CASE BASED REVIEWS

Eosinophilic Granulomatosis with Polyangiitis – description of a pediatric patient with severe disease

Barbosa Rodrigues A[1], Oliveira-Ramos F[1], Ferreira R[2], Camilo C[3], Oliveira T[4], Costa-Reis P[1]

ABSTRACT

Introduction: Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare vasculitis of small and medium sized blood vessels.

Case Description: Thirteen-year-old male, with history of rhinitis and asthma, who presented to the emergency department with one week of asthenia, arthralgias and myalgias and two days of fever. A diffuse petechial rash, palpable purpura and polyarthritis were detected on examination. Leukocytosis (34 990/µL) with eosinophilia (66%) and elevated C-reactive protein were identified. The patient was admitted and ceftriaxone and doxycycline were started. The clinical status deteriorated in the following days. The patient developed myopericarditis, bilateral pulmonary infiltrates and pleural effusion, requiring mechanical ventilation and aminergic support. Non-clonal eosinophils were detected on the bone marrow aspiration and the skin biopsy showed leukocytoclastic vasculitis with eosinophils. Antineutrophil cytoplasmic antibodies and genetic analysis for hypereosinophilic syndrome mutations were negative. After treatment with methylprednisolone for three days a fast clinical, laboratory and radiological improvement occurred. The patient started azathioprine and reduced steroids progressively. No relapses occurred since diagnosis five years ago.

Discussion: Clinical suspicion and early treatment of EGPA are crucial to improve prognosis.

Keywords: Adolescent Rheumatology; Cardiovascular; Paediatric/Juvenile Rheumatology; Respiratory.

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is a vasculitis of small and medium sized blood vessels, characterized by blood and tissue eosinophilia and extravascular granuloma formation[1-5].

It is one of the rarest, potentially life-threatening, systemic necrotizing vasculitis. It is particularly uncommon in children, with an incidence of 1:1 000 000.[2,6-7]

The respiratory system is the most frequently affected. Almost all patients have a history of asthma and its severity usually increases 3-6 months before the onset of the systemic manifestations[8]. Rhinosinusitis is also highly prevalent, and lung involvement ranges from migrating patchy infiltrates to severe complications, such as alveolar hemorrhage. Cardiac involvement should always be checked, since it is a major cause of death in EGPA. The skin, gastrointestinal tract, kidneys and the nervous system can also be involved (Table I)[9,10].

The diagnosis of EGPA is challenging, particularly the distinction from other vasculitis.

In 2022, the ACR/EULAR revised and validated the criteria for EGPA. These criteria are used for classification of a small or medium-vessel vasculitis when all potential other causes have been excluded, including other related hypereosinophilic syndromes or eosinophilic malignancies. The proposed criteria and their weight were: maximum eosinophil count $\geq 1 \times 10^9$/L (+5), obstructive airway disease (+3), nasal polyps (+3), cANCA or pANCA positivity (–3), extravascular eosinophilic predominant inflammation (+2), mononeuritis multiplex/motor neuropathy not due to radiculopathy (+1), and hematuria (–1). A patient would be classified as having EGPA if the cumulative score was ≥6 points. These criteria had 85% sensitivity (95% confidence interval [CI] 77–91%) and 99% specificity (95% CI 98–100%). ANCAs and hematuria are negative items in this classification criteria, since they can be present in EGPA but are less common in this disease compared to other vasculitis[11].

[1] Pediatric Rheumatology Unit, Pediatrics Department, Hospital de Santa Maria, Centro Hospital Universitário Lisboa Norte, Lisbon, Portugal; [2] Pediatric Pneumology Unit, Pediatrics Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal; [3] Pediatric Intensiv Care Unit, Pediatrics Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal; [4] Pathological Anatomy Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal

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Correspondence to: Ana Barbosa Rodrigues
E-mail: acatbrodrigues@gmail.com

In EGPA there is an eosinophil-mediated inflammation, where activated eosinophils release cytotoxic granule proteins and lipid mediators that induce tissue damage[9]. ANCAs are present in 30-60% of patients[6,12-14]. In ANCA-mediated inflammation, ANCAs activate neutrophils and cause endothelial damage that induces vasculitis through the production of reactive oxygen species, release of proteolytic enzymes and the formation of neutrophil extracellular traps (NETs)[9]. ANCAs are associated with higher risk of glomerulonephritis and peripheral nerve involvement[1,2,6,9]. ANCA negative patients are prone to cardiac disease[2,6] and poor prognosis, since cardiomyopathy is the main independent predictor of death in these patients[6].

A genome-wide association study showed that EGPA had two genetic subsets associated with different manifestations based on ANCA status. Patients with EGPA with ANCA-positive antibodies share similar major histocompatibility complex (MHC)associations with patients with microscopic polyangiitis, whereas ANCA-negative EGPA are genetically similar to patients with asthma and inflammatory bowel disease, suggesting that a mucosal barrier dysfunction may participate in the pathogenesis of this phenotype[9].

Some studies have suggested an association of leukotriene receptor antagonists (LTRAs) use with EGPA. LTRAs might activate neutrophils, through IL-8 production, with NETs'production[9], raising of ANCA titer and EGPA vasculitis outbreak. Nevertheless, a cause-effect connection has not been proven and LTRAs might be used more often in patients with more severe asthma and this may act as a confounding effect.

EGPA has a relapsing-remitting course with 35% of patients relapsing less than five years after the initial remission[2,15]. Treatment relies on immunosuppression in order to minimize relapses[2-4,15].

We present a patient with EGPA to raise awareness in the community for this disease, including in children and adolescents.

CASE DESCRIPTION

Thirteen-year-old male with rhinitis, asthma and dust mite allergy, treated with montelukast and nasal and inhaled corticosteroids. The patient had blood tests one year before presentation and eosinophilia was identified (eosinophils 13 670/µL). Chest and paranasal sinuses computed tomographies (CT) were normal. In the previous months, short-acting bronchodilators were frequently used due to multiple episodes of wheezing and shortness of breath.

The patient presented to the emergency department after one week of asthenia, arthralgias and myalgias and two days of low grade fever. On the physical exam, blood pressure was 103/52mmHg; heart rate 107 bpm; the cardiopulmonary auscultation was normal; the hepatic border was palpable three cm below the costal margin; a diffuse petechial rash, palpable purpura and extensive ecchymosis were detected (Figure 1), as well as polyarthritis, affecting mainly large joints. His blood tests revealed leukocytosis (34 990/µL) with eosinophilia (23 160/µL; 66%) without anemia (Hb 15.9g/dL) or thrombocytopenia (platelets 202 000mg/dL), high C-reactive protein [CRP](10.56mg/dL) without elevation of procalcitonin (0.6ng/mL), high transaminases (alanine aminotransferase 129UI/L, aspartate aminotransferase 92UI/L), lactate dehydrogenase [LDH](529UI/L) and creatine kinase [CK](515UI/L). Urea and creatinine (0.4 mg/dL) were in the normal range with glomerular filtrate rate> 90 mL/min/1.73m^2, without proteinuria or hematuria. The patient was admitted to the hospital and ceftriaxone and doxycycline were started. Blood cultures were negative, as well as the aspergillus galactomannan antigen and serologies for *Rickettsia conori, Erlichia, Brucella, Leptospira*, cytomegalovirus, Epstein Barr virus, parvovirus, adenovirus, cocsakie and echovírus.

Within 48 hours, there was a deterioration of the clinical status. The patient developed dyspnea, chest pain, hypoxemia, tachycardia, hipotension and olyguria. It was detected leukocytosis (48 390/µL), eosinophilia (30 000/µL) [confirmed by peripheral blood smear] and elevated CRP (16.5mg/dL), LDH (879UI/L), CK (962 mg/dL), troponin (1 686ng/L) and NT-proNBP (14 800pg/mL). There was an elevation of creatinine (0.86 mg/dL), with glomerular filtrate rate of 75 mL/min/1.73m^2, without proteinuria or hematuria. Tryptase was normal (3.9mcg/L). Bilateral pulmonary infiltrates with bilateral pleural effusion were identified

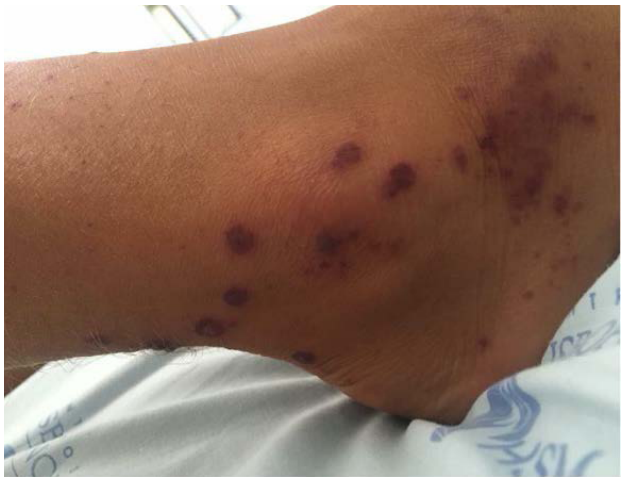

Figure 1. Diffuse petechial rash, palpable purpura and extensive ecchymosis presented by the patient.

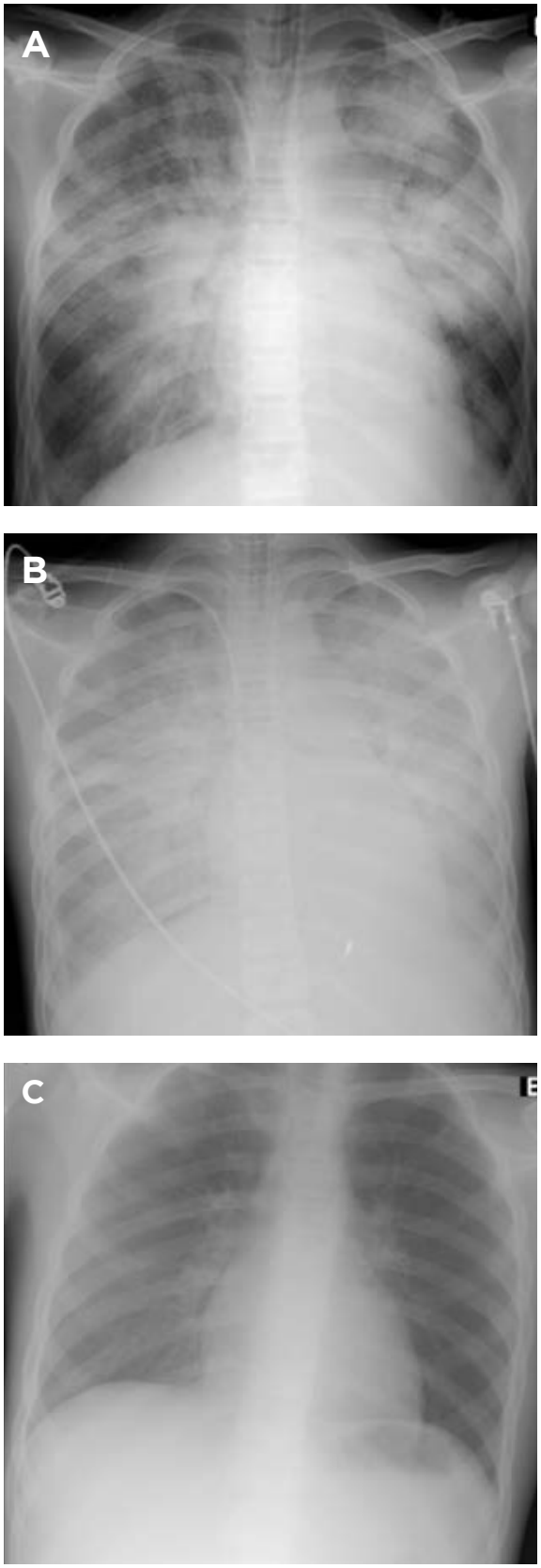

Figure 2. A, B – Chest x-ray with bilateral pulmonary infiltrates with bilateral pleural effusion. C - Chest x-ray with complete resolution of pleural effusion in five days.

on chest x-ray (Figure 2A); EKG and echocardiogram were suggestive of myopericarditis.

The patient was admitted to the paediatric intensive care unit. Antibiotic therapy was switched to meropenem plus vancomicin and non-steroidal anti-inflammatory drugs, furosemide, espironolactone and immunoglobulin were started. Mechanical ventilation and aminergic support were initiated.

Further exams were performed, namely bronchoalveolar lavage that was negative for bacteria and fungi; bone marrow aspirate that showed normal cellularity for the patient's age (Figure 3A) and a remarkable increase in eosinophils in various stages of maturation (Figure 3B and 3C). There was no fibrosis nor infiltration by atypical cells. The skin biopsy revealed leukocytoclastic vasculitis with eosinophils. ANCAs were negative. The genetic analysis for hypereosinophilic syndrome mutations (FIP1L1-PDGFRA/B) was negative.

The paediatric rheumatology team observed the patient and, according to the clinical presentation and laboratory results, established the diagnosis of EGPA. The patient was started on methylprednisolone, i.v., 1g per day, for three days and, afterwards, prednisolone 1 mg/kg/day. A fast clinical, laboratory and radiological improvement occurred. Aminergic support was discontinued one day after starting immunosuppression and mechanical ventilation two days later. There was complete regression of eosinophilia after 3 days of treatment with methylprednisolone (eosinophils 0/µL). There was complete resolution of pleural effusion on chest x-ray in five days (Figure 2B).

The patient was discharged 24 days after the symptoms began and returned to school six days later. Azathioprine was started (2mg/Kg) and the dose of steroids was progressively decreased.

The patient is currently followed by a multidisciplinary team that includes pediatric rheumatology, pneumology, cardiology and neurology, and is being treated with azathioprine (2mg/kg) and low dose prednisolone. He is also medicated with low doses of inhaled corticosteroid since, although the asthma has always been controlled, the last spirometry revealed mild bronchiolar obstruction with positive bronchodilation test, which indicates that there is a sign of reactivity. In addition, when this medication was stopped, the patient worsened his asthma symptoms.

More than five years after the diagnosis, there are no other signs of disease activity.

DISCUSSION

EGPA is a rare disease, characterized by vasculitic manifestations associated with eosinophilia, in a patient

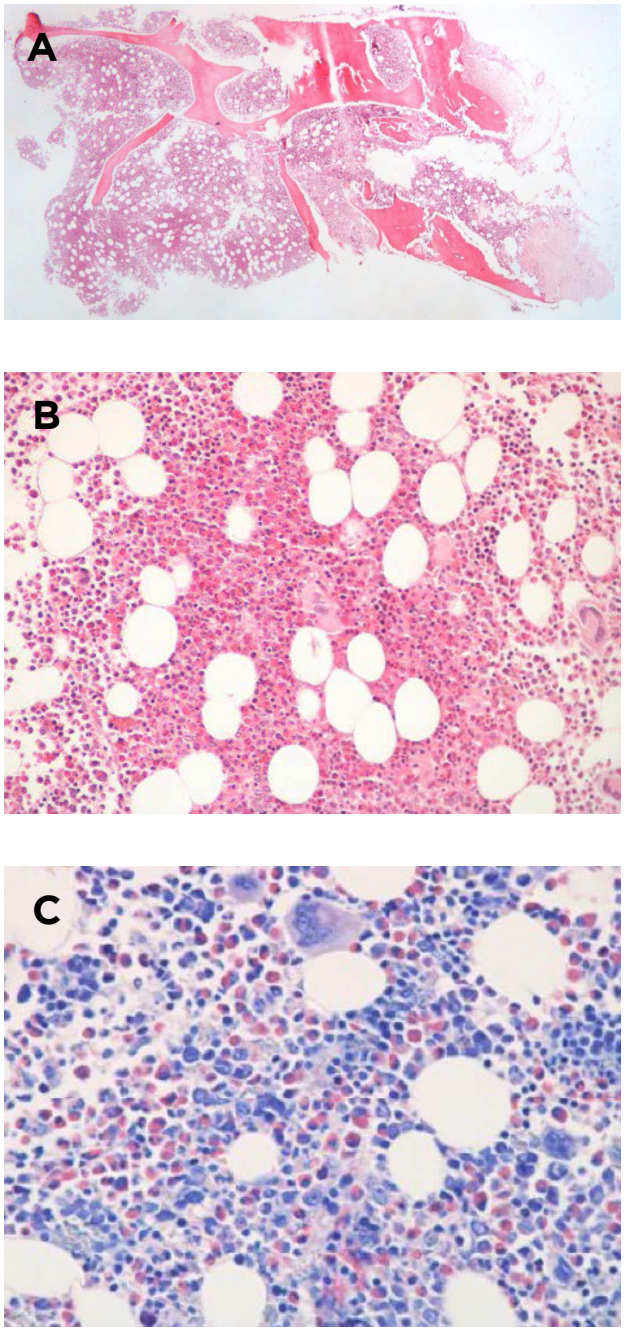

Figure 3. A – Normal cellularity of the bone barrow for the patient's age. B – Patient's bone marrow with remarkable increase in eosinophils in various stages of maturation C – Patient's bone marrow with remarkable increase in eosinophils in various stages of maturation

with asthma or allergic rhinitis[1,2,6].

EGPA is a systemic disease that can progress in different stages: asthma and sinusitis are usually the first manifestations, which in most of the cases are not valued due to their high prevalence in the general population; then, after a period of time, lung involvement with infiltrates occur and gastrointestinal and cardiac involvement can also be present; in later stages there are manifestations of vasculitis, including glomerulonephritis, palpable purpura and neuropathy[16].

Not all patients follow the different described phases and in some cases symptoms can overlap. Manifestations not related to an eosinophilic or vasculitic mechanism can also occur, such as thrombotic events[16].

It is important to differentiate EGPA from other systemic vasculitides. Skin biopsy is the gold standard for the differential diagnosis of cutaneous vasculitis and it may also be an informative tool in the absence of visible skin lesions[17].

Other eosinophilic disorders, like idiopathic chronic eosinophilic pneumonia and allergic bronchopulmonary mycosis, should also be excluded, if the clinical manifestations are exclusive to the lung. Hypereosinophilic syndrome (HES) and IgG4-related disease should be considered if there is extrapulmonary organ involvement. HES usually occurs in a patient without history of allergic disease. Bone marrow examination and search for FIP1L1-PDGFRa fusion gene are essential for diagnosis. IgG4-related disease can be distinguished by histopathologic examination (IgG4-secreting plasma cells and fibrosis) and measurement of serum IgG4 levels. Parasitic infections, drug allergy and haematological malignancies, such as Hodgkin lymphoma, should also be considered[5,18].

There are very few cases of EGPA occurring during childhood described in the literature[1]. The most common manifestations in children are respiratory (100%), cutaneous (71%), gastrointestinal (64%), and cardiac (57%)[19].

We present a patient with diagnosis of EGPA, presenting with a score of 10 according to 2022ACR/EULAR criteria for EGPA: obstructive airway disease, blood eosinophil count ≥ 109/liter and extravascular eosinophilic-predominant inflammation on biopsy, without ANCA or hematuria11.

In addition, the patient presented with history of allergy, pulmonary infiltrates, musculoskeletal and cardiac abnormalities, which, although they are not part of 2022 ACR/EULAR classification criteria for EGPA, are described as frequent in EGPA. Namely, cardiomyopathy is present in almost half of patients[9,10]. In the presence of myocardial disease associated with hypereosinophilia, the suspicion of EGPA should be therefore, raised, even in the absence of ANCA[20].

The patient had more asthma exacerbations in the previous months before presentation with an increased use of bronchodilators. This pattern had been frequently described in EGPA.

Treatment of EGPA is limited, due to its rarity and lack of studies on this disease. Glucocorticoids are used for induction of remission18. Disease-modifying

antirheumatic drugs (DMARDs), like azathioprine and mycophenolate mofetil, are used for induction and long-term maintenance therapy, since most patients with EGPA experience frequent relapses when glucocorticoids are reduced[17]. Rituximab, an anti-CD20 monoclonal antibody, can be effective in ANCA-positive patients, and cyclophosphamide and high-dose intravenous immunoglobulin therapy (IVIG) might be useful in refractory EGPA[18]. Mepolizumab, an anti-interleukin-5 monoclonal antibody, has proven to be safe and effective in EGPA, particularly in relapsing patients-who often experience recurrent respiratory manifestations[21,22].

Regarding outcomes, more than 90% respond to induction therapy with glucocorticoids, and consequently the prognosis is good in terms of survival[9,18]. The patient described had a dramatic improvement after starting immunosuppression, which shows that it is important to be alert and think about the possibility of the diagnosis of EGPA in order to start treatment as soon as possible and change the prognosis.

Nevertheless, the relapsing rate is high (25-40%) with significant morbidity if there is irreversible organ damage[9]. Cardiac involvement is a major determinant of mortality and long-term morbidity. Peripheral neuropathy is also an important morbidity factor, since it has a significant impact in patients' physical functioning[9]. Asthma in EGPA is classically severe and corticosteroid dependent[23]. There is persistent airflow obstruction despite oral corticosteroids in a significant proportion of patients[23].

The study of new therapies can potentially change the outcome of EGPA[18].

In conclusion, EGPA is a potentially life-threatening condition and clinical suspicion and early treatment of these patients are crucial.

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