



An overview of eosinophilic lung diseases

Eosinophilic lung diseases

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Abstract

Eosinophilic lung diseases describes a variety of lung diseases which can be idiopathic (simple pulmonary eosinophilia, acute eosinophilic pneumonia and chronic eosinophilic pneumonia and hypereosinophilic syndrome), secondary to various clinical entities (to drugs, parasites, fungal infections, irradiation or toxic product) or associated with diffuse lung diseases (connective tissue diseases and some neoplasms). Asthma, which is the most common cause of pulmonary eosinophilia, is frequently concomitant and can be a prerequisite, as in allergic bronchopulmonary aspergillosis (ABPA) and Churg-Strauss syndrome. Herein, we aimed to review the clinical findings and differential diagnosis of eosinophilic lung diseases.

Keywords

eosinophilic lung disease, eosinophilia, differential diagnosis

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Eosinophilic Lung Diseases

Eosinophilic lung diseases (ELD) are a group of pulmonary disorders associated with peripheral and/or tissue eosinophilia. ELDs are characterized by the accumulation of eosinophils in alveolar spaces, the interstitium, or both. ELD was first described as 'pulmonary infiltrates with (blood) eosinophilia syndrome'. Later, it was recognized that ELD consists of several lung diseases with eosinophil infiltration in the lungs and little or no increase in the peripheral blood eosinophil numbers.¹² In these patients, tissue eosinophil levels can be high while peripheral blood eosinophil levels are normal. The eosinophil count in the peripheral blood represents the balance between bone marrow production and tissue migration of eosinophils. In a healthy adult, peripheral blood eosinophil percentage can be 3-5% of white blood cells (WBC) with a corresponding absolute eosinophil count (#eosinophil) of 350-500/ μ L. Eosinophil amounts higher than these levels are accepted as eosinophilia.²⁻⁴ On the other hand, tissue eosinophil levels can be high while peripheral blood eosinophil levels are normal. This situation generally occurs as a result of accumulation of the eosinophils in tissues. Thus, in many ELDs blood eosinophil levels may not be an accurate indicator of eosinophil-related tissue injury. In such cases, eosinophilia must be shown by tests directly reflecting tissue contents.⁵⁻⁷ Lung biopsy is the most direct and reliable way to verify increased lung eosinophils. Considering that lung biopsy is an invasive test, it is only occasionally necessary to diagnose the various ELD or eosinophilic pneumonia (EP) cases. Instead, bronchoalveolar lavage (BAL) is frequently used to identify ELD or EP, and an increased BAL eosinophil level usually corresponds to increased lung tissue eosinophils. Accumulated eosinophils in tissues directly damage the epithelial and endothelial cells and promote the pro-inflammatory response resulting in the development of the clinical abnormalities attendant to the ELD.^{5,7,8} ELD can be idiopathic (simple pulmonary eosinophilia, acute eosinophilic pneumonia (AEP) and chronic eosinophilic pneumonia (CEP) and hypereosinophilic syndrome), secondary to various clinical entities (to drugs, parasites, fungal infections, irradiation or toxic products) or associated with diffuse lung diseases (connective tissue diseases and some neoplasms). Asthma, which is the most common cause of pulmonary eosinophilia, is frequently concomitant as in allergic rhinopulmonary aspergillosis (ABPA) and Churg-Strauss syndrome.⁹⁻¹² In this article, we review the clinical findings and differential diagnosis of ELDs.

Simple Pulmonary Eosinophilia (Löffler syndrome)

Simple pulmonary eosinophilia is characterized by patchy and migratory pulmonary infiltrates on chest radiographs with increased eosinophil counts in peripheral blood. Patients have few or no pulmonary symptoms and are often identified by incidental findings on chest x-rays or complete blood counts. It is usually associated with parasitic infections or drug reactions but can also be idiopathic. Although corticosteroids can be used for resolution of pulmonary infiltrates and blood eosinophilia, their use is rarely necessary.^{9,13-15}

Chronic Eosinophilic Pneumonia (CEP)

CEP, a chronic and ultimately life-threatening entity with severe dyspnea, high fever, night sweating and weight loss, is diagnosed with the presence of these criteria:

1. Progressive and dense pulmonary infiltrates arranged in a peculiar peripheral pattern,
2. rapid resolution with corticosteroid therapy,
3. pulmonary infiltration best described as a "photonegative" or "reversal" of the shadow seen in pulmonary edema or alveolar proteinosis and
4. recurrence of lesions in the same locations during relapse.¹⁶⁻¹⁸

Peripheral eosinophilia is common in CEP with a frequency of about 90%. BAL eosinophilia is also characteristic in CEP with an average per-

centage of 58%. Approximately half of the patients have preexisting asthma or atopic disease history. Unlike AEP, recently prior cigarette smoking or substance use is rarer, findings follow a slower course and remission may occur after corticosteroid therapy.^{19,20}

Acute Eosinophilic Pneumonia (AEP)

The onset of AEP is quite rapid, usually presenting within 1 to 5 days of symptom onset (average of 2.3 days). Patients can progress from mild shortness of breath to life-threatening respiratory failure in only a few hours. AEP was first recognized as a clinical entity in 1989.²¹ Various drugs, cigarette smoke, toxic gases and narcotics have been accused in the etiology of AEP. In the previous literature, AEP also has been reported to occur in human immunodeficiency virus (HIV) infection, military personnel in Iraq and a firefighter who worked in the World Trade Center rescue.^{22,23} AEP can be observed in all age groups with an average of 29 years and in both genders equally. Given that the cases reported throughout the Europe, United States and Japan, it is difficult to claim that there is a geographical endemicity.²³⁻²⁴ Diagnostic criteria of AEP consist of fever, hypoxemia, radiological diffuse alveolar or mixed alveolar-interstitial opacities, BAL eosinophilia (eosinophil >25%), exclusion of parasitic, fungal or other infections which may lead to eosinophilia, prompt and complete response to corticosteroid treatment and no relapse

after discontinuation of steroid therapy.^{23,25,26} On the other hand, in patients with AEP associated with a substance use or smoking, it is prudent to recommend future avoidance of these substances because relapses may occur if patients resume their use.²⁶ Lung biopsy is not necessary for the diagnosis but, eosinophilic infiltration of the pulmonary interstitium and alveolar spaces are the significant pathological findings of AEP.^{27,28} Radiological findings of AEP are not specific to AEP and vary in a range from extensive airspace opacities and ground-glass opacities to interlobular septal thickenings and/or pleural effusions; however, radiological infiltrates differ from CEP with their diffuse and not peripherally based localizations.²⁸ Corticosteroids are the main treatment in AEP. Most patients have significant clinical improvement within 24-48 hours with corticosteroid treatment. After the corticosteroid treatment AEP patients do not generally relapse and recurrence is exceedingly rare.²⁹⁻³² Patients with AEP have a rapid and striking response to corticosteroid therapy. Most patients will have significant clinical improvement within 24 to 48 hours, and some may improve within hours of the first dose.³³⁻³⁶

Churg-Strauss Syndrome (CSS) (Allergic angiitis and granulomatosis)

CSS is an antineutrophil cytoplasmic antibody (ANCA)-associated and necrotizing vasculitis affecting the small and medium-sized vessels with associated eosinophilic infiltrates and granulomas. Patients with CSS typically have an initial history of allergic diseases and/or asthma for 8-10 years. Diagnostic criteria of CSS include

1. eosinophilia of more than 10% in peripheral blood,
 2. pulmonary infiltrates (may be transient and migratory),
 3. asthma,
 4. paranasal sinusitis,
 5. histological proof of vasculitis together with extravascular eosinophils and
 6. mononeuritis multiplex or polyneuropathy.
- For the diagnosis of CSS, presence of at least four of these criteria is required.³⁷⁻⁴⁰

Idiopathic Hypereosinophilic Syndrome (HES)

HES is a rare clinical entity that is characterized by blood eosinophilia of $\geq 1500/\mu$ L for more than 6 months, absence of other etiologies for the eosinophilia and presence of the signs or symptoms of end organ damage.⁴¹ Allergic Bronchopulmonary Aspergillosis (ABPA): ABPA is a clinical entity caused by local airway hypersensitivity response to Aspergillus antigens colonized in airways. ABPA occurs most commonly in patients with asthma and cystic fibrosis. Diagnostic criteria of ABPA include proximal bronchiectasis (dilated bronchi in the inner two-thirds

of the chest field on CT chest), asthma, immediate cutaneous reactivity to *Aspergillus* species or *A. fumigatus* antigens, elevated total serum IgE (1000 ng/mL or >47 kU/L), elevated serum *A. fumigatus* specific IgE and/or IgG.⁴²⁻⁴⁴

Bronchocentric Granulomatosis

Bronchocentric granulomatosis is a clinical entity with destructive and granulomatous lesion of the airways which is generally thought to represent a nonspecific response to an airway injury.⁴⁵ Bronchocentric granulomatosis has to be taken into consideration in the differential diagnosis of pulmonary nodules and tumors. Because of the lack of a single clear clinical syndrome, the presence of this lesion should generally be considered a nonspecific manifestation of lung injury, not an etiologic diagnosis. In radiological imaging, nodular or mass lesions, usually solitary, were noted in 60% of patients while parenchymal infiltrates were noted in only 20%. CT scan findings consist of a focal mass or lobar consolidation with atelectasis.⁴⁶ Surgical biopsy is a requirement for diagnosis. Patients may present with several respiratory symptoms such as dyspnea or wheezing due to airway obstruction.⁴⁷

Parasitic and Fungal Infections

Parasitic and fungal infections are common causes of peripheral eosinophilia and ELD. In differential diagnosis, they should be carefully evaluated especially in immunosuppressive patients.^{5,48} In the United States, *Strongyloides*, *Ascaris*, *Toxocara*, and *Ancylostoma* are the most common causes of ELD. Peripheral blood eosinophilia and pulmonary eosinophilic infiltrates are noted in the majority of cases of primary coccidioidomycosis. The definitive diagnosis of these infections is based on the demonstration of the pathogen in the tissue.^{49,50} Administration of corticosteroids to these patients at this stage can result in an acceleration of the infection with mortal results, so these infections must be certainly excluded before the decision of corticosteroid therapy for other ELDs.⁴⁸

Drug-induced ELD:

Drug reaction is one of the most commonly reported etiological factors of pulmonary infiltrates with blood and/or alveolar eosinophilia in patients with no history of previous pulmonary diseases. However, most of this literature is in the form of case reports, which vary in terms of documentation.⁵¹ Over 150 drugs or categories of drugs have been associated with pulmonary eosinophilia.^{52,53} The mechanism is not known exactly for many drugs but the majority of the drugs are believed to provoke a hypersensitivity response in lungs. Patients with drug-induced ELD can vary in presentation from simple pulmonary eosinophilia to AEP-like syndrome.⁵³ Diagnosis is based on the responses of the lungs to withdrawal of the drug and, if possible, reintroduction to the suspected drug. Peripheral eosinophilia can be observed. Radiological findings may include ill-defined, soft, patchy, or linear /reticular infiltrates, occasionally associated with a pleural effusion. Many patients will improve by simply withdrawing the drug.⁵³

Corticosteroids are rarely required in these patients. Although drug-induced ELD is considered as a separate item in eosinophilic pneumonias, basically it can present as AEP or CEP.⁵⁴ The main reasons that drug-induced ELD is defined as a separate entity, are the drug use history for a certain period and clinical improvement with the cessation of the drug usually without need of additional treatment.^{54,55} As a conclusion, ELDs are a variety of lung diseases with common and distinct clinical features. Considering that there are differences between treatments, the differential diagnosis and rapid accurate diagnosis of ELDs are very important. We hope that this compilation may provide a quick overview to ELDs for clinicians.

Declarations

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed Consent

Informed consent was obtained from all participants.

Conflict of Interest

The authors declare no conflicts of interest.

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Scientific Responsibility Statement

The authors declare that they are responsible for the scientific content of the article, including the study design, data collection, analysis and interpretation, manuscript preparation, and approval of the final version of the manuscript.

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