

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;6:1455-61)

Key words: Eosinophilic pneumonias; Acute eosinophilic pneumonia; Chronic eosinophilic pneumonia; Parasites; Peripheral eosinophilia; Bronchoscopy; Bronchoalveolar lavage; Drug-induced eosinophilic pneumonia; Diagnosis; Prognosis; Treatment; Corticosteroids

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.

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

Löffler syndrome

The transient, transpulmonary passage of larvae, also known as Löffler syndrome, is a mechanism of parasite-induced pulmonary eosinophilia. *Ascaris lumbricoides*, hookworms such as *ancylostoma duodenale*, and *Strongyloides stercoralis* have all been associated with Löffler 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 anti-helminthic 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 Löffler 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

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication January 23, 2018; revised March 15, 2018; accepted for publication March 30, 2018.

Available online May 4, 2018.

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<https://doi.org/10.1016/j.jaip.2018.03.011>

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 μ L) 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

TABLE 1. Causes of eosinophilic pneumonia

Infections	Drug-induced eosinophilic lung disease
Helminthic infections	Nitrofurantoin
<i>Ascaris lumbricoides</i>	Minocycline/tetracyclines
Hookworm	Sulfonamides
<i>Strongyloides</i>	Ampicillin
Paragonimiasis	Daptomycin
Trichinellosis	Phenytoin
Cutaneous and visceral larva migrans	L-Tryptophan
Schistosomiasis	Methotrexate
<i>Wuchereria bancrofti</i>	NSAIDs
<i>Brugia malayi</i>	Anti-malarials (dapsone, pyrimethamine)
Nonhelminthic infections	Amiodarone
Coccidiomycosis	ACE inhibitors
Aspergillosis	H ₂ -receptor antagonists
Idiopathic	Allergen-related eosinophilic lung disease
Acute eosinophilic pneumonia	Allergic bronchopulmonary aspergillosis (ABPA)
Chronic eosinophilic pneumonia	
Idiopathic hypereosinophilic syndrome	Malignancy
	Leukemia
Interstitial lung diseases	Lymphoma
Cryptogenic organizing pneumonia	Primary lung cancer
Hypersensitivity pneumonitis	
Idiopathic pulmonary fibrosis	Associated with systemic vasculitis
Langerhans cell histiocytosis	Eosinophilic granulomatosis with polyangiitis (EGPA)
Sarcoidosis	Granulomatosis with polyangiitis

ACE, Angiotensin converting enzyme; NSAID, nonsteroidal anti-inflammatory drug.

Clinical presentation

AEP is a severe, rapidly progressive lung disease that can result in respiratory failure and death if not recognized early and treated appropriately. The majority of cases occur in patients between 20 and 40 years of age, and men are affected roughly twice as frequently as women.²⁴ Most patients diagnosed with AEP have few, if any, significant prior medical conditions. A small subset of patients do have a history of asthma or allergic disease.²⁵ Patients tend to present acutely, with the onset of symptoms within a few weeks, and often days, of presentation. Nonproductive cough, shortness of breath, and fever are almost universally present in all patients with AEP. In addition, patients may note more constitutional symptoms such as malaise, night sweats, pleuritic chest pain, and diffuse myalgias, similar to a flu-like illness. On physical examination, patients will appear physically ill. They may be in respiratory distress. Vital signs are notable for fever, tachypnea, and hypoxia. Bibasilar and possibly diffuse inspiratory crackles are often heard on lung auscultation. Patients may quickly progress from respiratory distress into overt respiratory failure, often requiring initiation of intubation and mechanical ventilation.

Laboratory studies

There are no laboratory studies specific for AEP and testing is obtained primarily to evaluate for alternative causes of eosinophilic lung disease and, more generally, respiratory failure. In contrast to the majority of other eosinophilic lung diseases, patients with AEP typically do not have a peripheral blood eosinophilia.¹⁶ Complete blood cell count may show a leukocytosis, but the differential will usually show a neutrophilia as opposed to an eosinophilia. Serum electrolytes, kidney function studies, and liver function studies are nonspecific and may even be normal in AEP. If urinalysis shows evidence of microscopic hematuria, alternative diagnoses such as vasculitic disease (ie, pulmonary-renal syndrome) should be suspected. Sputum cell count is infrequently obtained but may show an eosinophilia.²⁶ In addition, if a patient with AEP has pleural effusions, thoracentesis may reveal a marked pleural fluid eosinophilia.²⁷

Imaging

Chest radiographs often show bilateral, diffuse, mixed ground glass and reticular opacities (Figure 1).²⁸ Bilateral pleural effusions may also be present.²⁹ Chest CT, although not essential to the diagnosis of AEP, can be helpful to more precisely identify both the distribution of the airspace opacities and the best location to obtain BAL fluid for diagnosis. CT findings are characterized by diffuse, bilateral, randomly distributed patchy ground glass opacities.²⁹ Centrilobular nodules and bilateral pleural effusions may also be present. A significant number of patients with AEP, however, are acutely ill and often too unstable to tolerate CT scanning, so further imaging is not always available to clinicians.

Pathology

Lung biopsy is rarely performed in patients with AEP.³⁰ Pathology is not required for diagnosis, and patients are often too unstable to tolerate an open lung biopsy. If tissue is obtained, however, histopathological findings typically show acute and organizing diffuse alveolar damage with tissue and alveolar eosinophils. The extent of disease tends to be severe as well, as the changes are seen heterogeneously throughout the sampled lung.³¹

Diagnosis

A confident diagnosis of AEP can be made with the aid of bronchoscopy and BAL. BAL is frequently performed in patients with fevers, respiratory failure, and radiographic abnormalities. It can be useful to assess for an infectious process, alveolar hemorrhage, and malignancy. In AEP, BAL fluid shows a marked eosinophilia, often >25% of the total cell count.²³ There may be also increased BAL lymphocytes and neutrophils as well. Although a marked BAL eosinophilia is not 100% specific for AEP, a clinician can confidently make a diagnosis of AEP in the presence of a BAL eosinophilia >25% if the following additional criteria are met: (1) the patient presented with a febrile illness of relatively short duration (within days to weeks), (2) hypoxemic respiratory failure is present, (3) chest imaging shows diffuse pulmonary opacities, and (4) absence of other etiologies of eosinophilic pneumonia such as parasitic infection, drug toxicity, or asthma.³² Lung biopsy is only necessary if a patient suspected of AEP fails to demonstrate response to systemic corticosteroid therapy or if an infectious etiology cannot be quickly excluded by BAL.³³



FIGURE 1. Chest radiograph showing diffuse, bilateral airspace in a patient with acute eosinophilic pneumonia.

Differential diagnoses

The clinical syndrome of acute, progressive respiratory failure, diffuse radiographic opacities, and BAL eosinophilia is not unique to AEP. Diseases such as eosinophilic granulomatosis with polyangiitis (EGPA), fulminant fungal or parasitic infections, and eosinophilic pneumonia due to drugs or toxins all can present similarly to AEP. Although AEP can be relatively easily distinguished from most other eosinophilic lung diseases, it can prove difficult to discern from other causes of rapidly progressive respiratory failure. Several lung diseases have similar acute onset of symptoms and presence of diffuse bilateral infiltrates. None of these other processes, however, are associated with BAL eosinophilia. Acute respiratory distress syndrome, or ARDS, in contrast to AEP, is preceded by an inciting direct or indirect injury to the lungs such as pneumonia, sepsis, or aspiration. BAL in ARDS shows a neutrophil predominance. Goodpasture's syndrome and granulomatosis with polyangiitis (formerly Wegener's granulomatosis) can also present similarly to AEP. However, these diseases can be differentiated from AEP by the presence of alveolar hemorrhage in the BAL without BAL eosinophilia. In addition, patients with these diseases frequently develop renal failure, which is typically not seen in AEP.

Treatment

Although AEP can rapidly progress to fulminant respiratory failure, it fortunately is dramatically responsive to systemic glucocorticoid therapy. Supportive measures such as supplemental oxygen and potentially mechanical ventilation should be initiated early in the disease course. Empiric antibiotics are often given at the time of presentation as well, given that it is difficult to rapidly exclude infection in a patient presenting with fevers, diffuse radiographic opacities, and respiratory failure. Once bronchoscopy with BAL is performed, presumably ruling out an infectious process and demonstrating BAL eosinophilia, antibiotics can be stopped and systemic glucocorticoid therapy should be initiated. The optimal dose and length of steroid therapy are determined primarily by disease severity. Patients with severe hypoxemia or respiratory failure requiring mechanical ventilation should receive intravenous methylprednisolone (60-125 mg

every 6 hours) until respiratory failure resolves, which typically occurs within 1 to 3 days. In patients with milder disease, 40 to 60 mg of oral prednisone may be sufficient initial therapy. Oral prednisone in doses of 40 to 60 mg per day is typically given for 2 weeks after resolution of symptoms and improvement in radiographic abnormalities followed by tapering over the next 2 to 4 weeks.²³ Given the profound and dramatic response of AEP to steroids, if a patient demonstrates minimal improvement once therapy is initiated, an alternative diagnosis must be sought.

Prognosis/outcomes

Patients with AEP typically demonstrate rapid improvement in both symptoms and radiographic abnormalities within 24 to 48 hours of initiation of corticosteroids.^{34,35} Complete resolution is typically achieved by 1 to 2 months.²⁴ If left undiagnosed or untreated, AEP can lead to fatal respiratory failure. Fortunately, relapse is quite uncommon but can occur with resumption of cigarette smoking in cigarette-associated AEP.³⁶ This is in stark contrast to chronic eosinophilic pneumonia (CEP), in which recurrence is fairly common once steroid therapy is complete. Table II compares some of the clinical features of AEP and CEP.

CHRONIC EOSINOPHILIC PNEUMONIA

In contrast to AEP, CEP is an insidious disease with an average symptom duration of 7 to 8 months before clinical diagnosis is made. CEP should be suspected in patients experiencing several months of progressive shortness of breath with radiographic evidence of bilateral peripherally located opacities. In addition, it is associated with a peripheral blood eosinophilia. CEP is a rare disease with an estimated incidence of 0.23 cases/100,000 population between the years 1990 and 2014.³⁷ Early diagnosis and treatment is imperative as CEP rarely spontaneously resolves and, if untreated, can lead to irreversible pulmonary fibrosis.

Etiology/pathogenic factors

Like other eosinophilic lung diseases, CEP is caused by the abnormal accumulation of eosinophils in the lung tissue and the bloodstream. It has been hypothesized that some unidentified, nonspecific trigger leads to the overproduction and infiltration of eosinophils in the lung. The cytokine IL-5, known to be a regulator of the development and function of eosinophils, may play an integral role in the development of CEP.³⁸ In contrast to AEP, no significant temporal relationship between smoking or atypical environmental exposures and the development of CEP has been identified.

Clinical manifestations

CEP tends to affect patients in their 30s or 40s, though some childhood cases have been reported.³⁹ Women are affected about twice as frequently as men. In contrast to AEP, about half of patients have prior history of asthma or atopy.⁴⁰ The disease has a somewhat insidious onset with an average of 7 to 8 months between initial symptom onset and diagnosis. Symptoms may include productive cough, fever, dyspnea, weight loss, and night sweats. Hemoptysis, chest pain, and myalgias are rare.⁴¹ Physical examination may reveal wheezing and/or crackles but is otherwise unremarkable in most cases. Patients are usually not ill-appearing. CEP is typically a slowly progressive disease, but

TABLE II. Clinical features of AEP vs CEP

	AEP	CEP
Onset	Acute (days to weeks)	Insidious (months)
Symptoms	Fever, cough, pleuritic chest pain, myalgias, dyspnea (can progress to acute respiratory failure); pre-existing asthma rare	Dyspnea, low-grade fevers, pre-existing asthma common
Smoking history	Frequently affects smokers, particularly new smokers	Generally affects nonsmokers
Peripheral blood	Usually no eosinophilia	Eosinophilia >10%
Chest radiograph	Diffuse, bilateral interstitial and alveolar opacities, pleural effusions	Bilateral, migratory, peripheral opacities (“photographic negative of pulmonary edema”)
BAL	Eosinophils >25%; also with increased lymphocyte and neutrophil percentages	Eosinophils >25% with normal lymphocyte and neutrophil percentages
Lung biopsy	Diffuse alveolar damage (DAD), edema, eosinophilic infiltrate	Eosinophilic infiltration of parenchyma
Treatment	Corticosteroids for 2-6 wk	Corticosteroid treatment for 1-3 y
Response to treatment	Dramatic and rapid response to steroids	Good response to steroids, though relapses are common

AEP, Acute eosinophilic pneumonia; BAL, bronchoalveolar lavage; CEP, chronic eosinophilic pneumonia.

some patients have demonstrated more accelerated respiratory failure when the diagnosis was delayed or missed.

Laboratory studies

In contrast to AEP, the vast majority of cases of CEP (88% to 95%) are associated with a peripheral blood eosinophilia.⁴² The eosinophil proportion of the total circulating white blood cells will almost universally be greater than 6% (normal is 0% to 5%).⁴² The total blood eosinophil count is usually >1000/μL. Serum IgE levels are also elevated (mean 506 kU/L) in up to half of cases.⁴² In addition, elevated erythrocyte sedimentation rate, C-reactive protein, and platelet counts are all commonly seen in CEP. Importantly, none of these findings is specific for the diagnosis of CEP. Of note, sputum testing for eosinophilia is not particularly helpful for diagnosis as it is present in less than half of patients.^{30,43}

Pulmonary function testing

Pulmonary function tests (PFTs) are commonly performed in those patients being evaluated for CEP due to the chronic presentation of the disease. PFTs tend to be more valuable in ascertaining the degree of respiratory impairment rather than guiding the diagnosis, as patients with CEP can have either obstructive or restrictive impairments on spirometry.⁴⁴ The diffusing capacity can be reduced in approximately half of patients. PFTs remain an important diagnostic tool in CEP, both to determine the degree of initial impairment and to assess treatment response.

Imaging

Chest radiograph or CT scan of the chest may show bilateral peripheral opacities, often described as the “photographic negative” of pulmonary edema and “classic” for CEP (Figure 2).⁴⁵ It should be noted, however, that this “classical” finding is actually only present in approximately 25% of cases and is not specific for CEP.⁴⁶ Radiographic opacities are upper lobe predominant in half of cases and can often be migratory as well, if serial imaging is obtained. Less common findings include pleural effusions, nodules, cavities, and reticulations. Many eosinophilic lung diseases can share similar radiographic appearances to CEP, and thus diagnosis of CEP cannot be made on chest imaging alone.

Histopathology

Lung biopsy is usually not necessary to make a confident diagnosis of CEP. When tissue is obtained, however, characteristic findings include interstitial and alveolar eosinophils and histiocytes, including multinucleated giant cells. Pathology may also show features typical for organizing pneumonia and eosinophilic abscesses.⁴⁷ Unless the diagnosis is delayed, minimal interstitial fibrosis should be present.

Diagnosis

The diagnosis of CEP is made clinically, as there are no pathognomonic serologic or radiographic findings for the disease. When a patient presents with symptoms consistent with CEP along with a peripheral blood eosinophilia and abnormalities on chest imaging, a bronchoscopy with BAL should be performed next. This serves to both assess for BAL eosinophilia and to rule out infectious etiologies. In CEP, the BAL eosinophil count is almost always greater than 25%.⁴⁸ Some studies have reported a mean eosinophil count approaching 60%.⁴⁰ If BAL eosinophilia is absent, then an alternative diagnosis should be sought, or, if the suspicion for CEP remains high, lung biopsy should be pursued.⁴⁹

Differential diagnosis

CEP shares several clinical and radiographic features with other eosinophilic and noneosinophilic lung diseases. AEP is readily differentiated from CEP by its acute presentation, absence of peripheral blood eosinophilia, and diffuse radiographic opacities. Allergic bronchopulmonary aspergillosis (ABPA) is similar to CEP in that there is a pre-existing history of asthma, a peripheral blood eosinophilia, and upper lobe radiographic opacities.⁵⁰ However, in ABPA the serum IgE is typically greater than 1000 IU/L with serologic evidence of IgE antibodies to *Aspergillus* and a positive skin prick test to the *Aspergillus* antigen. Like ABPA and CEP, EGPA is also characterized by asthma and peripheral blood eosinophilia. EGPA tends to have more extrapulmonary manifestations than CEP, however, such as sinusitis or nephritis. It should be noted that there is an overlap between CEP and EGPA and that CEP could actually be a presenting feature of EGPA. It may be difficult to distinguish entities such as drug-induced eosinophilic pneumonia or



FIGURE 2. Chest radiograph representative of a patient with chronic eosinophilic pneumonia. Note the peripheral, bilateral opacities, often described as the “photographic negative” of pulmonary edema.

eosinophilic pneumonia due to fungal or parasitic infection based solely on clinical presentation and radiographic features, so a detailed medication and travel history is paramount in such cases. Among the noneosinophilic lung diseases, CEP is most similar in clinical and radiographic appearance to cryptogenic organizing pneumonia (COP). COP is not associated with BAL eosinophilia and tends to have a slower and less dramatic response to corticosteroids.

Treatment

Treatment should be initiated as soon as a diagnosis of CEP is made, as fewer than 10% of cases spontaneously improve or recover, and untreated CEP can lead to irreversible fibrosis.⁴⁸ Systemic corticosteroids have been the most well-studied and effective therapy for CEP and are the first-line treatment. For initial treatment, typical starting oral prednisone doses are 0.5 mg/kg per day. This dose is continued for at least 2 weeks after the complete resolution of both symptoms and radiographic abnormalities, which typically occurs 4 to 6 weeks after therapy has been started.⁴⁰ Oral steroids are sufficient in the vast majority of cases, though some patients do present with a fulminant, rapidly progressive form of CEP and may derive greater benefit from higher doses of intravenous methylprednisolone (ie, 250 mg every 6 hours) in the initial phase. Similar to AEP, patients with CEP often demonstrate a substantial and dramatic response once steroids are started with profound symptomatic relief within 48 hours in some cases.³⁸ If a patient has minimal to no improvement, an alternative diagnosis should be sought. Markers of disease improvement include the resolution of presenting symptoms such as dyspnea, cough, and fever; a decline in peripheral blood eosinophilia; marked reduction and even

resolution of radiographic abnormalities (though CT scan abnormalities may lag behind symptomatic improvement for weeks or months); and physiologic improvement in pulmonary function testing parameters. In most patients, monitoring of symptoms, plain chest radiographs, and peripheral blood eosinophil counts are sufficient to measure treatment response. Follow-up bronchoscopy with BAL is only necessary if symptoms persist or concern develops for a concomitant infectious process.⁵¹

Because of the relatively high rate of disease relapse, especially in comparison to AEP, the duration of therapy is less well established. The prednisone dose can be gradually tapered to the lowest dose necessary to control signs and symptoms of disease. Up to 75% of patients required prolonged, and even lifelong, glucocorticoid therapy, with a mean duration of 19 months.²⁶

As glucocorticoids can have several deleterious side effects, particularly at the doses and duration often required in CEP, alternative systemic steroid-sparing treatments have been sought. For instance, inhaled glucocorticoids such as beclomethasone at doses of 1500 mcg/day have shown some benefit in treating flares of CEP without an increase in the baseline dose of prednisone.⁵² Although inhaled steroids should not be used as initial or monotherapy, they may have some role in reducing the dose or duration of systemic steroid therapy. In addition, the recently FDA-approved monoclonal antibodies utilized in severe asthma, namely the IL-5 inhibitors benralizumab, mepolizumab and reslizumab, and the anti-IgE agent omalizumab, have shown some benefit in patients with CEP, particularly those with concomitant asthma and positive allergy tests, but more research is needed to confirm the true efficacy of these therapies.^{53,54}

Prognosis/outcomes

Symptomatic and/or radiographic relapse is quite common after reduction or cessation of steroid therapy with estimates ranging from 50% to 80% of cases.³⁷ Unfortunately, relapses can occur months to even years after initial presentation and often the diagnosis of CEP needs to be reconfirmed with each recurrence. Despite the risk of disease recurrence, the outcomes for most patients with CEP are excellent. Although the risk for recurrence is quite high, it fortunately does not portend treatment failure or a worse prognosis. Patients who do relapse tend to remain steroid-responsive at similar doses to those before the relapse.

Summary

A heterogeneous group of diseases can result in eosinophilic lung disease. Some eosinophilic pneumonias have defined etiologies, as certain parasitic infections and medications are known to induce pulmonary eosinophilia, whereas others are idiopathic, as in the cases of acute and chronic eosinophilic pneumonias. Most eosinophilic pneumonias are not immediately life threatening with the exception of AEP, in which prompt diagnosis and treatment with corticosteroids are imperative due to the potential severity of the respiratory failure. Diagnosis of eosinophilic lung disease can often be difficult and depends on a thorough history and physical examination, medication and travel history, laboratory evaluation to include assessment for peripheral blood eosinophilia, pulmonary function testing, chest imaging, and bronchoscopy.

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