Eosinophilic Lung Diseases

W. Michael Alberts, MD, MBA, FCCP

Objectives:

1. To highlight the heterogeneous nature of these disorders and suggest a usable classification system.
2. To discuss important aspects of the eosinophil.
3. To review diseases that involve the eosinophil and the airways.
4. To discuss known parenchymal lung disorders that are associated with peripheral and/or tissue eosinophilia.
5. To highlight the idiopathic eosinophilic lung diseases.

Key words: acute eosinophilic pneumonia; allergic bronchopulmonary aspergillosis; chronic eosinophilic pneumonia; eosinophil; Loffler's pneumonia

The eosinophilic lung diseases are a heterogeneous group of clinical entities in which there is an increased number of eosinophils in the airways and/or lung parenchyma. These disorders may or may not be accompanied by peripheral eosinophilia. The presence of eosinophils does not establish a cause-and-effect relationship. In some cases, the eosinophil is merely a part of the inflammatory process and may even be there to protect host tissues. In other cases, the eosinophil appears to be directly responsible for the tissue damage.

Classification of the Eosinophilic Lung Syndromes

There have been many attempts to create a clinically useful classification system. In the 1950s, the first classification systems were based on Crofton's five syndromes associated with peripheral blood eosinophilia and pulmonary infiltrates. The five categories were as follows: (1) simple pulmonary eosinophilia; (2) prolonged pulmonary eosinophilia; (3) pulmonary eosinophilia associated with asthma; (4) tropical eosinophilia; and (5) pulmonary eosinophilia with polyarteritis nodosa. These are the so-called "PIE syndromes" as coined by Reeder and Goodrich.

In the 1960s, a new group of diseases was included. These disorders had increased lung eosinophils but did not necessarily have peripheral blood eosinophilia. A lung biopsy specimen was needed to identify these disorders. "Chronic Eosinophilic Pneumonia" as reported by Carrington is an example. In the last few years, additional diseases have been added to this heterogeneous collection of syndromes by virtue of their association with an increased percentage of eosinophils in bronchoalveolar lavage specimens. The recently characterized "Acute Eosinophilic Pneumonia" is an example.

Currently, there is no universally accepted or optimal way to classify these disorders. In their state of the art review, Allen and Davis state that an improved understanding of the role of cytokines and the other factors that control eosinophil traffic in the lung may ultimately permit a scientifically plausible classification of these disorders. One suggested classification scheme is listed in Table 1 and will be used in this review. The entities listed in Table 1 include diseases in which the eosinophil is part of the definition of the disease and/or is thought to be of pathogenetic importance (these

Table 1—***Classification Scheme***

- Airway disorders
  - Asthma
  - Allergic bronchopulmonary aspergillosis
  - Bronchocentric granulomatosis
- Parenchymal disorders
  - Associated with known underlying disease processes
    - Bacterial infections (*eg,* brucellosis, mycobacterial)
    - Fungal infections (*eg,* coccidioidomycosis and Aspergillus)
    - Interstitial lung diseases
      - Idiopathic pulmonary fibrosis
      - Sarcoidosis
      - Systemic lupus erythematosus
      - Eosinophilic granuloma
    - Hypereosinophilic syndrome
    - AIDS associated *Pneumocystis carinii* pneumonia
    - Parasitic infections
    - Pulmonary vasculitis (*eg,* Churg-Strauss vasculitis)
    - Hodgkin's disease
    - Drug reactions
    - Lung cancer
    - Others
  - Idiopathic eosinophilic pneumonia
    - Simple pulmonary eosinophilia
    - Chronic eosinophilic pneumonia
    - Acute pulmonary pneumonia

disorders are highlighted). A number of other lung diseases that are variably associated with eosinophil involvement are listed, as well.

The Eosinophil

The eosinophil is a polymorphonuclear leukocyte that is produced in the bone marrow. The individual cell is 12 to 15 μm in diameter. The nucleus has two lobes. There is abundant endoplasmic reticulum and an active Golgi apparatus. Eosinophils contain three different types of granules: two smaller granule populations and a larger eosin-specific granule population. There are about 200 of these larger granules per cell. The larger granules are responsible for the characteristic red staining. The eosin-specific granule has a very characteristic electron microscopic appearance. The internal core of the eosin-specific granule is compromised primarily of major basic protein (MBP). MBP is an arginine-rich, highly cationic polypeptide that is highly toxic to parasites, tumor cells, and respiratory epithelial cells. The cell contains other cationic proteins such as eosinophil cationic protein, eosinophil peroxidase, eosinophil derived neurotoxin, and several collagenases. Another unique constituent of this cell is the membrane associated Charcot-Leyden crystal protein.

Differentiation of the eosinophil in the bone marrow is under control of IL-3, IL-5, and granulocyte macrophage colony-stimulating factor. There are two populations of circulating eosinophils that differ in their biochemical makeup and their functional activities. They are termed normodense cells and hypodense cells. An increased proportion of hypodense cells can be found both in the tissues and blood in eosinophilic disorders. These cells are more metabolically active and may represent "activated" cells.

The eosinophil is primarily a tissue cell. After a brief time in the peripheral circulation (usually 13 to 18 h), the cell moves into tissues and organs throughout the body. There are 100 to 400 times as many eosinophils in the tissues as compared to the circulation at any one time. The eosinophil tends to settle in submucosal areas of organs exposed to the environment such as the lungs, the GI tract, and the genitourinary tract. The movement of eosinophils into the tissues is controlled by many factors. Known chemotactic factors include complement components, histamine, ECF-A, platelet activating factor, leukotrienes, lymphokines, tumor associated factors, and IL-5.

There are several teleological theories of eosinophil function: host defense against parasites, modulator of inflammation, and tissue destructive cell. The host defense theory builds on the well-established clinical observation that the tissue invasive stages of parasitic infection are associated with a striking peripheral eosinophilia. *In vitro* studies have shown that eosinophils can degranulate into and kill parasites. The modulator of inflammation theory holds that the eosinophil protects host tissues by dampening the damaging effects of inflammation. Eosinophils contain a variety of substances that have been shown to dampen or modulate the effect of various inflammatory mediators. Eosinophils tend to encircle areas of acute and chronic inflammation, perhaps representing an attempt to contain inflammation. The tissue destructive cell theory holds that the eosinophil is activated at sites of inflammation and is directly responsible for the damage of host tissues.

Eosinophilic Lung Diseases

Airway Disorders

Asthma: Peripheral eosinophilia is present in many asthmatics and is independent of the type of asthma (intrinsic vs extrinsic). Eosinophil counts may, in fact, be used to follow the course of the disease in a given patient. In many cases, there is a quantitative linear relationship between the eosinophil count and the degree of expiratory airflow limitation. Asthma has been very appropriately referred to as "chronic eosinophilic bronchitis." Eosinophils appear in the sputum and BAL of asthmatic patients and an eosinophilic response has been observed in specific bronchoprovocation testing. Eosinophils may contribute to the increased bronchial responsiveness characteristic of asthma. For example, it is known that MBP is cytotoxic to airway epithelium. This substance damages epithelial cell tight junctions and can cause epithelial cell shedding. This shedding produces Creola bodies and airway plugs. Epithelial cell shedding may result in denuded airways with exposed nerve endings. Eosinophils also produce a number of other substances that have bronchoconstrictive and inflammatory properties.

Fungus-Induced Asthmatic Reactions: Inhalation of fungal spores by the asthmatic may result in

several types of reactions: (1) IgE-mediated allergic rhinitis and asthma and (2) allergic bronchopulmonary mycosis. Fungal IgE-mediated asthma is a noninfectious disease resulting from the immune response of the atopic host. The response to inhaled fungal spores or mycelial antigens resembles the response to other inhalant allergens, such as house dust mite. Allergic bronchopulmonary mycosis is an "infectious disease" characterized by periods of persistent fungal growth or colonization of the respiratory tract. Both types of disorders can cause long-standing asthmatic manifestations in susceptible individuals. These disorders are antigen-specific hypersensitivity disorders characterized by airway damage and/or eosinophilic consolidation.

Allergic Bronchopulmonary Aspergillosis: Allergic bronchopulmonary aspergillosis (ABPA) is the most common type of allergic bronchopulmonary mycosis. ABPA is a complication of allergic asthma in which the ubiquitous fungus, *Aspergillus fumigatus*, colonizes the lower respiratory tract. Patients with cystic fibrosis are particularly vulnerable. ABPA may been seen in up to 15% of patients with cystic fibrosis and 2 to 28% of asthmatics. An ABPA-like disorder may be caused by other fungi such as *Candida albicans*, Helminthosporium species, and *Curvularia lunata.* Each of these organisms is capable of hyphal growth at body temperature. The hyphae persist in the airways and continually release antigens. The antigen combined with specific IgG and IgE to cause actual tissue damage. This tissue damage may result in permanent damage as evidenced by proximal bronchiectasis and irreversible airways obstruction.

The factors that cause an atopic, fungus-sensitive individual to develop ABPA are unclear. Specific IgE-mediated type I and specific IgG-mediated type III hypersensitivity reactions are proposed to play an important role in the immunopathogenesis of ABPA. In addition, a TH2 CD4+ lymphocyte cellular immune response may be implicated. It appears that the clinical expression of ABPA results from the complex interaction of chronic colonization of the airways with *A fumigatus* , host factors allowing the colonization, and a host's genetically determined immune response.

To make a diagnosis of ABPA, patients should have most of the following: difficult to control asthma, peripheral blood eosinophilia, immediate skin prick test for Aspergillus antigens, serum precipitating antibodies against Aspergillus antigens, increased serum IgE (both total and specific to Aspergillus), and transient or fixed chest radiographic infiltrates. Other frequent findings include Aspergillus organisms in the sputum, a history of expectoration of brown plugs in the sputum, and a positive type III (Arthus) skin reaction for Aspergillus. It has become clear that patients may present with less than the full complement of diagnostic criteria. This continued diagnostic testing may be required for months or years to fulfill all the criteria.

Central bronchiectasis is the most characteristic feature of ABPA. This finding is a proximal saccular dilation of the bronchi with distal sparing that may be noted on CT or high-resolution CT. Central bronchiectasis often may not be evident early in the patient's presentation and as such is not a necessary criterion for diagnosis. . Central bronchiectasis and pulmonary fibrosis, when present, are irreversible.

Serum IgE levels may parallel disease activity and an increasing IgE level may portend a clinical exacerbation. A normal IgE level in a symptomatic patient virtually excludes the diagnosis. The chest radiograph may reveal a "gloved finger" picture due to mucoid impaction of bronchi, "ring shadows" with or without air fluid levels, a "tram track" appearance due to bronchial wall edema or bronchiectasis, and consolidation due to airway obstruction

The natural history of ABPA is currently not well characterized and is difficult to predict. ABPA has been divided into five stages to help categorize patients and guide therapy. The stages, however, are not phases of the disease and patients do not necessarily progress through them. Stage 1 (acute) is characterized by asthma, elevated IgE level, eosinophilia, and pulmonary infiltrates. The patient is rarely identified at this stage. Stage 2 (remission) is present when the total IgE level falls toward normal. Eosinophilia is absent, and the chest radiograph clears. A previously unrecognized case would not be identified at stage 2. Stage 3 (exacerbation) resembles stage 1 in a patient who carries a prior diagnosis of ABPA and is marked by a doubling of the stage 2 baseline IgE level. Stage 4 (corticosteroid-dependent) is recognized when attempts to taper steroid therapy are associated with worsening asthma symptoms or the redevelopment of pulmonary infiltrates. Stage 5 (fibrotic) is characterized by the findings of end-stage lung disease

with dyspnea, cyanosis, and cor pulmonale. The conditions of most patients are diagnosed at stage 4 or stage 5.

The overall treatment plan should be directed toward optimal control of asthma in the conventional manner, prompt management of exacerbations associated with radiographic abnormalities, and inhibition of tissue damaging reactions. The mainstay of treatment remains oral corticosteroids. The goal is to preserve lung function by suppressing both the inflammatory response of the underlying asthma and the immunologic response to the aspergillus antigens.

Active treatment may prevent progression. In the early stages of the disease, corticosteroids are very effective in promoting a prompt resolution of asthma symptoms, radiographic changes, and IgE levels. The best specific regimen for corticosteroids in ABPA has not been determined. High doses are used until the chest radiograph clears, which usually takes several weeks. The corticosteroid dose is then tapered to an every-other-day regimen for 3 months to be followed by a slow taper over the next 3 months. Relapses are common, however, and may occur after prolonged periods of remission. It has been suggested that a chest radiograph should be obtained every 4 months for 2 years, then every 6 months for 2 years, then annually thereafter. In addition, total serum IgE level should be measured monthly. A twofold to threefold rise in total IgE level suggests that recrudescence of ABPA is pending. A chest radiograph should be obtained. If infiltrates are present, steroid therapy should be reinitiated.

Theoretically, eradication of the fungus from the bronchial tree would be curative. This, however, is seldom possible. Reports of success with ketoconazole taken for a year have been published. This drug, however, carries significant side effects. Recent studies with itraconazole have suggested that this well-tolerated oral medication may have a role as a steroid-sparing agent in ABPA . Randomized controlled studies are ongoing to determine whether itraconazole is useful in the management of ABPA.

On occasion, relentless progression to permanent obstruction and restriction may occur despite therapy. In the latter stages of the disease, chronic interstitial and irreversible airway obstruction may be present. The place of long-term oral corticosteroids in the prevention of end-stage disease has not been formally evaluated. It has been suggested that maintenance therapy with oral prednisone may prevent progression to end-stage fibrotic disease. This remains an unproven speculation.

Bronchocentric Granulomatosis: Bronchocentric granulomatosis (BG)is a rare granulomatous disorder characterized by granuloma formation and necrosis centered around and limited to bronchi and bronchioles. Vasculitis is not a major component. BG may be a nonspecific response to a number of substances. A surgical biopsy specimen is required for diagnosis. The disease is defined by morphologic criteria and is not a clearly defined clinical syndrome. It has been debated whether BG is a separate disease entity or purely a pathologic description of one of the limited ways in which bronchi and bronchioles respond to injury.

There is limited information available on this disorder. The information that does exist suggests a variable presentation and course. Common symptoms include cough, chest pain, wheezing, dyspnea, fever, and malaise. The chest radiograph is highly variable and may show primarily upper lobe involvement, atelectasis, consolidation, and infiltrates.

Two main patient groups have been described. One group, comprising about one third of reported cases, tends to have tissue eosinophilia, asthma, peripheral eosinophilia, fungal hyphae on biopsy specimen, and positive sputum cultures for Aspergillus. This may actually be the tissue destructive phase of ABPA. The other group tends to have no eosinophils on biopsy specimen, no asthma, and no evidence of fungi. Such granulomatous inflammation of the bronchi can occur in several diseases, including mycobacterial and fungal infection, aspiration, Wegener's granulomatosis, and rheumatoid lung disease. BG is a diagnosis of exclusion.

Parenchymal Disorders (Associated With Other Known Disease Entities)

Interstitial Lung Diseases: Increased BAL eosinophils (>5%) may be present in about 10 to 20% of interstitial lung diseases. Common interstitial diseases associated with increased BAL eosinophils include idiopathic pulmonary fibrosis, sarcoidosis, systemic lupus erythematosus, and eosinophilic granuloma. The pathogenetic importance of eosinophils in these disorders is unknown. The presence of BAL eosinophilia in idiopathic pulmonary

fibrosis may correlate with clinical deterioration and may predict a poor response to therapy.

Drug Reactions: A number of drugs have been associated with the "PIE" syndrome. Most have been reported as isolated cases, such as nitrofurantoin, sulfasalazine, phenytoin, bleomycin, and tetracycline. The reactions are generally mild and, therefore, little is known about the pathologic condition of the pulmonary infiltrates or even if the reaction involves eosinophilic lung inflammation. The conditions of most patients with drug-induced eosinophilic lung disease will improve by simply discontinuing treatment with the medication. In severe or persistent cases, corticosteroids have been used on occasion with some success.

Pulmonary Vasculitis: Eosinophils may be associated with lung lesions that accompany pulmonary vasculitis syndromes. Pulmonary vascular inflammation is seen most frequently as a manifestation of primary systemic vasculitis, but also occurs in association with a number of conditions, including rheumatological disorders (*eg,* systemic lupus erythematosus and polymyositis), chronic infection, lymphoma, sarcoidosis, and extrinsic allergic alveolitis. Primary vasculitic processes affecting the lung include giant cell arteritis, pulmonary capillaritis, Takayasu's arteritis, and those associated with circulating antibodies to neutrophil cytoplasmic enzymes (*eg,* Churg-Strauss syndrome, Wegener's granulomatosis, and microscopic polyangiitis).

The Churg-Strauss syndrome, also known as allergic granulomatosis and angiitis, is a rare but distinctive disorder. Patients with the Churg-Strauss syndrome generally have long-standing established asthma and a dramatic peripheral eosinophilia. Manifestations of the disease appear to be due to a granulomatous inflammatory response that results in vascular necrosis, primarily involving the lungs. An open lung biopsy specimen is usually necessary for diagnosis. In the past, the pathophysiology of this disorder was presumed to be due to immune complex deposition in the walls of small- and medium-sized arteries and veins. More recent speculation involves the role of ANCA and the characteristic vasculitis. The association with asthma and eosinophilia is unexplained.

Clinical features include asthma, a history of atopic disease, fever, malaise, and weight loss. Systemic manifestations of the illness may include upper airway involvement (sinusitis, rhinitis, nasal polyps), skin changes (nodules, purpura, urticaria), arthralgias, myalgias, mononeuritis multiplex, abdominal symptoms (pain, diarrhea, bleeding), cardiac findings (heart failure, pericarditis, hypertension), and microscopic hematuria. Chest radiographs commonly reveal patchy and transient infiltrates but large and small nodules have been reported as well. Thin-section CT findings include bilateral subpleural consolidation with lobular distribution, centrilobular nodules (especially within the ground-glass opacity), or multiple nodules, especially in association with bronchial wall thickening. Pleural effusions may be noted in one third of cases. The effusions are exudative and may contain a significant number of eosinophils. Common laboratory abnormalities include leukocytosis with marked eosinophilia, a high percentage of BAL eosinophils, prolonged erythrocyte sedimentation rate, and anemia. The IgE level is often markedly elevated and appears to correlate with disease activity. In Churg-Strauss syndrome, the prevalence of a positive serum ANCA result ranges from 44 to 66%. The p-ANCA pattern is often present as opposed to the c-ANCA in Wegener's granulomatosis.

Clinically, there are three distinct phases: (1) a prodromal phase that may persist for many years, consisting of asthma, often preceded by allergic rhinitis; (2) a second phase of marked peripheral blood eosinophilia and eosinophilic tissue infiltrates resembling Loffler's syndrome, or chronic eosinophilic pneumonia, which may recur over a period of years; and (3) a third, life-threatening vasculitic phase.

Survival is dramatically enhanced with treatment. In the past, without treatment, 50% of patients died within 3 months of onset. Myocardial involvement was the most frequent cause of death. In patients treated with corticosteroids, a mean survival of 9 years has been reported. Corticosteroids alone are usually effective in the Churg-Strauss syndrome. The addition of oral cyclophosphamide may reduce the rate of relapse but has not been shown to improve survival. In patients who fail to respond to corticosteroid therapy, however, "pulse" methylprednisolone, azathioprine, or cyclophosphamide may be effective. It is important to separate the Churg-Strauss syndrome from other necrotizing vasculidites, such as Wegener's granulomatosis and polyarteritis nodosa, which may require treatment with cytotoxic agents.

The association of leukotriene antagonists with the Churg-Strauss syndrome originally described in

patients taking zafirlukast has now been recognized to occur with montelukast as well, and is therefore most likely an uncommon but documented class association with an incidence of about 1 in 20,000 patients. The pathophysiology is unknown but these patients may have had a primary eosinophilic infiltrative disorder that had been clinically recognized as asthma, was quelled by steroid treatment, and was unmasked following corticosteroid withdrawal facilitated by the initiation of the leukotriene inhibitor.

Parasitic Disease: The "PIE" syndrome (pulmonary infiltrates with eosinophilia) may develop in conjunction with a number of parasitic infections. In the United States, the most common infections are due to Strongyloides, Ascaris, Toxocara, and Ancyclostoma. The syndrome may arise because of the presence of the parasite in the lung at certain stages of its life cycle. At this point, eosinophils may be recruited to the lung to kill the parasite. Eosinophils have been shown to be present in the lung, however, when parasites are not demonstrable. This suggests that immunologic mechanisms may be involved. GI symptoms usually predominate the picture of parasitic infestation. Respiratory symptoms of cough and wheezing are usually mild. The lung disease commonly resolves with therapy directed at the specific parasite. Corticosteroids are usually not needed.

The most serious and best characterized parasitic eosinophilic lung disease is tropical pulmonary eosinophilia. This disorder is caused by the filarial worms *Wuchereria bancrofti* and *Brugia malayi*. These organisms are found primarily in India, Africa, South America, and Southeast Asia. Microfilariae released from adult worms cause an intense inflammatory reaction in the lung. This reaction commonly causes nocturnal cough, dyspnea, wheezing, fever, weight loss, and malaise. A history of residence in a filarial endemic region and a finding of peripheral eosinophilia >3,000 / mm^3 should initiate a consideration of this disease. Cases of tropical pulmonary eosinophilia have typically been reported to masquerade as acute or refractory asthma. The recommended treatment is diethylcarbamazine. If left untreated or treated late, the disease may lead to long-term sequelae of pulmonary fibrosis or chronic bronchitis with chronic respiratory failure.

Idiopathic Hypereosinophilic Syndrome: The idiopathic hypereosinophilic syndrome is a rare illness of unknown etiology. This disorder affects multiple organ systems primarily due to the infiltration of mature eosinophils. This disorder is likely related to unchecked T-cell secretion of IL-3, IL-5, or granulocyte macrophage colony-stimulating factor. Specific diagnostic criteria for the hypereosinophilic syndrome have been established: (1) peripheral eosinophilia (>1,500 cells per microliter) for 6 months; (2) involvement of various organ systems with evidence of end organ damage; and (3) no evidence of parasitic, allergic, vasculitic, or other known causes of eosinophilia.

The illness may be mild or fatal. The major cause of morbidity and mortality is cardiac disease where endocardial fibrosis, restrictive cardiomyopathy, valvular damage (supportive structures around the valves, especially the mitral valve, are prone to fibrosis), and mural thrombus formation occur. Lung involvement occurs in 40% of cases. Symptoms are nonproductive cough and dyspnea. The chest radiograph may show pulmonary edema and pleural effusions associated with cardiac dysfunction but may also reveal interstitial infiltrates presumably due to perivascular eosinophilic infiltration or fibrosis. Patients are usually treated with oral corticosteroids but only about 50% will have a good clinical response. Other drugs, such as busulfan and hydroxyurea, may be used in steroid-unresponsive patients.

Miscellaneous: Bronchogenic carcinoma is occasionally associated with lung and peripheral eosinophilia. Eosinophils have been shown to invade the tumor. This suggests that eosinophils may be involved in host defense against tumors. Hodgkin's disease may be associated with peripheral, BAL, and lung eosinophilia. Fungal disease may be associated with peripheral eosinophilia. Peripheral blood eosinophilia is noted in the majority of cases of primary coccidiomycosis. Pulmonary eosinophilic infiltrates may be noted on biopsy specimen or BAL. Administration of corticosteroids to patients early in their infection can result in an acceleration of the infection with possible fatal dissemination. In AIDS-associated *Pneumocystis carinii* pneumonia, 15% of patients had BAL eosinophils >5%. A number of other diseases have been reported to be associated with pulmonary infiltrates and blood or alveolar eosinophilia. They include bronchiolitis obliterans organizing pneumonia, ulcerative colitis, mycobacterial infection, Sjögren's syndrome, and postradiation fibrosis.

Parenchymal Disorders (Idiopathic)

Simple Pulmonary Eosinophilia (Loffler's Pneumonia): Simple pulmonary eosinophilia was originally described by Loffler in 1932. This disorder is characterized by migratory pulmonary infiltrates accompanied by peripheral eosinophilia. Respiratory symptoms are minimal or absent. Malaise, fever, and cough may be noted, At times, the chest radiographic pattern may be almost diagnostic with transitory and migratory ill-defined peripheral, nonsegmental, and relatively homogeneous densities. By definition, the disease resolves within 4 weeks. Afflicted patients have an excellent prognosis. Complete resolution with or without treatment is the rule. In the original description of this disorder, most of the patients likely had a parasitic infection or a drug reaction. Currently, it is estimated that up to one third of cases do not have a clinically identifiable cause. This latter group is included in the idiopathic eosinophilic pneumonias. Apparent simple pulmonary eosinophilia, however, should be viewed as a sign of possible underlying disease. A careful search for parasitic infection or drug reaction should be pursued.

Chronic Eosinophilic Pneumonia: Although uncommon, this entity is the best characterized of the idiopathic eosinophilic pneumonia syndromes. Both histologic and BAL studies strongly implicate the eosinophil in the pathogenesis of the disorder. A recent study found strikingly elevated levels of IL-5, IL-6, and IL-10 in BAL fluid recovered from involved lung segments. No such elevation was noted in serum or uninvolved lung segments. Furthermore, the presence of circulating immune complexes, elevated levels of IgE, and a frequently positive rheumatoid factor suggest an immunopathogenic mechanism. Although described earlier in the 1960s, chronic eosinophilic pneumonia (CEP) was best described by Carrington in 1969.

CEP is a serious disease that requires specific treatment. The disease usually affects middle-aged atopic women but the disease has been reported in both genders and all ages. Onset of the disorder is insidious with progressive respiratory and constitutional symptoms. Symptoms have been present for an average of 7.7 months before diagnosis. The most common symptoms are cough, dyspnea, fever, night sweats, malaise, and weight loss. Asthma is present in 50 to 60% of patients and is usually of recent onset. Laboratory evaluation may reveal elevated IgE level and the level may correspond to the clinical activity. Peripheral eosinophilia occurs in up to 88%.

Diffuse peripherally based infiltrates in the outer two thirds of the lung fields are found in 63% of patients. On occasion, the chest radiograph may be so characteristic as to be diagnostic. Bilateral peripheral or pleural-based dense infiltrates without segmental or lobar distribution may be noted. These infiltrates may form a pattern described as "the photographic negative of pulmonary edema." Unfortunately, less than 50% of patients demonstrate this classic plain radiographic picture. A CT scan will reveal peripheral infiltrates, however, in all afflicted. Biopsy specimens show interstitial and alveolar eosinophils that are degranulated. Common findings include eosinophilic microabscesses (which are aggregates of necrotic eosinophils surrounded by a rim of palisading histiocytes), low-grade vasculitis, and interstitial fibrosis. BAL specimens usually show eosinophilia that average 44%.

Fewer than 10% of patients will have spontaneous resolution, and deaths from CEP have been reported. The disease responds quickly and dramatically to corticosteroid therapy. The patient may become asymptomatic in hours or a few days. The prognosis is excellent but treatment for prolonged periods is usually necessary, at least 6 months. Steroid therapy must be tapered slowly as the disease tends to relapse. If a relapse occurs, treatment must be continued for a prolonged period before trying to taper again.

Acute Eosinophilic Pneumonia: In 1989, several well-documented cases of acute respiratory failure associated with increased BAL or tissue eosinophils were reported. The cause is unknown but may be a unique hypersensitivity reaction to an inhaled antigen. Various drug toxicities have been reported to produce this syndrome. The following diagnostic criteria have been suggested : (1) acute febrile illness of <5 days' duration; (2) hypoxemic respiratory failure; (3) diffuse mixed alveolar and interstitial chest radiographic infiltrates; (4) BAL eosinophilia (>25%); (5) no apparent infectious etiology; (6) rapid and complete response to corticosteroid therapy; and (7) no relapse after discontinuing corticosteroid therapy.

Patients typically present with an acute febrile illness accompanied by myalgias, pleuritic chest pain, and hypoxemic respiratory failure, often requiring mechanical ventilation Clinically, there is little to distinguish acute eosinophilic pnuemonia

from an acute infectious process or ARDS. It is the BAL that provides the clue to the diagnosis. Peripheral blood eosinophil percentage is usually normal but a very high percentage of BAL eosinophils is characteristic with an average of 42% in one series. Small-to-moderate pleural effusions are frequent. Fluid analysis may reveal a high percentage of eosinophils.

Patients usually respond rapidly to high doses of corticosteroids, usually within 24 to 48 h. The dose is then tapered but treatment is usually continued for 2 to 4 weeks. Most patients survive and recover normal lung function. Acute eosinophilic pneumonia is a diagnosis of exclusion. An infectious etiology should be pursued even after corticosteroid therapy is begun. It is especially important to look closely for disseminated fungal disease in all patients and *P carinii* in the HIV-positive patient.

Conclusion

In these disorders, teleologically, the eosinophil may be : (1) A "good guy," (2) a "bad guy," or (3) an "innocent bystander." The eosinophil may be a "good guy." The "host defense" theory builds on the clinical observation that the tissue invasive stages of parasitic infections are associated with a striking eosinophilia. *In vitro* studies have shown that eosinophils can kill parasites. Conversely, the eosinophil may be a "bad guy." The eosinophil is activated at sites of inflammation and thus may be responsible for the actual tissue damage. Alternatively, the eosinophil may be an "innocent bystander." The appearance of the cell may be part of the body's attempt to dampen or contain the effects of inflammation--the so-called "modulator of inflammation" theory.

Whatever the function of the eosinophil, it is important to remember that the disease processes lumped together as the eosinophilic lung diseases are a heterogeneous group of diseases. In an attempt to categorize these disorders, we may have either appropriately oartificially connected them by their association with the eosinophil.

Annotated Bibliography

"State of the Art" Review

Allen JN, Davis WB. Eosinophilic lung diseases. Am J Respir Crit Care Med 1994; 150:1423-1438
Most authoritative and complete, yet readable, review of the eosinophilic lung diseases. This article should be in your reprint collection as a ready reference.

The Eosinophil

Albera C, Ghio P. Eosinophils in eosinophilic pneumonia. Eur Respir J 1996(9); 2437-2439
Wardlaw AJ, Brightling C, Green R, et al. Eosinophils in asthma and other allergic diseases. Br Med Bull 2000; 56:985-1003
Weller PF. Human eosinophils. J Allergy Clin Immunol 1997; 100:283-287
All three reviews concentrate on the cell rather than the clinical syndromes.

Short Reviews

Allen JN, Davis WD. What is eosinophilic pneumonia? Arch Intern Med 1992; 152:1765-1766
Excellent short review that clearly discusses the various classification schemes.
Fujimura M, Yasui M, Shinagawa S, et al. Bronchoalveolar lavage cell findings in three types of eosinophilic pneumonia: acute, chronic, and drug-induced eosinophilic pneumonia. Respir Med 1998; 92:743-749
Discusses the clinical and bronchoscopic lavage findings in three of the more "common" eosinophilic pneumonia syndromes.
Greenberger PA. Immunologic aspects of lung diseases and cystic fibrosis. JAMA 1997; 278:1924-1930
Concise review of several of the entities included in the classification of esinophilic lung disease.
Sharma OP, Bethlem EP. The pulmonary infiltration with eosinophilia syndrome. Curr Opin Pul Med 1996; 2:380-389
Recent review with emphasis on the recent literature.

Acute Eosinophilic Pneumonia

Allen JN, Pacht ER, Gadek JE, Davis WD. Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. N Engl J Med 1989; 321:569-574
Original descriptions of the "newest" idiopathic eosinophilic pneumonia.

Badesch DB, King TE, Schwarz MI. Acute eosinophilic pneumonia: a hypersensitivity phenomenon? Am Rev Respir Dis 1989; 139:249-252
Pope-Harman AL, Davis WB, Allen ED, et al. Acute eosinophilic pneumonia : a summary of 15 cases and review of the literature. Medicine 1996; 75:334-342
Since the original descriptions in 1989, individual cases of acute eosinophilic pneuominia have been reported in the literature. This article reports 15 cases and reviews the literature concentrating on the typical presenting characteristics in hopes of facilitating early diagnosis and treatment.
Sarniak AP, Heideman SM. Acute eosinophilic pneumonia: a treatable cause of severe acute respiratory failure. Crit Care Med 1999; 27:2069-2070
Editorial that accompanies a case report of a patient with acute eosinophilic pneumonia associated with shock. Quick review of current thinking regarding pathogenesis and differential diagnosis.

Chronic Eosinophilic Pneumonia

Carrington CB, Addington WW, Goff AM, et al. Chronic eosinophilic pneumonia. N Engl J Med 1969; 280:787-798
*Original description of the most common idiopathic eosinophilic pneumonia syndrome.*Marchand E, Reynaud-Gaubert M, Lauque D, et al. Idiopathic chronic eosinophilic pneumonia: a clinical and follow-up study of 62 cases. Medicine 1998; 77:299-312.
Complete description of findings and natural history in a large number of documented cases.

Bronchocentric Granulomatosis

Ortiz-Saracho J, Vidal R, Delgado E, et al. Bronchocentric granulomatosis in a non-asthmatic patient without etiologic agent. Respiration 1996; 63:129-132
In a report of a nonasthmatic patient with bronchogenic granulomatosis, the authors discuss different proposed pathogenetic mechanisms.
Ward S, Heyneman LE, Flint JDA, et al. Bronchocentric granulomatosis: computed tomographic findings in five patients. Clin Radiol 2000; 55:296-300
Discussion of the radiographic findings in this rarely diagnosed disorder.

Allergic Bronchopulmonary Aspergillosis

Kauffman HF, Tomee JFC, Van der Werf, et al. Review of fungus-induced asthmatic reactions. Am J Respir Crit Care Med 1995; 151:2109-2116
*The authors classify "fungus-induced" obstructive airway disease in atopic individuals into two categories : (1) uncomplicated asthmatic reactions due to high but transient exposures to fungal spores (fungal asthma) and (2) more complex asthmatic reactions due to colonization of the mucus-epithelial surface by virulent protease-producing fungi. ABPA is the best recognized example of the latter.*Vlahakis NE, Aksamit TR. Diagnosis and treatment of allergic bronchopulmonary aspergillosis. Mayo Clin Proc 2001; 76:930-938
Short, but complete, update of this entity. Suitable for a quick review.

Classics in Eosinophilic Pneumonia

Crofton JW, Livingstone JL, Oswald NC, Roberts ATM. Pulmonary eosinophilia. Thorax 1952; 7:1-35*First attempt to categorize a group of disorders that shared the features of pulmonary infiltrates and peripheral eosinophilia*.
Reeder WH, Goodrich BE. Pulmonary infiltration with eosinophilia (PIE syndrome). Ann Intern Med 1952; 36:1217-1240
Reeder and Goodrich coined the term PIE syndrome in this article.

Churg-Strauss Syndrome

Conron M, Beynon HLC. Churg-Strauss syndrome. Thorax 2000; 55:870-877
Brief, readable review of this rare disorder.
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
Recent description of the clinical presentation and course in almost 100 patients.
Choi YH, Im JG, Han BK, et al. Thoracic manifestations of Chrug-Strauss syndrome: radiologic and clinical findings. Chest 2000; 117:117-124
Excellent short review of the pertinent literature with an emphasis on the thoracic manifestations.

Tropical Pulmonary Eosinophilia

Ong RK, Doyle RL. Tropical pulmonary eosinophilia. Chest 1998; 113:1673-1679
Excellent discussion of a rare, but becoming more common, cause of eosinophilia.

Notes