Idiopathic Acute Eosinophilic Pneumonia: An Uncommon Cause of Sudden Hypoxia

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Introduction

Pulmonary eosinophilic pneumonias include a heterogeneous group of disorders characterized by the presence of eosinophils in the lungs as detected by bronchoalveolar lavage or tissue biopsy, with or without blood eosinophilia (Tables 1 and 2).[1] Although the inflammatory infiltrate in the lungs is composed of macrophages, lymphocytes, neutrophils, and eosinophils, eosinophilia is an important marker for the diagnosis.

Idiopathic acute eosinophilic pneumonia (IAEP) is a rapidly progressive disease of healthy adults, described in 1989.[2,3] It is reported worldwide[4] and thought to be an allergic response to an environmental stimulus, sometimes associated with early cigarette smoking.[5] IAEP is a diagnosis of exclusion and should be considered in the differential of a sudden unexplained hypoxia and extensive pulmonary infiltrates.

Case Report

A 55-year-old Caucasian male presented with a seven-day history of losing ten pounds and night sweats. He had progressive shortness of air over the previous day and one-half. He was hypoxemic requiring 5-6 liters of oxygen by nasal canula and had bilateral infiltrates on chest x-ray (Figure 1) and computer tomography of the chest (Figure 2). Initial

Table 1. Classification of pulmonary eosinophilia based on clinical-radiological presentation.[1]

1) Simple pulmonary eosinophilia
2) Chronic eosinophilic pneumonia
3) Acute eosinophilic pneumonia
4) Allergic bronchopulmonary aspergillosis
5) Pulmonary eosinophilia associated with a systemic disease
   a) Churg-Strauss syndrome
   b) Hypereosinophilic syndrome

Table 2. Classification based on etiology of the forms of pulmonary eosinophilia.[1]

1) Primary or idiopathic
2) Secondary
   a) Known causes: drugs, parasites, toxic products/irradiation, fungal and mycobacterial infection
   b) Diffuse lung diseases: cryptogenic organizing pneumonia; hypersensitivity pneumonia; idiopathic pulmonary fibrosis; Langerhans cell histiocytosis; sarcoidosis
   c) Malignant diseases: leukemia, lymphoma, lung cancer, adenocarcinoma involving multiple organs, squamous carcinoma involving multiple organs
   d) Connective tissue diseases: rheumatoid arthritis, Sjögren's syndrome

laboratory work showed leucocytosis at 19,800 mcL without eosinophilia and bandemia of 16%. He had been exposed to tuberculosis in the past and tested positive on the tuberculosis skin test, however, he never had symptoms nor been treated. Active tuberculosis was ruled out. He also tested negative for atypical pneumonia including legionella, mycoplasma, and chlamydia. He also was checked for human immunodeficiency virus, vasculitis with antinuclear and antineutrophil cytoplasmic antibodies, and fungal infection including histoplasma. All tests were negative.

Sputum for gram stain and culture was positive for Staphylococcus aureus. Later, candida showed on culture which was thought to be commensal. The patient continued to be hypoxemic requiring about six liters of oxygen despite appropriate antibiotics and supportive treatment.

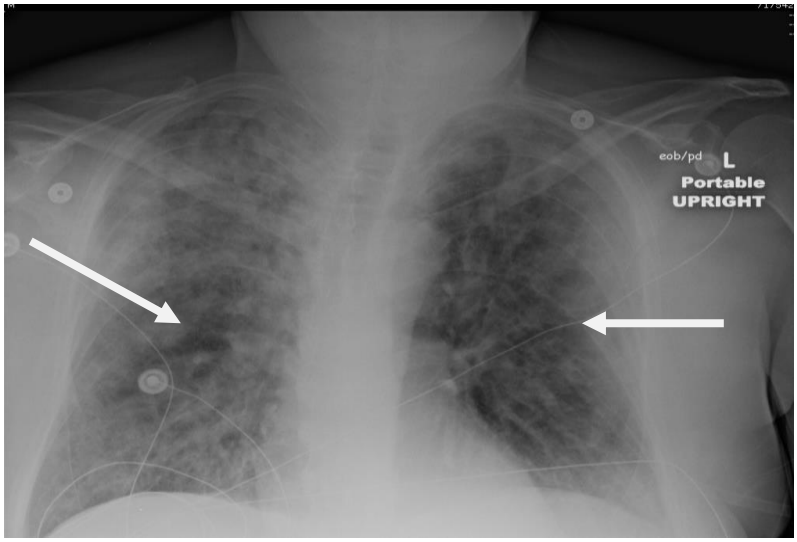

Figure 1 . Chest x-ray shows diffuse airspace consolidation.

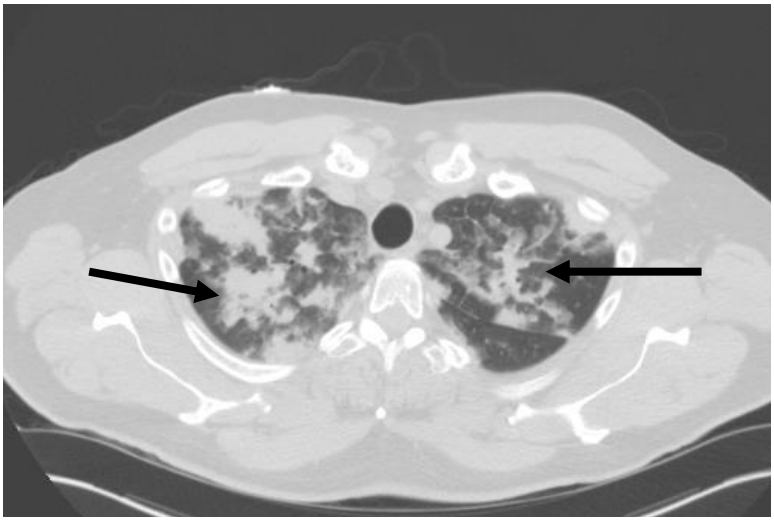

Figure 2. CT of the chest shows irregular, predominantly alveolar, infiltrate involving upper lobes bilaterally with lesser involvement of the lower lobes (not shown).

Bronchoalveolar lavage subsequently showed eosinophilia of 86%. A diagnosis of idiopathic acute eosinophilic pneumonia was made. The patient was started on IV steroid therapy as other causes for eosinophilia had been ruled out. The patient responded dramatically to steroids and was taken off oxygen in two days. He was sent home on tapering doses of steroids and antibiotics for methicillin resistant Staphylococcus aureus.

Discussion

Simple pulmonary eosinophilia is characterized by migratory pulmonary infiltrates in patients with eosinophilia and few or no pulmonary symptoms.[6,7] Pulmonary infiltrates are peripheral with a pleural base. Drugs and ascariasis are the most common causes. In one-third of cases, simple pulmonary eosinophilia is idiopathic. The prognosis is excellent. Corticosteroids are rarely necessary. Spon-taneous resolution occurs within 30 days.

Chronic eosinophilic pneumonia (CEP) is a severe disease of insidious onset with nonspecific respiratory and systemic symptoms.[8,9] Typically, CEP is idiopathic. The radiological profile is suggestive of peripheral consolidation that responds to corticosteroids, although it has a high recurrence rate. It can be secondary to drugs, parasites, and irradiation for breast cancer, or be associated with rheumatoid arthritis.[10] It has been described after childbirth[11,12] and desensitization using immunotherapy (allergy shots).[12]

The diagnosis is made on clinical criteria, a suggestive radiological profile, and the presence of peripheral eosinophilia or eosinophilia in the bronchoalveolar lavage fluid.[1] A rapid response to corticosteroids facilitates confirmation of the diagnosis. Spontaneous resolution is rare (occurring in only 10% of cases). There is a high recurrence rate after discontinuation of steroids.

Allergic bronchopulmonary aspergillosis (ABPA) is a complex hypersensitivity reaction that occurs when airways become colonized by aspergillus.[13] The following criteria are considered essential for a diagnosis of ABPA: asthma with central bronchiectasis or pulmonary infiltrates, positive skin test reactivity to aspergillus, total IgE levels greater than 1,000 U/L, and IgE or IgG against aspergillus in the blood. Based on disease activity, ABPA can be classified as having four distinct stages: remission, exacerbation, corticosteroid-dependent, and fibrotic phase.[1]

Chugg Straus Syndrome (CSS) or allergic granulomatosis and angiitis is a vasculitic disorder often characterized by sinusitis, asthma, and prominent peripheral blood eosinophilia.[14] CSS needs the following criteria for the diagnosis with confirmation of at least four being necessary: asthma, eosinophilia (greater than 1,500 cells/mm^3), paranasal sinus involvement, transient pulmonary infiltrates, mononeuropathy or poly-neuropathy, and biopsy findings of vasculitis. The disease pattern has such a distinct profile that it sometimes allows the diagnosis to be made clinically.[15] This syndrome is characterized by three phases: (1) allergic phase: presence of asthma or rhinitis, (2) eosinophilic phase: presence of severe persistent peripheral eosinophilia (greater than 1,500 cells/mm^3) for more than 6 months, and (3) vasculitic phase: presence of systemic manifestations and small vessel vasculitis, represented by the involvement of two or more extra pulmonary organs.

Hypereosinophilic syndrome (HES) is rare and typically results in death.[16] HES presents persistent eosinophilia (greater than 1,500 cells/mm^3; 30-70% of total leukocyte count) for more than six months. Organ involvement mainly includes the skin, the heart, the nervous system, and the

hematological system. The cytotoxicity of the major basic protein and eosinophil cationic protein content of eosinophils explains various instances of organ involvement in HES. The diagnosis is based on three criteria: persistent eosinophilia for at least six months or death within six months due to the signs and symptoms related to eosinophilia, eosinophilia-related involvement of at least one organ, and absence of a known cause of eosinophilia, such as drugs, parasites, malignancy, vasculitis, CEP, and CSS.[17]

Acute eosinophilic pneumonia (AEP) includes acute respiratory failure, fever, diffuse pulmonary infiltrate, and severe eosinophilia in the bronchoalveolar lavage (BAL) fluid or in lung tissue.[18,19] Histo-logical examination reveals eosinophil infiltration and edema in the alveolar spaces and interstitium, including the interlobular septa. In the lung tissues, there is a release of eosinophil chemotactic cytokines, granulocyte-macrophage col-ony-stimulating factor (GM-CSF), IL-3, IL-5, and IL-1B, all of which accumulate and are seen in the BAL fluid without an increase in the blood. This explains tissue eosinophilia without peripheral eosinophilia.

Pulmonary eosinophilia presents the greatest number of eosinophils in lung tissue. The granules containing toxic proteins explain why the tissue injury is so severe. Since the proteolytic potential of eosinophils is lower than neutrophils, the acute lung injury is reversible and there are no sequelae.[20] AEP can be caused by drugs as sertraline, BCG, minocycline, injectable progesterone, and inhaled cocaine. It also can be caused by passage of parasites through the lung, fungi, and inhalation of toxic products, but is most often idiopathic.[18]

Idiopathic acute eosinophilic pneumonia

IAEP is a treatable cause of acute hypoxic respiratory failure.[21] IAEP is a diagnosis of exclusion and consisting of an acute febrile illness of short duration (usually less than one week), hypoxemic respiratory failure, diffuse pulmonary opacities on chest radiograph, BAL eosinophilia great than 25 percent, lung biopsy evidence of eosinophilic infiltrates (acute and/or organizing diffuse alveolar damage with prominent eosinophilia as the most characteristic finding) and absence of known causes of eosinophilic pneumonia, including drugs, infections, asthma, or atopic disease. IAEP can occur at any age, even in previously healthy children, though most patients are between 20 and 40 years of age.[6,22] Men are affected approximately twice as frequently as women.[2,4,18,23]

Patients present with an acute febrile illness of less than three weeks duration, nonproductive cough and dyspnea.[23,24] Associated symptoms and signs include malaise, myalgias, night sweats, and pleuritic chest pain. Physical examination shows fever (often high) and tachypnea. Bibasilar inspiratory crackles and occasionally rhonchi on forced exhalation are heard upon auscultation of the chest.

Hypoxemic respiratory insufficiency is identified frequently at presentation and often requires mechanical ventilation.[5] Patients generally present with an initial neutrophilic leukocytosis.[5,25] In most cases, the eosinophil fraction becomes markedly elevated during the subsequent course of IAEP.[5,20,24] The erythrocyte sedimentation rate is elevated. The IgE level has been high in a majority of the patients in whom it was measured.[18,23,26] When pleural fluid is present, it may demonstrate a marked

eosinophilia with a high pH.[23] Diagnosis is based on analysis of the BAL fluid. Unlike in CEP (in which lymphocyte and neutrophil counts are normal), the severe eosinophilia in IAEP (percentage of eosinophils greater than 25%) is accompanied by about 20% lymphocytes and 15% neutrophils; whereas, in acute respiratory distress syndrome, there is a predominance of neutrophils.

At the onset of IAEP, the chest radiograph may show only subtle reticular or ground glass opacities, often with Kerley B lines.[21] Most often, bilateral diffuse mixed alveolar and reticular opacities are seen on plain chest radiographs.[2,3] Small bilateral pleural effusions are common (in up to 70 percent of patients).[5] CT findings in IAEP include ground-glass attenuation, airspace consolidation, poorly defined nodules, interlobular septal thickening, and pleural effusions. The triad of interlobular septal thickening, bronchovascular bundle thickening, and pleural effusions are most suggestive of IAEP.[27]

Lung biopsy when performed is mainly to rule out infection, especially by fungi such as aspergillus.[28] Biopsy findings of acute and organizing diffuse alveolar damage are common. Hyaline membranes and interstitial widening (due to a combination of edema, fibroblast proliferation, and inflammatory cells characteristic of the organizing phase of diffuse alveolar damage) is seen in most cases. Marked numbers of interstitial and lesser numbers of alveolar eosinophils are found. Other features include type II pneumocyte hyperplasia (55 percent of cases), interstitial lymphocytes (100 percent of cases), an organizing intraalveolar fibrinous exudate (100 percent of cases), and perivascular and intramural inflammation without necrosis (33 percent of cases). Granulomas and alveolar hemorrhage are absent.

Patients with IAEP can be treated with methylprednisolone (60-125 mg) every six hours.[4,29] Corticosteroids are the mainstay of treatment beside treating the underlying cause, if identified. Improvement occurs rapidly (1-3 days). The dose can be reduced to 40-60 mg/day and tapered over the subsequent 2-4 weeks. Although spontaneous remissions occur, most cases will be progressive if not treated. IAEP is not accompanied by multiple organ failure (as opposed to acute respiratory distress syndrome) if treated, therefore, it has a good prognosis. After treatment, there should be no relapse.

Conclusion

Idiopathic acute eosinophilic pneumonia is a treatable cause of acute hypoxic respiratory failure. It is important to recognize and treat this rare reversible non-infectious cause of pneumonia and respiratory failure, as not treating may lead to a chronic debilitating disease or death.

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