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Significant Response to Oral Etoposide in the Treatment of an Unresectable Cardiac Sarcoma

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Abstract

Primary cardiac sarcomas are rare and carry a poor prognosis. The standard of care is complete resection. Outcomes for patients without complete resection are dismal, and the benefit of adjuvant therapy is uncertain. A 9-year-old female presented with a large right-sided cardiac mass. Following biopsy, the tumor was classified as an undifferentiated sarcoma. Resection was not feasible due to apparent invasion of the right ventricle and atrioventricular groove. Treatment with oral etoposide resulted in a 97% reduction in tumor volume and allowed for complete resection of residual tumor. She is alive with no evidence of disease 25 months from diagnosis.

Keywords

Soft tissue sarcomas; rare tumors; chemotherapy

Introduction

Primary cardiac tumors are rare with an estimated prevalence of 0.02% in autopsy series.¹ The majority are benign, but approximately 25% are malignant.¹ Sarcoma is the most common primary cardiac malignancy, with one-third of these categorized as undifferentiated.² Given the rarity of these tumors, most data have been generated by small, single-institution series of adult patients.

Historically, median overall survival has been poor, ranging from 6–12 months.^{3–7} Studies show a survival benefit for patients who are able to undergo complete resection.^{3–9} From these reports, patients with incomplete or no resection have a median survival ranging from 4 to 10 months versus 12 to 27 months for those with complete resection.^{3–9}

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Several patients have been treated with chemotherapy, most commonly doxorubicin and/or ifosfamide-containing regimens, with no evident survival benefit, although studies are limited by small numbers.^{4-6, 8} The mainstay of therapy remains local control with complete surgical resection.^{4, 6-8} Limited efficacious options exist for patients presenting with unresectable tumors. The approach of using neoadjuvant oral etoposide for an unresectable cardiac sarcoma has not been previously described.

Case report

A 9-year-old female presented with a 6-month history of dry cough, a 2-week history of progressive dyspnea, fatigue, abdominal pain, anorexia and weight loss, and the acute onset of facial swelling. On exam, she was tachycardic with an irregular rhythm. She had obvious periorbital edema, breath sounds were decreased on the right and her liver was palpable 3cm below the right costal margin. A computed tomography (CT) scan revealed a large mass measuring 10.4×10.5×14.0cm occupying the majority of the right hemi-thorax with significant compression of the caval veins and right heart (Fig. 1A-D). CT of the abdomen and pelvis and bone scan were negative.

She had long runs of ventricular and supraventricular tachycardia and became hemodynamically unstable. The arrhythmia and facial swelling improved following the initiation of amiodarone therapy. She received dexamethasone and emergent radiation therapy for 2 fractions (600cGy total) without evidence of tumor lysis or shrinkage. A mediastinal needle biopsy was non-diagnostic and bone marrow aspirate and biopsy were normal. She underwent sternotomy with open biopsy and attempted resection. The tumor appeared to originate from the right ventricular myocardium and atrioventricular groove. The size of the tumor precluded manipulation without significant hemodynamic deterioration. Incisional biopsy was associated with significant bleeding. Given this constellation of findings, cardiopulmonary bypass and attempted resection would have been imprudent.

On light microscopy, the biopsy specimen showed a patternless, cellular tumor with foci of vague nesting and alternating thin fibrovascular septa (Fig. 2A). The tumor cells contained abundant clear to eosinophilic cytoplasm with variable-sized, rounded nuclei, granular to vesicular chromatin, and inconspicuous nucleoli. Immunostains for muscle specific actin and myoglobin were strongly positive (Fig. 2B-C). CD99 showed patchy staining. Myogenin, desmin, smooth muscle actin, S100, CD 31, CD 34, synaptophysin, epithelial membrane antigen, and cytokeratin were negative. INI-1 was retained. Fluorescence in-situ hybridization was negative for t (1;18) (SYT translocation seen in synovial cell sarcoma). 68% of cells had extra intact SYT signals, indicating polysomy or polyploidy of a presumed neoplastic clone. Four cells were karyotyped. These cells had 49 to 63 chromosomes. Each of the cells had several clonal abnormalities as well as a large number of non-clonal abnormalities, many too complex to be interpretable, with considerable cell to cell variation in the karyotype.

Immunohistochemical staining suggested muscle differentiation. However, the tumor failed to show any additional diagnostic histologic, immunohistochemical or cytogenetic features

of a recognizable line of differentiation. Consequently the tumor was categorized as an undifferentiated primary cardiac sarcoma.

She received a course of intravenous ifosfamide ($3\text{g}/\text{m}^2/\text{day} \times 3$), carboplatin ($635\text{mg}/\text{m}^2/\text{day} \times 1$) and etoposide ($100\text{mg}/\text{m}^2/\text{day} \times 3$) (ICE). A CT scan at 3 weeks and chest x-ray at 6 weeks following therapy showed no change. She began cycles of daily, oral etoposide ($50\text{mg}/\text{m}^2/\text{day}$) for 21 days then off for 7 days. After 3 cycles a CT scan demonstrated vast improvement in the size of the mass, measuring $4.4 \times 5.0 \times 9.0\text{cm}$. She continued on the same schedule of oral etoposide for 13 cycles for a total cumulative dose of almost $14\text{g}/\text{m}^2$. Interval CT scan demonstrated progressive reduction in tumor size, measuring $2.0 \times 3.0 \times 6.6\text{cm}$; a 97% reduction in tumor volume (Fig. 1E-H).

Given the significant decrease in tumor size and a negative metastatic workup, repeat exploration was indicated. The tumor originated from the atrial myocardium at the superior cavo-atrial junction with adherence to the superior vena cava, aorta, right atrioventricular groove, right atrium and inferior vena cava. Identifiable dissection planes permitted separation of the tumor from all structures except the right-sided pericardium and the right atrium. Pericardium was resected en bloc. Elevation of the tumor permitted application of a vascular clamp posterior to the tumor, which enabled resection of the right atrium en bloc with wide atrial margins and preservation of sinus rhythm and non-obstructed caval inflow. Cardiopulmonary bypass was not required. The resultant atriotomy was closed primarily. Cryotherapy of the atrioventricular groove (-90°C , 1 minute, two cycles) resection bed was utilized to ensure an adequate margin.

Pathological examination of the resection specimen revealed fibrotic and necrotic areas with a small, reddish-grey nodule ($2.4 \times 1.8 \times 1.3\text{cm}$) of viable tumor (Fig. 2D). The residual tumor was bordered by a fibrotic rim (Fig. 2E) and was histologically similar to the initial biopsy specimen. The resected margins were free of tumor involvement.

Postoperatively she did well with no significant complications. She was weaned off amiodarone with no re-emergence of arrhythmia. CT angiography 2 months after surgery demonstrated patency of the right coronary artery. No further adjuvant etoposide was prescribed. She has remained off chemotherapy for 11 months with no evidence of disease 25 months from diagnosis.

Discussion

This case presented diagnostic and therapeutic challenges. Given the lack of diagnostic histologic or cytogenetic features and the relative paucity of positive immunohistochemical markers, it was difficult to classify this tumor. The differential diagnosis included angiosarcoma, rhabdomyosarcoma, leiomyosarcoma, fibrosarcoma, synovial cell sarcoma, liposarcoma and rhabdoid tumor. CD31 and CD 34 are typically positive in angiosarcoma, and were negative in this tumor. The positive staining for muscle specific actin and myoglobin suggested a tumor of mesenchymal origin, possibly muscle, although a component of background staining could not be entirely ruled out. The tumor failed to stain for smooth muscle actin, myogenin and desmin, making rhabdomyosarcoma and

leiomyosarcoma less likely. The tumor was negative for vimentin, which did not support a diagnosis of fibrosarcoma, and also negative for cytokeratin and the (X;18) translocation, both typically seen in synovial cell sarcoma. The tumor was negative for S100, which, along with vimentin, is typically positive in liposarcoma. INI-1 was retained, ruling out malignant rhabdoid tumor. Given these findings, the tumor was best described as an undifferentiated sarcoma; a classification that accounts for one-third of all primary cardiac sarcomas.²

Therapeutically, complete resection is critical for any chance of survival beyond 1 year in patients with primary cardiac sarcomas.^{4, 6–8} However, our multi-disciplinary team deemed that initial resection posed an unacceptably high risk of mortality. Heart or combined heart and lung transplantation has been tried for patients with similarly unresectable tumors, although this strategy has met with limited success with the majority of patients experiencing local or distant disease recurrence.^{10–12} Additionally, the presence of active malignancy precluded heart transplant listing at our center. Our patient's response to oral etoposide permitted a pathologically complete resection. The use of cryotherapy with the intent of preventing local recurrence of a cardiac sarcoma is unique and based on clinical judgment and prior reports citing potential benefits in soft-tissue sarcomas or other cardiac tumors.^{13, 14}

Doxorubicin in combination with ifosfamide is a common regimen for the treatment of undifferentiated sarcoma.^{4–6, 8} The lack of compelling data for efficacy in this setting, in addition to her tenuous hemodynamic status, influenced the decision to avoid treatment with anthracyclines. Following a course of ICE there was no obvious treatment effect on the size or character of the tumor. It remains possible (especially in light of her subsequent response to oral etoposide) that the initial course of ICE had some delayed effect and/or that further cycles of ICE might have had some efficacy. Given the unresectability of the mass as well as uncertain benefit of further chemotherapy, we sought an approach to improve her symptoms and maximize her quality of life.

Previous studies have shown some efficacy and limited toxicity with daily oral etoposide in the treatment of a variety of solid tumors in the relapsed or refractory setting.^{15, 16} Kebudi et al demonstrated efficacy with the use of daily oral etoposide at 50mg/m²/day in the treatment of progressive or recurrent soft tissue sarcomas in children.¹⁵ In this study, 3 of 21 children experienced a complete or partial response to etoposide alone and an additional 8 children had some period of disease stabilization. Two patients were long-term survivors.

The incidence of secondary leukemia with high cumulative doses of etoposide limits its use. In a study of 18 patients treated with continuous etoposide, 5 developed secondary leukemia.¹⁷ In another study, patients treated with greater than 6g/m² of etoposide had 197 times the risk of secondary leukemia compared to those treated with less than 1.2g/m².¹⁸ Despite the risk of secondary leukemia, in patients with a poor prognosis and limited treatment options, daily oral etoposide should be considered early in their course as, in rare cases, it may result in durable remissions.

Oral etoposide induced significant tumor shrinkage in a case of an initially unresectable cardiac sarcoma allowing for later resection with negative surgical margins and no operative

morbidity. This therapy may be a viable option for patients with similar tumors and are unable to have complete initial resection. The benefit of a possible complete resection must be weighed against the risk of secondary malignancy with high cumulative doses of etoposide.

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Figure 1.

Computed tomography of chest with contrast. A-D) Radiographs at time of diagnosis: A) Coronal view B) Axial view the level of the aortic arch C) pulmonary arteries D) base of the heart. E-H) Radiographs following chemotherapy: E) Coronal view F) Axial view at the level of the aortic arch G) pulmonary arteries H) base of the heart

Figure 2.

A-C) Pathology images from open biopsy at diagnosis: A) Hematoxylin and eosin 20X B) Muscle specific actin 20X C) Myoglobin 20X. D-E) Pathology images following resection: D) Gross resection specimen E) Hematoxylin and eosin 10X