Eosinophilic Granuloma of the Lungs
Roentgenologic and Pathologic Features*

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In 1949, Parkinson reported roentgenographic changes in the lungs of patients having eosinophilic granuloma of bone and predicted that some cases would be seen in the future in which lung fibrosis and cyst formation would be the sole manifestation of the disease. It was but two years later when Farinacci et al. described fibrosing granulomatous lesions of the lungs infiltrated with eosinophils and resembling eosinophilic granuloma of bone. Since then, many cases involving only the lungs have been reported.

During the past two years, five patients have been admitted to the Municipal Tuberculosis Sanitarium suspected of having tuberculosis, but proved by lung biopsy to have eosinophilic granuloma. The problem of differential diagnosis in diffuse granulomatous disease of the respiratory tract poses a challenge to the clinician, radiologist and pathologist alike.

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ROENTGENOGRAPHIC FEATURES

The posteroanterior views of the chest roentgenograms on the five patients included in this report are illustrated in Figures 1 to 5. The earliest changes are considered to be a fine peribronchiolar lattice-work-like pattern of infiltration. Later on the appearance changes to that of a mixture of fine to nodular infiltrates combined with small cystic areas and eventually to a picture of cystic spaces of varying size compatible with the diagnosis of "honeycombed" lung. In reviewing the original x-ray reports, which were issued prior to lung biopsy, it was found that several different diagnoses were considered radiologically. These included sarcoidosis, cystic disease of the lung, miliary metastases, industrial diseases, fungus diseases and idiopathic pulmonary fibrosis.

PATHOLOGIC FEATURES

The pleural surface of the lung wedges showed a slight nodularity with some areas...
of fibrous thickening. In some, small subpleural cysts or blebs were seen. The lung tissue cut with slight resistance and the surfaces made by cutting contained some small pale gray firm infiltrates rather poorly delineated from the surrounding lung parenchyma. Some of these infiltrates could not be differentiated from vessels and bronchioles in cross section. Three of the specimens showed cystic spaces of varying sizes

**FIGURE 1C:** A three-fold magnification of the right lower lung field accentuates the changes noted above.

**FIGURE 2A:** Chest roentgenogram taken July 21, 1958 showing a diffuse, ill-defined pattern of infiltration with many areas of "honeycombing." **FIGURE 2B:** Four years later (September 5, 1962) the x-ray film shows the pulmonary lesions to be stable but a destructive lesion of the right transverse process of D-1 is present.
Figure 3A: Posteroanterior roentgenogram of the thorax taken September 27, 1954. A nonspecific infiltrate is present in the left apex. Figure 3B: Seven years later (August 15, 1961) one sees large and small cysts in the upper lobes.

with fibrosis of the intervening lung tissue (Figs. 6 and 7). Minimal degrees of anthracotic pigmentation were noted.

It was apparent from examining the sections of lung tissue that the disease process had been going on for an extended period. In some areas, however, there were collections of histiocytic cells within the walls of bronchioles and within the septa (Figs. 8 and 9) which appeared to be the

Figure 4A: A fine peribronchiolar lattice-work-like pattern of infiltration identical to Case 1 (Figs. 1A, B and C) is noted. Figure 4B: Approximately two years later the chest x-ray film shows a diffuse, ill-defined pattern of infiltration with areas of "honeycombing."
earliest lesion inasmuch as there was little evidence of proliferative changes in the surrounding tissue. The "typical" granulomata (Fig. 10) consisted of collections of histiocytic cells with varying numbers of eosinophilic granulocytes and an occasional plasma cell and lymphocyte. While some lipid-laden cells were found (Fig. 11) in most sections examined, the xanthomatous features of this disease were not prominent.

Figure 6: A macrophotograph of the lung tissue taken for biopsy on Case 4 showing marked alteration of the parenchyma with many dilated air spaces and bronchioles (Hematoxylin and Eosin x10).
Certainly one would not be tempted to classify any of the cases studied as one of the lipodystrophies. In some lesions there was dissolution of the central zone. These granulomata were usually surrounded by lung parenchyma which had undergone considerable alteration. Hyperplasia of bronchial epithelium and fetalization of alveolar epithelium was evident in many areas and very often this epithelial hyperplasia was accompanied by marked proliferation of fibroblasts (Fig. 12). Some air spaces could still be recognized by the presence of phagocytic cells containing pigment, but the structure of the lung in these areas was markedly altered due to the presence of many epithelial cells and fibroblasts. Some dilated bronchioles showed pronounced alteration of their walls due to the presence of histiocytic aggregates alternating with areas of fibrosis, with many skip areas in their lining where the epithelium was denuded. Many large dilated spaces could not be recognized as altered bronchioles save for the muscular pattern noted in the walls. There was evidence of smooth muscle proliferation (Fig. 13) and at some points, one could see bundles of muscle tissue which were not related to any bronchial structure. Capillary structures of the lung parenchyma were caught up in this proliferative process and larger vessels showed, in some instances, irregular thickening of their walls which was due to changes in all layers without any consistent pattern. These inflammatory changes in the larger vessels were felt to be secondary to the parenchymal lesions. While there was no evidence of necrosis, there was some evidence of stasis as some of the altered air spaces were packed with phagocytic cells. The transitional changes from the onset to the end point are illustrated in the diagram (Fig. 14) and are similar to the changes described by Engelbreth-Holm et al.⁶

**DISCUSSION**

The pulmonary manifestations of eosinophilic granuloma as seen on x-ray films are best described by Shanks and Kerley.⁷ In most of their cases, the lung lesions were diffuse and bilateral. Multiple granulomata were seen which measured from 0.5 to 2

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**Figure 7:** Note the marked bronchiolar dilatation in the section of the lung biopsy on Case 3. Some of the spaces are partly filled with serous material and blood cells (incidental to the surgical procedure). No semblance of normal lung is seen (Hematoxylin and Eosin x10).
mm. in diameter and the distribution was usually symmetrical, but often large groups were clustered together without coalescence. They state that the lesions are never quite as sharply defined or as dense as silicotic nodules and never as small or as dense as the lesions of miliary tuberculosis or some miliary forms of sarcoidosis. The delicacy of the lesions and the lack of definition may be similar to the picture of edema in chronic heart disease and there is always, at some stage, an additional fine linear infiltration. The lesions may heal without trace, but when they heal by fibrosis, the end result is the so-called "honeycombed" lung. The primary nodular phase of the disease is so similar to sarcoidosis that biopsy is essential to differentiate them; however, unlike sarcoidosis, glandular enlargement is not a feature of this disease. In the fibrotic stage, the delicate filigree honeycomb is characteristic as compared to post-sarcoid fibrosis which is not symmetrical and shows coarse fibrous strands.

The x-ray diagnosis of disseminated pulmonary disease in a hospital devoted primarily to tuberculosis resolves itself primarily into the problem of whether or not the lesion in question is or is not miliary or disseminated tuberculosis. Once the tentative decision has been made that the lesion does not look like tuberculosis then the whole gamut of disseminated pulmonary disease has to be considered. In our series of cases, the diagnosis was made easier in the initial case by the demonstration of coexisting pulmonary and bone lesions. A slowly growing expanding lytic lesion of the right transverse process of the first dorsal vertebra was demonstrated at one time during the course of this patient's pulmonary disease. Tissue taken from the lung for biopsy established the diagnosis of eosinophilic granuloma and made us aware of this disease entity as being compatible with the x-ray picture presented. This awareness and a high index of suspicion made the diagnosis less difficult in the other four cases, even though they were not associated with any bone lesion.

The pertinent clinical data are set forth in Table 1. The patients were all about 30 years of age, all had a positive tuberculin test, and in most instances, their disease had run a long and protracted course.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Nationality</th>
<th>Occupation</th>
<th>Duration Illness</th>
<th>Symptoms</th>
<th>M. tuberculosis</th>
<th>Tuberculin Test</th>
<th>Leukocyte Count</th>
<th>Eosinophil (Per Cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P.P.</td>
<td>29</td>
<td>M</td>
<td>Caucasian</td>
<td>Mechanic</td>
<td>7 years</td>
<td>Productive Cough, Dyspnea, Weight Loss</td>
<td>Negative</td>
<td>Tine-Positive</td>
<td>7100-16,750</td>
<td>0-4</td>
</tr>
<tr>
<td>2</td>
<td>R.O.</td>
<td>24</td>
<td>M</td>
<td>Puerto Rican</td>
<td>Paper Box Factory</td>
<td>4 years</td>
<td>Weight Loss, Bone Lesion</td>
<td>Three Positive Cultures</td>
<td>Positive 1:1000</td>
<td>7300-9850</td>
<td>4-12</td>
</tr>
<tr>
<td>3</td>
<td>J.C.</td>
<td>28</td>
<td>M</td>
<td>Negro</td>
<td>Leather Handler</td>
<td>7 years</td>
<td>Cough, Weight Loss</td>
<td>Negative</td>
<td>Positive 1:10,000</td>
<td>8900-9300</td>
<td>0-1</td>
</tr>
<tr>
<td>4</td>
<td>V.C.</td>
<td>29</td>
<td>F</td>
<td>Negro</td>
<td>Laundry</td>
<td>3 years</td>
<td>Productive Cough, Weight Loss, Fatigue</td>
<td>Negative</td>
<td>Tine-Positive</td>
<td>7850-10,550</td>
<td>1-4</td>
</tr>
<tr>
<td>5</td>
<td>M.P.</td>
<td>34</td>
<td>F</td>
<td>Caucasian</td>
<td>Clerical</td>
<td>6 months</td>
<td>Cough, Dyspnea, Fatigue, Weight Loss</td>
<td>Negative</td>
<td>Positive 1:10,000</td>
<td>5050-9900</td>
<td>0-1</td>
</tr>
</tbody>
</table>
Symptoms common to all cases were productive cough and weight loss. Only one patient had a history of having active pulmonary tuberculosis some time prior to the diagnosis of eosinophilic granuloma. In general, the white-cell count did not exceed 10,000 per cubic mm. and there was no appreciable blood eosinophilia save in one case, where the eosinophilic leukocytes ranged from 4 to 12 per cent. Occupation was not considered to be a factor in this disease nor was the disease limited to one sex or race.

The mechanism whereby the tissue changes are brought about is not known. Nor has a specific etiologic agent been found. It has been suggested that some micro-organism or noxious substance is responsible, but we have no proof of this. It has also been proposed that this represents an allergic response and in support of this notion is the marked tissue eosinophilia. While cavitary lesions are not generally noted in this disease, the pronounced alteration of many of the bronchioles, the dissolution of the center of the granulomatous lesions and the proliferative changes in the lung parenchyma certainly set the stage for cavitary lesions of the lung, especially those of a bronchiectatic nature. In resected lung tissue from one patient not included in this series we have observed changes compatible with the diagnosis of eosinophilic granuloma and a large cavity filled with debris containing many septated structures resembling aspergilli was present.

The end stage of eosinophilic granuloma—honeycomb lung—may be indistinguish-
able from silicar lung changes seen in sarcoidosis, pneucomoniosis, Hamman-Rich syndrome, bronchiolectasis, lipodystrophies, scleroderma and other disorders too numerous to mention. Of all these disorders, sarcoidosis most nearly resembles eosinophilic granuloma clinically and roentgenographically, but only in the terminal stages do the gross pathologic changes in the lung parenchyma appear the same in both diseases. One striking difference, however, is the marked lymph node involvement seen in sarcoidosis.

In the earlier stages, the histopathologic features are similar in many respects to those seen in some helminth infestations, viral infections, Hodgkins disease and hypersensitivity states to mention a few.

The diagnosis of eosinophilic granuloma can be entertained if certain clinical and

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**FIGURE 12 (upper):** The arrows point to the lumen of two small air passages which are markedly compressed due to the proliferation of fibroblasts (Hematoxylin and Eosin x250). **FIGURE 13 (lower):** Note bronchiolar dilatation and increase in smooth muscle. Some chronic inflammatory reaction is noted (Hematoxylin and eosin x100).

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**Schematic Representation of the Stages of Eosinophilic Granuloma of the Lung**

<table>
<thead>
<tr>
<th>Granulomatous Phase</th>
<th>Histioocytes + Foam cells Xanthomatous Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophils</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Plasma cells</td>
<td></td>
</tr>
</tbody>
</table>

**Proliferative Phase**

**Epithelial**

**Smooth muscle**

**Fibroblastic**

**Healing Phase**

**Interstitial fibrosis**

**Bronchiolectasis**

**"Honeycomb" lung**

radiographic features are present, but usually one has to resort to lung biopsy to establish or confirm the diagnosis.

**SUMMARY**

Five patients with diffuse pulmonary disease thought to be tuberculosis, but proved on lung biopsy to be eosinophilic granuloma were admitted to the Municipal Tuberculosis Sanitarium in the last two years. The x-ray findings were those of a fine peribronchiolar lattice-work-like pattern of infiltration which, in later stages, became a mixture of fine nodular infiltrates and small cystic areas, leading eventually to the diagnosis of honeycomb lung. Predominant findings on microscopic examination of the lung tissue were the presence of granulomata consisting of histiocytic cells with a large number of eosinophils, histiocytic aggregates in the alveolar septa and bronchial walls and marked fibrosis of the lung with resulting bronchiolectasis. There was hyperplasia of the smooth muscle and epithelial elements. In our experience, confirmation of the diagnosis of eosinophilic granuloma hinges on the histologic examination of lung tissue taken for biopsy.

**Resumen**

Se admitieron en el Sanatorio Municipal de Tuberculosis cinco enfermos con supuesta tuberculosis pulmonar difusa en los últimos dos años, los que resultaron después de biopsia pulmonar ser granulomas eosinofíllos.

El aspecto a los rayos X era el de fina infiltración peribronquiolar de punteado pequeño que
Eosinophilic Granuloma of the Lungs  

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more adelante se convierte en infiltrado nodular y pequeñas áreas quiticas que llevan acaso al diagnóstico de pulmón con aspecto de panal. Los hallazgos dominantes al examen microscópico del tejido pulmonar fueron la presencia de granulomas consistentes en células histiocióticas con gran número de eosinófilos, agregados histiocíticos en los tabiques alveolares y en paredes bronquiales y fibrosis acentuada del pulmón con bronquiolectasias resultante. Había hiperplasia del músculo liso y de los epitelios. Según nuestra experiencia la confirmación del diagnóstico de granuloma eosinófilo gira sobre el examen histológico del tejido tomado para biopsia.

RESUMÉ

Cinq malades atteints d'affectation pulmonaire diffuse prise pour une tuberculose, mais qui à la biopsie pulmonaire se révélèrent être un granulome eosinophile, furent admis au Sanatorium Tuberculeux Municipal pendant les deux dernières années. Les constatations radiologiques furent celles d'opacités périvbronchiales, qui dans les derniers stades, se transformèrent en un mélange de nodules fins et de petites zonas kystiques, conduisant éventuellement au diagnostic de "poumon en rayon de miel." Les constatations prédominantes, à l'examen microscopique du tissu pulmonaire, étaient la présence de granulomatoses consistent en cellules histiociytaires avec un grand nombre d'eosinophiles, d'agrégats histiociytaires dans les parois alvéolaires et les parois bronchiques, et une fibrose marquée du poumon, provoquant une bronchiolectasie. Il y avait une hyperplasie du muscle lisse et des éléments épitéliaux. Selon l'expérience de l'auteur, la confirmation du diagnostic de granulome eosinophile repose sur l'examen histologique du tissu pulmonaire prélevé par biopsie.

REFERENCES


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PULMONARY THROMBOEMBOLISM

The bronchial-pulmonary arterial vascular anastomoses in the normal lung were investigated and the earlier work of Miller confirmed. In the presence of disease, the size and site of these anastomoses are altered. Following pulmonary thromboembolism, systemic pulmonary arterial shunts are formed. Two of these systemic pulmonary arterial collaterals represent neovascular formations through vessels which under the light microscope appear as markedly enlarged capillaries. These collaterals are found passing from the systemic to the pulmonary circulation through areas of healed or healing infarcts and at sites of organizing thromboemboli. Only that portion of the bronchial circulation accompanying the thromboembolized artery participates in formation of a collateral circulation. The significance of the development of this collateral circulation appears to be to shunt blood away from the involved area and to prevent infarction should further thromboembolism occur. A patient may survive complete occlusion of a main pulmonary artery due principally to the extensive collateral circulation that develops in the manner described.


MIGRATION OF METALLIC PIN

A case of migration of a Steinmann pin from the right humerus into the right hemithorax in a 12-year-old girl is presented. The potential ability of metallic fixing pins to migrate within the patient must be recognized, and more frequent postoperative radiographic study performed after the insertion of such pins to permit earlier detection of bony resorption and migration, and thereby to permit earlier removal.