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Article type : Case Report

Title: Unexpected disseminated histoplasmosis detected by bone marrow biopsy in a solid organ transplant patient

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Key Clinical Message:

Disseminated histoplasmosis and hemophagocytic lymphohistiocytosis (HLH) show overlapping features, which require careful contextual interpretation. Histopathologic evaluation can

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1 potentially rapidly identify cases of possible histoplasmosis. A high index of clinical suspicion,
2 particularly in endemic areas and in a setting of immunosuppression, is critical to appropriate
3 diagnosis and treatment.

4
5 Keywords: histoplasmosis, hemophagocytic lymphohistiocytosis, ferritin, bone marrow

6
7 A 29- year- old male with a history of end stage renal disease secondary to minimal change
8 disease, status post renal transplant two years prior, presented with a one-week history of fever,
9 night sweats, chills, generalized aches and diarrhea. His immunosuppressive regimen included
10 tacrolimus, cyclosporine and prednisone. The patient lives in Michigan and works as a truck
11 driver with most recent travel to Arizona and Texas. Following admission, he was noted to be
12 tachycardic and febrile (up to 40.1°C), but his physical exam was otherwise unremarkable. CBC
13 showed mild anemia (Hgb as low as 11.1 g/dL) and variable thrombocytopenia (platelets as low
14 as 115 k/uL). Imaging studies were significant for ill-defined centrilobular groundglass opacities
15 in the lungs, although without any respiratory complaints or hypoxia initially. PET/CT also noted
16 hypermetabolic lymph nodes, spleen (without splenomegaly), and a soft tissue mass in the porta
17 hepatis, raising the possibility of a post-transplant lymphoproliferative disorder, however a
18 biopsy was not performed during the admission based on the subsequent findings.

19
20 He was initially placed on empiric therapy with vancomycin and piperacillin-tazobactam and
21 over the next 5 days underwent an extensive workup including blood and urine cultures; CMV,
22 HIV, EBV, HHV6, parvovirus, toxoplasma, adenovirus, and HSV PCR; Q fever, *Bartonella*,
23 *Brucella*, parvovirus and fungal serology; and *Clostridium difficile* antigen and toxin and serum
24 cryptococcal and urine *Legionella* antigen. These results were all negative. Concurrently, he
25 was found to have hyperferritinemia of 14914 ng/mL (normal range 18-320 ng/mL) and
26 triglycerides 228 mg/dL, concerning for hemophagocytic lymphohistiocytosis (HLH). To
27 evaluate for hemophagocytosis, soluble CD25 was measured at 2291 U/mL, fibrinogen was 415
28 mg/dL, and a bone marrow biopsy was performed; NK cell activity was not measured. The core
29 biopsy showed normocellular bone marrow with trilineage hematopoiesis.

1 A single histiocyte with oval-shaped organisms was seen on the aspirate smear (Figure 1A). The
2 morphological differential diagnosis included *Histoplasma capsulatum*, *Leishmania* species,
3 *Candida glabrata*, *Blastomyces dermatitidis*, among others¹. Grocott-methenamine silver stain
4 performed on the bone marrow core demonstrated additional histiocytes containing multiple
5 yeast forms exhibiting narrow based budding (Figure 1B). Rare hemophagocytes were noted
6 (Figure 1C). Based on these findings, intravenous liposomal amphotericin was started.
7 Subsequent urine *Histoplasma* antigen test results (above the limit of quantification) and fungal
8 blood culture results returned, confirming a diagnosis of *H. capsulatum*.

9
10 Disseminated histoplasmosis is predominantly seen in immunosuppressed patients, including
11 solid organ transplant patients². An association between hemophagocytic lymphohistiocytosis
12 (HLH) and *H. capsulatum* infection has been observed, commonly in the setting of AIDS^{3,4}. The
13 diagnostic criteria for HLH in the 2004 guidelines include fever, splenomegaly, cytopenias
14 affecting at least two of the three lineages, hypertriglyceridemia and/or hypofibrinogenemia,
15 hemophagocytosis in the bone marrow spleen or lymph nodes, low/absent NK-cell activity,
16 hyperferritinemia and high levels of sIL-2r⁵. The patient met 3 of these (fever, elevated ferritin,
17 and rare hemophagocytosis), which was insufficient for diagnosis of HLH, though soluble CD25,
18 triglycerides and cytopenias did approach meeting criteria. HLH can be seen either as a primary
19 hereditary disorder or secondary to a number of causes including infection (particularly viral, e.g.
20 EBV), malignancy, and rheumatologic disease. It is important to note that hyperferritinemia
21 alone is not specific for HLH, as this finding in isolation can be seen in the setting of
22 inflammation and infection, even with indolent course⁶. *Histoplasma* infection in particular can
23 cause elevated ferritin and fever without meeting other criteria for HLH. It is also important to
24 point out that hemophagocytosis seen on bone marrow aspirate is not specific to HLH^{7,8}. In a
25 study by Rivière et al.⁸, hemophagocytosis was found in 39.4% of patients where the diagnosis
26 of HLH was suspected but ultimately ruled out, as in this case.

27
28 This case demonstrates an instance where the bone marrow biopsy was particularly useful in
29 early detection of the patient's infection, as some of the confirmatory assays require more
30 extended periods of time to result. Though bronchoalveolar lavage (BAL) and respiratory
31 cultures were not performed in the current case, histopathologic evaluation of these samples

1 could also potentially have yielded similarly analogous information. A high index of clinical
2 suspicion for infection in potential HLH patients who are immunosuppressed is necessary, both
3 in the clinical and pathologic practice, especially in endemic areas. This patient was continued
4 on intravenous liposomal amphotericin followed by voriconazole. He exhibited complete
5 response with immediate reduction in fever and resolution of all imaging abnormalities and
6 symptoms.

7
8 In subsequent monitoring the ferritin initially increased to >16500 ng/mL in the two days prior to
9 bone marrow biopsy and decreased to 3602 ng/mL five days after the bone marrow biopsy was
10 performed with no additional follow-up.

11 12 13 **Authorship:**

14 Caroline T. Simon: Wrote the manuscript.

15 Carlos A. Murga-Zamalloa: Wrote the manuscript.

16 Michael A. Bachman: Provided additional comments, direction, and editing

17 Lindsey A. Petty: Provided additional comments, direction, and editing

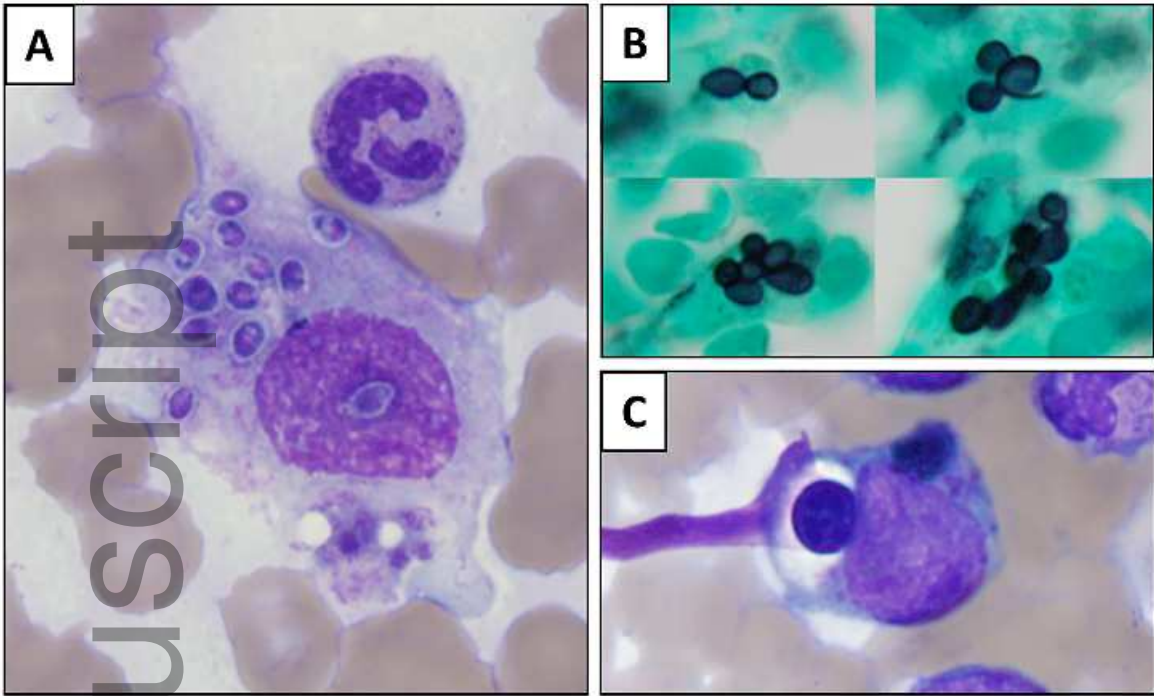
18 Sarah M. Choi: Wrote the manuscript and created the Figure.

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