Intrathoracic Fibrocaseous Granuloma of Obscure Origin

A Ten Year Survey*

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There is a group of patients with caseating, granulomatous disease of the lungs or mediastinal lymph nodes for whom an etiologic diagnosis cannot be established unequivocally even after exhaustive clinical investigation and examination of pathologic tissues. During the past ten years, 48 patients with intrathoracic fibrocaseous granulomata have been seen at this hospital for whom diagnostic surgical intervention was carried out. In no instance could a specific diagnosis be established. Of particular interest is the observation that recurrence or progression of disease has occurred in several of these patients subsequent to surgery.

The 48 patients included in this report were selected by diagnostic exclusion, that is, by the ability to find and identify causative organisms. In addition to the usual examinations of sputum, bronchial and gastric washings, the pathologic tissues obtained from these patients were subjected to intensive etiologic search by special culture methods and tissue stains. The tissue sections were reviewed by several pathologists and most were forwarded to the Armed Forces Institute of Pathology for further examination. The histologic characteristics of the granulomata obtained from these individuals were not unlike those of abnormal tissues received from patients with known tuberculosis, histoplasmosis or coccidioidomycosis. During the ten years of this survey, Coccidioides immitis was recognized in specimens from 115 patients, and Histoplasma capsulatum from 103 individuals. In addition, less commonly occurring organisms were occasionally identified. Also Mycobacterium tuberculosis was recognized and cultured from innumerable specimens. Despite an increased alertness for possible causative organisms on the part of this laboratory since 1950, the etiologic agent could not be demonstrated in these 48 patients.1,*

We have arbitrarily chosen to categorize these cases in accordance with the anatomic distribution of the disease (Table 1).

<table>
<thead>
<tr>
<th>Distribution of Disease</th>
<th>No of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Single Pulmonary Nodule</td>
<td>28</td>
</tr>
<tr>
<td>2. Mediastinal Disease</td>
<td>12</td>
</tr>
<tr>
<td>3. Multinodular Pulmonary Disease</td>
<td>8</td>
</tr>
</tbody>
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The majority of patients had what appeared to be a single peripheral pulmonary nodule on the chest roentgenogram. Those encountered with mediastinal or adjacent hilar involvement had primarily lymph node disease. A smaller group of individuals was encountered with diffuse or multinodular pulmonary granulomata.

Most of these patients were Caucasian men as might be anticipated in a military population. There were only six women in this series. It is interesting to note the disparity in distribution of the six Negroes with regard to the type of disease (Table 2). Four of them had multinodular granulomatous pulmonary disease. The average age of all patients was 32 years with a range of eight to 58 years. Epidemiologically, the various places of residence of this widely traveled group of military people

*From the Thoracic Surgery Service, Fitzsimons General Hospital.
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was of little aid diagnostically. Most of them lived for a time in the mid- or southwest section of this country, as well as in overseas areas.

Table 2—Distribution of Disease

<table>
<thead>
<tr>
<th>Distribution of Disease</th>
<th>Caucasian</th>
<th>Negro</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Single Pulmonary Nodule</td>
<td>27</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>2. Mediastinal Disease</td>
<td>11</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>3. Multinodular Pulmonary Disease</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>6</td>
<td>48</td>
</tr>
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**Single Pulmonary Nodule**

Twenty-eight patients in this series were observed to have a single pulmonary nodule as the roentgenographic abnormality. Fifteen were asymptomatic when the lesions were discovered. Thirteen had symptoms referable to the respiratory system, the most frequent complaint being cough. Two of these individuals developed acute symptoms with cough, pain and fever as the initial manifestation of disease. In addition, two had hemoptysis. Skin sensitivity to challenge injections of tuberculin PPD, histoplasmin and coccidioidin was recorded for 27 patients (Table 3). A negative reaction to PPD was recorded only after application of the second strength test material. In one, all three tests were negative and in five all three tests were positive. Eleven individuals had only one positive skin test, six to histoplasmin and five to PPD. The remaining ten had various combinations of two positive skin tests.

Table 3—Skin Sensitivity

<table>
<thead>
<tr>
<th>Test Material</th>
<th>Positive</th>
<th>Result</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PPD</td>
<td>19</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>2. Histoplasmin</td>
<td>19</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>3. Coccidioidin</td>
<td>8</td>
<td>19</td>
<td>27</td>
</tr>
</tbody>
</table>

The most frequently observed combination was positive PPD and histoplasmin tests in seven instances. Diagnostic serologic examinations were accomplished in nine of these patients and yielded positive information in two. In both instances, there was a significantly elevated serologic titer for histoplasmosis.

Surgery was offered to these patients as a diagnostic means. Although a majority were considered to be granulomata by the appearance on chest roentgenogram, carcinoma was not excluded as a possibility. Twenty-five were treated by local excision of the peripheral pulmonary nodule. This procedure was accompanied by the development of postoperative hemothorax in one individual. This complication was successfully managed by the instillation of a combination of streptokinase and streptodornase (Varidase) solution and several aspirations of the pleural space. The remaining three required segmentectomy to eradicate disease-bearing tissue. In addition to segmental resection, one also required decortication of a restricting fibrous peel, as well as a small concomitant thoracoplasty. This patient experienced a difficult postoperative course because of atelectasis, persistent pleural space and wound infection. These problems were eventually resolved by additional surgical collapse of the chest wall.

Subsequent observation of these patients by periodic examination at this institution, direct questionnaire or correspondence with the patient’s physician has been accomplished in all instances. Twenty-two have remained completely asymptomatic since surgery done one to seven and one-half years ago. One has symptoms suggestive of bronchitis nine years after surgery. Another continues to complain of intercostal pain six and one-half years after surgery. A third has cough and occasional hemoptysis three and one-half years after surgery. Possibly of greater interest is the observation that one of these patients developed symptoms and roentgenographic evidence clinically suggestive of tuberculosis of the third thoracic vertebra two years following removal of a peripheral pulmonary nodule. He became improved symptomatically following an appropriate course of adequate chemotherapy. In addition, two patients were ob-
served to have roentgenographic recurrence of a similar appearing lung nodule. One of these was re-excised (six years later) and the new specimen submitted to laboratory investigation. The prior nodule was removed from the lingula, the recurrent lesion was found in the adjacent anterior basal segment of the lower lobe. On this later occasion, special tissue stains revealed a suggestion of organisms resembling *Histoplasma capsulatum*. Two years after the second procedure, he was once again noted to have a pulmonary nodule in the left lower lung field in a similar position on the chest roentgenogram. After the administration of a systemic course of amphotericin-B, slight resolution of the infiltrate was thought to have occurred. This patient is still under observation. Finally, another of these patients developed roentgenographic evidence of a recurrent nodular lesion one year following local excision. He had a strongly positive skin reaction to histoplasmin initially. During a period of six months' observation, the recurrent lesion exhibited spontaneous regression on serial chest roentgenograms.

**DISCUSSION OF SINGLE PULMONARY NODULE GROUP**

Although the statistic probability of malignancy always exists in considering the etiology of the single pulmonary nodule, the importance of establishing an etiologic diagnosis of obscure pulmonary granuloma may be equally significant to the patient. Fortunately, the majority of these individuals have had no difficulty following surgical removal of the granuloma even though many have obviously been exposed to a known causative organism. On the other hand, subsequent observation of these patients reveals that local recurrence of a similar lesion may appear some years hence and becomes quite disconcerting. In addition, the subsequent appearance of a tuberculous-like process at another site points the finger of suspicion directly to the pulmonary granuloma previously removed. If the etiologic nature of the lesion can be established in a given patient, such a catastrophe might well be averted by the administration of appropriate therapy.

**MEDIASTINAL GRANULOMATA**

Twelve patients in this series were observed to have nonspecific granulomatous disease of the hilar or mediastinal lymph nodes. Half of these patients had symptoms; the others were seen because of abnormalities observed by chest roentgenogram. The symptoms noted were cough, hemoptysis, fever and chest pain in that order. One patient noticed increasing prominence of the veins about the head and neck which prompted him to seek medical advice. Skin sensitivity to challenge injections of tuberculin PPD, histoplasmin and coccidioidin was recorded for all patients in this group (Table 4).

<table>
<thead>
<tr>
<th>Table 4—Skin Sensitivity</th>
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<tbody>
<tr>
<td><strong>Test Material</strong></td>
</tr>
<tr>
<td>PPD</td>
</tr>
<tr>
<td>Histoplasmin</td>
</tr>
<tr>
<td>Coccidioidin</td>
</tr>
</tbody>
</table>

Two of these individuals were observed to have a negative reaction to all three materials tested. One was positive to all three tests. Only four individuals in this group had a single positive test; in each instance the patient reacted to histoplasmin. The remaining five were observed to have a combination of two positive tests. Serologic examinations were accomplished in four instances with a significantly elevated titer for histoplasmosis observed in two.

Surgery was offered to these patients for diagnosis and for relief of symptoms. Excision, either partial or complete, was accomplished in eight. Four had diagnostic tissue biopsy only because of the extent of the disease. Complete extirpation of all grossly evident abnormal tissue was accomplished for six. In one instance, the mass was removed except for areas of attachment along the superior vena cava and right atrium. The patient with obstruction of the superior vena cava required seg-
ment removal of this structure and repair with aortic homograft. No untoward effect of surgery was observed in this group.

These patients have now been observed for periods of one to nine years since operation. Of those for whom complete excision was possible all have done well, are asymptomatic and without evidence of disease. One died five years after surgery of myocardial infarction and at the time of postmortem examination, the thoracic viscera revealed no evidence of granulomatous disease. In contrast, several of those who had incomplete excision or biopsy only have not fared as well. The individual for whom the superior vena cava was replaced has done well from the standpoint of mediastinal disease, but has required hospitalization for adjustment of anticoagulant medication during the two-year period since surgery. An angiogram obtained recently revealed a patent graft. Two additional patients for whom incomplete excision was accomplished have done well for six and eight years, respectively. Two had diagnostic biopsy of nonresectable mediastinal masses both of whom continue to have recurrent hemoptyses. One of these individuals had a ten-year history of respiratory difficulties including recurrent pneumonia and hemoptysis prior to 1952 when thoracotomy was done and the patient was thought to have an inoperable carcinoma, although biopsy revealed nonspecific granuloma. A year later, he was seen at this hospital and a second diagnostic attempt was made. A biopsy obtained on this occasion again revealed an obscure granuloma. Finally, one is doing well symptomatically in spite of bronchial stenosis one year after surgical biopsy of a nonresectable mass about the mediastinum and right hilum.

**Discussion of Mediastinal Group**

The clinical history of the patients in this group with mediastinal or granulomatous lymph node disease strongly suggests that many of them may be the result of subclinical histoplasmosis. Ten of the 12 reacted to histoplasmin. Both of the individuals with elevated histoplasmin titer on serologic examination had severe mediastinal involvement, one of whom required aortic homograft replacement of the superior vena cava and the other could not be removed surgically. On the other hand, two individuals exhibited completely negative skin reactions to all three test materials.

The technical problems involved in surgical diagnosis and removal of disease-bearing tissue were considerably more complicated than in the patients with single pulmonary nodules. Not infrequently, vital structures were involved such as the vena cava, pulmonary artery or pericardium. Postoperative management of the patient with incompletely removed granulomatous disease becomes a serious problem in the absence of an established etiology. Several patients have received amphotericin-B with questionable benefit although the disease has not apparently been progressive during the period of observation since surgery.

**Multinodular Pulmonary Disease**

Eight patients have been seen with multinodular obscure granulomatous disease of the lung during the period of this survey. Five of these individuals were asymptomatic at the time an abnormal chest roentgenogram was discovered. Of the remaining three who were symptomatic, the most common complaint was cough which was occasionally associated with fever, pain or hemoptysis. Skin sensitivity to challenge injections of tuberculin PPD, histoplasmin and coccidioidin was recorded for seven (Table 5).

<table>
<thead>
<tr>
<th>Test Material</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PPD</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>2. Histoplasmin</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>3. Coccidioidin</td>
<td>1</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

Six individuals were observed to have two positive skin tests; the most frequent combination noted was to PPD and histoplasmin. Diagnosis serologic examinations were carried out in five instances. An
elevated serum titer for histoplasmosis was observed in one patient.

Surgery was accomplished in this group as a diagnostic procedure. At operation, lung biopsy by wedge excision was done on seven occasions. One of these patients was found to have two major nodules in the right lower lobe both of which were removed by local excision. The postoperative course in all instances was without complication.

This group of patients has been followed for periods varying from six months to nine years. One individual has been lost and one underwent surgery too recently to be of significance. Five are asymptomatic one and one-half, five, six, and nine years since operation. One was hospitalized at another institution five years after surgery here because of acute symptoms and roentgenographic evidence of progression of disease. He was treated with antituberculosis drugs at that time although the clinical diagnosis could not be confirmed bacteriologically.

DISCUSSION OF MULTINODULAR GROUP

The possibility of malignancy was not a strong consideration in this group of patients as contrasted to those with single pulmonary nodules or mediastinal masses evident by chest roentgenogram. However, the advantages of establishing a diagnosis where possible to determine appropriate management in each case are obvious. It is of some significance to note that the majority of these individuals have been symptomatically well during the period of observation in spite of the fact that a definitive, etiologic diagnosis has not been established.

SUMMARY

1. Surgical biopsy of fibrocaseous granulomata of the lung or mediastinum has been accomplished for 48 patients. A specific etiologic diagnosis could not be established by extensive investigation of tissues submitted to the laboratory.

2. Twenty-eight had excision of single peripheral pulmonary nodules. In two instances a recurrence of a similar lesion has been observed one to six years following surgery.

3. Of the 12 with mediastinal granulomata, surgery was of benefit in eight instances. Complete excision was possible in six.

4. Eight with multinodular fibrocaseous granulomata submitted to diagnostic lung biopsy. Subsequently, they have done well with the exception of one individual thought to have pulmonary tuberculosis five years later because of acute symptoms and roentgenographic progression of disease.

5. It is probable that many of these granulomata result from subclinical or unrecognized clinical infection by known pathogenic organisms. However, some of these patients may have had an encounter with an as yet unrecognized agent. The prognosis for the majority of them is excellent. A few will develop recurrence or progression of disease months or years later.

RESUMEN

1. Se hicieron biopsias quirúrgicas de granulomas fibrocaseos del pulmón o del mediastino en 48 enfermos. No se pudo hacer diagnóstico etiológico específico por investigación amplia de los tejidos enviados al laboratorio.

2. En 28 se hizo excisión de nódulos únicos pulmonares periféricos. En dos casos se observó recurrencia de una lesión semejante de uno a seis años después de la intervención.

3. De 12 con granulomas mediastinales, la cirugía fue benéfica en 8 casos. La excisión completa fue posible en seis.

4. Se sometieron a biopsia pulmonar ocho con granulomas múltiples. A estos, después les fue bien, con excepción de uno que se cree tuvo tuberculosis pulmonar cinco años después por síntomas agudos y evolución radiográfica de la enfermedad.

5. Es probable que muchos de esos granulomas resulten de infección clínica no reconocida, debida a organismos patógenos conocidos.

Sin embargo algunos de estos enfermos han sido invadidos por algún agente aun no conocido. El pronóstico para la mayoría es excelente. Unos cuantos desarrollarán recurrencia o progreso de la enfermedad meses o años después.

RESUME

1. Une biopsie chirurgicale d'un granuloma-tome fibrocaseux du poumon ou du médiastin a été pratiquée chez 48 malades. Le diagnostic
étologique spécifique ne put être établi par l'investigation attentive des tissus soumis au laboratoire.

2. 28 malades subirent l'exérèse de nodules pulmonaires périphériques isolés. Dans deux cas, on observa une recidive de lésions similaires un à six ans après intervention.

3. Sur 12 malades atteints de granulomatoses médiastinaux, la chirurgie eut un effet salutaire dans huit cas. L'exérèse complète fut possible chez 6 malades.

4. Huit malades porteurs de granulomatoses fibrocaseuses multinoдуaires furent soumis à une biopsie pulmonaire dans un but de diagnostic. Par la suite, ils se sont bien portés à l'exception d'un seul individu soupponé d'avoir eu une tuberculose pulmonaire cinq ans après, à cause de symptômes aigus et de la progression radiologique de l'affection.

5. Il est probable que beaucoup de ces granulomatoses résultent d'une infection subclinique ou clinique ignorée, produite par des germes pathogènes connus. Cependant, certains de ces malades peuvent avoir été infectés par un agent encore ignoré. Le pronostic pour la majorité des malades est excellent. Un petit nombre font nettement une récidive ou une progression de la maladie, des mois ou des années après.

ZUSAMMENFASSUNG


2. In 28 Fällen erfolgte die Exzision einzelner peripherer pulmonalner Knoten. Bei 2 Fällen ließ sich ein Recidiv in Form einer ähnlichen Läsion 1-6 Jahre nach dem Eingriff beobachten.


REFERENCES


FUNCTIONAL ALTERATIONS IN THE CARDIOVASCULAR SYSTEM

Serotonin is formed from triptophan in the chromatin cells of the intestine. It circulates in the blood almost exclusively attached to platelets. It increases notably in carcinoid. When carcinoid gives hepatic metastases, it exhibit functional disturbances of the liver and cardiac lesions.

In carcinoid syndrome, the following disturbances are seen: hot flashes, redness of the face, erythema, palpitations, asthmatic form crises and diarrhea. When the disease is advanced, there appear pulmonary stenosis and tricuspid regurgitation, ascites and edema of the lower extremities.

The experimental administration of serotonin produces tachycardia, increased force of the contraction of the myocardium, increased cardiac output and coronary vasodilatation. Pulmonary vascular resistance is also increased. It has a rather complex effect on the blood pressure: first, it produces vagal stimulation with slight hypotension; later, it stimulates the contraction of the nostril muscle of the arterioles with blood pressure elevation and finally it depresses blood pressure because it avoids the liberation of adrenergic mediators in the nerve endings.

The most common anatomic lesions in the carcinoid syndrome are pulmonary stenosis and tricuspid regurgitation. The pericardium may exhibit isolated fibrotic areas.