

# MALIGNANT PERICARDIAL MESOTHELIOMA. REPORT OF TWO CASES, REVIEW OF THE LITERATURE AND DIFFERENTIAL DIAGNOSIS

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Malignant pericardial mesothelioma is an uncommon variety of a primary malignant cardio-pericardial tumor and it is a highly lethal and fortunately rare cardiac neoplasm. The presentation of pericardial mesothelioma is aspecific and pathologically mesothelioma is not the most common among primary tumors of the pericardium. It is characterized by atypical solid growth of mesothelium with formation of atypical cavities surrounded by fibrous stroma. Antemortem diagnosis is difficult and dis-

tant metastases are extremely rare. Radical surgery can be used to treat localized mesothelioma. The treatment for advanced primary pericardial mesothelioma is usually palliative because the tumor is resistant to radiotherapy and chemotherapy. The prognosis is unfavorable. The median survival from the onset of symptoms is six months. In this paper we report two cases of patients with primary mesothelioma of the pericardium without a definite history of asbestos exposure.

**Key words:** asbestos exposure, malignant pericardial tumors, mesothelioma.

## Introduction

Mesothelioma is a malignancy deriving from the serous epithelial cells of the mesothelium; the most frequent sites are the pleura (60-70%) and the peritoneum (30-35%); mesothelioma of the pericardium or the vaginal epithelium of the testicle is very rare<sup>1</sup>. A study of about 500,000 autopsies revealed a pericardial mesothelioma incidence lower than 0.0022%, or about 2-3% if we consider only autopsies of patients who died of cancer<sup>2</sup>. Mirabella<sup>3</sup> carried out an epidemiological study of 206 cases of pericardial mesothelioma from 1875 to 1978.

The aim of this paper is to report two cases of pericardial mesothelioma with emphasis on some aspects of their clinicopathological presentation that complicated the diagnosis.

## Case 1: Clinical presentation

A 68-year-old retired man, ex smoker, came to our attention in October 1997. His history reported surgery for a right inguinal hernia at approximately 50 years of age and a gallbladder resection when the patient was in his sixties.

In May 1997 the patient complained of dyspnea, asthenia, evening fever and weight loss. Because of a general decline in his overall condition he was admitted to hospital, where a chest X-ray revealed an enlargement of the cardiac shadow due to massive pericardial effusion and moderate right pleural effusion. About 1000

mL of hemorrhagic effusion was obtained through pericardial drainage. Cytological analysis revealed the presence of epithelial tumor cells of unknown origin. The patient underwent a bronchoscopy, colonoscopy, abdominal ultrasonography and thoracic CT scan. Although these exams did not reveal the presence of malignancy, chemotherapy with cisplatin (80 mg/m<sup>2</sup> day 1) and navelbine (30 mg/m<sup>2</sup> day 1-8) every 28 days was started. After one month the patient was hospitalized following an inferior acute myocardial infarct. Echocardiogram and chest X-ray revealed pericardial effusion, hence the patient underwent pericardial resection and right ventricle suture. Histological examination demonstrated that the patient suffered from a pericardial mesothelioma. He returned to our department for the prescribed chemotherapy, but because of his worsening general condition it was decided to follow a palliative care protocol. Another chest X-ray confirmed the presence of bilateral pleural and pericardial effusion. About 1800 mL of serous effusion was collected through thoracentesis. The general condition of the patient worsened very rapidly and he died after admission to the Internal Medicine Department.

## Case 2: Clinical presentation

A 44-year-old male painter, a current smoker (about 30 cigarettes/day), came to our attention in 1998. His history reported a tonsillectomy at age 12. In October 1998 the patient had begun wide-spectrum antibiotic treatment for a tooth abscess. After seven days of treat-

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ment he manifested general malaise, chills, fever, asthenia, chest and joint pain that did not respond to anti-inflammatory drugs. The patient was hospitalized in the infectious disease ward, where he underwent a chest X-ray to exclude the presence of pneumonia. This only revealed pericardial effusion, so the patient was transferred to the cardiological intensive care unit where he underwent pericardial drainage which collected about 1100 mL of hemorrhagic effusion. Cytological analysis did not reveal atypical cells.

After one week it was necessary to perform a sternotomy with pericardial drainage and biopsy sampling because the patient manifested symptoms of cardiac tamponade. Histological examination revealed pericardial mesothelioma. Following surgery, given the worsening of his general condition, the patient was transferred to the Intensive Care Unit where he later died.

### Histopathological description

#### Case 1: Pathological findings (Figure 1)

Four biopsy samples of white-yellow fibrous tissue were analyzed, the largest measuring 8 × 4 × 2 cm. Mi-

croscopic examination revealed cancer infiltration of the pericardium with a multiple connected nodule morphology. These nodules consisted of large epithelial elements with well-marked vacuolated eosinophil cytoplasm, a vesicular nucleus and prominent nucleolus (Figure 1b). The cells formed cord-like or tubular-papillary structures, confirming the mesothelial origin of the malignancy. Foci of epithelial mesothelioma *in situ* were present (Figure 1a). Foci of atypical hyperplastic mesothelium were present in areas not affected by the malignancy.

Immunohistochemistry was positive for cytokeratin (AE1/AE3) (Figure 1c) and calretinin (Figure 1d); there was diffuse membrane positivity for EMA and HBME-1 and focal positivity for vimentin, while staining for CEA and CD15 was negative. The diagnosis was pericardial epithelial mesothelioma.

#### Case 2: Pathological findings (Figure 2)

Several hard pericardial samples with irregular shapes were analyzed, the largest measuring 7 × 4.5 × 2 cm. Histological examination revealed a pericardium affected by a malignancy lacking differentiation with

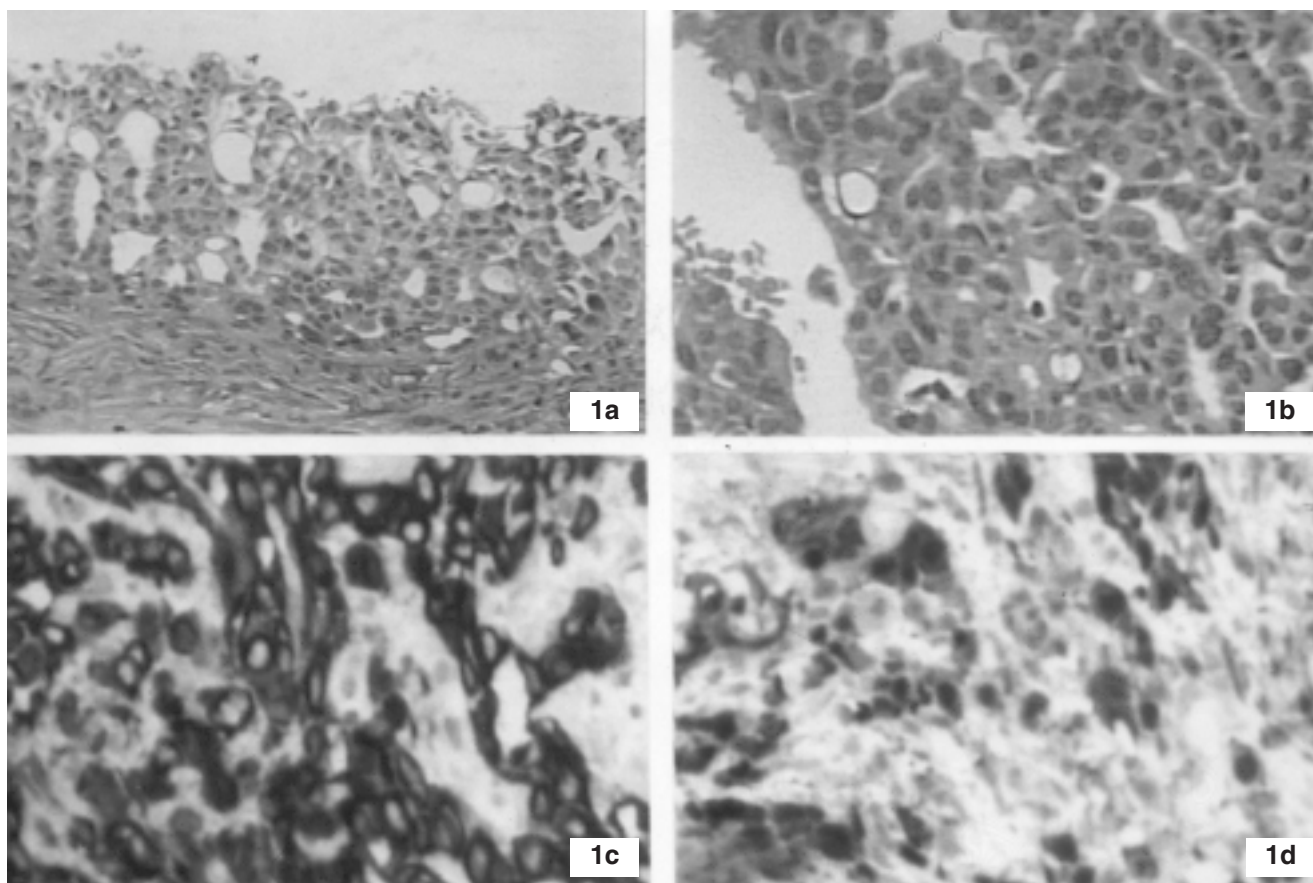


Figure 1 - Case 1: 1a) Epithelial mesothelioma *in situ* (EE). 1b) Atypical epithelial mesothelioma with tubular-papillary growth. 1c) Marked presence of cytokeratin (AE1, AE3). 1d) Many elements show calretinin.

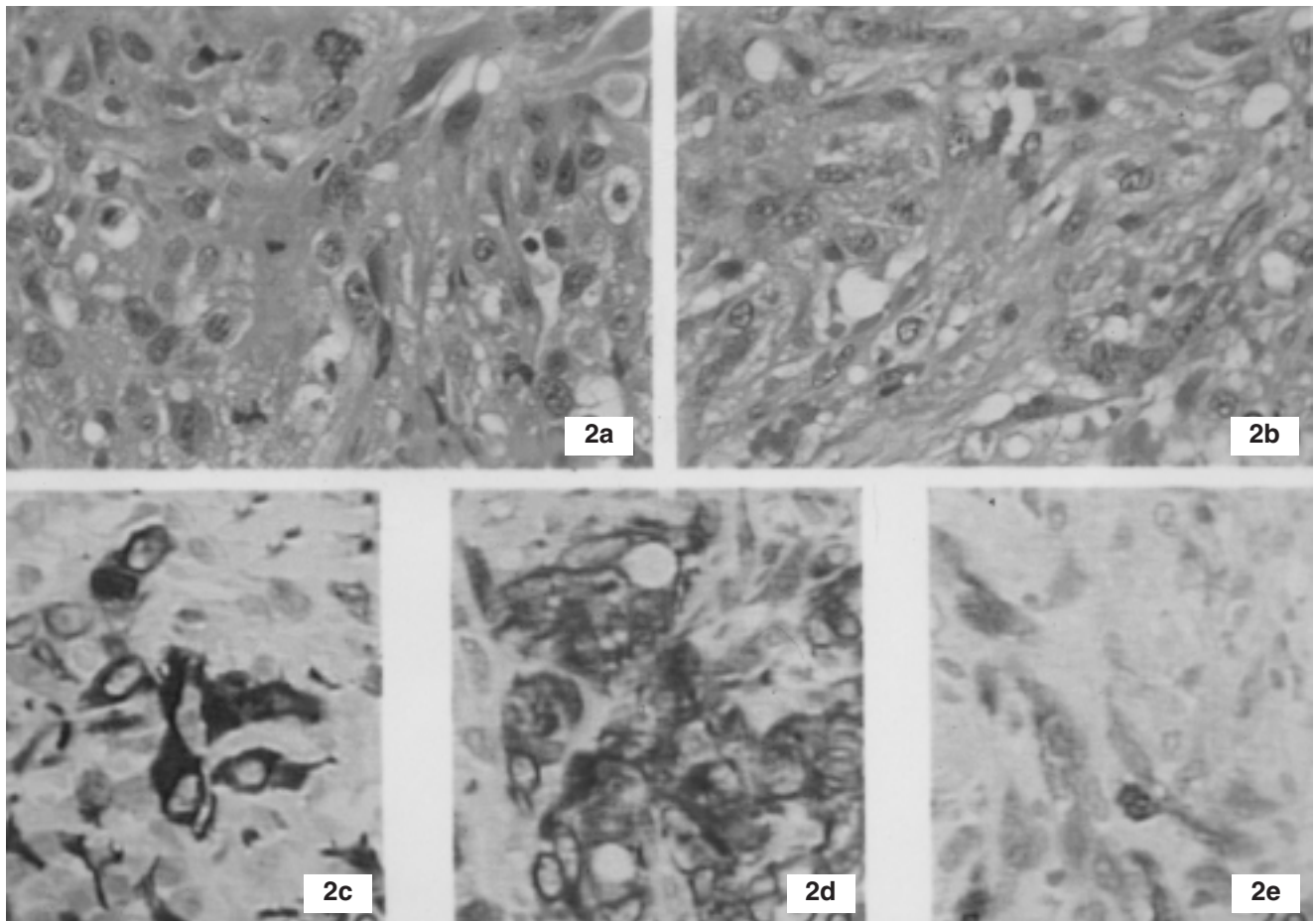


Figure 2 - Case 2: 2a-b) Mesothelioma with sarcomatoid appearance and areas with angiosarcoma-like differentiation. 2c) Diffusely positive for AE1/AE3. 2d) Diffusely positive for vimentin. 2e) Focally positive for calretinin.

confluent nodules and plaques. The cancer cells had an extended shape with a large nucleus, prominent nucleolus and vacuolated cytoplasm, and there was angioblastic differentiation (Figure 2a-2b); the neoplastic cells rarely had an extended shape and formed cord-like structures. The malignancy was positive for AE1/AE3 (Figure 2c), vimentin (Figure 2d), calretinin (Figure 2e), EMA and HMB-1, and negative for CEA, CD15, CD34 and Factor VIII. The diagnosis was biphasic mesothelioma, sarcomatous in the pericardium: this diagnosis was confirmed by the autopsy findings (Figure 3).

#### Discussion

The clinical features of pericardial effusion are chest pain, dyspnea, cough and sometimes paradoxical pulse. Pericardial effusion can be detected by chest X-ray, echocardiography and MRI or CT scan of the chest. The most frequent cause of effusion is *Mycobacterium tuberculosis* infection. Other frequent causes are myxedema, systemic lupus erythematosus, rheumatoid arthritis, severe chronic anemia, chylopericardium, mycetes/pyogenic infection, radiotherapy, and hypercholesterolemia.

The presence of hemorrhagic effusion may indicate an infection (eg tuberculosis) but also chronic hemorrhage due to an aortic aneurysm must be taken into account.

Hemorrhagic pericardial effusion could also be pro-

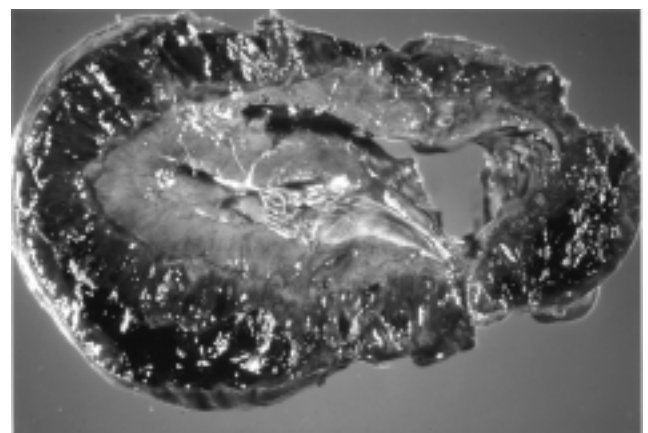


Figure 3 - Case 2: autopsy report.

duced by a distant malignancy that metastasized to the pericardial serosa; this process accounts for about 7% of all hemorrhagic pericardial effusion<sup>4</sup>. Also the heart could be affected by tumors that subsequently produce pericardial effusion. Autopsy studies found the heart to be affected by metastasis in 0.25% to 6.5% of all malignancies, with lung cancer being the prevailing primary site<sup>5</sup>. Primary heart malignancy accounts for 0.0017% to 0.28%, as was found on the basis of random autopsies (eight primary malignancies in a total of 480,000 autopsies performed in the US from 1938 to 1942)<sup>6</sup>.

Primary heart mesothelioma accounts for about 2-3% of all cardiac and pericardial primary tumors and about 1% of all mesotheliomas<sup>7</sup>: it is the third tumor after angiosarcoma (33%) and rhabdomyosarcoma (20%)<sup>8</sup>. Exposure to asbestos is correlated with the onset of pleural and peritoneal mesothelioma; however, the role of asbestos in pericardial mesothelioma is unclear.

The diagnosis is made on the basis of cytological examination, ultrasound or CT-guided biopsy, and MRI<sup>9</sup>; in only 10-20% of cases can a diagnosis be made before the death of the patient. It is important to differentiate between malignancy and mesothelial reactive hyperplasia associated with inflammatory disease<sup>10</sup>. Features that indicate the presence of a malignancy are infiltra-

tion of deep tissues, atypical cytoplasm, necrosis and confluent forms. If deep tissue infiltration is not present, the diagnosis can be based on severely atypical cytoplasm. Immunohistochemistry is useful for the differential diagnosis, but it is necessary to obtain additional information (anamnestic, clinical or radiological). Mesothelioma cells stain positive for cytokeratin, vimentin, epithelial membrane antigen (EMA) and calretinin, and negative for CEA, CD15 and S-100<sup>11,12</sup>. Pericardial mesothelioma infiltrates the myocardial and mediastinal structures. Metastases are present in about 25-45% of the cases and involve the regional lymph nodes, lungs and kidneys<sup>13</sup>.

As far as treatment is concerned, several studies have shown the efficacy of surgery, radiotherapy and chemotherapy, but the results are modest and provide no significant difference in prognosis, which remains poor (the median survival is about six months from diagnosis)<sup>14</sup>. Sometimes the malignancy involves the atria-ventricular nodes with a third-degree conduction block or the coronary circulation with ischemic heart attack<sup>15,16</sup>. The most frequent causes of death are cardiac tamponade, vena cava occlusion and congestive heart failure.

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