CHRONIC DIFFUSE INTERSTITIAL FIBROSIS OF THE LUNGS

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According to Mallory (1948) the term interstitial fibrosis when applied to the lungs should refer to fibrous proliferation in the alveolar walls or about the lymphatic vessels which run in relation to air passages and blood vessels. These two sites are frequently involved together, the thickening predominating around the bronchioles and arterioles and involving only those alveolar walls which are adjacent to the airways and vessels. An instance of such a condition is seen as a consequence of chronic venous congestion, but the fibrous proliferation in this case is usually of minor degree and, being a response to particulate matter, tends to be focal in distribution. Hamman and Rich (1944) first drew attention to a peculiar form of interstitial fibrosis, which principally affected alveolar walls more or less diffusely throughout the lungs and for which no cause was apparent. Other instances of this condition have since been reported from America (Eder, Hawn, and Thorn, 1945 ; Potter and Gerber, 1948 ; Beams and Harnos, 1949 ; Golden and Tullis, 1949), but none from this country. Previous cases have usually been described as acute, whereas in the present instance the duration of the illness and the character and extent of the pathological changes warrant the designation of chronic diffuse interstitial fibrosis of the lungs.

CLINICAL FINDINGS

The patient was a woman of 25, with no history of occupational exposure to dust or fumes. A month before the onset of the final illness her first child was born normally. Apart from a pulse rate of 100 per minute the early puerperium was also normal. She first complained of a pleuritic type of pain in the chest and a dry cough with sore throat, malaise, and lassitude. These symptoms appeared over the course of a few days, and her condition was diagnosed as pneumonia. The cough, however, became steadily worse and paroxysmal, and during the subsequent course of the illness there were several small haemoptyses. About three months after the onset dyspnoea on exertion first developed. The dyspnoea soon increased in severity until finally it was prominent even at rest and was accompanied by cyanosis. Recumbency did not aggravate the breathlessness, although paroxysmal exacerbations became increasingly frequent, sometimes without apparent cause, but mostly in association with the bouts of coughing. On these latter occasions the dyspnoea and cyanosis were extreme. Loss of weight was slight. The patient was under continuous medical care, being investigated as an in-patient at several hospitals. At no time was there evidence of dependent oedema, hepatic enlargement, or venous engorgement. Clubbing of the fingers and toes developed towards the end of the illness. Physical signs in the chest were slight and inconstant, although terminally those of bronchitis were found. Pyrexia was never observed, but the resting respiration rate

was often 40 and the resting pulse rate ranged between 90 and 140 per minute. Repeated radiographs of the chest showed no significant abnormality in the lungs until two days before death, when there were mottled opacities in the hilar regions with a diffuse network in the remainder of the lung fields. Radiological evidence of cardiac enlargement developed during the latter part of the illness. Many examinations of the sputum for tubercle bacilli and fungi were made microscopically, all with negative results. Eight months before death the Mantoux reaction (strength of tuberculin unrecorded) was negative. A throat swab on one occasion grew *Staphylococcus aureus* profusely. Apart from a mild terminal leucocytosis, blood counts were repeatedly normal. The erythrocyte sedimentation rate (Westergren) varied from 6 to 15 mm. in one hour. Two estimations of the basal metabolic rate eight and six months before death showed +18% and -4% of normal respectively. Death occurred in extreme respiratory distress 17 months after the onset without a diagnosis being reached.

PATHOLOGICAL FINDINGS

Gross Appearances.—The body weighed 47 kg. and showed little evidence of wasting. There was frothy muco-pus in the trachea and main bronchi, and a patchy fibrinous exudate on the visceral pleurae. The right lung weighed 530 g. and the left 500 g. On the cut surfaces the lungs were a mottled brick-red and grey. Both were firm, giving the initial impression of consolidation. Closer inspection, however, revealed a considerable degree of aeration in what appeared to be a very fine type of fibrosis more or less evenly distributed throughout both lungs. The features did not suggest an organized pneumonia. A little pulmonary oedema was noted. The lymph nodes at the pulmonary hila were enlarged and firm. The heart weighed 330 g. and showed considerable hypertrophy with some dilatation of the right ventricle. The left ventricle was normal in all respects and no congenital defects were present in the vascular system. The liver (1,600 g.) showed a typical nutmeg appearance and the spleen was chronically congested. All the other organs appeared normal.

Microscopical Appearances.—Preparations from upper and lower lobes of both lungs were stained by haematoxylin-eosin, Weigert's elastin, Lendrum's reticulin, and Masson's methods. In an endeavour to demonstrate micro-organisms, Gram's, Ziehl-Neelsen's, and Levaditi's stains were employed, whilst sections stained by Mann's and Lendrum's (1947) methods were searched for inclusion bodies.

The bronchi and bronchioles showed widely varying degrees of chronic inflammation, but there was no epithelial metaplasia. Most blood vessels were normal, but a few had slight intimal thickening and reduplication of the internal elastic lamina, whilst an occasional arteriole contained an organizing thrombus. Peribronchial and periarterial connective tissues showed variable fibrosis and chronic inflammatory cell infiltration. There was congestion and oedema in the septa, and an early fibrinous exudate of patchy distribution on the pleura. Reactive changes were found in a hilar lymph node with infiltration by plasma cells and in parts neutrophils.

It was, however, in the respiratory bronchioles and their subdivisions that the most pronounced and characteristic features were observed, although the severity of the involvement was not uniform. Thickening of the walls of the alveoli, alveolar ducts, and respiratory bronchioles occurred mainly as a result of fibrous proliferation of reticular rather than collagenous type (Fig. 1). Fibroblasts were little in evidence. It must be emphasized that the fibrosis was confined to the walls of air spaces, their lumina being quite free from this change. The thickening of alveolar walls was augmented by congestion of the capillaries, which were nevertheless reduced in number, by a mild oedema and by a pleomorphic cellular infiltration (Fig. 2). The latter consisted mainly of lymphocytes and plasma cells with some monocytes. There were eosinophils in places and a

FIG. 1

FIG. 2

FIG. 3

FIG. 4

few dust-laden phagocytes. Interstitial foci of lymphocytes were especially noticeable at the divisions of respiratory bronchioles. Smooth muscle appeared somewhat diminished in amount, but the elastica was normal. The alveolar spaces were lined by greatly swollen cells frequently forming continuous sheets (Fig. 3). The alveolar epithelium had proliferated in some places so that it partly occupied the alveoli. Separation of the epithelium from the thickened alveolar walls was often noted. There were a few intra-alveolar giant cells, presumably arising from the alveolar epithelium. In addition many alveoli contained an exudate of granular phagocytes with some lymphocytes, plasma cells, and eosinophils. A few foci of intra-alveolar calcification were also detected, but no ossification as described by Beams and Harnos (1949). Nowhere was there evidence of organization of the intra-alveolar exudate. There was emphysema of mild degree and patchy distribution throughout the lungs, principally affecting those vesicles whose walls showed least fibrosis. The respiratory passages appeared patent all along their courses and no evidence of obstruction by fibrosis was found.

FIG. 1.—Fibrous thickening of alveolar walls with reduction in the size of the alveoli. No organization of the alveolar exudate. Reticulin. $\times 65$.

FIG. 2.—General features of chronic diffuse interstitial fibrosis. Haemalum and eosin. $\times 65$.

FIG. 3.—Hypertrophic alveolar epithelium, lining greatly thickened alveolar walls. Haemalum and eosin. $\times 200$.

FIG. 4.—Area illustrating more acute reaction with the formation of hyaline membranes. Haemalum and eosin. $\times 65$.

Although the changes in the alveolar walls were mostly chronic in nature, evidence of a recent reaction was present in a few areas. This took the form of a mild neutrophil exudation into the alveoli and their walls, associated with a little haemorrhage and considerable oedema into the alveoli. The most impressive feature of the more acute process was the formation of thick, eosinophilic, hyaline membranes lying in close apposition to the alveolar walls, especially where the epithelium was detached or missing (Fig. 4). These membranes were apparently of a fibrinous nature, since they took up the red dye in Masson's method. There was a slight admixture of mononuclear cells, but even in this recent exudate no evidence of intra-alveolar organization was noticed. The acute reaction seemed to involve those parts of the lung least affected by the reticulin fibrosis.

As in previous cases special stains failed to demonstrate bacteria, including the tubercle bacillus and spirochaetes, and no definite cytoplasmic or nuclear inclusion bodies were revealed in the alveolar or bronchiolar epithelium. Unfortunately biological tests for the presence of virus could not be carried out, since all the material had been fixed before the nature of the condition was realized.

DISCUSSION

The pathological features of this case are similar in type to those characterizing cases previously reported, although, judging by published illustrations, the present instance appears to represent the most advanced stage of the disease so far recognized. The intensity of the changes varies considerably from one part of the lung to another and chronic features predominate over the acute ones. As indicated above, the more acute reaction tends to affect those parts of the lung where the chronic changes are least in evidence, suggesting that the disease progresses as a consequence of the cumulative effects of a series of minor insults which involve the lung irregularly. The appearances also suggest that the eosinophilic, hyaline membranes which lie in close apposition to the alveolar walls are fibrinous in nature, being formed by condensation of fluid exudate under the pressure of the inspired air. Although this feature is found in uraemia and in other forms of pulmonary oedema, it may be that organization of the membranes in places denuded of epithelium is responsible for the reticulin fibrosis of the alveolar walls in the advanced stage of the disease. The proliferation of the alveolar epithelium may likewise represent an attempt at healing.

Diffuse interstitial fibrosis of the lungs is readily distinguished from an organized bacterial pneumonia by the totally dissimilar reticulin pattern, the characteristic feature of the common bacterial disease being reticulin production in the intra-alveolar exudate with gradual obliteration of the alveolar spaces (Fig. 5). In both conditions the normal arrangement of the elastic tissue is preserved. It might be expected that an acute interstitial pneumonia, as described in influenza (Cole and MacCallum, 1918; McCordock and Muckenfuss, 1933; Scadding, 1937), in measles and pertussis (McCordock and Muckenfuss, 1933), and in atypical pneumonia (Drew, Samuel, and Ball, 1943; Perrone and Wright, 1943; Saphir, 1943; Dingle, Abernethy, Badger, Buddingh, Feller, Langmuir, Ruegsegger, and Wood, 1944; Needles and Gilbert, 1944; Golden, 1944) could initiate a diffuse fibrosis. The character and distribution of these acute lesions do not, however, seem consistent with this view, since in acute interstitial pneumonia there is a suppurative bronchiolitis with some reaction in the immediately adjacent alveolar walls and alveoli. These changes thus have a distinctly focal distribution centred on the

FIG. 5.—Bacterial pneumonia showing organization of intra-alveolar exudate and normal size of alveoli, for comparison with Fig. 1. Reticulin. $\times 65$.

bronchioles, quite unlike that found in diffuse interstitial fibrosis. Furthermore, as the bronchiolar lesion of acute interstitial pneumonia is characteristically suppurative, it might be expected to disrupt the elastica, which in diffuse interstitial fibrosis remains intact. The pneumonic lesion of Q fever (Lillie, Perrin, and Armstrong, 1941; Whittick, 1950; Niven, 1950) has not been observed in a chronic phase, but being lobar in distribution it can hardly be related to diffuse interstitial fibrosis. Gouley (1938) has discussed the evolution of lung lesions in rheumatic fever, which in its chronic phase bears a close resemblance to diffuse interstitial fibrosis. However, in the present instance of this latter condition there was none of the destruction of the elastic tissue with subsequent hyperplasia, which Gouley regards as characteristic of the rheumatic process, and no rheumatic stigmata were present at necropsy. Ellman and Ball (1948) refer to pulmonary changes, associated with polyarthritis of rheumatoid type, which appear indistinguishable from the features of diffuse interstitial fibrosis, and in their two necropsy reports no mention is made of any cardiac lesion. In the present case there was no history of allergy nor of sulphonamide therapy and the pathological features did not suggest a sensitization phenomenon. Radiation pneumonitis (Warren and Gates, 1940) also bears some resemblance to diffuse interstitial fibrosis, but irradiation can be excluded as an aetiological factor in this case. The possibility of an industrial origin for the fibrosis can be eliminated by the history. Intra-alveolar giant cells were not so numerous in the case under discussion as in the interstitial giant cell pneumonia (Dürck, 1896–7; Hecht, 1910), which may apparently arise independently or follow infectious fevers such as measles (Pinkerton, Smiley, and Anderson, 1945). Giant cell pneumonia is, however, reported as an acute condition of infancy and childhood, showing nuclear and cytoplasmic inclusions in the alveolar epithelium (Pinkerton and others, 1945), and hence is a most unlikely precursor of chronic diffuse interstitial fibrosis. It thus seems justifiable to regard diffuse interstitial fibrosis of the lungs as a distinct, though apparently rare, entity of uncertain aetiology.

The initial symptoms indicated a respiratory infection, but the clinical features were rapidly dominated by dyspnoea which ultimately became extreme. A respiratory rather than a cardiac origin for the dyspnoea is suggested by the absence of aggravation on lying down, together with the absence of any signs of heart failure

during life. The cardiac enlargement and lack of radiological evidence of a pulmonary lesion nevertheless distracted attention from the lungs. The pathological changes in the lungs are quite sufficient to account for the clinical features, the dyspnoea being primarily attributable to the widespread fibrosis of the alveolar walls coupled with reduction in the size of alveoli and the diminished capillary bed. Such emphysema as occurred may be regarded as compensatory in nature, there being no evidence to support Hamman and Rich's (1944) view that the emphysema is the result of fibrous stenosis of proximally placed respiratory bronchioles. In such a severe chronic pulmonary disorder it is not surprising that hypertrophic osteoarthropathy should develop.

With a single exception all the previous cases of this condition which have been identified in the literature pursued a considerably shorter course than did the present case. The cases of Hamman and Rich (1944) survived four to 24 weeks after the onset, that of Eder and others (1945) 17 weeks, and that of Potter and Gerber (1948) 32 weeks. The case of Beams and Harmos (1949) lived for 15 months, but it was only during the last four months that dyspnoea became incapacitating. The second case reported by Golden and Tullis (1949) had a course of nine months, but it is doubtful whether their first case, with an illness lasting about six years, represents a true example of diffuse interstitial fibrosis, since there was no increase of reticulin fibres in the alveolar walls and such thickening of the latter as occurred was apparently cellular in nature. The distribution of the changes in the two cases of Golden and Tullis (1949) is stated to be identical with that of the inflammatory elements in primary atypical pneumonia, which Golden (1944) himself describes as characteristically focal, resembling grossly a miliary granuloma. This differs from the diffuse involvement described by Hamman and Rich and in the present case. It is worth noting that, compared with the latter, the pathological changes found by Beams and Harmos in a case of 15 months' duration, and by Golden and Tullis in their case of nine months' duration, appear to be less severe and extensive. In the present case the history extends over 17 months, which appears to be the longest duration recorded in a definite instance of this condition.

SUMMARY

A case is presented showing features of chronic diffuse interstitial fibrosis of the lungs with such widespread involvement of the alveolar walls that dyspnoea dominated the clinical picture. No specific cause has been identified.

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