An adolescent with primary undifferentiated pleomorphic sarcoma of the heart with MDM2 amplification successfully treated with multimodal therapy: Case report and Review of Literature

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Abstract

Primary Undifferentiated pleomorphic sarcomas (UPS) of the heart extremely rare but aggressive tumors in the pediatric age group with an extremely poor prognosis and no clear guidelines available for best management. Diagnosis is often delayed, as they may be insidious and masquerade as other cardiac benign tumors. We present a rare case of cardiac UPS in a 13 year old with 40 months disease free survival following a combination of early gross total surgical resection followed by adjuvant chemotherapy and radiation therapy. The case highlights the importance of a timely diagnosis and multimodal multidisciplinary aggressive approach for improved survival.

Abstract

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Introduction

Primary malignant tumors of the heart in children and adolescents are exceedingly rare. Undifferentiated pleomorphic sarcomas (UPS) are cardiac sarcomas with no diagnostic histologic pattern or specific immunohistochemical profile. UPS generally arise in the left atrium, with a controversial prevalence depending on criteria adopted for diagnosis; in a broad definition, it represents the most common sarcoma type of the heart, accounting for 50% of cardiac sarcomas.[1, 2] On the other hand, benign cardiac tumors represent the majority of cardiac masses in children with myxomas being the most common.[3]

Cardiac sarcomas often present in an insidious manner in young adults and are characterized by a dismal prognosis.[4,5] It is difficult to provide insight into the biologic behavior, treatment, and prognosis of cardiac sarcomas in children because what is currently known is based on individual adult case documentations.

Treatment is often based on experiences from similarly labeled malignant tumors originating in other parts of the body. We are presenting a case of primary cardiac UPS with 40 months disease free survival following multimodal therapy provided by a multidisciplinary team.

Case

A 13-year-old female with no prior medical history presented to the emergency department with a two-month history of pallor, cough, fatigue, stomach pain and loss of appetite. Chest x-ray showed cardiomegaly at an outside cardiology office and she was referred to us. She denied chest pain, shortness of breath or palpitations. Patient endorsed a 5-pound weight loss over 2 months. There was no history of contact with tuberculosis, travel except Mexico and no exposure to pets. On examination, the patient was afebrile, breathing comfortably with a normal oxygen saturation. She was tachycardic and normotensive with no postural deficit. She, had a 3/6 diastolic murmur, hepatomegaly 3 cm below the costal margin, and jugular venous distension. There were no rubs or thrills and her lungs were clear to auscultation.

Laboratory results were significant for leukocytosis, anemia, hypophosphatemia, slightly elevated transaminases and dramatically elevated inflammatory markers. An ECG revealed sinus tachycardia with normal p-wave axis (+60°) and a low voltage QRS. Transthoracic echocardiogram, CT and cardiac MRI (Fig 1A-E) confirmed a large intracardiac mass that appeared to originate from the right sided atrial septum, occupied most of the dilated right atrium and protruded through the tricuspid valve into the RV outflow tract causing right tricuspid valve obstruction. There was a moderate pericardial effusion. Right ventricular ejection fraction (EF) and stroke volume and left ventricle EF were moderately reduced. Considering the location, size and nature of the mass, these findings were initially thought to be compatible with a large right atrial myxoma. A full-body CT scan revealed no evidence of distant metastasis.

After multidisciplinary discussions the patient underwent cardiac surgery with a cardiopulmonary bypass that included a gross total resection of the intracardiac mass, pericardial patch of the atrial septum and suture annuloplasty of the tricuspid valve. Tricuspid valve replacement was avoided due to risk of valve degeneration and calcification in the setting if anticipated adjuvant chemo radiotherapy. Histological analysis identified the tumor as an undifferentiated high grade (FNCLCC grade 3) pleomorphic sarcoma and FISH analysis revealed a MDM2 amplification (fig F -I). Post-operative course was uneventful and post-operative MRI and PET scans showed no residual disease. Patient developed moderate tricuspid regurgitation post operatively that improved with time. Combined modality adjuvant therapy with chemotherapy and radiation therapy (RT) followed recovery from surgery. She received 6 cycles of chemotherapy (21 day cycles of doxorubicin on Days 1, 2 (75 mg/m2/cycle) and Ifosfamide on Days 1, 2, 3 (9 g/m2/cycle) with G-CSF support). She was referred for concurrent RT after 1 cycle of chemotherapy. The 4D motion of the heart obtained from CT simulation was used to define the target volumes. The decision was made to initially include the entire heart to 25.2Gy) given the presence of a moderate amount of pericardial effusion at diagnosis, infiltrative nature of these tumors, inability to obtain negative resection margins in this location, possible inaccuracy of MRI scans for delineating actual cardiac tumor extent, intraoperative tumor spillage and targeting uncertainties due to the current inability to deliver cardiac gated IMRT. The RT planning target volumes and dose-volume histograms are shown in Fig 2. She received a cumulative dose of 54 Gy in 30 fractions from week 4 -10 of concomitant chemotherapy.

Her interval history was complicated by the development of post-radiation pericardial effusion that was observed on her surveillance echocardiograms starting 6 weeks post -radiation. She was started on systemic corticosteroids with concurrent increase in her Lasix dose and the effusion resolved within 10 weeks. The patient was monitored with three monthly MRI, CT chest and transthoracic echocardiograms for 24 months and then with six monthly MRI planned until 60 months post-surgery. She is now 40 months post therapy and continues to be in complete clinical and radiologic remission with normal cardiac function and no late effects.

Discussion

We present an extremely rare example of successful use of multimodal therapy and excellent survival outcome

in an adolescent patient with an aggressive primary cardiac UPS. Because of non-specificity of symptoms and rarity of these UPS, they are often difficult to diagnose preoperatively and are missed occasionally.[5, 6] The majority are presumed to be benign myxomas and the suspicion of sarcomas arises at the time of operation due to its invasive nature. Abnormal pre-operative imaging features (immobility of the mass, neovascularity, multicentricity, calcification and invasion into the heart structures) should raise the suspicion for a cardiac sarcoma.[6]Given the difficulty of biopsy in cardiac tumors, a presumptive diagnosis must be made based on radiologic appearance with surgery undertaken to provide both definitive diagnosis and therapy. Patients with localized disease amenable to complete resection experienced longer survival compared to incompletely resected disease.[7-9]However, UPSs are aggressive and locally invasive tumors, frequently making complete surgical excision unfeasible, leading to a poor prognosis.[9, 10]

Due to the lack of large of representative pediatric case-series, there is no uniform approach to treating these patients, and the benefits of adjuvant therapy are unclear.[11-13] First-line adjuvant treatment generally usually consists of chemotherapy with doxorubicin and ifosfamide.[13] Data on the role of radiation therapy (RT) in cardiac sarcoma management are also sparse.[14,15] There is widespread fear among oncologists to use high RT doses to large volumes of the heart due to the significant concerns for increased risks of cardiac toxicities, including pericarditis, cardiomyopathy, coronary artery and valvular injury that may be irreversible[16]. All modern advances in RT planning and delivery including IMRT, respiratory gating and Cine imaging patient immobilization techniques have been used in this patient.

Based on older retrospective and heterogeneous adult case series, sarcomas of the heart are aggressive tumors with frequent tumor recurrence (45%) and metastases (72%) and most patients die within 12–16 months after diagnosis. In more recent series, survival is slightly prolonged but only for patients who underwent complete resection in referral centers. [16, 17] Very few pediatric cases are reported and long term survival in pediatric and adolescent patients is extremely uncommon.[18-19] A case of disseminated metastatic undifferentiated sarcoma in a 13 year old was reported who could not undergo complete resection and after multiple rounds of chemotherapy succumbed to widespread disease .[21] Another 12-year-old boy with metastatic primary UPS of the left atrium died 41 days after diagnosis.[22] A pediatric patient with cardiac undifferentiated sarcoma had good response to oral etoposide, followed by complete resection. [23] This report has currently surpassed the median survival rates cited in literature for a patient even after complete resection of the tumor.

The advent of molecular analysis and targeted therapy offers some promise. *MDM2* regulates the cell cycle by inhibiting the tumor suppressor p53, through ubiquitin-mediated degradation and transcriptional suppression. When upregulated, *MDM2* results in aberrant cellular proliferation.[24] In recent years, a number of small molecule inhibitors of *MDM2* have been developed which function to stabilize p53 activity and present a promising option for recurrent disease .[24]

This rare case illustrates two crucial aspects of cardiac tumors in pediatric patients: they can masquerade as other conditions and modern aggressive multidisciplinary management of these tumors can result in long-term good quality survival. Longer-term follow up is required to determine the incidence of late toxicities of these treatments including cardiac, pulmonary and secondary malignancies.

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Figure 1. **(A)** . Trans-esophageal echocardiographic image of the cardiac mass showing the large atrial mass originating from the right sided atrial septum and protruding through the tricuspid valve and into the Right Ventricle. (**B)** . Pulse Wave Doppler showing the pressure gradient across the tricuspid valve with a mean gradient of 10 mmHg and a peak of 14 mmHg and some obstruction to the outflow tract (**C)** . Contrast enhanced CT image demonstrates a pedunculated low attenuation right atrial mass from the inter-atrial septum extending through the tricuspid valve in the right ventricle. Axial **(D).**and sagittal **(E)** T2 weighted MR images demonstrate same pedunculated, smooth bordered, right atrial mass arising from the inter-atrial septum projecting into the right ventricle. Also, moderate pericardial effusion.

Fig 1 **(F)** H&E (40X objective) The tumor shows a moderate cellularity of pleomorphic cells with mitotic activity (arrow) with myxoid matrix, prominent dilated capillaries, and areas of necrosis (left edge, asterisk) accounting for more than 50% of the tumor volume. The tumor did not show evidence of maturation, being negative for desmin, S100, myogenin and CD34 and only focally positive for smooth muscle actin. The tumor shows positive Fig 1**(G)** MDM2 and Fig 1**(H)** CDK4 Immunostains Fig 1 **(I)** The specimen was a 70g, 7.3 X 5.0 X 4.4cm smooth surfaced mass partly surrounded by a thin pseudo capsule. The cut surface shows hyperemic and myxoid pale yellow areas.

Figure **2(A)** Axial CT image showing the pre-operative gross tumor volume (GTV) and planning target volumes (PTV) for the different doses (25.2Gy, 41.4Gy and 54Gy) using IMRT

Figure **2(B)** Dose volume histograms for the various tumor target volumes and normal structures after IMRT 54Gy/30fr was delivered with concurrent chemotherapy.