DEFINITION AND CLASSIFICATION

Definition

Eosinophilic lung diseases are a group of diffuse parenchymal lung diseases characterized by the prominent infiltration of the lung interstitium and the alveolar spaces by polymorphonuclear eosinophils, with conservation of the lung architecture. As a corollary, a common denominator of eosinophilic lung diseases is represented by a dramatic response to systemic corticosteroid therapy and healing without any sequelae in most cases, despite frequent impressive impairment of lung function at presentation.

Blood eosinophilia is defined by an eosinophil blood cell count greater than 0.5 × 10⁹/L, and hypereosinophilia by an eosinophil blood cell count of greater than 1.5 × 10⁹ on 2 examinations over at least a 1-month interval. Alveolar eosinophilia is defined by differential cell count of at least 25% eosinophils at bronchoalveolar lavage (BAL), and typically greater than 40%.

Classification

Eosinophilic lung disorders can present as acute or chronic pneumonia or as the transient Löffler syndrome, which is most commonly of parasitic origin (Box 1). The main causes include exposure to drugs or toxins and fungal infection; however, chronic eosinophilic pneumonia is most often idiopathic, and acute eosinophilic pneumonia most often is related to drugs or tobacco smoke exposure. Eosinophilic lung disorders occurring in the
context of systemic conditions suggest the diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) or the idiopathic hypereosinophilic syndromes.

PATHOPHYSIOLOGY

Recruitment of Eosinophils to the Lung

Blood and tissue eosinophilia have long been identified as major players in immunity against parasites and in the pathogenesis of allergic diseases. Following differentiation of precursor cells in the bone marrow under the action of several cytokines, including interleukin (IL)-5, IL-3, and granulocyte macrophage colony-stimulating factor (GM-CSF), eosinophils are recruited in the blood and tissue, including the lung in response to circulating IL-5, eotaxins, and the C-C chemokine receptor-3 (CCR3). Because recruitment of eosinophils to tissues is organ-specific, tissue and blood eosinophilia are not necessarily associated. The prominence of IL-5 in eosinophil differentiation and recruitment has led to the development of anti–IL-5 monoclonal antibodies to selectively target the eosinophil lineage in humans with asthma.

Eosinophils and Immunity

Eosinophils are active participants in innate immunity. They interact with basophils, endothelial cells, macrophages, platelets, fibroblasts, and mast cells through cell membrane signaling molecules and receptors including Toll-like receptors and receptors for cytokines, immunoglobulins, and complement. Activated eosinophils release proinflammatory cytokines, arachidonic acid–derived mediators, enzymes, reactive oxygen species, complement proteins, chemokines, chemoattractants, metalloproteases, and cationic proteins. The latter are released by degranulation of activated eosinophils and exert a variety of effects, including direct cytotoxicity, upregulation of chemoattraction, expression of adhesion molecules, regulation of vascular permeability, and contraction of smooth muscle cells. Activated, degranulated (“hypodense”) eosinophils can be found in the bronchoalveolar lavage (BAL) and the lung tissue of patients with eosinophilic pneumonias. Tissue damage mediated by eosinophil cationic proteins is exemplified by the cardiac lesions that occur in the hypereosinophilic syndrome or in tropical eosinophilia.

Eosinophils are also involved in adaptive immunity against bacteria, viruses, and tumors through interaction with T-lymphocytes. They present antigens to T-helper-2 cells in tissues and in the draining lymph nodes in the context of major histocompatibility complex class II, thereby inducing T cell development, activation, and migration to sites of inflammation. Eosinophils secrete IL-4 and IL-13, amplifying the T-helper-2 response in the lung, and in turn are recruited and activated by T-helper-2 cell-derived cytokines (IL-4, IL-5, and IL-13).

IDIOPATHIC CHRONIC EOSINOPHILIC PNEUMONIA

First characterized by Carrington and colleagues, idiopathic chronic eosinophilic pneumonia (ICEP) is characterized by the onset over a few weeks of cough, dyspnea, malaise, and weight loss, with diffuse pulmonary infiltrates.

Epidemiology and Risk Factors

Although it is a rare disease, representing fewer than 3% of cases of various interstitial lung
diseases, ICEP is the most common of the eosinophilic pneumonias in nontropical areas where the prevalence of parasitic infection is low.\textsuperscript{20} It predominates in women (2:1 female/male ratio),\textsuperscript{21,22} and affects every age group with a mean age of 45 years at diagnosis,\textsuperscript{21} with no genetic predisposition. Two-thirds of patients with ICEP have a prior history of asthma,\textsuperscript{21,22} and approximately half a history of atopy, consisting in drug allergy, nasal polyposis, urticaria, and/or eczema.\textsuperscript{21,22} In contrast with idiopathic acute eosinophilic pneumonia (IAEP), most patients with ICEP are nonsmokers.\textsuperscript{21–23} It has been hypothesized that ICEP may occur predominantly in patients who are prone to develop a T-helper-2 response.\textsuperscript{24}

**Clinical Description**

The onset of ICEP is progressive or subacute, with several weeks or months between the onset of symptoms and the diagnosis.\textsuperscript{21,22} Shortness of breath is usually moderate and is the prominent clinical manifestation, present in 60% to 90% of patients. Cough (90%), rhinitis or sinusitis (20%), and rarely chest pain or hemoptysis (10% or less) may be present.\textsuperscript{21,22} Wheezes or crackles are found in one-third of patients at auscultation. Respiratory failure requiring mechanical ventilation is exceptional in ICEP, in contrast to the frequent respiratory failure that occurs in IAEP.\textsuperscript{25,26}

Approximately 75% of the patients with ICEP experience asthma at some time throughout the course of disease. Asthma frequently precedes the onset of ICEP, but occasionally occurs concomitantly with the diagnosis of ICEP (15%).\textsuperscript{27} Asthma in ICEP is often severe and can progress to long-term persistent airflow obstruction in approximately 10% of patients despite oral and inhaled corticosteroid therapy.\textsuperscript{27} Follow-up of patients, including pulmonary function tests is therefore necessary.

Systemic symptoms are frequently associated, with fatigue, malaise, fever, anorexia, night sweats, and weight loss (occasionally severe).\textsuperscript{21,22} Limited extrathoracic manifestations have been reported, including pericardial effusion, arthralgias, non-specific skin manifestations, and altered liver function tests\textsuperscript{19,21,28}, however, any significant extrathoracic manifestation should raise the suspicion of EGPA.

**Chest Imaging**

The imaging features of ICEP are often characteristic, albeit nonspecific, and are present on the chest radiograph in almost all cases before initiation of treatment.\textsuperscript{19,21,22,29–35} They consist of bilateral alveolar infiltrates with ill-defined margins, with a typical peripheral predominance in approximately 25% of patients.\textsuperscript{21,22,31,36,37} Spontaneous migration of the opacities observed in a quarter of the cases suggests the diagnosis of either ICEP or cryptogenic organizing pneumonia.\textsuperscript{21}

On high-resolution computed tomography (HRCT), typical features consist of confluent consolidations and ground-glass opacities (Fig. 1),\textsuperscript{21,30,34} almost always bilateral and predominating in the upper lobes and peripheral subpleural areas.\textsuperscript{30} Imaging abnormalities rapidly regress on corticosteroid therapy.\textsuperscript{30} This pattern is sufficiently typical to suggest the diagnosis of ICEP in approximately 75% of cases in the appropriate setting.\textsuperscript{33} Septal line thickening, band-like opacities parallel to the chest, mediastinal lymph node enlargement, or mild pleural effusion, may be found,\textsuperscript{21,29} but cavitary lesions are exceedingly rare.\textsuperscript{21,22,30}

**Laboratory Findings**

High-level peripheral blood eosinophilia present in most patients who have not yet received systemic corticosteroids\textsuperscript{22} is the key to the diagnosis, with mean values of 5 to 6000/mm\textsuperscript{3} in large series, representing 20% to 30% of blood leukocytes.\textsuperscript{21} BAL eosinophilia, defined as 25% eosinophils or
more at differential cell count, is found in all pa-
tients evaluated before any corticosteroid intake,
and confirms the diagnosis of eosinophilic pneu-
monia, especially when eosinophils represent the
predominant cell in BAL. The BAL eosinophil count
is commonly greater than 40%, with a mean of
58% in large series. Sputum eosinophilia may be
present but is less valuable for diagnosis. Increase
in blood C-reactive protein and total immunoglob-
ulin (Ig) E level are common but lack specificity.

Pathogenesis
The pathogenesis of ICEP is considered to be a
direct consequence of lung infiltration by eosino-
phils, and is reversible on corticosteroid treatment.
A number of studies have demonstrated the release
of proinflammatory molecules and increased
expression of activation markers by eosinophils
from patients with ICEP.1,9,38–40 Interestingly,
recent studies have suggested a possible role for
clonal blood and lung tissue T cells in ICEP,41,42
similarly to what seen in the lymphocytic variant
of the idiopathic hypereosinophilic syndrome.

Lung Function
Approximately half of patients with ICEP have
airflow obstruction, and the other half have a
restrictive ventilatory defect related to pulmonary
infiltration. In the latter case, multiple consolida-
tions are apparent on imaging, and reduced car-
bon monoxide transfer factor and coefficient are
present by pulmonary function testing. In addition,
many patients present with mild hypoxemia.21,22

Pathology
The diagnosis of ICEP does not typically require a
lung biopsy. When available, pathology is charac-
terized by prominent infiltration of the lung intersti-
tium and the alveolar spaces by eosinophils19,22
accompanied by a fibrinous exudate, with preser-
vation of the lung architecture. Eosinophilic micro-
abscesses, a non-necrotizing nongranulomatous
vasculitis, and occasional multinucleated giant
cells (but no granuloma) also can be found.
Some histologic overlap is common with orga-
nizing pneumonia.1 Eosinophil degranulation can
be demonstrated by immunohistochemical and
electron microscopic studies within the site of
eosinophilic pneumonia.17,43

Diagnosis
Working diagnostic criteria for ICEP are found in
Box 2.4,5 A thorough investigation for potential
causes of eosinophilia should be conducted
before the condition is considered idiopathic,
including drug intake, infections with parasites or

<table>
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<tr>
<th>Box 2</th>
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<tr>
<td><strong>Diagnostic criteria for idiopathic chronic eosinophilic pneumonia and for idiopathic acute eosinophilic pneumonia</strong></td>
</tr>
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</table>

**Idiopathic chronic eosinophilic pneumonia**

1. Diffuse pulmonary alveolar consolidation with air bronchogram and/or ground-glass opacities at chest imaging, especially with peripheral predominance.
2. Eosinophilia at bronchoalveolar lavage differential cell count ≥40% (or peripheral blood eosinophils ≥1000/mm³).
3. Respiratory symptoms present for at least 2 to 4 wk.
4. Absence of other known causes of eosinophilic lung disease (especially exposure to drug susceptible to induce pulmonary eosinophilia).

**Idiopathic acute eosinophilic pneumonia**

1. Acute onset with febrile respiratory manifestations (≤1 mo, and especially ≤7 d duration before medical examination).
2. Bilateral diffuse infiltrates on imaging.
3. PaO₂ on room air ≤60 mm Hg (8 kPa), or PaO₂/FiO₂≤300 mm Hg (40 kPa), or oxygen saturation on room air <90%.
4. Lung eosinophilia, with ≥25% eosinophils at BAL differential cell count (or eosinophilic pneumonia at lung biopsy when done).
5. Absence of determined cause of acute eosinophilic pneumonia (including infection or exposure to drugs known to induce pulmonary eosinophilia). Recent onset of tobacco smoking or exposure to inhaled dusts may be present.
fungi, and exposure to toxins or illicit drugs. In the setting of a characteristic clinical and radiologic presentation, the presence of marked eosinophilia at BAL (at least 25% but usually >40% of BAL cells), or when eosinophils are more numerous than neutrophils and lymphocytes, confirms the diagnosis of eosinophilic pneumonia, and obviates the need for lung biopsy.

Although performing a BAL is generally useful in patients with suspected eosinophilic pneumonia and those with diffuse alveolar opacities at imaging, the presence of markedly elevated peripheral blood eosinophilia together with typical clinical radiologic features also strongly suggest the diagnosis of ICEP. Diagnostic difficulties mainly arise in patients who are already receiving corticosteroid treatment, and therefore do not have peripheral or BAL eosinophilia at the time of clinical evaluation.

**Treatment and Outcome**

Although spontaneous resolution can occur, management of ICEP is based primarily on oral corticosteroids. The objective of therapy is to induce remission of disease and then to reduce the risk of relapse, while balancing the intensity of treatment with the need to minimize the side effects of corticosteroids.

There are no established dose and duration of systemic corticosteroids in ICEP. A typical regimen may include treatment with an initial dose of 0.5 mg/kg per day of oral prednisone for 2 weeks, followed by 0.25 mg/kg per day for 2 weeks, then corticosteroids are progressively reduced over a total duration of approximately 6 months and stopped. Response to corticosteroids is typically dramatic, with clinical improvement within 2 days, and clearing of chest opacities within 1 week. Most patients need corticosteroids for 6 to 12 months; however, a recent study found no difference in the relapse rate between a 3-month and a 6-month treatment regimen. Whether inhaled corticosteroids may be useful in nonasthmatic patients with ICEP is unknown.

Relapses occur in more than half the patients while decreasing or after stopping corticosteroids; however, they respond very well to resumed corticosteroid treatment. Relapses typically can be treated with a dose of 20 mg per day of prednisone. Patients should therefore be informed of the possibility of relapse while the corticosteroids are progressively tapered and then stopped. Such an approach reduces the overall patient’s exposure to long-term corticosteroids.

There are no long-term sequels of ICEP; however, clinical and functional follow-up is necessary to ensure that patients are asymptomatic with a normal chest radiograph and lung function. Potential morbidity is related to adverse events related to oral corticosteroids, and to possible persistent airflow obstruction that may develop despite bronchodilators and inhaled corticosteroids and often oral low-dose corticosteroids.

**IDIOPATHIC ACUTE EOSINOPHILIC PNEUMONIA**

IAEP, first described by Badesch and colleagues and later individualized by Allen and colleagues, is both the most dramatic and the most frequently misdiagnosed of eosinophilic pneumonias, because it mimics infectious pneumonia or acute respiratory distress syndrome in previously healthy individuals. It differs from ICEP by its acute onset, the severity of hypoxemia, the usual lack of increased blood eosinophils at the onset of disease, and the absence of relapse.

**Epidemiology and Risk Factors**

IAEP occurs acutely in previously healthy young adults, with a mean age of approximately 30 years, and with male predominance. Two-thirds of patients are smokers, but there is usually no history of asthma. The disease can be triggered by various respiratory exposures, especially a recent initiation of tobacco smoking (as in military or new college student settings). A change in smoking habits, smoking large quantities of cigarettes (or cigars), reintroduction to smoking (“rechallenge”), or even short-term passive smoking also can trigger IAEP. A variety of nonspecific environmental inhaled contaminants also have been demonstrated to induce IAEP. Whether this condition should be termed “idiopathic” acute eosinophilic pneumonia in cases clearly related to tobacco smoking or other exposures is debatable.

**Clinical Description**

IAEP is characterized by acute onset of dyspnea (100% of patients), fever that is usually moderate (100%), cough (80%–100%), and pleuritic thoracic pain (50%–70%), myalgias (30%–50%), or abdominal complaints (25%). Acute onset is an important criterion for the diagnosis of IAEP (see Box 2), with a delay between the first symptoms and hospital admission of less than 1 month and usually less than 7 days. Acute respiratory failure is frequent, often meeting criteria for acute respiratory distress syndrome, and admission to the intensive care unit and mechanical ventilation...
are often required. Crackles are present in most patients at lung auscultation.

**Chest Imaging**

The chest radiograph shows bilateral infiltrates, with mixed alveolar and interstitial opacities, especially Kerley lines. Chest HRCT demonstrates the typical combination of poorly defined nodules of ground-glass attenuation (100%), interlobular septal thickening (90%), bilateral pleural effusion (76%), and airspace consolidation (55%), which suggests the diagnosis in the appropriate setting. Thickening of bronchovascular bundles, lymph node enlargement, and centrilobular nodules also may be found.

**Laboratory Findings**

In contrast to other eosinophilic pneumonias, blood eosinophil count is normal at presentation in most cases of IAEP, a feature that contributes to misdiagnosis of IAEP as infectious pneumonia. Within days after presentation, the eosinophil count rises to high values, a finding that should suggest the diagnosis of IAEP. Given the usual lack of initial blood eosinophilia, BAL eosinophilia is often the key to the diagnosis of IAEP. With 37% to 54% eosinophils on average, BAL bacterial cultures are sterile. BAL eosinophilia usually resolves with corticosteroid therapy, but may persist for several weeks.

Biomarkers, especially serum levels of CCL17/TARC and KL6 (Krebs von den Lungen-6), have been proposed to discriminate IAEP from noneosinophilic causes of acute lung injury, but have not been validated. Thoracentesis when performed may show nonspecific pleural eosinophilia.

**Lung Function**

Pulmonary function tests are practical only in less severe cases, but typically reveal a mild restrictive ventilatory defect, with reduced carbon monoxide transfer capacity, and increased alveolar-arterial oxygen gradient of P<sub>A</sub>O<sub>2</sub>. Arterial blood gas demonstrates hypoxemia, which can be severe due to right-to-left shunting in areas of alveolar consolidation. Patients often meet diagnostic criteria for acute lung injury (including a P<sub>A</sub>O<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> ≤300 mm Hg) or for acute respiratory distress syndrome (P<sub>A</sub>O<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> ≤200 mm Hg).

**Pathology**

A lung biopsy is performed only in rare cases when the diagnosis of eosinophilic pneumonia has not been suspected. When performed, it shows acute and organizing diffuse alveolar damage together with interstitial-alveolar and bronchiolar infiltration by eosinophils, intra-alveolar eosinophils, and interstitial edema.

**Diagnosis**

BAL can both establish the presence of alveolar eosinophilia and exclude infection. Current working diagnostic criteria for IAEP and characteristics that differ between IAEP and ICEP are listed in Box 2 and Table 1, respectively. Some patients with moderate disease severity may not fit established criteria.

A variety of causes must be investigated, especially in the setting of acute-onset disease, including parasites, fungi, viruses, red spiders, drugs, over-the-counter drugs, and illicit drugs. The etiologic enquiry shall be repeated

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ICEP</th>
<th>IAEP</th>
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<tbody>
<tr>
<td>Onset</td>
<td>&gt;2–4 wk</td>
<td>&lt;1 mo</td>
</tr>
<tr>
<td>History of asthma</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Smoking history</td>
<td>10% of smokers</td>
<td>2/3 smokers, often recent initiation</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>Rare</td>
<td>Usual</td>
</tr>
<tr>
<td>Initial blood eosinophilia</td>
<td>Yes</td>
<td>Often No (typically delayed)</td>
</tr>
<tr>
<td>Bronchoalveolar lavage eosinophilia</td>
<td>&gt;25%</td>
<td>&gt;25%</td>
</tr>
<tr>
<td>Chest imaging</td>
<td>Homogeneous peripheral airspace consolidation</td>
<td>Bilateral patchy areas of ground-glass attenuation, airspace consolidation, interlobular septal thickening, bilateral pleural effusion</td>
</tr>
<tr>
<td>Relapse</td>
<td>Yes</td>
<td>No</td>
</tr>
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</table>
in case of poor response to therapy. AEP also may occur after allogeneic hematopoietic stem cell transplantation or in the context of acquired immunodeficiency virus infection.

**Treatment and Outcome**

Most patients receive systemic corticosteroids. A treatment duration of 2 weeks may be sufficient, with a starting dose of oral prednisone of 30 mg per day, or 1 to 2 mg/kg per day of intravenous methylprednisolone in patients with respiratory failure. Clinical recovery occurs within 3 days on corticosteroid treatment. Imaging and pulmonary function abnormalities resolve within less than a month. In contrast with ICEP, IAEP does not relapse. Patients should be informed about the etiologic role of tobacco in the disease process and should be strongly encouraged to quit.

Extrapulmonary organ failure or shock is exceptional, and only a couple of lethal cases have been reported. Extracorporeal membrane oxygenation has been used occasionally.

**EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS**

**Definition**

EGPA (formerly, Churg-Strauss syndrome), described in 1951, mainly from autopsied cases, is a systemic disease associated with asthma, eosinophilia, and eosinophil-rich and granulomatous inflammation involving the respiratory tract and a small-vessel, necrotizing small to medium-sized vessel necrotizing vasculitis. EGPA is associated in approximately 40% of cases with antineutrophil cytoplasmic antibodies (ANCA) and therefore belongs to the pulmonary ANCA-associated vasculitides.

**Epidemiology and Risk Factors**

EGPA predominates in the fourth or fifth decade, with no gender predominance. It is a rare condition, with an incidence of 0.5 to 6.8 cases per million inhabitants per year, and a prevalence of 10.7 to 13.0 cases per million inhabitants. A genetic predisposition has been linked to the major histopathology complex DRB4 allele. Familial EGPA has been reported. Association with a history of allergy is weak, as allergy can be evidenced by specific serum IgE with corresponding clinical history in fewer than one-third of patients. When present, allergy in EGPA mainly consists of perennial allergies, especially to *Dermatophagoides*, whereas seasonal allergies are less frequent than in control individuals with asthma.

Although the pathogenesis of EGPA is largely unknown, several triggering or adjuvant factors have been identified or suspected, including infectious agents (*Aspergillus, Candida, Ascaris, Actinomyces*), bird exposure, cocaine, and drugs (sulfonamides used together with antiserum, diflu- nisal, macrolides, diphenylhydantoin, and omalizumab) as well as allergic hyposensitization and vaccinations. Clonal T cells may play a role.

The possible link between leukotriene-receptor antagonists (montelukast, zafirlukast, pranlukast) and the development of EGPA is controversial, and the development of EGPA is controversial. EGPA may instead arise in patients taking these drugs due to the flare of smouldering preexisting disease as oral or inhaled corticosteroids are tapered rather than to a direct effect on the pathogenesis of vasculitis. However, a direct effect of montelukast cannot be excluded in individual cases, and it is reasonable to avoid leukotriene-receptor antagonists in asthmatic patients with eosinophilia and/or extrapulmonary manifestations compatible with smouldering EGPA.

**Clinical Description**

The natural course of EGPA has been described to follow 3 phases, with rhinosinusitis and asthma, blood and tissue eosinophilia, and eventually systemic vasculitis, but these often overlap in time. Asthma is always present in EGPA, occurring at a mean age of approximately 35 years, generally severe and becoming rapidly corticosteroid dependent, and often preceding the onset of the vasculitis by 3 to 9 years. Asthma may become attenuated after the onset of the vasculitis, likely reflecting the effect of systemic corticosteroids prescribed for EGPA. Eosinophilic pneumonia is the main pulmonary manifestation of EGPA other than asthma. It is often similar to ICEP in presentation, but may be acute in onset. The frequency of eosinophilic pneumonia may be underestimated in some series of EGPA, as it rapidly resolves on corticosteroid treatment, and because extrathoracic manifestations may be prominent clinically.

Chronic rhinitis or rhinosinusitis is present in approximately 75% of cases but lacks specificity. It may consist of chronic paraseptal sinusitis, crusty rhinitis, nasal obstruction, and nasal polyposis, often with eosinophilic infiltration at histopathology. Septal nasal perforation does not occur.
not occur in EGPA as opposed to granulomatosis with polyangiitis.

General symptoms are present in two-thirds of patients (asthenia, weight loss, fever, arthralgias, myalgias). Any organ system can be affected by the systemic disease through eosinophilic infiltration and/or granulomatous vasculitis.\textsuperscript{98,127} Heart and kidney involvement are frequently insidious and must be systematically investigated due to potential morbidity and mortality.

Cardiac involvement is often asymptomatic but can lead to sudden death or acute or chronic cardiac failure\textsuperscript{95–97,119,120,128,129} due to eosinophilic myocarditis and less commonly from coronary arteritis.\textsuperscript{130,131} Heart transplantation may be required.\textsuperscript{132} Therefore, any patient with suspected EGPA should undergo a systematic cardiac evaluation with electrocardiogram, echocardiography, N-terminal pro–brain natriuretic peptide, and serum level of troponin I. MRI of the heart is currently the preferred investigation when cardiac involvement is suspected.\textsuperscript{129,133–135} However, the clinical significance of subclinical abnormalities detected by MRI\textsuperscript{129,134,136} or echocardiography\textsuperscript{134,137} is unknown. Patients with EGPA are also at greater risk of venous thromboembolic events.\textsuperscript{92}

## Chest Imaging

Chest imaging abnormalities in patients with EGPA are twofold:

- Pulmonary infiltrates (50%–70%) corresponding to eosinophilic pneumonia and consisting of ill-defined opacities, sometimes migratory, with peripheral predominance or random distribution, and density varying from ground-glass opacities to airspace consolidation\textsuperscript{95,97,120,138–142} (Fig. 2). These abnormalities rapidly disappear on corticosteroid therapy.

- Airways abnormalities, including centrilobular nodules, bronchial wall thickening, and bronchiectasis.\textsuperscript{1,33,35,140}

Interlobular septal thickening, hilar or mediastinal lymphadenopathy, pleural effusion, or pericardial effusion also may be seen.\textsuperscript{35,139,140,142,143} Pleural effusion may correspond to eosinophilic pleural effusion or to a transudate caused by cardiomyopathy (see Fig. 2B).

## Laboratory Findings

Peripheral blood eosinophilia is a major feature of EGPA, with mean values generally between 5 and 20,000/mm\textsuperscript{3} at diagnosis.\textsuperscript{95,97,120} It is accompanied by BAL eosinophilia greater than 25% and usually greater than 40%.\textsuperscript{144} Increase in serum IgE and C-reactive protein levels is nonspecific. Biomarkers to reflect eosinophil degranulation and disease activity in vivo await prospective validation.\textsuperscript{145–147}

Although EGPA is one of the ANCA-associated pulmonary vasculitides, ANCA are found in only 40% of patients, and their absence does not exclude the diagnosis of EGPA. They are mainly perinuclear-ANCA with myeloperoxidase specificity.\textsuperscript{96,148–150} When present, ANCA support the diagnosis of EGPA; however, their titer does not correlate with the activity of disease. Different clinical phenotypes of disease have been reported in ANCA-positive and ANCA-negative patients\textsuperscript{148–152} (Box 3), possibly with a genetic correlate.\textsuperscript{99,153}

## Lung Function

Airflow obstruction is present in 70% of patients at diagnosis despite inhaled bronchodilator and high-dose inhaled corticosteroid therapy for asthma.\textsuperscript{121} Lung function improves with oral corticosteroid therapy given for the systemic disease; however,
mild airflow obstruction may persist. Low-dose long-term oral corticosteroids are required for asthma in most patients in addition to inhaled therapy, causing significant morbidity and susceptibility to infections. Persistent airflow obstruction may be present in 30% to 40% of patients with long-term follow-up.

Pathology

The diagnosis of EGPA is frequently based on the clinical presentation and marked eosinophilia, and lung biopsy is seldom necessary. Biopsy of more accessible tissues, such as skin, nerve, or muscle, has a better safety profile and can be useful. A single tissue specimen rarely contains all 3 defining characteristics: vasculitis (necrotizing or not, involving mainly the medium-sized pulmonary arteries), granulomata, and eosinophilic tissue infiltration (with palisading histiocytes and giant cells).

Diagnosis

Although the diagnosis is typically straightforward in patients with acute or chronic eosinophilic pneumonia and true vasculitis with positive ANCA, it may be more difficult in those with asthma, blood eosinophilia, negative ANCA, and mild extrathoracic manifestations; those with the so-called “forme fruste” of EGPA; or in subjects receiving corticosteroid treatment. Diagnostic difficulties thus largely depend on the stage of disease, yet it is crucial that this diagnosis be established before severe organ involvement develops, especially cardiac disease.

The diagnostic criteria proposed by Lanham and colleagues include (1) asthma, (2) eosinophilia exceeding 1.5 × 10^9/L, and (3) systemic vasculitis of 2 or more extrapulmonary organs; however, they are not applicable to patients with limited disease or those without a biopsy. Classification criteria have been established by the American College of Rheumatology; however, they can be applied only in cases with established systemic vasculitis. Working diagnostic criteria are proposed (Table 2), which include the diagnostic contribution of ANCA when present.

Treatment and Outcome

Corticosteroids remain the mainstay of treatment of EGPA, with oral prednisone typically initiated at a dose of 1 mg/kg per day for 3 to 4 weeks, then tapered to reach 5 to 10 mg per day by 12 months of therapy. An initial methylprednisolone bolus (15 mg/kg per day for 1–3 days) may be indicated in the most severe cases. Cyclophosphamide therapy (0.6–0.7 g/m² intravenously at days 1, 15, and 30, then every 3 weeks) should be added to corticosteroids to induce remission in patients with manifestations that could result in mortality or severe morbidity, especially heart failure, with 1 or more of the following “poor prognostic” criteria: age older than 65 years; cardiac symptoms; gastrointestinal involvement; renal insufficiency with serum creatinine greater than 150 µg/L; and absence of ear, nose, and throat manifestations. Subcutaneous interferon-α, high-dose intravenous immunoglobulins, plasma exchange, cyclosporine, and rituximab have been used successfully in a few cases refractory to corticosteroids. However, experience with rituximab is limited, and bronchospasm has been reported; rituximab should therefore not be used routinely in EGPA.

Once remission has been achieved, prolonged maintenance therapy is necessary to prevent relapse. Further research is needed to determine the optimal duration and dose of maintenance therapy.
relapses. Patients without poor prognosis criteria are generally treated by corticosteroids alone; the possible benefit of azathioprine to maintain remission in this setting (especially in patients who relapse despite 20 mg per day of prednisone or more) is currently being evaluated. In patients with poor prognostic criteria, maintenance therapy for 18 to 24 months (after remission has been obtained using cyclophosphamide) is generally based on azathioprine, which has a favorable risk/benefit ratio.98

Promising preliminary results have been obtained using the anti–IL-5 antibody mepolizumab.13,173,174 Drugs that target the eosinophil cell line may become part of the treatment strategy in the near future. In a retrospective multicenter study of 17 patients who received omalizumab for severe steroid-dependent asthma, alone or in association with other immunosuppressive agents, omalizumab treatment resulted in some efficacy and corticosteroid sparing effect, but severe flares occurred in a quarter of patients.176

Approximately 25% of patients experience at least 1 relapse, generally with peripheral eosinophilia, with or without new-onset systemic manifestations. The 5-year overall survival in EGPA is currently greater than 95%,159,177,178 with most deaths occurring during the first year of treatment due to cardiac involvement.179 Treatment-related side effects especially related to corticosteroids are the main cause of long-term morbidity. Difficult asthma and persistent airflow obstruction also cause significant morbidity.121,178

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Epidemiology and Pathogenesis

Allergic bronchopulmonary aspergillosis (ABPA) occurs almost exclusively in subjects with a prior history of chronic bronchial disease. It may occur in up to 1% to 2% of asthmatic adults and in up to 7% to 10% of patients with cystic fibrosis.180,181 Isolated cases have been reported in patients with chronic obstructive pulmonary disease, and in workers in bagasse-containing sites in sugar-cane mills.182

Chronic bronchial disease is associated with viscid mucus, which with exposure to fungal spores predisposes to this condition. In response to the presence of Aspergillus growing in mucous plugs in the airways of patients with asthma, complex chronic immune and inflammatory reactions develop in the bronchi and the surrounding lung parenchyma, causing local damage and impairment of the mucociliary clearance.183 Both type I hypersensitivity mediated by IgE antibodies, and type III hypersensitivity responses (with the participation of IgG and IgA antibodies and of exaggerated Th2 CD4+ T-cell–mediated immune response) are involved in the immunologic process. Excessive B-cell response, immunoglobulin production, and high levels of circulating IL-4 play a key role.183

As ABPA does not develop in all patients with asthma, genetic predisposition may have a role in conjunction with environmental exposure.183 An increased prevalence of heterozygotic cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations has been demonstrated in patients with ABPA without cystic fibrosis,184 as well as a polymorphism within the IL-4 receptor alpha-chain gene, the IL-10 promoter, and the surfactant protein A genes,185–187 and an association with HLA DR2/5 subtypes.188–190 Familial cases have been reported.191

ABPA may be associated with allergic Aspergillus sinusitis,192 resulting in a syndrome called sinobronchial allergic aspergillosis.193

Clinical Description

Patients with ABPA experience chronic cough, dyspnea, expectoration of brown or tan sputum plugs, low-grade fever, and chronic rhinitis. The
course of disease is chronic with repeated exacerbations, and does not necessarily follow the 5 classic stages of ABPA (acute, remission, recurrent exacerbations, corticosteroid-dependent asthma, and fibrotic end stage). Pulmonary infiltrates or peripheral blood eosinophilia may be only present during the acute phase or recurrent exacerbations of the disease. ABPA rarely progresses to chronic respiratory failure requiring oxygen supplementation.

Sputum production may be abundant in patients with bronchiectasis, with sputum cultures often positive for *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aspergillus fumigatus*, and/or nontuberculous mycobacteria.

**Chest Imaging**

Imaging abnormalities often suggest the diagnosis. Bronchial abnormalities are prominent at HRCT and include central cylindrical bronchiectasis (including in the upper lobes), bronchial wall thickening, mucous plugging (mucoid impaction) with “finger-in-glove” pattern, ground-glass attenuation, and airspace consolidation. The “finger-in-glove” sign present in approximately 25% of patients corresponds to bronchial mucous impaction radiating from the hilum to the periphery. Features of bronchiolitis are common, with centrilobular nodules and tree-in-bud pattern. Eosinophilic pneumonia can occur during the early course of the disease, but airspace consolidation should be differentiated from segmental or lobar atelectasis caused by mucus plugging (see Fig. 4).

**Laboratory Findings**

Blood eosinophils are usually greater than 1000/mm³ in the absence of corticosteroid treatment. Serum levels of total IgE may be particularly high and lead to suspicion of ABPA in patients with asthma. Skin-prick testing, and serum IgE and IgG (precipitin) reactions to *A fumigatus*, including antibodies specific for recombinant *Aspergillus* allergens (especially *Asp f4* and *Asp f6*), corroborate the diagnosis. Specific IgE against *A fumigatus* may be used to screen for ABPA in patients with asthma. Total and *Aspergillus*-specific IgE levels generally increase during exacerbations of ABPA. Fungal mycelia can be found by direct examination of sputum plugs.

**Pathology**

A lung biopsy is seldom necessary in patients with ABPA. Analysis of specimens from limited resection performed because of chronic pulmonary consolidation or atelectasis demonstrates bronchiectasis with mucus or mucopurulent plugs containing fungal hyphae, granulomatous inflammation of the bronchiolar wall, peribronchiolar chronic eosinophilic infiltrates with areas of eosinophilic pneumonia, exudative bronchiolitis, and mucus impaction of bronchi.

**Diagnosis**

The current primary diagnostic criteria are listed (Box 4). Cases without typical proximal bronchiectasis are designated ABPA-seropositive and may correspond to a distinct variant. Allergic bronchopulmonary syndromes similar to ABPA can be associated with yeasts or other...
fungi\textsuperscript{1,208}; the diagnosis is particularly challenging and based on repeated culture of the offending microorganism and serology if available.

\textbf{Treatment and Outcome}

Goals of treatment for ABPA includes the management of asthma exacerbations and prevention of progression to bronchiectasis and severe fibrotic lung disease while minimizing corticosteroid side effects. The mainstay of treatment for ABPA is the use of corticosteroids during ABPA exacerbations. Oral prednisone is preferred to intravenous methylprednisolone for typical episodes.\textsuperscript{209} Medium-dose oral glucocorticoids (oral prednisolone 0.5 mg kg\textsuperscript{-1} day\textsuperscript{-1} for 2 weeks followed by 0.5 mg kg\textsuperscript{-1} on alternate days for 8 weeks, then taper by 5 mg every 2 weeks and discontinue after 3–5 months) are as effective and safer than higher doses in acute-onset ABPA.\textsuperscript{210} Intravenous pulses of high-dose methylprednisolone may be used in refractory ABPA exacerbations.\textsuperscript{211} Long-term oral corticosteroids are maintained only in patients with frequent symptomatic attacks or evidence of progressive lung damage. Treatment of episodes of pulmonary consolidation may prevent the progression of ABPA to fibrotic end-stage disease.\textsuperscript{212} Inhaled corticosteroids may reduce the need for long-term oral corticosteroids; however, persistent airflow obstruction may develop over years. Oral itraconazole prescribed for 16 to 32 weeks to reduce the burden of fungal colonization in the lung is a useful adjunct to corticosteroids,\textsuperscript{213,214} allowing steroid dose reductions, and decreasing the frequency of exacerbations.\textsuperscript{213,214} Total serum IgE level is often used to monitor therapy.\textsuperscript{183} Experience with voriconazole in ABPA is limited. The anti-IgE recombinant antibody omalizumab may be useful especially in subjects with difficult asthma in ABPA.\textsuperscript{215–219}

\textbf{OTHER EOSINOPHILIC LUNG DISEASES}

\textbf{Idiopathic Hypereosinophilic Syndromes}

The idiopathic hypereosinophilic syndromes, historically defined as a persistent eosinophilia greater than 1500/mm\textsuperscript{3} for longer than 6 months, without a known cause of eosinophilia, and with presumptive signs and symptoms of organ involvement.\textsuperscript{220} now encompass 2 variants:\textsuperscript{221,222} (1) the “lymphocytic variant” (approximately 30% of cases), resulting from clonal Th2 lymphocytes bearing an aberrant antigenic surface phenotype;\textsuperscript{223} and (2) chronic eosinophilic leukemia or the “myeloproliferative variant” (approximately

\textbf{Box 4}

\textbf{Minimal essential diagnostic criteria of allergic bronchopulmonary aspergillosis}

\textit{Patients with asthma and central bronchiectasis}
1. Asthma
2. Central bronchiectasis (inner 2/3 of chest CT field)
3. Immediate cutaneous reactivity to \textit{Aspergillus}
4. Total serum IgE concentration greater than 417 kU/L (1000 mg/mL)
5. Elevated serum IgE-\textit{Aspergillus fumigatus} and/or IgG-\textit{A fumigatus} (infiltrates on chest radiograph and serum precipitating antibodies to \textit{A fumigatus} may be present but are not minimal essential diagnostic criteria)

\textit{Patients with asthma (ABPA seropositive)}
Patients with the preceding criteria 1, 3, 4, and 5 (infiltrates on chest radiograph may be present but are not a minimal essential diagnostic criteria)

\textit{Patients with cystic fibrosis}
1. Clinical deterioration (increased cough, wheezing, exercise intolerance, increase sputum, decrease in pulmonary function)
2. Immediate cutaneous reactivity to \textit{Aspergillus} or presence of IgE-\textit{A fumigatus}
3. Total serum IgE concentration \(\geq\) 1000 kU/L
4. Precipitating antibodies to \textit{A fumigatus} or serum IgG-\textit{A fumigatus}
5. Abnormal chest radiograph (infiltrates, mucus plugging, or a change from earlier films)

\textit{Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; CT, computed tomography; Ig, immunoglobulin.}
20% of cases) due to an interstitial chromosomal deletion in 4q12 encoding a constitutively activated tyrosine kinase fusion protein (Fip1L1-PDGFRα). At least half of the cases remain idiopathic and unclassified. Imatinib is used as first-line therapy in chronic eosinophilic leukemia, and can be stopped without relapse in some but not all patients. Corticosteroids are the mainstay of treatment of the lymphocytic variant. Mepolizumab is increasingly used.

Clinical manifestations mainly comprise fatigue, weight loss, and nonrespiratory involvement, especially targeting the skin, mucosa, heart, and nervous system. In older series, respiratory manifestations present in up to 40% of patients were nonspecific and included cough, dyspnea, and patchy ground-glass attenuation, consolidation, and small nodules at chest imaging. In more recent studies using current diagnostic standards, respiratory manifestations are generally of mild severity, with rare eosinophilic pneumonia if any. Chronic dry cough can be remarkable and may be a presenting feature.

**Idiopathic Hypereosinophilic Obliterative Bronchiolitis**

Hypereosinophilic obliterative bronchiolitis is a recently individualized entity, currently defined by demonstration of bronchiolitis, peripheral blood and/or alveolar eosinophilia, and persistent airflow obstruction despite high-dose inhaled bronchodilators and corticosteroids. Demonstration of a bronchiolitis may be obtained by lung biopsy and/or HRCT showing direct signs of bronchiolitis (eg, centrilobular nodules and branching opacities). Hypereosinophilic obliterative bronchiolitis can be idiopathic, but may also occur in the setting of EGPA, ABPA, drug-induced eosinophilic lung disease (such as minocycline), and possibly in severe asthma.

Patients report cough and exercise dyspnea but generally do not present with intermittent asthma symptoms or wheezes. The blood eosinophil cell count (with a mean value of 2.7 x 10^9/L), and the eosinophil differential percentage at BAL (with a mean value of 63%) are elevated. Airflow obstruction is often severe but reversible in all cases with oral corticosteroid therapy; however, clinical and functional manifestations often recur when the daily dose of oral prednisone is tapered to less than 10 to 15 mg. Unrecognized untreated hypereosinophilic obliterative bronchiolitis might be a cause of irreversible airflow obstruction in chronic eosinophilic respiratory diseases. Notably, whitish tracheal and bronchial granulations or bronchial ulcerative lesions can be present with prominent tissue eosinophils on bronchial biopsy.

**Eosinophilic Pneumonias in Parasitic Diseases**

Parasitic infection is the main cause of eosinophilic pneumonia in the world. However, it is less common in Europe and North America, and the diagnosis may be missed, especially because clinical and radiologic manifestations are nonspecific. Presentation is rarely as typical as that of ICEP or IAEP.

A detailed description can be found elsewhere. Briefly, infection with the nematode Ascaris lumbricoides mainly causes Löffler syndrome; for example, mild eosinophilic pneumonia with transient cough, wheezing, fever, high blood eosinophilia, and pulmonary infiltrates. Visceral larva migrans syndrome caused by Toxocara canis that occurs throughout the world causes fever, seizures, fatigue, blood eosinophilia, and transient pulmonary manifestations (cough, dyspnea, wheezes or crackles at pulmonary auscultation, and pulmonary infiltrates at chest radiograph). Hyperinfection syndrome caused by Strongyloides stercoralis is a severe disease in immunocompromised patients, which can affect all organs. Tropical pulmonary eosinophilia is caused by the filarial parasites Wuchereria bancrofti and Brugia malayi.

**Eosinophilic Pneumonias Induced by Drugs and Toxics**

A diligent search for the etiology of eosinophilic lung diseases is of paramount importance, as the identification of a potential cause may have practical consequences, especially when the disease is caused by drugs. When present, pleural effusion and extrapolmonary manifestations, including cutaneous rash, further suggest the possibility of drug-induced eosinophilic pneumonia. Therefore, a thorough investigation must be conducted for drugs taken in the weeks or days before an eosinophilic lung disease.

Although many drugs have been incriminated (www.pneumotox.com), causality has been established for approximately 20 agents. Those are mostly antibiotics (ethambutol, fenbufen, minocycline, nitrofurantoin, penicillins, pyrimethamine, sulfamides, sulfonamides, trimethoprim-sulfamethoxazole) and nonsteroidal anti-inflammatory drugs and related drugs (ace- tylsalcyclic acid, diclofenac, ibuprofen, naproxen, phenylbutazone, piroxicam, sulindac, tolfenamic acid). Other drugs can be involved, such as captopril, carbamazepine, or granulocyte-macrophage colony-stimulating factor.
An acute onset similar to the presentation to IAEP is common, especially with minocycline or nitrofurantoin, but the differential often includes chronic eosinophilic pneumonia. Presentation may be similar to that of ICEP, or have an acute onset similar to IAEP. Acute eosinophilic pneumonia may occur in the context of drug rash with eosinophilia and systemic symptoms.

Eosinophilic lung disease of varying presentation may be due to illicit drugs, especially cocaine or heroin, but also cannabis. The eosinophilia-myalgia syndrome that developed in 1989 in the United States was linked to impurities in L-tryptophan preparations in genetically susceptible hosts. One new case has been recently reported in a patient who had been taking L-tryptophan for 3 weeks, as well as other dietary supplements. The toxic-oil syndrome that affected approximately 20,000 people in Spain in 1981 is a sclerodermalike disorder characterized in the acute phase by diffuse parenchymal lung disease and possibly respiratory failure with interstitial-alveolar pattern on chest imaging and blood eosinophilia.

Radiation Therapy

A condition similar to ICEP has been reported after radiation therapy for breast cancer in women (similar to the syndrome of radiation-induced organizing pneumonia), with a median delay of 3.5 months after completion of radiotherapy. Relapse can occur after withdrawal of corticosteroid therapy.

Miscellaneous

ICEP may overlap with or mimic cryptogenic organizing pneumonia. Eosinophilia may be found in other bronchopulmonary disorders in which eosinophilic pneumonia is not prominent, including the eosinophilic phenotype of asthma, asthma with marked blood eosinophilia (ie, >1500/mm³) or “hypereosinophilic asthma,” eosinophilic bronchitis (without asthma), bronchocentric granulomatosis, isolated cases of idiopathic interstitial pneumonias (idiopathic pulmonary fibrosis/usual interstitial pneumonia, nonspecific interstitial pneumonia, and desquamative interstitial pneumonia), pulmonary Langerhans cell histiocytosis, sarcoidosis, and in lung transplant recipients.

Peripheral blood eosinophilia is an excellent diagnostic biomarker but may be absent at presentation, especially in IAEP and in patients who have already received corticosteroid treatment.

Defining the etiology of eosinophilic lung diseases has practical implications for therapeutic intervention, including interruption of a medicinal or illicit drugs, exposure to toxins, or treatment of infections with parasites or fungi. Laboratory investigations for parasites must take into account the epidemiology of parasites. Biological investigations for ABPA should be prompted by the presence of proximal bronchiectasis in patients with asthma or cystic fibrosis. When no cause is found, the eosinophilic lung disease is considered idiopathic. Extrathoracic manifestations are key to the diagnosis of EGPA. The diagnosis of ICEP or IAEP is considered only once all known causes of eosinophilia have been excluded.

Treatment of eosinophilic lung diseases involves oral corticosteroids in most cases, and withdrawal of the offending agent when appropriate. Cyclophosphamide treatment may be required in severe cases of EGPA. The development of therapies that more specifically target the differentiation, activation, or recruitment of eosinophils to the lungs is a promising new research direction for the eosinophilic lung diseases.

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