Pneumonia eosinophilic in pediatrics, clinical cases

Neumonía eosinofílica en pediatría, a propósito de dos casos clínicos

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Abstract

Eosinophilic Pneumonia (EP) is a very rare disorder in Pediatrics. It is characterized by the infiltration of eosinophils in the pulmonary and alveolar interstitium, and may be primary or secondary as well as present an acute or chronic progress. **Objective:** to present 2 pediatric EP clinical cases which were diagnosed at the pediatric intensive care unit of Clínica Indisa in Santiago, Chile between 2014 and 2017. **Clinical Cases:** Two older infants, who were hospitalized due to respiratory failure with a diagnosis of viral pneumonia. Both have asthmatic mothers. Additionally, they both had febrile syndrome, persistent condensation images in the chest x-rays, and peripheral eosinophilia throughout the course of the disease. One of the infants required oxygen for more than one month, and there was no eosinophilia in the bronchoalveolar lavage (BAL). In this case, the diagnosis of EP was reached via pulmonary biopsy. The other infant required mechanic ventilation for 28 days, and was diagnosed due to eosinophilia greater than 25% in the bronchoalveolar lavage. Both patients had excellent response to systemic corticosteroids. **Conclusion:** After ruling out other causes, EP should be suspected in children with pneumonia diagnosis, and persistent symptoms that do not respond positively to treatment, especially if associated with peripheral eosinophilia. The diagnosis of EP in pediatrics is confirmed with eosinophilia greater than 20% in BAL and, in some cases, it is necessary to perform a lung biopsy.

**Keywords:**
Eosinophilia;
Bronchoalveolar lavage;
lung biopsy;
persistent pneumonia;
corticosteroids
Introduction

Eosinophilic Pneumonia (EP) is a very rare entity in pediatrics. Most of the pediatric cases described in the literature are in children over 4 years of age, with clinical and laboratory characteristics that are partially different from adults.

It is part of the pulmonary infiltrates with eosinophilia (PIE) group, which can occur as primary or secondary cause. The primary cause may be due to eosinophilic granulomatosis with polyangiitis (EGPA), hypereosinophilic syndrome, or acute or chronic EP; and the secondary ones are parasites, drugs use or allergic bronchopulmonary aspergillosis (ABPA). In tropical countries, the first cause is parasites and in the rest of the countries, it is Chronic EP.

EP appears as pneumonia of torpid evolution, without response to treatment, presenting peripheral eosinophilia in bronchoalveolar lavage (BAL). In most patients, this entity has an excellent response to corticosteroids. Acute EP (AEP) is associated with hypersensitivity reactions triggered by inhaled agents, its onset is acute, and frequently requires mechanical ventilation (MV). Also, it may not initially present eosinophilia in BAL. Chronic EP (CEP) has a longer course and rarely requires MV. The differences between the CEP and the AEP are described in adults.

The objective of this article is to present two pediatric clinical cases of EP, both patients under 2 years of age, diagnosed between 2014 and 2017 in the pediatric intensive care unit of Clínica Indisa, in Santiago, Chile.

Clinical Case

Clinical case 1

20-months-old male infant diagnosed with Childhood Asthma (CA) treated with montelukast and desloratadine. His mother is asthmatic and he has no history of perinatal pathology.

The patient was hospitalized with diagnosis of pneumonia due to adenovirus, metapneumovirus, and bocavirus detected by polymerase chain reaction (PCR), with probable bacterial superinfection. The treatment was started with cefotaxime and invasive mechanical ventilation (IMV) for 3 days, followed by 10 days of oxygen administration through nasal cannula.

8 days after discharge, the patient was readmitted with febrile syndrome, thus an echocardiogram was performed, and he was diagnosed with Kawasaki Disease. He received treatment with gamma globulin and acetylsalicylic acid (ASA). The patient was discharged and after 48 hours, he was readmitted due to high fever, cough, and polypnea requiring oxygen therapy. A complete blood count (CBC) was performed which showed white blood cells count of 30,000 without bandemia and eosinophilia at 16%, PCR 5 mg/dl, and chest X-ray (CXR) showed bilateral interstitial infiltrates and right upper lobe consolidation. The patient was diagnosed with bacterial pneumonia and treatment was initiated with ceftriaxone and followed by ASA.

Due to fever persistence at 72 hours, BAL was performed, vancomycin was added to the treatment and a new gamma globulin push was administered. A CBC of later days showed leukocytosis with eosinophils count between 1600 and 3400. In the BAL was possible to observe: macrophages 50.2%, neutrophils 20.3%, lymphocytes 27.7%, eosinophils 1.8% and lymphocytes 12%, negative microbiological and fungal culture, PCR for Epstein-Barr, Pneumocystis jirovecii, Mycobacterium tuberculosis, Mycoplasma pneumoniae, and Chlamydia trachomatis was negative, and the PCR for quantitative cytomegalovirus (CMV) was positive. Ganciclovir was indicated for 21 days, however, the patient persisted febrile and requiring oxygen during treatment. Subsequently, quantitative PCR reported undetectable CMV in samples at the beginning and 6 days after treatment began.

Other studies were performed, all with negative results, such as HIV, blood cultures, myelogram, and marrow culture, in addition to full immunological study which was normal. Chest CT scan showed consolidation in both lower and upper lobes posterior segments and ground-glass opacity (figure 1).

Due to the persistence of fever for 27 days, oxygen requirement and pulmonary consolidation in the CXR despite treatment and without a clear etiological diagnosis, a pulmonary biopsy was performed, which resulted in nodular inflammatory interstitial lung disease with eosinophils predominance, diagnosing with eosinophilic pneumonia 30 days after the last hospitalization.

The child presented a rapid clinical response, with no fever and oxygen requirement 5 days after starting the treatment with systemic corticosteroids, and CXR with mild bibasilar interstitial infiltrate at 21 days. After 6 months of treatment, the oral corticosteroid was suspended and a control CT scan was performed, which showed almost complete regression of consolidation and ground-glass images.

Currently, the patient has been in follow-up for 3 years with treatment of inhaled corticosteroids and montelukast. He presented obstructive bronchitis and coughing triggered by exercise during the first 2 years of follow-up. During the third year, he presented only occasional cough and the inhaled corticosteroids dose was reduced. The child has normal spirometry, with no significant response to bronchodilator, negative skin test for inhalant agents, and 16 IU/ml IgE (figure 2).
Clinical case 2

15-month-old male infant, with no morbid history, normal perinatal period, and asthmatic mother.

He was hospitalized with diagnosis of pneumonia secondary to respiratory syncytial virus and parainfluenza detected by FilmArray® multiplex PCR system, with probable bacterial infection. The CXR showed consolidation of both the right and left lower lobe and right pleural effusion. The patient required IMV for 7 days and received ceftriaxone, cloxacillin, and clindamycin due to persistence of 10-days febrile symptoms. After extubation, he presented respiratory deterioration, poor respiratory mechanics, and pneumothorax, thus he required again IMV for 20 days. Change of antibiotics was indicated to vancomycin, piperacillin-tazobactam, and linezolid.

After 30 days of hospitalization, it was not possible to remove the IMV, thus BAL was performed, which found: macrophages 50.2%, neutrophils 20.3%, lymphocytes 27.7%, eosinophils 24%, and lipophages 12%, and PCR for CMV, Epstein-Barr, *Pneumocystis jirovecii*, atypical Mycobacteria, *Mycoplasma*, and *Chlamydia* was negative, microbiological, fungal, and *tuberculous Mycobacteria* culture were negative. Since more than 20% of eosinophils were observed in BAL, the diagnosis of eosinophilic pneumonia was confirmed. Chest CT scan showed consolidation and atelectasis in both lower lobes, pseudocyst images in the right upper lobe anterior segment, and right pleural effusion. Treatment with systemic corticosteroids was initiated with good evolution and withdrawal of mechanical ventilation on the sixth day of treatment. The patient was discharged 70 days after admission. He was on oral corticosteroids for 6 months. Currently, he has been in follow-up for a year, during which it has been observed that he is agitated while exercising. For this reason, and the history of asthmatic mother, the treatment continues with fluticasone and permanent montelukast, with good response.

Discussion

EP is very rare in children, with few cases reported in the literature. The CEP was first described by Carrington in 1969 and constitutes 3% of interstitial lung disease, which represents 3% of children under 20 years of age. It is more common in women, with an average age of 11.7 years in the pediatric population. AEP has a prevalence of 1/1,000,000 in children, and it is more frequent in male adolescents.

In these two cases, the patients are under 2 years of age, which contrasts with what has been published in the literature, where there was only one case of CEP in a one-year-old infant published in 1975 and another one of AEP in a 14-month-old girl.

Clinically, EP is characterized by cough, dyspnea, crackles, fever, weight loss, and night sweats that continue over time. It is confused with bacterial pneumonia without response to treatment which delays the diagnosis for 1 or 2 months, as occurred in our patients.

The CXR shows apical and peripheral bilateral alveolar infiltrate. The ‘photographic negative of pulmonary edema’, which is described in adults, is rare in pediatric patients. The chest CT scan shows patch-like alveolar filler lesions in upper and peripheral lo-
**Clinical Case**

In the AEP, it is possible to observe mild pleural effusion. Air bronchogram, nodules, mediastinal lymphadenopathy, and cavitations are less frequent. In the AEP, it is possible to observe mild pleural effusion. Our patients did not present all the radiological characteristics described in the literature, probably because of their age and the onset of the condition triggered by respiratory viruses.

The EP diagnosis is made through the presence of respiratory symptoms for more than 2 weeks, associated with peripheral eosinophilia and in the BAL, ruling out other causes of pulmonary infiltrates with eosinophilia. Lung biopsy is not required to diagnose CEP in adults, however, in pediatric cases, it should be considered when there is no clinical and radiological improvement with corticosteroids, or there is no eosinophilia in the BAL, which occurred in one of our patients. In children, 20% of eosinophils in BAL results is considered enough to diagnose EP, while in adults, the cut-off point is 40%. The biopsy describes alveolar and interstitial infiltrates of eosinophils and lymphocytes, with interstitial fibrosis, and preserved lung architecture. If the CEP is long-standing, it is possible to observe microabscesses, vasculitis, giant cells, and organizing pneumonia.

Regarding differential diagnoses, parasitosis was ruled out since Chile is not a tropical country and our children had not traveled to those areas and both had negative parasitological and serological tests for Toxocara. Allergic Bronchopulmonary Aspergillosis (ABPA) was ruled out since both patients had negative Sweat Test, IgE count less than 1000, low count of IgE specific for Aspergillus fumigatus, and absence of central cylindrical bronchiectasis in the chest CT scan. There were also no extrapulmonary manifestations, as described in eosinophilic granulomatosis with polyangiitis.

Exposure to drugs, days or weeks before the onset of symptoms, may appear as CEP or begin as AEP and, in some cases, pleural effusion may be observed and associated with rash. There is a website with a long list of medications that can cause eosinophilia with pulmonary infiltrates (www.pneumotox.com), however, the causality of this entity has been associated with less than 20 drugs. It is likely that the multiple antibiotic and nonsteroidal anti-inflammatory treatments received by the children may have played a role in the development of EP.

Although both children had viral pneumonia initially, we do not know if it triggered later the EP. We found two cases in the literature triggered by type A influenza and Bocavirus, the latter in a 14-month-old infant, similar to what happened with our patients. There are studies that prove the relationship between pulmonary viral infections, such as respiratory syncytial virus (RSV), coronavirus, influenza, and rhinovirus, and the eosinophil recruitment, especially in small infants when they are susceptible to asthma, as may be the case of our patients.

Eosinophils are classically involved in the reaction to parasites and allergens, but they also intervene in adaptive immunity against bacteria, viruses, and tumors due to the interaction of TH2 lymphocytes and interleukins 4, 5 and 13 in patients who have a predominantly TH2 lymphocyte response.

Both children had a history of having an asthmatic mother. The first one had a positive API (Asthma Predictor Index) and presented severe obstructive crises despite high doses of controller treatment in the first 2 years of follow-up, which is described in adult patients. Both children have presented symptoms compatible with asthma in the follow-up period after the EP picture, so they maintain controller treatment of asthma with inhaled corticosteroids and montelukast.

Regarding pulmonary function, mixed obstructive and restrictive patterns have been described in adults. In the first clinical case, after 3 years of the disease evolution, when the child was 4-1/2-years-old, spirometry was performed which was normal, without significant response to the bronchodilator. The child was on asthma controller treatment, which may explain the result.

The corticosteroid treatments have an excellent response, which are used for 6 weeks in adults, 9 to 12 months in case of recurrences, and 6 to 12 months in children. Symptoms improve in 2 days and CXR in 1 week. Inhaled corticosteroids are not useful as a single treatment for EP, but they are very useful in treating comitant asthma and subsequent relapses. Both patients received prednisone at 1 mg/kg/day dose for 6 months, with excellent clinical response in the first 3 days of treatment and a slower radiological response.

The relapses described in the adult population were not observed in our patients in a follow-up period of 4 years in the first case and 2 years in the second one.

**Conclusion**

The EP is a very infrequent pathology in pediatrics, which should be suspected in the child with pneumonia diagnosis with persistent symptoms and no response to treatment, having already ruled out other causes, especially if it is associated with peripheral eosinophilia. The diagnosis in pediatrics is confirmed by eosinophilia higher than 20% in BAL and, in some cases, lung biopsy is necessary and has an excellent response to corticosteroid treatment.
Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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