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EOSINOPHILIC GRANULOMA OF THE LUNG

by

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Two histologically proven cases of eosinophilic granuloma limited to the lung are reported. The roentgen examination of the chest reveals a generalized granulomatous infiltrate throughout the lung fields with a background pattern of fibrosis and localized areas of emphysema. Clinically, these patients are almost asymptomatic in spite of the extensive radiographic changes in the lungs. The pathological examination of the surgical specimens obtained from these cases reveals a process identical to that found in the lesions of eosinophilic granuloma of the bone.

One histologically proven case of eosinophilic granuloma of the bone with associated lung changes is reported. The roentgen examination of this patient's chest reveals identical changes to those found in the first two cases. Although no pathological confirmation of the lung changes was obtained, it is felt that this too represents a case of eosinophilic granuloma of the lung.

These lung lesions are identical to those found in the other members of xanthomatous group of diseases to which eosinophilic granuloma belongs. These also are identical to other cases reported in the literature of the lung lesions found in proven cases of eosinophilic granuloma of the bone. This is the first time that
histological confirmation of the lung lesions has been reported. It is felt that the term eosinophilic granuloma should be expanded to include those cases in which there are extra osseous lesions. It is suggested that these two cases of pulmonary eosinophilic granuloma are, like eosinophilic granuloma of the bone, the monosymptomatic form of a systemic xanthomatous disorder.

This abstract of about 250 words is approved as to form and content. I recommend its publication.

Signed [Signature]
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**Introduction**

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Eosinophilic granuloma limited to the lung has not to the author's knowledge been previously described. Two histologically proven cases have been recently observed and carefully followed. Eosinophilic granuloma involving both the lung and bone has been reported three times before (12, 13, 14). In these cases the diagnosis was made by biopsy of the bone lesions. To these three cases another is added, bringing the total reported to four. The cases presented here have all been confirmed by surgical biopsy and histological study. To the author's knowledge this is the first time that histological confirmation of the lung lesion has been reported.

Eosinophilic granuloma of bone was first recorded in the medical literature by Finzi (1) in 1929, whose diagnosis at that time was "a myeloma with preponderance of eosinophilic cells". However, it was not until 1940 that this condition was established as a well defined disease entity by the papers of Otani and Erlich (2) and Lichenstein and Jaffe (3). Since the first descriptions of the disease, there has been a tendency to expand the diagnosis of eosinophilic granuloma of bone to include those cases in which there are multiple bone lesions and even extra-osseous lesions, such as
those involving lymph nodes, skin, lungs and other organs (4). It is felt that with this report a step has been made in this direction.

Case Reports

Case 1: A 32-year-old white male developed a chronic productive cough during the winter of 1948-49. He produced from 30 to 150 cc. of sputum daily. He complained of fatigue and night sweats, but denied having fever or chills. A provisional diagnosis of pulmonary tuberculosis was made and he was admitted to magnificent army hospital. He had had a weight loss of 60 pounds. He gave a history of dust exposure from September 1947 to January 1948.

Physical examination was negative except for the presence of rales in both lungs.

X-rays revealed a general diffuse and patchy granulomatous type of pulmonary infiltrate (Figure 1) widely disseminated throughout both lung fields. This granulomatous infiltrate had a peculiar nodular quality about it. The nodules varied in size from almost visible to 1.5 cm. in diameter. Their margins were hazy. They were made more apparent by striking, by scattered areas of incision interpreted as apoplexy. In the background, throughout, the films showed a mild degree of fibrosis.

Laboratory findings were as follows: The total white blood count was 12,900 with 55% polymorphonuclear neutrophils but no
Case Reports

Case 1: A 32 year old white male developed a chronic productive cough during the winter of 1948-49. He produced from 50 to 120 cc. of sputum daily. He complained of fatigue and night sweats, but denied having fever or chills. A provisional diagnosis of pulmonary tuberculosis was made and he was admitted to Fitzsimons Army Hospital. He had had a weight loss of 40 pounds. He gave a history of dust exposure from September 1947 to January 1948.

Physical examination was negative except for the presence of rales in both lungs.

X-rays revealed a general diffuse and patchy granulomatous type of pulmonary infiltrate (Figure 1) widely disseminated throughout both lung fields. This granulomatous infiltrate had a peculiar nodular quality about it. The nodules varied in size from almost miliary to 1.5 cm. in diameter. Their margins were hazy. They were made more apparent, or striking, by scattered areas of lucency interpreted as emphysema. In the background, throughout, the films showed a mild degree of fibrosis.

Laboratory findings were as follows: The total white blood count was 18,500 with 83% polymorphonuclear neutrophils but no
Chest, Case 1, on admission shows a generalized patchy granulomatous infiltrate with components of fibrosis and emphysema.
eosinophils. Tuberculin (PPD 1st strength) skin test was 1 plus, Histoplasmin skin test was 2 plus, and Coccidioidin skin test was negative. Repeated examinations of sputum were negative for acid fast bacilli and fungi.

On 24 August 1949, a left thoracotomy was performed. Lung tissue from the left lower lobe was submitted for examination.

GROSS EXAMINATION: The specimen consisted of a wedge of lung tissue measuring 5 x 1.5 cm. Pea-sized hard nodules were felt scattered throughout. Over the nodules the pleura was thickened and hyalinized in some areas. The cut surface showed scattered irregular rounded grayish-white nodules. The largest nodule measured 1.0 x 0.7 cm. Those that reached the pleura merged with it.

HISTOLOGICAL EXAMINATION: There was a granuloma with an unusual eosinophilic polymorphonuclear infiltrate in the fibrosing miliary lesions (Figure 2). Many histiocytic cells and xanthomatous macrophages were seen. There were a few lymphocytes and some foreign body giant cells in among the fibrous trabeculae. The alveolar architecture in these areas was completely obliterated by this fibrous tissue containing the eosinophils, pigment laden macrophages and histiocytes (Figures 3 and 4).

Cultures from the lung tissues were negative for acid fast bacilli and fungi. No organisms or parasites were demonstrated in special stains.
Surgical specimen from Case 1 under low power showing the circumscribed granulomatous reaction in the lung tissue.
A high powered field from the granulomatous reaction shown in Figure 2. This shows the histiocytes, reticulum cells and large numbers of eosinophils throughout.
A high powered field from the granulomatous reaction shown in Figure 2. This field shows a predominance of histiocytes in contrast to Figure 3, but even here the eosinophils are prominent.
This lesion had the appearance of an inflammatory granulomatous process rather than being of a neoplastic origin. Its histological components of eosinophils and histiocytes lying in a fibrous stroma is similar to the histology characteristic of eosinophilic granuloma of bone.

Case 2: A 24 year old white male had a routine chest x-ray examination for re-enlistment in the army in September 1950. The x-ray (Figure 5) showed a widely disseminated diffuse and patchy granulomatous type of pulmonary infiltrate throughout all lung fields. The granulomatous nodules varied in size from miliary to 1.5 cm. in diameter. Their margins were ill defined and seemed to blend into the surrounding tissue. There were scattered areas of lucency throughout interpreted as localized areas of emphysema. In the background the lungs showed a slight degree of fibrosis.

The patient stated that he had had a cigarette cough with the production of 4-6 cc. of sputum (thin and whitish) for the past 2-3 years. He also stated that he had lost 5-6 pounds of weight in the preceding eight months but he denied having chills, night sweats, fever, hemoptysis and malaise. During his hospital course, his afternoon temperature varied between 99 and 100° Farenheit.

His past history was non-contributory except that he had been employed driving a truck carrying dry sand and cement. He had malaria in 1946 with recurrences in 1947 and 1948.
Chest, Case 2, on admission shows an extensive generalized granulomatous infiltrative process in the lungs with a slight degree of fibrosis and scattered areas of emphysema.
Physical examination was negative except for the presence of a small, non-tender, movable node in his left axilla.

Laboratory findings were as follows: The total blood count was 14,250 with 60% neutrophils and 10% eosinophils. The red blood count, hemoglobin and urine were normal. Tuberculin (PPD 2nd strength) test and skin tests for blastomycosis and histoplasmosis were positive. The coccidioidin skin test and the complement fixation test for histoplasmosis were negative. Repeated examination of sputum and gastric washings were negative for tuberculosis and fungi.

Repeat lung x-rays on October 24 showed no change. X-rays of the hands and feet showed no abnormalities. On November 20, post-operative x-ray studies of the long bones and skull revealed no abnormalities.

On November 13, a left thoracotomy was performed. Numerous buckshot sized firm nodules could be palpated throughout both lobes. The lung surface over these nodules was dimpled. The hilar lymph nodes were not enlarged. Tissue for biopsy was taken from the left upper and lower lobes.

GROSS EXAMINATION: The specimen consisted of two small pieces of lung tissue in which small, firm, but not stony hard, nodules could be palpated. Their cut surface was yellow and not sharply circumscribed. They varied in size from 0.4 to 1.5 cm. in diameter.
Smears and cultures for tuberculosis and fungi made from these lesions were negative.

HISTOLOGICAL EXAMINATION: These nodules were seen replacing the lung tissue (Figure 6). They consisted of bands of fibrous tissue containing in a lobulated fashion masses of eosinophils and histiocytic cells (Figures 7 and 8). The histiocytes had large vesicular nuclei and their cytoplasm was fragmented in some. In others, the cytoplasm was more abundant and vacuolated. Some large macrophages were laden with brown pigment. Scattered throughout were giant cells formed of nuclear aggregations with little cytoplasm. Occasionally typical foreign body giant cells were seen. The eosinophils were very numerous and in some areas they appeared in large clumps.

These eosinophils were mostly of the mature type. This granulomatous process was not circumscribed but in the sections one noted areas of lung wherein the architecture was completely destroyed, other areas adjacent which were atelectatic, and then normal or slightly emphysematous appearing lung tissue. No organisms or parasites have been demonstrated in the special stains prepared at the Armed Forces Institute of Pathology.

THE CLINICAL PICTURE: In both of these cases the clinical picture was minimal. Both complained of a mild cigarette cough with some sputum production. There was a low grade afternoon temperature from 99° to 100°. There was no chest pain and only minimal fatigue.
Surgical specimen from Case 2 under low power. This shows the granulomatous lesion surrounded by normal lung.
Section of the granulomatous lesion shown in Figure 2 illustrating the large numbers of eosinophils and scattered histiocytes. Compare with Figure 4.
Figure 8

Section of the granulomatous lesion shown in Figure 2. Here the histiocytes and reticulum cells predominate but the eosinophils are still numerous.
In Case 2 the condition was discovered entirely by accident. Physical findings were limited to Case 1 where scattered rales were found throughout the chest. In other words, the clinical picture is that of a very benign condition which belies the roentgen picture.

THE ROENTGEN FINDINGS: The lung findings in this condition are generalized and widespread. They are identical in both cases (Figures 1 and 5). They consist of a granulomatous infiltrate, nodular in character. The nodules vary in size from miliary to 1.5 cm. in diameter (Figure 9). They are not sharply demarcated but have rather hazy borders fading into the normal lung tissue surrounding them. There is evidence of associated localized areas of emphysema and fibrosis.

THE PATHOLOGICAL PICTURE: The pathological picture in these two cases was identical. It is of a granulomatous type, multiple and widely disseminated. It is not sharply circumscribed. There are areas showing fibrous tissue reaction, pigment laden macrophages and histiocytes. Eosinophils are a prominent feature of the picture being present both as scattered individual cells and, in some areas, sheets and large clumps. The picture is identical with that seen in eosinophilic granuloma of bone.

THE DIFFERENTIAL DIAGNOSIS: Since clinical and laboratory findings in these cases are more or less negative we are limited in our
An enlargement of lung fields on Case 1, showing distinctly the nodular or granulomatous pattern of the infiltrate. The hazy margins of the lesions are visualized as are the localized areas of emphysema and fibrosis.
discussion to a differential diagnosis of the above described roentgenological picture. In the differential diagnosis, therefore, one must include those conditions which give rise to (1) diffuse nodular granulomatous pulmonary infiltrate (2) pulmonary fibrosis and (3) emphysema of a scattered segmented type. This pattern has been described several times in the literature in various papers and the differential suggested. Most recently Robbins (19) touched upon the subject in his discussion of "Idiopathic Pulmonary Fibrosis". Perhaps, however, the most classic description is found in the article by Oswald and Parkinson (20) on Honeycomb Lungs. In both of these articles one gains the impression that the differential lies between those conditions more or less well known that produce the above mentioned pathological changes in the lungs.

Tuberculosis: When one is confronted with the radiograph of pulmonary eosinophilic granuloma (Figures 1 and 5) tuberculosis certainly must be considered. It may be ruled out with a fair degree of certainty because of the clinical picture (the eosinophilic granulomatous patient is almost asymptomatic) and the lack of a positive sputum for acid fast organisms (considering the very extensive lung involvement in the radiograph).

Sarcoidosis: This condition may present a difficult problem in the differential diagnosis of these cases. It is to be confessed that pre-operatively this was the diagnosis in the two cases cited above.
However, the lack of hilar and peritracheal adenopathy is suggestive of another diagnosis. The pulmonary infiltrate in eosinophilic granuloma is more widely disseminated than that usually encountered in sarcoid (it has a hematogenous rather than a lymphagenous distribution in the lung fields). These two factors when added to the underlying or background pattern of fibrosis and emphysema seen in all cases of eosinophilic granuloma point strongly away from a diagnosis of sarcoid.

Pneumoconiosis: Here again the differential diagnosis may be quite difficult. The distribution of the lesions in pneumoconiosis is seldom generalized or evenly distributed throughout the lungs. It strongly favors the hilar regions and the apices. Hilar masses are not uncommon and calcification particularly of the egg-shell type is the usual finding when the radiographs show as extensive changes as seen in eosinophilic granuloma. The history is of course very helpful in this instance and may settle the issue.

Bronchiectasis: This is to be considered, but in most instances may be ruled out on the basis of the clinical history and physical findings alone. The radiographs may only be confused with a very advanced generalized saccular type of bronchiectasis where symptoms and findings should be pronounced. Our cases were not even considered for bronchograms although this study would definitely eliminate this diagnosis.
Hodgkin's disease and other lymphomata: These seldom produce the extensive pulmonary changes seen in eosinophilic granuloma without showing some evidence of lymph node involvement either hilar or peripheral. The components of fibrosis and emphysema are usually missing in these conditions. A lymph node biopsy will usually establish the diagnosis.

Periarteritis nodosa: The lung findings do not usually present the picture seen in eosinophilic granuloma being more of a miliary peribronchial infiltrate sparing the periphery of the lung fields. The clinical picture will usually enable one to make the differential diagnosis. Periarteritis nodosa is a general disease - 75% showing kidney involvement, 60% heart changes, 30% G. I. Tract complaints compared to only 5% showing lung changes.

Rheumatic fever and Löffler's disease: These may be ruled out on a basis of the clinical picture and the transitory fleeting nature of their radiographic findings. (Löffler's pneumonia will be discussed in more detail later.)

Scleroderma: Here again the clinical picture helps to rule out the condition although the lungs may show a diffuse fibrotic "honeycombed" appearance.

Erythema nodosum: Although this condition may present a diffuse mottling of the lung fields with associated fibrosis the picture is not likely to be confused with eosinophilic granuloma. The clinical
picture in erythema nodosum is an acute one and the skin manifestations make the diagnosis.

Fibrocystic disease of the pancreas: This is characterized by fibrosis and emphysema of the lungs but it is not likely to be confused with eosinophilic granuloma due to its clinical picture and its lack of nodulation in the lung fields.

Coccidioides: Here, as in tuberculosis, the organisms should be found in the sputum when one considers the extensive radiographic involvement of the lungs. The clinical picture certainly is not compatible with extensive coccidioidomycosis of the lung. Coccidioidin skin tests and complement fixation tests may assume quite an important role in confirming the clinical impression.

Histoplasmosis: This usually does not present the fibrosis and emphysema one sees in eosinophilic granuloma. The Histoplasmin skin test may definitely rule out the condition. If there is any doubt blood cultures for Histoplasma capsulatum may be carried out as well as inoculations of mice with bronchial material.

Amyloidosis: This is a very rare condition, but then so is eosinophilic granuloma of the lung. The radiographic picture is not usually typical and in eosinophilic granuloma there is no evidence of involvement of the liver or kidneys. Clinical and laboratory studies will rule out this possibility.

Leukemia: This shows fine miliary-like lesions instead of the
nodules seen in eosinophilic granuloma. There are usually no components of fibrosis and emphysema. Blood studies will make the diagnosis.

Pulmonary adenomatosis: This is a generalized nodose condition of the lungs but it does not show the fibrotic or emphysematous components. In this condition the patient is usually dyspneic and acutely ill. It is progressive rather than static.

Xanthomatosis or reticulosis: This is the group of diseases that includes eosinophilic granuloma. If one studies the radiographs of patients with pulmonary involvement in any of these conditions, both lipoid and non-lipoid types, one finds that the lung picture is more or less the same. The radiograph of a patient with Gaucher's disease is included here as an example (Figure 12). The same diffuse pattern of fibrosis, emphysema and granulomatous infiltrate is well shown. The radiographic findings are identical in the entire group of the xanthomas and, like the pathological findings are almost inseparable from Letterer-Siwe and Hand-Schüller-Christian disease.

In this group the lipoid xanthomatosis: Gaucher's and Niemann-Pick's may be ruled out by studies of the blood cholesterols - they show hypercholesterolemia. In addition Niemann-Pick's shows an enlargement of the liver, spleen, nodes - anemia and leukocytosis which eosinophilic granuloma does not. Gaucher's is more common in
Figure 12

Chest of a patient with Gaucher's disease showing a generalized granulomatous infiltrate with fibrosis and emphysema. Compare with Figures 1, 5 and 13.
Jewish females in the first decade. It is insidious, chronic with marked splenic enlargement. There is a pancytopenia due to bone marrow replacements and or hypersplenism with resulting purpura. X-rays show the pathognomonic widening (Erlenmeyer flask type) of the lower end of the femur.

In the non-lipoid group we have Letterer-Siwe, Hand-Schüller-Christian and eosinophilic granuloma. Letterer-Siwe's disease is found almost exclusively in infants. There is generalized involvement of spleen, liver, lymph nodes, lungs and bones - this is not found in eosinophilic granuloma. It is progressive and fatal. Hand-Schüller-Christian's disease clinically shows diabetes insipidus in many cases as well as exophthalmos which is usually unilateral. There are usually found defects in the skull bones together with multiple areas of involvement of other bones. There are variable degrees of visceral involvement, liver, spleen and lungs. Anemia is frequent. It is progressive and usually fatal.

THE TREATMENT AND FOLLOW UP: Case 1 received no therapy for the condition. The pulmonary status was carefully followed by x-rays and gradually has cleared. His last film 12 December 1950 (Figure 10) approximately 16 months after thoracotomy shows almost complete clearing with some residual fibrosis. Case 2 has received ACTH therapy (800 mg. total 30 November - 9 December) and cortisone therapy (5,700 mg. total dose from 10 December - 23 February 1951).
Figure 10

Chest, Case 1, 16 months after thoracotomy shows considerable clearing from Figure 1. Some residual fibrosis is evident.
Chest film taken some 6 months after admission to the hospital shows definite evidence of clearing of the process (Figure 11) but at this date some of the granulomatous infiltrate is still present and the evidence of fibrosis has not changed. It is felt that the progress of these cases is very important as it is here the benign nature of eosinophilic granuloma is manifest as compared to Letterer-Siwe and Hand-Schüller-Christian disease. Also the chronicity is demonstrated and can be compared to the more transient Löffler's pneumonia. The course of these patients agrees in every way with the course of the patients who have monostatic eosinophilic granuloma of bone.
Chest, Case 2, 6 months after admission to the hospital. There is definite evidence of clearing of the process, but some of the infiltrate remains. Compare with Figure 5.
EOSINOPHILIC GRANULOMA OF THE BONE WITH PULMONARY CHANGES

The above mentioned pulmonary pattern in association with eosinophilic granuloma has been mentioned several times before in the literature. Three authors have reported this pulmonary picture in cases of biopsy proven eosinophilic granuloma of bone. To this group another case is added. It is to be emphasized that in none of these cases was lung biopsy performed and it can only be inferred that the lung lesions are of the same nature as those found in the bones.

Case Report

Case 3: A 19 year old white male was admitted to Fitzsimons Army Hospital on 24 May 1950. History dated back to November 1949 when he noted a soreness of the right lower gum margin. On 1 December 1949 he experienced general malaise, fatigability, pain in both shoulders and over the anterior chest. Chest pain was aggravated by coughing and deep inspiration. It was associated with a non-productive cough as well as a 20 pound weight loss. On 11 January 1950 he reported to the dental clinic because of continued gingival pain. X-rays of the mandible revealed destruction of the alveolar half of the mandible. Because of poor healing following the extraction of two loosened teeth, hospitalization was effected on 16 March 1950. X-rays of the
jaws revealed the upper border of the mandible to be eroded and reduced to two-thirds of normal with the bony outline hazy and irregular. His weight fluctuated between 126 and 128 pounds and he presented a daily temperature elevation of 99° to 99.6°. On 23 March a painless swelling not accompanied by inflammation appeared over the anterior end of the first left rib. Following poor results on antibiotic therapy a presumptive diagnosis of actinomycosis was made and the patient was evacuated to Fitzsimons Army Hospital.

Past history was non-contributory.

Physical examination revealed a well developed poorly nourished white male who appeared chronically ill. Positive findings were limited to the mouth and the chest. There were white, non elevated tender coalescent areas over the gingivae with areas of apparent necrosis in the region of the previous extraction. Scattered rales were present in both lungs.

Laboratory examinations showed a leukocyte count of 12,000 with 73% polys and 1% eosinophils. Tuberculin, histoplasmin, actinomycin and coccidioidin skin tests were negative. Sputum and exudate from the gingivae were culturally positive for Vincent's spirelli and fusiform bacilli.

Radiographic examinations revealed: (1) Destructive lesions of the bone of both mandibles (Figure 13). (2) Cyst-like destructive
Figure 13

Left mandible, Case 3, showing destructive lesion of the bone. A similar lesion was present in the right mandible.
lesion of the anterior one-third of the left first rib with expansion of, but no break in, the cortex (Figure 14). (3) Cyst-like areas of loss of bone substance in the proximal ends of the shafts of the humeri involving the heads (Figures 15 and 16). (4) A similar lesion in the left scapula (Figure 15). (5) General diffuse granulomatous nodular pulmonary infiltrate throughout all lung fields (Figure 14). The nodules varied in size from miliary to 1.5 cm. in diameter. There was a rather widely disseminated pulmonary emphysema, which, in areas showed cystic formation. Over the left apex was a localized area of pneumothorax (this cleared within a week). Fibrosis, as a background, was rather pronounced and generalized (Figure 14).

The course in the hospital was characterized by daily temperature elevations of 99° - 99.8° and a slight weight gain. Gingival biopsy on 6 June 1950 showed eosinophilic granuloma.

GROSS EXAMINATION: The specimen consists of a small wedge-shaped piece of formalin-fixed, firm tissue measuring 9 x 6 x 4 mm. The tissue appears to be covered on one surface by mucous membrane.

HISTOLOGICAL EXAMINATION: The stratified squamous epithelial surface is, in places, ulcerated and covered by a fibrino-purulent exudate. In the submucosal tissue there is a severe infiltration by large swollen histiocytic cells, clumps of eosinophils, some plasma cells, lymphocytes and polymorphonuclear neutrophils. The histological features are typical of eosinophilic granuloma.

This patient was treated by Roentgen therapy receiving:
Chest, Case 3, showing the cyst-like destructive lesion of the left first rib with expansion of the cortex. The diffuse granulomatous pulmonary lesions are quite prominent as is the fibrosis and emphysema of the lung.
Right shoulder, Case 3, showing the cyst-like area of destruction in the proximal end of the humerus.
Left shoulder, Case 3, showing the cyst-like destructive lesion in the proximal end of the humerus. A similar lesion is seen in the glenoid process of the scapula.
Factors: 200 KV, 15 Ma, 1/2 mm. Cu and 1 mm. Al added filtration, 50 cm. f.s.d. and Hvl 1.1 mm. Cu

The treatment plan consisted in delivering one or two courses of 600r in air to each port at the rate of 200r in air each day.

**Chest** - 2 courses: 17 July 1950 - 22 Aug. 1950

28 Dec. 1950 - 11 Jan. 1951

(Entire chest was treated - 4 anterior and 4 posterior ports 15x15 cm. each)

**Right and left shoulders** - 2 courses: 17 July 1950 - 25 July 1950


(One anterior and one posterior port (10x10 cm.) were used over each shoulder.)

**Right and left mandibles** - 1 course: 25 July 1950 - 2 Aug. 1950

(3x8 cm. ports)

**Right and left maxillae** - 2 courses: 26 Sept. 1950 - 30 Sept. 1950


**Sublingular area** - 1 course: 12 Jan. 1951 - 15 Jan. 1951

(7 cm. circle)
His lesions along the lower gingival margins have shown considerable regression, but two new lesions have appeared in the upper gingivae and involve the maxilla as evidenced by surgical exploration and roentgenographs. Recently, March 1951, a new lesion has appeared on the lower gingival margin anteriorly. The pulmonary picture has remained unchanged as have the lesions in the humeri. The rib lesion has recently showed signs of regression and re-ossification. The patient has been asymptomatic except for the slight temperature elevation the past six months. He has no cough and does not raise any sputum.

It is felt that this case, in view of the pulmonary radiographic findings identical with Cases 1 and 2, represents eosinophilic granuloma of the lung. It is felt that the cases reported by Weinstein (12), Schuknecht (13) and Parkinson (14), in view of the pulmonary picture and the positive bone biopsies also represent cases of eosinophilic granuloma of the lung.
PART III

GENERAL DISCUSSION

Farber, Green and McDermott in 1941 and Green and Farber (17) in 1942 studies pathological material from the bone lesions in thirteen cases of eosinophilic granuloma. They compared this pathological material with that obtained from the lesions in the viscera and bones in cases of Hand–Schüller–Christian's disease and Letterer–Siwe's disease. They were, as a result of these studies, the first to postulate that "all three conditions represent variations in degree, stage of involvement and localisation of the same basic process". Most authors (18) who have written since on eosinophilic granuloma of bone have accepted this point of view. Out of this voluminous literature have come some concepts that we may here review briefly.

Thannhauser and Magendanz (21) in 1938, in a detailed study of the xanthomatous diseases, evolved a clinical physiological classification of the entire group.

Classification

I. Primary essential xanthomatosis.
   A. Primary essential xanthomatosis of the hypercholesteremic type.
      1. Xanthomata of tendons.
      2. Xanthomata of tuberosa and plana.
3. Xanthomatous biliary cirrhosis.
4. Xanthomatosis of endocardium and blood vessels.
5. Nests in liver, spleen, etc.

B. Primary essential xanthomatosis of the normo-cholesteremic type.
1. Xanthomata disseminata.
2. Osseous xanthomata.
3. Xanthomatous involvement of the pituitary, brain, etc.
4. Xanthomatous involvement of the lungs and fibrosis.
5. Nests in the liver, spleen, etc.

C. Primary essential xanthomatosis of the combined types.

II. Secondary xanthomatous due to lipemia.
1. Xanthomata diabeticorum.
2. Nests in liver, spleen, etc.
3. Xanthomatous lymphangitis.

III. Localized xanthoma cell formation in true tumors (fibrosarcoma-xanthoma, etc.)

Since, in Letterer-Siwe, Hand-Schüller-Christian and eosinophilic granuloma normal cholesterol or high normal cholesterol in the serum
is the rule, these conditions fall into the above group of primary essential xanthomatosis of the normal cholesteremic type. It is to be noted that the further breakdown under this heading is only as to distribution of the lesions.

In practice, the cases seen seem to fall into more or less three distinct groups. There are, it is true, transition forms which bridge the various criteria but the patterns are constant enough to be classical and retain their identity.

Letterer-Siwe's disease was first called by this name by Abt and Denenholz (22) in 1936. They reviewed the nine cases observed up to that time. It was originally described as a non-lipoid reticuloendotheliosis characterized by a generalized hyperplasia of the reticulo-endothelial cells which, in some areas may assume tumor-like proliferation and show a hemorrhagic tendency. They demonstrate no constant storage of lipoid substance in the cells. Hepatomegaly and splenomegaly are characteristic as is generalized lymphadenopathy although the latter may not be too apparent in vivo. There is a secondary anemia which is of a progressive type with a normal leukocyte count. A hemorrhagic tendency is present which is chiefly manifested by petechial exanthem of purpura. The disease shows neither a heredity nor familial tendency and occurs exclusively in infants and young children. Its prognosis is fatal. The duration of the disease is from a few weeks to several years.
Hand-Schüller-Christian's disease is characterized by the classical triad:

1. Multiple defects in the skull.
2. Exophthalmos.
3. Diabetes insipidus.

The first case was reported by Hand in 1893 (23) who classified it as "polyuria and tuberculosis". He was not satisfied with this diagnosis. Schüller in 1915 described "peculiar defects of the membranous bones of the skull" and Hand referred later in 1921 (24) to "a peculiar syndrome of dyspituitarism". Christian in 1919 (25) called attention to a clinical syndrome consisting in "defects in membranous bones, exophthalmos and diabetes insipidus". It is now recognized, however, that the above members of the classical triad may occur singly, in any combination among themselves or with lesions involving other bones or the viscera. Wallgren (26) in 1944 stated that up to that time at least eight different clinical varieties had been seen and described.

The original description of eosinophilic granuloma as an entity described them as solitary lesions occurring only in bones, but this view was soon modified. Thannhauser (16a) was of the opinion that eosinophilic granuloma of bone was the monosymptomatic form of a systemic granulomatous disorder in which histiocytes, eosinophils and xanthoma cells are observed in the lesion at different phases. This, going back to his classification we quoted above, would permit it to
fall into any of the groups under the normocholesteremic type depending upon the organs involved.

By pathological studies it has been shown that these three conditions show definite phases which comprise the natural history of the disease:

1. A proliferative phase - here there is a stage of histiocytic proliferation which is associated with accumulation of eosinophilic leukocytes. There are no foam cells.

2. A granulomatous phase - there is an increase in blood vessels, reticular cells, histiocytes, eosinophilic leukocytes, and giant cells as well as lipid phagocytosis.

3. A xanthomatous phase - here there are nests and isolated foam cells interspersed among the above listed elements.

4. A fibrous stage - the above lesions heal by fibrosis.

There is no strict demarcation through the course of the disease. Wallgren in 1944 (24) pointed out that the histiocytic cells in Letterer-Siwe's disease could contain lipoid. He cited six cases which were clinically of this nature, but microscopically were identical to the histology accepted as that being of Hand-Schüller-Christian's disease. He, on the basis of these studies, concluded that these two diseases were expressions of the same basic process. This same view has been shared by Gross and Jacox (18c), Lichtenstein and Jaffe (18b) and Ponseti (16f) and others.
In addition, similar links have been described between eosinophilic granuloma and Letterer-Siwe’s disease on the one hand and Hand-Schüller-Christian’s disease on the other. Jaffe and Lichtenstein in 1944 (18b) described a case of a female child, age 10 months, who had a lesion of the left radial shaft which histologically was eosinophilic granuloma. Shortly afterward, the child developed an illness with a rapid downhill course, with fever, enlargement of liver, spleen and lymph nodes and skin rashes. Autopsy revealed a reticulo-endothelial proliferation throughout, of the Letterer-Siwe type.

From the above we may then assume that these three conditions are closely related, and are different clinical and anatomical expressions of the same basic process. Pathologically, four phases or stages have been described:

1. Histocytic proliferation.
2. Granulomatous phase.
3. Xanthomatous stage.
4. Healing by fibrosis.

The clinical features vary, but three main forms are recognized:

1. In infancy, the disease is acute and rapidly fatal (100%). Histologically, there is the proliferative phase with infiltration of the skin, bones, nodes, and viscera with histiocytes. This in its classical form is Letterer-Siwe’s disease.
2. In older children and adults the chronic complete type is encountered with widespread bone and visceral involvement. The histology in early cases is that of the granulomatous phase which later enters the xanthomatous stage. Thirty percent of these patients recover. The classical example is Hand-Schüller-Christian's disease.

3. In the chronic incomplete form, also found in older children and adults, solitary lesions are encountered. These have mainly been described in bones. The histology is that of the granulomatous phase. Either spontaneously or under x-ray therapy, these lesions go on to the fourth, the healing phase. This in its classical form is the eosinophilic granuloma.

That pulmonary infiltrations occur in eosinophilic granuloma has been recognized in retrospect since Rowland (15) in 1928 reported the case of a 5 year old male child who died from pulmonary fibrosis secondary to xanthomatosis. Since then many cases have been reported and reviewed (16). Parkinson (14) suggested the possibility of pulmonary infiltration occurring as the sole manifestation of the chronic form of eosinophilic granuloma. In two of our cases there was no evidence of coexistent osseous or other extra-osseous lesions so we must therefore conclude, for the present, that these patients have no manifestations of eosinophilic granulomatous involvement, other than the pulmonary lesions. These patients are being kept under observation
for any further progress of the disease.

A search of the literature for cases of extra-osseous eosinophilic granuloma is not very fruitful. In 1949 Vanek (5) described six cases of an eosinophilic granulomatous process involving the submucosa of the stomach, for which he suggested the term "gastric submucosal granuloma with eosinophilic infiltration". Histologically, the lesion was essentially that of a fibroblastic reaction with an even distribution of eosinophilic cells throughout the lesion. Vanek, himself considered these granulomatous lesions to be different from the "eosinophilic granuloma" such as found in bone.

Polayes and Kreiger (6) in 1950 described a case of a jejunal lesion which was histologically identical to that of Vanek's eosinophilic granuloma of the stomach and apparently did not have any relationship with eosinophilic granuloma of the bone.

In 1947 Curtis and Cauley (7) reported a case of widespread eosinophilic granulomatous infiltration of the skin in a 16 month old female infant who also had multiple skeletal defects. Biopsies of the cutaneous lesions revealed a picture compatible with eosinophilic granuloma of bone or Letterer-Siwe's disease manifesting cutaneous lesions. Biopsy of the skeletal lesions was not performed.

In 1947 Ackerman (27) reported a case of a 19 year old male showing areas of involvement in multiple bones and "with involvement of the lungs and diaphragm". Histopathological study of an affected
rib showed changes characteristic of an eosinophilic granuloma. In this case, the lung findings were not characteristic of this disease as shown by the cases we have presented. They were more or less limited to "moderate fibrosis in the dorsal segment of the left lower lobe and an associated "involvement of the diaphragm on the right". Although it is entirely possible that this was due to eosinophilic granulomatous infiltration, it is not characteristic and there is no proof.

The pulmonary syndrome described by Löffler (8) occurs as transient pulmonary infiltrations, often recurrent, accompanied by cough, pyrexia, asthmatic symptoms and a high peripheral eosinophilia. X-rays of the lungs show the picture of patchy transient areas of pneumonitis with streaking and soft lobular infiltration, more suggestive of pneumonia or of tuberculosis than of the picture described in eosinophilic granuloma. As stressed by Caffey (9) one of the main features in Löffler syndrome is the fleeting and migrating character of the roentgen changes. The morbid changes in the lungs have been examined in only a few cases (10); these studies revealed an exudative type of lesion. Specific allergenic factors such as amoebae, intestinal worms and plant pollens have been identified as causative agents in several cases (11). The elimination of these specific agents have resulted in permanent cure. On the basis of both histological and roentgenological findings, we are reasonably certain
that our cases resemble eosinophilic granulomas of bone rather than the "Eosinophilic Infiltrations" of Löffler and allied allergic reactions in the lung.

As pointed out by Robbins (19) and Oswald and Parkinson (2) numerous known causes of pulmonary fibrosis and/or honeycomb lungs exist. Also as pointed out by these authors in any large chest center, one is impressed by the not too infrequent cases of so-called idiopathic pulmonary fibrosis. It is to be suggested that with the advent of exploratory thoracotomy and lung biopsy, more and more of these cases will be solved and the true nature of their etiology recognized. It is felt that we have here made one step forward in this direction and that, in the future, with the advent of more cases this picture will be substantiated.
SUMMARY

Two cases of eosinophilic granuloma localized to the lungs are described.

An additional case of eosinophilic granuloma of bone with pulmonary findings is presented.

The roentgenological picture is identical to that of Letterer-Siwe's disease, Hand-Schüller-Christian's disease, Gaucher's disease and other xanthomatoses.

These lesions are histopathologically identical to the eosinophilic granuloma of bones.

The term eosinophilic granuloma should be expanded to include those cases in which there are extra-osseous lesions such as those involving lungs, skin and other organs.

It is suggested that these two cases of pulmonary eosinophilic granuloma are like eosinophilic granuloma of bone, the monosymptomatic form of a systemic xanthomatous disorder.
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