Mesothelioma of the Pleura

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History

Wagner in Germany in 1870 was the first to describe a tumor with the characteristics of a pleural mesothelioma and to recognize it as a pathological entity. He called it “a tubercle-like lymph adenoma.” From the time of this first description there has been a controversy among medical authorities until recently relative to the origin, histology and nomenclature of this disease. It has been variously called pleural carcinoma, mesothelioma, endothelial carcinoma, mesothelial carcinoma, endothelioma, carcinomatodes, adeno - endothelioma, sarco - endothelioma, perithelioma, lymph-angio - endothelioma, fibro - endotheliosis of pleura, lymphangitis proliferans and Cornil and his co-workers in France have suggested the name, pleuroma.

Although there have been many opinions, some authors even denying the existence of a primary pleural neoplasm, the names have narrowed down until the most common ones in use are: 1) Endothelioma, by those who believe the tumor originates from the endothelium of the pleural lymphatics and 2) Mesothelioma, by those who maintain the tumor originates from the lining epithelium of the pleura, since the latter are derived from the mesoderm in the embryo.

Ewing as late as 1940 states: “It is possible that two groups of serous endotheliomas should be recognized, one invasive with metastases and derived from the endothelium of the lymph spaces and another superficial, nodular or papillary, and originating from the lining cells.”

The confusing elements in the tumor seemed to be the mixture of epithelial appearing cells and connective tissue. The epithelial appearing cells at times arrange themselves as, and take on, glandular characteristics. The connective tissue stroma varies in amount and density and shows areas of hyalinization. How could a cell which is primarily epithelial in nature take on glandular and connective tissue elements?

Maximow demonstrated in 1927 that the covering cells of the serosal surfaces are pleomorphic and when cultured outside the body, in vitro, assume a fibroblastic nature and form collagen fibres. Twenty years later Maximow and Bloom stated, “The mesothelium is a simple, squamous cell layer which covers the
surface of all the serous membranes (peritoneum, pericardium, pleura). Its elements have the classical structure of true squamous epithelial cells. The prospective potencies of these elements are of dual nature—epithelial and fibroblastic. In tissue cultures the mesothelium of mammals may show for a certain time a purely epithelial type of growth in islands and sheets of polyhedral flattened cells. Tumors of epithelial character may develop from the mesothelium and, possibly, structures similar to uterine glands. On the other hand, in inflammation the mesothelial cells, after a period of contraction and of rounding off, finally give rise to typical fibroblasts, i.e. to connective tissue cells. The same occurs in tissue cultures. They are never transformed into ameboid phagocytes."

Young⁴ has shown that the pleural serosal cells of rabbits can undergo extensive hyperplastic and metaplastic proliferation, forming gland-like spaces lined with swollen epithelial-like cells.

Boyd⁷ now summarizes tumors of the pleura as “primary and secondary. The former are rare, while the latter (metastatic carcinoma) are fairly common. Primary tumors may be divided into two main groups, localized and diffuse. Localized tumors are of many histological types, but have one characteristic in common, in that they arise from the tissues beneath the surface lining of the visceral or parietal pleura, while the diffuse tumors arise from the surface lining, and are commonly known as an endothelioma. They would be better called mesothelioma, as the surface cells are mesothelial in character, the lining of the pleural cavity being derived from the coelomic epithelium, which in turn is developed by splitting of the mesoderm.

The diffuse tumor may present characteristics of either epithelial or connective tissue due to the varied potentialities of the mesothelial cells. Microscopically the tumor consists of large spherical cells arranged in solid masses and columns, often within the lumen of lymphatics they may have a definite glandular formation as in adenocarcinoma. The stroma is usually fibrous and abundant.”

Case Report

F.M., a 62 year old male passenger from France was admitted to the hospital January 8, 1949. He complained of cough, profuse expectoration, shortness of breath, pain in the left side of the chest, weakness and hoarseness. His past history was irrelevant, except that he had a dry cough for a number of months before departure from France 10 days before. Shortly after departure he developed a cold and his cough became worse. At this time he began to expectorate a great deal, his throat felt tight and he became hoarse.

Physical examination: The patient was an undernourished, small male, who appeared acutely ill. He was hoarse and dyspneic and coughed fre-
quently making a loud, hollow sound. His temperature was 100 degrees F., pulse 90, respirations 30 and blood pressure 105/80. His color was good. Examination of the head, including the eyes, ears, nose, pharynx and tongue was negative. He had many loose and carious teeth. The thyroid gland was normal in size and consistency. There was a round medium soft mass about the size of a hazelnut in the left anterior triangle of the neck, just above the medial portion of the left clavicle and under the distal end of the sternomastoid muscle. The trachea was in the midline.

The chest was symmetrical in form, but the expansions were abnormal, the left being greatly diminished and the right increased above normal. On the left side of the chest high-pitched bronchial breath sounds were heard over the upper lobe, with frequent rhonchi, and loud moist rales over the distal half of the chest posteriorly. Voice sounds and tactile fremitus were diminished, and there was marked dullness to percussion throughout the entire left side.

The right chest findings were normal. The abdomen showed a fullness in the upper part with no tenderness or masses. The skin, extremities and prostate were normal. The neurological examination was negative. The left vocal cord was paralyzed.

Laboratory findings: Sputum smears and cultures for acid-fast bacilli were negative. Other organisms found in the sputum were streptococcus, staphylococcus and pneumonococcus. The red cell count was 4,000,000 per cu. mm., hemoglobin was 80 per cent (Sahli) and the white blood cell count was 15,100 per cu. mm. The differential count showed 76 per cent neutrophiles, 1 eosinophil, 19 small mononuclear lymphocytes, 1 large mononuclear lymphocytes, and 3 per cent transitional. The urine showed no abnormality. Serological tests for syphilis were negative. The sedimentation rate was 30 mm. in one hour (modified Cutler). A chest x-ray film showed (Figure 1) a rather homogeneous haze in the upper two-thirds of the left lung field. There were mottled densities in the lower third of the lung field and a round density measuring approximately 3 cm. in diameter in the lateral aspect of the left base. The left half of the diaphragm was smooth. There was slight blunting of the left costo-

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21191/)
phrenic sinus. The trachea was approximately in the midline. The right
lung field was clear and the right half of the diaphragm was smooth.
The right heart border was normal in appearance. The left border was
obscured by adjacent pulmonary densities.

A tentative clinical diagnosis of inoperable neoplasm of the left lung
with secondary infection was made. Following administration of 40,000
units of penicillin every three hours for a few days, his breathing was
less labored and he attended to his own personal hygiene. His appetite
improved and he had less pain in the chest, but weakness continued and
his temperature continued to spike to 102 degrees F. He had a loud deep-
toned cough and expectorated about six ounces of white muco-purulent
sputum a day. Papanicalaou stains of sputum on two occasions were
negative for malignant cells.

On January 19, 1949 more chest x-ray films were inspected. The lateral
projection revealed a multi-lobulated mass in the upper two-thirds of
the left lung field, which extended from the posterior through the middle
into the anterior part of the chest.

On January 19, 1949 an 18 gauge needle was passed into the left sixth
intercostal space in the posterior axillary line. The needle at full length
could be moved in all directions without meeting resistance. There
seemed to be a pleural space but no fluid could be aspirated, only air.
The plunger of the syringe was withdrawn without resistance. The manom-
eter was attached, but the reading was zero. No biopsy was done be-
cause no solid tissue was found.

On January 21, 1949 an 18 gauge needle was passed into the left sixth
intercostal space in the mid-axillary line and 2 cc. of iodized oil and
5 cc. of 1 per cent solution of gentian violet were injected. No dye was
ever seen in the sputum.

The patient’s condition gradually became worse; he did not seem to
have much pain, but he became weak, cyanotic, with fast and weak pulse
and he expired on January 30, 1949 after 22 days in the hospital.

Pathology

The necropsy was performed by Dr. Louis Winkelman. The body
showed evidence of recent weight-loss. The skin was clear. The
gross findings were limited to the left thorax. The left lung was
atelectatic and retracted from the chest wall in the lower two-
thirds. The upper third of the lung was adherent to the chest
wall and there was about 300 cc. of brownish fluid in the pleural
cavity.

The pleura overlying the left lung was strikingly white and
markedly thickened. It was 1 cm. thick on the lateral wall and
at least 2 cm. in the interlobular fissure, moderately firm in con-
istency and exuded a whitish-grey fluid on pressure. This ab-
normal pleura extended over the apex and inferiorly towards the
lower lobe, where it appeared normal.

On removing the lung from the chest it was found that the
parietal pleura over the apex was involved and fused with the
visceral pleura. These were fused with four lymph nodes in the
superior aperture of the thorax and lower part of the neck. The
thickened pleura in other parts of the chest fused with large firm white lymph nodes in the hilar region, and could not be removed from these nodes. The thickened pleura was peeled from the apex and lateral surface of the lung. Although the pleura was smooth on its outer surface, the inner surface was nodular and indented the lung at numerous points as much as 2 cm. in depth. The lung was sectioned and the bronchial nodes were large and white.

The right lung was normal in appearance and consistency. All other organs were essentially normal. No metastases were found.

Microscopic examination showed that the pleural tumor was composed of two types of tissue, which followed a definite pattern. Varying sized nests of epithelial-like cells were seen enclosed within strands of connective tissue stroma (Figure 2). These cells were markedly basophilic, their nuclei varying from ovoid to round in shape. They often contained prominent nucleoli, occasional mitotic figures, and little cytoplasm. In some instances, a nucleus made up the entire cell, so no cytoplasm was seen. These cells were not arranged in any definite pattern and showed no signs of polarity. The connective tissue showed strands of collagen fibers and some hyalinization (Figure 3).

Sections of the bronchial, tracheal, and cervical lymph nodes showed a characteristic appearance. The architecture of the lymph follicle was still maintained, but by far the greater portion of the lymph follicle was replaced by malignant cells. A few tumor cells
had entered the bronchial muscles, but they were not distorted. Malignant cells were seen to reach the bronchi.

In some areas of the lung lymphatics the picture of necrosis and secondary infection was present, and there were few nests of discernible malignant cells. An unusual feature was seen in some of the sections, especially near the hilar region. Here irregular dark blue staining non-cellular areas were present. Those appeared to represent heterotopic calcification, a feature occasionally seen in endothelioma and described as osteoid production. The remainder of the lung showed areas of atelectasis and bronchopneumonia. No tumor cell was seen in the lung parenchyma.

Pathological diagnosis: Endothelioma of the left pleura with involvement of the left bronchial, hilar, and cervical lymph nodes.

Discussion

Every case of mesothelioma of the pleura that has been reported in the literature has been fatal. It is a rare malignant neoplasm occurring in about 1:1 cases per 1000 necropsies, and it occurs most frequently between the ages of 40 and 60 years. The right and left pleura are affected with equal frequency, but the rates of females to males are 1:1.8 according to Saccone and Coblenz.8

Clinical signs and symptoms as explained in the literature are most confusing. The onset of the disease is described as gradual, its duration is from six to nine months, only rarely over two years.
from the time of recognition. Our case and the one presented by Coulter was more rapid.

Cough seems to be a constant symptom. At first it may be dry and mild, and may remain this way throughout the course of the disease. The cough may, however, become hard, frequent, and produce a hollow sound. Stridor may develop due to the gradual pressure on and obstruction of the bronchi. Expectoration may be moderate, sometimes gelatinous in nature, depending upon the extent of the disease. In our case the expectoration was profuse, heavy, white, muco-purulent because of the secondary infection. Sputum is not blood-streaked and hemoptyisis is not the rule.

The temperature is usually normal. Where there is a secondary infection, as in our case, it will rise depending upon the severity and extension of the infection. Banyal and Grill presented a case with irregular, remittent fever, not unlike that seen in pulmonary tuberculosis. Our case was similar. Penicillin gave some temporary relief. Pain is pleuritic in type and may be severe over the affected side. Our case was similar in this respect to the one described by Coulter. There was little pain even with the secondary infection.

Dyspnea seems to be a constant symptom. It was severe in our case. The disease binds the lung with a constricting action, and prevents proper expansion. The elasticity of the pleura is gone. Expanding and enlarging lymph nodes produce obstruction of the bronchi with resulting obstructive emphysema and finally atelectasis. The function of the lung is lost and pulmonary insufficiency is pronounced. In our case the expansion of the chest wall on the affected side was greatly diminished. After our case received penicillin a few days, dyspnea became temporarily improved. The infection was apparently adding to the pulmonary insufficiency. Although the right lung was not involved cyanosis developed toward the last. His appetite remained fairly good until a few days before death. No other system seemed to be greatly affected by the disease; however, he may have been developing cor pulmonale.

Pleural effusion is given as one of the first signs in most of the cases reported. X-ray inspection of the chest gives a picture of pleural effusion although there may be no fluid. The thickened pleura is radio opaque. In our case the film showed a haze, except over the lateral part of the left base. Coulter found fluid and replaced it with air so as to obtain better x-ray visualization of the tumor. He recovered malignant cells from the fluid. Dyspnea was not relieved by aspiration and fluid reformed quickly.

A diagnostic feature according to Welsman is that the aspirating needle encounters great resistance in passing through the pleura. In our case, on two occasions a number 18 gauge needle
met no resistance. A biopsy of the node on the anterior triangle of the neck would have revealed the pathology as this node (when removed at necropsy) had the same structure as the bronchial and hilar lymph nodes. Papanicolaou stains may show malignant cells in the sputum, as this neoplasm does break into the bronchi.

There may be clubbing of the fingers and unilateral or bilateral vocal paralysis. Banyal and Grill\(^1\) described a condition of gradual compression of the larger thoracic veins, which was manifest by the appearance of dilated and enlarged skin veins over the abdomen on the same side, which carried the blood in reverse from the chest indirectly to the inferior vena cava.

X-ray inspection may not be helpful in the early stages when findings suggest pleural reaction with or without fluid. The aspiration of fluid and induction of artificial pneumothorax may aid diagnosis. It may show multiple smooth tumors, nodules of various sizes, and thicknesses. A small amount of iodized oil may help and gentian violet may determine whether broncho-pleural fistula is present. Later, the x-ray film may show evidence of markedly collapsed lung with atelectasis, displacement of the heart, shift of the mediastinum, enlarged hilar and mediastinal lymph nodes. The diaphragm may be affected, becoming immobilized and frequently depressed. Pulmonary abscess may develop from secondary infection.

Laboratory findings are not consistent. Anemia may or may not be present. The hemopoietic system may respond to the anoxia with increase in the number of red blood cells. The red cell sedimentation rate is increased. It is usually increased in pulmonary tuberculosis and pulmonary neoplasms.

Bronchoscopy will probably not be helpful in the early stages. It might show bronchial obstruction later, due to the enlarged lymph nodes. Exploratory thoracoscopy, however, should reveal the tumor. Sauerbruch\(^12\) states, "it is just as reasonable to establish a diagnosis in the chest by exploratory operation as it is to explore the abdomen." Biopsy of enlarged nodes near the tumor or even far from it may reveal the type of tumor.

Treatment is usually symptomatic. Deep x-ray irradiation has been tried, and found ineffective. Surgery may be of some avail if an early diagnosis could be made. There is no evidence to show that any of the drugs or radioactive substances used against neoplasms have been administered in this disease.

The findings at necropsy are fairly characteristic. There is the white thick evenly distributed pleura with nodular formation with metastases to the bronchial, axillary, cervical, mediastinal and retroperitoneal lymph nodes. The lung is not involved, but compressed and atelectatic. Cases have been reported showing metas-
tases to the brain, kidney, adrenals, thyroid, bone and Stout and Murry⁰ had a case where the malignant cells infiltrated the head of the pancreas and right ovary. In most cases, however, there is lymphatic infiltration, and little disturbance of other tissues.

Microscopic findings are less specific, but should be easily interpreted by a competent pathologist. The carcinomatous and sarcomatous elements in one tumor may be confusing. The tumor cells may vary from medium size, round to large, polygonal and medium-sized columns and are arranged in nests and broad sheets within connective tissue stroma. They may take the form of adenomatous tissue. The cytoplasm and chromoplasm of the tumor cells stain acidophilic and large nuclei are seen, but mitotic figures are often wanting.

SUMMARY

A case of mesothelioma of the pleura is presented together with a discussion of the clinical aspects of this disease.

RESUMEN

Se presenta y se discute un caso de mesotelioma de la pleura.

REFERENCES