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Eosinophilic granulomatosis with polyangiitis: sequential use of mepolizumab following rituximab for inadequate asthma control despite vasculitis remission

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SUMMARY

We report the case of a 54-year-old woman with antineutrophilic cytoplasmic antibody-negative eosinophilic granulomatosis with polyangiitis presenting with mononeuritis multiplex, intestinal hemorrhage, cardiomyopathy, fever, and worsening asthma symptoms. She was initially treated with steroids and cyclophosphamide but eventually required rituximab to control a vasculitis flare. However, her asthmatic symptoms did not improve, despite attaining vasculitis remission. Symptoms abated only after the treatment transition to mepolizumab. After a 1-year interval, there were no further episodes of asthma exacerbation and no requirement for systemic steroid therapy. This report reinforces the use of rituximab for induction and maintenance of remission in patients with eosinophilic granulomatosis with polyangiitis and predominant vasculitic manifestations, whereas mepolizumab demonstrated better control of the persistent eosinophilic manifestations, ensuing sustained remission and improved quality of life.

Key words: *Eosinophilic granulomatosis with polyangiitis, asthma, rituximab, mepolizumab, vasculitis.*

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INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare, immune-mediated systemic disease characterized by allergic rhinitis, asthma, and eosinophilia. It is characterized by a combination of systemic vasculitis that affects small and medium-sized vessels and eosinophilic tissue infiltration. In addition to the cardinal manifestations, it may present with cardiac, renal, cutaneous, gastrointestinal, peripheral, and central neurological manifestations (1, 2). Treatment of EGPA is directed according to the patient's risk of mortality, as assessed by the five-factor score (FFS), revised in 2011. It is noteworthy that there has been significant progress in understanding the pathophysiological mechanisms of EGPA, which has broadened the therapeutic options, including targeted therapies like monoclonal antibodies such as omalizumab, rituximab, and mepolizumab (3-5).

Rituximab, a first-line treatment for inducing remission in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, is a B-cell-targeted chimeric monoclonal antibody that induces effective remission of EGPA in patients refractory to standard therapy (1-4). However, few studies with an elevated degree of evidence have shown the potential benefit of rituximab when used against asthma, ear, nose, and throat manifestations, and/or organ impairment induced by EGPA (3). Studies have shown that mepolizumab, a humanized monoclonal antibody against interleukin (IL)-5, significantly reduced the eosinophil count and allowed a reduction in corticosteroid doses. The results support mepolizumab as a treatment for refractory or relapsing EGPA (3-8).

Herein, we report the case of a patient with EGPA and poor prognostic manifestations

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who required cyclophosphamide followed by rituximab to achieve remission of the vasculitic phase. However, due to severe persistent asthma, the treatment was switched to mepolizumab, and the patient achieved adequate symptom control and improvement in quality of life.

CASE REPORT

A 54-year-old woman was referred for evaluation in January 2012 because of generalized pain. Additionally, she referred a 3 kg (6 lb. 9.8 oz) weight loss, fever, dyspnea, worsening asthma, and allergic sinus symptoms. She had a history of asthma and allergic sinusitis since age 18, was treated intermittently with inhaled long-acting β2-agonists, corticosteroids, and topical nasal corticosteroids, and had frequent visits to the emergency room. There was no history of nasal polyps. She also had a history of hypertension and is currently on amlodipine. Six months prior to hospitalization, she presented with neuropathic pain affecting the upper and lower limbs, followed by paresthesia of the hands, legs, and feet. She complained of difficulties walking, climbing steps, and using fine motor skills. An electromyogram (EMG) revealed axonal motor neuropathy.

Her symptoms progressed, and she was admitted to an outside hospital. A complete blood count revealed 55,100 leukocytes/mm^3, 38,019 neutrophils/mm^3 and 11,020 eosinophils/mm^3, lactate dehydrogenase 849 units/L (range 200-480), and elevated inflammatory markers, C-reactive protein (CRP) 40 mg/L (range <6) and erythrocyte sedimentation rate of 35 mm in the first hour. Kidney function and liver enzymes were normal. Interestingly, a rheumatoid factor (RF) of 1024 units (range <8 U, latex) was present as opposed to one year before when its concentration was 21.6 units/mL (range <14) and ordered because of joint/limb pain. Total serum immunoglobulin E (IgE) levels were 2084 IU/mL (range <100 IU/mL) at presentation. Bone marrow aspiration did not reveal abnormal morphological features resembling myelodysplastic syndromes or myeloproliferative neoplasm, but findings of hypercellularity with marked eosinophilia, estimated at 55% of the total granulocyte count. The cerebrospinal fluid evaluation was normal.

Serology for human immunodeficiency virus (HIV), human T-lymphotropic virus (HTLV), hepatitis B, hepatitis C, syphilis, and schistosomiasis were negative. Fecal parasites were absent on stool analysis. She was discharged with prednisone 20 mg/day and pain modulators. Because of worsening symptoms, she was admitted to a tertiary care hospital. Her physical exam was compatible with atrophy of the thenar and hypothenar muscles of the right hand and of the right forearm muscles. Biceps and triceps deep tendon reflexes were present and normal bilaterally; however, left brachioradialis, bilateral patellar and Achilles reflexes were absent. Muscle strength was 5/5 on deltoids, 4/5 on biceps, triceps, and psoas bilaterally, as were right dorsiflexion and plantar flexion. Left dorsiflexion and plantar flexion were 0/0. She complained of lower intestinal hemorrhage without diarrhea, and an abdominal examination disclosed only mild generalized tenderness. Synovitis and skin disease were absent. Blood pressure remained stable on medication. Peripheral blood eosinophilia was confirmed. Additional exams included repeat EMG compatible with mononeuritis multiplex; echocardiography reporting an ejection fraction of 39% due to diffuse left ventricular hypokinesis, consistent with cardiomyopathy; and abdominal magnetic resonance angiography without evidence of large vessel vasculitis affecting the aorta or its branches or signs of atherosclerosis. Colonoscopy demonstrated rectal and sigmoid ulcers with pathology reports consistent with chronic erosive colitis and absence of granuloma or micro-abscess. Of note, tissue eosinophilia was absent. Computed tomography revealed maxillary sinusitis and right mastoiditis. Interestingly, no pulmonary infiltrates were present. ANCA was negative, as were anti-myeloperoxidase and anti-proteinase-3 antibodies.

A diagnosis of ANCA-negative EGPA was made, and based on an FFS score of 2 (gastrointestinal involvement and cardiomyopa-

thy), she was started on methylprednisolone pulse therapy with 1000 mg per day for 3 days. Her Birmingham vasculitis activity score, version 3 (BVAS) at diagnosis was 35 points for active disease (new or worse symptoms). Cyclophosphamide was added as a first-line therapy. Her symptoms gradually improved, and she was discharged for outpatient continued treatment with cyclophosphamide. She received a total of 7 doses at 3- to 4-week intervals, while prednisone was slowly tapered. After completing the induction period, she was switched to azathioprine as maintenance therapy. However, because of symptom relapse and the increasing need for higher doses of prednisone, rituximab was added. Administrative issues prevented a more regular prescription at the beginning of the treatment, but eventually, her vasculitic symptoms improved and she could be tapered off steroids. She received a total of 7 cycles (2 doses of 1000 mg 2 weeks apart) from 2012 to 2019. During this period, azathioprine was switched to methotrexate because of hepatotoxicity.

In the meantime, regular follow-up showed no evidence of pulmonary infiltrates, improvement of the cardiomyopathy, and no recurrence of intestinal hemorrhage. ANCA remained negative, and RF went into the normal range of 10.1 units/mL. She has persistent neuropathic pain and paresthesia as sequelae, controlled by gabapentin and occupational and physical therapies. Next, she was also diagnosed with knee osteoarthritis and osteoporosis, requiring specific treatment for both conditions. An immunoglobulin-G κ monoclonal peak was identified but remained stable throughout the years of follow-up. It corresponded to 3.7% of the total protein in 2022.

Conversely, her asthma and sinusitis symptoms persisted, requiring maintenance of the inhaled oral and nasal steroids and frequent use of short-acting β2-agonists, as well as short courses of high-dose oral steroids or intramuscular/intravenous steroids during emergency room visits. Montelukast was added without adequate control. Given frequent exacerbations necessitating systemic steroids and refractoriness to adequate therapy, a discussion about biological treatment modification was started. At this moment, her BVAS score was 4 for new or worse symptoms related to paranasal and wheezing features. The vasculitis damage index (VDI) was 9. Targeting refractory asthma at a dose of 100 mg per month, she started mepolizumab in July 2020, 16 months after the last dose of rituximab, and continued all inhaled drugs. The eosinophil count before mepolizumab initiation was 577 (range <500 cells/mm^3) and the IgE concentration was 307 (range <150 UI/mL). After a few months, the patient noted a significant improvement in allergic symptoms. One year later, there were no episodes of asthma exacerbation or use of systemic corticosteroid therapy. Her BVAS score is now 0. No definite change was seen in the lung function tests (Table I).

As of 2022, the patient presented with right otomastoiditis with otorrhea and developed peripheral facial palsy. It was consistent with a complicated infectious episode, and

Table I - Sequential results obtained from lung function tests from 2009 to 2020.

	October 2009	November 2010	August 2012	July 2020†	December 2020‡
FEV1 L (%), post-BD var, %	1,72 (71), 1	1,88 (79), 5	1,98 (86), 3	1,29 (61), 12	1,46 (60), 10
FVC L (%), post-BD var, %	2,49 (84), 4	2,58 (90), 3	2,73 (98), 7	2,16 (83), 3	2,21 (72), 12
FEV1/FVC, %	69	73	73	56	64
FEF25-75 L/s (%), post-BD var, %	1,10 (45), -1	1,30 (49), 13	1,44 (48), 9	0,61 (30), 38	0,81 (37), 7
DLCO mL/min/mmHg (%)	–	–	24,57 (113)	–	–
Conclusion	Mild obstruction	Mild obstruction	Mild obstruction	Moderate obstruction	Moderate obstruction

FEV1, forced expiratory volume in the first minute; FVC, forced vital capacity; FEF, forced expiratory flux; DLCO, diffusing capacity for carbon monoxide; BD, bronchodilator; var, variation; †pre-mepolizumab; ‡post-mepolizumab.

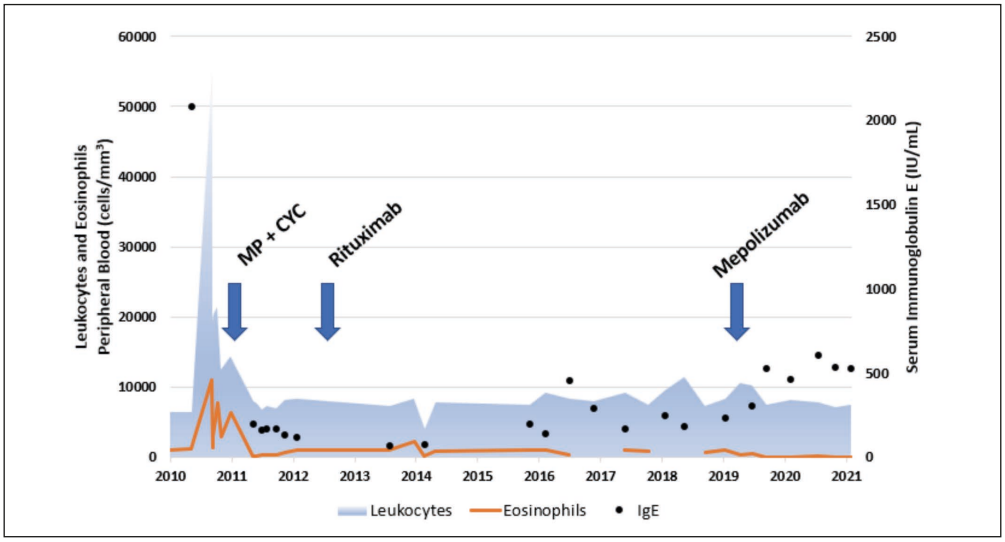

Figure 1 - Sequential results of total peripheral blood leukocytes, eosinophils, and serum immunoglobulin E from 2010 to 2022.
IgE, immunoglobulin E; MP, methylprednisolone; CYC, cyclophosphamide; IU, international units.

there was no evidence of vasculitis relapse. Azithromycin and then amoxicillin and clavulanate were prescribed, together with prednisone, and the patient recovered well without any permanent neurologic deficit. Figure 1 shows the sequential results of total peripheral leucocyte and eosinophil counts (obtained from complete blood counts) and IgE levels throughout the period from 2010 (before EGPA diagnosis) to 2022. Also, it can be noted that IgE concentrations were reduced with immunosuppressive therapy and steroids. After complete withdrawal of continuous steroid use, IgE levels increased, but not to those seen at EGPA diagnosis. Table 1 shows the sequential results obtained from lung function tests before and after mepolizumab.

DISCUSSION

This is a report about the long-term follow-up of a patient with ANCA-negative EGPA, severe disease, and the need for treatment adjustments based on vasculitic or eosinophilic preponderance. Conflicting results have been published regarding the efficacy of rituximab in EGPA. Mohammad et al. (9) described the results of a retrospective case series of rituximab in 41 EGPA patients, either on single or repeated courses. The authors reported that ANCA-positive patients were more likely to achieve remission in the first 12 months following the first rituximab dosing compared to ANCA-negative patients (80% *versus* 38%, p=0.013). Of note, no difference in the proportion of remission or partial response among patients who received rituximab for refractory or relapsing disease was seen (9). Akiyama et al. showed a consistent reduction in the absolute eosinophil count and improvement in the clinical manifestations of EGPA, including severe eosinophilic asthma, with rituximab (10). However, only half of the patients achieved protocol-defined remission, and less than one-third achieved the primary outcome. The study demonstrated that rituximab was effective in inducing and sustaining remission and that it also reduced the dose of glucocorticoid in patients with newly diagnosed disease or relapsing and refractory EGPA (10). Casal Moura et al. showed that in 17 patients included in their analysis of EGPA patients using rituximab, 13 patients (76.5%) had non-severe or controlled asthma, and remission was achieved in 12 (70.6%) by the end of the period of follow-up (11). Both eosinophils and CRP levels decreased, as did the steroid dose. They con-

cluded that patients receiving rituximab for EGPA maintenance required less than 10 mg of steroids for adequate asthma control. Moreover, the results of a phase 3 clinical trial assessing rituximab in EGPA (REOVAS) [NCT02807103] were presented as abstracts in recent meetings (12, 13). A total of 105 enrolled patients were divided into 2 arms: rituximab *versus* conventional therapy. 56% were ANCA-negative. The primary endpoint was the rate of patients who achieved remission at day 180 as defined by BVAS=0 and a prednisone dose ≤7.5 mg/day after induction treatment with rituximab (2×1 g doses, 2 weeks apart) or cyclophosphamide. Patients were followed for 12 months as part of the original study and later surveilled for a median of 45 months. The results showed that 63.5% of rituximab-treated patients achieved remission at day 180 compared to 60.4% of conventional strategy-treated patients treated with cyclophosphamide/azathioprine (p=0.75). No significant difference regarding corticosteroid use was seen between both arms, arguing that rituximab was not superior to conventional therapy based on FFS (12). Results of long-term follow-up confirmed the previous findings but showed that the analysis restricted to patients with anti-myeloperoxidase ANCA revealed a better survival without minor and major relapses for rituximab-treated patients compared to those treated with conventional strategy (92.3% *versus* 50%, p=0.02) (13).

Interestingly, RF was elevated at the initial flare in our patient, and titers decreased following rituximab therapy. RF positivity is present in 35-45% of patients with EGPA, questioning the possible immunological role of RF in the development of some EGPA manifestations (14). A recent publication compared patients with EGPA according to RF positivity. Importantly, patients with higher RF levels were usually ANCA negative, had higher eosinophil counts than those who were RF negative, and presented with more frequent gastrointestinal involvement. Instead, lower RF titers had more heart and renal involvement (14). Our patient had remarkably high levels of RF, was ANCA negative, and had evidence of heart, renal, and gastrointestinal involvement and relapsing disease. A possible implication in this setting is the assessment of RF in ANCA-negative patients, guiding treatment selection for vasculitis symptoms. Vasculitic manifestations were controlled with rituximab, but allergic manifestations persisted. This finding has been reported in the literature, as expected, in up to 50% of EGPA patients (15). Accordingly, Berti et al. described the predictors of long-term asthma severity in EGPA patients (16). Their cohort comprised 42.7% of patients with severe or uncontrolled asthma at baseline and 40.5% of patients with severe asthma after 3 years of treatment/follow-up, with increased airway resistance as assessed by pulmonary function tests, similarly to what we presented in this report. Regarding predictors of a worse outcome, our patient did not have severe asthma, pulmonary infiltrates, or was overweight at the initial presentation. However, she did have chronic rhinosinusitis. Due to its neutralizing effect on IL-5, mepolizumab is effective in patients with severe eosinophilic asthma and EGPA (5, 6). One year after starting mepolizumab 100 mg monthly and continuing all inhaled drugs, our patient no longer reported asthma exacerbations; her BVAS was 0, and systemic corticosteroid therapy was not required. Despite the approved dose for EGPA being 300 mg monthly, the patient responded well to 100 mg monthly and maintained vasculitis remission. This may indicate that the dose of mepolizumab aimed at EGPA control can be tailored according to the disease status, as postulated by Vergles et al. (17). Of note, there is one report of concurrent use of rituximab and mepolizumab for EGPA with favorable results, and a recent report from Aguirre-Valencia et al. illustrated a case in which the patient attained remission of the vasculitis with rituximab but required the addition of omalizumab, an anti-IgE monoclonal antibody, to improve asthma and rhinitis symptoms, corroborating the rationale of different targets (18, 19). Interestingly, the eosinophil count in our patient remained suppressed with mepolizumab, whereas the IgE concentra-

tions sequentially increased and pulmonary function tests stabilized or worsened, despite better clinical control, interrogating airway remodeling as proposed by Berti et al. (16).

CONCLUSIONS

This case report illustrates the response to rituximab for predominantly vasculitic manifestations in an EGPA patient and its lack of efficacy in controlling asthma and sinusitis symptoms or preventing allergic exacerbations. In contrast, we showed that lower-dose mepolizumab was a good option for controlling refractory asthmatic manifestations in the setting of low disease activity, resulting in sustained remission and improved quality of life.

Contributions
All the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict of interest
The authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate
This work was approved by the University of Santo Amaro Ethics Review Board, São Paulo, Brazil, under number 5.305.301 on March 22nd, 2022. The procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

Patient consent for publication
The patient read and signed informed consent for the study and publication.

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Availability of data and materials
Data available from the corresponding upon request.

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