Tumors of the Pleura

LOUIS L. FRIEDMAN, M.D., F.C.C.P.
Birmingham, Alabama

Tumors of the pleura may be primary or secondary. Primary tumors are exceedingly rare while secondary tumors are not uncommon. The most important and only primary malignancy of the pleura is the mesothelioma. In the 19th century the term, "tubercle-like lymphadenoma," was used to describe this tumor. Later the name, "endothelioma," was proposed for this malignancy because it was ascribed to a vascular origin. Recent reliable investigations together with the fact that the pleura is a mesodermal derivative have established the term mesothelioma as a more descriptive and appropriate identification of this tumor.

Epithelial and mesenchymal elements are both present in the pleura. The free surface is lined by a single layer of mesothelial cells which rest on a delicate elastic membrane. Beneath the membrane is found the loose connective tissue stroma. This is composed of collagenous and elastic fibers dispersed at various angles but generally parallel to the free surface of the pleura. Fibroblasts and macrophages constitute the predominant cellular elements. The subserous layer of tissue is responsible for the close adherence of the pleura to the related underlying structures. Tumors arising in the pleura will, consequently, display both epithelial and mesenchymal characteristics. Mesotheliomas are ordinarily composed of large epitheloid cells separated by collagenous fibers of tumor cell origin. The cellular elements have a tendency to arrange themselves as alveolar rests or rows. Unfortunately, not all pleural mesotheliomas present this typical histopathologic pattern. Pleomorphism and multidirectional lines of evolution complicate the proper identification and classification of this new growth. This tendency to frequent deviation has been paralleled by equally numerous attempts by well-intentioned investigators to prove the existence of more than one type of primary pleural malignancy. The problem of pleural malignancies, consequently, is clouded and confusing. Conclusive investigation and authoritative evaluation of this controversial problem have been limited by the paucity of cases available for study. Only one, and probably less than one, case in every one thousand postmortem examinations is a proved pleural mesothelioma. If primary malignancies of the pleura do occur, the weight of the available evidence supports the contention that they are all mesotheliomas with inherent possibilities of wide structural variation.
This opinion, however, is not shared by all clinicians and pathologists. There is a sizable group of reliable investigators who do not admit the possible existence of primary tumors of the pleura. This contention is a very disarming possibility when one considers the large volume of literature which has been written on the subject of pleural mesotheliomas by innumerable, usually reliable investigators. It is true, nevertheless, that many pleural tumors diagnosed originally as mesotheliomas are proved eventually to be metastatic lesions from the underlying bronchopulmonary tissue or neighboring thoracic and even more distant organs. A small primary malignant nodule in the lung is not infrequently the source of widespread pleural involvement. Unless the pulmonary tissue is examined diligently in all cases of suspected pleural mesothelioma, a small primary tumor nodule may be overlooked (Figs. 1 and 2). A high index of suspicion should be maintained at all times regarding this possibility in order to avoid erroneous diagnoses of pleural mesothelioma. Primary malignancies frequently arise in relation to the parietal pleura. They have their origin in the fascia of the intercostal muscles, nerve sheaths and other thoracic structures. Angiosarcomas, lipomyxosarcomas, neurosarcomas, round-cell or spindle-cell sarcomas, rhabdomyosarcomas or chondrosarcomas which arise from these tissues may be attributed erroneously to a pleural origin because of the intimate relationship of the parietal pleura to the structures of the thoracic wall. The known pleomorphic potentialities of pleural mesothe-

FIGURE 1: A diagnosis of pleural mesothelioma was considered in this instance based on the above histopathologic pattern observed in a section of tissue obtained from the region of the pleura. Recognizing the possibility of an erroneous conclusion, innumerable microscopic sections of the underlying bronchopulmonary tissue were examined. After diligent study, the lesion in the pleura was proved to be metastatic from a primary bronchogenic carcinoma. (Courtesy Dr. Joseph P. A. MacManus, Birmingham, Alabama).
llomas contribute to this pitfall in diagnosis. After careful consideration, this author is satisfied to concur in the opinion that such an entity as pleural mesothelioma does exist.\(^6\)\(^7\) That it probably occurs much less frequently than one in every one thousand postmortem examinations also appears to be a valid assumption.

There are no primary benign tumors of the pleura. Just as the tumors which arise in relationship to the parietal pleura are malignant, those which occur in association with the visceral pleura are ordinarily benign. Fibromas, lipomas and chondromas have their origin in the subserous connective tissues. Giant sarcomas which arise in relation to the visceral pleura do not possess metastatic or invasive properties.\(^5\) They grow slowly but may attain tremendous size. Primary tumors which arise in relation to the visceral pleura, with the possible exception of giant sarcomas, are asymptomatic. They are very small and usually discovered only by accident during surgical procedures or postmortem examinations. Surgical excision of these growths is the method of treatment.

Metastatic malignancies of the pleura are common. Any tumor which is capable of producing metastases may involve the pleura. Metastatic pleural lesions are most frequently secondary to the underlying bronchopulmonary tissue. Tumors of the breast also involve the pleura with great frequency. Malignant lesions of the esophagus are a frequent source of metastatic pleural involvement. Tumors of the other thoracic structures, stomach, adrenals, prostate, thyroid, pancreas and uterus are additional common sources of pleural metastases. Whenever a pleural malignancy is discovered it is imperative that these and other sites in the body be carefully scrutinized for a possible source of metastasis.

Primary, or metastatic malignant, lesions of the pleura may be

![Microscopic section correctly identifying this tumor as a bronchogenic carcinoma.](image-url)
diffuse or localized. Either variety produces hemorrhagic pleural effusions. Any unexplained pleural effusion, whether hemorrhagic or otherwise, however, in individuals past the age of 40, should arouse strong suspicions of a possible underlying malignant process. The chemical, physical and cytologic characteristics of the fluid depend upon the nature of the malignancy, duration, location and extent of pleural involvement. Occasionally the effusion develops the characteristics of a true hemothorax. The tendency to rapid reaccumulation following thoracentesis is a regular characteristic of effusions produced by malignant diseases of the pleura. Following the detection of hemorrhagic pleural effusion, indicated clinical and laboratory study to establish the correct etiology is in order. Since this discussion is concerned only with hemorrhagic effusions due to malignancies, those due to other causes are mentioned only for the sake of completeness. However, one should bear in mind that a hemorrhagic pleural effusion is not an uncommon manifestation of such clinical entities as pulmonary infarction, congestive heart failure, thrombocytopenic purpura hemorrhagica, cirrhosis of the liver, pneumonia, rheumatic fever, nephritis or pulmonary tuberculosis. Under certain conditions any pleural effusion may become hemorrhagic. Primary or metastatic malignancies of the pleura, however, are responsible for about 85 per cent of all hemorrhagic effusions. Although roentgenographic and fluoroscopic examinations of the chest are without rival in detecting pleural reactions, accurate identification of the etiologic factor depends upon other clinical and laboratory studies.

Diagnostic thoracentesis should be performed as soon as the presence of pleural effusion has been determined. An anticoagulant should be added to the aspirated material to avoid clotting. Complete withdrawal of the effusion should be attempted in order to facilitate more satisfactory roentgenographic examination of the underlying lung. There is a tendency among physicians to limit empirically the amount of fluid withdrawn during one thoracentesis. The author has practiced unlimited aspiration without any ill effects. Should the symptoms of dyspnea, cough, pulling sensation or pain in the chest develop during the procedure, the introduction of a small quantity of air usually suffices to control these manifestations of changing intrathoracic pressures and position of the heart and great vessels. Aspiration of the effusion may then be continued until all the fluid is withdrawn repeating small injections of air as necessary. The apprehensive patient may be calmed with suitable doses of a barbiturate or other sedative prior to thoracentesis. Production of pneumothorax in the presence of a hemorrhagic pleural effusion due to a malig-
nancy is actually desirable for diagnostic purposes. Introduction of air should be minimal or avoided after the diagnosis is established. Since bloody effusions are excellent culture media for bacteria, strict asepsis must be practiced in performing each thoracentesis. To avoid troublesome complications such as pyo-hemothorax, penicillin or any other suitable antibiotic agent should be instilled into the pleural cavity and along the needle tract when thoracentesis is completed.

A minimum of 5,000 to 6,000 red blood cells per cubic millimeter is required for the gross recognition of hemorrhagic effusions. The color of the fluid depends upon the number of red blood cells; their condition and length of confinement in the pleural cavity. Degeneration of the red corpuscles is followed by changes in the hemoglobin which may produce a brown or deep amber-colored effusion. Eosinophil cells may be present in unexplainably large numbers. Examination of the circulating blood in these instances may also reveal an absolute eosinophilia. When Hodgkin's disease is being considered, this finding may be misleading. The peripheral blood study is helpful, however, in cases of leukemia involving the pleura. Determination of the specific gravity and chemical analysis of hemorrhagic pleural effusions due to a malignancy are of no diagnostic value. The fluid may be thin and easy to aspirate or very thick and gelatinous and difficult to remove. Cytologic examination of properly prepared specimens of the hemorrhagic fluid by a competent histopathologist is the most important diagnostic study. Frequently malignant cells will be detected in the aspirated material. Tumor identification usually follows. Unfortunately, even in the presence of a known malignancy, malignant cells cannot always be detected in the pleural fluid in spite of repeated diligent study.

If identification of the tumor does not follow pleural fluid examination, other diagnostic studies should be considered. A careful search for enlarged lymph nodes or overt tumor growths in the immediate thoracic or more distant regions of the body may be fruitful. The breast, thyroid, uterus and prostate deserve special attention. Surgical biopsy of an abnormal lymph node or other lesion may provide the diagnosis after histopathologic study. Aspiration biopsies of the pleura are generally failures. Punch biopsies with a Vim-Silverman needle are more successful in these instances. Larger and more satisfactory pieces of tissue are made available for study by this latter procedure. Many condemn the use of aspiration or punch biopsies because of the possible danger of stimulating or actually producing metastatic lesions. In the presence of malignant pleural effusions one need not hesitate to perform either an aspiration or punch biopsy of the pleura.
This observer has heard and read many reports of secondary seeding and metastasis following either of these procedures but has never experienced or witnessed these misfortunes. Furthermore, how much significant harm can one produce in the presence of either a primary or secondary pleural malignancy? Actually, and with rare exceptions, determination of an accurate diagnosis in these instances is of academic interest only.

Since malignant tumors of the pleura are frequently secondary to primary lesions of the bronchopulmonary tissue, bronchoscopic examination should be performed routinely. The responsible primary tumor may be visualized. Specimens of bronchopulmonary secretions and frequently biopsy material may be obtained in this fashion for histopathologic review. Additionally, careful study of the position and configuration of the bronchoscopically accessible portions of the tracheo-bronchial tree may be of valuable diagnostic assistance. Bronchography should be used for indirect visualization of those portions of the tracheobronchial network which are inaccessible for direct bronchoscopic study. Carefully conducted x-ray and fluoroscopic examination of the lungs in various positions are especially helpful. Examination of the gastrointestinal tract with an opaque material may reveal the source of pleural metastasis. A high serum acid phosphatase level will incriminate the prostate. Alkaline phosphatase determination is of no special value. If existence and identification of a malignancy is not established or confirmed by the enumerated procedures, one should not hesitate to recommend thoracoscopic examination of the pleura and, preferably, a diagnostic thoracotomy. Many other diagnostic procedures may be attempted. In this presentation, however, only those procedures which are most frequently indicated, practicable and generally useful have been discussed and evaluated.

Since mesothelioma is considered the only primary malignancy of the pleura, it deserves some special attention. Pleural mesotheliomas may occur in all ages, but are most frequent in the adult age group.° Males are affected twice as often as females. Both hemithoraces are probably involved with equal frequency but opinion is divided on this point.°° The onset of the tumor is insidious. Nonproductive cough and pain in the chest are early symptoms. Fever becomes a manifestation when secondary infection supervenes but may occur without this complication. Later, the cough may acquire expectorant qualities. Massive accumulation of a hemorrhagic pleural effusion occurs with distressing regularity. Dyspnea ensues and quickly assumes the position of paramount concern among all other symptoms. The patient becomes cachetic with startling rapidity. Loss of weight, anemia
and weakness are typical observations. Dependent edema may occur at any stage of the illness. The panorama of symptoms changes frequently to correspond with the rapid growth of the tumor. Frequent thoracenteses are indicated for the palliative relief of dyspnea. Resistance to the introduction of the aspirating needle is usually very marked. As previously indicated, the benefits of thoracenteses are very temporary since the fluid re-accumulates rapidly. Occasionally daily thoracenteses are necessary to relieve the subsequent cardiorespiratory embarrassment. The fluid is easily aspirated early in the illness but gradually it becomes thicker and more difficult to remove. Re-accumulation has been observed to occur less rapidly after the pleural fluid assumes a thicker character. There is no effective treatment for pleural mesothelioma, or any other malignant involvement of the pleura. Metastases are common and the tumor may extend to involve the other pleural cavity, pericardium, peritoneum and capsules of abdominal viscera. Patients usually die within six to twelve months following detection of the tumor.

**SUMMARY**

1) The controversial subject of pleural tumors has been reviewed.
2) Although very rare, mesotheliomas are probably the only primary pleural tumors.
3) Malignant tumors of the pleura are predominantly metastatic or due to tissue continuity.
4) Clinical and laboratory aids most useful for accurate identification and evaluation of malignant growths of the pleura have been enumerated and discussed.

**RESUMEN**

1) Se revisa el asunto de la controversia de los tumores de la pleura.
2) Aunque muy raros, probablemente los mesoteliomas son los únicos tumores primarios de la pleura.
3) Los tumores malignos de la pleura son predominantemente metastáticos o debidos a continuidad tisular.
4) Se enumeran y se discuten los procedimientos de laboratorio y los clínicos que son útiles auxiliares para la identificación exacta de las neoplasias malignas de la pleura.

**REFERENCES**