Fever, Splenomegaly, and Pancytopenia: Histoplasma-Associated Hemophagocytic Lymphohistiocytosis

Arjun Gupta, MD¹, Mrinal Agrawal, BS², and Jesse Jaso, MD³

¹Department of Internal Medicine, University of Texas Southwestern Medical Centre, Dallas, TX, USA; ²Rutgers New Jersey Medical School, Newark, NJ, USA; ³Departments of Pathology, University of Texas Southwestern Medical Centre, Dallas, TX, USA.

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CASE

A 26-year-old man with acquired immunodeficiency syndrome (AIDS) taking no medications presented with fever and anorexia. Examination showed a febrile cachectic man with splenomegaly. Laboratory analysis revealed pancytopenia (white cell count $2.1 \times 10^3/\mu\text{L}$, hemoglobin 8.1 gm/dL, platelet count $49 \times 10^3/\mu\text{L}$) and CD4 count $2/\mu\text{L}$. Serum ferritin (8312 mcg/L) and fasting triglycerides (312 mg/dL) were elevated. Urinary *Histoplasma* antigen was positive. Bone marrow biopsy demonstrated histiocytes with intracellular yeast and ingested red blood cells (Figs. 1 and 2). The patient was diagnosed with disseminated histoplasmosis that

manifested as hemophagocytic lymphohistiocytosis (HLH) and was treated with antiretroviral therapy, intravenous amphotericin B for 2 weeks, and oral itraconazole for 1 year.

HLH is a hyperinflammatory disorder caused by uncontrolled proliferation of activated lymphocytes and macrophages secreting inflammatory cytokines.¹ Although a primary genetic form exists, secondary HLH is often associated with immunodeficiency, malignancy, and infection, commonly in patients with AIDS with histoplasmosis.^{2,3} Current diagnostic criteria require fulfillment of five out of eight criteria: fever, splenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia/hypofibrinogenemia, pathological evidence of hemophagocytosis, low natural killer cell activity, and elevated levels of soluble CD25.^{1,2} Treatment of HLH involves treating the underlying cause; additional therapy with corticosteroids, intravenous immunoglobulin (IVIG), etoposide, or cyclosporine may be required.¹

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Figure 1 Several enlarged histiocytes containing numerous yeast forms which are surrounded by a clear zone, characteristic of *Histoplasma* (red arrows). One histiocyte (at the top) also contains an engulfed red blood cell (black arrow). Bone marrow, Wright-Giemsa stain, $\times 1000$.

Figure 2 GMS stain highlights numerous fungal organisms identified as capsulated yeast (red arrows). Bone marrow, Gomori methenamine silver (GMS) stain, $\times 50$.

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Corresponding Author: Arjun Gupta, MD; Department of Internal Medicine University of Texas Southwestern Medical Centre, 5323 Harry Hines Blvd, Dallas, TX 75390-9047, USA (e-mail: guptaarjun90@gmail.com).

Compliance with Ethical Standards:

Conflict of Interest: The authors declare that they do not have a conflict of interest.

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