Desquamative Interstitial Pneumonitis Associated with Monomyelocytic Leukemia*

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We report two cases of desquamative interstitial pneumonitis (DIP) associated with chronic monomyelocytic leukemia. The coexistence of these two diseases may have implications for the origin of pulmonary alveolar macrophages and for the pathogenesis of DIP. Desquamative interstitial pneumonitis should be considered in the differential diagnosis of pulmonary infiltrates in patients with hematologic malignancy.

Desquamative interstitial pneumonitis (DIP) is an inflammatory process in the lung characterized histologically by massive accumulation of intra-alveolar mononuclear cells, predominantly alveolar macrophages (PAMs), without necrosis, fibrin exudes, hyaline membranes, or extensive fibrosis. Whether DIP is a distinct clinicopathologic entity or is merely part of a spectrum of fibrosing alveolitis remains controversial; however, patients with DIP tend to respond better to glucocorticoids, progress to "honeycomb lung" less frequently, and survive longer than patients with usual interstitial pneumonitis (UIP). The etiology of DIP is unknown, but more than one cause is likely since a variety of associated diseases and conditions have been noted in scattered cases. This report describes two patients with a previously unknown association—DIP and monomyelocytic leukemia. The findings in these cases provide additional evidence that alveolar macrophages and their precursors are still capable of responding to inflammatory stimuli even in the presence of hematologic malignancy.

METHODS

Open lung biopsies from both patients and autopsy lung tissue from case 2 were fixed in 10 percent buffered formaldehyde, processed routinely, and embedded in paraffin. Sections were stained with hematoxylin and eosin, periodic acid-Schiff, reticulin, trichrome, Prussian blue, gram, methenamine silver, and acid-fast stains. The lung biopsy from case 1 and post mortem tissue from case 2 were also studied by the chloroacetate esterase (CAE) technique and by immunoperoxidase for intracellular lysozyme.

CASE REPORTS

CASE 1

A previously healthy, 51-year-old woman who smoked, presented in February, 1978 with a three-week history of low grade fever, right pleuritic chest pain, and increasing dyspnea. The chest radiograph had the "classic" appearance for DIP: bilateral, hazy, ground glass infiltrates in the medial aspects of the lung bases. This illness was unresponsive to oral penicillin. After a white blood cell count was interpreted as acute leukemia, the patient was referred to the Peter Bent Brigham Hospital. Hepatosplenomegaly was present. White blood cell count was 50,000 with 30 percent atypical monocytes and 5 percent blasts. Bone marrow biopsy was interpreted as showing a myeloproliferative disorder most suggestive of chronic monomyelocytic leukemia, perhaps entering an acute phase. A Philadelphia chromosome was not present. Leukocyte alkaline phosphatase was decreased and serum lysozyme was elevated.

Because of progression of the pulmonary infiltrates over a two-week period (Fig 1A) and respiratory deterioration, an open lung biopsy was performed (described below). Therapy with prednisone was started the following day, and within one week clinical and radiographic resolution of the pulmonary abnormalities had begun. Dramatic improvement continued and the chest radiograph was nearly normal in three weeks (Fig 1B). Pulmonary problems did not recur subsequently.

On the 14th hospital day, a course of chemotherapy with cyclophosphamide, vincristine, arabinoside-C and prednisone was begun. Transient improvement of her peripheral blood counts followed, but a gradual increase in circulating blasts required a second course of the same therapy a year later, to which she did not respond. Hydroxyurea was begun in May, 1979, followed by splenic irradiation a month later, both without improvement. She was maintained with transfusions, but her condition deteriorated with cachexia, lethargy, probable radiation enteritis, and increasing circulating blasts. She expired 20 months after the onset of her illness; permission for postmortem examination was denied.

CASE 2

A 48-year-old woman was referred to the Robert Breck Brigham Hospital in 1968 with rheumatoid arthritis of approximately eight months' duration. On admission, she had...
a white blood cell count of 17,200 with 22 percent polys, 27 percent lymphocytes, and 51 percent immature monocytes. She was also anemic and mildly thrombocytopenic. A bone marrow aspirate revealed many immature myeloid and monocytoid cells, and a diagnosis of probable monomyelocytic leukemia was made. The karyotype was normal, but serum lysozyme was increased. Therapy was not recommended as the patient's hematologic condition was felt to be stable. The patient's past medical history was significant for hyperthyroidism, treated with propylthiouracil in 1965, and an undiagnosed fever of unknown origin in 1950, that remitted spontaneously. A brother died of acute leukemia at age 25.

The patient's hematologic status remained stable without treatment. White blood cell counts ranged between 10,000 and 20,000 with 20 percent to 70 percent monocytes. Anemia and thrombocytopenia persisted. The activity of her rheumatoid arthritis fluctuated, requiring hospitalization twice prior to her final admission. Rheumatoid nodules and a dermal vasculitis were documented by biopsy. Latex agglutination tests were initially positive at high titers, but later became negative, and she developed antinuclear antibodies and had positive LE preps. Between 1968 and May 1971, she received chloroquine, hydroxychloroquine, aspirin, and prednisone at various times.

In May, 1971, she presented with an exacerbation of her arthritic symptoms. White blood cell count was 16,700 with 24 percent polys, 4 percent bands, 9 percent lymphocytes, 2 percent atypical lymphocytes, and 61 percent monocytes. Diffuse bilateral reticular opacities were noted on chest radiograph. Her joint symptoms and the pulmonary infiltrates responded initially to prednisone. Two months later, however, shortness of breath began, eventually progressing over the next month to dyspnea at rest. By that time, the pulmonary infiltrates had become widespread and confluent. Clinical deterioration occurred over two days with Pco2 39, Pco2 26 mm Hg and pH 7.52. She was transferred to the Peter Bent Brigham Hospital for open lung biopsy (described below). On the first postoperative day, she became febrile, hypotensive, suffered a respiratory arrest, and could not be resuscitated. Postmortem examination was performed.

**Pathology**

The microscopic appearance of both lung biopsies and the lung autopsy sections from case 2 were similar (Fig 2). Large, round or polygonal cells filled the alveoli, including scattered multinucleated cells and cells in mitosis. Their cytoplasm contained periodic acid-Schiff (PAS) positive granules, and rare cells stained weakly positive with the Prussian blue reaction for iron. No necrosis or hyaline membranes were present. Hyperplastic, cuboidal, type II pneumocytes lined the alveolar septa, which were thickened with edema, a slight to moderate increase in reticulin, and patchy fibrosis. An interstitial cellular infiltrate composed of scattered lymphocytes, rare plasma cells, and immature myeloid and monocytoid cells was present. The latter were most evident on chloroacetate esterase (CAE) stains and im-

![Figure 1A](http://journal.publications.chestnet.org/pdaccess.ashx?url=/data/journals/chest/21277/)

**Figure 1A.** Case 1: Preoperative chest radiograph demonstrating bilateral interstitial infiltrates with more confluent alveolar opacities at the lung bases. B. Chest radiograph 3½ weeks after lung biopsy and glucocorticoid therapy. The infiltrates have resolved almost completely.

![Figure 2](http://journal.publications.chestnet.org/pdaccess.ashx?url=/data/journals/chest/21277/)

**Figure 2.** Desquamative interstitial pneumonitis with large accumulations of alveolar macrophages in the airspaces, type II pneumocyte hyperplasia (arrow), and alveolar septal thickening (Case 1, hematoxylin and eosin stain, original magnification × 50).
munoperoxidase stains for lysozyme (Fig 3). Myeloid (CAE-positive) cells were more numerous in case 1; most of the leukemic cells in case 2 had a monocytic appearance. Only rare intra-alveolar cells stained with CAE. Pulmonary macrophages, however, showed variable staining for lysozyme, most noticeable in case 2, and best seen with higher concentrations of antilysozyme antibody. Pulmonary macrophages always stained less intensely than the leukemic cells. Special stains for bacteria, fungi, and Pneumocystis were negative. Viral inclusions were not seen.

In addition, the biopsy in case 1 showed fibrinous pleuritis and subpleural fibrosis also accompanied by leukemic infiltrates. The post-mortem lung in case 2 had extensive intra-alveolar stasis of leukemic cells. Leukemic infiltration in this patient was also documented in the bone marrow, spleen, lymph nodes, and brain. The lungs in case 2 weighed 700 g each and were pale tan with granular consolidation most prominent in the lower lobes. Pulmonary rheumatoid nodules or vasculitis were not present. Joint and synovium sampled showed changes consistent with chronic rheumatoid arthritis, and a single palisading granuloma was found in a chordae tendineae of the mitral valve.

**DISCUSSION**

Both the underlying etiology and pathogenesis of DIP are unknown. Although the masses of intra-alveolar mononuclear cells were originally thought to be desquamated granular pneumocytes, subsequent ultrastructural studies have proven them to be alveolar macrophages. Farr et al suggested PAMs in DIP migrate into the air spaces in response to abnormal secretions produced by granular pneumocytes, which in turn may be reacting to an underlying immunologic, toxic, hormonal, or infectious stimulus. An immunologic injury is implicated in some cases by an association between DIP and rheumatoid arthritis, lupus erythematosus, or positive antinuclear antibody or latex agglutination tests in the absence of clinical manifestations of these disorders. Some patients have elevated IgA and others, circulating immune complexes and granular deposits of IgG within the alveolar septa. Altered immunity might also be invoked in single cases of DIP in children associated with chronic granulomatous disease, glomerulonephritis, tuberculosis and granulomatous lymphadenitis of unknown etiology.

Other cases of DIP have had assorted associations. Two children with DIP had congenital abnormalities. Tungsten carbide and asbestos rarely may cause a histologic appearance identical to DIP, as may nitrofurantoin and isoniazid. Although intranuclear inclusions were found in the cells in some DIP cases, viruses have never been conclusively identified or cultured. Recently, DIP-like reactions have been described surrounding pulmonary eosinophilic granuloma, rheumatoid nodules, and other localized lung lesions. In most cases, DIP occurs without extrapulmonary disease.

We are aware of only one case of DIP occurring in a patient with leukemia—a child with lymphoblastic leukemia in remission. Our patients are unique in that both had untreated, subacute, monomyelocytic leukemia at the onset of their pulmonary
symptoms. The association with monomyelocytic leukemia seems peculiar and raises interesting questions about both the etiology of DIP in these patients and the origin and activity of alveolar macrophages.

The histology in both our cases was similar to other patients with DIP, and patient 1 had a dramatic clinical and radiographic response to glucocorticoids, as previously seen with DIP. The intra-alveolar exudates were typical for DIP; it seems unlikely that these cells are malignant, especially since in case 1 the pulmonary abnormalities regressed without achievement of a hematologic remission. Immature leukocytes, however, were seen in the interstitium of both patients' lung biopsies, and extensive intravascular stasis of leukemic cells was present in the post mortem specimen in case 2.

Alveolar macrophages have a dual origin from circulating monocytes and their hematopoietic precursors, and from a population of pulmonary interstitial macrophages, which are long-term residents in the lung capable of replication that probably derive ultimately from monocytes also.18 Studies by Golde et al19 of leukemic patients with monocytopenia showed the number, morphology, and functional characteristics of their PAMs to be similar to control subjects, supporting the concept of a bone marrow independent source for some PAMs. Because alveolar macrophages obtained by lavage from other patients with DIP had normal in vitro phagocytic and bactericidal activity,20 and because it is unlikely immature, neoplastic monocytes would be capable of responding to a stimulus to migrate, differentiate, and function as PAMs, one might infer that the cells present within the alveoli in these cases may be derived from resident interstitial macrophages. Karyotyping of lavaged PAMs from patients whose leukemic clones bear chromosomal markers may provide direct evidence of the origin of alveolar macrophages in this setting.

The pathogenesis of DIP in these two cases, as in most cases, is uncertain. Clearly this reaction cannot be attributed to chemotherapeutic agents as neither patient's leukemia had been treated prior to the onset of respiratory symptoms. A leukemic origin of the cells is similarly excluded for the reasons discussed above. No occupational or environmental exposures were known, and a viral etiology, although possible, seems unlikely in the absence of inclusions and considering the failure of others to demonstrate viruses previously. One speculation is that the leukemic cells in the interstitium may have released or activated chemotactic factors, or injured the lung in some other way inducing the proliferation and migration of PAMs. The relatively rapid clinical deterioration and radiographic progression of the infiltrates seen in these two patients is unusual in idiopathic cases of DIP, suggesting a role for the leukemic cells in promoting the PAM reaction. Alternatively, this course may have resulted from leukemic infiltration superimposed on DIP.

Although pleuritis, usual interstitial pneumonitis, and rheumatoid nodules are more common pulmonary manifestations of rheumatoid arthritis, DIP has been reported occasionally.4,5 The relationship between rheumatoid arthritis, leukemia, and DIP in case 2 is unclear, but rheumatoid arthritis may have been important in the pathogenesis of DIP in this case. The association between DIP and monomyelocytic leukemia in these patients may be fortuitous especially considering the rheumatoid arthritis in case 2. Additional cases or experimental evidence is needed to clarify the relationship between DIP and monomyelocytic leukemia.

Desquamative interstitial pneumonitis should be added to the list of infectious, neoplastic, and therapeutic causes of pulmonary infiltrates in patients with hematologic malignancy. One of our patients suggests that DIP occurring in this setting behaves similarly to other cases of DIP with dramatic response to glucocorticoids and relatively small residual pulmonary abnormalities.

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