ISSN: 2619-9793 • E-ISSN: 2148-094X

istanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

VOLUME 21 • ISSUE 2 • MARCH 2020

Original Articles

istanbulmedicaljournal.org

galenos yayınevi

İstanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

Owned by on behalf of the University of Health Sciences Turkey, İstanbul Training and Research Hospital
Özgür YİĞİT

galenos yayınevi

Galenos Publishing House
Owner and Publisher
Derya Mor
Erkan Mor

Publication Coordinator
Burak Sever

Web Coordinators
Turgay Akpınar
Fuat Hocalar

Graphics Department
Ayda Alaca
Çiğdem Birinci
Gülşah Özgül

Finance Coordinator
Sevinç Çakmak

Project Coordinators
Pınar Akpınar
Gamze Aksoy
Saliha Tuğçe Evin
Melike Eren
Hatice Sever
Duygu Yıldırm

Project Assistants
Gülay Akın
Özlem Çelik
Rabia Palazoğlu
Ece Büşra Türkmen

Research&Development
Mert Can Köse
Mevlüde Özlem Akgüney

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Turkey
Phone: +90 (212) 621 99 25 **Fax:** +90 (212) 621 99 27
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Printing at: Üniform Basım San. ve Turizm Ltd. Şti.
Matbaacılar Sanayi Sitesi 1. Cad. No: 114 34204 Bağcılar, İstanbul, Turkey
Phone: +90 (212) 429 10 00
Certificate Number: 42419
Printing Date: March 2020
ISSN: 2619-9793 **E-ISSN:** 2148-094X
International periodical journal published three times in a year.

İSTANBUL MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

İstanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

istanbul
MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

AIMS AND SCOPE

İstanbul Medical Journal is the scientific, peer reviewed, open access publication of İstanbul Training and Research Hospital. The journal is printed six times in a year; on January, March, May, July, September, November and its publication language is Turkish and English.

The aim of the journal is to publish high level clinical and experimental studies conducted in all fields of medicine. Reviews comprising the latest research findings, reports on rare and educative cases and letters to the editor are also published.

The target population of the journal includes specialists in all fields of medicine, academicians and relevant health care professionals.

The İstanbul Medical Journal is indexed in Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, EBSCO, DOAJ, Hinari, ROOT INDEXING, Türk Atif Dizini, Türk Medline, J-GATE, Proquest, Ardi, Goali and Oare.

Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at www.istanbulmedicaljournal.org. The journal guidelines, technical information, and the required forms are available on the journal's web page.

All expenses of the journal are covered by the İstanbul Training and Research Hospital. Potential advertisers should contact the Editorial Office. The journal does not publish advertisement.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the İstanbul Training and Research Hospital, editors, editorial board, and/or publisher; the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

All published content is available online, free of charge at www.istanbulmedicaljournal.org. Printed copies of the journal are distributed to the members of İstanbul Training and Research Hospital as well as the members of the editorial board and the journal's reviewers, free of charge.

Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

Open Access Policy is based on the rules of the Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/. By "open access" to peer-reviewed research literature, we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over the integrity of their work and the right to be properly acknowledged and cited.

Editor: Feray AKBAŞ

Address: Clinic of Internal Diseases, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

E-mail: atlibatur@yahoo.com

Publisher : GALENOS PUBLISHING HOUSE

Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 Fındıkzade 34093 İstanbul, Turkey

Phone: +90 (212) 621 99 25 Fax: +90 (212) 621 99 27 E-mail: info@galenos.com.tr/yayin@galenos.com.tr Web: www.galenos.com.tr

OPEN ACCESS

İSTANBUL MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

Manuscripts submitted to İstanbul Medical Journal will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. In experimental animal studies, the authors should indicate that the procedures followed were in accordance with animal rights as per the Guide for the Care and Use of Laboratory Animals http://oacu.od.nih.gov/regs/guide/guide.pdf and they should obtain animal ethics committee approval. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, signed releases of the patient or of their legal representative should be enclosed.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors

(ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

İstanbul Medical Journal requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.istanbulmedicaljournal.org) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

İstanbul Medical Journal requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

istanbul MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

When submitting a manuscript to İstanbul Medical Journal, authors accept to assign the copyright of their manuscript to İstanbul Training and Research Hospital. If rejected for publication, the copyright of the manuscript will be assigned back to the authors. İstanbul Medical Journal requires each submission to be accompanied by a Copyright Transfer Form (available for download at www.istanbulmedicaljournal.org). When using previously published content, including figures, tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s).

Statements or opinions expressed in the manuscripts published in İstanbul Medical Journal reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2016 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.istanbulmedicaljournal.org. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:

- Copyright Transfer Form,
- Author Contributions Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors)

during the initial submission. These forms are available for download at www.istanbulmedicaljournal.org.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: A Turkish and an English abstract should be submitted with all submissions except for Letters to the Editor. Submitting a Turkish abstract is not compulsory for international authors. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

istanbul
MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Report, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or tatal of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Rankovic A, Rancic N, Jovanovic M, Ivanović M, Gajović O, Lazić Z, et al. Impact of imaging diagnostics on the budget – Are we spending too much? Vojnosanit Pregl 2013; 70: 709-11.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

istanbul MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed “Response to the reviewers” that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer’s comment, followed by the author’s reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal’s webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

Editor : Feray AKBAŞ

Address: Clinic of Internal Diseases, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Samatya, Fatih, İstanbul, Türkiye

E-mail: atlibatur@yahoo.com

Publisher : GALENOS PUBLISHING HOUSE

Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 Fındıkzade 34093 İstanbul, Turkey
Phone: +90 (212) 621 99 25
Fax: +90 (212) 621 99 27
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr

İSTANBUL MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

CONTENTS

Original Articles

istanbul
MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

CONTENTS

İstanbul Med J 2020; 21(2): 82-7
DOI: 10.4274/imj.galenos.2020.57984

Prognostic Analysis of Neutrophil/Lymphocyte Ratio and Thrombocyte/Lymphocyte Value Before Trimodal Treatment in Invasive Bladder Cancer

İnvaziv Mesane Kanserinde Trimodal Tedavi Öncesinde Nötrofil/Lenfosit Oranı ve Trombosit/Lenfosit Değerinin Prognostik Önemi

Berrin İnanç, Özlem Mermut

University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey

ABSTRACT

Introduction: To evaluate whether neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) ratios have prognostic value in patients undergoing bladder conserving treatment (trimodal therapy).

Methods: A total of 40 patients receiving trimodality treatment for invasive bladder cancer were included in the study retrospectively. NLR and PLR were obtained for every patient before trimodality treatment was applied. We investigated whether NLR and PLR values had prognostic value for survival.

Results: Gender, age, T stage, Histologic grade, radiotherapy dose, NLR and PLR values were evaluated in bladder cancer patients receiving trimodal therapy. In the receiver operating characteristic analysis, the optimum cut-off value for NLR was found to be 3.2 (sensitivity 71.4%, specificity 65.2% p<0.025). Area under the curve (AUC): 0.717, confidence interval (CI) 95% (0.557-0.877), the optimum cut-off for PLR was found as 152.25 (sensitivity 78.1%, specificity 64.2%, p<0.006), AUC: 0.764, CI 95% (0.610-0.917). Survival analysis showed that disease-free survival was 52.36±6 months and statistically significant in patients with an NLR value greater than 3.2 (p=0.023). PLR value above 152.25 was found to be an independent risk factor for disease-free survival (52.8±6.1 months) and overall survival (50.6±7.2 months) (p=0.043, p=0.011, respectively).

Conlusion: NLR and PLR before trimodal treatment in invasive bladder cancer patients may be considered as a prognostic factor for disease progression. NLR and PLR values should be taken into consideration when deciding on trimodal treatment.

Keywords: Bladder cancer, chemoradiotherapy, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio

ÖZ

Amaç: Mesane koruyucu tedavi (trimodal tedavi) uygulanan hastalarda nötrofil/lenfosit (NLR) ve trombosit/lenfosit (PLR) oranının prognostik bir değerinin olup olmadığını değerlendirdik.

Yöntemler: Bu retrospektif çalışmaya kasa invaze mesane kanseri tanısı alan ve trimodal (TUR + kemoradyoterapi) tedavi uygulanan 40 hasta dahil edildi. Trimodal tedavi uygulanmadan önce NLR ve PLR kan değerlerinden elde edildi. NLR ve PLR değerlerinin sağkalım açısından prognostik değeri olup olmadığı araştırıldı.

Bulgular: Trimodal tedavi alan mesane kanserli hastalarda, cinsiyet, yaş, T evresi, radyoterapi dozu, NLR ve PLR değerleri değerlendirildi. Alıcı işletim karakteristiği analizinde NLR için, optimum cut-off değeri 3,2 olarak bulundu. (sensitivite %71,4, spesifite %65,2 p<0,025). Eğri altındaki alan (AUC): 0,717, güven aralığı (CI): %95 (0,557-0,877), PLR için optimum cut-off 152,25 olarak bulundu (sensitivite %78,1, spesifite %64,2, p<0,006). AUC: 0,764, CI: %95 (0,610-0,917). Sağkalım analizlerinde NLR değeri 3,2 üzerinde olan hastalarda hastalıksız sağkalım 52,3±6 ay ve istatiksel olarak anlamlıydı (p=0,023). PLR değerinin 152,25 üzerinde olması hastalıksız sağkalım (52,8±6,1 ay) ve genel sağkalım (50,6±7,2 ay) için bağımsız bir risk faktörü olarak bulundu ve istatiksel olarak anlamlıydı (sırasıyla p=0,043, p=0,011).

Sonuç: İnvaziv mesane kanserli hastalarda trimodal tedavi öncesinde NLR ve PLR değeri hastalık progresyonunu göstermek için prognostik bir faktör olarak değerlendirilebilir. Trimodal tedavi kararı verilirken NLR ve PLR değerleri de göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Mesane kanseri, kemoradyoterapi, nötrofil/lenfosit oranı, trombosit/lenfosit oranı

Address for Correspondence/Yazışma Adresi: Berrin İnanç MD, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey
Phone: +90 532 704 79 50 **E-mail:** byalcin77@hotmail.com **ORCID ID:** orcid.org/0000-0002-6354-4609

Cite this article as/Atıf: İnanç B, Mermut Ö. Prognostic Analysis of Neutrophil/Lymphocyte Ratio and Thrombocyte/Lymphocyte Value Before Trimodal Treatment in Invasive Bladder Cancer. İstanbul Med J 2020; 21(2): 82-7.

Received/Geliş Tarihi: 11.05.2019
Accepted/Kabul Tarihi: 09.01.2020

Introduction

Invasive bladder cancer accounts for about 30% of all bladder cancers. In invasive bladder cancers, advanced treatment is needed after transurethral resection (TUR); in very rare cases, TUR is sufficient (1,2). These treatment regimens include radical cystectomy, partial cystectomy, bladder protective approaches and systemic treatments in advanced stage patients. Bladder protective treatments come to the forefront for patients who avoid radical surgical treatments due to the continuation of the patient's quality of life and maintaining organ function. With treatment applications (trimodality) including maximum TUR, radiotherapy (RT) and chemotherapy (CT), results similar to radical surgery are obtained in the treatment of invasive bladder cancer. In order to apply bladder protective treatment, the absence of small tumor (<5 cm), single focus disease, microscopic full TUR (R0-1), urethral obstruction or hydronephrosis, and the absence of pelvic lymph node metastasis and no reported *in situ* carcinoma are required.

It is known today that inflammation plays a critical role in the emergence, progression and metastasis of the tumor (3). While neutrophil count increases during systemic inflammation, neutrophil/lymphocyte (NLR) ratio and platelet/lymphocyte (PLR) ratio change with decreasing lymphocyte count. There are many studies suggesting that the rate of NLR is an effective predictive marker in many cancers (4,5) and bladder cancer (6,7). However, to date, there is no study investigating the rate of NLR and PLR rates together before trimodal treatment in patients with invasive bladder cancer.

In this study, we tried to reveal that NLR and PLR are a prognostic marker before the selection of trimodal treatment for invasive bladder cancer.

Methods

We retrospectively evaluated 52 patients who were diagnosed with invasive bladder cancer after TUR, who were not eligible for radical surgical intervention or who did not want it, or who were sent to University of Health Sciences Turkey, İstanbul Training and Research Hospital, Deparment of Radiation Oncology for bladder protective treatment between 2011 and 2018. While all relevant laboratory and pathology results were obtained from the hospital data, the data related to treatment follow-up were obtained from the clinical files. The recurrence and progression status for each patient was determined from these patient files.

Patients who were not eligible for bladder protective treatment (patients with the presence of carcinoma *in situ*, tumors larger than 5 cm, hydronephrosis, and pelvic lymph node metastasis, patients not undergoing microscopic full urethral resection) and those with any malignancy except bladder tumor, acute inflammatory diseases, bleeding disorders, and hematological disorders were excluded from the study after TUR. Of the 52 patients examined, we selected a total of 40 patients with clinically T2-T4a tumors after TUR. These patients received chemoradiotherapy after maximal TUR, and NLR and PLR ratios were determined from blood tests prior to the treatment.

The relationships between the patients' gender, age, T stage of the tumor, dose of RT, total follow-up time, overall survival and disease-free survival (regional and/or distant metastasis) times and NLR and PLR rates were examined.

Approval for this study was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (decision no: 12-04-2019/1792).

TUR and Chemotherapy Data

All patients received maximal TUR and then chemoradiotherapy. RT protocols; with a daily dose of 1.8-2 Gy/fraction, pelvic lymph nodes were sometimes included, and after 40-45Gy, it was applied to the bladder or tumor as to increase 65 Gy. The CT protocol of Cisplatin 35 mg/m^2 was applied weekly by the Medical Oncology Clinic. Patients were evaluated for acute toxicity every 10 days.

Blood Tests

Blood test results of a total of 40 patients who were eligible for trimodal treatment were examined before routine treatment. The data obtained included neutrophil count, lymphocyte count, and platelet count. NLR was determined by dividing absolute neutrophil count by absolute lymphocyte count and PLR was determined by dividing absolute platelet count by absolute lymphocyte count.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 18.0 for Windows. Receiver operating characteristic (ROC) analysis was performed to determine the cut-off values of the NLR and PLR values. Survival analyses were performed using the Kaplan Meier method. Log-rank test was used in univariate analyses. $P<0.05$ was considered statistically significant.

Results

Of the total 40 patients we included in the study, 5 were women and 35 were men. The mean follow-up period was 26 (5-72) months.

In almost all patients, the first complaint was hematuria. Their histopathologies were transitional epithelial cell carcinoma. Gender distribution, age distribution, hemoglobin values, T stage, RT doses, and the number of patients above and below the cut-off values of NLR and PLR are summarized in Table 1.

In univariate analysis, patients' being at T2 stage was found to be a prognostic value for overall survival ($p=0.003$).

In ROC analysis, optimum cut-off value for NLR was found to be 3.2 (Figure 1) (sensitivity 71.4%, specificity 65.2% $p<0.025$), Area under the curve (AUC): 0.717, confidence interval (CI): 95% (0.557-0.877). Local recurrence and metastasis were detected in 11 patients with a NLR value greater than 3.2, while local recurrence and metastasis were not detected in 9 patients. In the univariate analysis, disease-free survival was 52.3±6 months. While there were metastases and local recurrence in 3 patients with an NLR value below 3.2, no local recurrence and metastasis was detected in 17 patients with a value under 3.2. In this group of patients, disease-free survival was 27.6±6.6 months, which was statistically significant ($p=0.023$). While overall survival was 52±14.1 months in patients with an NLR value above 3.2, it was 14±2.08 months in patients with an NLR below 3.2, and this was not statistically significant ($p=0.075$) (Figure 3 and Table 2).

In the ROC analysis, the optimum cut-off for PLR was found to be 152.25 (Figure 2) (78.1% in sensitivity, 64.2% in specificity, p<0.006), AUC: 0.764, CI: 95% (0.610-0.917). Local recurrence and metastasis were detected in 11 patients with PLR value above 152.25, while local recurrence and metastasis were not detected in 12 patients. Disease-free survival was 52.8±6.1 months in univariate analysis. Local recurrence and metastasis were detected in 3 patients with PLR below 152.25, whereas local recurrence and metastasis were not detected in 14 patients. In this

Table 1. General and treatment features of the patients

	n=40 (number of patients)	%
Female	5	12.5
Male	35	87.5
Age (mean ± SD)	64±6.5 (50-76)	
Under the age of 65 years	21	52.5
Above the age of 65 years	19	47.5
Stage		
T2	33	82.5
T3	4	10
T4	3	7.5
RT dose		
60 Gy	4	10
66 Gy	36	90
Hemoglobin value (mean ± SD)	11.9±1.97 (7.6-16)	
NLR		
≥3.2	21	52.5
≤3.2	19	47.5
PLR		
≥152.25	23	42.5
≤152.25	17	57.5
Disease-free survival	21.10 (3-66)	
Overall survival	26.75 (5-72)	

SD: standard deviation, RT: radiotherapy, NLR: neutrophil/lymphocyte, PLR: platelet/lymphocyte

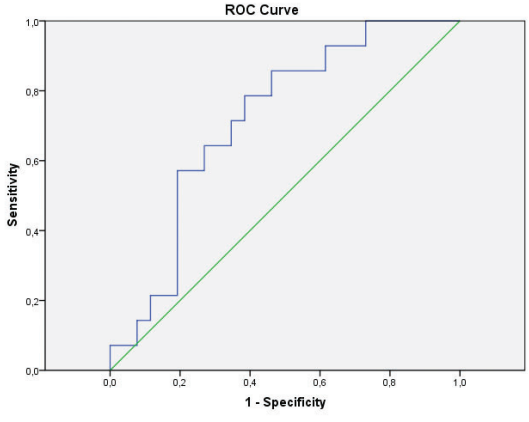

Figure 1. ROC Curve Analysis to determine the cut-off value of neutrophil/lymphocyte

ROC: Receiver operating characteristic

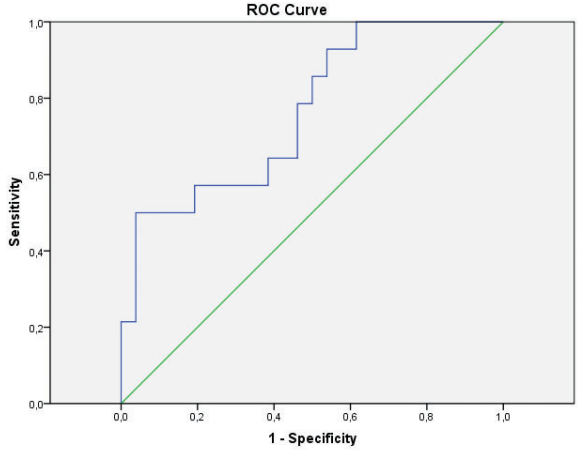

Figure 2. ROC Curve Analysis ROC Curve Analysis to determine the cut-off value of platelet/lymphocyte

ROC: Receiver operating characteristic

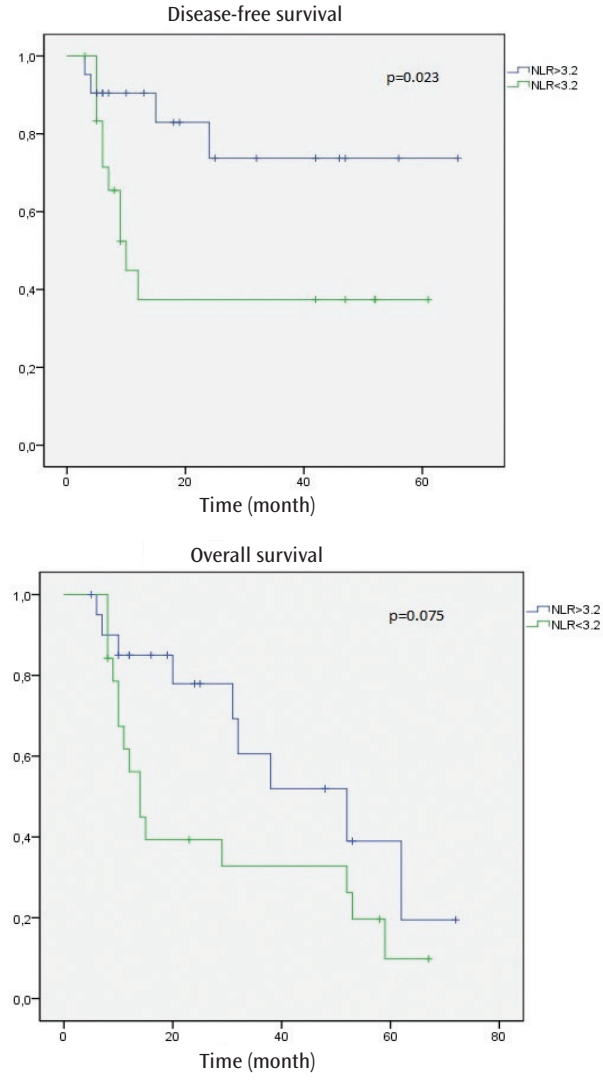

Figure 3. Kaplan-Meier curves for disease-free and overall survivals for neutrophil/lymphocyte value

NLR: neutrophil/lymphocyte

patient group, disease-free survival was 31.2±6.7 months and this was found to be statistically significant (p=0.043). While overall survival was 50.6±7.2 months in patients with a PLR value above 152.25, it was 27.5±4.4 months in patients with a PLR value below 152.25, and this was statistically significant (p=0.011) (Figure 4 and Table 2).

Discussion

In muscle-invasive bladder cancers, it is more common in men than in women, and patients receiving trimodal treatment are generally male patients (8). Similarly in our study, 35 patients were male and 5 were female. Bladder cancers can occur in any age group, but its frequency increases with age. It occurs around the age of 69 years in men and around the age of 71 years in women. Although it has a good prognosis in patients under 40 years of age, it is more aggressive in elderly patients (9). In our study, the mean age was found to be 65±6.5 (50-76) years and this was compatible with literature (9). While 21 of the patients were below the age of 65 years, 19 were above the age of 65 years. Pathological stage of the tumor in bladder cancer is the most important factor in determining its treatment. While TUR is sufficient in non-muscle invasive tumors, intravesical treatments are applied to reduce regional recurrence. In patients with muscle-invasive bladder cancer, trimodal treatment is usually used after the T2 stage. When we consider our study, while there were patients with T2 tumors (33 patients), 4 patients with T3 and 3 patients with T4 tumors were present. It is known that prognosis and overall survival in early stage tumors are good. In our study, overall survival was better in the T2 stage and this was statistically significant (p=0.003).

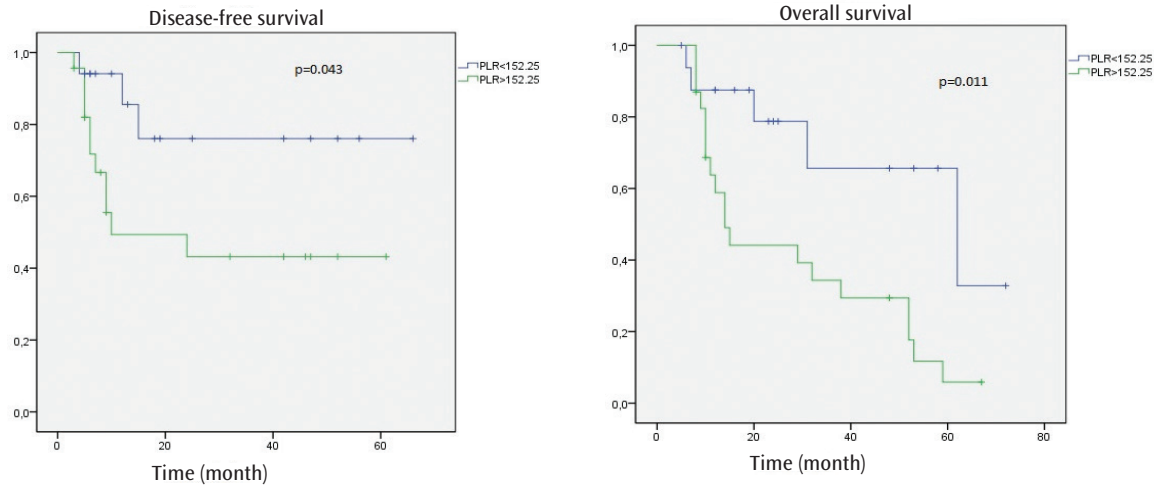

Figure 4. Kaplan-Meier curves for disease-free and overall survivals for platelet/lymphocyte value

PLR: platelet/lymphocyte

Table 2. Prognostic factors for disease-free survival and overall survival

		Number of patients	Disease-free survival (month)	p	Overall survival (month)	p
Gender	Female	5	23.2±9	0.285	29±10	0.121
	Male	35	42.4±5	-	38.0±4	-
Age	Under the age of 65 years	21	35±6	0.512	31±7	0.906
	Above the age of 65 years	19	46±7	-	52±27	-
Stage	T2	33	32±8	1.13	38±9	0.003
	T3	4	6±2.02	-	8±1.5	-
	T4	3	-	-	-	-
Dose of radiotherapy	60 Gy	4	38.5±4.8	0.863	35±4.0	0.762
	66 Gy	36	51.0±12.9		40±15.7	-
NLR	≥3.2	21	52.3	0.023	52±14.1	0.075
	≤3.2	19	27.6±6.6		14±2.08	-
PLR	≥152.25	23	52.8±6.1	0.043	50.6±7.2	0.011
	≤152.25	17	31.2±6.7	-	27.54.4	-
Final status	Alive	24	-	-	-	-
	Ex	16	-	-	-	-

NLR: neutrophil/lymphocyte, PLR: platelet/lymphocyte

RT dose is 60-66 Gy in patients with bladder cancer who receive trimodal treatment, and cisplatin or 5-Flurouracil is used as a radiosensitizer (10). In our study, cisplatin 35 mgr/m^2 was given weekly to all patients. Systemic CT was not applied weekly to some patients due to acute hematologic and gastrointestinal toxicity.

As a TR dose, 60 Gy was applied only in 4 patients, and in the remaining 36 patients, 66 Gy RT was applied externally (Table 1).

While non-invasive bladder cancers often recur after TUR, invasive bladder cancers and high grade tumors tend to make distant metastases. The regional recurrence and distant metastasis of the tumor depends on the characteristics of the tumor cell and the environmental conditions of the tumor (11). The presence of tumor cells and the behaviors of tumor cells, compared to normal cells, cause inflammatory reactions in the tissues surrounding the tumor. These inflammatory reactions cause an increase in the number of white blood cells in the bloodstream (12). There are many parameters to evaluate the systemic inflammatory response in peripheral blood tests. White blood counts consisting of fibrinogen, ferritin, albumin, C-reactive protein, transferrin, lymphocyte and neutrophil in the blood are examples for them.

There is growing evidence to support that systemic inflammation contributes to cancer development and progression (13). O'Toole et al. (14) reported that the increase in lymphocyte activity against bladder cancer tumor cells was associated with the clinical stage. In the peripheral blood count, the NLR value obtained by dividing the absolute neutrophil count by the lymphocyte count has been evaluated in many studies and its relationship with the recurrence of some types of cancer has been examined (15,16,17). Considering the studies in the literature, a cut-off value of NLR was determined for each cancer type and it was observed that recurrence was more frequent in patients over this value (15,16,17,18).

In our study, the cut-off value for NLR was found to be 3.2. While regional recurrence and distant metastasis were detected in 11 patients above this value, only 3 of the patients who were below this value had regional recurrence and distant metastasis. Disease-free survival was 52±3.0 months in patients with an NLR value above 3.2, while it was found to be 27.6±6.6 months in patients with a NLR value below 3.2, which was statistically significant (p=0.023)

NLR value was used in many studies and its relationship with regional recurrence was shown. However, our patients were high grade patients diagnosed with invasive bladder cancer. Even if trimodal therapy or radical cystectomy was performed in these patients, the major problem was the occurrence of distant metastases. Many studies have shown that platelets play an important role in the metastatic process (19). Todenhöfer et al. (20) showed that increasing number of platelets before radical cystectomy is a bad prognostic factor. For this reason, we also examined the PLR value to evaluate distant metastasis. The PLR value is obtained by dividing the platelet count in the blood by the lymphocyte count. We found our cut-off value for PLR to be 152.25. While 11 patients above this value had regional or distant metastases, 3 patients below this value did not have regional or distant metastases.

In patients with an NPLR value above 152.25, disease-free survival was 52.8±6.1 months and overall survival was 50.6±7.2 months. On the other hand, in patients with PLR value below 152.25, disease-free survival was 31.2±6.7 months and overall survival was 27.5±4.4, and this was statistically significant (p=0.043, p=0.011, respectively).

In the literature, studies with NLR have generally been found to be about non-invasive bladder cancer and they have shown that the NLR value may be a prognostic factor for regional recurrence (21). Studies examining the PLR value were generally performed about stomach, brain and colon cancer (22), and invasive bladder cancer was studied in very few studies.

Contrary to all the studies, we examined the PLR value in this study and included patients who received trimodal treatment for invasive bladder cancer. When considered from this point of view, it is the only study.

In the univariate log-rank analysis performed for patients above the cut-off values of NLR and PLR, NLR value is showed to be an independent prognostic factor for disease-free survival, while PLR can be a prognostic marker for both disease-free survival and overall survival.

The low number of patients in our study may be due to the lower number of patients receiving trimodal treatment in bladder cancer compared to radical cystectomy.

Conclusion

In patients with invasive bladder cancer, while NLR and PLR values can be used as a prognostic factor to show disease progression before trimodal treatment, further pathogenic and cytogenetic studies involving more patients are needed to use NLR and PLR as a prognostic marker for overall survival.

Ethics

Ethics Committee Approval: Approval for this study was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (decision no: 12-04-2019/1792).

Informed Consent: A total of 40 patients receiving trimodality treatment for invasive bladder cancer were included in the study retrospectively.

Peer-review: Externally peer-review.

Author Contributions: Concept - B.İ.; Design - B.İ.; Data Collection and/or Processing - B.İ., Ö.M.; Analysis and/or Interpretation - B.İ., Ö.M.; Literature Search - B.İ., Ö.M.; Writing Manuscript - B.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Solsona E, Iborra I, Collado A, Rubio-Briones J, Casanova J, Calatrava A. Feasibility of radical transurethral resection as monotherapy for selected patients with muscle invasive bladder cancer. J Urol 2010; 184: 475-80.
2. Leibovici D, Kassouf W, Pisters LL, Pettaway CA, Wu X, Dinney CP, et al. Organ preservation for muscle-invasive bladder cancer by transurethral resection. Urology 2007; 70: 473-6.
3. Herszényi L, Lakatos G, Hritz I, Varga M.Z, Cierny G,Tulassay Z. The role of inflam mation and proteinases in tumor progression. Dig Dis 2012; 30: 249-54.

4. Jaramillo-Reta KY, Velázquez-Dohorn ME, Medina-Franco H. Neutrophil to lymphocyte ratio as predictor of surgi- cal mortality and survival in complex surgery of the upper gas- trointestinal tract. Rev Invest Clin 2015; 67: 117-21.
5. Cho H, Hur HW, Kim SW,Kim SH, Kim JH, Kim YT, et al. Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. Cancer Immunol Immunother 2009; 58: 15-23.
6. Mano R, Baniel J, Shoshany O, Margel D, Bar-On T, Nativ O, et al. Neutrophil –to- lymphocyte ratio predicts progression and recurrence of non- muscle-invasive bladder cancer. Urol Oncol 2015; 33: 67.e1-7.
7. Krane LS, Richards KA, Kader AK, Davis R, Balaji KC, Hemal AK. Preopera- tive neutrophil/lymphocyte ratio predicts overall survival and extravesical disease in patients undergoing radical cystec- tomy. J Endourol 2013; 27: 1046-50.
8. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, et al. Cancer statistics, 2005. CA Cancer J Clin 2005; 55: 10– 30
9. Madeb R, Messing EM. Gender, racial and age differences in bladder cancer incidence and mortality. Urol Oncol 2004; 22: 86–92.
10. Mak RH, Zietman AL, Heney NM, Kaufman DS, Shipley WU. Bladder preservation: optimizing radiotherapy and integrated treatment strategies. BJU Int 2008; 102: 1345-53 .
11. Totterman TH, Loskog A, Essand M: The immunotherapy of prostate and bladder can- cer. BJU Int 2005; 96: 728–35.
12. Yamada H, Luo Y, Matsumoto T, O'Donnel M. A novel expression of macrophage derived chemo- kine in human bladder cancer. J Urol 2005; 173: 990–5.
13. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer related inflammation. Nature 2008; 454: 436–44
14. O'Toole C, Perlman P, Unsgaard B, Moberger G, Edsmyr F. Celllular immunity to human urinary bladder carcinoma. Correlation to clinical stage and radiotherapy. Int J Cancer 1972; 10: 77–91.
15. Motomura T, Shirabe K, Mano Y, Muto J, Toshima T, Umemoto Y, et al. Neutrophil-lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment. J Hepatol 2013; 58: 58–64.
16. Sejima T, Iwamoto H, Morizane S, Hinata N, Yao A, Isoyama T, et al.The significant immunological characteristics of peripheral blood neutrophil-to-lymphocyte ratio and Fas ligand expression incidence in nephrectomized tumor in late recurrence from renal cell carcinoma. Urol Oncol 2013; 31: 1343-9.
17. Mallappa S, Sinha A, Gupta S, Chadwick SJ. Preoperative neutrophil to lymphocyte ratio >5 is a prognostic factor for recurrent colorectal cancer. Colorectal Dis 2013; 15: 323-8.
18. Ohno Y, Nakashima J, Ohori M Gondo T, Hatano T, Tachibana M: Followup of neutrophil-to-lymphocyte ratio and recurrence of clear cell renal cell carcinoma. J Urol 2012; 187: 411–7.
19. Nieswandt B, Hafner M, Echtenacher B, Mannel DN: Lysis of tumor cells by natural killer cells in mice is impeded by platelets. Cancer Res 1999; 59: 1295–300.
20. Todenhöfer T, Renninger M, Schwentner C Stenzl A, Gakis G. A new prognostic model for cancer-spe- cific survival after radical cystectomy in- cluding pretreatment thrombocytosis and standard pathological risk factors. BJU Int 2012; 110: 533-40.
21. Ceylan C, Doluoglu OG, Keles I,Gazel E, Temucin T, Odabas O, et al. Importance of the neutrophil-to-lymphocyte ratio in muscle- invasive and non-muscle invasive bladder tumors. Urologia 2014; 81: 120-4.
22. Aldemir MN, Turkeli M, Simsek M, Yildirim N, Bilen Y, Yetimoglu H, et al. Prognostic Value of Baseline Neutrophil-Lymphocyte and Platelet-Lymphocyte Ratios in Local and Advanced Gastric Cancer Patients. Asian Pac J Cancer Prev 2015; 16: 5933-7.

İstanbul Med J 2020; 21(2): 88-91
DOI: 10.4274/imj.galenos.2020.51437

Unexpected Histopathological Findings After Laparoscopic Sleeve Gastrectomy

Laparoskopik Sleeve Gastrektomi Ameliyatı Sonrasında Görülen Beklenmedik Histopatolojik Bulgular

Burçin Batman, Hasan Altun

İstinye University Faculty of Medicine, Department of General Surgery, İstanbul, Turkey

ABSTRACT

Introduction: The prevalence of obesity is increasing all over the world. Laparoscopic sleeve gastrectomy (LSG) has become the most common bariatric surgery in the world today. Unlike other bariatric surgeries, laparoscopic sleeve gastrectomy yields a pathological examination. The aim of this study was to describe unexpected histopathological findings following LSG.
Methods: In this study, the pathologies of 1364 patients who underwent LSG between March 2013 and September 2019 were analyzed retrospectively. Patients were evaluated by a multidisciplinary team in the preoperative period. Patients who met the criteria for LSG were operated. These criteria were; Body Mass index (BMI) ≥40 kg/m^2 or BMI >35 kg/m^2 and comorbidities or BMI between 30 and 35 kg/m2 with accompanying Type 2 diabetes Mellitus or Metabolic syndrome. Two hundred four of the patients underwent gastroscopy preoperatively.

Results: One thousand three hundred sixty four patients underwent LSG. The mean age was 40.93±10.86 years; 974 patients (71.48%) were female. The mean BMI was 42.23±7.28. The most common findings in the pathologies were normal gastric specimen (50%), gastritis (30%) and changes due to proton pump inhibitor use (23%) respectively.
Conclusion: Gastroscopy should be added to the preoperative preparation process in cases where there is no gastric specimen after the operation. Preoperative gastroscopy is not a necessity for laparoscopic sleeve gastrectomy. It can be performed in selected cases.

Keywords: Laparoscopic sleeve gastrectomy, bariatric surgery, histopathological changes

ÖZ

Amaç: Obezite sıklığı tüm dünyada artmaktadır. Laparoskopik sleeve gastrektomi (LSG) günümüzde dünya genelinde en sık uygulanan bariatrik cerrahi olarak yerini almıştır. Diğer bariatrik cerrahilerin aksine LSG'de patolojik inceleme yapılabilecek bir piyes çıkmaktadır. Bu çalışmanın amacı LSG'yi takiben beklenmeyen histopatolojik bulguları tanımlamaktır.

Yöntem: Bu çalışmada Mart 2013 ile Eylül 2019 tarihleri arasında LSG uygulanan 1364 hastanın patolojileri geriye dönük olarak incelendi. Hastalar ameliyat öncesi dönemde multidisipliner bir ekip tarafından değerlendirildi. LSG'ye uygun kriterleri sağlayan hastalar Amerikan Metabolik ve Bariatrik Cerrahlar Birliği kriterlerine göre ameliyata alındı. Ameliyat öncesi dönemde 204 hastaya gastroskopi yapıldı.
Bulgular: Bin üç yüz altmış dört hastaya LSG uygulandı. Ortalama yaş 40,93±10,86 idi; 974 hasta (%71,48) kadındı. Ortalama Vücut Kitle indeksi 42,23±7,28 idi. Patolojilerdeki en sık bulgu normal mide piyesi (%50) olmakla birlikte bunu takip eden bulgular gastrit (%30) ve proton pompa inhibitörü kullanımına bağlı değişikliklerdi (%23).
Sonuç: Sleeve gastrektomi sonrasında beklenmedik histopatolojik bulgular saptanabilir. Ancak ameliyat öncesi yapılan gastroskopi ile saptanması zordur. LSG ameliyatı öncesinde böyle bir zorunluluk olmayıp seçilmiş olgularda ameliyat öncesi dönemde uygulanabilir.

Anahtar Kelimeler: Laparoskopik sleeve gastrektomi, histopatolojik değişiklikler, bariatrik cerrahi

Address for Correspondence/Yazışma Adresi: Burçin Batman MD, İstinye University Faculty of Medicine, Department of General Surgery, İstanbul, Turkey
Phone: +90 532 471 52 55 **E-mail:** drburcinbatman@yahoo.com **ORCID ID:** orcid.org/0000-0003-2245-3337

Cite this article as/Atıf: Batman B, Altun H. Unexpected Histopathological Findings After Laparoscopic Sleeve Gastrectomy. İstanbul Med J 2020; 21(2): 88-91.

Received/Geliş Tarihi: 10.10.2019
Accepted/Kabul Tarihi: 24.01.2020

Introduction

The incidence of obesity is increasing worldwide. More than one billion adults are thought to be obese or overweight. Obesity is associated with many diseases, including low life expectancy and arterial hypertension, hyperlipidemia, type 2 diabetes mellitus (T2DM) (1-3).

Bariatric surgery is the most effective technique to improve comorbidities associated with weight loss and obesity (4). Today, laparoscopic sleeve gastrectomy (LSG) is the most commonly applied bariatric surgery for obesity and associated comorbidities in the United States and Asia-Pacific region, with its relative ease of application and excellent results (5,6). Unlike Roux-en-Y gastric bypass, a specimen is removed that can be pathologically examined and unexpected pathological results can be encountered.

In most of the previously published series, it was reported that upper gastrointestinal system endoscopy was performed preoperatively, and fewer studies reported that there were few or no endoscopic examinations (7-11). However, this issue is still controversial. Although The American Association of Gastrointestinal and Endoscopic Surgeons and The American Gastrointestinal Endoscopy Society recommend preoperative endoscopy in patients with gastrointestinal symptoms, it is recommended to be performed routinely for all patients that will undergo Roux-en-Y gastric bypass because it is difficult to reach remnant stomach postoperatively (12). Similarly, The American Association of Metabolic and Bariatric Surgeons (ASMBS) recommends gastroscopy only in clinical necessity in the preoperative period (13).

The aim of this study is to identify unexpected histopathological findings following LSG.

Methods

Pathology reports of patients were retrospectively analyzed to identify all consecutive patients with morbid obesity who underwent LSG between March 2013 and September 2019. All patients were evaluated as suitable for bariatric surgery based on The American Association of Clinical Endocrinologists, The Obesity Association and ASMBS guidelines. Written and verbal surgical informed consent form was obtained from all patients before surgery. Approval was obtained from the ethics committee of Liv Hospital Ulus on 09.08.2019 for this study (decision no: 2019-23).

Patients meeting the following criteria were considered eligible for LSG;

Patients with Body Mass index (BMI) ≥40 kg/m^2 or BMI > 35kg/m^2 and accompanying comorbidities or BMI between 30 and 35 kg/m^2 and with accompanying T2DM or metabolic syndrome were operated. Patients other than these criteria were not operated. Patients who underwent revision surgery and those who underwent different bariatric procedures were not included in the study.

All patients were evaluated by a multidisciplinary team consisting of a cardiologist, endocrinologist, dietitian, psychologist, pulmonologist and anesthesiologist before surgery. All patients underwent blood tests and a chest X-ray; Abdominal ultrasonography (abdominal pain and/or suspected cholecystitis history) and gastroscopy were also performed in patients who were deemed necessary (reflux, suspected hiatal hernia, upper gastrointestinal system complaints, dyspepsia, family history of malignancy). All patients were examined macroscopically and histopathologically.

Statistical Analysis

In the statistical analysis of all data, IBM SPSS (Statistical Package for the Social Sciences) Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. was used. Mean and standard deviation values were calculated in the descriptive statistics of the data.

Results

Between March 2013 and September 2019, 1425 patients underwent different types of bariatric surgery and 1364 patients who underwent LSG were included in this study. Sixty one cases who were not included in the study were other bariatric surgeries or revision surgeries. The mean age was 40.93±10.86 years; 974 patients (71.48%) were women. The mean BMI was 42.23±7.28.

Most histopathological examinations of the specimens (682 patients, 50%) resulted in normal stomach tissue. The subsequent pathologies were gastritis (409 patients, 30%) and changes due to proton pump inhibitor (313 patients, 23%), respectively. Pathologies following them in decreasing rates are *Helicobacter pylori (HP)* infection (477 patients, 35%), intestinal metaplasia (20 patients, 1.5%), fundic gland polyp (5 patients, 0.36%), gastrointestinal stromal tumor (GIST) (6 patients, 0.44%), Schwannoma (1 patient, 0.073%), heterotopic pancreatic tissue (1 patient, 0.073%), duplication cyst (1 patient, 0.073%), and neuroendocrine tumor (1 patient, 0.073%) (Table 1). When the age distribution of tumoral results was evaluated, the patient diagnosed with Schwannoma was 49 years old and the tumor diameter was 0.4cm. In the patients in the GIST group, 2 patients were 45 years old and their tumor diameters were 0.6 and 0.5 cm. One patient was 49 years old and tumor diameter was 1cm; One patient was 64 years old and tumor diameter was 1.2 cm; one patient was 55 years old and tumor diameter was 0.7 cm; one patient was 56 years old and the tumor diameter was 0.7 cm. The patient with a neuroendocrine tumor was 48 years old and the tumor diameter was 1.2 cm.

Table 1. Histopathological findings

	n (number of patients)
Normal histopathology	682 (50%)
Gastritis	409 (30%)
Changes associated with proton pump inhibitor	313 (23%)
Helicobacter pylori (HP) infection	477 (35%)
Intestinal metaplasia	20 (1.5%)
Fundic gland polyp	5 (0.36%)
Gastrointestinal stromal tumor (GIST)	6 (0.44%)
Schwannoma	1 (0.073%)
Heterotopic pancreatic tissue	1 (0.073%)
Duplication cyst	1 (0.073%)
Neuroendocrine tumor	1 (0.073%)

Patients with macroscopically detected pathology during surgery underwent gastroscopy in the surgery. No pathology was found within the lumen.

In the existing cases, no additional treatment was required in the postoperative period. During the preoperative preparation period, 204 (15%) patients with gastrointestinal system complaints underwent gastroscopy. Medical eradication was not routinely applied to the patients with *HP* infection.

Discussion

After the increasing frequency of LSG in recent years, different histopathological results have begun to appear in gastric specimens. This resulted in an increase in parallel with incidental findings.

Although these findings may cause the surgeon to change the way of treatment in the postoperative period, most of the reported diagnoses do not require further clinical follow-up (14). In our series, there was no patient requiring treatment change in the postoperative period.

Some findings may vary according to geographic distributions. For example, the frequency of *HP* infections can vary from 3.2% to 64% (15-19,10,20-23). This rate was 35% in our series. Lee et al. (24) have shown that eradicating *HP* may reduce the risk of long-term malignancy, but this issue is still controversial. We did not apply routine eradication to patients who did not have clinical complaints among those with *HP* infection in our clinic.

Neoplasia was a rare finding in both our study and previous studies. While the frequency of GIST ranges from 0 to 1.2% (10,11,15,16,19,20,25) in the literature, we found 0.44% in our series. We detected all of these patients during the surgery and there was no need to change the treatment and follow-up protocol both in the surgical technique and in the postoperative period. All of them were early stage stromal tumors with low mitosis rate and low ki67 index. As in the study of Raess et al. (16), these incidentally detected histopathological findings gain more importance in surgical interventions that do not allow upper gastrointestinal system endoscopy in the future and in cases without stomach specimen. Routine gastroscopy in the preoperative period in LSG is a controversial issue. While a group of researchers advocated the necessity of performing routine gastroscopy to each patient preoperatively (26), another group shows a more conservative approach before LSG (27). The fact that we did not encounter any pathology in the gastric lumen in gastroscopy that we performed during the surgery for the lesions we detected incidentally on the stomach wall. This result questions the necessity of preoperative endoscopy.

In our series, we selectively applied upper gastrointestinal system endoscopy in 1364 patients in the preoperative period, as suggested by ASMBS (13), who had suspected hiatal hernia, family history of malignancy, and severe upper gastrointestinal complaints. We performed preoperative endoscopy only in 15% of patients.

We decided to perform Roux-en-Y gastric bypass instead of LSG upon the detection of grade C esophagitis according to the Los Angeles classification in only one of the patients who underwent gastroscopy in the preoperative period. LSG was applied to all other patients and a routine follow-up protocol was applied in the postoperative period. Although Safaan et al. (19) found an increase in abnormal pathologies detected with increasing age, we did not find any findings increasing with age in our series.

Conclusion

Preoperative endoscopy should be routinely performed especially in the types of surgery where endoscopic examination cannot be performed after surgery and a gastric specimen will not be removed. However, preoperative endoscopic evaluation is sufficient only in selected cases for LSG, since it does not cause much change in the decision of the type of surgery or in the postoperative follow-up.

Ethics Committee Approval: Approval was obtained from the ethics committee of Liv Hospital Ulus on 09.08.2019 for this study (decision no: 2019-23).

Informed Consent: Written and verbal surgical informed consent form was obtained from all patients before surgery.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.A.; Design - B.B.; Data Collection and/or Processing - B.B.; Analysis and/or Interpretation - H.A.; Literature Search - H.A.; Writing - B.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007; 49: 403-14.
2. Klijs B, Mackenbach JP, Kunst AE. Obesity, smoking, alcohol consumption and years lived with disability: a Sullivan life table approach. BMC Public Health 2011; 11: 378.
3. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body mass index and cause-specific mortality in 900,000 adults: collaborative analyses of 57 prospective studies. Lancet 2009; 373: 1083-96.
4. Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. Cochrane Database Syst Rev 2014; CD003641.
5. D'Hondt M, Vanneste S, Pottel H, Devriendt D, Van Rooy F, Vansteenkiste F. Laparoscopic sleeve gastrectomy as a single-stage procedure for the treatment of morbid obesity and the resulting quality of life, resolution of comorbidities, food tolerance, and 6-year weight loss. Surg Endosc 2011; 25: 2498-504.
6. Marceau P, Biron S, Bourque RA, Potvin M, Hould FS, Simard S. Biliopancreatic diversion with a new type of gastrectomy. Obes Surg 1993; 3: 29-35.
7. Miller GC, Reid AS, Brown IS. The pathological findings seen in laparoscopic sleeve gastrectomies for weight loss. Pathology 2016; 48: 228-32
8. Kinsinger LA, Garber JC, Whipple O. A review of sleeve gastrectomy specimen histopathology. Am Surg 2016; 82: 1101-4.
9. AbdullGaffar B, Raman L, Khamas A, AlBadri F. Should we abandon routine microscopic examination in bariatric sleeve gastrectomy specimens? Obes Surg 2016; 26: 105-10.

10. Dogan U, Suren D, Oruc MT, Gokay AA, Mayir B, Cakir T, et al. Spectrum of gastric histopathologies in morbidly obese Turkish patients undergoing laparoscopic sleeve gastrectomy. Eur Rev Med Pharmacol Sci 2017; 21: 5430-6.

11. Yardimci E, Bozkurt S, Baskoy L, Bektasoglu HK, Gecer MO, Yigman S. Rare entities of histopathological findings in 755 sleeve gastrectomy cases: a synopsis of preoperative endoscopy findings and histological evaluation of the specimen. Obes Surg 2018; 28: 1289-95

12. ASGE STANDARDS OF PRACTICE COMMITTEE, Anderson MA, Gan SI, Fanelli RD, Baron TH, Banerjee S, Cash BD, et al. Role of endoscopy in the bariatric surgery patient. Gastrointest Endosc 2008; 68: 1-10.

13. Mechanick JI, Youdim A, Jones DB, Garvey WT, Hurley DL, McMahon MM, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient-2013 update: cosponsored by American association of clinical endocrinologists, the obesity society, and American society for metabolic & bariatric surgery. Surg Obes Relat Dis 2013; 21 Suppl 1: S1-27.

14. Oner RI, Ozdas S. Histopathological findings in morbid obese patients undergoing laparoscopic sleeve gastrectomy: does H. pylori infection effective on pathological changes? Obes Surg 2018; 28: 3136-41.

15. Almazeedi S, Al-Sabah S, Al-Mulla A, Al-Murad A, Al-Mossawi A, Al-Enezi K, et al. Gastric histopathologies in patients undergoing laparoscopic sleeve gastrectomies. Obes Surg 2013; 23: 314-9.

16. Raess PW, Baird-Howell M, Aggarwal R, Williams NN, Furth EE. Vertical sleeve gastrectomy specimens have a high prevalence of unexpected histopathologic findings requiring additional clinical management. Surg Obes Relat Dis 2015; 11: 1020-3.

17. Ohanessian SE, Rogers AM, Karamchandani DM. Spectrum of gastric histopathologies in severely obese American patients undergoing sleeve gastrectomy. Obes Surg 2016; 26: 595-602

18. Lauti M, Gormack SE, Thomas JM, Morrow JJ, Rahman H, Mac- Cormick AD. What does the excised stomach from sleeve gastrectomy tell us? Obes Surg 2016; 26: 839-42.

19. Safaan T, Bashah M, El Ansari W, Karam M. Histopathological changes in laparoscopic sleeve gastrectomy specimens: prevalence, risk factors, and value of routine histopathologic examination. Obes Surg 2017; 27: 1741-9.

20. Aljerian K. Histopathological findings in laparoscopic sleeve gastrectomy specimens from patients with obesity in Saudi Arabia. Gastroenterol Res Pract 2018; 2018: 1702705.

21. Brownlee AR, Bromberg E, Roslin MS. Outcomes in patients with Helicobacter pylori undergoing laparoscopic sleeve gastrectomy. Obes Surg 2015; 25: 2276-9.

22. Rath-Wolfson L, Varona R, Bubis G, Tatarov A, Koren R, Ram E. Gastritis in patients undergoing sleeve gastrectomy: prevalence, ethnic distribution, and impact on glycemic. Medicine (Baltimore) 2017; 96: e6602.

23. Rossetti G, Moccia F, Marra T, Buonomo M, Pascotto B, Pezzullo A, et al. Does helicobacter pylori infection have influence on outcome of laparoscopic sleeve gastrectomy for morbid obesity? Int J Surg 2014; 12 Suppl 1: S68-71

24. Lee YC, Chiang TH, Chou CK, Tu YK, Liao WC, Wu MS, et al. Association between Helicobacter pylori eradication and gastric cancer incidence: a systematic review and metaanalysis. Gastroenterology 2016; 150: 1113-24.e5

25. Clapp B. Histopathologic findings in the resected specimen of a sleeve gastrectomy. JSLS 2015;19: e2013.00259

26. Peker KD, Sahbaz NA, Seyit H, Kones O, Gumusoglu AY, Alis H. An alternative view on the necessity of EGD before sleeve gastrectomy. Surg Obes Relat Dis 2017; 13: 1959-64.

27. Salama A, Saafan T, El Ansari W, Karam M, Bashah M. Is routine preoperative esophagogastroduodenoscopy screening necessary prior to laparoscopic sleeve gastrectomy? Review of 1555 cases and comparison with current literature. Obes Surg 2018; 28: 52-60.

İstanbul Med J 2020; 21(2): 92-6
DOI: 10.4274/imj.galenos.2020.40325

Smoking is a Strong Independent Predictor of Acute Coronary Syndrome Among Patients with Coronary Artery Ectasia

Koroner Arter Ektazisi Olan Hastalarda Akut Koroner Sendromun Güçlü Bağımsız Bir Öngördürücüsü: Sigara

Ahmet Gürdal, Serhat Sığırcı, Kadriye Orta Kılıçkesmez

University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey

ABSTRACT

Introduction: The independent relationship between smoking and Acute Coronary syndrome (ACS), among other risk factors, was investigated in patients with ectasic coronary arteries.

Methods: Between June 2015 and August 2018, 10.320 coronary angiography processes performed in our clinic were analyzed retrospectively. Coronary artery ectasia (CAE) was defined as the enlargement of a coronary artery to 1.5 times or more than that of the local or adjacent normal coronary artery segment. Patients were divided into two groups with (group 1) and without ACS (group 2). The two groups were compared in terms of demographic characteristics, laboratory findings and major risk factors such as hypertension, diabetes mellitus (DM) and smoking. Multivariate logistic regression analysis was used to evaluate independent predictors of ACS in patients with CAE.

Results: There were 189 (1.8%) patients with CAE and 143 (76%) of them were male. Of the patients, 107 (57%) were smoking, 106 (56%) had hypertension and 43 (22%) had DM. One hundred two (54%) of the patients presented with ACS. There was no significant difference between the groups in terms of hypertension, DM and basic laboratory characteristics. Smoking rate was significantly higher in the ACS group (66% and 34%, p=0.001). In multivariate logistic regression analysis, when hypertension, DM, age, gender and smoking were evaluated together, smoking was strongly predictive of ACS in patients with ectasic coronary artery [odds ratio: 2.34, (95% confidence interval), 1.093-4.983, p=0.028].

Conclusion: When the factors that play an important role in the etiology of ACS are evaluated together in patients with CAE, smoking predicts ACS strongly and independently.

Keywords: Acute coronary syndrome, coronary arteria ectasia, coronary artery disease, smoking

ÖZ

Amaç: Ektazik koroner arterlere sahip hastalarda, diğer önemli risk faktörlerinin yanında sigara ile Akut Koroner sendrom (AKS) arasındaki bağımsız ilişki araştırıldı.

Yöntemler: Kliniğimizde Haziran 2015-Ağustos 2018 tarihleri arasında yapılan 10.320 adet koroner anjiyografi geriye doğru analiz edildi. Koroner arter ektazisi, koroner arterin bölgesel ya da komşu normal koroner arter segmentinin 1,5 katı veya daha fazlası olacak şekilde genişlemesi olarak tanımlandı. Hastalar AKS olan ve olmayan olarak iki gruba ayrıldı. İki grup demografik özellikler, laboratuvar bulguları ve hipertansiyon, diabetes mellitus (DM) ve sigara gibi majör risk faktörleri açısından karşılaştırıldı. Çok değişkenli lojistik regresyon analizi ile ektazik koroner arterlere sahip hastalarda AKS'yi bağımsız öngördürücü risk faktörleri değerlendirildi.

Bulgular: Yüz kırk üçü erkek (%76), toplam 189 adet (%1,8) koroner ektaziye sahip hasta saptandı. Ektazi görülen hastaların 106'sı (%56) hipertansiyon, 43'ü (%22) DM tanılıydı ve 107'si (%57) sigara içmekteydi. Hastalardan 102'si (%54) AKS kliniği ile başvurdu. AKS olan (grup 1), AKS olmayan (grup 2) ile karşılaştırıldığında hipertansiyon, DM ve temel laboratuvar özellikleri açısından gruplar arasında anlamlı fark yoktu. Grup 1 daha genç (58±13 ve 63±10, p=0,016) ve erkek (%82 ve %67, p=0,027) ağırlıklıydı. AKS olan grupta sigara içme oranı anlamlı olarak yüksekti (%66 ve %34, p=0,001). Çok değişkenli lojistik regresyon analizinde hipertansiyon, DM, yaş, cinsiyet ve sigara birlikte değerlendirildiğinde, sigaranın ektazik koroner arterli hastalarda AKS'yi güçlü bağımsız bir şekilde öngördürdüğü saptandı [odds ratio: 2.34, (%95 güven aralığı), 1.093-4.983, p=0,028].

Sonuç: Ektazik koroner arterlere sahip hastalarda, AKS etiyolojisinde önemli rol oynayan etkenler birlikte değerlendirildiğinde, sigara AKS'yi güçlü ve bağımsız bir şekilde öngördürmektedir.

Anahtar Kelimeler: Akut koroner sendrom, koroner arter ektazisi, koroner arter hastalığı, sigara

Address for Correspondence/Yazışma Adresi: Ahmet Gürdal MD, University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
Phone: +90 506 478 14 41 **E-mail:** gurdal27@hotmail.com **ORCID ID:** orcid.org/0000-0002-2168-4937

Cite this article as/Atıf: Gürdal A, Sığırcı S, Orta Kılıçkesmez K. Smoking is a Strong Independent Predictor of Acute Coronary Syndrome Among Patients with Coronary Artery Ectasia. İstanbul Med J 2020; 21(2): 92-6.

Received/Geliş Tarihi: 29.09.2019
Accepted/Kabul Tarihi: 02.02.2020

Introduction

The role of smoking in the development of coronary artery disease (CAD) has been demonstrated in many studies (1). Smoking is held responsible for approximately one third of the deaths caused by cardiovascular diseases (2). Smoking primarily damages the cardiovascular system by increasing oxidative stress and inflammation, causing vasoconstriction and platelet dysfunction (3). It is known that major cardiac events and death are more common in those who have CAD and continue to smoke, but this risk is reduced by 40% in those who quit smoking (4).

Coronary artery ectasia (CAE) has been defined as the expansion of the coronary artery regionally or commonly to be 1.5 times or more of the adjacent normal coronary artery segment (5). Although CAE is often seen with CAD, it can also be detected as isolated. Isolated CAE is more rarely seen with a frequency of 0.1% to 0.79% among patients undergoing coronary angiography (6). When the etiology of CAE is examined, it is most frequently associated with atherosclerosis. Inflammation, oxidative stress, congenital anomalies, collagen tissue diseases and connective tissue diseases are among other causes (7).

In studies performed, it has been shown that ectasia leads to slow flow, thrombus formation and vasospasm in the coronary arteries, and perfusion defects can be observed in the myocardium due to the slow flow and possible microembolism (8,9). Coronary ectasias are mostly seen with CAD. Although there is no significant stenosis in the coronary arteries, dissection and thrombus occurring in the ectasia region can cause acute coronary syndrome (ACS) (10).

Many studies and researches have shown that smoking causes early atherosclerosis with a negative effect on the vascular wall, especially endothelial dysfunction, in early stage. Smoking causes coronary events by increasing inflammation in the vascular wall, causing vasospasm and leading to tendency to thrombosis. In ectasic coronaries, besides atherosclerosis, the frequency of coronary events increases due to negative factors such as slow flow, inflammation, dissection etc. (11). In our study, the independent relationship between smoking and ACS, among other important risk factors, was investigated in patients with ectasic coronary arteries.

Methods

Ten thousand three hundred twenty coronary angiographies performed between June 2015 and August 2018 in our clinic were analyzed retrospectively. In accordance with the angiographic definition of Hartnell et al. (5), CAE was defined as an expansion of the coronary artery diameter by 1.5 times or more than the adjacent normal segment. Regional or diffuse enlargement without significant coronary artery stenosis was considered as isolated ectasia. The presence of more than 50% narrowing in the coronary artery was considered as important obstruction and CAD. Patients presenting with ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (USAP) clinic were defined as ACS. The patients were divided into two groups, with and without ACS. The two groups were compared in terms of demographic features, laboratory findings, and major risk factors such as hypertension, diabetes mellitus (DM) and smoking. Risk factors predicting ACS were evaluated by multivariate logistic regression analysis in patients with ectasic coronary arteries. The study was approved by the ethics committee of University of Health Sciences Turkey, Şişli Hamidiye Etfal Education and Research Hospital (2534 / 17.09.2019). As it was a retrospective study, consent was not obtained from the patients.

Statistical analysis

SPSS Windows version 20 statistics program (SPSS, Inc. Chicago, IL, USA) was used to evaluate the data. Continuous variables were expressed as mean ± standard deviation and categorical variables as percentage values. The normal distribution analysis of the data was done with the Kolmogorov-Smirnov test. Independent t-test was used to compare continuous variables with normal distribution, and Mann-Whitney U test was used to compare continuous variables without normal distribution. Categorical variables were evaluated by the chi-square test. Pearson and Spearman correlation analysis was used for correlation analysis. The relationship between two variables was evaluated by univariate and multivariate logistic regression. P value ≤0.05 was considered significant.

Results

Ten thousand three hundred twenty coronary angiographies performed between June 2015 and August 2018 were analyzed retrospectively and 189 (1.8%) patients with coronary ectasia were detected. One hundred fourty three of the patients with ectasia were male (76%). While 107 (57%) of the patients were smoking, 106 (56%) were diagnosed with hypertension and 43 (22%) with DM. The number of dyslipidemic patients was 96 (51%) (Table 1).

While 43 (23%) of 102 (54%) patients presenting with ACS had ST STEMI, 59 (31%) had NSTEMI or USAP (Table 1). Of the patients admitted with ACS, CAD that did not cause significant stenosis was detected in 23

Table 1. Basal clinical and laboratory features of patients

Clinical features	Ectasia (N=189)
Age	61±12
Male	143 (76%)
Smoking	107 (57%)
Hypertension	106 (56%)
Diabetes mellitus	43 (22%)
EF (%)	52±10
Acute coronary syndrome	102(54%)
STEMI	43 (23%)
NSTEMI/USAP	59 (31%)
Glucose (g/L)	136±64
Hemoglobin (g/dL)	13.8±2.1
Leucocyte (g/dL)	9.6±3.7
Platelet (10^3/µL)	228±59
Total cholesterol(mg/dL)	193±57
HDL-k (mg/dL)	40±9
LDL-k (mg/dL)	123±54
Triglyceride (mg/dL)	161±96
Creatinine (mg/dL)	1.1±0.9

EF: ejection fraction, STEMI: ST segment elevation myocardial infarction, NSTEMI: non-ST segment elevation myocardial infarction, USAP: unstable angina pectoris

patients, single vascular disease in 35 patients, two vascular diseases in 23 patients, and three vascular diseases in 21 patients. Sixty eight of the patients (36%) had isolated ectasia without significant coronary stenosis.

When patients with ACS (group 1) and without ACS (group 2) were compared, there was no significant difference between the groups in terms of hypertension, DM, platelet count, lipid values and creatinine. While hemoglobin was slightly high in group 1 (14±2.1 and 13.5±2.0 p=0.040), the leukocyte count was significantly higher in group 1, as expected. (10.7±4.2 and 8.3±2.3 p=0.001). Group 1 was younger (58±13 and 63±10, p=0.016) and mostly male (82% and 67%, p=0.027). Smoking rate was significantly higher in the group with ACS (66% and 34%, p=0.001). Ejection fraction was detected to be slightly lower in group 1 (50±10 and 54±10 p=0.03). (Table 2). In the multivariate logistic regression analysis, when hypertension, DM, age, gender and cigarette were evaluated together, it was found that smoking predicted ACS strongly and independently in patients with ectasic coronary arteries [odds ratio:2.34, (95% confidence interval), 1.093-4.983, p=0.028] (Table 3).

Discussion

Although smoking is known to be a risk factor for ACS, its role and importance have not been clearly demonstrated in patients with ectasic coronary artery when evaluated with other known risk factors. In the literature review, it was observed that smoking was not discussed separately in terms of ACS in patients with ectasic coronary disease. In our study, it was found that smoking predicted ACS strongly and independently in this patient group.

Table 2. Comparison of demographic and laboratory features of patient groups

	ACS (+) N=102	ACS (-) N=87	p
Age	58±13	63±10	0.016
Gender (male)	84 (82%)	59 (67%)	0.027
Smoking	70 (66%)	37 (34%)	0.001
Hypertension	56 (53%)	50 (47%)	0.723
Diabetes mellitus	26 (60%)	17 (40%)	0.331
EF (%)	50±10	54±10	0.003
Glucose (g/L)	151±71	118±50	0.001
Hemoglobin (g/dL)	14±2.1	13.5±2	0.040
Leukocyte (10^3/µL)	10.7±4.2	8.3±2.3	0.001
Platelet (10^3/L)	230±55	226±63	0.460
T. Cholesterol(mg/dl)	196±68.7	189±40.9	0.870
HDL-k (mg/dL)	39.5±7.7	41±9	0.250
LDL-k (mg/dL)	127±65	119±35	0.757
Triglyceride (mg/dL)	170±119	150±57	0.776
Creatinine (mg/dL)	1.2±1.1	1.0±0.7	0.369

ACS: acute coronary syndrome, EF: ejection fraction, T. Cholesterol: total cholesterol

Table 3. Multivariate logistic regression analysis showing acute coronary syndrome predictive independent variables

Variables	Multivariate OR (95% CI)	p
Age	0.981 (0.956-1.008)	0.164
Gender	0.885 (0.379-2.065)	0.777
Smoking	2.334 (1.093-4.983)	0.028
Hypertension	1.014 (0.512-1.953)	0.969
Diabetes mellitus	1.384 (0.629-3.044)	0.419

OR: odds ratio, CI: confidence interval

Cardiovascular diseases are the major cause of mortality and morbidity in the world (12). In epidemiological studies, most of the cardiovascular risk consists of dyslipidemia, smoking, hypertension, DM, obesity, unbalanced diet and immobile life. While age, gender, family history at an early age, and race are the causes that cannot be modified, dyslipidemia, hypertension, smoking and DM are modifiable causes (13).

The frequency of CAE, which is detected in coronary angiographies performed for the suspicion of CAD, varies between 0.3-4.9% (14). In our study that we performed by analyzing the patients in our clinic, the frequency of ectasic coronary artery was found to be 1.8%. In addition to studies reporting that CAE is observed in similar rates in women and men (15), it was found more frequently in men in some studies (5). According to the The Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction (INTERHEART) case-control study, ACS is more common in young men (16). In our study, 76% of patients with CAE and 82% of patients with ACS were male.

Hypertension is responsible for 35% of all atherosclerotic cardiovascular events. Hypertension increases the risk of ACS 2-3 times in men and women (17). In a study by Markis et al. (18), hypertension was found to be more frequent in patients with ectasia and it was suggested that hypertension may play a role in the pathogenesis of coronary ectasia by accelerating the destruction of the media layer. In the study conducted by Sultana R. et al. (19), 55% of patients were diagnosed with hypertension, and similarly, in our study, 56% of patients had hypertension, and there was no significant difference in terms of hypertension between those with and without ACS.

DM is an independent risk factor for ACS, increasing the risk in men and women two and four times, respectively. According to the INTERHEART study, the prevalence of DM in patients with ACS has been shown to be 16% in men and 26% in women (16).

In the study of Sultana R. et al. (19), while 26% of patients with CAE were found to have DM, 22% of the patients were diagnosed with DM and no significant difference was found in terms of DM between those with and without ACS.

Atheromatous plaques are found on the basis of ACS. Dyslipidemia constitutes the basis of atherosclerosis. Although LDL is the primary lipid risk factor, other lipid parameters such as low HDL values and high triglyceride also pose a risk for CAD. Low HDL values, high triglycerides and high LDL values play an important role in the formation of atherogenic dyslipidemia (20). Many studies have demonstrated that each of these lipid parameters are independent risk factors for CAD (21,22). Atherosclerosis plays a major role in the etiology of CAE. In the pathological examination of ectasic coronary arteries, cholesterol crystals, calcification and fibrosis, intima and media destruction, lipid accumulation were found and these histological changes were observed to be the same as atherosclerotic process. (5). In a study by Sultana R.

et al. (19), dyslipidemia was reported in 58% of patients with CAE, and similarly in our study, 51% of patients had dyslipidemia. In our study, occlusive CAD was detected in 64% of patients with CAE, while 54% of patients presented with ACS. There was no difference in lipid parameters between the groups with and without ACS.

A strong relationship has been demonstrated between the number of cigarettes smoked and coronary heart disease in all groups independent of gender, age and race (23). Smoking increases the risk two to three times and increases the risk by interacting with other risk factors. The risk of myocardial infarction and cardiac death in smokers was found to be 2.7 times higher in males and 4.7 times higher in females compared to the non-smokers, and smoking is the most important preventable cause of mortality (24). The role and mechanism of smoking in atherosclerosis has been demonstrated by many studies. Smoking is known to initiate endothelial dysfunction and the inflammatory process in the endothelium. It has been shown in studies that cigarette smoke impairs vascular endothelial integrity and increases platelet activation and accelerates the entry of leukocytes into atherosclerotic lesions (25). In studies conducted, no difference was observed between patients with normal coronary artery structure and patients with CAE in terms of smoking. In the study of Yılmaz H. et al. (26), no significant difference was reported in patients with CAE in terms of gender, age, hyperlipidemia, DM and smoking compared to the control group. According to the Turkish Adult Risk Factor (TEKHARF) study (27), while the rate of smoking was around 30%, more than half of the patients were smoking in our study group. The rate of smoking was higher in patients presenting with ACS compared to the other group (66% vs. 34 %%). In multivariate regression analysis, it was found that smoking predicted ACS strongly and independently in patients with CAE.

Conclusion

Coronary artery ectasia is an important cause of mortality and morbidity, although it is not common in the community. In CAE, where many factors especially atherosclerosis play a role in the etiology, ACS can develop with or without obstructive CAD. Hypertension, DM, age, gender, dyslipidemia and smoking, which have an important place in the etiology of ACS, are also important in patients with CAE. In our study, it was found that smoking, which has an important place among these risk factors in patients with CAE, predicts ACS strongly and independently. Therefore, we think that smoking should be prevented in patients with CAE and rehabilitation for this issue should be given due importance for patients.

Ethics

Ethics Committee Approval: The study was approved by the ethics committee of University of Health Sciences Turkey, Şişli Hamidiye Etfal Education and Research Hospital (2534 / 17.09.2019).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - A.G., K.O.K.; Concept - A.G., Design - A.G., S.S.; Data Collection or Processing - A.G., S.S.; Analysis or Interpretation - A.G., K.O.K.; Literature Search - S.S.; Writing - A.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol 2004; 43: 1731–37.
2. CDC. Smoking-attributable mortality, years of potential life lost, and productivity losses—United States, 2000–2004. MMWR 2008; 57:1226-8.
3. Talukder MAH, Johnson WM, Varadharaj S, Lian J, Kearns PN, El-Mahdy MA, et al. Chronic cigarette smoking causes hypertension, increased oxidative stress, impaired NO bioavailability, endothelial dysfunction, and cardiac remodeling in mice. Am J Physiol Heart Circ Physiol 2011; 300: H388–96.
4. Shah AM, Pfeffer MA, Hartley LH, Moyé LA, Gersh BJ, Rutherford JD, et al. Risk of all-cause mortality, recurrent myocardial infarction, and heart failure hospitalization associated with smoking status following myocardial infarction with left ventricular dysfunction. Am J Cardiol 2010; 106: 911–6.
5. Hartnell GG, Parnell BM, Pridie RB. Coronary artery ectasia. Its prevalence and clinical significance in 4993 patients. Br Heart J 1985; 54: 392-5.
6. Al-Harthi SS, Nouh MS, Arafa M, al-Nozha M: Aneurysmal dilatation of the coronary arteries: diagnostic patterns and clinical significance. Int J Cardiol 1991; 30: 191–4.
7. Sayin T, Doven O, Berkalp B, Akyurek O, Gulec S, Oral D. Exercise-induced myocardial ischemia in patients with coronary artery ectasia without obstructive coronary artery disease. Int J of Cardiol 2001; 78: 143-9.
8. Papadakis MC, Manginas A, Cotileas P, Demopoulos V, Voudris V, Pavlides G, et al. Documentation of slow coronary flow by the TIMI frame count in patients with coronary ectasia. Am J Cardiol 2001; 88: 1030-2.
9. Kruger D, Stierle U, Herrmann G, Simon R, Sheikhzadeh A. Exercise-induced myocardial ischemia in isolated coronary artery ectasias and aneurysms ("dilated coronopathy"). J Am Coll Cardiol 1999; 34: 1461-70.
10. Mattern AL, Baker WP, McHale JJ, Lee DE. Congenital coronary aneurysms with angina pectoris and myocardial infarction treated with saphenous vein bypass graft. Am J Cardiol 1972; 30: 906-9.
11. Barbara Messner, David Bernhard. Smoking and Cardiovascular Disease Mechanisms of Endothelial Dysfunction and Early Atherogenesis. Arterioscler Thromb Vasc Biol 2014; 34: 509-15.
12. Naghavi M, Wang H, Lozano R, Davis A, Liang X, Zhou M, et al. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 385: 117–71.
13. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364: 937–52.
14. Oliveros RA, Falsetti HL, Carroll RJ, Heinle RA, Ryan GF. Atherosclerotic coronary artery aneurysm. Report of five cases and review of literature. Arch Intern Med 1974; 134: 1072-6.
15. Demopoulos VP, Olympios CD, Fakiolas CN, Pissimissis EG, Economides NM, Adamopoulou E, et al. The natural history of aneurysmal coronary artery disease. Heart 1997; 78: 136-41.
16. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, et al. Risk Factors for Myocardial Infarction in Women and Men: Insights from the INTERHEART study. Eur Heart J 2008; 29: 932-40.
17. Stratton JR, Chandler WL, Schwartz RS, Cerqueira MD, Levy WC, Kahn SE et al. Effects of Physical Conditioning on Fibrinolytic Variables and Fibrinogen in Young and Old Healthy Adults. Circulation 1991; 83: 1692-7.

18. Markis JE, Joffe CD, Cohn PF, Feen DJ, Herman MV, Gorlin R. Clinical significance of coronary arterial ectasia. Am J Cardiol 1976; 37: 217-22.

19. Sultana R, Sultana N, Ishaq M, Samad A. The prevalence and clinical profile of angiographic coronary ectasia.J Pak Med Assoc 2011; 61: 372-5.

20. Grundy SM. Hypertriglyseridemia, atherogenic dyslipidemia, and the metabolic syndrome. Am J Cardiol 1998; 81: 18-25.

21. Assmann G, Schulte H, Funke H, von Eckardstein A. The emergence of triglyserides as a significiant independent risk factor in coronary artery disease. Eur Heart J 1998; 19: 8-14.

22. Hokanson JE, Austin MA. Plasma triglyseride level as a risk factor for cardiovascular disease independent of highdensity lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996; 3: 213-9.

23. US Department of Health and Human Services. The Health Consequences of Smoking: Cardiovascular Disease_A Report of the Surgeon General. Washington, DC: Office of Smoking and Health, US government Printing Office; 1983.

24. U.S. Department of Health and Human Services. The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health; 1983. DHHS Publication No. (PHS) 84-50204.

25. Hurst's The Heart. Valentin Fuster, R. Wayne Alexander, Robert O'Rourke. 10. Baskısının Türkçe çevirisi. And Danışmanlık Eğitim Yayıncılık ve Organizasyon Ltd. Şti. 1. Basım. 2002; 1065-1109.

26. Yilmaz H, Sayar N, Yilmaz M, Tangürek B, Cakmak N, Gürkan U, et al. Coronary artery ectasia: clinical and angiographical evaluation. Turk Kardiyol Dern Ars 2008; 36:5 30-5

27. TEKHARF; Oniki Yıllık İzleme Deneyimine Göre Türk Erişkinlerinde Kalp Sağlığı. Prof. Dr. Altan Onat, Prof. Dr. Vedat Sansoy, Prof. Dr. İnan Soydan, Prof. Dr. Lale Tokgözoğlu, Prof. Dr. Kamil Adalet. Argos İletişim Hizmetleri Reklamcılık ve Ticaret Anonim Şirketi. Temmuz 2003, İstanbul.

İstanbul Med J 2020; 21(2): 97-103
DOI: 10.4274/imj.galenos.2020.13333

Role of Sentinel Lymph Node Biopsy During Contralateral Prophylactic Mastectomy

Kontralateral Profilaktik Mastektomide Sentinel Lenf Nodu Biyopsisinin Yeri

Halil Kara[1], Akif Enes Arıkan[2], Onur Dülgeroğlu[1], Cihan Uras[2]

[1]Acıbadem Mehmet Ali Aydınlar University, Vocational School of Health Sciences, İstanbul, Turkey
[2]Acıbadem Mehmet Ali Aydınlar University, Vocational School of Medicine, Department of General Surgery, İstanbul, Turkey

ABSTRACT

Introduction: Contralateral prophylactic mastectomy (CPM) is the removal of the opposite breast with the aim of risk reduction in cases of unilateral breast carcinoma. Routine use of sentinel lymph node biopsy (SLNB) at the time of CPM is controversial due to low occult breast cancer risk. This study aims to determine the rate of occult breast carcinoma and to evaluate whether SLNB should be performed during CPM.

Methods: Ninety-four patients who underwent CPM between 2009 and 2018 were evaluated retrospectively. Occult breast carcinoma detection rate and approach to axilla were evaluated.

Results: Occult invasive breast carcinoma was detected in three patients (3.2%): two invasive ductal carcinoma and one multifocal invasive lobular carcinoma. Axillary staging was performed in second session. SLNB was performed in two patients and a micro-metastasis in one of four sentinel lymph nodes (SLN) was detected in one patient. Axillary lymph node dissection was performed in one patient in whom SLN was not detected.

Conclusion: SLNB can be performed in patients with suspicious lesion in the absence of biopsy or in patients with high-risk of occult breast cancer (postmenopausal, high Gail score, lobular histology, multi-centric tumor, ipsilateral high-risk lesion); however, routine SLNB use during CPM is not recommended in patients with no risk. SLNB in second session by intradermic radioisotope injection in case of occult carcinoma can be an alternative solution to axillary staging.

Keywords: Sentinel lymph node biopsy, prophylactic mastectomy, breast cancer

ÖZ

Amaç: Kontralateral profilaktik mastektomi (KPM), tek taraflı meme kanseri saptanan hastalarda risk azaltılması amacıyla karşı memenin alınmasıdır. Okült meme kanseri riskinin düşük olması nedeni ile KPM sırasında rutin sentinel lenf nodu biyopsisi (SLNB) kullanımı tartışmalıdır. Bu çalışmada okült meme kanseri saptama oranı ve KPM sırasında SLNB gerekliliğinin araştırılması hedeflenmektedir.

Yöntemler: 2009 ile 2018 yılları arasında KPM uygulanan 94 hastanın verileri retrospektif olarak incelendi. Okült meme kanseri saptanma oranı ve aksillaya yaklaşım değerlendirildi.

Bulgular: Üç (%3,2) hastada okült invazif meme kanseri saptandı: iki invazif duktal karsinom ve bir multifokal invazif lobular karsinom. Aksiller evreleme ikinci seansta gerçekleştirildi. İki hastaya SLNB uygulandı ve hastaların birinde dört sentinel lenf nodunun (SLN) birinde mikrometastaz saptandı. SLN bulunamayan bir hastaya ise aksiller lenf nodu diseksiyonu uygulandı.

Sonuç: Biyopsi bulunmaksızın şüpheli lezyonu olan hastalara veya okült meme kanseri için yüksek riskli hastalara (postmenapozal, yüksek Gail skoru, lobular histoloji, multisentrik tümör, ipsilateral yüksek riskli lezyon) SLNB uygulanabilir. Bununla birlikte KPM sırasında rutin SLNB uygulaması önerilmemektedir. İkinci seansta intradermik radyoizotop enjeksiyonu ile SLNB yapılması okült meme kanserinde Aksiller evreleme için bir alternatif olabilir.

Anahtar Kelimeler: Sentinel lenf nodu biyopsisi, profilaktik mastektomi, meme kanseri

Introduction

Contralateral prophylactic mastectomy (CPM) is the removal of the opposite breast with the aim of risk reduction in cases of unilateral breast carcinoma. Patients with histories of breast carcinoma in one breast have an estimated risk of about 0.5% per year for developing contralateral breast cancer with a cumulative risk of about 6.9% at 10 years (1,2). This rate increases in high-risk patients, such as breast cancer gene (BRCA) carriers. The risk of breast cancer can be reduced by 90% to 95% with CPM (3).

Address for Correspondence/Yazışma Adresi: Halil Kara MD, Acıbadem Mehmet Ali Aydınlar University, Vocational School of Health Sciences, İstanbul, Turkey
Phone: +90 532 607 39 33 **E-mail:** halil.kara@acibadem.edu.tr **ORCID ID:** orcid.org/0000-0002-1527-7155

Cite this article as/Atıf: Kara H, Arıkan AE, Dülgeroğlu O, Uras C. Role of Sentinel Lymph Node Biopsy During Contralateral Prophylactic Mastectomy. İstanbul Med J 2020; 21(2): 97-103.

Received/Geliş Tarihi: 06.11.2019
Accepted/Kabul Tarihi: 04.02.2020

With increased breast cancer awareness and use of genetic tests, the use of CPM has become more popular. According to the review of the Surveillance, Epidemiology, and End Results database, there was an increase in CPM from 1.8% to 4.5% between 1998 and 2003 (4,5). However, in most patients, the risk of systemic metastasis from the index tumor is greater than the risk of contralateral breast cancer development, so no survival gains can be achieved with CPM and therefore, patient selection is important (6).

The patient's age, risk analysis, family history, genetic mutations, cosmetic concerns, or patient choice are important during decision making for undergoing (or not) CPM (7). Recommendations of the Society of Surgical Oncology can be summarized under three main headings (8):

1. Risk reduction: BRCA mutation or other genetic alterations, strong family history, high-risk lesions, such as atypical ductal hyperplasia.

2. Difficult surveillance: Clinically or radiologically dense breast tissue or diffuse micro-calcifications with negative biopsy.

3. Reconstructive issues: For symmetry or balance.

Occult breast cancer detection is an important issue for CPM. While occult breast malignancy risk varies between 0.5% and 8% in the literature, invasive disease detection rates are reported as 0.1%-3.5% (4,9-12). On the other hand, with the development of radiology, especially with the increase in the use of magnetic resonance imaging (MRI), the rate of occult malignancy detection rate decreases to 0.8%-2% (13).

Routine use of sentinel lymph node biopsy (SLNB) at the time of CPM is controversial due to occult breast cancer risk and morbidity. SLNB is routinely used for staging in patients with early stage breast carcinoma and has less complications than axillary lymph node dissection (ALND), especially in terms of lymphedema. However, many studies still report complications such as 5% lymphedema risk, 3% arm restriction, and 7% axillary paresthesia (9,14). Also, the increases in cost and patient anxiety are other factors that should be taken into consideration. On the other hand, when an occult invasive carcinoma is detected in patients who have undergone CPM, there is increased necessity for ALND and thus, morbidity increases.

This study aims to determine the rate of occult breast carcinoma and to evaluate whether SLNB should be performed during CPM.

Methods

A retrospective analysis of all patients with a diagnosed cancer in one breast, who underwent CPM between 2009 and 2018, was performed. All indications for CPM were included in this study. Patients younger than 18 years of age and patients with a history of breast cancer on the contralateral side were excluded from the study.

While all the patients were evaluated with both mammography and ultrasound, most of the patients had had breast MRI up to six months prior to surgery. Physical examination of the contralateral breast was negative in all of the patients. All of the patients underwent surgery by the same surgical team, and all specimens were evaluated by the same pathology team. All of the reconstructions were performed immediately with gel-based implants. CPM was performed as an immediate or delayed procedure. Routine SLNB was not performed during CPM. Axillary staging was performed at the second session but only if the patient had occult invasive breast carcinoma. If occult carcinoma was detected, the radioisotope method via intradermal injection was used for SLNB. Mastectomy type was chosen according to patients' preferences and comorbidities.

Mastectomy specimens were sliced into 2 mm-thick sections. Sliced specimens were first examined macroscopically, and then random sampling was done from four quadrants. Samples were also taken when suspicious areas were seen.

Age, type, CPM indications, presence of occult breast carcinoma, and approach to axilla were evaluated. Since the patients did not undergo routine SLNB, contralateral occult axillary lymph node (ALN) metastasis could not be evaluated.

All procedures performed in the study involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In addition, this study was approved by Ethic Committee of Acıbadem University on March 07, 2019 with number 2019-5/7. Informed consent was waived since the trial included retrospective data analysis.

Statistical Analysis

Statistical analysis program was not used to evaluate the study data. Continuous variables were expressed as median and categorical variables as percentage.

Results

Ninety-four patients who underwent CPM between 2009 and 2018 were evaluated. All of the patients were women. The median age was 43.7 (range: 28-78) years. Patient characteristics are summarized in Table 1. The most common indication for CPM was family history (Table 1). Thirteen patients underwent surgery after neoadjuvant chemotherapy due to local advanced breast cancer. While one patient preferred simple mastectomy and two patients preferred skin sparing mastectomy in order to sustain symmetry, the rest of the patients preferred nipple sparing mastectomy as the CPM procedure. CPM was performed immediately in 76 (80%) patients and in 18 (20%) patients as a delayed procedure.

Occult breast cancer was detected in four (4.2%) patients (Table 2). One of these patients had ductal carcinoma *in situ* (DCIS), two patients had invasive ductal carcinoma (IDC), and one patient had multifocal invasive lobular carcinoma (ILC). Axillary staging was performed for three patients (3.2%) with invasive occult malignancy in the second session with exception of the patient with DCIS. The radioisotope method was preferred for SLNB. After intradermic radioisotope injection, two of the three patients had sentinel lymph node(s) (SLN) in the preoperative lymphoscintigraphic examination, and SLNB was performed. ALND was performed in the patient in whom SLN was not detected; however, no metastasis was detected in ALND. Even though one of the patients who underwent SLNB had a micro-metastasis in one of four SLNs, no complete ALND was performed. The detection of occult breast cancer in the CPM did not alter the choice of patient treatment. One patient had chemotherapy because of the index tumor, while the other three patients received hormone therapy only.

Breast MRI had been obtained for 66 (70%) patients in the last six months. In 19 of 66 (29%) patients, MRI revealed lesions on the contralateral side. In 13 (68%) of these 19 patients, the lesions were defined as benign, and six (32%) were evaluated with preoperative biopsies due to suspicious lesions. Biopsy results were benign, but in one (16.7%) of the patients (n=6) who underwent biopsy, occult IDC was detected in the final pathology. However, in two patients with occult carcinoma, there were no suspicious lesions on MRI.

In 28 (30%) of 94 patients, breast MRIs had not been obtained. Only in one (3.6%) of these 28 patients, the pathology report revealed occult breast carcinoma.

Sclerosing adenosis was the most common finding in final pathology. Histological findings in the CPM specimen are summarized in Table 3.

In the median 41 (range: 4-96) -month follow-up of patients (n=4, 4.2%) with occult breast carcinoma on the contralateral side, no recurrence or new tumor development was seen in both breasts, and no distant metastasis was detected. Of patients without occult carcinoma, only one patient died at the 36th month of follow-up due to distant metastasis while five patients are still undergoing follow-up due to recurrence and three patients due to distant metastases.

Discussion

As breast cancer awareness increases, interest in CPM by both surgeons and patients has also increased. In general, survival gain cannot be achieved with CPM but can be applied especially in selected patient groups (8). CPM may be recommended for high-risk patients who have gene mutations, strong family history, and difficulty in radiological or clinical follow-up, and for symmetry, patient choice is also important. Anxiety about the potential development of contralateral breast cancer is a significant factor in patients' choice of CPM, especially in young patients with a long life expectancy (1).

In various publications, the risk of occult malignancy (*in situ* and invasive) varies between 0.5% and 8%; however, the detection of occult invasive disease has been reported at the rate of 0.1-3.5%. This rate can

Table 1. Characteristics of the patients

Age (years; median-range)		**43.7 (28-78)**
Menopausal status (n, %)	Premenopausal	78 (83%)
	Postmenopausal	16 (17%)
Family history (n, %)	Present	31 (33%)
	Absent	63 (67%)
Side of index tumor (n, %)	Right	46 (49%)
	Left	48 (51%)
Type of surgery (n, %)	Simple mastectomy	2 (2%)
	Skin sparing mastectomy	1 (1%)
	Nipple sparing mastectomy	91 (97%)
Stage of index tumor (n, %)	Early stage	81 (86%)
	Locally advanced	13 (14%)
Indications for contralateral prophylactic mastectomy (n, %)	Family history	23 (24%)
	Dense breast tissue	22 (23%)
	Gene mutation	13 (14%)
	Lobular histology	9 (10%)
	Patient's choice	9 (10%)
	Multi-centric/focal malignancy	8 (9%)
	Symmetry	4 (4%)
	Young age (<35-year-old)	4 (4%)
	Recurrence	2 (2%)

Table 2. Characteristics of patients with occult contralateral breast carcinoma

	Age (years)	Indication for CPM	Side of index tumor	Histology of occult tumor	Type of index tumor	Stage of index tumor	Stage of contralateral tumor	Follow-up (months)
Case 1	56	Patient's choice	Left	DCIS	DCIS	TisN0M0	TisN0	70
Case 2	54	Abnormal findings in MRI	Left	IDC	IDC	T1N0M0	T1N0	44
Case 3	43	Family history	Left	LCIS	DCIS	T1N0M0	T1Nmi	38
Case 4	38	Family history	Left	IDC	IDC	T2N1M0	T1N0	22

CPM: contralateral prophylactic mastectomy, DCIS: ductal carcinoma *in situ*, IDC: invasive ductal carcinoma, LCIS: lobular carcinoma *in situ*, MRI: magnetic resonance imaging

be as high as 5%-15% in high-risk patients (3,4,9-12). In current study, the rate of occult malignancy was found to be 4.2% (n=4) while the rate of invasive carcinoma was found to be 3.2% (n=3). Yi et al. (6) found three independent factors that predicted occult malignancy in the contralateral breast: 1) ipsilateral invasive lobular histology; 2) ipsilateral multi-centric tumor; and 3) a 5-year Gail risk score ≥1.67%. In that study, multivariate analysis also revealed that age ≥ 50 years at the time of the initial cancer diagnosis and an additional ipsilateral moderate to high risk pathology were independent predictors of moderate to high-risk histological findings in the contralateral breast (6). Boughey et al. (9) reported that older age (>60 years), postmenopausal status, and lobular type malignancy (ILC/lobular carcinoma *in situ*) were associated with occult breast cancer risk.

Table 3. Pathological findings in contralateral prophylactic mastectomy specimens

	Number of patients (%)
Sclerosing adenosis	29 (30%)
Stromal fibrosis	15 (16%)
Normal findings	15 (16%)
Fibroadenoma	10 (10.5%)
Apocrine metaplasia	6 (6.5%)
Intraductal papilloma	4 (4%)
Florid intraductal hyperplasia	3 (3%)
Flat epithelial hyperplasia	3 (3%)
Atypic ductal/lobular hyperplasia	2 (2%)
Lobular carcinoma *in situ*	2 (2%)
Invasive ductal carcinoma	2 (2%)
Invasive lobular carcinoma	1 (1%)
Ductal carcinoma *in situ*	1 (1%)
Tubular adenoma	1 (1%)

Today many surgeons use MRI for the evaluation of the breast before prophylactic mastectomy (PM). When compared to mammography, MRI has been shown to increase the detection rate of small cancers, especially in high-risk patients (3). Incidental contralateral breast cancer can be detected in 5% of patients with MRI (15,16). On the other hand, false negative and positive rates of MRI should be kept in mind. There are different opinions about the use of MRI in the detection of occult breast cancer in high-risk patients in addition to effects on decision making for selective SLNB indications in patients undergoing CPM. Black et al. (3) concluded that MRI significantly caused an increase in diagnostic costs and missed most occult cancers in PMs. In contrast, McLaughlin et al. (13) and Freitas et al. (16) concluded that MRI accurately ruled out the presence of invasive cancer in PM. While the use of MRI in cases without BRCA mutation is controversial due to costs and detection rates, it is recommended in patients with the BRCA mutation (17). In the current study, six of 66 patients with MRI had suspicious lesions

Table 4. Published reports investigating sentinel lymph node involvement in bilateral prophylactic mastectomy and/or contralateral prophylactic mastectomy (2000-2018)

Study	Year	PM/CPM	Number of cases	Total occult carcinoma	*In situ* occult carcinoma	Invasive occult carcinoma
Dupont (1)	2000	CPM	57	2 (3.5%)	0	2 (3.5%)
Boughey (9)	2006	PM	436	22 (5%)	14 (3.2%)	8 (1.8%)
Black (3)	2007	PM	192	19 (9.8%)	14 (7.2%)	5 (2.6%)
Soran (7)	2007	CPM	155	5 (3.2%)	3 (1.9%)	2 (1.3%)
McLaughlin (13)	2008	PM	613	33 (5.3%)	23 (3.7%)	10 (1.6%)
Yi (6)	2009	CPM	542	25 (4.6%)	NS	NS
Laronga (21)	2009	CPM	420	18 (4.2%)	12 (2.8%)	6 (1.4%)
		PM	28	0 (-)	0	0
Nasser (22)	2010	CPM	99	8 (8%)	6 (6%)	2 (2%)
Zhou (23)	2011	PM	1343	62 (4.6%)	41 (3%)	21 (1.6%)
Czyszczon (11)	2012	CPM	169	12 (7.1%)	10 (5.9%)	2 (1.2%)
Miller (4)	2012	CPM	106	8 (7.5%)	5 (4.7%)	3 (2.8%)
Burger (20)	2013	PM	83	1 (1.2%)	0	1 (1.2%)
Kuwajerwala (24)	2013	CPM	170	3 (1.8%)	1 (0.6%)	2 (1.2%)
Murthy and Chamberlain (25)	2013	PM	328	3 (0.9%)	3 (0.9%)	0
Bunting (26)	2014	PM	467	15 (3.2%)	9 (2%)	6 (1.2%)
Freitas (16)	2016	CPM	88	3 (3.4%)	2 (2.3%)	1 (1.1%)
Camara (17)	2018	PM	80	4 (5%)	2 (2.5%)	2 (2.5%)
Kara (current study)	2019	CPM	94	4 (4.2%)	1 (1%)	3 (3.2%)
Total		CPM	1522	88 (5.7%)	%4	%2.3
		PM	5092	237 (4.6%)	%3.2	%1.7

CPM: contralateral prophylactic mastectomy, PM: prophylactic mastectomy, NS: not specified

Table 5. Clinical arguments for and against the adoption of sentinel lymph node biopsy in prophylactic mastectomy

Arguments supporting the adoption of SLNB in PM	Arguments against the adoption of SLNB in PM
1. The morbidity of SLNB is low and can be safely performed with mastectomy.	1. The risk of occult invasive carcinoma is very low.
2. Axillary lymph node dissection can be avoided if occult invasive breast carcinoma is detected by simultaneous SLNB.	2. The detected occult lesions are early lesions (Ti or T1a-b) and the risk of SLN positivity is very low.
3. SLNB may detect occult contralateral nodal disease that has metastasized from the index tumor.	3. The effect of occult malignancies on the treatment is very low.
4. With simultaneous SLNB, the patient will not be exposed to a second operation and the risk of anesthesia.	4. SLNB has also complications.
5. Performing axillary staging in second session may cause delay in the treatment of patient.	5. Cost increases with routine SLNB.
	6. The operation time increases.
	7. The aesthetic importance of incision required for SLNB.
	8. In appropriate cases SLNB can be performed after mastectomy.

SLNB: sentinel lymph node biopsy, PM: prophylactic mastectomy

and were evaluated with preoperative biopsy. While all of the biopsies were benign, occult IDC was detected only in one patient in the final pathology. The identification rate of an occult carcinoma by MRI prior to CPM was quite low at 1.5% (1/66) in contrast to the current literature (13,16). Thus, MRI did not affect the decision of SLNB use in CPM.

Another issue that should be considered in the case of occult carcinoma is axillary staging. Patients with early -stage breast carcinoma routinely undergo SLNB for axillary staging since SLNB was first reported in the early 1990s (1). Although SLNB has lower complication rates when compared to ALND, 5.6% lymphedema and other minor complications are still observed. In addition, simple allergic (1%-2%) or anaphylactic reactions (0.25%-0.5%) can occur due to the blue dye. A false negative ratio of 8.4% (0%-29%) must also be kept in mind (18,19).

Routine use of SLNB at the time of CPM is controversial. Table 4 summarizes the studies covering occult breast carcinoma detection rates in PM or CPM without contralateral or bilateral discrimination. The surgeons using routine SLNB during CPM suggest that SLNB cannot be performed after mastectomy, so in case of occult invasive malignancy at CPM, ALND will be mandatory at the second session, which may cause an increase in morbidity. In addition, many authors suggest that they do not observe lymphedema or the risk is similar in the cases in which SLNB is not performed (1,4,20). They also state that SLNB is helpful to find possible cross-metastases from index tumor (1).

The group that does not recommend SLNB during CPM states that the risks of occult invasive carcinoma detection and SLN positivity in these tumors are too low because of the very early state. They also report that there is comorbidity associated with SLNB in the guidelines and that routine use is not appropriate. Another point is that the detection of occult breast cancer in CPM has minimal effects on the patient's treatment. Table 5 summarizes the clinical arguments for and against the adoption of SLNB in PM.

There are three prominent studies suggesting routine SLNB use during CPM. Dupont et al. (1) found two invasive occult carcinomas (3.5%) and two occult axillary metastases; however, patients with occult breast carcinoma did not represent metastasis in SLNB. They suggested SLNB because of lack of SLNB-induced lymphedema and change in treatment of four (7%) patients. Miller et al. (4) found three occult invasive carcinomas (2.8%) in 106 CPMs and micro-metastasis only in one patient during SLNB. Although the risk of lymphedema was high in the group with ALND, they suggested SLNB use during CPM because they did not find any differences in lymphedema between the groups with and without SLNB. Burger et al. (20) found only one occult ILC and three lobular *in situ* neoplasms in 83 PMs. They suggested SLNB because they did not see lymphedema in any patient and thought that adding SLNB did not prolong the duration of operation.

On the other hand, there are many studies in which routine SLNB during CPM is not recommended (3,6,7,9,11,13,16,17,21-26). In the meta-analysis by Zhou et al. (23), the occult breast carcinoma rate was found to be 1.6% in 1343 PMs. Four of the patients with invasive occult carcinoma and one of the patients with DCIS were found to have SLN positivity while 19 occult ALN metastases were found. Benefits from SLNB were obtained in 36 (2.8%) patients (17 SLN negative patients and 19 patients with occult lymph node metastasis). However, it should be noted that 12 (50%) of the patients with positive SLNB had advanced disease. Thus, they did not recommend routine SLNB. In most of the studies that identified occult lymph node metastasis in the contralateral axilla, it is mentioned that these metastases are probably due to advanced index tumor (11,21,22).

When studies involving only CPM are considered, the following outputs have yielded several findings. In the study of Yi et al. (6), the ratio of occult carcinoma was found to be 4.6% in the 542 CPMs although invasive/*in situ* discrimination was not performed. Laronga et al. (21) found this rate of invasive occult carcinoma to be 1.6% in their studies involving 420 CPMs. Occult SLN metastasis was detected in seven patients, and all of these patients presented with locally advanced breast cancer. In the same study, it was concluded that SLNB should not be indicated in patients who underwent bilateral PM or CPM associated with early stage disease. However, patients with locally advanced primary breast cancer had a significantly increased risk of contralateral occult ALN metastasis due most likely to crossover metastasis; this selected group of patients may benefit from SLNB. In another study conducted by Soran et al. (7), two invasive occult carcinomas (1.3%) were found in 155 CPMs, and two occult ALN metastases were found in patients who underwent surgery

for recurrent invasive carcinoma. Even though lymphedema was not seen in these patients, routine SLNB was not suggested as the risk of occult breast cancer was low. In the hypothetical cohort introduced by Boughey et al. (10), in cases in which the incidence of occult breast cancer was taken as 1.9%, the rate of SLN detection, the ratio of SLN positivity, and ratio of occult axillary metastasis were considered, and those complications would be seen in 680 of 10,000 patients with routine SLNB, only in 137 patients ALND could be avoided. In this study, three invasive occult carcinomas were detected among 94 CPMs. While SLNB was performed as second sessions in two patients, ALND was performed only in the patient in whom SLN was not found. In a total of 91 patients, SLNB and related complications were avoided and benefits from routine use of SLNB could be gained in only one patient. In a hypothetical proposition in which routine SLNB was performed during CPM and when the complication rate of SLNB was taken as 5%, there may be have been possible complications in five patients due to routine SLNB use; however, even if the SLN detection rate was accepted as 100%, ALND could have been avoided in only one patient.

The American Society of Breast Surgeons Consensus Meeting suggest that routine use of SLNB at the time of CPM is not necessary (12). Higher risks of occult malignancy in CPM are related to postmenopausal status, triple-negativity, locally advanced stage, and inflammatory or invasive lobular histology. They recommend biopsy if a suspicious lesion is detected in the preoperative MRI. Murphy et al. (27) investigated the role of intraoperative pathological examination of the resected breast tissue in PM. In 1900 cases (1410 CPM, 490 PM), 58 occult malignancies (32 invasive, 26 DCIS) were detected. Of these 58 cases, occult malignancies were found during surgery in 44 cases, and SLNB was performed. Facilitation of intraoperative pathology may prevent overtreatment in patients who have not been diagnosed with occult malignancy. Thus, they suggest SLNB use according to the results of the intraoperative pathological examination.

The most important consideration for authors who propose SLNB during CPM is that SLNB cannot be performed after a mastectomy in the case of an occult malignancy. Although the performance of SLNB in second session after mastectomy has not been extensively studied, a few case reports and very small series have reported a success rate of 65% to 100% (28-30). In the current study, SLN was detected by intradermic radioisotope injection in two of the three patients who underwent axillary staging. However, the studies related to SLNB after mastectomy has low power, and SLNB after mastectomy can be considered as an alternative solution for staging in selected cases.

Conclusion

The evaluation of the patients who are candidates for CPM is very important. If a suspicious contralateral breast lesion is found, a biopsy should be performed prior to surgery. SLNB can be performed in patients with suspicious lesions in the absence of biopsy or in patients with high risk for occult breast cancer (postmenopausal, high Gail score, lobular histology, multi-centric tumor, ipsilateral high-risk lesion). SLNB should also be considered when a second session would not be welcome, such as in cases of anticoagulant use, having comorbidities that would increase the risk factor for anesthesia, and local advanced breast cancer (due to cross-metastasis risk). However, routine SLNB use during CPM in patients with no risk is not recommended.

Ethics

Ethics Committee Approval: In addition, this study was approved by Ethic Committee of Acıbadem University on March 07, 2019 with number 2019-5/7.

Informed Consent: Informed consent was waived since the trial included retrospective data analysis.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Concept - H.K., A.E.A., O.D., C.U.; Design - H.K., A.E.A., O.D., C.U.; Data Collection or Processing - H.K., A.E.A., O.D., C.U.; Analysis or Interpretation - H.K., A.E.A., O.D., C.U.; Literature Search - H.K., A.E.A.; Writing - H.K., A.E.A., O.D., C.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Dupont EL, Kuhn MA, McCann C, Salud C, Spanton JL, Cox CE. The role of sentinel lymph node biopsy in women undergoing prophylactic mastectomy. Am J Surg 2000; 180: 274-7.
2. Kantor O, Chang C, Bleicher RJ, Moran M, Connolly JL, Kurtzman SH, et al; National Accreditation Program for Breast Centers Data Working Group. Physician Knowledge of Breast Cancer Recurrence and Contralateral Breast Cancer Risk is Associated with Increased Recommendations for Contralateral Prophylactic Mastectomy: a Survey of Physicians at NAPBC-Accredited Centers. Ann Surg Oncol 2019; 26: 3080-8.
3. Black D, Specht M, Lee JM, Dominguez F, Gadd M, Hughes K, et al. Detecting occult malignancy in prophylactic mastectomy: preoperative MRI versus sentinel lymph node biopsy. Ann Surg Oncol 2007; 14: 2477-84.
4. Miller CL, Specht MC, Skolny MN, Jammallo LS, Horick N, O'Toole J, et al. Sentinel lymph node biopsy at the time of mastectomy does not increase the risk of lymphedema: implications for prophylactic surgery. Breast Cancer Res Treat 2012; 135: 781-9.
5. Tuttle TM, Habermann EB, Grund EH, Morris TJ, Virnig BA. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. J Clin Oncol 2007; 25: 5203-9.
6. Yi M, Meric-Bernstam F, Middleton LP, Arun BK, Bedrosian I, Babiera GV, et al. Predictors of contralateral breast cancer in patients with unilateral breast cancer undergoing contralateral prophylactic mastectomy. Cancer 2009; 115: 962-71.
7. Soran A, Falk J, Bonaventura M, Keenan D, Ahrendt G, Johnson R. Is routine sentinel lymph node biopsy indicated in women undergoing contralateral prophylactic mastectomy? Magee-Womens Hospital experience. Ann Surg Oncol 2007; 14: 646-51.
8. Giuliano AE, Boolbol S, Degnim A, Kuerer H, Leitch AM, Morrow M. Society of Surgical Oncology: position statement on prophylactic mastectomy. Approved by the Society of Surgical Oncology Executive Council, March 2007. Ann Surg Oncol 2007; 14: 2425-7.
9. Boughey JC, Khakpour N, Meric-Bernstam F, Ross MI, Kuerer HM, Singletary SE, et al. Selective use of sentinel lymph node surgery during prophylactic mastectomy. Cancer 2006; 107: 1440-7.

10. Boughey JC, Cormier JN, Xing Y, Hunt KK, Meric-Bernstam F, Babiera GV, et al. Decision analysis to assess the efficacy of routine sentinel lymphadenectomy in patients undergoing prophylactic mastectomy. Cancer 2007; 110: 2542-50.

11. Czyszczon IA, Roland L, Sahoo S. Routine prophylactic sentinel lymph node biopsy is not indicated in women undergoing prophylactic mastectomy. J Surg Oncol 2012; 105: 650-4.

12. Boughey JC, Attai DJ, Chen SL, Cody HS, Dietz JR, Feldman SM, et al. Contralateral Prophylactic Mastectomy Consensus Statement from the American Society of Breast Surgeons: Additional Considerations and a Framework for Shared Decision Making. Ann Surg Oncol 2016; 23: 3106-11.

13. McLaughlin SA, Stempel M, Morris EA, Liberman L, King TA. Can magnetic resonance imaging be used to select patients for sentinel lymph node biopsy in prophylactic mastectomy? Cancer 2008; 112: 1214-21.

14. Lucci A, McCall LM, Beitsch PD, Whitworth PW, Reintgen DS, Blumencranz PW, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. J Clin Oncol 2007; 25: 3657-63.

15. Liberman L, Morris EA, Kim CM, Kaplan JB, Abramson AF, Menell JH, et al. MR imaging findings in the contralateral breast of women with recently diagnosed breast cancer. AJR Am J Roentgenol 2003; 180: 333-41.

16. Freitas V, Crystal P, Kulkarni SR, Ghai S, Bukhanov K, Escallon J, et al. The value of breast MRI in high-risk patients with newly diagnosed breast cancer to exclude invasive disease in the contralateral prophylactic mastectomy: Is there a role to choose wisely patients for sentinel node biopsy? Cancer Med 2016; 5: 1031-6.

17. Camara S, Pereira D, Andre S, Mira B, Vaz F, Oom R, et al. The Use of Sentinel Lymph Node Biopsy in BRCA1/2 Mutation Carriers Undergoing Prophylactic Mastectomy: A Retrospective Consecutive Case-Series Study. Int J Breast Cancer 2018; 2018: 1426369.

18. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013; 14: 500-15.

19. Lyman GH, Giuliano AE, Somerfield MR, Benson AB, 3rd, Bodurka DC, Burstein HJ, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 2005; 23: 7703-20.

20. Burger A, Thurtle D, Owen S, Mannu G, Pilgrim S, Vinayagam R, et al. Sentinel lymph node biopsy for risk-reducing mastectomy. Breast J 2013;19:529-32.

21. Laronga C, Lee MC, McGuire KP, Meade T, Carter WB, Hoover S, et al. Indications for sentinel lymph node biopsy in the setting of prophylactic mastectomy. J Am Coll Surg 2009; 209: 746-52; quiz 800-1.

22. Nasser SM, Smith SG, Chagpar AB. The role of sentinel node biopsy in women undergoing prophylactic mastectomy. J Surg Res 2010; 164: 188-92.

23. Zhou WB, Liu XA, Dai JC, Wang S. Meta-analysis of sentinel lymph node biopsy at the time of prophylactic mastectomy of the breast. Can J Surg 2011; 54: 300-6.

24. Kuwajerwala NK, Dekhne NS, Pentiak PA, Fend D, Callahan RE, Amine M, et al. Sentinel lymph node biopsy in contralateral prophylactic mastectomy: are we overtreating? Experience at a tertiary care hospital. Clin Breast Cancer 2013; 13: 287-91.

25. Murthy V, Chamberlain RS. Prophylactic mastectomy in patients at high risk: is there a role for sentinel lymph node biopsy? Clin Breast Cancer 2013; 13: 180-7.

26. Bunting PW, Cyr AE, Gao F, Margenthaler JA. Sentinel lymph node biopsy during prophylactic mastectomy: is there a role? J Surg Oncol 2014; 109: 747-50.

27. Murphy BL, Glasgow AE, Keeney GL, Habermann EB, Boughey JC. Selective Use of Sentinel Lymph Node Surgery in Patients Undergoing Prophylactic Mastectomy Using Intraoperative Pathology. Ann Surg Oncol 2017; 10: 3032-7.

28. Karam A, Stempel M, Cody HS, Port ER. Reoperative sentinel lymph node biopsy after previous mastectomy. J Am Coll Surg. 2008; 207: 543-8.

29. Intra M, Veronesi P, Gentilini OD, Trifiro G, Berrettini A, Cecilio R, et al. Sentinel lymph node biopsy is feasible even after total mastectomy. J Surg Oncol 2007; 95: 175-9.

30. Vicente DA, Henry LR, Hahm G, Soballe PW, Smart D. Axillary sentinel lymph node biopsy after mastectomy: a case report. World J Surg Oncol 2010; 8: 59.

İstanbul Med J 2020; 21(2): 104–8
DOI: 10.4274/imj.galenos.2020.26529

Prospective Outcomes of Arthroscopic Versus Open Resection of Dorsal Wrist Ganglions

El Bileği Dorsal Ganglionlarının Artroskopik ve Açık Olarak Eksizyonlarının Sonuçları

Tahsin Gürpınar, Engin Çarkçı

University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Turkey

ABSTRACT

Introduction: The aim of this prospective randomized study was to compare recurrence, pain and functional scores of the patients operated openly or arthroscopically due to dorsal wrist ganglion with a minimum of 18-month follow-up.

Methods: Twenty patients underwent arthroscopic and 20 patients underwent open excision after the failure of conservative treatment for a minimum period of six months. Patients' demographic characteristics, The Disabilities of the Arm, Shoulder and Hand score (QuickDASH), grip strength, Visual Analogue Pain scale (VAS), operation time, incision lengths, recurrence rates and treatment satisfaction rates were compared.

Results: In open and arthroscopy groups, age, gender, side distribution and dominant side distribution did not vary significantly ($p>0.05$). Although the postoperative QuickDASH score and VAS decreased significantly in the open and arthroscopic groups, there was no significant difference between the groups. The duration of operation was significantly higher and the incision length was lower in the arthroscopy group than in the open excision group ($p<0.05$). In the open and arthroscopic groups, time from diagnosis to surgery, grip strength, the rate of satisfaction with the treatment, and the recurrence rate were not significantly different ($p>0.05$). Furthermore, we diagnosed scapholunate interosseous ligament tear in seven patients and grade 1 triangular fibrocartilage complex tear in one patient who underwent arthroscopic ganglion excision. In both of the groups, there were two recurrences during follow-ups (10%), which were treated with open excision.

Conclusion: Arthroscopic ganglionectomy has the advantages of smaller incisions, diagnosing and intervention of other associated wrist pathologies. Disadvantages are steep learning curve and long operating time.

Keywords: Wrist arthroscopy, dorsal ganglion, arthroscopic ganglion excision

ÖZ

Amaç: Bu çalışmanın amacı artroskopik veya açık yöntemlerle el bileği dorsal ganglion eksizyonu yapılan ve minimum 18 ay takip süresi olan hastaları fonksiyonel skor, rekürrens ve postoperatif ağrı açısından karşılaştırmaktır.

Yöntemler: Bu çalışmada el bileği dorsal ganglionu nedeniyle en az altı aylık konservatif tedaviye yanıt alınamamış 20 hasta artroskopik olarak ve 20 hasta açık cerrahi ile opere edilmiştir. Hastaların demografik özellikleri, Kol, Omuz ve El Sorunları Anketi (QuickDASH) skorları, kavrama gücü ve görsel ağrı skorları (VAS) kaydedildi. Her iki grup klinik sonuçlar, operasyon süresi, insizyon uzunluğu, rekürrens ve hasta memnuniyetleri açısından değerlendirildi.

Bulgular: Açık ve artroskopik gruplar arasında yaş, cinsiyet ve taraf açısından anlamlı bir fark saptanmadı ($p>0,05$). Her iki grupta da post-op dönemde QuickDASH skoru ve VAS anlamlı olarak düştü, ancak her iki grup arasında fark saptanmadı. Artroskopik grupta operasyon süresi anlamlı olarak uzun ve insizyon uzunluğu anlamlı olarak kısa bulundu ($p<0,05$). Her iki grupta operasyona kadar geçen süre, kavrama gücü, hasta memnuniyeti ve rekürrens arasında anlamlı fark saptanmadı ($p>0,05$). Yedi hastada skafolunat ligament yırtığı ve bir hastada Triangular fibrokartilaj kompleks yırtığı saptandı. Her iki hasta grubunda da iki rekürrens saptandı (%10) ve açık olarak tedavi edildi.

Sonuç: Artroskopik ganglionektomi açık cerrahi ile karşılaştırıldığında daha az skar uzunluğu ve potasiyel ek yaralanmaların eş zamanlı tedavi edilmesi gibi avantajlar sunmakla beraber her iki cerrahi tedavide de benzer klinik sonuçlar elde edilmektedir. Operasyon süresinin daha uzun olması ve uzun öğrenme eğrisi artroskopik tedavinin dezavantajlarını oluşturmaktadır.

Anahtar Kelimeler: El bileği artroskopisi, dorsal ganglion, artroskopik ganglionektomi

Address for Correspondence/Yazışma Adresi: Tahsin Gürpınar MD, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Turkey
Phone: +90 505 685 64 39 **E-mail:** tahsingurpinar@msn.com **ORCID ID:** orcid.org/0000-0002-8194-6492

Cite this article as/Atıf: Gürpınar T, Çarkçı E. Prospective Outcomes of Arthroscopic Versus Open Resection of Dorsal Wrist Ganglions. İstanbul Med J 2020; 21(2): 104-8.

Received/Geliş Tarihi: 29.12.2019
Accepted/Kabul Tarihi: 07.02.2020

Introduction

Dorsal wrist ganglions are the most common benign tumour of the hand and they mostly remain asymptomatic (1,2). Most common causes of ganglion cysts are known as scapholunate ligament injuries, tendon stealth pathologies and synovial herniations (3).

Almost half of the wrist ganglions spontaneously disappear within time, but some can cause functional limitations, pain or cosmetic problems (3). Main symptoms are usually pain, reduced range of motion or decreased grip strength. The first-line of the treatment is non-surgical options like observation, aspiration or intralesional steroid injections but recurrences can be seen up to 78% of the cases (4). Open or arthroscopic surgery is the preferred treatment for recurrent cases and for patients who wish surgery as the initial treatment.

Open excision of wrist ganglions is the conventional method of surgical treatment but arthroscopic surgery has become popular since it was described by Osterman and Raphael (5). In the literature, the recurrence rates are similar but faster postoperative recovery time, decreased postsurgical pain, early return to work and less scar formation favours arthroscopic excision over open excision (6). The aim of this prospective randomized study was to compare recurrence, postoperative pain and functional scores of the patients operated with open or arthroscopically due to dorsal wrist ganglion with a minimum of 18-month follow-up.

Methods

The study was performed at a single institution between August 2017 and December 2017. All surgeries were done by the same surgeon. The Institutional Review Board of İstanbul Training and Research Hospital approved this study with the issue number 1042 and consent form was obtained from all patients. Fourty patients having dorsal wrist ganglion cysts, who failed conservative treatment for a minimum of six months, were prospectively registered in this study. Twenty patients had arthroscopic surgery and 20 patients had open excision. Conservative treatment involved anti-inflammatory drugs, splinting and aspiration. The exclusion criteria were previous surgery, a history of a fracture, ligamentous tears and wrist instability. Patients who agreed to partake in the study were randomly assigned to have open or arthroscopic excision. Randomization was performed at initial presentation by assigning patients with odd-numbered patient id numbers to the open excision group and even-numbered patient id numbers to the arthroscopic excision group.

All patients were examined just before the operation and at the postoperative last follow-up. The clinical and functional outcomes were measured with The Disabilities of the Arm, Shoulder and Hand (QuickDASH) score and grip strength. Pain was assessed with Visual Analogue Pain scale (VAS). Furthermore, patients' demographic characteristics, time from diagnosis to surgery, operation time, incision lengths, recurrence rates, and treatment satisfaction rates were compared.

Surgical Technique

The open technique was done under local anaesthesia. A transverse skin incision was made in 2 to 3 cm length (Figure 1A). Tourniquet was not used but meticulous homeostasis was achieved for visualization. The cyst was removed with the base of the ganglion stalk and with a portion of the dorsal wrist capsule (Figure 1B).

The arthroscopic technique was performed under general anaesthesia and traction. We used a 30° visual angle 2.7 mm arthroscope and isotonic saline solution. We used 4-5 portal for the purpose of visualization. 3-4 portal was then opened and used for instrumentation (Figure 2A). We used an arthroscopic shaver to debride the ganglion to scapholunate ligament and the stalk with a portion of the capsule (Figure 2B). After the excision of the ganglion, a 1-2 cm void was opened in the capsule. If dorsal synovitis was observed, it was also debrided. Meticulous care was taken to protect the extensor tendons. For both groups, splints were removed and active and passive exercises were started at the first visit at the 1st week and sutures were removed at the 2nd week.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum value frequency and percentage were used for descriptive statistics. The distribution of variables was checked with Kolmogorov-Simirnov test. Independent samples t-test and Mann-Whitney U test were used for the comparison of quantitative data. Wilcoxon test was used for the repeated measurement analysis. Chi-square test was employed for the comparison of the qualitative data. SPSS 22.0 was used for statistical analyses.

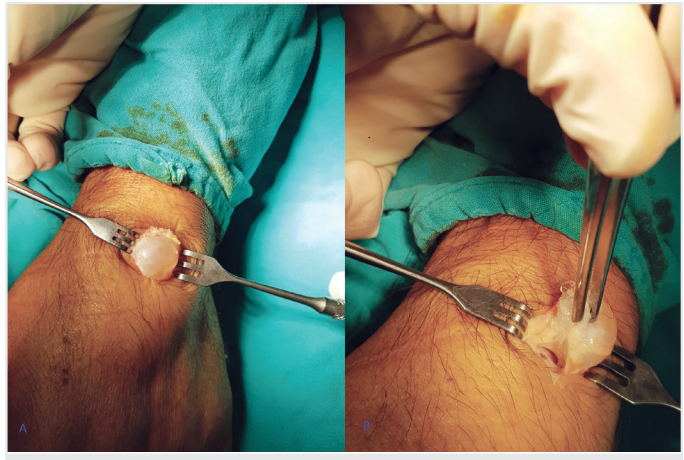

Figure 1A, 1B. Surgical images of open dorsal ganglion cyst excision

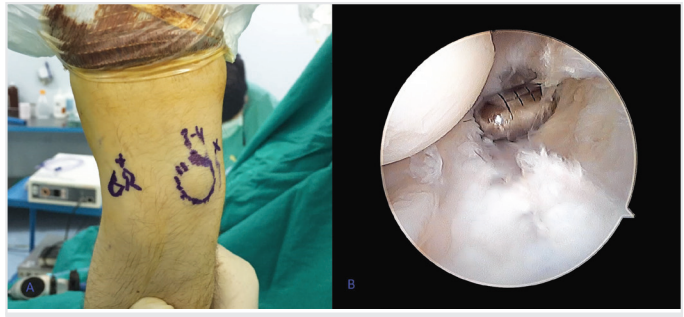

Figure 2A. Image of portals in the excision of arthroscopic dorsal ganglion cyst, **2B.** Arthroscopic view of the shaver excision of the dorsal ganglion cyst

Results

The study group consisted of 25 (62.5 %) female and 15 (37.5%) male patients with a mean age of 26.3±5.3 years (range, 18-43 years). In the open and arthroscopy groups, age, gender, side distribution and dominant side distribution were not significantly different (p>0.05).

Although the postoperative QuickDASH score and VAS decreased significantly in the open and arthroscopic groups compared to the preop period (p<0.05), there was no substantial difference between two groups regarding preop and postop values. In the open and arthroscopy groups, preop and postop grip strength values did not differ statistically (p>0.05). In the open and arthroscopy groups, the time from diagnosis to surgery did not differ statistically (p>0.05). The operative time was significantly longer in the arthroscopy group than in the open surgery group (p<0.05). In the arthroscopy group, the incision length was significantly lower than in the open surgery group (p<0.05). In the open and arthroscopic groups, the recurrence rate was similar (p>0.05). In the open and arthroscopy groups, the rate of satisfaction with the treatment did not change significantly (p>0.05) (Table 1).

In both of the groups, there were 2 recurrences during follow-ups (10%), which were treated with open excision. Extensor tendon rupture was not observed in any group; however, one of the patients had extensor tenosynovitis which lasted for 6 months after surgery and limited full flexion of the wrist. No other complications were reported.

Discussion

Arthroscopic surgery of the hand and wrist continue to expand in wrist pathologies such as triangular fibrocartilage complex (TFCC) injuries, intra-articular ligament tears and scaphoid fractures (7,8). Likewise arthroscopic dorsal ganglion resection has been performed with satisfactory outcomes since it was first described by Osterman and Raphael (5). The results of our study showed that arthroscopic excision of dorsal wrist ganglions provides respectable clinical outcomes with elevated patient satisfaction, as reported in previous studies (9-11). The

Table 1. Comparison of demographic characteristics, clinical and functional results of open and arthroscopic groups

		Open		Artroscopic		p	
Age		**Mean ± SD/ (n%)**	**Median**	**Mean ± SD /(n%)**	**Median**		
		26.9±5.7	26.0	25.8±4.9	26.0	0.537	t
Sex	Male	7 (35.0%)	-	8 (40.0%)	-	0.744	X^2
	Female	13 (65.0%)	-	12 (60.0%)	-		
Side	Left	8 (40.0%)	-	8 (40.0%)	-	1.000	X^2
	Right	12 (60.0%)	-	12 (60.0%)	-		
Dominant	Left	1 (5.0%)	-	3 (15.0%)	-	0.292	X^2
	Right	19 (95.0%)	-	17 (85.0%)	-		
QuickDASH score							
Preoperative		14.1±7.8	12.0	11.8±5.8	9.5	0.356	m
Postoperative		0.7±0.8	0.0	0.7±0.9	0.5	0.870	m
Intra group difference p		0.000	w	0.000	w	-	-
VAS							
Preoperative		4.2±0.7	4.0	4.2±0.8	4.0	0.834	m
Postoperative		0.4±1.0	0.0	0.4±0.8	0.0	0.791	m
Intra group difference p		0.000	w	0.000	w	-	-
Grip strenght							
Preoperative		29.9±8.6	26.5	31.5±7.9	29.0	0.378	m
Postoperative		30.4±7.8	28.0	31.6±7.5	30.0	0.480	m
Intra group difference p		0.303	w	0.322	w	-	-
Time from diagnosis to surgery (month)		11.7±3.6	12.0	10.9±3.4	10.0	0.442	m
Operation time (minute)		21.0±5.0	20.0	33.3±4.7	32.5	0.000	m
Incision length (mm)		34.5±4.1	34.0	9.3±1.2	9.0	0.000	m
Recurrence	(-)	18 (90.0%)	-	18 (90.0%)	-	1.000	X^2
	(+)	2 (10.0%)	-	2 (10.0%)	-		
Treatment Satisfaction	(-)	3 (15.0%)	-	2 (10.0%)	-	0.633	X^2
	(+)	17 (85.0%)	-	18 (90.0%)	-		

t: t-test, m: Mann-Whitney U test, X^2: chi-square test (Fischer exact), w: Wilcoxon test, SD: standard deviation, VAS: visual analogue pain scale

patients' reported outcome measures in both arthroscopic and open groups are also comparable in our study similar to the literature.

The pain was the main symptom in our cases. The mean VAS decreased from 4.2 to 0.4 at last follow-up in both arthroscopic and open groups. Chassat et al. (12) reported that the pain decreased from 3.37 to 1.76 after arthroscopic resection. Decreased pain scores are also reported in previous series (13). On the other hand, Lee et al. (14) reported 20% residual or persistent pain after arthroscopic excision whereas none in the open surgery group. In our study, the pain scores and postoperative alleviation of symptoms were comparable between the open and arthroscopic groups.

Recurrence of the ganglions is the most common reported complication of any treatment. (15,16) We reported 4 recurrences (10%): 2 in the arthroscopic and 2 in the open group in minimum of 18-month follow up. Rizzo et al. (17) reported 2 recurrences in 41 patients with a follow-up of 2 years. Mathoulin et al. (18) reported 4 recurrences in 96 patients with an average follow-up of 34 months. However, in another study, Chassat et al. (12) reported 16 recurrences in 54 dorsal wrist ganglia (29.7%) following arthroscopic excision at an average follow-up of 28 months. Recurrence rates after open excision are also variable. In a recent systemic review, Crawford et al. (19) found recurrence rate of arthroscopic excision as 7.9% whereas 9.8% for open excision when poor quality studies were excluded. Based on the relevant literature, arthroscopic excision of dorsal wrist ganglion has recurrence rates similar to the open technique. However, we believe that the most important reason of recurrence is incomplete excision of the stalk or the existence of multiple cysts which are not removed after arthroscopy or open surgery.

Dominant side, younger ages and female gender are reported to be the most substantial risk factors for recurrence following arthroscopic resection of wrist ganglions in the literature (20). In our small cohort, the mean age of the patients was 26.8 years in the arthroscopic group and 27 years for the open group. However, the ages of the patients with recurrence were 26, 32, 19 and 26 years, and no correlation was observed with age. On the other hand, all of the four recurrences were observed on the dominant side. In addition, three of the patients were female whereas one was male.

Complications such as stiffness, neuroma, hematoma, wound problems, neuropraxia or paresthesia, vascular injury, infection and extensor tenosynovitis were reported in the literature after open ganglion resections. (19,21,22) However, these complications are also possible after arthroscopic surgery. Kang et al. (6) compared outcomes of arthroscopic and open resection of 72 ganglions and they reported a case of neuropraxia of the superficial radial nerve, which was resolved after neurolysis in the arthroscopic group whereas no complication was reported in the open group. Fernandes et al. (11) reported one hypertrophic scarring after 34 arthroscopic resections. Edwards and Johansen (23) reported three extensor tenosynovitis after 55 arthroscopic surgeries. One of our patients had extensor tenosynovitis which lasted for six months after surgery and limited full flexion of the wrist. On the other hand, we did not observe any complication on the open group.

Post-surgical follow-up varies in the literature. We did not immobilize the wrist joint and only did a soft dressing as recommended by Nishikawa et al. (10). On the other hand, many authors choose immobilization for 7-10 days and avoid strenuous activity for few weeks (6,17).

An advantage of arthroscopic resection of dorsal ganglions are considered to be able to interfere coexisting intraarticular pathologies. Osterman and Raphael (5) reported that almost half of the patients had intraarticular pathologies and most commonly a scapholunate interosseous ligament tear. Likewise, Edwards and Johansen (23) claimed that all of the patients with dorsal wrist ganglions also had ligament instabilities. Kang et al. (24) reported intraarticular pathologies with dorsal wrist ganglions in 21 of 41 patients, such as TFCC and intrinsic ligament tears (23). We diagnosed scapholunate interosseous ligament tear in seven patients and grade 1 TFCC tear in one patient who underwent arthroscopic ganglion excision. We have not performed any arthroscopic repair to any identified coexisting intraarticular pathology; however, this may be because of our lack of experience in wrist arthroscopy and we may have underestimated the potential ligament laxity or other pathologies. On the other hand, a recent study showed that additional intraarticular pathologies did not affect functional outcomes after arthroscopic excision of dorsal ganglions (24).

One of the advantages of arthroscopic surgery is better cosmetic outcome. The small portals are only millimeters in length and scars are almost invisible after wound healing. In our study, the average scar length was 34.5 mm in the open group and 9.3 mm in the arthroscopic group. They healed faster and almost all of the patients in our study were satisfied with the cosmetic outcome.

Study Limitations

This study has some limitations. The main limitations are the small number of patients, the absence of a control group, and relatively short follow-up period. In addition, we could not repair interosseous ligamentous instability because of lack of experience.

Conclusion

Arthroscopic ganglionectomy has advantages of smaller scars, diagnosing and treating coexisting disorders of the wrist. Disadvantages are steep learning curve and long operating time.

Ethics

Ethics Committee Approval: The Institutional Review Board of University of Health Sciences Turkey, İstanbul Training and Research Hospital approved this study (Decision no: 1042, date: 21.07.2017).

Informed Consent: Consent form was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - T.G.; Concept - T.G.; Design - T.G.; Data Collection and/or Processing - T.G.; Analysis and/or Interpretation - T.G., E.Ç.; Literature Search - T.G., E.Ç.; Writing Manuscript - T.G., E.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Meena S, Gupta A. Dorsal wrist ganglion: Current review of literature. J Clin Orthop Trauma 2014; 5: 59-64.
2. Thornburg LE. Ganglions of the hand and wrist. J Am Acad Orthop Surg 1999; 7: 231-8.
3. Gude W, Morelli V. Ganglion cysts of the wrist: pathophysiology, clinical picture, and management. Curr Rev Musculoskelet Med 2008; 1: 205-11.
4. Suen M, Fung B, Lung CP. Treatment of ganglion cysts. ISRN Orthop. 2013; 2013: 940615.
5. Osterman AL, Raphael J. Arthroscopic resection of dorsal ganglion of the wrist. Hand Clin 1995; 11: 7-12.
6. Kang L, Akelman E, Weiss AP. Arthroscopic versus open dorsal ganglion excision: a prospective, randomized comparison of rates of recurrence and of residual pain. J Hand Surg Am 2008; 33: 471-5.
7. Wagner J, Ipaktchi K, Livermore M, Banegas R. Current indications for and the technique of wrist arthroscopy. Orthopedics 2014; 37: 251-6.
8. Wolf JM, Dukas A, Pensak M. Advances in wrist arthroscopy. J Am Acad Orthop Surg 2012; 20: 725-34.
9. Mathoulin C, Gras M. Arthroscopic Management of Dorsal and Volar Wrist Ganglion. Hand Clin 2017; 33: 769-77.
10. Nishikawa S, Toh S, Miura H, Arai K, Irie T. Arthroscopic diagnosis and treatment of dorsal wrist ganglion. J J Hand Surg Br 2001; 26: 547-9.
11. Fernandes CH, Meirelles LM, Raduan Neto J, Fernandes M, Dos Santos JBG, Faloppa F. Arthroscopic Resection of Dorsal Wrist Ganglion: Results and Rate of Recurrence Over a Minimum Follow-up of 4 Years. Hand (N Y) 2019; 14: 236-41.
12. Chassat R, Nourissat G, Chaumeil G, Dumontier C. [Arthroscopic treatment of dorsal ganglion cyst at the wrist. About 54 cases]. Chir Main 2006; 25: 146-51.
13. Rocchi L, Canal A, Pelaez J, Fanfani F, Catalano F. Results and complications in dorsal and volar wrist Ganglia arthroscopic resection. Hand Surg 2006; 11: 21-6.
14. Lee HLL, Lee KH, Koh KH, Won HJ, Cho HK, Park MJ. Excision of painful dorsal wrist ganglion by open or arthroscopic approach : a compariso n study. Acta Orthop Belg 2017; 83: 315-321.
15. Zeidenberg J, Aronowitz JG, Landy DC, Owens PW, Jose J. Ultrasound-guided aspiration of wrist ganglions: a follow-up survey of patient satisfaction and outcomes. Acta Radiol 2016; 57: 481-6.
16. Kulinski S, Gutkowska O, Mizia S, Gosk J. Ganglions of the hand and wrist: Retrospective statistical analysis of 520 cases. Adv Clin Exp Med 2017; 26: 95-100.
17. Rizzo M, Berger RA, Steinmann SP, Bishop AT. Arthroscopic resection in the management of dorsal wrist ganglions: results with a minimum 2-year follow-up period. J J Hand Surg Am 2004; 29: 59-62.
18. Mathoulin C, Hoyos A, Pelaez J. Arthroscopic resection of wrist ganglia. Hand Surg 2004; 9: 159-64.
19. Crawford C, Keswani A, Lovy AJ, Levy I, Lutz K, Kim J, et al. Arthroscopic versus open excision of dorsal ganglion cysts: a systematic review. J Hand Surg Eur Vol 2018; 43: 659-64.
20. Kim JP, Seo JB, Park HG, Park YH. Arthroscopic excision of dorsal wrist ganglion: factors related to recurrence and postoperative residual pain. Arthroscopy 2013; 29: 1019-24.
21. Balazs GC, Donohue MA, Drake ML, Ipsen D, Nanos GP, Tintle SM. Outcomes of Open Dorsal Wrist Ganglion Excision in Active-Duty Military Personnel. J Hand Surg Am 2015; 40: 1739-47.
22. Khan PS, Hayat H. Surgical excision versus aspiration combined with intralesional triamcinolone acetonide injection plus wrist immobilization therapy in the treatment of dorsal wrist ganglion; a randomized controlled trial. J Hand Microsurg 2011; 3: 55-7.
23. Edwards SG, Johansen JA. Prospective outcomes and associations of wrist ganglion cysts resected arthroscopically. J Hand Surg Am 2009; 34: 395-400.
24. Kang HJ, Koh IH, Kim JS, Choi YR. Coexisting intraarticular disorders are unrelated to outcomes after arthroscopic resection of dorsal wrist ganglions. Clin Orthop Relat Res 2013; 471: 2212-8.

İstanbul Med J 2020; 21(2): 109-14
DOI: 10.4274/imj.galenos.2020.47855

Electrocardiographic Alterations in Patients with Common Variable Immune Deficiency

Yaygın Değişken İmmün Yetmezliği Olan Hastalarda Elektrokardiyografik Değişikliklerin Değerlendirilmesi

Yakup Alsancak[1], Fatih Çölkesen[2]

[1]Necmettin Erbakan University Meram Faculty of Medicine, Department of Cardiology, Konya, Turkey
[2]Necmettin Erbakan University Meram Faculty of Medicine, Department of Clinical Immunology and Allergy, Konya, Turkey

ABSTRACT

Introduction: Common variable immunodeficiency (CVID) is the most heterogeneous group among the antibody deficiency syndromes, but its effects on the cardiovascular system have not yet been clearly identified. Here, we aimed to investigate the arrhythmogenic effects of this disease with electrocardiography.

Methods: The study included 30 CVID patients and 30 control subjects matched for age and comorbidities. Electrocardiographic and echocardiographic values of all participants were recorded. QRS, QT, Tp-e were measured manually. QTc was calculated using Bazett's formula. Then, Tp-e/QT, Tp-e/QTc, QT/QRS, and QTc/QRS ratios were calculated and compared between the groups.

Results: PR interval and P-wave dispersion were found to be higher in the CVID group. In addition, the QT interval and corrected QT interval, T peak-to-end interval were higher in the CVID arm, and the index of cardiac electrophysiological balance value obtained with the QT/QRS ratio was also higher in the CVID group. The number of patients with P terminal force was also higher in the CVID group.

Conclusion: As a result of this study, it was found that CVID patients have a higher incidence of developing arrhythmia than normal healthy individuals.

Keywords: Arrhythmia, CVID, electrocardiography

ÖZ

Amaç: Ortak değişken immün yetmezlik (CVID), antikor eksikliği sendromları arasında en heterojen gruptur, ancak kardiyovasküler sistem üzerindeki etkileri henüz net bir şekilde tanımlanamamıştır. Burada, bu hastalığın olası aritmojenik etkilerini, elektrokardiyografi ile değerlendirmeyi amaçladık.

Yöntemler: Çalışmaya 30 CVID hastası ile yaş ve komorbiditeleri eşleşen 30 gönüllü kontrol grubu dahil edildi. Tüm katılımcıların elektrokardiyografik ve ekokardiyografik değerleri kaydedildi. QRS, QT, Tp-e manuel olarak ölçüldü. QTc, Bazett formülü kullanılarak hesaplandı. Daha sonra, Tp-e/QT, Tp-e/QTc, QT/QRS ve QTc/QRS oranları hesaplandı ve gruplar arasında karşılaştırılma yapıldı.

Bulgular: CVID grubunda PR aralığı ve P dalga dispersiyonu daha yüksek bulundu. Ayrıca, QT aralığı ve düzeltilmiş QT aralığı, T peak-to-end interval, CVID kolunda daha yüksekti ve QT/QRS oranı ile elde edilen kardiyak elektrofizyolojik denge indeksi değeri CVID grubunda da daha yüksekti. CVID grubunda P terminal kuvveti olan hasta sayısı da daha fazla idi.

Sonuç: Bu çalışma sonucunda, CVID hastalarının normal sağlıklı bireylere göre aritmi gelişme sıklığının daha yüksek olabileceği bulunmuştur.

Anahtar Kelimeler: Aritmi, CVID, elektrokardiyografi

Introduction

Common variable immunodeficiency (CVID) is the most heterogeneous group among the antibody deficiency syndromes and the estimated prevalence is about 1:25.000 (1). Hypogammaglobulinemia is a primary immunodeficiency characterized by recurrent infections and increased risk of developing autoimmune diseases and malignancy (2). The presence of concomitant autoimmune diseases or chronic diseases has been associated with chronic inflammatory processes in patients (3). However, its effects on the cardiovascular system have not yet been clearly identified (4). However, it may be associated with immune deficiencies due to the known effects of systemic inflammation in the pathogenesis of atherosclerosis (5). In addition, inflammation plays a significant role in the pathogenesis of chronic arrhythmias, such as atrial fibrillation (AF) (6,7).

Standard surface electrocardiography is a simple diagnostic tool that is widely used in the detection of cardiac arrhythmias or coronary artery disease and in the evaluation of myocardial pathologies. Here, various

Address for Correspondence/Yazışma Adresi: Yakup Alsancak MD, Necmettin Erbakan University Meram Faculty of Medicine, Department of Cardiology, Konya, Turkey
Phone: +90 506 910 14 04 **E-mail:** dryakupalsancak@gmail.com **ORCID ID:** orcid.org/0000-0001-5230-2180

Cite this article as/Atıf: Alsancak Y, Çölkesen F. Electrocardiographic Alterations in Patients with Common Variable Immune Deficiency. İstanbul Med J 2020; 21(2): 109-14.

Received/Geliş Tarihi: 18.01.2020
Accepted/Kabul Tarihi: 07.02.2020

parameters have been identified on an electrocardiogram (ECG) that predicts sudden cardiac death or any arrhythmias. The best known of these is the prolongation of the QT interval, indicating sudden death or cardiac electrical instability (8). In addition, the T-wave peak-to-end (T_{p-e}) interval and T_{p-e}/QT ratio are novel proarrhythmogenic markers suggesting transmural dispersion of repolarization in the left ventricle (9). Moreover, P-wave dispersion (PWD) is known to predict the development of AF (10). More recently, the index of cardiac electrophysiological balance (iCEB), calculated by dividing the QT interval by the QRS duration, has been shown to be a predictor of ventricular arrhythmias (11,12).

Along with the changes observed in medical treatment, CVID awareness and the number of diagnosed patients are increasing day by day. Previously deceased due to various infectious diseases (brain abscess, endocarditis, pneumonia, etc.), antibiotic therapies and intravenous immunoglobulin treatments administered to these patients prolonged life expectancy. However, the effects of this disease, which can be a long chronic process, on the cardiovascular system are unknown. In our study, we aimed to investigate the effects of this disease on electrocardiography for the first time.

Methods

Patient Population

A total of 60 participants, including 30 patients who had undergone a cardiological examination for any reason and were being monitored for CVID and 30 healthy subjects who had been age and sex matched, were included in the study at the allergy and immunology clinic at our hospital. A standard 12-lead ECG was performed on the patients. The exclusion criteria were as follows: chronic renal failure; presence of electrolyte abnormalities; presence of active infection or malignancy; use of any drugs affecting the cardiac conduction system (treatment with beta-blockers, non-dihydropyridine calcium channel blockers or digital use) or use of prophylactic antibiotics with known efficacy on electrocardiography for protection from infections (erythromycin, azithromycin, etc.); regular use of an inhaler due to chronic obstructive pulmonary diseases; having undergone percutaneous coronary intervention or coronary artery bypass surgery for coronary artery disease; presence of documented AF; presence of a cardiac pacemaker; presence of a branch block on the ECG; presence of preexcitation syndromes; presence of left ventricular hypertrophy on an echocardiogram; and moderate or severe heart valve disease. Baseline demographic characteristics and electrocardiographic findings of the study population were recorded. Informed consent was obtained from all patients and healthy controls. The study was approved by the local ethics committee of Necmettin Erbakan University Faculty of Medicine the study was conducted according to the Declaration of Helsinki (decision no: 2019/1909).

Assessment of Electrocardiographic Parameters

A standard 12-lead surface ECG was performed after at least 1 hour of rest (10 mV/mm and 25 mm/s paper speed Marquette Case, Hellige Medical System, Cardiosmart Hellige Instrument Company, Freiburg, Germany). Heart rate, p-wave morphology, PR interval, QRS duration, QT distance and T-wave morphology were analyzed. All ECG samples were transferred to a digital platform to reduce the margin of error during measurement, and measurements were then taken using special software (Adobe Photoshop) to provide necessary magnification.

The beginning point of the P-wave was described as the first upward positive or downward negative deflection between the isoelectric line and the end of the P-wave was characterized as the point where the last deflection of the P-wave met the isoelectric line. Maximum P (P_{max}) and minimum P (P_{min}) wave durations were recorded. PWD was defined as the difference between the maximum and P_{min}-wave durations (10). Interatrial duration was regarded as the greatest duration of P-waves from D2, D3, AVF or V1 (13). P terminal force was defined as the terminal negative part of a biphasic P-wave in lead V1 being greater than 1 small square (40 mm) (14). The QT interval was conventionally obtained by manually measuring from the onset of the QRS complex to the crossing point of the T wave and isoelectric line. The heart rate-corrected QT interval was calculated using Bazett's formula ($cQT=QT\sqrt{}$ (R - R interval). QT dispersion (QTd) was obtained by measuring the longest QT interval (QT_{max}) and the shortest QT interval (QT_{min}) in any lead (15). QT interval measurements were taken by examining recordings from leads D2 and precordial V5, and the longer lead was recorded for statistical analysis (16). Changes in the T-wave in each cardiac cycle (shape, height, or duration) were termed macroscopic T-wave alternans (17). The distance from the peak of the T-wave (T_{peak}) to the endpoint of the T-wave (T end) ($T_{peak-end}$ or T_{p-e}) was obtained from the chest leads. The T_{p-e}/QT ratio was obtained by dividing the T_{p-e} duration by the QT interval in the precordial V5 lead (16,18). iCEB was obtained by dividing the QT interval by the QRS duration in the same lead (D2 or V5) (11,12).

Statistical Analysis

SPSS® version 16.0 statistical package software (SPSS Inc., Chicago, IL, United States) was used for statistical analyses. We presented normally distributed quantitative variables as mean ± standard deviation while we presented categorical variables in numbers and percentages. Normality of distribution was evaluated using the Kolmogorov-Smirnov test. Mean values of continuous variables were compared between independent groups using the Student's t-test, one-way ANOVA test, or Kruskal-Wallis test as appropriate. The chi-square test was performed to compare the study groups in terms of categorical variables. A p-value below 0.05 was considered statistically significant.

Results

The mean age of the patients included in the study was 38.76±13.59 years and 57% (n=34) were male. In addition, there was no statistically significant difference between the groups (CVID group and control group) in terms of age, gender, hypertension and smoking ($p>0.05$). The mean age of patients with CVID at the time of initial diagnosis was calculated as 28.03±15.29 years (minimum 1 year, maximum 60 years). The mean follow-up period of CVID patients was 8±6.58 years while the rate of patients with bronchiectasis whose clinical condition was not affected was 47% (n=14) in this patient group. The main demographic and characteristic features of the study population are shown in Table 1.

Table 2 shows a comparison of electrocardiographic parameters of the patient and control groups. Accordingly, the heart rate per minute and

P_{max} and P_{min} intervals were similar in both groups while the PR interval and PWD were found to be higher in the CVID group (p value; 0.009 and 0.005, respectively). In addition, the QT interval and corrected QT interval were higher in the CVID arm (p=0.021), and the iCEB value obtained with the QT/QRS ratio was also higher in the CVID group (p=0.031). T peak-to-end interval was higher in the CVID group (p=0.013) while the T peak-to-end/QT ratio was not statistically significant between the two groups although it was still high (p=0.093). The number of patients with P terminal force was higher in the CVID group (20% vs. 3%, p=0.044) while the number of patients monitored for macrovolt T-wave alternans was similar in both groups (p=0.519).

Depending on the presence of bronchiectasis, the QT interval and corrected QT interval were found to be longer in the presence of bronchiectasis when the subgroup analysis of the CVID group was performed (p values=0.011 and 0.013, respectively). All other electrocardiographic parameters were observed to be similar. Table 3 shows a comparison of the electrocardiographic parameters of the CVID group in the presence of bronchiectasis.

Discussion

As a result of our study, P-wave and QTd, a predictor of the development of arrhythmia in CVID patients, T_{p-e} interval and index of cardiac electrophysiological balance values have been shown to be higher. In addition, the QT interval was longer and P-terminal force frequency was higher in this patient group. Furthermore, none of these results varied, except for the QT interval, with bronchiectasis that does not require clinical treatment.

In CVID patients, the disease is usually diagnosed within about 8 years after first symptoms, and this diagnostic delay results in delayed initiation of standard treatments (immunoglobulin), thereby increasing

Table 1. Basale characteristic of study population

Variables	Control group (n=30)	CVID group (n=30)	p
Age (years, mean ± SD)	40.70±13.85	36.83±13.28	0.274
Gender (male, n%)	18 (60)	16 (53.3)	0.602
Diabetes Mellitus (n%)	3 (10)	2 (6)	0.640
Hypertension (n%)	4 (13)	3 (10)	0.688
Smoking (n%)	8 (26)	6 (20)	0.542
Ejection fraction (%, mean ± SD)	62.13±4.71	63.33±3.45	0.438
Age of diagnosis (years, mean ± SD, minimum-maximum)	-	28.03±15.29 (1-60)	-
Following period (years, mean ± SD)	-	8±6.58	-
The usage time of intravascular immunglobuline (years, mean ± SD)	-	7.69±6.88	-

CVID: common variable immunodeficiency, SD: standard deviation

Table 2. Comparison of electrocardiographic parameters of the study group

Variables	Control group (n=30)	CVID group (n=30)	p
Heart rate (beat/min, mean ± SD)	80.60±13.63	84.86±15.24	0.258
PR interval (msn, mean ± SD)	135.13±13.76	147.10±20	0.009
P maximum (msn, mean ± SD)	96.26±20.25	101.83±22.9	0.323
P minimum (msn, mean ± SD)	51±16.62	44.53±9.74	0.071
P wave dispersion (msn, mean ± SD)	44.7±13.29	57.8±20.38	0.005
Interatrial duration (≥110 ms) (n%)	8 (27)	10 (33)	0.389
P terminal force (n, %)	1 (3.3)	6 (20)	0.044
QT duration (msn, mean ± SD)	360.17±22.14	378.5±35.84	0.021
Corrected QT duration (msn, mean ± SD)	396.51±27.82	419.38±30.34	0.004
QT dispersion (msn, mean ± SD)	31±12.06	44.96±26.01	0.011
QRS duration (msn, mean ± SD)	82.90±10.81	77.66±14.82	0.124
T peak to T-end interval (msn, mean ± SD)	68.5±12.87	78.1±16.05	0.013
T peak to T-end interval/QT duration ratio	0.19±0.33	0.20±0.04	0.093
T peak to T-end interval/corrected QT duration ratio	0.17±0.33	0.18±0.03	0.185
Macrovolt T wave alternans (n/%)	7 (23)	5 (16)	0.519
Index of cardioelectrophsiyological balance (QT interval/QRS duration ratio)	4.41±0.64	4.92±1.07	0.031
Corrected Index of cardioelectrophsiyological balance (corrected QT interval/QRS duration ratio)	4.86±0.76	5.44±1.24	0.033

CVID: Common variable immunodeficiency, SD: standard deviation

Table 3. Comparison of CVID patients according to the presence of bronchiectasis

Variables	Patients with bronchiectasia (n=14)	Patients without bronchiectasia (n=16)	p
Age (years, mean ± SD)	36.5±13.71	37.12±13.34	0.912
Age of diagnosis (years, mean ± SD)	26.64±16.45	29.25±14.63	0.649
Following period (years, mean ± SD)	9.66±6.53	6.61±6.38	0.206
The usage time of intravascular immunglobuline (years, mean ± SD)	9.26±6.13	7.29±6.33	0.037
Heart rate (beat/min, mean ± SD)	85.14±15.56	84.62±15.47	0.928
Ejection fraction (%, mean ± SD)	63.21±4.13	63.43±2.87	0.864
PR interval (msn, mean ± SD)	147.29±20.93	146.94±19.85	0.963
P maximum (msn, mean ± SD)	108.50±25.16	96±19.69	0.138
P minimum (msn, mean ± SD)	46.92±12.33	42.43±6.44	0.213
P wave dispersion (msn, mean ± SD)	61.21±21.12	54.81±19.91	0.401
Interatrial duration (≥110 ms) (n, %)	3 (21)	7 (44)	0.041
P terminal force (n, %)	3 (21)	3 (19)	0.855
QT duration (msn, mean ± SD)	361.07±37.32	393.75±27.29	0.011
Corrected QT duration (msn, mean ± SD)	405.07±26.84	431.91±28.68	0.013
QT dispersion (msn, mean ± SD)	36.85±21.11	52.06±28.41	0.072
QRS duration (msn, mean ± SD)	77.28±10.17	78±18.31	0.898
T peak to T-end interval (msn, mean ± SD)	78.21±17.57	78±15.19	0.972
T peak to T-end interval/QT duration ratio	0.21±0.04	0.19±0.04	0.233
T peak to T-end interval/corrected QT duration ratio	0.19±0.04	0.17±0.03	0.353
Macrovolt T wave alternans (n, %)	3 (21)	2 (14)	0.743
Index of cardioelectrophsiyological balance (QT interval/QRS duration ratio)	4.73±0.73	5.08±1.3	0.382
Corrected Index of cardioelectrophsiyological balance (corrected QT interval/QRS duration ratio)	5.32±0.79	5.54±1.55	0.633

CVID: Common variable immunodeficiency, SD: Standard deviation

mortality and morbidity rates of the disease (19). Although the life expectancy of CVID patients increases with improved treatment methods, the presence of chronic inflammation leads to the development of different diseases in this patient group (20,21). In CVID patients, TNF-alpha and CRP levels were found to be higher as indicators of chronic inflammation compared to healthy subjects. The clinical presentation of this disease is known to be more severe in patients with high inflammation parameters (21,22). Inflammation parameters, such as TNF-alpha, CRP and IL-6 are also known to play an effective role in the pathogenesis of atherosclerosis which is a chronic disease. In addition, apo-A and high-density lipoprotein cholesterol levels and chronic inflammation were lower in this patient group (21). When evaluated with this evidence, atherosclerotic heart disease was considered to have started at an early stage in CVID patients and was thought to display a rapid course. On the other hand, it was thought that atherosclerosis and related diseases could be overlooked in these patients due to chronic respiratory infections (pneumonia, bronchiectasis, etc.), gastrointestinal system infections, autoimmune diseases and malignant diseases which are more common in early ages (23). As life expectancy was lower in this patient group, atherosclerotic cardiovascular diseases were thought to not display any clinical symptoms. In a comprehensive study, the age of mortality was shown to be between 40 and 50 years. However, with current immunoglobulin therapies and advanced antibiotic technologies, it is thought that the rate of patients presenting with cardiovascular diseases will increase in the near future (23,24). Another hypothesis was described as follows: "Endothelial dysfunction and endothelial inflammation in atherosclerosis cannot develop due to chronic immune dysregulation and immunodeficiency or the risk of atherosclerosis in these patients is similar in healthy individuals due to received immunoglobulin treatments" (23).

As atherosclerosis itself is known to be a risk factor for cardiac arrhythmias, the increased inflammatory response itself has also been shown to cause cardiac arrhythmias alone. For instance, inflammatory markers such as TNF-alpha, CRP, IL 6-8 were found to be higher in individuals with AF (25). Individuals with high CRP levels following myocardial infarction were more likely to suffer from ventricular tachycardia during clinical follow-up (26). At this point, it can be considered that the chronic inflammatory process in CVID patients provides a suitable basis for the development of cardiac arrhythmias.

Various parameters have been developed in standard surface electrocardiography to predict cardiac arrhythmias and pathologies. The main purpose of this study was to evaluate the effect of CVID on these parameters and to assess the arrhythmogenic risk in this patient population. Here, P-wave dispersion, a strong predictor of

the possibility of AF and the efficacy of which was demonstrated in various studies, was found to be higher in CVID patients (10,27). This supports the inflammatory process and risk of developing AF in CVID patients. Interatrial duration (interatrial block) and p-terminal force are parameters that were indicative of dilatation and dysfunction of the left atrium, atrial fibrillation and development of stroke (13,28,29). In our study, the frequency of P-terminal force was higher in CVID patients (3.3% vs. 20%, p=0.044); however, no statistically significant difference was determined in interatrial duration although the number thereof was higher (p=0.389). It should not be overlooked that the excess P terminal force supports the high probability of developing AF in this patient group. In addition, increased QTd detected in a surface ECG is associated with increased heterogeneity in ventricular repolarization and has an adverse impact on the development of ventricular arrhythmia (15,30). In our study, the QTd was higher in CVID. Moreover, iCEB, calculated as the QT/QRS interval, has been defined as a new risk predictor for malignant ventricular arrhythmias. Increased iCEB values have been shown to be associated with torsades de pointes while decreased iCEB values have been associated with non-torsades de pointes ventricular tachycardia or ventricular fibrillation (11,12). Again, this value was higher in the CVID patient group (p=0.031). The high QTd and iCEB values indicate that the incidence of ventricular arrhythmia is higher in this patient group than in the normal population. In addition to this information, the T_{p-e} interval is considered an index of transmural dispersion of repolarization in the left ventricle, and the T_{p-e}/QT ratio is used as a newer electrocardiographic index showing ventricular arrhythmias. Accordingly, a prolonged T_{p-e} interval and a higher T_{p-e}/QT ratio were associated with an increased risk of ventricular arrhythmia (9,31). In our patients, an increased T_{p-e} interval supported the risk of ventricular arrhythmia (p=0.013) while no statistical significance was observed (p=0.185) with an increased T_{p-e}/QT ratio.

The incidence of lung pathologies, particularly bronchiectasis, is high in CVID patients due to delayed diagnosis and treatment. Bronchiectasis is the most common pulmonary pathology in this patient group with a prevalence varying between 17 and 76% (32,33). In our patient population, this rate was 46.6%. There was no significant difference upon review of the ECGs of CVID patients with and without bronchiectasis. In patients with bronchiectasis, only the QT interval was shorter. Furthermore, as expected, the follow-up and treatment periods were slightly longer in the bronchiectasis group. Essentially, electrocardiographic changes should be more significant in the bronchiectasis group due to the longer duration of disease in patients with bronchiectasis. However, the small number of patients may be the most effective parameter to cause this condition. The high QT interval in CVID patients without bronchiectasis may be a coincidental result. More comprehensive and detailed studies are necessary to clarify this situation.

Conclusions

As a result of this study, it has been found that CVID patients have a higher incidence of developing arrhythmia than normal healthy individuals. Similar studies with a larger number of participants and longer follow-up period are needed to support our findings.

Ethics Committee Approval: The study was approved by the local ethics committee of Necmettin Erbakan University Faculty of Medicine the study was conducted according to the Declaration of Helsinki (decision no: 2019/1909).

Informed Consent: Informed consent was obtained from all patients and healthy controls.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - Y.A., F.Ç.; Concept - Y.A., F.Ç.; Design - Y.A., F.Ç.; Data Collection and/or Processing - Y.A., F.Ç.; Analysis and/or Interpretation - Y.A., F.Ç.; Literature Search - Y.A., F.Ç.; Writing Manuscript - Y.A., F.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Park MA, Li JT, Hagan JB, Maddox DE, Abraham RS. Common variable immunodeficiency: a new look at an old disease. Lancet 2008; 372: 489–502.
2. Cunningham-Rundles C, Knight AK. Common variable immune deficiency:reviews, continued puzzles, and a new registry. Immunol Res 2007; 38: 78–86.
3. Gathmann B, Mahlaoui N, Gérard L, Oksenhendler E, Warnatz K, Schulze I, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol 2014; 134: 116–26.
4. Human A, Murguia FL, Benson L, Roifman I, Grunebaum E. Cardiovascular abnormalities in primary immunodeficiency diseases. LymphoSign Journal 2015; 2: 107-34.
5. Libby P, Okamoto Y, Rocha VZ, Folco E: Inflammation in atherosclerosis: transition from theory to practice. Circ J 2010; 74: 213–20.
6. Fujiki A, Sakamoto T, Nishida K, Mizumaki K, Inoue H. Relation of interleukin-6 and C-reactive protein levels to sinus maintenance after pharmacological cardioversion in persistent atrial fibrillation. J Cardiovasc Pharmacol 2007; 50: 264-6.
7. Sata N, Hamada N, Horinouchi T, Amitani S, Yamashita T, Moriyama Y, et al. C-reactive protein and atrial fibrillation. Is inflammation a consequence or a cause of atrial fibrillation? Jpn Heart J 2004; 45: 441-5.
8. Straus SM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. J Am Coll Cardiol 2006; 47: 362–7.
9. Gupta P, Patel C, Patel H, Narayanaswamy S, Malhotra B, Green JT et al. T(p-e)/QT ratio as an index of arrhythmogenesis. J. Electrocardiol 2008; 41: 567–74.
10. Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M, et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. Am Heart J 1998; 135: 733–8.
11. Lu HR, Yan GX, Gallacher DJ. A new biomarker–index of cardiac electrophysiological balance (iCEB)–plays an important role in drug-induced cardiac arrhythmias: Beyond QT-prolongation and torsades de pointes (TdPs). J Pharmacol Toxicol Methods 2013; 68: 250–9.
12. Robyns T, Lu HR, Gallacher DJ, Garweg C, Ector J, Willems R et al. Evaluation of Index of Cardio-Electrophysiological Balance (iCEB) as a New Biomarker for the Identification of Patients at Increased Arrhythmic Risk. Ann Noninvasive Electrocardiol 2016; 21: 294-304.
13. Goyal Sb, Spodıck Dh. Electromechanical dysfunction of the left atrium associated with interatrial block. Am Heart J 2001; 142: 823-7.

14. E.W. Hancock, B.J. Deal, D.M. Mirvis, Okin P, Kligfield P, Gettes LS, et al. American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; American College of Cardiology Foundation; Heart Rhythm Society, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram J. Am. Coll. Cardiol 2009; 53: 992-1002.

15. Malik M and Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. J Am Coll Cardiol 2000; 36: 1749–66.

16. Shimizu M, Ino H, Okeie K, Yamaguchi M, Nagata M, Hayashi K, et al. T-peak to T-end interval may be a better predictor of high-risk patients with hypertrophic cardiomyopathy associated with a cardiac troponin I mutation than QT dispersion. Clin Cardiol 2002; 25: 335-9.

17. Narayan SM. T-wave alternans and the susceptibility to ventricular arrhythmias. J Am Coll Cardiol 2006; 47: 269–81.

18. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, Dorantes Sánchez M, Dorticós Balea F, Zayas Molina R, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol 2006; 47: 1828-34.

19. Seymour B, Miles J, Haeney M. Primary antibody deficiency and diagnostic delay. J Clin Pathol 2005; 58: 546–7.

20. Frostegard J. Immunity, atherosclerosis and cardiovascular disease. BMC Med 2013; 11: 117.

21. Vieira DG, Costa-Carvalho BT, Hix S, da Silva R, Correia MS, Sarni RO. Higher Cardiovascular Risk in Common Variable Immunodeficiency and X-Linked Agammaglobulinaemia Patients. Ann Nutr Metab 2015; 66: 237-41.

22. Trujillo CM, Muskus C, Arango J, Patino PJ, Montoya CJ. Quantitative and functional evaluation of innate immune responses in patients with common variable immunodeficiency. J Investig Allergol Clin Immunol 2011; 21: 207–15.

23. Ucar R, Arslan S, Turkmen K, Calıskaner AZ. Accelerated atherosclerosis in patients with common variable immunodeficiency: Is it overlooked or absent?. Med Hypotheses 2015; 85: 485-7.

24. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood 2012; 119: 1650-7.

25. Harada M, Van Wagoner DR, Nattel S. Role of inflammation in atrial fibrillation pathophysiology and management. Circ J 2015; 79: 495-502.

26. Blangy H, Sadoul N, Dousset B, Radauceanu A, Fay R, Aliot E, et al. Serum BNP, hs-CRP, procollagen to assess the risk of ventricular tachycardia in ICD recipients after myocardial infarction. Europace 2007; 9: 724-9.

27. Dilaveris PE, Gialafos JE. P-wave dispersion: a novel predictor of paroxysmal atrial fibrillation. Ann Noninvasive Electrocardiol 2001; 6: 159–65.

28. Agarwal Yk, Aronow Ws, Levy Ja, Spodıck Dh. Association of interatrial block with development of atrial fibrillation. Am J Cardiol 2003; 91: 882.

29. Spodıck Dh, Arıyarajah V, Goldberg R. Interatrial block: correlation with P-terminal force. Clin Cardiol 2009; 32: 181-2.

30. Lee KW, Okin PM, Kligfield P, Stein KM, Lerman BB. Precordial QT dispersion and inducible ventricular tachycardia. Am Heart J 1997; 134: 1005-13.

31. Hetland M, Haugaa KH, Sarvari SI, Erikssen G, Kongsgaard E, Edvardsen T. A novel ECG-index for prediction of ventricular arrhythmias in patients after myocardial infarction. Ann. Noninvasive Electrocardiol 2014; 19: 330–7.

32. Maarschalk-Ellerbroek LJ, Hoepelman AI, van Montfrans JM, Ellerbroek PM. The spectrum of disease manifestations in patients with common variable immunodeficiency disorders and partial antibody deficiency in a university hospital. J Clin Immunol 2012; 32: 907–21.

33. Ardeniz O, Başoğlu OK, Günşar F, Unsel M, Bayraktaroğlu S, Mete N, et al. Clinical and immunological analysis of 23 adult patients with common variable immunodeficiency. J Investig Allergol Clin Immunol 2010; 20: 222-36.

İstanbul Med J 2020; 21(2): 115-9
DOI: 10.4274/imj.galenos.2020.71463

Brain Death and Deceased Organ Donation in a Hospital in İstanbul, Turkey: The Effect of Early Identification of Brain Dead on Organ Donation Rates: A Retrospective Study

Beyin Ölümü Erken Tanısının Organ Bağış Oranına Etkisinin Retrospektif Analizi

Tuğçe Yeniocak[1], Perihan Ergin Özcan[2]

[1]Metin Sabancı Baltalimanı Bone and Joint Diseases Training and Research Hospital, Clinic of Anesthesiology, İstanbul, Turkey
[2]İstanbul University Faculty of Medicine, Department of Anesthesiology, İstanbul, Turkey

ABSTRACT

Introduction: The possibility of brain death (BD) among patients with a Glasgow Coma scale <7 must be considered by physicians who work in intensive care units. Deceased organ transplantation can be lifesaving so every BD patient should be seen as a potential donor. The aim of this study was to describe the causes of BD, rate of organ donation and to investigate the effect of diagnosis time on donation rates in our hospital over a 9-year period.

Methods: After obtaining Institutional Ethics Committee approval, we conducted a retrospective review of patients who had sustained BD in our hospital between January 1, 2004 and January 1, 2013. Patients' age, methods used to diagnose BD, duration of survival after diagnosis, whether patients' family members gave consent to organ donation, and organ donation rates were reviewed.

Results: Sixty patients were declared BD, of whom 21 (35%) were female and 39 (65%) were male. Their mean age was 28 years. Only 6 (10%) patients' families gave consent for donation. The most common cause of BD was traumatic brain injury (n=37, 62%). Internal carotid artery doppler ultrasonography was performed in 36 (60%) patients; cerebral angiography was performed in 14 (23%) patients; and electroencephalography was performed in two patients. The mean time from hospital admission to diagnosis of BD was 5.16±3.06 days overall; 5.5±0.4 days among non-donors; and 2.0±0.4 days among donors. The mean time from diagnosis of BD to death in non-donors was 2.4±0.3 days. In donors, the mean time from diagnosis of BD to harvesting of the patient's organs was 1.08±0.2 days.

Conclusion: In our hospital, the rate of organ donation after BD is low. It is found that the time to confirm the diagnosis of BD was significantly shorter in donors than non-donors. It is believed that early diagnosis of BD is associated with an increased rate of family approval for organ donation.

Keywords: Brain death, organ donation, deceased organ donation, transplantation

ÖZ

Amaç: Yoğun bakımda takip edilen Glasgow Koma skoru 7'nin altındaki hastalarda beyin ölümü gelişme ihtimaline karşı uyanık olunmalıdır. Kadavradan organ nakli; nakil sırası bekleyen hasta sayısını düşüreceğinden hayat kurtarıcıdır. Bu nedenle her beyin ölümü tanısı konan hastaya potansiyel donör gözüyle bakılmalıdır. Çalışmamızın amacı hastanemizde dokuz yıllık süreçte tanı alan beyin ölümü olgularını inceleyerek beyin ölümü nedenlerini araştırmak, tanı alma sürecindeki testleri ve kadavradan organ nakil oranını incelemektir. İkincil amacımız beyin ölümü tanı konma süresinin bağış oranına etkisini araştırmaktır.

Yöntemler: Etik Kurul onayı alınarak 1 Ocak 2004 ve 1 Ocak 2013 tarihleri arasında hastanemiz yoğun bakım ünitesinde beyin ölümü tanısı alan hastalar retrospektif olarak incelendi. Hastaların yaşı, beyin ölümü tanısında uygulanan testler, hastaneye gelişten beyin ölümü tanısı alana kadar geçen süre, tanı sonrası hastaların sağkalım süresi, ailelerin organ bağışına onay verip vermemeleri ve organ nakil oranları incelendi.

Bulgular: Altmış hasta beyin ölümü tanısı aldı, 21'i (%35) kadın, 39'u (%65) erkekti. Ortalama yaş 28'di. Sadece 6 (%10) aile organ bağışı için onay verdi. Beyin ölümünün en sık nedeni travmatik beyin hasarı (37; %65) olarak bulundu. Beyin ölümü klinik testlerin yanı sıra 36 (%60) hastaya internal karotis dopler, 14 (%23) hastaya serebral anjiyografi, 2 hastaya da elektroensefalografi yapılarak tanı konuldu. Hastaneye geliş ile tanı konmasına dek geçen süre ortalama 5,16±3,06 gün; donör grubunda 2,0±0,4 gün, donör olmayan grupta 5,5±0,4 gün olarak bulundu. Tanıdan kardiyak ölüme dek geçen süre donör olmayan grupta 2,4±0,3 gün olarak bulundu. Tanı konduktan sonra donör grubunda organ nakline kadar geçen süre 1,08±0,2 gündü.

Sonuç: Hastanemizde beyin ölümü sonrası organ bağış oranı oldukça düşük bulundu. Potansiyel donörlerin erken fark edilmesi ile organ bağış oranı artışı arasında istatistiksel anlamlı fark tespit edildi. Beyin ölümü tanısının erken konulması organ bağış oranını yükselterek nakil sırası bekleyen hastalar için umut ışığı olacaktır.

Anahtar Kelimeler: Beyin ölümü, organ nakli, kadavradan organ nakli, transplantasyon

Address for Correspondence/Yazışma Adresi: Tuğçe Yeniocak MD, Metin Sabancı Baltalimanı Bone and Joint Diseases Training and Research Hospital, Clinic of Anesthesiology, İstanbul, Turkey
Phone: +90 532 769 26 02 **E-mail:** tugcekusku@yahoo.com **ORCID ID:** orcid.org/0000-0001-9237-6424

Cite this article as/Atıf: Yeniocak T, Ergin Özcan P. Brain Death and Deceased Organ Donation in a Hospital in İstanbul, Turkey: The Effect of Early Identification of Brain Dead on Organ Donation Rates: A Retrospective Study. İstanbul Med J 2020; 21(2): 115-9.

Received/Geliş Tarihi: 29.09.2019
Accepted/Kabul Tarihi: 11.02.2020

Introduction

Brain death (BD) occurs as intracranial pressure increases due to the edema of brain tissue within the rigid borders of the skull. Once intracranial pressure equals or exceeds the systemic arterial pressure, the nutritional blood supply to brain tissue stops. This is followed by a rapid decrease in the intracranial pressure gradient and results as intracranial circulatory arrest. While death is traditionally characterized as cardiac arrest and loss of vital functions, advances in technology have made it possible to prevent somatic death despite an irreversible loss of brain function in the intensive care unit (ICU) setting. In these cases, providing prolonged life support can mislead family members about the severity of the patient's condition and give them false hope that the patient will recover. Also, the practice of providing life support after BD can cause spiritual distress among family members and long-term hospitalization increases the cost of ICU treatment (1).

Worldwide, hundreds of people on waiting lists for organ transplantation die of organ failure. There are currently insufficient organs donated by living donors to meet all of the demand for organ transplants. According to Turkish Ministry of Health figures, 779 people in Turkey died while awaiting organ transplants in 2018. In Turkey, there are currently 26,524 patients registered in organ and tissue information systems on waiting lists for organ transplants. Of these patients, 22,868 patients are on the waiting list for kidney transplant, 1,116 patients are on the list of heart transplant, 2,250 patients are on the list of liver transplant, 82 patients are on the list of lung transplant, 5 patients are on the list of bowel transplant and 289 patients are on the list of pancreas transplant (2).

The primary objective of this study was to analyze the causes of BD, the criteria used for determination of BD, ancillary tests for diagnosing BD, the duration of hospitalization before diagnosis, and the duration of survival after diagnosis. Secondary objective was to determine the rates of family consent for organ donation, and the effect of diagnosis time of BD in donation rates.

Methods

After obtaining Institutional Ethics Committee approval by İstanbul University Clinical Research Ethics Council (decision no: 2013/1748), we conducted a retrospective review of 60 patients diagnosed as brain dead in İstanbul Medical Faculty Hospital between January 1, 2004 and January 1, 2013. The hospital's Organ Transplant Coordinator provided data on all patients who had been diagnosed as brain dead while in the ICUs of the Departments of Anesthesiology, Neurosurgery, or Emergency Surgery.

Patients with metabolic endocrine disorders and affected by depressant drugs or neuromuscular block were excluded. Brainstem reflex tests were performed by ICU doctors to all patients who had Glasgow Coma scale <7 (Table 1). After declaration of BD, patients' families were informed about the option of deceased organ donation.

We reviewed patients' age at death, main diagnosis, length of stay in ICU, ancillary tests such as internal carotid artery doppler ultrasonography (ICAUSG), cerebral angiography (CA), electroencephalography (EEG), their religion and family consent for organ donation.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS software for Windows, version 22.0 Corp., Amonk, NY, USA). The mean, standard deviation and percentage values were calculated as descriptive statistics. Categorical data were compared using the independent sample t-test. $P<0.05$ were regarded as statistically significant.

Results

During the study period, 60 patients were declared as BD, of whom 21 (35%) were female and 39 (65%) were male. Their mean age was 28 years. The most common cause of BD was traumatic brain injury (n=37, 62%). ICAUSG was performed in 36 (60%) patients; CA was performed in 14 (23%) patients; both ICAUSG and CA were performed in 12 (20%) patients and EEG was performed in 2 (3.33%) patients. Only 6 (10%) patients' families gave consent to donation. Other patient characteristics are shown in Table 2. The mean time from hospital admission to diagnosis of BD was 5.16±3.06 days overall; 5.5±0.4 days among non-donor group; and 2.0±0.4 days among donor group. It is found that the time to confirm the diagnosis of BD was significantly shorter in donors than in non-donors (p=0.000). The mean time from diagnosis of brain dead to death in non-donor group was 2.4±0.3 days. In donor group, the mean time from diagnosis of BD to harvesting of the patient's organs was 1.08±0.2 days. Total hospitalization time in donor group was 3±0.6 and in 7.6±0.4 in non-donor group. As it is predicted, statically significant difference was found in total hospitalization time. It is related to immediate transplantation after consent in donor group (p=0.000) (Table 3) (Figure 1).

Discussion

The most common causes of BD among the patients in our study were traumatic intracranial hemorrhage (62%) and ischemic strokes (20%). These findings are similar to those of other studies. In a study conducted in Portugal, Eira et al. (3) found that the most common causes of BD were hemorrhagic strokes (55.3%) and ischemic strokes (17.4%). In Turkey, in a study by Karasu et al. (4), they found that 73% of patients who experienced BD in the ICU had been admitted for bleeding-obstructive

Table 1. Brain death confirmatory tests

• Brain stem reflexes • Pupillary reflex • Corneal reflex • Gag reflex • Occulovestibulary reflex • Cough reflex • Occulovestibulary reflex (caloric test)
Breath effort
Apnea test
Ancillary tests ICAUSG/CA/EEG

ICAUSG: internal carotid artery doppler ultrasonography, CA: cerebral angiography, EEG: electroencephalography

Table 2. Demographic characteristics of the patients

Variables	n	(%)
Gender		
Male	39	65
Female	21	35
Diagnosis		
Traumatic brain injury	37	61.67
Intracranial hemorrhages	12	20
Toxic gas inhalation*	4	6.67
Post CPR**	3	5
Intracranial tumor	2	3.33
Meningitis	1	1.67
Intracranial aneurism	1	1.67
Ancillary tests		
ICAUSG	36	60
CA	14	23
EEG	2	3.33
ICAUSG+CA	12	20
Donation		
Yes	6	10%
No	54	90%

ICAUSG: Internal carotid artery doppler ultrasonography, CA: cerebral angiography, EEG: electroencephalography, *carbon monoxide

**cardiopulmonary resuscitation

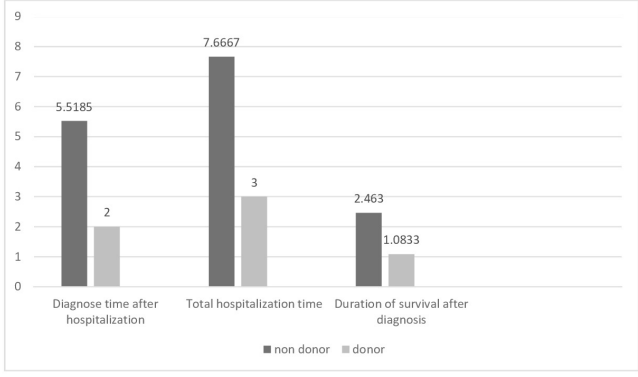

Figure 1. Hospitalization time and diagnosis

cerebrovascular disease, and in a study by Battal et al. (5), the most common cause of BD (58%) was reported to be intracranial hemorrhage.

The use of ancillary tests for diagnosing BD varies according to the experience of the clinicians and the settings. In our study, 83.3% of the patients had the diagnosis of BD confirmed by radiological examinations of cerebral blood flow, and 16.3% had BD diagnosed on clinical grounds alone. In the study by Karasu et al. (4), only 30.4% of the patients had BD confirmed by ancillary tests (13% ICAUSG and 13% CA); while in a study by Mutlu et al. (6), 76.2% of patients had BD confirmed using ancillary tests (22.3% CA, 13.8% ICAUSG, and 20% ICA and ICAUSG combined).

In our study, only 6 (10.0%) of the families gave consent for organ donation. This rate is quite low compared to other countries. Organ donation rates are measured as an organ donation per million population (ppm). Turkey has one of the lowest rates of deceased organ donation of all the countries in Europe with a rate of 2.2 ppm, compared to 15-20 ppm in other European countries (7). The rates differ among the hospitals in Turkey. In a 7-year study from Izmir, the families of 34.2% of patients diagnosed with BD consented to deceased organ donation (8). A study by Özmert et al. (9) in a tertiary pediatric ICU of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, they found a donation rate of 17% among children in a pediatric ICU. Another study found an organ donation rate of 23.8% in Ankara Numune Training and Research Hospital (6).

In Europe, a whole 80% of all organ donations are from deceased donors. Conversely, in Turkey, 75% of organ donations are from living donors, and only 25% are from deceased donors. Turkey had among the highest rates of organ donation by live donors of any country in the world in 2018, with a rate of 52 ppm (7). Nevertheless, waiting lists for organ transplants are long, and the demand far exceeds supply. The number of deceased organ donors would have to increase in order to meet the demand. In individuals with end-stage organ failure which requires supportive treatments such as hemodialysis, organ transplantation reduces the cost to the healthcare system and provides a better quality of life for the patient.

There are many reasons for low rates of deceased organ donation. One survey found that barriers included a limited understanding of the patient's prognosis and limited emotional readiness to donation on the part of family members, but staff also identified several facilitators

Table 3. Hospitalization time and diagnosis

Groups	N	Mean	Standard deviation	Standard error mean	p
Diagnose time after hospitalization (days)					
Non-donor	54	5.5185	3.01406	0.41016	0.000
Donor	6	2.0000	1.09545	0.44721	
Total hospitalization time (days)					
Non-donor	54	7.6667	3.59244	0.48887	0.000
Donor	6	3.0000	1.67332	0.68313	
Duration of survival after diagnosis (days)					
Non-donor	54	2.4630	2.91038	0.39605	0.074
Donor	6	1.0833	0.49160	0.20069	

of organ donation (10). Members of the general population do not understand that BD is irreversible and expect that individuals who are BD will recover completely because cardiac death has not occurred. Concerns about killing the patient to enable the patient's organs to be donated may be the reason for family veto.

Secondly, a delay in the diagnosis of BD may be as much of a contributor as family refusals. The interval between clinical suspicion of BD and confirmation of the diagnosis has varied widely across studies. In our study, it took a mean of 5.1 days to confirm the diagnosis of BD. This is a relatively short period compared to some other studies. A two-center study found that the interval between suspicion of BD and diagnosis was 6.7 days at the one center and 1.7 days at the other center (11). Tsai et al. (12) reported that this period was 6.6 days. Two other studies reported that the time taken from suspicion of BD to diagnosis was 5.9 days and 8.2 days, respectively (6,9).

The interval between confirmation of diagnosis of BD and terminating respiratory and circulatory support, known as somatic survival, has also varied across studies. In our study, the mean somatic survival was 2.5 days. In one study, somatic survival has been reported to be approximately 4 days (13) Özmert et al. (9) found that somatic survival was 6.9 days among non-donors and another study found that somatic survival was 6.8 days in patients <18 years, and 2.5 days in patients >18 years (4).

According to the world standards, at least one case of BD needs to be reported for each ventilatory ICU bed per year. Although there are >2,500 ventilatory ICU beds in Turkey, there are an average of only 500 BDs per year (14). The diagnosis of BD may be delayed if routine neurological examination is delayed while patients are being treated for other systemic disorders, and by a lack of communication with transplant coordinators (15). A review of cases of BD that occurred in emergency departments found that up to 84% of cases were not diagnosed due to failure of the diagnostic process (16).

In Turkey, organs of deceased patients cannot be used for transplantation without the consent of relatives, even if the deceased patient has an organ transplant volunteer card or has expressed a willingness to be an organ and tissue donor while healthy, or in a written will. Legal reforms are needed to prevent relatives from vetoing organ donation to which deceased patients have consented. In countries such as Belgium, Spain, and France, where an "opting out" or "presumed consent" model is used, there are a high number of cadaveric donors. According to this model, organs can be used for transplantation after death unless the individual has expressed an objection (17). Several studies have reported an association between assumed consent and high organ donation rates (18,19).

Although there have been many studies on organ donation after BD, the relationship between the time taken to confirm BD and the organ donation rate has not been studied. Our study differs from other studies in this regard. It was found that the time to confirm the diagnosis of BD was significantly shorter in donors than in non-donors. Early diagnosis of BD was associated with an increased rate of family approval for organ donation. Long hospitalization may lead relatives to veto organ donation because a longer stay provides greater hope of recovery and because of a lack of understanding of the situation by family members.

This study has some limitations. Firstly, we had no qualitative data to provide insight into the reasons for family members' reluctance to consent to organ donation by brain-dead patients. Similarly, we had insufficient information on the reasons why family members provided consent to organ donation among the family members who did consent. These reasons could be clarified by asking family members to answer a questionnaire about reasons for consenting to, or vetoing, deceased organ donation after informing them of the brain dead of their family member. This would clarify the ethical, religious, and sociological reasons for consenting to, or vetoing, organ donation by their deceased relative. Secondly; the study does not provide insight into quantifiable markers for early detection or diagnosis of BD, transplantation coordination, or changes to the legal framework. A prospective study should be conducted to gain a better understanding of these issues. Thirdly, it is unclear whether the results of this study are applicable to other hospitals, so a multicenter study is required.

Conclusion

In conclusion, in order to overcome the shortage of organ donations, a system should be established that protects donors and recipients. Early identification of potential donors, well-organized transplantation coordination systems, legal improvements, and measures to alter the perception of BD among the general public may increase deceased organ donation.

Ethics Committee Approval: The study was approved by İstanbul University Clinical Research Ethics Council (decision no: 2013/1748), we conducted a retrospective review of 60 patients diagnosed as brain dead in our hospital between January 1, 2004 and January 1, 2013.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - T.Y, P.E.Ö.; Concept - T.Y, P.E.Ö.; Design - T.Y, P.E.Ö.; Data Collection and/or Processing - T.Y, P.E.Ö.; Analysis and/or Interpretation - T.Y, P.E.Ö.; Literature Search - T.Y, P.E.Ö.; Writing Manuscript - T.Y, P.E.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Pestana AL, dos Santos JL, Erdmann RH, da Silva EL, Erdmann AL. Lean thinking and brain-dead patient assistance in the organ donation process. Re Rev Esc Enferm USP 2013; 47: 258-64.
2. 2. IÜ/İzleme ve Değerlendirme Birimi, Sayılarla TTDİS. Nakil Bekleyen Hasta Sayıları October 2019;10 (cited: 01/01/2019) Available from: URL: https://organ.saglik.gov.tr/ContentView.aspx?q=1
3. Eira CSLD, Barros MIT, Albuquerque AMP. Organ donation: the reality of an intensive care unit in Portugal. Rev Bras Ter Intensiva 2018; 30: 201-7.
4. Karasu D, Yılmaz C, Karaduman İ, Çınar YS, Buyukkoyuncu Pekel N. Retrospective analysis of brain death cases. Yoğun Bakım Journal 2015; 6: 23-6.
5. Battal M, Horoz A, Karatepe O, Çitgez, B. Beyin ölümü tespitinde araştırma hastanesi deneyimi. Şişli Etfal Hastanesi Tıp Bülteni 2013; 47: 59-62.

6. Mutlu, NM, Peker TT, Acar S, Koca B, Soyal ÖB, Titiz AP, et al. Brain Deaths and Donors in an Education and Research Hospital." Transplantation proceedings. Elsevier 2019; 51: 2176-9.

7. International Registry in Organ Donation and Transplantation. Turkey Deceased Organ Donor Evolution June 2019 (cited :01/07/2019) Available from: URL: http://www.irodat.org/?p=database&c=TR#data

8. Kıraklı C, Uçar ZZ, Anıl AB, Özbek İ. The effect of shortening the definitive diagnosis time on the organ donation rates in the intensive care unit, Yoğun Bakım Journal 2011; 1: 8-11.

9. Özmert S, Sever F, Ayar G, Yazıcı MU, Öztaş DK. Brain Death and Organ Donation in Paediatric Intensive Care Unit.» Turk J Anaesthesiol Reanim 2019; 47: 55-61.

10. Oczkowski SJ, Durepos P, Centofanti J, Arsenau E, Dhanani S, Cook DJ, et al. Multidisciplinary Survey to Assess Facilitators and Barriers to Successful Organ Donation in the Intensive Care Unit. Prog Transplant 2019; 29: 179-84.

11. Gündüz RC, Sahin S, Uysal-Yazıcı M, Ayar G, Yakut HI, Akman AÖ, et al. Brain death and organ donation of children. Turk J Pediatr 2014; 56: 597.

12. Tsai E, Shemie SD, Cox PN, Furst S, McCarthy L, Hebert D. Organ donation in children: role of the pediatric intensive care unit." Pediatr Crit Care Med 2000; 1: 156-60.

13. George S, Thomas M, Ibrahim EH, Abdussalam A, Chandra P, Ali HS, et al. Somatic survival and organ donation among brain-dead patients in the state of Qatar." BMC Neurol 2016; 16: 207.

14. Tepehan S, Elmas İ. Türkiye'de Beyin Ölümü Tanısına Güven Sorunu ve Organ Bağışına Yansımaları. Yoğun Bakım Hemşireliği Dergisi 2014, 18.1: 8-14.

15. Girlanda R. Deceased organ donation for transplantation: Challenges and opportunities. World J Transplant 2016; 6: 451-9.

16. McCallum, J, Ellis, B, Dhanani S, Stiell, IG. Solid organ donation from the emergency department–A systematic review. CJEM 2019; 21: 626-637.

17. Koçak Süren S. Organ ve doku naklinin yasal ve etik açıdan incelenmesi. Türkiye Barolar Birliği Dergisi 2007; 73: 174-95

18. 18. Rithalia A, McDaid, C, Suekarran S, Myers L, Sowden A. Impact of presumed consent for organ donation on donation rates: a systematic review. BMJ 2009; 338: a3162.

19. English V, Johnson E, Sadler BL, Sadler AM. Is an opt-out system likely to increase organ donation?. BMJ 2019; 364: l967.

İstanbul Med J 2020; 21(2): 120-5
DOI: 10.4274/imj.galenos.2020.32650

Comparison of Clinical and Biochemical Parameters in Atrial Fibrillation Patients Using Dabigatran and Rivoraxaban and Their Relationship with Complications

Acil Serviste Yeni Nesil Oral Antikoagülan Kullanan Hastaların Trombotik Komplikasyon Belirleyicilerinin Değerlendirilmesi

İrfan Aydın[1], Mehmet Kaan Poyraz[1], Abdullah Algın[2], Gökhan Aksel[2], Serkan Emre Eroğlu[2]

[1]Adıyaman University Training and Research Hospital, Clinic of Emergency Medicine, Adıyaman, Turkey
[2]University of Health Sciences Turkey, Ümraniye Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey

ABSTRACT

Introduction: Atrial fibrillation (AF) is a common disease that increases mortality and morbidity. New generation oral anticoagulants (NOACs) are agents that reduce ischemic events in patients with AF. In this study, we aim to compare biochemical and clinical parameters and examine the risk factors for thrombotic complications (such as stroke, myocardial infarction, systemic embolization) in patients using NOACs (dabigatran and rivaroxaban).

Methods: This study was designed as a retrospective, method development study. The study included 205 patients who were admitted to Emergency Service, Adıyaman University Training and Research Hospital, from January 2013 to December 2014. The patients were divided into two groups as rivaroxaban users and dabigatran users. The differences of laboratory parameters of patients before drug intake and during their emergency department visits were analyzed. [Δwhite blood cells, Δhemoglobin, Δhematocrit, Δplatelet, Δplatecrit, Δplatelet distribution width, mean platelet volume (ΔMPV)].

Results: There were no major differences between two groups in terms of CHA_2DS_2-VASc scores, complications and duration of drug intake. There was statistically significant decrease with regard to MPV ($p<0.001$), in both of the groups with the usage of NOACs. The optimal threshold point of ΔMPV in the prediction of the thrombotic complications was ≤0.7 fL, with 91.7% sensitivity and 62.2% specificity [area under the curve: 0.805, 95% confidence interval: 0.744-0.857, $p<0.001$).

Conclusion: As a result, the detection of high CHA_2DS_2-VASc score for the patients with AF using NOACs and visiting emergency department and less volume decline in previous MPV value are simple parameters to be used for predicting thrombotic cases and will be clinically useful.

Keywords: Atrial fibrillation, dabigatran, rivaroxaban

ÖZ

Amaç: Atriyal fibrilasyon (AF), mortalite ve morbiditeyi artıran yaygın bir hastalıktır. Yeni nesil oral antikoagülanlar, atriyal fibrilasyonu olan hastalarda iskemik olayları azaltan ajanlardır. Biz bu çalışmada yeni nesil oral antikoagülan (dabigatran ve rivaroksaban) kullanan ve acil servise gelen hastalarda trombotik komplikasyon risk faktörlerini (inme, miyokard infarktüsü, sistemik embolizasyon) incelemeyi amaçladık.

Yöntemler: Bu çalışma retrospektif olarak yöntem geliştirme çalışması olarak tasarlanmıştır. Çalışmaya Ocak 2013-Aralık 2014 yılları arasında Adıyaman Üniversitesi Eğitim ve Araştırma Hastanesi Acil Tıp Kliniği'ne başvuran 205 hasta dahil edilmiştir. Hastalar rivaroksaban kullanan ve dabigatran kullananlar olarak iki gruba ayrılmıştır. İlaç kullanımına başlamadan önceki laboratuvar parametreleri ile ilaç kullanırken acil servise başvuru esnasındaki laboratuvar parametreleri arasındaki farklılıklar analiz edildi. [Δbeyaz kan hücreleri, Δhemoglobin, Δhematokrit, Δtrombosit, Δplatecrit, Δtrombosit dağılım genişliği, ortalama trombosit hacmi (ΔMPV)].

Bulgular: İki grup arasında CHA_2DS_2-VASc skorları, komplikasyonlar ve ilaç alım süresi açısından anlamlı fark yoktu. Yeni nesil oral antikoagülan kullanan her iki grupta da MPV değeri ($p<0.001$) açısından istatistiksel olarak anlamlı bir azalma vardı. Trombotik komplikasyonların öngörülmesinde ΔMPV optimum eşik noktası 910,7 fL, %91,7 duyarlılık ve %62,2 özgüllükte saptandı (eğri altında kalan alan: 0,805, %95 güven aralığı: 0,744-0,857, $p<0,001$).

Sonuç: Sonuç olarak, acil servise başvuran ve yeni nesil oral antikoagülan kullanan atriyal fibrilasyonlu hastalar için yüksek CHA_2DS_2-VASc skoru ve önceki MPV değerinde beklenen düşüşün olmaması, trombotik olguları öngörmede kullanılacak basit parametreler olup klinik olarak kullanışlı olacağı düşünülmektedir.

Anahtar Kelimeler: Atrial fibrilasyon, dabigatran, rivaroxaban

Address for Correspondence/Yazışma Adresi: Abdullah Algın, University of Health Sciences Turkey, Ümraniye Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
Phone: +90 216 216 10 15 **E-mail:** dralgin@hotmail.com **ORCID ID:** orcid.org/0000-0002-9016-9701

Cite this article as/Atıf: Aydın İ, Poyraz MK, Algın A, Aksel G, Eroğlu SE. Comparison of Clinical and Biochemical Parameters in Atrial Fibrillation Patients Using Dabigatran and Rivoraxaban and Their Relationship with Complications. İstanbul Med J 2020; 21(2): 120-5.

Received/Geliş Tarihi: 13.05.2019
Accepted/Kabul Tarihi: 11.02.2020

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and related to serious morbidity and mortality (1). AF is a chronic disease which increases the formation of thrombosis in the left atrium and a significant risk factor in terms of stroke recurrence (2). One of the main aims of long-term anticoagulants treatment for patients with AF is to prevent thromboembolism attack and to reduce stroke risk (1).

New generation oral anticoagulants (NOAC) are agents that reduce stroke and systemic embolization in patients with nonvalvular AF (3). Dabigatran is direct thrombin inhibitor which is as efficient as vitamin K antagonist for reducing stroke risk without increasing bleeding risk in AF (4). In addition, dabigatran has been shown to be superior to warfarin in primary and secondary prevention of AF patients from ischemic events (5). Rivaroxaban is a factor Xa inhibitor which is as efficient as warfarin for preventing stroke without bleeding increase in AF patients (6). NOAC was found to be safer and more effective than warfarin to reduce the risk of thrombosis and complications in patients with non-valvular AF (7).

The international normalized ratio (INR) is the value of the warfarin level. In clinical practice, it is not possible to follow the NOAC level. In this study, we aimed to examine the risk factors and laboratory findings of the patients with AF who applied to emergency service with thrombosis related to the use of NOAC (dabigatran and rivaroxaban). We have investigated the availability of a simple usable parameter indicating NOAC activity. Besides, biochemical and clinical parameters were compared in the patients who used dabigatran and rivaroxaban.

Methods

The study included 205 consecutive patients who visited emergency department with chronic nonvalvular AF and were treated with rivaroxaban (15-20 mg) or dabigatran (110-150 mg) between the dates of 01.01.2013 and 31.12.2014. The patients were divided into two groups; group 1 using dabigatran and group 2 using rivaroxaban. The variation between laboratory parameters of patients existing before drug intake and acquired during their emergency department visits was also analyzed. Thrombotic cases were assessed according to type of thrombotic events such as myocardial infarction (MI), stroke, and systemic embolization. CHA_2DS_2-VASc scores were calculated for each patient and shown in Table 1 (8).

Table 1. CHA_2DS_2-VASc score

C	Congestive heart failure	1 point
H	Hypertension	1 point
A_2	Age (≥75 years)	2 point
D	Diabetes mellitus	1 point
S_2	Stroke/ TIA/ systemic embolization	2 point
V	Vascular disease (Old MI, PAH, aortic plaque)	1 point
A	Age (between 65-74 years)	1 point
Sc	Sexuality (Female gender)	1 point

MI: myocardial infarction, PAH: pulmonary arterial hypertension, TIA: transient ischemic attack

Patient Selection

The patients who were prescribed NOAC by the cardiologist and who had been using it for at least three months (dabigatran and rivaroxaban) were included in the study. Blood analyses of the patients before using dabigatran and rivaroxaban and during the emergency department visits were compared. The patients who had different risk factors which could cause thrombosis, such as hematologic diseases, chronic renal failure, hepatic failure, hyper- or hypothyroidism, active infection and malignancy, and who had been using NOAC irregularly or using for less than three months and the ones with missing data were excluded. The study was approved by Adıyaman University Faculty of Medicine Presidency of Ethics Committee of Biomedical Researches on 22.11.2016 with the decision number of 2016/7-1.

Data Collection

Age, gender, smoking status (Smoking +/-), chronic obstructive pulmonary disease (COPD) status (COPD +/-), white blood cells (WBC), hemoglobin (Hb), hematocrit (HTC), INR, prothrombin time (PT), activated partial thromboplastin time (aPTT), C-reactive protein (CRP), platelet (PLT), plateletcrit (PCT), platelet distribution width (PDW), mean platelet volume (MPV), CHA_2DS_2-VASc score, and time of used NOAC results were recorded from the patients' digital hospital files. ΔWBC, ΔHb, ΔHTC, ΔINR, ΔPT, ΔaPTT, ΔCRP, ΔPLT, ΔPCT, ΔPDW, and ΔMPV were calculated from the laboratory values.

Statistical Analysis

Collected data analysis was performed by using SPSS software (version 20.0, SPSS Inc., Chicago, Illinois). The Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables. Normally distributed continuous variables were compared with the Student's t-test while non-normally distributed continuous variables were compared with the Mann-Whitney U test. Categorical variables compared with the $\chi 2$ or Fisher's exact tests were summarized as percentages. Laboratory parameters of patient population before and three months after the emergency department visit were compared with paired t-test and/or Wilcoxon tests. Correlation analysis was performed using the Pearson's or Spearman's tests. Univariate analyses of all the parameters that might affect the thrombotic complications (age, gender, smoking status, COPD, CHA_2DS_2-VASc score, time of used NOAC, ΔWBC, ΔHb, ΔHTC, ΔINR, ΔPT, ΔaPTT, ΔCRP, ΔPLT, ΔPCT, ΔPDW, ΔMPV) were performed. Parameters having p values of <0.2 were included in the multivariate regression model. As the ΔHTC was highly correlated with ΔHb and ΔMPV with ΔPDW, ΔHTC and ΔPDW were excluded from the multivariate regression model although they both had p values of <0.2. Finally, multivariate regression analyses were performed on the parameters of CHA_2DS_2-VASc score, time of used NOAC, ΔMPV, ΔPT, ΔWBC, ΔHb, ΔPCT and ΔPLT. The fit of the multi regression analysis model was found good according to the Omnibus test. A value of $p<0.05$ was accepted as statistically significant.

Results

Demographic parameters of population included in the study are shown in Table 2. There is no significant difference between the groups with

respect to age, gender, diabetes mellitus, hypertension, cerebrovascular stroke, vascular disease, chronic obstructive pulmonary disease, CHA_2DS_2-VASc score and duration of drug usage. Congestive heart failure rate was higher in group 2 (p=0.006), whereas smoking rate was higher in group 1 (p=0.042).

The laboratory parameters of patient population are shown in Table 3. While the number of platelets was statistically reduced in the group using dabigatran in comparison with pre-treatment (p=0.001), there was no significant difference in the group using rivaroxaban (p>0.05).

Table 2. Basal demographic data of study population

	Group 1 (dabigatran)	Group 2 (rivoraxaban)	p
	(n=68)	(n=137)	
Age (years)	72 (67-77)	75 (65-83)	0.429
Gender (Male, %)	22 (32.4%)	58 (42.3%)	0.168
DM (n, %)	14 (20.6%)	16 (11.7%)	0.089
HT (n, %)	31 (45.6%)	74 (54.0%)	0.256
CHF (n, %)	16 (23.5%)	59 (43.1%)	0.006
CvS (n, %)	28 (41.2%)	43 (31.4%)	0.165
Vascular disease (n, %)	29 (42.6%)	59 (43.1%)	0.955
Smoke (n, %)	19 (27.9%)	19 (13.9%)	0.042
COPD (n, %)	14 (20.6%)	15 (10.9%)	0.062
CHA_2DS_2-VASc score	3.3±1.2	3.2±1.4	0.635
Duration of use (month)	66.4 (1-188)	59.4 (0-192)	0.306

DM: diabetes mellitus, HT: hypertension, CHF: congestive heart failure, CvS: cerebrovascular stroke, COPD: chronic obstructive pulmonary disease

*For categoric parameters $\chi 2$, student's t-test and Mann-Whitney U test were used

There is a statistically significant decrease with regard to MPV (p<0.001, for both group) and PCT (p=0.024, p=0.038, respectively), on the other side a significant increase in PDW value (p<0.001, for both group) in both groups taking NOACs.

As mentioned in Table 3 in detail, Hb, HCT, pentylenetetrazole and CRP did not show significant results in both groups. PCT, PDW and MPV were significantly different in both group 1 and group 2. PLT and aPTT were significant only in group 1 and WBC and INR were significant only in group 2.

In the univariate analysis performed to identify the complications cause p values of variables of <0.20 were included in the multivariate analysis (Table 4). In the logistic multiple regression analysis ΔWBC [odds ratio (OR)=1.163, confidence interval (CI) %95=1.005-1.346, p=0.043, CHA_2DS_2-VASc score (OR=2.195, CI %95=1.157-4.167, p=0.016) and ΔMPV (OR=0.235, CI %95=0.086-0.644, p=0.005)] were the independent predictors of the complications of NOACs (Table 5).

The optimal threshold point of ΔMPV in the prediction of the thrombotic complications was ≤0.7 fL, with 91.7% sensitivity and 62.2% specificity [area under the curve (AUC): 0.805, 95% CI: 0.744-0.857, p<0.001]. The optimal threshold point of CHA_2DS_2-VASc score in the prediction of the thrombotic complications was >3, with 83.3% sensitivity and 56.5% specificity (AUC: 0.731, CI: 0.701-0.857; p<0.001).

Discussion

According to the results of this study, ΔWBC, CHA_2DS_2-VASc score and ΔMPV predict the thrombotic complications which are seen during the process of total population of patients with nonvalvular AF using dabigatran and rivaroxaban (NOACs).

AF is the most common arrhythmia with continuity and its rate rapidly increases with the world-wide age average (9). Nowadays, atrial thrombosis and stroke are the most common reasons for mortality and

Table 3. Laboratory parameters of patient population

	Group 1 (dabigatran)			Group 2 (rivoraxaban)		
	(n=68)			(n=137)		
	Before	After	p	Before	After	p
WBC	8.6±2.4	8.9±3.1	0.313	8.4 (3.4-16.8)	9.6 (3.6-34.8)	0.001
Hb	13.3±1.7	13.1±1.9	0.292	13.4±2.0	13.2±2.2	0.189
HCT	40.9±5.1	39.7±7.1	0.130	41.5±6.1	41.2±6.1	0.562
INR	1.5±0.8	1.5±0.5	0.484	1.7±1.2	2.0±1.5	0.028
PTZ	17.6±7.0	17.4±4.5	0.826	18.7±9.7	20.7±11.9	0.063
aPTT	33.6±7.8	36.7±9.1	0.017	35.5±11.8	38.3±16.2	0.104
CRP	0.5 (0.1-6.6)	0.6 (0.2-10.2)	0.549	0.6 (0.1-19.4)	0.6 (0.1-33.1)	0.485
Plt	262.3±72.1	236.2±68.1	0.001	244.2±67.1	234.9±71.4	0.113
PCT	0.21±0.05	0.19±0.06	0.024	0.20 (0.06-0.37)	0.19 (0.05-0.36)	0.038
PDW	17.4 (10.1-24.8)	19.3 (10.2-23.4)	<0.001	18.5 (10.2-24.1)	20.1 (12.3-24.3)	<0.001
MPV	8.5±1.5	7.0±1.1	<0.001	8.4 (5.6-13.2)	7.1 (4.7-10.0)	<0.001

WBC: white blood cell, Hb: hemoglobin, HCT: hematocrit, INR: international normalized ratio

PT: prothrombin time, APTT: activated partial thromboplastin time, CRP: C-reactive protein, PLT: platelet, PCT: platecrit, PDW: platelet distribution width, MPV: mean platelet volume

*Paired t, t-test and Wilcoxon test were used

Table 4. Univariate regression analysis of parameters that may be associated with thrombotic complications

	p	OR	95% CI	
			Lower	Upper
NOAC type	0.990	0.992	0.288	3.419
Age (years)	0.438	0.983	0.941	1.027
Gender	0.847	0.890	0.272	2.906
Smoke	0.830	0.843	0.177	4.012
COPD	0.998	0.000	0.000	-
ΔWBC	0.101	1.102	0.981	1.237
ΔHb	0.099	0.801	0.616	1.043
ΔHCT	0.088	0.939	0.874	1.009
ΔINR	0.236	0.751	0.467	1.206
ΔPT	0.144	0.960	0.908	1.014
ΔAPTT	0.461	0.987	0.952	1.022
ΔCRP	0.461	0.934	0.780	1.119
ΔPLT	0.176	0.994	0.986	1.002
ΔPCT	0.026	0.000	0.000	0.232
ΔPDW	0.015	1.227	1.041	1.446
ΔMPV	0.004	0.380	0.196	0.736
CHA_2DS_2-VASc score	0.008	1.957	1.194	3.208
Time of use of NOAC	0.080	1.012	0.999	1.025

NOACs: new oral anticoagulants, COPD: chronic obstructive pulmonary disease, ΔWBC: magnitude of change in the white blood cell count, ΔHb: Magnitude of change in the Hemoglobin count, ΔHCT: magnitude of change in the hematocrit count, ΔINR: magnitude of change in the international normalized ratio count, ΔPT: magnitude of change in the prothrombin time count, ΔAPTT: magnitude of change in the activated partial thromboplastin time count, ΔCRP: magnitude of change in the C-reactive protein count, ΔPLT: magnitude of change in the platelet count, ΔPCT: magnitude of change in the platecrit count, ΔPDW: magnitude of change in the platelet distribution width count, ΔMPV: magnitude of change in the mean platelet volume count, CI: confidence interval, OR: odds ratio

Table 5. Multivariate regression analysis of parameters that may be associated with thrombotic complications

	p	OR	95% CI	
			Lower	Upper
CHA_2DS_2-VASc score	0.016	2.195	1.157	4.167
Time of use of NOAC	0.404	1.007	0.991	1.023
Δ MPV	0.005	0.235	0.086	0.644
Δ PT	0.429	0.974	0.914	1.039
Δ WBC	0.043	1.163	1.005	1.346
Δ Hb	0.293	0.847	0.623	1.154
Δ PCT	0.057	0.000	0.000	1.631
Δ PLT	0.456	1.005	0.992	1.018

NOACs: new oral anticoagulants, ΔWBC: magnitude of change in the white blood cell count, ΔHb: magnitude of change in the hemoglobin count, ΔPT: magnitude of change in the prothrombin time count, ΔPLT: magnitude of change in the platelet count, ΔPCT: magnitude of change in the platecrit count, ΔMPV: magnitude of change in the mean platelet volume count, CI: confidence interval, OR: odds ratio

morbidity (10). There are oral (warfarin and other vitamin K antagonists) and parenteral (unfractionated heparin, low molecular weight heparin, hirudin and argatroban) anticoagulant drugs with license to prevent systemic embolism in patients with non-valvular AF (11). Recently, NOACs which can be an alternative way of these treatment options are used. Among these drugs, dabigatran and rivaroxaban are two most frequently used agents (4,6). The measurement of thrombosis activation in patients with AF is significant because PLTs have an important role in thromboembolic cases (12). Many safe indicators have been recently examined to evaluate coagulation and PLT activation such as thrombin/antithrombin complex, b-thromboglobulin and soluble PLT P-selectin. However, these markers are not routine laboratory measurements and it is expensive to calculate the index. PLT index such as PCT, PDW, and MPV are routinely measured with complete blood cell count (CBC) without incremental cost (13).

AF increases the risk of thrombosis and causes platelet activation because of stasis in the left atrium and this is related to the risk of stroke and thromboembolic cases (9). MPV is an easy-measured marker that reflects platelet activation and reactivity. MPV is a significant predictive and prognostic marker in cardiovascular diseases (14). Large PLTs have higher thrombosis potential. Increasing MPV value is approved as an independent risk factor for MI and stroke (15). In another study, MPV has been shown to be increased in AF patients with stroke compared to those without stroke (16). In addition, increasing MPV is related to recurrent ischemia and mortality (17). Recent surveys have investigated the effects of some drugs on MPV. It is stated that the use of acetylsalicylic acid (ASA) for paroxysmal AF cases and dual antithrombocyte treatment for coronary artery disease has no significant effect on MPV (18). In the study conducted by Colkesen et al. (19), the effect of ASA on MPV value in paroxysmal AF patients was investigated and it was stated that MPV was not affected by ASA usage in these patients (19). In a different study, it is pointed that patients with MI that are cured with GP IIb/IIIa inhibitor abciximab and percutaneous coronary have lower MPV values (20). Unlike these studies, the effect of NOAC was evaluated in this study, and it was found that MPV was decreased in both groups using rivaroxaban and dabigatran during the process. However, to use MPV as a predictive factor for thrombotic effects of NOAC, prospective studies with wider populations are needed.

It is known that PLT activation causes morphological changes. PLTs with a bigger volume are more aggregate and active because of having increased the expression of PLT surface receptor (21). Also, larger platelets gather quicker than smaller PLTs. Therefore, higher MPV values are correlated with platelet activation and thrombosis tendency (22). That MPV decrease is lower in the patients with AF using NOAC refers that there is an independent predictor parameter of thrombotic cases, which supports the data in our study.

In a study, WBC has been shown to be a predictor of mortality in patients with stroke and the increase in WBC was found to be associated with high mortality (23). In a different study in which patients with cardiac pathology were followed, high WBC values were shown to be associated with higher rates of stroke (24).

In our study, it was observed that WBC increased significantly in the group using rivaroxaban unlike the group using dabigatran. This may

depend on different efficacy of the agents. However, it is necessary to investigate this with comprehensive studies.

Previous studies indicate that CHA_2DS_2-VASc score is a parameter that predicts hospitalization due to AF, and cardiovascular mortality. Many recent studies indicate that CHA_2DS_2-VASc score is an important parameter that helps to prevent stroke and also shows mortality and morbidity after stroke (8). Likewise, other studies mentioned in this study present that CHA_2DS_2-VASc score is a parameter that predicts the course of events in thrombotic cases in AF patients using NOAC (25).

Study Limitation

Relatively low number of the patients may be considered as a limitation. Another limitation is the inability of the patient to access the CBC before using NOAC. ΔWBC and ΔMPV cannot be calculated if patient's WBC and MPV values cannot be found before using NOAC. However, if the physician notes the WBC and MPV values before using NOAC, ΔWBC and ΔMPV can be used to predict the risk of thrombosis and complications due to use of NOAC drugs.

Conclusion

In conclusion, we found in this study that CHA_2DS_2-VASc score, ΔWBC and ΔMPV values predict the thrombotic complications in patients using NOAC. The results show that MPV change can be considered as an additional marker in the follow-up of patients with AF using NOAC in predicting thrombotic complications. In the follow-up with non-valvular AF patients visiting emergency department, we think it might be useful to evaluate these parameters in terms of the development of thrombotic complications.

Ethics

Ethics Committee Approval: The study was approved by Adıyaman University Faculty of Medicine Presidency of Ethics Committee of Biomedical Researches on 22.11.2016 with the decision number of 2016/7-1.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - İ.A., M.K.P., A.A., G.A., S.E.E.; Concept - G.A.; Design - M.K.P., S.E.E.; Data Collection or Processing - İ.A., M.K.P.; Analysis or Interpretation - A.A., G.A.; Literature Search - A.A.; Writing - A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). Eur Heart J 2006; 27:1979-2030.
2. Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. Neuroepidemiology 2003; 22:118-23.
3. Zemer-Wassercuq N, Haim M, Leshem-Lev D, Orvin KL, Vaduqanathan M, Gutstein A, et al. "The effect of dabigatran and rivaroxaban on platelet reactivity and inflammatory markers." Journal of thrombosis and thrombolysis 2015; 40: 340-6.
4. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-51.
5. Houston DS, Zarychanski R. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 2671; author reply 2674-5.
6. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012; 366: 9–19.
7. Hanley CM, Kowey PR. Are the novel anticoagulants better than warfarin for patients with atrial fibrillation? Journal of thoracic disease 2015; 7: 165.
8. Crandall MA, Horne BD, Day JD, Anderson JL, Muhlestein JB, Crandall BG, et al. Atrial fibrillation significantly increases total mortality and stroke risk beyond that conveyed by the CHADS2 risk factors. Pacing Clin Electrophysiol 2009; 32: 981-6.
9. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010; 31: 2369-429.
10. Friberg J, Scharling H, Gadsboll N, Truelsen T, Jensen GB. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (The Copenhagen City Heart Study). Am J Cardiol 2004; 94: 889-94.
11. Andersen LV, Vestergaard P, Deichgraeber P, Lindholt JS, Mortensen LS, Frost L. Warfarin for the prevention of systemic embolism in patients with non-valvular atrial fibrillation: a meta-analysis. Heart 2008; 94: 1607-13.
12. Ruf A, Patscheke H. Flow cytometric detection of activated platelets: Comparison of determining shape change, fibrinogen binding, and P-selectin expression. SeminThrombHemost 1995; 21: 146-51.
13. Arık OZ, Ozkan B, Kutlu R, Karal H, Sahin DY, Kaypaklı O, et al. Relationship between platelet indices and international normalized ratio in patients with non-valvular atrial fibrillation.Platelets 2014; 25: 311-6.
14. Park Y, Schoene N, Harris W. Mean platelet volume as an indicator of platelet activation: methodological issues. Platelets 2002; 13: 301-6.
15. Chu SG, Becker RC, Berger PB, Bhatt DL, Eikelboom JW, Konkle B, et al. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. J Thromb Haemost 2010; 8: 148-56.
16. Xu XF, Jiang FL, Ou MJ, Zhang ZH. The association between mean platelet volume and chronic atrial fibrillation and the presence of thrombotic events. Biomed Rep 2015; 3: 388-94.
17. Bath P, Algert C, Chapman N, Neal B. Association of mean platelet volume with risk of stroke among 3134 individuals with history of cerebrovascular disease. Stroke 2004; 35: 622-6.
18. Colkesen Y, Acil T, Abayli B, Yigit F, Katircibasi T, Kocum T, et al. Mean platelet volume is elevated during paroxysmal atrial fibrillation: A marker of increased platelet activation? Blood Coagul Fibrinolysis 2008; 19: 411-4.
19. Colkesen Y, Coskun I, Muderrisoglu H. The effect of aspirin on mean platelet volume in patients with paroxysmal atrial fibrillation. Platelets 2013;24: 263–6.
20. Estévez-Loureiro R, Salgado-Fernández J, Marzoa-Rivas R, Barge-Caballero E, Pérez-Pérez A, Noriega-Concepción V, et al. Mean platelet volume predicts

patency of the infarct-related artery before mechanical reperfusion and short-term mortality in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Thromb Res 2009; 124: 536-40.

21. Kamath S, Blann AD, Lip GY. Platelet activation: Assessment and quantification. Eur Heart J 2001; 22: 1561-71.
22. Karpatkin S, Khan Q, Freedman M. Heterogeneity of platelet function. Correlation with platelet volume. Am J Med 1978; 64: 542-46.
23. Furlan JC, Vergouwen MD, Fang J, Silver FL. White blood cell count is an independent predictor of outcomes after acute ischaemic stroke. Eur J Neurol 2014; 21: 215-22.
24. Koren-Morag N, Tanne D, Goldbourt U. White blood cell count and the incidence of ischemic stroke in coronary heart disease patients. Am J Med 2005; 118: 1004-9.
25. Hong HJ, Kim YD, Cha MJ, Kim J, Lee DH, Lee HS, et al. Early neurological outcomes according to CHADS2 score in stroke patients with non-valvular atrial fibrillation. Eur J Neurol. 2012; 19: 284-90.

İstanbul Med J 2020; 21(2): 126-31
DOI: 10.4274/imj.galenos.2020.33339

Short- and Long-term Outcomes After Curative Surgery for Rectal Cancer in Patients Under the Age of Fourty Years: A Stage Based Case-match Analysis

Kırk Yaş Altı Rektum Kanseri Olgularında Küratif Cerrahi Sonrası Kısa ve Uzun Dönem Sonuçlar: Evre Bazında Olgu Eşleştirme Analizi

Osman Civil, Mustafa Öncel

[2]İstanbul Medipol University Faculty of Medicine, Department of General Surgery, İstanbul, Turkey

ABSTRACT

Introduction: The aim of the study is to compare the short and long-term outcomes after curative surgery for rectal cancer in patients under the age of 40 years and over the age of 50 years.
Methods: A total of 46 patients with rectal cancer were retrieved from a prospectively designed database after the exclusion of stage 4 cases (<40 group). A case-match group (1:2) at similar stage was created among patients over 50 years of age (>50 group, n=92). Demographics, perioperative information, and oncological and pathological results were compared between the groups. The primary outcome measure was 5 year survival.
Results: The numbers of male cases were similar (59% vs 52%, p=0.468) between the groups. There were more patients who received preoperative radiation (98% vs 71%, p<0.001) in <40 group related to the location of the tumor and intolerance to the treatment. The tumors were closer to the dentate line [3 (0-15) cm vs 5 (0-15) cm, p=0.006)] and the rate of abdominoperineal resection was higher (39% vs 22%, p=0.031) in <40 group. Laparoscopy (72% vs 85%, p=0.069), conversion to open surgery (7% vs 10%), p=0.751), operation time (224±57 min vs 210±62 min, p=0.226), intraoperative bleeding [200 (10-1300) mL vs 200 (10-1500) mL, p=0.514], requirement of perioperative transfusion (30% vs 27%, p=0.688), reoperation (2% vs 2%, p=0.999) and 30 day mortality (2% vs 1%, p=0.333) rates, hospitalization period [7 (4-49) vs 7 (2-47) days, p=0.25] were similar. Tumor differentiation was poorer (p=0.046) in <40 group, but other pathological parameters were similar between the groups: number of harvested lymph nodes [14 (0-53) vs 12 (0-43), p=0172], number of malignant lymph nodes [1 (0-29) vs 1(0-11), p=0.616] and invasion rates [(0.09 0-0.93) vs 0.07(0-0.82), p=0.762]. Kaplan-Meier analysis revealed similar 5 year survival rates (63% vs 60%, p=0.052).
Conclusion: When similar tumor stages are considered, the survival is similar in rectal cancer patients below the age of 40 years and over the age of 50 years.

Keywords: Rectal cancer, young, survival, outcome

ÖZ

Amaç: Kırk yaş altı rektum kanseri olan hastalarda küratif cerrahi sonrası kısa ve uzun dönem sonuçları 50 yaş üzeri hastalar ile karşılaştırmaktır.

Yöntemler: Prospektif olarak tutulan veritabanından evre 4 hastalar dışlandıktan sonra 40 yaş altı (<40 grup) rektum kanseri olan hastalar ile 50 yaş üzeri (>50 grup) rektum kanserli hastalar 1:2 oranında patolojik evre bazında olgu-eşleştirme yöntemiyle demografik veriler, perioperatif veriler, onkolojik ve patolojik sonuçlar açısından karşılaştırıldı. Birincil sonlanım noktası beş yıllık sağkalım idi.
Bulgular: Gruplar arasında cinsiyet dağılımı benzerdi (%59 vs %52 erkek, p=0,468). <40 grupta daha yüksek oranda (%98 vs %71, p<0,001) neoadjuvan radyoterapi uygulanmıştı. <40 grubunda tümör dentate çizgiye daha yakın olup [3 (0-15 cm vs 5 (0-15) cm, p=0,006] abdominoperineal rezeksiyon daha yüksek orandaydı (%39 vs %22, p=0,031). Laparoskopik operasyon (%72 vs %85, p=0,069), açığa geçiş (%7 vs %10), p=0.751), operasyon süresi (224±57 dk vs 210±62 dk, p=0,226), kanama [200 (10-1300) mL vs 200 (10-1500) mL, p=0,514], kan transfüzyonu (%30 vs %27, p=0,688), reoperasyon (%2 vs %2, p=0,999) ve 30 günlük mortalite (%2 vs %1, p=0,333) oranları ile hastanede kalış süreleri [7 (4-49) vs 7 (2-47) gün, p=0,25] benzerdi. Tümör diferansiyasyonu <40 grupta daha kötü olup (p=0,046) diğer patolojik parametreler benzerdi: çıkarılan lenf nodu [14 (0-53 vs 12 (0-43), p=0,172], malign lenf nodu [1 (0-29) vs 1(0-11), p=0,616] ve invazyon oranları [0.09 (0-0,93) vs 0,07 (0-0,82), p=0,762]. Kaplan-Meier analizi benzer oranda beş yıllık sağkalım oranları (%63 vs %60, p=0,052) gösterdi.
Sonuç: Benzer tümör evreleri değerlendirildiğinden 40 yaş altı ve 50 yaş üzeri rektum kanseri olgularında sağkalım benzerdir.

Anahtar Kelimeler: Rektum kanseri, genç hasta, sağkalım, sonuç

Address for Correspondence/Yazışma Adresi: Osman Civil MD, İstanbul Medipol University Faculty of Medicine, Department of General Surgery, İstanbul, Turkey
Phone: +90 262 311 32 49 **E-mail:** dr.ocivil@hotmail.com **ORCID ID:** orcid.org/0000-0002-7780-4205

Cite this article as/Atıf: Civil O, Öncel M. Short- and Long-term Outcomes After Curative Surgery for Rectal Cancer in Patients Under the Age of 40 Years: A Stage Based Case-match Analysis. İstanbul Med J 2020; 21(2): 126-31.

Received/Geliş Tarihi: 12.12.2019
Accepted/Kabul Tarihi: 13.02.2020

Introduction

Rectum is one of the most common locations for adenocarcinoma, and colorectal cancer (CRC) continues to present among the leading tumors in Western World and developing countries, causing mortality (1). Recent studies have revealed a significant increase in the incidence of CRC in young population occurring over the past two decades (2-4). A recent report from United States nationwide Surveillance, Epidemiology and End Results cancer registry has indicated an annual increment of 2.6% in rectal carcinoma at younger ages (5).

The nature of CRC at younger ages may reveal several differences. Some have advocated that CRC at younger ages may have an aggressive histopathology and is diagnosed at more advanced stages (6). Several studies have shown that the rate of mucinous and signet-ring cell adenocarcinomas is higher in younger cases with CRC (7,8). Besides, there is conflicting information about survival with some studies suggesting a worse prognosis for young patients while other studies show no differences in long-term cancer outcomes among young and older cases with CRC (5,7,9,10). These contradictory reports may be related to the nature of the disease since younger people may have a more aggressive tumor behavior (9). Thus, current study aims to compare the short- and long-term outcomes of surgery in young (<40) and old (>50) patients in a case-match design considering the stages of the cancer.

Methods

All consecutive patients under the age of 40 years, operated for rectal cancer at Kartal Training and Research Hospital between 2003 and 2012 and Department of Oncological and Colorectal Surgery at Medipol University between 2012 and 2018, were retrospectively retrieved from our prospectively maintained database. A senior surgeon (MÖ) operated or supervised all procedures. Prior to the initiation of the data retrieval, the local ethics committee approved the content of the study (10840098-604.01.01-E21586). Because, there were no direct interactions with subjects and knowledge gained would not impact subject's clinical care, informed consent was not obtained. Patients with stage four tumors were excluded from further analyses, and a total of 46 cases under the age of 40 years were identified as the study group (group <40). A case-match analysis was completed with patients over 50-year-old from the same database for the creation of the comparison group (group >50) considering similar stage distribution between the groups and in a 1:2 ratio (n=92). Patients who were operated for benign conditions or premalignant lesions including *in situ* carcinomas, those receiving a palliative procedure (such as a diverting colostomy or exploration of the abdominal cavity because of carcinomatosis) or those having an emergent resection were excluded from the study. If the intended laparoscopic steps were not completed laparoscopically and necessitated any unplanned incision or the extension of a previously made incision to allow direct visualization for continued dissection, they were defined as conversion.

These outcome measures were compared between <40 and >50 groups: demographics, concomitant diseases (hypertension, diabetes mellitus (DM), chronic lung disease, chronic obstructive pulmonary disease, cerebrovascular accident, chronic liver disease, chronic renal failure, previous malignancy), American Society of Anesthesia (ASA) scores, tumor location (distance from the dentate line), neoadjuvant radiation therapy, operation technique (laparoscopic, conventional), conversion rate and causes, operation type (abdominoperineal resection, low anterior resection), anastomotic technique (stapled, handsewn), additional organ resection, operation time, intraoperative bleeding, rate and amount of perioperative blood transfusion, complications, reoperations, length of stay, 30-day mortality, pathological results [differentiation, T and N stages (and number of tumor positive lymph nodes), number of harvested lymph nodes, vascular and perineural invasion, and survival. The primary outcome measure was 5-year survival].

Statistical Analysis

Data were analyzed by using SPSS 21.0 for Windows (Armonk, NY, IBM Corp). Results were given as percentages, mean with standard deviations or median and ranges. Quantitative and qualitative variables were compared with Student's t-test, Mann-Whitney U test and chi-square (Pearson's or Fischer's Exact) tests, respectively. Kaplan-Meier analysis was used for survival analysis. A p value less than 0.05 was considered to be significant.

Results

There were 46 and 92 patients and the median (range) ages were 35.5 (24-40) and 63 (51-87) years in <40 and >50 groups, respectively. The number of male cases was similar. American Society of Anesthesiology score was higher and the number of patients with a concomitant disease was more in >50 group: hypertension [1 (2.2%) vs 34 (37%), p<0.001], DM [2 (4.3%) vs 19 (20.7%), p=0.012], chronic lung disease [0 vs 7 (7.6%), p=0.095], chronic obstructive pulmonary disease [0 vs 7 (7.6%), p=0.095], cerebrovascular accident [0 vs 3 (3.3%), p=0.551], previous malignancy [0 vs 3 (3.3%), p=0.551] chronic renal failure [0 vs 2 (2.2%), p=0.552] and chronic liver disease [1 (2.2%) vs 0, p=0.333], in groups <40 and >50, respectively. The tumors were closer to the dentate line and there were more patients who received preoperative radiation in <40 group related to the location of the tumor and intolerance to the treatment (Table 1).

Most of the patients were laparoscopically operated and conversion rates were less than 10% and similar between the groups (Table 2). The causes for conversion were T4 tumor (n=2) and bleeding (n=1) in <40 group and T4 tumor (n=5), bowel perforation (n=1), severe adhesions (n=1) and difficulty in creation of the anastomosis (n=1) in >50 group. A total of 29 cases required additional organ resection: vagina (n=5), bladder (n=2), uterus (n=1), and ovary (n=1) in <40 group and vagina (n=11), bladder (n=7), ovary (n=4), ureter (n=3), uterus (n=3), prostate (n=3) and small bowel (n=1) in >50 group. The rate of sphincter-saving procedure was more in >50 group. There were three patients necessitated a re-operation; one in <40 group for bowel obstruction and 2 in >50 group for stoma prolapse or anastomotic leak. Two patients

(one in each group) died during the postoperative period because of pulmonary embolism or intraabdominal sepsis secondary to an anastomotic leak. Other perioperative measures, length of stay, and rates of complications, reoperation and 30-day mortality were similar between the groups (Table 2). Tumor differentiation was significantly poorer in <40 group, but other pathological parameters were similar between the groups (Table 3). Kaplan-Meier analysis revealed similar 5-year survival rates (Figure 1).

Table 1. Demographics, patient-related information, tumor location and preoperative radiotherapy

	Group <40	Group >50	p
Gender (male) (%)	27 (58.7)	48 (52.2)	0.468
ASA score (%)	-	-	<0.001
1	20 (43.5)	5 (5.4)	-
2	19 (41.3)	52 (56.5)	-
3	7 (15.2)	34 (37)	-
4	0	1 (1.1)	-
Concomitant Diseases (%)	4 (8.7)	50 (54.3)	<0.001
Tumor location* [median (range)]	3 (0-15)	5 (0-15)	<0.001
Preoperative radiotherapy (%)	45 (97.8)	65 (70.7)	<0.001

ASA: American Society of Anesthesia, *distance from the dentate line

Table 2. Perioperative measures including intra-operative information, complications and post-operative outcomes

	Group <40	Group >50	p
Operation technique (%)	-	-	-
Laparoscopic	33 (71.7)	78 (84.8)	0.069
Conventional	13 (28.3)	14 (15.2)	-
Conversion (%)	3 (6.5)	9 (9.8)	0.751
Operation type (%)	-	-	0.031
Low anterior resection	28 (60.9)	72 (78.9)	-
Abdominoperineal resection	18 (39.1)	20 (21.7)	-
Anastomotic technique* (%)	-	-	0.276
Stapled	14 (50)	44 (62)	-
Hand-sewn	14 (50)	27 (38)	-
Operation time (min)	224±57	210.3±62.2	0.226
Intraoperative bleeding [median (range)] (mL)	200 (19-1300)	200 (10-1500)	0.514
Requirement of transfusion	-	-	-
Number of patients (%)	23 (50)	31 (34.1)	0.355
Amount (U)	0.5 (0-7)	0 (0-9)	0.099
Additional organ resection	7 (15.2)	22 (23.9)	0.237
Complications (%)	-	-	-
Surgical site infection	2 (4.3)	10 (10.9)	0.337
Wound infection	2 (4.3)	5 (5.4)	0.999
Evisceration	0	3 (3.3)	0.551
Intra-abdominal abscess	0	4 (4.3)	0.301
Urinary (fistula, retention, incontinence)	6 (13)	5 (5.4)	0.180
Prolonged paralytic ileus	3 (6.5)	4 (4.3)	0.686
Anastomotic leak*	2 (7.1)	5 (7)	0.999
Hemorrhage	2 (4.3)	4 (4.3)	0.999
Medical	1 (2.2)	3 (3.3)	0.999
Overall	14 (30.4)	25 (27.2)	0.688
Length of stay [median (range)]	6.5 (4-49)	6.5 (2-47)	0.250
Reoperation (%)	1 (2.2)	2 (2.2)	0.999
30-day mortality (%)	1 (2.2)	2 (2.2)	0.999

*considers only patients who had anastomosis

Table 3. Pathological outcomes

	Group <40	Group >50	p
ypT stage (%)	-	-	0.696
0	6 (13)	12 (13)	-
1	1 (2.2)	7 (7.6)	-
2	5 (10.9)	6 (6.5)	-
3	30 (65.2)	60 (65.2)	-
4	4 (8.7)	7 (7.6)	-
ypN stage (%)	-	-	0.787
0	20 (43.5)	38 (42.2)	-
1	16 (34.8)	36 (40)	-
2	10 (21.7)	16 (17.8)	-
TNM stage (%)	-	-	NA
0	6 (13)	12 (13)	-
1	5 (10.9)	10 (10.9)	-
2	10 (21.7)	20 (21.7)	-
3	25 (54.3)	50 (54.3)	-
Differentiation (%)	-	-	0.046
Poor	8 (17.4)	5 (5.4)	-
Moderate	17 (37)	51 (55.4)	-
Well	12 (26.1)	16 (17.4)	-
Unknown	9 (19.6)	20 (21.7)	-
Lymphovascular invasion (%)	14 (32.6)	28 (34.6)	0.822
Perineural invasion (%)	23 (53.5)	38 (46.3)	0.448
Number of harvested lymph nodes [median (range)]	14 (0-53)	12 (0-43)	0.172
Number of malignant lymph nodes [median (range)]	1 (0-29)	1 (0-11)	0.616
Lymph node invasion rate [median (range)]	0.09 (0-0.93)	0.07 (0-0.82)	0.762

*ypT stage: y- after neoadjuvant therapy, p- pathological evaluation, T - transmural invasion, **ypN stage: y- after neoadjuvant therapy, p- pathological evaluation, N-lymph node involvement

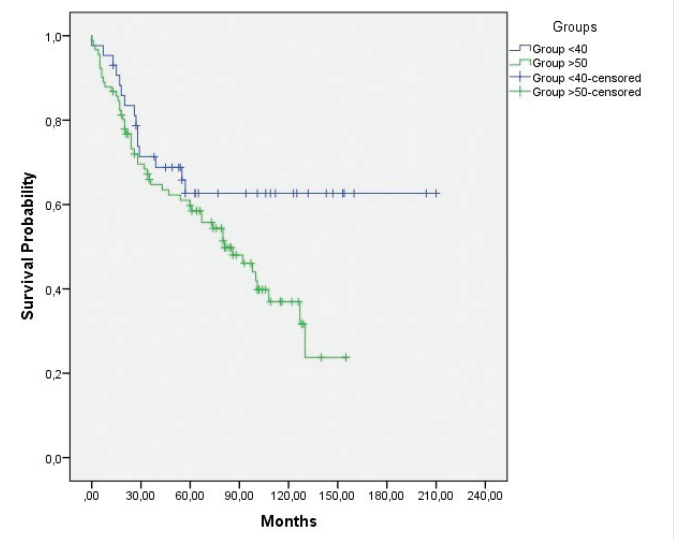

Figure 1. The 5-year survival rates after surgery were similar between the groups (62.7% and 59.8% in <40 and >50 groups, respectively, p=0.052)

Discussion

Current study evaluates the outcomes of curative surgery in rectal cancer patients younger than 40 years old. It is a comparative evaluation and the comparison group is composed of those older than 50 years old. In order to strength the homogeneity, the case-match of the comparison group is completed considering the stage of the tumor, since rectal cancer tends to be at more advanced stage at the time of diagnosis in younger population (8). In addition, a single surgeon has operated or supervised surgery in all patients in both groups; thus, surgeon has a minor impact on the results and conclusions of this study.

The patient and disease related measures are comparable between the groups. As expected, male gender rate is slightly higher in both groups, but the comparison between the groups does not reveal significance. Perioperative and pathological measures including operation time, intraoperative bleeding, requirement of transfusion, number of harvested lymph nodes are comparable between the groups. These findings make the conclusions of the postoperative outcomes and oncological measures more reliable. Besides -as expected- the rate of

having a concomitant disease and consequently ASA score is higher in >50 group. It is an interesting finding that patients' general condition and having additional diseases have not an impact on early postoperative results particularly on complication rates (data not shown). Thus, current study reveals that the postoperative complication profile may be similar in young and older patients.

Current study gives information about the nature of the rectal carcinoma in young population although the number of the patients and the case-match design of the study limit the conclusions. The number of T4 tumors and additional organ resections and the rate of preoperative radiotherapy show that the rate of advanced disease is probably higher in the studied population. In a recent study from SEER data has also revealed that the stage of the rectal cancer is more advanced in younger group between the ages of 20 and 39 years than in older patients over 40 years of age (8). The actual reason for this characteristic is not known but may be related to the screening programs that begins at the age of 50 years or to the behavior of the tumor at younger age. The higher incidence of more aggressive histological subtypes may also have a genetic basis (1). Other pathological measures have driven forward that the nature of the tumor may be different in younger population, since several parameters linked to poor pathological features are more common in younger CRC patients. These include poor differentiation, and mucinous and signet-ring cell histology (7,8,11). Current data support this information since poorly differentiated cancer rate is significantly higher in <40 group.

Several studies have advocated that the anatomic distribution of the tumor is moving to the rectum at younger ages (2,7,8). Two recent nationwide analyses have shown an increase in rectal cancer in patients under 40 years of age, while the incidence of colon cancer appears stable (8,12). Besides that, the location of rectal cancer (i.e. low, mid or upper) is extremely significant in routine practice since it is linked to the possibility of the sphincter preservation. However, whether or not the location of the rectal cancer and the operation type vary in younger population is not well studied. A recent single arm retrospective analysis on rectal cancer patients under 40 years of age has advocated that 87% of cancers are located at lower rectum, and two third of those necessitate an abdominoperineal resection (13). Current study has shown that tumors in younger patients are closer to dentate line, and consequently more often received an abdominoperineal resection than those over the age of 50 years. In our opinion, this may be a significant feature of rectal cancer at younger ages that has not been well analyzed in the literature, and has an impact on daily practice.

The primary outcome measure in the current study is survival. There is conflicting information about survival in the literature. Several institutional and nationwide studies have revealed no statistically significant difference in survival between young and elderly patients. Although may be biased due to the limited number of patients, at least two retrospective single institutional analyses have shown that survival is not impaired in young patients despite aggressive histological features of tumors in these cases (6,9). In contrast, another study from University of Erlangen (7) has revealed statistically significantly worse overall and cancer-related survival rates in non-metastatic rectal cancer patients under the age of 50 years than in those over the age of 50 years; however, this information may be criticized to include stage four cancer cases. This particular issue is also investigated with SEER data twice. The first study in 2004 has analyzed 466 and 11,312 cases between the ages of 20 and 40 years, and between the ages of 60 and 80 years, respectively, and revealed similar overall and stage-specific 5-year survival rates (5). In contrast, a recent analysis in 2015, comparing 1274 and 37,077 cases between the ages of 20 and 39 years and over the age of 40 years, respectively, underlines a significantly shorter median survival in young cases (28 vs 31 months) (8). This study may be biased since the tumors in young cases are associated with advanced stages and worse histological features. Current study is significantly related to its case-match design considering similar stages in the groups. Although it may be criticized because of the limited number of patients particularly in the study group, no statistical difference has been revealed between the groups. Kaplan-Meier figure has shown a decrease in older patients after the 5th year of follow-up. In our opinion, this finding is probably not related to the cancer recurrence, but the higher age in the >50 group. Thus, as the current information is supporting the same information, we believe that survival is similar in rectal cancer patients below the age of 40 years and over the age of 50 years, when similar tumor stages are analyzed.

Current study has some limitations. The retrospective design of the study and small number of patients are the paramount limitations. The lack of a power analysis is making some results questionable including operation technique, degree of differentiation and survival; where the statistical analysis is borderline significant or borderline not significant. Another important limitation of the current study is the lack of disease-free survival analysis, which would probably rule out the impact of age difference between the groups. Besides, in our opinion, the case-match design of the study considering similar stages and homogeneity of the groups still make the current information valuable.

Conclusion

Current study analyzes the perioperative measures and survival of rectal cancer patients younger than 40 years and older than 50 years, and reveals similar results. Because of the limitations in the study, and conflicting information in the literature, further investigations are needed.

Ethics

Ethics Committee Approval: The study was approved by İstanbul Medipol University Ethics Committee (10840098-604.01.01-E21586).

Informed Consent: There were no direct interactions with subjects and knowledge gained would not impact subject's clinical care, informed consent were not obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Concept - O.C.; Design - M.O.; Data Collection or Processing - O.C.; Analysis or Interpretation - M.O.; Literature Search - O.C., M.O; Writing: O.C.

Conflict of Interest: The authors declare that they have no conflicts of interest.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. P, Whitley A, Blaha M, Hoch J. Colorectal cancer in patients under the age of 40 years: experience from a tertiary care center in the Czech Republic. Acta Chir Belg 2017; 117: 356-62.
2. Segev L, Kalady MF, Church JM. Left-Sided Dominance of Early-Onset Colorectal Cancers: A Rationale for Screening Flexible Sigmoidoscopy in the Young. Dis Colon Rectum 2018;61: 897-902.
3. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin 2014; 64: 104-117.
4. Siegel RL, Jemal A, Ward EM. Increase in incidence of colorectal cancer among young men and women in the United States. Cancer Epidemiol Biomarkers Prev 2009; 18: 1695-1698
5. O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Ko CY. Are survival rates different for young and older patients with rectal cancer? Dis Colon Rectum 2004; 47: 2064-9.
6. Alici S, Aykan NF, Sakar B, Bulutlar G, Kaytan E, Topuz E. Colorectal cancer in young patients: characteristics and outcome. Tohoku J Exp Med 2003; 199: 85-93.
7. Schellerer VS, Merkel S, Schumann SC, Schlabrakowski A, Förtsch T, Schildberg C, et al. Despite aggressive histopathology survival is not impaired in young patients with colorectal cancer : CRC in patients under 50 years of age. Int J Colorectal Dis 2012; 27: 71-9.
8. Tawadros PS, Paquette IM, Hanly AM, Mellgren AF, Rothenberger DA, Madoff RD. Adenocarcinoma of the rectum in patients under age 40 is increasing: impact of signet-ring cell histology. Dis Colon Rectum 2015; 58: 474-8.
9. Lino-Silva LS, Salcedo-Hernández RA, Ruiz-García EB, León-Takahashi AM, García-Pérez L. Outcome of young patients with rectal adenocarcinoma. J Gastrointest Oncol 2017; 8: 96-101.
10. You YN1, Dozois EJ, Boardman LA, Aakre J, Huebner M, Larson DW.Young-onset rectal cancer: presentation, pattern of care and long-term oncologic outcomes compared to a matched older-onset cohort. Ann Surg Oncol 2011; 18: 2469-76.
11. O'Connell JB, Maggard MA, Livingston EH, Yo CK. Colorectal cancer in the young. Am J Surg 2004; 187: 343-8.
12. Meyer JE, Narang T, Schnoll-Sussman FH, Pochapin MB, Christos PJ, Sherr DL. Increasing incidence of rectal cancer in patients aged younger than 40 years: an analysis of the surveillance, epidemiology, and end results database. Cancer 2010; 116: 4354-9.
13. Haroon N, Khan S, Alvi R. Rectal carcinoma under 40 years of age: seven-year post-treatment follow-up at a tertiary care hospital in Pakistan. J Pak Med Assoc 2013; 63: 1460-3.

İstanbul Med J 2020; 21(2): 132-9
DOI: 10.4274/imj.galenos.2020.23427

Our Autoimmune Hepatitis Patients: Single Center Experience

Otoimmün Hepatit Hastalarımız, Tek Merkez Deneyimi

Osman Özdoğan, Serkan Yaraş
Mersin University Faculty of Medicine, Department of Gastroenterology, Mersin, Turkey

ABSTRACT

Introduction: Autoimmune hepatitis (AIH) is a form of chronic hepatitis of unknown etiology characterized by autoimmunological properties and circulating autoantibodies. It can be treated after early diagnosis and often requires a great effort during diagnosis and regular follow-up. In Turkey, the number of studies examining AIH patients from the point of diagnosis to treatment is very low. We retrospectively evaluated patients diagnosed with AIH in the last 10 years.

Methods: Between 2009 and 2019, AIH patients who were diagnosed in our hospital or applied for ongoing treatment were evaluated retrospectively from the hospital information system. Patients who responded were invited to the clinic and missing data were added.

Results: A total of 48 patients (10 males and 38 females) aged 18-73 years (44.8±14.8 years) were evaluated. Four patients (8.3%) were asymptomatic. In the pre-treatment evaluation, cirrhosis occurred in 31% of patients, acute hepatitis in 21% of patients, and chronic hepatitis in 39% of patients. Type 1 AIH was observed in 81.2% of patients, 4.2% had type 2 AIH, and 14.6% demonstrated autoantibody negative AIH. A total of 35.4% of patients (n=17) had overlap syndrome accompanied by biliary tract damage. A total of 68.8% of patients with type 1 AIH had antinuclear antibody, 41.7% were positive for anti-smooth muscle antibody, and 31.3% were positive for both autoantibodies. A total of 33.3% of patients had non-hepatic disease. The treatment response rates were: 68.8% (complete); 18.7% (partial); and 12.5% (non-responders). Of the patients with a mean follow up of 3.54±2.63 years, 37 patients continued the treatment.

Conclusion: Our data demonstrated similar findings to previously published literature in terms of the ratio of female-to-male presentation, type 1, type 2 rates, rate of concomitant non-hepatic autoimmune disease, and response to treatment. They were different in terms of the low number of asymptomatic patients, lower percentage autoantibodies, and high proportion of overlap syndrome.

Keywords: Autoimmune hepatitis, autoantibody, primary biliary cholangitis, cirrhosis

ÖZ

Amaç: Otoimmün hepatit (OIH) dolaşan otoantikorlar, otoimmünolojik tabloyla karakterize etiyolojisi bilinmeyen bir kronik hepatittir. Erken tanı ile çoğu kez tedavi edilebilen, tanısında birden çok değerin kullanıldığı, düzenli takip gerektiren bir hastalıktır. Ülkemizde OIH hastalarını tanısından tedaviye yanıtına kadar inceleyen çalışma sayısı yok denecek kadar azdır. Son 10 yılda OIH tanısı alan hastalarımızı retrospektif olarak değerlendirdik.

Yöntemler: 2009 ile 2019 yılları arasında kliniğimizde tanı almış veya takip amacıyla başvurmuş OIH hastaları, retrospektif olarak hastane bilgi sisteminden geriye dönük olarak değerlendirildi. Ulaşabilen hastalar kliniğimize davet edilerek, elde olmayan bazı tetkikleri eklendi.

Bulgular: 18-73 yaş arası (44,8±14,8 yıl) toplam 48 hasta (10 erkek ve 38 kadın) değerlendirildi. Dört hasta (%8,3) asemptomatik idi. Tedavi öncesi değerlendirmede hastaların %31'i siroz, %21'i akut hepatit, %39'u kronik hepatit idi. %81,2'si tip 1 OIH, %4,2'si tip 2 OIH iken %14,6'sında ise otoantikor negatif OIH saptandı. Hastaların %35,4'ünde (n=17) ise safra yolları hasarının eşlik ettiği overlap sendromu mevcut idi. Tip 1 OIH hastaların %68,8'inde antinükleer antikor, %41,7'sinde anti düz kas antikoru pozitifliği var iken her iki otoantikor pozitif olan hasta sayısı oranı %31,3 idi. %33,3'ünde karaciğer dışı hastalık mevcut idi. Tedaviye yanıt oranları tam yanıt %68,8, kısmi yanıt %18,7, yanıtsız hasta oranı ise %12,5 idi. Ortalama takip süresi 3,54±2,63 yıl olan hastaların halen 37'si tedaviye devam etmekte idi.

Sonuç: Kadın erkek oranı, prezetasyonu, tip 1, tip 2 oranları, eşlik eden karaciğer dışı otoimmün hastalık oranı ve tedaviye yanıt oranları bakımından çalışmamızın literatüre benzer şekilde olduğu görüldü. Asemptomatik hasta oranının düşük olması, otoantikorların daha düşük yüzdede saptanması, overlap sendromunun yüksek olması açısından farklılık göstermekte idi.

Anahtar Kelimeler: Otoimmün hepatit, otoantikor, primer bilier kolanjit, siroz

Address for Correspondence/Yazışma Adresi: Osman Özdoğan MD, Mersin University Faculty of Medicine, Department of Gastroenterology, Mersin, Turkey
Phone: +90 505 450 13 80 **E-mail:** osmanozdogan2000@gmail.com **ORCID ID:** orcid.org/0000-0002-8299-5341

Cite this article as/Atıf: Özdoğan O, Yaraş S. Our Autoimmune Hepatitis Patients: Single Center Experience. İstanbul Med J 2020; 21(2): 132-9.

Received/Geliş Tarihi: 21.12.2019
Accepted/Kabul Tarihi: 13.02.2020

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory disease of the liver that can occur at any age and may progress to cirrhosis if untreated. Females are more frequently affected than males. Difficulties in AIH diagnosis may be observed due to its heterogeneous nature, its prevalence, and the different ways in which AIH presents itself. Diagnosis is based on certain parameters such as the presence of characteristic autoantibodies, which is a specific feature in liver histopathology, abnormal serum globulin levels, and exclusion of other chronic liver diseases (1). The prevalence of AIH varies from 4 to 25 people per 100,000, although it varies among countries (2,3).

The symptoms and signs may occur in a a range from the findings of a normal physical examination to signs of cirrhosis or hepatic failure (e.g., jaundice, ascites, splenomegaly). Patients may be asymptomatic or experience non-specific symptoms such as loss of appetite, nausea, abdominal pain, fatigue, arthralgia, and itching (4). Autoimmunity-related diseases such as celiac disease, rheumatoid arthritis, type 1 diabetes, autoimmune thyroiditis, and ulcerative colitis may accompany AIH. In acute presentation, an increase in aminotransferases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] by 10-20 times the upper limit of the reference range is observed. The AST and ALT to alkaline phosphatase (ALP) ratio is generally <1:5. In patients with chronic symptoms or cirrhosis, the increase in AST and ALT is less pronounced while the ratio of ALP to AST (or ALT) is lower (approximately 1:2) (5). AIH is usually accompanied by hypergammaglobulinemia due to the elevation of immunoglobulin (Ig) G while Ig A and Ig M levels are normal (6). Antinuclear antibodies (ANA) are the most common circulating autoantibodies in AIH and may be the only autoantibodies detectable. Anti-smooth muscle antibodies (ASMA) are more specific but less common in AIH than ANA, especially when present at titers of 1:80 or are greater in adults. Anti-liver-kidney microsomal antibodies (anti-LKM) often occur in patients with type 2 AIH (7). Anti-liver cytosol antibody-1 is a marker of type 2 AIH. These antibodies usually coexist with anti-LKM-1 but may be the only detected autoantibody. Anti-soluble liver antigen/liver pancreatic (anti-SLA/LP) antibodies were found in 10%-30% of adult patients with type 1 AIH (8). Furthermore, different autoantibodies such as anti-actin antibodies, peripheral antineutrophil cytoplasmic antibodies, and anti-DNA antibodies may be found in some patients. Although liver histology is not specific, histopathological changes such as interface hepatitis (with lymphoplasmacytic infiltration rich in plasma cells), hepatocyte rosette formation, and zone 3 necrosis (central perivenulitis) support the diagnosis.

Almost 90% of AIH patients have type 1 AIH. Positive autoantibodies such as ANA, ASMA or anti-SLA/LP with HLA DR3, DR4 and DR13. Unresponsiveness to treatment is rare but post-treatment relapse and duration of treatment vary (9). Type 2 AIH occurs in approximately 10% of patients and is associated with HLA DR3 and DR7. Type 2 AIH is more common in children and young adults and has a more severe course and resistance to treatment than type 1 AIH (10). Type 3 AIH (anti-SLA/LP often accompanied by anti-Ro52 positivity) is rare while type 1 AIH has a similar but worse prognosis. Some authorities and guidelines accept it as if type 1 AIH. Autoantibody-negative AIH (or cryptogenic hepatitis) may also occur. Here, the response to treatment supports the diagnosis (4). Diseases such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) may accompany AIH. In these cases, overlap syndrome is observed. In patients with AIH/PBC overlap, histology may refer to AIH, serology may refer to PBC or histology may refer to PBC, serology may refer to AIH (11). In AIH/PSC overlap, serological and histological features are similar to those observed in AIH. When examined using imaging techniques, PSC has characteristic features. Survival rates were decreased in patients with overlap compared to AIH patients (12). It is necessary to differentiate drug-induced AIH from drug-induced liver damage, which differs in patophysiology. Corticosteroids and azathioprine are mainly used in treatment (4,10). In overlap syndromes, ursodeoxycholic acid (UDCA) may be added to the treatment regime. With early diagnosis and effective treatment, the disease can stabilize, fibrosis can regress histologically, and cirrhosis can be halted (6).

In Mersin University Hospital, Department of Gastroenterology, we investigated certain parameters such as the type of AIH that patients were diagnosed with and treated for over the last 10 years, their presentation at the time of diagnosis, the percentage of overlap syndrome, the types of given treatments, and the response of patients to treatment.

Methods

In our clinic, adult patients with AIH, who had been diagnosed over the last 10 years or who were continuing their follow-up, were retrospectively identified from the hospital information system. Complete blood counts; liver function tests; and measures of albumin, total protein, immunoglobulins, prothrombin time, alpha-1-antitrypsin, ferritin, copper, and ceruloplasmin were made in the biochemistry laboratory of Mersin University Hospital. The serology of hepatitis A, B, and C, cytomegalovirus, and the Epstein-Barr virus were examined in the microbiology laboratory of our hospital. ANA, ASMA, anti-LKM, anti-SLA/LP, and anti-mitochondrial antibody (AMA) were investigated by using an indirect immunofluorescence method in the microbiology laboratory of our hospital. Values above 1/40 for each antibody were considered positive. The sizes of the liver and spleen and the parenchymal status of all cases were examined using abdominal ultrasonography. Endoscopy was performed in patients with an enlarged spleen and/or cirrhosis.

The diagnosis of AIH was made according to the simplified scoring system published by the International Autoimmune Hepatitis Group (2008), which includes four basic components: autoantibody presence, Ig level, histopathology and viral hepatitis status (13). If the total score was 6, AIH was possible. On the other hand, if the total score was ≥7, definite AIH was diagnosed. The AIH subtypes were classified as follows: type 1, positive for ANA and/or ASMA; type 2, positive for LKM-1; type 3, positive for anti-SLA; autoantibody negative, negative for autoantibodies. The diagnosis of AIH was accepted as an overlap syndrome if there was associated biliary tract damage, enzyme height in a cholestatic pattern, and/or AMA positivity in histology. Magnetic resonance cholangiopancreatography (MRCP) was performed to rule out the possibility of PSC in suspected patients.

A total of 173 patients were evaluated. Fifty-six of these patients presented with incomplete data, 28 patients did not undergo regular follow-up, 13 patients refused biopsy, 11 patients demonstrated only

biliary changes in histology, and 17 patients had a simplified AIH score <6, and they were excluded from the study (Figure 1). A total of 48 patients were included in the study. This study was approved by the Ethics Committee of Mersin University (decision no: 2019/750).

Histological Evaluation

Before the treatment, liver biopsy was performed with a 16-g Menghini type needle under ultrasound guidance in Mersin University Hospital, Department of Gastroenterology and histopathological evaluation was carried out by medical pathology specialists in our hospital. Patients who underwent biopsy at the external center were asked for their preparations and were re-evaluated in our pathology unit. Pathological diagnoses were made according to pre-determined criteria (14).

Evaluation of Response to Treatment

According to serum ALT and AST and/or Ig G levels, cases that returned to normal values within 6-12 months and cases that were clinically asymptomatic were evaluated as a complete response. Cases that did not return to normal within 12 months but decreased according to baseline level were evaluated as a partial response. Cases that did not demonstrate any decrease during the two-year follow-up were considered non-responsive. If the increase in ALT and AST levels after receiving treatment, or discontinuation of treatment was greater than three times the normal values, this was classed as a relapse.

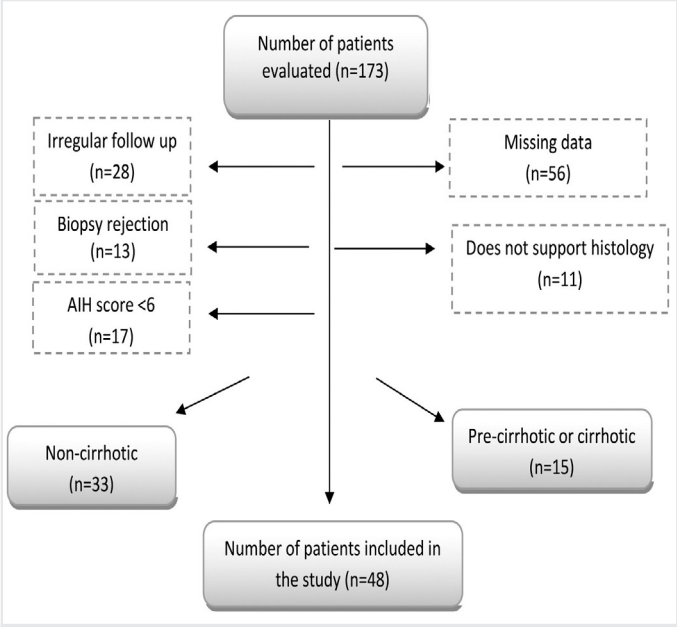

Figure 1. Patient selection (autoimmune hepatitis)

Statistical Analysis

Continuous variables were reported as mean ± standard deviation, and categorical variables were reported as percentages. A student's t-test and a Mann-Whitney test were used for continuous variables and a chi-square test was used for categorical variables. SPSS 20.0 for Windows (IBM Corporation, Armonk, New York, USA) was used to perform the statistical analyses.

Results

The study included 48 patients. Ten patients (20.8%) were male and 38 patients (79.2%) were female. The mean age was 44.8±14.8 years (range: 18-73 years). The period between symptomatic onset and patient diagnosis was 7.51±7.8 months. The main symptoms and signs at admission were fatigue (86%), mild abdominal pain (46%), pruritus (27%), muscle pain (25%), jaundice (14%), and ascites (10%). Diarrhea and fever were present in several cases. Four patients (8.3%) were asymptomatic and transaminase elevation was detected in screening tests. These patients were diagnosed with AIH due to the persistence of this elevation during follow-up. In the pre-treatment evaluation, cirrhosis or pre-cirrhosis was detected while 31.3% of patients and 68.7% of patients were non-cirrhotic. A total of 33% of patients who were non-cirrhotic presented with acute hepatic attack, which was also observed in 40% of cirrhotic patients (Table 1).

Biopsy was not performed in a patient who was cirrhotic due to refusal of the patient and a risk of complications. This patient was ANA and ASMA positive and demonstrated high transaminases, and other etiologic factors were excluded. This patient was diagnosed as having type 1 AIH and treatment was initiated. Biopsy was performed in 47 patients. Cirrhosis or pre-cirrhosis was detected by biopsy in eight patients whose conditions were classified as non-cirrhotic before the histologic evaluation. Interface hepatitis was detected in 45 patients (96%), plasmocytic infiltration in 39 patients (83%), and rosette formation in six patients (12.7%). AIH-compatible histology was not detected in one patient, but the patient had a simplified AIH score of 6. This patient was diagnosed with AIH and treatment was initiated. A complete response

Table 1. Gender complaints, presentation and histological characteristics of the patients

Gender		Complaints		Presentation		Histology	
Male	20.8%	Weakness	86%	Cirrhosis or pre-cirrhotic	31%	Interface hepatitis	96%
Female	79.2%	Abdominal pain	46%	Acute hepatitis	21%		
		Itching	27%	Chronic hepatitis	39%	Plasmocytic infiltration	83%
		Muscle pains	25%	Asymptomatic	9%	Rosette formation	12.7%
		Jaundice	14%	Fulminant liver failure	0%	Biliary tract changes	41.6%
		Ascites	10%			None	2.1%
		Fewer	8.3%				
		Asymptomatic	8.3%				

to treatment was achieved in this patient. Biliary duct changes were detected by histology on biopsies from 20 patients. Three patients were AMA negative and normal cholestatic enzymes were not accepted as representing overlap syndrome (Table 1).

In the pre-treatment evaluation, 81.2% of patients were diagnosed with type 1 AIH, 4.2% were diagnosed with type 2 AIH, and 14.6% were diagnosed with autoantibody negative AIH. A total of 68.8% of patients diagnosed with type 1 AIH were positive for ANA, 41.7% were ASMA positive, and 31.3% were both ANA and ASMA positive. A total of 35.4% of patients (n=17) had overlap syndrome with PBC. AMA was positive in 12 out of 17 patients (70.5%) with PBC. Histopathologic examination of AMA-negative patients showed bile duct damage and high cholestatic enzymes. In these patients, PSC was excluded by MRCP. Two patients who were AMA positive were not considered to have overlap syndrome because of the absence of bile duct changes and the normal range of cholestatic enzymes. No difference was observed between the cirrhotic and non-cirrhotic groups in terms of the type of AIH ($p>0.05$). Hepatitis B (HBV) was detected in two patients at the time of diagnosis, one of whom was cirrhotic. The HBV DNA of these patients was below 2000 IU/mL and hepatitis D antigen was negative. Both ANA and ASMA autoantibodies were detected in these patients, who also presented with acute hepatitis. Hepatitis C and HIV were not detected in any of the patients. In the non-cirrhotic group, albumin and platelet counts were high. In the cirrhotic group, ALP, total bilirubin and international normalized ratio levels were high ($p<0.05$). Data from all patients are presented in Table 2.

When we evaluated the accompanying diseases [diabetes mellitus (DM) in five patients, Hashimoto's thyroiditis in five patients, hypertension

Table 2. Demographic and laboratory patient data (prior to treatment)

		Total group (n=48)	Non-cirrhotic group (n=33)	Pre-cirrhotic and cirrhotic group (n=15)	p
Age (years)		44.8±14.8 49.3±9.82	45.7±13.6	42.6±17	0.253
Gender (female)		38 (79.2%)	25 (76%)	13 (86.7%)	0.389
AIH	Type 1 (%)	39 (81.2%)	27 (81.8%)	12 (80%)	0.881
	Type 2 (%)	2 (4.2%)	1 (3%)	1 (6.7%)	0.558
	Type 3 (%)	0	0	0	-
	Autoantibody negative	7 (14.6%)	5 (15.2%)	2 (13.3%)	0.676
Overlap syndrome (%)		17 (35.4%)	10 (30.3%)	7 (46.7%)	0.272
ANA positivity (%)		33 (68.8%)	24 (72.8%)	9 (60%)	0.379
ASMA positivity (%)		20 (41.7%)	14 (42.4%)	6 (40%)	0.874
Anti-LKM positivity (%)		2 (4.2%)	1 (3%)	1 (6.7%)	0.558
IgG		1.89±0.61	1.73±0.51	2.22±0.68	0.004
HBV positivity (%)		2 (4.2%)	1 (3%)	1 (6.7%)	0.558
HCV positivity (%)		0	0	0	-
ALT (U/L)		320±301	341±323	276±239	0.249
AST (U/L)		312±323	274±277	393±395	0.124
GGT (U/L)		188±146	170±131	228±165	0.107
ALP (U/L)		189±149	163±128	245±173	0.041
FBG		107±37	103±40	118±27	0.103
Creatinine (mg/dL)		0.64±0.16	0.66±0.18	0.62±0.11	0.227
Albumin (g/dL)		3.68±0.63	3.83±0.60	3.39±0.56	0.005
Total protein (g/dL)		7.42±1.17	7.39±1.33	7.51±0.65	0.371
Total bilirubin (mg/dL)		2.32±2.68	1.79±2.26	3.47±3.13	0.024
INR		1.13±0.25	1.08±0.22	1.23±0.25	0.025
Plt (x 10^3/µL)		222±82	257±71	146±49	0.000
HCT (%)		37.5±5.38	37.8±5.35	36.9±5.3	0.312
Wbc (µL)		7254±2623	7916±2550	5800±2152	0.004

AIH: autoimmune hepatitis, ALP: alkaline phosphatase, ALT: alanine aminotransferase, ANA: anti-nuclear antibody, ASMA: anti-smooth muscle antibody, AST: aspartate aminotransferase, FBG: fasting blood glucose, GGT: gamma glutamyl transpeptidase, HBV: hepatitis B virus, HCV: hepatitis C virus, HCT: hematocrit, IgG: immunoglobulin G, INR: international normalized ratio, LKM: liver-kidney microsomal antibody; Plt: platelet, wbc: white blood cell

(HT) in two patients, asthma in two patients, hypoparathyroidism in one patient, impetigo, diabetes insipidus, ulcerative colitis, Parkinson's disease, Guillain-Barre syndrome and coronary artery disease (CAD)] (Table 3), two of these patients had DM and hypothyroidism, one had DM and HT, one had hypothyroidism and hypoparathyroidism, and one had DM and CAD. No accompanying- extrahepatic disease was detected in 66.7% of patients.

Treatment was initiated with a combination of steroids (methylprednisolone and prednisolone), azathioprine (AZA), and UDCA (Table 4). Induction therapy was started with steroids (0.5-1 mg/kg), UDCA (15-25 mg/kg), and AZA (50 mg daily). For remission therapy, the steroid dose was adjusted (5-10 mg daily) and the AZA dose was adjusted (1.5 mg/kg) while the UDCA dose was unchanged. Twenty-nine of the patients were administered a steroid + AZA. Eleven patients were administered steroid + AZA + UDCA. Five patients (12.5%) who received this treatment were unresponsive. Of the five unresponsive patients, two responded to mycophenolate mofetil treatment while three were unresponsive despite different treatments being used. One of the three unresponsive patients had type 2 AIH with cirrhosis, developed sepsis and pancytopenia, and died. In another patient, cirrhosis developed. This patient died of esophageal variceal bleeding. The third unresponsive patient had liver transplantation and is now stable. Only AZA treatment could be administered in a cirrhotic patient who could not receive steroid treatment. Although other treatments were tested in this patient, the patient died within a year due to hepatic cirrhosis. In the seven patients who could not use AZA due to intolerance and hyperbilirubinemia, steroid treatment (plus UDCA in six cases) was administered. No patients were unresponsive to this regime. A complete response was observed in 68.8% of patients, a partial response was observed in 18.7% of patients, and 12.5% of patients were unresponsive (Table 4). One of the 17 patients with AIH-PBC was unresponsive while four demonstrated a partial response.

Table 3. Accompanying -extrahepatic diseases

Diseases	%
Diabetes mellitus	10.4
Hashimoto's thyroiditis	10.4
Hypertension	4.2
Asthma	2.1
Hypoparathyroidism	2.1
Impetigo	2.1
Diabetes insipidus	2.1
Guillain-Barre syndrome	2.1
Ulcerative colitis	2.1
Coronary artery disease	2.1
Parkinson's disease	2.1

One patient who received AZA developed lymphadenopathy in the neck and abdomen during follow-up, leading to treatment discontinuation. Lymph node excision was performed, and lymphoma was excluded. This patient relapsed after the discontinuation of treatment but went on to achieve a complete response with budesonide. Side effects such as weight gain, osteoporosis, and hyperglycemia developed in 13 patients (27%) while side effects such as skin rashes, cataracts, and fibromyalgia were noted in five patients (10.4%). These observations were most frequently observed in patients administered steroids. With a mean follow-up of 3.54±2.63 years, a healthy relapse rate could not be evaluated because 37 patients (77%) were still on treatment. Eleven patients whose treatments were discontinued had an average therapy time of 4.81±1.2 years. Four of these patients developed recurrence after treatment. The first treatment was started again for these patients. No patients who demonstrated a complete response showed loss of response to treatment during the treatment period.

Discussion

AIH is a preventable liver disease, which requires timely diagnosis and treatment. It is a disease that is difficult to diagnose because it presents with multiple non-specific symptoms and is rare (15). In admission to hospital, patients may show different presentation from asymptomatic presentation to cirrhosis of the liver.

In some previous studies, the ratio of females to males was 3.6:1 (3,12). Similar ratio was found in our study (3.8:1). In previous studies, the rate of asymptomatic AIH was 12%-35% (16,17). In the present study, this rate was 8.3%. The reason for this discrepancy was that the patients included in this study did not have regular follow-up appointments. This meant that asymptomatic enzyme elevation was not monitored by clinicians. Most of the patients that participated in this study had non-specific

Table 4. Drugs used and treatment response rates

Drugs	n (%)	Complete	Partial	Non-responders
Steroid + AZA	29 (60.3%)	n=20	n=5	n=4
Steroid + AZA + UDCA	11 (23%)	n=8	n=2	n=1
Steroid + UDCA	6 (12.5%)	n=4	n=2	n=0
Steroid	1 (2.1%)	n=1	n=0	n=0
AZA	1 (2.1%)	n=0	n=0	n=1
TOPLAM	48 (100%)	n=33	n=9	n=6

AZA: azathioprine, UDCA: ursodeoxycholic acid

symptoms such as fatigue and abdominal pain, and their incidence was consistent with previous studies (18). The detection rate of jaundice was low compared to other studies (19).

At the time of diagnosis, cirrhosis occurred in 31% of patients, which corroborates existing literature (17,20). The rate of acute hepatitis was 21% and the rate of chronic hepatitis was 39%. None of the patients included in this study developed fulminant hepatic failure. In a study carried out over approximately 20 years, 36.3% of patients had chronic hepatitis, 27.9% had acute hepatitis, 2.9% had fulminant hepatic failure, and 41% had cirrhosis (20). There is no typical morphological feature for the diagnosis of AIH. Histological changes include features such as interface hepatitis, rosette formation, zone three necrosis, and plasmocytic infiltration. They are necessary for the diagnosis of AIH (14). We detected interface hepatitis in 45 patients (96%), plasmocytic infiltration in 39 patients (83%), and rosette formation in six patients (12.7%).

In the present study, a total of 81.2% of patients had type 1 AIH, 4.2% had type 2 AIH, and 14.6% had autoantibody negative AIH. A total of 68.8% of patients in the present study with type 1 AIH had ANA, 41.7% were ASMA positive, and 31.3% of patients were tested as positive for both autoantibodies. In a study from Israel, ANA positivity was 79% and ASMA positivity was 56% (20). In another study, 78% of patients were tested as positive for ANA and 69% of patients were tested as positive for ASMA (17). In a study from North America, 96% of AIH patients were tested as positive for ANA, ASMA, or both (21). In these studies, the frequency of type 2 AIH was similar to the present study (approximately 4%). Type 2 AIH is more common in children (15%-20%). In our study, the frequency of autoantibody-negative AIH was found to be 14.6%, which was higher than the literature. However, certain studies conducted before the year 2000 reported that the incidence of seronegative AIH was approximately 10%-15% (22,23). In the autoantibody negative AIH patients enrolled in our study, the simplified AIH score was 6 and all patients responded to a standard treatment. We think that this ratio is remarkable. A limited number of studies were conducted in Turkey and these were usually carried out by pediatricians. In addition, some cases of AIH (e.g., acute hepatitis) may be ANA negative and present with normal Ig G levels in the initial stages (24).

Biliary duct involvement was identified in 35% of patients with AIH in the present study. This rate is higher than that reported in the literature. The prevalence of AIH-PBC is estimated at around 8%-10% (25,26). Previous studies have indicated that regional differences may occur. Studies from the Middle East and the Hispanics found that AIH patients demonstrated a high cholestatic pattern (27,28). In another study, approximately 20% of patients with phosphate buffered saline may have AIH (29). In a study carried out in the United States, AIH coexistence rate with PBC, PSC, and autoimmune cholangitis was 18% while the AIH: PBC ratio was 3.2% (23). Although PSC was excluded in the present study, non-exclusion of autoimmune cholangitis could be a reason for the high PBC ratio. Coexistence of AIH and PSC is more common in children, young adults, and those with ulcerative colitis (30). The patients in the present study were older and did not present with ulcerative colitis (except one patient). Therefore, regional differences may explain the absence of PSC. Five percent of patients were tested as positive for AMA. These patients did not present with bile duct damage when examined by histology (11). This rate was 4% in the present study. Combination therapies including UDCA are recommended for the treatment of overlap syndrome (28). We administered combination therapy to our patients, and only one (6%) was non-responsive, which is similar to that observed in the literature.

The rate of extrahepatic diseases accompanying AIH was 33.3%. Most of these cases were autoimmune diseases (e.g., hypothyroidism, ulcerative colitis). In a study conducted in Italy, the prevalence of non-liver autoimmune disease accompanying AIH was 42%, and autoimmune thyroiditis was common (31). In some studies, the rate of extrahepatic diseases was 29-38% (20,32). Studies have shown that patients with non-liver autoimmune disease do not differ in terms of disease progression and survival (31,33).

In the present study, 68.8% of patients demonstrated a complete response to induction-remission therapy, 18.7% demonstrated a partial response, and 12.5% were non-responsive. In a single-center study on approximately 68 patients with AIH from Israel, 70% of patients receiving steroid and/or AZA treatment demonstrated a complete response, 24% demonstrated a partial response, and 6% were non-responsive (20). In a study of 153 patients with AIH, 12 of whom had overlap syndrome, with a mean follow-up of 88 months, the remission rate was 70% and treatment failed in 13% (34). In this study, the relapse rate was 51%, the mortality rate due to hepatic failure was 7%, and the rate of transplanted patients was 3.2%. In another study involving 125 patients (4% type 2 AIH), 84.7% demonstrated a complete response, 13.3% demonstrated a partial response, and 2% were unresponsive (17). In this study, the relapse rate after treatment was 35%. Ten patients (8%) required liver transplantation. Nine of these patients had cirrhosis before treatment. In the present study, three patients (6%) died from liver cirrhosis and complications. One patient underwent liver transplantation. In our study, the likely cause of the low cirrhosis development rate and low transplantation rate was short-term follow-up. A healthy relapse rate could not be determined because 77% of patients in the present study had ongoing treatment. Of the 11 patients whose treatments were terminated, four patients relapsed within one year. This figure is similar to the literature in terms of the side effects of the drugs used.

Study Limitation

The limitations of our study are that it was designed retrospectively, the number of patients was low, and some data in the past were not available.

Conclusion

We found in our study that although rare papers on the evaluation of AIH patients in Turkey exist in the literature, the female to male ratio, presenting complaints, presentation, histology, incidence of type, concomitant non-hepatic autoimmune disease rate and treatment response rates were similar to those reported before. The patients in the present study differed in terms of the low number of asymptomatic

patients, detection of autoantibodies at lower percentages, and higher overlap syndrome.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Mersin University (decision no: 2019/750)

Informed Consent: Retrospective study. (Verbal consent was obtained from the patients).

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - O.Ö., S.Y.; Concept - O.Ö.; Design - O.Ö.; Data Collection and/or Processing - O.Ö., S.Y.; Analysis and/or Interpretation - O.Ö., S.Y.; Literature Search - O.Ö., S.Y.; Writing Manuscript - O.Ö., S.Y.

Acknowledgement: The authors are grateful to Dr. Orhan Sezgin, Dr. Engin Altıntaş, Dr. Fehmi Ateş, and Dr. Enver Üçbilek for their contributions, which have helped to improve the paper.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999; 31: 929-38.
2. Werner M, Prytz H, Ohlsson B, Almer S, Björnsson E, Bergquist A, et al. Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study. Scand J Gastroenterol 2008; 43: 1232-40.
3. Ngu JH, Bechly K, Chapman BA, Burt MJ, Barclay ML, Gearry RB, et al. Population-based epidemiology study of autoimmune hepatitis: a disease of older women? J Gastroenterol Hepatol 2010; 25: 1681-6.
4. Heneghan MA, Yeoman AD, Verma S, Smith AD, Longhi MS. Autoimmune hepatitis. Lancet 2013; 382: 1433-44.
5. Al-Chalabi T, Underhill JA, Portmann BC, McFarlane IG, Heneghan MA. Effects of serum aspartate aminotransferase levels in patients with autoimmune hepatitis influence disease course and outcome. Clin Gastroenterol Hepatol 2008; 6: 1389-95.
6. Manns MP, Lohse AW, Vergani D. Autoimmune hepatitis--Update 2015. J Hepatol 2015; 62: S100-111.
7. Homberg JC, Abuaf N, Bernard O, Islam S, Alvarez F, Khalil SH, et al. Chronic active hepatitis associated with antiliver/kidney microsome antibody type 1: a second type of "autoimmune" hepatitis. Hepatology 1987; 7: 1333-9.
8. Kanzler S, Weidemann C, Gerken G, Löhr HF, Galle PR, Meyer zum Büschenfelde KH, et al. Clinical significance of autoantibodies to soluble liver antigen in autoimmune hepatitis. J Hepatol 1999; 31: 635-40.
9. Zachou K, Muratori P, Koukoulis GK, Granito A, Gatselis N, Fabbri A, et al. Review article: Autoimmune hepatitis – Current management and challenges. Aliment Pharmacol Ther 2013; 38: 887–913.
10. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al. Diagnosis and management of autoimmune hepatitis. Hepatology 2010; 51: 2193–213.
11. O'Brien C, Joshi S, Feld JJ, Guindi M, Dienes HP, Heathcote EJ. Long-term follow-up of antimitochondrial antibody-positive autoimmune hepatitis. Hepatology 2008; 48: 550-6.
12. Al-Chalabi T, Portmann BC, Bernal W, McFarlane IG, Heneghan MA. Autoimmune hepatitis overlap syndromes: an evaluation of treatment response, long-term outcome and survival. Aliment Pharmacol Ther 2008; 28: 209-20.
13. Hennes EM, Zeniya M, Czaja AJ, Pares A, Dalekos GN, Krawitt EL, et al. Simplified diagnostic criteria for autoimmune hepatitis. Hepatology 2008; 48: 169-76.
14. Czaja AJ, Carpenter HA. Optimizing diagnosis from the medical liver biopsy. Clin Gastroenterol Hepatol 2007; 5: 898-907.
15. Czaja AJ.Diverse manifestations and evolving treatments of autoimmune hepatitis. Minerva Gastroenterol Dietol 2005; 51: 313-33.
16. Peng M, Li Y, Zhang M, Jiang Y, Xu Y, Tian Y, et al. Clinical features in different age groups of patients with autoimmune hepatitis. Exp Ther Med 2014; 7: 145-8.
17. Feld JJ, Dinh H, Arenovich T, Marcus VA, Wanless IR, Heathcote EJ. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. Hepatology 2005; 42: 53-62.
18. Lowe D, John S. Autoimmune hepatitis: Appraisal of current treatment guidelines, World Journal of Hepatology 2018; 10: 911-23.
19. Panayi V, Froud OJ, Vine L, Laurent P, Woolson KL, Hunter JG, et al. The natural history of autoimmune hepatitis presenting with jaundice. Eur J Gastroenterol Hepatol 2014; 26: 640-5.
20. Kogan J, Safadi R, Ashur Y, Shouval D, Ilan Y. Prognosis of symptomatic versus asymptomatic autoimmune hepatitis: a study of 68 patients. J Clin Gastroenterol 2002; 35: 75-81.
21. Martini E, Abuaf N, Cavalli F, Durand V, Johanet C, Homberg JC. Antibody to liver cytosol (anti-LC1) in patients with autoimmune chronic active hepatitis type 2. Hepatology 1988; 8: 1662-6.
22. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB, Homburger HA. The nature and prognosis of severe cryptogenic chronic active hepatitis. Gastroenterology 1993; 104: 1755–61.
23. Czaja AJ. Frequency and nature of the variant syndromes of autoimmune liver disease. Hepatology 1998; 28: 360-5.
24. Stravitz RT, Lefkowitch JH, Fontana RJ, Gershwin ME, Leung PS, Sterling RK, et al. Acute Liver Failure Study Group. Autoimmune acute liver failure: proposed clinical and histological criteria. Hepatology 2011; 53: 517-26.
25. Floreani A, Rizzotto ER, Ferrara F, Carderi I, Caroli D, et al. Clinical course and outcome of autoimmune hepatitis/primary sclerosing cholangitis overlap syndrome. Am J Gastroenterol 2005; 100: 1516–22.
26. Heurgue A, Vitry F, Diebold MD, Yaziji N, Bernard-Chabert B, Pennaforte JL, et al. Overlap syndrome of primary biliary cirrhosis and autoimmune hepatitis: a retrospective study of 115 cases of autoimmune liver disease. Gastroenterol Clin Biol 2007; 31: 17–25.
27. Zolfino T, Heneghan MA, Norris S, Harrison PM, Portmann BC, McFarlane IG. Characteristics of autoimmune hepatitis in patients who are not of European Caucasoid ethnic origin. Gut 2002; 50: 713-7.
28. Levy C, Naik J, Giordano C, Mandalia A, O'Brien C, Bhamidimarri KR, et al. Hispanics with primary biliary cirrhosis are more likely to have features of autoimmune hepatitis and reduced response to ursodeoxycholic acid than non-Hispanics. Clin Gastroenterol Hepatol 2014; 12: 1398–405.

29. Talwalkar JA, Keach JC, Angulo P, Lindor KD. Overlap of autoimmune hepatitis and primary biliary cirrhosis: an evaluation of a modified scoring system. Am J Gastroenterol 2002; 97: 1191-7.

30. Rojas CP, Bodicharla R, Campuzano-Zuluaga G, Hernandez L, Rodriguez MM. Autoimmune hepatitis and primary sclerosing cholangitis in children and adolescents. Fetal Pediatr Pathol 2014; 33: 202–9.

31. Muratori P, Fabbri A, Lalanne C, Lenzi M, Muratori L. Autoimmune liver disease and concomitant extrahepatic autoimmune disease. Eur J Gastroenterol Hepatol 2015; 27: 1175-9.

32. Wong GW, Heneghan MA. Association of Extrahepatic Manifestations with Autoimmune Hepatitis. Dig Dis 2015; 33: 25-35.

33. Wong GW, Yeong T, Lawrence D, Yeoman AD, Verma S, Heneghan MA. Concurrent extrahepatic autoimmunity in autoimmune hepatitis: implications for diagnosis, clinical course and long-term outcomes. Liver Int 2017; 37: 449-57.

34. Czaja AJ, Muratori P, Muratori L, Carpenter HA, Bianchi FB. Diagnostic and therapeutic implications of bile duct injury in autoimmune hepatitis. Liver Int 2004; 24: 322–9.

İstanbul Med J 2020; 21(2): 140-4
DOI: 10.4274/imj.galenos.2020.22220

The Usefulness of Endoscopic Retrograde Cholangiopancreatography at Preoperative or Postoperative Cystic *Echinococcus* Patients

Preoperatif veya Postoperatif Kistik *Echinococcus* Hastalarında Endoskopik Retrograd Kolanjiyopankreatografinin Faydası

Ekrem Çakar, Hasan Bektaş

University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey

ABSTRACT

Introduction: The aim of this study was to evaluate the efficacy of endoscopic retrograde cholangiopancreatography (ERCP) at cystic *echinococcus* (CE) patients in the preoperative or postoperative period.

Methods: Hepatic CE patients who underwent ERCP due to jaundice, bile leakage and rupture of the cyst to biliary tract between January 2010 and January 2018 were retrospectively evaluated in the study. Clinical status of the patients, ERCP, operation and radiology reports, and blood tests were assessed through hospital records and ERCP techniques, and ERCP success, complications and clinical situations of patients were noted.

Results: A total of 63 patients who participated in the study had 71 ERCP procedures and the mean age of the patients was 46.49±18.33 years and the W/M ratio was 31/32. ERCP were performed due to icter, bile leakage and opening to biliary tract at 38.28 and five patients respectively. Sphincterotomy and balloon application is the most frequently applied procedure in 40/71 patients. The mean time of closure of the bile leakage after ERCP was 19.29±10.64 days. ERCP was not successful in 4/63 patients (6.3%).

Conclusion: ERCP can be safely and successfully used for both diagnostic and therapeutic purposes in CE patients and CE complications.

Keywords: Cystic *echinococcus*, endoscopic retrograde cholangiopancreatography, icterus, bile leakage, magnetic resonance cholangiography, sphincterotomy

ÖZ

Amaç: Bu çalışmanın amacı, endoskopik retrograd kolanjiyopankreatografinin (ERCP) kistik ekinokok (KE) hastalarında preoperatif veya postoperatif dönemde etkinliğini değerlendirmektir.

Yöntemler: Ocak 2010-Ocak 2018 tarihleri arasında sarılık, safra kaçağı ve kistin safra yoluna rüptürü nedeniyle ERCP yapılan karaciğer KE hastaları retrospektif olarak çalışmaya dahil edildi. Hastaların klinik durumları, ERCP, operasyon ve radyoloji raporları, kan testleri hastane kayıtları ve ERCP teknikleri ile değerlendirildi, ERCP başarısı, komplikasyonlar ve hastaların klinik durumları kaydedildi.

Bulgular: Çalışmaya katılan toplam 63 hastaya toplam 71 ERCP prosedürü uygulandı ve hastaların ortalama yaşı 46,49±18,33 yıl ve K/E oranı 31/32 idi. ERCP sırasıyla 38, 28 ve 5 hastada ikter, safra kaçağı ve safra yollarına açılma nedeniyle uygulandı. Sfinkterotomi ve balon uygulaması 40/71 hastada en sık uygulanan işlemdir. ERCP sonrası safra kaçağının ortalama kapanma süresi 19,29±10,64 gündü. ERCP 4/63 hastada (%6,3) başarılı olamadı.

Sonuç: ERCP, KE hastalarında ve KE komplikasyonlarında hem tanı hem de tedavi amacıyla güvenle ve başarılı bir şekilde kullanılabilir.

Anahtar Kelimeler: Kistik ekinokok, endoskopik retrograd kolanjiyopankreatografi, ikter, safra kaçağı, manyetik rezonans kolanjiyografi, sfinkterotomi

Introduction

Cystic *echinococcus* (CE) is a disease caused by various species of the parasite *echinococcus* whose endemic range extends from South America to Africa and Eurasia (1-4). Being an endemic country, approximately 4,000 new cases are reported each year in Turkey (5). Though it is most frequently found in the liver, CE can affect many organs in the body. The complications of the disease can be life-threatening, with a 2-4% mortality rate (6,7). Diagnosis is usually incidental (8), as disease progression is slow in general.

In addition to incidental diagnosis in asymptomatic patients, CE can be diagnosed after the onset of symptomatic complications. The most common complications are allergic reactions due to cyst

Address for Correspondence/Yazışma Adresi: Ekrem Çakar MD, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey
Phone: +90 505 578 40 57 **E-mail:** ekremcakar@gmail.com **ORCID ID:** orcid.org/0000-0003-4447-0939

Cite this article as/Atıf: Çakar E, Bektaş H. The Usefulness of Endoscopic Retrograde Cholangiopancreatography at Preoperative or Postoperative Cystic *Echinococcus* Patients. İstanbul Med J 2020; 21(2): 140-4.

Received/Geliş Tarihi: 30.12.2019
Accepted/Kabul Tarihi: 13.02.2020

rupture, secondary infection of the cyst and jaundice with or without accompanying cholangitis due to the compression of the biliary tract by the cyst or by intrabiliary rupture. Among these complications, rupture of the cyst into the bile ducts is the most common, seen in 2-42% of the patients (9). Such cysts are usually located in the right lobe of the liver and can cause complications such as cholecystitis, cholangitis, liver abscess, sepsis and pancreatitis (9,10).

Once definitive diagnosis is made for CE, medical, percutaneous and surgical treatment methods are available (4). Endoscopic retrograde cholangiopancreatography (ERCP) is an appropriate diagnostic and therapeutic modality that can be used both preoperatively for cysts opening into the biliary tract and for the management of postoperative complications such as bile fistulae and jaundice (9). In this study, we examined patients who underwent ERCP due to CE in the preoperative or postoperative period and evaluated the efficacy of ERCP.

Methods

Data for the study were collected retrospectively from patient records. Ethics Committee Approval was obtained of by the University of Health Sciences Turkey, İstanbul University Training and Research Hospital (decision no: 2018, date: 11.10.2019) and informed consent from all patients were obtained. The study population consisted of patients who underwent ERCP because of liver CE between January 2010 and January 2018. Patients with bile leak due to bile duct injuries or jaundice associated with the obstruction of the common bile duct were excluded from the study. Hospital records of the patients were screened for demographic data, clinical conditions, endoscopic and surgical procedures, laboratory tests and imaging studies. Patients with incomplete records were also excluded from the study.

Statistical Analysis

Statistical analysis was performed with the IBM® SPSS® Statistics Version 21 (IBM, New York, USA) computer software. Normally-distributed continuous variables were expressed as mean ± standard deviation (SD) and variables without normal distribution were expressed as median and ranges. Paired t-test and Wilcoxon test were used for the comparison of numerical dependent variables between two groups. One-way ANOVA test was used to compare multiple groups. P value <0.05 was defined as indicating statistical significance.

Results

A total of 63 patients were included in the study, of which 31 were female and 32 were male. The mean age (± SD) of the patients was 46.49±18.33 years. The total number of ERCP procedures performed was 71. Thirty-four of these were performed in the postoperative period and 37 either preoperatively or on patients who were not operated. Regarding the indications, 38 procedures were performed because of biliary obstruction either before or after the operation, 28 were performed postoperatively because of bile leakage, and 5 were performed before surgery because of magnetic resonance cholangiopancreatography (MRCP) findings revealing communication between the cysts and the biliary tract. The mean duration between surgery and ERCP was 15.62±16.12 (6-90) days.

Majority of the patients (49 of the 63 total) had cysts in the right lobe of the liver. Only eight patients had cysts in the left lobe whereas in six patients, both lobes contained *echinococcus* cysts.

Table 1 lists the therapeutic procedures performed during ERCP for each ERCP indication. The most common procedure was sphincterotomy and balloon application, performed in 40 of the 71 ERCP procedures.

The mean diameter of the common bile duct was 10.19±4.44 mm as measured by ERCP. When calculated separately for each indication, the mean diameter of the common bile duct for biliary obstruction, bile leakage and preoperative diagnosis of intrabiliary rupture were 12.79±3.88 mm, 7.16±3.04 mm and 7±1.87 mm, respectively. Patients with biliary obstruction had a significantly more dilated common bile duct compared to the other patients (p<0.001).

Of the 27 patients who had surgery for CE followed by ERCP, 22 had endocystectomy with capitonnage; 3 had puncture, aspiration, injection and reaspiration, and 2 had endocystectomy with partial pericystectomy and omentoplication.

Levels of total and direct bilirubin, gamma-glutamyl transferase and alkaline phosphatase before and after the ERCP procedures were compared and a statistically significant decrease after ERCP was found in all 4 parameters (p <0.001 for all variables) (Table 2).

Eight patients required ERCP to be performed twice because of incomplete success in the first attempt. Of these, 4 patients had bile leakage after surgery, 3 had obstructive jaundice in the postoperative

Table 1. Distribution of therapeutic procedures performed during endoscopic retrograde cholangiopancreatography for each endoscopic retrograde cholangiopancreatography indication

ERCP procedures	Indications for ERCP		
	Biliary obstruction (n)	Bile leakage (n)	Radiological findings suggesting intrabiliary rupture (n)
Sphincterotomy alone	1	0	1
Sphincterotomy and biliary stent	5	10	0
Sphincterotomy and hydatic membrane extraction	1	3	0
Balloon application and biliary stent	4	4	0
Sphincterotomy and pus drainage	0	0	0
Sphincterotomy, hydatic membrane extraction and pus drainage	3	0	0
Sphincterotomy and balloon application	24	11	4

ERCP: endoscopic retrograde cholangiopancreatography

Table 2. The comparison of laboratory findings before and after the endoscopic retrograde cholangiopancreatography procedures

	Before ERCP	After ERCP	p
Total bilirubin (mg/dL) (mean ± SD)	3.62±3.17	1.18±0.69	<0.001
Direct bilirubin (mg/dL) (mean ± SD)	2.31±2.29	0.65±0.43	<0.001
GGT (U/L) (mean ± SD)	272.26±244.1	119.25±74.09	<0.001
ALP (U/L) (mean ± SD)	228.47±161.07	109.12±71.2	<0.001

ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, ERCP: endoscopic retrograde cholangiopancreatography

period, and 1 had obstructive jaundice in the preoperative period. The mean duration for the closure of biliary fistula after ERCP was 19.29±10.64 days ranging from 3 to 50 days.

As complications of the ERCP procedure, three patients developed mild to moderate pancreatitis that was treated conservatively. ERCP was not successful in 4 of the 63 patients (6.3%). Three of these 4 patients underwent ERCP because of postoperative bile leakage and 1 because of obstructive jaundice in the postoperative period. Surgical intervention was the treatment of choice in case ERCP was not successful. For the patients with bile leakage, the bile ducts communicating with the cyst were ligated, with common bile duct exploration and repair over T-tube added in one patient. In a patient with obstructive jaundice, bile duct exploration and T-tube drainage were performed.

Discussion

CE most commonly infects the liver and although the disease progresses slowly and insidiously, it may have various acute complications such as jaundice and cholangitis as a result of external compression or rupture into the bile ducts due to the elevated pressure in the cyst during growth (9). Intrabiliary cyst rupture is the most common complication, with rates reported as high as 42% in some series (9,11).

The communication between the cyst and the biliary tract can be classified as major and minor communications. Minor communications are usually not detectable in the preoperative period. They do not cause any symptoms preoperatively but might result in bile leakage in the postoperative period. Conversely, major communications are observed in 3-17% of CE patients and are usually diagnosed preoperatively. Obstructive jaundice, biliary colic, cholangitis, liver abscesses, sepsis and anaphylaxis are possible complications that can develop in the preoperative period due to the passage of the cystic content into the bile ducts (9,12,13).

ERCP has many uses in CE patients, including treatment of preoperative or postoperative biliary obstruction, treatment of biliary fistulae, prophylactic preoperative endoscopic sphincterotomy to prevent bile leakages in the postoperative period, and as a preoperative diagnostic tool (13-15).

However, the routine use of prophylactic endoscopic sphincterotomy (ES) for uncomplicated CE is not universally accepted. While some authors support the routine use of preoperative ERCP for prophylactic ES to reduce postoperative complications in uncomplicated cysts, others recommend that the preoperative use of ERCP is restricted to diagnostic purposes in demonstrating the anatomy of the bile ducts and their relationship with the cysts (9,14,16,17). Also of note is that the increasingly widespread use of MRCP provides a non-invasive alternative to ERCP for diagnostic purposes without the risk of potentially severe complications related to ERCP (9,18). In our study, MRCP was performed preoperatively in all patients and prophylactic ERCP for ES was performed in only five patients for whom rupture of the cyst into the biliary tract was radiologically demonstrated. Some studies showed that ERCP was used even in routine procedure to reduce post-operative complications. Bile fistulae can be observed in patients, and some of the fistulae will close spontaneously even though ES has not been performed (9,16).

The reported success rate of ERCP in the treatment of biliary obstructions observed in cholangiography prior to CE surgery is 80-100% (9,19). Sphincterotomy, extraction of cystic content using balloon or basket catheters, nasobiliary drainage and biliary stenting are possible treatment options. In our study, the complaints of all 31 patients with biliary obstruction were resolved after ERCP was performed preoperatively.

ERCP is an effective method for the treatment of obstructive jaundice and biliary fistulae which are the most common complications in the early postoperative period of CE surgery (5,11,14,20,21). ES alone is usually not adequate for the treatment of obstructive jaundice; extraction of cystic contents from the common bile duct and even biliary stenting might be necessary (22). One study reported the management of seven patients with CE developing obstructive jaundice and cholangitis after surgery, who were treated by ERCP. Within 36 hours of ES and clearing of the biliary tract of debris, normal bile flow was achieved and symptoms related to biliary obstruction were resolved (23). In our series, ERCP was performed in three patients in the postoperative period for biliary obstruction. Two of the patients were successfully treated by ES and extraction of cystic contents while the third patient underwent surgery because of failure of endoscopic treatment.

Bile leaks are encountered more frequently in the early postoperative period, with the output decreasing after the 10th postoperative day. However, it is difficult to consistently predict whether the leakage will continue or not. A biliary fistula with high output which is not steadily decreasing rarely closes spontaneously (24,25). In our series, ERCP for bile leak was performed for 27 patients, of whom 8 were within the first 10 days of the postoperative period as the output of leakage was high and spontaneous closure was not anticipated.

Surgery has traditionally been the standard treatment of fistulae not closing spontaneously. Thanks to advances in the field of endoscopic procedures, ERCP has become the first line treatment as it is not hindered by the difficulties of redo surgery such as adhesion and inflammation of tissues in the surgical field (17,26). The mechanism

of action of ERCP in treating biliary fistulae is to reduce the pressure in the bile ducts, which directs the bile flow to the duodenum and accelerates spontaneous closure (20,27,28). Delay in performing ERCP in high-output fistulae may result in infectious complications and cause the fistulae to become chronic (24,25). The success rate of ERCP in the treatment of biliary fistulae has been reported as high as 90% (14). Numerous studies in the literature have reported spontaneous closure of biliary fistulae after ERCP within 3 to 43 days (29,30). One study has reported that all cases of biliary fistulae were closed within 26 days following ES (14). In another study, a total of 46 ERCPs were performed on patients who were operated for CE and who developed postoperative biliary leakage. All cases of biliary leakage ceased in 2-21 days. The most commonly performed procedure in that study was ES (23). In our study, bile leaks were closed in an average of 19 days after ERCP, which is consistent with the literature. While ES was the most frequent procedure among ERCPs performed for postoperative bile leaks, which is in parallel with the literature, our series differed in that ES was combined with other procedures. We believe that combining ES with other procedures might be useful in avoiding the requirement for additional ERCPs due to inadequate treatment by ES alone. In addition, surgical treatment for biliary leakage was needed in three patients (12.5% of the total 24) as ERCP was not successful.

Conclusion

For the management of CE patients, ERCP is a useful tool for intrabiliary rupture of cysts used in the preoperative period for both diagnostic and therapeutic purposes. It is also an effective method for the treatment of biliary obstruction and bile leaks in the postoperative period, which can avoid unnecessary surgery. MRCP is a safe and viable alternative to ERCP for the diagnosis of minor communications between the cysts and the biliary tract which ERCP might fail to demonstrate. For patients with high-output biliary fistulae and obstructive jaundice, ES combined with biliary stenting or common bile duct exploration with a balloon catheter is effective at the preoperative and postoperative period. ERCP is a minimally invasive procedure that can be utilized safely and effectively; therefore, it should be the first line of treatment for the mechanical complications of CE.

Acknowledgements: This research did not receive any grants from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics

Ethics Committee Approval: It was obtained of by the University of Health Sciences Turkey, İstanbul University Training and Research Hospital (decision no: 2018, date: 11.10.2019).

Informed Consent: Informed consent from all patients were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - E.Ç., H.B.; Concept - E.Ç.; Design: E.Ç., H.B.; Data Collection or Processing - E.Ç., H.B.; Analysis or Interpretation - E.Ç., H.B.; Literature Search - E.Ç.; Writing: E.Ç., H.B.

Conflict of Interest: The authors declare that they have no conflicts of interest.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Eckert J, Deplazes P. Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. Clin Microbiol Rev 2004; 17: 107-35.
2. Zhang W, McManus DP. Recent advances in the immunology and diagnosis of echinococcosis. FEMS Immunol Med Microbiol 2006; 47: 24-41.
3. Işık A , Fırat D , Korkmaz S , Demiryıldız İ , Yılmaz İ . Atipik Prezente Kist Hidatik: Pankreas Başında Kitle. Sakarya Tıp Dergisi . 2018;8:149-52.
4. Mihmanli M, Idiz UO, Kaya C, Demir U, Bostanci O, Omeroglu S, et al. Current status of diagnosis and treatment of hepatic echinococcosis. World J Hepatol. 2016; 8: 1169-81.
5. Cicek B, Parlak E, Disibeyaz S, Oguz D, Cengiz C, Sahin B. Endoscopic therapy of hepatic hydatid cyst disease in preoperative and postoperative settings. Dig Dis Sci 2007; 52: 931-5.
6. Junghanss T, da Silva AM, Horton J, Chiodini PL, Brunetti E. Clinical management of cystic echinococcosis: state of the art, problems, and perspectives. Am J Trop Med Hyg 2008; 79: 301-11.
7. Belhassen-García M, Romero-Alegria A, Velasco-Tirado V, Alonso-Sardón M, Lopez-Bernus A, Alvela-Suarez L, et al. Study of hydatidosis-attributed mortality in endemic area. PLoS One 2014; 9: e91342.
8. Manzano-Román R, Sánchez-Ovejero C, Hernández-González A, Casulli A, Siles-Lucas M. Serological Diagnosis and Follow-Up of Human Cystic Echinococcosis: A New Hope for the Future? Biomed Res Int 2015; 2015: 428205.
9. Dolay K, Akbulut S. Role of endoscopic retrograde cholangiopancreatography in the management of hepatic hydatid disease. World J Gastroenterol. 2014; 20: 15253-61.
10. Dew H. Some complications of hydatid disease. Br J Surg 1930; 18: 275-93.
11. Lewall DB, McCorkell SJ. Rupture of echinococcal cysts: diagnosis, classification, and clinical implications. AJR Am J Roentgenol 1986; 146: 391-4.
12. Işık A, Sayar İ, Gülhan B, Fırat D. Fascioliasis: A Rare Case Mimicking Cholelithiasis. South. Clin. Ist. Euras 2016; 27: 145-6.
13. Deniz Fırat113. el-Tahir MI, Omojola MF, Malatani T, al-Saigh AH, Ogunbiyi OA. Hydatid disease of the liver: evaluation of ultrasound and computed tomography. Br J Radiol 1992; 65: 390-2.
14. El Malki HO, El Mejdoubi Y, Souadka A, Mohsine R, Ifrine L, Abouqal R, et al. Predictive model of biliocystic communication in liver hydatid cysts using classification and regression tree analysis. BMC Surg 2010; 10: 16.
15. Ozaslan E, Bayraktar Y. Endoscopic therapy in the management of hepatobiliary hydatid disease. J Clin Gastroenterol 2002; 35: 160-74.
16. Kilic M, Yoldas O, Koc M, Keskek M, Karakose N, Ertan T, et al. Can biliary-cyst communication be predicted before surgery for hepatic hydatid disease: does size matter? Am J Surg 2008; 196: 732-5.
17. Lygidakis NJ. Diagnosis and treatment of intrabiliary rupture of hydatid cyst of the liver. Arch Surg 1983; 118: 1186-9.
18. Kumar R, Reddy SN, Thulkar S. Intrabiliary rupture of hydatid cyst: diagnosis with MRI and hepatobiliary isotope study. Br J Radiol 2002; 75: 271-4.
19. Becker K, Frieling T, Saleh A, Häussinger D. Resolution of hydatid liver cyst by spontaneous rupture into the biliary tract. J Hepatol 1997; 26: 1408-12.
20. Giouleme O, Nikolaidis N, Zezos P, Budas K, Katsinelos P, Vasiliadis T, et al. Treatment of complications of hepatic hydatid disease by ERCP. Gastrointest Endosc 2001; 54: 508-10.

21. Somani SK, Srivastava AP. Resolution of hepatic hydatid cyst with biliary communication with ERCP. J Gastroint Dig Syst 2012; 2: 114.

22. al Karawi MA, Yasawy MI, el Shiekh Mohamed AR. Endoscopic management of biliary hydatid disease: report on six cases. Endoscopy 1991; 23: 278-81.

23. Akaydin M, Erozgen F, Ersoy YE, Birol S, Kaplan R. Treatment of hepatic hydatid disease complications using endoscopic retrograde cholangiopancreatography procedures. Can J Surg. 2012; 55: 244-8.

24. Zeybek N, Dede H, Balci D, Coskun AK, Ozerhan IH, Peker S, et al. Biliary fistula after treatment for hydatid disease of the liver: when to intervene. World J Gastroenterol 2013; 19: 355-61.

25. Dolay K, Akçakaya A, Soybir G, Cabioğlu N, Müslümanoğlu M, Iğci A, et al. Endoscopic sphincterotomy in the management of postoperative biliary fistula A complication of hepatic hydatid disease. Surg Endosc 2002; 16: 985-8.

26. Dawson JL, Stamatakis JD, Stringer MD, Williams R.. Surgical treatment of hepatic hydatid disease. Br J Surg 1988; 75: 946-50.

27. Bilsel Y, Bulut T, Yamaner S, Buyukuncu Y, Bugra D, Akyuz A, et al. ERCP in the diagnosis and management of complications after surgery for hepatic echinococcosis. Gastrointest Endosc 2003; 57: 210-3.

28. Inal M, Soyupak S, Akgül E, Ezici H. Percutaneous transhepatic endobiliary drainage of hepatic hydatid cyst with rupture into the biliary system: an unusual route for drainage. Cardiovasc Intervent Radiol 2002; 25: 437-9.

29. Vignote ML, Miño G, de la Mata M. de Dios JF, Gomez F. Endoscopic sphincterotomy in hepatic hydatid disease open to the biliary tree. Br J Surg 1990; 77: 30-1.

30. Spiliadis C, Georgopoulos S, Dailianas A, Konstantinidis A, Rimikis M, Skandalis N. The use of ERCP in the study of patients with hepatic echinococcosis before and after surgical intervention. Gastrointest Endosc 1996; 43: 575-9.

İstanbul Med J 2020; 21(2): 145-7
DOI: 10.4274/imj.galenos.2020.78466

Giant Polyostotic Fibrous Dysplasia: F-18-flourodeoxyglucose Positron Emission Tomography/Computerized Tomography and Radiologic Findings

Dev Poliostotik Fibröz Displazi: F-18-florodeoksiglukoz Pozitron Emisyon Tomografi/Bilgisayarlı Tomografi ve Radyolojik Bulgular

Melis Baykara Ulusan[1], Tevfik Fikret Çermik[2]

[1]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Department of Radiology, İstanbul, Turkey
[2]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Department of Nuclear Medicine, İstanbul, Turkey

ABSTRACT

A 40-year-old man with polyostotic fibrous dysplasia underwent F-18-flourodeoxyglucose (FDG) positron emission tomography/computed tomography imaging to rule out a possible malignancy. It showed lytic, expansile and moderate to high hypermetabolic bone lesions with "ground glass" pattern and surrounded by a distinct rim of reactive bone in the right temporal bone, 8th and 9th ribs on the left hemithorax, T8 vertebra and sacrum. As some lesions had high F-18-FDG uptake, it was recommended to repeat the histopathological examination with suspicion of sarcomatous pathology. A second biopsy of the mass on the 8th rib was confirmed the diagnosis of fibrous dysplasia.

Keywords: Polyostotic fibrous dysplasia, F-18 FDG PET/CT, CT, MRI

ÖZ

Poliostotik fibröz displazili 40 yaşında erkek hastaya, olası bir maligniteyi ekarte etmek için F-18-florodeoksiglukoz (FDG) pozitron emisyon tomografisi-bilgisayarlı tomografi görüntülemesi yapılmıştır. Yapılan incelemede sağ temporal kemikte, sol 8. ve 9. kostalarda, T8 vertebra ve sakrumda litik, ekspansil, "buzlu cam" paterninde reaktif sklerotik rim ile çevrili orta-yüksek metabolizma gösteren lezyonlar saptanmıştır. Bazı lezyonlarda F-18-FDG tutulumu yüksek olduğundan, sarkomatöz patoloji şüphesiyle histopatolojik incelemenin tekrarlanması önerilmiştir. Sekizinci kostadaki kitleden yapılan ikinci biyopside fibröz displazi tanısı doğrulanmıştır.

Anahtar Kelimeler: Poliostotik fibröz displazi, F-18 FDG PET/BT, BT, MR

Introduction

Fibrous dysplasia (FD) is a benign congenital non-neoplastic condition of children and young adults characterized by the replacement of normal cancellous bone by abnormal fibrous tissue. FD can affect one bone (monostotic, 80%) or multiple bones (polyostotic, 20%). When polyostotic, it tends to be unilateral. It can literally affect all bones but is mainly seen in long bones, craniofacial bones, and ribs. The polyostotic form can be seen in McCune-Albright and Mazabraud syndrome with endocrinopathies (1,2).

Lesions of FD continue to grow until bone maturation occurs; they regress in adulthood or remain silent. FD is usually an incidental finding in adults and asymptomatic but it may become symptomatic with pathological fractures, secondary aneurysmatic bone cysts and very rarely with malignant transformation (0.5%) (3,4).

The diagnoses of FD and its complications are based on physical, radiological, and histopathological examination. The use of the whole body F-18-flourodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) imaging is not rare because FD shows various FDG uptake and can mimic multiple bone metastases, especially in polyostotic form (5,6).

This article presents a case of polyostotic FD in a patient with the imaging and histopathological features, diagnosed during the investigation of a giant rib mass.

Case Report

A 40-year-old man presented with chest pain and a big, firm swelling on his left flank area. Magnetic resonance imaging (MRI) examination images showed a heterogenous, expansile bone mass involving the left eighth and ninth ribs and T8 vertebra. The lesion was expanding from

Address for Correspondence/Yazışma Adresi: Melis Baykara Ulusan MD, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Department of Radiology, İstanbul, Turkey
Phone: +90 535 272 58 22 **E-mail:** melis@baykara.com **ORCID ID:** orcid.org/0000-0002-4728-1802

Cite this article as/Atıf: Baykara Ulusan M, Cermik TF. Giant Polyostotic Fibrous Dysplasia: F-18 FDG PET/CT and Radiologic Findings. İstanbul Med J 2020; 21(2): 145-7.

Received/Geliş Tarihi: 14.11.2019
Accepted/Kabul Tarihi: 06.01.2020

the bottom of left scapula level posteriorly to the midclavicular line anteroinferiorly. The bone mass showed heterogenous intermediate signal on T2W images with cystic areas and mainly heterogenous avid enhancement with concomitant mild enhancement areas on postcontrast T1W images (Figure 1). The lesion was limited to the bone without a soft tissue component and mostly well-demarcated. However, giant cell bone tumor could not be excluded due to vertebral destruction and signal similarities. Aneurysmal bone cyst findings and some bone-forming regions were reported in the first histopathological examination. No primary tumor was found but FD and giant cell tumor of bone were highlighted as differential diagnosis.

The patient was referred for F-18-FDG PET/CT imaging to rule out a possible malignancy. It showed lytic, expansile and moderate to intense hypermetabolic bone lesions with "ground glass" pattern and surrounded by a distinct rim of reactive bone in the right temporal bone, left hemithorax, left T8 vertebra and sacrum (Figure 1-2). The F-18-FDG uptake in the right temporal bone was variable, with the maximum standardized uptake value (SUV_{max}) of 11.9. The right hemithorax lesions appeared to arise from the left eighth and ninth ribs (SUV_{max}: 15.1), with the involvement of the T8 vertebra (SUV_{max}: 9.6). FDG-avid lesions were also noted in bilateral sacral wings with a maximum SUV_{max} of 9.8 in the right sacral wing. As the heterogeneous and intense F-18-FDG uptake in the lesions raised concern of sarcomatous degeneration, secondary histopathological examination was recommended.

On microscopic examination, the tissue revealed irregular, bony trabeculae in a collagenous stroma with no evidence of osteoblastic rimming and lamellar bone were evident. The mesenchymal stroma surrounding the dysplastic trabeculae was relatively hypocellular. Both features were characteristics of FD. A diagnosis of polyostotic FD was made with a second biopsy of the rib mass. Informed consent was obtained from the patient to use his data in this study.

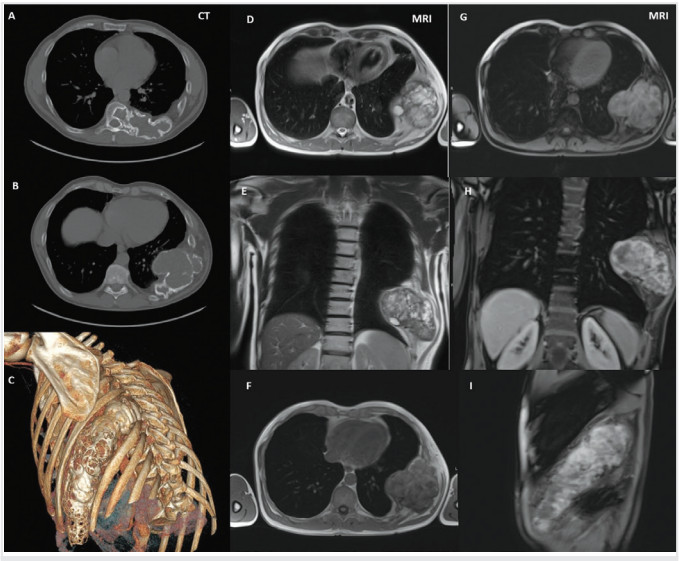

Figure 1. On the computerized tomography images, lesion affects the posterior ends of the eighth and ninth ribs, and extends to the eighth vertebral body through the costovertebral joint (A, B). Volume rendered images demonstrating heterogenous expansion of whole rib (C). In magnetic resonance imaging T2W axial and coronal images, expanse rib mass is heterogeneously hyperintense. It abuts lung. On unenhanced magnetic resonance imaging T1-weighted images the lesion is isointense with bone (D, E, F). On axial, coronal and sagittal enhanced series showing avid heterogenous enhancement on the magnetic resonance imaging images (G, H, I)

Discussion

FD accounts for approximately 7% of benign bone tumors and is caused by an activating mutation of *GNAS* gene, encoding α-subunit of stimulatory G protein seen in both mono and polyostotic forms, resulting in abnormal osteoblastic differentiation and increased bone turnover (2,6).

The gross histological picture of FD constitutes a firm solid tan-gray mass which gradually replaces the medullary cavity and the surrounding cortical bone. It consists of uniformly cellular fibrous tissue, cytologically bland spindle cells with sparse mitotic activity. Irregular curvilinear woven bones are also present without any significant osteoblastic rimming (7).

A sudden increase in the size of a previous FD maybe due to a superimposed aneurismatic bone cyst or malignant transformation. Malignant transformation is rarely seen with an incidence of 0.5% in patients with FD. The incidence increases in patients with McCune-Albright syndrome by nearly 4%. It may develop after radiation therapy. Although the most common malign transformation is osteosarcoma, fibrosarcoma and chondrosarcoma can also be seen. Radiographic changes suggesting malignancy are lytic regions, intralesional calcification, periosteal reaction, and a cortical disruption (4,8-13). Radiologic differential diagnoses of FD include paget disease (mostly skull), simple bone cyst, giant cell tumor (mostly pelvis), non-ossifying fibroma, neurofibromatosis, and osteoblastoma. In tibia, when originates in cortex, FD is indistinguishable from adamantinoma. This distinction can be made pathologically (5,11,12,14).

X-ray imaging may show not specific but characteristic features. The density of lesions varies from lytic to sclerotic. Mostly central lesions show

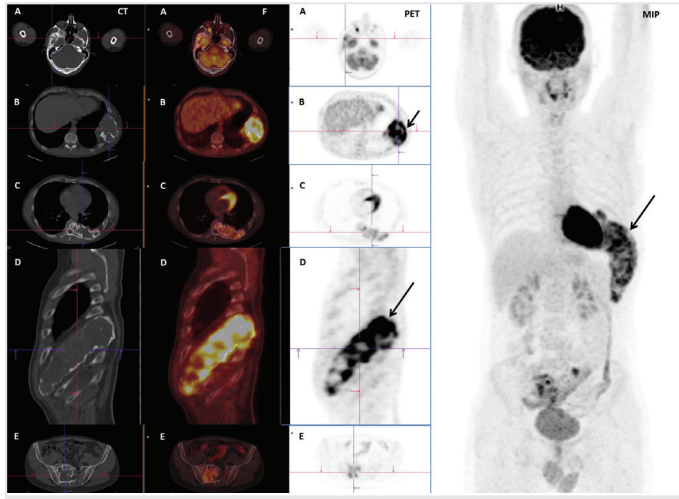

Figure 2. Positron emission tomography / computerized tomography images showed heterogeneously moderate or high pathological fluorodeoxyglucose uptake in lesions located in the right temporal bone, the 8th and 9th ribs at left hemithorax, 8th thoracic vertebral body and sacrum (A, B, C, D, E and MIP). The most intense uptake was observed in lesion along the 8th rib in the left hemithorax (arrows) (MIP: maximum intensity projection, F: fusion).

enlargement of medulla, deformity with endosteal thinning, increased trabeculation to a characteristic "ground-glass" appearance which is formed by a mixture of immature bone and fibrous tissues (2,4,8).

The conventional three-phase bone scan shows markedly increased uptake of tracer in both perfusion and the delayed phase. This high uptake is related to the bone turnover characteristic for the disorder. CT is still the best technique for delineating the extent of involvement with the typical ground glass pattern of the bone. The lesion is surrounded by a reactive sclerotic bone (5,14).

F-18-FDG PET/CT imaging is also used to make a differential diagnosis. Benign bone lesions like giant cell tumor of bone can show high F-18-FDG uptake, and the SUV_{max} values vary according to the different stages of disease and remodeling (15).

In cases of FD, a highly variable F-18-FDG uptake was identified, between none and avid, especially in cases mimicking metastatic disease (3,16-18). The highest SUV_{max} value of 15.1 for a benign FD in our study was higher than most of the benign and some of the malignant lesions reported in the literature (18,19). The report of Su et al. (19) and many other publications have discussed the necessity and usefulness of PET/CT. The lesion diversity among the body parts and the distribution of hyper- and hypometabolic areas inside the lesions made it impossible to diagnose a lesion by PET/CT. They argued that the correct diagnosis could only be made by biopsy (17).

In patients who were followed up with FD, focal increase in SUV_{max} was evaluated in favor of early malignant transformation, while some authors reported that patients with benign proven lesions showed F-18-FDG activity changes in follow-up examinations (15).

CT and MRI imaging features in our case suggested FD in the first differential diagnosis when multiple lesions were considered. The 40-year-old patient presented with a growing lesion, and high F-18-FDG uptake of the lesions compared to the literature increased the suspicion of malignant transformation. When both pathology results are evaluated together, this patient with undiagnosed polyostotic FD is likely to become symptomatic due to aneurysmal bone cyst secondary to the left hemithorax lesion. In addition, repeat biopsy results from different locations were not found in favor of malignant transformation. This case shows the potential pitfalls in the interpretation of F-18-FDG PET/CT when multiple increased uptake is seen in the skeleton, particularly in the context of suspected malignancy.

In conclusion, on F-18-FDG PET/CT imaging, the quantity of radiopharmaceutical uptake of FD lesions does not distinguish between a benign lesion and a lesion that has undergone malignant transformation. However, PET/CT imaging can lead to biopsy by identifying the maximum F-18-FDG-avid bone lesions and it may show multifocality of an undiagnosed polyostotic FD. And also, PET/CT may be useful for long-term follow-up of low F-18-FDG-avid FD lesions.

Informed Consent: Informed consent was obtained from the patient to use his data in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - M.B.U., T.F.Ç.; Concept - M.B.U., T.F.Ç.; Design - M.B.U., T.F.Ç.; Data Collection and/or Processing - M.B.U., T.F.Ç.; Analysis and/ or Interpretation - M.B.U., T.F.Ç.; Literature Search - M.B.U., T.F.Ç.; Writing Manuscript - M.B.U., T.F.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Mandell, Jacob. Core radiology: A visual approach to diagnostic imaging. University Printing House, Cambridge: Cambridge University Press, 2013. ISBN 978-1-107-67968-9, Paperback 376-78.
2. Manaster, B. J. Diagnostic imaging. Musculoskeletal: non-traumatic disease, Second edition. Salt Lake City, UT: Elsevier, Inc., 2016. ISBN 978-0-323-39252-5. Pages:376-82.
3. Makis W, Probst S. Extensive polyostotic fibrous dysplasia evaluated for malignant transformation with 99mTc-MDP bone scan and 18F-FDG PET/CT. BJR Case Rep 2016; 2: 20150440.
4. Khanna V, Shori A. Case Report JOJ Case Stud Polyostotic Fibrous Dysplasia: A Case Report. JOJ Case Stud 2017;3. doi:10.19080/JOJCS.2017.03.555601.
5. Aras M, Ones T, Dane F, Nosheri O, Inanir S, Erdil TY, et al. False Positive FDG PET/CT Resulting from Fibrous Dysplasia of the Bone in the Work-Up of a Patient with Bladder Cancer: Case Report and Review of the Literature. Iran J Radiol 2012; 10: 41-4.
6. Hosalkar RM, Pathak J, Swain N, Mohanty N. Pagetoid polyostotic fibrous dysplasia. BMJ Case Rep 2015; 2015. pii: bcr2014209149.
7. Kamaleshwaran KK, Joseph J, Kalarikal R, Shinto AS. Image Findings of Polyostotic Fibrous Dysplasia Mimicking Metastasis in F-18 FDG Positron Emission Tomography/Computed Tomography. Indian J Nucl Med 2017; 32: 137-9.
8. Traibi A, El Oueriachi F, El Hammoumi M, Al Bouzidi A, Kabiri el H. Monostotic fibrous dysplasia of the ribs. Interact Cardiovasc Thorac Surg 2012; 14: 41-3.
9. Hughes EK, James SLJ, Butt S, Davies AM, Saifuddin A. Benign primary tumours of the ribs. Clin Radiol 2006; 61: 314-22.
10. Diercks RL, Sauter AJ, Mallens WM. Aneurysmal bone cyst in association with fibrous dysplasia. A case report. J Bone Joint Surg Br 1986; 68: 144-6.
11. Tateishi U, Gladish GW, Kusumoto M, Hasegawa T, Yokoyama R, Tsuchiya R, et al. Chest Wall Tumors: Radiologic Findings and Pathologic Correlation. Radio Graphics 2003; 23: 1477-90.
12. DiCaprio MR, Enneking WF. Fibrous Dysplasia.Pathophysiology, Evaluation, and Treatment. J Bone Jt Surg 2005; 87: 1848.
13. Fitzpatrick KA, Taljanovic MS, Speer DP, Graham AR, Jacobson JA, Barnes GR, et al. Imaging Findings of Fibrous Dysplasia with Histopathologic and Intraoperative Correlation. Am J Roentgenol 2004; 182: 1389-98.
14. Kransdorf MJ, Moser RP, Gilkey FW. Fibrous dysplasia. Radiographics 1990; 10: 519-37.
15. Berrebi O, Steiner C, Keller A, Rougemont A-L, Ratib O. F-18 Fluorodeoxyglucose (FDG) PET in the Diagnosis of Malignant Transformation of Fibrous Dysplasia in the Pelvic Bones. Clin Nucl Med 2008; 33: 469-71.
16. von Falck C, Rosenthal H, Laenger F, Lotz J, Knapp WH, Galanski M. Avid uptake of [18F]-FDG in fibrous dysplasia can mimic skeletal involvement in Hodgkin's disease. Eur J Nucl Med Mol Imaging 2008; 35: 223.
17. Basu S, Baghel N, Puri A, Shet T, Merchant N. 18F-FDG avid lesion due to coexistent fibrous dysplasia in a child of embryonal rhabdomyosarcoma: Source of false positive FDG-PET. J Cancer Res Ther 2010; 6: 92.
18. Charest M, Singnurkar A, Hickeson M, Novales JA, Derbekyan V. Intensity of FDG uptake is not everything: synchronous liposarcoma and fibrous dysplasia in the same patient on FDG PET-CT imaging. Clin Nucl Med 2008; 33: 455–8.
19. Su MG, Tian R, Fan QP, Tian Y, Li FL, Li L, et al. Recognition of fibrous dysplasia of bone mimicking skeletal metastasis on 18F-FDG PET/CT imaging. Skeletal Radiol 2011; 40: 295–302.

İstanbul Med J 2020; 21(2): 148-51
DOI: 10.4274/imj.galenos.2020.99907

A Rare Cause of Acute Abdomen: Small Intestine Perforation Due to Metastasis of Lung Cancer

Nadir Bir Akut Batın Sendromu Sebebi: Akciğer Kanserinin İnce Barsak Metastazına Sekonder Perforasyon

Elchin Alizade, Mehmet İlhan, Baran Mollavelioğlu, İsmail Cem Sormaz, Erhan Eröz, Recep Erçin Sönmez
İstanbul University Faculty of Medicine, Department of General Surgery, İstanbul, Turkey

ABSTRACT

Approximately 50% of lung cancer patients have distant metastases at diagnosis. Intestinal metastasis of lung cancer is quite rare and mostly asymptomatic as well. A 65-year-old male patient had been referred to a peripheral hospital with the complaint of abdominal pain. A mass lesion located on the apex of the right lung had been detected; as well as brain and abdominal metastases had been documented and oncotherapy had been planned accordingly. Several days later, he was referred to emergency surgery department due to the symptoms of acute abdomen. Tests showed hollow organ perforation, and the patient underwent operation later on. Perforation secondary to metastatic small intestine implant was observed per-operatively and so, small bowel resection was performed accordingly. The pathology revealed metastatic adenocarcinoma of lung cancer. The prognosis of lung cancer patients having bowel metastasis is poor with a low rate of survival. In this study, we aimed to present a case of metastatic lung cancer patient who had Acute Abdomen syndrome due to perforation secondary to small bowel metastasis.

Keywords: Acute abdomen, intestinal perforation, metastatic lung cancer

ÖZ

Akciğer kanseri hastalarının yaklaşık %50'sinde tanı sırasında uzak metastazlar vardır. Akciğer kanserinin barsak metastazı oldukça nadirdir ve çoğunlukla asemptomatiktir. Altmış beş yaşında erkek hastanın karın ağrısı şikayeti ile başvurduğu periferik bir hastanede yapılan tetkiklerinde sağ akciğer apeksinde yer alan kitle lezyonu saptandı; beyin ve abdominal metastazları da bulunan hastaya onkolojik tedavi planlandı. Birkaç gün sonra, akut batın semptomları nedeniyle acil cerrahi birimine başvurdu. Yapılan tetkikler sonucu içi boş organ perforasyonu saptandı ve hasta ameliyata alındı. Operasyonda metastatik ince barsak implantına sekonder perforasyon görüldü ve bu nedenle ince barsak rezeksiyonu yapıldı. Patolojik değerlendirmesi, akciğer kanserinin metastatik adenokarsinomu olarak sonuçlandı. Barsak metastazı olan akciğer kanseri hastalarının prognozu kötü ve sağkalım oranı düşüktür. Bu çalışmada akciğer kanserinin ince barsak metastazına sekonder perforasyon nedeniyle Akut Batın sendromu gelişen bir hastayı sunmayı amaçladık.

Anahtar Kelimeler: Akut batın, ince barsak perforasyonu, metastatik akciğer kanseri

Introduction

Approximately 50% of lung cancer patients have distant metastases at diagnosis. The most common organ metastases are the brain, liver, bones and adrenals. Approximately one third of lung cancer patients have symptoms due to distant metastases. Intestinal metastasis of lung cancer is very rare and usually asymptomatic (1,2). Most of the lung cancers causing intestinal metastasis are squamous cell carcinomas according to literature and it is followed by large cell lung cancer. In 70% of cases, extra-intestinal metastases are seen along with small intestine. Generally, bowel perforation and obstruction of the cases can be observed.

Case

A 65-year-old male patient had been referred to a peripheral hospital because of abdominal pain. A mass lesion located on the apex of the right lung had been detected on his chest X-ray (Figure 1). Afterwards, further investigations had been done accordingly and many other widespread lesions had been observed located in brain and abdominal cavity which all were compatible with metastasis (Figure 2,3). The bronchoscopy procedure had been consistent with primary lung tumor. The biopsy confirmed adenocarcinoma. Radiotherapy along with anti-edema treatment (Dexamethasone 4*4 mg, Levetirasetam 2*500) had

Address for Correspondence/Yazışma Adresi: Elchin Alizade MD, İstanbul University Faculty of Medicine, Department of General Surgery, İstanbul, Turkey
Phone: +90 538 383 70 84 **E-mail:** drelializade@gmail.com **ORCID ID:** orcid.org/0000-0002-7404-9304

Cite this article as/Atıf: Alizade E, İlhan M, Mollavelioğlu B, Sormaz İC, Eröz E, Sönmez RE. A Rare Cause of Acute Abdomen: Small Intestine Perforation Due to Metastasis of Lung Cancer. İstanbul Med J 2020; 21(2): 148-51.

Received/Geliş Tarihi: 26.01.2019
Accepted/Kabul Tarihi: 31.01.2020

been given for brain metastases. His chemotherapy had been postponed since he had had pneumonia after bronchoscopy.

Later on, he was admitted to our emergency surgery department with the complaint of abdominal pain prolonging for 3-4 days which had aggravated for the last day. Physical examination revealed acute abdomen mimicking symptoms like widespread tenderness, defense and rebound during palpation. Plain graph showed free air under the right hemi-diaphragm. Oral/iv contrast-enhanced thoracic and abdominal computerized tomography (CT) revealed an image of pneumoperitoneum located mostly around anterior surface of the liver. No contrast extravasation was observed. Heterogenic mass lesion having an approximate diameter of 7*6 cm was detected on apical segment of the right lung (Figure 4).

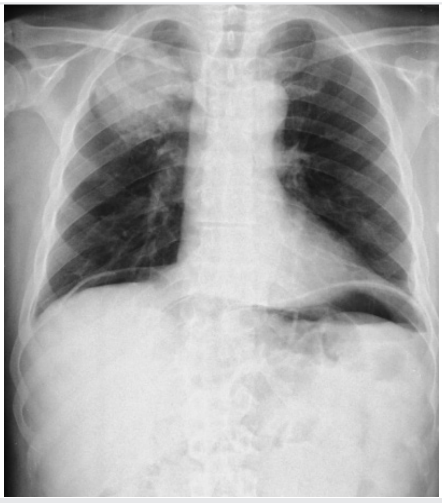

Figure 1. Posteroanterior chest X-ray showing free air under the diaphragm. Blue arrow showing the mass lesion located on the apex of the right lobe of the lung

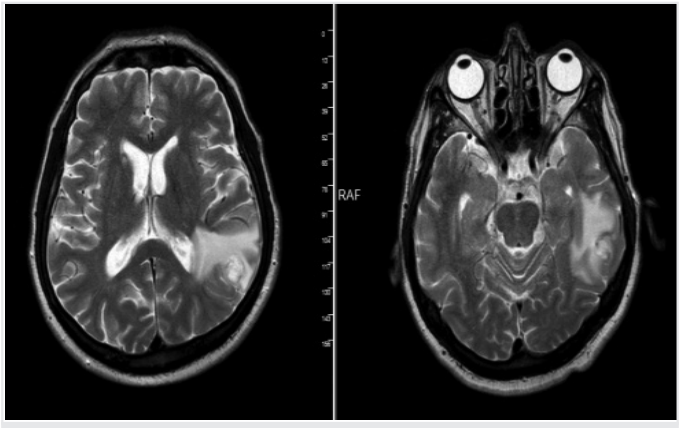

Figure 2. Metastases in the brain left parietal and temporal lobes

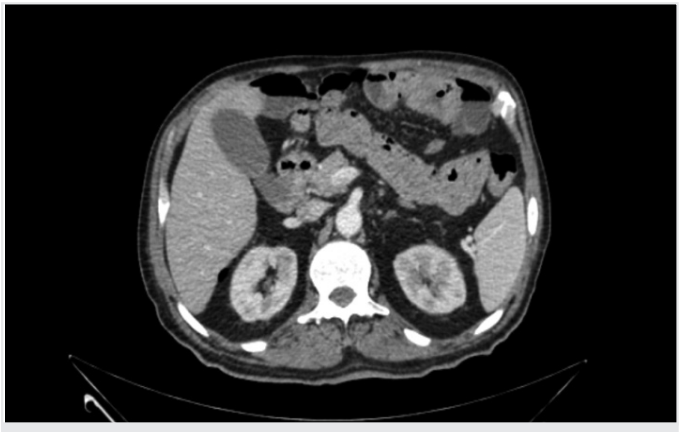

Figure 3. Small intestinal wall thickening surrounded by free air in left upper quadrant. Free air in the abdomen

Necessary blood samples were taken during admission, and laboratory values were as follows; Hb/Htc: 9.4/28.9 White blood cell: 7000 C-reactive protein: 80. A detailed informed consent had been taken from the patient and his relatives after giving information about the risks and complications. Later on, he underwent operation due to pre-op diagnosis of hollow organ perforation.

After a laparoscopic exploration, the operation was converted to laparotomy due to dens adhesions which prevented adequate exposure. Abdominal exploration revealed a micro-perforation located on the anti-mesenteric site of the small bowel which was 190 cm distal to Treitz ligament. Multiple implants were observed along the serosa of the small bowel. All small bowel segments beginning from Treitz ligament till the ileocecal valve were explored carefully. Perforated small bowel segment was resected, and functional end-to-end anastomosis with stapler was performed accordingly. Afterwards, the patient was taken to intensive care unit for post-operative follow-up.

The patient was taken to the ward on the following day. Oral intake was initiated on the second day of operation. The patient did not have any problems during the hospitalization period and was discharged uneventfully. The patient was referred to the oncology department for systemic chemotherapy. He died 4 months after the surgery because of terminal disease. Pathological findings were consistent with adenocarcinoma metastasis of lung cancer (Figure 5,6).

Discussion

The most common sites for distant metastasis of lung cancer are the lymph nodes, liver, adrenal glands, skeletal system, and brain respectively. Gastrointestinal metastases are very rare (3,4,5,6). It has

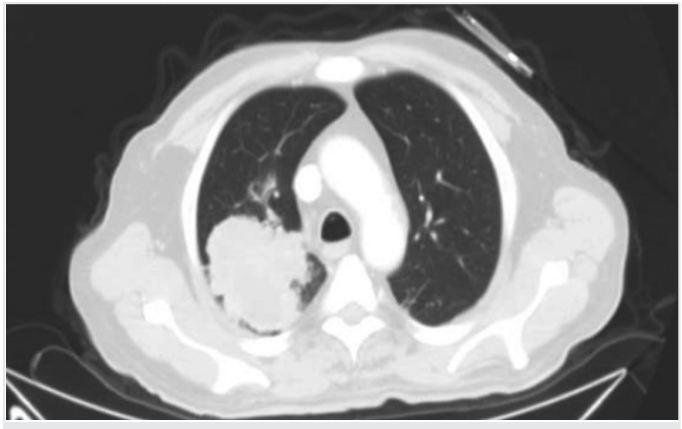

Figure 4. Heterogen mass lesion with 75*56 mm in widest place axially, starting from right lung

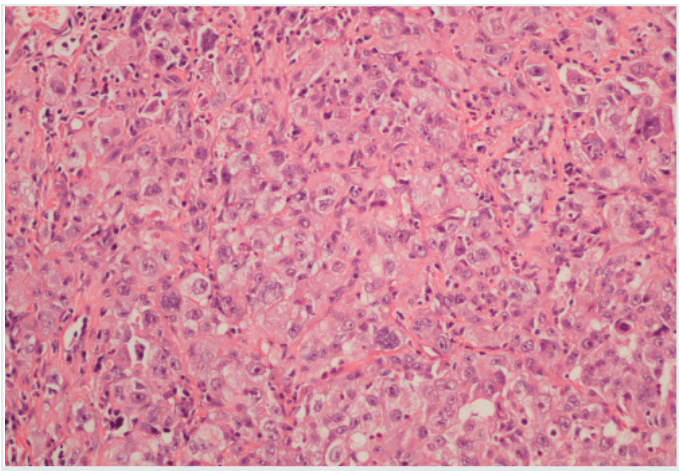

Figure 5. (A)X200. Hematoxylin and eosin. Lesion with prominent nuclear pleomorphism, nucleol distinction, wide eosinophilic and few clear cytoplasmic eithelioid cells. Small vacuoles are seen in cytoplasm, more prominent in some cells

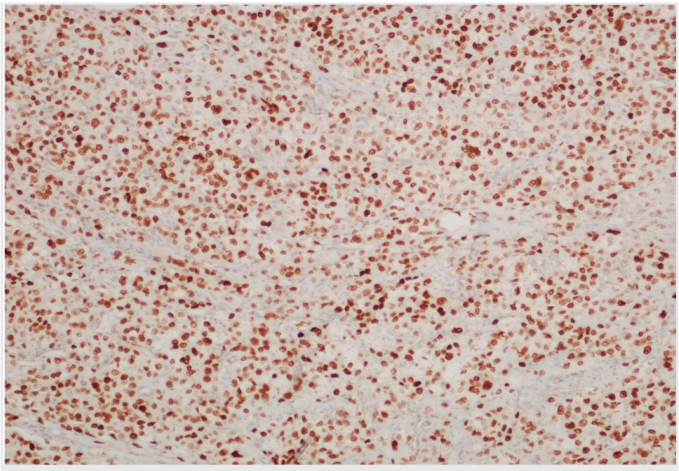

Figure 6. X100. Thyroid transcription factor-1 immunohistochemistry stain. The staining in the nucleus indicates that the tumor is of lung origin

been reported in some autopsy studies that it has a prevalence range between 4.7% and 14% (7,8). In the present study, we discussed the clinical course of an adult male patient having small bowel perforation due to metastasis originated from a lung cancer. According to our research in recent literature, about 1/3 of the intestinal metastases originated from lung cancers are asymptomatic, and the diagnosis is usually made following the autopsy. Tumor necrosis induced by chemotherapy has also been claimed to have led to perforation. Gastrointestinal system metastasis of lung tumors occur via hematogenic and/or lymphatic route. Most common symptoms are abdominal pain, nausea/vomiting, anemia and weight loss (9-11). These findings mostly occur after the diagnosis of the primary disease and, sometimes, are seen before or simultaneously with the diagnosis of the primary disease as in our case. Yang et al. (12) scanned 399 lung carcinoma cases between 2003 and 2005, and found six (1.77%) cases who had symptomatic gastrointestinal system metastasis. The diagnosis was made by using gastroscopy for three patients who had gastric metastasis and by colonoscopy for one patient (cecum involvement), and two patients underwent operation due to small bowel perforation and intussusception respectively (13,14).

Histological subtypes of bronchogenic carcinomas leading to metastasis differ among studies regarding theirs frequencies. In one study, it was observed that large cell carcinoma of lung metastasized more than the others, whereas in other studies, squamous subtype was to be found more aggressive regarding metastasis. Yang et al. (12) reported squamous cell lung carcinoma to be the most common type of lung cancer having distant metastasis (15-17).

It is difficult to diagnose intestinal metastasis at an early stage before serious complications occur (18). Conventional CT, which is mostly the preferred imaging modaliy, has a low sensitivity to detect small intestine metastases. In some instances, certain indirect findings such as intestinal intussusception are more informative.

No significant pathology was detected after the evaluations done by the peripheral center. The patient was referred to our institute with the persistent complaint of abdominal pain later on. Pathological flourodeoxyglucose uptake in the region fitting ileum on positron emission tomography was helpful reaching the diagnosis. It was not clear whether the lesion was a primary tumor of the gastrointestinal tract or a metastatic lesion (19). Diagnosis was established later on by immunohistochemical examination of the specimen.

Conclusion

The disease has a low rate of overall survey since it has an insidious clinical course despite distant metastasis mostly. Gastrointestinal metastases are very rare. It is difficult to diagnose intestinal metastasis at an early stage before complications occur. If the diagnosis is established at an early period, the life expectancy may be prolonged.

Informed consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - B.M., İ.C.S., E.E.; Concept - E.A., R.E.S.; Design - E.A., M.İ., R.E.S.; Data Collection and/or Processing - E.A.; Analysis and/ or Interpretation - E.A.; Literature Search - E.A.; Writing Manuscript - E.A.

Conflict of interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Hsing CT, Kim HY, Lee JH, Han JS, Lee JH, Chang JS, et al. Gastrointestinal metastasis from a primary adenocarcinoma of the lung presenting with acute abdominal pain. Korean J Gastroenterol 2012; 59: 382–5.
2. Akyildiz HY, Akcan AC, Sözüer E, Küçük C, Yilmaz N, Artiş T. Unusual causes of intestinal perforation and their surgical treatment. Ulus Travma Acil Cerrahi Derg 2009; 15: 579-83.
3. Di JZ, Peng JY, Wang ZG. Prevalence, clinicopathological characteristics, treatment, and prognosis of intestinal metastasis of primary lung cancer: A comprehensive review. Surg Oncol 2014; 23: 72-80.
4. McNeill PM, Wagman LD, Neifeld JP. Small bowel metastases from primary carcinoma of the lung. Cancer. 1987; 59: 1486-9.

5. Berger A, Cellier C, Daniel C, Kron C, Riquet M, Barbier JP, et al. Small bowel metastases from primary carcinoma of the lung: clinical findings and outcome. Am J Gastroenterol1999; 94: 1884-7.

6. Garwood RA, Sawyer MD, Ledesma EJ, Foley E, Claridge JA. A case and review of bowel perforation secondary to metastatic lung cancer. Am Surg 2005; 71: 110-6.

7. Mao Y, Yang D, He J, Krasna MJ. Epidemiology of Lung Cancer. Surg Oncol Clin N Am 2016; 25: 439-45.

8. Siegel RL, Miller KD, Jemal A. Cancer statistics 2017. CA Cancer J Clin. 2017; 67: 7-30.

9. Pezzuto A, Mariotta S, Fioretti F, Uccini S. Metastasis to the colon from lung cancer presenting with severe hyponatremia and dyspnea in a young male: A case report and review of the literature. Oncol Lett 2013; 5: 1477-80.

10. Jevremovic V, Abboud A, Krauss S. Colonic Metastasis with Anemia Leading to a Diagnosis of Primary Lung Adenocarcinoma. Case Rep Oncol Med 2016; 2016: 5275043.

11. Bouzbib C, Chaput U, Jarrin I, Lavergne-Slove A, Marteau P, Dray X. "Bleeding from gastroduodenal metastases as the first manifestation of lung adenocarcinoma. Endoscopy 2014; 46 Suppl 1 UCTN: E474-5.

12. Yang CJ, Hwang JJ, Kang WY, Chong IW, Wang TH, Sheu CC, et al. Gastrointestinal metastasis of primary lung carcinoma: clinical presentations and outcome. Lung Cancer J 2006; 54: 319-23.

13. Pratto D, Resial M, Wulfson A, Gennaro M, Brarda M, Schmidt A. Jejunojejunal intussusception as presentation of a primary lung carcinoma: a case report. Acta Gastroenterol Latinoam 2012; 42: 50-2.

14. Kaswala DH, Patel NR, Shah SS, Razack RM, Fitzhugh VA, Brelvi ZS. Metastatic lung adenocarcinoma mimicking a colonic polyp. N Am J Med Sci 2013; 5:3 06-7.

15. Cedres S, Mulet-Margalef N, Montero MA, Martinez P, Martinez A, Felip E. Rectal metastases from squamous cell carcinoma: A case report and review of the literature. Case Rep Med 2012; 2012: 947524.

16. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JH, Beasley MB, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015; 10: 1243-60.

17. Frank CD, Roy HD, Lynn T, Rogerio CL. DeVita, Hellman and Rosenberg's Cancer: Principles & Practice of Oncology. 10th Edition. Wolters Kluwer Health Corp.; Philadelphia: 2015. Non-small Cell Lung Cancer; pp. 495-502.

18. Işık A, Eken H, Demiryıldız I, Yılmaz I, Fırat D, Çimen O, et al. Rectum, Lymphoma, Adenocancer. Turk J Colorectal Dis 2015; 25: 106-8.

19. Huang YM, Hsieh TY, Chen JR, Chien HP, Chang PH, Wang CH, et al. Gastric and colonic metastases from primary lung adenocarcinoma: A case report and review of the literature. Oncol Lett 2012; 4: 517-20.

İstanbul Med J 2020; 21(2): 152-4
DOI: 10.4274/imj.galenos.2020.24356

Renal Involvement in Chronic Lymphocytic Leukemia: A Case Report

Kronik Lenfositik Lösemi'de Böbrek Tutulumu: Olgu Sunumu

Sinan Demircioğlu[1], Mesut Özgökçe[2], Ali Doğan[3], İrfan Bayram[4], Cengiz Demir[3]

[1]Necmettin Erbakan University Meram Faculty of Medicine, Department of Hematology, Konya, Turkey
[2]Van Yüzüncü Yıl University Faculty of Medicine, Department of Radiology, Van, Turkey
[3]Van Yüzüncü Yıl University Faculty of Medicine, Department of Hematology, Van, Turkey
[4]Van Yüzüncü Yıl University Faculty of Medicine, Department of Pathology, Van, Turkey

ABSTRACT

Chronic lymphocytic leukemia (CLL) is a neoplastic condition of B cells that frequently affects the lymph nodes, liver, spleen and bone marrow. The extranodal involvement of CLL is most commonly observed in the skin, whereas gastrointestinal and genitourinary involvement is rare. Renal involvement may not always present with renal failure. In this study, we aimed to present a patient with CLL infiltration in the kidney without renal failure and proteinuria.

Keywords: Chronic lymphocytic leukemia, extranodal, kidney, involvement

ÖZ

Kronik lenfositik lösemi (KLL) lenf bezlerini, karaciğer, dalak ve kemik iliğini sıkça etkileyen B hücrelerinin neoplastik bir durumudur. KLL'nin ekstranodal tutulumu en sık ciltte görülür. Gastrointestinal ve genitoüriner tutulum nadir izlenir. Böbrek tutulumu karşımıza her zaman böbrek yetmezliği ile gelmeyebilir. Bu çalışmada böbrek yetmezliği ve proteinürisi olmayan hastada böbrekte KLL enfiltrasyonu saptadığımız bir olguyu sunmayı amaçladık.

Anahtar Kelimeler: Kronik lenfositik lösemi, ekstranodal, böbrek, tutulum

Introduction

Chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) is a mature B-cell neoplasm characterized by the progressive accumulation of monoclonal B lymphocytes. Malignant cells in CLL and SLL have the same pathological and immunophenotypic properties. CLL/SLL accounts for approximately 25%-30% of all leukemias (1) and is more common in men than in women (male: female ratio is between 1.3:1 and 1.7:1) (1,2). It is considered to occur commonly in older adults, and the median age of incidence is 70 years (3). In most cases, diagnosis is made by the investigation of lymphocytosis identified during routine examination. Symptomatic cases may present with complaints related to lymphadenomegaly or organomegaly (splenomegaly or hepatomegaly) and/or general symptoms, such as fatigue, weight loss, anorexia and fever (4). CLL/SLL cells can infiltrate into any organ, but because of its ease of examination, the most frequently involved non-lymphoid tissue at the time of diagnosis is the skin. Skin lesions (leukemia cutis) on the face are most common and present as maculae, papules, plaques, nodules, ulcers or blisters (5). Unlike other lymphomas, clinically significant gastrointestinal mucosal involvement is rare in CLL/SLL. Similarly, meningeal leukemia is not expected at the time of diagnosis (6).

Case Report

A 63-year-old male patient was being followed up with a diagnosis of Stage 2 CLL since 2016. The patient complained of night sweats for several years. Physical examination revealed cervical, axillary and inguinal lymphadenopathies (LAP) that were painless, soft and mobile, with the largest being 2 cm in diameter. In addition, masses of 3-5 cm were palpated on the liver and spleen and under the ribs. Leukocyte count was 44.160/microL, lymphocyte count was 32.870/microL, hemoglobin level was 12.40 g/dL, platelet count was 272.120/microL, creatinine was 1.14 mg/dL and lactate dehydrogenase was 189 U/L. Complete urinalysis did not reveal proteinuria. The results of bone marrow biopsy were suggestive of CLL. In the genetic examination, 90% of the analyzed cells had a deletion in the 13q14.3 region, and 11q22.3, trisomy 12, 17p13.1 deletion and p53 mutation were not observed. Abdominal ultrasonography (USG) revealed hepatosplenomegaly, LAPs in the abdomen and a heterogeneous lesion (17 mm in diameter) in the

Address for Correspondence/Yazışma Adresi: Sinan Demircioğlu MD, Necmettin Erbakan University Meram Faculty of Medicine, Department of Hematology, Konya, Turkey
Phone: +90 555 432 44 74 **E-mail:** sinandemircioglumd@gmail.com **ORCID ID:** orcid.org/0000-0003-1277-5105

Cite this article as/Atıf: Demircioğlu S, Özgökçe M, Doğan A, Bayram İ, Demir C. Renal Involvement in Chronic Lymphocytic Leukemia: A Case Report. İstanbul Med J 2020; 21(2): 152-4.

Received/Geliş Tarihi: 10.10.2019
Accepted/Kabul Tarihi: 11.02.2020

left kidney upper pole. Abdominal computed tomography (CT) revealed a hypodense lesion of approximately 22×18 mm, with a mean density of 69 Hounsfield units in the left kidney upper pole posterior (Figure 1). Needle biopsy was performed on this lesion, and the following results were reported: CD20 (+), CD5 (+), CD23 (+), Bcl2 (+), CD3 (−), CD10 (−), Bcl6 (−), cyclin D1 (−), TdT (−) and Ki67 proliferation index was 5%. A diagnosis of CLL/SLL was made (Figure 2). The overall condition of the patient was good, with an Eastern Cooperative Oncology Group performance score of 1. Thus, rituximab-bendamustine chemotherapy was started. Informed consent was obtained from the patient.

Discussion

Renal insufficiency is common in patients with CLL, with a prevalence of 7.5% at the time of diagnosis and 16.2% over the course of the disease (7). The mechanism of renal insufficiency in these patients is variable. CLL infiltration can cause compression on renal tubules and microvasculature, resulting in renal obstruction and ischemia. Other potential causes of renal insufficiency in patients with CLL include contrast-induced nephropathy, treatment-induced tumor lysis, chemotherapy-induced toxicity and ureteral obstruction with lymphadenopathy (8). CLL can also result in various glomerular pathologies, including acute glomerulonephritis, nephrotic syndrome and chronic glomerulonephritis (8).

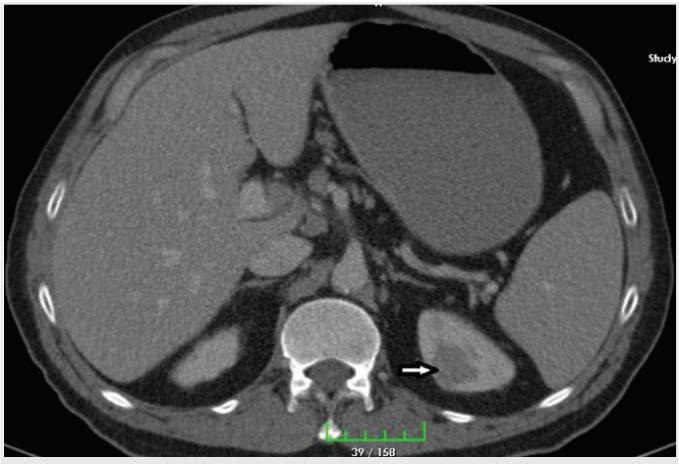

Figure 1. Focal hypodense area of hypodense localized in the upper pole of the left kidney (White arrow)

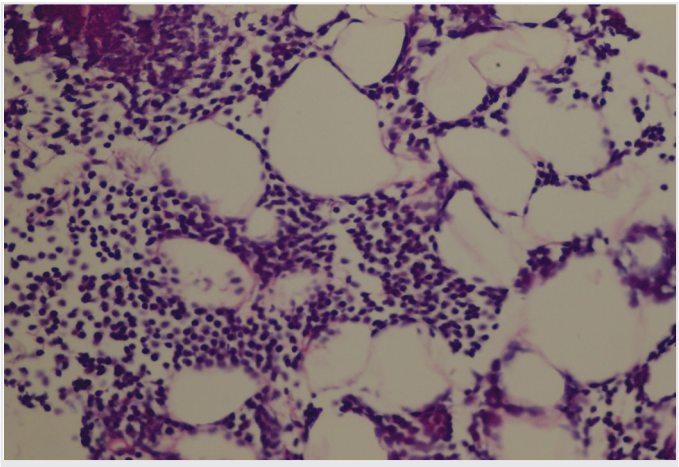

Figure 2. Chronic lymphocytic leukaemia/small lymphocytic lymphoma infiltration in the renal hilar fatty tissue. Mature-looking lymphocytes that show infiltration between fat cells can be observed in the section (hematoxylin and eosin staining, x40 magnification)

In a previous study, among the 4024 patients diagnosed with CLL and monoclonal B-cell lymphocytosis at Mayo Clinic, renal biopsy was performed in 49 patients (1.2%) due to renal insufficiency and nephrotic syndrome. Biopsy results revealed membranoproliferative glomerulonephritis (20%), CLL interstitial infiltration as primary etiology (12%), thrombotic microangiopathy (12%) and minimal change disease (10%) (9). In another study, renal biopsy was performed in 15 patients diagnosed with CLL, and CLL infiltration was detected in 10 of these patients (10). In a study on 700 patients with non-Hodgkin's lymphoma and CLL, renal infiltration was detected only in five patients (11). The retrospective evaluation of 52 patients with malignant B-cell infiltration in the kidney revealed that patients were diagnosed with Waldenström's macroglobulinemia (n=21), CLL (n=11), diffuse large B-cell lymphoma (n=8), other lymphomas (n=11) and multiple myeloma (n=1) (12). Contrary to these data, autopsy studies have indicated that 60%-90% of the patients have leukemic cell infiltration in the kidneys, but renal function remains intact even in late stages (13).

Renal insufficiency at diagnosis was found to be associated with male sex, advanced age, more advanced disease and CD49d positivity. Acute kidney injury developed in 16% of the patients during follow-up. The development of renal insufficiency during follow-up was shown to be associated with advanced age, male sex and certain CLL characteristics (Immunoglobulin heavy chain variable region genes unmutated, $CD49d^+$, $CD38^+$, $ZAP\text{-}70^+$, $del17p^-$ and $del11q^-$) (7). It has been reported that renal function improves with CLL treatment in several patients with infiltrative disease on biopsy (10).

In a study, the presence of renal disease was found to be independently associated with adverse patient outcomes in CLL. It was shown that overall survival is significantly lower in patients with renal disease at the time of CLL diagnosis or during follow-ups than in patients without renal disease (9).

The most common imaging finding of renal involvement in leukemia is nephromegaly, which can affect one or both kidneys and is caused by widespread or nodular parenchymal infiltration of leukemic cells (14). However, the sensitivity and specificity of this finding remain unknown. For example, nephromegaly was detected only in 1 of the 10 patients with proven renal infiltration on biopsy (10). Obstructive uropathy can also be observed in CLL. Diagnosis can be made using imaging methods, such as USG, CT and magnetic resonance imaging (15).

In conclusion, renal involvement is rarely observed in CLL. Each case of renal insufficiency observed in CLL may not be related to infiltration. Post-renal renal insufficiency due to paraneoplastic syndromes, tumor lysis syndrome, chemotherapy-related toxicity and lymphadenopathies should not be overlooked.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - S.D., M.Ö., A.D., C.D.; Concept - S.D., İ.B., C.D.; Design - S.D., A.D., İ.B., C.D.; Data Collection or Processing - S.D., A.D., İ.B., C.D.; Analysis or Interpretation - S.D., M.Ö., İ.B.; Literature Search - S.D., M.Ö., C.D.; Writing - S.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Referanslar

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69: 7-34.
2. Hernandez JA, Land KJ, McKenna RW. Leukemias, myeloma, and other lymphoreticular neoplasms. Cancer 1995; 75(1 Suppl): 381-94.
3. Smith A, Howell D, Patmore R, Jack A, Roman E. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. Br J Cancer 2011; 105: 1684-92.
4. Soysal T. Kronik Lenfositik Lösemi-Küçük Lenfositik Lenfoma. Hematolog 2013; 3: 253-70.
5. Agnew KL, Ruchlemer R, Catovsky D, Matutes E, Bunker CB. Cutaneous findings in chronic lymphocytic leukaemia. Br J Dermatol 2004; 150: 1129-35.
6. Strati P, Uhm JH, Kaufmann TJ, Nabhan C, Parikh SA, Hanson CA, et al. Prevalence and characteristics of central nervous system involvement by chronic lymphocytic leukemia. Haematologica 2016; 101: 458-65.
7. Strati P, Shanafelt TD. Monoclonal B-cell lymphocytosis and early-stage chronic lymphocytic leukemia: diagnosis, natural history, and risk stratification. Blood 2015; 126: 454-62.
8. Hricik DE, Chung-Park M, Sedor JR. Glomerulonephritis. N Engl J Med 1998; 339: 888-99.
9. Strati P, Nasr SH, Leung N, Hanson CA, Chaffee KG, Schwager SM, et al. Renal complications in chronic lymphocytic leukemia and monoclonal B-cell lymphocytosis: the Mayo Clinic experience. Haematologica 2015; 100: 1180-8.
10. Poitou-Verkinder AL, Francois A, Drieux F, Lepretre S, Legallicier B, Moulin B, et al. The spectrum of kidney pathology in B-cell chronic lymphocytic leukemia / small lymphocytic lymphoma: a 25-year multicenter experience. PLoS One 2015; 10: e0119156.
11. Da'as N, Polliack A, Cohen Y, Amir G, Darmon D, Kleinman Y, et al. Kidney involvement and renal manifestations in non-Hodgkin's lymphoma and lymphocytic leukemia: a retrospective study in 700 patients. Eur J Haematol 2001; 67: 158-64.
12. Javaugue V, Debiais-Delpech C, Nouvier M, Gand E, Chauvet S, Ecotiere L, et al. Clinicopathological spectrum of renal parenchymal involvement in B-cell lymphoproliferative disorders. Kidney Int 2019.
13. Barcos M, Lane W, Gomez GA, Han T, Freeman A, Preisler H, et al. An autopsy study of 1206 acute and chronic leukemias (1958 to 1982). Cancer 1987; 60: 827-37.
14. Bach AG, Behrmann C, Holzhausen HJ, Katzer M, Arnold D, Spielmann RP, et al. Prevalence and patterns of renal involvement in imaging of malignant lymphoproliferative diseases. Acta Radiol 2012; 53: 343-8.
15. Sheth S, Ali S, Fishman E. Imaging of renal lymphoma: patterns of disease with pathologic correlation. Radiographics 2006; 26: 1151-68.

İstanbul Med J 2020; 21(2): 155-9
DOI: 10.4274/imj.galenos.2020.78785

Recurrent Angioedema with Abdominal and Genital Involvement in Childhood: Hereditary Angioedema Type 2 Disease due to C1 Inhibitor Functional Deficiency

Genital ve Karın Bölge Tutulumuyla Giden Çocukluk Çağında Tekrarlayan Anjioödem: C1 İnhibitör İşlevsel Eksikliğine Bağlı Herediter Anjioödem Tip 2 Hastalığı

Öner Özdemir[1], Halime Çiçek[2]

[1]Sakarya University, Sakarya Training and Research Hospital, Clinic of Pediatric Allergy and Immunology, Sakarya, Turkey
[2]Sakarya University, Sakarya Training and Research Hospital, Clinic of Pediatrics, Sakarya, Turkey

ABSTRACT

Hereditary angioedema is a rare disorder characterized by recurrent angioedema attacks due to C1 inhibitor antigen or functional deficiency. Here, two cases with recurrent swelling on extremities, genital organs and face that were later diagnosed with C1 inhibitor functional deficiency (hereditary angioedema type 2) were presented. The first patient was an 8-year-old boy complaining of hand and foot swelling recurring once a year for the last 4 years. He was more frequently brought to outpatient pediatric clinics because of his recurring complaints in the last 5 months. In prodromal period, he had erythema marginatum-like rash and sometimes described abdominal pain with swelling. The second patient was an 11-year-old girl complaining of abdominal pain and facial swelling recurring in a couple of months for the last 8 years. Her grandfather, father and uncle had the same angioedema. In their laboratory evaluation, complement C4 levels were both found as low at <0.07 g/L (>0.1). Although C1 inhibitor antigen levels were both in reference range, its function tests were detected as low at 31% and 43% (>70%), respectively. Therefore, in cases with pediatric recurrent angioedema without urticaria, hereditary angioedema should be considered. After screened with C4 level, if required, both C1 inhibitor antigen and function tests are evaluated.

Keywords: Hereditary angioedema, abdominal pain, genitalia, childhood, C1 inhibitor

ÖZ

Herediter anjioödem C1 inhibitor antijen ya da işlevsel eksikliğine bağlı tekrarlayan anjiyoödem ataklarıyla bilinen nadir bir bozukluktur. Burada ekstremitelerde, genital organlarda ve yüzde tekrarlayan şişlikleri nedeniyle C1 inhibitor işlevsel eksikliği (herediter anjiyoödem tip 2) tanısı konulan iki olgu sunulmuştur. Sekiz yaşındaki erkek çocuk el ve ayaklarında şişliklerin yılda bir kere son 4 yıldır tekrarladığından şikayet etmekteydi. Son beş ayda tekrarlayan şikayetlerinden dolayı daha sık pediyatri polikliniğine başvurmuştur. Olgu prodrom döneminde eritema marginatum-benzeri döküntü ve şişlikleri esnasında karın ağrısından şikayet etmekteydi. On bir yaşında kız çocuk olan ikinci olgu son 8 yıldır birkaç ayda bir tekrarlayan karın ağrısı ve yüzde şişmeden şikayet ediyordu. Dede, baba ve amcada benzer anjiyoödem mevcuttu. Olguların laboratuvar değerlendirmesinde, kompleman C4 düzeyi <0,07 (>0,1) g/L olarak düşüktü. Her ikisinde C1 inhibitor antijen seviyesi referans aralığı içinde olmasına rağmen fonksiyon testi sırasıyla %31 ve %43 (>%70) olarak düşük bulundu. Dolayısıyla, çocukluk çağı tekrarlayan ürtikersiz anjiyoödemlerinde, herediter anjiyoödem düşünülmelidir. Kompleman C4 düzeyi ile tarama sonrasında, gerekirse, hem C1 inhibitor antijen ve hem de fonksiyon testleriyle değerlendirilmelidir.

Anahtar Kelimeler: Herediter anjioödem, karın ağrısı, cinsel organ, çocukluk çağı, C1 inhibitor

Introduction

Hereditary angioedema (HAO) is an autosomal dominant inherited disease with recurrent angioedema attacks. HAO is characterized by C1 inhibitor (C1 INH) antigen level deficiency or dysfunction, which regulates the starting proteins of the classical complement system (1). Two main groups of the disease are defined according to whether C1 INH has a protein or functional deficiency. In the main group (C1 INH-HAO), which leads to a deficiency of C1 INH, there is a decrease in absolute antigen concentration of C1 INH in Type 1 and a decrease in C1 INH function in Type 2. Besides inhibiting the first element of complement, C1 INH leads to inhibition on coagulation factors, plasminogen, etc. in the coagulation-fibrinolysis activation system. In its deficiency, due to

Address for Correspondence/Yazışma Adresi: Öner Özdemir MD, Sakarya University, Sakarya Training and Research Hospital, Clinic of Pediatric Allergy and Immunology, Sakarya, Turkey
Phone: +90 533 137 12 74 **E-mail:** oner.ozdemir.md@gmail.com **ORCID ID:** orcid.org/0000-0002-5338-9561

Cite this article as/Atıf: Özdemir Ö, Çiçek H. Recurrent Angioedema with Abdominal and Genital Involvement in Childhood: Hereditary Angioedema Type 2 Disease due to C1 Inhibitor Functional Deficiency. İstanbul Med J 2020; 21(2): 155-9.

Received/Geliş Tarihi: 23.09.2019
Accepted/Kabul Tarihi: 12.02.2020

the overwork of this system, bradykinin accumulation occurs in the body and angioedema occurs. The main group of HAO (nC1 INH- HAO), formerly referred to as Type 3, where C1 INH protein level and function is within the reference range, is mainly due to the mutation in the coagulation factor 12, plasminogen or angiopoietin-1 genes and mostly triggered by angiotensin converting enzyme (ACE) inhibitor or estrogen-containing drugs, particularly in women. Rarely, it has been reported to be seen in male cases (1-3).

HAO is a disease seen equally in both sexes and at all ages. Angioedema attacks can affect any part of the body; however, it occurs mostly on the extremities, face, airways, visceral organs, trunk, neck and genital area. Edema in the airways, laryngeal edema is the most common cause of fatality (2). Although its frequency varies from society to society, it is believed that C1 INH-HAO, which is the most common type, has a frequency of 1/50,000-150,000 people in the society. The frequencies of some other types are much rarer (2). Since it is a very rare disease, its diagnosis may be delayed from time to time. Here, a boy with a complaint of swelling in the hands and feet, who has had many polyclinic applications in the last 4 years, and a girl with more facial involvement are presented due to the functional deficiency of C1 INH and the diagnosis of HAO type 2, and being rarely seen in the clinic.

Case 1

An 8-year-old boy complained of swelling in the hands and feet, which repeated once a year for 4 years. Because his complaints became more frequent in the last 4-5 months and he had swelling of the hands and feet 4 times in the last 1 month, he applied to the child outpatient clinic (Figure 1 a,b). The patient had a complaint of rash before the complaint of swelling, but never itching (Figures 2a, b). No previous history of infection, exposure to a known allergen, trauma and drug use was described. There was no known history of the disease in his background and family history. In laboratory examinations, hemogram evaluation and biochemical tests were within the reference range. C-Reactive protein, erythrocyte sedimentation rate, serum rheumatoid factor, serum immunoglobulin and C3 values were found to be normal. Thyroid function tests were within the reference range and viral hepatitis serology was negative. There was no positivity in skin prick tests (SPT) and allergen-specific IgE studies applied to the patient. C4 requested for the diagnosis of HAO was <0.07 g/L (0.1-0.4) and was low. C1 INH antigen level was detected as 24.7 (18- 40 mg/dL), which was in the reference range. The patient was followed up with a pre-diagnosis of chronic urticaria-angioedema in the outpatient clinic. Because C4 and C1 INH antigen level tests that could be performed in the hospital were within the reference range, the diagnosis of HAO was avoided in the first plan. C1 INH activation/function test was requested because when the boy presented to the child allergy outpatient clinic, a typical rash during the prodrome period (Figures 2a, b) was observed and he stated that he sometimes had abdominal pain with swelling. Considering C1 INH function test result of 31% (70-130%), the patient was diagnosed with C1 INH-HAO type 2 and Icatibant therapy was started. The case was admitted to the Pediatric Emergency Department with a complaint of swelling in his hand after a few weeks and he was evaluated to have had

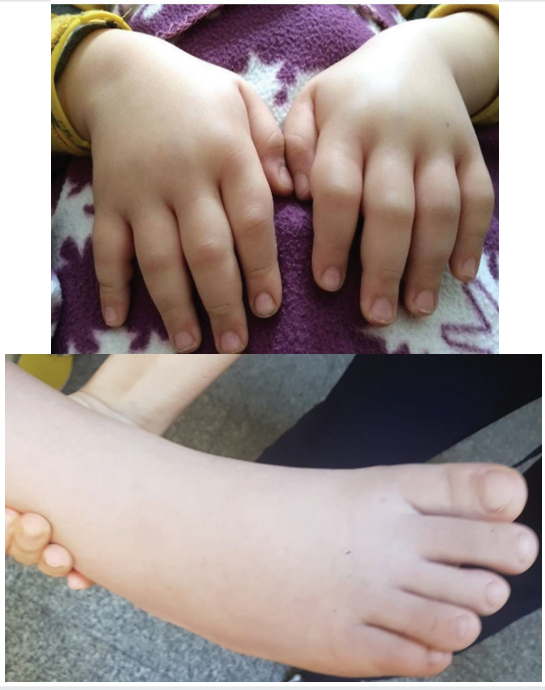

Figure 1a, b. Edema in the hands and feet seen in the attack period of the first case

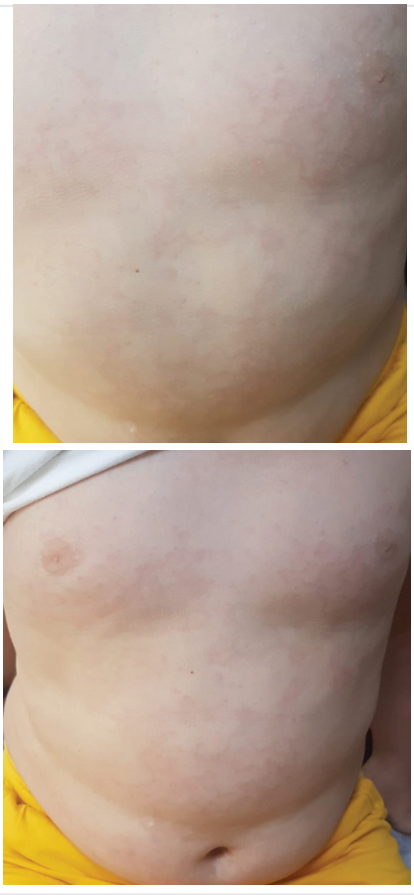

Figure 2a, b. Erythema marginatum-like rash in the body seen in the prodrome period of the first case

a HAO attack and Icatibant 15 mg was administered subcutaneously. Two-three days after this treatment, the patient complained of swelling and mild pain in the penis and scrotum area and he applied to the child allergy outpatient clinic. His physical examination revealed no signs of pathological examination except for tenderness with palpation and edema in the scrotum and penis (Figures 3a, b). Scrotal ultrasonography which was performed for ruling out epididymitis revealed edema in the scrotum wall. Complete urine test was evaluated within the reference range. The complaints of the patient were thought to be related to angioedema. The patient was hospitalized in the child allergy clinic and 15 mg Icatibant was subcutaneously administered to the patient in accordance with the drug posology (weight) (0.4 mg/kg; maximum 30 mg). Because the edema in the penis and scrotum was reduced in the follow-up, the patient was discharged with healing. The follow-up of the patient is still ongoing, and his attacks are under control (written informed consent was obtained from the child's family for the presentation).

Case 2

An 11-year-old girl had recurrent abdominal pain, swelling in the face and eyes for 7-8 years. Since the age of 3-4 years, she had abdominal pain that lasted two days every 2-3 months. While teething in the 1st and 3rd grades of primary education, she had swelling on the face. Her most recent complaint was swelling on the face, lips and eyelids 15 days before applying to us (Figure 4). The swelling first started from the cheeks, lips and eyes, and spread to the entire face, then regressed. Previously, she had no redness, itching, history of an infection, or a history of exposure to a known allergen. There was no known history of the disease in her background. Her family history included a diagnosis of angioedema in the father, grandfather and uncle, but its type was unknown. At admission to the Pediatric Allergy and Immunology Outpatient Clinic, in the laboratory examinations requested with the preliminary diagnosis of HAO, C4 was <0.07 g/L (0.1-0.4) and was low. C1 INH antigen level was 38.2 (18- 40 mg/dL) and within the reference range. The clinical and examination results of the case were compatible with HAO, and C1 INH activation/function test was requested for the purpose of typing HAO. Because C1 INH function test result was reported as 43% (70-130%), the patient was diagnosed with C1 INH-HAO type 2 and Icatibant treatment was started. The follow-up of the case is still ongoing (written informed consent was obtained from the child's family for the presentation).

For complement tests studied in these cases, fresh serum samples were collected in Vacutainer dry tubes and within 6 hours, 3 mL serum was stored at -20 °C. Frozen serum samples were studied in 72 hours to determine the level of C4, C1 INH antigenic and function levels. C4 serum level was measured in the Cobas c 501 autoanalyzer by turbidimetric method and by using the Cobas C4-2 kit (Roche, Rotkreuz, Switzerland). The C1 INH antigen level was determined on the BN II / BN ProSpec® system nephelometry instrument and using the N AS C1IN kit (Siemens, Marburg Germany). C1 INH function test was performed by working with the chromogenic Berichrom® C1-Inhibitor kit (Siemens, Marburg Germany) on the Berichrom® C1 INH coagulation automatic analyzer. To obtain plasma, 1 unit of sodium citrate solution (0.11 mol/L) was carefully mixed with 9 units of venous blood, avoiding foam formation. After the blood sample was centrifuged at room temperature for at least 15 minutes with 1500xG, absorbance was measured on the photometer. The lower limits of the three tests were as follows. Serum C4 level: ≤0.1g/L, C1 INH antigenic level: ≤0.21 g/L, C1 INH function: ≤%70. The values below these limits were considered low (4).

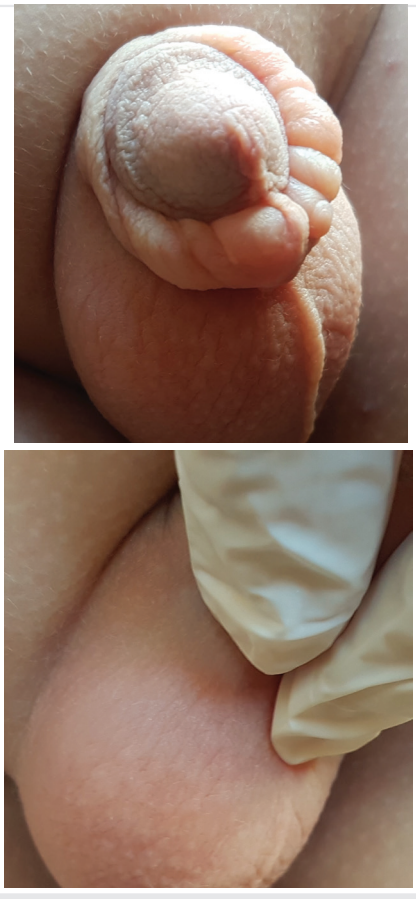

Figure 3a, b. Edema of the skin on the penis and redness in the scrotum seen during an attack of the first case

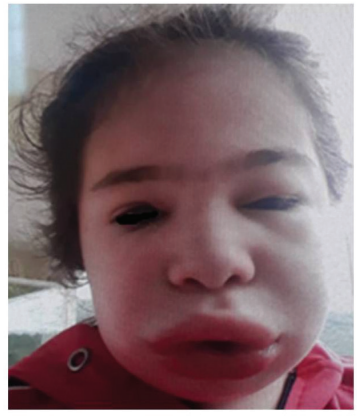

Figure 4. Angioedema in the face, eyelid and lips seen in the attack period of the second case

Discussion

HAO was first described by William Osler in 1888 (1-3). HAO is a hereditary disease that recurs, has boundaries not clearly selected, and has a course with angioedema attacks not accompanied by pain and itching (urticaria). Although it is a rare disease, it most often develops due to a qualitative or quantitative protein deficiency in C1 INH. C1 INH is a serine protease inhibitor and is produced primarily in the liver. C1 INH deficiency or dysfunction causes the production of vasoactive and anaphylactic peptides and the increase of vascular permeability by the release of mediators such as bradykinin due to the elevated kallikrein. As a result, angioedema occurs due to plasma leaking from postcapillary venules between the dermal layers of the skin (3). Edema developing in the disease can often occur in the subcutaneous tissues, gastrointestinal tract and respiratory system. More rarely, it may appear as bladder, urethra, shoulder, hip swelling or pleural effusion. In a typical attack, angioedema is most commonly seen in the hands and feet (2,3). The reason for our cases to apply to the outpatient clinic was recurrent swelling on the extremities and face. The most feared complication of HAO is laryngeal edema and has never happened in our cases. In some cases, the most common symptom may be abdominal pain due to edema in the gastrointestinal tract. Often, cases of HAO are accidentally diagnosed as acute abdomen or "FMF: familial Mediterranean fever". Considering acute abdomen, unnecessary laparoscopy and / or appendectomies are frequently performed in these cases (5). It was stated in our cases that there was sometimes abdominal pain with swelling. However, as seen in the first case, involvement of the scrotum or genital area is not a widely reported form of involvement in HAO. Rare case reports are encountered in the literature (6,7).

HAO is a disease that is not known when and how often it will recur, sometimes fatal, and progresses with angioedema attacks. An attack usually reaches its peak within 24 hours. It follows a slow recovery in the next 48-72 hours and ends in 72-96 hours. In our case, the attack lasted an average of 48-72 hours. The frequency of attacks varies from person to person, from weekly episodes to monthly episodes (6,7). Our first case generally described attacks once a year until the last 4-5 months. Our second case described an attack every 2-3 months. A prodrome stage usually leads to angioedema attacks in HAO. There may be a feeling of numbness in the area where the attack will begin about an hour before the attack. In 1/3 of the cases, erythema marginatum-like rash may appear on the skin during the onset of the attack (8). Rashes are not puffy from the skin and are not accompanied by itching. It is important to differentiate erythema marginatum-like rash from urticaria before attack because urticaria plaques do not accompany attacks and itching does not occur in cases with HAO. Although our first case had erythema marginatum-like rash before swelling in the hands and feet (Figure 2a, b), our second case did not mention the rash.

If the following points are taken into consideration, HAO attack can easily be distinguished from other causes of angioedema in childhood. HAO attacks are the types of attacks that last longer (3-5 days) without any urticaria, are triggered by factors such as trauma or stress and sometimes medication in adults, and have a course with swelling in which the attack does not respond to anti-histamine, corticosteroid and adrenaline. It differs from other shorter types of angioedema, which is frequently seen in childhood due to infection or allergic-immunological mechanisms and is seen with urticaria. In adults or older children, it can also be confused with acquired or drug-induced angioedema such as ACE-inhibitor (1-3). In our cases, there was no obvious trigger for attacks.

Routine laboratory tests related to chronic urticaria-angioedema are in the reference range in HAO. On the other hand, SPT used for triggering allergens is negative. Complete blood count and biochemical values of both cases were within the reference range limits and SPT was negative. In almost all cases with HAO, serum C4 levels are low both between and during attacks. Complement C4 is a very good screening test in the diagnosis of HAO. Complement C2 and C3 levels are in the reference range (1-3). In both of our cases, C4 level was low, C1 INH antigen level was in the reference range and C1 INH function was low. Determination of C1 INH level and function helps both make a diagnosis and make the distinction between Type 1 and Type 2 C1 INH-HAO. In Type 1, C1 INH antigen level is decreased; however, in Type 2, C1 INH level is in the reference range, but its function is decreased. Accordingly, both of our cases were Type 2 C1 INH-HAO. The nC1 INH-HAO group, which is more common in adolescents and adults, has not been reported much in childhood in the literature (9,10).

Treatments used in other angioedemas (corticosteroids, antihistamines and epinephrine) are not effective in the treatment of HAO. The treatment approach in HAO can be divided into four steps: i-) prevention treatment, ii-) treatment of acute attacks, iii-) short-term prophylaxis for the prevention of acute attacks, and iv-) long-term prophylaxis. Prevention measures begin with education, which includes explaining the disease to the patients and their relatives. The factors that trigger attacks should be taught to the cases. It should be kept in mind that some drugs can trigger attacks. Sick individuals' families should also be screened. A card that tells the patients what their illnesses are and which drugs and how to use in emergencies can be prepared. In acute attack treatment, the goal is to replace C1 INH, which is deficient. In the treatment of attack, plasma-derived C1-INH (Berinert®, Cinryze®) or recombinant C1-INH (Ruconest®) replacement, selective bradykinin B2 receptor antagonist (Firazyr®, Icatin®), and selective plasma kallikrein inhibitor (Kalbitor®) can be used. In our country, recombinant C1-INH and kallikrein inhibitor are still not available. On the other hand, İcatin has been covered by SGK since the beginning of 2019. For this purpose, primarily plasma-induced or recombinant C1 INH replacement is preferred; but when it is not available, bradykinin B2 receptor antagonist, kallikrein inhibitör or as a last resort, fresh frozen plasma (FFP) can be given (2). In our country, Cinryze®/İcatin® can be used in attacks and is present in emergency units. In general, long-term prophylaxis is recommended for patients who experience more than one attack per month, are affected by these attacks for more than 5 days a month, or have a history of respiratory obstruction, but the criteria are not clear (2). Three groups of drugs are used in long-term prophylaxis. These are products that contain weak androgens (danazol, stanozolol), anti-fibrinolytics (aminocaproic acid, tranexamic acid) and C1 INH. Another treatment approach in cases with HAO is short-term prophylaxis to prevent acute attacks during interventions such as tooth extraction or surgical operation known to trigger attacks or immediately

after trauma. FFP, weak androgens and C1 INH replacement can also be used for short-term prophylaxis (10). In our country, drugs such as weak androgens and anti-fibrinolytics can be used for short or long term prophylaxis, but C1-INH products from plasma are not covered by SGK.

Despite the fact that C1-INH antigen level of the laboratory tests used in the diagnosis is easier and can be studied in most university hospitals around the world and Turkey, C1-INH function is widely studied with chromogenic method in private laboratories in the world, as in our cases.

Although ELISA test is also used to measure activity (function), it has not been found as sensitive as the chromogenic method (11-13). Although ELISA and chromogenic method have been reported to have similar positive predictive value in previous publications, the chromogenic method has been found to have a higher negative predictive value (12). In our study, C1 INH function could only be studied with the chromogenic method. With the chromogenic method, the sensitivity of the C1 INH function test is given as 57% and the specificity as 100%. The sensitivity of C1 INH antigen test has been reported as 97% and its specificity as 100% (11). Serum C4 level was found to be 85.7% sensitive and 85% specific in detecting C1 INH deficiency in asymptomatic HAO cases (11, 13).

If possible, both (chromogenic and ELISA) test results should be evaluated together with clinical history, family history, and C4 levels. It is recommended to repeat the suspicious ELISA test results with the chromogenic method. Especially, the chromogenic method stands out as a method that needs more attention in terms of correct storage and working of the sample. Genetic testing is the confirmatory and diagnostic test that will be applied when necessary (13). Our cases did not use any medication at the time of the tests and they did not have any disease other than HAO.

The strength of our case report is that a very rare clinical picture could be confirmed by laboratory findings made from serum, and the weak side is that the genetic Type 2 HAO-specific mutation could not be studied due to financial impossibility.

Conclusion

In cases where recurrent angioedema is not accompanied by urticaria, HAO should be considered and serum complement C4 level should be evaluated as screening test in the first stage. In cases with low complement C4 levels, C1 INH antigen level should be examined, and even if it is within reference range, C1 INH activity test should be kept in mind since C1 INH- HAO Type 2 can occur. Where all of these levels are within the reference range, further investigations (investigating whether factor 12, plasminogen and angiopoietin mutations are available) for the nC1 INH-HAO group, formerly called Type 3, should be requested (14-15).

Informed Consent: Written informed consent was obtained from the child's family for the presentation.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ö.Ö.; Design - Ö.Ö.; Data Collection and/or Processing - Ö.Ö.; Analysis and/ or Interpretation - Ö.Ö., H.Ç.; Literature Search - Ö.Ö., H.Ç.; Writing - Ö.Ö., H.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Ozdemir O. New developments in type of hereditary angioedema with normal CI-inhibitor level. MOJ Immunol 2019; 7: 1-2.
2. Bowen T, Cicardi M, Bork K, Bork K, Zuraw B, Frank M, et al. Hereditary angiodema: a current state-of-the-art review, VII: Canadian Hungarian 2007 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. Ann Allergy Asthma Immunol 2008; 100(1 Suppl 2): S30-40.
3. Zuraw BL, Christiansen SC. HAE pathophysiology and underlying mechanisms. Clin Rev Allergy Immunol 2016; 51: 216-29.
4. Özdemir Ö, Elmas B. Prevalence and Clinical Manifestations of Hereditary Angioedema in Untested Close and Distant Blood Relatives of Hereditary Angioedema Index Patients in a City, Turkey. JAREM 2017; 7: 51-7.
5. Bahceci SE, Genel F, Gulez N, Nacaroglu HT. Coexistence of hereditary angioedema in a case of familial mediterranean fever with partial response to colchicine. Cent Eur J Immunol 2015; 40: 115-6.
6. Abuzakouk M, AlMahmeed N, Memisoglu E, McManus M, Alrakawi A. Hereditary angioedema Type II: First presentation in adulthood with recurrent severe abdominal pain. Case Reports Immunol 2018; 2018: 7435870.
7. Iwanami K, Okano T, Ohara O, Morio T. Recurrent acute abdomen as the main manifestation of hereditary angioedema. Intern Med 2019; 58: 213-6.
8. Martinez-Saguer I, Farkas H. Erythema marginatum as an early symptom of hereditary angioedema: Case report of 2 newborns. Pediatrics 2016; 137: e20152411.
9. Longhurst HJ, Bork K. Hereditary angioedema: an update on causes, manifestations and treatment. Br J Hosp Med (Lond) 2019; 80: 391-8.
10. Jose J, Zacharias J, Craig T. Review of select practice parameters, evidence-based treatment algorithms, and international guidelines for hereditary angioedema. Clin Rev Allergy Immunol 2016; 51: 193-206.
11. Tarzi MD, Hickey A, Forster T, Mohammadi M, Longhurst HJ. An evaluation of tests used for the diagnosis and monitoring of C1 inhibitor deficiency: normal serum C4 does not exclude hereditary angio-oedema. Clin Exp Immunol 2007; 149: 513-6.
12. Wagenaar-Bos IG, Drouet C, Aygoren-Pursun E, Bork K, Bucher C, Bygum A, et al. Functional C1-inhibitor diagnostics in hereditary angioedema: assay evaluation and recommendations. J Immunol Methods 2008; 338: 14-20.
13. Li HH, Busse P, Lumry WR, Frazer-Abel A, Levy H, Steele T, et al. Comparison of chromogenic and ELISA functional C1 inhibitor tests in diagnosing hereditary angioedema. J Allergy Clin Immunol Pract 2015; 3: 200-5.
14. Ozdemir O. Tekrarlayan anjiyoödem atakları ile başvuran hastaya akılcı yaklaşım. Klinik Tıp Pediatri Dergisi 2019; 11: 64-73.
15. Öner Özdemir. Innovations in Hereditary Angioedema Pathophysiology. SCIE 2019; 30: 355-61.