Diffuse Interstitial Fibrosis of the Lungs*
(Report of a Case with Unusual Features)

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Hamman and Rich1 (1944), first described a series of four cases of diffuse interstitial fibrosis of the lungs of unknown etiology. All cases manifested distinctive clinical and pathological features. The lungs showed a widespread connective tissue hyperplasia throughout the interstitial structures. The alveolar walls were greatly thickened, in the early stages there were many fibroblasts which were later replaced by scar tissue. The alveoli contained little or no exudate. These pathologic changes were progressive in character as evidenced by different gradations in the anatomic age of the fibrous tissue in various sections of the lungs. They resulted in an extreme degree of dyspnea and cyanosis, and finally in myocardial insufficiency due to right ventricular hypertrophy and dilatation.

Reports with essentially similar clinical and pathological features have recently been published by Golden and Tullis,2 Beams and Harmos,3 Ferrar et al.,4 and Potter and Gerber.5 The duration of the disease from the onset of symptoms to death varied from one to six months in Hamman and Rich's patients,1 from four to nine months in the two cases described by Golden and Tullis,2 and 15 months in the one described by Beams and Harmos,3 and eight months in Potter and Gerber's patient.5

Our case is unusual in that the duration of life from the onset of symptoms to death was 36 months. In addition, this patient manifested structural osseous changes, muscular atrophies, and contracture deformities of the hands not previously reported in this disease.

Case Report

A 51 year old white male was admitted to Halloran Veterans Administration Hospital on January 14, 1950, with the complaint of extreme shortness of breath and weakness. The onset of these symptoms dated

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from February 1947, when he first noticed exertional dyspnea. Cardiac disease was suspected at that time but all studies including electrocardiographic tracings were normal. The dyspnea and weakness progressively increased in severity, causing marked limitation of his activities. By early Spring of 1949, he became almost completely bed ridden, and oxygen by mask or tent was administered at intervals for the alleviation of dyspnea.

In March 1949, he was hospitalized at another institution for observation and study. During his stay there, the patient had frequent episodes of night sweats and intermittent temperature elevations to 105 degrees F. He was treated with penicillin (200,000 units q.2.h. for one week), and later with streptomycin (one gram daily for one week) without evident effect on the temperature elevation or clinical course of the disease.

In May 1949, he developed sharp pain and swelling in the joints of both hands, left wrist, right elbow, both feet, ankles, and knees. The pain was at first migratory but soon became persistent and dull in nature. In the subsequent months, there was progressive development of flexion deformities of both hands, generalized muscular and subcutaneous atrophy, clubbing of the fingers and toes, and cyanosis of the nail beds and mucous membranes. In July 1949, he developed a cough, at first non-productive, which later became paroxysmal and productive of a moderate amount of mucoid and tenacious sputum.

Past History consisted of usual childhood diseases including whooping cough and scarlet fever. He had pneumonia at the age of 10 years, and attacks of influenza at 19 and 30 years. He had intermittent asthmatic episodes of moderate severity in childhood, these persisted at irregular and infrequent intervals until the age of 20 years. From 1922 to 1924, he was employed as a sandblaster and factory worker. For a period of about 20 years, he had been essentially asymptomatic and in good health until the onset of the present illness. The family history was non-contributory.

Physical Examination: On admission to this hospital, the patient

\[\text{Figure I: Chest roentgenogram, September 13, 1949. There are diffuse mottled and patchy infiltrations, particularly in the lower half of both lung fields. The hilar markings are accentuated. The heart is moderately enlarged.} \]

\[\text{Figure II: Chest roentgenogram, February 4, 1950. Clearer definition of the infiltrations but their extent and nature appear unchanged in both lung fields.} \]
appeared chronically ill, markedly emaciated, dyspneic, and cyanotic. Weight, 103 pounds. Pulse, 130 per minute. Respiration, 40 per minute. Blood pressure, 104/72. There was a marked generalized muscular weakness, subcutaneous as well as muscular atrophy and wasting. The right pupil was smaller than the left and the right lens showed cataract formation. The chest was of emphysematous contour. The diaphragmatic leaves were markedly limited in motion, and the lungs were hyperre-

### TABLE I

<table>
<thead>
<tr>
<th>ESSENTIAL LABORATORY FINDINGS</th>
<th>1-16-50</th>
<th>1-20-50</th>
<th>2-15-20</th>
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</thead>
<tbody>
<tr>
<td><strong>R.B.C. (X1000) (cu. mm.)</strong></td>
<td>4,300</td>
<td>4,140</td>
<td>4,100</td>
</tr>
<tr>
<td><strong>Hemoglobin (gm.) (per cent)</strong></td>
<td>14.2</td>
<td>13.6</td>
<td>14.6</td>
</tr>
<tr>
<td><strong>W.B.C. (cu. mm.)</strong></td>
<td>9,400</td>
<td>8,400</td>
<td>9,300</td>
</tr>
<tr>
<td>Neut. (per cent)</td>
<td>88</td>
<td>69</td>
<td>73</td>
</tr>
<tr>
<td>Lymph.</td>
<td>8</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>Mono.</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Eos.</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (per cent)</td>
<td>48</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>E.S.R. (mm./hr.)</td>
<td>9</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Glucose (mgm. per cent)</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mgm. per cent)</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein (grm. per cent)</td>
<td>5.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Globulin</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO₂ (Vol. per cent)</td>
<td>73</td>
<td>65</td>
<td>68</td>
</tr>
<tr>
<td>Chlorides (m.eq./L)</td>
<td>86</td>
<td>102</td>
<td>94</td>
</tr>
<tr>
<td>Potassium (m.eq./L)</td>
<td>4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (m.eq./L)</td>
<td>148</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

sonant to percussion. Loud rhonchi were audible bilaterally, and crackling rales were present at both bases. The heart was moderately increased in size and showed normal rhythm, but the cardiac sounds were distant, and a soft apical systolic murmur was audible. There was marked clubbing and cyanosis of the fingers and toes, and cyanosis of the mucous membranes. The interosseous muscles of both hands were markedly atrophic. There were flexion deformities, tenderness, and periarticular swelling of the metacarpal phalangeal joints with hyperextension of the interphalangeal joints. All the deep reflexes were hyperactive and equal bilaterally.

**Laboratory Findings:** Table I summarizes the essential laboratory findings during the patient's present hospitalization. Sputa cultures were repeatedly negative for tubercle bacilli and pathogenic fungi. The dominant sputa flora consisted of pleomorphic diphtheroid bacilli and beta hemolytic streptococci. The tuberculin test (PPD .00002 mg.) gave a two plus reaction. The histoplasmin (1 to 1,000) and coccidioidin (1 to 100) skin reactions were negative. Spinal puncture (1/18/50) showed a fluid pressure of 156 mm. of water and essentially normal chemical and cyto logical findings. Culture of the spinal fluid was negative for tubercle bacilli, fungi, and pyogenic organisms.

A chest roentgenogram at the time of the first hospitalization on September 13, 1949 (Figure I), revealed diffuse, finely mottled and patchy nodular infiltrations throughout both lung fields, particularly in the region of the bases. Roentgenograms of the chest at this hospital on January 15, and on February 4, 1950 (Figure II), showed these infiltrations to be essentially unchanged in extent and distribution. Roentgenogram of the hands on January 18, 1950 (Figures III, IV and V), showed considerable demineralization of the osseous structures, particularly, about the articulations and broadening of the middle and terminal phalanges of the right fifth digit. Deformities of the hands and atrophy of the soft tissue structures were evident.

Serial electrocardiographic tracings showed the following: January 14, 1950: Regular sinus rhythm, S-1 S-2 S-3 pattern; PR interval, 22 seconds; QRS complexes of low voltage (less than 5 mm. in all limb leads). Pre cordial leads, small R; Large S in V2, V4 and V5. January 22, 1950: Slight increase in voltage of all complexes in limb leads. February 22, 1950: No significant change.

**Course in Hospital:** Throughout the entire hospital course the patient manifested persistent and severe dyspnea. Oxygen was administered by mask or tent during the major portion of his stay. The administration of a saturated solution of potassium iodide (10 gtt. t.i.d.) for the first two weeks resulted in the expectoration of less viscid sputum. This medication was discontinued because of iodide sensitivity, manifested by lachrymation, fine macular skin eruption, and temperature elevation. Additional therapy consisted of intravenous infusions of aminophyllin in dextrose solution, and intramuscular injections of adrenal cortical extract. This medications were without effect on the patient's general clinical status. Penicillin therapy (300,000 units b.i.d.) and streptomycin (0.5 gram b.i.d.) were administered for two weeks. During this period, his temperature remained at normal levels with only an occasional rise to 102 degrees F. A skin and muscle biopsy was performed on February 2, 1950. Gross and microscopic examination of the tissue revealed it to be normal.
Figures III, IV and V: Roentgenograms of the hands, January 18, 1950. There is demineralization of the osseous structures, particularly about the articulations. The flexion and contracture deformities of the hands as well as the muscular and subcutaneous atrophy are evident.
On February 20, 1950, the patient developed ankle edema, and the liver edge was slightly tender and palpable one finger below the right costal margin. He manifested all signs of congestive heart failure, secondary to cor pulmonale. He was treated with digitalis, mercurhydridin, and a salt free diet without apparent clinical improvement.

On March 1, 1950, after a brief period of restlessness, marked increase in cyanosis and dyspnea, mental clouding and lethargy, he became comatose and expired, on the 45th day of hospitalization and 36 months following the onset of respiratory symptoms.

Necropsy Findings: The necropsy was performed four hours after death. The body was emaciated with a great wasting of muscles of the extremities. There was marked deformity of all the fingers, with hyperextension of the phalanges and flexion of the metacarpal phalangeal joints.

Both pleural spaces contained blood tinged fluid (200 cc. in the left and 500 cc. in the right). Microscopically the pleural surface was thickened by collagen connective tissue and attached to its surface was a large mass of red blood cells, polymorphonuclear leucocytes and fibrin. Many histiocytes and fibroblasts were present at its attachment to the pleura.

The lungs weighed 1800 grams and one section the parenchyma was crepitant and varied in color from grey-black to rust-brown. The tissue was traversed by irregular zones of translucent grey-white connective tissue varying in length from five mm. to two cm. and in thickness from less than one mm. to two mm. The air spaces throughout both lungs were dilated and measured up to three mm. in diameter. The bronchi and bronchioles were irregularly dilated and trabeculated, and the mucous membrane was smooth.

Figure VI: Coronal sections showing a diffuse fibrosis of the lungs more advanced in the lower lobes. The emphysema gives the lung parenchyma a spongy appearance.—Figure VII: Photomicrograph of the lung showing great thickening of the interstitial tissue by connective tissue.
Microscopically a diffuse fibrosis was present in all lobes. The alveolar septa were irregularly and extensively thickened by an increase of loose and dense connective tissue. Within these septa were numerous capillaries, fibroblasts, histiocytes, lymphocytes and some plasma cells. In some areas were dense collections of lymphocytes. Some of the alveoli were lined by low cuboidal cells. The connective tissue septa of some of these alveoli had a pink hyaline appearance. Some of the air spaces were partially filled with alveolar phagocytes, red blood cells and occasional polymorphonuclear leucocytes. The alveoli in the intervening portions of the lung parenchyma were irregularly dilated and many of the septa were fragmented. The walls of the arteries and arterioles within the region of connective tissue were extensively thickened by an increase of connective tissue within the intima and adventitia. The lumina of some of the smaller arteries were obliterated by collagenous connective tissue in which were histiocytes and fibroblasts and capillaries.

The pericardial cavity contained 300 cc. of clear yellow fluid. The pericardial surface was smooth and there was a moderate decrease in the amount of subepicardial fat. The heart weighed 350 grams. The endocardial surface was smooth and the valves showed no abnormalities. The wall of the right ventricle measured up to four mm. in thickness, the apex was rounded and the papillary muscles were somewhat flattened. The inflow tract measured seven cm., while the outflow tract measured 10 cm. The wall of the left ventricle measured one cm. in thickness and the apical angle was acute. The inflow and outflow tract each measured seven cm.

The pulmonary artery and all its branches within the lungs showed a moderate loss of elasticity. They contained numerous atheromatous yellow plaques which varied in size from two mm. to one cm. An advanced arteriosclerotic process was also present in the coronary arteries as well as the aorta and its branches.

The liver weighed 1350 grams and the spleen 200 grams. Grossly as well as microscopically these organs showed moderate passive congestion.

The other significant findings in this case included: an encapsulated, calcified focus in a right peribronchial lymph node and one in the spleen (remnants of a primary infection); an atrophy (slight) of the frontal lobe of the brain and dilatation of the lateral ventricles.

Discussion

The features of the cases of diffuse interstitial fibrosis of the lungs which have thus far been reported are as follows:

A) Clinical:
1. Advanced and progressive dyspnea as well as cyanosis.
2. Cor pulmonale.
3. Polycythemia, which is not a consistent finding. It was absent in the cases described by Golden and Tullis, and Ferrar et al.
4. The average duration of life from the onset of pulmonary symptoms has been reported as being from four to six months. In some instances the process had been fulminating and lasted only a few weeks.
B) Anatomic Features:

1. The pathologic findings characteristic of this process as set forth by Hamman and Rich\(^1\) are: 1) extensive, diffuse and progressive interstitial proliferation of fibrous tissue throughout all lobes of the lungs, associated with focal organization of intra-alveolar hemorrhage, 2) necrosis of alveolar and bronchial epithelium, 3) a hyaline membrane which lines the alveoli, 4) enlargement of the lining alveolar epithelial cells, 5) edema and fibrin deposit in the alveolar walls, 6) eosinophiles in the interstitial tissue may be present, 7) stenosis of small bronchi and bronchioles by mucous plugs and cellular debris or by the interlacing bands of fibrous tissue. The adjacent alveoli show emphysema changes of varying degree.

The gross and microscopic features in our case are those of an interstitial fibrosis of the lungs in which none of the acute changes described by Hamman and Rich\(^1\) are present. Thus we see no edema, fibrin, or eosinophiles in the alveolar walls, nor a hyaline membrane lining the alveoli. These changes were observed in the case of Beams and Harmos\(^3\) where the duration was considered as being 15 months with a latent period of 11 months. The question thus naturally arises as to whether this case is a chronic stage of the process originally described by Hamman and Rich or is an end-stage of some other disease within the lungs.

**Differential Diagnosis:** Robbins\(^6\) and Mallory\(^7\) in their studies on pulmonary fibrosis and its causes emphasize that the following should be considered as possible causes: tuberculosis, pneumoconiosis, sarcoidosis, chronic pulmonary granulomatosis (beryllium), organized pneumonia (bacterial or viral), fungus disease (aspergillosis), dermatomyositis, scleroderma, periarteritis nodosa, Raynaud's disease, lupus erythematosus, lymphatic spread of carcinomatous metastases, vascular occlusion of idiopathic pulmonary arteriosclerosis, and bronchiolitis obliterans.

Many of the clinical, roentgenographic, and pathologic features in our case described resembled those of scleroderma. The duration of the disease, the osseous changes, the muscular atrophy, and contracture deformities of the hands are more commonly seen in scleroderma than in idiopathic pulmonary fibrosis. The essential differential diagnostic features of the two diseases are summarized in Table II.

The anatomic changes in scleroderma as described by Getzowa,\(^8\) Spain and Thomas,\(^9\) indicate a close similarity to those of idiopathic pulmonary fibrosis. The pulmonary changes in scleroderma consist primarily of cystic changes as well as dense fibrosis in the pulmonary parenchyma. There is an associated diffuse peribron-
Chiolar fibrosis, bronchiolectasis, bronchiolar epithelial hyperplasia, obstructive emphysema, as well as atrophy and fibrosis in the musculature of the bronchial tree.

Chronic pulmonary granulomatosis due to beryllium, sarcoidosis, dermatomyositis, and the collagen diseases were considered in this case and were excluded by the clinical manifestations, course of the disease, and necropsy findings. Silicosis was also considered because of the occupational history 20 years previous to the onset of the present illness. However, the long latent period as well as the pathologic findings were not consistent with the diagnosis.

_Etiology and Pathogenesis:_ The etiology of this disease remains obscure. The pulmonary fibrous tissue is non-specific in appearance. The predominance of peribronchial fibrosis is consistent, however, with the end-result of organizing pneumonitis or unresolved primary atypical pneumonia.

Mallory7 in a review of 6,000 postmortem examinations found that the anatomic diagnosis of pulmonary fibrosis was made in

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**TABLE II**

**DIAGNOSTIC FEATURES OF IDIOPATHIC PULMONARY FIBROSIS AND SCLERODERMA**

<table>
<thead>
<tr>
<th></th>
<th><strong>Idiopathic Pulmonary Fibrosis</strong></th>
<th><strong>Scleroderma</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Predilection</td>
<td>Respiratory System</td>
<td>Generalized connective tissue disease with predilection for skin, muscles, subcutaneous tissue, and gastrointestinal tract.</td>
</tr>
<tr>
<td>Course</td>
<td>Average duration from four to six months</td>
<td>Usually two to three years</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Deformities</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Muscular atrophy</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>Absent</td>
<td>Induration and edema</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Heart</td>
<td>Cor pulmonale</td>
<td>Focal or diffuse myocarditis in addition to cor pulmonale</td>
</tr>
<tr>
<td>Raynaud's features</td>
<td>Absent</td>
<td>Common</td>
</tr>
<tr>
<td>Red blood cell count</td>
<td>Polycythemia</td>
<td>Anemia</td>
</tr>
<tr>
<td>Remissions</td>
<td>Rare. Progressive disease</td>
<td>Occasional</td>
</tr>
<tr>
<td>Chest roentgenogram</td>
<td>Cystic changes are rare</td>
<td>Common</td>
</tr>
</tbody>
</table>
only 59 instances. In these cases there was a multifocal or generalized involvement of the lungs of sufficient extent to be of clinical significance. In 19 instances the fibrosis was the result of organized pneumonia, and in 10 of these there was an associated history of chronic bronchial asthma.

The past history of an allergic and asthmatic background in our case with superimposed pneumonic and influenzal infections may well have served as the basis for the pulmonary fibrosis. Asthmatic bronchitis delays resolution of a pneumonic process because of a mechanical impediment to drainage of the affected alveoli and bronchioles. Hamman and Rich noted the presence of eosinophilic infiltrations of the interstitial tissue as one of the features of the disease, a finding compatible with an allergic manifestation. Our case did not manifest this finding on histologic study. However, the non-specific diffuse fibrosis undoubtedly represents the end-stage of a previously existing active process of which an allergic reaction may have been a part.

In the cases of primary atypical pneumonia reported by Knee-land and Smetana, Longcope, Saphir, and Golden, the typical anatomic lesion was that of an interstitial pneumonitis in various stages of development. In the early stages the inflammatory process was found chiefly in the interstitial tissues. There was a marked tendency to proliferation of fibroblasts and deposition of collagen fibers in the alveolar walls and peribronchial regions. The appearance and distribution of the lesions as well as the peribronchial predilection of the fibrosis in this case is thus consistent with the end-result of organization of the inflammatory elements in recurrent interstitial pneumonitis.

Extrapulmonary Manifestations: The skeletal, muscular, and trophic disturbances of the hands have not been previously described in cases of idiopathic interstitial pulmonary fibrosis. The question arises as to whether these changes are coincidental findings in this case or whether they occur in this disease when it is of long standing. The changes noted consisted of generalized muscular and subcutaneous tissue atrophy, particularly of the hands, with resulting severe contracture deformity. There was also an osteoporosis of the articular portions of the metacarpal and phalangeal bones and a loss of the regular bone trabeculation. Holt and Hodges list similar skeletal changes in cases with syringomyelia, leprosy, erythromelalgia, Raynaud's disease, acrosclerosis, thromboangitis obliterans, dermatomyositis, and scleroderma.

Cause of Death: Pulmonary or myocardial insufficiency is the usual cause of death in this disease. The diffuse pulmonary fibrosis causes marked loss of pulmonary elasticity and reduction in ventilatory reserve. In addition, the reduction in the functional alve-
olar capillary bed results in interference with the exchange of
gases in the alveoli. The compression and reduction in the number
of pulmonary capillaries with its subsequent increase in the pul-
monary arterial pressure leads to right ventricular dilatation and
hypertrophy. This steadily progresses until myocardial insuffi-
ciency results. The anoxemia serves as a contributory factor in
the genesis of the myocardial insufficiency and heart failure.

SUMMARY

1) A case of idiopathic interstitial pulmonary fibrosis with
autopsy findings is presented.

2) This case is unusual in that the duration of the disease from
the onset of pulmonary symptoms was 36 months. The greatest
duration previously reported was 15 months.

3) There was marked muscular and subcutaneous atrophy and
contracture deformities of the hands. This finding has not been
previously reported in this disease.

RESUMEN

1) Se presenta un caso de fibrosis pulmonar intersticial idiop-
ática.

2) Este caso es extraordinario porque la duración de él desde la
aparición de los primeros síntomas fue de 36 meses. La duración
mayor antes referida fue de 15 meses.

3) Había marcada atrofia muscular y subcutánea así como con-
tractura y deformación de las manos. Este hallazgo no se había
referido antes en la literatura.

RESUME

1) Les auteurs présentent un cas de fibrose pulmonaire intersti-
tielle idiopathique avec les constatations d'autopsie.

2) Il s'agit d'un cas inhabituel en ce sens que l'affection s'est
étendue pendant 36 mois après l'apparition du premier symptôme
pulmonaire. La plus longue durée qui ait été précédemment rap-
portée avait été de 15 mois.

3) On constate une atrophie musculaire et sous-cutanée très
importante et des contractions déformantes des mains. Ces cons-
statations n'avaient pas été faites antérieurement dans cette affec-
tion.

REFERENCES

1 Hamman, L. and Rich, A. R.: “Acute Diffuse Interstitial Fibrosis of
2 Golden, A. and Tullis, I. F. Jr.: “Diffuse Interstitial Fibrosis of the
3 Beams, A. J. and Harmos, O.: “Diffuse Progressive Interstitial Fibrosis