

Long-term omalizumab use in the treatment of exercise-induced anaphylaxis

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ABSTRACT

Reported is a case of a 39-year-old male who was diagnosed with exercise-induced anaphylaxis (EIA). He was initially treated prophylactically with fexofenadine, montelukast, and ranitidine. He also used an epinephrine autoinjector as needed. He was refractory to these medications and continued to have episodes of EIA. He was then started on a trial of omalizumab, an immunoglobulin E monoclonal antibody, and had resolution of the EIA episodes. After discontinuation of the omalizumab, the EIA episodes returned. He was restarted on omalizumab and since that time, has had 5 years free of EIA episodes and can now exercise without any symptoms. To our knowledge, this is only the third case in the literature of successful treatment of EIA by using omalizumab. This case was unique because it provided successful long-term use of omalizumab for EIA. Further studies are recommended for the use of omalizumab in the treatment of EIA.

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Omalizumab is an immunoglobulin E (IgE) monoclonal antibody that is approved for allergic asthma and chronic idiopathic asthma. Omalizumab has also been used successfully in the treatment of idiopathic anaphylaxis, systemic mastocytosis, and venom-induced anaphylaxis.^{1–6} We are aware of two other reported cases of successful use of omalizumab in treating exercise-induced anaphylaxis (EIA).^{1,2} We present a case of EIA successfully treated with omalizumab with long-term follow-up.

CASE PRESENTATION

A 39-year-old male referred to the allergy clinic due to an episode of diffuse urticaria, periorbital edema, and a globus sensation, 15 minutes after running 2 miles on the treadmill. He was seen in the emergency department for the episode and received intramuscular epinephrine, intravenous steroids and diphenhydramine, which resolved his symptoms within 1 hour. Over the previous 3 months, he had reported many episodes of lightheadedness and patches of urticaria, with chest tightness that happened either with or

shortly after exercise. With these episodes, he would also have associated rhinitis and, at times, dysphagia and throat tightness. The dysphagia would also happen without exercise. He did have a history of allergic rhinitis and was on cetirizine. He had normal spirometry results, negative methacholine challenge and vortex stimulation results.

Due to the dysphagia, the patient had a skin-prick test for many foods and had positive results for almond, carrot, celery, egg white, egg yolk, peanut, pistachio, shrimp, soybean, black walnut, whole wheat, orange, potato, and, by history, for gluten and chickpea. He did not have any history of anaphylactic episodes with eating these foods. It was presumed that he had an episode of EIA and, in addition, dysphagia, which was separate. It was thought that, with the positive skin-prick test results to many foods, these may have contributed to the episode of EIA. The patient was given an epinephrine autoinjector, fexofenadine, montelukast, and ranitidine. These medications helped with the throat and chest tightness with exercise, but did not completely resolve his symptoms to include the dysphagia without exercise. He continued to have urticaria and some chest tightness with occasional throat tightness, only associated with exercise for at least 15 minutes. He was later diagnosed with eosinophilic esophagitis *via* biopsy as the cause of his dysphagia. He was lost to follow-up for awhile.

Four years later, the patient returned to the allergy clinic and reported every 3 months, he would have one to two episodes of urticaria with shortness of breath, periorbital edema, and a globus sensation. All episodes required epinephrine use and one required hospitalization. The patient was a physician and, due to a previous concern for possible food-induced EIA and his diagnosis of eosinophilic esophagitis, he had been


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avoiding wheat and, later, all food for up to 12 hours before exercise, which helped with the throat tightness, but not the frequency of EIA symptoms and the need for epinephrine. The episodes mostly occurred with running, with one episode with walking and another with cycling.

The patient's laboratory evaluation included a normal complete blood cell count, a tryptase level of 4 ng/mL, and a serum IgE level of 393.8 IU/mL. The tryptase level was not assessed during an acute episode due to either not being seen or having gone to the emergency department. Discussed completing exercise testing with and without food challenge in a controlled setting to see if EIA could be induced, but the patient declined; he felt that he had already challenged himself. Levocetirizine was added in place of fexofenadine to his medications listed earlier, but he continued with more-frequent episodes of urticaria and difficulty breathing, and these episodes were becoming more severe as well, requiring epinephrine nearly every time he exercised. Because of worsening episodes despite treatment and wanting to continue to exercise due to being in the military, he wanted to try something more. There was literature that indicated success with the use of omalizumab in treating EIA, but this was off-label use. The patient signed a consent form and elected to start a trial of omalizumab.

The patient was started on omalizumab injections of 300 mg every 2 weeks, with the dose being based on weight and total IgE levels, as done for asthma. There were no food restrictions given during this time. At a 3-month follow-up, the patient reported marked improvement. He had been exercising three times a week and had one episode of mild urticaria, but it happened when he had missed one of his omalizumab injections. There were no episodes of anaphylaxis. He had been able to tolerate eating normally even just before exercise. Omalizumab helped reduce his dysphagia as well. To determine if the omalizumab was what was truly helping reduce his symptoms, omalizumab was discontinued and he continued on levocetirizine, fluticasone propionate, and montelukast sodium for his allergic rhinitis.

The patient returned to the clinic after 4 months off omalizumab and reported that at just 1 month off, he started with episodes of urticaria, markedly increased chest tightness, and periorbital edema after at least 15 minutes of exercise. His dysphagia symptoms also increased, as did his throat tightness with exercise. He ultimately had an episode of anaphylaxis with urticaria, difficulty breathing, and facial swelling that required epinephrine, steroids, diphenhydramine, ranitidine, and intravenous fluids in the emergency department. After this episode, omalizumab was restarted at the same doses and intervals. Five years later, the patient continues on omalizumab with no further

episodes of anaphylaxis and has been able to return to full activity level with no restrictions. He will continue to be followed up monthly and exercise normally, reporting any symptoms that he has.

DISCUSSION

EIA is a rare, but potentially life-threatening syndrome. There are a variety of symptoms that present during or shortly after exercise. These symptoms include but are not limited to pruritus, urticaria, wheezing, chest tightness, nausea, diarrhea, angioedema, and ultimately, airway compromise and circulatory collapse.⁷⁻⁹ It can happen independently, but there also is a food-dependent EIA (FdEIA). In this type of EIA, ingestion of certain foods before exercise induces the anaphylactic episodes. It has been seen in most cases that symptoms occurred when food was consumed between a few minutes to 2 hours before exercise, with a few cases occurring up to 6 hours after exercise.¹⁰ Typically, if the food is avoided for 4-6 hours before exercise, the symptoms do not occur, which is the treatment of choice for FdEIA. Many patients will have positive skin-prick test results or IgE immunoassays to the triggering foods. Some triggers include wheat, seafood, nuts, seeds, alcohol, and some vegetables and fruits. Wheat has been found to be one of the most prevalent triggers and best studied cause of FdEIA.¹¹ It was found that omega-5 gliadin, which is a major protein of wheat, is a contributing factor in >80% of patients with wheat allergy that caused FdEIA.^{12,13}

The pathophysiology of EIA and FdEIA is not fully understood, but is thought to be mediated by mast cell activation and subsequent histamine release.¹⁴ Other theories regarding the pathophysiology are exercise-induced antigen release and changes in blood flow and pH. Increased gut permeability is also a proposed mechanism because gastrin is released with exercise and is a known mast cell secretagogue. The increased gut permeability may also increase the absorption of food allergens into the circulation and cause a higher antigen load, which results in symptoms.^{8,15} Prophylactic therapies that have been tried include histamine blockers, leukotriene inhibitors, oral steroids, epinephrine, and the cessation of activity as soon as symptoms begin to occur. There also has been the successful use of omalizumab.

Our patient was thought to have FdEIA and thus was counseled to avoid food 4-6 hours before exercise and to remove foods from his diet to which he had tested positive, which included wheat. He did this and extended to 12 hours with no food consumption before exercise by not eating at night and exercising in the morning, but the symptoms continued. He was prophylactically taking a H₁ and H₂ antihistamine and a leukotriene inhibitor, and continued with no change in

frequency or severity of symptoms. Due to exhausting all recommended therapies with no success, it was conjointly determined by the patient and physician that a trial of omalizumab should be taken because there was one reported successful case.¹ Omalizumab offered relief of all of his symptoms, which provided a second successful case with long-term follow up.

Omalizumab does not treat or block all of the proposed pathways that could cause EIA. It is thought that mast cell stabilization plays a key role. There also is a case that showed improvement in symptoms of EIA with montelukast, a leukotriene inhibitor, which would decrease the stimulation and subsequent degranulation of mast cells.¹⁶ With these methods, there is a decreasing rate of mast cell degranulation, and this is a presumed pathway involved in EIA. The European Academy of Allergy and Clinical Immunology released a position statement stating that the proposed mechanisms of EIA that are popular today lack validity.¹⁷ More research is needed to better understand the pathophysiology of EIA and to offer better diagnostic and treatment options. Our patient also had resolution of his dysphagia symptoms as well after starting on the omalizumab. There is a recent study that demonstrated improvement in the symptoms of eosinophilic esophagitis,¹⁸ which seems to have been the case in our patient.

CONCLUSION

We concluded that omalizumab was helpful in the resolution of EIA symptoms. This case provided evidence of the successful use of omalizumab over a long period of time. We suggest that mast cell stabilization may be the main contributing factor in reducing the symptoms of EIA, but more research needs to be done to validate this presumption. We also recommend further clinical studies of treatment of EIA with omalizumab.

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