Primary Cardiac Sarcoma*
A Novel Treatment Approach

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Primary cardiac sarcomas carry a dismal prognosis with no known curative therapy using standard treatment approaches. By its very location, the possibility of a radical complete resection—the underlying principle in the management of any soft-tissue sarcoma—is precluded. While literally in a continuous "blood bath," cardiac sarcomas are associated with a very high rate of hematogenous metastases. This report describes the management of a case in a 51-year-old white man with a high-grade unresectable cardiac sarcoma who was treated with hyperfractionated (twice daily) radiotherapy to a total dose of 70.50 Gy along with a radiosensitizer, (5'-iododeoxyuridine. The patient currently is disease-free and functioning well more than 5 years following this novel treatment approach.

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Primary sarcomas of the heart are a rare entity associated with a uniformly dismal prognosis. The standard modalities of therapy, surgery and adjuvant radiotherapy or chemotherapy, have been consistently unsuccessful. In a large review of 75 primary sarcomas of the heart, Burke et al1 reported a median survival of only 6 months. Cardiac sarcomas thus present a challenge to those faced with the management of these patients who typically present in the third to fifth decade of life. This study shows an innovative plan that was used at the National Cancer Institute in the management of a patient with a primary cardiac sarcoma.

CASE HISTORY

CLINICAL DATA

The patient is a 51-year-old white man who presented in May of 1992 with pleuritic substernal chest pain, low-grade fevers, night sweats, a persistent nonproductive cough, and dyspnea on exertion. These symptoms were initially thought to be pericardial in origin. However, further workup with an echocardiogram showed a large tumor invading the right atrium and right ventricle extending across the tricuspid valve. An MRI confirmed the presence of a large intracardiac mass (Fig 1). On selective right coronary artery injection and catheterization, this mass was found to extend the entire length of the atrioventricular groove from near the ostium of the right coronary artery all the way into the distal portions of the right coronary circulation. The tumor extended into both the right atrium and right ventricle, impinging on the tricuspid annulus and causing some degree of regurgitation.

The patient's past medical history disclosed no abnormalities. He never smoked and occasionally drank alcohol. He worked for a gas and electric company installing gas lines and he reports a history of asbestos exposure. Other than 2+ bilateral lower extremity edema, the remainder of the physical examination was within normal limits with no evidence of any heart murmur. The patient had intermittent episodes of atrial fibrillation that responded well to a combination of digoxin (Lanoxin) and diltiazem hydrochloride. A metastatic workup (including CT scans of the chest, abdomen, and pelvis; a bone scan; and a laboratory workup) disclosed no abnormalities. A right ventricular endomyocardial biopsy was attempted. Normal myocardium was obtained, but this procedure inadvertently caused pericardial tamponade that required pericardial drainage for approximately 1 day. An open myocardial biopsy was performed in August 1992 which showed that the tumor was far too extensive to consider resection.

PATHOLOGIC FINDINGS

Examination of the sections stained with hematoxylin-eosin (Fig 2) showed a uniform population of large atypical cells with prominent nucleoli. There was no light microscopic evidence of smooth muscle formation, storiforming, or pleomorphism. The vessels appeared to be separate from the tumor. No intranuclear inclusions were noted. The differential diagnosis included sarcoma (rhabdomyosarcoma, angiosarcoma, or undifferentiated), metastatic carcinoma, amelanotic melanoma, and anaplastic lymphoma. Immunohistochemical stains were negative for leukocyte common antigen (LCA-CD45), S-100 protein, CAM 5.2, keratin, EMA, HPCA-1CD34, factor VIII, and KPI/CD68. Tumor cells showed staining for Ulex Lectin and equivocal staining for desmins and actin.

By electron microscopy, the tumor cells showed abundant lysosomal vacuoles, neutral lipid, and intermediate filaments. There was no evidence of skeletal muscle or gap junctions noted, and the intermediate filaments were interpreted as most likely representing vimentin in light of the focal desmin reactivity. Based on the severe degree of anaplasia, this tumor was believed to be a high-grade sarcoma.

TREATMENT

The patient was treated according to the Radiation Oncology Branch protocol for unfavorable neoplasms with iododeoxyuridine, a halogenated pyrimidine analogue of thymidine with radiosensitizing properties,2 and with hyperfractionated radiotherapy. After receiving 48 h of iodouridine to allow adequate time for uptake of the drug, hyperfractionated radiotherapy was begun on September 18, 1992, using 150 cGy twice daily (with 6 h between fractions). The iododeoxyuridine infusion was continued for almost 2 weeks, and then a second cycle was administered halfway through the course of radiation. Initially, the entire heart was treated to 3,000 cGy using anteroposterior-posteroanterior fields (Fig 3). A left ventricular block was then added (on October 1, 1992), for the next 600 cGy (Fig 3). Using left anterior oblique-right posterior oblique fields, a shrinking
field technique was then used to take the tumor volume to a total dose of 7,050 cGy (Fig 4). The entire treatment involved 47 fractions over 37 days and was completed on October 28, 1992.

The patient tolerated the treatment well, except for moderately severe radiation esophagitis that required a soft diet, and resolved 2 to 3 weeks after treatment. Due to a drop in his platelet count, the patient’s iododeoxyuridine cycles were curtailed by 1 day per the protocol specifications. By the 3rd week of treatment, the patient’s lower extremity edema had resolved, and he no longer had the daily episodes of low-grade fevers and night sweats.

**FOLLOW-UP**

Over the initial 15 months, there was a gradual decrease in the size of the lesion on the MRI until it reached approximately half its original size (approximately 4 cm) in early 1994. Figure 5 is a recent MRI showing the residual abnormality in the right side of the heart; this abnormality has remained unchanged. As with other soft-tissue sarcomas, there is rarely complete resolution of the mass following radiation since the tumor is also composed of extracellular matrix material which does not necessarily regress following radiation treatment. Follow-up echocardiograms also demonstrated the slow shrinkage over time. The right atrium has become dilated, but the left ventricular function has remained intact. Also noted are mild aortic and mitral regurgitation as well as moderate tricuspid regurgitation.

The patient has done reasonably well after therapy and remains clinically disease-free more than 5 years after diagnosis. In the initial period following his treatment, the patient gradually resumed an active lifestyle including playing golf. In early 1994, the patient developed several recurrent right pleural effusions requiring multiple thoracenteses, all of which did not disclose malignant tumors. The patient had a pleural biopsy which showed fibrosis with reactive mesothelial cells but no evidence of malignant tumors. Talc pleurodesis was performed, and the patient has not had a recurrent symptomatic pleural effusion since that time. In July 1997, pneumonia was diagnosed, and the patient had a protracted recovery period. A thorough evaluation at the National Cancer Institute revealed evidence of severe restrictive lung disease and reduced diffusion capacity compatible with radiation fibrosis. He now requires supplemental oxygen with exertion and has adjusted to being more sedentary.

**DISCUSSION**

Approximately 25% of primary cardiac tumors are malignant. The vast majority of malignant tumors of the heart are sarcomas. Although sarcomas can occur at any age, the majority of cases occur between the third and fifth decades of life, as in this patient. The most common site of involvement is the right side of the heart, such that the most frequent presentation is right-sided congestive heart failure.

Cardiac sarcomas have a dismal prognosis. Applying the general principles of treatment of soft-tissue sarcoma occurring outside the heart, the most critical element is a complete surgical resection. Yet, there is perhaps no location more difficult for obtaining a margin of resection than the heart itself. The use of radiotherapy also is restricted in many ways. Typically, a dose of 6,000 to 6,500 cGy is required as adjuvant therapy following complete resection of a high-grade sarcoma. In unresectable lesions, or those with gross residual disease, most investigators suggest increasing the dose to greater than 7,000 cGy. Such high doses of radiation, though, are not tolerated well by the heart. Stewart has shown that 6,000 cGy to the whole heart is associated with an approximately 40% incidence of pericarditis. The most active chemotherapy

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**FIGURE 1.** Pretreatment MRI showing a large (7.5 cm) right-sided intracardiac mass.

**FIGURE 2.** Tumor cells are pleomorphic with abundant cytoplasm and distinct nucleoli. Areas of necrosis and mitotic figures classify the tumor as a high-grade sarcoma (hematoxylin-eosin, original ×40).
agent in the treatment of sarcoma is doxorubicin hydrochloride (Adriamycin), which is itself associated with significant cardiotoxicity.

Based on the previously mentioned facts, it is not surprising that the treatment of cardiac sarcomas has been uniformly unsuccessful. In one study of 125 patients, McAllister\textsuperscript{5} found that the vast majority of the patients died within a year of diagnosis. Similarly, Burke et al\textsuperscript{5} reviewed 75 primary sarcomas of the heart and reported a median survival of only 6 months. In their multivariate analysis, a low level of mitotic activity and any therapy were the only significant factors affecting survival rate. Survival rates appeared to be better in patients receiving chemotherapy and radiation therapy.

The key to any successful treatment regimen employing radiation or chemotherapy or both depends on the therapeutic ratio, ie, the ability to sterilize the tumor while sparing surrounding normal tissues. One class of radiation sensitizers, the halogenated pyrimidines, allows for a differential effect between the tumor and normal tissues as these compounds sensitize cells based on the amount of the analog incorporated. Halogenated pyrimidines are thymidine analogues in which a methyl group is replaced by a halogen, such as chlorine, bromine, or iodine. Since the halogen is very similar in size to the methyl group, such fraudulent bases (eg, 5'-iododeoxyuridine) are incorporated into the DNA chain in place of thymidine. This substitution creates a "weak link" in the DNA chain such that labeled cells are more susceptible to damage by irradiation. As the percentage of the analog incorporated into the DNA increases, so does the extent of radiosensitization.\textsuperscript{2} In principle, tumor cells grow faster and, thus, incorporate more of the drug than the surrounding normal tissues. This strategy was thus exploited in the mediastinum, where the majority of the surrounding tissues (lung, heart, and spinal cord) are comprised of cells that are slowly dividing. The only exception is the esophagus, in which the cells of the mucosal lining regenerate rapidly in response to damage. It is of interest that this patient

**Figure 3.** Initial anteroposterior-posteroanterior radiotherapy fields. The white rectangle delineates the radiation port. The black cross-hatched areas at the field edges correspond to the custom-made blocks to protect adjacent normal structures. A left ventricular block was added after treatment with 3,000 cGy (on October 1, 1992) for the next 600 cGy. TV=tumor volume.

**Figure 4.** Left anterior oblique and right posterior oblique fields used to boost the tumor volume to a total dose of 7,050 cGy.

**Figure 5.** Posttreatment MRI showing significant shrinkage of the intracardiac mass to 4 cm in diameter.
experienced moderately severe esophagitis during treatment that may have been exacerbated by the use of iododeoxyuridine.

Another strategy to avoid late complications is to carefully aim the radiation to treat the tumor yet spare as much of the normal surrounding tissue as possible. As can be seen from the 3-dimensional reconstruction (Fig 6), the 90% isodose line (depicted in blue) encompasses the tumor volume (depicted in red), while sparing much of the normal heart tissue (depicted in yellow), especially the left ventricle. A dose-volume histogram shows that while essentially 100% of the tumor volume received the full prescribed dose, approximately 50% of the heart received less than 6,000 cGy (Fig 7). Moreover, hyperfractionated radiotherapy (employing more than one fraction of radiation per day) has been found to reduce the late effects of radiotherapy while achieving the same or better tumor control.

The patient's history of asbestos exposure is of interest because there have been case reports of cardiac sarcomas associated with asbestos exposure. In one study, cytogenetic analysis of a primary cardiac spindle cell tumor demonstrated a translocation (X;18), an aberration almost exclusively reported in synovial sarcomas. Pathologic examination revealed amphibole asbestos within the lungs and diaphragmatic pleural plaques indicative of asbestos exposure. These findings raise interesting questions about the possible cause of this tumor.

**Addendum**

Following submission of this report, the patient entered a period of accelerated clinical decline due to the chronic cardiopulmonary toxicity resulting from his intensive therapy. In March 1998, he was admitted to the hospital for a syncopal episode, while in the process of being evaluated for heart/lung transplant as an attempt to prolong his life in the face of end stage pulmonary hypertension. Although he was able to leave the hospital, his condition never became stable enough to allow the transplant, and 1 month later he was readmitted for respiratory failure with an admission chest radiograph most consistent with pulmonary edema superimposed on severe pulmonary fibrosis. He then developed most likely an aspiration pneumonia and died shortly thereafter.

An autopsy was performed, and on gross examination, the thoracic organs were encased in a bed of adhesions, making it difficult to dissect the lungs from the pleural surfaces and the heart from the mediastinum. Gross examination of the heart revealed marked right ventricular hypertrophy. The area corresponding to the original intracardiac tumor was a cavity filled with a cream-colored necrotic material. Examination of this material showed it to be acellular. The remaining cardiac tissue showed microscopic characteristics of radiation effect. There was no evidence of sarcoma within the heart, and the remaining gross and microscopic examinations did not detect any evidence of distant metastases, thus pathologically confirming that the patient had been rendered free of malignant disease by the combination of iododeoxyuridine and radiotherapy.
Although, in principle, we have demonstrated that this novel treatment approach can eradicate a primary cardiac sarcoma, this patient ultimately died more than 5½ years following diagnosis from the complications resulting from intensive thoracic irradiation. Our experience at the National Cancer Institute has been that iododeoxyuridine does not contribute to the development of late effects. Future attempts with this approach will need to incorporate recent advancements with sophisticated 3-dimensional conformal radiotherapy planning techniques in order to further reduce the radiation dose to surrounding normal structures.

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