



Successful Use of Multimodal Therapy for an Adolescent with Primary Undifferentiated Pleomorphic Sarcoma of Heart with MDM2 Amplification: Case Report and Review of Literature

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Abstract

Primary Undifferentiated Pleomorphic Sarcomas (UPS) of the heart are rare in the pediatric age group with an aggressive course, a dismal prognosis and no standard recommendations present for best management. Diagnosis is often difficult and late, as they may be insidious and masquerade as other benign cardiac tumors. We present a rare case of cardiac UPS with MDM2 amplification in a 13 year old girl with 3.5 year survival with complete remission following a combination of early gross total surgical resection followed by adjuvant chemoradiation therapy. The case highlights the importance of an accurate and early diagnosis and an aggressive multimodal approach for improved survival with the assistance of a multidisciplinary team.

Keywords: Cardiac sarcoma; Pleomorphic undifferentiated sarcoma; Cardiac gated IMRT

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Background

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

Cardiac sarcomas often present insidiously on adolescents and young adults and are characterized by a very poor prognosis [4,5]. Most of the available literature on this diagnosis is from individual case reports and therefore it is difficult to provide clear insights into biologic behavior, management and prognosis of cardiac sarcomas in children. 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 3.5 year disease free survival following management by a multidisciplinary team using multimodal therapy.

Case Presentation

A 13-year-old female with no prior medical history presented to the hospital emergency room 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, dyspnea, orthopnea or palpitations. Patient endorsed a 5-pound weight loss over 2 months. There was no history of travel except Mexico and no exposure to pets. On examination, the patient was afebrile, breathing comfortably with 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

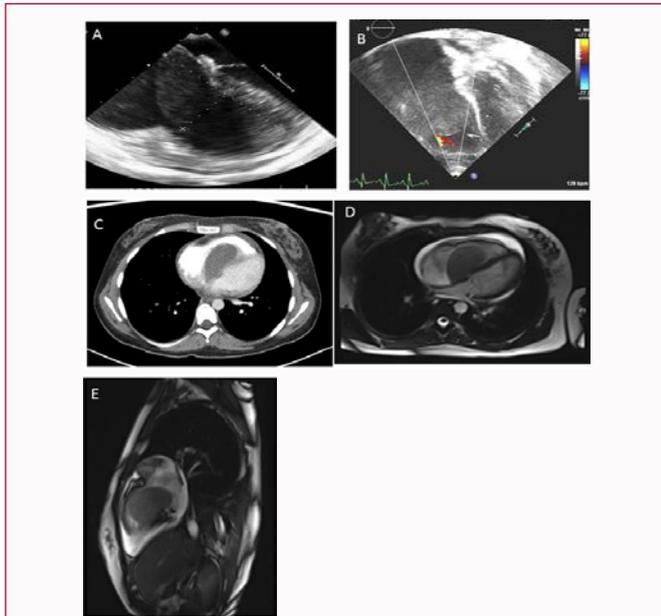


Figure 1: A: Trans-esophageal echocardiographic image of the cardiac mass showing the large atrial mass originating from the right sided atrial septum and protruding through the tricuspid valve and into the Right Ventricle. B: Pulse Wave Doppler showing the pressure gradient across the tricuspid valve 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. D: Axial 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.

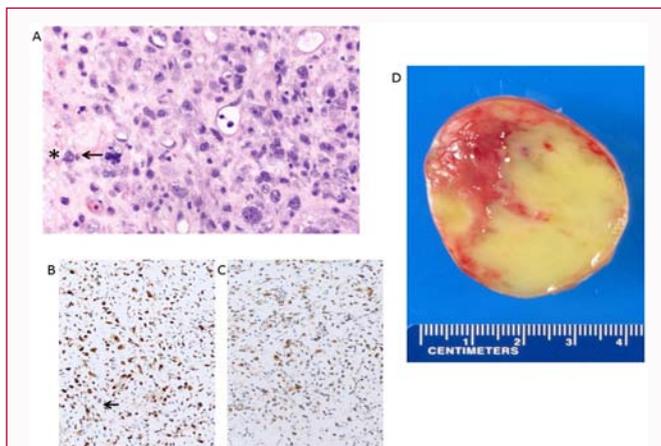


Figure 2: A: H&E (40x objective) The tumor shows a moderate cellularity of pleomorphic cells with mitotic activity (arrow) with myxoid matrix, prominent dilated capillaries, and areas of necrosis (left edge, asterisk) accounting for more than 50% of the tumor volume. The tumor did not show evidence of maturation, being negative for desmin, S100, myogenin and CD34 and only focally positive for smooth muscle actin. The tumor shows positive. B: MDM2 and C: CDK4 Immunostains, D: The specimen was a 70 g, 7.3 cm x 5.0 cm x 4.4 cm smooth surfaced mass partly surrounded by a thin pseudo capsule. The cut surface shows hyperemic and myxoid pale yellow areas.

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 (Figure 1A-1E) confirmed a

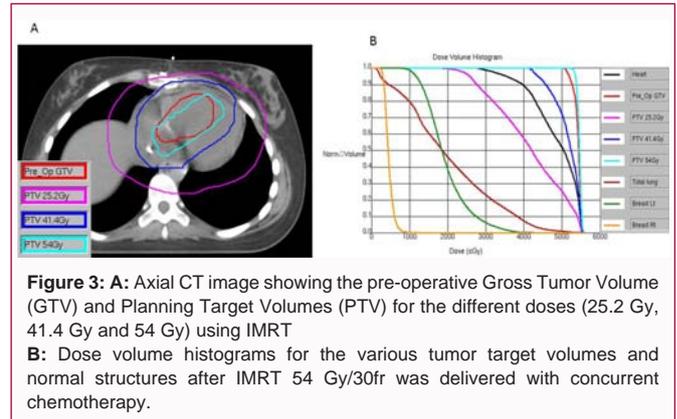


Figure 3: A: Axial CT image showing the pre-operative Gross Tumor Volume (GTV) and Planning Target Volumes (PTV) for the different doses (25.2 Gy, 41.4 Gy and 54 Gy) using IMRT. B: Dose volume histograms for the various tumor target volumes and normal structures after IMRT 54 Gy/30fr was delivered with concurrent chemotherapy.

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. There was no evidence of distant metastasis on a full body CT.

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 chemoradiotherapy. Histological analysis identified the tumor as an undifferentiated high grade (FNCLCC grade 3) pleomorphic sarcoma and FISH analysis revealed a MDM2 amplification (Figure 2A-2D). 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 1cycle of chemotherapy. The 4D motion of the heart obtained from CT simulation was used to define the target volumes. The team decided to initially include the entire heart to 25.2 Gy) 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 Figure 3. She received a cumulative dose of 54 Gy in 30 fractions from week 4 to 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 24months 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. UPS are often difficult to diagnose and missed preoperatively due to the non-specific symptoms and rare diagnosis [5,6]. Many masses are presumed to be benign myxomas and their invasive nature during surgery leads to the suspicion of sarcoma. On pre-operative imaging abnormal features such as neovascularity, multicentricity, immobility, calcification and invasion into the cardiac structures should raise the index of suspicion for a 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].

There are no large representative pediatric case-series reported, therefore there is no uniform approach to treating these patients, and the approach to type of adjuvant therapy is unclear [11-13]. First-line adjuvant treatment generally includes chemotherapy with ifosfamide and doxorubicin [13]. The role of Radiation Therapy (RT) in cardiac sarcoma is also not well reported [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 [14]. All modern advances in RT were planning and delivery including IMRT, respiratory gating and Cine imaging patient immobilization techniques has been used in this patient.

Based on older retrospectives 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 to 16 months after diagnosis. In more recent series, for patients who underwent complete resection in large referral centers, survival might be slightly better [14,16]. Very few pediatric cases are reported and prolonged survival in pediatric and adolescent patients is rare [17,18]. A 13 year old with disseminated metastatic undifferentiated sarcoma was reported who could not undergo total resection and succumbed to widespread disease after multiple rounds of chemotherapy [19]. Another 12-year-old boy with metastatic primary UPS of the left atrium survived only 41 days after diagnosis [20]. A pediatric patient with cardiac undifferentiated sarcoma had good response to oral etoposide, followed by complete resection [21]. This report has currently surpassed the median survival rates cited in literature for a patient even after complete resection of the tumor.

The use of targeted therapy based on molecular analysis offers some promise. MDM2 is an inhibitor of the tumor suppressor p53 and it regulates the cell cycle through ubiquitin-mediated degradation and transcriptional suppression. MDM2 results in abnormal cellular proliferation if it is upregulated [22]. 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 [23].

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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