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REFERENCES

1. Simon D, Simon HU. Eosinophilic disorders. J Allergy Clin Immunol 2007;119:1291-300.
2. Kasinath BS, Lewis EJ. Eosinophilia as a clue to the diagnosis of atheroembolic renal disease. Arch Intern Med 1987;147:1384-5.
3. Sari I, Pabuccuoglu U, Akkoc ND. Cholesterol crystal embolism in a patient with suspected vasculitis. J Rheumatol 2007;34:229-30.
4. Cogan E, Schandené L, Papadopoulos T, Crusiaux A, Goldman M. Interleukin-5 production by T lymphocytes in atheroembolic disease with hypereosinophilia. J Allergy Clin Immunol 1995;96:427-9.
5. Ochiai K, Omura M, Mochizuki A, Ito M, Tomioka H. Human umbilical vein endothelial cells support interleukin-3- and interleukin-5-induced eosinophil differentiation from cord blood CD34+ cells. Int Arch Allergy Immunol 1999;120(S1):2-6.
6. Freidlin IS. Immunophysiology of endothelial cells. Hum Physiol 2006; 32:357-67.
7. Mohle R, Salemi P, Moore MAS, Rafii S. Expression of interleukin-5 by human bone marrow microvascular endothelial cells: implications for the regulation of eosinophilopoiesis in vivo. Br J Haematol 1997;99:732-8.

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Reply

To the Editor:

We appreciate the positive comments of Cecioni et al[1] regarding our suggested new classification of eosinophilic disorders.[2] The authors report about a patient suffering from the atheroembolic disease associated with eosinophilia or ''blue toe syndrome.'' We agree with Cecioni et al that the current available data suggest that the eosinophilia in atheroembolic disease is most likely cytokine-mediated.

However, we see the atheroembolic disease in the case presented by Cecioni et al[1] more as a complication or part of underlining eosinophilic and cardiovascular diseases and not as a clinical entity on its own. Unfortunately, the authors have not been able to identify the cause of eosinophilia in their patient. Similarly, how the thrombotic complication developed remains unclear. Because the patient did not appear to suffer from an eosinophilic endomyocardial disease,[3] it might have been due to thrombi, which dislodged as emboli as a result of a large-vessel endothelial disease, in which eosinophils somehow contributed to the pathogenesis. For instance, eosinophils have been described to release tissue factor (TF),[4] the major initiator of coagulation, and to increase TF activity in endothelial cells,[5] thereby provoking a thrombotic diathesis. Such a mechanism might also play a role in the atheroembolic disease, which has been described in association with deep vein thrombosis in hypereosinophilic syndrome.[6]

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REFERENCES

1. Cecioni I, Fassio F, Gori S, Giudizi MG, Romagnani S, Almerigogna F. Eosinophilia in cholesterol atheroembolic disease. J Allergy Clin Immunol 2007;120:1470-1.
2. Simon D, Simon HU. Eosinophilic disorders. J Allergy Clin Immunol 2007;119:1291-300.
3. Leiferman KM, Gleich GJ. Hypereosinophilic syndrome: case presentation and update. J Allergy Clin Immunol 2004;113:50-8.
4. Moosbauer C, Morgenstern E, Cuvelier SL, Manukyan D, Bidzhekov K, Albrecht S, et al. Eosinophils are a major intravascular location for tissue factor storage and exposure. Blood 2007;109:995-1002.
5. Wang JG, Mahmud SA, Thompson JA, Geng JG, Key NS, Slungaard A. The principal eosinophil peroxide product, HOSCN, is a uniquely potent phagocyte oxidant inducer of endothelial cell tissue factor activity: a potential mechanism for thrombosis in eosinophilic inflammatory states. Blood 2006;107:558-65.
6. Liao YH, Su YW, Tsay W, Chiu HC. Association of cutaneous necrotizing eosinophilic vasculitis and deep vein thrombosis in hypereosinophilic syndrome. Arch Dermatol 2005;141:1051-3.

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Omalizumab for drug allergy

To the Editor:

Casale et al[1] have recently shown that pretreatment with omalizumab decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. Although the US Food and Drug Administration has approved only specific indications for omalizumab, including treatment of patients with moderate persistent to severe persistent asthma with a positive skin test response to a perennial aeroallergen, anti-IgE appears to provide a therapeutic option for many allergic diseases and conditions in which IgE plays a significant role.[2] This potential use of omalizumab is being investigated,[3] with ongoing trials in patients with allergic rhinitis and studies for treating food allergy, atopic dermatitis, and chronic urticaria under evaluation.[3] However, the potential use in severe cases of drug allergy, in which the need for the drug is essential, has not been evaluated.

We present the case of a 27-year-old man with type I diabetes mellitus, intermittent mild allergic asthma with dust mite sensitization, and contact sensitization to nickel sulphate. He was assessed because he was using oral corticosteroids and antihistamines daily for 6 months because of itching, hives, and some episodes of anaphylaxis coinciding with insulin bolus. A diagnosis of insulin allergy was made after positive skin prick test responses to all kind of insulins, *in vitro* testing with positive IgE levels (determined by means of RAST; Phadia, Uppsala, Sweden), and a positive challenge result with 2 U of regular insulin. He required 2.5 IU/kg of insulin per day at the time of diagnosis. Desensitization was performed as described previously.[4] Six months after desensitization, 0.8 IU/kg of insulin per day was required, and the patient was free of symptoms without medication. Nevertheless, 9 months later, he began to experience similar symptoms after an episode of diabetic ketoacidosis. Antihistamines did not control his full symptoms. Corticosteroids were

avoided to prevent any increase in insulin requirement. Omalizumab was offered, and specific written informed consent was obtained from the patient and his family. The hospital committee and Spanish Health Authorities approved treatment. Omalizumab (300 mg) was administered subcutaneously every second week. After 20 weeks, the patient was taking only 5 mg of levocetirizine every 24 hours, with no allergic symptoms.

Omalizumab, an anti-IgE mAb, is designed to treat IgE-mediated diseases.[2] However, the mechanism of action is not well known, although omalizumab downregulates dendritic cell FcεRI expression on basophils,[5] B cells, $CD4^+$ cells, $CD8^+$ cells, and IL-4^+ cells. Omalizumab is a recombinant humanized mAb that blocks free serum IgE through the high-affinity Fc receptor from attaching to mast cells and prevents IgE-mediated inflammatory changes.[1]

Insulin allergy is uncommon, even though 2% of diabetic patients have antibodies against insulin. Switching to other types of insulin or introducing a subcutaneous pump usually solves any problems. In a few cases desensitization is the final approach, with good results. However, symptoms appeared again in this patient. Trying to avoid oral corticosteroids to avoid an increase in insulin requirements, we offered omalizumab as a novel therapy. Although omalizumab is currently approved to treat moderate-to-severe IgE-mediated asthma, its use in the treatment of other IgE-mediated conditions, such as severe drug allergy, has a promising future.[2]

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REFERENCES

1. Casale TB, Busse WW, Kline JN, Ballas ZK, Moss MH, Townley RG, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2006;117:134-40.
2. Chang TW, Wu PC, Hsu CL, Hung AF. Anti-IgE antibodies for the treatment of IgE-mediated allergic diseases. Adv Immunol 2007;93:63-119.
3. Mankad VS, Burks AW. Omalizumab: other indications and unanswered questions. Clin Rev Allergy Immunol 2005;29:17-30.
4. Matheu V, Perez E, Hernandez M, Diaz E, Darias R, Gonzalez A, et al. Insulin allergy and resistance successfully treated by desensitisation with Aspart insulin. Clin Mol Allergy 2005;3:16.
5. Lin H, Boesel KM, Griffith DT, Prussin C, Foster B, Romero FA, et al. Omalizumab rapidly decreases nasal allergic response and FcepsilonRI on basophils. J Allergy Clin Immunol 2004;113:297-302.

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Reply

To the Editor:

Matheu et al[1] report an interesting case of insulin allergy treated successfully with omalizumab. Although omalizumab is only approved by the US Food and Drug Administration for moderate-to-severe persistent allergic asthma, there has been an increase in the use of this agent for the management of many disorders thought to be IgE mediated.

Omalizumab has been shown to be effective for the treatment of both seasonal and perennial allergic rhinitis.[2] Indeed, early studies indicated a clear dose-response relationship between omalizumab dose, suppression of IgE, and clinical efficacy.[2] In addition, a 9-week pretreatment period with omalizumab has been shown to inhibit approximately 80% of acute allergic reactions caused by rush allergen immunotherapy with ragweed in patients with seasonal allergic rhinitis.[3]

Because of these and other data, the utility of omalizumab in preventing acute anaphylactic events attributed to allergen immunotherapy is being studied in greater detail. An ongoing multicenter study using omalizumab pretreatment in patients with chronic persistent perennial allergic asthma and FEV_1 values of greater than 75% will hopefully answer whether pretreatment with omalizumab for 12 weeks can inhibit cluster allergen immunotherapy–induced allergic reactions in this patient population. A recent open-label study of 8 patients with moderate-to-severe persistent asthma examined whether acute allergic reactions caused by a modified cluster immunotherapy regimen with multiple allergens could be prevented by omalizumab pretreatment for 2 months. The results presented at the 2006 American College of Allergy, Asthma & Immunology meeting by Sekhsaria et al indicated that all patients tolerated the immunotherapy well, and no systemic reactions occurred.[4]

These studies in patients with allergic rhinitis and asthma indicate that omalizumab can be an effective agent to prevent acute allergic reactions caused by allergen immunotherapy. However, there are many unanswered questions that are pertinent to these studies, as well as the report by Matheu et al,[1] including the following: (1) What is the optimal duration of pretreatment with omalizumab before initiating allergen immunotherapy or treatment with a drug to which a patient is allergic? (2) Once maintenance immunotherapy or maintenance dosage with a drug, such as insulin, is reached without adverse consequences, can you stop the omalizumab and still tolerate the immunotherapy or drug? (3) What immunologic and clinical end points of interest could help predict the ability to use omalizumab in this fashion and to possibly stop the omalizumab after reaching maintenance therapy?

As omalizumab's use becomes more widespread, additional anecdotal case reports will be forthcoming. For example, omalizumab's successful use in patients with chronic idiopathic urticaria (presented by Shapiro et al at the 2007 American Academy of Allergy, Asthma & Immunology Annual Meeting),[5] cold-induced urticaria,[6] and latex allergy[7] have been reported. Although all of these reports will help us better define the utility of strategies to block IgE in diseases other than chronic persistent allergic asthma, one still needs to exercise caution.