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# Primary Malignant Pericardial Mesothelioma

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## 1. Introduction

### 1.1 Epidemiology

Primary malignant pericardial mesothelioma is an extremely rare tumour. One of the largest autopsy series including about 500,000 cases gave an incidence of primary pericardial tumours of <0.0022% (Gossinger et al., 1998). However, it accounts for approximately 2-3% of all cardiac and pericardial primary tumours being the third tumour after angiosarcoma and rhabdomyosarcoma (Karadzic et al., 2005; Papi et al., 2005).

Mesothelioma arises from the serous epithelial cell of the mesothelium. The most common sites for this malignancy include the pleura (60-70%) and the peritoneum (30-35%). Primary pericardial mesothelioma accounts for only about 1% of all mesotheliomas (Karadzic et al., 2005; Papi et al., 2005).

Approximately 200 cases have been described in literature, of which most have been reported as case studies. The majority of diagnoses occur in the fourth to seventh decades of life with a median age of 46 years (Nilsson & Rasmuson, 2009) and on average, tends to develop in fairly young people compared to pleural or peritoneal mesothelioma. The male-to-female ratio is nearly 2:1, lower than the ratio of approximately 3.5:1 for mesotheliomas of the pleura.

The higher proportion of women suggests that the link with asbestos exposure is weaker for pericardial than for pleural mesothelioma, or that some pericardial mesotheliomas are pathogenetically distinct from their pleural counterparts (Burke et al., 1995). The etiology of malignant pericardial mesothelioma is not completely known. No obvious relationship between asbestos exposure and the development of pericardial mesothelioma has been established due, in part, to the very small number of cases reported (Kaul et al., 1994). An example of this is a recent article published by Nilsson et al., 2009, where they presented a case report and review of 29 primary pericardial mesotheliomas in English literature from 1993 through to 2008. They found that most of the reviewed articles contained no information about asbestos exposure and that only three cases were reported with known exposure to asbestos and 11 were reported with no known exposure (Nilsson et al., 2009), Table 1.

Furthermore, pericardial malignant mesothelioma has been described in patients with a prior history of irradiation showing pericardial effusion (Bendek et al., 2010; Yildirim et al., 2010). A rare association with pericardial mesothelioma and tuberculosis has also been reported (Narayanan et al., 1972).

Exposure to asbestos	n	%
Exposure	3/14	21
No known exposure	11/14	79
Not mentioned	16/30	53

Table 1. Asbestos exposure and primary pericardial mesothelioma

2. Clinical presentation

Symptoms arising from primary pericardial mesothelioma usually result from constriction of the heart or compression of surrounding structures, ranging from dyspnoea, cough, dysphagia, orthopnoea and chest pain (Aggarwal et al.,1991). The onset of symptoms is usually insidious. Common clinical manifestations of pericardial mesothelioma are constrictive pericarditis, pericardial effusion, cardiac tamponade and heart failure caused by myocardial infiltration (Suman et al., 2004). Compression of coronary arteries and local spread of the disease to surrounding large vessels can result in additional symptoms.

As with symptoms, the majority of physical findings are nonspecific. Tachycardia (a heart rate of more than 90 beats per minute) is usually present. Heart sounds may be attenuated if pericardial fluid is present. Clinically significant tamponade produces jugular venous distension, hypotension or even shock. A key diagnostic finding for tamponade is pulsus paradoxus, defined as an exaggeration (more than 10 mmHg) of the normal variation during the inspiratory phase of respiration, in which the blood pressure declines as one inhales and increases as one exhales, and is often palpable in muscular arteries. Sometimes, pulsus paradoxus can be caused by other pathologies, such as asthma, COPD, superior vena cava obstruction, pulmonary embolism or anaphylactic shock.

Additionally, distant metastasis, conduction blockade due to myocardial infiltration and tumour embolism causing neurological deficits have also been reported (Szczechowski et al., 1992). Metastases are present in about 25-45% of the patients and involve regional lymph nodes, lung and kidney (Karadzic et al., 2005; Lagrotteria et al., 2005).

3. Diagnosis

Diagnosis of the disease can be challenging because of nonspecific symptoms and therefore usually only detected at an advanced stage. Usually, tumour presentation consists of coalescent irregular lobular masses that obliterate the pericardial space and tend to constrict the heart. Although a mild infiltration into the subepicardial muscle may occur, the underlying myocardium is frequently not affected. The malignant involvement of pericardium may lead to the development of pericardial effusion, which results from blockage of venous and lymphatic circulation of pericardial fluid.

Often, a multimodal imaging approach, including echocardiography, computed tomography (CT), magnetic resonance imaging (MRI) and FDG-PET scans, is required. Chest radiography of patients reveals cardiomegaly, an irregular cardiac silhouette or diffuse mediastinal enlargement. Transthoracic echocardiography is the mainstay imaging technique for cardiac tumour detection. Although generally robust, it carries several well-described limitations, including operator dependence, restricted field of view and occasional limited imaging of the right heart chambers. Transesophageal echocardiography improves

image quality considerably, but is more invasive and carries a restricted field of view. CT scan can demonstrate the extent of the cardiac tumour, the extent of pericardial thickening, the mediastinal lymph node and the extracardiac lesions, Figure 1. These can be useful in distinguishing primary pericardial tumours from other causes of constrictive pericarditis. Cardiovascular magnetic resonance imaging is the reference non-invasive imaging technique for assessment and characterization of a suspected cardiac mass. It allows accurate confirmation of the presence of a space occupying lesion, localization and assessment of the extent of involvement, evaluation of the functional impact of the lesions, as well as tissue characterization, Figure 2. Such information is important not only for diagnosis, but also determination of prognosis and in planning of therapy (Randhawa et al., 2011). Integrated positron-emission tomography (PET)/Computed tomography (CT) imaging has not established itself in routine evaluation, probably due to their low frequency. However, in a recent report, PET-CT was useful in the staging and preoperative evaluation of pleural or pericardial mesothelioma, detection of unsuspected nodal and occult distant metastases (Ost et al., 2008).

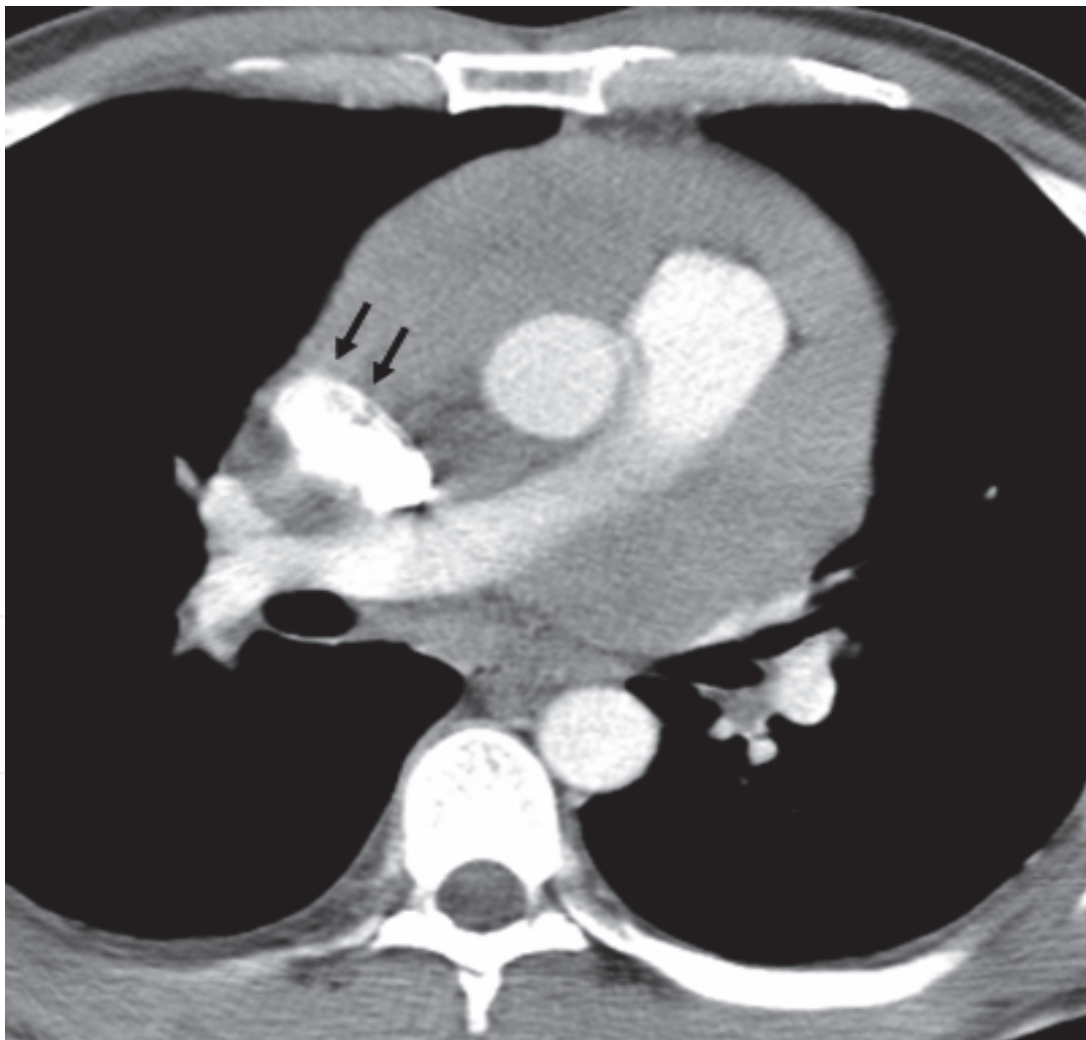


Fig. 1. Axial contrast-enhanced chest CT scan (mediastinal window) shows a soft-tissue mass with homogenous enhancement that encases the ascending aorta and right pulmonary artery. The mass is compressing the right atrium (arrows).

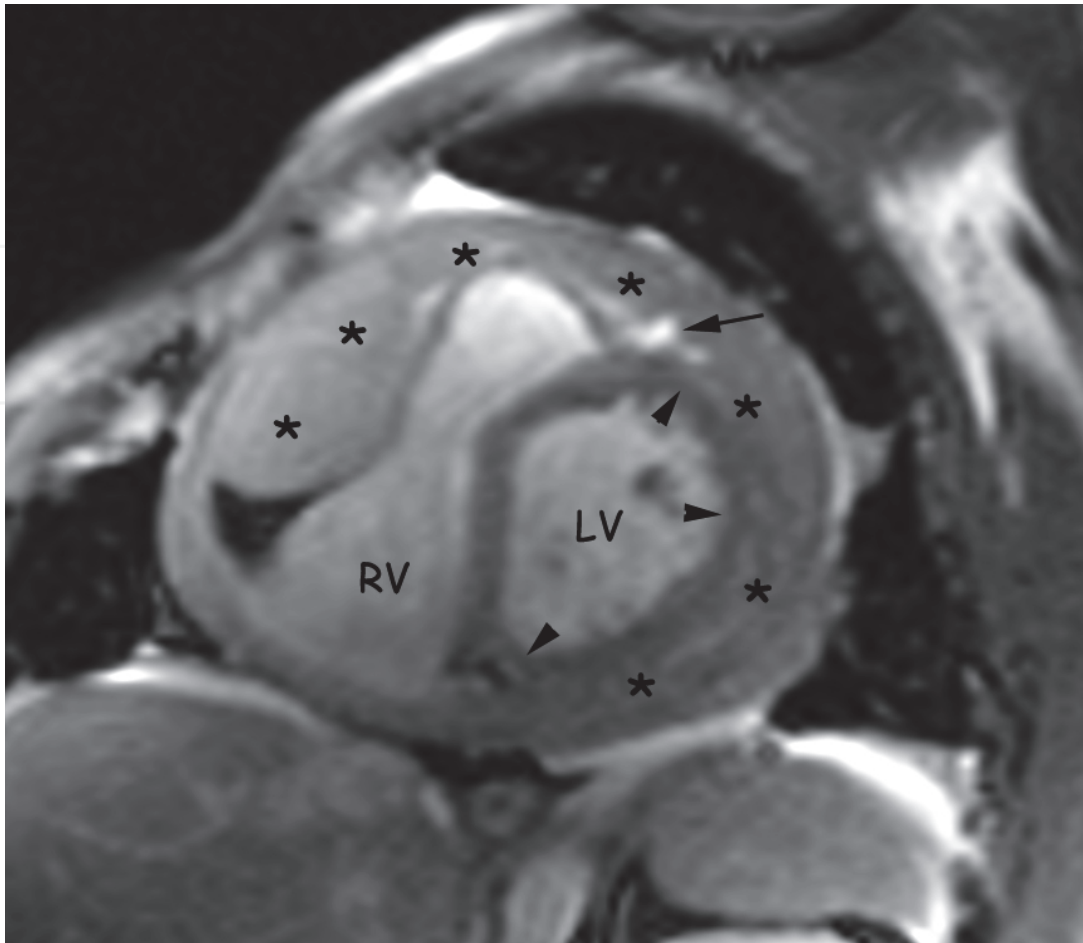


Fig. 2. Contrast-enhanced short-axis steady-state free precession MR image, demonstrates extensive pericardial involvement of the tumour that encases the ventricles and also compresses the right ventricle. It is possible to differentiate the myocardium (arrowheads) from the mass (asterisks). In this sequence, liquids show high attenuation and only minimal pericardial fluid is seen (arrow). RV: right ventricle; LV: left ventricle.

The diagnosis of the disease is made as a result of the pathologic assessment of pericardial fluid or tissue generally obtained with the guidance of echocardiogram, ultrasonography or CT scans. Moreover, cytological examination, immunohistochemistry and the high pericardial hyaluronic acid content of the pericardial aspirate can be diagnostic. As with any tumour, reliable diagnosis of mesothelioma depends on obtaining adequate and representative tissue samples. Antemortem diagnosis is notoriously difficult because the clinical presentation is nonspecific, the radiological findings are sometimes non-contributory and the cytological analysis of pericardial fluid is often inconclusive. In only 10-20% of cases can the diagnosis be made before the death of the patient (Papi et al., 2005). It is important to differentiate between malignancy and mesothelial reactive hyperplasia associated with inflammatory disease. In biopsy specimens, features that indicate the presence of a malignancy are infiltration of deep tissues, atypical cells, necrosis and confluent forms. In these cases it is useful to obtain additional anamnesis, clinical and radiological information. Immunohistochemistry has a limited role and the more useful antibodies have diagnostic sensitivity and specificity < 90% (table 2).



Antibody	Sensitivity (%)	Specificity (%)
Epithelial membrane antigen	74	89
p53	58	91
Desmin	83	83

Table 2. Antibodies distinguishing between malignant mesothelioma and reactive mesothelial hyperplasia (Addis B & Roche H, 2009).

On microscopy, malignant mesotheliomas of the pericardium resemble pleural mesotheliomas. Mesotheliomas are divided into epithelial, mixed (biphasic) and sarcomatous types on the basis of histologic growth patterns, Figure 3,4. The less common mixed and sarcomatous variants show poorer survival. Immunohistochemically, almost 100% of pleural mesotheliomas express cytokeratin in epithelioid areas. Sarcomatoid cells express cytokeratin in about 75% of cases, vimentin is preferentially expressed in the spindle cell areas and epithelioid membrane antigen (EMA) is frequently present in the epithelioid areas. With pericardial mesotheliomas, EMA and vimentin are present in fewer than 50% of pericardial cases. As with pleural mesothelioma, a panel of antibodies should be used for differential diagnosis with metastatic pericardial tumours, so much frequent than mesothelioma. For adenocarcinoma, the most common metastatic pericardial tumour, a panel of positive (CK5/6, calretinina) and negative (CEA, ber-EP4 y CD15) antibodies allow the diagnosis of mesothelioma in the context of the morphologic findings. In this case, antibodies usually positive in epithelial mesothelioma are presented in Table 3 (Addis & Roche, 2009).

Antibody	Sensitivity (%)	Specificity (%)
CK5/6	83	85
Calretinin	82	85
HBME 1	85	43
Thrombomodulin	61	80
N-cadherin	78	84
Wilms tumour product-1	77	96

Table 3. Antibodies usually positive in epithelial mesothelioma.

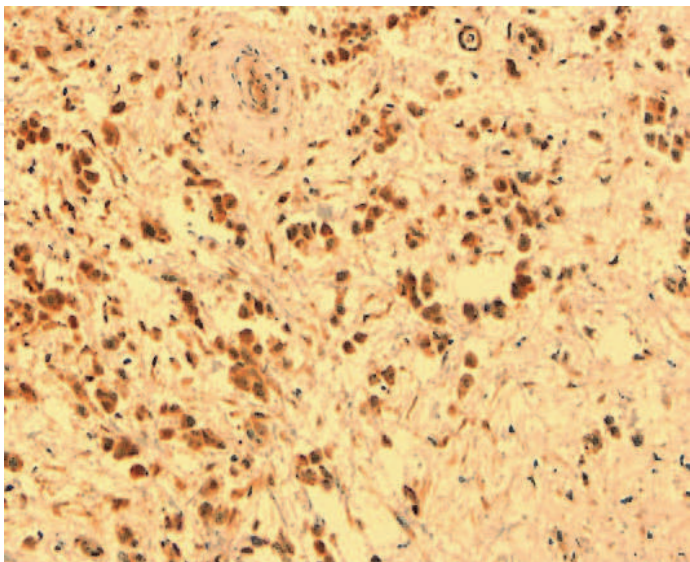


Fig. 3. Positivity for calretinin in neoplastic cells of epithelial mesothelioma.

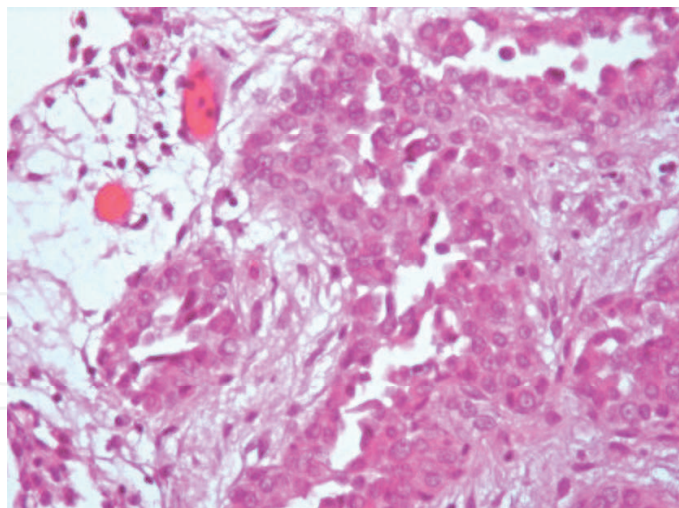


Fig. 4. Epithelial mesothelioma in invasive pattern. Hematoxylin-eosin x 200.

#### 4. Treatment and prognosis

Pericardial mesothelioma is a highly aggressive tumour with global survival of less than 6-12 months, depending on histological type, tumour stage, performance status and treatment, and other factors, such as gender and age (Papi et al., 2005; Suman et al., 2004). Its molecular profile indicates that most of the known genes for radio- and chemoresistance are overexpressed (Roe et al., 2009). Treatment tends to be mainly palliative rather than radical and based on surgery, chemotherapy and radiotherapy. However, despite best efforts, no significant difference has been achieved in regards to prognosis.

Surgery plays a limited role as the disease is often locally advanced when diagnosis is reached. Its main role is therefore to control symptoms, as in the case of partial pericardiectomy in cardiac tamponade (Vigneswaran et al., 2000).

Treatment options for the control of malignant pericardial effusions or tamponade should be individualized to maximize symptom relief and minimal impact in quality of life. Several techniques have been used, percutaneous pericardiocentesis, pericardial sclerosis, subxiphoid pericardial window, pericardiectomy or pericardiectomy by thoracotomy or video-assisted thoracoscopy. However, a retrospective comparison of cases published in 1998 by Girardi, showed that pericardiocentesis with intrapericardial sclerotherapy was as effective as open surgical drainage for the management of malignant pericardial effusions and also showed similar rates of complications (Girardi et al., 1997). Surgical drainage is desirable in patients with intrapericardial bleeding and in those with clotted hemopericardium or thoracic conditions that make needle drainage difficult or ineffective. If treatment is indicated for management of tamponade, percutaneous subxiphoid pericardiocentesis is the treatment of choice in the acute setting, guided by echocardiography. Recurrent pericardial effusion occurs in approximately 21-50% of cases (Anderson et al., 2001; Tsang et al., 2000). Limited cases suggest rates of pericardial fluid reaccumulation at 30 days ranging 5-33% after pericardiocentesis and intrapericardial treatment with sclerosing drugs versus more than 50% in cases treated with pericardial drainage alone (Anderson et al., 2001). Several sclerosing agents have been used, tetracycline, bleomycin, thiotepa, mitoxantrone, docetaxel, among others. Some cases may

required three or more treatments to achieve adequate sclerosis. A prospective comparison study of doxycycline versus bleomycin showed a similar rate of success, but less morbidity in cases treated with bleomycin, especially in severe retroesternal chest pain, 70% of patients treated with tetracyclines versus 0% with bleomycin (Liu et al., 1996).

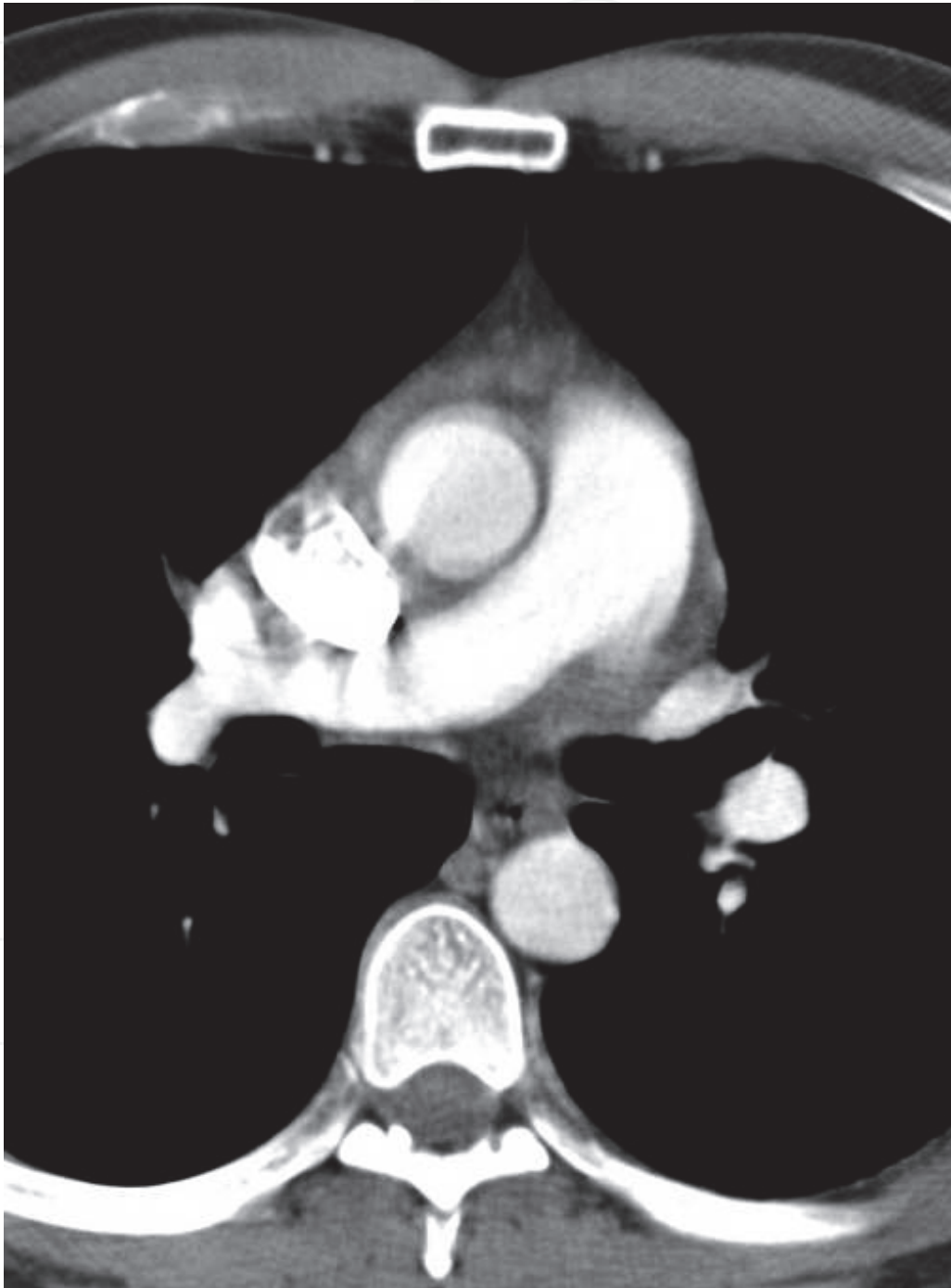


Fig. 5. Chest CT scan performed after three cycles of chemotherapy. Axial contrast enhanced CT scan (mediastinal window) at the same level as Figure 1 shows marked improvement in the mass (Santos et al., 2008).



Scheme of bleomycin chemical sclerosis: after catheter is correctly placed and drainage is effective, bleomycin 10 to 20mg dissolved in 10 to 20 mL of normal saline is inserted through the catheter into the pericardial sac. The catheter is clamped for 1 to 2 hours and then reopened and allowed to drain. Special positioning of the patient is not required. Procedure could be repeated every 24-48h until volume of drainage was less than 25 mL per 24 hours. Maximum number of procedures is 3 or 4. Catheter is definitively removed when the echocardiogram confirms that the effusion is resolved.

Radiation therapy has been used as adjuvant treatment in patients with incomplete tumour resection with or without chemotherapy (Papi et al., 2005; Suman et al., 2004) but pericardial mesothelioma responds poorly to radiotherapy and we have to be cautious with the side effects of such radiation that can cause primarily pericarditis or myocarditis.

The use of new drugs offers further treatment options. The therapeutic schemes generally used are the same as those used in pleural mesothelioma, mainly a combination of platin-infusion plus gemcitabine or paclitaxel with and objective response rates of 16-48% and median survivals of 9.6-11.2 months. Recently, pemetrexed, a multitargeted antifolate, has demonstrated modest activity against malignant pleural mesothelioma in combination with cisplatin (Volgenzang et al., 2003) or carboplatin (Ceresoli et al., 2006). Some cases report excellent tumour response with a combination of carboplatin and pemetrexed unusual in this type of tumours with progression-free survival and overall survival of 10 and 18 months, respectively (Doval et al., 2007; Fujimoto et al., 2009; Santos et al., 2008), Figure 5.

## 5. Conclusion

Malignant pericardial mesothelioma is a rare malignancy with a poor prognosis. Diagnosis procedures are sometimes difficult and a multidisciplinary approach, including pathologists, clinicians and radiologist, is often required. Due to few cases being described, management is based on knowledge obtained from usual presentations of malignant mesothelioma, such as pleural or peritoneal. Systemic treatments can be used and tumoural responses have been described, especially with new antineoplastic agents. With respect to the treatment of local complications as pericardial effusions with tamponade, options include pericardiocentesis with or without chemical sclerosis as an initial procedure. Other more aggressive surgical approaches may be recommended in selected cases.

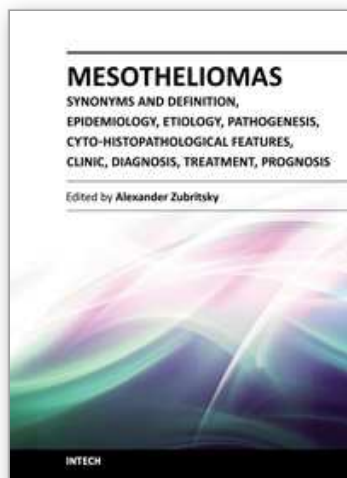
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**Mesotheliomas - Synonyms and Definition, Epidemiology, Etiology, Pathogenesis, Cyto-Histopathological Features, Clinic, Diagnosis, Treatment, Prognosis**

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Mesotheliomas are mysterious mesothelial tumors in that they are relatively rare, difficult to diagnose, with a large number of synonyms, and the etiology and pathogenesis of the disease are still not fully disclosed. This problem attracts the attention of various specialists in the field of medicine and biology every year. In recent years there has been a significant increase of mesothelioma morbidity in most of the countries, due to the further industrialization of society. In this regard, this book has been published with the participation of an international group of experts with rich experience from around the world . The book consists of 14 chapters containing the most advanced achievements of all aspects of the various types of mesotheliomas, both in humans and domestic animals, at a high methodological level. This book is intended for biologists and all health care workers, mostly oncologists of different profiles, as well as students of medical educational institutions engaged or even just interested in the problems of mesotheliomas.

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