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ARTICLE



Effective treatment with omalizumab of a patient with spontaneous chronic urticaria and eosinophilic esophagitis

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ABSTRACT

This article reports the clinical history of a patient who had been affected by chronic spontaneous urticaria for 13 years, resistant to currently recommended therapy, and who was also diagnosed eosinophilic esophagitis. The anti-IgE monoclonal antibody omalizumab was rapidly effective and induced the clinical remission of both diseases.

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Chronic spontaneous urticaria; eosinophilic esophagitis; omalizumab; esophagogastro-duodenoscopy

Introduction

Omalizumab is a humanized monoclonal antibody directed against E immunoglobulin (IgE), recommended for the treatment of allergic asthma and of chronic spontaneous urticaria (CSU) resistant to treatment with antihistamines (1). Urticaria is a series of skin conditions characterized by itching wheals, possibly associated with angioedema. Urticaria recurring for longer than 6 weeks is defined chronic, while acute urticaria usually lasts less than 3 weeks (2). Chronic urticaria heavily affects the quality of life of the patient and it is not easily managed. Eosinophilic esophagitis is a chronic inflammatory disease, characterized clinically by dysphagia and pathologically by eosinophilia of the esophagus. Diagnosis is made by 3 criteria: symptoms of esophageal dysfunction; presence of ≥ 15 eosinophils/high power field in at least 1 esophageal biopsy, with few exceptions; eosinophilia limited to the esophagus, with exclusion of other possible causes of esophageal eosinophilia, including proton pump inhibitors (PPI) responsive esophageal eosinophilia. It may be associated with allergy and epigastric pain, and symptoms do not respond to proton pump inhibitors (PPI) (3). This article reports the history of a patient affected by antihistamines-refractory CSU and eosinophilic esophagitis, who had remission of both diseases after therapy with omalizumab.

Patient and treatments

A 67-year-old woman, affected by allergic rhinitis and chronic urticaria (Figure 1) reported recurrent episodes of urticaria since 2003, and heartburn; other symptoms of esophageal dysfunction: dysphagia, regurgitation, and abdominal pain were present. Remission of episodes was obtained with administration of oral corticosteroids, antihistamines, and PPI for several months. Starting from 2004 oral corticosteroids stopped to control urticaria (single administration, combination, or association with low dose drugs, were all ineffective). The patient was hospitalized 3 times

between 2004 and 2006, for chronic urticaria episodes. A skin biopsy was taken during a period free from urticaria and drug administration; histology ruled out urticarial vasculitis. Autologous serum test was also performed in the same period, and was negative. Esophagogastroduodenoscopy showed the presence of duodenitis, inflammation of the gastric antrum with *Helicobacter pylori* isolates. Blood examination demonstrated the absence of antinuclear antigen and antibodies against the gastric wall; C3 and C4 levels were normal as well circulating immune complexes (6, 3 EU/ml); normal levels of IgE were detected. Moreover, the patient has not showed any sensitization to allergens. Pulmonary involvement was excluded by function tests and thorax radiography. Type 2 diabetes mellitus was diagnosed during hospitalization. The patient has been resistant to the treatment with second-generation antihistamines since the second admittance to hospital and only high dose corticosteroids have been subsequently effective. In order to reduce corticosteroids dosage, the anti-leukotriene drug montelukast 10 mg was associated, but no improvement of outcomes was obtained. Cyclosporine A 3 mg/kg/day was started in September 2005, and urticaria and heartburn remitted completely. Cyclosporine A therapy was repeated several times with lower doses, for 3–4 months, and each time remission lasting for 6–7 months was obtained. No adverse events occurred, blood examination and renal function tests were normal, and blood pressure level did not change, during therapy with cyclosporine A. In 2006, the eradication of *H. Pylori*, evidenced through the breath test, was obtained after a first cycle of 5 days of therapy with amoxicillin 2 g/day, clarithromycin 1 g/day and omeprazole 20 mg/day, followed by another 2 cycles of 5 days each of amoxicillin 1 g/day and PPI (omeprazole 2 mg/day). The use of PPI was discontinued during remission periods without heartburn rebound. As corticosteroids were administered only in concomitance with urticaria recurrences, and heartburn was present only in the same periods, it was thought that pain could be due to intolerance to oral corticosteroids. Esophagogastroduodenoscopy was repeated in November 2012,



Figure 1. Skin area affected by itching wheals, at patient presentation.

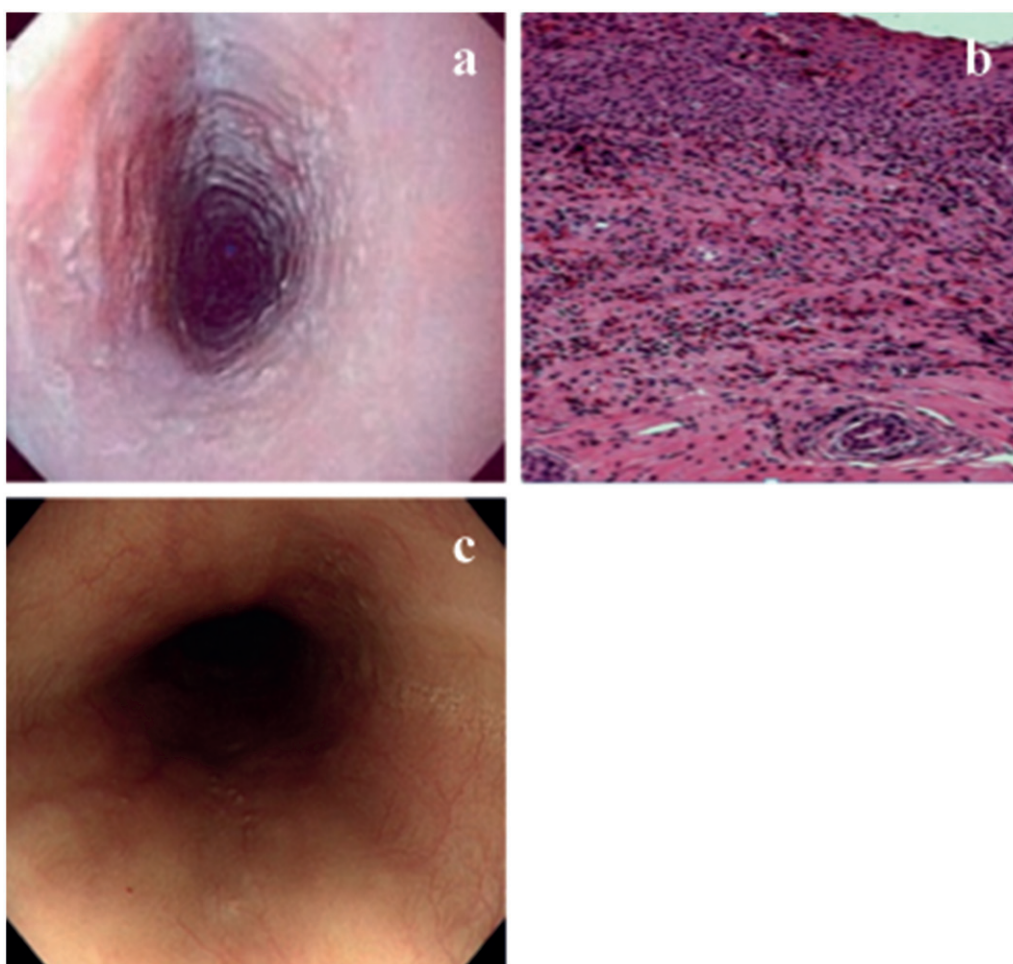


Figure 2. Endoscopic appearance of eosinophilic esophagitis, as shown by esophagogastroduodenoscopy before omalizumab treatment (a), and its resolution after omalizumab treatment (c). Esophageal biopsy showed inflammatory infiltrate, with high concentration of eosinophils, before omalizumab treatment (b). Haematoxylin and eosin staining.

and it showed a light hyperemia of the distal esophagus, a little sliding hiatal hernia, hyperemic and polypoid-like mucosa of the pylorus, and two little ulcers of the upper duodenum. A hyperplastic polyp was demonstrated by the histologic examination of a biopsy of distal esophagus. These results suggested a gastroesophageal reflux disease without time. Clebopride malate 0.5 mg twice a day and pantoprazole 40 mg/day were prescribed for

11 months, with adequate dietary recommendations. Cyclosporine A was administered for one or two periods/year until 2015. A new urticaria episode occurred and did not remit after therapy with cyclosporine A and oral corticosteroids, and heartburn recurred. After this episode, urticaria recurrence and heartburn responded only to high oral or e.v. dose of corticosteroids. A new therapy was initiated: flunarizine 5 mg/day, dimethindene maleate 1 g/day,

and ebastine 10 mg/day, for 21 days to be repeated after 7 days of discontinuation. A slight improvement of urticaria symptoms was obtained after 3 runs of this treatment. As heartburn persisted notwithstanding corticosteroid discontinuation, a new esophagogastroduodenoscopy was performed. Linear furrowing, scattered white spots, granularity, and felonization of esophagus mucosa were seen (Figure 2(a)). The histologic examination of a biopsy in this site demonstrated an inflammatory infiltrate with more than 15 eosinophils/high resolution field, some lymphocytes and rare macrophages in the squamous epithelium (Figure 2(b)). Based on these histology findings, history of allergic rhinitis and symptoms, eosinophilic esophagitis was diagnosed.

Chronic spontaneous urticaria persisted in January 2016, with weekly urticaria activity score (UAS7)=30, and treatment with omalizumab 300 mg subcutaneously every 4 weeks was started.

Results

Itching wheals and heartburn rapidly remitted after the first injection of omalizumab. Omalizumab was injected once a month for 6 times, discontinued for 2 months, and repeated 6 more times. At the end of the discontinuation period, some wheals were present, and omalizumab treatment was repeated. Both CSU and eosinophilic esophagitis were completely remitted 9 months after the end of the treatment with omalizumab. Esophagogastroduodenoscopy showed a normal mucosa of the esophagus (Figure 2(c)). Remission was continuing when this report was written (June 2017), and the patient reported a relevant improvement of her quality of life at the last follow-up visit.

Discussion

This article reports the complete remission of CSU and eosinophilic esophagitis in a woman, after treatment with omalizumab. Omalizumab is a monoclonal antibody directed against IgE that is recommended as a third line, add-on therapy for CSU in patients resistant to second-generation antihistamines. This experience confirms the effectiveness of this therapeutic approach, as our patient rapidly responded to the first administration of omalizumab. She was one of those patients who may be identified as early responders to omalizumab, and may have a particularly high benefit (4,5). Based on this experience, we suggest that patients affected by CSU who report persistent heartburn and have no benefit by PPI administration, should be suspected to have eosinophilic esophagitis; esophagogastroduodenoscopy should be performed to rule out this condition. Moreover, in our patients, eradication of *H. pylori*, evidenced through the breath test, was obtained in 2006, and the esophagogastroduodenoscopy showed a negative test for *H. pylori*, in 2012. In our case, not only gastric pyrosis but also epigastric pain was present. The clinical and histological features of eosinophilic esophagitis are typical compared to the common esophageal reflux. In our case, the intake of PPI determined only a slight improvement of gastric pyrosis but did not modify epigastric pain. The association of CSU and eosinophilic esophagitis may suggest that both conditions are mediated by mechanisms activated by IgE. Loizou et al. speculated that IgE may have a pivotal role in the pathophysiology of eosinophilic esophagitis of a group of patients, and these subjects

should be eligible to effective treatment with omalizumab (6). Our patient had a rapid remission of symptoms due to eosinophilic esophagitis and to CSU after the administration of omalizumab, in agreement with this hypothesis. It must be mentioned that the literature reports only a few cases of eosinophilic esophagitis treated with omalizumab, and results were not consistent (6–8). It is possible that different mechanisms are involved in subgroups of patients, and different treatments should be identified.

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Patient consent

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

Disclosure statement

No potential conflict of interest was reported by the authors.

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