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A Patient with Asymptomatic Connective Tissue Disease Coursing with Angioedema

Anjioödemle Seyreden Asemptomatik Bağ Dokusu Hastalığı

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Abstract / Öz

Here we present the case of a patient who was diagnosed with non-familial angioedema (AE) and who had a high risk of connective tissue disease. The patient had recurrent AE and arthritis attacks. C1 inhibitor level was found to be borderline low, and the antinuclear antibody (ANA) level was significantly high. The patient is being followed up with an antihistaminic treatment. The association of AE with systemic lupus erythematosus (SLE) is a rare condition. The possibility of collagen tissue disease, especially SLE not reflected in the clinic in our case, is strong.

Biz burada ailesel olmayan anjioödem (AE) tanısı alan ve bağ dokusu hastalığı riski yüksek bir olguyu sunduk. Hastada tekrarlayan AE ve artrit atakları mevcuttu. C1 inhibitör (inh.) düzeyi sınırda düşük bulundu ve beraberinde Anti-Nükleer Antikor (ANA) düzeyi anlamlı yüksekti. Antihistaminik tedavi ile takip ediliyor. AE ve Sistemik Lupus Eritemasus (SLE) birlikteliği nadir görülen bir durum olarak bilinmektedir. Bizim olgumuzdaki C1 inh. düzeyi düşük AE vakasında kliniğe yansımayan SLE başta olmak üzere kollagen doku hastalığı şüphesi kuvvetlidir.

Keywords: Antinuclear antibody, angioedema, C1 inhibitor deficiency

Anahtar Kelimeler: Anjioödem, C1 inhibitör eksikliği, Anti-nükleer antikor

Introduction

The association of angioedema (AE) with systemic lupus erythematosus (SLE) is rarely seen (1). Collagen tissue diseases, particularly SLE, exhibit a multisystemic involvement. Their etiologies have not yet been clarified, and they may course with various clinical variations. AE is a life-threatening and serious immunological disease that may cause dyspnea in the respiratory tract (2).

Also in this case report, the probability of a connective tissue disease, particularly SLE, seems to be quite high in a patient diagnosed with AE and followed up by the immunology clinic.

Case Report

A female patient aged 32 years visited our allergy and clinical immunology polyclinic with the complaint of a recurrent swelling in her right (Figure 1) and left (Figure 2) eyelids and in the ocular area. She had persistently complained of AE for 9 years. Nine years ago, she had AE on the upper lip and recovered in 3 days. She had received intravenous pheniramine maleate (47.5 mg) and dexamethasone (8 mg) as treatment. During the same period, she had suffered from pain and diarrhea that had lasted for 2 days. At intervals, she also had arthritis attacks in her patellar region as well as hands and shoulders. For the last 4 years, she had edema only in her eyelids. She has never had laryngeal edema. Although she has dyspnea was episodic, an organic cause was not identified. Afterward, her complaints disappeared along with the medications advised by the department of psychiatry. However, those complaints recurred when she discontinued the medication.

She took ketotifen and hydroxychloroquine sulfate tablets as well, but without any effects. She had no familial history of AE. The AE attacks had nothing to do with tooth pull and surgical operation. From time to time, red lesions with no itching and unassociated with AE were identified. Results of laboratory examinations were as follows: C4: 20.9 mg/dL (10–40); C1q:133 mg/dL (70–350); C1 functional: 104.4% (70%–130%); and C1 inhibitor: 20.5 g/l (21–39) were determined. The patient's examinations were repeated, and the results were as follows: C4: 20 mg/dL; C1 inhibitor: 0.2 g/L (0.15–0.35); ANA: 1/100 positive, nucleolar pattern; and complete blood count, normal. Glucose, liver function tests, and kidney function tests were normal, and IgE:169 IU/mL (0-100), CRP:3,45 mg/l (0-5) and Sedimentation: 2 mm/h (0-20). Complete urinalysis proved normal. Then, treatment with 180 mg of fexofenadine was started. ANA profile was requested. Abdominal ultrasonography and Posterior Anterior chest radiography findings were normal. Anti-dsDNA (4.70 IU/mL; N, <5 IU/mL) proved to be normal as well. Anti-Smooth Muscle Antikor (ASMA), histidyl-tRNA synthetase antibody (Anti-Jo-1), Anti–topoisomerase I (Anti–Scl-70), and Anti- Small nuclear RNP particles antibody (Anti-Sm-RNP) were negative. Anti Sjögren Syndrome Antibody A and B (Anti-SSA) and (Anti-SSB) were positive. When the patient described dryness in her right eye, she

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was referred to the rheumatology clinic with a diagnosis of Sjögren syndrome. In the examinations performed in the rheumatology clinic, C3:94.39 mg/dL (90–180), C4:18.8 mg/dL (10–40), and ANA: 1/320 proved to be positive, and a nuclear pattern was detected. The patient was followed up by the rheumatology clinic for the development of the connective tissue disease. Treatment was not initiated, as the disease was asymptomatic. We obtained verbal consent from the patient as well as pictures, documents, and information about her illness.

Discussion

Chronic angioedema is common in the population and frequently recurs. It can be hereditary, acquired, idiopathic, or drug-induced. Hereditary AE develops as a result of C1 inhibitor abnormalities. However, drug-induced and idiopathic AE development mechanisms have been less understood. In recent years, there have been significant developments in the diagnosis and treatment of these diseases to reduce mortality and morbidity. However, there is still a lot to learn about the pathophysiology, diagnosis, and treatment of chronic AE (3). AE is the edema seen in the deeper parts of the subcutaneous tissues and dermis. In general, it occurs with the acute release of mast cell mediators activated as a result of exposure to allergens, such as medications, pollen, foods, and animal epithelium and hair/fur. Apart from the fact that AE can be an acute condition due to angiotensin-converting enzyme inhibitor (ACE inhibitor), it may also be a chronic reaction due to acquired diseases that is characterized by hereditary or abnormal complement response. The main symptom is the edema at rather severe level (4).

Angioedema is a condition with life-threatening potential. Most patients present with urticaria (5). Severe attacks may lead to airway obstruction and even death. There are two types of AE: histaminergic and non-histaminergic AE. Both of these types are dangerous and require an aggressive approach in diagnosis and treatment (2). Frequent careful examination will often help identify the etiology of the agent and will also help take preventive measures against the disease.

According to in the guidelines published by the World Allergy Organization (WAO), examinations of the patients with the symptoms and findings of angioedema such as urticaria, flushing, itching, bronchospasm, sore throat, and/or hypotension were described. This examination must be comprise a detailed history of having been exposed to some potential agents, such as foodstuff, medications, inhaled materials, latex, and insect sting in particular.

Figure 1. Swelling in the right eyelid and ocular area

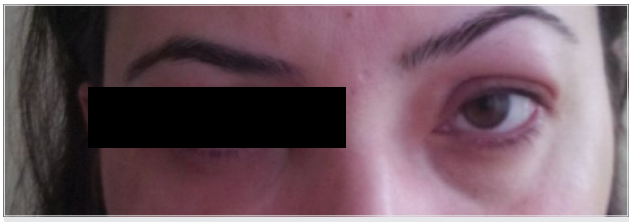

Figure 2. Swelling in the left eyelid and ocular area

These patients require additional examinations at given intervals, such as immunocomplex levels, thyroid function tests and autoantibodies, breast and abdominal graphs, biopsies, stool examination for parasites, and bone marrow aspiration. The value of aeroallergen screening tests for patients with AE is limited (6). Idiopathic AE is defined as AE attacks without urticaria and even nothing may be found in all the evaluations (7). The treatment currently recommended is empirical to a large extent. Current treatment modalities involve non-sedative antihistamines, combination of a leukotriene antagonist with non-sedative antihistamines as well as systemic corticosteroids and immunosuppressant therapies. Plasmapheresis or intravenous immunoglobulin has also been used (8). In any of these treatments, no generally accepted success was seen. Notably characterized by the edema in the head–neck region and in the extremities, AE is a rarely seen clinical picture that is also characterized by edema of the dermis, upper airways, and mucosal and submucosal layers in the gastrointestinal tract and genital region (9). Since the airway patency is impaired under the terms in which there is laryngeal edema involvement in the head–neck region, a life-threatening situation is likely to develop, and the immediate intervention to be performed can be life-saving. AE, according to the clinical picture, can be classified as "allergic AE" mainly accompanied by urticaria and "non-allergic AE" without the accompaniment of urticaria. Allergic AE is a type 1 immunoallergic reaction that develops through the medium of IgE (2). In this case, AE is accepted as another finding of urticaria, and the approach to the patient in diagnosis and treatment is the same as that of urticaria (2). AE can be acute and chronic (<6 weeks). Almost 90% of the cases with acute AE are mast cell mediated. Mast cell-mediated mechanisms involve acute allergy. These are typical IgE-mediated reactions. IgE-mediated AE is usually associated with urticaria. The same allergens frequently give rise to acute IgE-mediated urticaria. Acute AE may also be caused by direct mast cell stimulation without IgE. Other causes could be opiates, radiocontrasted substances, aspirin, and nonsteroidal anti-inflammatory drugs. The term "non-allergic AE," however, is used to determine clinical themes that various mechanisms in which mainly bradykinin and other vasoactive peptides play a role are responsible. These are divided into four groups: (i) acquired AE, (ii) AE due to the renin angiotensin aldosterone system blockers, (iii) pseudoallergic AE, and (iiii) idiopathic AE (2). Approximately 30% of cases with acute AE who are brought to the emergency department are due to ACE inhibitors. ACE inhibitors directly increase bradykinin level. The face and lower airways are often affected; the intestines may also be affected. AE may occur immediately or even after years of treatment. The cause of chronic AE is unknown (>6 weeks). IgE-mediated mechanisms are rare. However, the intake of suspected drugs and chemicals may sometimes be the cause (penicillin, milk, unprescribed drug, preservatives, and other food additives). A few cases may be due to hereditary reasons or acquired C1 inhibitor deficiency.

Idiopathic AE occurs without urticaria; it is chronic and recurrent, and no cause can be found (4). All the unnecessary secondary medications must be stopped if there is no reason what so ever during the treatment. The medications involving also H1 blockers for all the mast cell-mediated AEs eliminate the symptoms. Prednisone

(30–40 mg/day) is a proper treatment for more serious reactions. In those with serious symptoms, 125 mg of methylprednisolone and 50 mg intravenous diphenhydramine should be administered. A long-term treatment process requires H1 and H2 blockers as well as corticosteroids. The fact that epinephrine, corticosteroid, and antihistamines were effective on bradykinin-mediated AE was not shown. AE induced by ACE inhibitors generally clears up 24–48 h after the medications are stopped. If the symptoms are serious, progressive, or resistant, then the treatments applied in hereditary or acquired AE should be tried. These treatments involve fresh-frozen plasma, C1 inhibitor concentrate, and, possibly, ecallantide and icatibant. For idiopathic AE, a high dose of oral non-sedative antihistamine can be tried (4). Another type of kinin-mediated AE is well-defined (10). This can be caused by anti-C1 inhibitor antibodies or increased C1 inhibitor catabolism associated with lymphoproliferative diseases. In the event that the onset is seen at later ages, it is distinguished from hereditary AE due to the lack of a familial history and the low level of C1q. As for our patient, she had no familial history but had late onset. With these characteristics, her ailment was distinguished from the diagnosis of hereditary AE. Contrary to hereditary AE, there is the association of lupus in acquired AE; yet, it is rarely seen in 2%. There was no finding to suggest a rheumatologic disease in our patient either, except for the arthralgia of inflammatory character in her knee joints. As for a third type of acquired AE in lupus, it was suggested that there was the association of classic path-related hypocomplementemia (low C3 and C4), a temporary decline in antigenic, and/or functional levels of C1 inhibitor C1q antibody/IgG anti-CLR elevation, and the absence of anti--C1 inhibitor antibodies with the conditions in which no clinics of a lymphoproliferative disease or SLE is seen in the course of acute AE. In our patient, the functional levels of C4, C1q, C1 inhibitor and C1 inhibitor were within normal limits. The laboratory examinations also pushed us away from establishing a diagnosis of hereditary AE. The recovery of AE is related with the normalization of C3, C4, and C1 inhibitor levels through immunosuppressive treatment (1).

Conclusion

In our case, an idiopathic AE was considered in the first place due to the fact that she had response to the antihistaminic therapy and that no other etiological factors were found. However, since, in her repeated tests, ANA, which once proved to be negative, turned out to be positive afterward in 1/320 dilution, this was considered by the rheumatology department as an asymptomatic connective tissue disease, and thus, an unmedicated follow-up was recommended, since it has been argued that acquired AE could still be seen even during the period when the clinics in lupus disease has not yet been established and the disease is not yet symptomatic (1). Since there was still no finding in our patient in asymptomatic and laboratory sense to consider an acquired AE except for ANA positivity, it was recommended that the patient's rheumatologic and immunological follow-ups be continued in terms of the symptoms likely to develop later on as well as the low C1q level.

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