

FILE NAME: Oil Industry and American Petroleum Institute (API)

DATE: 1956 Nov

DOC#: API114

DOCUMENT DESCRIPTION: Journal Article - Malignant Mesothelioma of the Pleura

Malignant Mesothelioma of the Pleura

H. B. EISENSTADT, M.D., F.C.C.P.

Port Arthur, Texas

Primary mesothelioma of the pleura is a controversial entity referring to a growth originating from the mesothelium, the cell layer covering the inner surface of the pleural, pericardial and peritoneal cavities which are derived from the celomic space of the embryo. Willis¹ denies their existence entirely and considers isolated masses of the pleura as metastatic deposits of some distant asymptomatic primary focus. Anderson² believes that in most instances neoplastic involvement of the pleura originates from a bronchial cancer, but he admits that in a small number of cases no intrapulmonary growth can be detected with a most meticulous examination. Ackerman and del Regato³ are convinced that primary pleural mesothelioma exists but consider it a rare disorder. It may be benign appearing as a fibrous mass or malignant showing alveolar, follicular or papillary patterns. Even the latter types have a tendency to remain localized and to expand by invasion of the neighboring structures rather than by distant metastases. However, metastases do occasionally occur into almost any part of the body. Undoubtedly, benign primary tumors of the pleura have been repeatedly recognized;⁴⁻⁹ therefore, the controversy between the various pathologists must refer to the malignant types which are difficult to classify on account of the great variability of their microscopic appearance.⁴⁻¹² These may be localized tumors varying from coin lesions¹³ to huge masses occupying one hemithorax, or they may appear as diffuse thickening of the pleura with or without effusion. Their consistency varies from soft to hard, from brittle to elastic; their color has been described as white, grey, yellow, orange, red, or bluish. Their microscopic picture may resemble carcinoma, endothelioma, epithelioma, sarcoma, fibroma, fibromyoma and giant cell tumor.

Stout and Murray¹⁰ believe to have solved the puzzle of the variable appearance of these tumors by demonstrating in tissue cultures that mesothelioma cells can develop into solid, tubular, or glandular structures of epithelial character as well as into mesenchymal tissues with fibroblasts, collagen, and reticulum fibers. Sometimes one form of growth predominates but more often there is a mixture present causing a great variability of different sections of the same tumor. Other authorities,² however, are of the opinion that bronchogenic cancers may reveal all the pathological features described as characteristic of mesothelioma. This confused status of the pathology of pleural tumor masses makes their clinical evaluation difficult and is apparently responsible for the scarcity and brevity of reports describing their symptomatology during lifetime which is in contrast to the extensive literature discussing their autopsy appearance. Nevertheless, the practicing physician will have to face from time to time the problem of dealing with such isolated pleural growth deserving the

name of malignant mesothelioma.

Considering the great variability of the pathological picture one should expect a multitude of clinical manifestations, laboratory and x-ray findings. It has been stated that some benign types of pleural mesothelioma are asymptomatic and only accidentally discovered during an x-ray investigation. If symptomatic, these tumors are usually responsible for various types of discomfort in the chest and epigastrium among which the typical pleurisy pain aggravated by coughing, sneezing and deep breathing is quite uncommon. Various respiratory disturbances may occur such as dyspnea, cough, hemoptysis and mucoid, purulent or blood-streaked sputum; digestive discomfort may be present in the form of anorexia, nausea, vomiting, belching and epigastric fullness; general malaise may be noticeable with fever, chills, anemia and weight loss. Clubbing of fingers and osteoarthropathy have also been reported.^{7, 8, 11} In the malignant cases invasion of the diaphragm, the chest wall, the pericardium and the peritoneum is responsible for additional symptomatology. Clinical and roentgenological findings are either those of single or multiple solid tumors or of pleural effusions with various types of exudates that are resistant to a conservative treatment.

In contrast to those features considered to be characteristic of mesothelioma, the presented case shows quite a few different findings worth reporting. The diagnostic difficulties of this disease are clearly demonstrated by the fact that it escaped recognition over a period of several

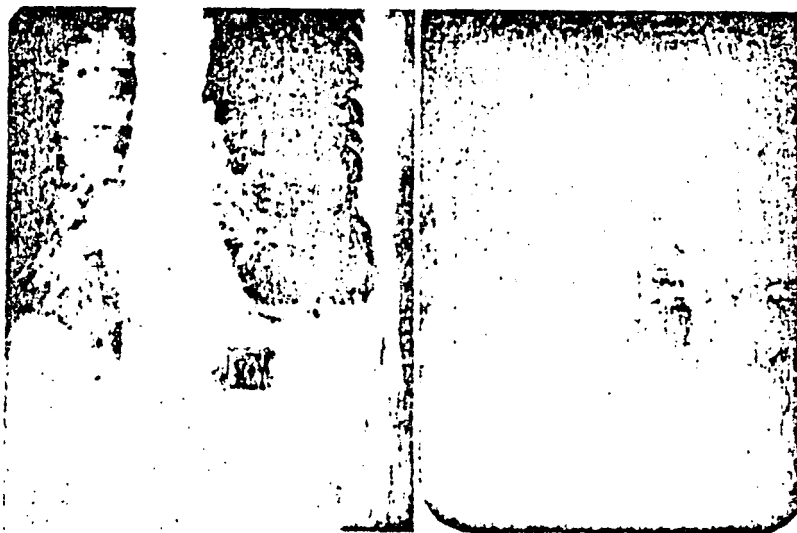


FIGURE 1

FIGURE 2

Figure 1: Chest film of August 1952, showed pneumothorax and small fluid level. Left hemidiaphragm was slightly elevated (see position of "magenblase") and was immovable.—Figure 2: Chest film of August 19, 1954: destruction of lower ribs with soft tissue mass adjacent to them.

years in spite of the most thorough investigations including exploratory laparotomy and thoracotomy. The patient was seen by a number of physicians including specialists of almost any field of medicine:

Case Report: A 57 year old male refinery foreman was treated on May 5, 1950, for acute posterior coronary artery occlusion with myocardial infarction.

Marital and family history were non-contributory. In 1918 he had suffered from a severe attack of influenzal pneumonia. For about 20 years he had been suffering from spells of indigestion with "gas pain" in the left upper abdomen and mucus in the stool.

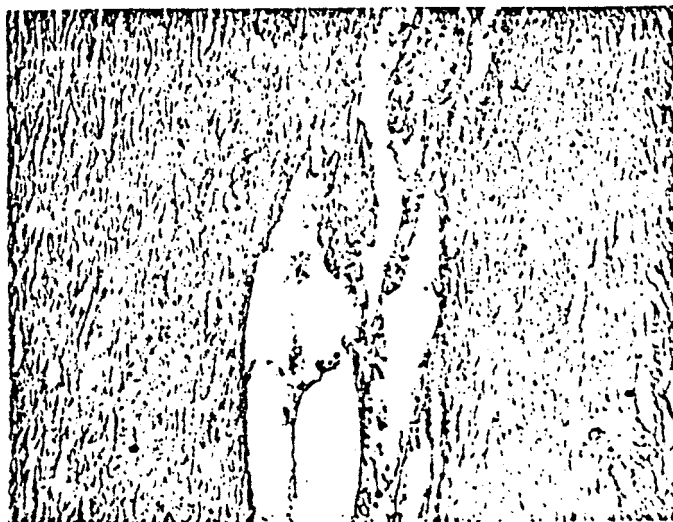


FIG.
3

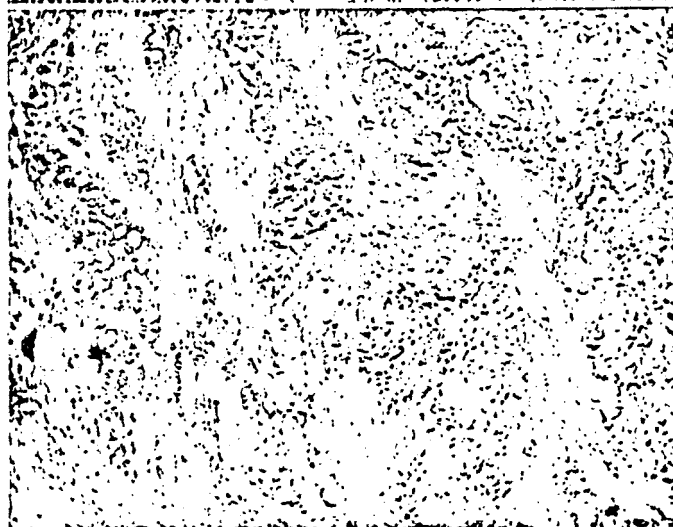


FIG.
4

Figure 3: Section of first biopsy: alveolar pattern invading dense fibrous tissue. Dr. Vernie A. Stembridge (X 48 magnification).—*Figure 4:* Section of second biopsy: medullary pattern. Dr. Vernie A. Stembridge (X 110 magnification).

These attacks of bowel dysfunction were frequently associated with urticaria and attributed to an irritable bowel syndrome associated with food allergy. The heart attack proved to be severe and was followed by a prolonged period of disability with persistent hypotension and marked Q and T wave changes in the electrocardiogram. There remained a stubborn discomfort from the left lower chest as well as the left epigastrium. It was difficult to decide if this was an aftermath of the occlusion or an exaggeration of the previously encountered left flexure syndrome. The patient himself attributed it mostly to the intake of incompatible food as well as to his constipation and gas formation. In the following years thorough clinical studies were repeated several times but no additional pathology could be elicited.

In April 1952, however, the discomfort from the left side of the trunk had become so severe that he consulted three large medical centers in succession. Here, he underwent thorough examinations, but only the previous diagnoses of old myocardial infarction of the diaphragmatic surface, functional bowel disturbance, food allergy and anxiety neurosis could be confirmed. Nevertheless, the treatment suggested on the basis of these investigations failed to bring him relief. Shortly after returning from these clinics to his home city, a routine fluoroscopic checkup revealed unexpectedly a left spontaneous pneumothorax with small fluid level and slightly deformed, elevated and immovable diaphragm. However, neither the collapsed lung nor the visible part of the pleura showed any abnormality (Figure 1). The air was aspirated together with the fluid; the latter contained five grams of protein per 100 cc. and quite a few cells, 80 per cent of which were lymphocytes and 20 per cent eosinophils. Smears, culture, guinea pig inoculation and special studies for tumor cells were unrevealing. The origin of the pneumothorax as well as the exact time of its onset could never be clearly elucidated. An x-ray film taken about four weeks prior to the accidental discovery of this disorder showed a completely normal chest. The patient himself attributed it to an accident which he had sustained in February 1952, when he slipped from a scaffold and tried to grab a brace to hold himself. At this time he felt a sudden severe pain in the left side. However, an x-ray film taken immediately following this fall had been entirely negative. The pneumothorax disappeared after several aspirations but the drawing and pulling pains persisted. It was worse in the evening after moving about all day and was temporarily relieved by bed rest as well as by intercostal nerve blocks.

In the following weeks a progressive deformity of the left hemithorax was noticed apparently caused by pleural contraction. It was so severe that he walked with his trunk bent over to the left and that he developed marked scoliosis with the convexity to the right. As this finding seemed to be an unusual sequela of a simple pneumothorax, an exploratory thoracotomy was advised in July 1953. This operation was preceded by bronchography and bronchoscopy which, however, yielded no additional information. The only finding at the time of the surgical exploration appeared to be an extreme fibrothorax which was treated with decortication. The pathologist noticed severe fibrous thickening of the pleura (Figure 3). The pericardium, the left lung and the subphrenic space were carefully palpated during the operation but no abnormality could be demonstrated. Unfortunately, these surgical efforts brought no relief and he then started to consult various chiropractors and cultists, but was unable to get help; neither did psychiatric consultation and shock treatment change his symptomatology. Contrary to expectations, the fibrothorax recurred and the scoliosis as well as the shrinking of the left hemithorax were soon worse than ever before. Physiotherapy and various muscular exercises did not improve the misery; neither did x-ray therapy of the bones and a brace prescribed by an orthopedic surgeon. In the meantime a considerable loss of weight and strength was apparent approaching the state of cachexia. This was to a large extent caused by the patient's attempt to relieve his "gas pains" by restriction of food as well as by excessive purging. After a neurosurgical consultation had yielded no new clues to his trouble, he underwent an exploratory laparotomy July 7, 1954, which revealed no pathology except masses of adhesions extending from the lower surface of the diaphragm to the spleen and the left flexure of the colon. These were severed but the course of the disease was not changed. The origin of his suffering remained obscure until August 19, 1954, when x-ray films revealed some osteolytic lesions as well as pathological fractures of the left lower ribs (Figure 2). Therefore, on September 14, 1954, another operation was performed (Dr. L. R. Lancaster) to obtain specimens of these destroyed bones. The microscopic examination showed "mesothelioma of the pleura" attached to the destroyed ribs (Dr. Ellen Forey, Pathologist, Hotel Dieu, Beaumont, Texas; Dr. Vernie A. Stembridge, University of Texas Medical School, Galveston, Texas) (Figures 4 and 5.) On November 26, 1954, he passed away in a state of extreme cachexia. Permission for an autopsy was not obtained.

Comment: It must be admitted that the presented case does not fulfill all the requirements of the diagnosis of primary mesothelioma of the pleura

because no autopsy was available excluding any other primary malignancy. Nevertheless, the latter disorder is unlikely on account of the surgical explorations, the pathological findings and the most complete clinical investigations. It may be argued that this tumor did not originate from the mesothelium itself but from the peripheral pulmonary tissue.² This possibility would be of much more concern to the pathologist than to the clinician. The latter is mainly interested in the fact that apart from the absence of respiratory symptoms no intrapulmonary tumor could be found on x-ray films before, during and after pneumothorax and with bronchoscopy, and palpation of the lung during exploration. Thoracotomy showed only an extensive pleural thickening with adhesions.

This growth and similar ones described in the literature should at least deserve special recognition as a clinical entity in order to facilitate the diagnosis even if their origin is uncertain. Any persistent, or recurrent pain and discomfort from one side of the trunk not explainable by abnormal findings of the thoracic cage, the intrathoracic and intraabdominal organs, the spine, or the central and peripheral nervous system should alert the investigator to the possibility of pleural mesothelioma. If the x-ray film of the chest is entirely negative one has to realize that the initial lesion may be in the hidden diaphragmatic or mediastinal section of the pleura. In addition, Rabin¹⁴ has emphasized that the majority of pleural x-ray shadows are caused by effusions or by inflammatory granulation tissue, and that even an extremely thickened and indurated pleura may fail to be visible on the x-ray film. Therefore, it seems plausible that in the initial stage a diffusely growing pleural tumor without effusion may not possess enough opacity to be recognized roentgenologically.

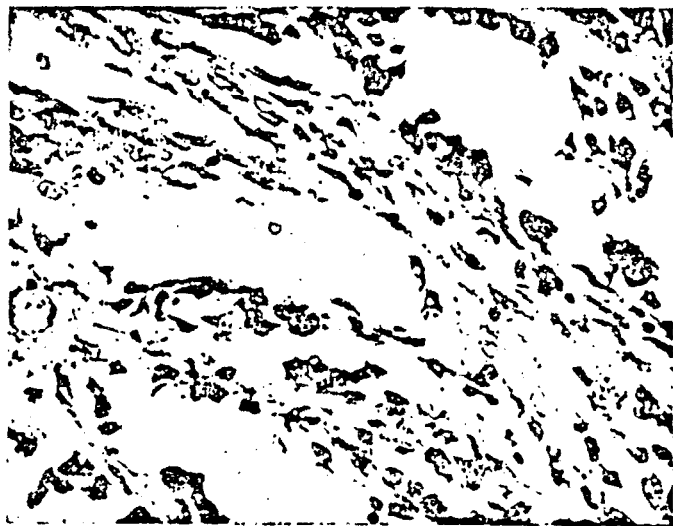


FIGURE 5: Section of second biopsy: alveolar pattern removed from skeletal muscle tissue. (X 473 magnification).

One could speculate about the connection between an infarction of the diaphragmatic surface of the heart and a tumor manifesting itself initially in the phrenicocardiac region. However, the heart attack had all the features of a classical coronary occlusion, and there was never any pericardial involvement in spite of repeated clinical, cardiographic and roentgenologic investigations. Therefore, one must assume that this association is fortuitous. Unfortunately, there was no clearcut clinical evidence of the beginning of the pleural tumor, because the various diseases leading to pain and discomfort in the left hemithorax and upper abdomen overlapped each other. Initially, the patient was suffering from gastrointestinal spasms, left flexure syndrome, food allergy and mucous colitis for several decades. Later, after the sudden coronary occlusion he seemed to have an anginal type of distress which could be easily correlated with the persistence of the electrocardiographic abnormalities. In the final stage all these disorders caused symptoms concomitantly with those originating from the tumor predominating.

Of considerable interest was the spontaneous pneumothorax as the initially presenting sign of the tumor. Such occurrence has apparently not been described in the literature. It is well known that spontaneous pneumothorax can occasionally appear in the beginning as well as during the course of a bronchogenic cancer, and that it is more frequently observed in metastatic pulmonary sarcomas.¹⁵ It is supposedly due to the infiltration of the lung bordering the pleura by malignancy followed by tissue destruction leading to bronchopleural fistula. A similar mechanism could be operating in mesothelioma which invades the parenchyma from the periphery.

In addition to the spontaneous rupture of the lung our case was distinguished from the majority of the mesotheliomas reported in the literature by the formation of a progressing constrictive pleurisy leading to a severe deformity of the chest as well as the whole body. Such a finding depends obviously on the character of the tumor: a solid growth of tubular and glandular elements will either appear as an expanding mass or as an intractable pleural effusion while the formation of mesenchymal tissue with innumerable fibrous layers will lead to chronic fibrothorax. The latter form of growth was present in our patient with such a marked degree of fiber production that at first the diagnosis of benign constrictive pleurisy and later of massive peritoneal adhesions was entertained and that the true character of the disease was not recognized until bone destruction occurred.

SUMMARY

A case of a malignant mesothelioma is described starting in the diaphragmatic portion of the pleura and invading the left hemidiaphragm and the peritoneal cavity. Malignant pleural tumor is a definite clinical entity even if its pathological classification remains a matter of speculation.

Persistent or recurrent discomfort from one hemithorax or one side of the epigastrium may be the initial symptom of such a growth in the absence of positive roentgenologic findings.

Spontaneous pneumothorax may occur at any time during the course of this disease or may be the initial feature.

Mesothelioma must be included in the differential diagnosis of solid intrathoracic masses, persistent pleurisy with effusion, and progressive fibrothorax.

RESUMEN

Se describe un caso de mesotelioma que empezó en la parte diafragmática de la pleura e invadió el hemidiafragma izquierdo así como la cavidad peritoneal. El tumor maligno de la pleura es una entidad clínica definida aunque su clasificación patológica siga siendo motivo de especulación.

Las molestias persistentes o recurrentes en un hemitórax o en un lado del epigastrio, pueden ser el síntoma inicial de tal neo formación en ausencia de hallazgos positivos a los rayos X.

El neumotórax espontáneo puede ocurrir en cualquier tiempo en el curso de esta enfermedad o puede ser el accidente inicial.

El mesotelioma debe incluirse en el diagnóstico diferencial de las masas sólidas intratorácicas o cuando hay pleuresia persistente con derrame y fibrotórax progresivo.

RESUME

L'auteur décrit un cas de mésothéliome malin qui, son point de départ étant localisé à la portion diaphragmatique de la plèvre, a fini par envahir l'hémi-diaphragme gauche et la cavité péritonéale. La tumeur pleurale maligne est une entité clinique bien certaine même si la classification pathologique reste matière à discussion.

La gêne continue ou intermittente d'un hémithorax ou d'un côté de l'épigastre peut être la manifestation initiale en l'absence de constatations radiologiques positives.

Un pneumothorax spontané peut survenir à tout moment de l'évolution et peut réaliser le symptôme initial de l'affection.

Le mésothéliome peut être compris dans le diagnostic différentiel des masses intrathoraciques, des épanchements pleuraux chroniques, et du fibro-thorax progressif.

ZUSAMMENFASSUNG

Beschreibung eines Falles eines malignen Mesothelioms, ausgehend vom Zwerchfellteil der Pleura mit Durchsetzung der linken Zwerchfellhälfte und der Bauchhöhle. Der bösartige pleurale Tumor ist eine wohl abgegrenzte klinische Einheit, auch wenn seine pathologische Einordnung eine Sache der Vermutung bleibt.

Anhaltende oder wiederkehrende Beschwerden auf einer Brustkorbhälfte oder einer Seite des Epigastriums können das Initial-Symptom eines solchen Wachstums sein bei Fehlen positiver röntgenologischer Befunde.

Ein Spontan-Pneumothorax kann zu jeder Zeit im Verlauf dieser Krankheit auftreten oder kann auch das initiale Merkmal sein. Ein Mesotheliom muss in die Differential-Diagnose einbezogen werden bei soliden intrathorakalen Massen, anhaltender Pleuritis mit Erguss und fortschreitendem Fibrothorax.

REFERENCES

- 1 Willis, R. A.: *Pathology of Tumors*, C. V. Mosby Company, St. Louis, Mo., 1948.
- 2 Anderson, W. A. D.: *Pathology*, 2nd edition, St. Louis, Mo., 1954.
- 3 Ackerman, L. V. and Regato, J. A. del: *Cancer, Diagnosis, Treatment and Prognosis*, C. V. Mosby Company, St. Louis, Mo., 1954.
- 4 Stout, A. P. and Himadi, G. M.: "Solitary (Localized) Mesothelioma of the Pleura," *Ann. Surgery*, 133:50, 1951.
- 5 Stout, A. P.: "Mesotheliomas of the Pleura and Peritoneum," *J. Tenn. Med. Assoc.*, 44:409, 1951.
- 6 Stout, A. P.: "Tumors of the Pleura," *Harlem Hosp. Bull.*, 5:54, 1952.
- 7 Clagett, O. T., McDonald, J. R. and Schmidt, H. W.: "Localized Fibrous Mesothelioma of the Pleura," *J. Thoracic Surg.*, 24:213, 1952.
- 8 Benoit, H. W. and Ackerman, L. V.: "Solitary Pleural Mesotheliomas," *J. Thoracic Surg.*, 25:346, 1952.
- 9 Bogardus, G. M., Knudtson, K. T. and Mills, W. H.: "Pleural Mesothelioma," *Am. Rev. Tuberc. and Pul. Dis.*, 71:280, 1955.
- 10 Stout, A. P. and Murray, M. R.: "Localized Pleural Mesothelioma: Investigation of its Characteristics and Histogenesis by Method of Tissue Culture," *Arch. Path.*, 34:951, 1942.
- 11 Yesner, R. and Hurwitz, A.: "Localized Pleural Mesothelioma of Epithelial Type," *J. Thoracic Surg.*, 26:325, 1953.
- 12 Sharkey, B. E.: "Malignant Mesothelioma of the Pleura," *Med. J. of Australia*, 1:706, 1954.
- 13 Ross, C. A.: "The Coin Lesion," *Dis. Chest*, 28:114, 1955.
- 14 Rabin, C.: *X-ray Diagnosis of Chest Diseases*, The Williams and Wilkins Company, Baltimore, 1952 (pp. 191 S and 191 T).
- 15 Heimlich, H. J. and Rubin, M.: "Spontaneous Pneumothorax as a Presenting Feature of Primary Carcinoma of the Lung," *Dis. Chest*, 27:457, 1955.