Case Report Section

Report of a Case of Diffuse Interstitial Pulmonary Fibrosis ("Hamman-Rich Syndrome")

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During 1954, the following case of Hamman-Rich Syndrome was admitted to Fitzsimons Army Hospital. We are reporting the findings so that the accumulation of data in the literature may ultimately lead to a more complete understanding of this condition.

Case Report

A 41 year-old white man was admitted to PAH on October 25, 1954 from USAH Landstuhl, Germany, complaining of soreness of the chest.

He stated he "felt perfectly well" until June, 1954, when he noticed the onset of increasing fatigability. During the next three months, he lost 13 pounds in weight. About September 1, 1954, a generalized aching and soreness developed in his left chest laterally, and over the left base posteriorly. This gradually increased to a generalized tightness of the entire chest. Two weeks later, a slight cough developed, productive of about one tablespoonful of clear mucous daily. With the onset of cough, there was a change in character of the chest pain: it had become pleuritic. This was accompanied by fever, night sweats, and dyspnea on exertion. There was no history of hemoptysis or wheezing. On September 18, 1954 he reported to the dispensary, where a chest roentgenogram was taken and read as suspicious of pulmonary tuberculosis. He was immediately hospitalized at the 97th General Hospital in Germany. Repeated sputa examinations were positive for acid-fast bacilli by smear. On September 23, 1954, streptomycin, 1 gram every third day and isoniazid, 300 mgs daily were started and continued to July 3, 1955.

He denied all other illness, except "pneumonia" in 1951 while in Korea, for which he was not hospitalized and no x-ray films were taken. He was treated on quarters with Aureomycin, and returned to duty after a few days without further symptoms.

Prior to entering the Army, he worked as a farmer. In the military service, he worked as a supervisor in garages where painting and remodeling was done to Army vehicles. The work was supervisory and he was never exposed to paint spraying. During 1951 and 1952, there was periodic breaking of fluorescent lights within the shop; averaging two to four times weekly. He denied close contact to any of these incidents.

On examination he was a well developed, and well nourished white man of 41, who did not appear acutely or critically ill. His temperature was 98.6°F; pulse, 70 per minute; respirations, 17 per minute; blood pressure, 110/80.

He was a small, slender white man who appeared 8 to 10 years older than his stated age. There was moderate clubbing of all fingers which he thinks has been present for many years and he recalled that two siblings have similar fingers. Pleural friction was elicited over the left lower chest laterally. Extensive post-tussive rales were heard over the left lower third of the chest bilaterally without regard to lobar distribution. Breath sounds were decreased over the left lower chest with impaired resonance to percussion in this area. Chest expansion seemed normal on both sides. Vital capacity was two liters, 66 per cent of the predicted and slow. No other abnormal findings were noted.

Purified protein derivative first strength and histoplasmin (1:100) were positive; coccidioidin (1:100) was negative. Serology for histoplasmosis, blastomyosisis, and coccidioidomyosisis were negative. The white blood cell count was 16,850; 63 per cent neutrophils, 31 per cent lymphocytes, 4 per cent monocytes, and 2 per cent eosinophils. They were with 5.26 million red blood cells. The erythrocyte sedimentation rate was 15 mm/hr. Hematocrit 50 mm. Urine normal. Sputum specimens collected during October, November and December, 1954 were repeatedly positive for tubercle bacilli by concentrated smear and culture. Sputa collected during the same period were negative by culture for fungi. Repeated sputum specimens collected from January through June, 1955 were negative by concentrated smear and culture for tubercle bacilli. Bronchial washings were negative for malignant cells.

A review of chest x-ray films taken in 1948, 1949, and 1949 revealed a small, round, calcific density in the lower left lung field and calcium deposits in the left hilum.

From the Pulmonary Disease Service, Fitzsimons Army Hospital
region. Otherwise, the heart and lungs appeared normal. The first "positive" x-ray film, dated September 18, 1954, revealed a hazy density obscuring the lower one third of the left lung field, with soft nodular densities in the third anterior interspace on the left and a finely reticulated pattern throughout all lobes of both lungs. The mediastinum and heart appeared within normal limits. The calcific densities seen on previous films were present and unchanged. Lateral and oblique views revealed that the homogeneous density seen on the routine postero-anterior x-ray film was confined principally to the lingula of the left upper lobe. The reticulated pattern described in the postero-anterior x-ray film throughout the remainder of the lung fields was particularly prominent on the lateral and oblique views. He had diffuse disease scattered throughout all lobes of both lungs.

Serial monthly roentgenographs through May 27, 1955 revealed no clearing. Instead, there had been a generalized progression of the disease. The reticulated pattern had increased in all lobes of both lungs, and numerous, small, soft nodular densities had developed throughout both lung fields.

Bronchoscopy, on October 28, 1954, revealed on the right a small tubercle superior to the middle lobe orifice and another small tubercle superior to the anterior basilar segmental orifice. The left lower lobe bronchus was mildly stenotic, permitting the passage of a 7 mm bronchoscope with difficulty. Granulations were seen in this area. Bronchial washing cultures were positive for M. tuberculosis and negative for fungi. Bronchoscopy on May 3, 1955 revealed no endobronchial disease.

The organisms were sensitive to streptomycin and isoniazid which were started on September 23, 1954 and continued until June 18, 1955. After eight months of anti-microbial therapy for tuberculosis the sputum had been negative for acid-fast bacilli for five months, but the roentgenograms showed progression of the lesions in all lobes of both lungs.

At conference on June 16, 1955 the history and clinical course were reviewed. Except for the possible exposure to beryllium, nothing significant was found. Physical examination revealed a chronically ill-appearing, white man, with slight clubbing of his fingers and toes. Cyanosis of the nailbeds and marked clubbing of all fingers and toes were present. There was marked dysnea after walking up one flight of stairs. The chest appeared to expand equally bilaterally. Decreased resonances and pronounced post-tussive rales were found at the left base posteriorly. Heart appeared to be normal. Abdominal examination was within normal limits.

The pulmonary tuberculosis, documented by 10 positive sputum examinations over a four month period, apparently was adequately controlled. The fine lacy reticulated pattern seen in the chest roentgenogram had increased, so this was probably due to a second and actively progressive disease process. The interstitial nature of the lesion, and the possibility of alveolar-capillary blocking made consideration of a large number of disease entities mandatory. However, possibility was reduced to fungus infection, neoplasia, beryllium granulomatosis, and Hamman-Rich Syndrome. The following studies were done to assist in making a definitive diagnosis:

1. Three sputum specimens examined for tumor cells: Negative.
2. Bronchial washings examined for tumor cells: Negative.
4. Laminograms revealed a fine, lacy network throughout all lobes which was interpreted to suggest fibrosis and emphysematous blebs.
5. EKG on June 20, 1955 was within normal limits. No evidence of right heart strain.
6. Oxygen saturation tests: Resting arterial O₂ saturation 71 per cent. The standard bicycle exercise was planned for six minutes, but after two and one half minutes extreme dyspnea and fatigue developed, so it was stopped. Approximately one minute later a sample of blood from the right femoral artery revealed O₂ saturation of 65 per cent.

On June 24, 1955, following walking down and up one flight of stairs, he became extremely dyspneic and was relieved by lying flat in bed. This was accompanied by the development of a slight hacking cough; mild precordial pain which disappeared with rest; marked cyanosis of lips, earlobes, and nailbeds. Blood pressure was 117/80; temperature 99.4°; pulse, 120/min.; respirations, 28/min.; dyspnea and cyanosis persisted. Three hours later he developed fever of 102°F, pulse 140/minute, respirations 36/minute, and blood pressure 120/60. There were moist rales throughout both lung fields. The liver was not palpable and there was no ankle edema. An EKG revealed a rate of 150/minute, with a slight change in the electrical position and slight elevation of the ST segments over precordial areas when compared with a previous EKG. There was no evidence of myocardial infarction.

He was definitely more comfortable lying absolutely flat in bed. The neck veins were not distended. He was treated symptomatically and observed closely. Mercaptopurin grs. IV intravenously, mercurophylline 1 cc intramuscularly and morphine sulphate grs. ½ subcutaneously were given. He became comfortable and slept well throughout the night.
The following morning the temperature was 98.6°F, pulse 124/minute, respirations 28/minute, and blood pressure was 104/76. Rales were present at both bases, but the upper lung fields seemed to be clearer. The cyanosis had markedly decreased. There was no detectable enlargement of the liver and no ankle edema. There was no tenderness of the calf muscles and pulsations in femoral regions were equal and forceful. Laboratory studies revealed: white blood cells 15,600; PMNS 78 per cent, lymphocytes 20 per cent, monocytes 2 per cent, and eosinophils 2 per cent. There were 6.34 million red blood cells. Hgb 17.2 grams per cent. Hematocrit 55 mm. Bleeding time 20 seconds, coagulation time eight minutes. Chest film revealed no change from previous serial films. He rested comfortable for the next five days so long as he remained in bed, but any slight exertion caused extreme dyspnea. On June 30, 1955 the consensus of opinion was that he had multiple pulmonary emboli and pulmonary edema. Coumadin 76 mgms was administered.

Following examination, the cardiologist stated that he doubtedly had pulmonary hypertension, probably on a chronic basis. In addition there had been some additional insult to the pulmonary circuit, most likely on the basis of a small pulmonary embolus. The EKG's were in keeping with right ventricular ischemia, probably of the strain pattern, although subendocardial infarction of the septum could not be ruled out. The whole picture was more in keeping with the former. Although there was no evidence of right heart failure at the moment, it probably was incipient. It was thought he should be digitalized and the anticoagulant therapy continued.

At noon digitoxin 0.6 mgm was given. Throughout the afternoon and early evening there was no change, but at 2000 hours, respirations increased to 40/minute, pulse 120/minute, and temperature 100.8°F. Digitoxin 0.2 mgm was given and oxygen, by face mask was started. After five minutes respirations decreased to 18/minute and cyanosis markedly decreased. He stated he felt much better. During the remainder of the night, the dyspnea and cyanosis were markedly relieved by intermittent oxygen, and he slept for long intervals. Continuous oxygen therapy in a tent was instituted the following morning.

His condition remained unchanged under supportive therapy until the afternoon of July 3, 1955 when there was a sudden increase in dyspnea. This was accompanied by evidence of venous engorgement and slight tenderness in the liver area, although the liver was not palpable. It was our impression that he had cor pulmonale with heart failure.

Two hours later he began to gasp for breath and stopped breathing within a few minutes.

**CLINICAL DIAGNOSES:**

1. TUBERCULOSIS, pulmonary, far advanced, bilateral, all lobes.
2. FIBROSIS, pulmonary, interstitial, unknown etiology.
3. ENLARGEMENT OF THE HEART due to pulmonary disease (cor pulmonale).

An autopsy was performed on July 4, 1955 and the following significant pathologic findings, gross and microscopic, were observed:

**GROSS:** There was no fluid in either thoracic cavity. The right lung was free; the left lung was bound down by fibrinous adhesions in all areas. These adhesions can be broken easily by hand.

The right lung weighs 970 grams, the left 580 grams. Both lungs were firm to palpaton but crepitant. On the external surface of each lung were multiple solid pink nodules extending above the surface of the red-blue background. At the apex of the left lung there were several small blebs, the largest measuring 0.7 cm in diameter. There were several fairly firm areas in the neighborhood of the lingula. On probing the bronchi, there was no evidence of endobronchial disease except in the left lung. There were several nodules encroaching upon the lingular bronchus and compressing blood vessels in this area. The bronchi to the left lower lobe did not appear to be encroached upon, but the nodules in the lingula extended to this area. Examination of the pulmonary vascular tree revealed no evidence of thrombosis, embolism or infarction of lung parenchyma. The parenchyma is moderately edematous in both upper lobes, and there is congestion of a moderate degree in both lower lobes. Section of lung parenchyma revealed diffuse fibrosis, emphysema, and greyish discoloration throughout. Although the lungs floated in water, there was little available space for respiration to occur. The heart weighed 365 grams and the right ventricular wall measures 0.4 cm in thickness, which for an individual weighing 135 pounds, probably represents mild hypertrophy. The liver and spleen were markedly congested.

There were several nodes at the hilus of the left lung measuring approximately 2.0 cm in diameter and one lymph node at the carina measuring 4.0 cm in diameter. These nodes were soft with no calcific areas palpable. Section reveals a mottled grey cut surface.

Eight sections of lung showed essentially the same changes: the bronchi in some areas had preserved their cuboidal epithelium, but in most areas bronchial epithelium was denuded. Bronchioles in most areas had preserved their epithelium, and in many areas broncholar epithelium was seen to have extended to line the alveoli. In many
areas this epithelium had undergone squamous metaplasia. Almost all the alveoli were airless, and were filled with blood in some areas and with pigment-laden macrophages in others. In some areas the alveolar exudate was undergoing organization by fibrin deposition and occasionally by fibroblastic proliferation, and here occasional multinucleated giant cells were seen. The alveoli which were not lined by the broncholar or squamous epithelium were lined by a homogenous hyaline-like membrane. The interstitial tissue of the lung showed increased fibrous tissue, fibroblastic proliferation and neovascularization. Inflammatory change was minimal and consisted of a few monocytes. The pleura did not appear to be thickened but the diffuse lesion previously described extended up to a subpleural location. Four sections stained for acid-fast bacilli were negative. Stain for iron was also negative.

Sections of four lymph nodes removed from the thorax showed essentially the same picture. The capsules were intact. Germinal centers were visible but were considerably distorted by a marked congestion associated with an ingrowth of new blood vessels. There was also a moderate increase in fibrous tissue. A generous amount of anthracotic pigment was present. On one slide four old, healed granulomata were seen, but their etiology was not known.

The pathologic cause of death was diffuse interstitial fibrosis of the lungs of the type described by Hamman and Rich. The immediate cause of death was acute right heart failure. The entire case was reviewed by the Armed Forces Institute of Pathology and the diagnosis of Hamman-Rich Type of diffuse interstitial pulmonary fibrosis was confirmed.

Discussion

Extensive pulmonary fibrosis as a cause of respiratory insufficiency may appear in several different forms and have many different causes. The original description of the Hamman-Rich type of diffuse interstitial pulmonary fibrosis remains essentially unchanged. However, it is now known that the disease may run a protracted course, and that the apparently acute fulminating cases may be the terminal phase of a more chronic illness.

The present case is interesting in that the admission diagnosis was proved pulmonary tuberculosis.Repeated sputum cultures during the first four months were all positive for acid-fast bacilli, which morphologically and culturally resembled M. tuberculosis. However, throughout the remainder of hospitalization the sputum was persistently negative for acid-fast bacilli. The patient had received more than nine months of continuous anti-tuberculosis chemotherapy, which apparently accounted for the permanent conversion of the sputum and the absence of pathologic evidence of tuberculosis. The only possible remote evidence of tuberculosis infection was "healed granulomata of unknown etiology" seen in one section of a lymph node.

Whereas, after eight months of treatment, the tuberculosis had been apparently controlled, the roentgenographic findings remained unchanged. It was this fact that led us to the conclusion that the reticulated pattern seen throughout all lobes of both lungs was probably due to an interstitial pulmonary fibrosis of unknown etiology. The second diagnosis was not established until after necropsy.

Although the clinical course and roentgenographic findings are characteristic during the late stages of Hamman-Rich Syndrome, the diagnosis can be established only by histologic examination. Furthermore, it must be borne in mind that there are numerous other diseases entities which can produce similar clinical and roentgenographic patterns.

Although the cause of this disease is unknown, many theories have been postulated but none has been proved. Bacteria have not been demonstrated in the lesions. No common chemical irritant or occupation has been identified. The lesions do resemble those seen in influenzal and atypical pneumonias. The possibility of a hypersensitivity or allergic reaction, or a nonspecific reaction initiated by a variety of substances have been suggested as etiologic agents, but the cause still remains unidentified.