Pathology of Pulmonary Disease, edited by Mario J. Saldana.
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Eosinophilic Pneumonia

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In 1952, Crofton and colleagues proposed a classification of pulmonary eosinophilia that still serves as a framework for the study of these disorders.[1] These investigators wrote, "We would emphasize that we are not trying to fossilize these conditions into rigidly separate categories but are merely proposing convenient labels as a necessary preliminary to the further discussion and investigation of an obscure group of diseases."[1] In the same year, Reeder and Goodrich coined the catchy term "PIE syndrome" (*i.e.*, pulmonary infiltrates with eosinophilia) to encompass the same group of diseases.[2] Their observation that "original concepts of readily definable entities are changing as more protean cases are encountered" remains as true today as it was when originally written.[2]

Problems are encountered with the classification of pulmonary eosinophilia. A significant number of cases remain idiopathic, there is considerable overlap between the various syndromes, clinical asthma is an inconstant feature of these syndromes, different etiologic agents may cause similar clinical and pathologic findings, and pulmonary eosinophilia may occur in several conditions that are not necessarily associated with blood eosinophilia.

There has been a shift in what is meant by the term "pulmonary eosinophilia." Although Crofton and colleagues defined it as pulmonary infiltrates seen on the chest x-ray film associated with peripheral blood eosinophilia, it is better defined as pulmonary eosinophilia with or without circulating eosinophilia.[1] An updated classification of pulmonary eosinophilia based on current understanding of these disorders is presented in Display 64-1.

The main two entries in Display 64-1 refer to the clinical syndromes of acute and chronic eosinophilic pneumonia. Although many are idiopathic, some cases of acute eosinophilic pneumonia may have identifiable etiologic agents (*e.g.*, drugs, parasites, bacteria, fungi). Less commonly, some cases of chronic eosinophilic pneumonia have an identifiable etiologic agent. There is an overlap between idiopathic syndromes of eosinophilic pneumonia and those with specific etiologies or associated diseases. The clinicopathologic features of pulmonary eosinophilia in this context are discussed in this chapter.

ACUTE EOSINOPHILIC PNEUMONIA

Acute Transient Eosinophilic Pneumonia

Acute eosinophilic pneumonia (*i.e.*, Löffler syndrome) can be divided into two groups: the transient form (*i.e.*, Löffler pneumonia) and progressive acute eosinophilic pneumonia with respiratory failure.[1,3–8] The diagnostic criteria for Löffler syndrome are shown in Display 64-2. Clinical symptoms are mild, and some patients are entirely asymptomatic. Cough is the most common symptom; in most cases, it is dry, but in some patients, there is production of mucoid sputum containing eosinophils. A few patients complain of chest tightness or pain; headaches, malaise, and night sweats are reported as systemic complaints, and these patients may be afebrile or have low-grade fevers. On physical examination, signs of consolidation are absent. By definition, all patients have peripheral eosinophilia. The leukocyte count is usually in the upper range of normal or slightly elevated, with eosinophilia usually in the range of 6% to 20%.

Chest x-ray films show bilateral or unilateral infiltrates that are described as fan shaped with irregular borders and that are occasionally nodular. The disorder resolves spontaneously, and the eosinophilia usually disappears within 2 to 4 weeks. The patients feel better in 1 to 3 weeks, and there is radiographic clearing of infiltrates by 4 weeks. Several etiologic agents have been identified as causative for Löffler syndrome (see Display 64-2). Many cases remain idiopathic.

Because of the mild, transient nature of the illness, the pathology of Löffler syndrome is not well described. The few reports that have been published indicate that the pathology is similar to that of chronic eosinophilic pneumonia.[9] More neutrophils may be associated with the eosinophilic infiltrate than with most cases of chronic eosinophilic pneumonia. There is also more edema and fibrinous exudate (Fig. 64-1). However, these differences are subtle, and in many areas, the findings are indistinguishable from chronic eosinophilic pneumonia.

DISPLAY 64-1. CLASSIFICATION OF PULMONARY EOSINOPHILIA

Clinical Syndromes

Acute eosinophilic pneumonia
- Transient (*i.e.*, Löffler syndrome)
- Progressive

Chronic eosinophilic pneumonia

Specific Causes and Diseases

Parasite-related eosinophilic pneumonia
Eosinophilic pneumonia with infection other than parasitic
Drug-related eosinophilic pneumonia
Allergic bronchopulmonary aspergillosis
Vasculitis-associated eosinophilic pneumonia
Hypereosinophilic syndrome
Miscellaneous causes

DISPLAY 64-2. LÖFFLER SYNDROME

Clinical Manifestations

Mild clinical symptoms
Transient pulmonary infiltrates
Peripheral eosinophilia
Spontaneous resolution
Time course <1 month

Causes

Parasites
Drugs
Chemicals
Pollen
Poison ivy desensitization
Smoke inhalation
Idiopathic

Acute Progressive Eosinophilic Pneumonia

There have been several reports emphasizing a form of acute eosinophilic pneumonia that progresses to acute respiratory failure.[10–14] The clinical presentation is similar to that for Löffler syndrome, but it is more severe. Patients present with dyspnea, cough, sputum production, and chest pain. Systemic signs and symptoms are prominent, and these patients invariably have significant fevers and myalgias. Laboratory findings include significant leukocytosis, but peripheral blood eosinophilia is an inconstant finding.

The radiographic appearance is one of diffuse, nonspecific, interstitial and alveolar infiltrates. These patients progress to acute respiratory failure (*i.e.*, $Po_2 < 60$ mm Hg) in less than 1 week. Exclusion of infection is important, because there are several infectious causes of acute eosinophilic pneumonia. How completely infection is excluded is frequently dictated by the severity of the patient's illness. Useful techniques to help in the differential diagnosis include bronchoalveolar lavage, transbronchial and open lung biopsies, culture, serology, and skin tests.

Patients with acute eosinophilic pneumonia respond rapidly to steroid therapy, with dramatic clinical improvement over the first week. The chest radiographs may take a few weeks to normalize. The duration of steroid therapy has varied, with a course as short as 10 days reported. Unlike chronic eosinophilic pneumonia, none of the reported patients with acute progressive eosinophilic pneumonia have had recurrences after recovery and withdrawal from steroid therapy.

The pathology of acute progressive eosinophilic pneumonia has not been well documented. In the largest series of four patients, there were no tissue biopsies.[11] Diagnosis was made on the basis of bronchoalveolar lavage eosinophilia (*i.e.*, eosinophils > 25% of cell differential). In three patients in whom biopsy tissue was obtained, the findings included interstitial and intraalveolar eosinophils admixed with histiocytes, diffuse alveolar edema, and intraalveolar fibrin.[10,12,14] I have observed two cases that met the clinical criteria for acute progressive eosinophilic pneumonia in which an open lung biopsy specimen was obtained. The findings include striking interstitial inflammation with numerous eosinophils admixed with other inflammatory cells, including lympho-

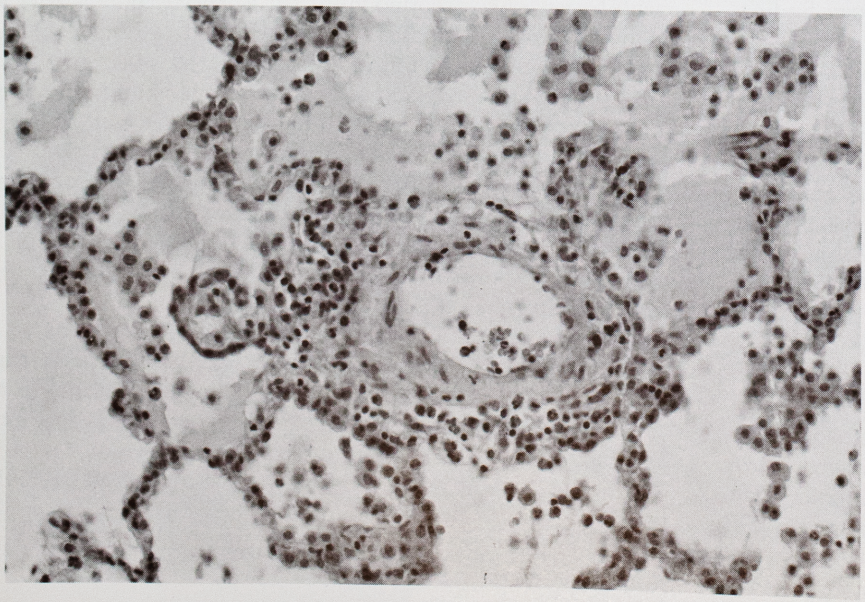

FIGURE 64-1. The Löffler syndrome is manifested by a prominent perivascular and interstitial inflammatory infiltrate with numerous eosinophils. Notice the alveolar edema and early exudate of inflammatory cells, including eosinophils. (H & E stain; intermediate magnification.)

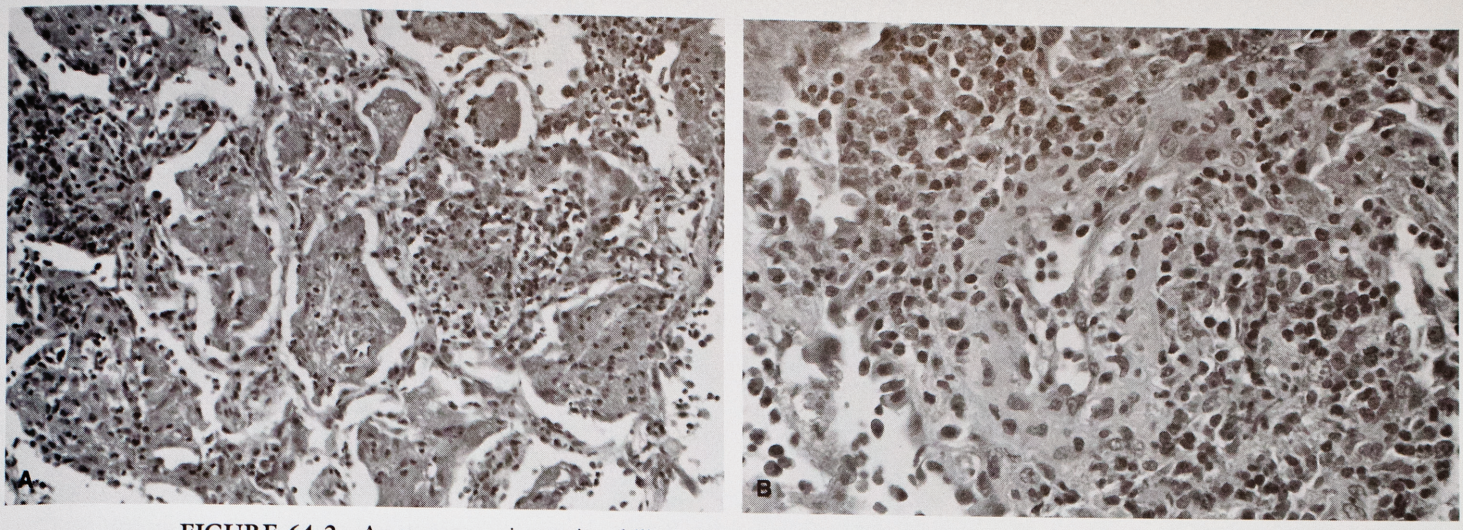

FIGURE 64-2. Acute progressive eosinophilic pneumonia. (**A**) Interstitial inflammation with prominent eosinophils and intraalveolar fibrinous exudate. (H & E stain; low magnification.) (**B**) Eosinophilic vasculitis with subtotal vascular occlusion. Lymphocytes, plasma cells, and eosinophils extend to the adjacent alveolar tissue. (H & E stain; intermediate magnification.)

cytes and plasma cells. The inflammatory infiltrate was most prominent around vessels and airways. Eosinophils and lymphocytes infiltrated the walls of small vessels without causing vascular wall necrosis or thrombosis. Intraalveolar edema and fibrinous exudate were also prominent. In some areas, changes similar to those seen in chronic eosinophilic pneumonia were observed, such as intraalveolar collections of eosinophils and histiocytes (Fig. 64-2).

CHRONIC EOSINOPHILIC PNEUMONIA

Chronic eosinophilic pneumonia was originally described by Carrington and colleagues in 1969.[15] Subsequently, numerous reports of this disease have appeared.[16–20] Gaensler and colleagues summarized the features of chronic eosinophilic pneumonia seen in more than 119 patients.[21] The diagnostic criteria for chronic eosinophilic pneumonia requires exclusion of acute eosinophilic pneumonia (*i.e.*, symptoms must exist for at least 2 weeks). The mean duration of symptoms is about 8 months (range, 1–48 months). Peripheral eosinophilia and peripheral pulmonary infiltrates are required for the diagnosis; in the absence of these combined findings, additional evidence of biopsy-proven pulmonary eosinophilia is necessary. Although open lung biopsy provides the best basis for a pathologic diagnosis, transbronchial biopsy, bronchoalveolar lavage, and sputum have been used to support the diagnosis, depending on the clinical setting.

There are several important conditions that must be excluded before diagnosis. Patients with human immunodeficiency virus infection and *Pneumocystis carinii* pneumonia may have significant eosinophilia revealed by bronchoalveolar lavage. Many infections are associated with significant peripheral and pulmonary eosinophilia, and drugs are known to produce eosinophilic hypersensitivity reactions that may be difficult to interpret. I know of one woman who for years had been diagnosed with recurrent chronic eosinophilic pneumonia before she told her pulmonologist that it seemed to her that whenever she got a vaginal infection, these pulmonary infiltrates reappeared. Sulfonamide vaginal suppositories are reported to cause eosinophilic pneumonia. Malignant diseases and vasculitides associated with eosinophilia must also be excluded.[5]

Chronic eosinophilic pneumonia most commonly presents as a subacute respiratory illness with fever, cough, dyspnea, and weight loss. In a few patients, more severe symptoms such as drenching night sweats, chills, myalgia, chest pain, hemoptysis, and rapid progression to respiratory failure have been reported. Most patients have had symptoms for several months before diagnosis. Approximately one half of the patients have an allergic diathesis, and 40% have asthma.

Patients of virtually every age group from infants to octogenarians have been reported with this disease, but 80% of the patients are between 30 and 70 years of age. Two times more women than men are reported. The radiographic appearance of chronic eosinophilic pneumonia is frequently helpful in making the diagnosis; it has been described as the photographic negative of pulmonary edema. Although this appearance is reported to be diagnostic, it occurs in fewer than 25% of cases. The most common radiographic picture is one of peripheral pulmonary infiltrates with bilateral upper lobe involvement (Fig. 64-3).

Using routine radiographic techniques, about 30% of patients are found to have nonperipheral infiltrates, but when studied by computerized tomography, many of them are reclassified as having peripheral infiltrates (Fig. 64-4). A variety of unusual radiographic appearances have been associated with chronic eosinophilic pneumonia, including nodular infiltrates, consolidation, fibrosis, and pleural effusion. Cavitation has not been well documented, and caution should be exercised before accepting as idiopathic a case of chronic eosinophilic pneumonia with lung cavities.

It is particularly important to exclude infections, vasculitides, and neoplasms mimicking or associated with chronic eosinophilic pneumonia. Steroid therapy results in rapid and dramatic improvement in the clinical condition of these patients. In two thirds of patients, there is complete clinical resolution of symptoms within the first 2 weeks, and in the remaining third, there is significant improvement, with most patients reporting a clinical cure after 1 month of therapy. Eighty percent of patients suffer recurrences of disease on tapering or discontinuation of steroid

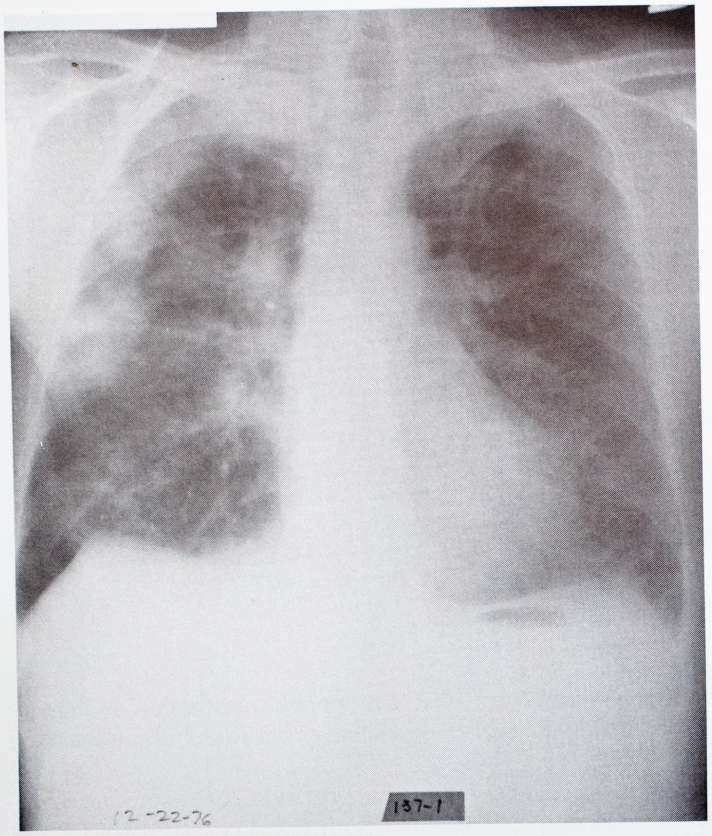

FIGURE 64-3. A radiograph of a patient with chronic eosinophilic pneumonia shows bilateral, upper lobe, peripheral, fluffy infiltrates, which are most prominent on the right side. The interstitial markings are increased.

therapy. The radiographic appearance of the recurrent disease appears similar in distribution to the initial radiographic presentation of the disease. Because there is an increased awareness of this disease and more cases are diagnosed on a clinical basis, there is an increased risk of misdiagnosis as well.

A therapeutic trial of steroids is recommended only in the proper clinical setting. Failure of the patient to improve after 1 week of therapy or any clinical deterioration, whether there was initial improvement in the clinical condition or not, should prompt aggressive diagnostic intervention, with open lung biopsy offering the greatest diagnostic yield.

The pathology of chronic eosinophilic pneumonia has been described, and the salient features are illustrated in Color Figure 64-1 and Figure 64-5.[15] The most prominent finding is that of alveolar filling by eosinophils admixed with histiocytes and a smaller number of other inflammatory cells. Multinucleated giant cells are commonly present and may contain eosinophilic, Charcot-Leyden crystals. In some cases, eosinophilic microabscesses are seen within air spaces, with histiocytes palisading around the eosinophilic debris. The second component of this disease is a significant interstitial pneumonitis, which is often obscured by the air space infiltrate. It includes eosinophils and histiocytes and an increased number of lymphocytes and plasma cells, which are sparse in the alveolar infiltrate. Perivascular and peribronchial cuffing by inflammatory cells are also common, and vascular infiltration by lymphocytes and eosinophils vary in severity. Vascular wall necrosis is not a feature of this disease.

Despite the marked inflammatory infiltrate and the long duration of symptoms, the underlying architecture of the lung remains intact. Significant fibrosis with restructuring of the pul-

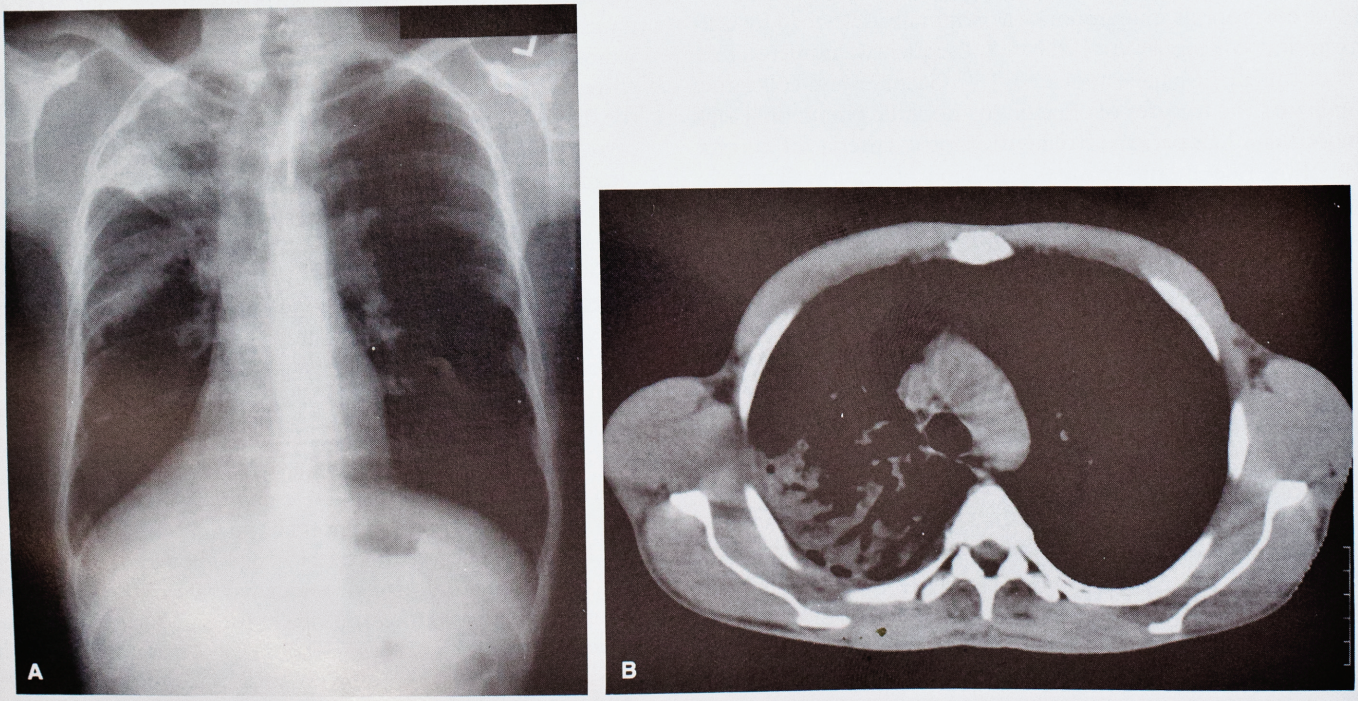

FIGURE 64-4. (**A**) A radiograph of a patient with chronic eosinophilic pneumonia demonstrates a right upper lobe infiltrate that does not appear to be peripheral. (**B**) A computed tomography scan of the same patient better demonstrates the peripheral distribution of the infiltrates.

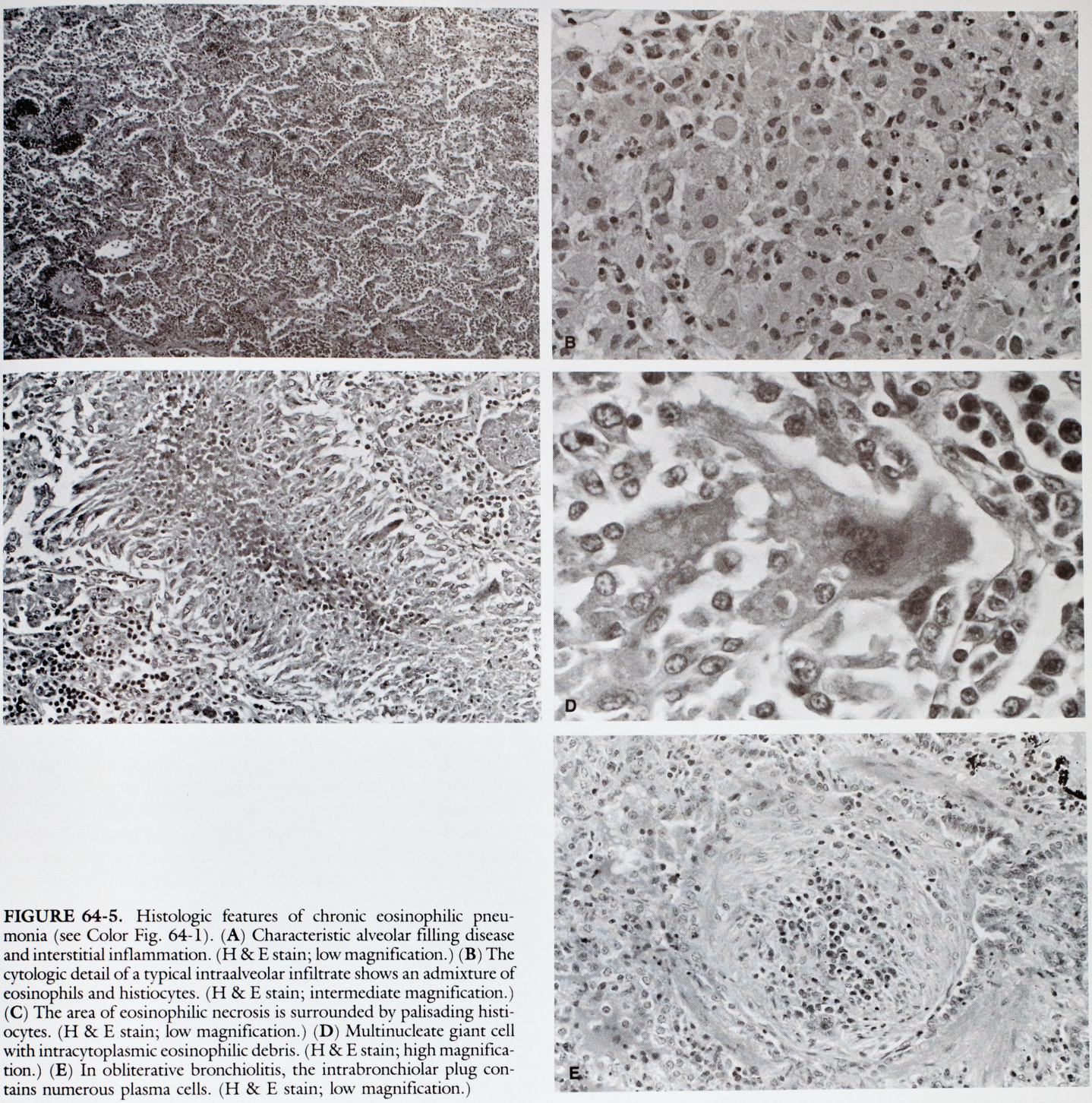

FIGURE 64-5. Histologic features of chronic eosinophilic pneumonia (see Color Fig. 64-1). (**A**) Characteristic alveolar filling disease and interstitial inflammation. (H & E stain; low magnification.) (**B**) The cytologic detail of a typical intraalveolar infiltrate shows an admixture of eosinophils and histiocytes. (H & E stain; intermediate magnification.) (**C**) The area of eosinophilic necrosis is surrounded by palisading histiocytes. (H & E stain; low magnification.) (**D**) Multinucleate giant cell with intracytoplasmic eosinophilic debris. (H & E stain; high magnification.) (**E**) In obliterative bronchiolitis, the intrabronchiolar plug contains numerous plasma cells. (H & E stain; low magnification.)

monary architecture is not observed. The subsidiary pathologic findings include bronchiolitis obliterans, which may be prominent in as many as 25% of samples. Bronchiolar mucus plugs are also a common finding. Edema is uncommon, but small amounts of fibrinous exudate are frequently seen. Rare cases have had small, scattered, sarcoid-type granulomas.

After treatment with steroids, the eosinophils rapidly lyse. Patients are occasionally biopsied after initiation of steroid therapy for several reasons, and the histologic appearance is one of an eosinophil-depleted eosinophilic pneumonia. Frequently, the only evidence of the prior eosinophilia is the presence of eosinophilic crystals in macrophages (Fig. 64-6). Some researchers have postulated that eosinophil-depleted eosinophilic pneumonias may occur secondary to spontaneous regression of the disease.

In cases of slowly resolving eosinophilic pneumonia that have been biopsied, bronchiolitis obliterans is a significant feature;

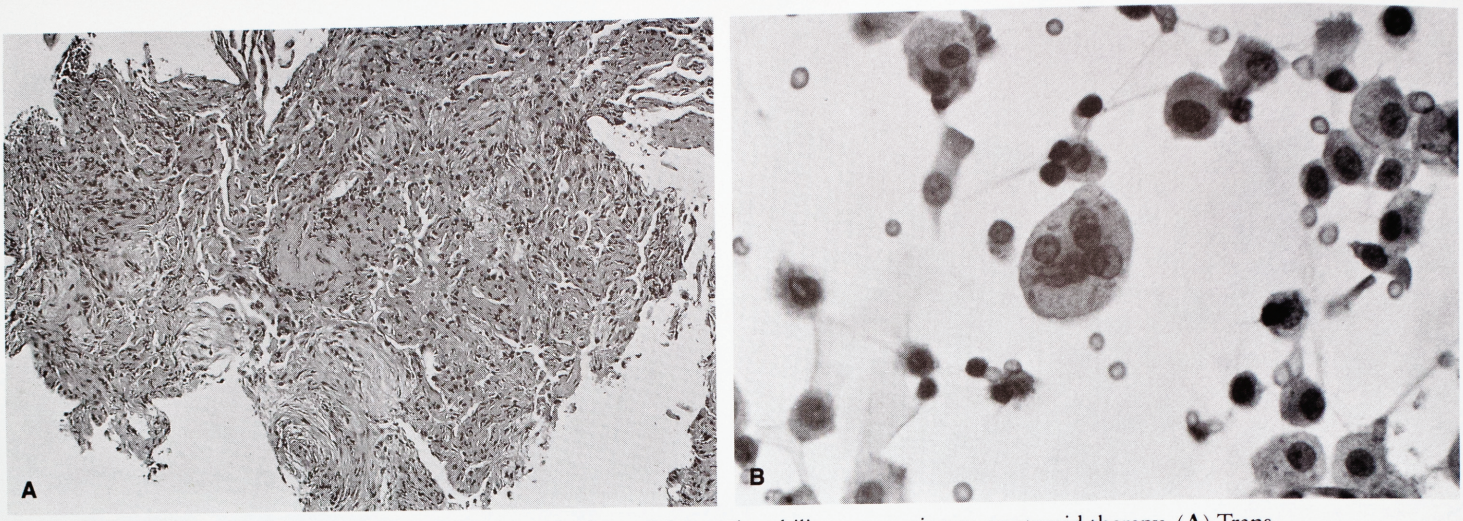

FIGURE 64-6. This patient with a slowly resolving eosinophilic pneumonia was on steroid therapy. (**A**) Transbronchial biopsy revealed an eosinophil-depleted organizing pneumonitis. (H & E stain; low magnification.) (**B**) Bronchoalveolar lavage demonstrates multinucleate histiocytes with intracytoplasmic eosinophilic crystals (*i.e.*, Charcot-Leyden). (H & E stain; high magnification.)

there appears to be some degree of overlap between these conditions, but the finding of eosinophilic crystals in histiocytes favors the diagnosis of partially treated eosinophilic pneumonia.

OVERLAP SYNDROMES

Although acute transient eosinophilic pneumonia, acute progressive eosinophilic pneumonia, and chronic eosinophilic pneumonia have been discussed as separate entities, they form a continuous spectrum of hypersensitivity disease involving the lung. Several reports have drawn attention to the possible overlap between the syndromes of bronchiolitis obliterans organizing pneumonia (BOOP) and chronic eosinophilic pneumonia.[22,23] There are several lines of evidence supporting the association. Both diseases usually present as subacute respiratory illnesses with similar nonspecific complaints. BOOP may also present with peripheral pulmonary infiltrates. Chronic eosinophilic pneumonia seen on biopsy commonly has areas of obliterative bronchiolitis identical to that seen in BOOP, and both diseases are responsive to steroid therapy.

Although less commonly than eosinophilic pneumonia, BOOP may recur after withdrawal from steroid therapy, and the recurrence is frequently in the same location as the initial infiltrates. In some cases, the lung biopsy histopathology has shown features of BOOP and eosinophilic pneumonia, and these observations led to the hypothesis that some cases of BOOP may represent an evolution of chronic eosinophilic pneumonia.[22,23] This theory has merit, but it has not been unequivocally established; the possibility deserves further investigation.

PARASITE-RELATED EOSINOPHILIC PNEUMONIA

Tropical eosinophilia was described in 1943 by Weingarten and subsequently incorporated into Crofton's original classification of pulmonary eosinophilia.[24] It has since been recognized to be caused in most cases by filarial organisms. Many parasitic infections and infestations are associated with pulmonary eosinophilia. Table 64-1 summarizes the most important sources of infections.[25,26]

Although trematodes may cause pulmonary disease with eosinophilia, they rarely mimic one of the idiopathic eosinophilic pneumonias. Nematodes are the most common parasites to cause pulmonary eosinophilia, and *Ascaris*, *Strongyloides*, *Ancylostoma* and *Toxocara* sp., as well as *Necator americana*, can all produce eosinophilia with transient pulmonary infiltrates characteristic of Löffler syndrome. Although most cases of parasite-associated Löffler syndrome are thought to coincide with migration of larval forms through the lung, it is likely that at least some cases represent hypersensitivity reactions to circulating parasite antigens.[27]

The syndrome of tropical eosinophilia due to filarial organisms, particularly *Brugia malayi* and *Wuchereria bancrofti*, can also be caused by parasitic organisms such as *Strongyloides* and *Ancylostoma* species.[28] Tropical eosinophilia most commonly has an insidious, subacute onset, and it is slowly progressive. Patients report low-grade fever and myalgia that antedate respiratory complaints by 1 to 2 weeks. As the disease progresses, cough (usually dry) and dyspnea become prominent. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea may complicate the course. Localized or generalized lymphadenopathy may ensue. Peripheral blood eosinophilia is the rule, with total eosinophil counts greater than 3000/mm^3. Leukocytosis is also common, and counts ranging up to 70,000 to 90,000 leukocytes/mm^3 with eosinophils comprising 70% to 90% of the circulating cells have been recorded. Specific filarial antibody tests have proved helpful in confirming the diagnosis.

Chest x-ray films of these patients show a wide range of changes; they may be normal or show interstitial infiltrates, patchy areas of alveolar filling disease, or diffuse miliary nodular infiltrates. Histologically, the lungs show a striking eosinophilic infiltration in the interstitium and in the alveolar spaces. Eosinophilic microabscesses cause destruction of the lung architecture. Granulomas, some with necrosis and refractile eosinophilic strands of tissue, are a feature of some cases. It is unusual to find an identifiable filarial organism in lung biopsy tissue. The organisms have been found in the lung, but examination of thousands of sections

TABLE 64-1
Parasite-Related Eosinophilic Pneumonia

Parasite	Peripheral Eosinophilia	Lung Eosinophilia	Most Common Lung Disease
Ascaris species	+ +	+ +	Infiltrates
Strongyloides species	+ +	+ +	Infiltrates
Ancylostoma duodenale	+ +	+ +	Infiltrates
Necator americanus	+ +	+ +	Infiltrates
Ancylostoma braziliense	+ +	+ +	Infiltrates
Toxocara canis and cati	+ +	+ +	Infiltrates
Brugia malayi and Wuchereria bancrofti	+ +	+ +	Infiltrates; miliary nodules
Dirofilaria species	+/−	+/−	Coin lesion
Schistosoma species	+	+	Miliary nodules; pulmonary hypertension
Paragonimus westermani	+ +	+ +	Infiltrates; nodules
Sparganum species	+ +	+ +	Infiltrates; nodules

+, usually present; + +, always present; +/−, variably present.

are required, and lung biopsy has little role in the diagnosis of this disease.

If untreated, some cases progress to significant interstitial fibrosis, and the histologic analysis shows progressively more histiocytic and granulomatous inflammation. Pulmonary function tests reflect a significant restrictive pattern with superimposed mild to moderate obstructive changes.

Patients with filaria-associated tropical eosinophilia respond dramatically to chemotherapy with diethylcarbamazine. Untreated patients may undergo spontaneous resolution of their symptoms, but the eosinophilia usually persists, and these patients frequently have recurrences or relapses of their symptoms.[28] Even in patients treated with diethylcarbamazine, there is often persistent mild and subclinical interstitial inflammation as assessed by bronchoalveolar lavage.[29]

INFECTION-ASSOCIATED EOSINOPHILIC PNEUMONIA

Several infections have been associated with significant peripheral and pulmonary eosinophilia. These include *Aspergillus fumigatus*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Corynebacterium pseudotuberculosis*, *Mycobacterium simiae*, and *Brucella* species.[30–35] Although this is an unusual occurrence and the number of cases small, the potential for misdiagnosing is great. Several points may be helpful in the differential diagnosis.

The chest roentgenogram may provide valuable clues. The classic pattern of bilateral peripheral infiltrates found in cases of idiopathic eosinophilic pneumonia is not seen in infection-associated eosinophilic pneumonia. Although atypical radiographic appearances of chronic eosinophilic pneumonia have been described, they deserve special scrutiny to exclude an identifiable etiologic agent. A detailed history with particular attention to travel to areas endemic for parasitic or fungal organisms associated with infectious eosinophilic pneumonia should be elicited.

Appropriate skin and serologic tests may provide important information. It is important to recognize that an initially favorable response to steroid therapy does not guarantee that the eosinophilic pneumonia is not infection related. Deterioration of the patient's clinical situation while on steroid therapy should prompt an aggressive diagnostic workup for an infectious cause.

DRUG-RELATED EOSINOPHILIC PNEUMONIA

Adverse reactions to drugs have been extensively reviewed.[36–46] A growing number of drugs have been implicated in the pathogenesis of eosinophilic pneumonia. Drug-related eosinophilic pneumonia is discussed in relation to drug-induced pulmonary disease in Chapter 16.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Eosinophilic pneumonia occurs as part of the spectrum of changes seen in allergic bronchopulmonary aspergillosis (ABPA), which is discussed in Chapter 63.[47] When seen in the context of ABPA, the eosinophilic pneumonia is usually patchy and always associated with other features of ABPA, such as mucoid impaction, bronchocentric granulomatosis, and exudative bronchiolitis.[48]

VASCULITIS-ASSOCIATED EOSINOPHILIC PNEUMONIA

Most cases of vasculitis associated eosinophilic pneumonias fall into the group of Churg-Strauss allergic granulomatosis and angiitis.[49] However, cases of generalized polyarteritis nodosa associated with eosinophilic pneumonia have been reported. An eosinophilic variant of Wegener granulomatosis has been described, but typical areas of eosinophilic pneumonia are not found in these cases.[50] Pulmonary vasculitides are discussed in greater detail in Chapters 68 through 70.

HYPEREOSINOPHILIC SYNDROME

The criteria for the diagnosis of the hypereosinophilic syndrome includes persistent eosinophilia greater than 1500/mm^3 for longer than 6 months.[51] Critical to the diagnosis is the exclusion of the many causes of secondary eosinophilia, the most important of which are listed in Display 64-3. There is still uncertainty about the relation between the idiopathic hypereosinophilic syndrome and eosinophilic leukemia, a chronic myeloproliferative disorder. There is evidence that a subset of patients with the hypereosinophilic syndrome are suffering from eosinophilic leukemia, but patients with eosinophilic leukemia have had cytogenetic abnormalities (*e.g.*, trisomy 8 or 21, various translocations) that are not seen in patients with hypereosinophilic syndrome.

Patients with chronic myelogenous leukemia with significant eosinophilia usually demonstrate *BCR*—gene rearrangement by Southern blot analysis and the polymerase chain reaction; the abnormality is not present in patients with the hypereosinophilic syndrome. The clinical course of patients with hypereosinophilia due to eosinophilic leukemia is similar to that of other chronic myeloproliferative disorders, including transformation to an acute blastic leukemia.[52]

Patients with the hypereosinophilic syndrome present with constitutional symptoms of fever, fatigue, and weight loss.[51–54] The disease has a male predominance, and most patients are between 20 and 50 years of age at diagnosis. In addition to the peripheral eosinophilia, these patients commonly have anemia with poikilocytosis and thrombocytopenia. The eosinophils may show some vacuolization, hypogranularity, and hypersegmentation. Bone marrow aspiration usually shows a degree of eosinophilia of greater than 30%. Cardiac involvement occurs in as many as 90% of patients and includes endomyocardial fibrosis with restrictive cardiomyopathy and mural thrombi with associated outflow obstruction. Thromboembolic complications and a variety of valvular abnormalities, including aortic, mitral, and tricuspid valve regurgitation, and mitral and aortic valve stenosis are also seen. However, these abnormalities are nonspecific and have been associated with secondary hypereosinophilias.

Pulmonary involvement occurs in about one half of patients with the hypereosinophilic syndrome. The involvement may be secondary to the cardiac disease (*e.g.*, edema, thromboembolism) or a primary involvement with patchy infiltrates similar to those seen in chronic eosinophilic pneumonia. To exclude cases of chronic eosinophilic pneumonia from the hypereosinophilic syndrome, organ system involvement other than the lung is required for diagnosis. About one half of these patients suffer from neurologic involvement. This may be central (*e.g.*, generalized encephalopathy, reversible dementia, infarcts or hemorrhage secondary to thromboembolic events) or peripheral (*e.g.*, sensory polyneuropathy, radiculopathy). Cutaneous involvement is also found in about one half of the patients. The disease may manifest as urticaria or angioedema or as pruritic erythematous papules and nodules involving the extremities and trunk. Other organ system involvement is less common but includes the gastrointestinal tract, liver, kidney, and eye.

The natural history of untreated hypereosinophilic syndrome is one of progressive disease with a median survival of 12 months. Most deaths are secondary to advanced cardiac involvement. In the largest series of patients with this syndrome, the mortality rate was only 4% at 3 years.[55] A variety of treatments have been employed. Almost 40% of patients respond to steroid therapy alone. Most patients who do not respond to steroids have a satisfactory response to hydroxyurea. Other options are various cytotoxic chemotherapeutic agents, interferon, cyclosporine, and bone marrow transplantation.[51]

DISPLAY 64-3. SECONDARY EOSINOPHILIAS

Addison disease
Allergies
Autoimmune diseases
Collagen-vascular diseases
Drug reactions
Immunodeficiency syndromes
Infections
Neoplasms
Parasites
Vasculitis

MISCELLANEOUS CONDITIONS

Collagen-vascular diseases frequently have an associated peripheral eosinophilia, but pulmonary eosinophilia has been only infrequently documented. Rare cases of rheumatoid arthritis have been associated with biopsy-proven eosinophilic pneumonia.[22] Similarly, patients with sarcoidosis occasionally present with circulating eosinophilia, and some of these patients have peripheral pulmonary infiltrates in a distribution similar to that seen in chronic eosinophilic pneumonia.[56] However, pulmonary eosinophilia has not been demonstrated. When examined histologically, the samples show alveolar filling with protein-rich fluid and interstitial inflammation characteristic of sarcoidosis with active mononuclear infiltrates admixed with confluent noncaseating granulomas. Eosinophils are inconspicuous.

There are a variety of conditions in which pulmonary eosinophilia occurs but are not regarded as cases of eosinophilic pneumonia. These conditions include pulmonary histiocytosis X (*i.e.*, Langerhans cell granulomatosis) and neoplasms associated with eosinophilia, including Hodgkin disease, non-Hodgkin lymphoma, leukemic infiltrates, and various solid tumors including carcinoma of the lung.[51]

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