Omalizumab's role in the treatment of steroid dependent malignant idiopathic anaphylaxis

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Abstract

If an anaphylaxis episode is not caused by an identifiable trigger, it is defined as idiopathic anaphylaxis. Although it is rarely observed, idiopathic anaphylaxis is clinically significant because of its morbidity and fatality risk. No effective treatment has been demonstrated to date. We report a girl aged 16 years who had had malignant idiopathic anaphylaxis since the age of 12 years who was treated successfully with omalizumab. Although she avoided allergic trigger foods such as tomato and seafood, she used to have these attacks twice a week. Attacks were averted by taking 60 mg prednisone. When prednisone was tapered down to 5 mg on every alternate day, the episodes recurred. Later, attacks could not be controlled on <30 mg of prednisone daily. After being steroid-dependent for 4 years, subcutaneous omalizumab 225 mg every two weeks was started. Under omalizumab therapy, the attacks disappeared and prednisone was discontinued. (Turk Pediatri Ars 2017; 52: 105-7)

Keywords: Anti-IgE, idiopathic anaphylaxis, omalizumab, steroid

Introduction

Idiopathic anaphylaxis is an anaphylaxis syndrome in which no specific triggering cause can be demonstrated. It was described for the first time in 1978 in adults and subsequently in pediatric patients. Clinically, it is characterized by symptoms that may also be observed in allergic anaphylaxis including urticaria, angioedema, erythema in the face, syncope, hypotension, tachycardia, wheezing, stridor, pruritus, dysphagia, nausea, vomiting and diarrhea (1). Similar findings are observed as recurrent episodes. The frequency of episodes may change treatment protocols; generally, steroid treatment is planned for patients who have ≥ 6 episodes a year. If the daily steroid dosage cannot be reduced below 30 mg/day (1 mg/kg), this condition is called malignant idiopathic anaphylaxis (2).

Recently, success of anti-immunoglobulin (Ig) E treatment (omalizumab) has been reported in complex and difficult-to-treat urticarial/anaphylactic cases (3). Here, we discuss the effect of omalizumab in malignant idiopathic

anaphylaxis in light of recent literature by presenting our treatment experience in a patient with steroid-dependent malignant idiopathic anaphylaxis.

Case

A girl aged 16 years was being followed up for urticaria, angioedema, and anaphylaxis episodes, which she had had from the age of 12 years. In her medical history, she had food allergy including tomato and sea products (fish and shellfish) and house dust allergy. In addition, the patient had a history of severe persistent allergic rhinitis and asthma attacks. It was suspected that the anaphylaxis episodes were triggered by many factors including cold, pressure, vibration, exercise, and consumption of shellfish. As the asthma attacks became more severe, she started to avoid tomato and sea products. The patient had to continue her education at home because she had had 2-3 attacks a week in the last one year. The attacks initiated with stretching, rash, and hot flash in the skin in any part of the body. Following a rash in the arms, legs, hands and face, swelling

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in the skin, a sense of choking in the throat and finally respiratory distress developed. The attacks could generally be overcome with prednisolone treatment and using an epinephrine auto-injector when prednisolone was not sufficient. The attacks continued in the first two months of home education, although the suspected trigger factors were avoided.

Among the laboratory tests, hemogram and erythrocyte sedimentation rate values were found as normal. Immunoglobulin G, A, M values were normal. IgG1 (4.3 g/L) and IgG3 (0.5 g/L) subgroups were found slightly low and the other subgroups were normal. Total IgE was high (408 IU/mL). Specific IgE tests directed to food previously revealed positivity for seafood (fish and shellfish), tomato, and house dust. Class 2 positivity was found for seafood (fish and shellfish) and class 3 positivity was found for tomato and house dust. In the tests, which were repeated periodically, these positivities disappeared despite the absence of a strict diet. C1 esterase function and antigen level, C1q, CH50, C2, C3, and C4 levels were found as normal. The triptase and histamine levels measured during an attack were normal. Thyroid-stimulating hormone (TSH), T3 uptake, sT4, and total T4 levels were found as normal. Anti-nuclear antibody (ANA), ribonucleoprotein (RNP), Sjögren-syndrome-related antigen A (SS-A), Sjögren-syndrome-related B (SS-B), scleroderma antibodies, anti-dsDNA, anti-Smith antibody, thyroglobulin antibody, and anti-thyroid peroxidase antibodies were negative. The autologous serum test was also negative. Hepatitis B and hepatitis C virus DNA tests were negative. On punch (skin) biopsy, an increase in perivascular neutrophilic and eosinophilic cells was demonstrated in accordance with urticarial vasculitis.

With these clinical and laboratory findings, a diagnosis of idiopathic anaphylaxis was made, because no relationship with any known triggering factor could definitively be demonstrated. Treatment with 60 mg prednisolone + 25 mg hydroxyzine/day was initiated and the patient benefited greatly from this combination treatment. She had no further attacks after the first two months of home education.

In the following period, we tried to reduce the steroid dosage to 5 mg every other day, but we had to continue steroids when the attacks started again. The patient was thought to have steroid-dependent malignant idiopathic anaphylaxis because the prednisolone dose could not be reduced below 30 mg daily. Despite steroid treatment, the patient had an attack once a week or every two weeks, mostly of low severity. In this way, we followed up the patient as steroid-dependent for four years. Subsequently, subcutane-

ous omalizumab treatment at a dosage of 225 mg every two weeks was initiated. An improvement was found in the frequency and severity of the attacks compared with the periods when we used prednisolone. After the first 15 days when attacks did not occur, the prednisolone dose could be tapered over four weeks. The patient had no attack during the following 6-month period during which omalizumab treatment was continued alone (Figure 1). Afterwards, the patient was lost to follow-up because she moved to another province. Verbal consent was obtained from the patient's family for this presentation.

Discussion

Anaphylaxis is defined as a life-threatening systemic hypersensitivity reaction. Anaphylaxis is a syndrome rather than a disease and it is difficult to relate the pathophysiology to a single factor. Most of the time, it may be related with many unknown triggering factors. In anaphylaxis, mediators are released from mast cells by way of IgE, and these mediators play a key role in the development of anaphylaxis (4).

Idiopathic anaphylaxis is a type of anaphylaxis in which specified triggering causes cannot be found. Although it is IgE-mediated, the mechanism is not known exactly. Treatment and care is difficult because the etiology is not fully known. Prednisolone, H1 antihistamines, and adrenalin are recommended for treatment according to the frequency of attacks. In recent years, anti-IgE treatment has come to the fore in idiopathic anaphylaxis (5). In fact, recent studies have shown that use of omalizumab gives positive results in many allergic diseases, mainly including asthma, atopic dermatitis, allergic rhinitis, latex allergy, chronic urticaria, nasal polypsis, systemic mastocytosis, and idiopathic allergy (3).

Omalizumab is a molecule that acts as anti-Ig E. It prevents the release of mediators from mast cells and basophils by

Figure 1. Number of anaphylaxis attacks in our patient in the six-month period

binding to free IgE in the circulation and preventing it from binding to specific receptors on mast cells and basophils. It is known that serum free IgE levels are reduced in patients treated with omalizumab (6). However, it is interestingly observed that the clinical results in patients receiving omalizumab treatment are not related with reduced IgE levels. This leads to contemplation regarding the other immunomodulator effects of omalizumab (7). Therefore, it is thought that the success of omalizumab in idiopathic anaphylaxis is enabled by reducing total IgE level, and especially by mast cell stabilization and reducing the number of FcεR receptors. Again, it is thought that FcεRIs agglomerate by autoimmune mechanisms and omalizumab may be efficient with its immunomodulator action, especially in idiopathic anaphylaxis (4, 5). However, further clinical and laboratory studies are needed, though there are case reports from different countries.

Treatment of idiopathic anaphylaxis with anti-IgE (omalizumab) was tried in the past, but Jones et al. (5) reported in 2008 for the first time that omalizumab treatment was successful in a 12-year-old male patient who had uncontrolled asthma, allergic rhinitis, multiple food allergies, and anaphylactic episodes. Although some food products were found to be the cause of some attacks of anaphylaxis in this case, the cause could not be found for some other attacks. Our patient, who had anaphylactic attacks 4-5 times monthly and was diagnosed as having idiopathic anaphylaxis was successfully treated with anti-IgE. Pitt et al. (8) showed the effect of omalizumab in a 15-year-old female patient who was diagnosed as having idiopathic anaphylaxis because of systemic mastocytosis. Similar examples are also present for adult patients. Demirtürk et al. (9) reported the success of omalizumab in prophylaxis of idiopathic anaphylaxis in a 46-year-old female patient. The number of case reports supporting omalizumab as an efficient treatment option is increasing day by day in the literature. Lee et al. (10) reported that they treated a 41-year-old patient who was diagnosed as having idiopathic anaphylaxis with omalizumab at a monthly dose of 300 mg, and this patient who had had six attacks in the previous seven months did not have another attack in 13 months following omalizumab prophylaxis. Although the most appropriate dose is not known, there has been no documented need for additional doses in cases presented in the literature. Our patient had an attack weekly or every two weeks at the longest, despite steroid treatment. Our patient, who was followed up by us with a diagnosis of steroid-dependent idiopathic anaphylaxis, had no attack in the six-month follow-up period with the anti-IgE treatment. Omalizumab was administered at a dosage of 225 mg every two weeks and there was no need for additional doses.

In conclusion, the cases presented in the literature provide a treatment option for physicians, especially for patients with recurrent or malignant idiopathic anaphylaxis, though they do not prove causality and efficiency of this treatment. We think that omalizumab is promising for the future, especially in treatment-resistant patients. Ongoing and future studies will be directive.

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