Therapy-related myelodysplastic syndrome presenting as fulminant heart failure secondary to myeloid sarcoma

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Abstract Rapidly progressive heart failure is commonly caused by an extensive myocardial infarction, a mechanical complication of infarction, myocarditis, or acute valvular insufficiency. We present an unusual case that was caused by a diffuse infiltration of the myocardium with leukemic cells (myeloid sarcoma). The patient presented with

episodic shortness of breath, he was anemic and thrombocytopenic, and his bone marrow biopsy revealed myelodysplastic syndrome from treatment for oligodendroglioma. His clinical course was characterized by a chronic leak of cardiac enzymes, a new right bundle branch block, and a large pericardial effusion causing tamponade and death from fulminant heart failure and ventricular arrhythmias within 2 weeks. At autopsy, the heart was massively infiltrated with myeloblasts and other immature myeloid cells. There was no evidence of acute leukemia in the bone marrow or peripheral blood. Cardiac infiltration in a patient with myelodysplastic syndrome is extremely rare, especially in the absence of bone marrow involvement by blasts. The recognition of this entity is becoming increasingly important as the incidence of cardiac myeloid sarcoma may be on the rise as the number of patients receiving chemotherapy increases.

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Introduction

Leukemic cells can infiltrate virtually any organ in the body. A collection of neoplastic, immature myeloid cells found outside the bone marrow is termed an extramedullary myeloid tumor or a myeloid sarcoma [1, 2]. The tumors can arise during the active phase of acute leukemia, they can be the first manifestation of blastic transformation of chronic leukemia, or they can present as a relapse in patients previously treated for leukemia. Although the underlying disorder is most frequently acute myelogenous leukemia, myeloid sarcoma has also been found in myeloproliferative

neoplasms and in myelodysplastic syndromes. The most common sites of occurrence are bone, lymph nodes, and skin (leukemia cutis). Cardiac involvement without marrow involvement is extremely rare [3, 4]. We describe a patient with fulminant heart failure who was found at autopsy to have diffuse infiltration of the myocardium with leukemic cells. The case was remarkable for the rapidly progressive symptoms, the absence of acute leukemia in the blood and bone marrow, and the fact that the underlying disorder was a chemotherapy-related myelodysplastic syndrome.

Clinical history

The patient was a 59-year-old male schoolteacher with a history of anaplastic oligodendroglioma diagnosed 3 years before admission. He had been treated by primary resection and chemotherapy with temozolomide, lomustine, and vincristine. The last dose was administered 2 years prior to his current hospitalization. He presented to the emergency department complaining of brief episodes of shortness of breath for 10 days without associated chest pain, fever, edema, or weight loss. Medical history was significant for a postoperative seizure disorder, hypertension, hyperlipidemia, and osteoarthritis. On physical examination, the pulse was 84 beats/min and blood pressure was 150/78 mm Hg. The chest was clear to auscultation, and the cardiac examination showed a regular rhythm and an S4

gallop without a murmur. There was no evidence of lower extremity edema. Laboratory studies revealed a white blood cell count of 6.1 K/ μ l, a macrocytic anemia (hemoglobin 8.3 g/dl), and thrombocytopenia (platelets 126 K/ μ l). The serum troponin I (TnI) was slightly elevated at 1.2 ng/ml, but the creatine kinase MB (CK-MB) was within normal limits. The brain natriuretic peptide (BNP) level was 443 pg/ml. His electrocardiogram (ECG) showed sinus rhythm and new T-wave inversions in the inferior and lateral leads (Fig. 1a). A transthoracic echocardiogram (TTE) revealed a normal ejection fraction, no wall motion abnormalities, and a small pericardial effusion (Fig. 1b). The patient was diagnosed as having a small non-ST-segment elevation myocardial infarction from demand ischemia in the setting of anemia. He was admitted to the coronary care unit, given heparin, and transfused 1 unit of packed red cells.

In working up his anemia, the peripheral blood smear showed mild monocytosis, a prominent basophilia, and a rare dyspoietic neutrophil myelocyte (Fig. 2a). A bone marrow aspirate and biopsy showed 7% blasts, dysgranulopoiesis, dyserythropoiesis, and dysplastic megakaryocytes (Fig. 2b, c). Flow cytometric analysis of the marrow aspirate identified a population of myeloblasts that were partly CD34 positive and expressed dim CD45 and CD15, positivity for CD13, CD33, myeloperoxidase (MPO) (Fig. 3d–f) and CD11b, and absence of CD3, CD20, and CD117. Cytogenetic studies demonstrated an abnormal mosaic male karyotype (46,XY

Fig. 1 Echocardiographic still images and electrocardiographic data. **a** ECG tracings demonstrate the development of a right bundle branch block then VT. **b** Echocardiographic frames taken during diastole (*left*)

and systole (*right*) demonstrate deteriorating LV systolic function between the first and second hospital admissions

Fig. 2 Hematologic findings. **a** Peripheral blood smear demonstrating a dyspoietic, hypolobate neutrophil (*center*). Macrocytic anemia and thrombocytopenia were also present. Bone marrow aspirate (**b**) illustrating a blast (*white arrowhead*) with other myeloid precursors, and bone marrow core biopsy (**c**) illustrating normal bone marrow cells with decreased numbers of mature segmented neutrophils indicating a myeloid shift to immaturity, but no obvious acute

leukemia. Black size bars for **a–c** represent 20 μ m. Flow cytometric plots (**d–f**) illustrating a population of blasts depicted in *red*. The blasts are dim CD45 positive (**d**: upper quadrants), partially MPO positive (**d**: right upper quadrant), partially CD34 positive (**e**: right upper quadrant), and CD33 positive (**f**: right upper quadrant) supporting that they are myeloblasts

and 45,XY,-7). Because of these findings, the patient was diagnosed with therapy-related myelodysplastic syndrome (t-MDS) secondary to previous alkylating-agent chemotherapy. The subtype of MDS was refractory anemia with excess blasts (RAEB). The diagnosis of acute leukemia was excluded because the number of blasts in the bone marrow aspirate and peripheral smear was less than 20%.

Over the next few days, the patient developed increasing fatigue and shortness of breath. There was a gradual rise in his TnI and CK-MB without changes in his ECG (peak TnI 4.41 ng/ml; peak CK-MB 12.9 ng/ml). A catheterization of the left side of the heart revealed insignificant coronary artery disease and a mildly elevated left ventricular (LV) end-diastolic pressure (LVEDP) of 15 mm Hg. He was started on indomethacin for presumed myopericarditis. On the 7th hospital day, a repeat TTE showed a large pericardial effusion with early tamponade (image not shown). Pericardiocentesis was performed, and 600 mL of serous fluid was drained, with a drop in the pericardial pressure from 15 to 0 mm Hg. Cytologic examination of the fluid demonstrated 6,000 white blood cells/mm³ with 36% basophils, 28% lymphocytes, 28% macrophages, 3% neutrophils, 2% mono-

cytes, and 1% eosinophils. The patient's symptoms improved after the procedure. The drain was removed, and he was discharged home on the 10th hospital day.

Within 18 hours of discharge, the patient developed acute onset shortness of breath at rest, orthopnea, increasing abdominal girth, and bilateral lower extremity edema. He returned to the emergency department. On physical examination, his pulse was 98 beats/min and his blood pressure was 127/77 mm Hg. There was jugular venous distention to the angle of the jaw, decreased breath sounds at both lung bases, distant heart sounds, and 4+ pitting edema in the lower extremities. Laboratory tests revealed a TnI of 8.02 ng/ml, CK-MB of 47.0 ng/ml, brain natriuretic peptide (BNP) of 4,438.2 pg/ml, and C-reactive protein of 29.3 mg/dl. His hemoglobin was 9.2 g/dl, and white blood cell count was 9,200/ μ L. His ECG showed a new right bundle branch block and new ST-segment depression in leads I, II, and V4–V6 (Fig. 1a). Chest x-ray demonstrated cardiomegaly and a left-sided pleural effusion. A TTE revealed a trace pericardial effusion and new global hypokinesis with regional variation in the wall motion. The ejection fraction was 35%, down from 65% measured

by TTE 5 days previously (Fig. 1b). The patient was readmitted to the CCU but developed worsening respiratory distress despite treatment with intravenous diuretics. Intravenous dobutamine was started but stopped because of runs of ventricular tachycardia (VT). About 24 hours after admission, he suffered a cardiac arrest characterized by episodes of sustained VT with intermittent bouts of pulseless electrical activity (PEA; Fig. 1a). Despite successful resuscitation, he quickly developed worsening lactic acidosis with acute renal failure, shock liver, and a coagulopathy that precluded placement of an intra-aortic balloon pump. His blood pressure fell inexorably. After consultation with the patient's wife, supportive measures were withdrawn and he was allowed to expire.

Postmortem examination

Gross pathological examination showed bibasilar pulmonary congestion ($R=770$ g, $L=610$ g) and bilateral serosanguineous pleural effusions ($R=570$ mL, $L=1,300$ mL). There was also portal and splenic vascular congestion. A previous left craniotomy site was identified, and a portion of the left temporal lobe was surgically absent. There was a small serous pericardial effusion (30 mL) with fibrinous exudate. The heart was enlarged (712 g) with LV and septal wall hypertrophy (Fig. 3a). On sectioning, there was mottling of the myocardium throughout its full thickness in both the left and right ventricular walls and in the septum. There was minimal coronary atherosclerosis.

Microscopic examination of the left ventricle, septum, and right ventricle revealed extensive myocyte necrosis. The myocardium was predominantly infiltrated by medium- to large-sized blastic cells with scant cytoplasm (Fig. 3b, c).

There were occasional mature and immature neutrophils and rare eosinophils and megakaryocytes. Immunohistochemical (IHC) studies demonstrated that the blasts stained positively with an antibody for MPO, and no staining was detected against CD3, CD20, CD34, CD45, CD68, CD117, hemoglobin A, and factor VIII (data not shown). These IHC stains were very useful to determine that the infiltrating blasts present in the heart were of myeloid lineage. The CD34 stain on the cardiac tissue was negative by IHC; however, the blasts were only partially positive by flow cytometry performed on the bone marrow. IHC can be less sensitive than flow cytometry since fixation techniques, and processing of the tissue may destroy some of the antigenic epitopes. Taken together with the patient's history of t-MDS, these findings indicate that the patient died of a myeloid sarcoma with blastic transformation involving the heart.

Discussion

Myeloid sarcoma is a destructive, focal tumor mass composed of immature myeloid cells that most commonly occurs during the active phase of acute myelogenous leukemia. It can also be the first manifestation of blastic transformation in patients with chronic myeloproliferative disorders or myelodysplastic syndrome, or can present as relapse in patients previously treated for leukemia. Although myeloid sarcoma has been reported in almost every site of the body, cardiac involvement is unusual [4, 7, 9–18]. We report the case of a 59-year-old man with a history of t-MDS who died of rapidly progressive heart failure. His LV ejection fraction (LVEF) was decreased from 65% to 35% over the course of a few days as documented by serial echocardiograms. At autopsy, the

Fig. 3 Autopsy findings. **a** Gross specimen of the heart showing circumferential LV hypertrophy and mottling of the myocardium (size bar represents 1 cm). **b** Microscopic view from mottled area demonstrating a mixed inflammatory infiltrate and myocyte necrosis

(size bar represents 40 μ m). **c** Higher power view reveals a cellular infiltrate with predominantly medium to large-sized blastic cells with scant cytoplasm and finely dispersed nuclear chromatin, occasional neutrophils, and rare eosinophils (size bar represents 20 μ m)

heart was diffusely infiltrated with myeloblasts and other immature myeloid cells, confirming the diagnosis of myeloid sarcoma. The diagnosis was unexpected given the diagnosis of t-MDS, but no evidence of acute leukemia in the blood or bone marrow and the lack of a distinct cardiac mass on transesophageal echocardiography. The development of cardiac myeloid sarcoma in patients with myelodysplastic syndrome is extremely rare [5, 6, 18].

The reason for the patient's fulminant course and rapid deterioration in cardiac function is unclear. The patient's continuous elevation of troponin I and CK-MB was too small to account for the deterioration in LV function, and his coronary angiogram showed no significant arterial obstructions. These observations argue against an ischemic etiology. The pericardial effusion did not reaccumulate after it was drained. It is also unlikely that he had developed a restrictive cardiomyopathy given the appearance of his transthoracic echocardiogram, his mildly elevated LV filling pressures, and the rapid pace of the deterioration. It is possible that the leukemic cells physically interfered with cardiac contraction/electrical activity or that they secreted a substance/cytokine that was toxic to the myocytes or decreased their contractility. Near the time of his death, systemic hypotension and a severe metabolic acidosis (arterial pH 7.00) may have also have contributed to the deterioration in LV function.

Extensive infiltration of the heart by a myeloid sarcoma is distinctly rare (Table 1). Although 30%–50% of patients with leukemia are found to have microscopic collections of leukemic cells in the myocardium or endocardium at autopsy, the incidence of gross infiltration is only about 0.7% [7, 8]. In many instances, an asymptomatic mass is discovered during routine echocardiography or at autopsy (Table 1). Patients come to clinical attention when the mass obstructs blood flow or compromises valvular function. Typically, the right-sided chambers are affected, and the presenting symptoms are fatigue and pedal edema. In one case, several distinct masses compressed the superior vena cava, pulmonary artery, and aorta causing pulsus paradoxus [9]. Only one case of successful treatment has been reported [4]. In this patient, the tumor caused tricuspid valve stenosis and was treated with radiation and chemotherapy. Eight years later, the tumor recurred. Rarely leukemic infiltration causes complete heart block, which can resolve once the tumor is treated [10]. A similar case in a patient with myelodysplastic syndrome was reported by Mateen et al. [18], with extensive myocardial infiltration by hematopoietic precursors. In our patient, we preferred to use the term myeloid sarcoma since we found leukemic cells diffusely infiltrating the entire heart and markedly effacing the myocardium, despite the lack of a focal, discrete tumor mass.

Table 1 Previous case reports of extramedullary myeloid tumor of the heart

Age (y)	Sex	Hematologic diagnosis	Previous chemotherapy	Clinical presentation	Cardiac pathology	Reference
48	M	None	No	SOB, cough, weakness, VT, death	Encasement of the SVC, PA, and aorta	Foucar et al. [4]
12	F	APML	Yes	Heart failure, death	Right-sided intracardiac mass	Jankovic et al. [11]
72	M	Agnogenic myeloid metaplasia	ND	RV failure, encasement	Encasement of the heart and great vessels	Tillawi and Variakojis [9]
28	M	Not reported	ND	Dyspnea on exertion	Masses causing tricuspid and mitral stenosis	Ichikawa et al. [12]
48	M	AML FAB M4 subtype	ND	Fatigue, positional dyspnea, headache	RA mass	Erdol et al. [13]
34	M	AML FAB M1 subtype	Yes	None	Masses in all cardiac chambers	Makaryus et al. [14]
39	M	AML FAB M1 subtype	Yes	Edema, fatigue, dyspnea	ND	Marcos-Alberca et al. [15]
28		Acute monoblastic leukemia	ND	Noncardiac (sepsis)	ND	Orts et al. [16]
28	M	AML FAB M2	Stem cell transplantation	Noncardiac and dyspnea	ND	Kara et al. [17]
64	F	MDS (RAEB)	No	Lethargy, weakness, SOB	Diffuse infiltration of the myocardium	Mateen et al. [18]

RAEB refractory anemia with excess blasts, *SOB* shortness of breath, *VT* ventricular tachycardia, *PA* pulmonary artery, *ND* not documented, *RV* right ventricle, *APML* acute promyelocytic leukemia, *AML FAB* acute myeloid leukemia, French-American-British classification, *RA* right atrium, *MDS* myelodysplastic syndrome

Although cardiac involvement by a myeloid sarcoma is unusual, this case demonstrates the importance of keeping this diagnosis in mind in patients with myelodysplastic syndrome or patients who present with heart failure of uncertain etiology. The incidence of myelodysplastic syndrome is rising as the population ages and as the number of long-term cancer survivors who received alkylating chemotherapy increases. These trends may portend an increase in the number of patients with cardiac myeloid sarcoma.

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