patients. There is a high procedure-related mortality for lung transplantation in SCD patients.

Sudden death in SCLD patients with pulmonary hypertension is common due to pulmonary thromboembolism, systemic hypotension, and cardiac arrhythmia. The mortality of patients with pulmonary hypertension is seven times greater than that of SCD patients without pulmonary hypertension. The mean survival of SCD patients with chronic lung disease and elevated pulmonary artery pressures can be as little as 2 years.


Further Reading


Eosinophilic Lung Diseases

J P Lynch III, M C Fishbein, and R D Suh, The David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

© 2006 Elsevier Ltd. All rights reserved.

Abstract

Eosinophilic lung diseases are a diverse group of disorders characterized by eosinophilic infiltration of the airways or lung parenchyma, with or without extrapulmonary involvement. Some pulmonary eosinophilic disorders are due to specific causes or exposures (e.g., parasitic, fungal, or mycobacterial infections; hematological or solid malignancies; connective tissue disorders; drugs; environmental exposures) whereas in others no cause or inciting factor is recognized. Eosinophils are pro-inflammatory and may cause tissue injury, but may also be helpful to eradicate parasites or specific infections. Irrespective of cause, clinical, pathologic, and radiographic features of eosinophilic syndromes overlap extensively. In this article, we discuss the salient clinical features and management of the following pulmonary eosinophilic syndromes: tropical pulmonary eosinophilia, a hypersensitivity response caused by parasites (helminths); acute eosinophilic pneumonia due to other infectious causes (e.g., mycobacteria, fungi, Pneumocystis carinii); idiopathic eosinophilic pneumonias, which comprise simple pulmonary eosinophilia, acute eosinophilic pneumonia, and chronic eosinophilic pneumonia; allergic angitis and granulomatosis (Churg-Strauss syndrome); allergic bronchopulmonary aspergillosis; idiopathic hypersensitivity pneumonitis; eosinophilia-myalgia syndrome; and toxic oil syndrome.

Introduction

Eosinophilic lung diseases are a diverse group of disorders characterized by eosinophilic infiltration of the airways or lung parenchyma, with or without extrapulmonary involvement. Eosinophilic lung diseases were first described as ‘PIE’ syndromes, or pulmonary infiltrates with (blood) eosinophilia. Subsequently, pulmonary eosinophilic disorders without blood eosinophilia were recognized. Some pulmonary eosinophilic disorders are due to specific causes or exposures (e.g., parasitic, fungal, or mycobacterial infections; hematological or solid malignancies; connective tissue disorders; drugs; and environmental exposures) whereas in others no cause
or inciting factor is recognized. Eosinophils are pro-inflammatory and may cause tissue injury, but may also be helpful in eradicating parasites or specific infections. Irrespective of cause, clinical, pathologic, and radiographic features of eosinophilic syndromes overlap extensively.

Pathogenesis of Eosinophilic Lesions

Eosinophils are derived from myeloid progenitors in bone marrow, via the action of three hematopoietic cytokines, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), and IL-5. T-helper type 2 (Th2) lymphocytes orchestrate the recruitment of eosinophils (and other effector cells) by releasing cytokines such as IL-4, IL-5, and IL-13. IL-4 is required for class switching from immunoglobulin G (IgG) to IgE. IL-5, in association with IL-3 and GM-CSF, regulates eosinophil proliferation. Following IgE-triggered activation, mast cells may promote eosinophilic inflammation of the airways by producing proinflammatory cytokines. In several types of eosinophilic pneumonias, elevations in serum IgE, activated CD4 T cells, CC chemokines (e.g., eotaxin, monocyte chemoattractant protein-1 (MCP-1), thymus- and activation-regulated chemokine (TARC), and CCR4), Th2 cytokines (e.g., IL-5, IL-13, IL-10), and interferon-γ-inducing factor (IL-18) have been found, suggesting their importance in the pathogenesis of these disorders. The release of constituents of eosinophilic granules such as major basic protein (MBP), eosinophilic cationic protein (ECP), eosinophil-derived neurotoxins, reactive oxygen radicals, and proinflammatory cytokines may cause tissue injury. The life span of eosinophils in tissue is prolonged by IL-3, IL5, or GM-CSF, which inhibit apoptosis. In addition, tissue eosinophils can regulate their own survival through an autocrine pathway.

Pulmonary Eosinophilia due to Specific Causes

Eosinophilic pneumonia may be a response to infection (most commonly helminthic), as a reaction to drugs, chemotherapy, or radiation therapy, or in the context of atopy, allergies, asthma, connective tissue disease, or malignancy. Given the space constraints of this article, our discussion is limited to a few specific forms of eosinophilic pneumonias (discussed below).

Pulmonary Eosinophilia due to Parasitic Infections

Worldwide, helminthic infections are the most common cause of pulmonary and blood eosinophilia. Tropical pulmonary eosinophilia (TPE) is a hypersensitivity response caused by the filarial worms Wuchereria bancrofti or Brugia malayi, which are endemic in India, Africa, South America, and South East Asia. With increasing travel and immigration, TPE may occur even in nonendemic regions. In this context, an erroneous diagnosis of asthma is often made. Laboratory findings include high levels of serum IgE and eosinophilia in blood and bronchoalveolar lavage fluid (BALF). Microfilariae can be found in lung, liver, or lymph nodes in affected patients. Treatment with diethylcarbamazine (6–12 mg kg⁻¹ day⁻¹ in three divided doses for 1–3 weeks) is highly effective. Untreated TPE can lead to progressive pulmonary fibrosis and respiratory failure. Other less common parasites that might evoke pulmonary eosinophilia include Schistosoma, Trichinella spiralis, Paragonimus westermanni, Echinococcus granulosus, Dirofilaria immitis, Clonorchis sinensis, and Opisthorchis. Although parasitic infections are rare in the US, Strongyloides, Ascaris, Toxocara, and Ancylostoma may be implicated in eosinophilic lung disorders.

Acute Eosinophilic Pneumonia due to Other Infectious Causes

Acute eosinophilic pneumonia (AEP) may complicate infections due to mycobacteria, fungi (e.g., Coccidioides immitis or Histoplasma capsulatum), or Pneumocystis jiroveci (formerly P. carinii). These causes should always be excluded before accepting the diagnosis of ‘idiopathic’ AEP.

Idiopathic Eosinophilic Pneumonias

The idiopathic eosinophilic pneumonias include simple pulmonary eosinophilia, chronic eosinophilic pneumonia (CEP), and AEP.

Simple Pulmonary Eosinophilia (Loeffler’s Syndrome)

Simple pulmonary eosinophilia (also termed Loeffler’s syndrome) is characterized by migratory, patchy pulmonary opacities, peripheral blood eosinophilia, and few or no respiratory symptoms (Figure 1). The course is self limited. Given the mild and transient nature of this condition, treatment is not warranted.

Idiopathic Chronic Eosinophilic Pneumonia

CEP is a rare disorder of uncertain etiology characterized by cough, wheezing, migratory alveolar infiltrates, constitutional symptoms, and peripheral blood eosinophilia.
Etiology  The cause is unknown, but a heightened allergic diathesis likely plays a contributory role.

Histopathological features Lung biopsies in CEP demonstrate dense aggregates of eosinophils, histiocytes, and multinucleated giant cells within bronchioles and alveolar spaces and septa (Figures 2–4). Additional features include intra-alveolar eosinophilic abscesses, degenerating necrotic eosinophils, Charcot–Leyden crystals, alveolar macrophages containing eosinophilic fragments, foci of organizing pneumonia, scattered lymphocytes and plasma cells, and ill-defined granulomatous inflammation. Well-formed granulomata are rare as are extensive fibrosis or parenchymal necrosis. Small and medium-sized arteries may be infiltrated by eosinophils, but fibrinoid necrosis or true vasculitis are not found. When vasculitis is present, allergic angiitis and granulomatosis (Churg–Strauss syndrome) (Figure 5) is more likely. Bronchial asthma, with smooth muscle hyperplasia and mucus-containing Charcot–Leyden crystals and eosinophils, may be present (Figure 6). Surgical lung biopsy is usually not necessary, since the diagnosis of CEP can usually be established by bronchoscopic techniques (e.g., transbronchial biopsies and/or BAL) provided clinical and radiographic features are consistent.

Clinical features Most common symptoms of CEP are cough (>90%), dyspnea (>90%), fever (>75%), and weight loss (>70%). The course is subacute or chronic, with symptoms developing over several weeks to months. Extrapulmonary involvement is lacking. Atopy or asthma antedate CEP in >50% of patients. CEP typically occurs in the 4th–6th decade of life, but all ages can be affected. There is a 2:1 female:male predominance. The disease is less common in cigarette smokers. Chest radiographs reveal patchy, subpleural alveolar opacities, with a predilection for the upper lobes (Figures 7–10). The peripheral distribution of alveolar opacities, with central sparing, is evident in 50–70% of patients and is termed the ‘photographic negative of pulmonary edema’. Less common patterns include focal lobar consolidation or reticulonodular opacities. Pleural effusions are not found. Chest computed tomographic (CT) scans demonstrate peripheral consolidations, ground-glass opacities (GGO), and reticular opacities (mimicking cryptogenic organizing pneumonia (COP)) (Figure 9(b)). A striking feature of CEP is the rapidity of radiographic improvement (within hours to days) following institution of corticosteroid therapy (Figure 11).

Pulmonary function tests may reveal restriction and/or obstruction, but are normal in a third of patients. BAL demonstrates marked eosinophilia (often >50%), often with degranulation and hypersegmentation of eosinophils; lymphocyte and neutrophil percentages are normal or mildly elevated. Elevations in the peripheral blood eosinophil counts and erythrocyte sedimentation rate (ESR) are noted in >80% of patients with CEP, and parallel the course of the disease. Serum IgE is increased in 50–75% of patients but severe elevations (>2000 ng ml⁻¹) are rare.

Management and current therapy Corticosteroids are the cornerstone of therapy for CEP and are highly efficacious. Optimal dose and duration of therapy have not been studied in randomized trials. An initial dose of prednisone of 40–60 mg day⁻¹ or equivalent is adequate; lower doses may be used in patients at...
increased risk for side effects. Responses are usually dramatic (within 24–72 h). Relapses occur in 80% of patients as corticosteroids are tapered or discontinued. Some patients require long-term (sometimes indefinite) therapy with low-dose prednisone (e.g., 10–20 mg every other day) to maintain remissions.

**Idiopathic Acute Eosinophilic Pneumonia**

Idiopathic AEP, first described in 1989, is a rare acute febrile illness with cough, dyspnea, fever, diffuse infiltrates on chest radiographs, pronounced BAL eosinophilia (typically >25% eosinophils), and
hypoxemic respiratory failure, often requiring mechanical ventilatory support.

**Etiology** The cause is unknown.

**Histopathology** The histopathological features of AEP demonstrate extensive interstitial and intra-alveolar eosinophils resembling CEP but neutrophils, interalveolar septal edema, and fibrin deposition.
within alveolar spaces are more prominent in AEP. Hyaline membranes and diffuse alveolar damage (DAD) may also be present. Granulomata or vasculitis are not found in AEP. The diagnosis of AEP does not require surgical lung biopsy, as marked BAL eosinophilia (often >50%) in the appropriate clinical context is sufficient to establish the diagnosis.

Clinical features The onset of AEP is rapid, and most patients present within 1–7 days of onset of


Figure 7 (a) Chronic eosinophilic pneumonia. Chest radiograph of a 26-year-old woman demonstrates a focal infiltrate in the apical region of the left upper lobe (arrow). She improved promptly with corticosteroid therapy. Reproduced with permission from: Lynch JP III and Flint AF (1984) Sorting out the eosinophilic pulmonary syndromes. Journal of Respiratory Diseases 5: 61–78. (b) Chronic eosinophilic pneumonia. Chest radiograph from the same patient 5 months later, with three small focal alveolar infiltrates (arrows) in the right apex, right axillary region, and left axillary region. Note the peripheral, subpleural location of the infiltrates. Reproduced with permission from Lynch JP III and Flint AF (1984) Sorting out the eosinophilic pulmonary syndromes. Journal of Respiratory Diseases 5: 61–78. (c) Chronic eosinophilic pneumonia. Chest radiograph from the same patient during a relapse. Arrows depict the alveolar infiltrate with a distinct predilection for the subpleural region on the left and the left apex. There is a small nodular infiltrate in the right apex (arrow).
symptoms. However, the course may be subacute, evolving over 7–30 days. Acute hypoxemic respiratory failure ensues; mechanical ventilatory support is required in two-thirds of patients. The presentation of AEP resembles acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). However, extrapulmonary organ dysfunction or shock is not a feature of AEP. Chest pain, often pleuritic, occurs in 50–70% of patients and myalgias occur in 50%. There is a slight male predominance. Antecedent asthma is not a feature of AEP.

Chest CT in AEP resembles pulmonary edema, with bilateral extensive alveolar opacities and interlobular septal thickening (i.e., Kerley B lines). The opacities lack the peripheral distribution characteristic of CEP. Pleural effusions are evident on CT in 70% of cases.

BAL demonstrates striking increases in eosinophil number (often exceeding 50%). This feature distinguishes AEP from other clinical syndromes such as ARDS or pneumonia, which exhibit marked neutrophilia with normal or low eosinophil counts. Modest elevations in lymphocytes and neutrophils are also typical of AEP. Eosinophils in CEP and AEP may be degranulated and possess multiple lobes. Peripheral blood eosinophilia is present in only 40–65% of patients with AEP. Elevations in serum IgE may be striking.

Pathogenesis Other causes of AEP include human immunodeficiency virus (HIV) infection, cigarette smoke, fireworks, exposure to noxious occupational agents, drugs, and microbial pathogens.

Management and current therapy Idiopathic AEP is rare, and controlled therapeutic trials are lacking. However, corticosteroids are highly efficacious, with response rates approaching 100%. With severe cases, initial treatment with intravenous methylprednisolone (60–125 mg every 6 h) is advocated, until respiratory failure resolves. At that point, the corticosteroids are converted to oral prednisone. Responses to corticosteroids are usually dramatic with symptoms improving within hours to days of treatment; chest radiographs normalize within 1–4 weeks. Pulmonary function normalizes and late sequelae are rare. A brief course of corticosteroid therapy (6–12 weeks) is adequate, as late relapses are rare.
Churg–Strauss Syndrome

Churg–Strauss syndrome (CSS), also termed allergic angiitis and granulomatosis, is a rare disease characterized by blood and tissue eosinophilia, asthma, and a multisystemic necrotizing vasculitis.

Etiology
The cause is unknown.

Histopathological features
Histopathological features of CSS include a necrotizing eosinophilic and granulomatous vasculitis involving small vessels (capillaries, arterioles, venules); extravascular granulomas with pallisading histiocytes and multinucleated giant cells; eosinophilic infiltrates; and varying degrees of necrosis, hemorrhage, and fibrosis (Figures 5 and 12). The prominent eosinophilic and granulomatous components and propensity for small vessel involvement distinguish CSS from classic polyarteritis nodosa. Pulmonary involvement may include CEP, necrotizing vasculitis, or capillaritis (with alveolar hemorrhage).

Clinical manifestations
Asthma is invariably present in CSS, and usually antedates the development of vasculitis by several years. Pulmonary opacities are present in 30–70% of patients and pleural effusions in 20–30%. Transient alveolar opacities, often in a peripheral distribution, are characteristic (Figure 13). In contrast to other granulomatous vasculitides, nodular densities and cavitation are unusual in CSS. Extrapulmonary sites of organ involvement include constitutional symptoms (90%); mononeuritis multiplex (63–92%); skin lesions (e.g., petechiae, purpura, ulcerations, miscellaneous) (50–70%); cardiac involvement (15–56%); central nervous system (CNS) involvement (8–27%); arthralgias or myalgias (30–50%); systemic hypertension (50%); gastrointestinal (GI) tract (30–60%); renal failure (<5%); and ocular involvement (<5%). Prior to the availability of effective therapy, most deaths were ascribed to cardiac involvement (cardiac failure, pericarditis, coronary vasculitis, eosinophilic endocarditis).

Typically, three phases of CSS can be identified. The prodromal period consists of an atopic or allergic diathesis (e.g., allergic rhinitis, nasal polyps, asthma), which antedates vasculitis by months to years. Later in the course of illness, blood and tissue eosinophilia (e.g., Loeffler’s syndrome, CEP, or eosinophilic gastroenteritis) develop. The vasculitic phase occurs as a late event, 10 or more years after the onset of allergic rhinitis and 3–5 years after the onset of asthma. Increasingly, severe and more frequent attacks of asthma are harbingers to the development of CSS. A shorter duration from the onset of asthma to the development of vasculitis is associated with a worse prognosis.

Laboratory studies in CSS demonstrate elevated ESR and blood eosinophil counts in >80% during

Figure 11  (a) Chronic eosinophilic pneumonia. Chest radiograph demonstrating widespread but focal, dense alveolar opacities in a 28-year-old woman with fever, wheezing, and dyspnea. Transbronchial lung biopsies were compatible with CEP. The chest radiographs normalized within 3 weeks following institution of corticosteroid therapy. Reproduced from Shannon JJ and Lynch JP III (1995) Eosinophilic pulmonary syndromes. Clinical Pulmonary Medicine 2: 19–38, with permission from Lippincott Williams & Wilkins. (b) Chronic eosinophilic pneumonia. PA chest radiograph from a 47-year-old man showing confluent bilateral alveolar infiltrates. Peripheral blood eosinophil count was markedly elevated at 6600 per ml. Transbronchial lung biopsies showed extensive eosinophilic infiltration and consolidation of the alveolar spaces. Following institution of corticosteroid therapy, partial clearing of chest radiographs was noted within 36 h. Reproduced with permission from Lynch JP III and Flint AF (1984) Sorting out the eosinophilic pulmonary syndromes. Journal of Respiratory Diseases 5: 61–78.
acute exacerbations. Both the ESR and blood eosinophil counts correlate with disease activity. Serum IgE is elevated in >50% of patients. Circulating antineutrophil cytoplasmic antibodies (ANCA) (primarily p-ANCA) are present in 40–70% of patients with CSS.

Pathogenesis The immunopathogenesis of CSS involves a chronic allergic diathesis that evolves over time (often years). Th2 cells are pivotal to the early asthmatic phase and recruitment of eosinophils to tissues. During the later phases of the disease, circulating myeloperoxide (MPO)-ANCA antibodies likely play key contributory roles in the pathogenesis of glomerulonephritis and vasculitis. Possible contributory factors include repeated antigen stimulation, vaccination, and cysteinyl leukotriene receptor antagonists (LTRAs).

Management and current therapy Corticosteroids are the cornerstone of therapy for CSS, and achieve remissions in >80% of patients. Immunosuppressive or cytotoxic agents are employed for more severe or steroid-recalcitrant cases or when unfavorable prognostic factors are present. Factors associated with a worse prognosis include older age (>65 years), CNS involvement, cardiomyopathy, severe GI tract involvement, proteinuria (>1 g day⁻¹), and renal insufficiency. In several prospective studies employing various therapeutic regimens, 3- and 10-year survival rates exceeded 80% and 70%, respectively. Relapses occur in 20–40% as the corticosteroids or immunosuppressive therapy is tapered or discontinued. Long-term low-dose prednisone is usually required as maintenance therapy for chronic asthma.

Allergic Bronchopulmonary Aspergillosis Allergic bronchopulmonary aspergillosis (ABPA) is a clinical syndrome that occurs in 2–8% of patients with chronic asthma or cystic fibrosis (CF). It is characterized by repetitive episodes of bronchospasm, mucus plugging, blood and tissue eosinophilia, and airflow obstruction.

Etiology The immunopathogenesis of ABPA involves an exaggerated host response to endobronchial Aspergillus antigens. Eosinophils, basophils, mast cells, lymphocytes, mononuclear phagocytes, and humoral antibodies participate. The hyphae of Aspergillus fumigatus grow saprophytically in the bronchial lumens, and elicit a CD4⁺ Th2 immune response characterized by production of the cytokines IL-4, IL-5, IL-13, and Aspergillus-specific and polyclonal IgE. Release of fungal proteases, host-derived proinflammatory cytokines (e.g., IL-8, IL-6, MCP-1), and mast cell degranulation results in persistent bronchial inflammation, central bronchiectasis, and ultimately pulmonary damage. These immunopathogenetic mechanisms are not unique to Aspergillus, because other fungi or molds may elicit...
identical hypersensitivity reactions (e.g., Candida, Helminthosporium, Curvularia, Dreschlera, and Steemphyllum species).

**Histopathological features** Histopathological features of ABPA include dilated bronchi; endobronchial mucus; dense peribronchiolar cellular infiltrates composed of eosinophils, mast cells, and mononuclear cells; Charcot–Leyden crystals; Curschmann’s spirals; and degenerating eosinophils (Figure 14). Fungal hyphae may be observed within bronchial lumens or the inflammatory exude. Vasculitis or extensive necrosis are not features of ABPA. The surrounding lung parenchyma may reveal CEP, organizing pneumonia, or foreign body giant cell reactions. Mucoid impaction of bronchi is characterized by filling of bronchiecstatic bronchi and bronchioles with mucin, eosinophils, and inflammatory exudate. Lung biopsy is not necessary to make the diagnosis of ABPA, which is established by clinical and laboratory tests (discussed below).

**Clinical manifestations** In contrast to other eosinophilic lung diseases, the eosinophilic infiltration in ABPA is largely confined to the airways (bronchi and bronchioles). Consequently, the main symptoms of ABPA are difficult-to-treat or recurrent episodes of asthma. Major diagnostic criteria for ABPA include asthma, immediate cutaneous reaction to Aspergillus, precipitating IgG antibodies to A. fumigatus, proximal (central) bronchiectasis, chest radiographic infiltrates, blood eosinophilia, elevated serum total IgE, and increased A. fumigatus-specific IgE or IgG.

![Figure 13 Churg–Strauss syndrome. (a) PA radiograph shows ill-defined and faint consolidation within the right mid and upper lung. (b) Axial CT confirms and better delineates right upper lobe airspace consolidation. The left upper lobe contains ground-glass densities, consistent with both areas of lesser consolidation and air trapping.](image)

![Figure 14 Allergic bronchopulmonary aspergillosis. Mucus plug from bronchopulmonary aspergillosis: note numerous eosinophils and Charcot–Leyden crystals entrapped in mucus (H&E, × 400). Inset shows typical features of Aspergillus fungal forms in mucus (methenamine silver stain, × 400).](image)
antibodies. Immediate skin test reactivity and precipitating antibodies are sensitive but not specific for ABPA. Additional criteria required to establish the diagnosis of ABPA include airflow obstruction, elevations in serum IgE or *Aspergillus*-specific IgE, and chest radiographic infiltrates or bronchiectasis. Typical chest radiographic features include peribronchiolar thickening (most evident in the upper lobes), ring shadows, ‘tram lines’ (parallel linear shadows caused by inflamed bronchi), ‘finger-in-glove’ sign (medium-sized bronchi filled with mucus), segmental consolidation, atelectasis, and mucoid impaction (Figure 15(a)). However, chest radiographs may be normal, even during acute flares of the disease. Chest CT scans reveal thickened and dilated bronchial walls, proximal bronchiectasis, centrilobular nodules, and mucus impaction (Figure 15(b)). Additional findings include expectoration of mucus plugs, sputum flecked with brown or black elements, sputum cultures yielding *A. fumigatus*, and sputum smears showing fungal hyphae or eosinophils. ABPA is characterized by acute flares with cough, wheezing, and airflow obstruction, which may resolve with corticosteroid therapy. Repetitive flares of ABPA, often evolving over years, may cause irreversible bronchial injury, central bronchiectasis, pulmonary dysfunction, pulmonary fibrosis, and emphysematous changes. Secondary complications include atypical mycobacteriosis, secondary infections, and cor pulmonale. With severe chronic disease, fatalities due to respiratory failure may occur. Extrapulmonary involvement does not occur. Serum IgE levels and blood eosinophil counts correlate with disease activity. During acute flares, marked elevations of serum IgE (> 2000 ng ml⁻¹) are typical. Serum IgE levels fall in response to therapy, and serial studies are invaluable to assess disease activity.

Management and current therapy  Corticosteroids are the cornerstone of therapy for ABPA, and chronic corticosteroid therapy is often required. Initial treatment with prednisone 0.5–1.0 mg kg⁻¹ day⁻¹ (or equivalent) is usually adequate to achieve remissions. The corticosteroids are tapered to alternate day dosing over the next several weeks to months, with an attempt to control symptoms and maintain acceptable lung function. Inhaled corticosteroids have a modest steroid-sparing effect. Spirometry and serum IgE levels are helpful in following the disease. These parameters should be followed at least once monthly following an acute flare, with less frequent measurements once the disease is controlled. Poor control of ABPA leads to irreversible bronchiectasis, pulmonary fibrosis, and permanent airflow obstruction. Because chronic corticosteroid therapy has cumulative side effects, it is not practical to aim for normal serum IgE levels. The extent and rate of corticosteroid taper needs to be gauged by clinical symptoms, chest radiographs, pulmonary function, serum IgE levels, and the presence or absence of adverse effects of corticosteroids. Relapses require
retreatment with high-dose corticosteroids. Oral itraconazole (200 mg b.i.d.) may be efficacious as adjunctive therapy to reduce airway colonization with aspergilli, but is expensive.

**Idiopathic Hypereosinophilic Syndrome**

Idiopathic hypereosinophilic syndrome (IHES) is a rare and complex chronic disorder characterized by severe hypereosinophilia (>1500 per mm\(^3\)) for >6 months, diffuse organ infiltration by mature eosinophils, anemia, and constitutional symptoms.

**Etiology** The cause of IHES is unknown, but recent studies support segregating IHES into two major variants (myeloproliferative and lymphocytic). The myeloproliferative variant (m-HES) is associated with clonal proliferation of eosinophils; additional features found in some patients with m-HES include deletions in chromosome 4q12, a fusion gene encoding a protein displaying constitutive tyrosine kinase activity, and male predominance. Some patients with m-HES probably have chronic eosinophilic leukemia. By contrast, the lymphocytic variant (l-HES) is associated with abnormal clonal proliferation of activated T cells that produce IL-5 and IL-4; chromosomal abnormalities are present in some cases. Evolution of l-HES to T-cell lymphomas occurs in a minority of cases. m-HES and l-HES exhibit differences in prognosis and responsiveness to therapy.

**Histopathology** Large quantities of eosinophils, eosinophilic metamyelocytes, and myelocytes are observed in bone marrow, peripheral blood, and affected tissues. In the myeloid variant (discussed below), bone marrow biopsies may show atypical, dysplastic mast cells and myelofibrosis. Fibrosis of affected tissues (e.g., heart) may be prominent.

**Clinical features** The course and prognosis of IHES are strikingly heterogeneous. The heterogeneity in part reflects distinct hematological disorders involving either myeloid or lymphoid cells as the cause of IHES. The m-HES is more aggressive, often resistant to CS therapy, associated with an increased incidence of fibrotic complications, and may evolve to myeloid malignancy. By contrast, the l-HES is less aggressive and more often responsive to CS.

Common presenting features of IHES include night sweats, anorexia, weight loss, pruritis, fever, and cough. Cardiac involvement (e.g., endocardial fibrosis, restrictive cardiomyopathy, valvular damage, and mural thrombus) is the major cause of morbidity and mortality in m-HES but is uncommon in l-HES. Features associated with m-HES include involvement of liver or spleen (80%), nervous system (67%), thromboembolic disease (65%), lung (40%), and skin (40–60%). Other sites of eosinophilic infiltration include GI tract, kidneys, joints, and muscles. Among patients with l-HES, skin lesions (e.g., urticaria, angioedema, erythromelalgia) are invariably present. Other cardinal features of l-HES include eosinophilic infiltration of lung and the GI tract. Lung involvement in IHES may reveal marked BAL eosinophilia (>70%), interstitial infiltrates and/or pleural effusions on chest radiographs, small pulmonary nodules, and focal GGO on CT. Peripheral blood eosinophilia is usually striking (30–70%) in both m-HES and l-HES. Serum IgE levels are markedly elevated in most patients with l-HES; this is variable with m-HES. Serum levels of the chemokine TARC are often elevated in l-HES. Serum vitamin B\(_12\) levels and tryptase levels are often elevated with m-HES.

**Management and current therapy** IHES is rare and controlled therapeutic studies are lacking. Treatment should be stratified based upon subtype (i.e., m-HES or l-HES). Therapy with corticosteroids alone is efficacious in a majority of patients with l-HES but not with m-HES. Since the 1980s, anecdotal successes have been cited with hydroxyurea, vinca alkaloids, chemotherapeutic agents, and \(\alpha\)-interferon for IHES. Over the past 3 years, clinical successes were noted with the tyrosine kinase inhibitor, imatinib-mesylate, which is now considered first-line therapy for m-HES. By contrast, monoclonal antibodies against IL-5 may be efficacious for l-HES, although rebound hypereosinophilia may occur. Leukopheresis may be necessary when blood eosinophil counts are exceptionally high (>100,000 mm\(^3\)). Bone marrow or stem cell transplantation has been successful in refractory cases.

**Eosinophilia–Myalgia Syndrome**

Eosinophilia–myalgia syndrome (EMS), initially described in New Mexico in 1989, is characterized by the abrupt onset of severe myalgias, eosinophilia, paresthesias, rash, constitutional symptoms, and multisystemic involvement.

**Etiology** A relationship between ingestion of l-tryptophan and EMS was recognized, and the epidemic ceased after the Centers for Disease Control (CDC) recalled l-tryptophan-containing products.

**Clinical features** Criteria for the diagnosis established by the CDC in Atlanta included blood eosinophil count >1000 per mm\(^3\), incapacitating myalgias, and no other identifiable etiology (e.g., parasitic reaction or drug hypersensitivity). Within a few weeks
of being described, EMS assumed epidemic proportions in the US. One third of patients required hospitalization, and more than 30 patients died.

**Toxic Oil Syndrome**

Toxic oil syndrome was described in the spring of 1991 as an epidemic illness in Spain characterized by blood eosinophilia, pulmonary infiltrates, and diverse musculoskeletal manifestations.

**Etiology** Ingestion of contaminated rapeseed oil was implicated in June 1991, and the epidemic resolved quickly following withdrawal of the agent from the marketplace.

*See also: Asthma: Overview; Allergic Bronchopulmonary Aspergillosis. Colony Stimulating Factors. Interleukins: IL-1 and IL-18; IL-4; IL-5; IL-10; IL-13. Leukocytes: Eosinophils. Pneumonia: Mycobacterial. Pulmonary Fibrosis. Viruses of the Lung.*

**Further Reading**


