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Myeloid sarcoma of the heart

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A 42-year-old Hispanic man was referred from an outside hospital for evaluation of a large mediastinal and intracardiac mass. He was in his usual state of health until 4 months previously when he developed facial flushing and swelling. One month prior to admission, he developed a dry cough and progressive dyspnea, with lightheadedness and hemoptysis over a 2-week period. He also complained of orthopnea and mild chest pain. A chest X-ray revealed a right-sided pleural effusion and right lung opacities [Figure 1(A)]. Symptoms worsened despite a week of antibiotics, and a computed tomography (CT) scan revealed a mediastinal mass invading the heart, prompting hospital transfer for further management. Radiographic studies upon admission to our hospital confirmed the presence of a large pleural effusion, and demonstrated a large soft tissue mass with transmural cardiac invasion involving the bilateral atrial walls and the intra-atrial septum with lobulated extension into the right atrium [Figure 1(B)]. There was encasement and marked narrowing of the right anterior descending artery, right pulmonary artery, right bronchus, and inferior pulmonary veins as well as complete occlusion of the distal superior vena cava extending cranially from the superior vena cava into the azygos origin and the left subclavian vein. A positron emission tomography (PET) scan revealed a large area of contiguous hypermetabolic activity involving the right heart, with extension into the intra-atrial septum and medial aspect of the left atrium, with a maximum standardized uptake value (SUV) of 6.0 [Figure 1(C)]. A transthoracic echocardiogram revealed a moderate pericardial effusion over the right ventricle, collapse of the right atrium, and severe reduction in cardiac input due to a mass in the right atrium. Radiographically, no abnormalities were found in his brain, abdomen, or pelvis. Laboratory evaluation showed a white blood cell count (WBC) of $8.03 \times 10^9/L$ with 74% neutrophils, 19% lymphocytes, 4% monocytes, 2% eosinophils, 1% basophils and no immature forms; he had a mild normocytic anemia (hemoglobin 12.1 g/dL, mean corpuscular volume [MCV] 88 fL) and a normal platelet count ($297 \times 10^12/L$). His lactate dehydrogenase (LDH) was 173 U/L. Telemetry revealed a junctional rhythm alternating with sinus rhythm and frequent premature atrial contractions.

Pleural fluid cytology was negative for malignant cells. A right atrial mass biopsy revealed the presence of a relatively homogeneous population of non-cardiac, large, immature-appearing cells characterized by a high nucleus:cytoplasm (N:C) ratio with fine, open

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chromatin and prominent nucleoli [Figure 2(A)]. Immunohistochemical studies were positive for CD45, CD34 and myeloperoxidase (MPO), an immunophenotype indicative of immature hematopoietic cells of myeloid lineage, most consistent with myeloblasts. Cells also weakly expressed PAX5 (with nuclear staining) but not the other lymphoid markers CD20, CD30, CD15, CD10, BCL6 or CD3, and fewer than 5% of the cells were positive for CD79a and terminal deoxynucleotidyl transferase (TdT) (not shown). Multi-parametric flow cytometry of the peripheral blood revealed a small population of abnormal myeloid blasts, constituting 2.8% of the total leukocytes, with an immunophenotype of the blasts similar to the intracardiac mass, showing abnormal expression of CD7 (low), CD19 (low), CD33 (low), CD34 (increased) and CD56 (uniform), with normal expression of CD13, CD38, CD45, CD71, CD117, CD123 and human leukocyte antigen (HLA)-DR, without CD2, CD3, CD4, CD5, CD8, CD14, CD15, CD16, CD20, CD64 or surface light chains [Figure 2(B)]. A subsequent bone marrow biopsy revealed a normocellular marrow with trilineage hematopoiesis and myeloid blasts (estimated at 4% morphologically and 5.7% flow cytometrically, respectively) with a similarly aberrant immunophenotype. Cytogenetic analysis of the bone marrow revealed a normal male karyotype of 46,XY; however, 17 of 200 cells (8.5%) analyzed were positive for the t(8;21)(q22;q22); *RUNX1/RUNX1T1* translocation by interphase fluorescence *in situ* hybridization (iFISH). Given these findings, a diagnosis of myeloid sarcoma with t(8;21) translocation was established.

Because of the invasive nature of the cardiac mass and the presence of cardiac arrhythmias, anthracyclines were avoided and induction therapy with high-dose cytarabine (HiDAC) only (1 g/m² per day for 2 days followed by 2 g/m² twice a day [BID] every other day for six additional doses) was initiated. CT scans on days 4 and 17 showed progressive shrinkage of the intracardiac mass, with increased size of both atria, as well as decreased narrowing of the right superior pulmonary vein. There was no azygos vein dilatation or collateral vessels to indicate superior vena cava (SVC) obstruction. Cardiac arrhythmias resolved around day 14 of therapy. Magnetic resonance imaging (MRI) obtained on day 34 confirmed the presence of blood flow between the atria and SVC and pulmonary veins, although the vessels remained narrowed, and a large T2 hyperintense, gadolinium-enhancing heterogeneous mass was still seen [Figure 1(D)]. Bone marrow biopsy on day 34 revealed no evidence of disease by flow or morphology; however, 0.3% of cells were still positive for t(8;21) by iFISH. The patient then underwent further chemotherapy with fludarabine/cytarabine/granulocyte-colony stimulating factor (G-CSF)/idarubicin (FLAG-Ida), with clearance of minimal residual disease from his bone marrow. He subsequently received one course of consolidation therapy with HiDAC (1 g/m² BID × 6 days). His chemotherapy course was complicated by pulmonary aspergillosis and persistent thrombocytopenia. Eight months after the initial diagnosis, he remains without evidence of disease in the marrow; his tumor mass has continued to decrease in size and the hypermetabolic fluorodeoxyglucose (FDG) activity has resolved, although there is residual mass radiographically. Given the normalization of FDG activity, external beam radiation has thus far been deferred because of the delicate location of the tumor mass and the likely associated toxicities of radiotherapy.

As an extramedullary manifestation of acute myeloid leukemia (AML), myeloid sarcoma (MS; also known as granulocytic sarcoma or chloroma) can occur concurrently with, prior to, or after the onset of marrow disease [1]. These tumors of immature myeloid cells most commonly involve the skin, lymph nodes, spine, gastrointestinal tract, and orbits, and are found in 2.5–9.1% of patients with AML [1–3]. Although microscopic leukemic cell infiltrates are commonly present in the heart, intracardiac tumor masses are rare and have been found in < 1% of patients with AML in larger autopsy series [4,5].

Consistent with this, only a small number of case reports of cardiac MS have been published in the English literature [6–28]. Among the 25 identified cases (two with acute

promyelocytic leukemia [APL], 23 with non-APL AML), the median age was 35 years (range, 7–72 years) at diagnosis of the cardiac MS, with a marked male predominance (21 males, four females). Cytogenetic information was provided on only four non-APL AML cases, with two patients being positive for t(8;21) by iFISH. Cardiac MS was found both at initial disease presentation as well as at relapse, where it was often noted as a late relapse manifestation. The reported cases suggest a striking predisposition for the right atrium, with occasional extension into the superior vena cava and pulmonary veins, similar to our case. Less frequently affected structures included the septum, epicardium, and ventricles. Most commonly reported symptoms were chest pain, fatigue, and dyspnea, whereas superior vena cava syndrome, tachycardia, heart failure, and tamponade were less common.

Certain cytogenetic abnormalities have been associated with a higher incidence of MS, in particular those that disrupt one of the core binding factor (CBF) transcription factor genes, most notably t(8;21)(q22;q22), as in our patient, but also inv(16)(p13q22) [1,29]. Expression of neural cell adhesion molecule 1 (NCAM1; CD56) may play a role in the pathogenesis of extramedullary disease in cases with t(8;21) (q22;q22), and has been associated with worse outcome in this AML subset [1,30,31]. Our patient thus had features characteristically associated with a higher risk for MS. However, given the paucity of cytogenetic and immunophenotypic information provided in previously reported patients with cardiac MS, it is unknown whether these abnormalities also predispose to this specific extramedullary manifestation.

In patients without a known history of AML, establishing a diagnosis of MS can be challenging, and a tissue diagnosis (using immunohistochemistry, flow cytometry, iFISH or molecular analyses) is warranted [1]. For cardiac MS, multimodality imaging (echocardiography, CT and MRI) has proved useful for evaluation [32,33]; yet, biopsies are associated with morbidity, and incorrect and delayed diagnoses do occur. Possible misdiagnoses may include acute lymphoblastic lymphoma, non-Hodgkin lymphoma, classical Hodgkin lymphoma or thymic neoplasms. In our patient, the initial finding of weak expression of the B-cell transcription factor, PAX5, in conjunction with dim expression of CD19, raised suspicion of a B-cell neoplasm such as diffuse large B-cell lymphoma and, more specifically, primary mediastinal large B-cell lymphoma, given the location of this tumor. However, subsequent studies established the presence of an abnormal myeloid blast population with aberrant expression of lymphoid markers, as often observed in t(8;21) AML [34]. Even in patients with established AML, diagnostic confirmation of MS via biopsy is necessary to rule out inflammatory or infectious processes that could have a similar appearance [1].

MS remains clinically challenging: most importantly, it continues to be controversial whether the presence of extramedullary disease portends a worse prognosis than what is predicted based on cytogenetic/molecular abnormalities in cases with marrow-only disease involvement [1]. Because of this uncertainty, the optimal treatment approach has yet to be developed, and it is unclear to what extent the established risk-stratified treatment algorithms that incorporate intensive chemotherapy and possibly hematopoietic cell transplant for AML can be utilized. Nevertheless, it has been recommended to consider additional therapy, including local radiotherapy, if less than a complete response is achieved with standard anti-AML therapy [1]. Radiotherapy is exquisitely effective for MS and results in rapid symptomatic relief, but its impact on overall survival is uncertain [1].

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Figure 1.

Radiographic studies. (A–C) Imaging studies at disease presentation: (A) chest X-ray (anterior–posterior) showing right-sided pleural effusion (dashed arrow) and right lung opacities (arrow); (B) CT scan (axial, sagittal and coronal views) demonstrating right-sided pleural effusion (dashed arrow) and large cardiac soft tissue mass with lobulated extension into the right atrium and encasement as well as narrowing/occlusion of adjacent vascular structures (arrows); (C) FDG-PET scan (axial view). (D) Cardiac MRI (axial view) at follow-up showing residual soft tissue mass.

Figure 2.

Pathologic studies. (A) Routine hematoxylin and eosin (H&E) stain and immunostains for CD45, MPO and CD34 ($\times 400$, insert $\times 630$). H&E stain showing population of cells with high N:C ratio, fine, open chromatin and prominent nucleoli. Immunostains demonstrating expression of CD45, MPO and CD34, consistent with immature hematopoietic cells of myeloid origin. (B) Multi-parametric flow cytometry evaluation of peripheral blood at diagnosis. CD45/side scatter (SSC) identifies the presence of a small, abnormal blast population with decreased CD45 expression (shown in red, with arrow), estimated to represent 2.8% of the total white blood cell count (normal hematopoietic cell populations [lymphocytes, monocytes and granulocytes] shown in light gray; first panel from left). Gating on this abnormal blast population reveals that these cells express CD34 (strong), CD117, CD56 (strong), CD7 (dim) and CD19 (dim-variable).