Acute Panmyelosis with Myelofibrosis: An Unusual Cause of Pancytopenia

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Introduction

Pancytopenia is a common clinical scenario whose etiology is often difficult to establish. The following case report illustrates the evaluation of a case of pancytopenia, leading to the diagnosis of a rare form of acute leukemia. A basic approach to pancytopenia is also presented.

Case Description

A 56-year-old woman presented to her family physician with a 2-month history of dizziness, palpitations, dyspnea on exertion, and episodic chest discomfort. Initial investigations revealed a mild pancytopenia. Two days later, she presented to emergency with a low-grade fever (37.8°C), left-sided chest discomfort, and weakness. She denied any infectious or bleeding symptoms and had no significant past medical history, including no medications.

On examination, the patient had no lymphadenopathy, and her cardiac, respiratory, and abdominal examinations were unremarkable, with no hepatosplenomegaly. Her investigations revealed a pancytopenia (see Table 1). On the basis of her neutropenia and low-grade fever, she was admitted for intravenous antibiotics and work-up of her pancytopenia.

In hospital, her pancytopenia persisted; her counts reached a nadir of hemoglobin (Hgb) 46 g/L, platelets (Plt) 16 X 10^9/L, and white blood cells (WBC) 1.88 X 10^9/L (neutrophils 0.54 X 10^9/L). An abdominal ultrasound revealed normal liver and spleen size, with no focal lesions. Her peripheral smear revealed no poikilocytes (tear drop red cells) or blasts, and serum protein electrophoresis identified a polyclonal gammopathy with no paraproteins.

A bone marrow aspirate was a “dry tap” and found to be hypocellular; however, a mild plasmacytosis (5%) and mild increase in blasts (5%) was noted. The bone marrow biopsy demonstrated variable cellularity (0-40%) and increased reticulin (marker of marrow fibrosis), with focal megakaryocyte hyperplasia and a reactive lymphocyte aggregate (see Figure 1). Peripheral blood flow cytometry was unremarkable, with no evidence of abnormal lymphocytes or myeloid blasts. No JAK2 V617F mutation was detected, reducing the likelihood of a myeloproliferative neoplasm such as idiopathic myelofibrosis.1

The patient was discharged with no infectious etiology identified, but was readmitted with dyspnea and weakness associated with persistent pancytopenia. Her peripheral smear contained a few bands, myelocytes and atypical lymphocytes with no blasts, and abdominal CT revealed no enlarged mediastinal nodes or splenomegaly.

Figure 1. Pathologic bone marrow biopsy specimen. 
(A) displays hematoxylin-eosin stain demonstrating cellular as well as fibrotic areas. (B) displays reticulin stain of the same field, highlighting fibrosis. (C) displays CD34 immunostain of the same field, highlighting occasional blasts (note: CD34 also stains blood vessels).
A second bone marrow biopsy was conducted, in which a significant amount of myelofibrosis and increased blasts were identified. The pathology favoured a diagnosis of acute pancytopenia with myelofibrosis (APMF), a rare form of acute myeloid leukemia (AML).2,3

The diagnosis was discussed with the patient, and she was offered a course of AML-type induction chemotherapy with eventual bone marrow transplantation, if needed, along with continued best supportive care with red cell and platelet transfusions as required. She is currently deciding her course of action with respect to treatment.

**Table 1. Initial Laboratory Values**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial</th>
<th>Normal</th>
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<tbody>
<tr>
<td>Hemoglobin (Hgb)</td>
<td>99 g/L</td>
<td>120 – 160 g/L</td>
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<tr>
<td>White Blood Cells (WBC)</td>
<td>2.5 x 10^10/L</td>
<td>4 – 11 x 10^10/L</td>
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<tr>
<td>Neutrophils</td>
<td>0.5 x 10^10/L</td>
<td>1.9 – 8.0 x 10^10/L</td>
</tr>
<tr>
<td>Platelets (Plt)</td>
<td>37 x 10^9/L</td>
<td>150 – 400 x 10^9/L</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>30 x 10^9/L</td>
<td>10 – 100 x 10^9/L</td>
</tr>
<tr>
<td>LDH</td>
<td>213 U/L</td>
<td>100 – 200 U/L</td>
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**Discussion**

Pancytopenia is a common clinical problem with a wide differential diagnosis (see Table 2). This particular case was notable because the initial clinical impression was not matched by expected findings on physical examination and bloodwork. It highlights the importance of identifying the cause of persistent pancytopenia, which is usually caused by chronic diseases but can be a sequela of acute hematologic disease.

**Table 2. Selected Differential Diagnosis of Pancytopenia**

<table>
<thead>
<tr>
<th>Primary Bone Marrow Disorders</th>
<th>Myelophthisis</th>
<th>Myeloproliferative Disease</th>
<th>Metastatic Disease</th>
<th>Hematologic Malignancies</th>
<th>Granulomatous Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocellular Bone Marrow</td>
<td>Idiopathic Myelofibrosis</td>
<td>Solid Tumour</td>
<td></td>
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<tr>
<td>(incl. Aplastic Anemia, Hypoplastic Myelodysplasia)</td>
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<tr>
<td>Cellular Bone Marrow (incl. Myelodysplasia, PNH)</td>
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**Systemic Disease**

- Hypersplenism
- Alcoholism
- Rheumatologic Diseases (incl. RA, SLE)
- Immunodeficiency (incl. AIDS)
- Nutritional Deficiencies (Vitamin B12, Folate)
- Systemic Infections (Sepsis)

One of the more common causes of pancytopenia in older adults is idiopathic myelofibrosis (IMF), a chronic fibrosis of the bone marrow, which was the initial consideration in this patient. However, while IMF is most often associated with splenomegaly due to extramedullary hematopoiesis, this patient’s clinical examination and imaging studies were normal. The peripheral smear in IMF also exhibits poikilocytes, while our patient demonstrated normal erythrocyte morphology.4–5 Due to these discrepancies, a bone marrow biopsy was conducted, revealing a pathologic diagnosis of APMF, a rapidly progressive leukemia with a poor prognosis.

APMF is classified as a form of AML by the World Health Organization. It is a condition in which pancytopenia rapidly develops, due to an associated pancytopenia proliferation within the bone marrow, and variable marrow fibrosis,2 with both phenomema leading to myelofibrosis (bone marrow displacement). APMF can arise de novo or in patients previously treated with radiation or myelotoxic agents, including alkylating agents.6 This condition is rare (<1% of all AML cases), and a PubMed and MedLine literature search reveals only a few descriptive studies and no management guidelines.

Clinically, APMF patients typically present with symptoms of pancytopenia – fatigue (anemia), infections (neutropenia), and bleeding (thrombocytopenia). Physical examination generally reveals little or absent splenomegaly, unlike IMF. The peripheral blood contains few or absent myeloblasts (<5%), although there is usually a “left shift” with circulating immature neutrophils and erythrocyte precursors.7 The myeloid cells are often dysplastic, while the erythrocytes display normal morphology.8

The diagnosis of APMF is made on pathologic analysis of the marrow. Bone marrow aspirates are frequently difficult, and our patient’s “dry tap” was not uncommon. The bone marrow biopsy in APMF is notable for its lack of marked increase in blasts, unlike conventional AML. Rather, the marrow typically contains foci of blasts with variable reticulin and collagen fibrosis.8 The marrow contains maturation defects in all three hematopoietic lineages, especially in the megakaryocytes.4–5 Thus, bone marrow biopsy is essential to the diagnosis of APMF, as in all the hematologic malignancies.

The natural history of APMF is rapid and aggressive. It has been reported to respond poorly to chemotherapy, and to have a median survival of less than 1 year, as it evolves to bone marrow failure and/or AML.7 In terms of management, there is little evidence regarding successful treatment for APMF. The most common course of action has been induction chemotherapy as in AML.6,8,9 Other approaches have included autologous stem cell transplantation following chemotherapy, and zoledronate,10 which have shown some benefit in inducing remission. Overall, however, APMF is a rapidly fatal condition whose outcomes remain poor.

**Conclusion**

While APMF is an uncommon cause of pancytopenia, this case illustrates that such a hematologic presentation must be investigated until a satisfactory etiology is established. While pancytopenia is most often caused by chronic hematologic and systemic disorders, the possibility of acute hematologic malignancy exists and must always be excluded.

**References**