

Sequential rituximab and omalizumab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

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Abstract Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome (CSS), is a small vessel vasculitis associated with eosinophilia and asthma. Clinical manifestations commonly seen in patients presenting with EGPA range from upper airway and lung involvement to neurological, cardiac, cutaneous, and renal manifestations. Treatment for severe presentations includes steroids, cyclophosphamide, plasmapheresis, and recently, rituximab. Rituximab is associated with a good response in the treatment of vasculitis, but a variable response for the control of allergic symptoms. Here, we report a 16-year-old female patient with severe EGPA (gastrointestinal and cutaneous vasculitis, rhinitis and asthma) refractory to conventional treatment. She was treated with rituximab, which enabled rapid control of the vasculitis component of the disease, but there was no response to rhinitis and asthma. Additionally, she developed severe bronchospasm during rituximab infusion. Sequential rituximab and omalizumab were initiated, leading to remission of all manifestations of vasculitis, rhinitis, and asthma, in addition to bronchospasm related to rituximab infusion.

Keywords Churg-Strauss syndrome · EGPA · Eosinophilic granulomatosis with polyangiitis · Omalizumab · Rituximab

Introduction

ANCA-associated vasculitis (AAV) is a heterogeneous group of autoimmune diseases, sharing the feature of small vessel vasculitis. The spectrum of AAV comprises granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA)—formerly known as Churg-Strauss syndrome (CSS). In EGPA, small vessel vasculitis is associated with eosinophilia and asthma [1]. The clinical manifestations commonly seen in patients presenting with EGPA range from upper airway and lung involvement to neurological, cardiac, cutaneous, and renal manifestations [2]. Mortality without treatment is approximately 50% at 3 months [3]. Treatment of this vasculitis is complex, and a positive response to conventional immunosuppressive drugs is not always expected [4]. Recently, for vasculitis associated with ANCAs, including EGPA, rituximab was recommended as an effective therapeutic option [4, 5]. As these patients have an allergic condition, hypersensitivity reactions to rituximab, including severe bronchospasm, are not uncommon and have been reported [6].

Here, we report the case of a patient with severe EGPA who required sequential treatment with rituximab and omalizumab in order to achieve control of severe vasculitis and the allergic components/hyperreactivity of the disease, including rhinitis, asthma, and bronchospasm associated with rituximab infusion.

Case report

A 16-year-old female patient was attended at our site, due to a clinical presentation of 1 year of evolution of asthma and progressive rhinitis, treated with various conventional treatments, including oral steroids, steroid inhalers with

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betamimetics, with no favorable response. The patient required numerous hospitalizations for severe bronchospasm. Five months before admission, she developed vasculitic lesions in the lower limbs and trunk. Three days before admission, she presented melena and hematemesis; thus, she was referred to our institution. An endoscopy of the upper gastrointestinal tract revealed necrotizing vasculitic ulcers. The initial physical examination showed regular clinical condition, cardiopulmonary auscultation with bronchospasm, and cutaneous vasculitis in the abdomen and extremities (Fig. 1). Laboratories reported the following: WBC 19,600/ μ L, neutrophils 8800/ μ L, lymphocytes 3600/ μ L, eosinophils 6600/ μ L, hemoglobin 7.6 g/dL, platelets 308,000/ μ L, erythrocyte sedimentation rate 40 mm/h, C-reactive protein (CRP) 2.9 mg/dL, creatinine 0.61 mg/dL, BUN 12.7 mg/dL, AST 36.8 U/L, ALT 25.4 U/L, Ig E 844 IU/mL (normal to 100 UI/mL), and all autoantibodies, including anti-DNA, ANAS, anti-ENAS, p-ANCA, and c-ANCA, being negative. Biopsies of the stomach and skin showed leukocytoclastic vasculitis with eosinophilia (Fig. 2). An EGPA diagnosis was made based on 4/6 1990 ACR diagnosis criteria (i.e., asthma, eosinophilia of more than 10% in peripheral blood, paranasal sinusitis, histological proof of vasculitis with extravascular eosinophils) (Masi et al., 1990). Pulses of methylprednisolone 1 g daily for 3 days were initiated, in addition to plasmapheresis (with 5% albumin for five sessions). After the end of the cycle of plasmapheresis, cyclophosphamide 500 mg IV was prescribed. The patient presented a good evolution and was discharged with prednisone 0.5 mg/kg daily.

One month later, the patient presented again vasculitic lesions of the skin. Three additional pulses of methylprednisolone 500 mg were indicated, in addition to a second

dose of cyclophosphamide. Upon improvement, prednisone 0.5 mg/kg was prescribed.

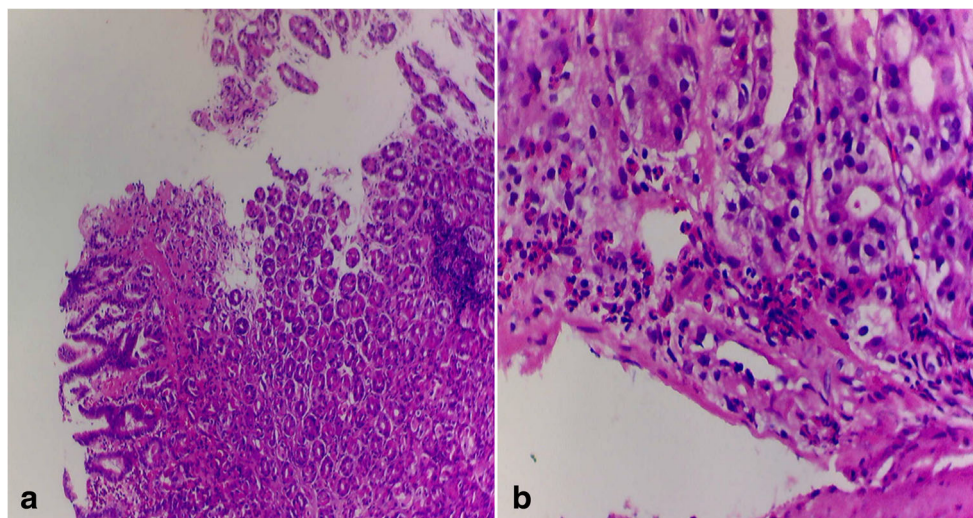
In the following 3 months, the patient presented multiple flare-ups and progressive eosinophilia, requiring an increase in the oral steroid dose to 1 mg/kg, with no adequate response. The cyclophosphamide pulses were continued each month. Additionally, she developed symptoms and signs related to iatrogenic Cushing syndrome. A new hospitalization was necessary, due to vasculitic lesions of the skin and worsening of rhinitis and bronchospasms. It was decided to start rituximab at the initial dose of 1000 mg. After rituximab onset, she presented severe bronchospasm, which led to suspension of the infusion and initiation of systemic steroids and respiratory therapy. Rituximab was resumed as desensitization scheme, improving tolerance to the infusion [7]. The second dose of rituximab 1000 mg was indicated 2 weeks later, with better tolerance. Premedication was performed with hydrocortisone 100 mg and nebulizations. She continued ambulatory management with prednisone 0.5 mg/kg, azathioprine 2 mg/kg/day, with better control of the vasculitis but not of the allergic symptoms. Three months later, it was decided to change from azathioprine to mycophenolate mofetil 1 g BID. With this treatment, remission of the vasculitic symptoms continued but not the allergies. The steroid dose was gradually reduced. It was further decided that the administration of rituximab 2000 mg every 9 months would be beneficial, as indicated in rheumatoid arthritis patients, given the severity of the clinical picture and the possibility of relapse.

Two years later, allergic symptoms worsened progressively, and 4 years after the initial visit, surgery to remove multiple polyps from the nasal cavity was necessary. During the

Fig. 1 Vasculitic lesions in the abdomen and extremities



Fig. 2 Gastric pathology. **a** The oxyntic gastric mucosa has necrosis, fibrin deposits in the lamina propria, and inflammatory infiltrate predominantly of neutrophil and eosinophil polymorphonuclear cells. (H & E stain, orig. mag. $\times 100$). **b** Small vessel in the muscularis mucosae with a marked inflammatory infiltrate, predominantly of eosinophils with necrotizing vasculitis (H & E stain, orig. mag. $\times 400$)



seventh cycle of rituximab, 2 years after surgery, the patient experienced severe bronchospasm which required non-invasive mechanical ventilation. A new scheme of desensitization was successful and the treatment was administered. One year later, the patient presented severe relapse of asthma and the emergence of new nasal polyps. It was therefore decided to add omalizumab 150 mg subcutaneously every month, with excellent clinical results. The asthma and rhinitis were quickly controlled, achieving a progressive decrease in steroid usage until its withdraw, 2 months after initiation of omalizumab. Two additional cycles of rituximab were undertaken, with 9-month intervals, with no bronchospasm. Currently, the patient is controlled and still receiving omalizumab and rituximab.

Discussion

Some patients with EGPA may have life-threatening manifestations due to both the vasculitic component and the allergies. Despite the fact that corticosteroids and cyclophosphamide have significantly improved the prognosis and survival rates [8], some patients are refractory and have severe relapses that are treated with variable responses with plasmapheresis [4], and more recently, with rituximab [9]. The degree of evidence regarding the use of rituximab in the induction of remission and relapse in EGPA is lower than that in GPA and in MPA, with referral rates at 6 months of 34% and at 12 months of 49% [4, 5]. Rituximab induced a significant reduction in eosinophil counts and also led to a decrease in interleukin-5 (IL-5) serum levels. Since IL-5 is essentially produced by T cells, this finding indirectly suggests that B cells may activate T cells, which ultimately secrete IL-5, the main survival factor for eosinophils [3]. In a study by Mohammad et al. [4], with 41 patients with EGPA who received rituximab, 31 adverse events were

reported, including 15 infections and 10 infusion-related reactions in 7 patients (17%), of which 8 were mild and improved after suspending rituximab infusion, and 2 were severe reactions requiring hospital admission (ICU) and intravenous glucocorticoids [4]. In addition, it is noted that rituximab is less effective in controlling asthma and chronic rhinosinusitis.

In EGPA, there is an important increase in IgE and IgG4 levels. The IgE may be responsible for dependent cell degranulation of the IgE receptor (eosinophils, basophils and mast cells) and can be associated with rhinitis and asthma occurring in these patients. The use of omalizumab, a recombinant humanized monoclonal antibody that works against the high-affinity IgE binding, is therefore effective in controlling this component of the disease. Omalizumab binding to free IgE prevents its interaction with both high- and low-affinity FC ϵ RI (and FC ϵ RII) receptors, which occurs on the surface of mast cells, basophils, eosinophils, and B cells. In addition, omalizumab induces apoptosis of eosinophils and decreases the production of inflammatory cytokines, having therefore both anti-allergic and anti-inflammatory effects. The efficacy of omalizumab for the treatment of allergic asthma and allergic rhinitis has been proved with a favorable safety profile [10, 11]. For this reason, the sequential addition of omalizumab was decided for the patient. In the study by Jachiert et al. [10], which included 17 patients with EGPA, 6 patients (35%) achieved complete response, and 5 patients (30%) achieved partial response of allergic manifestations, mainly within 3–6 months after the start of treatment with omalizumab. Six patients (35%), however, had refractory disease. It was possible to decrease the dose of steroids, due to a decrease in the number of asthma exacerbations, increased FEV1 at 3 months and also at 12 months of treatment. In contrast to the effect on manifestations of asthma and steroids, there was a decrease in eosinophil count and serum IgE.

Due to the formation of IgE-anti-IgE immune complexes, IgE serum levels may remain high despite treatment with omalizumab, justifying the concomitant use of anti-CD20 to deplete IgE and avoid complications as a result of immune complexes [12]. In this case, IgE levels should not be used to monitor the therapeutic response of omalizumab [13].

Taking account of the persistence of high IgE levels, and according to the mechanisms described above, the sequential use of rituximab before omalizumab, with the aim of decreasing total IgE levels, was reported with success in insulin allergy refractory to management [12]. Also, there is a report of the sequential use of omalizumab and rituximab in severe atopic dermatitis, avoiding co-stimulation of T cells and Th1/Th17, with good clinical evolution in 3 of 4 patients [14]. In the case report by Iglesias et al. [15], the use of rituximab in EGPA was not favorable, and remission was only achieved after initiation of omalizumab therapy, but no sequential therapy was done such as in our case. In addition, paradoxical development of eosinophilic granulomatosis following the use of omalizumab has been described in eight cases [16, 17]. The pathogenesis of this association is poorly understood. Two mechanisms have been hypothesized: first, omalizumab has a direct casual effect in the development of EGPA; second, reduction of steroid use, achieved by omalizumab treatment, could reveal EGPA that beforehand manifested only as asthma. Although uncommon, omalizumab-prescribed patients should be closely monitored for the appearance of EGPA signs and symptoms [17].

In this report, we describe the favorable response to treatment of both vasculitis and allergic manifestations in a patient with severe and refractory EGPA.

Compliance with ethical standards

Disclosures None.

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