Eosinophilic Pneumonia-like Areas in Idiopathic Usual Interstitial Pneumonia

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Usual interstitial pneumonia is the most common idiopathic chronic interstitial pneumonia, characterized by a temporally heterogenous pattern of interstitial injury with interstitial mononuclear infiltrates, septal fibromyxoid nodules, and parenchymal scarring. This report details the presence of focal eosinophilic pneumonia in six cases of usual interstitial pneumonia in the absence of known causes of this reaction. The relationship of eosinophilic infiltrates in usual interstitial pneumonia with regard to pathogenesis, differential diagnosis, and prognosis is discussed.

KEY WORDS: Chronic interstitial pneumonia, Usual interstitial pneumonia, Eosinophilic pneumonia, Idiopathic pulmonary fibrosis.

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Usual interstitial pneumonia (UIP) is the most common histologic pattern of chronic interstitial injury seen in patients with clinical idiopathic pulmonary fibrosis (1–6). Although this pattern of interstitial damage may have a variety of causes, most cases are cryptogenic. UIP has a distinctive histology with a peripheral subpleural and periseptal distribution of patchy interstitial injury that displays temporal heterogeneity—zones of mononuclear cell infiltration alternate with areas of old scarring, with honeycomb fibrosis and fibromyxoid connective tissue nodules within the interstitium. The mononuclear infiltrate consists largely of lymphocytes, especially T cells, and of plasma cells, with frequent lymphoid follicles. In most cases, eosinophils are quite inconspicuous, although they have been noted in up to 25% of patients examined histologically (7). Studies of bronchoalveolar lavage fluid (BALF) in UIP have shown that a level of eosinophils >3% is associated with a poor response to steroids, more severe functional abnormalities, and a worse prognosis (8–16). Despite the increased percentages of eosinophils in up to 45% of idiopathic UIP cases studied by BALF, the significance of eosinophils in tissue sections has been largely ignored (17–20). In this report, six patients with idiopathic UIP are described who had patchy zones of eosinophilic pneumonia superimposed on the underlying UIP.

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MATERIALS AND METHODS

The consultation files of the author and the Department of Pathology at the University of Pittsburgh Medical Center were searched for all cases of UIP in which prominent eosinophils were noted. Of 124 patients with UIP, 17 cases were identified. In six of these cases, eosinophils consolidated air spaces in a patchy distribution, and these cases form the basis of this report. To be considered eosinophilic pneumonia, it was required that there be (1) more than three sites of discrete alveolar consolidation and (2) filling of >100 air spaces with eosinophils at each site. Eosinophilic pneumonia-like areas occupied approximately 10–30% of tissue available for review in the six cases. Medical records were obtained from patient files and contributing physicians, and follow-up information and drug histories were specifically requested from primary case providers. In no instance was there clinical evidence that the cause of the patient's pulmonary disease was drug induced, according to the referring pulmonologist or pathologist. Similarly, no patient had a history of connective tissue or autoimmune disease or had documented previous or current parasitic infection.

Records focused on clinical findings at presentation, smoking history, white blood cell counts with cell differential, radiographic abnormalities, therapy, and survival/outcome data. Information was obtained on all six patients. Open-lung biopsies were performed in five patients, and single-lung

transplantation with explant examination was done in one patient.

RESULTS

The clinical data on the six patients in the study are presented in Table 1. Five of the six patients were men, with an average age of 49 years (range: 38–58 y). All patients presented with longstanding pulmonary complaints (average: 2.1 y; range: 0.7–4.6 y), chiefly progressive shortness of breath and dyspnea on exertion that had worsened recently. A dry cough accompanied these symptoms in four of the six patients (67%). No patient gave a history of recent infection, although Patient 3 had a history of a pneumonic process treated with trimethoprim-sulfamethoxazole 4 months before biopsy. No evidence of asthma or wheezing was described in the clinical histories. Five patients were cigarette smokers. Laboratory studies showed that no patient (none of six) had a history of peripheral blood eosinophilia, antinuclear antibodies (none of five), anti-neutrophil cytoplasmic antibodies (none of two), or rheumatoid factor (none of three). No patient had a known autoimmune disorder. No patient was on a known pulmonotoxic drug. In four studies, pulmonary function tests were reported to show restrictive lung disease.

Reports of radiologic studies, including chest radiographs and high-resolution computed tomography scans, were available in five cases. All five reports emphasized the bilateral, particularly basilar, reticulonodular infiltrates associated with honeycomb cystic change in the subpleural areas. Three reports described focal ground-glass infiltrates in a patchy random distribution. No emphasis on the peripheral nature of these alveolar infiltrates was made.

The lung biopsies and explants showed the characteristic features of usual interstitial pneumonia. At low magnification, there was a subpleural and periseptal pattern of parenchymal scarring that culminated in zones of honeycomb fibrosis (Fig. 1). The pulmonary interstitium was expanded by a patchy infiltrate of small round and centrocyte-like lymphocytes associated with plasma cells. In the subpleural zones, the pulmonary lobules were disrupted by broad bands of dense eosinophilic scar tissue accompanied by mononuclear cells and lymphoid aggregates in six of seven (86%) cases. At the advancing front of this dense scar tissue and in zones of mononuclear cell infiltration were foci of young loose fibromyxoid connective tissue containing a proliferation of reactive spindle fibroblasts/myofibroblasts within the edematous matrix (Fig. 2). At the edges of these foci, alveolar pneumocytes were reactive. In these areas of septal injury, air space macrophages were prominent, as they were in the peribronchiolar zones of the cigarette smokers. The temporal heterogeneity of interstitial injury and subpleural and peripheral lobular distribution was typical of UIP. Pertinent negative findings included the absence of granulomas, ferruginous bodies, cannibalistic giant cells, anthracosilicotic nodules, and pleuritis.

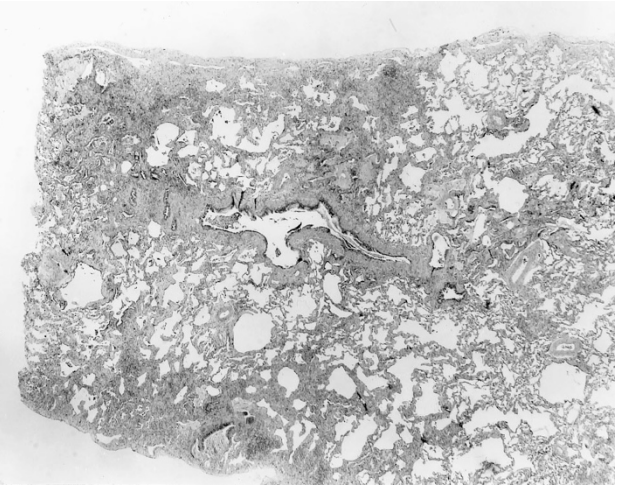

FIGURE 1. Usual interstitial pneumonia. Low magnification demonstrates the patchy, predominantly subpleural distribution of interstitial injury (hematoxylin and eosin staining, 40×).

Against this background of UIP were multifocal patchy areas, especially adjacent to subpleural zones of fibrosis, of air space consolidation by bilobed eosinophils (Fig. 3). Macrophages were admixed in all cases and often contained cytoplasmic

TABLE 1. Data in Patients with Coexistent Eosinophilic Pneumonia and Idiopathic UIP

Case	Age (yrs)/ Race/Sex	S&S	Smoking History	Peripheral Blood Eosinophilia	Therapy	Current Status
1	50 WM	DOE	+	−	Steroids	AWED, 4 months
2	44 WM	DOE, fatigue	+	−	Steroids, cyclophosphamide	DOD, 13 months
3	38 WM	DOE, cough	+	−	Single lung transplantation	AWED, 2 years
4	58 WF	DOE, cough	−	−	Steroids, cyclophosphamide	DOD, 18 months
5	48 WM	Dyspnea, DOE	+	−	Steroids, methotrexate	DOD, 4 months
6	56 WM	DOE, cough	+	−	Single lung transplantation	AWED, 4 years

W, caucasian; M, male; F, female; DOE, dyspnea on exertion; +/−, positive/negative; DOD, dead of disease; AWED, alive with evidence of disease.

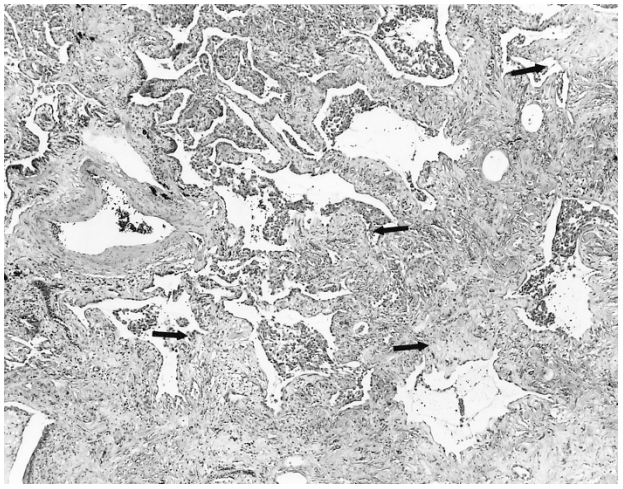

FIGURE 2. Usual interstitial pneumonia. Zones of damage were characterized by a nonuniform pattern of fibrosis with dense irreversible scarring, interstitial organization (arrows), and mononuclear infiltrates (hematoxylin and eosin staining, 48×).

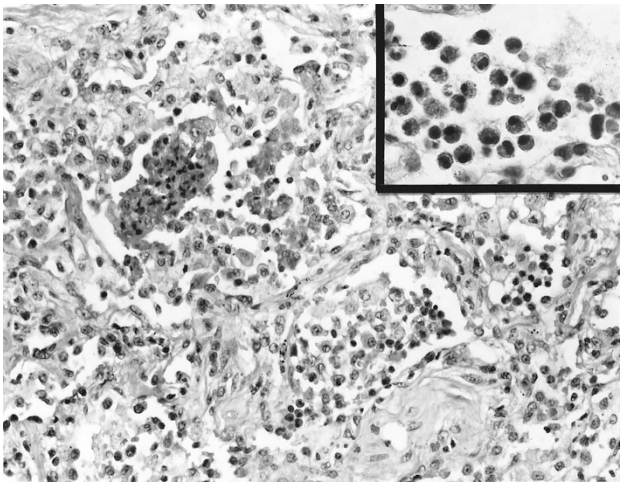

FIGURE 3. Eosinophilic pneumonia. Air space filling by eosinophils with microabscess formation (inset) and macrophages were diagnostic (hematoxylin and eosin staining, 120×; inset, 480×).

granules resembling those in the eosinophils. Loose granulation tissue was noted within air spaces in two instances. In these sites of eosinophilic pneumonia, the interstitium contained prominent intravascular and septal eosinophils. No Charcot-Leyden crystalloids, filaria, eggs, fungi, or protozoa were seen with routine or special, such as silver, stains.

DISCUSSION

Since Liebow's initial description of the categories of chronic interstitial pneumonias, idiopathic UIP has remained the most common cause of clinical idiopathic pulmonary fibrosis (1–2). In recent years, emphasis has focused on identifying pathologic mimics of UIP (*e.g.*, bronchiolitis obliterans organizing pneumonia, acute interstitial pneumonia, nonspecific interstitial pneumonia) in an attempt to better define the clinicopathologic significance and behavior of these idiopathic patterns of lung injury (1, 7). With this effort has come only minor changes in our understanding of the histologic spectrum of UIP itself. Particular emphasis has focused on acute exacerbations and organizing pneumonia-like injury patterns in UIP that are accompanied by relatively rapid declines in clinical pulmonary function (21–24). This report describes one peculiar histologic manifestation of idiopathic UIP with coexistent eosinophilic pneumonia.

The histologic pattern of injury recognized as UIP can be caused by a variety of conditions, and yet there are extremely few histologic features that suggest the underlying etiology. Eosinophilic infiltrates raise the possibility of connective tissue disease and drug-induced lung disease, and yet the presence of eosinophils in idiopathic UIP has been recognized in lavage studies for many years (10, 15, 25). A recent study found rare eosinophils in 25% of cases of UIP (7). In this current report, the six patients with UIP had no clinical evidence of drug injury or autoimmune disease and manifested a distinct consolidation of alveolar spaces and pulmonary parenchyma histologically identical to eosinophilic pneumonia.

The significance of eosinophilic pneumonia in UIP is unclear. From BALF studies, increases in eosinophils are seen in up to 45% of UIP cases and appear to be a marker of more severe impairment of pulmonary function and of poor response to immunosuppressive therapy (10–14, 17, 26). Histologic correlations with lavage studies fail to show associations of BALF eosinophilia with specific morphologic patterns of injury (8, 14, 18–20). Unfortunately, none of our six patients had bronchoalveolar lavage performed before biopsy. BALF eosinophilia is often seen with connective tissue disorders, especially scleroderma, acquired immunodeficiency syndrome, mucous hypersecretion, drug-induced lung disease, asthma, and chronic eosinophilic pneumonia (16, 17, 26). These possibilities were excluded in this series.

It is of some interest that four of the six patients in this study were 50 years of age or younger. In studies of UIP, most patients are diagnosed in their mid to late fifties (3). This raises the possibility that some early presentations with UIP may be tied to this unusual variant described in this report.

Recent clinical and radiologic studies of UIP have described markers of activity in UIP that relate to zones of interstitial injury and clinical decompensation (9, 27, 28). Clinically, UIP patients often have an acute onset of fever and dyspnea that evolves over days to weeks and that resembles a persistent viral infection in the terminal stages of their dis-

ease. High-resolution computed tomography scans show peripheral zones of ground-glass opacity superimposed on background changes of chronic lung damage, especially honeycomb fibrosis (9, 28). Rare morphologic correlates of this radiographic change have been described, but these areas are thought to show increased interstitial mononuclear cells, air space organization, and hyaline membrane formation (27–29). Diffuse alveolar damage is observed when extensive portions of both lungs are affected. This study suggests that eosinophilic pneumonia may be one histologic correlate of these zones of activity.

The pathogenesis of idiopathic UIP is unclear but has most often been attributed to mononuclear, especially T-cell, injury to the pulmonary interstitium (30–31). Activation of T cells is accompanied by elevations of cytokines, including IL-5, that may be chemotactic for other inflammatory cells, including eosinophils (32–39). Eosinophils elaborate a variety of agents that have a known cytotoxic effect on pulmonary epithelium, including eosinophilic cationic protein and major basic protein, and others that are fibrogenic, especially TGF-β (35–37).

Treatment of isolated eosinophilic pneumonia requires steroids. Such therapy would seem to be indicated in these special cases as part of conventional therapy for aggressive chronic interstitial pneumonias. There is some data too that cyclophosphamide is helpful in reducing cell counts and eosinophil numbers in the BALF of UIP patients (15).

Eosinophilic pneumonia occurring in the setting of idiopathic UIP raises several differential diagnostic possibilities (40–44). First, Langerhans' cells histiocytosis (LCH) is one cause of interstitial scarring that may have a prominent eosinophilic component. The nodular aggregates of Langerhans' cells in a bronchiolocentric distribution differs from the subpleural, peripheral lobular, and periseptal pattern of interstitial fibrosis in UIP, and Langerhans' cells do not form large coalescent aggregates in UIP. Pneumothorax can occur in both LCH and idiopathic UIP and may be one cause of pleural and subpleural air space collections of eosinophils (45). Similarly, reactive airway disease inpatients with UIP could have increased peribronchiolar and interstitial eosinophils, but alveolar eosinophils would be unusual. Cigarette smoking has been associated with increased BALF eosinophils in the setting of UIP, but masses of air space eosinophils are not seen in smokers' bronchiolitis. Chronic eosinophilic pneumonia, if untreated, can lead to irreversible pulmonary fibrosis (43, 46). These patients tend to have a history of asthma and peripheral blood eosinophilia and evanescent episodes of a febrile debilitating illness and would not have the progressive downhill clinical course and unique pattern of subpleural, temporally heterogenous scarring of UIP.

In summary, this report describes six patients with UIP who had coexistent eosinophilic pneumonia as part of their histologic presentation. The interstitial and air space damage associated with air space eosinophils may represent an atypical form of active interstitial injury in some cases of idiopathic UIP.

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