Primary Interstitial Pulmonary Fibrosis:
Clinico-Pathologic Aspects of the Disease*

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INTRODUCTION

There has been a trend in recent years to consider the diffuse and circumscribed forms of interstitial pulmonary fibrosis as two different evolutions of a common disease process. This view has been based on observation of only a few cases. 1,7

While the etiology still remains obscure, a thorough study of more cases, especially of the circumscribed form, is desirable, to further understanding of the nosologic and pathogenetic aspects of an admittedly puzzling chronic pulmonary disease.

The following four cases are part of a common pathogenetic process which manifested itself in apparently unrelated clinical forms. Although the etiology may have differed from case to case, they are all related in that the lesions, allowing for the time factor, presented a common pathologic substratum.

CASE 1

This 40-year-old woman developed mild fever accompanied by anorexia, shortness of breath and non-productive cough, in June, 1960. She was admitted to hospital in July, 1960. Physical examination disclosed only nonrepetent rales over the lower lung fields. Routine laboratory tests were within normal limits. Chest x-ray film revealed infiltrations of the entire left lung and of the upper portion of the right lung. A left thoracotomy and a biopsy from the upper lobe were performed. Most of the upper and lower lobes were found to be moderately infiltrated. The postoperative course was uneventful, and she was discharged from hospital, to be followed by chest x-ray film at intervals. In the ensuing months, while the infiltrations in the left lung and upper middle lobe of the right lung were receding, ground glass opacities appeared in the lower portions of the right lung. Within a period of seven months from the onset of the disease, the infiltrations in both lung fields progressively disappeared.

CASE 2

This 42-year-old woman developed nonproductive cough, general malaise and weight loss, in April, 1959. She continued to lose weight, and shortness of breath developed in the following months. Admission to hospital occurred in November, 1959. The leukocyte count was 15,000 per mm.3 with a normal differential ratio; sedimentation rate 115 mm. in one hour. Other laboratory findings were within normal limits. There was fever on admission. This receded within one week. Physical examination of chest and other systems was not relevant. Chest x-ray film revealed diffuse infiltrations in both lungs. Left thoracotomy was performed and a biopsy specimen was taken from the upper lobe. Infiltration of the posterior segment of the upper lobe and upper portion of the lower lobe was noted at the time of operation. She was discharged one month after surgery, and was followed-up by repeated chest x-ray examinations. About one year after the onset of the disease, there was radiologic evidence of interstitial fibrosis in both lungs, although she was clinically improved.

CASE 3

A 52-year-old woman complained of productive cough and general malaise of three months' duration. She was admitted to a sanatorium hospital on May 5, 1960. Physical examination was non-contributory. There was a low-grade fever on admission. Chest x-ray film showed an inflammatory process in the upper lobe of the left lung, in the line of the second rib. Leukocytes numbered 19,300, with a normal differential ratio; hemoglobin 9.13 gm., and sedimentation rate 60 mm. in one hour. Other laboratory tests were within normal limits. She was placed on antituberculosis therapy. On June 8, chest x-ray film showed extension of the lesion. She was started on erythromycin. This was followed by some clearing of the lesion. On July 8, the upper lobe of the left lung was resected. The lung was found to be adherent to the parietal

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pleura over the posterolateral surface of the upper lobe.

**CASE 4**

This 60-year-old machinist had an infiltration in the upper lobe of the right lung of approximately eight years' duration. The lesion remained stationary until the past year, when it began to enlarge. In November, 1960, right upper lobectomy was performed. The lobe of the lung weighed 330 gm. A hard mass, measuring 5 cm. in its superior anterior diameter was found, 2.6 cm. below the apex. Six months after the operation, the patient was reported to be in good health.

**DISCUSSION**

The first two cases are examples of an interstitial pulmonary process which slowly spread to both lungs, but became a crippling disease only in the second case.

In the first case, microscopic examination of the lung tissue showed fibroblastic proliferation of the alveolar septa and infiltration of lymphocytes, with a few granulocytic leukocytes and eosinophiles. In places, the air sacs contained dense proteinaceous fluid and desquamated alveolar cells with foamy cytoplasm. There was a slight hyperplasia of the alveolar epithelium and loss of reticulum fibers. "Masson bodies" were noted in the alveolar lumens, alveolar walls and alveolar ducts. Some of the bronchioles contained organized plugs of exudate in the lumen (Figs. 1 and 2). Except for the presence of fibroblastic proliferation, the lesion in Case 1 was comparable in many aspects to that in acute interstitial pneumonitis. The absence of collageniza-
tion may account for the regression of the process in this case.

Similar histologic lesions were encountered in Case 2. Here, however, lipophagic cells in the air sacs were copious; collagenization of the alveolar septa, with focal loss of lung parenchyma, had also occurred (Figs. 3 and 4).

The absence of allergic phenomena, organizing exudate, granulomatous lesions, necrotizing arteritis and phlebitis, and the paucity of eosinophilic infiltration, differentiate both cases from the Loeffler's syndrome. The intra-alveolar and intraductal "Masson bodies" and the bronchiolar plugs of organizing exudate are nonspecific lesions, inasmuch as they have been described in a variety of pulmonary disorders.11,12

Case 3 is an example of the circumscribed form of primary interstitial pulmonary fibrosis.

The resected portion of lung exhibited the features of chronic interstitial pneumonitis with marked lymphoid infiltration, fibrosis and destruction of large areas of lung tissue. Numerous lipophages and hemosiderin-laden macrophages were in the alveolar spaces and in the fibrous tissue. The alveolar cells displayed marked hyperplasia. There was no evidence of intra-alveolar fibrosis. Destruction of the lung tissue occurred in a concentric fashion, mainly due to widening of the alveolar septa, and obliteration of the alveolar lumens (Fig. 5).

Geever et al.10 pointed out the similarity, except for the absence of foamy macro-

Figures 3 and 4: Case 2—Microscopic sections (×160 and ×320) of lung biopsy showing collagenization and widening of alveolar septa with focal loss of parenchymal tissue and lipophagic cells in the alveolar lumens.
phages, of one of their cases of atypical pneumonia to those reported by Waddell et al., under the descriptive term of "chronic pneumonitis, cholesterol type." It is felt that the term "cholesterol pneumonia" should be applied only to cases with massive infiltration of foamy macrophages. The pathologic significance of finely vacuolated macrophages remains unknown, inasmuch as they are found in a variety of lung disorders. We have found them in typical cases of primary interstitial pulmonary fibrosis of the Hamman-Rich type; they begin to appear in Case 1, and are also present in larger numbers in Case 2 of this report. It was quite evident to us that the interstitial fibrosis is the primary pathologic lesion, while the other changes developed during the evolution of the disease. In the present case, the exuberant growth of fibrous tissue and the hyperplasia of the respiratory epithelium supports our impression of an early inflammatory pseudotumor.

Case 4 typifies the evolution of circumscribed interstitial pulmonary fibrosis into alveolar cell carcinoma.

Microscopic examination of the lung lesion showed atypical and pleomorphic cells lining the alveolar spaces and featuring an alveolar cell carcinoma (Fig. 6). In the central zone of the tumor, the lung tissue was replaced by connective tissue, with occasional alveolar-like structures and nests...
of epithelial cells with anaplasia and hyperplasia. At the margin of the lesion, the lung tissue exhibited a transitional zone of septal fibrosis, with atypism of the alveolar cells. The long history and the histology of the lesion suggests that a "pseudo-tumor" had preceded the development of an epithelial neoplasm.

It has been pointed out that cases of primary interstitial pulmonary fibrosis with hyperplasia of alveolar epithelium may simulate or progress to1,3,4,15,17 an alveolar cell carcinoma. This applies also to the focal forms of the disease.

The malignant potentialities of this type of pseudo-tumor are proved by the peculiar proclivity of the bronchoalveolar epithelium to metaplasia, metaplasia and neoplasia. The concept of "cicatrization" cancer5,18 has been substantiated by several reports of peripheral lung cancer associated with scar.19 A full scale of lesions from simple hyperplasia to alveolar cell carcinoma has been described in the healing infarctions of the lungs. The experimental evidence that fibrosis of the septal walls and epithelialization of the alveoli is enhanced by the chronic pathologic stimuli and/or by delay of scar formation4,19 is a further indication of the variegated response of the alveolar epithelium to a number of stimuli. The frequent association of pulmoceriosis in systemic scleroderma with alveolar cell carcinoma further indicates that simple fibrosis and hyperplasia may evolve into a malignant adenomatous growth.4,18

**SUMMARY**

The clinico-pathologic aspects of one case of protracted interstitial pneumonia and three cases of interstitial pulmonary fibrosis have been discussed. Further evidence of the pathogenetic relationship between the diffuse and the circumscribed forms of interstitial pulmonary fibrosis has been presented. Progression to an alveolar cell carcinoma occurred in one case.

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**Zusammenfassung**

Klinisch-pathologische Gesichtspunkte eines Falles einer verzögerten interstitiellen Pneumonie und von 3 Fällen einer interstitiellen pulmonalen Fibrose wurden diskutiert. Weitere Anhaltspunkte einer pathogenetischen Beziehung zwischen oder diffusen und der umschriebenen Form der interstitiellen pulmonalen Fibrose wurden vorgebracht. Eine Progression zu einem Alveolarzell-Carzinom erignete sich in einem Fall.

**References**


RADIOLOGIC APPEARANCES OF LYMPHANGITIS CARCINOMATOSA OF LUNG

The chest radiographs of 20 patients, subsequently proved at necropsy to have lymphangitis carcinomatosa, were examined. Abnormalities were found to be slightly more common in the right lung than in the left. No single radiographic change was diagnostic, but the combination of abnormalities was sufficiently characteristic to suggest the diagnosis in about half the cases. The lungs of five of these patients were studied radiographically and histologically at necropsy. It was shown that tumor-filled pleural lymphatics cast no recognizable shadow and that "B" lines are due to the interlobular septa, thinned by fibrous and inflammatory tissue around tumor-stuffed lymphatics. "A" lines appear to be due to "anastomotic" lymphatics, which run an independent course through the lung when they are similarly surrounded by fibrous tissue and chronic inflammatory cells. TRAPPENELL, D. H.: "Radiological Appearances of Lymphangitis Carcinomatosa of the Lung." Thorax, 19:251, 1964.

EFFECT OF EXTRACORPOREAL CIRCULATION ON FORMED BLOOD ELEMENTS

The authors studied the effect of extracorporeal circulation upon formed blood elements in experiments and actual clinical conditions by using an apparatus devised by the Research Institute of Experimental Surgical Equipment and Instruments (1959 model). Extracorporeal circulation was found to cause changes in all types of formed blood elements. In the overwhelming majority of cases, their numbers are seen to diminish. In clinical perfusions, however, leukocyte alterations are insignificant. The degree of hemolysis during perfusion is, in the main, contingent upon the biologic compatibility of the donor's and recipient's blood and the cleanliness of all parts of the apparatus, coming in contact with the blood. To achieve prophylaxis of hemolysis and reduction of post-perfusion reactions, it is necessary that the polyvinyl and polyethylene tubings be used but once each time.


RECOVERABILITY OF ACID FAST BACILLI

The recoverability of acid-fast bacilli by smear and/or culture of resected tuberculous pulmonary lesions was evaluated in a series of 405 patients. Acid-fast bacilli were demonstrable consistently in a higher incidence by smear than by culture of the resected specimen. The incidence of recoverability of acid fast bacilli by smear of the resected lesion did not vary greatly with the duration of preoperative drug therapy except when the duration of therapy was greater than one year, under which circumstances there was a somewhat greater incidence of positive smears. The incidence of recoverability of acid-fast bacilli by culture of the resected specimen decreased with increase of the duration of preoperative drug therapy up to six to ten months. KILLEN, D. A., FOSTER, J. H., RHEA, W. G. JR., MCCracken, R. C., Dively, W. L. AND HUBBARD, W. W.: "Recoverability of Acid-fast Bacilli from Resected Pulmonary Tuberculous Lesions as Related to the Duration of Preoperative Antituberculous Drug Therapy," J. Thor. and Cardiovas. Surg., 47:610, 1964.