MAJOR ARTICLE

Histoplasmosis-Induced Hemophagocytic Syndrome: A Case Series and Review of the Literature

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Background. Histoplasmosis-associated hemophagocytic lymphohistiocytosis (HLH) is a relatively rare disorder for which data are limited regarding optimal treatment and clinical outcomes in adults. We describe the clinical features, treatment, and outcomes of patients with histoplasmosis-associated HLH at our institution.

Methods. We performed a retrospective chart review of all inpatients at Parkland Hospital diagnosed with HLH associated with *Histoplasma capsulatum* from 2003 to 2013.

Results. Eleven cases of histoplasmosis-associated HLH over this time period were identified. Nine of eleven cases were males (82%). Nine of these patients had human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), 1 was a renal transplant patient on immunosuppressants, and the other had no documented immunocompromise. The most common HLH criteria were splenomegaly (n = 10), fever (n = 10), and ferritin >500 ng/dL (n = 9). Urine *Histoplasma* antigen was positive in every patient tested (n = 9 of 9), and most antibodies for *Histoplasma* were positive if checked (n = 4 of 5). A majority of patients received liposomal amphotericin B (n = 9) with an average treatment duration of 11 days, and 5 patients also received prednisone, intravenous immunoglobulin (IVIG), or both. Overall, 5 patients died within 30 days (45.5%), and 7 patients died within 90 days (63.6%). Of the 5 patients that received immunosuppression, 4 died (80%), whereas in the group not given additional immunosuppression (n = 5), 2 died (40%).

Conclusions. Histoplasmosis-associated HLH among adults is a lethal disease of highly immunocompromised patients, especially patients with HIV/AIDS. Clinical features such as splenomegaly, elevated ferritin, and cytopenias should prompt evaluation for HLH in this population. Further data are needed to define the role of immunosuppression, IVIG, and highly active antiretroviral therapy in treating this condition.

Keywords. disseminated histoplasmosis; hemophagocytic syndrome; HIV.

Hemophagocytic syndrome, also called hemophagocytic lymphohistiocytosis (HLH), is a rare syndrome characterized by a hyperstimulated but ineffective immune response with characteristic signs of fever, hepatosplenomegaly, and cytopenias. A majority of cases occur in children and are triggered by primary genetic disorders ("primary HLH") that cause defects in cytotoxic functioning of natural killer (NK) and T lymphocytes. In adults, "secondary HLH" can be triggered by hematologic malignancies and autoimmune diseases, but more often it occurs with various bacterial infections, fungi, and viruses [1, 2]. Although aggressive chemotherapy treatment protocols and allogeneic stem cell transplant have been shown to decrease mortality in children with HLH due to a genetic predisposition, optimal treatment of infection-related HLH in adults is not clear [3, 4]. Some physicians treat only the underlying infection, whereas others use immune suppression in addition to antimicrobials. The literature presents scant evidence regarding the efficacy of chemotherapy in infection-related HLH.

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Rather than a disease on its own, HLH can be viewed as an immune derangement and hypercytokinemia caused by various triggers. Under normal conditions, intracellular infections are controlled by a complex interaction of cell types, to which NK cells are central. In HLH, defects in NK cell cytotoxicity result in a positive feedback loop of uncontrolled intracellular infection, ongoing immune activation, and a lack of immune down-regulation. Without NK cell removal of cytotoxic T lymphocytes (CTLs), a sustained increase in activated lymphocytes generates a cytokine storm and unopposed macrophage activation that damage end organs of the host [5, 6].

Clinical and laboratory findings in HLH include markers of immune activation as well as end organ damage. High levels of tumor necrosis factor (TNF)-α production by macrophages stimulates fever and inhibits the ability of lipoprotein lipase to remove triglycerides from the serum. Activated macrophages phagocytose erythrocytes and scavenge heme, but they also secrete ferritin and contribute to hyperferritinemia. Cytopenias are not just a result of hemophagocytosis, but they also related to suppression of normal hematopoiesis by cytokines. Macrophages may also secrete plasminogen activators that accelerate the conversion of plasminogen to plasmin, causing hyperfibrinolysis and leading to characteristically low fibrinogen levels. Soluble interleukin (IL)-2 receptor, which is secreted by activated macrophages and lymphocytes, is extremely high in HLH as well [5].

In cases of secondary HLH, the pathophysiology is thought to be from temporary acquired immunodeficiency states that result in NK cell defects. In HLH, the perforin-mediated killing function is blocked leading to an accumulation of activated T lymphocytes and activated histiocytes with increasingly high levels of cytokines. Human immunodeficiency virus (HIV), for instance, is known to cause NK cell defects, which may explain the higher incidence of HLH in HIV patients [7–11].

With the understanding that HLH is a result of defective NK cell function, it becomes clear that intracellular organisms are uniquely positioned to trigger HLH, because NK cells are essential for clearing infected somatic cells and activated CTL. All of the pathogens currently described as triggers of HLH are either intracellular or facultatively intracellular, including viruses (Epstein-Barr virus [EBV], cytomegalovirus, HIV), parasites (malaria, leishmania), mycobacteria, fungi, and bacteria (*Babesia*, *Listeria*, *Coxiella*). Without functioning NK cells, a host suffers a double defect of an exuberant but ineffective immune response that damages the host without clearing the infection.

The existing treatment and outcomes data for histoplasmosis-associated HLH in adults consist of 27 reported cases (summarized in Table 1). Seventeen of the cases occurred in HIV patients, a majority from before the era of highly active antiretroviral therapy (HAART). The mortality rate for all reported cases was 10 of 26 (38%). Treatment is not always detailed, but half of cases report using antifungal therapy alone. Five of 26 cases report using antifungal therapy in addition to immune suppression. The remainder did not diagnose the condition premortem or did not detail a treatment regimen. The paucity of data highlights the need for reporting of more cases in the current era to examine whether any treatments can aid in survival of these patients.

In this study, we sought: (1) to identify cases of histoplasmosis-associated HLH at our large urban safety net hospital, (2) to describe the clinical characteristics of patients with histoplasmosis-induced HLH including diagnostic criteria, and (3) to describe the treatment regimens and clinical outcomes of this study population.

METHODS

We performed a retrospective chart review of cases of histoplasma-associated HLH at Parkland Hospital in Dallas, Texas, a large urban hospital that is the sole public safety net provider in Dallas County. Records were reviewed from December 2003 to February 2013. Cases were identified searching the results of bone marrow biopsy specimens from 2003 to 2013 for the key term "hemophagocytosis." This was the time period during which the pathology department electronically coded cases in a searchable database. The reports of bone marrow specimens with mention of hemophagocytosis were reviewed for evidence of histoplasmosis infection and absence of malignancy. The last case that did not have a bone marrow specimen was included because the patient was seen by the authors as an inpatient consultation during the time of the review, and the patient was found to have evidence of HLH by laboratory criteria. This study was approved by the UT Southwestern Medical Center Institutional Review Board.

Patients were excluded from review if they were <18 years of age, and if no clinical records were available. Record review was via paper charts, which often contained limited data, and the electronic medical record for patients after 2006. Patients were considered to have possible (4 of 8 criteria) or confirmed (5 of 8 criteria) HLH according to the HLH-2004 criteria: (1) Fever; (2) Splenomegaly; (3) Cytopenias affecting 2/3 cell lines in the peripheral blood; (4) Hypertriglyceridemia and/or hypofibrinogenemia; (5) Hemophagocytosis in the spleen, bone marrow, or lymph nodes, with no evidence of malignancy; (6) Low or absent NK cell activity (not available at our facility); (7) Ferritin >500 ng/dL; (8) Soluble IL-2 receptor >2400 U/mL (not available at our facility) [3]. Patients were considered to have disseminated *Histoplasma capsulatum* if any of the following were true as per Infectious Diseases Society of America guidelines: (1) cultures from sputum or a sterile body site (bone marrow, lymph node, biopsy specimen) grew *H capsulatum*; (2) biopsy specimens contained granulomas with yeast morphologically consistent with *H capsulatum*; or (3) urine or serum *Histoplasma* antigen was positive [30].

Table 1. Previous Cases of *Histoplasma*-Associated HLH Reported in the Literature[a]

Author	Year	Underlying Disease	CD4	Treatment	Outcome
Majluf-Cruz [12]	1993	HIV	NR	Fluconazole	Survived
		HIV	NR	Amphotericin B	Survived
		HIV	NR	none	Died
Keller [13]	1994	CMC	N/A	Amphotericin B	Survived
Koduri [14]	1995	None	N/A	Amphotericin B/solumedrol	Died
Koduri [15]	1995	HIV	36	ART/Amphotericin B/ IVIG × 2d	Died
		HIV	4	ART/Amphotericin B/ IVIG × 2d	Died
		HIV	6	ART/Amphotericin B/ IVIG × 2d	Died
		HIV	22	ART/Amphotericin B/ IVIG × 2d	Survived
		HIV	32	ART/Amphotericin B	Survived
		HIV	44	ART/Amphotericin B	Survived
Chemlal [16]	1997	HIV	34	NR	NR
Kumar [17]	2000	None	N/A	None	Died
		HIV	NR	None	Died
Rao [18]	2002	CLL	N/A	Amphotericin B	Survived
Masri [19]	2003	Heart transplant	N/A	Amphotericin B	Survived
Gil-Brusola [20]	2007	HIV	39	None	Died
Guiot [21]	2007	HIV	66	Abelcet × 36d –> itraconazole	Survived
Sanchez [22]	2007	HIV	NR	Amphotericin B × 6 wks	Survived
Wang [23]	2007	CKD/ fungal endocarditis	N/A	None	Died
Phillips [24]	2008	Sarcoidosis on chronic steroids	N/A	NR	Survived
De Lavaissiere [25]	2009	HIV	NR	ART/IVIG × 2 g/Amphotericin B × 4 wks –> itraconazole	Survived
Lo [26]	2010	Renal transplant	N/A	Ambisome × 2 wks –> itraconazole; reduced immunosuppression (IS)	Survived
		Renal transplant	N/A	Amphotericin B × 1 wk –> itraconazole; reduced IS	Survived
Van Koeveringe [27]	2010	CLL	N/A	Amphotericin B	Survived
Vaid [28]	2011	HIV	153	Antifungal and ART	Died
Chandra [29]	2012	HIV	NR	Ketoconazole	Survived

Abbreviations: ART, antiretroviral therapy; CKD, chronic kidney disease; CLL, chronic lymphocytic leukemia; CMC, chronic mucocutaneous candidiasis; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; IVIG, intravenous immunoglobulin; N/A, not applicable; NR, not reported.

[a] Underlying disease, treatment, and outcomes.

For all patients meeting inclusion criteria, data were collected on patient demographics, comorbidities, presence of fever, presence of organomegaly, laboratory values (complete blood counts, ferritin, lactate dehydrogenase [LDH], triglycerides, fibrinogen), microbiologic data, diagnostic procedures (bone marrow biopsy, bronchoscopy), treatment course (antifungal medication, chemotherapy), and outcomes (survival to hospital discharge). Immunosuppression included corticosteroids, TNF inhibitors, calcineurin inhibitors, cytotoxic chemotherapy, intravenous immunoglobulin (IVIG), and methotrexate.

RESULTS

Eleven cases of histoplasmosis-associated HLH were identified: 10 patients with hemophagocytosis on bone marrow examination, and 1 patient reported by the Infectious Disease consult service at the time of our search who did not undergo a bone marrow biopsy but met other laboratory criteria for HLH. Cases occurred between December 2003 and February 2013. The demographics and clinical characteristics of these patients are presented in Table 2. A majority of the patients had HIV (9 of 11). One was a renal transplant recipient, and the other had no known immunosuppression. A majority were male (9 of 11), with a mean age of 43.9 years. The majority of HIV patients were not on HAART at diagnosis (6 of 9), and the mean CD4 count was very low at 14.3. The average time between admission and bone marrow biopsy was 9 days (range, 3–15). Antifungal start dates were not routinely available.

Results of the microbiology and radiologic testing done during inpatient evaluation are shown in Table 3. The most consistent diagnostic finding was a positive urine *Histoplasma* antigen, which was positive in 100% of the specimens that were sent (9 of 9). Eight patients had *H capsulatum* visualized on bone marrow biopsy (Figure 1), 7 had positive blood cultures

Table 2. Characteristics of Patients With Histoplasmosis-Induced HLH, 2003–2013

Case Number	Age	Gender	Ethnicity	Country of Origin	HIV	Immunosuppressive Medications at Diagnosis	CD4 Count	HIV VL	ART at Time of dx
1	31	Female	Hispanic	Mexico	Yes	No	1	None	Yes
2	53	Male	Non-Hispanic/White	USA	Yes	No	6	205 000	Yes
3	33	Female	Non-Hispanic/Black	USA	Yes	No	1	750 000	No
4	47	Male	Hispanic	Mexico	No	Yes	N/A	N/A	N/A
5	28	Male	Non-Hispanic/Black	USA	Yes	No	Unknown	Unknown	Yes
6	60	Male	Hispanic	Unknown	No	Yes	N/A	N/A	N/A
7	44	Male	Hispanic	Unknown	Yes	No	2	190 000	No
8	52	Male	Non-Hispanic/White	USA	Yes	No	16	6 440 000	No
9	52	Male	Non-Hispanic/White	USA	Yes	No	16	6 440 000	No
10	32	Male	Hispanic	El Salvador	Yes	No	50	>10 000 000	Yes
11	51	Male	Non-Hispanic/White	USA	Yes	No	9	6036	No

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; N/A, not applicable; VL, viral load.

for *H capsulatum*, and 4 had intracellular yeast seen on peripheral smear (Figure 2). A bronchoalveolar lavage specimen from one of the patients is shown in Figure 3. On chest radiography, the most common finding was bilateral infiltrates (6 of 11), but other findings included pleural effusions (n = 5), pulmonary nodules (n = 3) (Figure 4), lymphadenopathy (n = 4), pneumothorax (n = 1), cardiomegaly (n = 3), and pulmonary edema (n = 1).

Specific laboratory values included in the HLH-2004 criteria are reported in Table 4. Soluble IL-2 receptor levels and NK cell activity were not available. All patients had fever documented except for 2 patients, who had sparse medical records available. Cytopenias were universal and severe, with most patients having platelet counts $<50 \times 10^3/\mu L$. The mean ferritin level was extremely high at 30 722 ng/mL (range, 1713–100 000+). All but one patient had documented splenomegaly.

From the available treatment data, the most commonly reported treatment regimen was liposomal amphotericin B (n = 9) for a mean of 11 days (range, 3–21), followed by oral antifungals (most commonly itraconazole) for 3–12 months

Table 3. Microbiologic and Radiologic Findings in Patients With *Histoplasma*-Associated HLH

Case Number	Bone Marrow With Yeast	*Histoplasma* on Peripheral Smear	Bone Marrow With Hemophagocytosis	*Histoplasma* Antibody[a] (<1:8)	Urine *Histoplasma* Ag (<2.0 EIA)	Sites Growing *Histoplasma*	CXR Findings
1	Yes	Yes	Yes	N/A	N/A	Blood, bone marrow,	BI, B effusions, CM
2	Yes	Yes	Yes	Positive	Positive	None	BI, LAD
3	No	No	Yes	N/A	>13	Blood	Hemothorax, right pneumothorax
4	No	No	Yes	Positive	Positive	None	BI, L effusion
5	Yes	Yes	Yes	N/A	>13	Blood, bone marrow	Clear
6	Yes	No	Yes	N/A	>13	Bone marrow, skin	CM
7	Yes	No	Yes	N/A	11	Sputum, blood	Edema, BI, effusions
8	Yes	No	Yes	Positive	>19	Bone marrow	Miliary nodules, effusions, LAD
9	Yes	No	Yes	N/A	>19	Blood, bone marrow	Miliary nodules
10	Yes	No	Yes	Positive	N/A	Respiratory blood, bone marrow	CM, BI, nodules, L effusion
11	No	Yes	Not done	Negative	4.9	Respiratory, blood, gastric tissue	BI, nodules

Abbreviations: Ag, antigen; B, bilateral; BI, bilateral infiltrates; CM, cardiomegaly; EIA, enzyme immunoassay; HLH, hemophagocytic lymphohistiocytosis; L, Left; LAD, lymphadenopathy; N/A, not applicable (not reported).

[a] Complement fixation titer, ARUP laboratories.

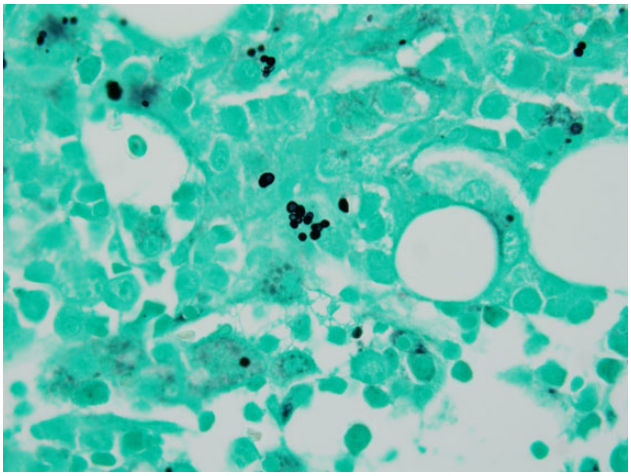

Figure 1. Gomori methenamine silver stain of bone marrow, 40×. Intracellular yeast consistent with *Histoplasma capsulatum*.

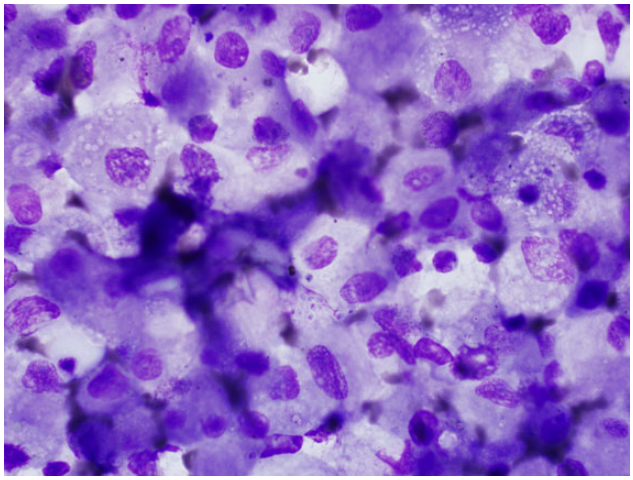

Figure 3. Bronchoalveolar lavage specimen showing intracellular yeast. Wright stain, 1000×.

(n = 5) (see Table 5). Three patients died during the initial amphotericin course.

In addition, 2 HIV patients received steroids, 1 received IVIG alone, and 1 received steroids in addition to IVIG. One renal transplant patient continued on his home regimen of prednisolone and tacrolimus, whereas the other renal transplant patient had no documented immunosuppressive treatment. One patient was started on HAART during the admission, whereas 4 others were continued on their outpatient HAART regimens. One patient presented with HLH within 3 weeks of starting HAART, which is consistent with an immune reconstitution inflammatory syndrome (IRIS).

Of the 5 patients that received immunosuppression during admission (including prednisone, IVIG, or both), 4 died (80%), whereas in the group not given additional immunosuppression (n = 5), 2 died (40%). The remaining patient survived but his treatment course was not available for review. Overall 30-day mortality was high (5 of 11 patients, 45.5%). Four patients died during the admission (within 16 days), while one patient died 7 months later. There was not a significant difference in mortality between patients who did or did not receive immunosuppression ($P = .24$, 2 tailed Fisher's exact test) although the comparison was underpowered.

DISCUSSION

We report eleven cases of *Histoplasma*-associated HLH, the largest case series of this clinical phenomenon that has been reported to date. The relatively large number of *Histoplasma*-associated HLH cases at our hospital, compared with the number of cases reported at other institutions in the literature, may be

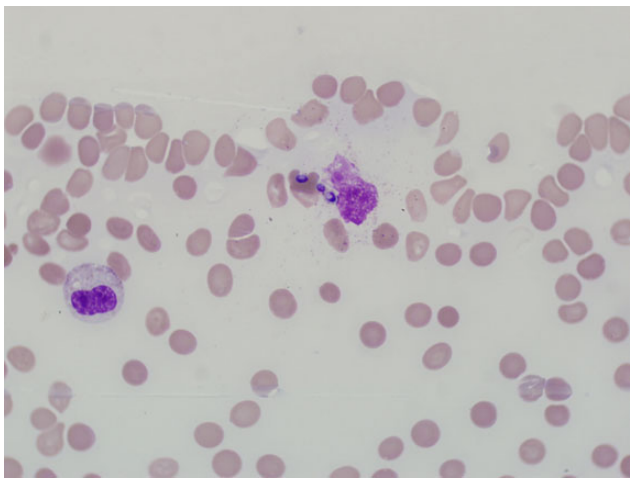

Figure 2. Peripheral blood smear showing intracellular yeast. 100× oil. Modified Wright-Giemsa stain.

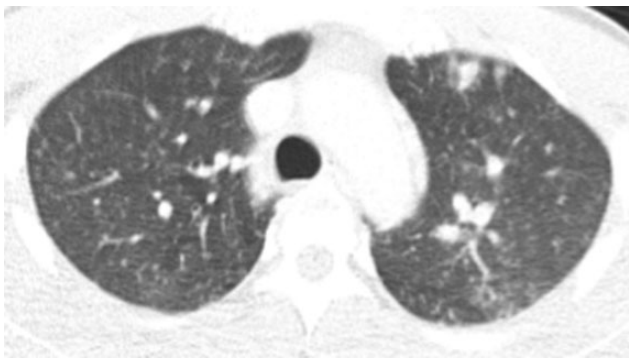

Figure 4. Chest computed tomography with mixed pattern of large and small nodules.

Table 4. Clinical Features and Diagnostic Criteria for HLH-2004

Case Number	T_{max} During Admission	Rash	Splenomegaly	Hemoglobin Nadir (12.4–17.3 g/dL)	Platelet Nadir (150–450 $\times 10^3$/μL)	Peak Ferritin (30.0–400.0 ng/mL)	LDH (135–225 U/L)	HLH Criteria
1	39.8	No	Yes	6	12	Unknown	1336	5 of 8
2	38.6	No	Yes	7.1	9	>16 500	971	5 of 8
3	37	No	Yes	6	48	1713	227	4 of 8
4	39.2	No	Yes	5.9	16	>16 500	1815	6 of 8
5	37.3	No	Yes	7.3	70	>16 500	1277	4 of 8
6	38.5	Yes	No	8.8	45	Unknown	971	5 of 8
7	39.9	No	Yes	6.3	<5	>16 500	1402	5 of 8
8	38.7	No	Yes	7	4	4392	402	6 of 8
9	39.4	No	Yes	7	4	4400	402	5 of 8
10	101.9	No	Yes	5.7	7	>100 000	2517	5 of 8
11	39.5	No	Yes	5.7	10	>100 000	8004	5 of 8

Abbreviations: HLH, hemophagocytic lymphohistiocytosis; LDH, lactate dehydrogenase; *T*, temperature.

due to the geographic overlap of histoplasmosis and HIV as well as the under-recognition of this condition in other settings [31, 32]. We hypothesize that this condition may be even more prevalent than we found in our series, given our somewhat limited case finding strategy. In addition, while many clinicians recognize that disseminated histoplasmosis causes high fevers, an

Table 5. Treatment and outcomes of *Histoplasma*-associated hemophagocytic lymphohistiocytosis

Case Number	Antifungal drug used	Liposomal amphotericin B duration (days)	Oral antifungal duration (days)	Immuno suppressive treatment	HAART at time of diagnosis	Immuno suppressive duration	HAART started during admission	Outcome at 30 days	Survival from admission (days)
1	Liposomal amphotericin B	Unknown	0 days	None	Yes	None	No	Died	16
2	Liposomal amphotericin B; itraconazole	14	Unknown	None	Yes	None	Yes	Alive	2168
3	Liposomal amphotericin B; fluconazole	21	>1 year	Prednisone 20 mg PO daily	No	Unknown	No	Died	221
4	Itraconazole	0	Unknown	None	N/A	None	N/A	Alive	44
5	Unknown	Unknown	Unknown	Unknown	Yes	Unknown	Unknown	Alive	3560
6	Liposomal amphotericin B; voriconazole	Unknown	Unknown	Prednisolone 10 mg po BID, Tacrolimus 1.5 mg PO daily	N/A	5 months	N/A	Alive	2849
7	Liposomal amphotericin B; itraconazole	16	12 weeks	None	No	None	No	Alive	86
8	Liposomal amphotericin B; itraconazole	5	0 days	IVIG × 1; prednisone 40 BID	No	9 days	No	Died	9
9	Liposomal amphotericin B; itraconazole	3	Unknown	IVIG 1gm × 1	No	1 day	No	Died	9
10	Liposomal amphotericin B; itraconazole	18	>1 year	None	Yes	None	No	Alive	408
11	Liposomal amphotericin B	11	0 days	Prednisone 40 mg PO BID; solumedrol 60 mg IV q6hrs	No	11 days	Yes	Died	13

Abbreviations: HAART, Highly active antiretroviral therapy; IVIG, intravenous immunoglobulin.

elevated LDH, and a high ferritin, they may not consider HLH in this clinical scenario. In our series, the mean time from presentation to bone marrow was >1 week, which may have led to treatment delays. It remains to be seen if early diagnosis could lead to improved outcomes with earlier institution of antimicrobial and possibly immunsuppressive therapy.

In our series, uncontrolled HIV was the dominant risk factor for this condition, while renal transplant patients are also at risk [33]. HIV patients may be uniquely vulnerable to HLH given the depletion of NK cells in HIV, which has been connected to multiple manifestations of immune dysregulation [20, 34, 35]. The predominance of males is difficult to explain, as no gender predilection has been reported for HLH or histoplasmosis, but may be related to a higher prevalence of HIV in males in Dallas. Guidelines do not recommend routinely screening for disseminated histoplasmosis in HIV patients before starting HAART [36], nor is this done in renal transplant patients. However, it may be reasonable to screen patients with severe anemia or thrombocytopenia with a urine *histoplasma* antigen, especially those planned for intense immunosuppression, so that their infection might be recognized and treated prior to immunosuppression.

One interesting clinical finding in our series that has not been described previously is the occurrence of a cardiopulmonary syndrome in patients with HLH. Several patients had either cardiomegaly, pleural effusions, or pulmonary edema on their chest radiographs. A high output state related to anemia in these patients may be contributing, possibly in addition to the cytokine storm causing leaky vasculature.

Treatment for the triggering condition is recommended as first line therapy for patients with HLH, although indications for initiating chemotherapy directed at HLH is less clear in the adult population with the sporadic (rather than inherited form) of the disease. Although all patients in our series received antifungal treatment with amphotericin products and/or azole treatment, there was wide variability on whether or not immunomodulation was used. None of the patients in this series were treated with the chemotherapy protocols such as those recommended for HLH in children (etoposide, dexamethasone with or without intrathecal therapy),although half of patients in our series received steroids, IVIG, or both. Given the small sample size, no benefit or harm could be attributed to IVIG or steroids. Since a majority of tissue damage is caused by cytotoxic lymphocytes, therapies such as corticosteroids and cytotoxic chemotherapies such as those used in children make sense as strategies to control the inflammation, but have not been established in adults. More targeted immunosuppression in macrophage activation syndrome (a similar pathologic process) is being evaluated in studies underway using cytokine antagonists and IL-1 receptor antagonists [37].

The role of HAART for treatment of this condition is not clear. Although HAART may improve outcomes in patients not receiving HIV treatment at the time of developing HLH, it also may precipitate HLH. In our series, one patient presented with HLH within 3 weeks of starting HAART, which is consistent with an immune reconstitution inflammatory syndrome (IRIS). Prior publications have reported HLH as a manifestation of IRIS in HIV-positive patients, 2 with HIV alone, 1 associated with leishmania, 1 with EBV, and 1 with lymphoma [25, 38–43]. As with other chronic fungal and mycobacterial diseases that have a strong potential to cause IRIS, it may be reasonable to wait for the acute phase of HLH to resolve before instituting HIV treatment.

There remains considerable controversy surrounding treatment of adult patients with HLH related to infectious triggers. Our comparison between patients who did or did not receive additional immunosuppression detected more survivors in the non-immunosuppression group, although the analysis is underpowered and may reflect treatment bias of individuals who were more ill. Additional data, even if retrospective, must be compiled to help guide decisions in this difficult-to-treat group.

This study has several limitations. First, our search strategy focused on bone marrow biopsy results, which may have missed patients with histoplasmosis-associated HLH who did not undergo bone marrow biopsy. Nonetheless, we were able to identify 11 cases over an approximately 10-year period, which is the largest case series of histoplasmosis-associated HLH to date. Second, the medical records from patients occurring before implementation of the electronic medical record had less detailed information about treatment regimens. Finally, because this is a retrospective review with a small sample size, no conclusions can be reached on the impact of different treatment regimens on clinical outcomes. Prospective treatment studies would be ideal, but they are unlikely given the rarity of this disease.

CONCLUSIONS

Histoplasma-associated HLH was relatively common at our large urban safety net hospital in Dallas, Texas, and uncontrolled HIV patients make up the majority of patients, whereas solid organ transplant patients also seem to be at risk. Key features that should prompt evaluation for this condition are splenomegaly, an extremely elevated ferritin, and cytopenias in an immunocompromised patient. Fungal blood cultures and urine *Histoplasma* antigen are high-yield tests in this setting for diagnosing *H capsulatum* as the underlying trigger for HLH. The mortality rate is high despite the use of antifungal agents and immune suppression. More data on treatment for this condition are needed in adults. The role and timing of HAART initiation in treatment of this condition remains unclear.

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