Bronchopulmonary Sarcoïdosis Confirmed by Bronchoscopic Biopsy

A Report of Two Cases with a Review of the Gross and Histologic Descriptions of All 28 Previously Recorded Cases in the Literature

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It is less than a score of years (1941)' since the first confirmatory bronchial biopsy was obtained from a case of pulmonary sarcoïdosis. The literature concerning means of effecting a diagnosis in this pleomorphic, often systemic disease, is voluminous. In three large series including a combined study from the Johns Hopkins Hospital and the Massachusetts General Hospital, a series by Riley from New York City and one from the Veterans Hospital, totaling 321 cases, only one positive bronchial biopsy compatible with a sarcoïd lesion was described. This case was the first described in the literature. It is curious that with hilar lymph node involvement and parenchymal changes listed in the majority of the cases, only one other case even mentions bronchoscopic abnormalities in these three series, without substantiation of biopsy. In the series reported by Riley, 6 of 52 cases (14 per cent) had symptoms of wheezing, suggestive of stenotic bronchial processes. This alone would indicate that with routine bronchoscopy and biopsy the yield of positive biopsy material would have been substantial in the 45 of Riley's 52 cases presenting pulmonary involvement. It is known that sarcoïd changes in the respiratory mucosa occur more frequently than is generally realized. A positive laryngeal biopsy was obtained relatively early. It was not until Kalbian made a routine bronchoscopic study on 11 known cases of sarcoïdosis, finding abnormalities in nine and positive biopsies in three cases, that the significance of bronchial biopsy as a source of diagnostic material was realized. In the Dunner et al.7 series of 109 cases, 131 positive biopsies were obtained from various sites, namely, 56 per cent from lymph nodes, 15 per cent from the liver, 12 per cent from the lung by needle biopsy, 9 per cent from the skin and 8 per cent from other sites. Bronchial biopsies were not mentioned in spite of a high percentage of lung and hilar lymph node involvement, more than any other organic system.

The following two cases (1956-57 and 1959), with histories and illustrations, are presented with suggestive findings on bronchoscopy and the positive diagnostic evidence obtained through biopsy material.

Case 1: I.M.C., a white woman, age 28, was first seen in August, 1956. Her illness began in mid-1954 when she developed wheezing respiration accompanied by dry cough. Early in 1956 she was referred to a chest clinic where a chest x-ray film was taken and she was told that she had tuberculosis. Sputum studies were negative by culture and guinea pig inoculation. She was placed immediately on streptomycin twice weekly and PAS daily. An x-ray film of her chest on August 7, 1956 showed a fairly dense, somewhat rectangular parenchymal infiltration in the right upper lung field, bilaterally enlarged hilar nodes, and a fibrous infiltrate in the left subapical region with a general increase of the markings in the lower lung fields. Bronchoscopic examination was made at the Maryland General Hospital on September 11, 1956. The findings were a foreshortened, broadened and edematous carina without the usual

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sharp spur. There was mild edema of the right bronchus and the telescopic view of the upper lobe of this bronchus showed a thickened projecting margin, with several round projections seen particularly on the inferior and anterior circumferences. The lumen was narrowed to one-half its normal size and only the posterior division of the bronchus could be seen. From it exuded some bubbly purulent material. An attempt at biopsy was made and several small shreds of tissue were obtained from the rather firm margin of the upper lobe of the right bronchus. The left bronchus was examined and except for slight edema of the left basilar divisions and a somewhat broadened left upper lobe divisional spur, no gross abnormality was detected. At the time it was felt that there was stenosis of the upper lobe branch of the right bronchus and mildly allergic (asthmaoid) bronchial mucosa, as suggested by the edema and spasm of both bronchi. The biopsy material proved insufficient for diagnosis and was described by the pathologist as showing tiny shreds of epithelium, with a large amount of fibrin and a blood clot. Bronchoscopic secretions were reported negative for tubercle bacilli by culture and guinea pig inoculation, also by the three gastric washings which were done during this hospitalization. She was then placed on isoniazid and PAS instead of streptomycin. She was followed until early 1957. After another chest x-ray film (Fig. 1) she was admitted to Church Home and Hospital on January 29, 1957. This chest film showed an increase in the amount of infiltration in the right and left upper lobes with persistence of the hilar adenopathy. Upon admission, the pertinent history was the same as previously reported, with emphasis on the absence of tuberculosis in the family. Physical examination revealed a fairly well developed, well nourished, slightly obese woman. Her vital signs were normal except for a temperature of 99.2°F. The physical examination proved negative except for positive findings in the chest. The lungs showed dullness in the right upper part of the chest and increased tactile fremitus at the left interscapular area and the left base. Bronchial breath sounds were heard over the left upper lung field and inspiratory wheezes bilaterally. Rales were not elicited on either side. Blood cell counts and chemistries including serum calcium and A/G ratio, as well as blood sugar and NPN were essentially normal. The sputum was negative for acid-fast bacilli. A second strength PPD tuberculin test was reported negative after 48 hours. This was repeated and again was negative. Histoplasmin skin tests were negative on two occasions. On January 30, 1957, a second bronchoscopy was performed and revealed the following: Secretions were seen coming from the lower

![Image](image-url)

**FIGURE 1:** Chest roentgenogram January 19, 1957, after 4 months of streptomycin-isoniazid therapy and prior to admission to Church Home and Hospital. Evidence of increase in the upper lobe infiltrations as well as the size of the hilar lymph nodes as compared with pre-admission findings.
lobe of the left bronchus, which was moderately irritated and considerably contracted by edema. The mucosa of this lower lobe had a velvety appearance and the lumen of the intermediary bronchus was reduced by 50 per cent. This reduction was even more noticeable below the superior segment branch and extended into the basilar divisions. The velvety red mucosa was friable and hemorrhagic secretions were obtained as a result of the instrumentation. Right angle telescopic visualization at this time showed the right upper lobe orifice fixed with a triangular contracted outline. On the inferior and anterior portions of its margins there was a whitish scar, probably the result of the previous biopsy attempt. The right upper lobe bronchus was definitely elongated and still reduced by 50 per cent with only 1 subdivisional spur recognizable. A biopsy was taken from the velvety mucosa of the lower lobe of the left bronchus, namely a basilar divisional spur. The bronchial biopsy (Fig. 2) on pathologic section was interpreted as chronic granulomatous tuberculoid reaction of the bronchial mucosa, compatible with the diagnosis of sarcoidosis. During her hospital stay, she was placed on steroids (prednisone, 40 mgm. daily), as well as isoniazid (100 mgm. daily). Some objective improvement occurred. The cough decreased and wheezing disappeared by the time she was discharged on February 21, 1957. She remained on Prednisone for six weeks, followed by maintenance doses of 15 mgm. daily for 10 months. A chest film after seven weeks of steroid therapy showed slight improvement. During the 10 months of steroid maintenance she complained of loss of libido, epigastric distress, weight gain and irritability. Prednisone therapy was discontinued after 10 months, when it was felt that maximum benefit was obtained, and she became free of com-
plants. However, there was a moderate increase in the roentgenographic findings throughout 1958. When this became more noticeable in early 1959, a re-appraisal was deemed necessary and she was admitted to the Maryland General Hospital in February of 1959. A third bronchoscopy was performed on March 2, 1959. As seen telescopically, the right upper lobe orifice again showed a stenosis of 50 per cent with considerable elongation and over-hanging of a whitish, fibrotic anterior margin. No longer could any portion of the subdivisions be seen. The firmness of the margin made it impossible to attempt a biopsy from this region. The left bronchus was then examined and showed stenosis of about 40 per cent of the intermediary left lower lobe bronchus. The individual basilar divisions, of which only two could be seen, were stenosed by more than 50 per cent. The mucosa no longer showed the previous velvety red appearance, but was whitish, pale, edematous with a tendency to fibrous contraction. Again a biopsy attempt was made from the left basilar divisions and three small shreds of mucosa were obtained. Pathologically, this second bronchial biopsy (Fig. 3) no longer showed specific sarcoid tissue although the granulomatous pattern could still be recognized. The tissue showed partial fibrosis and was considered to represent non-specific granulomatous mucosa. On March 6, 1959, a right cervical gland biopsy was done, which histologically showed typical sarcoid follicles, non-caseating, consisting of epitheloid cells as well as giant cells. Schaumann bodies could be demonstrated within the giant cells. Sputa and gastric washings were negative by smear and culture and the histoplasmin and tuberculin skin tests, which were repeated again proved negative. It is interesting to note, however, that the bronchial secretions grew out a single colony of acid-fast bacilli, which on culture and guinea pig inoculation proved to be virulent tubercle bacilli. She has remained asymptomatic since, with little or no change in the x-ray films. It has not been possible to demonstrate tubercle bacilli again in any of her secretions. However, a prophylactic course of isoniazid is being continued. This relates to the concept of Scadding and Citron who believe in a close relationship of sarcoidosis with tuberculosis.

Case 2: J.A.S., a 20 year-old white woman, was first seen on July 3, 1959, when her chest x-ray film (Fig. 4) showed suggestive changes of pulmonary sarcoidosis. She was admitted to Church Home and Hospital on July 9, 1959 with the chief complaint of intermittent chest pain of about 18 months' duration associated with progressive shortness of breath unrelated to effort. The family history was unrevealing except for the death of one sister at the age of 23 of carcinoma of the stomach. The past history was interesting since she is said to have had five attacks of pneumonia before the age of 10. Married for four years, she had one pregnancy resulting in a healthy child. She worked for a manufacturer of plastics, but insisted that she had not been in contact with any toxic airborne substances. A chest x-ray film in mid-1958 was

**FIGURE 4:** Case 2. Initial chest roentgenogram July 3, 1959, showing diffuse infiltrations of small patchy and streaky areas throughout both lung fields.
said to have shown "spots on both lungs." On the basis of a second chest film in March of 1959 at a chest clinic, the probable diagnosis of pulmonary tuberculosis was considered and she was so informed. Sputum examinations were carried out and reported negative for tubercle bacilli by culture. The vital signs were normal; the temperature was 99°F. The physical examination of this well developed, slightly obese female was essentially negative except for moderately harsh breath sounds and an occasional muffled wheeze, heard bilaterally. Laboratory data: The urine was free of sugar and albumin. Hematologic findings were within normal limits. Blood chemistries showed: Blood sugar 95, NPN 28, total proteins 8, albumin 5.3, calcium 10.2, phosphorus 3.8, sodium 145 m.Eq./l, potassium 4.9 m.Eq./l. The A/G ratio was 1.9. Alkaline phosphatase was 3.3 units, thymol turbidity 0.3 units. There were no LE cells seen. The PPD tuberculin concentration test and the electrocardiogram were normal. A chest x-ray film following admission showed that there were diffuse changes seen throughout both lung fields, consisting of fine linear and interlacing densities, with superimposed small nodular lesions. The changes were more pronounced on the right than on the left and extended peripherally from both hilus. The cardiovascular structures were found to be normal. The radiologist's impression was: Bilateral pulmonary changes which were most likely caused by sarcoidosis. Upon x-ray examination of the paranasal sinuses an unusual incidental finding in the skull was observed. Diagnostic skull x-ray films showed two spherical areas, 1.5 cm. in diameter, of mottled calcification within the cranial cavity. They were symmetrically placed, and therefore from their location they were presumed to represent calcification in the gloma of the choroid plexuses. Their significance at this time was doubtful, but the possibility of a disturbed calcium metabolism in the past raised interesting questions in relation to similar disturbances seen in some cases of sarcoidosis. A second strength PPD tuberculin test was done as well as a histoplasmin skin test. Both were reported negative after forty-eight hours. The tuberculin test was repeated after several days, resulting in a negative response again. The hospital course was as follows: On July 13, 1959 the patient was bronchoscooped and a bronchial biopsy was taken. The bronchoscopic report showed the following highlights: The carina was broadened, thickened and blunted. The right upper lobe orifice showed moderate thickening of the mucosa; the right middle lobe orifice also was thickened and showed edema. The right lower lobe bronchus showed considerable edema with projection of the edematous mucosa anteriorly. The color of the mucosa was whitish and pale. Seen teleoscopically, the left bronchus showed minimal edematous thickening of the upper lobe divisional spur and some edematous changes in the basilar divisions. A bronchial biopsy was obtained from the projecting anterolateral portion of the right lower lobe bronchus, near the basilar divisions. Histologically, the bronchial biopsy (Fig. 5) showed within the submucosal zones several structures of tubercle-like origin, revealing a layer of epitheloid cells irregularly arranged. According to the pathologic report, the appearance was suggestive of tuberculous, but the multiplicity of tubercles and atypical caseation suggested that this lesion was of sarcoi'd type rather than tuberculous. Therefore, the diagnosis made from biopsy of the bronchus was probable sarcoi'd tissue. On July 14, 1959, a right cervical lymph node biopsy was performed. The nodes as exposed were grossly abnormal and histologically showed clear cut evidence of non-caseating epitheloid-type follicles with giant cells, typical findings of sarcoidosis. In addition, it was also reported that the cultures of the bronchoscopic secretions and of three gastric washings were reported negative for tubercle bacilli by culture. The patient

FIGURE 5: Case 2, Bronchoscopic biopsy, July 13, 1959, showing a non-caseating epitheloid follicle with giant cell.
was placed on steroid therapy (Dexamethasone, 3 mgm, daily) and given isoniazid (300 mgm, daily) for prophylaxis. Upon discharge from the hospital on July 29, 1959, the patient was asymptomatic. She was continued on the same dosage of steroids at home. A chest film on September 3, 1959 showed slight but definite generalized improvement of the diffuse pulmonary sarcoid lesions.

The 28 previously documented cases reported in the interim are shown in Table 1.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of Cases</th>
<th>Bronchoscopic Appearance</th>
<th>Histology</th>
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<tbody>
<tr>
<td>Benedict &amp; Castleman</td>
<td>1941</td>
<td>Bled-like, gray intrinsic lesions, whitish fibrous stenosis</td>
<td>Chronic epitheloid cell granuloma, non-caseating.</td>
</tr>
<tr>
<td>Olsen</td>
<td>1946</td>
<td>nodular mucosa</td>
<td>Chronic granuloma Absence of caseation.</td>
</tr>
<tr>
<td>Jacobs</td>
<td>1949</td>
<td>Extrinsic compression of bronchus flat, faintly hemorrhagic areas</td>
<td>Non-caseating tubercles.</td>
</tr>
<tr>
<td>Harvier</td>
<td>1950</td>
<td>Thickened mucosa, Rt. bronchus</td>
<td>Non-caseating epitheloid cell follicles, surrounded by hyalinization.</td>
</tr>
<tr>
<td>Siltzbach, Som</td>
<td>1952</td>
<td>Thickening and stenosis of Right middle lobe bronchus</td>
<td>Epitheloid cell follicles Schaumann bodies.</td>
</tr>
<tr>
<td>Turial et al.</td>
<td>1952</td>
<td>1 necropsy: Diffuse invasion of both bronchi by granulations, narrowing of main stem bronchi.</td>
<td>Various epitheloid-cell infiltrates extending into submucosa. Non-caseating granulation tissue, typical of sarcoïdosis.</td>
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<tr>
<td></td>
<td>1955</td>
<td>6</td>
<td></td>
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<tr>
<td>Cowdell</td>
<td>1954</td>
<td>Not given</td>
<td>Granulation tissue typical of sarcoïdosis.</td>
</tr>
<tr>
<td>Grimminger</td>
<td>1955</td>
<td>Mucosal infiltrates of carina</td>
<td>Epitheloid-cell infiltrates, no giant cells, no caseation, tendency to scar formation and sclerosis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>left main and portions of right main bronchus, 40 per cent stenosis of Rt. upper lobe by conical, glassy-edematous, rose colored nodules, later seen as brownish-flat projections.</td>
<td></td>
</tr>
<tr>
<td>Citron &amp; Scadding</td>
<td>1957</td>
<td>Stenosing, stricturing endobronchial granulomatous lesions, some showing fibrosis.</td>
<td>Non-caseating epitheloid tubercles.</td>
</tr>
<tr>
<td>Honey &amp; Jepson</td>
<td>1952</td>
<td>Generalized inflammation, slit-like narrowing of upper lobe bronchus. Severe distortion and rigidity of entire bronchial tree.</td>
<td>Discrete epitheloid-cell follicles, giant cells with asteroid bodies, some necrosis no caseation, some hyalinization.</td>
</tr>
<tr>
<td>Dijkstra</td>
<td>1958</td>
<td>Edematous, redened mucous membrane; occasionally areas of granulation or stenotic divisional branches. Sometimes severe stenosis.</td>
<td>Non-caseating tubercles, confirmatory of sarcoïdosis.</td>
</tr>
</tbody>
</table>

Total documented cases exclusive of necropsies Total: 28
Discussion

Kalbian4 in his discussion believes that there are three possible abnormal bronchoscopic findings, in pulmonary sarcoidosis, namely: 1. Signs of external pressure from enlarged lymph nodes; 2. Granular, nodular, rough-looking mucous membrane with small blebs; 3. Thickened, edematous mucous membrane with stenosis of the bronchus. Grimmer concluded his attempt to arrive at a characteristic classification on the strength of his two cases with multiple observations. One would tend to identify his cases with Kalbian's first and second categories respectively. Turaif et al.16 in their series report findings which would fit into the classification mentioned above, but some of their findings are minor and localized, similar to those in our two cases. Their positive biopsies encourage one to attempt biopsy from even a trivial variation of normal if one considers sarcoidosis as a possible etiology. Citron and Scadding22 rightly conclude that bronchoscopic appearance of the mucosa varies with the stage of the disease. They feel that bronchial involvement is widespread and ranges from acute changes with edema, granulation tissue and nodular areas to fibrotic, firm, smooth or irregular areas of distortions and strictures. One would be inclined to agree with the French authors19-21 that endobronchial sarcoid infiltrations are analogous to those elsewhere in the respiratory apparatus such as nasal accessory sinuses, tonsils and larynx and it is believed they often reflect the sarcoid changes in the lung. Their location helps to explain the presence of respiratory symptoms such as wheezing, the accompanying atelectasis that is occasionally found or frequent obstructive emphysema. Thus, these lesions tend to explain further the polymorphy of the pulmonary form of Boeck's sarcoid.

Most authors feel that when pulmonary sarcoidosis is suspected, a bronchoscopic biopsy should be attempted.19,21-23 One author advocates19 bronchoscopy and biopsy in those cases that have clinical features of recurrent bronchopulmonary infection, stridor and progressive dyspnea. Another23 advocates a relatively large biopsy bite to provide a reasonably large portion of tissue, since a small specimen may contain insufficient granulomata to show the general uniformity of the disease pattern. The authors of this paper believe that the only logical approach is that of careful small, possibly multiple biopsies from areas suggestive of involvement. The judicious use of this method will frequently confirm or lead to a correlation with the clinical and roentgenologic diagnosis of sarcoidosis. Therefore this is considered the procedure of choice.

REFERENCES