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

doi: 10.18176/jiaci.0436

Key words: Wells syndrome; eosinophilic cellulitis; omalizumab; successful treatment.

Palabras clave: Síndrome Wells. Celulitis eosinofílica. Omalizumab. Tratamientoeficaz.

Eosinophilic cellulitis (Wells syndrome) is an uncommon rare recurrent inflammatory dermatosis that is characterizedby a great clinicalvariability described as itching and/or burningtender erythematous lesions, sometimes with urticaria, vesicles and/or bullae, and granulomatous eosinophilic infiltrates in the dermis. This conditionwas first described by Wells in 1971 and to date, less than 200 cases have been reported in the literature. The histological features are dependent of 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 inperipheral blood did not show any signs for monoclonal lymphocytic population. Autoimmune testing for anti-nuclear antibodies and extractable nuclear antigens was negative.Parasitic infectionswere 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 2007revealed a dense dermal perivascular and interstitial lymphocytic and

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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 acidup to 1000mg 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 up10 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 activationwas suspected.In this contextomalizumab 300mg per month subcutaneouslywas 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 24months.Actually, we are trying to discontinue omalizumab by interval prolongation. He is treatednow 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 identifya 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 ratesin the literature. Due to the rarity of the disease, no randomized placebo controlled clinical trialhas been conducted to date. In general, ifa trigger factorcannot be detectedoreliminated, first line treatments are topical or systemic

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corticosteroidsand 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. Omalizumabbinds free IgE resulting in down-regulation of FcεRI-expression on mast cells and basophils, preventing their activationwith a beneficial effect on the development of urticaria[6].Other potential mechanisms of action of omalizumabhave 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 (FcεRI) 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 assumethat the skin eosinophils inWells syndrome may have an upregulation of the FcεRIwith a subsequent downregulation underomalizumab treatment which may explain the beneficial effect as previously described in atopic dermatitis, bullous pemphigoid andespecially in chronic spontaneous urticaria.However, our hypothesis is speculative andneeds tobe provenwith studies by characterization of FcεRI on eosinophils in Wells syndromeon 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 omalizumabis not understood in Wells syndrome, our case demonstrates thatomalizumabmight be an effective alternative in refractory Wells syndrome.

doi: 10.18176/jiaci.0436

Funding sources: No funding.

Conflict of interest: No relevant conflict of interest

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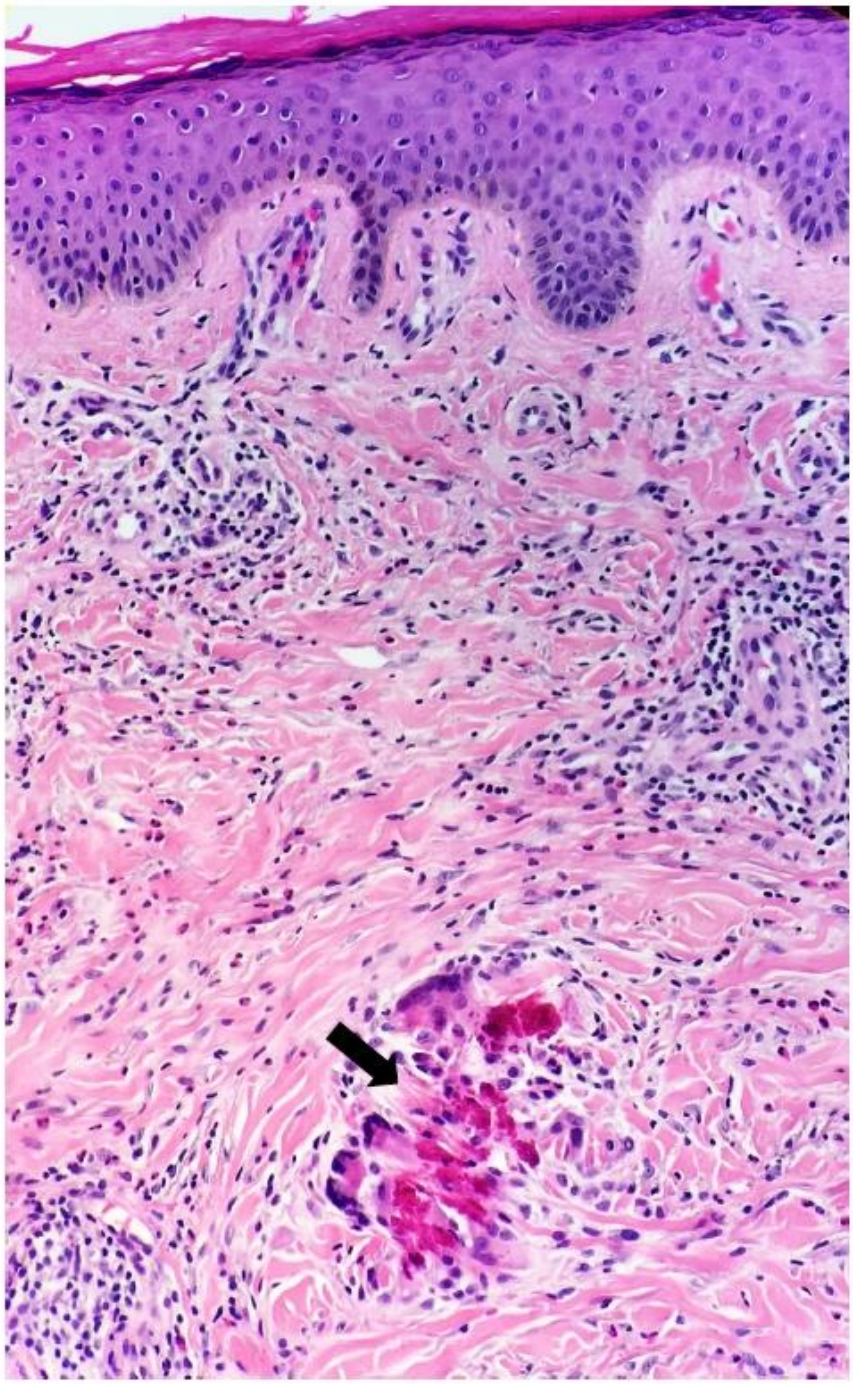
doi: 10.18176/jiaci.0436

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).



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