

# Silent acute myocarditis in eosinophilic granulomatosis with polyangiitis

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## ABSTRACT

Eosinophilic granulomatosis with polyangiitis is a rare multisystemic disorder, characterized by necrotizing vasculitis affecting small to medium-sized vessels, associated with asthma and eosinophilia. Cardiac involvement is the most important predictor of mortality and it seems to be more frequent in anti-neutrophil cytoplasmic antibodies-negative patients. Cardiomyopathy and congestive heart failure can occur but a significant proportion of patients are asymptomatic. We present a case of this condition in a 65-year-old woman with a past medical history of rhinosinusitis and recent episodes of asthma, that developed palpable purpura, sensory deficiency and excruciating pain mainly in the lower limbs. A significant hyper eosinophilia and elevated troponin level were found, although she had not cardiac symptomatology. Cardiovascular magnetic resonance revealed late gadolinium enhancement and a severe reduction of the left ventricular ejection fraction. Mononeuritis multiplex was documented and diagnosis was confirmed by biopsy. Complementary cardiac investigation is mandatory in any patient with suspicion of eosinophilic granulomatosis with polyangiitis. Early detection and the appropriate treatment are crucial due to the possible life-threatening manifestations.

**Keywords:** Churg-strauss syndrome; Eosinophilic granulomatosis with polyangiitis;

## INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss Syndrome, is a rare systemic vasculitis, characterized by necrotizing eosinophilic and granulomatous tissue infiltration, which can affect small and medium-sized vessels. Respiratory involvement with presentation of rhinitis and/or asthma is practically universal. Although cardiac involvement is less common, it is the main cause of morbidity and mortality of this pathology<sup>1,2</sup>.

## CASE REPORT

A 65-year-old caucasian woman, with a past medical history of allergic rhinosinusitis since the age of 27, was followed by a pneumologist for a recent diagnosis of asthma and recurrent periods of exacerbation treated with montelukast, fluticasone/formoterol and hydroxyzine. She was admitted in the emergency department presenting a lancinating neuropathic pain and asymmetrical lower limb oedema more pronounced on the left side with 2 days of duration. Fifteen days prior she developed multiple purpuric lesions and dysesthesias of the upper and lower limbs (Figure 1). The patient reported unproductive cough, with no chest pain, dyspnea or palpitations. She denied fever or other constitutional complaints.

On admission to the rheumatology department, the patient presented hemodynamic stability, saturation 98% and body temperature 36.5°C. Cardiac auscultation showed rhythmic beats, without murmurs and pulmonary auscultation revealed diffused wheezing and inspiratory basilar crackles. Some petechiae and purpuric lesions were evident at the palmar and dorsal side of the hands and feet with extension to the pretibial region bilaterally. A muscular strength deficit was also found- right hand flexion grade 3 and left foot dorsiflexion grade 4 - and a hypoesthesia area in the right

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palm and left foot.

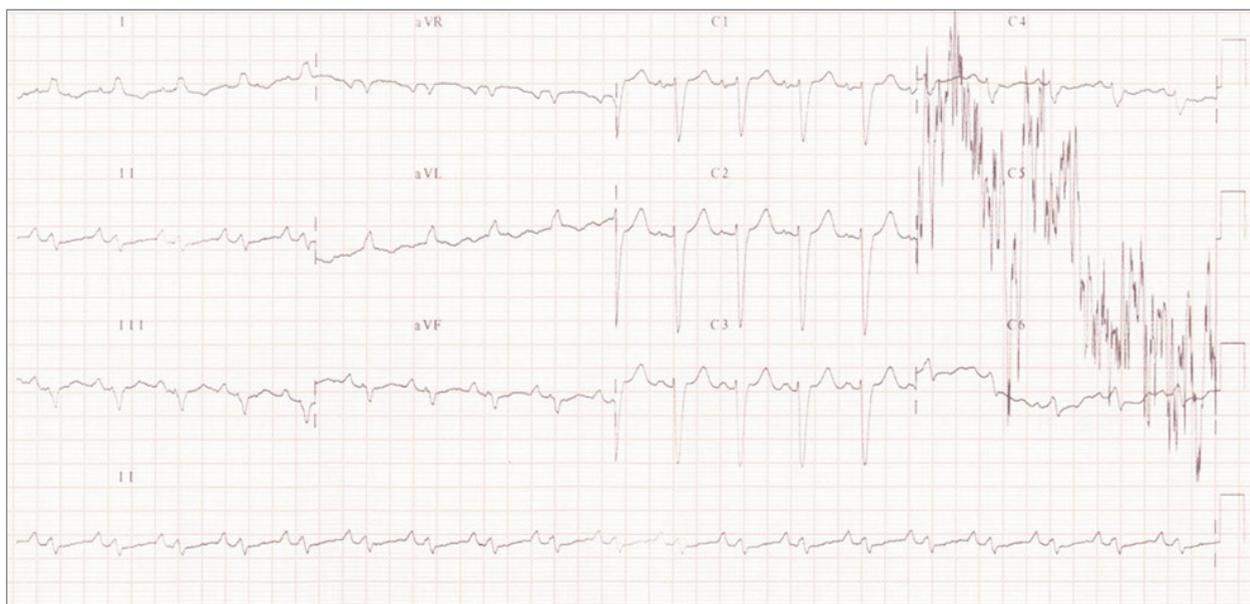
A complete blood count stood out leukocytosis of  $18.8 \times 10^9/L$  with hypereosinophilia of  $11.28 \times 10^9/L$



**FIGURE 1.** Palpable purpuric lesions on the lower limbs of the patient

(59.8%), without anemia (hemoglobin 14,7g/dL) or thrombocytopenia (platelets  $234 \times 10^9/L$ ). The erythrocyte sedimentation rate was 35mm/hr and the C-reactive protein of 147.2mg/L. Despite the absence of chest pain or other cardiac symptoms, serum troponin I level was markedly increased to 11429ng/L (normal <16) and also muscle enzymes were elevated - aspartate aminotransferase 133U/L, alanine aminotransferase 51U/L, lactate dehydrogenase 782U/L, creatine kinase 1579U/L, aldolase 28U/L, myoglobin 575ng/mL, creatine kinase-MB 123ng/mL. B-type natriuretic peptide (BNP) was increased by 543pg/mL as well as the serum IgE level (843kU/L). Renal function was preserved (creatinine 0,75mg/dL, urea 26mg/dL, creatinine clearance 73ml/min), urinalysis and lipid profile were normal. Anti-neutrophil cytoplasmic antibodies (ANCA) and anti-nuclear antibodies were absent. Serological tests for Epstein Barr, Parvovirus B19, Cytomegalovirus, syphilis, hepatitis B and C and HIV were negative. Blood cultures were sterile.

The electrocardiogram documented sinus tachycardia of 114bpm and left bundle branch block (Figure 2). Transthoracic echocardiography revealed moderate to severe left ventricular systolic dysfunction (LVSD) with ejection fraction ~32%, mild to moderate mitral regurgitation and a small volume pericardial effusion. Cardiac catheterization ruled out coronary disease. Cardiac magnetic resonance confirmed the severe



**FIGURE 2.** Electrocardiogram of the patient showing sinus tachycardia, heart rate 114bpm and left bundle branch block

re LVSD. On T2-weighted sequence no areas of hyperintensity suggestive of myocardial oedema were found, although a low image quality of that sequence was noticed. Post-contrast imaging clearly showed a late gadolinium enhancement pattern of subendocardial predominance and also in the papillary muscles, compatible with fibrosis and suggestive of a vasculitic process (Figure 3). The chest computed tomography scan revealed some subsegmental atelectasis of the lower lobes, without consolidations or nodularities. She presented a moderate obstructive pattern on the spirometry - forced vital capacity 1.64L (1.71-3.12), forced expiratory volume in 1 second 1.07L(1.39-2.64), tiffeneau index 56%, maximum mid expiratory flow 75/25 22%, without arterial blood gas changes (pH 7.4, pO<sub>2</sub> 81.7mmHg, pCO<sub>2</sub> 36.4mmHg, HCO<sub>3</sub> 24.9mmol/L, satO<sub>2</sub> 95.2%).

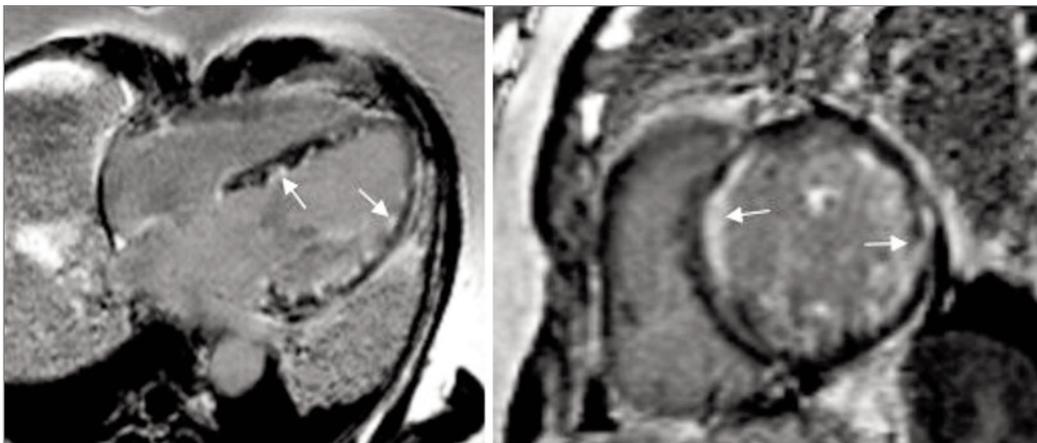
Electromyography of the upper and lower limbs recorded low amplitude nerve conduction, fitting with an acute multiple mononeuropathy. Doppler ultrasound test showed no signs of recent venous thrombosis. Due to the high diagnostic suspicion of EGPA presenting with major organ involvement, immunosuppressive therapy was instituted on the 2nd day of hospitalization with 3 pulses of methylprednisolone 1g/day, followed by oral prednisolone 1mg/kg/day and cyclophosphamide 1g/month. Montelukast was suspended. In addition, she started treatment with bisoprolol, acetylsalicylic acid, gabapentin and integrated a functional rehabilitation program. A rapid decrease of the inflammatory parameters was seen, as well as normalization of eosinophilia and muscle enzymes de-

cline. Subsequently, the patient was submitted to sural nerve and muscle biopsy. The histological exam revealed a severe asymmetric neuropathy with signs of activity (findings of demyelination of nerve fibers and axonal degeneration). The muscle tissue expressed very slight alterations. Although no granulomas or infiltrates were found in the sample, the characteristics described were consistent with a vasculitic process. The clinical condition of the patient significantly improved, with progressive regression of cutaneous lesions and a dramatic recovery of sensitivity and muscular strength. After 5 months of follow-up, the echocardiographic re-evaluation demonstrated a preserved left ventricular function (ejection fraction ~55%).

## DISCUSSION

EGPA is included in the heterogeneous group of vasculitis associated with ANCA. It typically manifests in the 5th decade of life, with identical sex distribution. Classically, the syndrome occurs in three sequential phases. The initial or prodromal phase is characterized by the presence of allergic rhinitis, sinusitis, nasal polyps and asthma. The latter often of adult-onset and difficult control. The second phase is marked by peripheral eosinophilia and tissue eosinophilic infiltration. Finally, the third phase can progress to potentially life-threatening vasculitic lesions, involving multiple organs, such as the heart and nervous system<sup>1-3</sup>.

Despite the absence of ANCA antibodies, our case



**FIGURE 3.** Long and short-axis of cardiac magnetic resonance imaging images showing patchy subendocardial late gadolinium enhancement in the left ventricle (arrows)

fulfils the American College of Rheumatology classification criteria for EGPA: past medical history of asthma, eosinophilia > 10%, mononeuropathy and alterations of the paranasal sinuses<sup>4</sup>. To respect to histological findings of muscle and nerve biopsy, although typical eosinophilic infiltration was not found in the tissue sample, we underline that the procedure was performed fifteen days after initiating glucocorticoid and immunosuppressive treatment which can influence the results.

The underlying pathophysiological mechanisms of the vasculitis and its frequent association with asthma are still poorly understood. The hypothesis of a causal relationship between the exposure to anti-leukotrienes, such as montelukast, and the development of the syndrome have been discussed over the years. Some speculations point to the unmasking of EGPA as a result of steroids tapering or discontinuation, enabled by the newer asthma therapeutics introduction. However, in other cases, there is a temporal relationship with the use of these anti-asthmatics in patients not previously medicated with corticosteroids. Due to this unclear association, we chose to discontinue montelukast as recommended by the literature<sup>3, 5</sup>.

Recent studies have showed some particularities of cardiac involvement in EGPA, which may be important in the patient clinical approach. The cardiovascular manifestations can occur in approximately 15 to 60% of cases and are variable. The disease has been associated with pericarditis, myocarditis, pericardial effusion, acute coronary syndrome, heart failure, valvulopathy, intracardiac thrombi, arterial hypertension and electrical conduction disorders<sup>1,2,6,7</sup>. Nevertheless, its course can often be silent, as it happened in the case described. We emphasize that the patient had no cardiac symptoms since her hospital admission. This finding is consistent with the study developed by Robet M. Dennert *et al.*, which reported that in the absence of symptoms and major electrocardiographic abnormalities, cardiac involvement could still be detected by echocardiography or cardiac magnetic resonance imaging (MRI) in 38% of the cases<sup>7</sup>.

In fact, MRI has emerged as the gold standard imaging test, due to its ability to assess a detailed anatomical description of the cardiac lesions. The technique allows the identification of pericardial leaflets inflammation, microvasculature changes, the existence of intraventricular thrombi, inflammation and/or fibrosis of myocardial tissue and detection of late gadolinium enhancement, despite the meaning of some findings

remain to be defined. Myocardial fibrosis appears to develop rapidly during the course of the disease and, consequently, an aggressive and immediate immunosuppressive treatment may be warranted, in order to prevent progression to chronic heart failure<sup>1,2,6</sup>. In this case, an endomyocardial biopsy was not performed, to avoid the inherent risks of an invasive technique and a delay of treatment initiation, since the whole clinical picture was very characteristic of EGPA and the myocardial involvement was supported by cardiac MRI.

Hypereosinophilia is the hallmark of the pathology, whereas ANCA, predominantly antimyeloperoxidase, are found in only 30-40% of the patients. Besides that, its prevalence seems to vary according to major organs involvement. Some series have shown that negativity for ANCA is more common in cardiac involvement, on the other hand, the presence of positive ANCA is more frequent in renal and neurological involvement. The data regarding cardiac complications also point to an association with higher serum eosinophilia (percentage > 20%), especially in myocarditis. The significant increase in intravascular eosinophilic proliferation that progressed to the infiltration of extravascular space, namely the cardiac muscle, seems to represent the pathogenic phenomenon. All these aspects support the analytical and clinical phenotype of the case presented<sup>1,8,9</sup>.

We therefore suggest the laboratory analysis of BNP and cardiac muscle enzymes, especially troponin I, in the initial approach, even in asymptomatic patients. Complementary imaging investigation is mandatory to evaluate cardiac function and structure, with chest x-ray, electrocardiogram and echocardiogram, in any patient with suspected EGPA. Cardiac catheterization can be used to exclude coronary abnormalities and cardiac MRI is a useful non-invasive modality to confirm myocardial involvement. ANCA assay should be performed, but its result deserves a careful interpretation, since clinical characteristics seem to differ according to this antibodies status remembering that their positivity is not imperative for establishing the diagnosis<sup>1,2,7</sup>.

Assessment of organ involvement is also extremely important for the therapeutic decisions. Steroid therapy constitutes the first-line treatment. The choice of concomitant immunosuppressants is dictated by the spectrum of manifestations. For remission-induction, cyclophosphamide is recommended in patients with severe systemic manifestation, as observed in the presented case with cardiac and neurologic involvement,

but in non-organ-threatening EGPA either methotrexate or mycophenolate mofetil can be used<sup>10</sup>. The French Vasculitis Study Group Cohort identified some poor prognostic factors, such as age > 65 years, cardiac involvement, gastrointestinal manifestations or renal failure, and for some authors cardiomyopathy remains the main independent predictor of mortality in this pathology<sup>9,11</sup>.

It is peremptory to perform a careful investigation in the suspicion of EGPA, because of its multisystemic involvement and the challenge of possible occult clinical manifestations. An early diagnosis is similarly essential given the association of cardiac involvement with poor prognosis and the efficacy of immunosuppressive therapy recommended in the treatment of this vasculitis.

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#### REFERENCES

- Mahr A, Moosig F, Neumann T, Szczeklik W, Taille C, Vaglio A, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): evolutions in classification, etiopathogenesis, assessment and management. *Curr Opin Rheumatol*. 2014;26(1):16-23.
- Dunogue B, Pagnoux C, Guillevin L. Churg-strauss syndrome: clinical symptoms, complementary investigations, prognosis and outcome, and treatment. *Semin Respir Crit Care Med*. 2011;32(3):298-309.
- Weller PF, Plaut M, Taggart V, Trontell A. The relationship of asthma therapy and Churg-Strauss syndrome: NIH workshop summary report. *J Allergy Clin Immunol*. 2001;108(2):175-183.
- Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis and Rheumatism*. 1990;33:1094-1100.
- McDanel DL, Muller BA. The linkage between Churg-Strauss syndrome and leukotriene receptor antagonists: fact or fiction? *Therapeutics and Clinical Risk Management*. 2005;1(2):125-140.
- Cereda AF, Pedrotti P, De Capitani L, Giannattasio C, Roghi A. Comprehensive evaluation of cardiac involvement in eosinophilic granulomatosis with polyangiitis (EGPA) with cardiac magnetic resonance. *Eur J Intern Med*. 2017;39:51-56.
- Dennert RM, van Paassen P, Schalla S, Kuznetsova T, Alzand BS, Staessen JA, et al. Cardiac involvement in Churg-Strauss syndrome. *Arthritis Rheum*. 2010;62(2):627-634.
- Qiao L, Gao D. A case report and literature review of Churg-Strauss syndrome presenting with myocarditis. *Medicine (Baltimore)*. 2016;95(51):e5080.
- Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viillard JF, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term follow-up of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum*. 2013;65(1):270-281.
- Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis*. 2016;75(9):1583-1594.
- Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P, et al. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine (Baltimore)*. 2011;90(1):19-27.