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.

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 episodes 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 palpable purpura, sensory deficiency and excruciating pain mainly in the lower limbs. A significant hypereosinophilia 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;

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palm and left foot. A complete blood count stood out leukocytosis of 18.8 x 10^9/L with hypereosinophilia of 11.28 x 10^9/L (59.8%), without anemia (hemoglobin 14.7 g/dL) or thrombocytopenia (platelets 234 x 10^9/L). The erythrocyte sedimentation rate was 35 mm/hr and the C-reactive protein of 147.2 mg/L. Despite the absence of chest pain or other cardiac symptoms, serum troponin I level was markedly increased to 11429 ng/L (normal <16) and also muscle enzymes were elevated - aspartate aminotransferase 133 U/L, alanine aminotransferase 51 U/L, lactate dehydrogenase 782 U/L, creatine kinase 1579 U/L, aldolase 28 U/L, myoglobin 575 ng/mL, creatine kinase-MB 123 ng/mL. B-type natriuretic peptide (BNP) was increased by 543 pg/mL as well as the serum IgE level (843 kU/L). Renal function was preserved (creatinine 0.75 mg/dL, urea 26 mg/dL, creatinine clearance 73 mL/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 114 bpm 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 seve-
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, pO₂ 81.7mmHg, pCO₂ 36.4mmHg, HCO₃ 24.9mmol/L, satO₂ 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 decline. 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.

Despite de absence of ANCA antibodies, our case...
fulfils the American College of Rheumatology classification criteria for EGPA: past medical history of asthma, eosinophilia > 10%, mononeuropathy and alterations of the paranasal sinuses⁴. 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 literature⁵–⁷.

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 disorders¹,²,⁶,⁷. 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 cases⁷.

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 failure²,⁶. 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 EPGA and the myocardial involvement was supported by cardiac MRI.

Hypereosinophilia is the hallmark of the pathology, whereas ANCA, predominantly antimielylperoxidase, 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 presented¹,⁸,⁹.

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 diagnosis¹,²,⁷.

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. 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.

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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