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CASE REPORT

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Eosinophilic vasculitis of aortic valve in EGPA: a life-threatening onset of disease

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ABSTRACT

Objective: Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss Syndrome, is an anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis that can manifest with a wide spectrum of clinical presentations. Indeed, EGPA is characterized by eosinophil-rich inflammation and systemic necrotizing vasculitis affecting small-to-medium-size vessels of different organs. Cardiac involvement is associated with a poor prognosis, and it is mainly described in the form of myocardial eosinophilic infiltration. Aortic valve involvement of EGPA is exceedingly rare.

Methods: Here, we describe a clinical case of a 51-years-old man with eosinophilic severe asthma and chronic rhinosinusitis with nasal polyps presented to the Emergency Department with worsening dyspnea after a two months history of low-grade fever and malaise; home therapy included anti-IL-5 monoclonal antibody (100 mg every four weeks). At the Emergency Department, the patient developed cardiac arrest and, after advanced life support maneuvers, he underwent surgery for acute torrential aortic regurgitation.

Results: Pathological examination of native aortic valve showed widespread vasculitis with eosinophilic inflammatory infiltrate and ANCA antibodies (anti-MPO), previously negative, tested positive. A diagnosis of EGPA was therefore made, despite low blood eosinophils probably due to mepolizumab therapy. Mycophenolate mofetil and high dose mepolizumab (300 mg every 4 wk) were started and the patient was discharged with full resolution of his clinical picture even at the three months follow-up visit.

Conclusions: To our knowledge, this is the first reported case demonstrating angioplasia and vasculitis on the aortic valve. Our case report shows the importance of appropriate mepolizumab dose to improve EGPA clinical outcomes; moreover, severe disease activity despite low dose mepolizumab could underline the role of alternative pathogenic mechanisms beyond IL-5 pathway, at least in some patients.

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angioplasia; aortic regurgitation; CRSwNP; EGPA; severe eosinophilic asthma

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic vasculitis characterized by granulomatous and eosinophil-rich inflammation affecting small-to-medium-size vessels of different organs. The disease typically develops in patients with a history of asthma and eosinophilia. Cardiac involvement, more frequent in anti-neutrophil cytoplasmic antibodies (ANCA) negative patients, is associated with a poor prognosis, and represents the major cause of early death (1). It is mainly described in the form of myocardial eosinophilic infiltration. Early recognition and prompt treatment are crucial to improve patient outcomes. We here describe a clinical case: 1) to highlight the importance of early diagnosis and correct management, even in case of atypical and rare EGPA presentations; 2) to underline the importance of appropriate anti-IL-5 dosing in EGPA patients.

Case study

In November 2021 a 51-year-old man was referred to our attention due to worsening of daily and nocturnal asthma symptoms with asthma control test (ACT) of 15 despite maximal dose of inhaled therapy, according

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to step 5 of GINA recommendations (2). Beside severe eosinophilic asthma (SEA) with sensitization to grass, olive tree and Parietaria officinalis pollens, patient's medical history was also significant for chronic rhinosinusitis with nasal polyps (CRSwNP), previously treated with FESS thrice. Blood tests showed eosinophilia corresponding to 730 cells/mm^3 (8.2%), serum total IgE 240 kU/L, eosinophil cationic protein (ECP) 29 U/mL and p-ANCA negativity. The clinical history also included hypertension and mild aortic regurgitation with preserved left ventricular ejection fraction. He was a former smoker (15 packs/year) and led an active life, working as a blacksmith. His pharmacological daily therapy included the following medications: fluticasone salmeterol 250/25 µg 2 × 2, mometasone 100 µg, ramipril 5 mg. In April 2022, due to poor asthma control, the anti-interleukin-5 monoclonal antibody mepolizumab was prescribed at the dose of 100 mg every 4 wk. After the initial improvement of respiratory symptoms over the first year, the patient demonstrated poor adherence to the protocol of clinical follow-up visits.

In February 2024 the patient was admitted to the Emergency Department (ED) with new-onset chest pain and rapidly worsening dyspnea. He also reported intermittent fever in the last two months associated with malaise, cough, weight loss and fatigue.

Upon admission, the patient was tachypnoic, hypoxemic (SaO_2 92%) and with normal blood pressure (101/60 mmHg). An electrocardiogram (ECG) performed in the ED showed junctional ectopic tachycardia and incomplete left bundle branch block. Blood tests revealed a significant increase in Hs-TnI values (from 616 to 2993 pg/ml) and high NT-pro BNP levels (14970 pg/ml). A transthoracic echocardiography performed in the ED revealed severe aortic regurgitation (Figure 1), an ejection fraction of 40-45%, bilateral pleural effusion, and a floating image on the ascending aorta consistent with an intimal flap (Figure 2). The patient was initially treated with oxygen therapy using a 60% Ventimask and received intravenous furosemide and morphine. Due to the high suspicion of type A aortic dissection, a CT angiogram of the thoraco-abdominal aorta was performed. The exam ruled out acute aortic dissection but showed incomplete coaptation of the aortic valve cusps. Consequently, he was admitted to the cardiothoracic surgery ward. Shortly after returning from the radiology department, the patient developed orthopnoea and was placed on non invasive ventilation (NIV), invasive blood pressure monitoring and aggressive diuretic therapy. Despite these measures, the patient's hemodynamics kept rapidly deteriorating, eventually leading to cardiac arrest with pulseless electrical activity (PEA). Advanced life support (ALS) maneuvers successfully ensured the return of spontaneous circulation (ROSC) after approximately ten minutes. Following intubation, trans-oesophageal echocardiogram (TEE) showed torrential aortic regurgitation. An urgent coronary angiography showed intact coronary arteries. Emergency surgery was performed to replace the aortic valve with a bio-prosthesis. Intraoperatively, the ascending aorta presented a dense fibrinoid layer, and the native valve exhibited retraction of the left coronary cusp.

Results

Histopathological examination of the native aortic valve revealed areas of fibrinoid necrosis, dense lymphoplasmacytic and eosinophilic infiltrates, angioplasia and widespread vasculitis (Figure 3A-B). Blood and valve

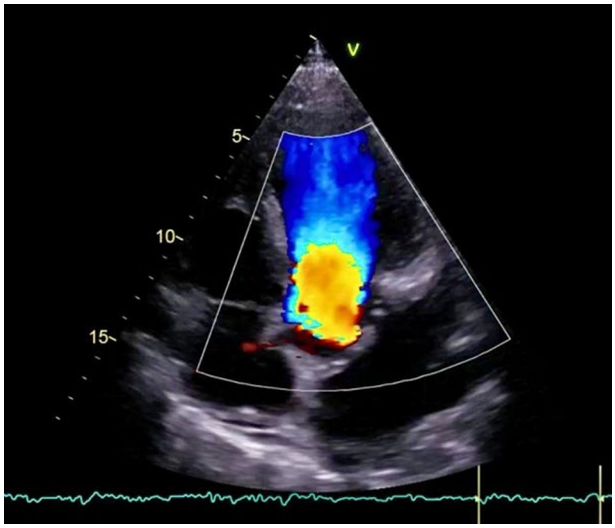

Figure 1. Dilated, hypocontractile left ventricle and severe aortic regurgitation.

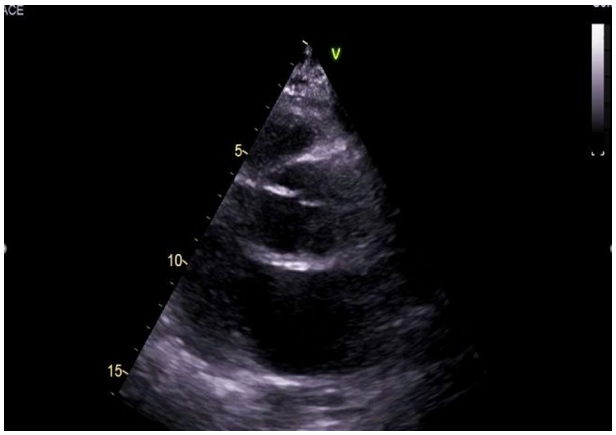

Figure 2. Floating image on the ascending aorta consistent with an intimal flap.

tissue cultures and pathological examination ruled out infective endocarditis. Blood tests revealed ANCA positivity and blood eosinophils count of 1% corresponding to 220 cells/mm^3. After uncomplicated surgery, the subsequent hospital stay was uneventful. A diagnosis of EGPA was made according to the American College of Rheumatology (ACR) criteria (3) due to the presence of: a) severe asthma; b) CRSwNP; c) fibrinoid necrotic vasculitis; d) ANCA positivity despite the low value of blood eosinophils, likely related to the ongoing mepolizumab treatment. Due to the high Five Factor Score (FFS = 2), according to the 2009 version (4), the therapy was then intensified by raising the dose of mepolizumab (300 mg every 4 wk, the dose currently approved for EGPA) and adding immunosuppressive therapy with mycophenolate mofetil (2000 mg/day); considering the good clinical results of heart surgery, we decided not to add glucocorticoids to the therapeutic regimen. Echocardiogram at discharge showed an EF of 54% and a well-seated normally functioning aortic bio-prosthesis.

The three months post-surgery follow up visit showed stable clinical and echocardiographic findings as well as a complete control of asthma (ACT: 23/25) and sinonasal symptoms [Sinonasal outcomes tests (SNOT)-22: 9].

A follow-up cardiac MRI performed one year after the procedure showed normal native T1 and extracellular volume (ECV) values, with no T2-weighted evidence of edema. Late gadolinium enhancement (LGE) sequences revealed no significant myocardial enhancement, except for enhancement of the papillary muscles (see Figure 4).

Discussion

The spectrum of cardiac manifestations in EGPA varies from acute, life-threatening eosinophilic myocarditis to subtle, asymptomatic lesions detected by cardiac magnetic resonance imaging (5). Cardiac involvement in EGPA is usually more common in ANCA-negative patients, and accounts for around 50% of mortality (6). Conversely, ANCA+ patients often present with vasculitic manifestations of the disease, such as mononeuritis or purpura. However, extra-pulmonary involvement including peripheral neuropathy or other organs manifestations can be directly related to the high number of blood eosinophils independently from ANCA status (7).

To date, only three cases of EGPA-related aortic regurgitation have been reported (8–10), but, to our knowledge, this represents the first described case of EGPA with a clear demonstration of a angioplasia and vasculitic process involving the aortic valve, causing severe acute aortic regurgitation with subsequent cardiogenic shock. Considering the three cases previously reported, histopathology of aortic valve was available only in 2 out of 3 patients, and showed granulomatous inflammation with abundance of eosinophils. Of note, our patient developed cardiac valve eosinophilic vasculitis despite low peripheral blood eosinophils, likely linked to the ongoing mepolizumab treatment, unlike the blood hypereosinophilia present in other published cases; in the other cases, mepolizumab treatment was not used, so the patients were treated with cyclophosphamide and corticosteroids (2 out of 3) or methotrexate and corticosteroids (1 out of 3).

This case clearly shows that, in EGPA, tissue injury due to vasculitis and eosinophil tissue accumulation can occur also in the presence of low blood eosinophil count. Indeed, several other mechanisms, largely distinct from IL-5 mediated eosinophilic pathways, have been described in EGPA pathogenesis, including ANCA mediated neutrophils priming, Th1/Th17 altered immune responses, Th17/Treg imbalance and B cells dysregulation (11).

On the other hand, we must underline that our patient was receiving mepolizumab 100 mg for the

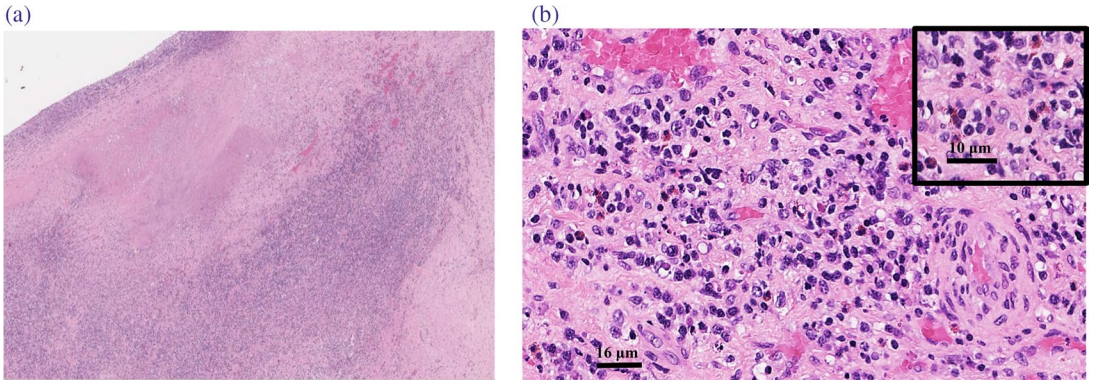

Figure 3. Histopathology of the left coronary cusp: A: An ample area of fibrinoid necrosis surrounded by dense inflammatory infiltrate; B: Angioplasia with signs of vasculitis. Numerous eosinophils admixed with lymphocytes and plasmacells.

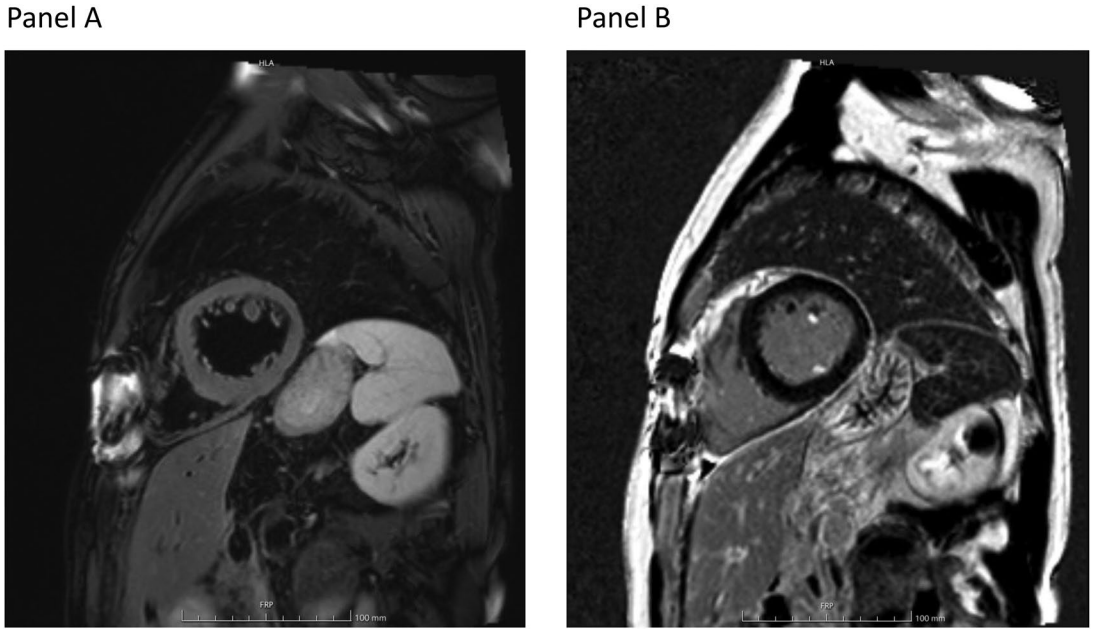

Figure 4. heart MRI performed one year after emergency aortic valve surgery, showing normal native T1 and extracellular volume (ECV) values, no edema in T2-weighted images and absence of late gadolinium enhancement.

diagnosis of severe eosinophilic asthma, that could not have been sufficient to prevent EGPA onset. Althought several case series including EGPA patients treated with Mepolizumab 100 mg have been published (12,13), relapse of the disease in patient treated with Mepolizumab 100 mg have already been described (14), suggesting the idea that, at least in a subset of patients, Mepolizumab 100 mg dose could be too low to stop EGPA disease activity. In our patient the occurrence of vasculitis was associated with ANCA development, thus it is not easy to understand the precise sequence of pathogenic events involving both eosinophils and ANCA. The different weight of the two factors must be understood as it is unclear what the most important trigger actually is, eosinophils or ANCA.

The strengths of this case are the availability of heart valve pathology allowing a definite diagnosis of EGPA as well as the presence of a careful clinical and imaging follow up data; these data allow to effectively show the effectiveness of patient's management. The main limitations of our case are the rarity of this EGPA clinical presentation, preventing us to generalize our clinical approach, and the inability to define the exact role of Mepolizumab low dose on the natural history of our patient's disease.

Conclusions

Cardiac involvement in EGPA patients represents a major complication with potential life-threatening manifestations and affects long-term prognosis. Early diagnosis, prompt treatment, and close collaboration between immunologists and cardiologists are pivotal. This case highlights the severity of EGPA-related cardiac involvement, underlining the need for heightened awareness and proactive management in these often young patients.

In conclusion, our case demonstrates that EGPA can rarely involve cardiac valves and the valvular involvement of EGPA can progress with extreme severity, leading to life-threatening heart manifestation. Therefore, in EGPA patients presenting in an acute setting, the evaluation of valvular function is mandatory.

Ethical Approval statement

Ethical Approval is not applicable for this manuscript.

Disclosure statement

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