

Wells syndrome and Chronic Spontaneous Urticaria: report of four cases successfully treated with omalizumab

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Conflicts of interest

Ogueta I, No conflict of interest to declare

Spertino J, has participated in educational activities and clinical trials sponsored by Novartis

Deza G, has participated in educational activities and clinical trials sponsored by Novartis

Alcantara Luna S, has participated in educational activities and has attended congresses and courses sponsored by Novartis.

Zaragoza Ninet V , No conflict of interest to declare

Pujol RM, No conflict of interest to declare

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Medical Advisor for Uriach Pharma, Genentech, Novartis, FAES, GSK, Sanofi Regeneron Research . Grants supported by Uriach Pharma, Novartis, Grants from Instituto Carlos III-FEDER. Educational activities for Uriach Pharma, Novartis, Genentech, Menarini, LEO-PHARMA , GSK, MSD, Almirall, Sanofi

Financing: authors deny any type of funding for the development of this publication

Key words: chronic spontaneous urticaria / Wells's syndrome / omalizumab

Word count: 587

Well's syndrome (George Wells, 1971) or eosinophilic cellulitis is an idiopathic dermatosis characterized by edematous urticarial plaques, simulating bacterial cellulitis or urticaria. It shows diagnostic pathological features and its treatment is difficult and even frustrating. (1,2) Peripheral eosinophilia (15-67%) and diffuse dermal infiltrate of eosinophils with "flame figures", without vascular damage can be present (3). Commonly, WS is diagnosed in adults. The success treating WS with topical and systemic corticosteroid, antihistamines, cyclosporine, dapsone, antimalarials or colchicine is not guarantee in most cases.(4) Although unknown etiology, a type IV hypersensitivity reaction has been suggested. (1) Once WS is clinically suspected, other diseases where eosinophils plays a pathogenic role should be ruled out, including chronic spontaneous urticaria (CSU), insect bites and other eosinophilic syndromes. Concomitant WS with CSU is an uncommon association. Nevertheless we present four patients, objectively documented of CSU and WS, refractory to conventional treatment with optimal therapeutic results with omalizumab.

Clinical features and treatment approach from these four patients is summarized in Table 1. Three women and one man, all of them older than 60 years old, were diagnosed of concomitant CSU with WS, in three Dermatology Departments from different Spanish areas. CSU was present for more than 1 to 20 years with well-defined hives and sometimes angioedema. Concomitantly acute cutaneous eruption of pruritic and painful non-evanescent erythematous and edematous plaques of 2 to 10 days' evolution, mainly in trunk and legs, were observed. Oedema and a dense interstitial and perivascular inflammatory infiltrate with eosinophils, neutrophils, lymphocytes and histiocytes with degranulated eosinophilic material developing "flame figures" were noted in the upper and mid dermis in the forth cases. Because CSU was very active being refractory to antihistamines H1 and even to oral corticosteroids or dapsone, omalizumab was introduced at 300 mg each four

weeks. All the patients achieved in few weeks the complete resolution of CSU and also the WS plaques disappeared. Nowadays the four the patients remain free of symptoms in continuous treatment with omalizumab .

WS is considered as an independent disease excluded from the diagnosis of CSU. In rare instances urticarial lesions (wheals) simulating true urticaria has been reported in patients with WS (5), along with the evidence of a combination of urticarial lesions and eosinophilic cellulitis plaques after episodes of acute sinusitis (6). We suggest that this concomitant rare association is maybe underreported and should be always suspected once wheals and long lasting itchy and painful plaques appear concomitantly.

A type IV hypersensitivity reaction mechanism has been postulated in WS . Environmental and autoimmune trigger factors interacting with tissular mast cells receptors (e.g FcεRI, TLR4, EP1/EP3, etc.) induce the immediate release of mediators, increasing vascular permeability and recruiting inflammatory cells, mainly eosinophils. (7). IL-5 by Th2 cells would exacerbate eosinophils maturation, migration and activation. Some therapeutic options have been postulated as effective for either WS or CSU. Monoclonal antibodies anti-IL5 showed optimal results in eosinophilic diseases (8). Herout et al. published a successful treated case of WS with mepolizumab (9). Egeland et al. reported an optimal response of WS with omalizumab (10). Omalizumab has been demonstrating extremely efficient treating CSU and WS for the four patients enrolled in this communication. Omalizumab may interact directly with eosinophils or through its effect binding tissular IgE, stabilizing the mast cell's degranulation and modifying pro-inflammatory Th2-mediated cytokines/interleukins (IL-5, IL-13, IL-4 and IL-2) that modulate eosinophils and mast cells survival.

CSU and WS is a rarely reported association. Omalizumab is a therapeutic option in patients with WS refractory to conventional treatments, and / or in concomitance with CSU.

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Table 1: Summary of the four cases, with their clinical, histopathological characteristics, laboratory test and evolution.

Figure 1. A. Case 1 Generalized erythematous and edematous plaques in trunk long lasting few days. **B.** Case 1 Higher magnification showing a typical flame figure. HE, 200x. **C.** Case 3 Infiltrated itchy plaques in legs combined with evanescent wheals. **D.** Case 3 Higher magnification with numerous eosinophils and scant lymphocytes; note dermal edema. HE. 200x

Supplementary Figures

Figure 1 supplementary . A. Case 2 Generalized erythematous and edematous plaques in trunk long lasting few days. **B.** Case 2 Higher magnification showing a typical flame figure. HE, 200x.

Figure 2 supplementary A. Case 4 Infiltrated itchy plaques in legs combined with evanescent wheals. **B.** Case 4 Higher magnification with numerous eosinophils and scant lymphocytes; note dermal edema. HE. 200x