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To cite this article: T. Grieco, C. Chello, V. Faina, V.V. Gomes, L. Alei, A. Sernicola, V. Panasiti & S. Calvieri (2018): Omalizumab Therapy in a Patient with Chronic Spontaneous Urticaria, Ulcerative Colitis, Hypereosinophilia and Prurigo Besnier: A Case Report, Journal of Dermatological Treatment, DOI: [10.1080/09546634.2018.1527990](https://doi.org/10.1080/09546634.2018.1527990)

To link to this article: <https://doi.org/10.1080/09546634.2018.1527990>



Accepted author version posted online: 26 Sep 2018.



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OMALIZUMAB THERAPY IN A PATIENT WITH CRONIC SPONTANEOUS URTICARIA, ULCERATIVE COLITIS, HYPEREOSINOPHILIA AND PRURIGO BESNIER: A CASE REPORT

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Abstract

The case of a woman who suffered from CSU and prurigo Besnier, with a history of chronic hyper-eosinophilia, ulcerative colitis and thyroiditis, unresponsive to anti-histamines and steroids is reported. The patient received omalizumab treatment, and obtained resolution of urticaria along with improvement of cutaneous symptoms of prurigo.

Key words

Urticaria, prurigo nodularis, hypereosinophilia

Introduction

Chronic urticaria is a dermatological disorder characterized by the onset of itchy wheals and/or angioedema recurring for at least 6 weeks, with periods of exacerbation and remission. It affects approximately 2-3% of the world population, with a higher prevalence in females.

Chronic urticaria can be divided into inducible urticaria (CIndU) when identifiable trigger factors lead to the cutaneous manifestations and spontaneous urticaria (CSU) when there is no correlation between trigger factors and the disease (1).

The pathophysiology of chronic spontaneous urticaria (CSU) is still unclear, although it is known that autoimmunity plays a pivotal role and that urticaria often coexists with autoimmune diseases such as thyroiditis, vitiligo, or systemic lupus erythematosus (SLE). CSU affects daily activities and social life, leading to reduced quality of life (QoL). Treatment is mandatory, but often unsatisfactory, and management is very challenging when comorbidities induce polytherapy and increase the risk of adverse events.

According to the European Academy of Allergy and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum, World Allergy Organization (EAACI/GA₂LEN/EDF/WAO) guidelines, the treatment of CSU has a multi-step approach.

Use of second-generation anti-H1 histamines is a first line therapy; anti-H1 histamines are titrated up to a four-fold dose, if symptoms persist after two weeks; third line treatment with immunosuppressors, or omalizumab, in case of refractory disease, is recommended (1).

The case of a woman who suffered from CSU and prurigo, with a history of chronic hyper-eosinophilia, ulcerative colitis and thyroiditis, unresponsive to anti-histamines and steroids is reported. The patient received omalizumab treatment, and obtained resolution of urticaria along with improvement of cutaneous symptoms of prurigo.

Case report

A 49-year-old woman first presented to our department in February 2017. At clinical examination, typical itching wheals were present, with many nodular brownish lesions with hematic crusts, widely spread on the skin surface, especially on the trunk and the buttocks, but sparing the face (Figure 1 A, B and C). Wheals had frequently recurred since 2015, and nodular lesions had been present since 2013.

CSU had been diagnosed in 2015, and the patient had been treated with high doses of anti-H1 histamines and systemic corticosteroids, without any improvement. The patient reported that nodular lesions had been diagnosed as prurigo nodularis.

In addition, the patient had suffered from ulcerative colitis since she was 24 years old, and had been treated with Mesalazine 500 mg/day. Chronic hyper-eosinophilia had been present for some years. A hemolymphoproliferative disorder had been previously excluded based on a CT scan and bone marrow examination and parasitic infection was ruled out thanks to negative fecal examination, so a diagnosis of idiopathic hypereosinophilia was established.

The patient was admitted to hospital for laboratory tests. Blood tests showed hyper-eosinophilia (9.2%), D-dimer elevation (869 μ g/L fibrinogen-equivalent units [FEU], normal range 50-420), polyclonal γ -globulin elevation (19.3%) and high levels of thyroid peroxidase autoantibodies (TPO 49 UI/ml (reference values 0.00-34.00), with normal values of thyroid hormones (TSH 1.47 μ UI/ml, reference values 0.27-4.20, FT3 2.2 pg/ml, reference values 2.00-4.40) except for low levels of FT4 (0.85 ng/dl, reference values 0.93-1.70). Data suggested the presence of autoimmune thyroiditis. In addition, levels of vitamin D in the lower range, with increased parathyroid hormone (PTH): vitamin D3 7 ng/mL (reference values 6.23-49.9), PTH 69.8 pg/ml (reference values 15 - 65). Folic acid was deficient: 2.8 ng/mL (reference values 3.80-16.00) and vitamin B12 increased (>2000 pg/ml (reference values 191.00-663.00). Total IgE levels was increased (1243.00 U/ml, reference values 4.00-100.00), while anti-nuclear antibodies (ANA) and extractable nuclear antigen antibodies (ENA) were negative.

We decided to perform an incisional biopsy of one of the nodular lesions. Histopathologic examination demonstrated subacute and chronic dermatitis, with hyperkeratosis, papillomatosis, dermal T cell infiltrate and eosinophil deposits.

Radio-allergosorbent test (RAST) was positive for *Dermatophagoides farinae* (++) and *Dermatophagoides pteronyssinus* (++) , supporting an atopic condition. Patch tests could not be performed because of the severity of the cutaneous involvement. BAT (Basophil activation test) was above the normal range: 18 (normal values < 15).

Considering the laboratory data and the cutaneous manifestations, the diagnosis of Chronic Spontaneous Urticaria in a patient with Ulcerative Colitis, idiopathic hypereosinophilia, autoimmune thyroiditis and prurigo Besnier (atopic dermatitis), was made.

UAS7 was 42, and high dose antihistamines were prescribed, but the patient was unresponsive. Therefore, according to EAACI/GA₂LEN/EDF/WAO guidelines recommendations, omalizumab was chosen as a third-line treatment at the dose of 300 mg sc once a month. One week after the first injection of omalizumab, the patient reported an improvement of the urticaria symptoms, especially itching.

Figure 2 shows itch intensity at baseline and during the 24 weeks after initiation of treatment, recorded by a score from 0 = absence of itch to 30 = severe itch.

Moreover, after the administration of the second dose of omalizumab, the patient noticed a reduction of prurigo lesions (Figure 3, A-B). At the end of 24 weeks of therapy, we observed a resolution of CSU and a significant reduction of dermatological lesions of prurigo (Figure 3, C-D).

Discussion

We describe our experience with effective treatment of CSU in a woman who was also affected by prurigo Besnier (atopic dermatitis) and autoimmune diseases.

Omalizumab is a humanized anti IgE monoclonal antibody approved as third-line, add-on therapy for CSU/CIU in adults and adolescents (>12 years) who fail to respond to H1- antihistamine

treatment (EEACI/GA2LEN/EDF/WAO guidelines) (1).

Omalizumab binds to free IgE, preventing its link to high or low affinity receptors (FcεRI and FcεRII) on mast cells, basophils, eosinophils, and lymphocytes. Consequently, free IgE level is reduced and receptors on cell membranes are downregulated (2, 3). In addition, several effects of omalizumab have been demonstrated: reduced mast cell releasability, reversal of basopenia, improved basophil IgE receptor function, reduced activity of IgG autoantibodies against FcεRI and IgE, reduced activity of IgE autoantibodies against unknown antigens, and decreased role of coagulation involvement (4).

Omalizumab was first used for persistent allergic asthma and was later approved for CSU in patients resistant to anti-H1 histaminic therapy (5).

Conventionally, the activation cascade of mast cells and basophils, leading to release of mediators and clinical manifestations of urticaria, has been considered as IgE mediated, a classical example of type I hypersensitivity reaction. Recent studies revealed a pivotal role of autoimmunity in the pathogenesis of CSU that was thus correlated with autoimmune diseases, including thyroiditis, systemic lupus erythematosus, celiac disease, type I diabetes. Specifically, two subtypes of auto-reactivity were identified: in the first subtype, named type I immunoreaction or "autoallergy", patients produce IgE autoantibodies against autoantigens, most frequently thyroid peroxidase (TPO) (6); in some patients with CSU high levels of IgE against dsDNA were also found. In the second subtype, named type II immunoreaction, affected patients produce IgG autoantibodies against FcεRI, IgE, or both, which can cross-link IgE-occupied or barren FcεRI to activate mast cells and basophils (7).

These findings suggest that, besides the cross linking of FcεRI-bound IgE by antigens, autoantibodies also play an important role in the activation of mast cells, binding to IgE, FcεRI or both (7).

Hyde and Montgomery first described prurigo nodularis in 1909. Multiple hyperkeratotic, erosive papules and nodules, distributed symmetrically on the extensor surface of the limbs, characterize it.

It mainly affects middle-aged women (8). These lesions are characteristically highly pruriginous. Etiopathogenesis is still unknown, although the disease is associated to different disorders: atopic dermatitis, kidney disease, and autoimmune diseases, such as Hashimoto Thyroiditis (9).

In our case, the patient had nodular lesions, together with signs of lichenification and eczema on typical sites, such as popliteal and antecubital fossa and neck; these signs, in association with laboratory data of increased total IgE levels, RAST positive for *Dermatophagoides pter. and far.*, are important features of atopic dermatitis.

No recent literature reports the coexistence between this condition and CSU. TH2-related cytokines are activated and expression of IL-31 is increased both in patients with prurigo nodularis and in those with atopic condition (10). The cell infiltrate of prurigo lesions is predominantly composed of T-lymphocytes, eosinophilic granulocytes and mast cells (11). In addition, increased NGF (nerve growth factor) release by mast cells and eosinophils leads to the activation of nerve fibers and proliferation of keratinocytes (11). Prurigo nodularis has been treated with topical steroids, antihistamines, antidepressants, opioid receptor antagonists, but control of itching and skin lesion regression are seldom achieved (8).

Some cases of omalizumab treatment in patients with atopic dermatitis have been reported with discordant conclusions¹².

Conclusion

Treatment with omalizumab provided complete remission of CSU, along with reduction of prurigo nodularis lesions, in a patient affected by autoimmune diseases. Omalizumab was administered in monotherapy, while no immunosuppression was present. The Authors speculate that omalizumab, in addition to being a suitable and safe option for resistant CSU, may be helpful for diseases that share physiopathologic mechanisms of CSU.

Patient consent

The patient gave consent to the inclusion of material pertaining to herself into this article, she acknowledged that she cannot be identified via the paper; the Authors fully anonymized patient's material.

Disclosure of interest

The authors report no conflict of interest.

Acknowledgements

Laura Brogelli, PhD, on behalf of Content Ed Net, provided editorial assistance for the preparation of this manuscript; this assistance was funded by Novartis Farma Italy.

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Figure legends:

Figure 1. Skin lesions at presentation. A) wheals on the lower limb. B) brownish papules and nodules spread on the upper limbs. C) papules and nodules on back and buttocks.

Figure 2. ITCH score during treatment with Omalizumab. The score is described as a weekly score, reporting the sum of the ITCH score in each day of the week. 0=no itch; 10=mild itch; 20=moderate itch; 30=severe itch

Figure 3. A) and B) Three months after the first administration of omalizumab, both urticaria and prurigo were improved; C) and D) Six months after the first administration of omalizumab, urticaria had remitted and nodular lesions were scant.

Figure 1

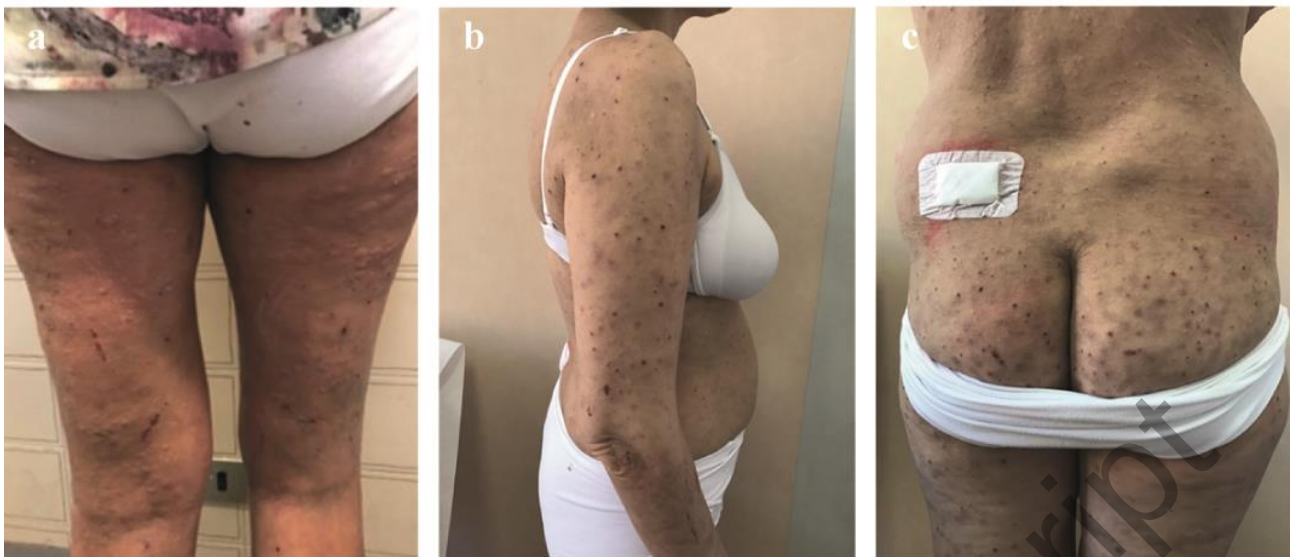


Figure 2

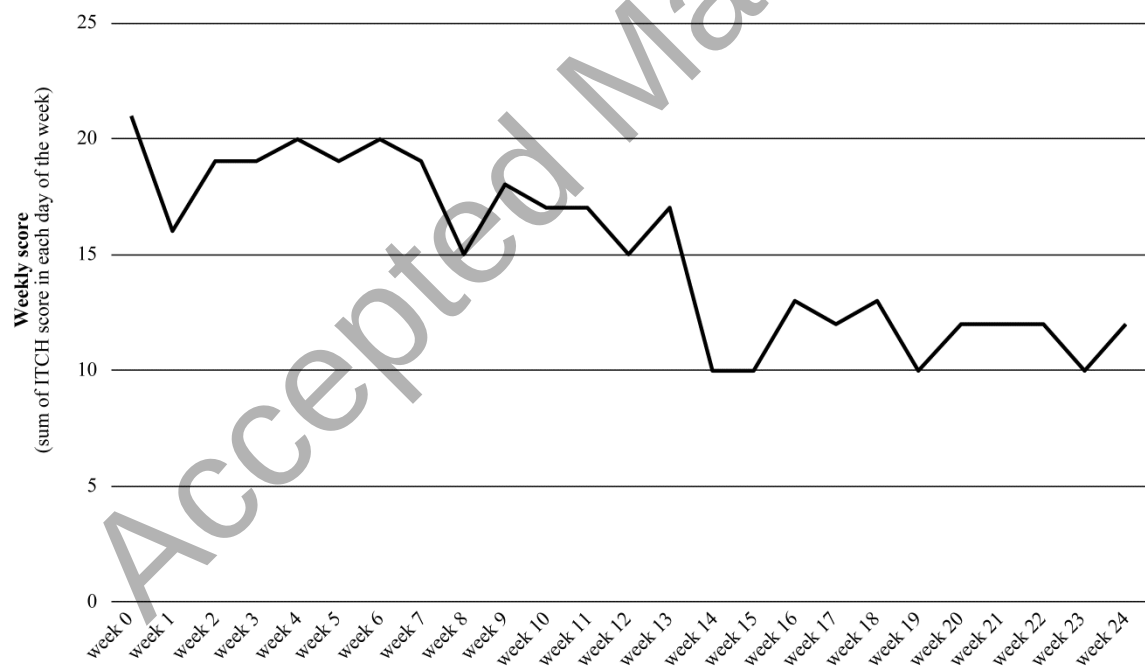


Figure 3

