Clinical Case Report: Hemophagocytic Syndrome in a Patient with Acquired Immunodeficiency Syndrome and Acute Disseminated Penicilliosis

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Abstract. Penicilliosis marneffei, which is caused by the opportunistic fungus *Penicillium marneffei*, is one of the troublesome infections in patients infected with human immunodeficiency virus (HIV) in southeast Asia. We report an HIV-positive patient with acute disseminated penicilliosis marneffei that manifested as hemophagocytic syndrome. Numerous nucleated erythrocytes were also found in peripheral blood of the affected patient. Bone marrow aspirate histopathologically showed hemophagocytosis and abundant *P. marneffei*. The hemophagocytic syndrome and peripheral nucleated erythrocytes improved after therapy with amphotericin B. Our report underscores the importance of recognition of this peculiar phenomenon in penicilliosis marneffei. This awareness may alert clinicians to potential penicilliosis marneffei in HIV-positive patients, therefore making early diagnosis and timely effective treatment of the infectious disease possible.

Penicilliosis marneffei, an opportunistic infectious disease caused the dimorphic fungus *Penicillium marneffei* that grows as a mold at 25°C and as a yeast at 37°C. It is encountered in human immunodeficiency virus (HIV)-infected patients in southeast Asia,1 and is an emerging infectious disease among immunocompromised patients in Taiwan.2,3 The mortality rate in patients with acute disseminated penicilliosis marneffei is high if the infection is not diagnosed early enough and a timely and effective anti-fungal therapy is not used.1,4 We report a case of acute disseminated penicilliosis marneffei that manifested as hemophagocytic syndrome (HPS) in a patient with acquired immunodeficiency syndrome (AIDS). Numerous circulating nucleated erythrocytes were also found in the peripheral blood of this patient. The implications of this case are discussed.

A 34-year-old homosexual man visited our emergency service with the chief complaint of a two-week fever with respiratory distress and a weight loss of approximately 15 pounds in the previous two months. Physical examinations showed oral thrush, hepatosplenomegaly, and diffuse cutaneous erythematous papular lesions with or without central umbilication over his face and body (Figure 1). A chest radiograph showed consolidation in the lower lobe of his right lung. His hemogram values at admission were a leukocyte count of 8.25 × 10^3 cells/µL (normal range = 4–11 × 10^3 cells/µL) comprising 85% neutrophils, 5% bands, 4% myelocytes, 3% lymphocytes, and 3% monocytes; hemoglobin level = 7.8 g/dL (normal range = 13.5–17.5 g/dL); mean corpuscular volume = 70.8 fl (normal range = 80–100 fl); erythrocyte distribution width = 17.4% (normal range = 11.0–14.0%); reticulocytes = 1.96%; platelet count = 64 × 10^3 cells/µL (normal range = 150–400 × 10^3 cells/µL); and peripheral nucleated erythrocytes = 3/100 leukocytes. Blood chemistry data showed an aspartate aminotransferase level of 128 U/L (normal range = 0–37 U/L), an alanine aminotransferase level of 26 U/L (normal range = 0–40 U/L), and a creatinine level of 2.6 mg/dL (normal range = 0.4–1.4 mg/dL). The patient was serologically positive for HIV and his CD4 T lymphocyte count was 119 cells/µL. Because of oral candidiasis and systemic fungal infection was suspected, parenteral fluconazole (600 mg/day) was empirically prescribed. Three days later, his circulating peripheral nucleated erythrocytes increased to 202/100 leukocytes; his hemoglobin level decreased to 7.1 g/dL; his platelet count decreased to 10 × 10^3 cells/µL; and his leukocyte count decreased to 2.3 × 10^3 cells/µL, with 1% metamyelocytes, 2% bands, 76% segments, 8% lymphocytes, and 13% monocytes.

A skin biopsy specimen showed suppurative necrosis of dermis and the deeper subcutaneous tissue; numerous small round-shape microorganisms were seen in necrotic areas and in histiocytes. His bone marrow aspirate showed histiocytic hyperplasia and marked hemophagocytosis, and HPS was thus diagnosed. In addition, elongated or sausage-shaped microorganisms (3–6 μm in size) with a visible septum were found in both intracellular and extracellular spaces of histiocytes (Figure 2A). Periodic acid-Schiff staining of bone marrow aspirate showed a prominent central septum in some of the non-budding yeasts (Figure 2B). Therefore, the prescribed fluconazole was switched to amphotericin B. Subsequently, cultures of peripheral blood, skin biopsy specimens, bone marrow, and sputum all showed *P. marneffei*.

Three days after the patient received treatment with amphotericin B, fever and respiratory distress improved and the skin lesions began to resolve, and the pancytopenia and leukoerythroblastosis disappeared one week later, indicating that he had a rapid favorable response to treatment. When released from the hospital three weeks later, the patient received oral itraconazole (200 mg twice a day) and highly active antiretroviral therapy with zidovudine, lamivudine and efavirenz.

Hemophagocytic syndrome is characterized by fever, cytopenia, splenomegaly, abnormal liver function, and the pathologic finding of hemophagocytosis (phagocytosis of erythrocytes, leukocytes, platelets, and their precursors by macrophages) in bone marrow.5 This uncommon clinicopathologic entity is associated with lymphoma (T cell lymphoma in particular), autoimmune diseases, and an array of infections.6 As for infections, etiologies known to be inducers of HPS include a variety of viruses, bacteria, rickettsiae, fungi, and parasites.7 An HIV-negative woman with Sjögren’s syndrome treated with prednisolone and cyclophosphamide was...
reported to have penicilliosis-mediated HPS in which *P. marneffei* was absent from bone marrow. The bone marrow of our patient showed hemophagocytosis and *P. marneffei* (Figure 2). These findings suggested the high burden of *P. marneffei* and the severely immunocompromised status of the host, and this observation is consistent with a report that among patients suffering with penicilliosis, higher *P. marneffei* antigen titers and lower *P. marneffei* antibody titers were found in HIV-infected patients than in non–HIV-infected patients.

The presence of circulating peripheral nucleated erythrocytes usually indicates bone marrow infiltration if severe hemolysis, bleeding, or sepsis is absent. The common causes of extensive marrow infiltration include leukemia, lymphoma, fibroblasts, metastatic neoplasms, and infections (e.g., military tuberculosis and disseminated fungal infection). The high ratio of peripheral nucleated erythrocytes to leukocytes (202/100) detected in our patient is a valuable clue for potential bone marrow infiltration. This finding warrants further research for confirming and identifying its cause once bone marrow infiltration is confirmed.

The incidence of penicilliosis marneffei has increased over the past few years. Skin lesions are of particular importance for rapid diagnosis of disseminated penicilliosis because they draw the clinician’s attention and provide an easily accessibly biopsy specimen. *Penicillium marneffei* in biopsy specimens should be differentiated from other possible pathogens that include *Histoplasma capsulatum*, * Blastomyces dermatidis*, *Candida glabrata*, *Cryptococcus neoformans*, *Leishmania* spp., *Pneumocystis jirovecii*, and *Toxoplasma gondii*. The yeast form of *P. marneffei* proliferates by fission, and the yeast form of *H. capsulatum* proliferates by budding.

Special stains such as periodic acid-Schiff or Gomori-methamin silver may be helpful in highlighting the central transverse septum of *P. marneffei*. Unfortunately, papules with or without central necrotic umbilication, maculopapular rash, or folliculitis were nonspecific for penicilliosis marneffei, and were found in only approximately 50% of affected patients outside disease-endemic regions and in approximately 70% of affected patients in Thailand. Because of the extreme importance of timely effective therapy for which an early diagnosis is prerequisite in lowering the mortality rate in patients with acute disseminated penicilliosis marneffei, and because of the suboptimal incidence and nonspecificity of skin lesions in the affected patients when it comes to diagnosis, HPS may play a complementary role in alerting clinicians to the potential of acute disseminated *P. marneffei* infection, and a workup for confirmation may be conducted. In the AIDS era, any clue that suggests a possible opportunistic infection and the underlying HIV infection should be highly valued.

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