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Can Platelet Indices and Serum Lactate Dehydrogenase Levels be Used for the Differential Diagnosis of Malignancy in Children with Lymphadenopathies?

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Abstract

Introduction: Platelet indices such as the mean platelet volume (MPV) and platelet distribution width (PDW) have been reported to have a diagnostic value in some cancer types and inflammatory diseases. In this study, the platelet indices and serum lactate dehydrogenase (LDH) levels were investigated in children with reactive lymph node hyperplasia and lymphoma.

Methods: In total, 102 children were enrolled in this study. Overall, 30 healthy children and 72 children, who had undergone excisional lymph node biopsy between October 2011 and 2016, were enrolled this study. File records were retrospectively reviewed.

Results: Histopathologically, 50 (69.4%) of the 72 patients were diagnosed with reactive lymph node hyperplasia, and 22 (30.5%) were diagnosed with lymphoma. Of the cases diagnosed with lymphoma, 15 (68%) were those of Hodgkin's lymphoma and 7 (32%) were those of non-Hodgkin's lymphoma. There was no difference between the patients diagnosed with reactive lymph node hyperplasia and those with lymphoma in terms of leukocyte counts, MPV and PDW values, and serum LDH levels ($p>0.05$, for all). The serum LDH levels of both groups were statistically significantly higher than those of the control group ($p<0.001$, for both).

Conclusion: Platelet indices and serum LDH levels are not useful in the differentiation of malignant and non-malignant differentiation in children with unexplained lymphadenopathies. Serum LDH levels may remain within the normal range in low-grade tumors such as Hodgkin's lymphoma.

Keywords: Lymphadenopathy, reactive, malignant, platelet index, lactate dehydrogenase

Introduction

The most common cause of lymphadenopathies is reactive lymph node hyperplasia (1-3). Although the prevalence of malignancy among these patients is low, it is worrying for both doctors and patients. In cases of unexplained etiology, numerous laboratory tests, imaging methods, and tissue biopsies are required (4).

Platelet volume values, which are mean platelet volume (MPV) and platelet distribution width (PDW), are parameters that are easily obtained from blood counts and are associated with platelet function and activity (5, 6). Platelet indices have been shown to have diagnostic value in malignancies and inflammatory diseases (7-11).

Lactate dehydrogenase (LDH) is found in all tissues, but the highest level of LDH is seen in the liver, muscle tissue, heart, and kidney. Temporary elevations can occur in any case where cell damage develops (12). LDH is thought to be an important indicator in forecasting the prognosis of patients with lymphoma (12).

In this study, we aimed to investigate the usability of platelet indices, such as MPV and PDW, and serum LDH levels in the differentiation of malignancy and non-malignancy in children with idiopathic lymphadenopathy.

Methods

Between October 2011 and 2016, children diagnosed with reactive lymph node hyperplasia who underwent lymph node excision due to unexplained etiology and children diagnosed with lymphoma were included in the study. A control group comprised 30 children without any health problems who visited the polyclinic. Patient files were retrospectively reviewed. Patients' age, gender, location of the lymph node excision, clinical diagnosis, pathology results, blood count results, and serum LDH levels were recorded.

Blood specimens were obtained from the antecubital vein using vacuum tubes. In all study groups, within 2 hours after the blood samples were taken, whole blood counts were studied in the hema-

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tology laboratory, and LDH levels were studied in the biochemistry laboratory. Blood samples for complete blood count were taken into tubes containing ethylene diamine tetra acetic acid and studied with the electrical impedance method on a Beckman Coulter LH750 (Kraemer Blud, Brea, CA, USA) device. Blood samples for the LDH analysis were taken into gel-filled biochemical tubes and centrifuged at 1500 g for 15 min. The resulting serum was photometrically studied on a Cobas C 702 (Roche, Germany) device.

White blood cell and platelet count, MPV and PDW values, and serum LDH levels of the patients who had been diagnosed with reactive lymph node hyperplasia, patients with lymph node, and control group were compared. For the study, an ethics committee approval was obtained on 05.06.2017 with 80558721/G-172 number. In addition, written informed consent was obtained from the parents of all the children who participated in the study.

Statistical Analysis

Data analysis was performed using the SPSS 21 (IBM SPSS Corp.; Armonk, NY, USA) packet program. The qualitative characteristics of the patients were shown as the number (n) and frequency (%) in the tables. Normal distribution of quantitative variables was assessed using Shapiro-Wilk test. For non-normal distribution variables, descriptive statistics was used, and for intergroup comparisons, median and 25%-75% interval were used. Kruskal Wallis test was used in the comparison of the groups. Paired comparisons were performed using Dunn's test. $p<0.05$ was considered to be significant.

Table 1. Clinical follow-up diagnosis of patients diagnosed with reactive lymph node hyperplasia

Clinical diagnosis	Number	%
History of URTI	31	62
History of URTI+adenotonsillar hypertrophy*	6	12
Tooth decay	3	6
Congenital malformation	2	4
Pulmonary infection	3	6
Polyarticular juvenile rheumatoid arthritis**	1	2
Autoimmune lymphoproliferative syndrome**	1	2
Unidentified	3	6
Total	50	100

URTI: upper respiratory tract infection
*Adenotonsillar hypertrophy diagnosis was made by otorhinolaryngology polyclinic, and adenotonsillectomy was performed on all patients.
**Diagnosis was made during clinical follow-ups, after biopsy was performed.

Results

A total of 72 patients and 30 healthy children were included in the study. Of the 72 patients, 50 had cervical (69.4%), 8 had submandibular (11.1%), 7 had supraclavicular (9.7%), 4 had axillary, and 3 had inguinal lymph node excision. Fifty patients (69.4%) were diagnosed with reactive lymph node hyperplasia, and 22 patients (30.5%) were diagnosed with lymphoma. The most frequent complaints in the clinic were swelling in the neck (65 patients, 90.2%), swelling under the arm (4 patients, 5.6%), and swelling in the groin (3 patients, 4.2%).

Eighteen (36%) patients diagnosed with reactive lymph node hyperplasia were female, 32 (64%) were male, and their median age was 7.5 (6-10) years. When their clinical diagnosis was taken into consideration, 31 patients (62%) had recurring upper respiratory tract infection, 6 patients (12%) had recurring upper respiratory infections with adenotonsillar hypertrophy, and 3 patients (6%) had tooth decay that needed intervention. In 2 patients (4%), since the swelling was in the midline of the neck, a congenital malformation, such as thyroglossal cyst, was considered during pre-diagnosis. During the clinical follow-up, 1 patient (2%) was diagnosed with polyarticular juvenile rheumatoid arthritis and 1 (2%) with autoimmune lymphoproliferative syndrome. Three patients (6%) who underwent an axillary lymph node biopsy had a history of pulmonary infection. However, for 3 patients (6%) who had an inguinal lymph node biopsy, there was no clinical diagnosis. Table 1 shows the clinical follow-up of patients diagnosed with reactive lymph node hyperplasia before the biopsy.

Of the patients diagnosed with lymphoma, 9 patients (41%) were female and 13 (59%) were male, and their median age was 12.5 (7-13,5) years. Of the 22 patients, 15 (68%) were diagnosed with Hodgkin's lymphoma and 7 (32%) with non-Hodgkin's lymphoma. Among the patients diagnosed with non-Hodgkin's lymphoma, 3 had T-cell lymphoma, 3 had B-cell lymphoblastic lymphoma, and 1 had follicular lymphoma. Four of these patients had Stage II, 12 had Stage III, and 6 had Stage IV lymphoma.

In the control group, 15 patients were (50%) female 15 (50%) were male, their mean age was 8.5 (6.7-10) years, and there was no statistically significant difference between the groups in terms of age

Table 2. Comparison of laboratory parameters of patients with reactive lymph node hyperplasia and lymphoma diagnosis with control groups

	Group 1 n=22	Group 2 n=50	Control n=30	p
Gender (F/M)	9/13	18/32	15/15	>0.05
Age (year)	12.5 (7-13.5)	7.5 (6-10)	8.5 (6.7-10)	>0.05
Leukocyte (/109L)	8.60 (6.5-11.5)	7.81 (6.2-11.7)	7.4 (6.3-8.1)	>0.05
Platelet (x109L)	318 (201.0-436.0)	322a (271.0-418.0)	264a (208.0-319.0)	<0.05
MPV (fl)	8.0 (7.4-8.5)	7.8 (7.3-8.3)	8.1 (7.6-9.3)	>0.05
PDW (%)	16.6 (16.1-17.2)	16.70 (16.1-17.1)	16.4(16.0-17.0)	>0.05
LDH (U/L)	458b (324.50-782.0)	499a (440.50-529.0)	259ab (204.0-310.0)	<0.001

MPV: mean platelet volume; PDW: platelet distribution width; LDH: lactate dehydrogenase
Reference values: MPV (7.5-11.5 fl), PDW (10%-17.9%), platelet count (150-400x109/L), LDH (220-500 U/L)

and gender (p>0.05; Table 2). There was no difference in the white cell count and MPV and PDW values between patient groups and control groups (p>0.05, for all). Platelet counts of patients with reactive lymph node hyperplasia were higher than those in the control group (p=0.018). The LDH levels of the patient groups were significantly higher than those of the control group (p<0.001, for both). However, there was no statistically significant difference between the groups in terms of the LDH levels (p>0.05; Table 2).

Discussion

Lymphadenopathies may occur secondary to local or systemic inflammation, as a result of lymphatic malignancy and metastatic malignancy, or in response to autoimmune diseases and vaccination (13). Most of children with lymphadenopathy have underlying infectious or benign causes (14). There are three studies evaluating the risk of malignancy in patients with unexplained lymphadenopathy. In the first study, 3 of 238 patients were diagnosed with malignancy. In the second study that included 80 patients, none of them was diagnosed with malignancy, and in the third study, the malignancy prevalence was 1.1% (15-17). In our study, the frequency of malignancy was 30.5% among the patients who underwent the lymph node biopsy. It is not possible to generalize in this respect as our study is not a prevalence study. The most possible reason for this is that the patients with suspected malignancy were referred to our clinic.

Studies have increasingly focused on the fact that platelet indices are easily obtained from blood counts and that it has been discovered that some changes in these parameters occur in some diseases. In recent years, it has been acknowledged that platelet count and platelet indices can be used as inflammatory markers in cancer patients.

The platelet volume in circulation is heterogeneous. Their structure and metabolic activities are different. The average platelet volume in healthy subjects is 7.2-11.7 fl (18, 19). MPV is determined by megakaryocytes. It has been suggested that some cytokines stimulate megakaryocyte maturation and stimulate the production of younger and larger platelets in cancer patients (20). Elevated MPV can be used as an indication of an increased platelet diameter production rate and platelet activation. MPV has been shown to be significantly higher in endometrial, ovarian, colorectal, and gastric cancers than in healthy control group members (21).

Platelet distribution width shows the platelet distribution volume. PDW elevation indicates that small and large platelets are present at abnormal levels in the circulation. Compared to healthy control group members, PDW has been shown to be higher in patients with ovarian cancer and lower in patients with lung, breast, and malignant adnexal tumors (22-24). It has been reported that, of the hematologic malignancies in acute leukemia, MPV is similar to the control group, PDW is low, and there is no difference between MPV and PDW in lymphoblastic leukemia and myeloblastic leukemia (25). As per our knowledge, no study has evaluated platelet indices in patients with lymphadenopathies. In our study, we could not identify any difference regarding MPV and PDW values in patients with reactive lymph node hyperplasia, patients with lymphoma, and the healthy control group members. Lactate dehydrogenase plays a role in the reduction of pyruvate to lactate in the final step of glycolysis and in the conversion of lactate to pyruvate during gluconeogenesis (12). Increased LDH levels have been reported in solid tumors, leukemias, and diffuse lymphomas, particularly in the Burkitt lymphoma (26-30).

In the studies investigating laboratory parameters of non-malignant and malignant lymphadenopathies, it has been shown that serum LDH levels and lymph node diameters are higher in the malignant group than in the non-malignant group (26-28). However, these groups were not compared with a healthy control group, and the level of difference was not reported (26-28). In one study, it was shown that LDH levels were not more than the normal limits in any of the cases with Hodgkin's lymphoma, LDH levels were not significant in terms of histological subtype of lymphomas, but there was a significant correlation between the disease progression and LDH levels (12). In addition, there was no difference in serum LDH levels between the cases responsive and non-responsive to chemotherapy, and no difference was reported regarding LDH levels (12). According to the results of our study, serum LDH levels in patients with lymphoma were higher than that in the control group, but they were similar to the patients' with reactive lymph node hyperplasia. It is likely that since the majority of our patients (68%) had Hodgkin's lymphoma and these tumors were not aggressive, LDH levels were not very high.

Bozlak et al. (26) reported in their study investigating the causes of cervical lymphadenopathy and risk factors for malignancy in children that serum LDH levels were above normal limits in more than half of the children with benign lymphadenopathy. In a study investigating the importance of diagnostic serum LDH levels, it was reported that among patients with the LDH levels two times higher than normal, 60% were benign, 36% had malignant causes, and 5% had unexplained etiology (31). The fact that our study had LDH levels more than normal limits in patients with reactive lymph node hyperplasia is consistent with the results obtained in these studies, which can be explained by the knowledge of the LDH elevation in many lymphoproliferative diseases (32).

Conclusion

The results of our study showed that platelet indices were not useful in the differential diagnosis of malignancy in unexplained lymphadenopathies, elevated LDH levels were not a specific lymphoma symptom, and LDH levels could be elevated in inflammatory events. LDH should be measured in cases where malignancy is suspected, but it should be carefully evaluated with other diagnostic tests and clinical findings. Working with a small number of patients was a limitation in our study, and extensive studies that involve a larger number of patients are required.

Ethics Committee Approval: Ethics committee approval was received for this study from Eskişehir Osmangazi University School of Medicine Clinical Researches Center (Approval Date: June 5th, 2017; Approval No: 80558721/G-172).

Informed Consent: Informed consent was obtained from the parents of the patient who paticipated in this study.

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