Acute, Diffuse, Interstitial Fibrosis of the Lungs

REPORT OF A CASE

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The syndrome of acute, diffuse, interstitial fibrosis of the lungs, first described by Hamman and Rich in 1935¹ and 1944,² is still essentially unaffected by therapy and obscure in etiology, despite its rather distinctive clinico-pathological picture. A recent review analyzes all of the previous case reports and treats extensively the possible etiologies.³ However, in view of several remarkable features, it was felt worthwhile to present briefly this one additional case. These include a 19-year hospital confinement for mental illness with consequent opportunity for close observation, an unusual combination of laboratory and pathological findings, and a strikingly rapid onset and short course documented by chest films.

The case which follows bears a close similarity to those of Hamman and Rich, both clinically and histologically, and particularly in its brief duration. Their four patients had unexplained cough and dyspnea, while other symptoms were minimal, and all died of pulmonary insufficiency and/or right heart failure from 31 days to six months after the onset of symptoms. The characteristic pathological changes in the lungs were: (1) Edema and fibrin deposit in alveolar walls followed by extensive, diffuse interstitial proliferation of fibrous tissue; (2) enlargement of alveolar lining cells; (3) minimal leukocytic infiltration; (4) necrosis of alveolar and bronchiolar epithelium; and (5) alveolar hyaline membranes.

The illness as described in the original cases, and also in a relatively few others, including the present one, can properly be called “acute.” This is in contrast to a majority of the reports, which are concerned with courses of years in duration.

Case Report

A white widowed woman, a former domestic, was admitted to Taunton State Hospital (case No. 33642) in July of 1938 at the age of 62 because of agitated behavior in response to hallucinations. She remained hospitalized for 19 years, with her fatal illness occurring at age 81. She was diagnosed as suffering from psychosis with cerebral arteriosclerosis, and initial therapy was aimed at controlling overactivity. Later, she was generally pleasant and cooperative, with a much clearer sensorium; she no longer reacted to hallucinations, but indulged only in occasional temper tantrums. There was history of cancer in two sisters; her own medical history was marked by an oophorectomy, said to be for an ectopic pregnancy. Admission physical examination and laboratory determinations did not indicate any noteworthy physical illness. Mild diabetes mellitus was manifested within two years after admission. An epidermoid carcinoma was removed from the left hand nine years after admission and a benign intraductal papilloma from the right breast about four and one half years later. She was given intermittent “cardiac” therapy for an illness said to be characterized by “hepatomegaly, ascites and peripheral edema,” but had required no such treatment for the past 15 years.

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FIGURE 1: Posteroanterior X-ray film on the 14th day of illness (December 23, 1957).

FIGURE 2: Posteroanterior X-ray film one year before illness (December 12, 1956).

FIGURE 3: Posteroanterior X-ray film on the third day of illness (December 12, 1957).

FIBROSIS OF THE LUNGS
Her first chest film, taken four years after admission, showed no evidence of pulmonary disease. The heart showed left ventricular hypertrophy and dense calcification in the aortic arch. Just a year before her final illness, another film again showed normal lung fields (Figure 1). She remained asymptomatic, with diabetes well controlled, and with no other abnormality reflected by routine laboratory tests, until the onset of the final illness. A blood study a week before fever began gave a red cell count of 3,500,000 with a hematocrit of 30 per cent and a hemoglobin of 10.6 gm; and 4,300 white cells, of which 39 per cent were neutrophils, 7 per cent stab forms, 1 per cent eosinophils, and 53 per cent lymphocytes. Blood urea nitrogen was 14 mg per cent. During this period, she responded to treatment for aphthous buccal ulcers. She also had vague complaints of malaise, non-localized chest pain, and joint pain suggestive of arthritis, but without objective signs. Paget's disease of the pelvis was an incidental finding.

Her febrile illness began with a temperature of 101.2°F, and treatment included Tetracyn, 250 mg q.i.d. A white blood cell count two days after onset was 3,800 with 39 per cent neutrophils, 10 per cent stab forms, 1 per cent eosinophil, and 50 per cent lymphocytes. On the next day, a chest film was interpreted as showing only minimal congestion (Figure 2). Physical examination gave evidence of moderate hepatosplenomegaly, but was not otherwise remarkable until terminal cyanosis and pulmonary congestion developed three days before death. On the eighth day, the hematocrit was 23 per cent, hemoglobin 7.9 gm per cent, white cell count 2,300 with a full differential count not performed, but frequent primitive cells seen. Marked cyanosis and dyspnea developed on the 14th day with moist rales scattered throughout all lung fields and an x-ray film showed diffuse infiltration, appearing somewhat coarser than miliary dissemination, involving almost the entire lung fields bilaterally (Figure 3). Oxygen and digitalis were added to the treatment and bone marrow aspirated. Following blood transfusion, the hematocrit on the 15th day was 34, with white count 4,700, again including many primitive forms. A direct serum bilirubin was 2.20 mg per cent and indirect was 2.95 mg per cent.

The hematologic abnormalities dominated the early clinical considerations so that leukemic leukemia and aplastic anemia were tentative diagnoses. With the physical and x-ray findings of pulmonary infiltration, infection, such as staphylococcal pneumonia, was felt to be associated. Hematological review of peripheral blood and marrow slides confirmed the presence of primitive white cells, but the diagnosis was felt to be aplastic depression of the bone marrow in the face of toxicity from overwhelming pulmonary disease.

A septic course continued until the final days of illness, with rectal temperatures usually reaching 102-103 daily. Diabetes remained controlled as indicated by relatively normal blood sugars. The disease was progressive, with little response to any of the therapeutic measures and she died on the 17th day after onset of fever.

**Necropsy Findings**

There were petechial hemorrhages of the pericardium, which was otherwise thin and transparent. The heart weighed 380 grams. None of the heart chambers was dilated, and the right and left ventricular walls were 4 mm. and 12 mm. thick, respectively. There was no hemorrhage of the myocardium. Microscopically there was fatty infiltration of the myocardium. Except for slight calcification of the aortic valve, the valve leaflets were thin and pliable. There was minimal atherosclerosis of the coronary arteries.

There was no free fluid in either pleural cavity. The lungs weighed 940 and 780 grams. The pleural surfaces were dull with small patches of fibrin on them. All pulmonary tissue was diffusely subcrepitant with a firm, unyielding consistency, and on sectioning was uniformly light gray. The histologic appearance was striking, giving an overall impression that the entire lung parenchyma was rapidly turning into fibrous connective tissue. Alveolar septa were thickened and contained proliferating fibroblasts, lymphocytes, and neutrophilic polymorphonuclear leukocytes (Figure 4). Eosinophils were not numerous. In some alveolar walls there were already mature collagenous fibers in association with fibroblasts. Alveolar lining cells were greatly hypertrophied and had large, vesicular nuclei. Many of these had exfoliated into the alveolar spaces, and some showed phagocytic activity. Most of the alveoli contained only these bizarre cells, but a few contained clumps of fibrin in various stages of resolution. There was no cellular intra-alveolar exudate, nor were there hyaline membranes. There was no exudate or aspirated material in the bronchi. There were no emboli in pulmonary arteries. An enlarged mediastinal lymph node showed extensive caseation necrosis, epithelioid reaction, and Langhans giant cells. Tubercles were not found in the lung parenchyma.

There was no free fluid in the peritoneal cavity. The liver weighed 1310 grams. Its surface was finely nodular and the parenchyma had a "nutmeg" appearance. Microscopically there was moderate degenerative fatty infiltration of the central portions of the lobules. Multiple sections of liver disclosed two microscopic non-caseous tubercles.

The spleen was soft and enlarged, weighing 205 grams, and the pulp was infiltrated by polymorphonuclear leukocytes. The kidneys weighed 120 and 140 grams and their surfaces were granular. There was hyaline fibrosis of occasional glomeruli and ad-
FIGURE 4: A characteristic alveolar septum showing the hypertrophied alveolar lining cells and the thickening by edema, fibroblasts, and occasional inflammatory cells.

advanced intimal thickening of small arteries. There was a small endometrial polyp. Ovaries were absent. The vertebral bone marrow was slightly paler than usual. Other organs showed no abnormality.

The principal pathologic diagnoses were:
1. Acute, diffuse, interstitial pulmonary fibrosis with associated interstitial pneumonitis.
2. Fibrinous pleuritis.
3. Active tuberculosis of mediastinal lymph node with recent dissemination to liver.
4. Acute toxic splenitis.
5. Low grade right heart failure with chronic passive congestion of liver and edema of lower extremities.
6. Arteriopathy.
7. Endometrial polyp.

Discussion

As has been mentioned, the relatively abrupt onset and fulminating course of 17 days, believed to be the shortest on record, is consonant with the original description but in contrast to the majority of later cases.14 No prior sign or symptom of pulmonary disease was evidenced. Laboratory and particularly x-ray film studies were similarly negative. The changes in chest film findings during the febrile illness were remarkable. (See illustrations.) There are, however, several other reports of courses of six months or less, and recently illnesses of 29 and 25 days have been described.5 In the more chronic form of the disease, a patient was treated with corticotropin and cortisone, with improvement to the point that an x-ray film showed reduction in a previous fairly extensive process to a few fibrous strands. After cessation of therapy, rapid exacerbation led to death in five days. The total length of illness was, of course, much greater; nevertheless, the rapidity with which the disease may progress from a few findings to a fatal outcome is again illustrated.15

No aplastic anemia or leukopenia has been described previously; on the contrary, a tendency toward leukocytosis and polycythemia has been variably present. The leukopenia with relative lymphocytosis and the progressive anemia with chemical jaundice apparently represented toxic depression of the bone marrow.

Also unusual was the presence of active tuberculous foci in a mediastinal lymph node, with tubercles (but probably not actual miliary spread) in the liver. Pulmonary tuberculosis has been an occasional finding, and the patient of Hamman and Rich with the shortest course had a cavity, but this has not been considered significant. A tuberculous basis for the illness in the present patient again seems unlikely.

A definite etiology has never been proved in any of the cases reported so far, and, indeed, the frequent assumption that this syndrome represents a disease entity with one etiology is unfounded.

The group of acute reactions into which the present fulminating case falls might presumably have a different cause than the more chronic group. Diffuse interstitial pulmonary fibrosis may very well be a type of non-specific reaction to a wide variety of pulmonary insults. In this respect, it could be somewhat analogous to keloid for-
mation in the skin. The tendency to react in this way may be a constitutional or familial trait, as evidenced by the occurrence of the relatively rare disease in siblings.\(^{11,12}\)

In the acute group, an infectious agent is possible, although none is demonstrable. Viral etiology is perhaps the leading possibility but it remains so more by virtue of exclusion of other causes than by positive evidence. Primary atypical pneumonia may resemble this syndrome, however, and viral infections characterizedly cause an interstitial inflammatory reaction, often with cuboidal metaplasia of the alveolar lining cells, and with the alveolus usually free from significant inflammatory exudate.

Lack of demonstrable inclusion bodies in the Hamman-Rich syndrome is not conclusive, since they are absent in some diseases known to be viral in origin. It must be emphasized, however, that these similarities are only suggestive.

A relationship to the collagen diseases is again speculative. Fibrosis of the alveolar walls has been described in scleroderma, and reported cases of Hamman-Rich syndrome have had associated diagnoses of scleroderma and periarteritis nodosa. (These have been tentatively excluded on examples of this syndrome by some authors because of this associated collagen disease.) Response to steroids, with relapse following discontinuance, in consistent with this etiology, although such result is far from uniform and may be exceptional. The frequency of associated rheumatoid arthritis and the histological similarities to rheumatic pneumonia may be significant. Hypersensitivity reactions again may have some similar features. Reaction to a toxic agent appears less likely. It must be concluded that the syndrome remains obscure and perhaps varied in its etiology.

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