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Primary Malignant Mesothelioma of the Pleura

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THE DIAGNOSIS OF primary malignancy of the pleura continues to be quite a difficult problem in spite of all modern clinical skills and advanced laboratory and x-ray facilities. Unfortunately, this disease is quite uncommon, and few investigators have been able to accumulate a broad knowledge of its characteristic features. Nevertheless, mesothelioma is perhaps not as rare as the literature reports and probably may be seen but not recognized properly.

This tumor is most frequently confused with benign lesions of the pleura or the mediastinum, with primary malignancy of the underlying lung tissue as well as of the enclosing rib cage, and, finally, with metastatic disease from a distant tumor. Many diagnostic difficulties are created by the great variety of clinical, roentgenologic and pathologic manifestations of this tumor that may puzzle clinicians, chest surgeons, roentgenologists, and pathologists. This peculiar behavior was explained at first by Maximow[1] and later by Stout and Murray[2] with the aid of cell culture methods.

The growth originates from mesothelial (cemic) cells that are multipotential and can form a great variety of mesothelial as well as mesenchymal tissues in manifold combinations.[3] Thus, mesotheliomas not only differ from each other but also may show amazing differences in microscopic sections of the same growth.[3]

Clinically, 2 types can be distinguished: a localized and a diffuse mesothelioma. The localized form is usually benign, fibrous, and asymptomatic until late and is often discovered during routine chest x-ray examinations. It forms a nodular density attached to the chest wall or the diaphragm. There are all kinds of transitions between this tumor and the malignant types which grow diffusely, invade rapidly, and show early symptomatology. The latter may be responsible for chest pain and discomfort before being visible on roentgenograms. Later, they make themselves known by pleural effusions, idiopathic pneumothorax, or dense massive shadows covering a large portion of the hemithorax.

Microscopically, the benign mesotheliomas form fibrous masses, while those that are malignant consist either of solid conglomerations or glandular and follicular arrangements of epithelial cells or, more rarely, of fibrosarcomatous tissue. The localized tumors can be eradicated surgically; the diffuse types, however, have been considered inoperable until recently when Harris and associates[4] reported a cure, or at least a long-term survival, after radical pleuropneumonectomy during the early stage of the development. In addition, Richert and Sherman[5] reported a long-term arrest after early administration of radioactive gold.

If the experience of these investigators can be confirmed by others, it seems mandatory for all physicians who may encounter mesotheliomas in their practice to acquaint themselves with the symptomatology and natural history of this growth. It is obvious that a tumor of such great variability will produce a different picture in each individual case. However, the experience gained from the observation of 2 patients with malignant mesothelioma showed a characteristic similarity that makes it worthwhile to review them. The first case was previously reported in detail,[6] while the second is a new case.

CASE REPORTS

Case 1. A 57-year-old oil refinery foreman noticed a diffuse pain in his left upper chest and upper abdomen, which gradually increased in intensity. The onset was very insidious, and his initial discomfort was at first not clearly separated from a previously present angina pectoris, in spite of the fact that the chest pain had changed in character and persistence and no longer responded to vasodilating remedies.

Initially, an x-ray film of the chest was normal, but soon this patient experienced a "spontaneous" pneumothorax without a history of trauma or physical exertion. A roentgenogram taken at this time showed a partly collapsed lung without abnormal shadows in this organ, in

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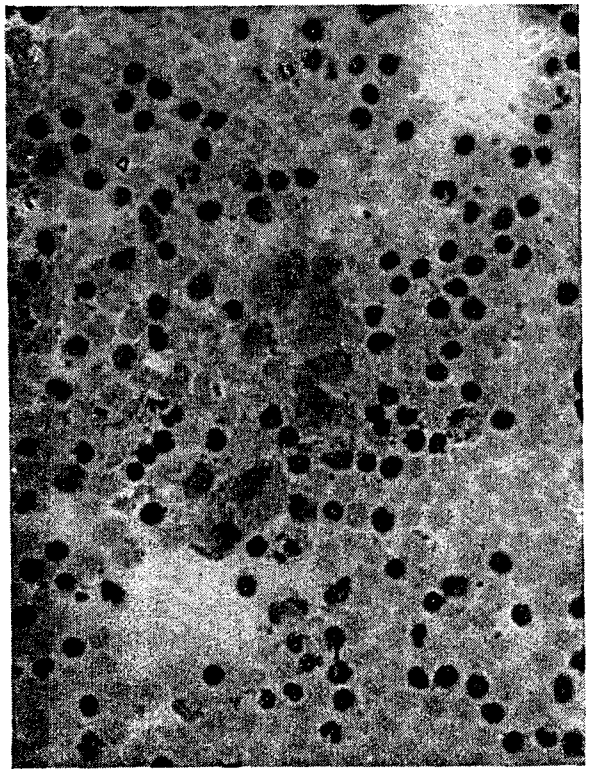


Fig. 1. Large mesothelial cells noted in the bloody pleural effusion.

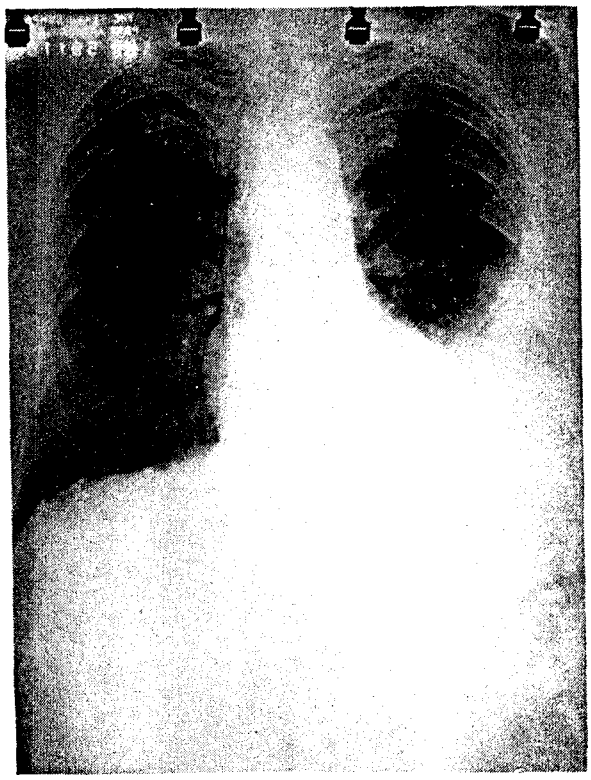


Fig. 2. Upper scalloped border of the pleural walls.

the pleural space, or in the bony rib cage. A small amount of serous fluid was aspirated but not examined for tumor cells. The chest pain persisted after the air had been absorbed, and a dense fibrothorax gradually developed with shrinking of the entire hemithorax and inward retraction of the lateral chest wall.

Thoracic exploration was performed because of unbearable pain, but this revealed only a dense fibrothorax with massive adhesions. Decortication gave no relief. Anorexia and weight loss became marked and led to severe cachexia. Neither large doses of narcotics nor neurosurgical procedures reduced the pain. An exploratory laparotomy followed, but only similar adhesions were encountered. No diagnosis was made until a routine stomach x-ray film unexpectedly revealed that several ribs were destroyed. Biopsy of this region revealed pleural mesothelioma.

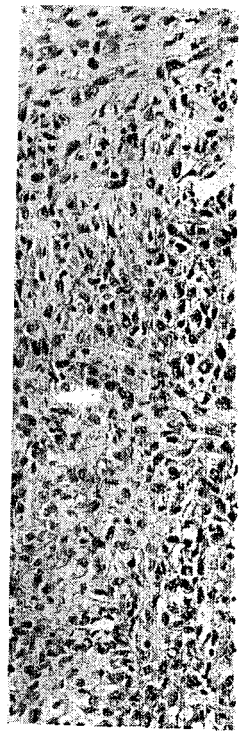
Case 2. A 58-year-old oil refinery foreman who had worked with asbestos insulating material for quite a while noticed soreness and a rattling noise in the left hemithorax. Chest examination in January 1959 revealed a bloody pleural effusion. This fluid was bacteriologically negative but contained large mesothelial cells, which our pathologist suspected were malignant (figure 1). However, his suspicion was not shared by a number of other pathologists who were consulted. The patient's pain continued to increase and radiated over the whole left hemithorax. The pleural fluid reaccumulated in spite of repeated thorough paracenteses. Some dyspnea but little cough was noted.

Exploratory thoracotomy in a large medical center revealed multiple hard plaques covering the entire pleural space and extensive pleural adhesions. A portion of the pleura was removed for microscopic studies. The pathologist reported "granulomata of unknown origin." A lung biopsy performed at the same time revealed asbestos bodies in the bronchioles. In spite of negative skin and bacteriologic tests, the patient was placed on an antituberculous regime after the operation. The fluid did not return, but a dense fibrothorax developed with shrinking of the entire hemithorax. The pleural density increased on successive x-ray films and finally revealed an upper scalloped border (figure 2). The pain was constant day and night and did not respond to large doses of narcotics.

In November 1959, intercostal blocks were performed followed by nerve sections. These procedures were without benefit, and, in December 1959, a chordotomy was also done. Shortly after this operation, x-ray examination revealed that several ribs were destroyed. Similar roentgenograms had been previously made almost at monthly intervals, but no bony defect had ever been noted. Excisional biopsy of these bones revealed a malignant growth interpreted as "fibrous sarcoma" by the pathologist (figures 3 and 4).

In the following weeks, various other parts of the bony thoracic cage were destroyed, particularly the lower dorsal vertebrae and the upper sternum. This led to cord compression and transection as well as to obstruction of the trachea and esophagus. The patient suffered unbearable pain until his demise in May 1960.

The essential findings at autopsy were "Mesothelioma of the left pleura invading mediastinum, ribs, vertebrae, liver, spleen, and lungs. Hypostatic pneumonitis, asbestosis of the lungs. The primary tumor and the mestastases consisted of irregular bundles of spindle cells of atypical character with hyperchromatic bizarre nuclei" (figures 3 and 4).



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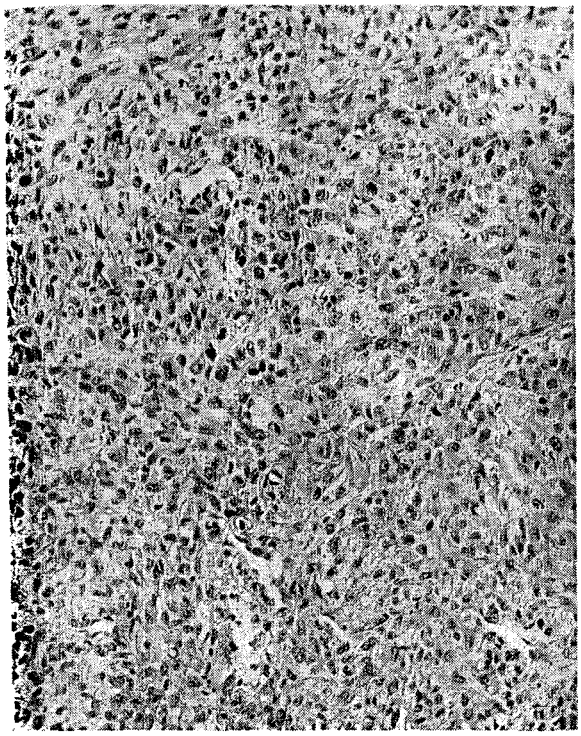

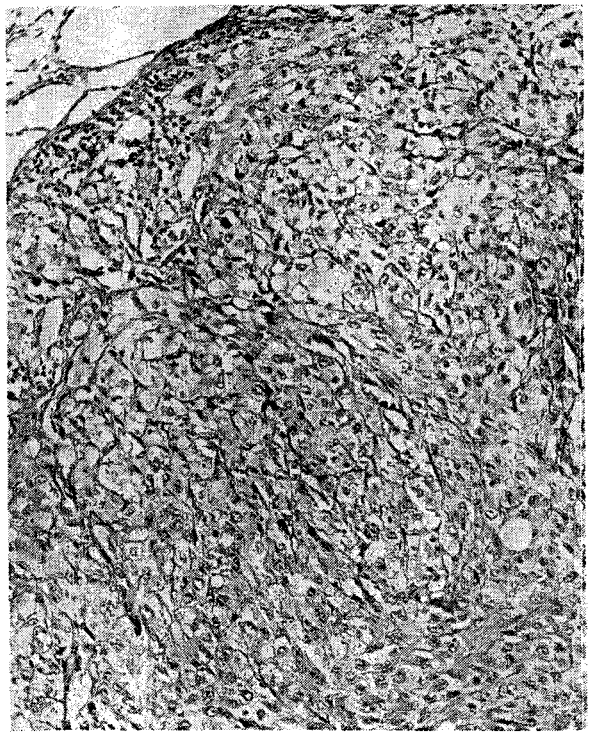

Fig. 3 *(left)* and Fig. 4 *(right).* Fibrosarcoma composed of irregular bundles of spindle cells with hyperchromatic bizarre nuclei.

DISCUSSION

The similarity of these 2 cases of diffuse malignant mesothelioma and of some of the others reported in the literature,[7–10] is striking. Only the lack of familiarity with this entity can explain why both of the medical centers caring for these patients failed to make an early diagnosis, in spite of the fact that the referring physician alerted them to the possibility of such a growth. These patients were observed for months by various specialists who failed to recognize this entity until bone destruction, which was noted on roentgenograms, and excisional biopsy confirmed the correct diagnosis.

Any attempt to give these patients the benefit of radical surgery or successful radiation therapy would require a thorough knowledge of the early symptomatology of this tumor. The clinician must be alerted to a diffuse unilateral chest pain of recent origin gradually increasing in intensity in a middle-aged or elderly person. His physical examination may be negative, or there may be an unexplained pleural effusion and, occasionally, a spontaneous pneumothorax. The bacteriologic examination of the pleural fluid will be negative. It remains to be seen whether the cells present in this fluid can be recognized as malignant by the pathologists (figure 1).

The pain is not markedly relieved by paracentesis or aspiration of the pneumothorax. Anorexia, weight loss, and cachexia gradually develop. Administration of narcotics and neurosurgical procedures are without benefit or only slightly useful to the patient. Percussion density and shrinking of the hemithorax, with or without scoliosis, may be observed. Clubbing of fingers, articular rheumatism, and osteoarthropathy have been reported in some cases but have not been observed in our patients. They are apparently more often seen with the localized benign mesotheliomas. Chills, fever, cough, dyspnea, and cyanosis are usually mild or absent.

The roentgenologist should be aware of the fact that the chest x-ray may be entirely negative for some time. Pleural effusion, fibrothorax or pneumothorax are nonspecific. However, the increasing density of the fibrothorax, particularly after surgical exploration and the shrinking and narrowing of the entire hemithorax may be significant. Either the mediastinum is pulled toward the lateral chest wall or vice versa. Scalloped margins of the pleural walls or of the fibrothorax (figure 2) are late manifestations. Bone destruction should be constantly looked for with repeated Bucky exposures. If present, this announces the final, probably incurable stage.

Thoracic exploration is always necessary to confirm the diagnosis. Therefore, the chest sur-

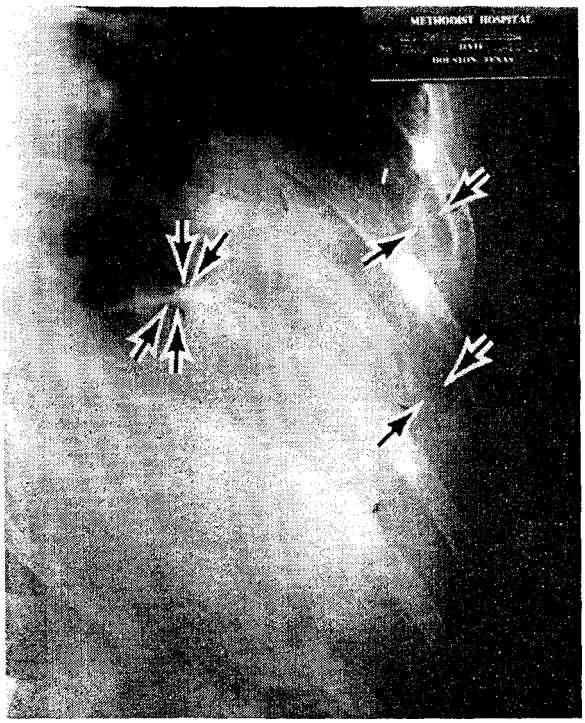

Fig. 5. Calcium deposit along the diaphragmatic surface of the pleural space.

geon must be familiar with the various macroscopic features of the growth which forms fine nodules, large plaques, massive adhesions, and a dense fibrothorax.

Of utmost importance is, of course, the correct pathologic interpretation of the pleural biopsy on which the decision for radical treatment depends. In the majority of cases, the specimens have been misinterpreted as fibrous pleural thickening, pleural adhesions, granulomatous tissues, or metastatic malignancy. The careful pathologist can only state that the lesions are compatible with malignant mesothelioma, because this diagnosis actually requires a complete autopsy excluding any other primary neoplasm. However, in practice, one should proceed with surgical therapy if a thorough clinical investigation has eliminated any distant malignancy.

Our second case is particularly interesting because of the history of long-time exposure to asbestos and the discovery of asbestos bodies in the lung biopsy specimen. The etiologic association of asbestos and malignant mesothelioma has been repeatedly discussed in the literature.[11–15] Not all investigators agree that exposure to asbestos predisposes to malignancy of the pleura.[15] However, such history alerted the suspicion of the authors in the second case.

On the basis of his autopsy, our pathologist considered it "very unlikely that the pathogenesis of the tumor could be related to the asbestos fibers since they were located in the bronchioles and not in the pleura." However, asbestos material could have reached the pleural tissues without being demonstrable microscopically.[11] In addition, along the diaphragmatic surface of the pleural space there was a "thick grey rind which was partially calcified" at autopsy. This calcium deposit could be demonstrated on the initial x-ray pictures (figure 5, double arrows), indicating some pleural scarring prior to the development of the malignant growth.

SUMMARY

The symptomatology and natural course of primary malignant mesothelioma has been illustrated by 2 case reports. In spite of early clinical suspicion, early thoracic exploration, and continuous care by various specialists, these patients progressed to an advanced hopeless stage with destruction of the bony thorax before the correct diagnosis was established. The early clinical, roentgenologic, and pathologic characteristics of this neoplasm must be kept in mind in order to bring these patients in time to radical surgical procedures or effective irradiation therapy that may be curative or at least prolong life.

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