Histoplasmosis-Associated Hemophagocytic Lymphohistiocytosis: A Review of the Literature

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Received 20 June 2019; Accepted 30 August 2019; Published 1 October 2019

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Background. Histoplasmosis is an endemic fungal disease with diverse clinical presentations. Histoplasmosis-associated hemophagocytic lymphohistiocytosis (HLH) is a rare disorder with limited data regarding treatment and outcome. We described the clinical features, treatment, and outcomes of five patients in our institution with histoplasmosis-associated HLH. This review also summarizes the current literature about presentation, treatment, and outcome of this infection-related HLH entity.

Methods. We searched the electronic medical records for patients with histoplasmosis-associated HLH at our institution from 1/1/2006 to 9/30/2017. Diagnosis of HLH was confirmed by chart review using the HLH-04 criteria. We also searched the current literature for case reports and case series.

Results. Five cases of histoplasmosis-associated HLH were included from our institution. All five patients were diagnosed after 2010. The literature review yielded 60 additional cases of histoplasmosis-associated HLH. The most common underlying condition was HIV in 61% of cases. The majority of histoplasmosis patients (81%) were treated with amphotericin B formulations. Documented specific treatments for HLH were as follows: nine patients received steroids only, six patients received intravenous immunoglobulin (IVIG) only, three patients received dexamethasone and etoposide, two patients received etoposide, dexamethasone, and cyclosporine, two patients received steroids and IVIG, and one patient received Anakinra and IVIG. The inpatient case fatality rate was 31% with most of the deaths occurring within two weeks of hospital admission.

Conclusions. Histoplasmosis-associated HLH among adults is an uncommon but serious complication with high associated mortality. Early antifungal therapy with a lipid formulation amphotericin B is critical. The initiation of immunosuppressive therapy with regimens like HLH-04 in this disease entity should be individualized.

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare but often life-threatening syndrome of excessive immune activation. Primary HLH is triggered by genetic disorders and usually manifests in children below the age of 18 months. The term secondary (acquired) HLH has generally been used to describe cases in adults without known genetic predisposition and a clear trigger for HLH. This trigger is often an infection or an alteration in immune homeostasis (e.g., malignancy, rheumatologic conditions, or immunodeficiency syndromes) [1]. HLH may present as a single episode of disease or recurrent episodes. Histoplasmosis-associated HLH is a relatively rare disorder with limited data about treatment [2, 3]. We describe the clinical features, treatment, and outcomes of cases seen at the University of Kansas Medical Center (KUMC). In addition, we reviewed the current literature about diagnosis and treatment of histoplasmosis-associated HLH.

2. Methods

We searched our medical informatics HERON (Healthcare Enterprise Repository for Ontological Narration) database for the following ICD9/ICD10 terms: “hemophagocytic syndrome,” “hemophagocytosis,” “hemophagocytic lymphohistiocytosis” or
4. Results

We identified five cases of histoplasmosis-associated HLH. The clinical characteristics are summarized in Table 1. All patients had disseminated histoplasmosis and were immunosuppressed. Human immunodeficiency virus (HIV) infection was the underlying condition in 2/5 patients (40%); the diagnosis of HIV in both patients was new. The other three patients were on steroids in addition to other immunosuppressive agents. There was a male predominance 4/5 (80%). All patients 5/5 (100%) had positive blood cultures for histoplasma, and the histoplasma antigen (blood or urine) was above the limit of quantification. Histoplasma was seen on bone marrow (BM) biopsy in 3/4 (75%) patients.

Four patients (80%) met at least 5 out of 8 criteria for the diagnosis of HLH as shown in Table 2. The IL2-receptor, cytopenia, and ferritin criteria were met in all five patients. Peak ferritin level was above the limit of quantification in 4/5 (80%) patients. One patient met only four criteria, but the hematology consulting team felt that it was highly likely secondary HLH.

The treatment and outcomes are shown in Table 3. Most patients were started on liposomal amphotericin B for at least 2 weeks and then transitioned to an oral azole. One patient received only voriconazole. Three out of five patients survived to hospital discharge.

The literature review yielded 60 cases from 39 papers; most of them were case reports and few were case series. Table 4 summarizes the patients baseline characteristics, treatment used, diagnostic tests for histoplasmosis, and outcomes. Five papers were published before 2000, and 18 papers were published since 2015. We report five patients at our institution from 1/1/2006 to 9/30/2017 (Table 1). All 5 cases at KUMC were diagnosed after 2010. Adding our five cases to the 60 reported previously, the median age of cases was 41 years and 72% (37/52) were men. The most common underlying immunosuppressive condition was HIV in 62% (36/58). Six patients had solid organ transplant, and there was no clear underlying immunodeficiency described in seven patients. In eleven patients, there was no mention of the host immune status.

The median CD4 count in HIV patients was 17 cells/μL. The majority of patients had disseminated histoplasmosis. Five patients were diagnosed by either lymph node biopsy or histoplasma urine Ag only and not proven to have disseminated histoplasmosis.

Initial antifungal treatment consisted of amphotericin B formulation in 48 cases and only azoles in four cases. The specific treatment for HLH was as follows: nine patients received steroids only; six patients received intravenous immunoglobulin (IVIG) only, three patients received dexamethasone and etoposide, and two patients received etoposide, dexamethasone, and cyclosporine, two patients received steroids and IVIG, and one patient received Anakinra and IVIG.

The overall inpatient case fatality rate was 31% (20/64) and 37% (13/35) among HIV patients. The mortality rate

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**Table 1: Clinical characteristics of histoplasmosis-induced HLH patients at our institution (n = 5).**

| Case | Year | Age | Gender | Race | Comorbid conditions | Immunosuppressive agent | Yeast in BM | Urine histoplasma Ag | Sites growing histoplasma | CXR findings |
|------|------|-----|--------|------|---------------------|-------------------------|-------------|---------------------|--------------------------|-------------|
| 1    | 2011 | 48  | M      | White | HIV/CD4 count 50    | None                    | Yes         | Above LoQ           | Blood                    | No infiltrates |
| 2    | 2014 | 48  | F      | White | MCTD                | HCQ/prednisone 10mg daily | No          | Above LoQ           | Blood                    | LAD without infiltrates |
| 3    | 2016 | 75  | M      | White | Crohn’s             | Prednisone              | Yes         | N/A (serum Ag: above LoQ) | Blood and BM | No infiltrates |
| 4    | 2017 | 46  | M      | African American | Sarcoid                | None                    | N/A         | Above LoQ           | Blood                    | Diffuse infiltrate |
| 5    | 2017 | 41  | M      | White | HIV/CD4 count 10    | None                    | Yes         | Above LoQ           | Blood                    | Diffuse infiltrate |

M: male; F: female; HIV: human immunodeficiency virus; MCTD: mixed connective tissue disease; N/A: not applicable; BM: bone marrow; dexe: dexamethasone; CXR: chest X-ray; Ag: antigen; LAD: lymphadenopathy; LoQ: limit of quantification; HCQ: hydroxychloroquine.

“macrophage activation syndrome” and “histoplasmosis” or “disseminated histoplasmosis.” We included patients older than 18 years and seen at our institution from 1/1/2006 to 9/30/2017. All patients who satisfied the HLH-04 criteria [4] for a diagnosis of HLH (i.e., 5 of 8 criteria) and confirmed to have histoplasmosis by retrospective chart review were included. HLH-04 criteria include (1) fever; (2) splenomegaly; (3) cytopenia in two or more cell lines; (4) hypertriglyceridemia (triglyceride level ≥265mg/dL or hypofibrinogenemia (fibrinogen level ≤150 mg/dL); [5] hemophagocytosis in the bone marrow, spleen, or lymph nodes; [6] hyperferritinemia (ferritin level ≥500ng/mL); [7] impaired NK cell function; and [8] elevated soluble CD25 (soluble IL-2 receptor alpha) two standard deviations above age-adjusted laboratory-specific norms. This study was approved by the University of Kansas Medical Center institutional board review.

3. Literature Review

We searched PubMed for “histoplasmosis” and “hemophagocytic syndrome,” “histoplasmosis” and “secondary hemophagocytic syndrome,” “histoplasmosis induced hemophagocytic syndrome,” “disseminated histoplasmosis” and “hemophagocytic syndrome,” “HLH” and “histoplasmosis,” and “histoplasma associated HLH.” Few papers were only available by a published abstract in English.

The overall inpatient case fatality rate was 31% (20/64) and 37% (13/35) among HIV patients. The mortality rate
was 25.0% (12/48) in patients who received amphotericin B, 20% (1/5) in patients who received steroids and etoposide with or without cyclosporine (all received amphotericin B), 62% (5/8) in patients who received IVIG, and 31% (5/16) in patients who received steroids. One patient received Anakinra and IVIG and survived. Only 14/21 patients had available date of death; of those, 10 patients died within two weeks of admission and four patients died at hospital days 16, 18, 43, and 44.

5. Discussion

Histoplasmosis-associated HLH is rare but likely underdiagnosed given the nonspecific clinical and laboratory presentation. The diagnosis is challenging because high fever, peripheral blood cytopenia, splenomegaly, and elevated ferritin are very common in patients with disseminated histoplasmosis. We report the second largest case series of histoplasmosis-induced HLH. About half of the cases (29/60) were reported after 2014, and all five cases at our institution were diagnosed after 2010. This may be explained by an increased awareness of this entity. Almost all cases of histoplasmosis-associated HLH occurred in patients with disseminated histoplasmosis. Most patients were relatively young. HIV and its numerous related opportunistic infections remain the most common underlying immunodeficiency that triggers HLH, but the recent literature showed an increasing number of non-HIV patients (organ transplant, patients receiving chemotherapy, or other immunosuppressive treatments). This is likely caused by the recent increase in disseminated histoplasmosis among non-HIV infected patients [43, 44]. Only few patients had no clear underlying immunodeficiency. The male predominance may be related in part to the higher incidence and prevalence of HIV in men in the United States.

Human immunodeficiency virus (HIV) could trigger hemophagocytic syndrome by itself, or secondary to ART initiation or opportunistic infections [45]. In a retrospective study to evaluate the triggers of HLH among HIV patients in Brazil, opportunistic infections were the most common factors (59%) including Mycobacterium (34%), Cytomegalovirus (14%), and Cryptococcus neoformans (11%) [46].

Macrophage activation syndrome (MAS) is a form of HLH that is usually associated with rheumatologic diseases and inflammatory bowel diseases (IBD). In a review of literature of 50 cases of HLH or MAS, the association between HLH and IBD was thought to be secondary to infections, the effect of immunosuppressive therapy, and the potential presence of a genetic susceptibility [47]. The majority of cases were Crohn’s disease (CD) rather than ulcerative colitis; this was attributed to the more frequent use of immunomodulators in CD.

The number of patients in each treatment group and the noncontrolled nature of this review hinder making conclusions about the most effective therapy. Patients who received amphotericin B had a slightly lower case fatality rate compared to the whole group. It is unclear if the addition of etoposide and steroids was helpful, but 4/5 patients with such regimen survived. We suggest starting a lipid formulation of amphotericin B as soon as possible, as recommended by the Infectious Diseases Society of America guidelines [48] for the treatment of moderate to severe disseminated histoplasmosis. There are limited data to establish the best treatment protocol and the role of immunosuppressive therapy and IVIG for histoplasma-associated HLH [1].

The treatment of secondary HLH is most effective when the inciting disease can be treated and controlled. If effective histoplasmosis treatment fails to demonstrate improvement after 48–72 hours, clinician often consider initiation of

| Table 2: Diagnosis of HLH (n = 5). |
|-----------------------------------|
| Case # | Fever | Cytopenia (2 lines) | IL2-receptor (pg/mL) | Peak triglycerides (mg/dL) | BM with hemophagocytosis | Splenomegaly | Peak ferritin (ng/mL) | Nadir fibrinogen (mg/dL) |
|-------|-------|---------------------|----------------------|---------------------------|--------------------------|-------------|---------------------|--------------------------|
| 1     | Yes   | Yes                 | 5167                 | 258                       | Yes                      | No          | >15,000             | 95                       |
| 2     | Yes   | Yes                 | 115,900              | 329                       | Yes                      | Yes         | 4487                | 265                      |
| 3     | No    | Yes                 | 958                  | 227                       | Yes                      | No          | >7500               | 384                      |
| 4     | Yes   | Yes                 | 1648                 | 192                       | No                       | Yes         | >7500               | 168                      |
| 5     | No    | Yes                 | 15,540               | 246                       | N/A                      | Yes         | >7500               | 51                       |

| Table 3: Treatment and outcome of histoplasmosis-associated HLH patients at our institution (n = 5). |
|---------------------------------------------------------------|
| Case # | Antifungal drug | HLH specific treatment | Outcome (hospital discharge) |
|-------|----------------|------------------------|-----------------------------|
| 1     | Liposomal amphotericin B for 2 weeks, then itraconazole for 12 months | None | Survived |
| 2     | Liposomal amphotericin B for 4 weeks, then oral azoles for 4 years | Dexamethasone 10 mg/m² for 2 days | Survived |
| 3     | Voriconazole PO (discharged to hospice, patient preference) | None | Discharged to hospice |
| 4     | Liposomal amphotericin B for 2 weeks then itraconazole for 4 months | Dexamethasone 10 mg/m² | Survived |
| 5     | Liposomal amphotericin B for 2 weeks then oral azoles | None | Died (day 43) |

Notes. BM: bone marrow, IL: interleukin, N/A: not applicable.
| Author                        | Year | Country   | Age, gender | Underlying disease | CD4 | Treatment          | Histoplasma diagnosis | Outcome |
|------------------------------|------|-----------|-------------|--------------------|-----|--------------------|-----------------------|---------|
| Majluf-Cruz et al. [5]        | 1993 | Mexico    | 37y, M      | HIV                | NR  | Fluconazole        | Liver Bx              | Survived |
|                              |      |           | 49y, M      | HIV                | NR  | Amphotericin B     | BM Bx                 | Survived |
|                              |      |           | 36y, M      | HIV                | NR  | None               | BM Bx                 | Died (NR) |
| Keller and Kurtzberg [6]      | 1994 | USA       | 6y          | Chronic mucocutaneous candidiasis | N/A | Amphotericin B     | BM Cx/blood Cx/BAL Cx | Survived |
| Koduri et al. [7]             | 1995 | USA       | NR          | None               | N/A | Amphotericin B/solumedrol | NR                  | Died (NR) |
| Koduri et al. [8]             | 1995 | USA       | NR          | HIV                | 36  | Amphotericin B/IVIG × 2d | Blood smear/BM path and Cx | Died (NR) |
|                              |      |           |             | HIV                | 4   | Amphotericin B/IVIG × 2d | Blood smear/BM path/BM Cx/CSF Cx | Died (HD 6) |
|                              |      |           |             | HIV                | 6   | Amphotericin B/IVIG × 2d | Blood smear/BM path and Cx | Died (NR) |
|                              |      |           |             | HIV                | 22  | Amphotericin B/IVIG × 2d | BM path and Cx/skin Cx | Survived |
|                              |      |           |             | HIV                | 32  | Amphotericin B      | BM path and Cx         | Survived |
|                              |      |           |             | HIV                | 44  | Amphotericin B      | BM path and Cx         | Survived |
| Chemlal et al. [9]            | 1997 | Africa    | 50y         | HIV                | 34  | NR                 | Blood Cx/BM and skin path | NR       |
| Kumar et al. [10]             | 2000 | India     | 50y, M      | None               | N/A | None               | Splenic aspirate smears | Died (within 48 hours) |
|                              |      |           | 40y, M      | HIV                | NR  | None               | LN Bx                  | Died (within 48 hours) |
| Rao et al. [1]                | 2002 | USA       | 68y, M      | CLL on cyclophosphamide and fludarabine | N/A | Amphotericin B     | BM and lung Bx (path) | Survived |
| Masri et al. [11]             | 2003 | USA       | 47y, M      | Heart transplant   | N/A | Liposomal amphotericin B | BM (path and Cx)/peripheral smear/lung Bx (path and Cx) | Survived |
| Gil-Brusola et al. [12]       | 2007 | Ecuador   | 33y, M      | HIV/disseminated TB | 39  | None               | Blood smear/BM path    | Died (HD 18) |
| Guiot et al. [13]             | 2007 | Puerto Rico | 43y, M     | HIV/ileal perforation | 66  | None               | Gl (path)/BAL (cytology)/BM path and Cx, histoplasma PCR | Survived |
| Sanchez et al. [14]           | 2007 | USA       | 61y, M      | HIV/pulmonary TB   | 4   | Amphotericin B      | Blood and BM (? Cx or path) | Survived |
| Wang et al. [15]              | 2007 | USA       | 52y, M      | HCV, CKD           | N/A | None (postmortem diagnosis) | Autopsy diagnosis/postmortem blood and spleen Cx | Died (HD 12) |
| Phillips et al. [16]          | 2008 | USA       | 69y, M      | Sarcoidosis on chronic steroids | N/A | Amphotericin B/steroids/cyclophosphamide | BM path and Cx/blood smear | Survived |
| De Lavaissiere et al. [17]    | 2009 | France    | 33y, M      | HIV                | NR  | Amphotericin B/itraconazole/ART/IVIG | Blood and BM (Cx or path?) | Survived |
| Lo et al. [18]                | 2010 | USA       | 22y, F      | Renal transplant   | N/A | Liposomal amphotericin | BM path/Blood Cx/urine Ag | Survived |
|                              |      |           | 18y, M      | Renal transplant   | N/A | Liposomal amphotericin for 2 weeks/itraconazole | LN path/BM Cx/urine Ag | Survived |
| van Kooleringe and Brouwer [19]| 2010 | Holland   | 50y, M      | CLL-alemtuzumab/fludarabine/cyclophosphamide | N/A | Dexamethasone/cyclophosphamide/amphotericin | BM path confirmed by PCR and culture | Survived |
| Vaid and Patel [20]           | 2011 | UK        | 25y, M      | HIV                | 153 | Antifungal         | Skin/BM/oral mucosa path | Died (NR) |
| Author et al. [21] | Year | Country | Age, gender | Underlying disease | CD4 | Treatment | Histoplasma diagnosis | Outcome* |
|-------------------|------|---------|-------------|--------------------|-----|----------|-----------------------|---------|
| Chandra et al. [21] | 2012 | India | 38y, F | HIV | NR | Ketoconazole | NR | Survived |
| Nieto-Rios et al. [22] | 2012 | Colombia | 30y, F | Renal transplant | N/A | Amphotericin B/itraconazole | Blood Cx | Survived |
| 41y, F | Renal transplant | N/A | None (died the same day of positive Cx) | Blood Cx | Died (HD 3) |
| Telfer and Gulati [23] | 2012 | USA | 28y, M | HIV | 12 | Voriconazole | BM path/urine Ag | Died (NR) |
| Huang [24] | 2014 | Guatemala | 25y, M | HIV | 4 | Antifungals/dexamethasone | Urine Ag/BM path | Survived |
| Subedee and van Sickels [25] | 2015 | USA | 34y, M | AIDS | N/A | Liposomal amphotericin B/itraconazole | Blood Cx | Survived |
| Rajput et al. [26] | 2015 | USA | 42y, F | HIV | 40 | Liposomal amphotericin B/itraconazole | Blood Cx | Survived |
| Kashifet al. [27] | 2015 | USA | 41y, F | Renal transplant | N/A | None (died the same day of positive Cx) | Blood Cx | Died (HD 3) |
| Huang [24] | 2014 | Guatemala | 25y, M | HIV | 4 | Antifungals/dexamethasone | Urine Ag/BM path | Survived |
| Subedee and van Sickels [25] | 2015 | USA | 34y, M | AIDS | N/A | Liposomal amphotericin B/itraconazole | Blood Cx | Survived |
| Rajput et al. [26] | 2015 | USA | 42y, F | HIV | 40 | Liposomal amphotericin B/itraconazole | Blood Cx | Survived |
| Kashifet al. [27] | 2015 | USA | 41y, F | Renal transplant | N/A | None (died the same day of positive Cx) | Blood Cx | Died (HD 3) |
| Telfer and Gulati [23] | 2012 | USA | 28y, M | HIV | 12 | Voriconazole | BM path/urine Ag | Died (NR) |
| Huang [24] | 2014 | Guatemala | 25y, M | HIV | 4 | Antifungals/dexamethasone | Urine Ag/BM path | Survived |
| Subedee and van Sickels [25] | 2015 | USA | 34y, M | AIDS | N/A | Liposomal amphotericin B/itraconazole | Blood Cx | Survived |
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| Telfer and Gulati [23] | 2012 | USA | 28y, M | HIV | 12 | Voriconazole | BM path/urine Ag | Died (NR) |
| Huang [24] | 2014 | Guatemala | 25y, M | HIV | 4 | Antifungals/dexamethasone | Urine Ag/BM path | Survived |
| Subedee and van Sickels [25] | 2015 | USA | 34y, M | AIDS | N/A | Liposomal amphotericin B/itraconazole | Blood Cx | Survived |
| Rajput et al. [26] | 2015 | USA | 42y, F | HIV | 40 | Liposomal amphotericin B/itraconazole | Blood Cx | Survived |
| Kashifet al. [27] | 2015 | USA | 41y, F | Renal transplant | N/A | None (died the same day of positive Cx) | Blood Cx | Died (HD 3) |
| Telfer and Gulati [23] | 2012 | USA | 28y, M | HIV | 12 | Voriconazole | BM path/urine Ag | Died (NR) |
| Huang [24] | 2014 | Guatemala | 25y, M | HIV | 4 | Antifungals/dexamethasone | Urine Ag/BM path | Survived |
| Subedee and van Sickels [25] | 2015 | USA | 34y, M | AIDS | N/A | Liposomal amphotericin B/itraconazole | Blood Cx | Survived |
| Rajput et al. [26] | 2015 | USA | 42y, F | HIV | 40 | Liposomal amphotericin B/itraconazole | Blood Cx | Survived |
| Kashifet al. [27] | 2015 | USA | 41y, F | Renal transplant | N/A | None (died the same day of positive Cx) | Blood Cx | Died (HD 3) |
| Telfer and Gulati [23] | 2012 | USA | 28y, M | HIV | 12 | Voriconazole | BM path/urine Ag | Died (NR) |
| Huang [24] | 2014 | Guatemala | 25y, M | HIV | 4 | Antifungals/dexamethasone | Urine Ag/BM path | Survived |
| Subedee and van Sickels [25] | 2015 | USA | 34y, M | AIDS | N/A | Liposomal amphotericin B/itraconazole | Blood Cx | Survived |
| Rajput et al. [26] | 2015 | USA | 42y, F | HIV | 40 | Liposomal amphotericin B/itraconazole | Blood Cx | Survived |
| Kashifet al. [27] | 2015 | USA | 41y, F | Renal transplant | N/A | None (died the same day of positive Cx) | Blood Cx | Died (HD 3) |
| Telfer and Gulati [23] | 2012 | USA | 28y, M | HIV | 12 | Voriconazole | BM path/urine Ag | Died (NR) |
| Huang [24] | 2014 | Guatemala | 25y, M | HIV | 4 | Antifungals/dexamethasone | Urine Ag/BM path | Survived |
| Subedee and van Sickels [25] | 2015 | USA | 34y, M | AIDS | N/A | Liposomal amphotericin B/itraconazole | Blood Cx | Survived |
| Rajput et al. [26] | 2015 | USA | 42y, F | HIV | 40 | Liposomal amphotericin B/itraconazole | Blood Cx | Survived |
| Kashifet al. [27] | 2015 | USA | 41y, F | Renal transplant | N/A | None (died the same day of positive Cx) | Blood Cx | Died (HD 3) |
| Author                  | Year | Country  | Age, gender | Underlying disease | CD4 | Treatment                                      | Histoplasma diagnosis                  | Outcome* |
|------------------------|------|----------|-------------|--------------------|-----|-----------------------------------------------|----------------------------------------|----------|
| Ferguson-Paulet et al. | 2016 | USA      | 6 months, F | MRSA bacteremia    | N/A | Liposomal amphotericin B/itraconazole/etoposide/steroids | Urine serum Ag/BM and CSF Cx          | Survived |
| Dao and He [35]        | 2016 | USA      | 21y, M      | Crohn disease      | N/A | Antifungal therapy                            | BM (cx and path)/Blood and BAL Cx     | Survived |
| Schulze et al. [36]    | 2016 | Germany  | 59y, F      | Steroids for suspected IBD | N/A | Liposomal amphotericin B/posaconazole/steroids | Colon, liver, LN, lung path/blood Cx | Survived |
| Gómez-Espejo et al. [37]| 2017 | Venezuela| 23y, M      | HIV               | 7   | Liposomal amphotericin B/dexamethasone/IVIG    | Liver Bx                              | Survived |
| Karthik Bommanan et al. | 2017 | India    | 32y, M      | Healthy           | N/A | Amphotericin B                                 | BM Bx path                           | Survived |
| Souto Filho et al. [39]| 2017 | Brazil   | 40y, F      | SLE                | N/A | Amphotericin B/steroids                       | BM Bx path                           | Died (within 48 hrs)          |
| Ocon et al. [40]       | 2017 | Guyana   | 49y, M      | HIV                | 7   | Liposomal amphotericin B/ART/IVIG/anakinra    | Blood cx                             | Survived |
| Loganantharaj et al. [41]| 2017 | Dominican Republic | 46y, M | HIV       | 54  | Liposomal amphotericin B                       | Urine Ag/LN bx                      | Survived |
| Huapaya et al. [42]    | 2017 | USA      | 46y, M      | Kidney transplant  | N/A | Amphotericin B                                 | Urine and serum Ag/BAL cytology       | Survived |

Abbreviations: y, year; M, male; F, female; HIV, human immunodeficiency virus; NR, not reported; BM, bone marrow; N/A, not applicable; BAL, bronchoalveolar lavage; ART, antiretroviral therapy; IVIG, intravenous immunoglobulin; d, days; wks, weeks; Cx, culture, Bx, biopsy; path, histopathology; CSF, cerebrospinal fluid; CLL, chronic lymphocytic leukemia; TB, tuberculosis; GI, gastrointestinal; PCR, polymerase chain reaction; HCV, hepatitis C virus; CKD, chronic kidney disease; Ag, antigen; LN, lymph node; MCTD, mixed connective tissue disease; HD, hospital day; IBD, inflammatory bowel disease.
immunosuppressive therapy with regimens such as the HLH-94 protocol [49]. Once clinical improvement is noted, we believe immunosuppressive therapy can be tapered, and the full protocol is often not required.

We report a small number of cases at our institution and it is possible that we could have missed cases in our retrospective search. In published case reports and case series, some data were lacking and few articles were not in English.

6. Conclusions

Histoplasmosis-associated HLH among adults is an uncommon but serious disease with high mortality. The clinical and laboratory findings that should prompt evaluation for HLH are splenomegaly, highly elevated ferritin, and cytopenia in an immunocompromised patient with disseminated histoplasmosis. The delay in diagnosis of HLH may affect outcomes and patients with suspected HLH should have a prompt hematology consultation. HLH appears to be a disease of excessive immune activation, and the optimal treatment and duration of immunosuppressive therapy remains unknown. Early antifungal therapy with a liposomal formulation amphotericin B is critical. Multicenter prospective studies are needed to help define the role and duration of immunosuppressive therapy for this disease.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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