Granulomatous foreign-body reaction with facial dermal fillers after omalizumab treatment for severe persistent allergic asthma: a case report

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MADAM, During the past few decades, an increasing number of soft-tissue filler substances have been introduced to the beauty market worldwide for treating age wrinkles, correcting atrophic scars or small cutaneous defects, and cosmetically augmenting soft tissue of different parts of the body.[1] Although these injectable fillers are considered safe, significant adverse reactions may occur.[2] As was reported with interferon alfa, new immunomodulatory therapies used for inflammatory and allergic disease may produce a foreign-body granulomatous reaction in patients injected with dermal fillers.[3]

We report on a case of a patient who had received hyaluronic acid (HA) and calcium hydroxylapatite injections and showed foreign-body granulomatous reaction after omalizumab administration for severe persistent allergic asthma.

A 50-year-old white woman with facial erythematous nodules was referred to our clinic. She had received treatment for adult-onset severe allergic asthma with maximal inhaled corticosteroids and montelukast, but the asthma remained poorly controlled, with frequent exacerbations requiring monthly courses of oral steroids. A 16-week trial treatment with omalizumab (300 mg subcutaneously per month) was started. The last short course of oral steroids for an exacerbation was stopped 10 days before the first administration of omalizumab.

Oedema, first localized on the eyelids, appeared 2 weeks after the first administration of omalizumab and disappeared after application of a topical steroid. The facial oedema recurred after the second monthly injection, but was more extensive, and persisted. The patient had blue-red swelling mainly on the eyelids and upper and lower lips (Fig. 1). On palpation, these nodules were painful and moved but were not well defined. Neither fever nor lymphadenopathy was noted.

The patient had received annual cosmetic filler injections in the nasolabial folds, lips and eyelids since 2006. The dermal fillers were HA in 2006, 2008 and 2009, and calcium hydroxylapatite in 2008.

Results were normal for all laboratory tests, including serum chemistry, full blood cell count, erythrocyte sedimentation rate and levels of angiotensin-converting enzyme and C-reactive protein. Histopathological examination of a lip nodule by a 4-mm punch biopsy revealed a foreign-body granulomatous reaction at the dermal–subcutaneous fat border that was composed of histiocytic cells and lymphocytes surrounding densely packed, small, round cystic spaces that contained translucent, nonbirefringent, uniformly sized microspheres (Fig. 2). The patient received prednisone (1 mg kg^{-1} daily) for 15 days with gradual reduction of the dose, combined with doxycycline (100 mg daily) for 3 months. Despite improvement in asthma control with the first omalizumab injection, it was decided to withdraw omalizumab. Clinical improvement was noted after 2 weeks of oral steroid treatment. Further improvement was noted at 8 months, but fibrous nodules were still palpable.

Omalizumab is considered a safe and well-tolerated treatment for asthma. However, several cases of Churg–Strauss syndrome have been reported after treatment in patients with severe eosinophilic asthma.[4] To the best of our knowledge, our case is the first report of a foreign-body granulomatous response to dermal filler injection after omalizumab treatment.

Our histological findings suggest that the granulomatous reaction was mainly due to calcium hydroxylapatite microspheres. Only a few macrophages were observed around the particles, and the microspheres appeared to be packed

Fig 1. Inflammatory facial oedema after the second monthly omalizumab administration for severe persistent allergic asthma in a 50-year-old woman who had received multiple cosmetic filler injections for 4 years without previous side-effects.

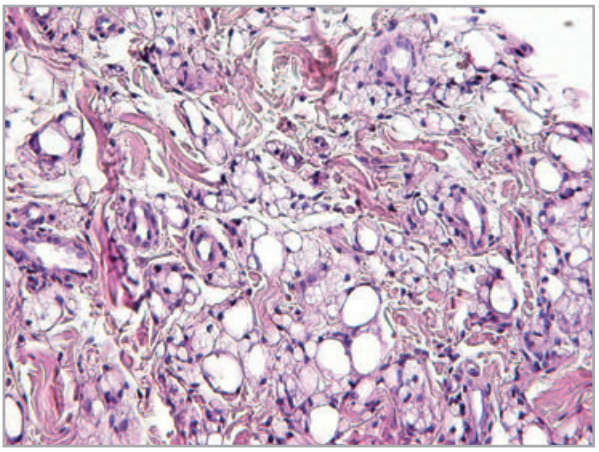

Fig 2. Histology of a skin nodule showing foreign-body granulomatous reaction composed of histiocytic cells and lymphocytes surrounding small, round microspheres after omalizumab administration.

together, had a round or oval shape, and were surrounded by some fibrin fibres, with little cellular infiltrate.[5] Granulomas develop from a delayed hypersensitivity phenomenon. The induction of dermal filler granuloma by an immunomodulatory drug has been observed with interferon treatment.[3] Interferon may induce systemic sarcoidosis, especially in patients with chronic hepatitis C. Dermal fillers may be a target in the interferon-induced granulomatous reaction.

Omalizumab is a monoclonal anti-IgE antibody which reduces exacerbations and the need for inhaled or systemic corticosteroids in patients with moderate to severe allergic asthma.[6,7] The inflammatory granulomatosis facial reaction occurred only 2 weeks after the first omalizumab injection. We cannot exclude that frequent use of systemic corticosteroid treatment could have masked the foreign-body granulomatous reaction in our case, but the rapid and enhanced development of this reaction after omalizumab initiation, as well as the worsening after the second administration, suggests the direct responsibility of omalizumab. A deviation of immunity from T helper (Th) 2 to Th1 cells may explain the granulomatous reaction as proposed in interferon-induced granuloma.[3] Rapid reduction in systemic steroid use may participate in this process, as was reported for Churg–Strauss syndrome masked by long-term corticosteroid treatment.[4]

Clinicians and patients must be aware of the risk of foreign-body granulomatous reactions after omalizumab treatment. In the same way that we think dermatologists should inform patients who receive interferon alfa of the risk of any filler injection and may exclude them, asthmatic patients who are candidates for omalizumab treatment should also receive this information. Before initiation of omalizumab treatment for asthma, patients should be asked about previous use of dermal fillers, and patients with dermal fillers must be monitored during omalizumab administration, especially when steroid use can be reduced.

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Blaschkoid distribution of cylindromas in a germline *CYLD* mutation carrier

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Madam, Familial cylindromatosis (FC; OMIM 605018), also known as 'turban tumour' syndrome, is characterized by the development of multiple cylindromas as the only tumour type. FC is caused by mutations in the gene encoding the CYLD protein.[1] More than 75 different mutations in the *CYLD* gene of patients with FC have been reported to date. This report presents a Japanese case with multiple cylindromas developing along Blaschko's lines, which contained a novel *CYLD* gene mutation.

A 75-year-old Japanese woman presented with multiple nodular tumours on her right arm and chest. She had first