Vilaça J, et al., J Neonatol Clin Pediatr 2022, 9: 102
DOI: 10.24966/NCP-878X/100102

HSOA Journal of Neonatology and Clinical Pediatrics

Case Report

Two-year follow-up of the use of mepolizumab in a pediatric patient with eosinophilic granulomatosis with polyangiitis: a case report

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Abstract

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic eosinophilic necrotizing vasculitis of small-to-medium blood vessels, with multiorgan involvement. The incidence of this disease in children is unknown, but it is thought to be rare and the clinical presentation is variable. Even though mepolizumab has been indicated as an add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory EGPA, its safety and efficacy data in this population have not been fully clarified.

Purpose

We hypothesized that mepolizumab would be an effective therapeutic option to achieve remission in an adolescent with antineutrophil cytoplasmic antibody (ANCA)-negative EGPA.

Method

We, herein, report the case of a 13-year-old girl with asthma, admitted to the emergency department (ED) for respiratory distress. After the first relapse, the patient was diagnosed with ANCA-negative EGPA with pulmonary and cutaneous involvement, nasal polyposis, pansinusitis, and pericardial effusion.

Results

Remission was only achieved after off-label introduction of mepolizumab, and it was sustained over two and a half years.

Conclusions

EGPA is a rare vasculitis in children. In this case, despite the presence of relapsing disease, remission was achieved with off-label use of mepolizumab in combination with azathioprine and prednisolone. Early recognition of childhood EGPA is a priority since delays in diagnosis can lead to severe organ involvement and, ultimately, death.

Keywords: ANCA; Case report; Refractory asthma; Eosinophilic granulomatosis with polyangiitis; Mepolizumab

List of non-standard abbreviations

ACR: American College of Rheumatology

ANA: antinuclear antibodies

ANCA: antineutrophil cytoplasmic antibody

BVAS: Birmingham Vasculitis Activity Score

CT: computed tomography

ED: emergency department

EGPA: Eosinophilic granulomatosis with polyangiitis

ELD: eosinophilic lung disease

EMA: European Medicines Agency

EULAR: European Alliance of Associations for Rheumatology

FFS: five-factor score

GPA: granulomatosis with polyangiitis

IL-5: anti-interleukin-5

MPA: microscopic polyangiitis

Key messages

Eosinophilic granulomatosis with polyangiitis (EGPA) is rare in pediatric patients, with very heterogeneous clinical manifestations. With off-label treatment with mepolizumab, it was possible to control the disease maintaining remission two and a half years later.

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Citation: Vilaça J, Miranda SB, Correia M, Lima R, Balona F, et al. (2022) Two-year follow-up of the use of mepolizumab in a pediatric patient with eosinophilic granulomatosis with polyangiitis: a case report. J Neonatol Clin Pediatr 9: 102.

Received: December 24, 2022; **Accepted:** December 29, 2022; **Published:** December 31, 2022

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), previously called Churg-Strauss syndrome or allergic granulomatosis angiitis, is a systemic eosinophilic necrotizing vasculitis of small-to-medium blood vessels with multiorgan involvement [1–3]. The common presentation of EGPA includes asthma, allergic rhinitis, and peripheral blood eosinophilia. Along with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), EGPA is an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Among these conditions, EGPA is the least prevalent, with an extremely low incidence, ranging from 0.18 to 4 new cases per million patients per year and an estimated overall prevalence between 5.3 to 38 per 1 million people, varying by location [1,2,4]. The mean age at diagnosis is 48 years and both sexes are equally affected [1]. The incidence of this disease in children is unknown but is thought to be rare and the clinical presentation can be quite diverse [5,6]. In children with EGPA, ANCAs are only found in 40% of the cases [2,7], which creates additional challenges to diagnosis in this population.

In terms of therapeutic approaches for severe EGPA, current guidelines recommend the combination of corticosteroids with immunosuppressive drugs, such as cyclophosphamide or rituximab, to achieve remission. In non-severe disease, mepolizumab shall be preferred over methotrexate, azathioprine, or mycophenolate mofetil and glucocorticoids [8].

Mepolizumab is an anti-interleukin-5 (IL-5) humanized monoclonal antibody that binds to free IL-5. It induces bone marrow eosinophil maturation arrest and decreases eosinophil precursors and subsequent maturation in the blood and bronchial mucosa [9]. In the European Union, mepolizumab was approved, in 2018, to treat patients with eosinophilic asthma aged 6 years and older [10]. By the end of 2021, the European Medicines Agency (EMA) has granted an extension of mepolizumab´s indication as add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory EGPA. Although, safety and efficacy data in children have been extrapolated from clinical trials with adult patients and, as such,, further evidence is warranted [4].

We, herein, report the case of a 13-year-old girl with asthma, from admission to disease remission. The patient was admitted for respiratory distress and diagnosed with ANCA-negative EGPA with pulmonary and cutaneous involvement, nasal polyposis, pansinusitis, and pericardial effusion.

Materials and Methods

The case herein reported followed the principles of clinical assessment including medical history, diagnosis, observation, and treatment.

Case report

We present a 13-year-old girl, with a family history of atopy, who was diagnosed with asthma and treated with inhaled salmeterol and fluticasone eight months before the first observation in our emergency department (ED), in August 2018.

Medical history

During the summer holidays, the patient had been observed, in the ED of another hospital, with dyspnea, dry cough, and interdigital itchy violaceous maculopapular skin lesions in hands and feet, without fever; she was treated with azithromycin and hydroxyzine. Five days later, and due to persistent symptoms, the patient performed a chest radiography that which revealed bilateral infiltrates. She was medicated with oral amoxicillin/clavulanate, clemastine, and inhaled salbutamol.

After five more days, the patient presented at our ED without any improvement. Physical examination revealed no respiratory distress, transcutaneous oxygen saturation of 95%, wheezing at pulmonary auscultation, and several interdigital skin lesions on the hands and feet. White blood cell differentiation and blood smear revealed leukocytosis ($23.6x10^9$/L) and eosinophilia ($11.4x10^9$/L), with exuberant granulations. C-reactive protein and erythrocyte sedimentation rate were raised (29 mg/L and 37mm/h, respectively). Renal function, coagulation tests (prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimer test), transaminases and albumin were normal. Chest radiography and computed tomography (CT) revealed perihilar mediastinal adenopathy, bilateral multiple peripheral consolidation focus, and air-trapping. A small pericardial effusion was confirmed by echocardiogram; electrocardiogram and cardiac enzymes were normal. The patient was admitted for investigation, keeping treatment with salbutamol, clemastine, and amoxicillin/clavulanate. On the first day of hospitalization, she developed respiratory distress and hypoxemia and started systemic corticotherapy (methylprednisolone 60 mg/day). Significant clinical improvement was observed within a few hours, reinforcing the suspected diagnosis of eosinophilic lung disease (ELD). In this setting, the team decided to extend the study; IgG and IgE levels were elevated (2110 mg/dL and 1552 U/ml, respectively), C3 and C4 complement were normal, and antinuclear antibodies (ANA), ANCA, and rheumatoid factor were negative. The analysis of bronchoalveolar lavage fluid evidenced 51% eosinophils, and negative mycobacterial and microbiological cultures. Bronchial biopsy revealed inflammatory infiltrate of eosinophils. Blood eosinophilia disappeared within 4 days, showing a fast response to steroids. Extensive cultures and serologic tests showed no evidence of infectious diseases, including negative fecal parasitology, specific IgE to *Aspergillus* and interferon gamma release assay. After 14 days of hospitalization, the adolescent was discharged with oral prednisolone 1 mg/kg/day (50mg/day), for 1 month; after that period, the dose should be slowly reduced to 0.2 mg/kg/day (10mg/day).

Six months after diagnosis, in March of 2019, the adolescent presented the first relapse with cough, hemoptysis, reappearance of cutaneous lesions, and blood eosinophilia ($7x10^9$/L). She was hospitalized and required supplemental oxygen. Symptoms improved rapidly and blood eosinophilia disappeared within 10 days, after increasing prednisolone to 0.6 mg/kg/day (40mg/day). Paranasal sinus CT revealed pansinusitis and slight polypoid degeneration adjacent to the middle meatus. Skin biopsy showed abundant perivascular superficial and deep interstitial inflammatory infiltrate with a predominance of eosinophilic polymorphonuclear cells.

Diagnosis

Although no vasculitis or granulomatous lesions were observed during the first relapse, the findings were suggestive of EGPA. The patient was discharged with prednisolone (0.6 mg/kg/day; 40mg/day), which was slowly reduced to 0.15 mg/kg/day (12.5mg/day). The use of corticosteroid in monotherapy led to a large weight gain and appearance of stretch marks, which interfered with her body image and, consequently, with self-esteem.

After five months, in August of 2019, the patient had a second relapse of the disease with cough, nasal obstruction, and cutaneous lesions. She was treated with oral prednisolone 0.78 mg/kg/day (60 mg/day) in association with progressively increasing doses of azathioprine up to 2 mg/kg/day (150 mg/day), as maintenance therapy. At this time, spirometry revealed small airway obstructive ventilatory syndrome with bronchodilator response.

Treatment

In the presence of a third relapse in April of 2020, again with alveolar hemorrhage and difficulty in corticosteroids weaning, treatment was adjusted to intravenous methylprednisolone pulses (500mg/day) for three days and subcutaneous off-label mepolizumab in a dose of 300 mg, every four weeks.

Outcomes and follow-up

Mepolizumab enabled the progressive reduction of the dose of azathioprine and prednisolone, with suspension of the last one. As of December 2022, three years after the diagnosis and two and a half years after starting treatment with mepolizumab, the patient is clinically stable, without asthma exacerbations. She is still on mepolizumab (300 mg subcutaneously, every four weeks), azathioprine (50 mg/day), budesonide (200 mcg/twice a day inhaled), and long-acting bronchodilators. The spirometry is normal without response to bronchodilator and the patient features zero on the five-factor score (FFS) scale and on the Birmingham Vasculitis Activity Score (BVAS).

Discussion

In accordance with the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, EGPA is a form of vasculitis histologically defined by eosinophil-rich necrotizing granulomatous inflammation, primarily involving the respiratory tract along with necrotizing vasculitis of small- to medium-sized vessels [11].

The exact pathogenesis of EGPA is still unknown. The disease is generally presented in three sequential phases: i) allergic rhinitis and asthma, in the prodromal phase; ii) eosinophilic infiltration in multiple organs, especially in the respiratory and gastrointestinal tract, in the eosinophilic phase; and iii) systemic small and medium vessels vasculitis, in the vasculitic phase [2].

The diagnosis of the case herein reported was based on the current adopted criteria. In 2022, the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) proposed new classification criteria that are to be applied when small-vessel or medium-vessel vasculitis are diagnosed, with a sensitivity of 88% and a specificity of 98%. The criteria and their weights include obstructive airway disease (+3), nasal polyps (+3), mononeuritis multiplex (+1), and laboratory and biopsy criteria like the presence of serum eosinophil count ≥ $x10^9$/L (+5), extravascular eosinophilic-predominant inflammation on biopsy (+2), positive test for cytoplasmic ANCA or antiproteinase 3 antibodies (anti-PR3) (-3), and hematuria (-1) (Table 1).

A score ≥ 6 is needed for classification of EGPA [7]. The previous 1990 ACR proposed the following six criteria for the diagnosis of Churg-Strauss syndrome: asthma (wheezing, expiratory rhonchi), eosinophilia of more than 10% in peripheral blood, paranasal sinusitis, pulmonary infiltrates (may be transient), histological proof of vasculitis with extravascular eosinophils, and mononeuritis multiplex or polyneuropathy. The presence of four or more criteria yields a sensitivity of 85% and a specificity of 99.7%, for the diagnosis [12]. Our patient met EGPA criteria according to both classifications.

Clinical Criteria	
Obstructive airway disease	+3
Nasal polyps	+3
Mononeuritis multiplex	+1
Laboratory and biopsy criteria	
Blood eosinophil count ^{3}1x109/L	+5
Extravascular eosinophilic – predominant inflammation on biopsy	+2
Positive test for cytoplasmatic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-3
Hematuria	-1

Table 1: Classification criteria for eosinophilic granulomatosis with polyangiitis (adapted from the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology criteria).

Despite the uncertain diagnosis, during the first hospitalization, glucocorticoids were used as induction and maintenance therapy, with clinical improvement. After the first relapse, the patient was diagnosed with EGPA, according to the abovementioned criteria. At this point, she was presented with active refractory disease, with new clinical signs and symptoms attributed to EGPA, like hemoptysis. Considering that the vasculitis was non-life- or organ-threatening, the team decided to initiate azathioprine with glucocorticoids. However, the relapsing nature of the disease kept hindering glucocorticoid tapering. At the moment of the third relapse, an extensive literature review followed by a multidisciplinary discussion culminated in consensus regarding the initiation of *off-label* mepolizumab. This strategy resulted in disease remission that remained until the elaboration of this report (December 2022). The outcome achieved with this drug demonstrated its effectiveness in patients with relapsing non-severe EGPA on immunosuppressive therapy, as recommended in the 2021 ACR/Vasculitis Association Guideline for the Management of ANCA-Associated Vasculitis [8].

As of December 2022, the patient presents a FFS score of 0. Even though the applicability of FFS to more recent therapies is still unconfirmed, this value (FFS=0) seems to indicate good prognosis. In fact, FFS is primarily a prognostic tool (higher scores are associated with worse outcomes) and it has been used to guide treatment [8].

In conclusion, we, herein, present a 13-year-old girl with an ANCA-negative EGPA, with the onset of symptoms at an atypical age, but presenting the most prevalent initial manifestations of this disease: pulmonary and rhino-sinus involvement. The adopted therapeutic approach, based on the off-label use of mepolizumab, enabled the safe tapering, and finally suspension, of systemic steroids, avoiding the development of additional steroid-related side effects, such as Cushing's syndrome, osteoporosis, growth delay, and infections.

In the last two years, the patient did not have any disease relapse or infectious complications. The absence of infectious disease is relevant considering that she started mepolizumab at the beginning of

COVID era. EGPA is a rare vasculitis in children. Early recognition of childhood EGPA is mandatory since delayed diagnosis can lead to severe organ involvement and fatal outcomes. Our case emphasizes the importance of considering the diagnosis of EGPA in children presenting with refractory asthma and unexplained manifestations. This approach enabled the implementation of appropriate and timely treatment, which proved to be determinant to avoid relapses and progression of the vasculitis process.

In this case report, disease remission was achieved only after the use of mepolizumab. Remission was maintained over the last two and a half years, allowing azathioprine´s tapering and systemic corticosteroids' suspension.

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