**CLINICAL CASE**

**Eosinophilic granulomatosis polyangiitis (EGPA) complicated with periaortitis, precipitating role of dupilumab? A case report a review of the literature**

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**ABSTRACT**

Eosinophilic granulomatosis with polyangiitis (EGPA) is an ANCA-associated vasculitis that affects small size vessels. Only four cases of periaortitis associated with EGPA have been reported in the literature. We report the case of a 67-year-old woman with EGPA who developed periaortitis 11 months after the initiation of dupilumab for uncontrolled asthma with hypereosinophilia. Complete remission of the periaortitis, and of EGPA, was obtained after switching from dupilumab to mepolizumab combined with oral prednisone therapy. Dupilumab has been associated with hypereosinophilia, that is usually asymptomatic and transitory, but symptomatic cases including EGPA were exceptionally reported. Although causality has not yet been established, caution is advisable when prescribing dupilumab for uncontrolled asthma with features that might suggest EGPA.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

⇒ Periaortitis have rarely been described with Eosinophilic granulomatosis with polyangiitis.

**WHAT THIS STUDY ADDS**

⇒ We describe a case of periaortitis associated with Eosinophilic granulomatosis with polyangiitis and discuss the precipitating role of dupilumab.

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ Caution is advisable when prescribing dupilumab for uncontrolled asthma with features that might suggest EGPA.

**INTRODUCTION**

Eosinophilic granulomatosis with polyangiitis (EGPA) is an ANCA-associated vasculitis (AAV) that affects small blood vessels.1 Large vessels involvement, including periaortitis, has been described in AAVs, mainly in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).2,3 With regard to EGPA, only four cases of periaortitis have been reported in the literature.4–7

Dupilumab is a human monoclonal IgG4 antibody that targets the interleukin-4 receptor subunit α of the IL-4 and the IL-13 receptors. It is used in the treatment of atopic dermatitis, uncontrolled asthma with hypereosinophilia and chronic sinusitis with nasal polyposis.8 Its use has been associated with hypereosinophilia, that is usually asymptomatic and transitory, but symptomatic cases were reported, including EGPA.9

We report a case of EGPA with periaortitis that appeared 11 months after the initiation of dupilumab for uncontrolled asthma. We then discuss the association of periaortitis and EGPA and the potential role of dupilumab in inducing or exacerbating EGPA.

**CASE DESCRIPTION**

A 67-year-old female patient presented to our department in September 2022 with abdominal and back pain that was localised in the left lower quadrant and had been evolving for 3 weeks.

The patient’s medical history is relevant for severe asthma diagnosed at the age of 50, with hypereosinophilia fluctuating in numbers (12.18×10^9/L in March 2020), nasal polyposis and chronic rhino sinusitis with crust formation and a history of polyarthritis that was diagnosed as polymyalgia rheumatica, anti-neutrophil cytoplasmic antibodies (ANCA) were tested negative. She was treated with inhaled corticosteroid/long-acting beta-agonist, long-acting muscarinic antagonist, oral corticosteroids and was well controlled since the introduction of dupilumab in October 2021. She also presented an episode of haemoptysis in August 2021, with a chest
CT scan showing ground glass opacities in the left lower lobe.

She did not have fever, diarrhoea, haematuria or symptoms of urinary tract infection. She initially presented to the emergency department where a blood analysis showed an elevated level of C reactive protein (CRP) (22.5 mg/L), and an abdominal CT scan showed a peri-adventitial thickening of the aorta and the left common iliac artery. She was then referred to our department for further investigation.

She had mild diffuse joint pain and fatigue but had a stable appetite and weight. Physical examination was normal except an abdominal tenderness in the left lower quadrant without signs of peritoneal irritation, a diffuse expiratory wheezing on pulmonary auscultation and a tenosynovitis of the left elbow. ECG was normal.

Laboratory analysis revealed eosinophilia (1.09x10^9/L), no anaemia, an elevated CRP level (25.89 mg/L; N<5 mg/L), a serum creatinine level of 96 µmol/L. Urine analysis showed no leucocyturia, no microscopic haematuria and no proteinuria. Liver function tests were normal. Antinuclear antibodies, ANCA, rheumatoid factor and ACE were all negative. Serum protein electrophoresis showed a normal gamma fraction level. The IgG, level was elevated (1.9 g/L, N<0.864 g/L). Thyroid-stimulating hormone level was normal. Microbiological investigations were negative: syphilis, Coxiella, hepatitis C and B, HIV 1 and 2 seralogies, blood cultures, tuberculosis interferon-gamma release assay.

The CT aortic angiography showed the hypodense circumferential irregular infiltration of the infrarenal abdominal aorta and the common and external left iliac arteries without significant luminal narrowing, compatible with periaortic fibrosis (figure 1A). The left renal pelvis and ureter were dilated being in contact with the infiltration around the iliac artery. The periaortic and peri-iliac artery fibrosis was highly metabolic on the Fluorodeoxyglucose positron emission tomography (FDG PET) (figure 1B). A sinus CT scan showed polypoidal lesions in the maxillary sinuses and the left sphenoid sinus.

A biopsy of the periaortic mass was performed and showed a fibroinflammatory tissue with non-specific subacute inflammatory changes. There was no granuloma, no signs of malignity, no vasculitis lesions, no eosinophilic cells, no storiform fibrosis. There were no IgG+ plasma cells excess on the immunohistochemical studies with anti-IgG, IgG, and anti-CD138, in the limit of the small number of plasma cells present. Culture of the specimen remains sterile.

The final diagnosis was a periaortitis associated with an EGPA. The patient was treated with oral corticosteroid, at a dose of 0.5 mg/kg/day (30 mg/day) of prednisone and was switched to mepolizumab (100 mg every 4 weeks) due to the potential role of dupilumab in inducing or exacerbating EGPA.

After 6 months, the patient was still taking steroids at a dose of 5 mg per day and mepolizumab. She did not have abdominal or back pain. She had no asthma attacks or other clinical manifestations of EGPA. Eosinophilic count was normal and CRP level was normal. The FDG PET scan showed a complete remission of the periaortitis (figure 1C, D).

**DISCUSSION**

As a part of the aetiological differential diagnosis of periaortic fibrosis, secondary causes must be ruled out before the condition is termed chronic periaortitis (CP) (infections, neoplasia, radiotherapy, major abdominal surgery or trauma, histiocytosis and drug induced). CP per se is an inflammatory condition that originates in the adventitia of the aortic wall and then extends to the periaortic space, forming a fibroinflammatory tissue that usually develops around the infrarenal abdominal aorta and the common iliac arteries. Depending on the aspect of the aorta (dilated or not), three different conditions can be described in CP: idiopathic retroperitoneal fibrosis, inflammatory abdominal aortic aneurysms and periadventitial retroperitoneal fibrosis. CP can be isolated or associated with other conditions such as organ-specific autoimmune disorders, systemic autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis and small vessel vasculitis) and IgG-related disease (IgG4 RD). In our case, the two main diagnoses that could be discussed were EGPA and IgG4 RD.

EGPA is an AAV that affects small blood vessels, together with GPA and MPA. However, although rare, large
Vessels involvement, including aortitis and peri-aortitis, has been described in AAVs, mainly in GPA and MPA, and is usually non-stenosing, consisting of perivascular soft tissue masses, aneurysms, dissection and rupture. With regard to EGPA, to our knowledge, only four cases of peri-aortitis have been reported in the literature, and are summarised in table 1. The suggested underlying pathophysiology is a vasa-vasoritis of the aorta. In our case, the patient met the ACR 2022 criteria for EGPA.

The second hypothesis that can be discussed in our case is IgG4-RD. Indeed, it is known that IgG4 levels can be elevated in EGPA patients without IgG4-RD and can be associated with EGPA disease activity and organ involvement. Furthermore, IgG4-RD is considered as a diagnosis of exclusion; in other words, EGPA must be excluded before IgG4-RD can be diagnosed. However, in a retrospective case series, Danlos et al point to the possibility of an overlap syndrome between AAV and IgG4-RD. In this retrospective multicentre observational study including of 18 patients fulfilling the criteria for IgG4-RD and AAV criteria, 14 cases were GPA, 3 MPA and only 1 EGPA. Interestingly, 50% of the patients (9 patients) had CP. Our patient had mild increased level of IgG4, but no IgG4 on the biopsy, nor storiform fibrosis or obliterator phlebitis. Given the whole presentation, we did not retain the diagnosis of IgG4-RD.

Lastly, our case highlighted the potential role of dupilumab in inducing or exacerbating EGPA. Our patient developed CP 11 months after the introduction of dupilumab and without change in her corticosteroids dose.
### Table 2  Case reports describing EGPA cases diagnosed after dupilumab initiation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex</th>
<th>Age</th>
<th>Reason for prescribing DPM</th>
<th>Time from DPM initiation to EGPA onset</th>
<th>EGPA manifestations</th>
<th>ANCA status</th>
<th>Histopathology</th>
<th>Corticosteroids tapered before or during EGPA onset?</th>
<th>Switch from anti-IL5/IL5R to DPM?</th>
<th>Corrective treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persaud et al(^\text{15}) 2022</td>
<td>M</td>
<td>58 years</td>
<td>Chronic sinusitis</td>
<td>1–2 weeks</td>
<td>Weakness, arthralgia, skin rash, lung and renal involvement</td>
<td>pANCA MPO (+)</td>
<td>Skin (eosinophilic vasculitis) and renal (pauci-immune glomerulonephritis)</td>
<td>No</td>
<td>No</td>
<td>High dose MPL for 3 days then oral prednisone, plan for long-term RTX</td>
</tr>
<tr>
<td>Tanaka et al(^\text{16}) 2022</td>
<td>M</td>
<td>50s</td>
<td>Asthma and eosinophilic rhinosinusitis with nasal polyposis</td>
<td>5 months</td>
<td>High-grade fever, dyspnoea, interstitial pneumonia</td>
<td>(−)</td>
<td>Transbronchial lung biopsy: interstitial pneumonia with eosinophilia and no vasculitis.</td>
<td>No</td>
<td>No</td>
<td>High-dose MPL for 3 days then prednisolone 1 mg/kg</td>
</tr>
<tr>
<td>Murag et al(^\text{17}) 2021</td>
<td>M</td>
<td>41 years</td>
<td>Uncontrolled asthma</td>
<td>3 months</td>
<td>Polyneuropathy and lung involvement</td>
<td>(−)</td>
<td>None</td>
<td>possible</td>
<td>No</td>
<td>Switch from Dupilumab to MPZ</td>
</tr>
<tr>
<td>Milne et al(^\text{18}) 2022</td>
<td>M</td>
<td>63 years</td>
<td>Severe persistent asthma and nasal polyposis</td>
<td>7 months</td>
<td>Fatigue, purpura, pulmonary nodules, eosinophilic myocarditis</td>
<td>(−)</td>
<td>Skin (small-vessel vasculitis with eosinophilic infiltrate)</td>
<td>Yes</td>
<td>Yes (MPZ)</td>
<td>High-dose MPL for 3 days then oral prednisone, CYC than AZA and MPZ</td>
</tr>
<tr>
<td>Anai et al(^\text{19}) 2022</td>
<td>M</td>
<td>42 years</td>
<td>Uncontrolled asthma</td>
<td>3 weeks</td>
<td>Fever, sinusitis, lung involvement</td>
<td>(−)</td>
<td>Transbronchial lung biopsy: eosinophilic pneumonia, possible features of healed arteritis</td>
<td>?</td>
<td>Yes (MPZ then benralizumab)</td>
<td>High-dose MPL for 3 days then oral prednisolone, intravenous CYC and MPZ instead of DPM (reintroduced later)</td>
</tr>
<tr>
<td>Eger et al(^\text{20}) 2021</td>
<td>F</td>
<td>63 years</td>
<td>Uncontrolled asthma</td>
<td>After 8 administrations of dupilumab</td>
<td>Dysarthria, left-sided neurological deficit, bilateral pulmonary consolidations</td>
<td>(−)</td>
<td>None</td>
<td>Yes (cautiously)</td>
<td>Yes (Benralizumab)</td>
<td>Increase in prednisone dose, switch from DPM to MPZ</td>
</tr>
</tbody>
</table>

ANCA, antineutrophil cytoplasmic antibodies; AZA, azathioprine; CYC, cyclophosphamide; DPM, dupilumab; EGPA, eosinophilic granulomatosis with polyangiitis; F, female; M, male; MPL, methylprednisolone; MPZ, mepolizumab; RTX, rituximab.
In our case, EGPA was probably pre-existing before the onset of dupilumab, as she had uncontrolled asthma with hypereosinophilia, a history of polyarthritis and haemoptysis with ground glass opacities. Thus, dupilumab may have exacerbated her EGPA. Dupilumab allowed a good control of her steroid dependent asthma that was previously poorly controlled.

Dupilumab is a human monoclonal IgG4 antibody that targets the interleukin-4 receptor subunit α (IL-4Rα) of the IL-4 and the IL-13 receptors, thus inhibiting their signalling. Hypereosinophilia has been described in dupilumab use and one more than 300 days after a single dose.9 In the LIBERTY NP SINUS-52 clinical trial, two cases of EGPA were reported on dupilumab, one during dupilumab use and one more than 300 days after a single dose.14 Table 2 summarises six case reports describing EGPA diagnosed after initiation of dupilumab.15–20 In the case presented by Anai et al, dupilumab was first switched to mepolizumab after EGPA onset, and reintroduced later concomitantly with mepolizumab giving the insufficient control of asthma, with good results, pointing to the possibility of combination therapy.19

The pathophysiology of the hypereosinophilia induced by dupilumab can be partially explained by an inhibition of the migration of eosinophils to tissues without inhibition of eosinophilopoiesis, resulting in accumulation of eosinophils in the blood.9 However, this mechanism cannot fully explain the pathophysiology since eosinophils were found in tissues in patients developing EGPA while on dupilumab.19 Whether dupilumab induces EGPA or whether it accelerates the course of a previously non-diagnosed ANCA-negative EGPA is still unclear.

Finally, we did not find any case of a periaortitis caused by dupilumab. On the contrary, there are some reports of effective treatment with dupilumab in IgG4-RD.21

CONCLUSION

In conclusion, we presented a case of an EGPA with periaortitis that appeared 11 months after initiation of dupilumab. Periaortitis can be an atypical manifestation of EGPA. EGPA has been described in patients treated with dupilumab, but causality has not yet been established. Caution is advisable when prescribing dupilumab for uncontrolled asthma with features that might suggest EGPA.

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