Letter to the Editor

Profound neutropenia and atypical lymphocytosis in a traveller to Ghana

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A previously healthy 27-year-old African American male returned from a 3-month stay in Ghana where he travelled extensively in the countryside, sustained insect bites, ingested local food and water, and held infants and young children. On the day of his return, he experienced a sudden onset of fever to 104°F, headache, myalgias, chills, and sweats and was admitted to the hospital for evaluation.

He had been vaccinated against hepatitis A, yellow fever, and typhoid fever prior to travelling and denied any sexual encounters during his stay. He had taken mefloquine prophylaxis intermittently and had a febrile illness while in Ghana, 6 weeks before his return. He was treated with three unknown medications, which he discontinued because of side effects after 2 days. There was no diarrhea, rash, cough, or vomiting.

Upon admission to hospital, the patient’s temperature was 39.5°C and his heart rate was 80 bpm. Physical examination was significant for profuse sweating, rigors, hepatomegaly, and mild diffuse abdominal pain. There was no adenopathy, skin rash, or jaundice. Laboratory examination revealed mild hepatitis (aspartate aminotransferase 53 U/L), and an abdominal ultrasound showed hepatosplenomegaly. The patient’s hematologic parameters during the first 4 days of hospitalization are shown in Table 1. Admission hematologic findings included leukopenia, neutropenia, and atypical lymphocytosis. Renal function tests and chest radiograph were normal.

Major differential diagnoses included malaria, dengue, typhoid fever, cytomegaloviral infection, hepatitis A, toxoplasmosis, mononucleosis secondary to Epstein-Barr virus, and human immunodeficiency virus (HIV) seroconversion syndrome.

The clinical syndrome was consistent with malaria except for the relative bradycardia and the severe hematologic abnormalities. Infection with dengue virus was considered because of the fever, malaise, myalgia, and headache. Rash occurs in almost one half of travellers with dengue, and lymphopenia, but not neutropenia, is common. Hemoglobin levels are usually normal as seen initially in this patient. Typhoid fever is associated with a relative bradycardia and hepatosplenomegaly but not with severe hematologic abnormalities, and the fever usually rises in a stepwise manner and not abruptly as in this patient. In addition, he had been vaccinated against this infection. Agents causing a mononucleosis-like syndrome, such as cytomegalovirus, Epstein Barr virus, toxoplasmosis and primary HIV infection, can all cause atypical lymphocytosis and various hematologic abnormalities.

The lack of pharyngitis and lymphadenopathy mitigated against the diagnosis of Epstein-Barr infection and toxoplasmosis, and lack of sexual contact or exposure to blood products made HIV infection unlikely. Cytomegalovirus infection can cause hepatitis, malaise, and fever, and the patient’s exposure to babies and young children made this a consideration. Vaccination is usually effective in preventing hepatitis A, and the height of fever and mild transaminase elevations would be atypical for this infection.

Blood and cerebrospinal fluid were sent for culture and were sterile. Smears from four blood specimens taken during the first 36 hours of hospitalization and examined by experienced technicians were negative for malarial parasites. Doxycycline was begun and one dose of granulocyte colony stimulating factor was administered because of neutropenia. A fifth peripheral blood smear and a bone marrow biopsy revealed Plasmodium falciparum with a parasitemia of less than 1%. There were increased numbers of immature myeloid cells. Serologic studies were negative for acute infection with Epstein-Barr virus, dengue, Ehrlichia and Brucella. Review of the initial four negative smears again showed no evidence of malaria.

The patient responded completely to therapy with quinine and doxycycline, had normal hematologic and hepatic function 2 weeks after treatment, and has remained well.

Plasmodium falciparum infection has been associated with a wide variety of hematologic alterations, such as thrombocytopenia, anemia, leukocytosis, and leukopenia. Neutrophil kinetic studies have provided data supporting one mechanism for the neutropenia sometimes encountered in malaria, namely that there is a premature release of bone marrow neutrophils with a
Table 1. Hematologic values during the first 4 days of hospitalization

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Day of hospitalization</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>43.2</td>
<td>37.7</td>
</tr>
<tr>
<td>WBC count (mm³)</td>
<td>1800</td>
<td>2000</td>
</tr>
<tr>
<td>Granulocytes (%)</td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td>Band forms (%)</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>48</td>
<td>74</td>
</tr>
<tr>
<td>Atypical lymphocytes (%)*</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Platelets (mm³)</td>
<td>115</td>
<td>84</td>
</tr>
</tbody>
</table>

concentration of these neutrophils in the marginal pool, especially the spleen, which is expanded to approximately four times normal.1,2 Absolute neutropenia, however, has not been previously described.

Atypical lymphocytes were first described by Turk in 1907, who saw them in the peripheral blood of patients with mononucleosis. They are a manifestation of a polyclonal proliferative response to some antigenic stimulus.3 Although usually associated with viral infections, they have been described in parasitic diseases such as toxoplasmosis, babesiosis,4 and malaria.5 Studies of cultured lymphocytes of patients with malaria show rapid transformation into blasts even without mitogenic stimulation.6 Nevertheless, the percentage of atypical lymphocytes reported in malaria infection has been less than 30% of lymphocytes,5,7 unlike the 100% seen in this patient.

The malaria infection was most likely acquired 6 weeks before presentation and was partially suppressed by 2 days of unknown antimalarial therapy in Ghana and intermittent mefloquine. The duration of severe neutropenia was brief, 1 day, and was associated with a reactive bone marrow, suggesting sequestration or marginalization.

Plasmodium falciparum-induced neutropenia and atypical lymphocytosis can be profound and may suggest alternative diagnoses. Awareness of this unusual hematologic presentation may assist clinicians in pursuing the diagnosis of malaria. Multiple blood specimens may be required to detect low levels of parasitemia.

REFERENCES