Pseudomonas sepsis simulating acute promyelocytic leukemia

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Pseudomonas aeruginosa is an opportunistic organism that has become an increasingly important cause of infection since the advent of antibiotics.1,2 It remains an uncommon systemic infection in healthy children but is a frequent pathogen in patients with cystic fibrosis, burns, trauma, immunodeficiencies or malignancies.2 We report a previously healthy infant who presented with P. aeruginosa sepsis and a clinical picture resembling a leukemic process, including pancytopenia, hepatomegaly and hyperuricemia. A bone marrow aspirate was performed and was suggestive of acute promyelocytic leukemia. However, because no Auer rods or abnormal granules were seen in these promyelocytes, the diagnosis of acute promyelocytic leukemia could not be established. A repeat bone marrow examination 24 hours later revealed normally differentiating granulocyte precursors consistent with resolving maturational arrest due to sepsis. Supportive care and systemic antibiotic therapy resulted in the gradual normalization of all symptoms and laboratory abnormalities.

CASE REPORT

This 6-month-old previously healthy white male was referred to our institution after 2 days of low grade fever, increasing lethargy and loose, green, mucous-containing stools. On arrival his body temperature was 101.8°F, blood pressure 88 mm Hg systolic and heart rate 160 beats/minute. He was listless and in respiratory distress. The liver was palpated 5.5 cm below the right costal margin. No splenomegaly, lymphadenopathy or skin lesions were apparent.

The patient’s hemoglobin was 7.2 g/dl and the platelet count was 80,000 cells/mm³. Many spiculated red blood cells as well as Döhle bodies were noted. The white blood cell count was 2700 cells/mm³ with 4% neutrophils, 9% band forms, 5% metamyelocytes, 74% lymphocytes, 4% reactive lymphocytes and 4% monocytes. The serum glucose was 50 mg/dl, the sodium 133 mmol/liter, potassium 3.6 mmol/liter, chloride 100 mmol/liter, bicarbonate 16 mmol/liter, blood urea nitrogen 42 mg/dl, serum creatinine 1.3 mg/dl and uric acid 15.4 mg/dl. Prothrombin time was 14.4 seconds and partial thromboplastin time was 52.5 seconds; fibrinogen and fibrin split products were normal. Chest radiographs were consistent with pulmonary edema or a bilateral diffuse pneumonitis. Serum haptoglobin, Coombs test, liver function studies and cerebrospinal fluid were normal. Cultures of urine, blood, tracheal secretions and stool were positive for P. aeruginosa, prompting a change in antibiotics from ampicillin and chloramphenicol that were initially started to ceftazidime and tobramycin.

Within 24 hours of admission a repeat hemogram showed an increase in circulating myeloid precursors (Table 1). Because of the hematologic and clinical abnormalities including an unusual bacterial pathogen, a bone marrow aspiration was performed. This revealed a hypercellular marrow showing prominent promyelocytes (43.2% of nucleated cells) and few mature myeloid elements (4.1%). The myeloid:erythroid ratio was increased at 19:6:1. The abundance of promyelocytes in the marrow, the pancytopenia, organomegaly and hyperuricemia were all consistent with acute promyelocytic leukemia. However, the adequate number of megakaryocytes and the absence of Auer rods, bizarre bilobed nuclear forms or abnormal cytoplasmic granules suggested a diagnosis of maturational arrest. Monoclonal antibody phenotyping of these cells was nondiagnostic.

Supportive care including fluids, antibiotic therapy and mechanical ventilation was used to stabilize the child; no antileukemic chemotherapy was initiated. A repeat marrow aspirate 24 hours later revealed a morphologically similar marrow but with more myelocytes and fewer promyelocytes, again without Auer rods. Cytogenetic analysis of this marrow showed a normal 46,XY karyotype. This was consistent with a resolving bone marrow arrest probably associated with Pseudomonas sepsis. Serial hemograms showed an eventual
TABLE 1. Serial hemograms in a patient with pseudomonas sepsis

The patient received a transfusion of packed red cells on admission and two more on Day 1. In addition a transfusion of platelets was administered on the evening of Day 1 and again on Day 2.

<table>
<thead>
<tr>
<th>Day of Hospitalization</th>
<th>Total Blood Cell Count</th>
<th>% of Segmented Forms</th>
<th>% of Band Forms</th>
<th>% of Precursor</th>
<th>% of Lymphocytes</th>
<th>% of Monocytes</th>
<th>ANC/µl</th>
<th>Hemoglobin (g/dl)</th>
<th>Platelets/µl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>2 700</td>
<td>4</td>
<td>9</td>
<td>5</td>
<td>78</td>
<td>4</td>
<td>351</td>
<td>7.2</td>
<td>80 000</td>
</tr>
<tr>
<td>Day 1</td>
<td>2 600</td>
<td>1</td>
<td>6</td>
<td>19</td>
<td>53</td>
<td>20</td>
<td>182</td>
<td>10.8</td>
<td>21 000</td>
</tr>
<tr>
<td>Day 2</td>
<td>8 900</td>
<td>0</td>
<td>34</td>
<td>24</td>
<td>18</td>
<td>24</td>
<td>3026</td>
<td>13.4</td>
<td>90 000</td>
</tr>
<tr>
<td>Day 4</td>
<td>12 000</td>
<td>3</td>
<td>52</td>
<td>0</td>
<td>30</td>
<td>10</td>
<td>6000</td>
<td>12.6</td>
<td>60 000</td>
</tr>
<tr>
<td>Day 8</td>
<td>11 900</td>
<td>5</td>
<td>52</td>
<td>1</td>
<td>29</td>
<td>12</td>
<td>6726</td>
<td>11.9</td>
<td>167 000</td>
</tr>
<tr>
<td>Day 12</td>
<td>20 700</td>
<td>13</td>
<td>31</td>
<td>6</td>
<td>36</td>
<td>13</td>
<td>7038</td>
<td>10.7</td>
<td>Mod inc</td>
</tr>
<tr>
<td>Day 17</td>
<td>13 500</td>
<td>24</td>
<td>19</td>
<td>2</td>
<td>42</td>
<td>13</td>
<td>5805</td>
<td>11.6</td>
<td>998 000</td>
</tr>
</tbody>
</table>

Precor., Granulocyte precursors, i.e. metamyelocytes, myelocytes; ANC, absolute neutrophil count; Mod inc, no numerical value available. Platelets estimated as moderately increased.

clearing of the circulating myeloid precursors (Table 1). He was discharged 19 days after admission in good condition with no medications.

Further testing including quantitative immunoglobulins, IgG subclasses, total hemolytic complement, C3, C5 and sweat testing were normal. A urine culture was positive for cytomegalovirus and an ECHO 22 virus was grown from the stool. Seven months after his illness the patient was well with no recurrence of serious infection.

**DISCUSSION**

*P. aeruginosa* is a rare cause of systemic infection in childhood, constituting 0.7 to 3.0% of cases of bacteremia.1–6 Recent reviews of *Pseudomonas* sepsis in children and adults have discussed patients with cancer, prolonged hospitalization or underlying illnesses.7–11 Earlier reports have described occasional cases of *Pseudomonas* in apparently healthy infants.12–14 Chusid and Hillman15 recently reported three cases of infants with systemic *Pseudomonas* infections, two apparently healthy and one with hypogammaglobulinemia. Two of these patients also had neutropenia. In addition Lanham et al.16 reported two children with *Pseudomonas* sepsis, pancytopenia and bone marrow aspirates suggestive of acute promyelocytic leukemia.

Pseudomonal infections in burn patients have been reported to result in granulocytopenia,17 and *Pseudomonas* has been shown to suppress the production of platelets and granulocytes in burned rats.18 The multiple physiologic changes caused by *Pseudomonas* sepsis are in part the result of a number of virulence factors produced by *Pseudomonas*, including proteases, phospholipases, pili, endotoxin and exotoxin A.1 Injection of endotoxin causes an initial decrease in circulating white blood cells as they shift to the marginating pool, although this is generally followed by granulocytic proliferation and a subsequent leukocytosis.16,18,19 Exotoxin A is an extremely toxic extracellular product of *Pseudomonas*1 and appears to be cytotoxic as well as an inhibitor of protein synthesis.17,20 Stuart et al.17 demonstrated that purified exotoxin A produced leukopenia in mice in addition to suppressing the proliferation of human bone marrow, suggesting that exotoxin A may be responsible for causing the bone marrow suppression seen in human pseudomonal infections.

The source of the pseudomonal infection in this patient remains unknown, although it seems probable that it was a gastrointestinal illness initially, which led to bacteremia and hematogenous spread. Because of the unusual nature of the illness an inherited immune defect was considered, but this was not supported by immunologic testing.

It is of interest that cytomegalovirus was isolated from the urine and an ECHO 22 virus was isolated from the stool. Chusid and Hillman15 similarly reported viruses isolated from two of three infants with systemic *Pseudomonas* infections. However, 10 to 15% of infants in the United States acquire cytomegalovirus from maternal sources, and the vast majority of these are asymptomatic;21 ECHO viruses are common causes of gastrointestinal disease or asymptomatic infection.22 Although viral infections could potentially play a contributory role in the development of *Pseudomonas* sepsis, we believe the *Pseudomonas* infection was the cause of the severe symptoms and hematologic anomalies.

In summary systemic illnesses due to *P. aeruginosa* in healthy children are uncommon. Neutropenia or pancytopenia may be associated with pseudomonal infections, possibly caused by exotoxin A, endotoxin or another bacterial toxin. The absence of Auer rods and abnormal appearing granules in granulocytic precursors may indicate bone marrow suppression due to infection. Before initiating antileukemic chemotherapy in such a clinical situation, a repeat marrow aspirate 1 to 2 days later is helpful in establishing whether the diagnosis is leukemia or primary sepsis.

**ACKNOWLEDGMENTS**

The authors thank Dr. G. Sekhon for marrow cytogenetic evaluation, Dr. D. Norback for marrow flow cytometry analysis and Ms. Judy Setzkorn for marrow histochemistry. This work was supported in part by NIH Grant CA 32685 and American Cancer Society Grant CH-237.
REFERENCES


Wheeler Wildlife Range, Alabama

Photograph by Joe Rutledge, M.D.
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