Primary Mesothelioma of the Pericardium

By John Thomas, M.D., and James M. Phytyon, M.D.

Mesotheliomas of the pericardium are one of the causes of sanguineous pericardial effusion. Clinical and pathologic features of a case of this rare condition are presented. Certain clinical manifestations and laboratory findings that may serve as a basis for future antemortem diagnosis are emphasized.

A patient with a pericardial effusion may frequently present a diagnostic problem. A primary malignancy of the heart or pericardium is one of the rare causes of such an effusion. Lymburner at the Mayo Clinic reported an incidence of .05 per cent in 8,500 consecutive autopsies. Mesotheliomas compose only a small percentage of the primary tumors of the heart and pericardium. Dawe, Wood, and Mitchell in a recent and excellent review of the literature could find only 24 cases that conformed to the category of primary mesothelioma of the heart or pericardium.

This case of a mesothelioma of the pericardium is reported because it is typical of a rare condition, there is no doubt regarding the origin of the tumor, and in the hope that this clinicopathologic picture of persistent bloody pericardial effusion may serve as the basis for future antemortem diagnoses.

Case Report

K. C., a 78-year-old retired fireman, entered the George W. Hubbard Hospital on November 3, 1955, complaining of dyspnea of about 3 months' duration. He had been well until about 5 or 6 months prior to admission, when he began to tire easily. At the onset there was only exertional dyspnea; later, attacks of wheezing and a dry hacking cough. Two weeks before admission orthopnea and paroxysmal nocturnal dyspnea began. Very slight exercise precipitated attacks of breathlessness. At that time he also developed swelling of the abdomen and edema of the feet and legs. He lost approximately 18 pounds during his illness.

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In the past, he had always been in good health. There was no known contact with tuberculosis.

Physical examination revealed a well developed, well nourished patient who appeared younger than the stated age. He was dyspneic, and there was an occasional dry cough.

The blood pressure was 130/100 mm. Hg. The pulse was 96/min. and weak. The neck veins were moderately distended and the chest was well developed and muscular. The area of cardiac dullness was increased both to the left and right of the sternum. The heart sounds were muffled, especially at the apex, and no friction rub or murmurs were heard. There was sinus rhythm with an occasional premature beat. A moderate number of moist and also dry rales were heard at the bases of both lungs. There were dullness and bronchial breathing posteriorly at the angle of the left scapula. Examination of the abdomen revealed a suggestion of ascites. The liver edge was palpable below the right costal border and it was firm, smooth and nontender. There was pitting edema of the feet and legs. There were freely movable nodes about 0.5 cm. in diameter in both axillae. The inguinal nodes were slightly enlarged, firm, and discrete. The cervical lymph nodes were not enlarged.

Laboratory Findings. The hemoglobin was 13.7 Gm./100 ml.; the hematocrit value was 45 volumes per cent; the white blood cells numbered 14,300/mm.4, neutrophils 67, lymphocytes 26, basophils 1, and monocytes 6 per cent. A urinalysis was not remarkable. A serologic test for syphilis (VDRL) was negative. The nonprotein nitrogen was 41 mg./100 ml.; blood sugar was 130 mg./100 ml.; chlorides, sodium, and potassium were normal. Sputum cultures and smears were negative for tubercle bacilli. The venous pressure was 240 mm. of water and the circulation time was 22 sec. by the arm-to-tongue (Decholin) method.

X-ray examination of the chest revealed massive enlargement and globular configuration of the cardiac shadow, slight congestion in both lung bases, and left pleural effusion (fig. 1). There was a suggestion of pericardial calcification.

The initial electrocardiogram showed low voltage T waves in all leads. Later there was a decrease in voltage of the QRS complexes. The histoplasmin and coccidiodin skin tests were negative and the tuberculin skin test was moderately positive.
Hospital Course. The patient was treated for congestive heart failure. The following morning 300 ml. of serosanguineous fluid were aspirated from the left pleural space. Analysis of the fluid revealed a specific gravity of 1.013; white blood cells numbered 1,077/mm.³, with 92 per cent lymphocytes and 8 per cent neutrophils; protein content was 6.5 Gm./100 ml.; chlorides were 97 mEq./L.

Three days after admission the signs of cardiac compression had increased. A pericardial paracentesis yielded 700 ml. of sanguineous fluid containing large amounts of fibrin. Air was injected into the pericardial sac. Examination of the pericardial fluid revealed the specific gravity of the centrifuged specimen to be 1.021, of the whole fluid 1.028; the white blood cells were 5,550/mm.³ with 9 per cent neutrophils and 91 per cent lymphocytes, and the hematocrit level was 15 volumes per cent; the hemoglobin was 5.53 Gm., the protein was 8 Gm., the sugar was 96 mg./100 ml., and the chlorides were 92 mEq./L. The patient's symptoms were greatly relieved by this pericardial paracentesis.

Radiologic examination of the chest then revealed a hydropneumopericardium, slight left pleural effusion, and plural thickening at the right base (fig. 2). There was no parenchymal lesion of the lungs and no hilar adenopathy. Because of the lymphocytic nature of the fluid, the thickening and questionable calcification of the pericardium, and the pleural thickening a tentative diagnosis of tuberculous pericarditis was made. This diagnosis was supported somewhat by a report that 1 acid-fast bacillus was seen on direct smear of the pericardial fluid. The administration of isonicotinic acid hydrazid and para-aminosalicylic acid was begun.

The rectal temperature ranged from 99 to 101 F. The fluid in the pericardial sac reaccumulated and within a week it was necessary to perform another aspiration. During the 10-day period of hospitalization 2,050 ml. of fluid were withdrawn from the pericardial sac and 650 ml. were taken from the left pleural space (fig. 3). After 10 days the patient was discharged to his home.

Pericardial paracentesis was performed every 7 to 10 days on an out-patient basis. At each visit 700 to 1,200 ml. of fluid were removed. One month...
after discharge from the hospital, and 7 days after the last aspiration (1,300 ml.), on December 13, 1955, the patient appeared with severe symptoms of cardiac tamponade. He was again admitted to the hospital. On examination, the blood pressure was found to be 100/90 mm. Hg and there was a paradoxical pulse. Left thoracentesis yielded 500 ml. of serosanguineous fluid. A pericardial paracentesis yielded 1,000 ml. of sanguineous fluid. The patient was symptomatically improved following these procedures.

No apparent improvement had resulted from the antituberculosis therapy but it was continued for want of a more tenable diagnosis. Some type of malignant disease was suspected, though biopsy of scalenus, inguinal, and axillary nodes revealed no disease.

During the next week pericardial paracentesis was performed twice. The fluid removed was similar to that removed on previous occasions and the relief of symptoms was only temporary.

Three days later on December 31, 1955, he complained of an increase in dyspnea. Early the next morning while at stool he summoned his wife, who found him in respiratory difficulty. He died within a few minutes.

**Autopsy.** At autopsy, both lungs were displaced laterally by a bulging, taut pericardial sac. The left pleural space contained approximately 500 ml. of serosanguineous fluid. The pleura was firmly adherent to the diaphragm. The pericardial sac contained over a liter of bloody fluid. The heart, pericardium, and 12.0 cm. of aorta weighed 900 Gm. The pericardial sac was thickened, markedly roughened internally, and densely adherent posteriorly to the right ventricle and around the entry of the inferior vena cava. No calcification was present. The free portion varied between 2.0 and 5.0 mm. in thickness.

The epicardial surface was covered by small whitish granular excrescences. There were several distinct nodules over the surface of the right atrium (fig. 4). The right coronary artery was partially buried in this portion of the tumor. The right atrium and the area of the pericardial reflection over the aorta for a distance of 7.0 cm. were thickened. They appeared hemorrhagic and necrotic. This change extended through the wall of the right atrium to present just beneath the endocardial surface. The remainder of the heart was encased in a mantle of tumor measuring 4 to 6 mm. in thickness. Over the apex of the heart the tumor was 15 mm. thick and portions were seen to be grossly hemorrhagic. At the base of the heart all the great vessels were surrounded by tumor but did not seem to be compressed. The endocardial surfaces showed no changes. The valves were normal in appearance. The coronary arteries showed moderate atherosclerosis. There appeared to be no invasion into the ventricular musculature.

**FIG. 4.** Gross appearance of the heart. The anterior pericardium has been reflected.

Both lungs showed a moderate amount of edema. The bronchi were opened and examined for tumor but none was found. The liver was moderately congested. The gastrointestinal tract, spleen, pancreas, adrenal glands, kidneys, prostate, testes, larynx, thyroid gland, and vertebral marrow were completely examined without discovery of tumor or other significant change. The cranial contents were not examined.

**Microscopic Examination.** Blocks of tissue were fixed in 10 per cent formalin, imbedded in paraffin, and stained with hematoxylin and eosin. Microscopically, the individual cellular characteristics varied only slightly from one area of the tumor to another. The cells were round to oval, sometimes irregularly indented. They varied through all gradations to elongated spindle-shaped forms in the more highly cellular areas. The nuclei were pale with a moderate peripheral condensation of chromatin and a finely dispersed basophilic stippling. The cytoplasm was faintly eosinophilic with indistinct cellular borders. Mitotic figures were present, but rare (fig. 5).

Large areas of the tumor were composed of spindle-shaped forms arranged in bundles and clusters. In areas where the cells were most elongated they were usually arranged in parallel bundles with delicate eosinophilic cytoplasmic processes.

In other areas the tumor had a more distinctive appearance (fig. 6). The cells were arranged in cords and small bundles forming clefts and glandlike spaces with small papillary projections into the lumina. Here, the stromal cells appeared more rounded and plump. The lining cells, while retaining their general nuclear characteristics, tended to be somewhat flattened. There were wide areas of necrosis. Throughout all areas there was considerable
that mesothelium can give rise to both epithelial and spindle cells seems well established.3-5 This concept has led to the classification of such tumors occurring in the pleura into fibrous or glandular types; diffuse or localized; and benign or malignant.3 Ackerman6 gave essentially the same classification for tumors arising from the peritoneum. In a recent review, Dawe, Wood, and Mitchell2 divided primary mesotheliomas of the pericardium into epithelial, fibrous, and mixed types. They assembled 24 cases from the literature and added 1 of their own. Of these, 14 were of the spindle-cell type, 6 of the epithelial type, and the remainder were composed of both elements in approximately equal amounts. Our case would seem to fulfill all the criteria for the mixed type of pericardial mesothelioma.

About half of the cases showed no metastases. When present these were usually found in adjacent structures, i.e., pleurae, lungs, and mediastinal lymph nodes. Only 2 cases7-8 showed multiple distant metastases. A thorough search disclosed no evidence of metastasis in our case.

The majority of the cases in the review cited above2 were diffuse tumors covering most of the heart, often obliterating the pericardial cavity and constricting the great vessels. When obliteration of the pericardial sac did not occur, a bloody pericardial effusion was generally present. Seven of the patients died of cardiac tamponade. The course of the patient diagnosed ante mortem by Shelburne9 was marked by the rapid accumulation of sanguineous pericardial fluid. Lisa, Hirschhorn, and Hart10 listed the presence of serosanguineous pericardial effusion as typical of malignancy of the pericardium. They stressed the rapid recurrence of the effusion after aspiration as being almost diagnostic. This was also emphasized by Shelburne.9 Others11-13 have also emphasized the diagnostic implication of the presence of a bloody pericardial fluid in any patient. In

Discussion

congestion and atelectasis. The liver showed marked central congestion. The prostate showed benign hyperplasia. Examination of the remaining organs showed no tumor and no other significant findings.

Fig. 5. Top. High power magnification. H. and E. X 470.

Fig. 6. Bottom. Lower magnification showing varied appearance from area to area. Note numerous cleft-like spaces at left and more solid area at right. H. and E. X 120.

hemorrhage. Even the more viable areas of tumor contained small necrotic foci.

Sections of the myocardium showed moderate hypertrophy of the fibers. The lungs showed mild

Fig. 5. Top. High power magnification. H. and E. X 470.

Fig. 6. Bottom. Lower magnification showing varied appearance from area to area. Note numerous cleft-like spaces at left and more solid area at right. H. and E. X 120.
Whorton’s review of malignant tumors of the heart, of the 100 cases analyzed 25 had pericardial effusion. All but 3 had hemorrhagic pericardial fluid; the rapid formation was very significant. In our patient, on 1 occasion 1,300 ml. of fluid were removed from the pericardium. Seven days later he returned again with symptoms of cardiac compression. Fluoroscopy revealed the fluid had reaccumulated to the previous level and another 1,000 ml. of fluid were aspirated. This rapid formation of fluid in the presence of an adequate antituberculous regimen was considered very strong evidence of malignancy in our case.

The character of the fluid is also worthy of comment. The pericardial and pleural fluid were similar. The pericardial fluid, however, was the more hemorrhagic. A large amount of fibrin was present. The pericardial fluid contained 5,500 white blood cells with 91 per cent lymphocytes and 9 per cent polymorphonuclear cells. The predominance of lymphocytes has been characteristic in most of the reported cases. The lymphocytosis is one of the findings that influenced the institution of antituberculous therapy. Sarrell also began antituberculous therapy on a patient with a similar type of fluid.

The injection of air into the pericardial sac at the time of aspiration is a valuable procedure. As can be seen in the above figures, it helps to estimate the amount of fluid present, the size of the heart, and the thickness of the pericardium. Also, irregularity of the heart border caused by a tumor growth may occasionally be seen.

Meyer and Chaffee have reported hyaluronic acid in the effusion produced by a mesothelioma of the pleura. We attempted to find this polysaccharide in fixed tissue sections, using a modification of the periodic acid-Feulgen fuchsian method. We could not demonstrate polysaccharide of any type.

SUMMARY

A case of mesothelioma of the pericardium occurring in a 78-year-old Negro man is presented. The tumor was composed of epithelial and fibrous elements in approximately equal proportions. This corresponds to the mixed type of mesothelioma described by Dave and his associates. The clinical course was marked by the rapid reaccumulation of massive amounts of bloody pericardial fluid. Death was caused by cardiac tamponade. Such a course of events strongly suggests the presence of an intrapericardial neoplasm.

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SUMMARY IN INTERLINGUA

Es presentate un caso de mesothelioma del pericardio in un negro mascole de 78 annos de etate. Le tumor eseva composit de elementos epithelial e fibrose in proportiones plus o minus equal. Isto corresponde al typo mixte de mesothelioma descrit per Dave e su associatos. Le curso clinico eseva marcate per le reaccumulation rapide de massive quantitates de fluido pericardial sanguinose. Le morte occurreva in consequentia de tamponamento cardiac. Le curso clinico del caso suggereva fortemente le presentia de un neoplasma intra-pericardial.

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Essential pulmonary hypertension is a condition in which the elevation in pulmonary artery pressure results from an increase in the vascular resistance in the lung. The exact cause of the pulmonary vascular changes is not definitely established, but the possibility exists that in some instances repeated asymptomatic pulmonary embolization can produce the vascular changes found in this disease. Prior to the introduction of cardiac catheterization, primary pulmonary hypertension was considered rare. The present paper is a report dealing with clinical and physiologic studies on 3 patients, and with postmortem studies in 2 of them. Two of the patients were under 15 years of age; the third was 33 years old. All 3 patients died after cardiac catheterization had been completed.

The histories of the 3 patients described in this report show certain common features. Two of them, both children, suffered from effort syncope. All 3 patients had a history of shortness of breath, which was particularly severe in the adult. Physical examination revealed that all patients of this series had a systolic murmur. In 2 a diastolic murmur was also heard. The systolic murmur may be the result of a relative tricuspid insufficiency or of a dilation of the pulmonary artery. The diastolic murmur may be produced by relative insufficiency of the pulmonary valve. The electrocardiograms in the patients of this series showed right axis deviation and right ventricular hypertrophy. However, during attacks the electrocardiogram showed marked alterations. Case 1 during catheterization first developed sinus tachycardia, followed by 2:1 or 3:1 A-V block, with a ventricular rate of 125 per minute. Following this, a 2:1 block with ventricular rate of 50 per minute was observed. Finally, ventricular standstill occurred with an atrial rate of 50 per minute. In case 2 a sudden decline in ventricular rate from 140 to 30 beats per minute, with a complete cessation of atrial complexes, was recorded. Case 3 developed ventricular fibrillation. The findings on fluoroscopy obtained on the patients in this series are characteristic of the syndrome. The hilar markings are increased but the peripheral pulmonary vascular markings are diminished. Right ventricle and the pulmonary artery segment are prominent. The relatively clear peripheral lung fields distinguish this condition from congenital heart disease with a large left-to-right shunt. On cardiac catheterization, the most significant finding was marked increase in pulmonary artery pressure. The microscopic findings recorded on 2 patients revealed medial and intimal thickening of the pulmonary arterioles. The proliferation in the walls of the arterioles was particularly conspicuous, leading to almost complete occlusion of the lumina. The stem of the pulmonary artery showed arteriosclerotic changes. This report again stresses the fact that the life of patients with essential pulmonary hypertension is continually menaced. In over 900 patients on whom catheterization of the heart has been performed within the last 3½ years at the Medical College of Alabama, the 3 cases described represent the only fatalities encountered.

WENDKOS
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