Histiocyticneoplasia in the heart

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Abstract

Introduction: Histiocytic sarcomas are malignant proliferation of cell showing morphological and immunophenotypic characteristics of mature tissue histiocytes.

Objective : Is to report 3 years old girl presented with pyrexia of unknown origin and after echocardiography, MSCT on heart and MRI heart, the case was reported to have cardiac mass then after excisional biopsy of the mass and immunohistochemisrtry,histiocysticneoplasia was diagnosed.

Conclusion: Cardiac tumor should be excluded in the case of pyrexia of unknown origin.

Introduction

Cardiac tumors are rare in children and consist of both primary and secondary tumors, with the majority being benign primary tumors. Primary cardiac tumors in the pediatric population have a prevalence of 0.0017–0.28 in autopsy studies and an incidence of 0.14% during fetal life **(1)**. The majority of primary cardiac tumors in children are benign, with rhabdomyoma and fibroma being the most common, accounting for up to 80% of cases of all cardiac tumors.The most common malignant primary cardiac tumor in both children and adults is sarcoma.Histiocytic sarcomas are malignant proliferation of cell showing morphological and immunophenotypic characteristics of mature tissue histiocytes**(2).**

3 years old girl admitted to our pediatric department in sohag university hospital with complain of persistent fever about 2 and half month ago. Fever was from 38.5 -39.5 ^{0}c. It was persistent all over the day (no diurnal variation). Temperature was decreased with antipyretic and never returns to normal. There were no respiratory, cardiac, gastrointestinal, Neurological, musculoskeletal symptoms and no past history of medical diseases or surgical operations.In examination, the patient was general well, weight 13 kg and her height was 134cm (25 centile&50 centile). Head and neck examination was normal while during chest examination there was mild tachypnia RR 35 cycle\min. On cardiac examination, there was mild tachycardia HR 130 beats\min, pulse was regular, average volume, equal in both sides with no special characters. Abdomenal , Neurological, Endocrinal and Musculoskeletal examination was completely normal. Her blood pressure was normal 90/50.Her investigations were as follow: complete blood count(WBCS 6.8*10^{9} \liter,HgB 11gm\dl and plt 289 *10^{9}\liter ، CRP was 96 mg\ liter, ESR 120 mm\hr,Urinanalysis was normal and urinculture showedno growth, Blood culture (twice) showed no growth. Multa and widal tests were normal, also T.B PCR was normal. CMV and HSV antibodies were normal but EBV IgG and IgM were positive.Her

imaging investigations include chest X ray, Abdominal U/S, CT chest and abdomen all were normal. Lastly we decided to do echocardiography to the heart which was done by one of our pediatric cardiologist and showed increase velocity at Junction of SVC to RA and recommends for MSCT, other findings in the heart were completely normal and ECG was normal.When we do MSCT, it shows a soft tissue mass lesion posterior to the right atrium at SVC drainage site insinuated between the two atria and splaying them, possibility of being intra pericadial lesion for farther assessment and cardiac MRI. The MRI report show A well circumscribed rounded, heterogeneous lesion is seen arising at the SVC/RA junction, likely intra atria (RA), for anatomical correlation with CT. No CMRI features of aggressive tumor behavior (no effusion, no metastases). Despite their rareness, according to location and age; a fibroma and myxoma are to be considered, in absence of central line insertion's history a thrombus is to be excluded.After 3 months from the MRI of the heart, complete excision of the mass was done and mass was send for gross and microscopic analysis. Grossly it showswell circumscribed mass measure 3*2*1.5cm with rubbery grey yellow cut section. Microscopically, there were fragmented tumor tissue formed of nodules of spindle cells with large vesicular nuclei and pale eosinophilic cytoplasm with many aggregates of histiocytoid cells and scattered plasma cells and eosinophilesfor immunophenotyping. In Immunohistochemistry, sections were treated against S100, CD163,CD138,LCA, CD20, CD21, CD3,KI67, CD1A, fascin and MCM2. Results showed that there are CD163 strongly positive histiocytes with fascinfocally positivehistiocytes with proliferation index 8 which are consistant with histiocysticneoplasia.Possibility of LCH, RDD, interdigitatingdendrtic sarcoma, follicular dendritic sarcoma, intimal sarcoma and T and B cell lymphoma are totally excluded. Tumor show low mitotic activity and relative low proliferation index

Discussion

Cardiac tumors are benign or malignant neoplasm arisingprimarily in the inner lining, muscle layer, or the surroundingpericardium of the heart. Cardiac tumors can be primary or metastatic. Primary cardiac tumors are rarein pediatric practice with a prevalence of 0.0017 to 0.28in autopsy series. In contrast, the incidence of cardiac tumors during fetal life has been reported to be approximately0.14% **(3, 4).**

The vast majority of primary cardiac tumors in childrenare benign, whilst approximately 10% are malignant. Secondarymalignant tumors are 10–20 times more prevalentthan primary malignant tumors **(5)**.Sarcomas make up 75% of malignant cardiac masses **(6, 7).**The clinical presentation depends on the age of the patient as well as the size and location of the cardiac tumor. Children with cardiac tumors may present with arrhythmias, heart failure, heart murmur, valvular insufficiency, or, rarely, sudden death.

Echocardiography and MR imaging are the most commonly used imaging modalities for evaluation of cardiac masses in children However, limitations of echocardiography include relatively

poor soft-tissue characterization in larger patients and inadequate evaluation of extracardiac structures **(8)** as in our case echocardiography show only increase velocity at junction of SVC to RA. Cardiac MR imaging is the modality of choice for further characterization of cardiac masses, especially in children, as it does not involve the use of ionizing radiation. Although cardiac MR imaging is the preferred modality, CT can also play an important role in the evaluation of cardiac masses **(8).** In our case we did first MSCT on the heart which show the soft tissue mass but the exact localization could be done by CMRI. Malignant histiocytosis is a neoplasm composed exclusivelyof cells showing morphological and immunophenotypicfeatures similar to those of mature tissue histiocytes**(2).**

Malignanthistiocytosis and true histiocytic lymphoma are now generallyconsidered to be neoplasms of similar cell types,differing only in their presentation as disseminated (malignanthistiocytosis) or localised (true histiocytic lymphoma)**(9, 10).** The term histiocytic sarcoma was introduced in1970 by Mathe et al**(11)**to include the whole spectrum ofdisseminated and localised forms from true histiocyticlymphomas to malignant histiocytosis. Other authors, however,serve to confuse the picture by limiting the term‘‘histiocytic sarcoma’’ to the localized lesion previously calledtrue histiocytic lymphoma, while classifying cases with multiple sites of involvement as ‘‘malignant histiocytosis’’.Histiocytic sarcoma (HS) is a rare neoplasm, first termed histiocytic medullary reticulosis, appearing in the medical literature in 1939 **(12).** The tumors, initially considered histiocytic in origin on the basis of morphology alone, have now been shown to represent diffuse large B-cell lymphomas or peripheral T-cell lymphomas (most commonly anaplastic large cell lymphoma), by immunohistochemistry **(13).**

The etiology and pathogenesis of HS is unknown. Common associations include midline germ cell tumors, preexisting lymphoma/leukemia, viral infection, and transplantation **(14).**Solid organ presentation is not as frequent. There are only 3 published case reports in English literature that have documented the occurrence of HS post renal transplantation**(15, 16).** One of the three cases was diagnosed within one year of transplantation and was thought to be related to Epstein-Barr virus infection **(16)** and in our case EBV IgG and IgM were both positive and may be related to the tumor.Kramer et al. **(15)** described an EBV associated HSalmost 3 decades back, but presently there is compelling evidence for a lack of relationship between EBV infection and an increased risk for HS **(15)**. Thediagnosis ofHS is based onmorphology supported by an extensive immunophenotypic analysis to establish histiocyticlineage and the exclusion of other, poorly differentiated, large cell malignancies **(17).**The main differential diagnosis when encountering a case of HS includes Langerhans cell histiocytosis, dendritic cell sarcoma, diffuse large Bcelllymphoma, anaplastic large T-cell lymphoma, myeloid sarcoma/AML, undifferentiated carcinoma, and malignantmelanoma **(13, 17).**There is a wide age range, with a predilection for patients in their second and third decades**(8).**Constitutional symptoms are common, with most patients presenting with fever, night

sweats and weight loss**(18, 19)** as in our case fever was the only clinical presesntation.The consistently similar morphologic findingsdescribed in literature can assist a pathologist in suspectingHS at the time of first encounter either on cytology or on needle core biopsy Moreover, themorphologic features also aid in making the distinction fromreactive histiocytic proliferations.This tumor is characterizedby mainly dissociated single, large neoplastic cells, one ormore large pleomorphic nuclei, prominent nucleoli, andabundant eosinophilic to vacuolated cytoplasm.

Nonspecific findings on electron microscopy and lack of universal genetic markers for detection of clonal histiocyticproliferation highlight the importance of immunohistochemistry in the diagnosis of HS **(20).** A strict criterionis that the neoplastic cells must express at least twospecific macrophage-associated antigens and typically lackof B-cell and T-cell markers and Langerhans cell (CD1a,langerin/CD207), follicular dendritic cell (CD21, CD23,CD35, and CAN.42), and epithelial (pancytokeratin, EMA),melanocytic (HMB-45, Melan A), and myeloid cell (CD13, CD33,myeloperoxidase)markers has been proposed to diagnose rare cases of bona fide histiocytic tumor **(20–22)**. Potential pitfalls include occasional expression of CD45 and CD4. Langerhans cell markers CD1a and S100 and the follicular dendritic cell marker podoplanin (D2-40) are expressed by a subset of HS (**20, 21).** CD163, a hemoglobin scavengerreceptors has been recognized as a new macrophage-related differentiation marker, with higher specificity for histiocyticorigin in comparison to other histiocytic markers such asCD68 (**22**) and in our case cells were strongly CD163 positive. More recently, T-cell immunoglobulin mucin 3and T-cell immunoglobulin mucin 4 (TIM-3 and TIM-4)were described to be markers of histiocytic and dendriticneoplasms; however, due to their expression on dendritic cellneoplasms, Langerhans cell histiocytosis, and cases of acute monocytic leukemia, they might not be ideal to confirm HS (**23**).There are no guidelines or established standard of care for treatment of HS. For historical reasons, principally misdiagnosis of non-Hodgkin lymphomas as HS, lymphoma directed therapy such as CHOP-like regimens has been used despite a lack of data for superiority over histiocytic-directed therapies. Outcomes have thus far been poor with multifocal disease, with nearly all patients reported to experience local or distant recurrence of disease within months following therapy.

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