Allergol Immunopathol (Madr). 2014;42(1):78–87

Allergologia et immunopathologia

www.elsevier.es/ai

RESEARCH LETTERS

Successful treatment of severe delayed pressure angio-oedema with omalizumab

To the Editor,

Delayed pressure angio-oedema (DPA) is a very rare form of physical cutaneous disorder.[1] The symptoms typically occur 4 to 6 h after applying any type of pressure such as wearing tight clothing, hammering, walking or sitting down. Therapeutic management is complex and frustrating and the impairment of quality of life is very relevant. Omalizumab is a recombinant, humanised, monoclonal antibody directed towards Immunoglobulin E (IgE), approved as an option for the treatment of severe allergic asthma.[2] It has also been used in the treatment of other cutaneous diseases like atopic dermatitis, mastocytosis and chronic urticaria. We present a unique case of complete symptom relief from DPA 48 h after the first dose of omalizumab.

We present the case of a 45-year-old woman suffering from isolated delayed pressure angio-oedema without urticaria during the previous 11 years. At first, symptoms occasionally occurred after intensive and prolonged pressure on different body regions, afterwards those episodes appeared while performing daily activities, to such an extent as to alter and void the patient daily work activities as a highway cashier, as they appeared almost daily. She did not have hives in any of the episodes. Not immediate but delayed dermographism appeared; pressure test was positive. Pressure test was performed using a forearm sling with a 4 kg weight attached for 10 min, local forearm angio-oedema was observed 6 h after the pressure had been applied (Fig. 1). This test was later reproduced in the same patient and was negative in two controls. The carried out study revealed an increased of total IgE of 600 UI/mL (<100 UI/mL). Skin-prick-testing was negative both against a common battery of aeroallergens and of foods. Moreover, the assessment included thorax X-rays, blood count and biochemistry, renal, hepatic and thyroid function analyses, stool parasite exam, hepatitis B and C serologies, Antinuclear-Antibody-Test, cryoagglutinins, complement (C3, C4, C1-inh, C1q), Immunoglobulins G, A, M. All the results were within the normal range or negative. Initially, symptoms became occasionally evident during moderate exercise and were controlled with antihistamines H1-blockers, but subsequently they increased

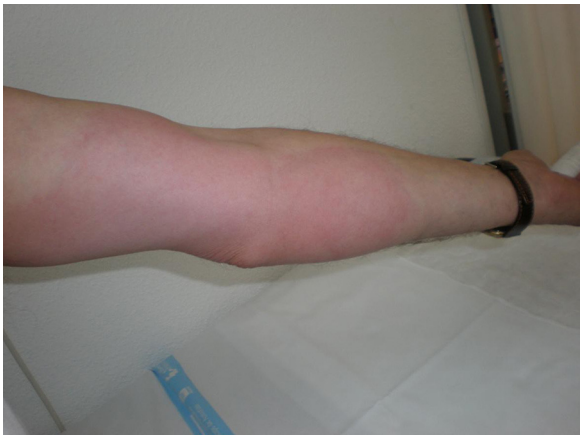

Figure 1 Pressure test was performed using a forearm sling with a 4 kg weight attached for 10 min and local forearm angio-oedema was observed 6 h after pressure had been applied.

their frequency until they disrupted her daily work activities, not achieving enough therapeutic response, although the patient was taking maximum daily doses of H1-blockers. Therefore, she required oral corticosteroids, firstly on a tapered basis and later on a daily basis (prednisone 5–25 mg/day). After three years of daily intake of corticosteroids, methotrexate (7.5 mg/week) was added to the former medication and attained total control of the symptoms just after 24 h of the first dose, the patient was able to discontinue the corticosteroids treatment. After five months of treatment, methotrexate had to be suspended due to hepatotoxicity and four months later we had to reintroduce oral corticosteroids. Two years later, despite taking daily corticosteroids treatment the patient showed an intense decrease of her Quality of Life, measured by Dermatology-Life-Questionnaire: 20 (0–30). Finally, omalizumab 300 mg fortnightly was initiated as an off-label therapy.

Patient's symptomatology disappeared 48 h after the first dose, letting us taper off oral corticosteroids until complete discontinuation. Our patient remained symptom-free for five months, while using omalizumab, the anti-IgE treatment was stopped after these five months. However, two months after the anti-IgE last dose extremely intense symptoms reappeared, eliciting delayed pressure angio-oedema, the patient required an increase on the dosage

of prednisone up to 1 mg/kg/day without symptomatic control. Omalizumab was then reinstated at the same dose as had been used previously (300 mg fortnightly), due to the total IgE level maintenance. The patient's symptoms disappeared after six days of the reinstatement of omalizumab attaining total control of the symptoms which continues at present, so as to avoid corticosteroids intake. Nine months later she remained asymptomatic receiving monotherapy with omalizumab and we could prescribe it monthly, at a dose of 300 mg/month. We tried to increase the dose interval to five weeks, inducing symptoms relapse at the end of the fourth week, probably due to the 26-day half-life previously described for omalizumab[2]. Therefore we prescribed omalizumab at a fixed four-week interval showing effectiveness, as to maintain total symptomatic control.

Recently, the utility of omalizumab as a treatment for chronic urticaria has been described.[3] There is a general consensus that, in chronic urticaria the underlying cause is never an allergy, despite the fact that high levels of total IgE and several autoallergic mechanisms have been identified and reported as autoimmune chronic urticaria.[4] Omalizumab has been used to treat both severe and antihistamine-resistant chronic urticaria. A total amount of 63 patients with chronic urticaria treated with omalizumab have been reported in the literature. Although several clinical trials have been developed demonstrating a satisfactory response to omalizumab, no studies have been performed with this drug to treat DPA.[3,4] The former results have demonstrated that the use of omalizumab as a treatment for chronic urticaria, which seemed a promising therapeutic option, has become a recommended therapeutic option for those patients who do not achieve total control of their symptoms after using conventional treatments, as stated by the recent EAACI/GA^{2}LEN/WAO/EDF guidelines as fourth-line therapy.[5]

However, this has not happened to the same extent to angio-oedema, presumably due to the small number of patients reported in the literature.[6] When conventional treatment included in current guidelines for angio-oedema management such as corticosteroids and antihistamines are not effective, some therapies, namely immunosuppressive agents (i.e. cyclosporine and methotrexate) are used.[7] Nevertheless, potential severe side effects shall arise due to the high doses of this drugs required and their long-term use. Cyclosporine has been used, showing no response. Non-responsive patients may require alternative therapies such as methotrexate, which elicited hepatotoxicity in our patient. Therefore, omalizumab constitutes a safer option and, on a long-term basis, and demonstrates cost-effectiveness for delayed pressure angio-oedema.

The unusual nature of this case of severe long standing delayed pressure angio-oedema, together with the exclusivity of its rapid and spectacular preliminary response to omalizumab, similar to that achieved with methotrexate, and the fast response after its reinstatement, following a cessation and severity relapse, reinforces the theory of immunomodulation beyond the presumed free-IgE blockage mechanism. Additional mechanisms of action which have been suggested for omalizumab are the reduction of expression of *FcεRI* on the surface of basophils and the prevention of the release of mast cell mediators[2,8] induction of eosinophil apoptosis and the downregulation of the inflammatory cytokines IL-2 and IL-13.[9] Moreover, a reduction in B-cell activation and homing and in TNF-α and IL-4 production has been proven as well as an increase in INF-γ synthesis and an enhancement of the activity in peripheral blood CD4+ by measurement of ATP release.[10]

The aetiopathogenesis of DPA is still unclear and different mediators could play a significant role. The demonstrated and sustained efficacy of omalizumab in the treatment of DPA in our case suggests an immunomodulator mechanism that needs further observations. Omalizumab could be a valid, safe and an effective therapeutic option for patients suffering from DPA who do not respond to conventional treatment.

Ethical disclosures

Patients' data protection. Confidentiality of Data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Protection of human subjects and animals in research. Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Author's contribution

MRR, JBE and DAA were involved in patient follow-up, pharmacologic advisory and data analysis.

MRR, DAA, JBE, MJSG and MAMS were involved in patient follow-up and writing manuscript.

Conflict of interest

There are no known conflicts of interest for the authors.

References

1. Kaplan AP. Urticaria and angioedema. In: Adkinson Jr NF, Brochner BS, Busse WW, et al., editors. Middleton's allergy principles & practice. 7th ed. Philadelphia: Elsevier, Inc.; 2009. p. 1071–2.
2. Bang LM, Plosker GL. Spotlight on omalizumab in allergic asthma. BioDrugs. 2004;18:415–8.
3. Cassano N, Mastrandrea V, Vestita M, Vena GA. An overview of delayed pressure urticaria with special emphasis on pathogenesis and treatment. Dermatol Ther. 2009;22 Suppl. 1:S22–6.
4. Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatmen of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol. 2008;122:569–73.
5. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau, et al. EAACI/GA^{2}LEN/EDF/WAO guideline: management of urticaria. Allergy. 2009;64: 1427–43.

6. Sands MF, Blume JW, Schwartz SA. Successful treatment of 3 patients with recurrent idiopathic angioedema with omalizumab. J Allergy Clin Immunol. 2007;120:979–81.
7. Metz M, Maurer M. Omalizumab in chronic urticaria. Curr Opin Allergy Clin Immunol. 2012;12:406–11.
8. Rodríguez-Trabado A, Fernández Pereira LM, Romero-Chala S, García-Trujillo JA, Cámara Hijón C. Monitoring omalizumab treatment efficacy in chronic urticaria by the basophil activation test. Allergol Immunopathol (Madr). 2011 [Epub ahead of print].
9. Lemoli E, Piconi S, Fusi A, Borgonovo L, Borelli M, Trabattoni D. Immunological effects of omalizumab in chronic urticaria: a case report. J Investig Allergol Clin Immunol. 2010;20:252–4.
10. Sánchez-Machín I, Iglesias-Souto J, Franco A, Barrios Y, González R, Matheu V. T cell activity in successful treatment of chronic urticaria with omalizumab. Clin Mol Allergy. 2011;9:11.

M. Rodríguez-Rodríguez*, D. Antolin-Amerigo, J. Barbarroja-Escudero, M.J. Sánchez-González, M. Alvarez-Mon

Servicio de Enfermedades del Sistema Inmune-Alergia, Hospital Principe de Asturias, Departamento de Medicina, Universidad de Alcalá, Hospital Universitario Príncipe de Asturias, Madrid, Spain

* Corresponding author.
E-mail addresses: mercedesrr@gmail.com (M. Rodríguez-Rodríguez), dario.antolin@gmail.com (D. Antolin-Amerigo), jose.barbarroja@uah.es (J. Barbarroja-Escudero), medicimj@yahoo.es (M.J. Sánchez-González), mademons@gmail.com (M. Alvarez-Mon).

http://dx.doi.org/10.1016/j.aller.2012.11.001

Occupational airborne contact dermatitis caused by usnic acid in a domestic worker

To the Editor,

Lichens are composite organisms consisting of the permanent association between a fungus and an alga. The fungus component is called mycobiont and the algal component is called phycobiont; both grow in a symbiotic relationship[1], usnic acid is one of their main components and it is found in different types of lichens.[2] In Portugal, there are four predominant species of lichens: *Parmelia reticulata*, *P. caperata*, *Ramalina lusitana*, and *R. usnea*, which grow mainly on olive trees.[3,4] Airborne allergic contact dermatitis (AACD) caused by lichens[4,5] may simulate photodermatitis due to its preferential location in exposed areas of the skin. In rural workers, AACD may appear in the context of an occupational dermatitis, which is sometimes disabling, or it may affect those involved in outdoor leisure activities.[5]

Herein, we described the case of a 46-year-old Caucasian woman, rural domestic worker, who carried oak and olive wood for fireplaces, mainly between the months of October and March.

The patient was referred to the dermatology department because of an intensely pruritic erythematous scaling dermatitis, involving the face, neckline, and extensor surface of the hands, forearms and lower limbs. On the face, the eyelids, earlobes, and retroauricular fold were affected. The extensor surface of the forearms and hands showed extensive lichenification (Fig. 1). The dermatitis had started in the autumn, and persisted throughout the winter, with worsening on the uncovered areas in the beginning of the spring.

The patient had a history of asthmatic bronchitis and allergic rhinitis in childhood and had been followed for her respiratory allergies since 1993. Her most recent laboratory investigations showed: D2-*Dermatophagoides farinae* specific IgE 90.10 kU/L (class 5); D1 *D. pteronyssinus* specific IgE > 100 kU/L (class 6), and total Ig E 1977 U/mL (ref < 87).

The patient underwent patch testing with the Basic Series adopted by the GPEDC (Grupo Português das Dermites de Contacto), and the Gloves and Clothing Series, all of which were negative.

Faced with the possibility of photodermatitis, the patient performed tests with the Photo Allergen Series, which showed the following positivities: lichen acid mix and usnic acid, after UVA irradiation with 5 J/cm^2 (Table 1 and Fig. 2).

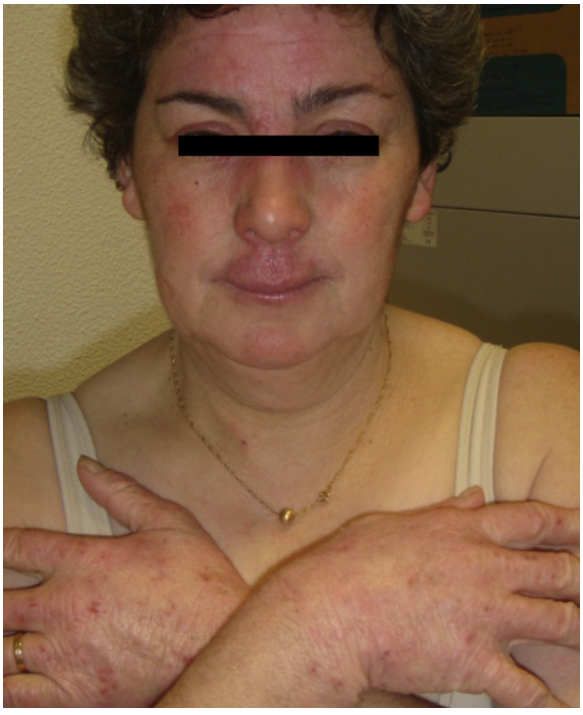

Figure 1 Erythemato-squamous dermatitis, involving the face, eyelids, earlobes, retroauricular fold, neckline, extensor surface of the hands and forearms.