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MESOTHELIOMA ASSOCIATED WITH ASBESTOSIS

A Report of 3 Cases

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A study of 34 autopsies of patients dying with pulmonary asbestosis disclosed 3 cases of peritoneal mesothelioma, one of which was complicated by a mesothelioma of the pleura. In 2 of the 3 patients there was an occupational exposure history of 20 and 34 years in an asbestos textile plant. Although the remaining patient had classical asbestosis of the lungs at autopsy, there was no known history of industrial exposure to asbestos. The authors think asbestos can produce mesothelioma of either peritoneum or pleura; they present 3 cases to support the concept of a causal relationship. The increased utilization of asbestos material and the recent demonstration of asbestos bodies in the lungs of urban dwellers may have significant implications for cancer epidemiology in the future.

THE ASSOCIATION OF MESOTHELIOMA OF THE peritoneum and pleura with asbestosis has been recognized recently. The number of cases reported to date has been small and the causal relationship requires additional confirmation.

Recent reports from South Africa,^{1,4,14} Great Britain^{2,3,5,7,11} and this country^{5,9} have incriminated pulmonary asbestosis in a causal role with respect to pleural and peritoneal mesothelioma. Wagner et al.¹⁴ described 33 cases of pleural mesothelioma, which they related to asbestos exposure. Thomson¹² associated 7 cases of mesothelioma, 4 in the pleura and 3 in the peritoneum with pulmonary asbestosis.

Selikoff, Churg and Hammond³ described 4 cases of pleural mesothelioma and 6 of peritoneal mesothelioma in 307 consecutive deaths among asbestos insulation workers from January 1943 through August 1964. The same authors found asbestos bodies in 12 of the 45 mesotheliomas in the Armed Forces Institute of Pathology material upon review. These investigators emphasized the importance of a diligent search for asbestos bodies in the lungs of autopsied patients who have mesothelioma.

In a study⁶ covering 1940 through 1965 autopsies were performed on 34 patients with pathologic evidence of asbestosis at the Lancaster General Hospital; 22 patients had bronchogenic carcinoma; 3 individuals had

mesotheliomas of the peritoneum and one had associated mesothelioma of the pleura.

The 3 patients with mesothelioma had been admitted to the medical or surgical service of the Lancaster General Hospital. Two of the 3 individuals had been employed in the same plant involved in the textile phase of the asbestos industry. We do not know the manner of exposure of the third patient.

CASE REPORTS

Case I (S.B., D-65820). A 53-year-old male factory worker was admitted to the hospital in October 1964 with a chief complaint of abdominal distress and distention of 2-week duration. He gave a history of smoking a pack of cigarettes daily for most of his adult life.

On physical examination, the patient appeared to be chronically ill. Rales and coarse rhonchi were heard throughout both lung fields. The abdomen was distended; shifting dullness was present in the flanks and tympanic percussion was elicited over the anterior portion of the abdomen. There were no palpable organs or masses in the abdomen. The bowel sounds were normal.

The blood count, urinalysis and blood indices were within normal limits. An x-ray of the colon was not remarkable except for evidence of ascites. Infiltration of the bases of both lungs, blunting of the costophrenic angles and adhesions to the diaphragm were present on x-ray study. Calcification over the right diaphragmatic and mediastinal areas was present. The x-ray findings were interpreted as compatible with the fibrosis associated with asbestosis. A history of exposure to asbestos

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II. Section of lung showing asbestos bodies in a

FIG. 2. Case II. Section from lung showing the mesothelioma growing on the capsule. The neoplasm has an adenomatous pattern.



nodules. The incision was 1 cm in diameter

weighed 350 Gm. The parenchyma was of increased consistency.

on—The serosal surface showed marked proliferation of cells and strands of fibrous tissue. The neoplastic cells had foamy or vacuolated cytoplasm. The neoplasm was in the liver substance. The cells were large and polygonal but in some areas they were arranged in cords. Where the neoplasm was in the appendix. Several of the nodules contained metastatic

fibrotic and the tissue was extensively replaced by fibrous tissue. The lungs were free of neoplastic nodules. The mesothelioma of the stomach was tension into the mesentery; moderately differentiated; acute purulent inflammation; coagulation necrosis; pulmonary artery

Case II (R.B., D-57201). A 49-year-old male, employed in an asbestos manufacturing plant, was admitted to the Lancaster General Hospital in June 1962, with a diagnosis of pneumonia involving the base of the left lung. His chief complaint was fever and distress involving the lower anterior chest. The pain became particularly acute about one week prior to admission and was aggravated by deep breathing. He had a cough until about 4 weeks prior to admission. The cough subsided when he stopped smoking cigarettes.

On physical examination the patient was afebrile and moist rales were heard in the lung fields on auscultation. The chest x-ray was interpreted as showing fibrosis in the lower portions of both lungs and the changes were thought to represent asbestosis. The chest films showed no change from those taken in 1960 and in 1961. The patient had been an asbestos worker since 1929 and still was so employed. Bronchoscopy, sputum culture and cytology were essentially negative.

In March 1964 the patient was readmitted with a 3-week history of swelling of the abdomen, anorexia and malaise. Cough and dyspnea developed as the abdomen distended more.

Physical examination disclosed bilateral crackles. The abdomen was distended markedly and signs of ascites were present. The blood counts, blood indices and urinalysis were not remarkable. The heart was not enlarged. An x-ray film of the chest showed considerable elevation of the diaphragm. Multiple densities were present in the lower lobe of the left lung; otherwise, the chest film was unchanged from the one taken in 1962. The heart was not enlarged. On the fourth hospital

day, paracentesis was attempted. A small amount of thick mucinous material was obtained, which on cytologic examination showed clumps of malignant cells. On the tenth hospital day the patient had exploratory surgery. There was extensive carcinomatosis with "sheets" and "cakes" of tumor tissue over the mesentery, peritoneal and omental surfaces. The pathologic report on the biopsied material was poorly differentiated carcinoma. The patient was discharged, but was seen for periodic removal of ascitic fluid. On June 14, 1964 the patient was readmitted for terminal care; he expired 5 days later.

Postmortem examination (R.B., A-64-152). The external examination showed marked atrophy of the skeletal musculature and pitting edema of the lower extremities. There was a healed right rectus scar of the abdomen.

Thorax—There was an extensive adhesive pleuritis in the right chest and, in the left, a marked fibrous pleuritis with focal loculation of about 600 ml of brown serous fluid between the pleural membranes. Both lungs were of increased consistency and the parenchyma was reddish-brown. An 8 cm white fibrous plaque covered the lateral aspect of the lower lobe of the left lung. The visceral pleura of both lungs was thickened and opaque. Some hilar lymph nodes were replaced by gray tissue.

Abdomen—The abdominal contents had to be removed en masse because the visceral organs were matted together by tumor. The peritoneum covering the stomach, intestines, liver, spleen and mesentery was studded by the neoplasm distributed as sheets, plaques and nodules of gray-white or pale pink tissue. The plaques varied from 0.5 to one cm in

thickness and in some areas the neoplasm was seen as rubbery nodules measuring up to 8 cm in diameter. Covering the inferior surface of the diaphragm was gray-white tissue about one cm in thickness. Some of the para-aortic lymph nodes were enlarged and replaced by neoplasm. Gray-white nodules were present on the parietal peritoneum. There was no evidence of gross invasion of visceral organs although both liver and spleen were encased almost completely by the tumor.

Histopathologic examination—Sections of stomach, intestines, diaphragm, mesentery and spleen revealed neoplasm in the serosal surfaces. The diaphragm and colon were the only organs invaded by tumor. Much of the serosa of the abdomen showed hypertrophy and proliferation of its cells. The neoplastic cells formed papillary excrescences which consisted of connective tissue cores covered by cuboidal mesothelial cells. In some areas the tumor was solid, consisting of large cells with eosinophilic cytoplasm and oval, vesicular, bland-appearing nuclei. Many of these cells had vacuolated cytoplasm. In the colon and diaphragm the neoplasm invaded the muscular layers and the pattern which the cells assumed was pleomorphic, pseudoglandular, solid and papillary. The capsules of liver and spleen were thickened and invaded by papillary mesothelial tissue.

There was moderate hypertrophy and hyperplasia of the serosal cells covering the visceral pleura. At some levels the neoplastic cells had proliferated into clumps. A similar change was seen in the parietal pleura and in some of the alveoli. No neoplasm was found in the bronchial epithelium or walls. Many asbestos bodies were seen in the bronchioles and there was a moderate degree of diffuse fibrosis of the lungs. Hilar and para-aortic abdominal lymph nodes contained papillary neoplastic metastases.

Essential pathologic diagnoses included the following: diffuse malignant mesothelioma involving the peritoneum and pleura; neoplastic invasion of the colon, diaphragm and lungs; neoplastic metastases to hilar and para-aortic abdominal lymph nodes; pulmonary asbestosis; bilateral chronic adhesive fibrous pleuritis; cachexia and marked edema of the lower extremities.

Case III (B.M., C-6761). A 60-year-old laundry worker was admitted to the hospital in 1956. He had an acute onset of right upper quadrant and right lower chest pain with chills and fever. On examination a pneumonitis in the lower lobe of the right lung was indicated. Chest x-ray revealed an elevated right diaphragm and mottled abnormal densi-

ties lying above and posteriorly. The patient improved on antibiotic treatment and was discharged.

In November 1958 this patient was readmitted because of right upper quadrant distress. Gallbladder x-ray and intravenous urogram were negative. A stomach and duodenal x-ray showed a small duodenal ulcer in the duodenal cap. The chest x-ray revealed elevation of the right diaphragm and scarring of the right lower lung field. The patient improved on an ulcer program and was discharged.

In January 1959 the patient was admitted again because of right upper quadrant distress. On physical examination the patient was obese and had generalized abdominal tenderness. No palpable masses or organs were found.

On January 20, 1959 an exploratory laparotomy was done and extensive carcinomatous was seen over the omentum, gallbladder and liver. Several liters of serous fluid were removed. The pathologic study of the biopsied material disclosed a papillary malignant neoplasm, probably a mesothelioma. The patient was discharged and had multiple abdominal paracenteses as an outpatient. He was readmitted in June 1959 for terminal care and expired 3 days later.

Postmortem examination (G.M., A-59-13). The body was fairly well developed. A 15 cm scar was seen in the right upper quadrant of the abdomen.

Abdomen—About 400 ml of turbid fluid was present in the greater peritoneal space. The abdominal viscera were encased by tumor tissue. Both visceral and parietal peritoneum were studded widely with gray plaques and nodules. Similar masses were seen in the serosa covering liver, spleen, gallbladder, stomach, intestines and urinary bladder. Omentum was replaced by solid gray-white tissue.

Thorax—Grossly there was a moderately advanced bilateral fibrous pleuritis. The lungs were reddish-brown and of increased consistency.

Histopathologic examination—The serosal cells which made up these tumor masses had a mixed pattern—papillary, adenomatoid and solid masses of mesothelial cells. The neoplasm was confined to the capsules or serosa of all visceral organs except the colon. In the organ the malignant cells invaded the outer muscular layer. Asbestos bodies were evident in the fibrous tissue seen in the lungs.

Essential pathologic diagnoses included the following: diffuse malignant peritoneal mesothelioma; neoplastic extension into the wall of the colon; old bilateral fibrous pleuritis and pulmonary asbestosis.

DISCUSSION

These 3 patients had mesotheliomas. In addition to the abdominal configuration of the tumor, except for the spinous process seen in the liver.

In the second patient, a peritoneal arrangement was found at solid masses of adenomatoid pattern. The mesothelioma was involved in the morphologic features of the fibrotic pleura and parenchyma. Small nodules were present in some instances, we think that independent nodules in the serosal and pleura. The tumor was recognized only in the pleura.

The third patient had a mesothelioma which was a histopathologic pattern. The only organ involved was the pleura.

All 3 patients had asbestos bodies. Many asbestos bodies and diffuse fibrosis were seen in these individuals.

No asbestos bodies were seen in the peritoneum, the peritoneal and pleura, hilar or mediastinal structures. In the intestinal tract. In the presence of asbestos bodies in the lung parenchyma.

CONCLUSION

The exact period of exposure is known for only one patient (B) had been employed for 20 years (1926 to 1946) in a 6-year exposure to asbestos. Mesotheliomas were recognized in these individuals, after the fact. There is no information about our third patient. The local asbestos plaques. The patients with an asbestos textile exposure since the

DISCUSSION OF PATHOLOGY

These 3 patients had malignant diffuse mesotheliomas. In case I the neoplasm was limited to the abdomen. The morphologic configuration of the tumor was adenomatoid except for the spindle cells in a fibrous stroma as seen in the liver substance.

In the second patient the mesothelioma was primarily a peritoneal growth. The structural arrangement was for the greater part papillary but solid masses of large eosinophilic cells and adenomatoid patterns were seen. The pleura also was involved and the serosal cells were hypertrophic and showed focal hyperplasia. The morphologic pattern was tubular where the fibrotic pleura was invaded. In the lung parenchyma small clumps of mesothelial cells were present in some of the alveoli. In this instance, we think the mesothelioma originated independently and perhaps simultaneously in the serosal membranes of peritoneum and pleura. The pleural involvement was recognized only in the microscopic study.

The third patient had a diffuse abdominal mesothelioma which was also seen as a mixed histopathologic pattern. The colonic wall was the only organ involved by invasion. The neoplasm was confined to the abdomen.

All 3 patients had pulmonary asbestosis. Many asbestos bodies were seen in bronchioles and diffuse fibrosis of the lung was present in these individuals.

No asbestos bodies were found in the peritoneum, the peritoneal mesotheliomas, parietal pleura, hilar or abdominal lymph nodes. These structures were not seen in the gastrointestinal tract. In our experience the presence of asbestos bodies has been limited to the lung parenchyma.

COMMENT

The exact periods of exposure to asbestos dust is known for 2 of our patients. Case I (S.B.) had been employed in an asbestos mill for 20 years (1926 to 1946). Case II (R.B.) had a 34-year exposure (1929 to 1963). The mesotheliomas were recognized 38 and 35 years, respectively, after the first known exposure. There is no information available to confirm that our third patient had been employed in the local asbestos plant.

The patients with known exposure worked in an asbestos textile mill which had been in operation since the turn of the century. This

plant was concerned with weaving, carding and spinning of asbestos. In the early years the potential danger of inhalation of asbestos dust was not known. The concentration of "asbestos dust" before the mid-1930's was of such degree that several departments were referred to as "dust holes." It has been said that individuals working in this atmosphere "could not see beyond an arm's length." In 1935 asbestos was recognized as a cause of pneumoconiosis and measures then were initiated to minimize the environmental pollution.

We think mesothelioma of the peritoneum is a definite pathological entity as seen in these 3 patients. Metastatic malignancy mimicking mesothelioma is not likely in the absence of a demonstrable primary lesion at autopsy. Mesothelioma of the peritoneum is so infrequent, except in association with asbestosis, that a causal relationship seems acceptable. In our hospital we have not seen a case of mesothelioma without asbestosis.

Thomson¹² and Selikoff et al.⁹ have pointed out that asbestosis frequently may be overlooked in mesotheliomas. This occurred in our third case. Initially, the pulmonary asbestosis had been overlooked. On reviewing the lung sections, definite evidence of asbestosis was present.

In 2 of the 3 cases the patients, when seen, were no longer in an occupation associated with exposure to asbestos dust. Two patients had x-ray changes sufficiently characteristic to suggest asbestosis but the third did not, even to radiologists who see many cases of pulmonary asbestosis. A high index of suspicion is needed in relating asbestosis to mesothelioma. The frequency with which occupations are changed, as well as the widespread use of asbestos, necessitates a detailed history of possible exposure. At autopsy the presence of pulmonary asbestosis may be overlooked very easily.

Our 3 patients had extensive fibrosis of the lung parenchyma and characteristic asbestos bodies, presenting the typical changes of pulmonary asbestosis usually seen as a result of occupational exposure. Recently, however, several investigators have presented evidence that asbestos fibers may be air-borne and as such present a modern urban hazard. Reports from Cape Town,¹³ Miami¹⁰ and Pittsburgh¹ showed 26.4, 27.9 and 41%, respectively, of the subjects studied to have asbestos bodies in the lung tissue at autopsy. The implications in cancer epidemiology are significant since

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there has been a marked increase in the utilization of asbestos in the past generation. Pleural or peritoneal mesothelioma may be seen in increased frequency as a result of non-occupational exposure on the basis of environment contamination.

Since asbestosis is primarily a pulmonary disease, an explanation is needed for its carcinogenic relationship to the peritoneum. The lymphatic vessels of the diaphragm form 2 plexuses—one on the thoracic and one over the abdominal surface. These plexuses communicate freely with one another on the parts covered by the pleura and the peritoneum.⁴ Asbestosis involves mainly the bases of the lungs. It is postulated that a carcinogenic substance is released in asbestosis, which, through access to the lymphatic channels in the diaphragm, may produce mesothelioma of the peritoneum.

The South African and British reports deal primarily with the crocidolite type of asbestosis. Chrysotile type asbestos fiber is used primarily by the United States asbestos industry. Our findings support the concept of Selikoff et al.⁹ that mesothelioma is a hazard of asbestos exposure in general, rather than one type of asbestos fiber in particular.

ADDENDUM

Since the preparation of this report, a fourth case of pulmonary asbestosis with pleural mesothelioma has been seen in a patient at surgery. It occurred in a patient with a history of occupational exposure to asbestos. Since a primary bronchogenic carcinoma cannot be excluded completely at this time, the case has not been included in this report.

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