Title: Extensive myocardial infiltration by hemopoietic precursors in a patient with myelodysplasia

Authors and Author affiliations

Farrah J. Mateen MD¹, Sheila R. Harding MD, FRCPC², ³, Anurag Saxena MD, FRCPC²

Resident, Department of Neurology, Mayo Clinic¹, Rochester, Minnesota, USA, College of Medicine and Departments of Pathology² and Internal Medicine³, Royal University Hospital, University of Saskatchewan, Saskatoon, Saskatchewan, Canada..

Emails:
Farrah J. Mateen: farrah_mateen@hotmail.com
Sheila R. Harding: Sheila.harding@usask.ca
Anurag Saxena: anurag.saxena@usask.ca

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Corresponding Author:

Anurag Saxena, MBBS, MD, FRCPC, FCAP
Professor and Hematopathologist
Head, Division of Hematopathology
Department of Pathology and Laboratory Medicine
Royal University Hospital
103 Hospital Drive
Saskatoon, Saskatchewan, S7N 0W8. CANADA.

Tel: 001-306-655-2157
Fax: 001-306-655-2223
E-mail: saxena@sask.usask.ca
Abstract

**Background:** Although myocardial infiltration with leukemic blasts is a known finding in patients with acute leukemia, this phenomenon in myelodysplasia is not reported in the literature. Cardiac symptoms in patients with myelodysplasia are often due to anemia and may be due to iron overload and side effects of therapy.

**Case Presentation:** Herein we report the first case of neoplastic infiltration of the heart with associated myocardial necrosis in a patient with myelodysplasia. It was associated with unicellular and multifocal geographic areas of necrosis in the left ventricle and the interventricular septum. It is likely that cardiac compromise in our patient was due to a combination of restrictive cardiomyopathy due to leukemic infiltration, concomitant anemia, cardiac dilatation, conduction blocks and myocardial necrosis. Myocardial necrosis was most likely due to a combination of ischemic damage secondary to anemia and prolonged hypotension and extensive leukemic infiltration. Markedly rapid decrease in ejection fraction from 66% to 33% also suggests the role of ischemia, since leukemic infiltration is not expected to cause this degree of systolic dysfunction over a 24-hour period. The diagnosis was not suspected during life due to concomitant signs and symptoms of anemia, pulmonary infections, and pericardial and pleural effusions. The patient succumbed to cardiac failure.

**Conclusions:** Hemopoietic cell infiltration was not considered in the differential diagnosis and contributed to this patient’s morbidity and mortality. This case
highlights the clinical importance of considering myocardial infiltration in patients with myelodysplasia and cardiac symptoms.

**Background:**

Myelodysplastic syndromes are hematologic malignancies characterized by dyspoiesis, a progressive clinical course and usually a fatal outcome due to either transformation to acute leukemia or bone marrow failure [1, 2]. The patients often present with symptoms attributable to cytopenias and the clinical course reflects progression to bone marrow failure or transformation to acute leukemia [3]. The patients usually managed with supportive care and sometimes novel treatments [4] are monitored for evolution to acute leukemia and progressive marrow failure using some risk stratification scheme, for instance the International Prognostic Scoring System [5].

Cardiac symptoms in patients with myelodysplasia are usually due to anemia [6] or iron overload [7] and sometimes due to toxic effects of drug treatment. The
latter include cardiac arrhythmias due to a hemopoietic growth factor, IL-11 [8], bradycardia and orthostasis due to immunomodulating thalidomide [9], exacerbation of congestive cardiac failure to immunomodulating infliximab [10], cytotoxic chemotherapy e.g. cytarabine related cardiotoxicity [11], and conduction abnormalities due to a putative differentiating agent arsenic trioxide [12]. Although infiltration by leukemic blasts is a known phenomenon in patients with acute leukemia [13-15], to the best of our knowledge our’s is the first case report of cardiac infiltration by malignant hemopoietic cells in a patient with myelodysplasia. The extensive hemopoietic cell infiltration was not considered in the differential diagnosis and contributed to this patient’s morbidity and mortality. This case, therefore, highlights the importance of considering this phenomenon in patients with myelodysplasia who develop cardiac symptoms.

**Case Presentation:**

A 64-year-old woman with increased lethargy, generalized weakness, and shortness of breath on exertion was found to have pancytopenia on a routine blood count; hemoglobin 80 g/L, white blood cells $3.2 \times 10^9$/L, platelets $98 \times 10^9$/L. After bone marrow examination a diagnosis of refractory anemia with excess blasts (RAEB) was made. The symptoms were attributed to anemia and she received 5 units of packed red cells.

Approximately 2 months later, she developed a 4-day course of intermittent chills and sweating but was afebrile when she came to the local emergency
department. The CBC at admission demonstrated $6.9 \times 10^9$ white blood cells with left shift and $0.21 \times 10^9$ blasts, $76 \text{ g/L}$ hemoglobin and $65 \times 10^9$ platelets. During her hospital stay the white blood cells increased to $16.9 \times 10^9$ with increasing left shift; anemia and thrombocytopenia persisted. There was central bronchial wall thickening and interstitial prominence in the chest radiograph suggestive of an early viral infectious process. The cardimediastinal silhouette was within normal limits (Figure 1a). The electrocardiogram (ECG) showed normal sinus rhythm. The patient was started on oral levofloxacin.

Four days later, the patient became febrile (38.8 degrees) and developed increasing shortness of breath and retrosternal chest pain that radiated to both arms. There were bilateral crepitations and decreased breath sounds. Repeat chest radiograph demonstrated bilateral pleural effusions, basal consolidation of the left lower lobe and left ventricular enlargement. There was no evidence of cardiac failure (Figure 1b). Right bundle branch block (RBBB) with sinus tachycardia was identified on ECG. An echocardiographic study identified a moderate pericardial effusion with no cardiac tamponade; the left ventricular ejection fraction was 66% and there were no regional wall motion abnormalities. The next day, a repeat echocardiographic study identified a 33% ejection fraction with left ventricular global hypokinesia and a moderate sized pericardial effusion without tamponade. The patient was treated for pneumonia, hypotension, acute renal failure, and myelodysplastic syndrome but developed heart block and
cardiorespiratory compromise. Her condition deteriorated rapidly and she died five days post-admission.

Peripheral blood and bone marrow, ante-mortem (Figures 2 -5): In the peripheral blood there was dysplasia in the leukocytes, platelets and red cells was associated with a left shift and circulating blasts. The bone marrow was hypercellular with trilineage dysplasia. Blasts were increased (18.2%) and there was abnormal localization of immature precursors (ALIP).

Post-mortem examination was limited to heart and lungs at the request of the family. The heart lay free in the pericardial sac, surrounded by 300 mL of straw-colored pericardial effusion. There was fibrinous pericarditis. The free wall of the left ventricle and the interventricular septum had soft and hemorrhagic areas scattered throughout, with no definite transmural focus. The major coronary arteries (right coronary, left anterior descending, and left circumflex arteries) were involved to only a minor degree by old eccentric atherosclerotic plaques (maximum stenosis of 25 to 30%) with no evidence of an acute event (thromboembolus, hemorrhage, rupture). There was bilateral pulmonary edema and left lower lobe congestion and consolidation.

Microscopic examination of the heart (Figures 6-9) revealed a diffuse interstitial infiltrate of immature dysplastic hemopoietic cells involving the myocardium, endocardium and the pericardium. Cells of myeloid, erythroid and
megakaryocytic lineages were present. These infiltrates were associated with single fibre myocyte necrosis as well as larger foci of necrosis. A majority of these cells were immunopositive for myeloperoxidase consisted with myeloid lineage.

Pancytopenia associated with peripheral blood features including dysplastic changes in the granulocytes, <19% blasts and <1 x 10⁹/L monocytes coupled with multilineage dysplasia and 18.2% blasts in the bone marrow was in keeping with the diagnosis of refractory anemia with excess blasts-2 (RAEB-2) [1]. Clinical presentation and clinical course of RAEB is typically related to the symptoms of decreased counts of one or more cell lineages and blast count [3, 4]. The symptoms of lethargy, shortness of breath, and generalized weakness in this patient may be attributed to both anemia and cardiac infiltration by malignant cells, although the former is much more common clinically [6]. Her cardiac symptoms were not due to drugs sometimes used in patients with myelodysplasia, since the patient had not received cytotoxic, immunomodulatory, putative differentiating agent, or hemopoietic growth factor therapy [8-12].

Although cardiac involvement in leukemic extramedullary spread is relatively common (ranging from 37-44%) [13-15], clinical signs are found in less than 1% of cases [16-18] and leukemic cardiac involvement antemortem is usually not suspected [19]. The most likely reason for this is the subclinical nature of the symptoms and signs in cardiac leukemic infiltration [20]. This is in keeping with
the observation that gross infiltrative disease at the time of initial diagnosis in patients with acute leukemia is rare [14, 19, 21].

Although cardiac infiltration is usually associated with high WBC count (mostly due to blasts) and advanced disease [14], the presence of a high circulating white blood cell count is not a necessity for developing cardiac infiltration as infiltration has been shown to be present in aleukemic leukemia [21] as well as in patients with very low white cell counts [22]. The development of cardiac infiltration in our patient with myelodysplasia and pancytopenia would be consistent with this observation keeping with this phenomenon; the rising white late in the course of the disease was predominantly due to neutrophilia and left shift and not due to a large blast population.

The effects of hemopoietic cell infiltrate in the heart are varied. Leukemic deposits may form mass lesions [23] or thrombi [24]. Pericardial involvement may lead to pericardial effusion contributing to restrictive myocardial dysfunction [19, 25]. Reports of heart block in extramedullary cardiac leukemic involvement are few [22, 26, 27]. Heart block has been observed in patients with both very high and very low peripheral blood white cell counts [22] and may be reversible after local radiotherapy to the heart despite persistence of leukemic infiltration [22]. However, infiltration of the conduction system is a potentially serious complication that may be fatal [28]. Leukemic infiltration is a rare cause of restrictive cardiomyopathy [18]. An antemortem study of 18 patients with acute
leukemia (6 ALL, 12 AML) demonstrated no significant difference from controls in LV systolic function parameters including LV ejection fraction, similar to what was observed in our patient at initial echocardiography [18]. However, LV diastolic dysfunction has been observed in 38 percent of leukemic patients, independent of age and heart rate. It is likely that cardiac compromise in our patient was due to a combination of restrictive cardiomyopathy due to leukemic infiltration, concomitant anemia, cardiac dilatation, conduction blocks and myocardial necrosis. Myocardial necrosis was most likely due to a combination of, a) ischemic damage secondary to anemia and prolonged hypotension and b) extensive leukemic infiltration. Markedly rapid decrease in ejection fraction from 66% to 33% also suggests the role of ischemia, since leukemic infiltration is not expected to cause this degree of systolic dysfunction over a 24-hour period.

Usual causes of death in patients with myelodysplasia are related to bone marrow failure and transformation to acute leukemia [3, 4, 29], however, in this patient, death was attributed to cardiac failure. It is likely that the rising white blood cell count during second admission, although predominantly due to neutrophilia and left shift, was associated with early transformation- in view of increased peripheral blood blast percentage - the limited autopsy did not permit evaluation of the bone marrow.

Cardiac involvement in by malignant hemopoietic cells is of more than just academic interest, since cardiac function has been shown to improve following
therapy directed against malignant infiltrate [22, 30]. Incorrect diagnosis during life and the fatal outcome highlight the clinical importance of considering myocardial infiltration in patients with myelodysplasia and cardiac symptoms.

**Conclusions:**
Infiltration of heart tissues by malignant hemopoietic cells can occur in patients with myelodysplasia. This case highlights that in a patient with myelodysplasia, leukemic cardiac infiltration should be considered in the differential diagnoses when investigating cardiac symptoms and signs, particularly heart block.

**Competing interests:**
The authors declare that they have no competing interests.

**Authors’ contributions:**
SRH was responsible for the initial assessment and management of the patient. AS was responsible for the initial diagnosis of myelodysplasia and also performed the autopsy on the deceased. FM was responsible for review of the patient’s clinical charts and interpretation of data. All authors have contributed equally in the preparation of the manuscript. All authors read and approved the final manuscript.
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Figure legends

Figure 1
Plain radiographs of the chest (PA views) at admission (a) and four days later (b) with noticeable increase in the cardiac silhouette.

Figures 2 - 5
Peripheral blood and bone marrow findings;
2) circulating blast and a pseudo Pelger-Huet cell, peripheral blood (Giemsa x 500),
3) bone marrow aspirate with marked erythroid dysplasia (Giemsa x 500),
4) core biopsy, megakaryocytic and erythroid dysplasia (H&E x 300),
5) core biopsy, abnormal localization of immature precursors (H&E x 300).

Figures 6 - 9
Cardiac infiltration by hemopoietic precursors;
6) epicardial involvement with fibrinous pericarditis (H&E x 50),
7) extensive septal and intercellular myocardial infiltration with vascular wall and myocardial necrosis (H&E x 50),
8) dysplastic megakaryocyte and myeloid precursors (H&E x 300),
9) Myeloperoxidase positive myeloid precursors (Immunoperoxidase x 300).
Figure 6