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MEDICAL IMAGERY

"Disseminated histoplasmosis and erythrophagocytosis in an immunocompromised host: the role of bone marrow evaluation for prompt diagnosis of invasive fungal infections"

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A 44-year-old woman came to our service with fever, fatigue, and weight loss lasting 3 months. Blood count demonstrated severe pancytopenia. Bone marrow (BM) aspirate revealed granulocytic maturation arrest, plasmacytosis, increased macrophage activity with erythrophagocytosis, and rounded fungal structures inside the histiocytes [Figure 1]. Computed tomography scans showed splenomegaly and abdominal lymphadenomegaly. HIV serology was positive, CD4 count was 16 cells/mm^3, and HIV viral load was 2.880,000 copies/mL. Serum ferritin was 10.015 ng/mL, triglycerides were 369 mg/dL, and fibrinogen was 77 mg/dL. The patient had an H-Score of 317 points, with hemophagocytic lymphohistiocytosis (HLH) probability >99% (Fardet et al., 2014). According to criteria for HLH proposed by the Histiocyte Society in 2004 (HLH-2004) (Henter et al., 2007), a diagnosis of secondary HLH was defined in this case by the presence of 6/8 criteria: fever, splenomegaly, pancytopenia, hypertriglyceridemia, ferritin ≥500 ng/mL, and presence of hemophagocytosis figures in BM aspirate, in addition to the absence of associated malignancy.

Histoplasma capsulatum was isolated in peripheral blood cultures. After diagnostic confirmation of disseminated histoplasmosis, the patient was promptly treated with liposomal amphotericin B at a dose of 3 mg/kg/day I.V. for 2 weeks, followed by maintenance with itraconazole, 200 mg P.O. twice daily for 12 months. Anti-retroviral therapy (ARVT) was also promptly initiated with a triple-regimen based on dolutegravir, abacavir, and lamivudine. Three weeks after the beginning of antifungal therapy, the patient no longer had fever, there was an improvement in her general condition, there was no longer any hepatosplenomegaly on physical examination, and there was an increase in cytopenias. There was also laboratory improvement of HLH markers, with normalization of aminotransferases, triglycerides and fibrinogen, and reduction of ferritin levels to <500 ng/mL. Six months have passed since completing treatment for disseminated histoplasmosis, and she currently remains asymptomatic, using ARVT regularly, with CD4 count of 213 cells/mm^3 and an undetectable HIV serum viral load.

Histoplasmosis is a granulomatous disease caused by the fungus *Histoplasma capsulatum* (Wheat et al., 2016). Its disseminated form occurs when 2 or more organs are affected, and predominates in immunocompromised patients (Azar et al., 2020). It is associated with high morbidity and mortality, therefore rapid identification and treatment are essential to improve clinical outcomes (Wheat et al., 2016). Although the gold-standard for diagnosis is isolation of the fungus in cultures or histopathological identification

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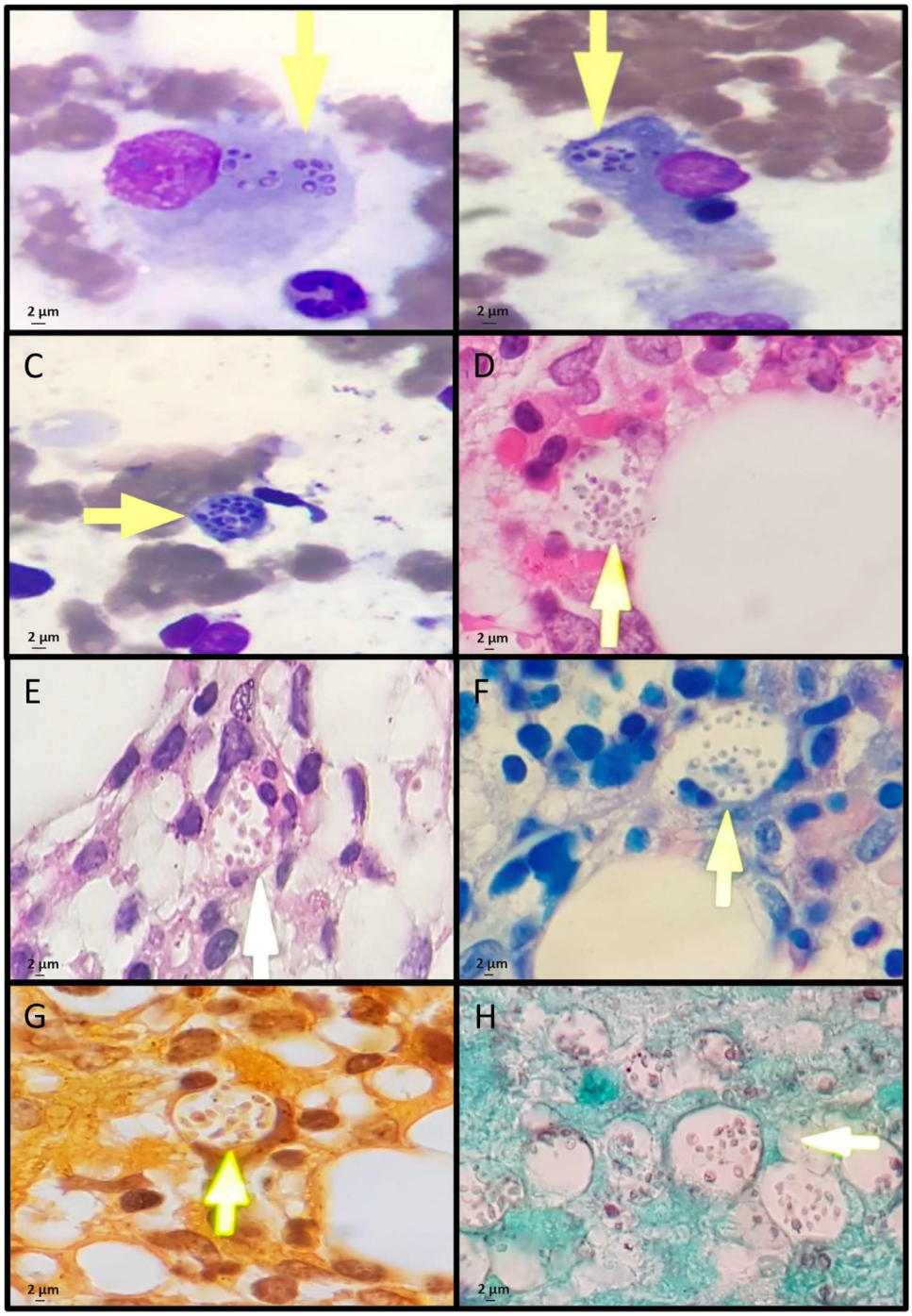

Figure 1. A, B, and C: bone marrow aspirate (Leishman staining, optical microscopy, 100 x magnification) - several rounded fungal structures with birefringent membrane inside the cytoplasm of bone marrow histiocytes, in **B** a histiocyte phagocytizing an orthochromatic erythroblast (figure of erythrophagocytosis), as well as histiocytic inclusion vacuole with several parasitic structures. **D, E, F, G and H**: bone marrow biopsy (optical microscopy, 100 x magnification) - **D**: positivity for periodic acid-Schiff staining (PAS); **E**: Hematoxylin-Eosin (HE) staining; **F**: Giemsa staining with identification of *H. capsulatum* inside bone marrow macrophages; **G**: negativity of fungal structures in mucicarmine staining; **H**: Grocott-Gomori staining demonstrating numerous silver-stained intracytoplasmic fungal structures.

by Grocott-Gomori staining [Figure 1], BM aspirate can strongly contribute to a faster diagnosis, allowing the institution of prompt specific therapy (Kauffman, 2007).

HLH in HIV-infected patients is a rare condition associated with poor outcomes. Recently, Nguyen et al. (2020) reported 14 cases of HIV-associated HLH in the Amazon region. According to these authors, 12/14 cases had associated disseminated histoplasmosis (10 confirmed cases and 2 suspected cases). As in our case, >90% of patients had a CD4 count <200 cells/mm^3 and a HIV viral load >100,000 copies/mL. In this case series, most patients had a favorable response to therapy with amphotericin B, similarly to our patient. We highlight the fact that in the Amazon cohort the authors were less restrictive in establishing a diagnosis of HLH, using the presence of 3/8 criteria of the HLH-2004 classification, as opposed to the recommended minimum of 5/8 criteria used in diagnosing our patient. Therefore, we emphasize the utility of considering histoplasmosis as an important etiologic factor in secondary HLH in HIV-infected patients, particu-

larly in endemic areas and with regard to *Histoplasma capsulatum* infection.

Declaration of Competing Interest

No conflict of interest was declared by the authors.

Informed Consent

Obtained.

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Authorship Contributions

Concept: LAPCL; Design: LAPCL, HFC; Data Collection or Processing: GGML, GG; Analysis or Interpretation: LAPCL, JP; Literature Search: LAPCL; Writing: LAPCL, JP. Acknowledgments to Dr. Sheila Aparecida Coelho Siqueira for the photographs of bone marrow biopsy (Department of Pathology – University of São Paulo).

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