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Hemophagocytic Lymphohistiocytosis Secondary to Disseminated Histoplasmosis

A Report of 3 Cases and Review of the Literature

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Abstract: Hemophagocytic lymphohistiocytosis is a syndrome of immune dysregulation that can lead to an overwhelming inflammatory state. In this case series, we describe 3 cases in which disseminated *Histoplasma capsulatum* infection caused hemophagocytic lymphohistiocytosis.

Key Words: histoplasmosis, *Histoplasma capsulatum*, hemophagocytic lymphohistiocytosis, HLH, immunocompromised

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Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome of immune overactivation in which a defective cytotoxic T-cell response leads to an uncontrolled inflammatory state.[1–3] This syndrome can mimic severe sepsis and overwhelming infection but can be triggered by any immune stimulating event, including malignancy, autoimmune disease, or infection, with cytomegalovirus and Epstein-Barr virus being the most frequently described.[2,3] Disseminated histoplasmosis is an uncommon cause of HLH; a large case review suggests that less than 1% of cases of HLH worldwide are due to histoplasmosis.[3] Histoplasmosis associated with HLH has been primarily reported in patients infected with HIV.[4,5]

In this case series, we present 3 immunocompromised patients with HLH secondary to disseminated histoplasmosis, all without HIV infection, who presented in the fall of 2019 to two tertiary care centers in southeastern Michigan.

CASE 1

A 68-year-old man, with psoriatic arthritis on tumor necrosis factor (TNF)-α inhibitor therapy with golimumab presented in mid-October with fevers and malaise that did not respond to broad-spectrum antibiotics and a 6-day methylprednisolone dose pack. On admission, he was febrile and ill appearing. Examination showed bilateral pulmonary rhonchi and splenomegaly. Laboratories on admission were notable for thrombocytopenia and elevated transaminases (Table 1). Chest x-ray demonstrated a pulmonary infiltrate in the right lower lobe. He had progression of thrombocytopenia and transaminitis despite antibiotic treatment; workup for atypical pulmonary infection was initiated. Bronchoscopy was unremarkable. β-D-Glucan was positive at 368 pg/mL, and fungal serologies showed positive histoplasma H and M bands, with mycelial titers of 1:16 and yeast titers of 1:256. Urine and serum *Histoplasma* antigens were greater than the upper limit of detection (MiraVista Labs, Indianapolis, Ind). Bone marrow biopsy was performed given thrombocytopenia and showed hemophagocytosis; ferritin was greater than 10,000 ng/mL and interleukin 2 (IL-2) receptor antibodies were positive at 3686 IU/mL. Bone marrow culture grew *Histoplasma capsulatum*. The patient was started on intravenous liposomal amphotericin B 3 mg/kg per day and was transitioned to itraconazole solution 200 mg twice a day at discharge; an itraconazole level checked 1 week into therapy was 4.4 μg/mL. The patient did not receive any immunosuppression as treatment for HLH.

CASE 2

A 42-year-old woman with ankylosing spondylitis on methotrexate 10 mg weekly and infliximab 400 mg every 8 weeks presented with 5 days of fever, headaches, malaise, nausea, and abdominal pain. On admission, she was febrile to 40°C; laboratories showed mild thrombocytopenia with elevated transaminases and bilirubin (Table 1). Computed tomography (CT) of the abdomen was concerning for cholecystitis with choledocholithiasis; splenomegaly was noted. Despite treatment with broad-spectrum antibiotics for 7 days, initially piperacillin-tazobactam 4.5 g every 6 hours, followed by ertapenem 1 g daily, she had persistent fever and worsening transaminase elevation and renal failure. She subsequently became hypoxic with altered mentation and required intubation; a CT chest showed diffuse ground-glass changes bilaterally. Her renal injury progressed requiring hemodialysis, and she developed lactic acidosis and hemodynamic instability requiring vasopressor support. Ferritin level was 26,918 ng/mL and triglycerides were 1409 mg/dL, which raised concern for HLH (Table 1). Liver biopsy showed marked granulomatous inflammation with numerous intracellular organisms consistent with *H. capsulatum*. Bone marrow biopsy showed hemophagocytosis, and Grocott methenamine silver (GMS) stain showed intracellular yeast forms consistent with *Histoplasma* species. Patient's urine and serum histoplasma antigen were both strongly positive (MiraVista Labs; Table 1). The patient was treated with intravenous liposomal amphotericin B 3 mg/kg per day for disseminated histoplasmosis, as well as etoposide 72 mg intravenously every 3 days ×2 doses, and dexamethasone with a taper for HLH. Her mental status, hemodynamics, and laboratory parameters all improved, and she eventually had full renal recovery. She was transitioned to itraconazole solution 200 mg twice daily and ultimately discharged from the hospital with good recovery.

CASE 3

A 56-year-old woman with systemic lupus erythematosus complicated by lupus nephritis and antiphospholipid antibody syndrome managed with hydroxychloroquine 200 mg daily

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Written consent was obtained from the applicable patients for publication of the case series. The design of this work conforms to standards currently applied in the country of origin.

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TABLE 1. Clinical Characteristics of the Patients With Disseminated Histoplasmosis and HLH

Case	Age/ Sex	Comorbidities and Immunosuppression	Social and Travel History	Presenting Symptoms	Routine Laboratories at Diagnosis	HLH-Specific Testing	Microbiologic Diagnosis	Urine/Serum *Histoplasma* Antigen*	Chest Imaging Findings	Treatment	Outcome at 1-Year Follow-up
1	68/M	Psoriatic arthritis on golimumab	Lives in central Michigan	Fever, malaise	WBC 3.2, Hgb 7.5, Plt 42, AST 522, ALT 303	TG 283 mg/dL, hemophagocytosis present on BMBx, ferritin >10,000 ng/mL, soluble IL-2 receptor 3686 IU/mL	Bone marrow culture: *H. capsulatum*	Urine >19.0 ng/mL; serum, >19.0 ng/mL	R lower lobe infiltrate	Liposomal amphotericin B 3 mg/kg daily followed by itraconazole 200 mg twice a day	Alive
2	42/F	Ankylosing spondylitis on MTX 10 mg weekly and infliximab 400 mg every 8 wk	Lives in rural Michigan, recently traveled to IN and AL, maintains chicken coop	Fever, headaches, nausea, abdominal pain	WBC 18.6, Hgb 6.4, Plt 43, AST 613, ALT 60	TG 1409 ng/mL, hemophagocytosis present on BMBx, ferritin 26,918 ng/mL	Liver biopsy: granulomatous inflammation with numerous intracellular organisms consistent with *H. capsulatum*; BMBx: GMS stain with intracellular yeast forms consistent with *H. capsulatum*	Urine >19.0 ng/mL; serum >19.0 ng/mL	Diffuse ground-glass opacities with consolidation in the upper lobes bilaterally	Liposomal amphotericin B 3 mg/kg daily followed by itraconazole 200 mg twice a day; etoposide IV 72 mg every 3 d ×2 doses and dexamethasone taper for HLH	Alive
3	56/F	Systemic lupus erythematous on MMF 500 mg twice a day and hydroxychloroquine 200 mg daily	Lives in southeast Michigan	Fevers, fatigue, cough	WBC 1.6, Hgb 10.1, Plt 49, AST 305, ALT 221	TG 314 ng/mL, hemophagocytosis on BMBx, ferritin 14,964 ng/mL, NK cell function decreased	BMBx: intracellular yeast on GMS and PAS stains; BAL and fungal blood cultures: *H. capsulatum*	Urine 14.91 ng/mL; serum >19.0 ng/mL	Centrilobular nodules and ground-glass opacities, most prominent in the L upper lobe, and mild mediastinal lymphadenopathy	Liposomal amphotericin B 3 mg/kg daily; dexamethasone 20 mg daily followed by methylprednisolone 1 g daily, ruxolitinib 15 mg twice a day for HLH	Deceased

*Upper limit of quantification is 19.0 ng/mL.

AL, Alabama; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BAL, bronchoalveolar lavage; BMBx, bone marrow biopsy; Hgb, hemoglobin; IN, Indiana; MMF, mycophenolate mofetil; MTX, methotrexate; PAS, periodic acid–Schiff; Plt, platelets; TG, triglycerides; WBC, white blood cell.

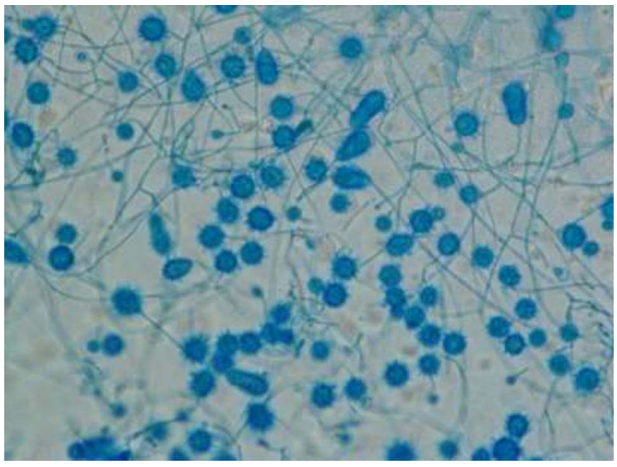

FIGURE 1. *Histoplasma capsulatum* organisms isolated from bronchoalveolar lavage fluid. This lactophenol aniline blue stain demonstrates the characteristic tuberculate macroconidia seen in the mold phase.

and mycophenolate mofetil 500 mg twice a day presented in early December with a 2-week history of high fever, fatigue, and dry cough. On admission, she was febrile to 39.3°C and hypoxic requiring 15 L of O_2. She was pancytopenic with acute kidney injury and elevated transaminases (Table 1). International normalized ratio (INR) was greater than 9.0. Ferritin was 14,964 ng/mL and triglycerides were elevated at 314 mg/dL. A CT scan of the chest demonstrated centrilobular nodules and ground-glass opacities, most prominent in the left upper lobe, and mild mediastinal lymphadenopathy. The patient was started on dexamethasone 20 mg daily given concern for HLH; this was increased to methylprednisolone 1 g daily after 2 days. Bone marrow biopsy was initially deferred because of supratherapeutic INR. Three days later, she was started on ruxolitinib 15 mg twice a day given lack of improvement on corticosteroids. However, she continued to have progressive hypoxia and required intubation. Once patient's INR had normalized, bone marrow biopsy was performed; this demonstrated intracellular yeast, positive on GMS and periodic acid–Schiff stains, and macrophages with hemophagocytosis were present. The patient's serum histoplasma antigen was greater than the upper limit of quantification, and the histoplasma urine antigen was 14.91 ng/mL (MiraVista Labs). Both fungal blood cultures and bronchoalveolar lavage cultures ultimately grew *H. capsulatum* (Fig. 1). The patient was started on intravenous liposomal amphotericin B at a dose of 3 mg/kg per day but continued to have worsening respiratory and renal function. She required initiation of hemodialysis. Eight days after admission, in the face of worsening hypoxia and increasing vasopressor requirements, her family decided to withdraw care and the patient died.

DISCUSSION

When reviewed together, these 3 cases illustrate a broad range of clinical presentations associated with secondary HLH caused by disseminated histoplasmosis. In all 3 cases, an immunocompromised patient presented with a nonspecific syndrome of fevers, malaise, and respiratory symptoms. Diagnosis of HLH was made early in the patients' clinical courses, but awareness of histoplasmosis as the inciting event happened later in the clinical course.

The pathophysiology of HLH is related to excessive immune stimulation and dysregulation. Typically, antigens are presented to cytotoxic T cells and natural killer (NK) cells, leading to the production of perforins, triggering cell lysis.[2,3] This exerts negative feedback and dampens the subsequent immune response.[1,6] In HLH, defective cytotoxic T and NK cells do not exert negative feedback, leading to uncontrolled immune activation and aberrant activity.[2] Unlike primary HLH in which the negative feedback response to cytotoxic T cell and NK cells is impaired because of genetic defects, the mechanism of secondary HLH varies depending on the etiology. The NK cells are thought to be particularly relevant for HLH triggered by infection, as NK cells conduct surveillance to remove activated cytotoxic T cells and infected macrophages.[6]

The exact mechanism as to how histoplasmosis triggers HLH is unclear. However, defense against *Histoplasma* is mediated by T cells and activated macrophages.[7,8] Macrophages phagocytose *Histoplasma* yeast forms and eventually triggers a T helper 1 cell–mediated immune response that leads to the release of cytokines including interferon γ and TNF-α, which are integral to granuloma formation.[7] Other intracellular pathogens that cause granuloma formation like *M. tuberculosis,* leishmaniasis, and *Rickettsia* infection have also been implicated in causing HLH.[3,9] Hemophagocytic lymphohistiocytosis could be caused by either excessive antigen presentation or excessive cytokine release as part of an aberrant response to disseminated histoplasmosis.

One might expect that patients with a healthy immune system would be more likely to develop HLH, because they may have a stronger cytokine response. However, in cases where histoplasmosis is the triggering agent of HLH, patients are often heavily immunosuppressed, suggesting that HLH is more related to immune dysregulation rather than immune activation.[5,6] Most reported cases of histoplasmosis-associated HLH are in the setting of HIV with depressed CD4 cell count.[4–6,10,11] In our series, 2 of the patients were on TNF-α inhibitors for autoimmune disease, which would presumably blunt cytokine release, and the third was broadly immunosuppressed. Tumor necrosis factor α inhibitors are a well-described risk factor for histoplasmosis.[12] Another series noted a high rate of TNF-α inhibitor use in patients who developed HLH secondary to infection, even those infections not significantly modulated by granuloma formation.[9] Perhaps the impairment of the granulomatous response in some patients on TNF-α inhibitors contributes to loss of negative feedback and triggers HLH.

Clinical manifestations of HLH may be subtle and can include fever, fatigue, and splenomegaly (Table 2).[13,14] Laboratory investigation may demonstrate pancytopenia, elevated triglycerides, significantly elevated ferritin, low NK cell activity, and elevated

TABLE 2. Clinical and Laboratory Criteria for the Diagnosis* of HLH

1. Fever >38.5°C
2. Splenomegaly
3. Cytopenia with at least 2 of the following:
   Hemoglobin <9.0 g/dL
   Platelets $<100 \times 10^9$ cells/L
   Absolute neutrophil count $<1.0 \times 10^9$ cells/uL
4. Hypertriglyceridemia
   Fasting triglycerides ≥265 mg/dL
   Hyperfibrinogenemia (fibrinogen ≤150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph node, or liver
6. Low or absent NK cell activity
7. Ferritin ≥500 ug/L
8. Elevated soluble CD25 (soluble IL-2 receptor α) ≥ 2400 U/mL

*Diagnosis requires fulfillment of 5 criteria.

soluble CD25 (soluble IL-2 receptor α).[13,14] If left untreated, HLH can rapidly progress to hemodynamic instability and multiorgan failure. The clinical manifestations of HLH are similar to sepsis and can be difficult to recognize clinically, especially in the setting of infection as trigger for HLH. Prompt identification and treatment are warranted to minimize morbidity and mortality.

The current recommended therapy for HLH, HLH-2004, involves chemo-immunotherapy and subsequent hematopoietic stem cell transplantation.[13,14] However, the original treatment guideline draws from data on primary HLH, which may not apply to all patients.[13,14] There are currently no evidence-based treatment recommendations for HLH related to an infectious process, and the widely accepted HLH-2004 guidelines do not have a strong recommendation for how to balance treating an underlying infection with suppression of the overwhelming immune response. The American Society of Hematology encourages use of the full HLH-2004 chemotherapy protocol in the setting of viral infections, specifically Epstein-Barr virus and HIV, but acknowledge that HLH induced by intracellular infections may respond to directed antimicrobial therapy.[4,11,15] This alludes to the importance of a rigorous infectious workup when managing adults with HLH. This includes not only testing for viral infections but also workup for histoplasmosis in the appropriate geographical location. In our case series, all 3 patients lived in Michigan, where histoplasmosis is endemic; 2 had notable outdoor exposures. Physicians caring for patients with HLH should elicit pertinent travel and exposure histories and consider whether a patient has resided in an area considered to be endemic for histoplasmosis.[8,16] In addition, changing patterns of human land use and possibly climate change may lead to expansion of the area in which *Histoplasma* is considered to be endemic, and physicians outside the classic range will need to be aware of the association between HLH and histoplasmosis.[17]

Given the lack of clear guidance on management of HLH related to underlying infection, it is not surprising that our 3 cases were all managed differently. One patient improved with antifungal therapy alone, 1 received steroids prior to identification of histoplasmosis and subsequently died, and 1 received concomitant antifungal therapy as well as full HLH-2004 protocol (dexamethasone and etoposide) with improvement. Our experience adds weight to the theory that some cases of HLH secondary to histoplasmosis can be managed with treatment of the underlying infection alone and without HLH-2004 protocol chemotherapy.[4,6,11] More study is needed to determine which patients with HLH triggered by histoplasmosis are likely to improve with antimicrobial therapy alone as opposed to those who require additional immunosuppressive therapy.

It is known that secondary HLH can be triggered by underlying infection, most commonly viral infections. However, it is imperative to consider histoplasmosis as an infectious trigger of HLH, particularly in patients who are immunocompromised and who live in an endemic area, which our case series illustrates. As HLH is a condition with a high rate of morbidity and mortality, it requires prompt recognition. If histoplasmosis is identified early as a cause of secondary HLH, early initiation of active antifungals can be lifesaving and may prevent the need for further administration of immunosuppressive chemotherapy.

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