Atypical Pneumonitis with Interstitial Fibrosis: An Unusual Case Receiving Prolonged Corticosteroid Therapy*

Pulmonary Alveolar Proteinosis

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Recently Rosen and coworkers1 reported an unusual histologic pattern in the lungs consisting of alveolar deposition of a granular proteinoid material. They designated their findings as "pulmonary alveolar proteinosis." These changes were found in biopsy or autopsy specimens of the lung which were referred primarily for tissue diagnosis. One of these patients was under our care. Since their description is primarily pathologic, and because our patient was under prolonged, close clinical observation, it is considered worthwhile to present this case in detail.

Case Report

A white, electrical appliance repairman, aged 35 years, was admitted to the hospital on March 9, 1956, for evaluation of an abnormality detected on a chest roentgenogram from a mass survey unit in January 1956. He dated his illness to June 1955, when he had multiple alveolar abscesses and underwent extractions of the upper teeth. His weight declined from 165 pounds in the summer of 1955 to 138 pounds by Christmas 1955.

In December, 1955, he had an illness, diagnosed as pneumonia, which consisted of fever, pain in the chest, cough, malaise, and muscular aches. He was treated with sulfa drugs and penicillin. He returned to work in six days but did not feel as well as prior to his illness; also, he noticed dyspnea on exertion. He had no current symptoms of orthopnea, paroxysmal nocturnal dyspnea, wheezing, pedal edema, known allergy, chills, pleuritic pain, or expectoration. He did have a chronic cough, however, aggravated by

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FIGURE 1: Normal chest x-ray on left, taken 1950. Film on right taken on admission to hospital 1956.
cigarettes, but this was essentially non-productive and unchanged from what it had been through the years. He smoked one package of cigarettes daily.

As a result of wartime service in the Pacific, he suffered a missile wound to the jaw and throat with subsequent osteomyelitis of the mandible. He gave no history of exposure to insecticides or contact with pets, farm animals or animal quarters. He had questionable exposure to broken fluorescent bulbs.

*Systemic review* revealed the presence of indigestion and heartburn of one year's duration. The symptoms were relieved by "Tums" or milk and were unrelated to specific foods.

On *physical examination*, he was well developed and well nourished and did not appear ill. Deformity of the left mandible from the previous injury and osteomyelitis were noted. Questionable dullness was present over the right lung base posteriorly and in this area there was slight decrease in tactile fremitus and slight decrease in breath sounds. Scattered throughout both lungs, particularly in the basilar portions, were terminal expiratory fine rales, cleared by coughing. No wheezing was present. Blood pressure was 118/76 mm. of mercury. A; was equal to P; No abdominal organs or masses were palpable. Lymphadenopathy was not present.

*Laboratory examinations.* Upon admission, the white blood cell count was 6,800 per cu. mm. with a normal differential blood smear; hemoglobin was 17.8 Gm. per 100 ml. and the hematocrit was 51 per cent. Sedimentation rate (Wintrobe) was 13 mm. in one hour. Urine specimen was normal. Serologic tests for syphilis were negative. Sputum smears and cultures of 72-hour specimens were negative for acid fast bacilli. Serum calcium and phosphorus determinations were 9.9 and 3.9 mg. per 100 ml. respectively. Alkaline phosphatase (Bodansky method) was three units per 100 ml. Serum albumin was 4.7 Gm. per 100 ml. and globulin was 2.0 Gm. per 100 ml. Electrocardiogram was within normal limits. Pulmonary function studies showed a moderate restrictive defect.

*Chest roentgenograms* on admission showed a fine granulomatous type of infiltration with a tendency to confluency. This infiltration was scattered throughout the left and the lower two thirds of the right lung (Fig. 1). A normal chest roentgenogram of March 9, 1950, was available for comparison. Planigrams did not show evidence of cavitation or significant hilar adenopathy.

*Course in the Hospital.* At the time of admission, he was relatively asymptomatic, although he did complain of some shortness of breath. He had been afebrile and his weight had been steady. In view of the paucity of symptoms, together with the rather striking bilateral pulmonary infiltrate, a diagnosis of sarcoidosis was considered. A supraventricular biopsy on April 3, 1956, showed normal tissue. On April 16, 1956, an exploratory thoracotomy with biopsy of the lung was performed.

The findings at operation showed some filmy adhesions between the anterior and

![FIGURE 2: Lung biopsy (68X) showing pink-staining material in some alveoli and foamy histiocytes in others. Interstitial fibrosis is present in some areas but is not prominent.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21328/ on 06/24/2017)
posterior segments in the right upper lobe to the chest wall. The entire right lung, especially the lower lobe and anterior segment of the right upper lobe, had fine nodularity and various degrees of thickening and nodules measuring from fine seeds to several cm. in diameter. In some areas, these were subpleurally located. The lung did not exhibit normal resiliency and crepitation. The hilum was normal. No enlarged nodes were visible.

Microscopically (Fig. 2), the striking feature was deep pink-staining material filling the air spaces. Many of the air spaces were slightly, but uniformly, distended, and the adjoining septae were not remarkable. In the mid-lateral aspects, surrounded by the areas described above, were air spaces containing moderate numbers of foamy histiocytes and the neighboring septae were thickened slightly, and the alveolar lining cells were moderately prominent. Small groups of air spaces contained both the pink-staining material and foamy histiocytes. Special staining procedures revealed normal findings (Sudan IV, crystal violet, congo red, mucicarmine, alcian blue). Smears and cultures for bacteria (aerobes and anaerobes), fungi and acid fast bacilli were negative. Granuloma or foreign material such as asbestos were not seen. The slide was interpreted to show: 1) Unidentified intra-alveolar material, and 2) Pulmonary fibrosis (slight).

Following the lung biopsy, a chest roentgenogram showed some increase in the diffuse infiltrate. Liver function studies at this time showed a normal bilirubin; thymol turbidity of 6.7 units and cephalin flocculation of 3-plus in 48 hours. Corticosteroid

FIGURE 3: Gross appearance of lung at autopsy. Lung sectioned (at left) showing diffuse involvement.

FIGURE 4: Photomicrograph (26x). Section of lung at autopsy showing three main pathologic features (1) pink-staining material in alveoli in central area, (2) alveoli filled with foamy histiocytes (upper right), and (3) moderate interstitial fibrosis (lower left).
therapy in the form of prednisone (50 mg. a day in four equally divided and equally spaced doses) was started on May 21, 1956. On June 25, he complained of nervousness, easy fatigability, and sensations of fever. Temperature of 100° F. was documented; he had purulent sputum and was cyanotic. Laboratory examinations then showed a red blood cell count of 6.7 million per cu. mm. with a hemoglobin of 17.8 Gm. per 100 ml. and hematocrit of 57 per cent. White blood cell count was 14,700 per cu. mm., with 81 per cent polymorphonuclear neutrophils, 13 per cent lymphocytes and 6 per cent monocytes. Platelets were 366,000 per cu. mm.

Because severe secondary infection was thought to be present, the dose of prednisone was gradually reduced. By July 8 it had been decreased to 15 mg. a day. On July 3 he had been placed in an oxygen tent because of cyanosis. On July 10 it was noted that he was markedly cyanotic even while in the oxygen tent. On July 13 prednisone was increased to 20 mg. a day. By July 25 he appeared slightly improved and less cyanotic. By August 8 he was out of the tent for short intervals. Chest roentgenogram on August 20 showed some clearing of the bilateral infiltrate. By August 27

**Figure 5**: Higher power (112X) of part of field seen in Fig. 4, showing pink-staining material in some alveoli and foamy histiocytes in others. Note the slight fibrous thickening of the septae.—**Figure 6**: Autopsy section of lung (244X) showing fibrous thickening of alveolar septae and pronounced alveolar lining cells.
he was out of the oxygen tent up to 10 minutes. During the period from July 13 to October 23, the dose of prednisone was 20 mg. daily.

On August 30, the left mandible had some swelling at the angle and an abscessed tooth was removed. On September 7, he had incision and drainage of the left mandible at the angle. About this time, he was able to get out of the tent for up to 20 minutes, four or five times a day; and he was sitting in a chair for 15 minutes, two or three times a day. He had gained about three or four pounds in weight. On October 10 he had another flare-up of osteomyelitis with drainage from the jaw, and he became more dyspneic. He was unable to be out of the tent more than 10 or 15 minutes at a time. On October 23 the dosage of prednisone was increased to 30 mg. a day. By November 22 he was short of breath and cyanotic even in the oxygen tent. On December 5 corticosteroids were increased to 40 mg. a day. A week later he had slight mental aberrations. The dosage was cut to 35 mg. daily, and the mental symptoms seemed to improve. His condition continued to deteriorate and by January 18, 1957, he was receiving 45 mg. of corticosteroids daily. By January 25 he was alternately comatose and conscious. On February 2, 1957, he expired.

Additional laboratory and clinical data. During his entire stay in the hospital from May 1956 until death in early February 1957, this patient was on continued antibiotic therapy with most of the known antibiotic agents being given in full therapeutic dosages at one time or another. Beginning in September the chronic infection in the left jaw necessitated three or four procedures for incision and drainage. During the last month of his life, discharge was minimal. Cultures from the jaw were negative for anaerobic organisms and aerobic cultures showed a light growth of coagulase negative Staphylococcus aureus. Cultures on Sabouraud's medium were negative.

Blood pressure was stable throughout his hospital course. He had a slight cough, usually non-productive. The slightest exertion, even while in the tent, produced shortness of breath. In July, the second rales accentuated and was louder than the aortic second sound. Scattered throughout both lung fields were small fine, moist inspiratory rales, more prominent over the lower portions of the chest, bilaterally.

During hospitalization, he received other medications in addition to the corticosteroids and antibiotics. These included small amounts of antacids and therapeutic vitamins, plus continuous oxygen in the tent. With the oxygen, he had a combination of Isuprel (1:200) and Alevaire in a mixture of 1:5, respectively, administered by a Mist-O-Gen nebulizer for four hours and then omitted for four hours.

Blood electrolytes ranged within normal limits except for the serum bicarbonate which was elevated to 30-36 milliequivalents per liter during the last two weeks of his life. His serum globulin values never were elevated. Liver function studies in January 1957 were normal. After June 1956, white blood cell counts were consistently elevated to as high as 25,000 per cu. mm., and one before death was 50,000 per cu. mm.; differential blood smears showed increased polymorphonuclear neutrophils without eosinophilia. Blood morphology was not remarkable. Smears of peripheral blood for lupus erythematosus cells (LE preparation) were negative on two occasions.

About 12 days before death, he developed fever and his pulse rate rose to levels of 120 to 140, having previously varied from 80 to 130 per minute, with an average range of 90 to 110.

At autopsy (Fig. 3), the lungs weighed 3100 Gm. A few fibrous pleural adhesions were present over the right upper lobe area. The lungs were non-crepitant. A few distended air spaces were present in the upper portions of both upper lobes. In the lateral and medial aspects of the lower lobe of the right lung were a few cysts, ranging in diameter from 3 to 12 mm. The remaining cut surface was dry, grey-white, firm, nodular and mottled. In the lower medial aspect of the upper lobe of the left lung, was an abscess measuring 5 cm. and containing about 30 cc. of turbid, green-yellow fluid. Bacteriologic studies of the fluid (including fungus studies) were negative. The bronchial system, the pulmonary arterial and venous trees, periarchial and tracheo-bronchial lymph nodes were not remarkable.

Microscopically, all sections showed a similar pathologic process. The main features were similar to the lung biopsy; intra-alveolar deposition of a proteinoid material, interstitial fibrosis, prominent cells lining the alveoli, and large numbers of foamy macrophages (Figs. 4 and 5). Fibrous thickening of the alveolar walls was slight to moderate and in some areas the interstitial fibrosis was quite severe (Fig. 6), particularly in those areas where more of the pink proteinoid material appeared. In these same areas the alveolar cells were more prominent and some distended capillaries were on the thickened septae. The pink-staining proteinoid material tended to fill most alveolar spaces but did not stream through or "bridge" the interalveolar pores. Multinucleated giant cells were seen rarely. Terminal bronchioles contained very little of the proteinoid material. Inflammatory reaction was minimal to absent except in the neighborhood of the abscess which had the appearance of being moderately old. Sclerosis of the pulmonary vessels was not noted. Mediastinal lymph nodes showed no evidence of the proteinoid material. Special stains revealed normal findings except the Masson trichrome stain which documented the interstitial fibrosis. Other stains...
were Turnbull's blue, McManus periodic acid, Heidenhain's iron hematoxylin, Gram-Weigert, Sudan IV, Schults, Mayer's mucicarmine and Dopa.

Other autopsy findings consisted of a shallow chronic peptic ulcer of the stomach, and some thinning of the adrenal cortex. The kidneys were normal grossly, but microscopically a fine scarring extended from the subcapsular area toward the pelvis. An occasional mildly dilated tubule, lined by atrophic or irregular epithelium and containing hyaline scars, was nearby. Renal vascular changes had not occurred. The heart weighed 325 Gm. and the thickness of the right and left ventricles was 2 and 16 mm., respectively. The liver and spleen were normal.

COMMENT

The longer this patient was observed, two clinical impressions assumed prominence. At first, berylliosis was considered a definite possibility, in view of his contact with fluorescent lights; however, since granulomas suggestive of berylliosis were not seen at any time, the presence of this condition was thought unlikely. Secondly, Hamman-Rich syndrome was contemplated.

At the time of lung biopsy, the description of the gross appearance of the lung was compatible with the Hamman-Rich syndrome, but microscopic sections showed only slight fibrosis of the alveolar walls and the most outstanding finding was pink-staining material in the alveolar spaces. A diagnosis of Hamman-Rich syndrome could not be ruled out completely, however, as only one case of the syndrome in which lung biopsy had been done soon after onset of symptoms had been reported in the literature. This case was reported by Pinney and Harris, and biopsy had been obtained within four months after the onset of symptoms and before treatment was begun. Since the early microscopic picture of the Hamman-Rich syndrome was essentially unknown, our case could have represented early findings. Subsequently, at least two other cases in which lung biopsy was done soon after onset of symptoms have been reported. These, together with Pinney's case, indicate that the fundamental microscopic and pathologic features of the Hamman-Rich syndrome are seen early and do not change markedly with the duration of symptoms.

In sections of the lungs at autopsy, the outstanding feature again was the pink-staining intra-alveolar material as seen in the biopsy. Numerous special staining techniques failed to identify its nature or origin. Interstitial fibrosis, while greater than in the biopsy specimen, was present only to a moderate degree and did not appear to be of the type originally described by Hamman and Rich. However, our patient received prolonged (eight months) corticosteroid and oxygen therapy, and these may have influenced the final microscopic picture in the lungs. Although it is doubtful that corticosteroid therapy alters the fundamental pathologic features of the Hamman-Rich syndrome, it is conceivable that this therapy could alter the tissue response in other conditions.

REFERENCES


