Long-term remission of Wells syndrome with omalizumab

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0436
Key words: Wells syndrome; eosinophilic cellulitis; omalizumab; successful treatment.


Eosinophilic cellulitis (Wells syndrome) is an uncommon rare recurrent inflammatory dermatosis that is characterized by a great clinical variability described as itching and/or burning tender erythematous lesions, sometimes with urticaria, vesicles and/or bullae, and granulomatous eosinophilic infiltrates in the dermis. This condition was first described by Wells in 1971 and to date, less than 200 cases have been reported in the literature. The histological features are dependent on the disease stage, but dermal edema, marked eosinophilic infiltrate without signs of vasculitis, and flame figures are characteristic. Peripheral eosinophilia is often reported[1].

We describe the case of a 67-year-old man with history of recurring episodes of erythema with a duration of 1-3 days, with occasional concomitant edema of the limbs, tongue or face, occurring approximately every two weeks for the last 30 years. No trigger factors, including drugs, could be identified. Complete white cell blood count (including eosinophils), tryptase, functional C1-inhibitor esterase, and C4 were within normal range. CT scan of thorax and abdomen was inconspicuous without any signs for malignancy or inflammatory lesions. Analysis of lymphocyte populations with flow cytometry in peripheral blood did not show any signs for monoclonal lymphocytic population. Autoimmune testing for anti-nuclear antibodies and extractable nuclear antigens was negative. Parasitic infections were excluded by stool and serological tests. Prick-tests and specific IgE for food allergy were negative and total IgE was not elevated. Skin biopsy of the arm performed in 2007 revealed a dense dermal perivascular and interstitial lymphocytic and
histiocytic inflammatory infiltrate associated with many eosinophils and “flame figures” compatible with Wells syndrome. Initially, he was treated with antihistamines up to fourfold higher than the licensed doses, then with topical and systemic corticosteroids, later with azathioprine up to 150 mg daily, tranexamic acid up to 1000 mg three times daily and finally with a gluten free diet without any success. Despite a Helicobacter pylori eradication his recurrent skin lesions and edema persisted. He was lost to follow-up and treated by different doctors. Detailed information are not available. Finally, he showed up 10 years later in 2017 because of exacerbating skin symptoms under antihistamines and topical corticosteroids.

New skin biopsy was performed (Figure 1) and showed a dermal infiltrate of perivascular and interstitial lymphocytes and histiocytes with numerous eosinophils, some multinucleate giant cells and typical “flame figures”. At this time, due to recurrent edema and strong pruritus, a concomitant mastcell activation was suspected. In this context, omalizumab 300 mg per month subcutaneously was started. After a few days, the patient felt a dramatic improvement of his skin manifestations and remained asymptomatic under omalizumab during a follow-up of 24 months. Actually, we are trying to discontinue omalizumab by interval prolongation. He is treated now every eight weeks without any sign of recurrence. A complete discontinuation will be attempted in the next 6 months.

The pathogenesis of Wells syndrome remains unknown. One hypothesis is that Wells syndrome is caused by a nonspecific hypersensitivity reaction to different endogenous or exogenous stimuli including infection, vaccination, medication, insect bite, myeloproliferative disorder or malignant disorders. However, despite extensive investigations it is often not possible to identify a trigger factor. A dysregulation of tissue eosinophilia with high IL-5 production may also play a role in the pathogenesis[2, 3].

Multiple treatment regimens have been used with variable success rates in the literature. Due to the rarity of the disease, no randomized placebo controlled clinical trial has been conducted to date. In general, if a trigger factor cannot be detected or eliminated, first line treatments are topical or systemic...
corticosteroids and antihistamines. If the disease recurs, immunomodulatory or immunosuppressive therapies such as dapsone or cyclosporine have been reported as therapeutic options. Other alternative treatments include azathioprine, antimalarial drugs, tacrolimus, interferon alpha and gamma, anti-TNF alpha and colchicine[4].

In 2018, Egeland et al. published the first case of a successfully treated patient with omalizumab[5]. This drug is well established as second line treatment of chronic spontaneous urticaria. Omalizumab binds free IgE resulting in down-regulation of FceRI-expression on mast cells and basophils, preventing their activation with a beneficial effect on the development of urticaria[6]. Other potential mechanisms of action of omalizumab have been mentioned. Eosinophils have been shown to play a role in a multitude of inflammatory and/or autoimmune diseases. Upregulation of the high affinity IgE receptor (FceRI) on skin infiltrating eosinophils has been reported in atopic dermatitis[7] and also in bullous pemphigoid[8]. A small number of patients with these skin diseases have been successfully treated with omalizumab[9, 10]. Therefore, we assume that the skin eosinophils in Wells syndrome may have an upregulation of the FceRI with a subsequent downregulation under omalizumab treatment which may explain the beneficial effect as previously described in atopic dermatitis, bullous pemphigoid and especially in chronic spontaneous urticaria. However, our hypothesis is speculative and needs to be proven with studies by characterization of FceRI on eosinophils in Wells syndrome on treatment.

According to current literature, our patient is the second described case of Wells syndrome with the longest follow-up, successfully responding to omalizumab. Although the mechanism of action of omalizumab is not understood in Wells syndrome, our case demonstrates that omalizumab might be an effective alternative in refractory Wells syndrome.
**Funding sources:** No funding.

**Conflict of interest:** No relevant conflict of interest

**References**


Table Legends

Figure 1. Skin biopsy with marked dermal eosinophilic infiltrate, some multinucleate giant cells and typical “flame figures” (arrow) (hematoxylin and eosin stain, original magnification x200).