

## Primary pericardial malignant mesothelioma and response to radiation therapy

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### Abstract

We report a case of a primary pericardial malignant mesothelioma. A 59-year-old male presented with episodic chest pain and dyspnea on exertion. Cardiac magnetic resonance imaging revealed a large mass in the pericardium attached to the right ventricle. Partial resection of the mass was undertaken revealing malignant mesothelioma, biphasic type. The patient was treated with chemotherapy intermittently over a period of 3 years, but his disease continued to progress. The patient was then treated with definitive radiation therapy to 64 Gy to the primary tumor using a six field 3D conformal technique. The patient remains free of progressive disease 86 months from the time of diagnosis and 50 months from the completion of his radiotherapy.

### Case Report

A 59-year-old African American male with essentially no significant past medical history except for hypertension and obesity presented to the emergency room on April 27, 2003 with a complaint of episodic chest pain and increasing dyspnea on exertion over the previous month. An EKG revealed sinus tachycardia but was otherwise within normal limits. A chest x-ray was performed and revealed a bottle-shaped heart consistent with a pericardial effusion. The echocardiogram subsequently performed showed a right ventricular pericardial mass. A CT of the patient's chest, abdomen, and pelvis revealed a moderate pericardial effusion and high attenuation focally in the anterior pericardium consistent with a pericardial mass. The scan revealed an otherwise normal abdomen and pelvis examination

with no evidence of metastatic disease. Subsequently a cardiac magnetic resonance image (MRI) was performed revealing a mass within the pericardial space measuring 7.7×3.6 cm, adhering to the right ventricle epicardium without myocardial infiltration and compressing the right ventricular apex. The mass was not lipomatous and took up contrast consistent with vascularity (Figure 1A). A moderate pericardial effusion was also present.

### Pathological findings

The patient was subsequently taken to the operating room to create a pericardial window to alleviate his pericardial effusion, as well as a partial resection of his tumor. An aggregate of approximately 6.5×6.5×2.5 cm of tumor was removed. However, a complete resection could not be performed due to tumor adherence to the right ventricular muscle. On gross review of the pathology specimen, the interior of the mass appeared necrotic with outer tissue showing smooth, glistening serosal surfaces with small papillary excrescences. Pathology demonstrated a biphasic (epithelial and spindle cell) histology characteristic of mesothelioma, with immunohistochemistry showing cytokeratin positivity in both cellular components, and calretinin (a mesothelioma-specific immunohistochemical stain) positivity in the epithelioid cells. The final pathology of the tumor specimen was reported as a malignant mesothelioma: biphasic type (Figure 2).

### Therapeutic intervention

The patient was treated initially with eight cycles of gemcitabine and cisplatin, with a good partial response to treatment. This treatment ended in March 2004. The patient was subsequently followed with serial imaging, which showed stable disease until January 2005, when an increase in size of the patient's pericardial mass was appreciated. An additional six cycles of chemotherapy was administered with gemcitabine and carboplatin. The last cycle was given in July 2005. No further disease progression or regression was appreciated until November of 2005, when once again, the patient was noted to have disease progression. He subsequently received two cycles of permerted, but a MRI in January 2006 revealed that the anterior pericardial mass located in the interventricular groove had increased in size to 7.4×4.8×4.2 cm (previous 3.3×4.6×5.4 cm). There was continued compression of the right ventricle, slightly increased from prior examination. The right atrium was mildly enlarged, which was new from prior examination (Figure 1B). The patient was also beginning to once again experience increasing dyspnea on exertion and was then referred to Radiation Oncology and treated on an Elekta SL-18 linear accelerator from March 2, 2006 until April 18, 2006. He was pre-

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scribed a total dose of 64 Gray in 32 fractions yielding a daily dose of 2 Gray per fraction delivered to the 100% isodose line using 6 MV photons. He was treated using a 6-field non-coplanar 3D conformal technique with a right anterior oblique field measuring 12.2×9.6 cm, a right superior anterior oblique field measuring 10.5×12.3 cm, a left inferior anterior oblique field measuring 12.1×10.7 cm, a right inferior anterior oblique field measuring 14.2×10.7 cm, a left superior anterior oblique field measuring 13.9×10.6 cm and a left lateral field measuring 13.5×10.8 cm. Sixty-degree wedges were used on all fields to improve dose homogeneity and blocks were used to spare normal tissues (Figure 3). Overall, the patient tolerated his radiation treatments quite well and noted improvement in his dyspnea at the end of treatment.

### Radiographic response assessment

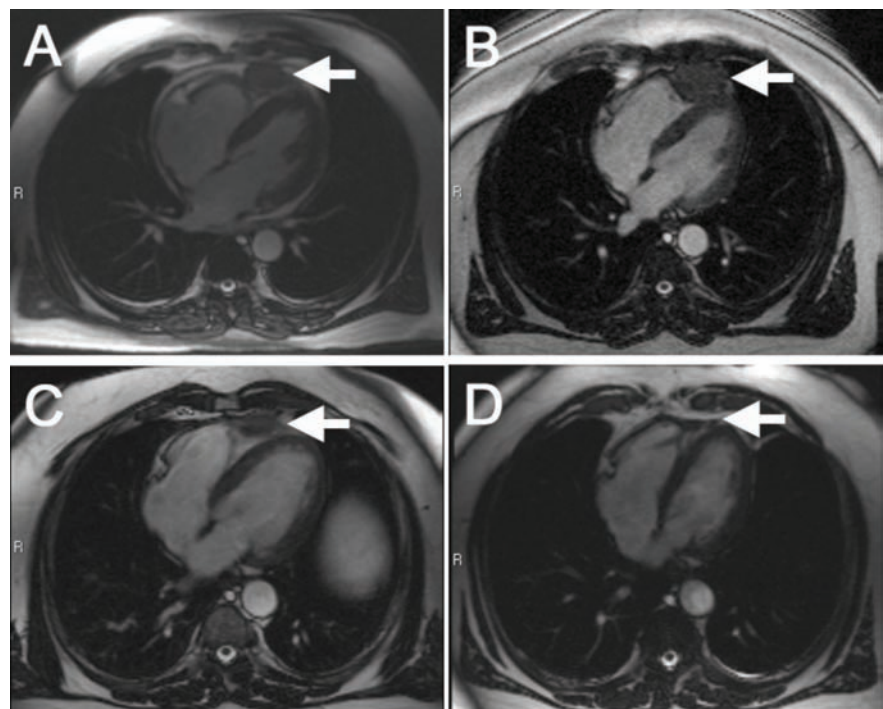
At the completion of his radiation therapy a cardiac MRI was performed, which again identified a solid enhancing pericardial mass along the anterior/apical region of the right ventricle. The mass had decreased in size, now measuring 2.1×3.5×5.2 cm. Volumetric measurements of the mass demonstrated the mass to be 1/5 the volume compared to pretreatment examination

(Figure 1C). The patient was subsequently followed with serial imaging after the completion of his radiation therapy. At 40 months post-radiation treatment, imaging revealed a small amount of anterior pericardial thickening with a maximal thickness of 8 mm, which had remained unchanged since December 2007. No discrete mass lesion was identified, and the remainder of the pericardium was unremarkable. Given the stability of the thickening, this was felt to most likely represent post-radiation changes (Figure 1D). The patient is now 86 months from diagnosis and 50 months from the completion of his radiation therapy with no evidence of progressive disease. Additionally, the patient has minimal symptoms with no baseline shortness of breath and stable dyspnea on exertion since the completion of his radiation therapy. He has had no late lung radiation toxicity, and his most recent cardiac ejection fraction was found to be 48% (normal 56-78%) in February 2010, which was only slightly decreased from prior to radiation, where it was found to be between 50-55% in February 2006.

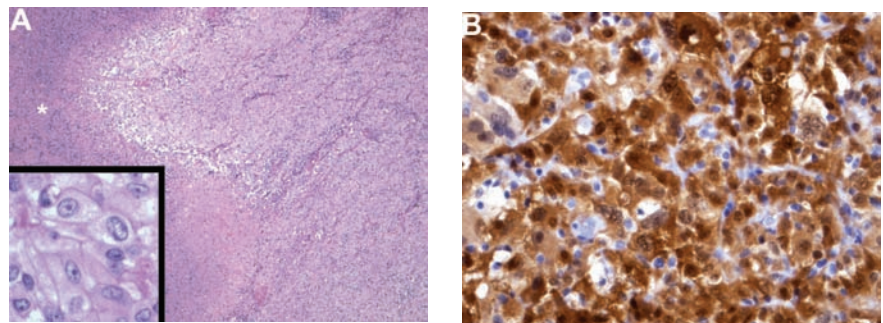
## Discussion

The most common tumor arising from the pericardium is a secondary tumor with metastases most frequently arising from lung, breast, melanoma, and lymphoma.<sup>1</sup> In a study of 2649 autopsies performed in patients with malignant tumors, there were 407 cases of secondary involvement of the heart and/or pericardium but only 1 case of a primary tumor (malignant mesothelioma).<sup>2</sup> Primary pericardial tumors are rare entities, and include benign (teratomas, fibromas, angiomas and lipomas) and malignant (mesothelioma and sarcoma) tumors.<sup>3</sup>

Although primary pericardial mesothelioma is infrequent, it is the third most common tumor of the heart/pericardium after angiosarcoma (33%) and rhabdomyosarcoma (20%).<sup>4</sup> In a study of about 500,000 autopsies, its incidence was <0.0022%<sup>5</sup> however, it accounts for approximately 2-3% of all cardiac and pericardial primary tumors.<sup>4,6</sup> Mesothelioma arises from the serous epithelial cells 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.<sup>4,6</sup> Pericardial mesothelioma can present as a localized lesion or a diffuse infiltration of the pericardium. Four histological types have been described including epithelioid, sarcomatoid, desmoplastic and biphasic.<sup>7</sup> Pleural and peritoneal mesothelioma development has been correlated with exposure to asbestos; however, the role of asbestos in pericardial mesothelioma is



**Figure 1. Cardiac magnetic resonance imaging. (A) At diagnosis. (B) Pre-radiation. (C) Post-radiation. (D) 40 months post-radiation.**



**Figure 2. Tumor histology. (A) The tumor was composed of sheets of large pleomorphic epithelioid cells with abundant pale cytoplasm and well demarcated cell borders. The tumor demonstrated geographic areas of necrosis (\*). Hematoxylin and eosin stain, original magnification x40 (inset x400). (B) In an immunohistochemical stain for calretinin, a marker of mesothelial differentiation, the tumor cells showed strong and diffuse brown staining. Hematoxylin counterstain, original magnification x200.**

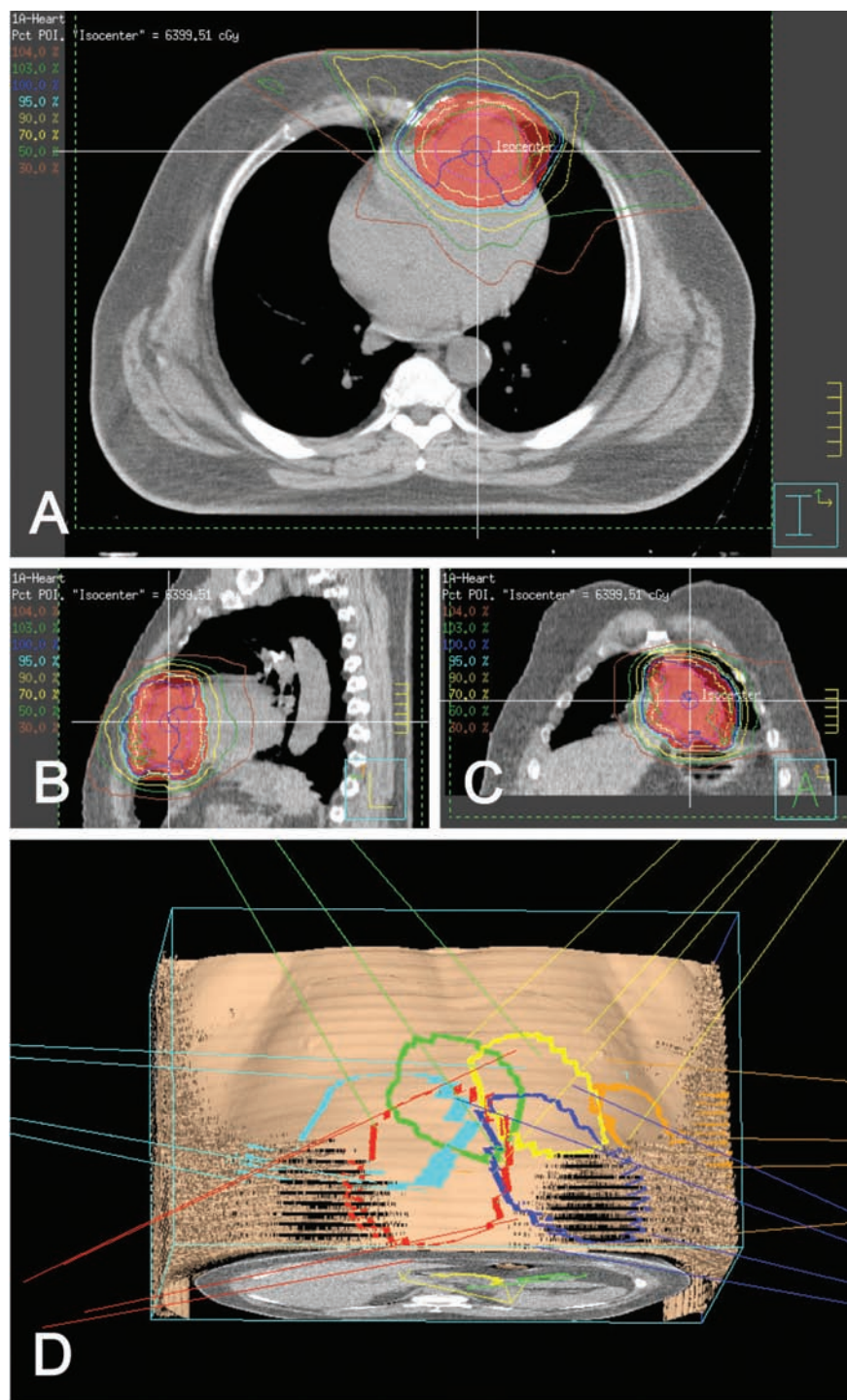
unclear.<sup>6,8</sup> A rare association with pericardial mesothelioma and tuberculosis has been reported.<sup>9</sup>

Symptoms arising from primary pericardial mesothelioma usually result from constriction of the heart or compression of surrounding structures, ranging from dyspnea, cough, dysphagia and chest pain.<sup>8</sup> The onset of symptoms is usually insidious. Constrictive pericarditis, pericardial effusion, cardiac tamponade and heart failure can all be clinical manifestations of pericardial mesothelioma. Compression of coronary arteries and local spread of the disease to surrounding large vessels can result in

additional symptoms.<sup>3</sup> Additionally, distant metastases, myocardial infarction secondary to conduction blockade, as well as tumor embolism causing neurological deficits have been reported.<sup>10,11</sup>

Diagnosis of the disease can be challenging, and in only 10-20% of cases a diagnosis is made prior to the patient's death.<sup>6</sup> The initial test usually consists of an echocardiogram. Imaging such as MRI and CT can be helpful in identifying the extent of disease and infiltration into adjacent structures; an ultrasound or CT guided biopsy of the pericardium can also be performed. Moreover, cytological examina-





**Figure 3. Representative isodose plan for treatment using 3D conformal radiation. (A) Axial view. (B) Sagittal view. (C) Coronal view. (D) Beam arrangement.**

tion, immunohistochemistry, and high pericardial hyaluronic acid content of the pericardial aspirate can be diagnostic; however, pericardial fluid in pericardial mesothelioma can be difficult to aspirate.<sup>3</sup> Mesothelioma cells stain positive for cytokeratin, vimentin, epithelial membrane antigen and calretinin, and negative for CEA, CD15 and S-100.<sup>12,13</sup> The tumor can readily metastasize and involve regional

lymph nodes, lungs and kidneys, doing so in approximately 25-45% of patients.<sup>14</sup>

In regards to treatment, surgical resection can be curative in localized cases. Reduction of the mass has been achieved with cyclical combination chemotherapy with doxorubicin, vincristine, and cyclophosphamide as well as with radiotherapy.<sup>3,6</sup> However, despite the best efforts, no significant difference has been

achieved in regards to prognosis, and the median survival time is approximately 6 months from diagnosis.<sup>7,15</sup> Ongoing research for this disease includes such devices as intracavitary chemotherapy and irradiation, photodynamic therapy, inhibition of growth factors, and vaccines.<sup>16</sup>

## Conclusions

Primary pericardial mesotheliomas are rare tumors. We report a case of a patient with primary pericardial malignant mesothelioma with a complete clinical response and local control at 50 months following high dose radiation. Modest benefits are generally reported with chemotherapy and radiation, and median life expectancy is very low. Despite these facts, we recommend consideration of curative high dose radiation as a reasonable treatment option for patients with unresectable or recurrent primary pericardial mesotheliomas.

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