Nongranulomatous Interstitial Pneumonitis in Sarcoidosis*

Relationship to Development of Epithelioid Granulomas

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Nongranulomatous, nonspecific interstitial pneumonitis was a predominating or prominent histopathologic finding in 62 percent of 128 granuloma-containing specimens from open lung biopsies obtained from patients with sarcoidosis. Data from this study, combined with observations by others on the evolution of experimentally induced granulomas, indicate that interstitial pneumonitis represents a very early lesion, possibly the initial lesion, in pulmonary sarcoidosis. Because of the relative-large error of sampling inherent in the currently increasing practice of obtaining small specimens for lung biopsy via the flexible fiberoptic bronchoscope, we anticipate that interstitial pneumonitis will be seen as the only histopathologic finding in these specimens with increasing frequency. It is therefore important to recognize that interstitial pneumonitis is a characteristic, although nondiagnostic, morphologic feature of pulmonary sarcoidosis.

In reviewing the specimens from open lung biopsy obtained from 128 patients with clinical findings consistent with sarcoidosis, we found that a substantial number exhibited pulmonary lesions consisting predominantly of nonspecific, nongranulomatous interstitial inflammation. A similar observation was briefly mentioned and illustrated in a recent publication by Carrington et al. We designated this histopathologic feature as interstitial pneumonitis. The present investigation was undertaken to study the prevalence of interstitial pneumonitis in our material from biopsy and to attempt to elucidate the relationship of this finding to both the radiographic findings and the evolution of the characteristic sarcoid lesions, i.e., epithelioid granulomas. Based partly on our observations and partly on information derived from studies by others on experimentally induced granulomas, we suggest that interstitial pneumonitis represents a very early lesion in the evolution of pulmonary sarcoidosis.

Materials and Methods

This was a predominantly a retrospective study. One hundred twenty-eight specimens from open lung biopsies obtained from 128 different patients with the clinical diagnosis of sarcoidosis were studied. These specimens were obtained during the ten-year period from 1966 to 1975. The patients ranged in age from 16 to 60 years, with a mean age of 28 years. Eighty-seven (68 percent) were female patients.

A mean of 1.5 ± 0.4 slides stained with hematoxylin-eosin were examined per case. All showed epithelioid granulomas. The results of staining and cultures for mycobacteria and fungi on these specimens from lung biopsy, the results of cultures for mycobacteria and fungi from specimens of lymph nodes, sputum, and gastric washings, and the results of cutaneous testing on these patients have been previously reported. The findings from chest x-ray films taken immediately prior to lung biopsy were available for 107 patients.

The interstitial pneumonitis observed in our material was characterized by a mixed mononuclear cellular infiltrate consisting of macrophages and lymphocytes within the alveolar walls, with a predominance of macrophages (Fig 1). Little or no exudate or inflammatory cells were present in the alveoli, and hyaline membranes were not seen. Interstitial pneumonitis was usually focal, with intervening areas of normal-appearing pulmonary parenchyma usually seen. There was no apparent perivascular or peribronchial localization of interstitial pneumonitis. The interstitial pneumonitis was clas-
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Interstitial pneumonitis. Interstitial mononuclear infiltrate consists mostly of macrophages, with some lymphocytes (hematoxylin-eosin, × 160).

sified as "predominating" if it was present in a greater amount than the granulomas, as "prominent" if it was present in a lesser amount than the granulomas but nevertheless quite conspicuous, and as "absent" if it was present in a very minimal amount or not at all.

In each case the slides were examined under a dissecting microscope in order to estimate the percentage of the area of the specimen occupied by granulomatous lesions. The extent of parenchymal granulomas was graded as follows: minimal, if there were no more than a few granulomas in the entire specimen from biopsy; 1+, if the granulomas numbered more than a few but occupied less than one-third of the area of the specimen; 2+, if the granulomas occupied one-third to two-thirds of the area of the specimen; or 3+ if the granulomas occupied more than two-thirds of the area of the specimen. Fibrosis of the pulmonary parenchyma was noted as being present or absent.

RESULTS

Interstitial pneumonitis predominating was present in 31 (24 percent) of the specimens from biopsy, interstitial pneumonitis prominent was present in 48 specimens (38 percent), and interstitial pneumonitis was classified as absent in 49 specimens (38 percent). Interstitial pneumonitis predominating was seen in 11 (61 percent) of 18 specimens showing minimal parenchymal granulomas, in 14 (30 percent) of 47 specimens with 1+ granulomas, and in six (19 percent) of 31 specimens with 2+ granulomas (Table 1). The differences between the incidence of interstitial pneumonitis predominating in the groups with minimal and with 1+ and 2+ granulomas is significant (P < 0.05). The difference in incidence of 11 percent between the groups with 1+ and 2+ granulomas is not significant. The difference between the incidence of interstitial pneumo-

Table 1—Relationship of Interstitial Pneumonitis to Extent of Parenchymal Granulomas

<table>
<thead>
<tr>
<th>Data</th>
<th>Extent of Parenchymal Granulomas*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. in group</td>
<td>Minimal 1+ 2+ 3+</td>
</tr>
<tr>
<td>Interstitial pneumonitis</td>
<td>18 47 31 32</td>
</tr>
</tbody>
</table>

Predominating          11 (61) 14 (30) 6 (19) 0
Prominent               2 (11) 19 (40) 11 (35) 16 (50)
Absent                  5 (28) 14 (30) 14 (45) 16 (50)

*Table values are numbers of specimens; numbers within parentheses are percentages of group.

monitis prominent in the group with minimal granulomas compared to the other three groups taken together is significant (P < 0.05).

When the various categories of interstitial pneumonitis were related to the findings from chest x-ray films taken before biopsy, it was seen that interstitial pneumonitis predominating occurred with significantly (P = 0.05) greater frequency in radiographic stage 1 (41 percent; 9/22 specimens) than in stages 2 and 3 (19 percent [10/54] and 17 percent [5/29], respectively) (Table 2). No other significant relationships of interstitial pneumonitis to radiographic findings were noted.

Fibrosis was seen in ten (32 percent) of 31 specimens with interstitial pneumonitis predominating, in 29 (60 percent) of 48 specimens with interstitial pneumonitis prominent, and in 40 (82 percent) of 49 specimens with interstitial pneumonitis absent. The differences between these groups are significant (P = 0.05).

Detailed study of the cases with interstitial pneumonitis predominating afforded us the opportunity to observe the evolution of pulmonary sarcoid lesions. Small lesions which we interpreted as representing developing granulomas were frequently and readily seen in the midst of the mixed macrophage-

Table 2—Relationship of Interstitial Pneumonitis to Radiographic Stage of Sarcoidosis

<table>
<thead>
<tr>
<th>Data</th>
<th>0 1 2 3 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No in group</td>
<td>1 22 54 29 1</td>
</tr>
</tbody>
</table>

Interstitial pneumonitis          1 (100) 9 (41) 10 (19) 5 (17) ...
Prominent                         7 (32) 24 (44) 10 (35) 1 (100)
Absent                            6 (27) 20 (37) 14 (48) ...

*Table values are numbers of specimens; numbers within parentheses are percentages of group. Stage 0, normal; stage 1, hilar lymphadenopathy only; stage 2, hilar lymphadenopathy and pulmonary infiltrates; stage 3, pulmonary infiltrates only; and stage 4, cystic pulmonary lesions.
lymphocyte cellular infiltrate (interstitial pneumonitis) in the alveolar walls. When first recognizable, these lesions consist of a poorly circumscribed group of mononuclear cells that appear somewhat larger, contain more cytoplasm, and stain paler than the surrounding cells (Fig 2). As these cells enlarge, their nuclei become vesicular, and their nucleoli become more prominent. The cells are then readily recognized as epithelioid cells and the lesions as epithelioid granulomas (Fig 3). The epithelioid granulomas enlarge as increasing numbers of epithelioid cells develop; simultaneously, the granulomas become increasingly well circumscribed and compact, and the surrounding population of macrophages and lymphocytes diminishes substantially (Fig 4). Necrosis is not seen in the early developing epithelioid granulomas. The presence of giant cells is variable; occasionally, they appear to be the predominating cellular element of the granuloma.

**DISCUSSION**

Our findings strongly suggest that interstitial pneumonitis represents a very early lesion, possibly the initial lesion, in pulmonary sarcoidosis, antedating the appearance of the characteristic epithelioid granulomas. This conclusion is supported by our data showing that the incidence of interstitial pneumonitis predominating decreases as the density of parenchymal granulomas increases and that interstitial pneumonitis predominating is significantly more prevalent in patients with sarcoidosis of radiographic stage 1 (41 percent; 9/22 specimens) than stage 2 (19 percent; 10/54 specimens) or stage 3 (17 percent; 5/29 specimens). Furthermore, the findings of pulmonary fibrosis in 32 percent (10) of the 31 specimens showing interstitial pneumonitis predominating, compared to fibrosis in 82 percent (40) of those 49 with interstitial pneumonitis absent, is additional evidence for interstitial pneumonitis being a relatively early lesion. Because interstitial pneumonitis is invariably associated with granulomatous lesions, it appears unlikely that it repre-
sents a nonspecific or unrelated intercurrent interstitial pneumonitis.

Our conclusion that interstitial pneumonitis is an early lesion of pulmonary sarcoidosis is supported by Takahashi's study of the evolution of sarcoid lesions in lymph nodes, in which he observed that formation of discrete epithelioid granulomas was preceded by a diffuse proliferation of mononuclear cells, which he termed "diffuse lymphoreticular histiocytosis." In 1964, Teilmum stated that "It seems that granuloma formation is preceded by a diffuse mononuclear cell infiltration in all the sites where granulomas are found."

Further support for interstitial pneumonitis being an early sarcoid lesion comes from observations of granulomas induced experimentally, either by cellular or humoral immune factors. Spector and Heesom noted that preparations of antigen-antibody complexes prepared at antibody equivalence or excess and injected intradermally into rats resulted in formation of granulomas at the site of injection. Early in the response, Spector and Heesom noted a diffuse inflammatory infiltrate consisting mostly of macrophages, similar in appearance to the interstitial pneumonitis seen in our material from lung biopsy. Later, the lesions acquired the characteristics of typical granulomas, consisting of epithelioid cells and giant cells, with some lymphocytes located at the periphery. Similar findings were reported by Unanue and Benacerraf in experimental granulomas mediated by cellular, rather than humoral, immune factors.

In the examination of material from lung biopsy, it is therefore important for the pathologist to be aware that interstitial pneumonitis may be a common finding in specimens from lung biopsy obtained from patients with sarcoidosis, especially those who have relatively early disease by radiographic criteria. In our material, interstitial pneumonitis was present as either a predominating or prominent finding in 62 percent of the specimens from biopsy. Because of the increasing tendency to perform a biopsy of the lung through the flexible fiberoptic bronchoscope, the procedure of open lung biopsy is currently assuming a lesser role in the diagnosis of many types of pulmonary disease, and specimens from biopsy are generally smaller than previously. Since the potential error of sampling is inversely proportional to the size of the specimen, it is likely that with increasing utilization of bronchoscopic procedures for lung biopsy, pathologists will encounter specimens from patients with sarcoidosis that show interstitial pneumonitis as the only pathologic finding. Thus, the finding of interstitial pneumonitis in a specimen from lung biopsy obtained from a patient with strong clinical indications of sarcoidosis should prompt a careful search of the entire specimen, with serial section, to identify early developing granulomas.

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REFERENCES