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Dilated Cardiomyopathy in a Patient with Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)

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Abstract: Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a rare pathology that belongs to a group of diseases characterized by necrotizing vasculitis of small and medium-sized systemic blood vessels. Symptomatic cardiovascular involvement occurs in 27%–47% of cases of EGPA and is one of the most severe manifestations. The diagnosis is usually confirmed by eosinophilic infiltration observed in tissue biopsy, but with the recent inclusion of cardiac magnetic resonance imaging (MRI), the former can be replaced. Early diagnosis is important because timely treatment is often associated with improvement.

Keywords: Dilated cardiomyopathy; Churg-Strauss syndrome; Heart failure

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1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, belongs to a group of diseases characterized by necrotizing vasculitis of small and medium-sized blood vessels [1]. Its prevalence and annual incidence are 7.3–17.8 and 0.9–2.4 per million population, respectively [2]. The organs most commonly affected in EGPA are the lungs and skin. Symptomatic cardiovascular involvement occurs in 27%–47% of cases [3] and is one of the most severe manifestations, accounting for approximately 50% of deaths from this disease [4]. Pericarditis, arterial hypertension, valvular heart disease, eosinophilic myocarditis, arrhythmias, and/or congestive heart failure are some of its manifestations [2]. We present a case of EGPA with cardiovascular involvement in a patient who showed good response to timely pharmacological treatment.

2. Case

A 49-year-old man with history of ischemic stroke five years ago, asthma, chronic sinusitis, and EGPA diagnosed by right sural nerve biopsy performed in view of lower limb polyneuropathy associated with systemic eosinophilia complaint of epigastralgia for 4 months associated with progressive functional class III dyspnea and edema in the lower limbs for which he was hospitalized in another institution with presumptive diagnosis of decompensated heart failure secondary to dilated cardiomyopathy with severely impaired systolic function (ejection fraction of 31%). He was referred to our institution for further

investigations and treatment.

Physical examination showed lower limb edema, jugular vein distention, hepatojugular reflux, and crepitus in both lung fields up to the middle one-third of the lungs.

Laboratory investigations on admission showed eosinophilia and elevated levels of high-sensitivity troponin T (22.5 ng/L), N-terminal prohormone of brain natriuretic peptide (Nt-proBNP; 6,546 pg/mL), and D-dimer (1,260 ng/mL). His rheumatology profile showed marked elevation of immunoglobulin E (IgE; 1,556 IU/mL, normal value of IgE < 100 IU/mL). Viral and Chagas serologies were negative.

Electrocardiogram showed frequent ventricular extrasystoles alternating with sinus rhythm and fusion beats, complete right bundle branch block and left anterior hemiblock. Doppler echocardiogram showed biventricular dilatation with impaired left ventricular systolic function (ejection fraction 25%) and moderately dilated left atrium. No angiographically significant coronary lesions were observed on coronary angiography; thus, coronary involvement as a cause of ventricular dysfunction was ruled out.

Cardiovascular magnetic resonance imaging (MRI) with gadolinium was performed given the history. The results were consistent with non-ischemic/necrotic dilated cardiomyopathy, with severe dilatation and functional impairment of the left ventricular cavity (ejection fraction 16%); apical subendocardial fibrosis and small foci of late intramyocardial enhancement in the basal region were also observed (**Figures 1** and **2**).

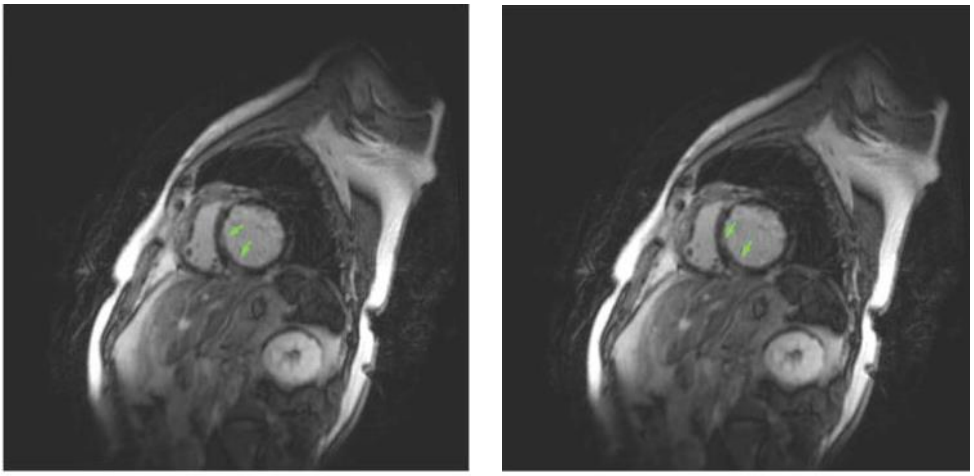

Figure 1. Short-axis phase-sensitive inversion recovery (late enhancement) sequences showing focal intramyocardial fibrosis in basal septal and anteroseptal regions (arrows)

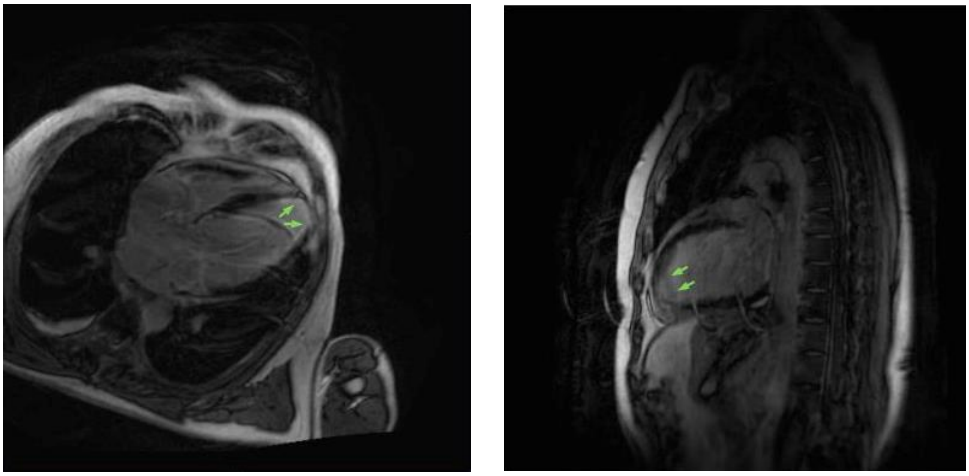

Figure 2. Long-axis phase-sensitive inversion recovery (late enhancement) sequences showing subendocardial fibrosis in the apical region (arrows)

We then decided to evaluate for respiratory involvement by means of chest and paranasal sinus computed tomography. The former reported diffuse ground-glass opacities, with central distribution, in both lung parenchyma, and granulomas in both lungs; in addition, moderate right pleural effusion associated with subtotal atelectasis of the right lower lobe and multiple mediastinal lymph nodes were observed. Signs of chronic sinusitis were observed on paranasal sinus CT.

Given the findings, a diagnosis of EGPA with cardiovascular involvement was made. Treatment was initiated with corticosteroids (methylprednisolone 500 mg intravenous pulses for 3 days and subsequent maintenance with meprednisone 40 mg per day), immunosuppressants (azathioprine 50 mg every 12 hours orally), and heart failure medications (spironolactone 25 mg per day, bisoprolol 5 mg twice a day, and sacubitril/valsartan 50 mg every 12 hours).

Subsequent follow-up after 9 months of treatment showed marked clinical improvement (functional class I) and improved ventricular function (ejection fraction 40%) on echocardiogram.

3. Discussion

EGPA, formerly known as Churg-Strauss syndrome, is a specific variant of a group of systemic diseases characterized by necrotizing vasculitis of medium- and small-sized vessels associated with antineutrophil cytoplasmic antibodies (ANCA). The other subtypes include granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis [1,2].

The diagnosis of EGPA is based on the presence of asthma, peripheral eosinophilia, and systemic vasculitis, along with an anatomopathological study showing necrotizing vasculitis, inflammatory infiltrate consisting of eosinophils, and extravascular granulomas [6].

The diagnostic criteria are shown in **Table 1**.

Table 1. American College of Rheumatology (ACR) diagnostic criteria for eosinophilic granulomatosis with polyangiitis

American College of Rheumatology (ACR) diagnostic criteria
(i) Previous history of asthma
(ii) Peripheral eosinophilia > 10%
(iii) History of allergy
(iv) Mono- or polyneuropathy
(v) Migratory pulmonary infiltrates
(vi) Paranasal sinus abnormalities
(vii) Typical anatomopathological findings, such as eosinophilic vasculitis and fibrinoid necrosis

Note: With 4 or more criteria, eosinophilic granulomatosis with polyangiitis is diagnosed with a sensitivity of 85% and a specificity of 99.7%.

EGPA is a rare condition; its incidence is 0.9–2.4 cases per million people, while its prevalence is 7.3–17.8 cases per million [2]. It tends to affect men more than women, with a mean age of presentation at 45.5, and it is more common in people of European descent [7].

Patients who are positive for ANCA (about 40%) usually have a vasculitic phenotype and often present with myalgia, migratory polyarthralgia, weight loss, mononeuritis multiplex, and renal involvement, such as necrotizing or crescentic glomerulonephritis. In contrast, patients without ANCA usually have an eosinophilic phenotype, with a higher incidence of myocarditis [8]. EGPA is one of the most common systemic vasculitides affecting the heart. The reported frequency of cardiac involvement is 62%, with symptomatic cases ranging from 27% to 47% [3]. This manifestation is of great clinical importance, as it

represents the main cause of morbidity and mortality (50%) in these patients despite the overall favorable prognosis of the disease [4]. The lesion is caused both by mediators released by activated eosinophils and by vasculitic lesions in the myocardium and coronary arteries [9].

The cardiac manifestations include pericarditis, arterial hypertension, valvular heart disease, eosinophilic myocarditis, arrhythmias, congestive heart failure, coronary artery disease, cardiomyopathies, and eosinophilic pericardial effusion [2]. Among them, myocarditis is the most common in EGPA, and patients may present with mild symptoms, such as precordial pain and palpitations, or even life-threatening conditions, such as cardiogenic shock, in severe cases [11].

The risk of myocarditis increases in patients between 20 and 30 years of age, and cardiac manifestations occur later in women than in men [3]. Cardiac involvement in EGPA may also mimic acute coronary syndrome. Electrocardiography may reveal nonspecific ST-T changes or, rarely, ST elevation due to coronary vasospasm or intracoronary thrombi. Coronary angiography, on the other hand, may show stenotic lesions, coronary ectasia, or vasospasm.

Significant coronary involvement is seen in 36.4% of patients [10]. Coronary vasospasm has been considered the main cause of chest pain in patients with EGPA without significant coronary artery disease. Coronary ectasia has been previously described in many systemic inflammatory vasculitides and is associated with ectasia in other arterial beds, such as the renal and cerebral vasculature [10]. At the laboratory level, eosinophil count is markedly higher in patients with myocarditis, as is the white blood cell count due to eosinophilia. In addition, erythrocyte sedimentation rate and C-reactive protein are often elevated, indicating an active inflammatory response. Patients with EGPA and myocarditis are usually negative for ANCA [3].

The use of Doppler echocardiography is very useful for the initial evaluation of these patients [10]. Echocardiographic findings consist of left ventricular systolic dysfunction (83.9%), significant diastolic dysfunction (3.2%), segmental wall motion disorders (9.7%), ventricular hypertrophy and valvular insufficiency (12.9%), pulmonary hypertension (6.5%), pericardial effusion (37.1%), and intracardiac thrombi (22.6%).

Cardiac MRI with gadolinium is indicated in cases of EGPA with electrocardiographic or echocardiographic abnormalities, since it correlates with eosinophilic infiltration in endomyocardial biopsy [12] and with evidence of fibrosis and necrosis in advanced cases [13]. MRI may be useful for stratification of patients with EGPA and individualization of treatment [14]. However, in many cases, further studies are needed to differentiate the active phases of fibrosis. The exact sensitivity and specificity of MRI in EGPA with cardiac involvement is still unknown; however, there are studies that have reported a sensitivity of 88% and specificity of 72% [15].

The treatment of EGPA with cardiac involvement depends on the stage of the disease; the suggested regimens are shown in **Table 2** [5].

Table 2. Recommended treatment regimens according to the stage of disease

Stage	Recommended treatment regimen
No indicators of poor prognosis	Regimen 1: Oral prednisone 1 mg/kg per day for 3 weeks, and then reduce to 0.5 mg/kg and until cessation. Regimen 2: Intravenous methylprednisolone (15 mg/kg), followed by oral prednisone as in Regimen 1.
With poor prognostic indicators	3 pulses of intravenous methylprednisolone (15 mg/kg) + 12 pulses of cyclophosphamide (600 mg/m^2) every 2 weeks for 1 month, and then every 4 weeks, or 1 short cycle of cyclophosphamide (oral 2 mg/kg) for 3 months, or 6 pulses of cyclophosphamide (600 mg/m^2) every 2 weeks for 1 month, and then every 4 weeks + azathioprine 2 mg/kg for 1 year or more.

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Stage	Recommended treatment regimen
Relapses	Oral azathioprine 2 mg/kg per day for at least 6 months, or cyclophosphamide pulses (600 mg/m^2) every 2 weeks for 1 month, and then every 4 weeks.
Maintenance for remission	Methotrexate (10–25 mg per week). Cyclosporine A (1.5–2.5 mg/kg per day). Azathioprine (2 mg/kg per day).
Refractory disease	Plasmapheresis. Intravenous immunoglobulin (0.4 g/kg per day for 5 days). Interferon-alpha (3 million IU, 3 times per week subcutaneously). Tumor necrosis factor inhibitors: infliximab, etanercept, adalimumab, or rituximab (325 mg/m^2 for 4 consecutive weeks).

Our patient was considered to have poor prognosis due to cardiac involvement, as assessed by MRI, with confirmed EGPA by sural biopsy. However, a favorable outcome was observed with the combined treatment as demonstrated by the increase in ventricular function from 25% to 40% in the last follow-up. The use of cardiac MRI made it possible to rule out any other cardiac conditions that could lead to confounding diagnosis and thus delay treatment.

With early detection and timely treatment, EGPA has a favorable prognosis with a 5-year survival of 90%. The relapse rate is estimated at approximately 20%–30% and is often lower with fever, joint pain, and constitutional symptoms [5].

4. Conclusion

Cardiac involvement in EGPA can manifest in a highly variable manner but it remains subclinical in most cases. This warrants an in-depth cardiac evaluation of all patients with a confirmed diagnosis of EGPA regardless of symptom status to detect cardiac involvement in its early phase and thus begin optimal treatment.

We present a case of decompensated heart failure secondary to non-ischemic/necrotic dilated cardiomyopathy in a patient diagnosed with EGPA. The therapeutic response showed improvement in symptoms and ventricular function on echocardiographic follow-up.

Disclosure statement

The authors declare no conflict of interest.

Author contributions

All authors contributed to the conceptualization, data collection, and preparation of the manuscript, taking public responsibility for its content and approving its final version.

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