

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., Editor

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CASE 62-1963

PRESENTATION OF CASE

A fifty-six-year-old plumber was admitted to the hospital because of pain in the chest.

The patient had been in good health until twenty-one months previously, when he began to experience right-sided chest pain. Six months later he was told that an x-ray film of the chest was abnormal. Twelve months before admission he entered another hospital because of persistent chest pain accompanied by dyspnea and a cough productive of white sputum. There had been no chills, fever, weight loss or fatigue. A tuberculin skin test (second-strength PPD) was reported as strongly positive, but studies of the sputum and gastric washings for tuberculosis were negative. X-ray films of the chest demonstrated a pleural density on the right side, which was thought to represent partially organized hydrothorax; bronchoscopic and bronchographic studies were negative. Right-sided exploratory thoracotomy was performed, with decortication of the pleura; the pathological diagnosis was "dense fibrotic pleuritis." He was discharged home on isoniazid, 100 mg. three times daily.

Nine months after discharge the patient re-entered the same hospital because of continuing chest pain, which had not been improved by nerve block performed in a surgeon's office. An x-ray film of the chest revealed thickening of the apical pleura on the left side and a linear density overlying the diaphragm adjacent to the left cardiac border; on the right side a dense, homogeneous shadow compressed the lung downward and medially and extended from the apex to the level of the second rib; another density extended from the third costal interspace to the diaphragm. The fourth, fifth and sixth intercostal nerves were divided in an attempt to relieve the pain, and histologic examination of a specimen of the pleura revealed "chronic inflammation and fibrosis." Shortly after discharge his wife observed that the patient's pupils were unequal in size. The chest pain was not

relieved by the operation, and he was referred to a psychiatrist for further evaluation and treatment. Two weeks before admission he entered a mental hospital for management of depression. Anisocoria was observed on admission. An x-ray film of the chest showed a decrease in volume of the right hemithorax, with partial collapse of the right lung, pleural effusion, shift of the mediastinum to the right and an extensive density in the right-middle-lung field. Transfer to this hospital was arranged.

Bilateral nerve deafness had been present for seventeen years. The patient had worked as a plumber for forty years, having spent about half of that period installing insulation on boilers and pipes. He had smoked 1½ packages of cigarettes daily for many years. Five years previously x-ray films were interpreted as showing a peptic ulcer. There had been a loss of 30 pounds in weight during the three months before entry.

Physical examination disclosed a pleasant man who did not appear depressed. A right-sided Horner syndrome and drooping of the right shoulder were observed. Dullness and diminished breath sounds were heard over the lower third of the right lung; the heart was normal, and there were no murmurs. The liver edge was felt 2 fingerbreadths below the right costal margin.

The temperature was 98.6°F., the pulse 113, and the respirations 22. The blood pressure was 120 systolic, 70 diastolic.

The urine was normal except for a rare red cell and 1 or 2 white cells per high-power field in the sediment. The hematocrit was 38 per cent, and the white-cell count was 11,830. The fasting glucose was 100 mg., the urea nitrogen 15 mg., the calcium 9.0 mg., the phosphorus 3.0 mg., the bilirubin 0.5 mg., and the protein 6.8 gm. (the albumin 4.4 gm.,

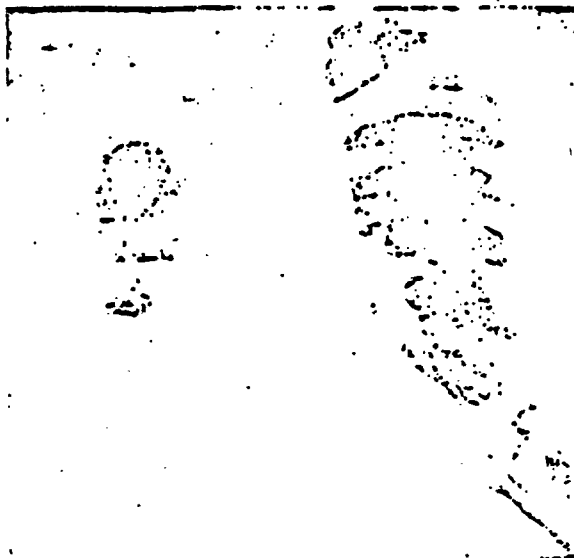
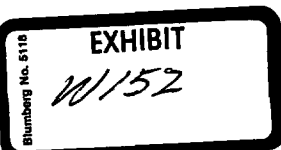


FIGURE 1. Posteroanterior Film of the Chest Taken on Admission, Showing an Extensive Pleural Reaction on the Right Side and a Scattered Pulmonary Infiltration.

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and the globulin 2.4 gm.) per 100 ml. The serum glutamic oxalacetic transaminase (SGOT) was 14 units, and the alkaline phosphatase was 8.4 Bodansky units. Culture of the sputum yielded a moderate growth of pneumococci. X-ray films of the chest (Fig. 1) disclosed irregular thickening of the pleura on the right side, with elevation of the right hemidiaphragm and a slight shift of the mediastinum and heart to the right; a lesser degree of pleural thickening was visible on the left side. X-ray films of the bones (Fig. 2) revealed destruction of the fourth through the seventh ribs on the right side; the dorsal spine was not well seen, but the lumbar spine, pelvis and skull were normal. Fluoroscopic study of the chest showed infiltrations within the parenchyma of the right lung (Fig. 3), with mild compensatory emphysema of the left lung; the left ventricle was slightly enlarged; the left hemidiaphragm moved normally with respiration, but the right hemidiaphragm was obscured by a large quantity of fluid and pleural thickening extending to the apex of the lung. An electrocardiogram was within normal limits. Tuberculin (intermediate-strength PPD), histoplasmin, blastomycin and coccidioidin skin tests were negative. Ventilatory studies, which were unsatisfactory because of severe pain, revealed a one-second vital capacity of 1.50 liters, a total vital capacity of 1.62 liters (43 per cent of predicted nor-

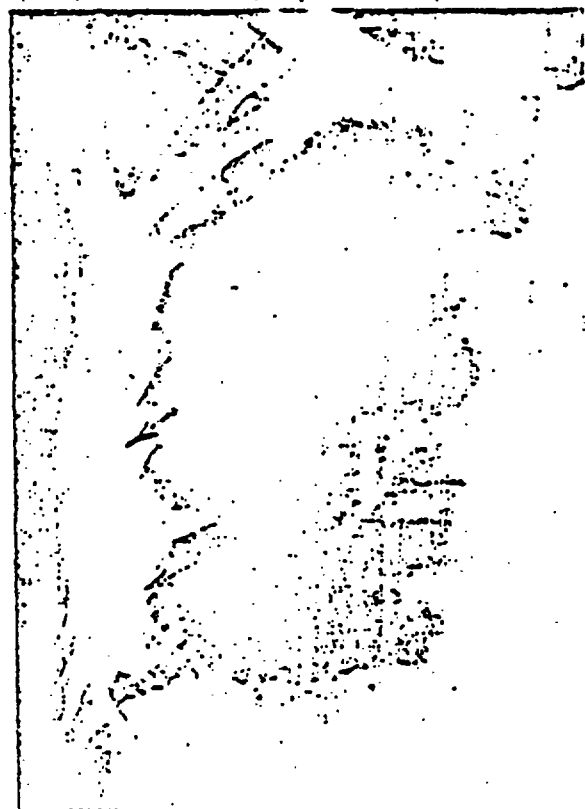


FIGURE 2. Overpenetrated Film of the Right Hemithorax, Defining the Extent of the Pleural Thickening. There is cortical destruction of portions of the right fourth and fifth ribs (arrows).

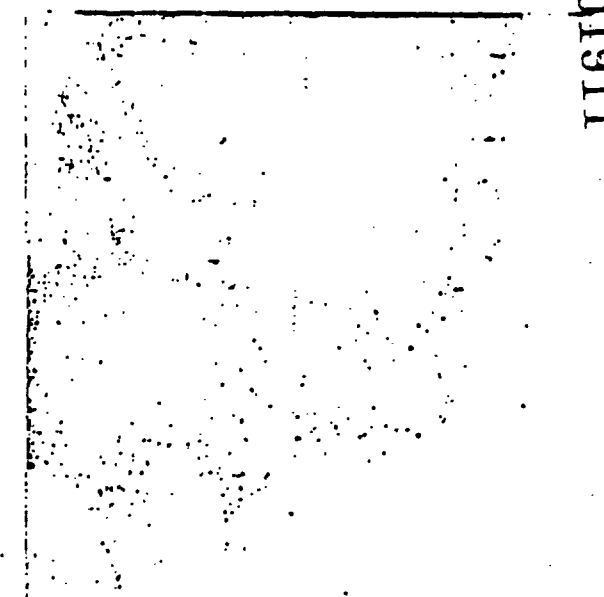


FIGURE 3. Fluoroscopic Spot Film of the Right Lung, Showing a Reticular Pattern of Fibrosis and a Nodular Infiltration.

mal value) and an estimated maximum breathing capacity of 60 liters per minute. Bronchoscopic examination and cytologic studies of bronchial washings and sputum were negative. Biopsy of the right scalene fat pad revealed no evidence of tumor.

An operation was performed on the ninth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JOHN H. KNOWLES*: This fifty-six-year-old plumber of forty years' standing was a heavy smoker and, even more importantly, had spent a great deal of time installing insulating material on pipes and boilers. It is probable, therefore, that he was heavily and chronically exposed to the inhalation of asbestos fibers, since asbestos is by far the most common material used for insulating purposes. The history of his illness spanned a year and three quarters and began with chest pain, which apparently persisted throughout the course. Symptoms and signs of an infectious process were entirely lacking. The chest pain, which is not fully described, was unrelieved by division of the fourth, fifth and sixth intercostal nerves. When I read that he underwent psychiatric care, the thought transiently entered my mind that this man had enough disease and chronic pain to result in an exogenous depression. The second thought that occurred to me is that the use of isoniazid occasionally is associated with mental irritability and even the production of psychosis. However, I doubt very much that this episode was significant in terms of the patient's basic disease.

DR. DREYFUSS: May we review the x-ray films now?

DR. JACK R. DREYFUSS: The films taken on admission

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sion provide several interesting findings. First of all, we see a fairly extensive reaction along the periphery of the right lung (Fig. 1). Its outline is irregular, and it seems to be a soft-tissue reaction extending around the entire lung. This change means a decrease in volume of the lung, which is further indicated by elevation of the right leaf of the diaphragm and by retraction of the heart and mediastinum toward the right side. Within the lung field there is a pattern of fine fibrosis and perhaps a nodular infiltrate. I am less certain about the findings on the left side, but there appears to be pleural thickening along the left lateral chest wall, as well as a similar but much less marked pattern of fibrosis and nodular infiltrate. The abnormality is confined almost entirely to the perihilar and basal regions of the lungs. The lateral film of the chest taken at the same time again demonstrates the elevation of the diaphragm and the extensive alteration that is apparently a pleural reaction. A fluoroscopic spot film (Fig. 3) taken shortly thereafter reveals a fine, linear, reticular pattern that is probably indicative of fibrosis, and mixed in with that change or superimposed upon it we see a pattern composed of very small nodules, which in some areas, particularly in the lower zones, coalesce into conglomerate shadows. Finally, a high-penetrating film (Fig. 2), which was taken primarily to show the extent of the apparent pleural reaction, also demonstrates very nicely that in at least two ribs, the right fourth and the right fifth, the anterior part of the cortex is missing. This picture is certainly consistent with erosion or destruction, and there is probably also slight erosion of the sixth and seventh ribs.

Dr. KNOWLES: The films demonstrate that this man had bilateral pleural involvement, but predominantly of the right side. Furthermore, he had bilateral parenchymal changes that were largely confined to the lower lobes. He also had erosive dissolution of at least two ribs on the right side. I'd like to ask a few questions pertaining to the radiologic studies because the crux of the problem, as I see it, is whether the patient had either bronchogenic carcinoma or a pleural mesothelioma as a complication of what I believe was diffuse pulmonary asbestosis. Dr. DREYFUSS, will you tell me about the character of the carina, in view of the fact that there might have been metastatic malignant disease in the contiguous lymph nodes, which would distort it?

Dr. DREYFUSS: The outline of the carina is sharp, and that fact is against significant subcarinal adenopathy.

Dr. KNOWLES: Secondly, would you say that the pleural fibrosis on the right side definitely extends into the mediastinal structures and even into the thoracic inlet on that side?

Dr. DREYFUSS: The change that appears to be pleural fibrosis or thickening definitely, and probably significantly, extends along the medial surface of the lung, and it is particularly striking at the base of

the right lung along the cardiac and mediastinal border.

Dr. KNOWLES: Do you see any evidence of a Pancoast tumor, or so-called superior-sulcus tumor, invading the soft tissues of the right thoracic inlet and thereby giving rise to the Horner syndrome?

Dr. DREYFUSS: Of course, a soft-tissue lesion above the apex of the lung always raises the suspicion of a superior-sulcus tumor, but I interpret the alteration in this case as a continuous process actually encasing the lung. Another clue that I should like to see before making a diagnosis of a Pancoast tumor is evidence of erosion or destruction of the first, second or third rib, which is not indicated on these films.

Dr. KNOWLES: Can you state fairly definitely that fluid was absent and that the major portion of the change was due to fibrotic disease?

Dr. DREYFUSS: I am quite certain of the absence of a significant amount of fluid. The left leaf of the diaphragm is very sharp, and the usual tapered sign of fluid extending up the posterior gutter is lacking on the right side.

Dr. KNOWLES: One other point is that even though the right hemidiaphragm was elevated the liver extended 2 fingerbreadths below the right costal margin. So I assume that there was significant hepatomegaly.

Dr. DREYFUSS: It is certainly suggested.

Dr. KNOWLES: As I see it, the argument in this case rests on four key findings: the disease was bilateral and both pleural and parenchymal; the patient had persistent chest pain; erosive dissolution of the ribs had occurred; and a right-sided Horner syndrome had developed. The last three features suggest a malignant process and remove the disease from the simple class of just a fibrotic reaction to asbestosis. The only conclusion that I can reach is that he had chronic pulmonary asbestosis, and that a complication of some type had developed.

At this point perhaps a brief historical review of asbestosis is in order.¹ Asbestos is a Greek word meaning unquenchable or unconsumable in the sense of being indestructible. In +30 B. C. the Romans discovered that clothing made of this flexible fiber facilitated the collection of the ashes after cremation. Its contemporary use is as insulating material for pipes, linings for chemical containers and brakes on automobiles, insulating slabs and shingles, firefighter suits, theater curtains and undercoating for ships and automobiles.² Two years ago, pulmonary asbestosis was reported in Massachusetts in a man whose occupation included spraying undercoating on cars;³ the material used had an asphalt base with about 30 per cent asbestos, and he had true pulmonary asbestosis. Asbestos is the name given to a series of minerals composed of certain fibrous silicates, magnesium and iron. It is mined as crushed rock and is then carded, woven and spun or ground and mixed with cement or plastics. Cana-

da, Italy and South Africa produce most of the mineral. The dust given off during the manufacture or even during the installation of insulating material is usually around 5 to 10 millimicrons in diameter and may be as long as 50 millimicrons. The longer fibers seem to be the most disease provoking. According to the current view the disease is produced purely by mechanical irritation by the inhaled fibers, although chemical irritation is considered an important factor by some authorities. The asbestos body is found either under the skin or actually in the pulmonary parenchyma and consists of a central asbestos fiber surrounded by a protein sheath heavily laden with iron salt. In addition, there may be true granulomatous inflammation around the asbestos bodies. The disease is most heavily confined to the lower lobes of the lungs and may give rise to both extensive pleural fibrosis and nodular interstitial parenchymal fibrosis.

The first case of asbestosis was described as recently as 1907,² even though the material has been used for centuries. The disease may develop anywhere from ten months to as long as twenty years after exposure. The most common symptoms are dyspnea and a dry cough, although the disease may remain asymptomatic and be recognized incidentally on a routine radiologic examination of the chest. The x-ray films show a variety of findings. There may be striking pleural fibrosis, with or without calcification, or a diffuse interstitial fibrosis or a fine nodular fibrosis with a ground-glass appearance may predominate. The lower lobes are most heavily involved. Pleuropericardial adhesions giving a very shaggy appearance to the left heart border on the x-ray films sometimes serve as a clue to the diagnosis. In a case that was reported from England³ post-mortem pictures of the lungs dramatically illustrated the tremendous pleural fibrosis that sometimes occurs as a manifestation of asbestosis, with heavy involvement of the lower lobes and the fissures, in addition to the characteristic interstitial pulmonary fibrosis with a fine, reticular, mottled appearance.

Asbestosis may be associated in more than a fortuitous fashion with a pleural mesothelioma. Investigators in South Africa⁴ found 33 cases of mesothelioma over a period of four years among the people who worked or lived in the Cape asbestos-mining fields. Asbestos fibers adjacent to the developing mesothelioma were demonstrated in only 8 of them, however. Regardless of whether or not the pleural mesothelioma is causally related to asbestosis, we must consider whether the nonspecific pleural fibrosis of asbestosis existed in this patient or whether the pleural disease was a true pleural mesothelioma. The two pleural biopsies leave us with only a slim chance that a mesothelioma was missed, although the neoplastic cells may be so sparse and the fibrosis so predominant in these tumors that even two negative biopsies do not rule out the diagnosis. The clinical course is compatible with this type of tumor, as is the associated asbestosis. Mesotheliomas are

capable of invading the chest wall, the mediastinum and even the diaphragm and on rare occasion extend through the diaphragm into the liver. Perhaps the eroded ribs, the Horner syndrome and the hepatomegaly in this case indicate invasion of all three of these areas by such a tumor.

There seems to be general agreement at the present time that bronchogenic carcinoma is associated with asbestosis. The evidence is inferential but persuasive. The incidence of bronchogenic carcinoma in cases of asbestosis is 13.8 per cent.^{4,7} and there is a much higher incidence in the female afflicted with asbestosis than in the female population at large. The cancer is almost invariably found in the lower lobes, where the concentration of asbestos fibers is greatest, in contrast to the predilection of bronchogenic carcinoma for the upper lobes of the lung in the general population. In 1953 Isselbacher and his associates,⁷ in studying this association in a case from this hospital, observed coexistent squamous metaplasia in the affected air tubes and speculated that the chronic mechanical irritation by the asbestos fibers produces the cancer. The average period of continuous exposure to asbestos fibers before the development of the cancer is between sixteen and eighteen years.

In this case I suspect that a pleural mesothelioma or, less likely, a bronchogenic carcinoma was superimposed on chronic pulmonary asbestosis, as judged by the persistent chest pain, the erosive dissolution of the anterior ribs and the development of the Horner syndrome. These three findings take the pleural disease out of the realm of the simple pleural fibrosis of asbestosis. Can the chest pain be characterized further? Was it so-called post-thoracotomy chest pain engrafted on the initial chest pain, or did it start and finish in the area corresponding to the destroyed ribs?

DR. EARL W. WILKINS: It was my impression from talking with the patient that he initially experienced a sensation of tightness in the chest, not a real pain, and then superimposed on this discomfort he did have post-thoracotomy pain. The thoracic surgeon who saw him apparently thought so, too, because he performed an intercostal neurectomy.

DR. KNOWLES: Did the pain ever correspond to the area of the eroded ribs?

DR. WILKINS: By the time that we saw him it did.

DR. KNOWLES: Was there any pain whatsoever in the inner arm, the shoulder or the upper portion of the thorax?

DR. WILKINS: No.

DR. KNOWLES: That information is helpful in a negative way. I'd also like to ask if clubbing was present. Clubbing can accompany asbestosis, and it is particularly common with pleural mesothelioma occurring in over half the cases.

DR. BENJAMIN CASTLEMAN: There was no clubbing.

DR. KNOWLES: Was the sputum examined for asbestos fibers?

Dr. CASTLEMAN: The sputum was examined for both tumor cells and asbestos fibers, and neither were found.

Dr. KNOWLES: My argument is becoming less tenable by the moment. Were the so-called asbestos corns observed on physical examination? These are small, nodular fibrous areas that may develop on the hands, arms and legs of people who work with asbestos fibers.

Dr. CASTLEMAN: None were found.

Dr. KNOWLES: I should like to say a word about the pathologic physiology of this disease, although it requires extraordinary courage to stick with my original premise after all these questions have been answered in the negative. Pulmonary asbestosis is commonly associated with the alveolar-capillary-block syndrome.⁶ The full-blown syndrome is characterized by reduction in lung volume, unobstructed air flow, increased respiratory rate and ordinarily cyanosis on exercise, but with a normal carbon dioxide level or even mild respiratory alkalosis since there is no obstruction to the diffusion of carbon dioxide.

What else should be considered in the differential diagnosis? Tuberculosis and fungous disease such as actinomycosis are possibilities, since both cause pleural fibrosis and bilateral chronic disease, but there was no evidence of chronic infection in this patient. Fungous disease, with the exception of actinomycosis, does not erode ribs but causes a periosteal proliferative reaction. So I can dismiss those two diagnoses.

The presence of the Horner syndrome bothered me considerably, but there is no question that a neoplastic mesothelioma, by invading the lower cervical ganglions and sympathetic fibers or the upper thoracic fibers, could be responsible for this condition. The fact that it was noticed soon after the operation made me worry about metastatic disease or even a little infarct in the medulla, but with no other associated neurologic findings of the so-called lateral medullary or Wallenberg syndrome one has to place the cause of the Horner syndrome peripheral to the spinal cord and to the medulla. A superior-sulcus tumor with invasion of the sympathetic stellate ganglion or compression of the stellate ganglion by a cervical rib, perhaps due to manipulation during the operation, seems unlikely on both clinical and radiologic grounds. A final point to be explained is the elevated alkaline phosphatase level. It is possible that the high value reflected metastases to the bone or the liver from a bronchogenic carcinoma, but I interpret the elevation of the right leaf of the diaphragm as a sign of significant hepatic enlargement and choose to say that a pleural mesothelioma invaded the diaphragm and also the liver.

My conclusion is that this man suffered from pulmonary asbestosis, with diffuse parenchymal interstitial and nodular fibrosis as well as extensive pleural fibrosis. In addition, I believe that he had a pleural mesothelioma rather than a bronchogenic carcinoma tucked away in the right lower lobe. I base that

choice on the negative evidence — that is, the negative bronchoscopic study, the nonspecific radiologic findings with no suggestion of a localized mass and the negative sputum examinations. I think that the operation was another right-sided thoracotomy, with, I hope, pleural and pulmonary biopsies and perhaps even biopsy of a diseased rib. I doubt whether curative surgery could be done.

Dr. LAMAR SOUTTER: Why do you think the patient lost so much weight?

Dr. KNOWLES: I attribute the weight loss to the debilitating effects of chronic pain and ultimate invasion of the liver, either by metastatic disease or by direct extension. Loss of appetite may be the key symptom of hepatic involvement.

Dr. KENNETH T. BIRD: Diffuse lung disease, whether or not of occupational origin, may result in weight loss. This effect is probably a manifestation of persistent hypoxia. For example, the presenting complaint of the patient with pulmonary emphysema is often progressive weight loss.

It is important to note that the crystalline form and size of inhaled particles may determine the response of the host in pulmonary disease associated with occupational exposure. Crocidolite, one of the several varieties of asbestos fibers, may give rise not only to parenchymal and pleural disease but also to peritoneal manifestations.⁷ Chrysotile, $3MgO \cdot 2SiO_2 \cdot 2H_2O$, is the main asbestos of commercial use.

Dr. CASTLEMAN: Dr. Isselbacher, do you have a comment?

Dr. KURT J. ISSELBACHER: As Dr. Knowles mentioned, in 1933 we became interested in a possible relation between asbestosis and the development of bronchogenic carcinoma. It seemed important to document such a relation, if it existed, because of the magnitude of the asbestos industry in this country. We were impressed by the preponderance of involvement of the lower lung when the carcinoma occurred in association with asbestosis. Another factor pointing toward an association of the two entities was the high incidence of bronchogenic carcinoma — namely, 13.8 per cent. A third feature, which Dr. Knowles has emphasized in this case, was the bilateral nature of the disease. In view of the occupational history in the present case, I find Dr. Knowles's diagnosis most attractive.

CLINICAL DIAGNOSES

? Asbestosis.

? Carcinoma of lung.

Dr. JOHN H. KNOWLES'S DIAGNOSES

Pulmonary asbestosis.

Pleural mesothelioma, with invasion of mediastinum, chest wall, right hemidiaphragm and liver.

PATHOLOGICAL DISCUSSION

Dr. CASTLEMAN: Dr. Monaco, will you tell us what you found at the first operation?

Dr. ANTHONY P. MONACO: The operation performed at this hospital was, as Dr. Knowles has foretold, an open biopsy of the pleura and lung. The parietal pleura was markedly thickened, in some areas to a thickness of 2 or 3 cm. It was markedly fibrotic, but also nodular and in some portions stony hard, and a generous biopsy of a stony-hard area was taken. The underlying lung was also fibrotic and nodular, and we made a wedge excision of a nodular area. It was our impression at the time that the lung changes were most consistent with some type of granulomatous disease of the lung, and that the pleural changes were most consistent with either severe chronic pleuritis or metastatic involvement of the pleura.

Dr. CASTLEMAN: Examination of the biopsy specimen revealed very dense pleuritis. There were masses of collagen with a few scattered lymphocytes, which are characteristic of the dense, fibrous, chronic pleuritis that one commonly finds in patients with asbestosis (Fig. 4). In fact, when the pathologist sees this type of pleuritis he should look very carefully for asbestos bodies. We searched for evidence of a mesothelioma, but in most of the fields found only a pleural reaction with normal mesothelial cells, as is seen with any chronic pleuritis. The mesothelial cells were small and perfectly normal and certainly did not suggest a mesothelioma. Knowing that asbestos bodies are often covered with iron and appear brown or very dark in the section, we hunted for pigmented areas and in one field were rewarded by finding long, corrugated, brown structures that did prove to be asbestos bodies (Fig. 5). At the time of this operation, therefore, we were able to make a diagnosis of severe, chronic pleuritis, undoubtedly associated with asbestosis. No tumor cells were seen.

Dr. Wilkins, will you tell us the follow-up?

Dr. WILKINS: After discharge the patient was followed at first in the clinic. He did not do well. The pain was not relieved, and the dyspnea became more marked. He began to complain of abdominal pain and distention, and at one time intestinal obstruction seemed to be developing. When he returned to the hospital three weeks after the operation we rapidly determined that he did not have intestinal obstruction. It was hard to escape the clinical impression that this man had a malignant process, as Dr. Knowles has implied. The only other avenue that we could pursue to establish that diagnosis was study directed toward the liver. By means of a peritoneoscope we surveyed the surface of the liver, which was studded with little white nodules that looked like metastatic tumor, and we were actually able to do a needle-aspiration biopsy of these nodules through the peritoneoscope. In addition, the peritoneal surface of the entire upper portion of the abdomen was covered with what appeared to be carcinoma, and we took a direct biopsy of a nodule in that region.

Dr. CASTLEMAN: I assume, Dr. Knowles, that you are reassured now that you know that a nodule, at

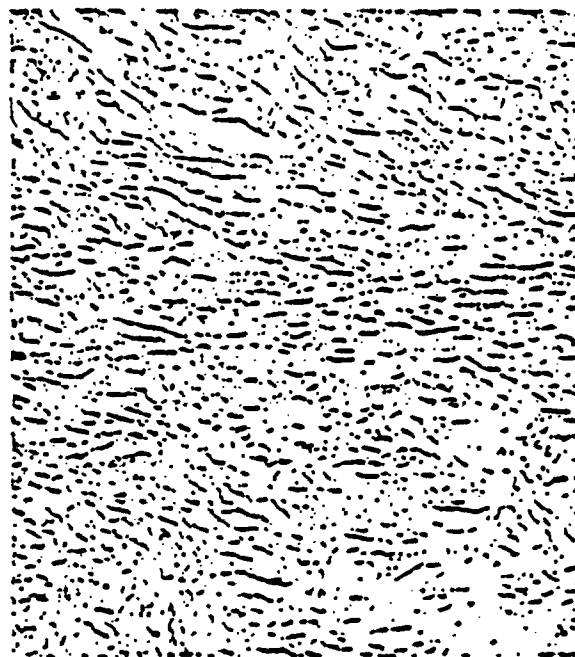


FIGURE 4. Dense, Collagenous Pleuritis. (X200)



FIGURE 5. Small Group of Asbestos Bodies. (X10)
Note the reactive non-neoplastic mesothelial cells below. At least, was removed from the abdomen. Microscopical examination of this nodule revealed, in addition to the previously observed collagen, large epithelial-like cells, which were much larger than those seen on the pleura, and on the basis of this biopsy we could say definitely that this was a malignant lesion. We were not certain whether it was a mesothelioma or carcinoma, but because of the dense collagen we leaned a little toward a mesothelioma, which can be predominantly fibrous.

The patient died ten days after this operation. At autopsy the entire right side of the chest was obliterated by dense fibrous tissue that in many places was obviously neoplastic. In the region of the right lower lobe the pleura had a thickness of as much as 5 cm. As Dr. Knowles surmised, the pleural tumor had extended through the diaphragm and overlay the surface of the liver (Fig. 6). However, the parenchyma of the liver was spared except for a few small metastatic nodules. The neoplastic tissue extended into the lower lobe of the right lung, producing the serrated or cobblesone margin, as it projected from the pleura into the lung, that is characteristic of the mesothelioma. The left lung was also involved by this dense pleural tumor, and there were a few small metastatic nodules within its parenchyma.

The tremendous mass of the mesothelioma involved the entire mediastinum, and compression of the subclavian veins on the right side accounted for the Horner syndrome. The tumor extended down to involve the pericardium as well, and there were two small nodules on the epicardium. From the pleura it extended into the ribs, as was seen on the x-ray films, and two of the ribs were completely destroyed. The vertebrae were also involved, not by direct extension but by actual metastasis. As I mentioned, the huge tumor extended down from the chest and overlay the right lobe of the liver, and when it was peeled off nodules were seen on the surface of the liver. The omentum was completely covered

with mesothelioma implants, which were present throughout the abdomen, especially in the region of the right lower quadrant over the cecum, the ascending colon and the terminal ileum.

Microscopical examination of one of the metastases within the left lung (Fig. 7) revealed mesothelial cells with a tremendous fibrous-tissue counterpart, which is characteristic of the mesothelioma, as I indicated (Fig. 8). In fact, an occasional mesothelioma is almost entirely fibrous, and at times it is very difficult for the pathologist to differentiate it from merely dense collagen or a fibrosarcoma. We know from experimental evidence that the mesothelioma cell, when grown on tissue culture, may produce collagen, and that is what it was doing in this metastasis. On the other hand, other mesotheliomas are predominantly made up of large mesothelial cells,



FIGURE 6. Sagittal Section through the Lower Lobe of the Right Lung, Diaphragm and Liver.

The mesothelioma encircles the lung (above) and overlies the anterior surface of the liver (below). Note the pleural nodules extending into the lung parenchyma.



FIGURE 7. Metastatic Nodule in the Left Lung. (X15)

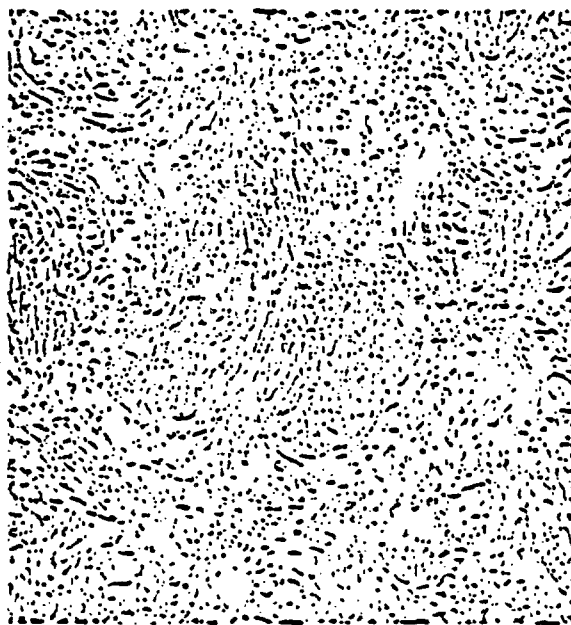


FIGURE 8. Mesothelioma with Preponderance of Fibrous-Tissue Elements. (X120)

sometimes in an acinar or papillary arrangement. In fact, many of the cases in which a tumor has been described as a complication of asbestosis and called an adenocarcinoma of the lung probably belong in the category of mesotheliomas rather than adenocarcinomas. In this metastasis we were able to find a very nice asbestos body among the mesothelial tumor cells (Fig. 9).



FIGURE 9. Asbestos Body within a Fibrous Area of the Mesothelioma (the Club-Shaped Horizontal Structure in the Lower Third of the Photograph). (X600)

Just a few months ago we saw another case of mesothelioma. That patient had not been exposed to asbestos, but the case brought out a number of interesting points about this type of tumor. The pleura was very dense, as in the case under discussion today, and the tumor had similarly extended down through the diaphragm to the abdominal cavity, where loops of small bowel were interadherent because of the resultant peritoneal thickening, which was composed of malignant mesothelioma cells. There has been some discussion regarding whether a mesothelioma of the peritoneum can occur without involvement of the pleura in cases of asbestosis. In all the cases that I have seen the tumor has extended down from the pleura, as it had in the case discussed by Dr. Knowles.

I might point out that mesothelioma cells secrete hyaluronic acid, whereas carcinoma cells do not. Thus, if one has fresh tissue one can stain it metachromatically with toluidine blue, and if the hyaluronic acid in the cells is digested by spermatid hyaluronidase it indicates that the cell is mesothelial rather than epithelial.

Dr. Knowles, do you want to comment further?

Dr. Knowles: I'm a little distressed that on two pleural samples we still couldn't hit something that told us that this patient's lesion was a mesothelioma, although I realize that there may be a relative paucity of cells, with fibrous disease predominating. The

other important point is that a mesothelioma can indeed metastasize, as has been emphasized by the studies in South Africa. Regarding your point about adenocarcinoma, in view of the squamous metaplasia that is associated with chronic irritation by these fibers I would expect to see squamous-cell carcinoma more often than adenocarcinoma. Is that not true?

Dr. Castleman: In about half the reported cases the tumor has been squamous-cell carcinoma, and I agree that it is what one would expect. If we believe that the asbestos body is an irritant, it is logical to assume that it stimulates squamous metaplasia in the bronchial or the bronchiolar epithelium, which then may progress to carcinoma, but in the case that Dr. Isselbacher and his associates reported, for example, although there was squamous metaplasia the carcinoma was an adenocarcinoma. Perhaps the lesion was a mesothelioma!

Dr. Paul S. Russell: Dr. Castleman, I know that the degree of invasiveness of these tumors varies considerably, and that they sometimes remain confined to the pleural space for a remarkably long time, whereas I've encountered some that invaded into the chest wall and even into the abdomen, as in the case that you referred to. But I have never seen a mesothelioma with involvement of the bone. Is that a common occurrence in your experience?

Dr. Castleman: In the cases in which the mesothelioma does metastasize bone involvement is not infrequent.

Dr. Soutter: Isn't there a benign type of mesothelioma also?

Dr. Castleman: There is a lesion that is characterized by proliferation of benign mesothelial cells. This may occur with any chronic infection; for example, tuberculosis can stimulate the mesothelial cells sufficiently to provoke an appearance that is almost neoplastic. It probably is not a true tumor, but there are cases of so-called benign mesothelioma.

ANATOMICAL DIAGNOSES

Pulmonary asbestosis.

Pleural mesothelioma, bilateral, with extension into lung, mediastinum, pericardium, ribs, diaphragm and liver and with metastases to lungs, liver and vertebrae.

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