Eosinophilic Lung Diseases: I

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Cover Illustration by Catherine Twomey
INTRODUCTION

Eosinophils are terminally differentiated, nondividing granulocytes that normally constitute a tiny proportion of the peripheral blood leukocyte population. They spontaneously undergo apoptosis in the absence of specific cytokine factors, including interleukin (IL)-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-3; IL-5 is the prototypical eosinophil-viability enhancing factor. The physiologic role of the eosinophil appears to be in the host defense against parasitic infections, where they may effect the death of the organism by releasing toxic granule proteins (eg, major basic protein, eosinophil-derived neurotoxin, eosinophil cationic protein, eosinophil peroxidase).

Normal values for circulating eosinophils are generally considered to be 0% to 6% of the leukocyte differential, or more relevantly, an absolute count of blood eosinophils below 500/mm$^3$, with some variation in normal values among different laboratories. These cells are not found in appreciable numbers in the normal human airway or alveolus: bronchoalveolar lavage (BAL) fractions typically range between 0% and 1%. Peripheral eosinophilia refers to abnormally elevated levels of circulating eosinophils and is broadly characterized as mild (500–1500/mm$^3$), moderate (1500–5000/mm$^3$), or severe (> 5000/mm$^3$). An elevated lung lavage eosinophil fraction above 5% or peripheral eosinophilia implies the presence of disease. Two common etiologies of peripheral and tissue eosinophilia are allergic disease (eg, rhinitis and asthma) and parasitic infection. Both helminth infection and the response to simple allergens have been extensively modeled and provide a basis for understanding tissue eosinophilia in general. Recruitment of these cells to sites of inflammation requires the induction of specific patterns of adhesion molecules along with local generation of eosinophil-active chemoattractants and cytokines in a process that is orchestrated by T helper type 2 (Th2) lymphocytes.¹

Although the list of disorders associated with peripheral eosinophilia is long, pneumonia with excess accumulation of eosinophils in the lung suggests a limited number of diagnoses. These diagnoses are clinically and pathogenically varied but have been classically grouped under the headings pulmonary eosinophilia,² pulmonary infiltration with eosinophilia (PIE syndrome),³ or simply eosinophilic lung diseases,⁴ implying that the eosinophil is involved in disease pathogenesis and is not simply a bystander. The major categories of eosinophilic lung diseases have been modified since the useful initial efforts by Reeder³ and Crofton² and currently include (1) simple pulmonary eosinophilia, (2) asthma, (3) tropical pulmonary eosinophilia, (4) Churg-Strauss syndrome (CSS), (5) allergic bronchopulmonary aspergillosis (ABPA), (6) chronic eosinophilic pneumonia, (7) acute eosinophilic pneumonia, and (8) hypereosinophilic syndrome.⁴ In this review, drug reactions and parasitic infections (other than filarial) are discussed in the section on simple pulmonary eosinophilia, and bronchocentric granulomatosis is discussed in the section on ABPA.

This manual is the first of a 2-part review of the eosinophilic lung diseases. Part 1 discusses a general initial approach to patients with eosinophilia, with a focus on simple pulmonary eosinophilia, tropical pulmonary eosinophilia, CSS, and ABPA. Prototypical cases are presented to introduce each topic. Part 2 will review acute and chronic eosinophilic pneumonia and hypereosinophilic syndrome.

INITIAL WORK-UP OF PULMONARY EOSINOPHILIA

Eosinophilic lung disease is typically considered when a patient presents with peripheral eosinophilia in the setting of pulmonary symptoms. However, certain disorders may have trivial peripheral eosinophilia and thus may not be considered initially (eg, acute eosinophilic pneumonia). In the evaluation of pulmonary eosinophilia, important information is usually found in the history. When considering eosinophilic lung disease, special consideration should be given to the presence of asthma or rhinitis, symptoms in other organ systems besides the lungs, and the patient’s medication history. A detailed social history is critical, with special attention to country of origin, lifelong travel experience, unusual
The patient completes a 3-day course of mebendazole, and on follow-up, both the symptoms and infiltrates have resolved.

**CLINICAL AND LABORATORY FEATURES**

Simple pulmonary eosinophilia encompasses a group of disorders that can be associated with transient, migratory pulmonary infiltration and peripheral eosinophilia. This term has been applied based on the typically benign natural history of these disorders. The prototypic simple pulmonary eosinophilia syndrome was first described in the early 20th century by Löffler. While studying tuberculosis at his clinic in Switzerland, he observed a condition characterized by fleeting shadows on chest radiograph with peripheral eosinophilia, either as an incidental finding during screening of asymptomatic patients or with associated symptoms that included mild cough, malaise, chest pain, or fever. In classic Löffler’s syndrome, the cough can be productive with rare hemoptysis; sputum eosinophils have been demonstrated. The radiographic appearance of the infiltrates is highly variable, with consolidations of different sizes and shapes rapidly appearing and disappearing over the course of 3 to 8 days (Figure 1). The extent of disease on radiograph is often disproportionate to the mild symptoms and signs.

Seasonal clustering of cases was appreciated in these early series, causing investigators to postulate that Löffler’s syndrome was a hypersensitivity response to the migration of certain intestinal parasites through the lung. This theory has been abundantly confirmed for *Ascaris lumbricoides*, a ubiquitous helminth that affects approximately 25% of the world’s population and subsequently is believed to be the etiologic agent in the majority of cases in Löffler’s original series.

An adult *Ascaris* worm parasitizing the human small intestine can lay upwards of 200,000 eggs per day, which can infect others via a fecal-oral route (hand-to-mouth) or by ingestion of contaminated food. Once ingested, the eggs hatch in the duodenum and larvae migrate through the intestine, entering the portal circulation where they make their way through the liver, heart, and lungs, ultimately burrowing out into the alveoli. The developed larvae ascend the airways, are eventually swallowed, and mature into adult worms in the small intestine. In support of this model, typical respiratory symptoms, radiographic infiltrates, and recovery of larvae from the lungs can be demonstrated following intentional or accidental ingestion of *Ascaris* eggs by humans. The pulmonary inflammation from *Ascaris* is the result of the Th2-mediated host response to larval antigens as indicated by a rise in precipitating antibodies to parasite-specific antigens, elevated IgE levels, and associated peripheral eosinophilia.

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**SIMPLE PULMONARY EOSINOPHILIA**

**CASE PRESENTATION**

A previously healthy 24-year-old male medical student presents after slight hemoptysis complicated the course of mild cough with occasional wheeze. His symptoms began approximately 5 days ago. On examination, he is well developed and breathing comfortably and has a temperature of 100°F. Lung auscultation reveals a few scattered squeaks and crackles but good air movement overall. A chest radiograph reveals bilateral ill-defined consolidations; a complete blood count (CBC) is significant for 15% eosinophils (absolute, 1350/mm³). Upon repeat questioning, the patient reports that he recently returned from a primary medicine experience in rural Brazil. A direct fecal smear reveals helminth ova, and a diagnosis of simple pulmonary eosinophilia is made. The patient completes a 3-day course of mebendazole, and on follow-up, both the symptoms and infiltrates have resolved.
Diverse infectious and noninfectious agents have been associated with simple pulmonary eosinophilia, and we have grouped several of them together with the understanding that an individual host response to a given antigen is highly variable and that the quality, duration, and symptoms of lung disease may not always conform to the classic pattern. The “dose” of the offending antigen also appears to be an important determinant of the intensity of the illness. For example, even generally innocuous parasites such as *Ascaris* or hookworm can cause severe illness if the inoculum is large. Consequently, these pneumonias may not always be simple. Diagnostic considerations are listed in Table 1.

### Parasites

Any parasite with obligate lung migration as part of its life cycle can potentially induce a Löffler’s-type pneumonia. Parasites other than *Ascaris* that are endemic in the United States or that should be considered in certain immigrant populations include *Trichinella* species, hookworms (*Ancylostoma duodenale* and *Necator americanus*), the dog roundworm (*Toxocara canis*), *Strongyloides stercoralis*, and the trematodes *Schistosoma* species and *Paragonimus westermani*. Because of its tendency for persistent lung disease, the tropical eosinophilia induced by endemic filariasis is treated as a separate topic (see page 5).

Although a detailed description of each of these organisms is beyond the scope of this review, *Strongyloides stercoralis* deserves mention. *Strongyloides* is an intestinal nematode endemic to the tropics that is also found in the southeastern United States, Puerto Rico, and Central America. Humans are infected via penetration of the skin by infective filariform larvae that enter the circulation, traverse the lungs, and ascend the airway. After being swallowed, the adult parasite ultimately

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**Table 1. Simple Pulmonary Eosinophilia: Diagnostic Features**

<table>
<thead>
<tr>
<th>Feature</th>
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<tr>
<td>Mild to moderate peripheral eosinophilia</td>
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<tr>
<td>Fleeting pulmonary infiltrates that completely resolve after several days without specific therapy</td>
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<tr>
<td>Mild or no respiratory symptoms, minimal findings on physical examination</td>
</tr>
<tr>
<td>Typically self-limited disease</td>
</tr>
<tr>
<td>IgE level is often elevated; a search for intestinal parasites is warranted</td>
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</tbody>
</table>

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**Figure 1.** Classic pattern of rapidly waxing and waning pulmonary infiltrates in Löffler’s syndrome. Radiographs A–D were obtained over 12 days in a patient who had recently immigrated to the United States. (Adapted with permission from Ascariasis. In: Palmer ES, Reeder MM, editors. Imaging of tropical disease. 2nd ed. New York: Springer; 2001:11–39.)
resides in the small intestine. Unlike Ascaris, Strongyloides eggs can hatch in the intestine, and the resultant larvae have the potential to penetrate the gut and repeat the cycle (autoinfection), which may account for the well-described persistence of Strongyloides infection many years after its original acquisition. For this reason, even a remote travel history to an endemic area may be relevant. Mild symptoms and simple pulmonary eosinophilia are the rule in strongyloidiasis, but the infection may be complicated in patients with preexisting pulmonary disease, which can result in retention and maturation of the worms in the lung with respiratory compromise. Similarly, overwhelming systemic dissemination of larvae (hyperinfection syndrome) with severe pneumonia is well described in patients on corticosteroids or with other forms of immunosuppression. In these conditions, Strongyloides larvae often can be readily demonstrated in BAL fluid or even on sputum Gram’s stain.

Drugs

Hypersensitivity to drugs and unknown causes probably are the most common noninfectious etiologies of transient pulmonary opacities with eosinophilia. While attention is often focused on hypersensitivity to certain antibiotics (eg, sulfonamides), diverse drug classes have been reported to cause this syndrome and it is unwieldy to list them all. Interrogation of the DRUGDEX system yields over 250 medications with the reported adverse effect of eosinophilia, with or without associated pulmonary disease. Previous reviewers have singled out sulfasalazine, a drug commonly used to treat ulcerative colitis, as there are multiple well-documented reports of eosinophilic pneumonia and peripheral eosinophilia associated with its use. Similarly, numerous cases of PIE syndrome have been documented in patients taking minocycline, a drug commonly used to treat acne. The unique pulmonary toxicities and associated eosinophilia observed with contaminated L-tryptophan (eosinophilia-myalgia syndrome) and rapeseed oil (toxic oil syndrome) also warrant mention from a historical and mechanistic perspective.

Asthma and Inhalant Allergens

Inhalant allergens are implicated in the pathogenesis of asthma and in asthma exacerbations, and mucosal infiltration with eosinophils is a characteristic feature of the asthmatic airway. The more recently described entity eosinophilic bronchitis is also characterized by eosinophil infiltration of the bronchial mucosa but lacks the obstructive pattern and hyperresponsiveness typical of asthma. In contrast to Löffler’s syndrome and the other eosinophilic pneumonias, BAL and tissue eosinophilia are generally mild in asthmatic patients in the absence of status asthmaticus. Although mucoid impaction is well described, alveolar consolidations are not characteristic of asthma.

There is a dearth of literature consistently linking any inhalant allergen to Löffler’s-type pneumonia. Ford noted instances of Löffler’s syndrome among a large group of asthmatic patients, and similar reports have been mentioned in review. The affected subjects appeared to be highly atopic with some seasonal variation in their symptoms. There is at least a theoretical basis from the antigen challenge literature for an IgE-mediated eosinophilic pneumonitis, where experimentally administered antigen can recruit eosinophils (often in large numbers) in a sensitive subject. Thus, it is plausible that an unusually large or persistent exposure might result in pulmonary infiltration in a sensitive individual.

TROPICAL PULMONARY EOSINOPHILIA

CASE PRESENTATION

A 42-year-old man without a previous history of lung disease is referred by his primary care physician for evaluation of asthma. He has just arrived in the United States from southern India to work as a computer consultant. The onset of his symptoms occurred 1 month prior and included a febrile prodrome with malaise and prominent dry cough; at the time, he was treated symptomatically for the flu. Currently, he complains of cough, wheeze, mild exertional dyspnea, and a 15-lb weight loss. His examination is remarkable for normal vital signs, scattered wheezes, bibasilar crackles, and mild hepatosplenomegaly. A chest radiograph reveals diffuse reticulonodular shadows similar to those shown in Figure 2. Pulmonary function testing shows a mixed obstructive/restrictive pattern with a reduced diffusion capacity for carbon monoxide (DLCO). Peripheral eosinophilia is present (40%; absolute, 4000/mm³), with IgE levels over 4000 ng/mL. Antifilarial titers are strongly positive.

CLINICAL AND LABORATORY FEATURES

A syndrome whose onset is characterized by evening fevers, anorexia, weight loss, and occasional splenomegaly, followed by a dry, hacking cough and prominent wheezing was detailed by Weingarten in 1943 while stationed in India. Indeed, the vast majority of the literature regarding what is now known as tropical eosinophilia is derived from the Indian medical
literature, pointing to South Asia as a principal area of endemicity. Marked peripheral blood and sputum eosinophilia are seen in these patients (usually > 3000/mm³). A typical radiograph demonstrates increased bronchovascular markings with or without symmetric nodular consolidations (2–5 mm). These nodular infiltrates constitute the classic “mottled” appearance described in the literature; they occur predominantly at the bases and have a tendency to follow the distribution of the airways. Hilar prominence and pleural effusion are also reported. The chest radiograph occasionally may be normal, as infiltrates tend to appear later in the course of the disease when respiratory symptoms peak.

It is now recognized that tropical eosinophilia represents an alternative manifestation of lymphatic filariasis in which hypersensitivity to the parasite dominates the clinical picture rather than lymphatic obstruction (ie, lymphedema and elephantiasis). It has been referred to as “occult” or “unusual” filariasis in that microfilaria are not seen on blood smears, although the offending organisms have been observed in affected tissues (lymph nodes, lung, spleen, liver), usually surrounded by an intense eosinophilic reaction. The usual etiologic agents include *Wuchereria bancrofti*, which is encountered worldwide, and *Brugia malayi*, which is limited to Asia. Lung biopsy reveals patchy interstitial and peribronchial inflammation, composed principally of eosinophils, with spillover into the airspaces; necrotizing granulomatous foci also are frequently present without vasculitis. Very high total IgE levels can be seen in tropical eosinophilia, with a mean of up to 8000 ng/mL observed in acute cases; complement-fixing antibodies to filarial antigen are also detectable. General diagnostic considerations are listed in Table 2.

**PROGNOSIS AND TREATMENT**

If tropical pulmonary eosinophilia is untreated, the respiratory symptoms may relapse for months or years and mimic chronic asthma. Unlike with asthma, tropical eosinophilia is characterized by notable lung restriction and obstruction, especially with chronic untreated disease; mild to moderate fibrosis can result. Early treatment is important. Most studies report an excellent clinical response after early treatment with diethylcarbamazine, with resolution of peripheral eosinophilia, decrease in total IgE levels, and normalization or near-normalization of lung function.

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**Table 2. Tropical Pulmonary Eosinophilia: Diagnostic Features**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>Prodrome of weight loss and fever followed by symptoms and signs of asthma with prominent cough</td>
<td></td>
</tr>
<tr>
<td>History of travel or residence in an area endemic for filarial disease, particularly <em>Wuchereria bancrofti</em> or <em>Brugia malayi</em></td>
<td></td>
</tr>
<tr>
<td>Very high peripheral eosinophil counts are common</td>
<td></td>
</tr>
<tr>
<td>High total IgE levels and positive filarial titers</td>
<td></td>
</tr>
<tr>
<td>Symmetric infiltrates on chest film ranging from interstitial prominence to miliary consolidations (mottled chest radiograph)</td>
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<tr>
<td>Positive clinical response to therapy directed against filariasis</td>
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**Figure 2.** (A) Shadows typically seen in recently acquired tropical eosinophilia include symmetrically increased interstitial markings (“striations”) emanating from prominent hila. (B) This finding is frequently associated with 2- to 5-mm nonconfluent nodular opacities, resulting in a “mottled” appearance on the chest radiograph. (Adapted with permission from Herlinger H. Pulmonary changes in tropical eosinophilia. Br J Radiol 1963;36:889–901.)
CHURG-STRAUSS SYNDROME

CASE PRESENTATION

A 40-year-old woman presents with a past medical history of poorly controlled asthma and rapidly progressive left lower extremity weakness. She reports a history of asthma for the past 20 years with associated allergic rhinitis and frank sinusitis that required several endoscopic procedures for palliation. More recently, she has developed mild fever, increasing malaise, and intermittent blood-streaked sputum. On examination, she is ill appearing with a temperature of 101°F, respiratory rate of 22 breaths/min, blood pressure of 115/70 mm Hg, and pulse of 120 bpm. Lungs and heart are remarkable for diffuse wheeze and pericardial friction rub. Her skin shows several tender red nodules over the arms and legs. Neurologic examination reveals a left foot drop. A chest radiograph shows bibasilar patchy consolidation similar to that shown in Figure 3. CBC is significant for 62% eosinophils (absolute, 9300/mm³).

CLINICAL AND LABORATORY FEATURES

CSS, or allergic granulomatosis, refers to migratory eosinophilic pneumonia in the setting of clinical asthma and frank systemic vasculitis. The pathologic features were described in 1951 in a series of patients with severe asthma symptoms and associated fever, hypereosinophilia, cardiac failure, renal failure, and peripheral neuropathy. Purpuric skin rash and gastrointestinal symptoms, including pain and diarrhea with hematochezia, were common. Peripheral eosinophil counts varied but in general tended to be very high (eg, > 3000/mm³). Histologic examination of affected organs revealed a necrotizing vasculitis and extravascular granulomata with an eosinophil-predominant infiltrate. In addition to vasculitis involving medium to small vessels, there was pneumonia characterized by eosinophil exudation in the alveolar spaces (Figure 4). Deposition of toxic eosinophil granule products has been documented in areas of tissue injury, supporting a pathogenic role for these cells.

CSS affects men and women equally and begins with a prodrome of adult-onset (~ age, 20–35 yr) allergic rhinitis and asthma, which is typically poorly controlled. This prodrome may last for years before significant hypereosinophilia and finally vasculitis develop. A Löffler’s-type pneumonia may be observed during the hypereosinophilic phase. Of note, transient resolution of asthma symptoms may presage the onset of the vasculitic phase along with signs of systemic disease, including skin rash, mononeuritis multiplex, and cardiac dysfunction. Cardiac dysfunction is the leading cause of death in untreated disease. The “classic” histopathologic features of CSS (particularly granulomata) may not be demonstrable in an individual patient, and the importance of diagnostic clinical features has been stressed. The American College of Rheumatology diagnostic criteria for CSS are listed in Table 3.

The etiology of CSS is not known. Antineutrophil antibodies, particularly p-ANCA, are seen in some but not all patients with CSS. While p-ANCA are helpful in supporting a diagnosis of vasculitis if present, their pathogenic significance is unclear. Mild to moderate elevations in IgE (eg, up to 1000 ng/mL) have been noted. Given its strong association with atopic disease, hypereosinophilia, and elevated IgE levels, CSS might represent an aberrant response to some environmental antigen, but this remains unproven. Recent reports have linked the initiation of leukotriene antagonist therapy for asthma with the onset of CSS in patients who were actively tapering corticosteroid therapy and in those who were not using steroids. A direct cause and effect is not at all clear in these cases, and this phenomenon may simply be due to unmasking during steroid withdrawal or to coincidence.
Prognosis and Treatment

CSS is fatal if left untreated but demonstrates an excellent response to high-dose prednisone (ie, 1–2 mg/kg), with long-term survival being the rule.\textsuperscript{50,53,54} Steroids are generally required for 3 to 6 months, with the rate of taper dictated by the type and extent of end organ dysfunction at the time of presentation. Adjunctive cytotoxic therapy (usually with cyclophosphamide as daily oral therapy or monthly bolus) is recommended by some experts from the outset, while others reserve combination therapy for patients with multiple end-organ involvement.\textsuperscript{55–57}

Allergic Bronchopulmonary Aspergillosis

Case Presentation

A 45-year-old man who is a life-long nonsmoker and has a 15-year history of difficult to control bronchial asthma presents with cough productive of mucopurulent sputum and worsening asthma symptoms. An initial chest radiograph shows a small infiltrate in the middle portion of the right lung. He is treated with several courses of antibiotics and high-dose inhaled corticosteroids with minimal improvement. Laboratory data show a normal CBC except for 10% eosinophils, negative antinuclear antibodies, negative ANCA, and an IgE level of 1750 ng/mL. Chest CT scan shows bronchus intermedius central bronchiectasis. Bronchoscopy is performed and shows normal airways except for inflamed proximal airways on the right side. Cultures of a bronchoscopy sample are positive for \textit{Aspergillus fumigatus}. Immediate skin test and serum precipitins are positive for \textit{Aspergillus}. The patient is started on oral corticosteroids (1 mg/kg), with substantial improvement in symptoms and a fall in the IgE level to less than 1000 ng/mL.

Clinical and Laboratory Features

ABPA is a form of \textit{Aspergillus} lung disease that is clinically and pathologically distinct from invasive and chronic necrotizing aspergillosis, aspergilloma (mycetoma), hypersensitivity pneumonitis, and mold-sensitive asthma. It was first described by Hinson et al.\textsuperscript{58} in 1951, and the clinical and diagnostic features have been subsequently detailed.\textsuperscript{59,60} Patients present with poorly controlled asthma symptoms, mild to moderate peripheral eosinophilia (~ 1000/mm\textsuperscript{3} in some series), and remarkable mucous production with migratory pulmonary infiltration and intermittent lobar atelectasis. The phlegm is purulent and contains aspergillus mycelial elements appearing either as flecks or aggregated in larger plugs along with eosinophils, mucous, and other cellular debris. These expectorated plugs represent portions of larger masses that tend to obstruct the distal bronchi. Intermittent mild hemoptysis is common. Cultures of patients with ABPA overwhelmingly yield \textit{Aspergillus fumigatus},

Table 3. American College of Rheumatology Criteria for Diagnosis of Churg-Strauss Syndrome (1990)

<table>
<thead>
<tr>
<th>Churg-Strauss syndrome is likely when 4 of 6 following features are present:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Eosinophilia &gt; 10%</td>
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<tr>
<td>Paranasal sinus abnormality</td>
</tr>
<tr>
<td>Pulmonary infiltrates</td>
</tr>
<tr>
<td>Mononeuropathy or polyneuropathy</td>
</tr>
<tr>
<td>Extravascular eosinophils on biopsy of affected tissue</td>
</tr>
</tbody>
</table>

Figure 4. Pathology of Churg-Strauss syndrome. Micrographs of lung parenchyma show (A) typical extravascular granulomata (white arrowheads) and an area of eosinophilic pneumonia (black arrowhead) as well as (B) vasculitis (white arrows). (Adapted with permission from Conron M, Beynon HL. Churg-Strauss syndrome. Thorax 2000; 55:870–7, with permission from the BMJ Publishing Group.)
although other *Aspergillus* species, other molds, and yeast are occasionally demonstrated.\(^6\)\(^5\)\(^6\) Aspergillus *fumigatus* is ubiquitous in the environment, and ABPA has not been strongly linked to any particular exposure. Skin prick tests to *Aspergillus* *fumigatus* extracts are uniformly positive, and serum precipitins to *Aspergillus* are demonstrable in over 90% of patients.\(^5\)\(^9\)

Bronchial biopsies in ABPA demonstrate mucosal infiltration with neutrophils and eosinophils, mucous gland hyperplasia, and no fungal invasion. Lesions of bronchocentric granulomatosis also have been associated with ABPA.\(^6\)\(^5\)\(^6\) The radiographic abnormalities in ABPA tend to have an upper lobe predominance and include consolidations of various sizes, evidence of bronchial dilatation (tram tracking and ring shadows), and evidence of mucoid impaction (eg, “gloved finger” shadows) with or without frank atelectasis.\(^6\)\(^6\)\(^7\) The tendency for central bronchiectasis in ABPA has been confirmed by bronchograms and more recently by CT scanning.\(^6\)\(^8\)\(^\text{70}\) When present, central bronchiectasis is highly supportive of the diagnosis in combination with the other signs and symptoms (Figure 5). Lung function testing reveals a predominantly obstructive picture; concomitant restriction with diminished DLCO is seen in more advanced disease. Total IgE levels in patients with ABPA tend to be very high (usually > 1000 ng/mL), compared to uncomplicated asthma or other antigen-driven diseases like hypersensitivity pneumonitis.\(^7\)\(^1\) Levels of *Aspergillus*-specific IgE and IgG also have been found to be higher in ABPA than in simple asthma and may be helpful in supporting the diagnosis.\(^7\)\(^2\) Diagnostic features of ABPA are summarized in Table 4.

### Table 4. Diagnostic Features of Allergic Bronchopulmonary Aspergillosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Asthma present, usually poorly controlled/steroid dependent</td>
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<tr>
<td>History of transient pulmonary infiltration</td>
<td></td>
</tr>
<tr>
<td>Fixed radiologic defects, especially central bronchiectasis</td>
<td></td>
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<tr>
<td>Peripheral eosinophilia, typically mild to moderate</td>
<td></td>
</tr>
<tr>
<td>Immediate skin prick reaction to <em>Aspergillus</em> <em>fumigatus</em></td>
<td></td>
</tr>
<tr>
<td>High serum IgE levels (&gt; 1000 ng/mL)</td>
<td></td>
</tr>
<tr>
<td>Presence of <em>Aspergillus</em>-specific IgE or IgG antibodies</td>
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### PROGNOSIS AND TREATMENT

If untreated, ABPA results in progressive lung destruction characterized by central bronchiectasis with progression to fixed airway obstruction and ultimately lung fibrosis and cor pulmonale. The majority of patients with active ABPA characterized by wheezing, pulmonary infiltrates, peripheral eosinophilia, and high IgE levels will have good clinical response to systemic corticosteroids in addition to standard asthma therapy. Prednisone is initially dosed at 0.5 mg/kg for several weeks and then tapered after symptoms and infiltrates resolve; a typical course of treatment spans several
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months. A concomitant fall in total IgE level is expected with successful treatment (eg, ≤ 35% baseline) but will usually remain above normal during remission. Accordingly, a rising IgE level in a patient with known ABPA is a useful indicator of disease activity and is associated with relapse. Adjunctive use of antifungal chemotherapy in patients resistant to steroid alone has shown potential clinical benefit in short (16 wk) prospective trials in terms of reduced sputum eosinophilia and decreased total IgE levels compared with steroids alone.

SUMMARY

Eosinophilic lung diseases are a group of clinically and pathogenically varied disorders characterized by abnormal accumulation of eosinophils in the lungs as well as signs and symptoms of pneumonia. Causes of pulmonary eosinophilia include parasitic or fungal infections and hypersensitivity drug reactions. Integration of clinical, laboratory, and radiologic findings enables the diagnosis of the various eosinophilic lung diseases. Identifying the underlying cause of pulmonary eosinophilia is necessary to select appropriate therapy, which ranges from specific antiparasitic drugs to glucocorticoid therapy. Corticosteroids remain the treatment of choice for most forms of eosinophilic lung disease. Adjunctive treatments include immunosuppressive therapy for CSS and antifungals for ABPA. In general, the 4 eosinophilic lung diseases discussed in this manual (simple pulmonary eosinophilia, tropical pulmonary eosinophilia, CSS, and ABPA) have an excellent clinical response to early, appropriate treatment.

REFERENCES

27. Belongia EA, Hedberg CW, Gleich GJ, et al. An inves-


