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CASE REPORT

INTERMEDIATE

CLINICAL CASE

A Journey Across Oceans With a Heavy Heart

Rare Presentation of a Pediatric Malignancy

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ABSTRACT

Myeloid sarcoma, due to extramedullary deposition of myeloblasts, is one of the rare presentations in acute myeloid leukemia. We present an extremely rare case of a 5-year-old boy with cardiac myeloid sarcoma. Noninvasive mode of diagnosis, timely initiation of chemotherapy and meticulous supportive care are the keys to successful outcome. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2021;3:1221–6) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Extramedullary presentation of acute myeloid leukemia (AML) labeled as myeloid sarcoma (MS) involving the heart is exceedingly rare in children (1). We report a successful outcome with the use of chemotherapy in a boy with cardiac MS.

HISTORY OF PRESENTATION

A 5-year-old boy of Indian origin was retrieved from Dubai by air ambulance to our center in a sick condition with an underlying cardiac mass. In Dubai, the child had presented with a 2-week history of fever, breathing difficulty, and edema. The child had anasarca, respiratory distress, and hepatomegaly. With chest x-ray revealing right pleural effusion, he was treated with antibiotics for pneumonia with synpneumonic effusion. However, his respiratory distress progressed and eventually developed thrombocytopenia, transaminitis, disseminated intravascular coagulation (DIC) with elevated prothrombin time and activated partial thromboplastin time, and hypofibrinogenemia and required multiple transfusions. Chest computed tomography showed an ill-defined solid mass in the right atrium (RA) of size 5 × 6 × 3 cm, engulfing the right coronary artery and obstructing tricuspid inflow with multiple mediastinal lymph nodes and bilateral pleural effusion. With a plan of cardiac mass biopsy, child was transported via air ambulance as per the parents' request.

LEARNING OBJECTIVES

- To understand the various cardiac tumors and approach to diagnosis of very rare/critical masses infiltrating cardiac chambers and causing congestive failure.

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ABBREVIATIONS AND ACRONYMS

AML = acute myeloid leukemia

BMA = bone marrow aspiration

DIC = disseminated intravascular coagulation

MS = myeloid sarcoma

RA = right atrium

RV = right ventricle

On arrival at our center, child had pallor, anasarca, tachypnea, elevated jugular venous pressure, hepatomegaly, and a short mid-diastolic murmur at the tricuspid area. Electrocardiogram and blood pressure were normal.

DIFFERENTIAL DIAGNOSIS

With this constellation of bicytopenia, DIC requiring transfusions and right heart failure secondary to an infiltrating RA mass, the possibility of a leukemia/lymphoma with extramedullary deposits or sarcoma infiltrating bone marrow was considered.

INVESTIGATIONS

Hemogram showed anemia and thrombocytopenia with leukocytosis. Peripheral smear showed leukocytosis with myeloid left shift. Blood investigations are summarized in **Table 1**. Chest x-ray showed bilateral pleural effusion without cardiomegaly. Pleural fluid cytology was negative for malignant cells.

On echocardiography, a large mass measuring 20 × 32 mm was seen arising from the RA free wall immediately superior to the anterolateral tricuspid leaflet. Except for a narrow stream, it was completely obstructing the tricuspid valve inflow, causing significant dilation of RA, inferior vena cava, and hepatic veins. There was no other chamber involvement. There was an additional thick-walled cystic mass measuring 20 × 21 mm superior to the above-mentioned mass. There was only a thin layer of pericardial effusion without any apparent infiltration of the pericardial space (**Figure 1,** Video 1). Right ventricular (RV) systolic function was preserved and there was mild left ventricular systolic dysfunction with an ejection fraction of 48%. The inflow velocity of the tricuspid valve was increased (a′-wave = 1.7 m/s) (**Figure 2**). He was started on intravenous furosemide, oral spironolactone, and dobutamine infusion (8 μg/kg/min).

Multidisciplinary team of pediatric cardiologist, hemato-oncologist, intensivist, and cardiothoracic surgeons considered bone marrow aspiration (BMA)/biopsy to be more definitive and less risky than cardiac mass biopsy since he had bicytopenia and DIC.

BMA and biopsy revealed hypercellular marrow infiltrated by blasts with eosinophilic cytoplasm with large nuclei and prominent nucleoli suggestive of myeloid blasts (**Figures 3 and 4**). Flow cytometry was suggestive of AML with monocytic differentiation. Cytogenetics revealed inv(16), a favorable prognostic marker in AML.

TABLE 1 List of Blood Investigations Done at Diagnosis

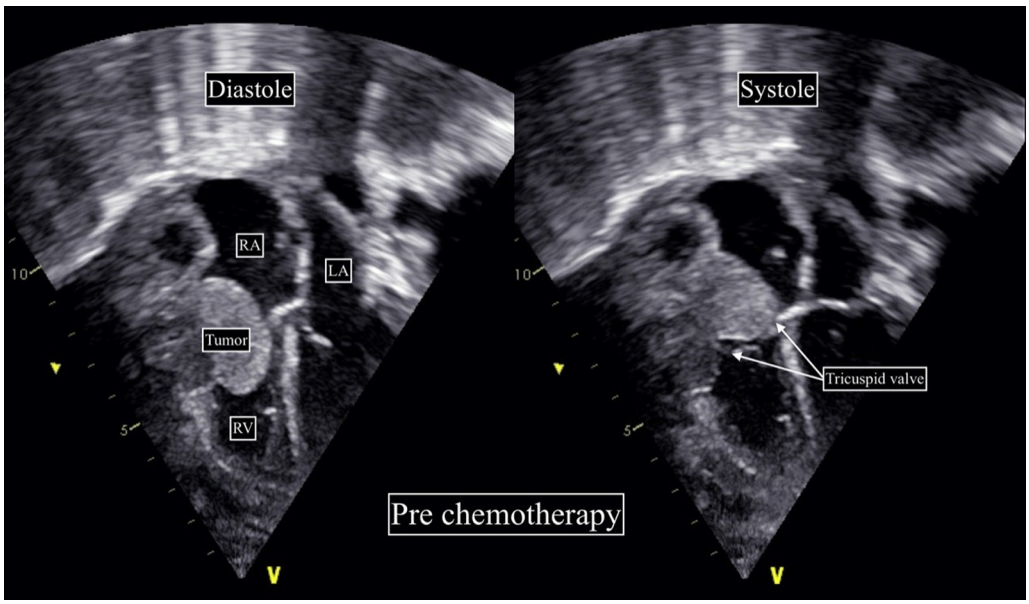
	November 7, 2018	November 19, 2018
WBC, 10^9/l	8.8	19.5
Hb, g/dl	12	9.5
Platelets, 10^9/l	154	29
PCV	36.5	30.3
MCV (fl)	76.9	82.5
Differential count		neutrophil: 3%; lymphocyte: 16%; monocyte: 10%; eosinophil: 1%; basophil: 0%; promyelocyte: 25%; myelocyte: 6%; metamyelocytes: 3%; nucleated red blood cells: +
Liver function tests		
ALT, IU/l	128	801
AST, IU/l	56	422
Serum albumin, g/dl	3.2	3.7
Serum bilirubin, mg/dl, total/direct		0.77/0.21
Serum ALP, U/l	155	150
Coagulation profile		
PT, s	22.7	23
aPTT, s	43	34
INR	2	2
Serum fibrinogen in ng/l	105	43.1
Renal function tests		
BUN, mg/dl		11
Serum creatinine, mg/dl		0.3
LDH, U/l	5,107	2,213
Ferritin, ng/ml	921.3	491.4
Uric acid, mg/dl	8.5	1.8
Electrolytes		
Sodium, mEq/l	138	142
Potassium, mEq/l	3.8	3.2
Chloride, mEq/l	101	98
Bicarbonate, mEq/l	22.8	27.5
Calcium/phosphorus, mg/dl	8.1/2.6	8.4/4.9

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; aPTT = activated partial thromboplastin time; BUN = blood urea nitrogen; Hb = hemoglobin; INR = international normalized ratio; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; PCV = packed cell volume; PT = prothrombin time; WBC = white blood cells.

MANAGEMENT

With a final diagnosis of AML-M4 with cardiac MS, the child was started on chemotherapy according to the United Kingdom Medical Research Council protocol with cytarabine and etoposide. Daunorubicin was deferred in the first cycle of induction because there was a mild left ventricular systolic dysfunction. After the first cycle of induction, the solid mass decreased in size and the obstruction resolved gradually (**Figure 5**). BMA revealed only 0.9% minimal residual disease. For the next cycle, daunorubicin was added as there was significant

FIGURE 1 Echocardiography at Diagnosis



Mass arising from RA wall, almost totally obstructing tricuspid valve orifice and causing significant dilation of RA, inferior vena cava, and hepatic veins. LA = left atrium; RA = right atrium; RV = right ventricle.

improvement in systolic function. Over the course of induction chemotherapy, the solid mass further shrank to a small echocardiographically dense opacity with total regression of cystic mass on echocardiography and non fluorodeoxyglucose avidity on positron emission tomography-computed tomography, suggesting fibrotic change (**Figure 6**). He was consolidated with 2 more cycles of high-dose cytosine arabinoside.

FOLLOW-UP

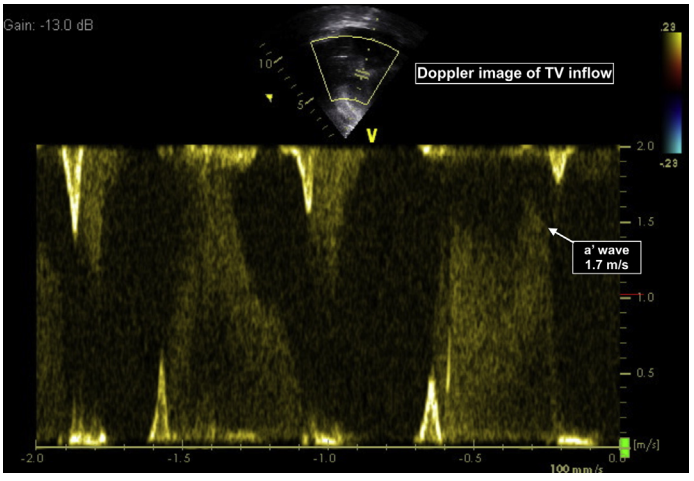
His bone marrow at the end of treatment was in remission and is doing well on follow-up for the past 2.5 years with good cardiac function without any sequelae (Video 2).

DISCUSSION

AML accounts for 15% to 20% of pediatric acute leukemias. MS, seen in 2% to 8% of AML, is also referred to as chloroma or granulocytic sarcoma and is characterized by deposition of myeloblasts in an extramedullary site (2). MS can be an initial manifestation of AML in children and young adults, especially in boys (1). Expression of CD56 helps to invade/infiltrate extramedullary tissues and is common with French-American-British AML types M2, M4, and M5 (3).

MS can occur with (acute/chronic myeloid leukemia) or without (isolated, nonleukemic, de novo) concurrent marrow disease at diagnosis, or relapse after chemotherapy or hematopoietic stem cell transplantation. MS may also occur in association with myeloproliferative neoplasm (4).

FIGURE 2 Doppler Echocardiography



Tricuspid valve (TV) inflow velocity of 1.7 m/s (a′-wave).

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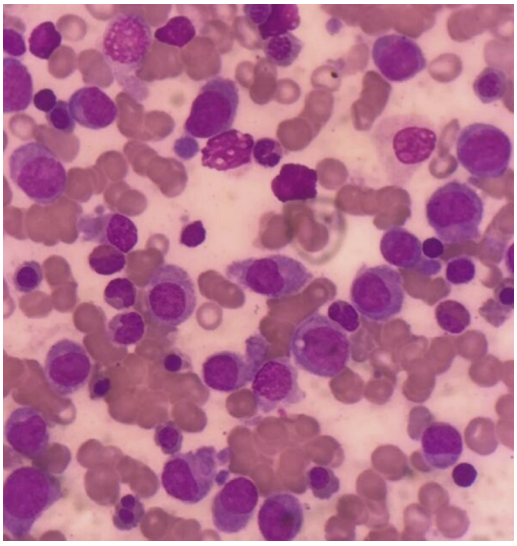
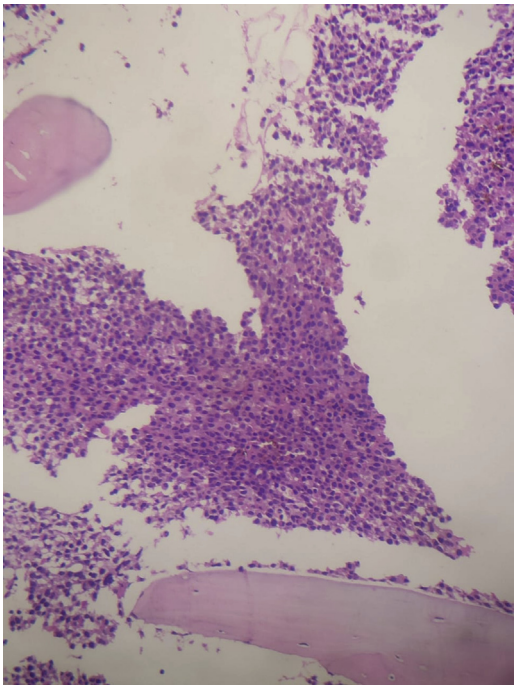
FIGURE 3 Bone Marrow Aspirate



With monocytic blasts, MGG stain, ×100 magnification.

FIGURE 4 Bone Marrow Trephine Biopsy



Hypercellular marrow replaced by blasts, hematoxylin and eosin stain, ×20 magnification.

In a study of 33 MS patients, the most common site of involvement was skin, followed by orbit and lymph nodes, and rare sites included central nervous system, genitourinary tract, chest wall, lungs, lacrimal gland, and breast (1). In another series of 9 patients, 2 were children with MS in the right middle meatus and orbit (5).

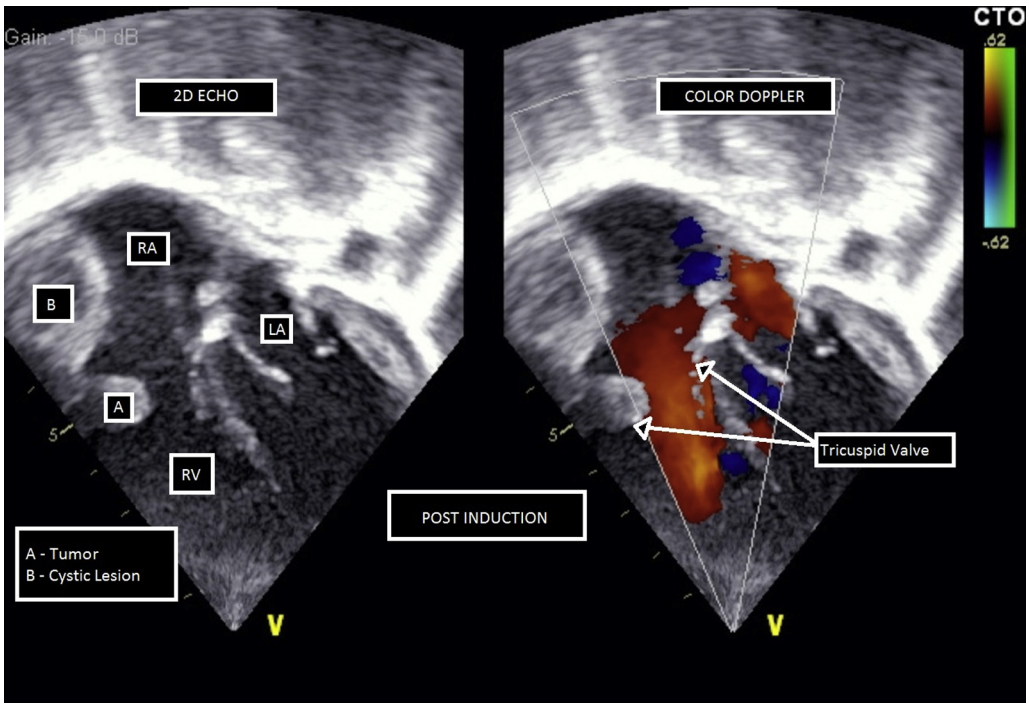
In a known patient with myelodysplastic syndrome/AML, diagnosis is straightforward; however, significant challenges and delays are evident in isolated MS, because the differential diagnosis includes soft tissue sarcoma, neuroblastoma, and primitive neuroectodermal tumors (6). Technical difficulties like biopsy from inaccessible/deep tissues pose a significant challenge. Less invasive techniques to arrive at a diagnosis are to be resorted to avoid a procedure-related complication, as in the present patient with RA mass or mediastinal mass with superior mediastinal syndrome.

Most cardiac tumors in children are benign, rhabdomyoma being the most common, whereas metastatic cancers are the most common malignant tumors. Rhabdomyomas and fibromas arise from the ventricles and myxomas arise from the interatrial septum or LA. Myxomas are often associated with low-grade DIC and usually arise as pedunculated mobile masses. Metastases often involve the RA and RV. Very rarely, cardiac metastases may be the first manifestation of malignancy, as in the present patient (7). This patient had a sessile mass arising from the RA free wall, causing significant prolonged obstruction with bicytopenia, coagulopathy, elevated lactate dehydrogenase, and hyperuricemia, prompting us toward a diagnosis of an unusual malignancy.

Coagulation abnormalities such as DIC and hyperfibrinolysis that are commonly seen in AML-M3 occur in 7% to 9% of non-M3 AML; possible factor X-activating enzymes in monoblasts and liver dysfunction have been proposed as underlying mechanisms (8).

Cardiac MS is exceedingly rare, comprising <1% cases of MS and predominantly diagnosed on autopsy. To our knowledge, the number of children with cardiac MS is very small. In the largest meta-analysis including 30 studies over 10 years, only 3 were children among 32 patients with cardiac-MS (9), including a 7-year-old boy with involvement of myocardium and sinoatrial and atrioventricular nodes, a 12-year-old girl with intracardiac mass involving right-side chambers, and 1-year-old girl with pericardial invasion. Unfortunately, none of those children survived.

FIGURE 5 Echocardiography After Induction of Cycle 1 of Chemotherapy



Significant reduction in the size of mass to 10 × 10 mm. Abbreviations as in Figure 1.

Histopathology remains the criterion standard for diagnosis, and yield of biopsy is increased by image-guided techniques. Least invasive technique is the best strategy to avoid morbidities, because the procedure could be fatal owing to the location and proximity to vital structures.

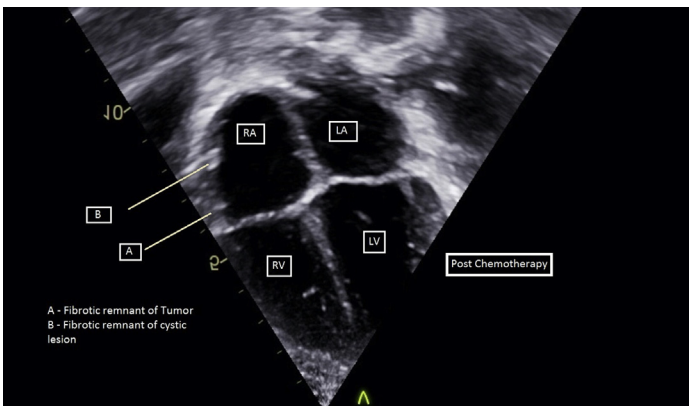
Chemotherapy remains the mainstay of treatment and includes cytarabine and anthracyclines. With a fear of cardiotoxicity, other regimens, such as etoposide/mitoxantrone/cytarabine, have been used (3,10). Fractionated radiotherapy up to 24 Gy for symptomatic relief and as consolidation has been found to be effective (11). The role of hematopoietic stem cell transplantation is well documented in relapsed/refractory and high-risk AML.

Extramedullary disease is considered to have a poor prognosis; however, in the presence of favorable cytogenetics, there was no significant difference in survival between those with and without MS (1,12). Reported poor prognosis in cardiac MS has been due to difficult/delayed diagnosis or treatment-related complications. Long-term survival rate according to available literature is only 20% to 25% (13).

CONCLUSIONS

Meticulous examination and careful scrutiny of baseline laboratory investigations will help to avoid

FIGURE 6 Echocardiography at End of Treatment



Shrunken hyperdense lesion suggesting a residual scar tissue. Abbreviations as in Figure 1.

invasive, potentially life-threatening diagnostic procedures such as cardiac mass/mediastinal mass biopsy. Multidisciplinary team approach and accurate histopathologic diagnosis with cytogenetics are crucial for a successful outcome of rare diseases such as MS. To the best of our knowledge, this is the first child with cardiac MS with successful outcome/prolonged remission.

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KEY WORDS acute myeloid leukemia, myeloid sarcoma, cardiac myeloid sarcoma, chloroma, right atrial mass

APPENDIX For supplemental videos, please see the online version of this paper.