Successful Treatment of Hypocomplementemic Urticarial Vasculitis With Omalizumab: A Case Report

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Hypocomplementemic urticarial vasculitis syndrome (HUVS) is a rare small-vessel vasculitis of unknown etiology. It affects the superficial dermis, causing itchy papular lesions that last more than 24 hours, with residual hyperpigmentation. Up to 40%-50% of patients may also have angioedema. The diagnosis requires the simultaneous presence of 2 major criteria (recurrent urticaria >6 months and hypocomplementemia) plus 2 or more minor criteria (biopsy-proven vasculitis of the dermis, positive C1q antibody and/or suppressed C1q titer, glomerulonephritis, arthralgia/arthritis, ocular inflammation, and recurrent abdominal pain). Mild forms are usually treated with antihistamines (frequently ineffective) or indomethacin (25 mg 1-3 times/d). Moderate forms usually respond to corticosteroids (such as prednisone 1 mg/kg/d), colchicine (0.6 mg/12-24 h), dapsone (50-100 mg/d), or hydroxychloroquine (200-400 mg/d). Severe types usually require immunosuppressants such as mycophenolate mofetil (500 mg-1000 mg/12 h), methotrexate (15 mg/d), or azathioprine (1 mg/kg/d).

We present the case of a 60-year-old woman with a history of recurrent urticarial lesions that first appeared in 2014 (Supplementary Figure 1). The lesions lasted more than 24 hours and were sometimes accompanied by facial and neck angioedema. The clinical diagnosis was Sweet syndrome, and a skin biopsy was performed (Supplementary Figure 2). The biopsy revealed a superficial and deep perivascular infiltrate, predominantly lymphocytic, with occasional neutrophils and some eosinophils. The infiltrate permeated some vascular walls, which showed prominent endothelium, although we did not observe fibrinoid necrosis with extravasation of red blood cells, which is consistent with leukocytoclastic vasculitis (Figure). The patient was eventually diagnosed with HUVS.

Two separate blood tests revealed complement depletion (C1q <5 mg/dL [10-25], C3 58 mg/dL [88-165], C4 <0.8 mg/dL [14-44], with C1 inhibitor of 40.50 mg/dL [16.00-33.00]), and normal thyroid-stimulating hormone (2.56 µIU/L [0.55-4.58]). The antinuclear antibody titer was negative (<0.50 IU/mL [<25.00]).

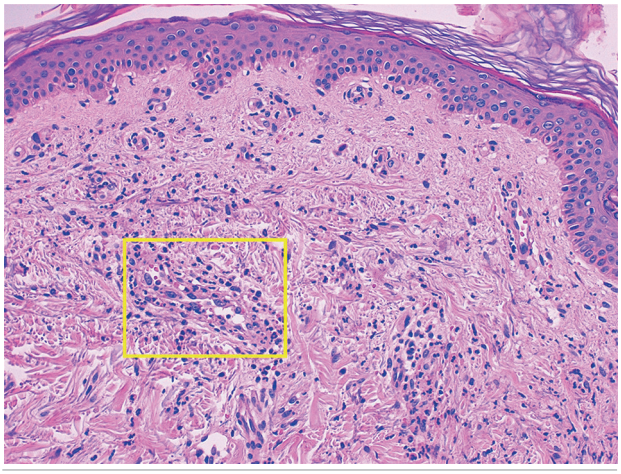

Figure. Superficial and deep perivascular infiltrate, predominantly lymphocytic, with occasional neutrophils and some eosinophils.

It should also be noted that the patient did not develop major organ involvement at any time.

Initially, the patient was treated with prednisone (60 mg/d), although she experienced new flares of erythematous-edematous lesions when the dose was reduced to below 10 mg/d. Levocetirizine was used as an antihistamine. Since she had elevated intraocular pressure, hydroxyzine was contraindicated by her ophthalmologists due to its anticholinergic effect. She continued treatment with prednisone (10-15 mg/d), which was subsequently combined with azathioprine (150 mg/d) and dapsone (100 mg/d). Despite treatment with these drugs, the pruritic maculopapular lesions persisted and were subsequently treated with intramuscular corticosteroids. The patient also began to experience severe corticosteroid-induced adverse effects such as polymyalgia, corticosteroid-induced diabetes (with hospital emergency care for secondary hyperosmolar syndrome), weight gain (20 kg) with cushingoid appearance, and increased intraocular pressure.

Given the poor response to corticosteroids and immunosuppressants, we requested off-label treatment with omalizumab. After we received authorization, the patient started with 300 mg every 4 weeks in 2015. Azathioprine (150 mg/d) and prednisone (10-15 mg/d) were maintained until the skin lesions improved. Both treatments were discontinued after 7 months without symptoms.

Five months later, the patient experienced a severe flare of the skin lesions on her hands and arms that required treatment with prednisone (80 mg/d). As her condition worsened, we increased the dose of omalizumab to 450 mg every 4 weeks. After the third dose, the skin lesions resolved; therefore, we decreased prednisone over 2-3 months and replaced it with hydrocortisone until recovery of hypothalamic-pituitary-adrenal axis function. Corticosteroid-induced diabetes and cushingoid appearance resolved after discontinuation of corticosteroids, and the patient lost 18 kg of weight.

A year later, the patient experienced several episodes of facial angioedema and tongue swelling (treated with prednisone 80 mg/d) and reported maculopapular lesions on both arms and the abdomen. Onset was always around the fifteenth day after administration of omalizumab. Therefore, we decided

to increase the frequency of omalizumab 450 mg to every 2 weeks; this led to complete remission of the skin lesions and angioedema. Nevertheless, complement levels remained low in the last blood sample (C3 62.8 mg/dL [75-140 mg/dL], C4 6.2 mg/dL [10-34 mg/dL]). Both the Weekly Urticaria Activity Score (UAS7) and Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) are validated tools for chronic spontaneous urticaria (CSU) but not for urticarial vasculitis, so they were not used in the clinical assessment [1]. The patient has remained asymptomatic with the same therapeutic protocol (omalizumab alone) since 2017.

Omalizumab is a monoclonal antibody that binds to IgE, thus blocking its action and preventing mast cell degranulation. This in turn leads to a decrease in serum IgE and downregulation of mast cells and basophils. European guidelines support the use of omalizumab as a third-line treatment for patients with CSU. These patients typically respond to omalizumab within the first 4-8 weeks of treatment, and the response is often evident within the first week [2].

Omalizumab has also proven effective in normocomplementemic urticarial vasculitis syndrome (NUVS). Three patients with NUVS experienced complete remission with 300 mg of omalizumab every 4 weeks [3-5], and 1 experienced remission with 150 mg [6]. Evidence regarding HUVS is very scarce. Del Pozo et al [7] reported complete remission in a woman with HUVS and systemic lupus erythematosus after 3 doses of omalizumab (300 mg/mo). Aurich et al [8] reported the absence of response in a patient with C3 depletion after 19 months of up to 600 mg of omalizumab every 4 weeks. Furthermore, Nucera et al [9] reported complete remission of intestinal symptoms, arthralgia, and skin lesions with omalizumab 300 mg/mo.

Although the exact role of omalizumab in HUVS remains unknown, it is believed to hamper cellular activation by reducing chemotaxis and immunocomplex formation. This in turn might suppress basophil activation and degranulation, which are thought to be associated with the cutaneous manifestations of the syndrome. Unfortunately, we cannot explain yet why omalizumab seems to work better for some HUVS patients than for others.

We report the case of a woman with HUVS who responded poorly to immunosuppressants and corticosteroids, both of which induced severe adverse effects. The patient achieved complete remission after therapy with omalizumab 450 mg every 2 weeks. This finding contrasts with those of previous case reports, where remission was reached with monthly doses of 300 mg. Although more studies are needed on treatment of HUVS with omalizumab, the safety and lack of known adverse effects [10] of this monoclonal antibody lead us to propose it as a possible alternative treatment for HUVS in patients with no major organ involvement.

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Conflicts of Interest

EGF has been paid for consultancy by and participated in speakers' bureau for Novartis.

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