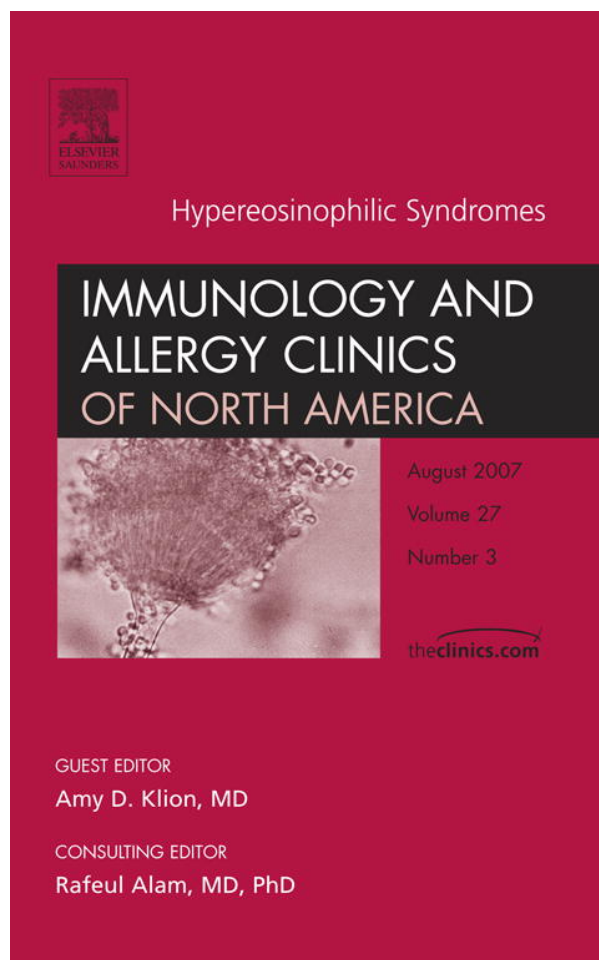




This article was published in an Elsevier journal. The attached copy is furnished to the author for non-commercial research and education use, including for instruction at the author's institution, sharing with colleagues and providing to institution administration.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>



Immunol Allergy Clin N Am
27 (2007) 477–492

IMMUNOLOGY
AND ALLERGY
CLINICS
OF NORTH AMERICA

Pulmonary Eosinophilic Syndromes

Michael E. Wechsler, MD, MMSc

*Pulmonary & Critical Care Division, Harvard Medical School,
Brigham & Women's Hospital, 15 Francis Street, Boston, MA 02115, USA*

Although eosinophils are normal constituents of the lungs, several pulmonary eosinophilic syndromes are characterized by an increased number of eosinophils in peripheral blood, in lung tissue, in sputum, in bronchoalveolar lavage (BAL) fluid, or in all of these. These pulmonary eosinophilic syndromes generally are characterized by increased respiratory symptoms, abnormal radiographic appearance, and the potential for systemic manifestations. Because the eosinophil plays such an important role in each of these syndromes, it often is difficult to distinguish between them. Nonetheless, there are important clinical and pathologic differences, and because of differences in prognosis and treatment paradigms, it is important to understand and appreciate the distinguishing features of each of these conditions. This article focuses on the clinical manifestations of these syndromes, ways to distinguish between them, and on the general diagnostic approach to the patient eosinophilia and lung disease.

Classifying pulmonary eosinophilic syndromes and general approach

Eosinophilia is a feature of many different lung diseases. In some conditions, eosinophils are increased in the blood but not in the lung tissue; in other diseases, there may be significant eosinophilia in the lung tissue but not in the peripheral blood. In others, there may be lung eosinophilia without any radiographic evidence of disease. Because eosinophilia is a prominent feature of so many different diseases, the first step in classifying pulmonary eosinophilic syndromes is distinguishing between primary pulmonary eosinophilic lung disorders and those in which eosinophilia is secondary to a specific cause such as a drug reaction, an infection, a malignancy, or another pulmonary condition such as asthma. **Box 1** lists primary and secondary pulmonary eosinophilic disorders, the former of which are the main focus of this article.

E-mail address: mwechsler@rics.bwh.harvard.edu

Box 1. Pulmonary eosinophilic syndromes*Primary pulmonary eosinophilic disorders*

Acute eosinophilic pneumonia
Chronic eosinophilic pneumonia
Churg-Strauss syndrome
Hypereosinophilic syndrome

Pulmonary disorders of known cause associated with eosinophilia

Asthma and eosinophilic bronchitis
Allergic bronchopulmonary aspergillosis
Bronchocentric granulomatosis
Drug/toxin reaction
Infection

- Parasitic/helminthic disease
 - Löffler's syndrome
 - Tropical pulmonary eosinophilia
 - Ascaris
 - Paragonimus
 - Strongyloides
 - Trichinosis
- Nonparasitic infection
 - Tuberculosis
 - Coccidioides

Lung diseases associated with eosinophilia

Bronchiolitis obliterans organizing pneumonia
Hypersensitivity pneumonitis
Idiopathic pulmonary fibrosis
Pulmonary Langerhans cell granulomatosis

Malignant neoplasms associated with eosinophilia

Leukemia
Lymphoma
Lung cancer
Adenocarcinoma of various organs
Squamous cell carcinoma of various organs

Systemic disease associated with eosinophilia

Postradiation pneumonitis
Rheumatoid arthritis
Sarcoidosis
Sjögren's syndrome

For each patient, a detailed history is of utmost importance and can help elucidate the origin of the underlying disease. Details regarding onset, timing, and precipitants of specific symptoms can help distinguish one diagnosis from another. History regarding pharmacologic, occupational, and environmental exposures is instructive, and family and travel history is crucial. In addition to details about the sinuses and lungs, it is important to inquire about systemic manifestations and to assess for physical findings of cardiac, gastrointestinal, neurologic, dermatologic, and genitourinary involvement, all of which may give clues to specific diagnoses. Once the details from history and physical examination are teased out, laboratory testing (including measurements of blood eosinophils, cultures, and markers of inflammation), spirometry, and radiographic imaging can help distinguish between different diseases. Often, however, BAL or transbronchial or open lung biopsies are required. In many cases, biopsies or noninvasive diagnostic studies of other organs (eg, echocardiogram, electromyogram) can be helpful.

Acute eosinophilic pneumonia

First described in the 1980s, acute eosinophilic pneumonia is a syndrome characterized by fevers, acute respiratory failure that often requires mechanical ventilation, diffuse pulmonary infiltrates (Fig. 1), and pulmonary eosinophilia in a previously healthy individual (Box 2) [1,2].

Clinical features and etiology

At presentation, acute eosinophilic pneumonia often is mistaken for acute lung injury or acute respiratory distress syndrome until BAL is performed and reveals more than 25% eosinophils. The predominant symptoms of acute eosinophilic pneumonia are cough, dyspnea, malaise, myalgias, night sweats, and pleuritic chest pain. Findings on physical examination include high fevers, basilar rales, and rhonchi on forced expiration. Acute eosinophilic



Fig. 1. Diffuse pulmonary infiltrates in a patient who has acute eosinophilic pneumonia.

Box 2. Diagnostic criteria of acute eosinophilic pneumonia

Acute febrile illness with respiratory manifestations of more than 1 month's duration
Hypoxemic respiratory failure
Diffuse pulmonary infiltrates on chest radiograph
BAL eosinophilia > 25%
Absence of parasitic, fungal, or other infection
Absence of drugs known to cause pulmonary eosinophilia
Quick clinical response to corticosteroids
Failure to relapse after discontinuation of corticosteroids

pneumonia most often affects men between ages of 20 and 40 years who have no history of asthma. Although no clear etiology has been identified, several case reports have linked acute eosinophilic pneumonia to recent initiation of tobacco smoking or exposure to other environmental stimuli including dust from indoor renovations [3] or even World Trade Center dust [4].

Laboratory and radiologic features

In addition to a suggestive history, the key to establishing a diagnosis of acute eosinophilic pneumonia is the presence of more than 25% eosinophilia in BAL fluid. Lung biopsies show eosinophilic infiltration with acute and organizing diffuse alveolar damage, but it generally is not necessary to proceed to biopsy to establish a diagnosis [5]. Although patients present with an elevated white blood cell count, in contrast to other pulmonary eosinophilic syndromes, acute eosinophilic pneumonia often is not associated with peripheral eosinophilia on presentation. Peripheral eosinophilia often occurs, however, between 7 and 30 days after disease onset, with mean eosinophil counts of 1700 cells/mm³ [3]. The erythrocyte sedimentation rate (ESR) and C-reactive protein and IgE levels are high but nonspecific; high-resolution CT is always abnormal with bilateral random patchy, ground-glass, or reticular opacities and small pleural effusions in as many as two thirds of patients [6]. Pleural fluid is characterized by a high pH with marked eosinophilia. Pulmonary function testing is notable for a restrictive defect with a reduced diffusion capacity.

Clinical course and response to therapy

Although some patients improve spontaneously [3], most patients require admission to an ICU and respiratory support with either invasive (intubation) or noninvasive mechanical ventilation. What distinguishes acute eosinophilic pneumonia from other cases of acute lung injury and from some of the other pulmonary eosinophilic syndromes is the absence of organ dysfunction or multisystem organ failure other than respiratory failure. One

of the other characteristic features of acute eosinophilic pneumonia is the high degree of corticosteroid responsiveness and the excellent prognosis. Another distinguishing feature of acute eosinophilic pneumonia is the complete clinical and radiographic recovery without recurrence or residual sequelae that occurs in almost all patients within several weeks of initiation of therapy.

Chronic eosinophilic pneumonia

In contrast to acute eosinophilic pneumonia, chronic eosinophilic pneumonia is a more indolent syndrome that is characterized by pulmonary infiltrates and eosinophilia in both the tissue and blood (Box 3) [7]. Most patients are female nonsmokers with a mean age of 45 years, and patients usually do not develop the acute respiratory failure and significant hypoxemia seen in acute eosinophilic pneumonia [5]. As in Churg-Strauss syndrome (CSS), most patients have asthma, and many have a history of allergies. The airflow obstruction tends to worsen with disease activity but responds to corticosteroids.

Clinical and radiographic features

Patients present with a subacute illness over weeks to months, with cough, low-grade fevers, progressive dyspnea, weight loss, wheezing, malaise, night sweats, and a chest radiograph with migratory bilateral, peripheral, or pleural-based opacities. Although this “photographic-negative pulmonary edema” appearance on chest radiograph and chest CT is pathognomonic of chronic eosinophilic pneumonia, fewer than 25% of patients present with this finding (Fig. 2) [8]. Other radiographic findings include atelectasis, pleural effusions, lymphadenopathy, and septal line thickening [9].

Laboratory features

Almost 90% of patients have peripheral eosinophilia with mean eosinophil counts of more than 30% of the total white blood cell count [10]. BAL eosinophilia is also an important distinguishing feature with mean BAL eosinophil counts close to 60%. Both peripheral and BAL eosinophilia are very responsive to treatment with corticosteroids. Other laboratory features of chronic eosinophilic pneumonia include increased ESR, C-reactive protein, platelets,

Box 3. Chronic eosinophilic pneumonia

1. Respiratory symptoms of usually more than 2 weeks' duration
2. BAL and/or blood eosinophilia
3. Pulmonary infiltrates (often with a peripheral predominance on chest imaging)
4. Exclusion of any known cause of eosinophilic lung disease.

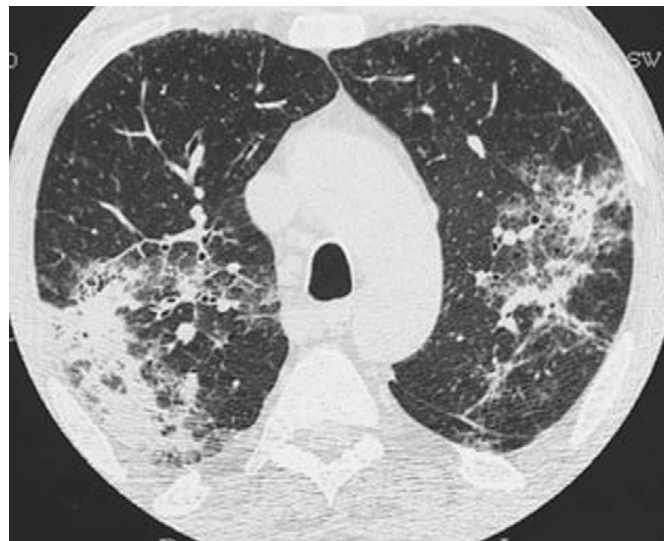


Fig. 2. Peripheral pulmonary infiltrates in a patient who has chronic eosinophilic pneumonia. (From Cottin V, Cordier JF. Eosinophilic pneumonias. *Allergy* 2005;60:844; with permission.)

and IgE. Often lung biopsy is not required to establish a diagnosis but may show accumulation of eosinophils and histiocytes in the lung parenchyma and interstitium, as well as bronchiolitis obliterans organizing pneumonia, but with minimal fibrosis (Fig. 3).

Systemic manifestations and treatment response

Similar to acute eosinophilic pneumonia, nonrespiratory manifestations are uncommon, but arthralgias, neuropathy, and skin and gastrointestinal symptoms have been reported [5]; their presence may suggest CSS or hyper-eosinophilic syndrome (HES). Another similarity is the rapid response to corticosteroids with quick resolution of peripheral and BAL eosinophilia

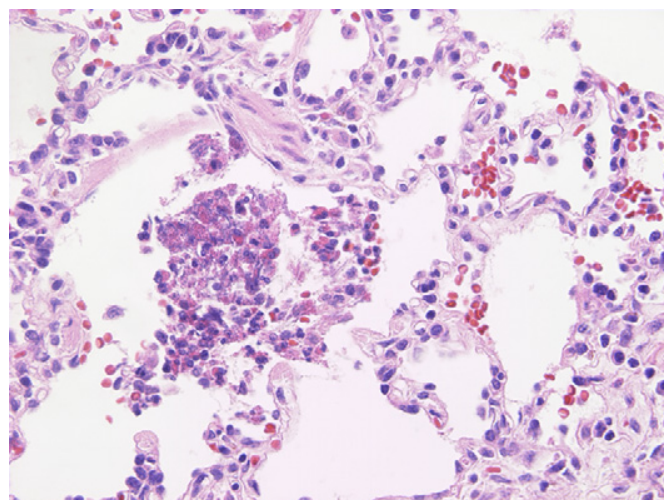


Fig. 3. Accumulation of intra-alveolar eosinophils in chronic eosinophilic pneumonia (hematoxylin and eosin, original magnification $\times 40$). (Courtesy of Yadira Sanchez and Sara Vargas, Boston Children's Hospital, Boston, MA.)

and improvement in symptoms. In contrast to acute eosinophilic pneumonia, however, more than 50% of patients relapse, and many require prolonged courses of corticosteroids for months to years [10].

Churg-Strauss syndrome

Also known as “allergic angiitis granulomatosis,” CSS is a complex syndrome characterized by eosinophilic vasculitis that may involve multiple organ systems including the lungs, heart, skin, gastrointestinal tract, and nervous system. Although CSS is characterized by peripheral and pulmonary eosinophilia with infiltrates on chest radiograph, the primary features that distinguish CSS from other pulmonary eosinophilic syndromes are the presence of eosinophilic vasculitis in the setting of asthma and the involvement of multiple end organs (a feature it shares with HES). Although perceived to be quite rare, the incidence of this disease seems to have increased in the last few years, particularly in association with various asthma therapies [11].

Diagnostic criteria

Diagnostic criteria have included both clinical and pathologic features (Box 4), but the criteria most commonly used to describe CSS are those adopted by the American College of Rheumatology in 1990 [12]. These criteria include both clinical and pathologic features and define CSS as the presence of four of the following six features: asthma, eosinophilia, neuropathy, pulmonary infiltrates, paranasal sinus abnormality, and presence of eosinophilic vasculitis (Fig. 4).

Clinical features

CSS occurs with equal frequency in men and women and typically occurs in several phases [13]. The prodromal phase is characterized by asthma and allergic rhinitis and usually begins when the individual is in his/her 20s or 30s, typically persisting for many years. The eosinophilic infiltrative phase is characterized by peripheral eosinophilia and eosinophilic tissue infiltration of various organs including the lungs and gastrointestinal tract. The third phase is the vasculitic phase and may be associated with constitutional signs and symptoms including fever, weight loss, malaise, and fatigue. The mean age at time of diagnosis is 48 years with a range of 14 to 74 years; the average length of time between diagnosis of asthma and vasculitis is 9 years [14].

Similar to other pulmonary eosinophilic syndromes, constitutional symptoms are common in CSS and include weight loss of 10 to 20 lb, fevers, and diffuse myalgias and migratory polyarthralgias. Myositis may be present with evidence of vasculitis on muscle biopsies. In contrast to the eosinophilic pneumonias, CSS involves many organ systems including the lungs, skin, nerves, heart, gastrointestinal tract, and kidneys.

Box 4. Criteria used in diagnosis of Churg-Strauss syndrome*Churg and Strauss, 1951*

1. Asthma
2. Necrotizing vasculitis of small and medium arteries and veins
3. Eosinophil infiltration around involved vessels and tissues
4. Extravascular granulomas
5. Fibrinoid necrosis of involved tissues

Lanham, 1984

1. Asthma
2. Eosinophilia $> 1.5 \times 10^7$
3. Systemic vasculitis involving two or more organs

American College of Rheumatology, 1990

1. Asthma
2. Eosinophilia $> 10\%$
3. Neuropathy
4. Pulmonary infiltrates
5. Paranasal sinus abnormality
6. Extravascular eosinophil infiltration on biopsy

Chapel Hill, 1994

1. Asthma
2. Eosinophilia
3. Eosinophil-rich granulomatous inflammation involving the respiratory tract
4. Necrotizing vasculitis affecting small- to medium-sized vessels

Data from Wechsler ME, Pauwels R, Drazen JD. Leukotriene modifiers and Churg-Strauss syndrome: adverse effect or response to corticosteroid withdrawal? Drug Saf 1999;21:241–51.

Respiratory. Almost all patients who have CSS have asthma that arises in adulthood with a mean age of onset of 35 years. It often occurs in individuals who have no family history of atopy. The asthma is usually severe; oral corticosteroids often are required to control symptoms but may lead to suppression of vasculitic symptoms. Although the severity of asthma may increase as the underlying disease progresses, asthma symptoms may abate in some instances as the vasculitis becomes manifest. Common symptoms include cough, dyspnea, sinusitis, and allergic rhinitis; alveolar hemorrhage and hemoptysis also may occur.

Neurologic. More than three fourths of patients who have CSS have neurologic manifestations [14]. Mononeuritis multiplex often involves the

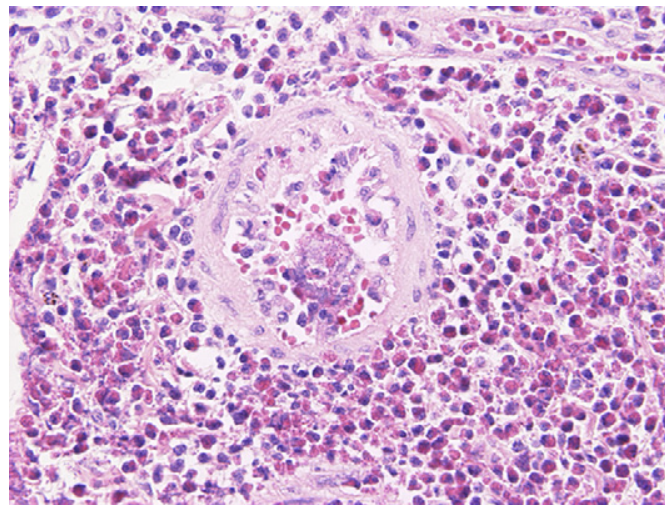


Fig. 4. Eosinophilic vasculitis in the lung of a patient who has Churg-Strauss syndrome. (Courtesy of Yadira Sanchez and Sara Vargas, Boston Children's Hospital, Boston, MA.)

peroneal nerve but also can affect the ulnar, radial, internal popliteal, and, occasionally, cranial nerves. Polyneuropathy often develops in the absence of treatment and may be symmetric or asymmetric. Cerebral hemorrhage and infarction can be important causes of death in these patients. Despite treatment, neurologic sequelae are common.

Dermatologic. Approximately half of patients who have CSS develop dermatologic manifestations. These manifestations include palpable purpura, skin nodules, urticarial rashes, and livedo.

Cardiovascular. The heart is a primary target organ in CSS, and heart involvement often portends a worse prognosis [13]. Granulomas, vasculitis, and widespread myocardial damage may be found on biopsy or at autopsy. Cardiomyopathy and heart failure may be seen in up to half of all patients but often are at least partially reversible. Acute pericarditis, constrictive pericarditis, myocardial infarction, and other electrocardiographic changes may occur.

Gastrointestinal. Eosinophilic infiltration of the gastrointestinal tract may result in abdominal pain, diarrhea, gastrointestinal bleeding, and colitis. Ischemic bowel, pancreatitis, and cholecystitis also have been reported in association with CSS and usually portend a worse prognosis [15].

Renal. Renal involvement is more common than once thought. Approximately 25% of patients have some degree of renal involvement that may include proteinuria, glomerulonephritis, renal insufficiency, and, rarely, renal infarct. Systemic hypertension also is common.

Laboratory abnormalities

Eosinophilia greater than 10% is one of the defining features of this illness and may be as high as 75% of the peripheral white blood cell count. It is present at the time of diagnosis in more than 80% of subjects but may respond quickly (often within 24 hours) to initiation of systemic corticosteroid therapy. Even in the absence of systemic eosinophilia, tissue eosinophilia may be present.

Although not specific to CSS, antineutrophil cytoplasmic antibodies (ANCA), mostly with a perinuclear staining pattern, are present in up to two thirds of patients [16]. Nonspecific laboratory abnormalities that may be present in patients who have CSS include a marked elevation in ESR, a normochromic normocytic anemia, an elevated IgE, hypergammaglobulinemia, and positive rheumatoid factor and antinuclear antibodies. BAL often reveals significant eosinophilia, but this sign may be seen in the other eosinophilic lung diseases. Pulmonary function testing often reveals an obstructive defect similar to asthma.

Radiographic features

Chest radiographic abnormalities are extremely common in CSS and consist of bilateral, nonsegmental, patchy infiltrates that often migrate and may be interstitial or alveolar in appearance. Reticulonodular and nodular disease without cavitation can be seen, as can pleural effusions and hilar adenopathy. The most common CT findings include bilateral ground-glass opacity and airspace consolidation that is predominantly subpleural [17]. Other CT findings include bronchial wall thickening, hyperinflation, interlobular septal thickening, lymph node enlargement, and pericardial and pleural effusions. Angiography may be used diagnostically and may show signs of vasculitis in the coronary, central nervous system, and peripheral vasculature.

Etiology and pathologic features of Churg-Strauss syndrome

Like other pulmonary eosinophilic syndromes, the exact etiology of CSS is unknown. CSS probably represents an autoimmune process because of the prominence of allergic features and the presence of immune complexes, heightened T-cell immunity, and altered humoral immunity, as evidenced by elevated levels of serum IgE and rheumatoid factor. The presence of ANCA in about half of patients also suggests an immune-mediated mechanism. Although the exact role of ANCA in CSS and other vasculitides remains unclear, the binding of ANCA to vascular walls is thought to contribute to vascular inflammation and injury as well as to chemotaxis of inflammatory cells. CSS has been associated with various asthma therapies, including leukotriene modifiers [18,19] and inhaled corticosteroids [20], but no causal link has been established. It seems either that the syndrome occurs coincidentally to the use of these medications or that these medications facilitate systemic steroid withdrawal that unmasks the syndrome.

Pathologically, CSS is characterized by tissue infiltration by eosinophils, extravascular granulomas, and necrotizing vasculitis, which may occur in isolation or may coexist and commonly are found in the lungs, heart, skin, muscle, liver, spleen, and kidneys. The eosinophilic vasculitis predominantly affects small and medium-sized arteries and veins and may include fibrinoid necrosis and thrombosis. Granulomas are not seen in many patients but when present are peri- or extravascular and are characterized by degenerated eosinophils with necrotic collagen at the center, surrounded by epithelioid cells and giant cells.

Treatment and prognosis of Churg-Strauss syndrome

Most patients diagnosed as having CSS have been diagnosed previously as having asthma, rhinitis, and sinusitis and have received treatment for these disorders with inhaled or systemic corticosteroids. In patients who have CSS but who are perceived to have severe asthma, these therapies may delay the diagnosis of CSS by masking the signs of vasculitis. Corticosteroids dramatically alter the course of CSS: up to 50% of those who are untreated die within 3 months of diagnosis [21], but in treated patients the 6-year survival rate exceeds 70% [14]. Common causes of death include heart failure, cerebral hemorrhage, renal failure, and gastrointestinal bleeding. Recent data suggest that clinical remission may be obtained in more than 90% of patients treated. Approximately 25% of those patients may relapse, often because of corticosteroid tapering; a rising eosinophil count heralds the relapse [14]. Myocardial, gastrointestinal, and renal involvement most often portends a poor prognosis. In such cases, treatment with higher doses of corticosteroids or the addition of cytotoxic agents such as cyclophosphamide often is warranted. Although survival does not differ between those treated or not treated with cyclophosphamide, treatment is associated with a reduced incidence of relapse and an improved clinical response to treatment [15]. Other therapies that have been used successfully in the management of CSS include azathioprine, methotrexate, mycophenolate, intravenous gamma globulin, and interferon alpha. Plasma exchange has not been shown to provide any additional benefit [14].

Hypereosinophilic syndrome

A detailed overview of the main HES (those not primarily involving the lung) is given elsewhere in this volume. Briefly, HES constitutes a heterogeneous group of disease entities manifest by persistent eosinophilia in excess of 1500 eosinophils/mm³ in association with end-organ damage or dysfunction, in the absence of secondary causes of eosinophilia [22]. In addition to familial, undefined, and overlap syndromes with incomplete criteria, the predominant HES subtypes are the myeloproliferative and lymphocytic variants (Box 5). The myeloproliferative variant may be divided into three subgroups: (1) chronic eosinophilic leukemia with demonstrable cytogenetic

Box 5. Hypereosinophilic syndromes*Myeloproliferative variants*

Etiology unknown

PDGFRA-associated HES

Chronic eosinophilic leukemia

Lymphocytic variants

Familial

Undefined

- Benign
- Complex
- Episodic

*Overlap/organ-restricted eosinophilic disorders (including eosinophilic pneumonia)**Associated conditions (including CSS)*

abnormalities and/or blasts on peripheral smear; (2) the PDGFRA-associated HES attributed to a constitutively activated tyrosine kinase fusion protein (Fip1L1-PDGFR α) caused by a chromosomal deletion on 4q12; and (3) the FIP1-negative variant associated with eosinophilia and at least four of the following: dysplastic peripheral eosinophils, increased serum B₁₂, increased tryptase, anemia, thrombocytopenia, splenomegaly, bone marrow cellularity in excess of 80%, spindle-shaped mast cells, and myelofibrosis. In the lymphocytic variant, hypereosinophilia seems to occur in response to the production of eosinophilopoietic cytokines, particularly interleukin-5, by clonal populations of phenotypically abnormal, activated T lymphocytes [23]. In these patients T-cell receptor rearrangement analysis often demonstrates T-cell clonality, and serum IgE and thymus- and activation-regulated chemokine levels are elevated.

Extrapulmonary manifestations of hypereosinophilic syndrome

More common in men than in women, HES occurs between the ages of 20 and 50 years and is characterized by significant extrapulmonary involvement, including infiltration of the heart, gastrointestinal tract, kidney, liver, joints, and skin. Cardiac involvement includes myocarditis and/or endomyocardial fibrosis, as well as a restrictive cardiomyopathy [23].

Pulmonary manifestations of hypereosinophilic syndrome

As in other pulmonary eosinophilic syndromes, patients who have HES manifest high levels of blood, BAL, and tissue eosinophilia. Lung involvement occurs in 40% of these patients and is characterized by cough, dyspnea, and pulmonary infiltrates [5]. Although it often is difficult to discern

the pulmonary infiltrates and effusions seen on chest radiography from pulmonary edema resulting from cardiac involvement, findings on CT scan include interstitial infiltrates, ground-glass opacities, and small nodules. HES typically is not associated with ANCA.

Course and response to therapy

Unlike the other pulmonary eosinophilic syndromes, less than half of patients who have HES respond to corticosteroids as first-line therapy. Treatment options include hydroxyurea, cyclosporine, and interferon, but imatinib has emerged as an important therapeutic option for patients who have the myeloproliferative variant. Anti-interleukin-5 therapy with mepolizumab also holds promise for these patients and is being investigated currently.

Diagnosis and differential diagnosis of pulmonary eosinophilic syndromes

The key to managing the pulmonary eosinophilic syndromes is establishing a firm diagnosis. The first step in this process is excluding secondary causes of pulmonary eosinophilia, as listed in [Box 1](#). One must exclude one of the many medications or toxins that have been associated with eosinophilic lung diseases. One must rule out parasitic involvement caused by infestation by nematodes such as *Ascaris* and *Strongyloides* and other parasites that can cause tropical eosinophilia or Löffler's syndrome. One must exclude *Aspergillus* colonization that may be associated with allergic bronchopulmonary aspergillosis, as well as infection with other micro-organisms. Finally, one must take a careful history and perform a detailed evaluation to exclude malignancies, other systemic conditions such as sarcoidosis, and other lung diseases such as pulmonary fibrosis and bronchiolitis obliterans, each of which may present with eosinophilia.

Because all of the pulmonary eosinophilic syndromes are characterized by blood and BAL eosinophilia as well as pulmonary infiltrates, it can be difficult to differentiate between them. Indeed, it often is speculated that all these conditions are related and on a continuum, with some unknown mechanism responsible for targeting eosinophils and their toxins to specific organs, such as the lung. Nonetheless, one can often establish a diagnosis by using a combination of clinical, laboratory, pathologic, and radiographic criteria ([Table 1](#)).

For instance, isolated pulmonary involvement with peripheral eosinophilia is associated with either acute or chronic eosinophilic pneumonias, depending on the relative acuity of symptoms. Generally, the presence of ANCA or vasculitis and eosinophilia in an individual who has airway obstruction is sufficient for a diagnosis of CSS. Patients who have HES have eosinophilia with multiorgan involvement and may present in a manner similar to CSS; however, these entities are not associated with vasculitis and often do not have asthma as a primary disease feature. Bronchoscopy with

Table 1
Distinguishing features of various eosinophilic lung diseases

Feature	Acute eosinophilic pneumonia	Chronic eosinophilic pneumonia	Churg-Strauss syndrome	Hypereosinophilic syndrome
Onset	Acute (days)	Indolent (weeks/months)	Indolent (months/years)	Indolent (months/years)
Imaging	Diffuse	Peripheral	Patchy	Patchy
Fulminant respiratory failure	++	—	—	—
Asthma/allergy history	—	+	++	—
Smoking history	+	—	—	—
Vasculitis	—	—	++	—
Antineutrophil cytoplasmic antibody	—	—	+	—
Cardiac involvement	—	±	+	++
Neurologic	—	±	++	++
Requirement for therapies other than corticosteroids	—	—	+	++

Abbreviations: —, rarely occurs; +/—, occasionally occurs; +, commonly occurs; ++, occurs most of the time.

BAL should be considered in cases of lung disease with eosinophilia. If the BAL is unrevealing, consideration should be given to obtaining lung tissue by means of a transbronchial or open-lung biopsy, depending on the clinical and radiographic findings. Video-assisted thoracoscopic surgery (VATS) can substitute for a thoracotomy to provide tissue. If disease is more parenchymal and peripheral, a transbronchial biopsy is less likely to be revealing, and VATS or a limited thoracotomy should be considered.

Although a biopsy specimen often can help tease out differences, non-invasive surrogates including CT scan, electromyogram, nerve conduction studies, or other blood tests often can be used to establish a diagnosis. Once the proper diagnosis is established, one can treat the specific disease entity appropriately. Work-up of the patient who has eosinophilia and lung disease thus should include the following laboratory studies: complete blood cell count with differential, ESR, C-reactive protein, ANCA, vitamin B₁₂, immunoglobulins including IgE, electrolytes and liver enzymes, tryptase, urinalysis, stool assessment for ova and parasites, and strong consideration of bone marrow analysis. All organ systems should be evaluated including consideration of the following: dilated eye examination, EKG, echocardiogram, pulmonary function studies, detailed skin, vascular, and neurologic

examinations, and consideration of imaging of specific organs such as the lungs, heart, kidney, and gastrointestinal tract.

Summary

Pulmonary eosinophilic syndromes are a heterogeneous group of disorders that are associated with peripheral blood and/or tissue eosinophilia. It is critical to make a quick diagnosis and to treat aggressively with corticosteroids and other therapies to prevent long-term sequelae. Establishing a diagnosis is facilitated by the use of noninvasive and invasive markers and by judicious use of CT scans and other tests.

References

- [1] Badesch DB, King TE, Schwarz MI. Acute eosinophilic pneumonia: a hypersensitivity phenomenon. *Am Rev Respir Dis* 1989;139:249–52.
- [2] Allen JN, Pacht ER, Gadek JE, et al. Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. *N Engl J Med* 1989;321:569–74.
- [3] Philit F, Etienne-Mastroianni B, Parrot A, et al. Idiopathic acute eosinophilic pneumonia: a study of 22 patients. The Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires (GERMO'P). *Am J Respir Crit Care Med* 2002;166:1235–9.
- [4] Rom WN, Weiden M, Garcia R, et al. Acute eosinophilic pneumonia in a New York City firefighter exposed to World Trade Center dust. *Am J Respir Crit Care Med* 2002;166:797–800.
- [5] Cottin V, Cordier JF. Eosinophilic pneumonias. *Allergy* 2005;60:841–57.
- [6] Cheon JE, Lee KS, Jung GS, et al. Acute eosinophilic pneumonia: radiographic and CT findings in six patients. *Am J Roentgenol* 1996;167:1195–9.
- [7] Carrington CB, Addington WW, Goff AM, et al. Chronic eosinophilic pneumonia. *N Engl J Med* 1969;280:787–98.
- [8] Jederlinic PJ, Sicilian L, Gaensler EA. Chronic eosinophilic pneumonia. A report of 19 cases and a review of the literature. *Medicine (Baltimore)* 1988;67:154–62.
- [9] Arakawa H, Kurihara Y, Niimi H, et al. Bronchiolitis obliterans with organizing pneumonia versus chronic eosinophilic pneumonia: high-resolution CT findings in 81 patients. *Am J Roentgenol* 2001;176:1053–8.
- [10] Marchand E, Reynaud-Gaubert M, Lauque D, et al. Idiopathic chronic eosinophilic pneumonia. A clinical and follow-up study of 62 cases. The Groupe 'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires (GERMO'P). *Medicine (Baltimore)* 1998;77:299–312.
- [11] Wechsler ME, Pauwels R, Drazen JD. Leukotriene modifiers and Churg-Strauss syndrome: adverse effect or response to corticosteroid withdrawal? *Drug Saf* 1999;21:241–51.
- [12] Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum* 1990;33(8):1094–100.
- [13] Lanham JG, Elkon KB, Pusey CD, et al. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine* 1983;63:65–81.
- [14] Guillevin L, Cohen P, Gayraud M, et al. Churg-Strauss syndrome: clinical study and long-term follow-up of 96 patients. *Medicine* 1999;78:26–37.
- [15] Conron M, Beynon HLC. Churg-Strauss syndrome. *Thorax* 2000;55:870–7.
- [16] Hagen EC, Daha MR, Hermans J, et al. The diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. *Kidney Int* 1998;53:743–53.

- [17] Choi YH, Im JG, Han BK, et al. Thoracic manifestations of Churg-Strauss syndrome. *Chest* 2000;117:117–24.
- [18] Wechsler ME, Garpestad E, Flier SR, et al. Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. *JAMA* 1998;279:455–7.
- [19] Wechsler ME, Finn D, Gunawardena D, et al. Churg-Strauss syndrome in patients receiving montelukast as treatment for asthma. *Chest* 2000;117:708–13.
- [20] Le Gall C, Pham S, Vignes S, et al. Inhaled corticosteroids and Churg-Strauss syndrome: a report of five cases. *Eur Respir J* 2000;15(5):978–81.
- [21] Allen JN, Davis WB. Eosinophilic lung diseases. *Am J Respir Crit Care Med* 1994;150:1423–38.
- [22] Klion AD, Bochner BS, Gleich GJ, et al. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. *J Allergy Clin Immunol* 2006;117:1292–302.
- [23] Klion AD. Recent advances in the diagnosis and treatment of hypereosinophilic syndromes. *Hematology* 2005;209–14.