Severe heart failure and intracardiac thrombosis: going beyond the appearance for diagnosis and treatments

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Abstract

We describe the case of a 45-year-old female affected by asthma and nasal polyposis who presented to the emergency department because of worsening dyspnea and paresthesia of the left lower limb. Comprehensive instrumental examinations revealed the presence of severe left ventricle dysfunction, intracardiac thrombus, deep vein thrombosis, pulmonary embolism, lung infiltrates, polyserositis, and neurological involvement. Finally, the patient was diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA), formerly Churg-Strauss syndrome, a rare vasculitis of small-medium blood vessels with several organ involvements.

Treatment with anticoagulants, corticosteroids, and cyclophosphamide led to a significant clinical improvement. However, a subcutaneous cardiac defibrillator was implanted because of the persistence of severe left ventricular dysfunction and the high cardiovascular risk phenotype. Indeed, several cardiac manifestations may occur in EGPA, particularly in patients with anti-neutrophil cytoplasmic antibody-negative disease. Therefore, clinicians should have high clinical suspicion because cardiac involvement in EGPA results in a poor prognosis if not diagnosed and adequately treated.

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly Churg-Strauss syndrome, is a systemic syndrome characterized by eosinophil-rich granulomatous inflammation and necrotizing small-vessel vasculitis. It was first described in 1951 by Jacob Churg and Lotte Strauss in patients affected by asthma, hypereosinophilia, cardiac failure, and renal and neurological involvement [1].

EGPA's estimated annual incidence is between 0.5 and 4.2 cases per million [2]. Due to its rarity and the ample clinical, laboratory, and pathological variability, it is essential to recognize this syndrome to start promptly adequate treatment; indeed, the disease is frequently characterized by heart and lung involvement with possible severe and fatal complications.

In the present article, we describe a case of a 45-year-old female who presented to the Emergency Department because of worsening dyspnea, deep vein thrombosis, and left lower limb paresthesia. Comprehensive clinical and instrumental evaluations led to a diagnosis of anti-neutrophil cytoplasmic antibodies (ANCA)-negative EGPA with critical cardiovascular, neurological, and respiratory involvement.

Case Report

A 45-year-old woman, former smoker, affected by bronchial asthma and nasal polyposis, experienced gradually worsening dyspnea, hepatomegaly, and paresthesia on the left lower limb that was

hot and edematous. A total body positron emission tomography/computed tomography showed left segmental pulmonary thromboembolism associated with patchy pulmonary infiltrations, pericardial and pleural effusions, cardiogenic liver cirrhosis, and thrombosis of the right uterine vein and left gonadal vein.

Therefore, she was admitted to the Emergency Department. At admission, general conditions were mediocre; blood pressure was 100/70 mmHg, heart rate 111 bpm, oxygen saturation 98% at room air, and blood temperature 36 C. Cardiac examination revealed muffled heart sounds without murmurs, while chest examination showed dullness to percussion and decreased breath sounds at the lung bases.

The admission electrocardiogram (EKG) showed sinus bradycardia, low QRS voltages in the peripheral leads, normal atrioventricular and intraventricular conduction, poor r-wave progression in the precordial leads, and diffuse repolarization abnormalities (Figure 1). The trans-thoracic echocardiography revealed a dilatated and hypokinetic left ventricle, thrombotic stratification at the apex, bi-atrial and bi-ventricular dilation, severe reduction of bi-ventricular global systolic function, and circumferential pericardial effusion not determining chambers compression (Figure 2). Blood tests revealed marked eosinophilia (1900 cell/µL, relative value 11%), a marked increase of N-terminal pro-B-type natriuretic peptide (26200 pg/mL), and a mild increase of troponin I HS (56 pg/mL).

The patient was transferred to the coronary intensive care unit. The heart/coronary computed tomography documented epicardial coronaries free from significant atheromatous pathology and confirmed the presence of endocavitary thrombosis. The cardiac magnetic resonance (CMR) better characterized the left ventricle thrombus and showed the presence of a dilated cardiomyopathy with a severe reduction in systolic biventricular function (left ventricular ejection fraction = 14%, right ventricular ejection fraction = 26%), late gadolinium enhancement (LGE) in the sub-endocardial area with diffuse involvement of the mid-apical ventricular segments and in the infra-myocardial area at the level of the lower basal and mid-apical intraventricular septum (Figure 3).

The autoantibodies ANCA were negative. According to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2022 criteria [3], in the presence of bronchial asthma, nasal polyposis, motoneuritis, and hypereosinophilia, a diagnosis of ANCA-negative EGPA with cardiac involvement was made.

Genetic testing was negative for *FIP1L1-PDGFRA*; Leiden V Factor, II factor, C and S protein mutations, and antiphospholipid antibodies were excluded. Therefore, anticoagulants and immunosuppression therapy with corticosteroids and cyclophosphamide were started. However, although medical treatment for ventricular dysfunction was optimized, the implantation of a subcutaneous cardiac defibrillator was indicated for primary prevention of arrhythmias, in accordance with the 2022 European Society of Cardiology (ESC) ESC guidelines [4].

Discussion

EGPA is a rare vasculitis of small-medium blood vessels occurring in patients with asthma and hyper-eosinophilia [2,5]. Histologically, it is characterized by necrotizing vasculitis and tissue eosinophil-rich granulomatous inflammation [5]. EGPA usually

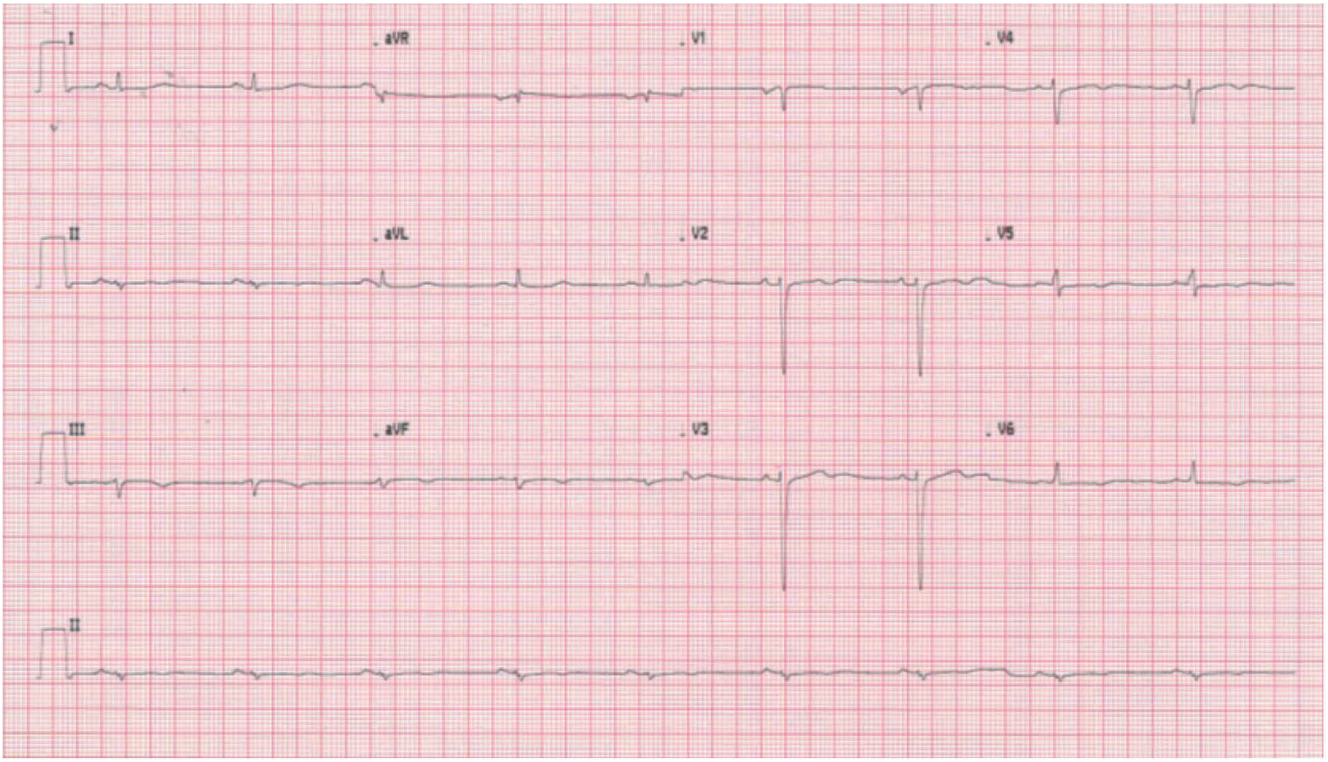

Figure 1. Admission electrocardiogram showing low QRS voltages in the peripheral leads, normal atrioventricular and intraventricular conduction, poor r-wave progression in the precordial leads, and diffuse repolarization abnormalities.

involves three steps that can also overlap [5]. The prodromic "allergic" phase can last several years and is characterized by asthma [2]. The "eosinophilic" phase is marked by blood hyper-eosinophilia, systemic involvement, and organ dysfunction. The "vasculitic" phase (not present in all the patients) is characterized by clinical manifestations due to small-vessel vasculitis [5].

In addition to asthma, respiratory involvement included lung infiltrates (radiologically patchy, peripheral, and migratory), pleural effusions secondary to eosinophilic pleurisy or eosinophilic cardiomyopathy-associated congestive cardiac failure, chronic recurrent rhinosinusitis, and nasal polyposis [2]. Other clinical manifestations may be possible, depending on the vasculitic involvement of cardiovascular, neurological, renal, gastrointestinal, and dermatological organs.

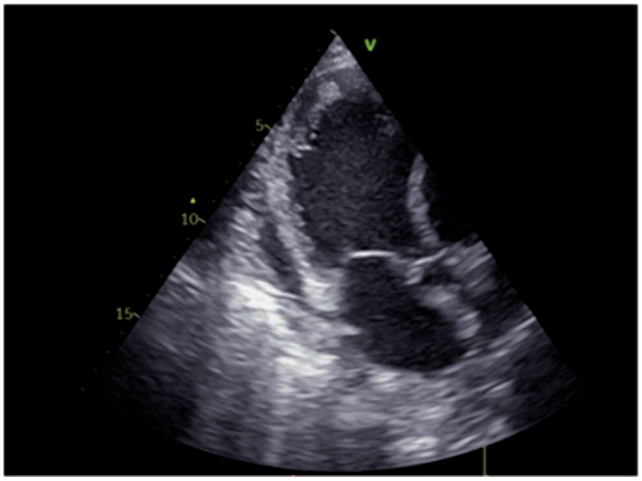

Figure 2. Trans-thoracic color Doppler echocardiogram showing left ventricle apical thrombus and pericardial effusion.

Cardiac involvement is present in one-third of cases and may range from silent to severe forms; it is the most adverse prognostic indicator because it is associated with severe complications and disease relapse [2,5-7]. Approximately 50% of deaths in EGPA patients are directly attributed to cardiac involvement and occur mainly within the first few months following diagnosis [6].

The most severe form of cardiac involvement is cardiomyopathy secondary to endomyocardial eosinophilic infiltration (*i.e.*, Loeffler endocarditis), causing impaired left ventricular function at diagnosis [6]. Other features of heart involvement may include valvular insufficiencies, eosinophilic coronaritis, constrictive or acute pericarditis, conduction defects, ventricular or supraventricular arrhythmias, intraventricular thrombosis, and sudden death [2,6,8].

Causes of cardiac damage in EGPA include initially direct damage by eosinophilic myocardial infiltration with consequent necrosis. Then, an ischemic mechanism may be involved; this induces inflammation and thrombotic obstruction of epicardial coronary arteries or perforating myocardial vessels and the development of fibrosis on the endocardium, myocardium, and tendon cords. Finally, systemic inflammation and steroid therapy may favor the onset of other cardiovascular risk factors such as diabetes, dyslipidemia, hypertension, and obesity [8].

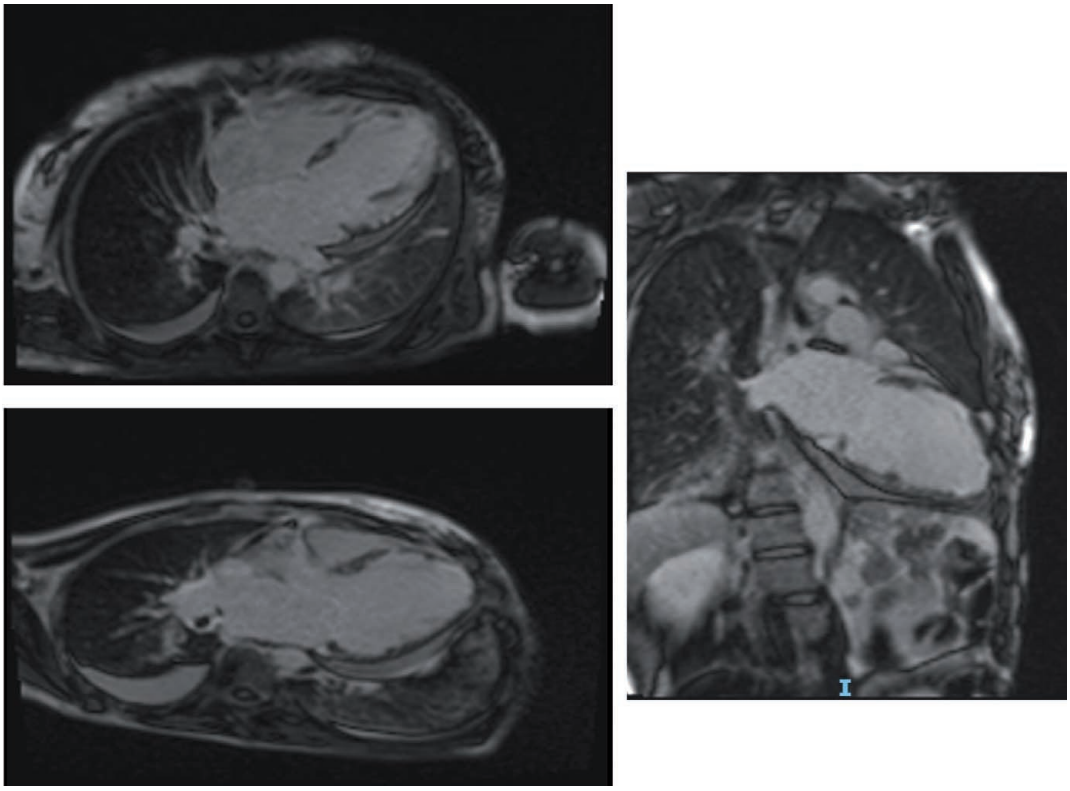

Figure 3. Cardiac magnetic resonance showing infra-myocardial late gadolinium enhancement and pleuropericardial effusion.

Our patient had a biventricular cardiomyopathy with a hypokinetic-dilated phenotype and a thromboembolic status (intraventricular thrombus, pulmonary embolism, uterine and gonadic vein thrombus). So, hypereosinophilia must have been responsible for the thromboembolic status. In the present case, a particular sign of severity and adverse outcomes was represented by an intracardiac thrombus, favored by several factors inducing the alteration of all three components of the Virchow triad. In particular, severe ventricular dysfunction favors stasis, and eosinophil and eosinophil-derived products can cause endothelial damage and favor a prothrombogenic state through different mechanisms [6,9].

ANCA autoantibodies, usually against myeloperoxidase, are detectable in only ~40% of EGPA cases [2,5]. EGPA patients with negative ANCA, as in the case report, have more severe eosinophilic lung and heart involvement [6]. In particular, EGPA patients with negative ANCA demonstrated a higher inflammatory cardiac disease (coronary arteritis, myocarditis, and pericarditis), leading to a worse prognosis than those with positive ANCA [8].

Because of the possible cardiac involvement, the initial evaluation and follow-up of patients with EGPA requires the measurement of serum troponins (TnIs) and brain natriuretic peptides (BNPs) [10]. Indeed, although these markers are not specific, they are high in patients with EGPA and cardiac involvement. Also, they are helpful markers for patient follow-up, prognostic assessment, and identification of possible adverse cardiac events. BNP levels increase in ventricular pressure or volume overload and, therefore, in the case of heart failure. Instead, TnI levels rise due to myocardial injury and, in the context of EGPA, may increase because of arthritis or myocarditis [10]. Therefore, both BNP and TnI levels may be helpful as markers to identify cardiac involvement and as a marker for patient monitoring.

Concerning instrumental diagnostic tools, cardiac alterations depend on the type of heart involvement. In the current case, the EKG showed diffuse ST-T alterations with poor r-wave progression in precordial leads. Other alterations include first-degree atrioventricular block, atrial dilation, ventricular hypertrophy, incomplete BBDx, poor R-wave progression in precordial leads, and negative T-waves.

A structured imaging assessment is necessary to identify the impaired cardiac function and endomyocardial abnormalities in EGPA [6]. The trans-thoracic echocardiogram may reveal left ventricular hypertrophy, left atrial dilation, right ventricular dilation, pericardial effusion, and a paradigmatic sign represented by an apical intraventricular thrombus [9]. Instead, the most common CMR findings are sub-endocardial LGE and left ventricular dilation with globally reduced ejection fraction. Finally, although more invasive, endomyocardial biopsy represents the gold standard for diagnosing eosinophilic infiltration of the cardiac tissue in addition to endocardial fibrosis, intramural thrombosis, small vessel inflammation, and thrombosis [6].

EGPA diagnosis is based on the following criteria coded by the ACR/EULAR 2022 guidelines (a score ≥6 is required) [3]: obstructive airway disease (+3); nasal polyps (+3); mononeuritis multiplex (+1); blood eosinophil count ≥ 1×10^9/L (+5); extravascular eosinophilic-predominant inflammation on biopsy (+2); positive test for cytoplasmic ANCA or antiproteinase 3 antibodies (-3); hematuria (-1).

In the present case report, clinical and laboratory criteria supported the diagnosis (score = 12), so the biopsy was unnecessary, even considering the intracardiac thrombus and the high thrombotic phenotype.

Established treatments for EGPA include glucocorticosteroids and cyclophosphamide, which usually result in a significant reduction of eosinophils and clinical improvement. In addition, recombinant humanized antibodies like omalizumab and mepolizumab or chimeric monoclonal antibody Rituximab may be used as an add-on therapy with steroid-sparing and in cases of refractory or relapsing disease [2]. In particular, omalizumab targets the high-affinity receptor binding site on free immunoglobulin E (IgE), preventing allergen-specific IgE from attaching to FcεRI on mast cells and basophils (with a consequent downregulation of FcεRI and inhibition of mediator release) [11]. Also, interleukin (IL)-5 is highly expressed in patients with EGPA; therefore, mepolizumab (anti-IL-5) is also a valid therapy for EGPA since it binds to free IL-5, preventing the association between IL-5 and IL-5 receptors on the surface of eosinophils and basophils (reducing their activation) [12]. Finally, rituximab may be used to target B-lymphocytes' surface CD20 antigen, resulting in B-cell suppression [13]. In our patient, we also excluded the *FIP1L1-PDGFRA* mutation, a hypereosinophilia genetic variant associated with beneficial therapy with imatinib [14].

Considering the severe and multi-organ involvement, anti-inflammatory/immunosuppressant therapy with glucocorticoids and cyclophosphamide was started, in addition to guideline-directed medical treatment for heart failure and therapeutic dose anticoagulation. We observed a reduction of blood eosinophils with a simultaneous improvement of respiratory and neurological involvement. However, despite optimizing treatment for heart failure, no significant improvement in biventricular function was observed (persistence of left ventricular ejection fraction <35%); this finding, in addition to extended LGE at CMR, suggested poor reversibility of the cardiomyopathy with medical therapy. Therefore, the implantation of a subcutaneous defibrillator for primary prevention of sudden cardiac death was necessary, as recommended by the 2022 ESC guidelines [4].

Conclusions

EGPA may heterogeneously involve the cardiovascular system and lead to severe complications. Therefore, a high clinical suspicion is necessary to diagnose this multi-faced vasculitis, to start treatment promptly, and prevent clinical deterioration and complications.

References

1. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. Am J Pathol 1951;27:277-301.
2. White J, Dubey S. Eosinophilic granulomatosis with polyangiitis: a review. Autoimmun Rev 2023;22:103219.
3. Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. Ann Rheum Dis 2022;81:309-14.
4. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2022;43:3997-4126.
5. Emmi G, Bettiol A, Gelain E, et al. Evidence-based guideline for the diagnosis and management of eosinophilic granulomatosis with polyangiitis. Nat Rev Rheumatol 2023;19:378-93.
6. Neumann T, Manger B, Schmid M, et al. Cardiac involvement

in Churg-Strauss syndrome: impact of endomyocarditis. Medicine (Baltimore) 2009;88(4):236-43.
7. Guillevin L, Cohen P, Gayraud M, et al. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine (Baltimore) 1999;78:26-37.
8. Garcia-Vives E, Rodriguez-Palomares JF, Harty L, et al. Heart disease in eosinophilic granulomatosis with polyangiitis (EGPA) patients: a screening approach proposal. Rheumatology (Oxford) 2021;60:4538-47.
9. Maino A, Rossio R, Cugno M, et al. Hypereosinophilic syndrome, Churg-Strauss syndrome and parasitic diseases: possible links between eosinophilia and thrombosis. Curr Vasc Pharmacol 2012;10:670-5.
10. Bond M, Fagni F, Moretti M, et al. At the heart of eosinophilic granulomatosis with polyangiitis: into cardiac and vascular involvement. Curr Rheumatol Rep 2022;24:337-51.
11. Jachiet M, Samson M, Cottin V, et al. Anti-IgE monoclonal antibody (omalizumab) in refractory and relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss): data on seventeen patients. Arthritis Rheumatol 2016;68:2274-82.
12. Faverio P, Bonaiti G, Bini F, et al. Mepolizumab as the first targeted treatment for eosinophilic granulomatosis with polyangiitis: a review of current evidence and potential place in therapy. Ther Clin Risk Manag 2018:2385-96.
13. Mohammad A, Hot A, Arndt F, et al. Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg–Strauss). Ann Rheum Dis 2016;75:396-401.
14. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med 2003;348:1201-14.