

THERAPEUTIC HOTLINE: LETTER

A severe adverse reaction to omalizumab therapy in chronic spontaneous urticaria

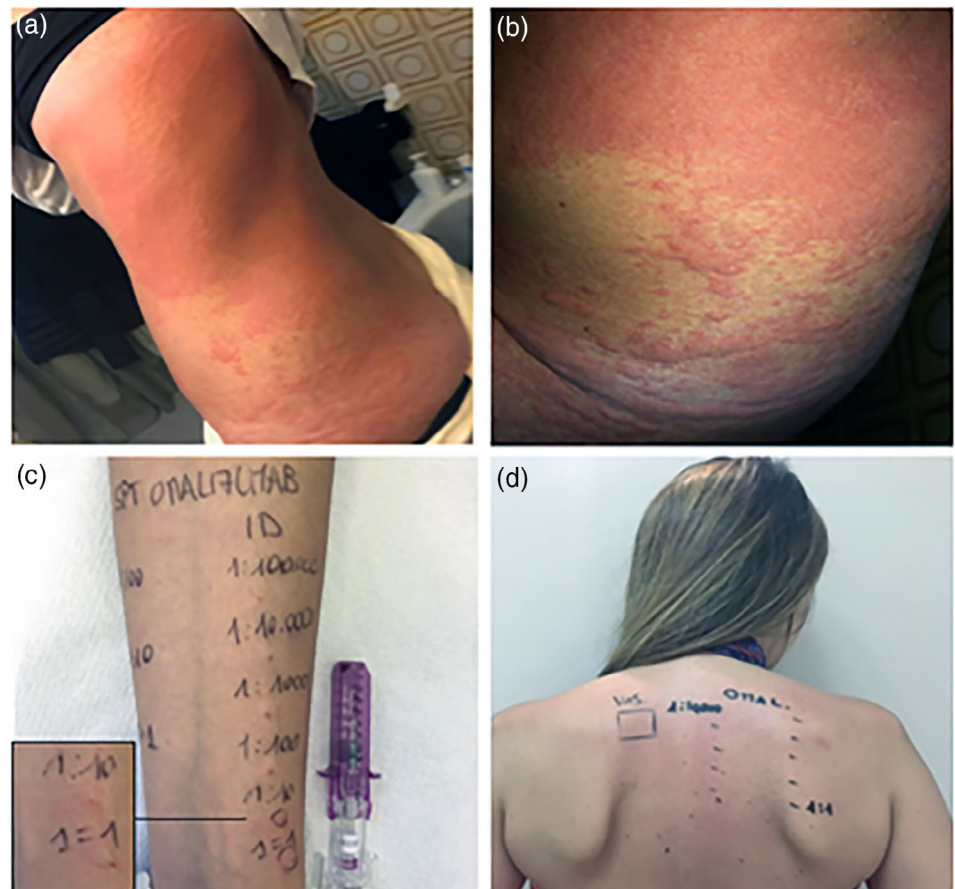
Omalizumab is a humanized IgG1-k monoclonal antibody(mAb), which binds the C3 domain of free IgE, inhibiting its interaction with the high-affinity IgE receptor (FcεRI) on the surface of basophils, mast cells, and dendritic cells (Lieberman, Jones, Rajwanshi, Rosén, & Umetsu, 2017). Adverse events to omalizumab have been rarely described (Lieberman et al., 2017; Perino, Freymond, Devouassoux, Nicolas, & Berard, 2018). Specifically, anaphylaxis was reported in 0.1 to 0.2% of patients, but the underlying mechanism remains unknown (Lieberman et al., 2017). Adverse events of omalizumab may depend on the murine component of the drug or may be due to specific excipients (Lieberman et al., 2017).

A 33-year-old Caucasian woman presented to our department in February 2019 with a 2-year history of antihistamine-resistant chronic spontaneous urticaria (CSU) with only partial response to oral corticosteroids. The patient underwent screening tests for CSU. Laboratory

investigations for basophil activation test (BAT) and for an autoimmunity panel were negative. Total IgE count was 187 UI/mL, while D-dimer, fibrinogen, and eosinophils were in the normal range.

According to the personal medical history, we decided to start subcutaneous omalizumab 300 mg. About 12 hr after the first administration, the patient experienced pyrexia (body temperature: 37.5°) and headache with resolution after a few days. A general remission of urticaria was also observed.

About 24 hr after the second administration, the patient developed a severe diffuse painful urticarial rash (UAS7: 42) (Figure 1) associated with systemic symptoms of vomiting, mucous diarrhea, and diffuse muscular pain, poorly responsive to both oral antihistamine (ebastine 10 mg twice/day) and steroids (methylprednisolone 16 mg twice daily for a week, then betamethasone 4 mg intramuscular twice daily for 2 days). Blood tests were performed, resulting within normal range, except for an



FIGURES 1 (a,b) Severe diffuse painful urticarial rashes. (c) Negative skin prick test (SPT) and positive intradermal test (ID) to omalizumab. Inset, lower left: note the positivity to omalizumab at the intradermal test. (d) Negative patch test to omalizumab

increase of total IgE (645.20 UI/mL). Although omalizumab was already immediately discontinued and intravenous (i.v.) treatment with betamethasone 4 mg $\times$ 2/day, chlorpheniramine 10 mg/day, ranitidine 50 mg/day, and saline solution 500 ml/day were performed for 1 week, the reaction continued to be refractory and persistent.

Despite the patient refused a cutaneous biopsy, we studied the patient for antidrug antibodies (ADA), skin prick test (SPT), intradermal test (IDT), and patch test. IDT resulted positive at the concentrations of 1:10 and 1:1, while ADA, SPT to omalizumab, and patch test at concentrations from 1:10.000 to 1:1 were negative (Figs1-1).

Two weeks after the interruption of i.v. treatment with antihistamines and steroids, we observed a relapse of urticarial lesions, preceded by diarrhea. Consequently, we recommended cyclosporine at the dosage of 4 mg/kg per day, observing only the persistence of urticarial lesions, after 50 days of follow-up.

Although rare, severe side effects can be present in patients treated with omalizumab. Many factors can influence the onset of adverse reactions: protein structures, glycosylation, degradation products, route of administration, dosage, treatment scheme, excipients, and concomitant use of other immunomodulators (Perino et al., 2018). In this regard, delayed-onset anaphylaxis after 1 day from the administration of omalizumab has also been reported, mainly due to excipients such as polysorbate (Limb, Starke, Lee, & Chowdhury, 2007; Price & Hamilton, 2007).

Analyzing signs and symptoms presented by our patient and considering the current classifications of mAbs adverse reactions (Patel & Khan, 2017), the patient's reaction can be classified either as a "type α overstimulation", "cytokine release syndrome or as a type β hypersensitivity reaction IgE", "IgG or immune complexes mediated as a serum-sickness like reaction" (Patel & Khan, 2017). In any case, despite the negativity of the tryptases and ADA, according to IDT positivity, as well as to the clinical aspects of the reaction, we can describe our patient's reaction a possible IgE-mediated delayed-onset anaphylaxis to omalizumab.

In conclusion, omalizumab is a very effective drug that has deeply changed the history of patients with severe allergic asthma and chronic urticaria. Given the possibility, albeit rare, of both immediate and delayed drug-related adverse events, patients should be made aware of the occurrence of adverse events. In case of adverse reactions, it is always advisable to precisely assess whether the drug is the cause of the reaction, if it is an exacerbation of the disease or there are external factors possibly related to adverse event, before discontinuing therapy, especially in cases where omalizumab is effective.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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