The hemophagocytic syndrome in an immunocompromised patient: A diagnostic challenge

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CASE PRESENTATION

A 23-year-old woman was admitted to hospital because of intermittent fever up to 40°C accompanied by significant arthralgia and myalgia for the previous seven days. She had been receiving azathioprine 100 mg per day and prednisone 60 mg per day for Harada’s disease with frequent bouts of recurrent uveitis for the past two years. She had been complaining of diffuse muscle and joint pain, stiffness and general weakness for the previous seven months, which prevented her from walking. Steroids had been tapered during the previous several weeks for suspected iatrogenic myopathy, although there had been no improvement. She denied cough, chest pain, headache or other symptoms. She had no pets, except contact with a friend’s dog, and had not travelled recently. Physical examination revealed a cushingoid woman in no distress with no adenopathy. Chest, cardiovascular, skin and abdominal exams were normal, and no hepatosplenomegaly was noted. Blood analysis revealed pancytopenia (hemoglobin 5.4 mmol/L; leukocytes 2×10⁹/L [0.4×10⁹/L lymphocytes]; platelets 38×10⁹/L), elevated liver enzymes (aspartate aminotransferase 561 U/L; alanine aminotransferase 451 U/L; lactate dehydrogenase 2300 U/L) and an increased prothrombin time by 56%. The erythrocyte sedimentation rate was 120 mm/h. Total gamma globulins were decreased (10 g/L) with low immunoglobulin G (6.53 g/L) and normal albumin (45 g/L). Triglycerides and fibrinogen were normal. Urine analysis, other routine biochemical markers and renal function were normal, as were the assays for rheumatoid factor, total complement activity, reticulocyte count and vitamin B₁₂ levels. Autoimmune studies (ie, antinuclear antibody, anti-DNA) and a Coomb’s test were negative, as was serology for common endemic infectious diseases (ie, Brucella species; Cytomegalovirus; Epstein-Barr virus; hepatitis A, B and C viruses; leishmania). Blood and urine cultures for bacteria were negative. A radiograph of the chest was normal, although echocardiography revealed a mild pericardial effusion. A computed tomography scan of the chest did not reveal any abnormalities. A diagnostic procedure was performed. What is the diagnosis?
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**DISCUSSION**

Hemophagocytic syndrome is characterized by uncontrolled nonmalignant proliferation of histiocytes and macrophages in bone marrow, lymphoid tissues or other organs, accompanied by clinical events such as fever, lymphadenopathy or hepatosplenomegaly. Pancytopenia develops due to activation of the mononuclear phagocytic system, with overproduction of cytokines and phagocytosis of erythrocytes, platelets and leukocytes (1). The histopathological and cytological findings of hemophagocytosis may be found in conjunction with malignant reactive histiocytosis, histoicytic medullary reticulosis, familial lymphohistiocytosis, or sinus histiocytosis associated with massive lymphadenopathy or lymphoproliferative processes, such as Hodgkin’s disease and T-cell or B-cell lymphomas. These hematological syndromes can cause the same clinical syndrome as seen in visceral leishmaniasis (VL) (2,3). Our patient with VL did not present with lymphadenopathy, and there had been no family history of such a disorder, making these hematologic processes unlikely. Hemophagocytosis may also occur in serious infections such as brucellosis, tuberculosis, rubella, Epstein-Barr virus, Cytomegalovirus, schistosomiasis, salmonellosis and leishmaniasis (1,2). Brucella species cultures and serology were negative in our patient, as were mycobacterial cultures, polymerase chain reaction for *Mycobacterium tuberculosis* complex, Salmonella species cultures and various viral serological assays (although the patient’s immunocompromised state may have affected the reliability of such serological studies). Pancytopenia can also present in autoimmune diseases, especially systemic lupus erythematosus, but negative antinuclear antibody and anti-DNA tests made this group of illnesses unlikely.

Only very prolonged and thorough review of the bone marrow aspirate produced the correct diagnosis in this patient. The diagnosis of VL is based on the demonstration of amastigotes in tissue samples (eg, liver, spleen and bone marrow) or the identification of promastigotes in a tissue culture (4). Specific serology is useful in immunocompetent patients, but seroconversion can be delayed or nonexistent in immunocompromised individuals (5). Polyclonal B-cell activation by this parasite produces hypergammaglobulinemia and high titers of antileishmania antibodies, except when hemophagocytosis develops (5,6). The hemophagocytic syndrome seldom occurs in VL but, if present, parasites become very scarce in bone marrow smears for unexplained reasons and, thus, are difficult to detect (7,8). The diagnosis in the presence of hemophagocytosis is elusive and usually delayed, with one study showing delays of up to 134 days (5). In addition, the absence of parasite visualization may lead to an erroneous diagnosis of one of the hematological neoplasms which display hemophagocytosis, resulting in aggressive chemotherapy treatments and/or bone-marrow allografting, as some authors have reported (1,2,5,6,8,9).

Our patient did not present with hepatosplenomegaly, hypergammaglobulinemia or weight loss, which are usually seen in VL. This may have been due to the previous corticosteroid administration. The normalization of all blood parameters and bone marrow histology after therapy with antimony salts supports *Leishmania* species as the responsible agent for her syndrome (2). The present case highlights the importance of prolonged and in-depth bone marrow review in immunocompromised patients with pancytopenia. Although unusual, VL may be masked by hemophagocytic events mimicking malignant histiocytosis. Clinicians and pathologists must be aware of this possible association between VL and hemophagocytic syndrome as a diagnostic challenge and include VL in the differential diagnosis of hemophagocytosis, especially in patients living in or having previously travelled to endemic areas.

**Figure 1** May-Grünewald-Giemsa stain of bone marrow aspirate, disclosing a mononuclear cell containing two *Leishmania* amastigotes (arrow) (Magnification ×1000)
REFERENCES


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