Clinical Management Review

Eosinophilic Pneumonias

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The eosinophilic pneumonias are a heterogeneous group of diseases characterized by an increase in eosinophils in lung tissue or bronchoalveolar lavage fluid. Many, but not all, of the eosinophilic pneumonias are also associated with a peripheral blood eosinophilia. The etiologies of eosinophilic lung disease are wide ranging and include parasitic infections, medications or other toxins, autoimmune and inflammatory disease, and malignancies. Some eosinophilic pneumonias have no proven cause or inciting event and are classified as idiopathic. An accurate diagnosis can prove difficult and often relies on a combination of a thorough history and physical examination, including travel and medication history, laboratory and radiographic evaluation, and, in some instances, bronchoscopic and histologic evaluation. Early and accurate diagnosis is imperative in certain diseases, such as acute eosinophilic pneumonia, as delayed diagnosis and treatment can lead to fatal lung disease. Corticosteroids are the mainstay of treatment for many of the eosinophilic pneumonias, particularly for both acute and chronic eosinophilic pneumonias, and prognosis is typically excellent provided treatment is initiated in a timely manner. © **2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;■:■-■)**

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Eosinophilic lung disease is characterized by the presence of lung tissue eosinophilia on histopathology or by increased eosinophils in bronchoalveolar fluid. It can additionally be inferred when there are increased peripheral blood eosinophils along with infiltrates on chest radiographs. This article will discuss parasitic and medication-related etiologies of eosinophilic lung disease and focus on the diagnosis and management of acute and chronic eosinophilic pneumonias. Table I shows the causes of eosinophilic pneumonia.

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INFECTIONS

Among infectious etiologies of pulmonary eosinophilia, parasitic disease has historically had the strongest association with eosinophilic pneumonias. In the Western world, the most common parasitic causes of eosinophilic lung disease include *Ascaris, Ancylostoma, Toxocara*, and *Strongyloides* infection, whereas in India and Southeast Asia, microfilaria-induced tropical pulmonary eosinophilia is more common.[1]

Loffler syndrome

The transient, transpulmonary passage of larvae, also known as Loffler syndrome, is a mechanism of parasite-induced pulmonary eosinophilia. *Ascaris lumbricoides*, hookworms such as ancylostoma duodenale, and *Strongyloides stercoralis* have all been associated with Loffler syndrome. Patients can be asymptomatic but may complain of a persistent dry cough and nonspecific chest discomfort.[2] Dyspnea, wheezing, fevers, and hemoptysis may also be present. Chest imaging often shows bilateral, rounded opacities. These opacities may appear migratory or fleeting when chest imaging is obtained serially. Diagnosis often requires detection of parasitic larvae in respiratory secretions, as stool examination for ova and parasites may be nondiagnostic, with the exception of strongyloidiasis. Treatment is usually not necessary given the self-limited nature of the disease, but antihelminthic therapy for intestinal infection may be appropriate after resolution of respiratory symptoms.

Strongyloidiasis deserves special mention because of its relatively higher incidence in the United States, particularly in the southeastern states.[3] Infection is acquired most commonly through skin contact with soil contaminated with larvae. Pulmonary manifestations of *Strongyloides* infection are clinically similar to other causes of Loffler syndrome. Importantly, patients with asthma and peripheral eosinophilia who reside in endemic areas should be screened for strongyloidiasis before initiation of steroid therapy. Unrecognized infection can worsen and quickly disseminate with immunosuppression.[4] Peripheral eosinophilia and elevated serum IgE in patients from endemic areas should raise suspicion for strongyloidiasis. Definitive diagnosis requires demonstration of larvae in stool specimens or *Strongyloides* IgG antibodies in blood samples. All patients with strongyloidiasis should be treated, mainly to reduce the risk of autoinfection and dissemination. Ivermectin is the treatment of choice.

Direct pulmonary parenchymal invasion

Some parasites, such as paragonimus lung flukes and echinococcus cestodes, directly invade the pulmonary parenchyma and can have long-lasting pulmonary sequela. Patients infected by these parasites may complain of recurrent hemoptysis or a chronic cough productive of "chocolate-colored" sputum, which results from a mixture of blood, inflammatory cells, and parasite eggs.[5] Peripheral blood eosinophilia may be present early in the disease course but is usually absent with established

Abbreviations used
ABPA- Allergic bronchopulmonary aspergillosis
AEP- Acute eosinophilic pneumonia
ARDS- Acute respiratory distress syndrome
BAL- Bronchoalveolar lavage
CEP- Chronic eosinophilic pneumonia
COP- Cryptogenic organizing pneumonia
EGPA- Eosinophilic granulomatosis with polyangiitis
NSAID- Nonsteroidal anti-inflammatory drug
PFT- Pulmonary function test
TPE- Tropical pulmonary eosinophilia

disease. Chest imaging will often show peripheral nodular lesions. Diagnosis of paragonimiasis can be confirmed by detection of eggs in fecal matter or bronchoalveolar lavage (BAL) fluid. Patients should be treated with antihelminthic therapy.

Hematogenous seeding

Ascarids, such as toxocara canis, which typically causes visceral larva migrans, can spread hematogenously to the lungs.[6] Schistosomiasis, prevalent in sub-Saharan Africa, can also cause eosinophilic pneumonia via hematogenous spread. Patients with cirrhosis and portal hypertension are at increased risk for this infection. Schistosomal adult worms infect the lungs via collateral vessels in this setting. Chest imaging findings in schistosomiasis are nonspecific. Treatment is imperative, as chronic untreated schistosomiasis can lead to severe pulmonary hypertension. The treatment of choice is praziquantel.[7]

Tropical pulmonary eosinophilia

This disease results from a hypersensitivity response to the filarial parasites *Wuchereria bancrofti* and *Brugia malayi*.[1] Filarial infections are typically endemic to the tropical and subtropical regions such as Central Africa and the South Pacific islands. Clinical manifestations develop months to years after the initial filarial infection and include cough, dyspnea, wheezing, malaise, and fever. Tropical pulmonary eosinophilia (TPE) can clinically mimic asthma. Laboratory evaluation may reveal a dramatic peripheral eosinophilia (frequently >3000 μL) and a markedly elevated serum IgE (>1000 U/mL).[1] Chest imaging is nonspecific and can even be normal in some cases. Diagnosis is made clinically based on pertinent exposure and travel history as well as clinical presentation. Serologic testing is helpful in situations when a diagnosis is unclear, as patients with TPE should have markedly elevated antifilarial IgG antibodies. Tropical pulmonary eosinophilia requires treatment with antihelminthic therapy.[8] Occasionally, systemic glucocorticoids are used for persistent wheezing and bronchoconstriction.

DRUG-INDUCED PULMONARY EOSINOPHILIA

Drug-associated eosinophilic pneumonia can have wide-ranging clinical manifestations. Patients may have asymptomatic pulmonary eosinophilia, chronic cough or shortness of breath, or acute and rapidly progressive hypoxia. A thorough medication history is paramount for all patients with evidence of either pulmonary or peripheral blood eosinophilia. Nonsteroidal anti-inflammatory drugs (NSAIDs) and antimicrobials are most commonly associated with eosinophilic pneumonia.[9-11] Among the antimicrobials, nitrofurantoin, minocycline, the sulfonamides, ampicillin, and daptomycin have been linked to the most cases of pulmonary eosinophilia.[12] Isolated cases have also been attributed to anti-epileptics, angiotensin-converting enzyme inhibitors, antimalarial medications, methotrexate, amiodarone, and bleomycin.[9,12,13] Some antiepileptics and antibiotics have been associated with a syndrome known as "drug reaction with eosinophilic and systemic symptoms," or "DRESS." This syndrome should be suspected in a patient presenting with respiratory symptoms, pulmonary infiltrates, skin eruptions, fevers, facial edema, lymphadenopathy, and recent initiation of a culprit medication within the past 2 to 6 weeks. The treatment of medication-induced pulmonary eosinophilia usually requires only cessation of the offending agent. Corticosteroids are often used concomitantly, but there are no placebo-controlled studies assessing their efficacy. If steroids are used, infectious etiologies must be ruled out first. There is also no consensus on the dose or duration of corticosteroid usage. Some studies have suggested higher doses of steroids, such as 60 to 90 mg of prednisone, to treat NSAID-induced pulmonary eosinophilia.[14] Recommendations regarding treatment duration range from 2 to 6 weeks, though some patients with chronic medication-induced eosinophilic pneumonia require long-term steroids.[15]

ACUTE EOSINOPHILIC PNEUMONIA

Acute eosinophilic pneumonia (AEP) is a severe, rapidly progressive lung disease that, if not recognized or treated, can result in fatal respiratory failure. The precise pathogenesis and etiology of AEP is still unknown, but there is some correlation between AEP and preceding exposure to inhalational agents, such as cigarette smoke. The diagnosis of AEP is dependent on maintaining a high index of clinical suspicion as well as characteristic findings in BAL fluid. Although the disease can progress rapidly toward fatal respiratory failure if untreated, patients with AEP do fortunately respond dramatically well to treatment with systemic corticosteroids with minimal risk of recurrence.

Etiology and pathogenic factors

AEP was first identified as a cause of acute respiratory failure in the 1980s.[16] Although the exact etiology is unknown, it has been hypothesized that an acute hypersensitivity reaction to an unidentified inhaled antigen in otherwise healthy individuals leads to AEP.[17,18] Some evidence points to a possible temporal relationship between the development of AEP and the recent onset of cigarette smoking.[19] Regardless of the exact etiology, a link between AEP and exposure to a particular culprit inhaled pathogen does seem to exist, and the exposure tends to occur just before the onset of AEP. For example, AEP has been reported in Iraqi war veterans in the early 2000s, the vast majority of whom smoked cigarettes and reported recent significant exposure to fine airborne sand or dust particulate matter.[1] AEP was also seen in several firefighters among the first responders after the collapse of the World Trade Center towers in 2001, all of whom were exposed to dust and smoke almost immediately before symptom onset.[20] Interestingly, the culprit pathogen is not always an atypical or unusual one. A study in 1996 demonstrated that environmental factors within the home, such as mildew, cockroaches, and even fabric protection agents such as Scotchguard, have been associated with AEP.[21,22] Other inhalational exposures that have been associated with AEP include firework smoke, cave exploration, and gasoline tank cleaning.[23]