Case Report

Hemophagocytic Lymphohistiocytosis Due to Disseminated Histoplasmosis in a Young Patient with AIDS

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome of immune dysregulation that results in multiorgan failure; HIV and histoplasmosis are known triggers of HLH. A young patient with AIDS was found to have disseminated histoplasmosis and met criteria for HLH. Despite 10 days of treatment with liposomal amphotericin B, she developed shock and acute respiratory distress syndrome and ultimately died. The few reported cases of HLH due to histoplasmosis in AIDS offer a variety of treatment approaches. There have been successful outcomes combining amphotericin with chemotherapies for HLH. Targeted therapies for HLH may be considered on a case-by-case basis in the setting of concurrent disseminated histoplasmosis and HIV/AIDS.

Keywords: AIDS, amphotericin B, hemophagocytic lymphohistiocytosis, histoplasmosis, HIV

Introduction

Histoplasma capsulatum is a dimorphic fungus with a worldwide distribution but is highly endemic to the midwestern United States and Central and South America.[1] The fungus has a predilection for infecting the lungs and gastrointestinal tract; infection is typically more severe in immunocompromised hosts.[2] Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by persistent activation of the mononuclear phagocytic cascade which causes an uncontrolled, hyperinflammatory response.[3] HLH can be familial (primary) or acquired (secondary) due to infections, malignancies, and autoimmune diseases.[3] A diagnosis is made by either having a genetic mutation associated with HLH or by meeting 5 of 8 diagnostic criteria. These criteria include: fever, splenomegaly, ≥2 cell lineage cytopenia, hypertriglyceridemia or hypofibrinogenemia, hyperferritinemia, hemophagocytosis seen on biopsy, low natural killer cell activity, and/or elevated soluble interleukin-2 (IL-2) receptor (CD25).[4] The H-score is a validated set of weighted criteria for the diagnosis of a reactive hemophagocytic syndrome; it was developed because the HLH criteria were nonspecific, gave equal weight to each criterion, and were difficult to apply in common practice.[5] Here, we present a unique case of one of the youngest patients in the literature with HLH in the setting of disseminated histoplasmosis and AIDS.

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Case Report

The patient was a 24-year-old woman who was born in Ecuador, lived on a farm, and had moved to the United States 8 months prior. She had no past medical history, did not take prescription or recreational drugs, and worked in a restaurant. Her symptoms were fevers, fatigue, cough, diffuse abdominal pain, vomiting, and diarrhea for 1 month and an unknown quantity of weight loss. She denied night sweats, neck swelling, chest pain, dyspnea, hemoptysis, dysuria, joint pains, prior treatment for tuberculosis, or sick contacts.

Her temperature on arrival was 40°C and she was lethargic and ill-appearing. Cardiopulmonary examination revealed

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tachycardia without murmurs and her lungs were clear to auscultation bilaterally. Her abdomen was soft with diffuse tenderness to palpation and a palpable spleen.

Initial laboratory findings were significant for white blood cell count 1.43 × 10^3 cells/μL, hemoglobin 8.4 g/dL, MCV 81.9 fl, platelet count 93 × 10^3 g/dL, AST 93 U/L, and albumin 2.2 g/dL. Basic metabolic panel, hemoglobin A1c, and thyroid stimulating hormone were all normal. HIV 1, 2 antigen/antibody test was reactive. CD4 cell count was 5 cells/μL and HIV viral load was 25 million. Initial blood cultures were without growth. Hepatitis B and C serologies, heterophile antibody, parvovirus serology, serum cryptococcal antigen, peripheral blood and sputum cultures for acid-fast bacilli, blood parasite smear, stool ova and parasite, urine Legionella antigen, and Coxiella and Brucella serologies were all not detected. Syphilis treponemal antibody was detected and rapid plasma reagin (RPR) was not detected. Computed tomography (CT) of the chest with contrast showed diffuse ground glass and reticulonodular opacities in the lungs with small pleural effusions [Figure 1]. CT of the abdomen and pelvis showed hepatosplenomegaly and numerous enlarged retroperitoneal and mesenteric lymph nodes.

On hospital day #9, yeast forms were detected in neutrophils in the complete blood count and peripheral blood smear confirmed the finding [Figure 2]; liposomal amphotericin B (AMB) was started for presumptive disseminated histoplasmosis. On hospital day #10, blood cultures grew yeast [Figure 3]. On hospital day #11, urine histoplasma antigen resulted as positive and, on day #12, serum histoplasma antigen resulted as above the limit of quantification. Further laboratory investigations were notable for triglyceride 142 mg/dL, fibrinogen 136 mg/dL, ferritin 14,971 ng/mL, and soluble IL-2 receptor 26,274 pg/mL. Antiretroviral therapy was initiated after histoplasmosis was confirmed and a diagnostic lymph node biopsy was scheduled. On hospital day #18, the patient became delirious and hypoxic due to acute respiratory distress syndrome. She was intubated and given vasopressors, vancomycin, and meropenem for presumptive septic shock; despite these measures, she had cardiac arrest and expired. Postmortem blood cultures grew extended-spectrum beta-lactamase producing *Klebsiella pneumoniae* and *Escherichia coli*.

Figure 1: Computed tomography chest with contrast with diffuse ground glass and reticulonodular opacities in the lungs

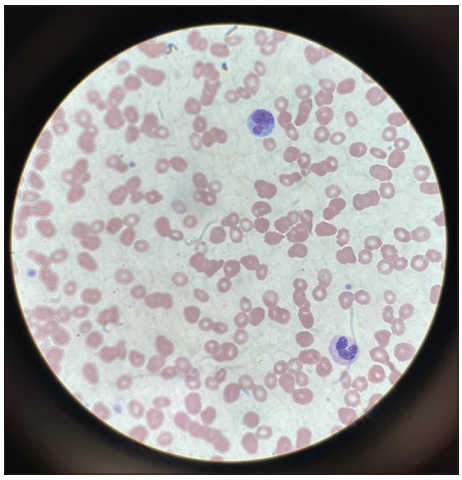

Figure 2: Peripheral blood smear with yeast forms in neutrophils

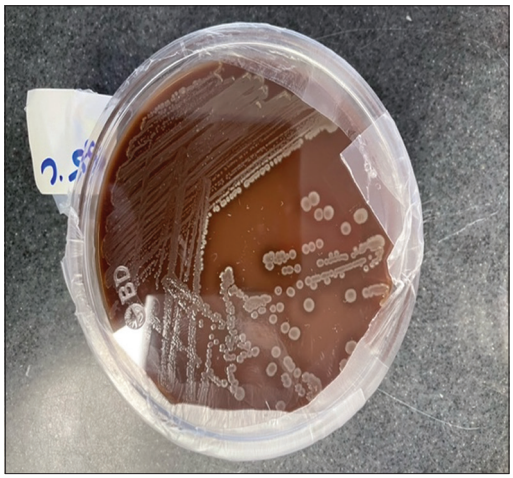

Figure 3: Agar culture plate growing yeast

Discussion

AMB is first-line therapy for disseminated histoplasmosis; the mainstay of therapy for secondary HLH is treatment of the underlying cause.[6] Our patient received 10 days of AMB then rapidly decompensated and died. Six criteria for HLH were fulfilled; her total H-score was 282 which has a >99% probability of HLH. Her H-score was calculated as follows: known underlying immunosuppression (+18), temperature >39.4°C (+49), hepatosplenomegaly (+38), 3 cell-lineage cytopenia (+34), ferritin >6,000 ng/mL (+50), triglyceride 132.7–354 mg/dL (+44), fibrinogen <250 mg/dL (+30), and AST >30 U/L (+19). Thus, the question was raised whether she would have benefited from HLH-directed therapy. A review of HLH in histoplasmosis found the inhospital mortality rate for those with HLH and histoplasmosis without HIV was 31% (20/64) and 37% for those with HIV (13/35).[7]

Table 1: Therapeutic regimens and outcomes for hemophagocytic lymphohistiocytosis -associated disseminated histoplasmosis in HIV/AIDS

Regimen	Survived	Died
AMB±ICZ7[8-11]	25	8
AMB + steroids[7,11,12]	4	1
AMB + IVIG[7]	2	4
AMB + IVIG + steroids[7,11,13-15]	4	2
AMB + etoposide±steroids[7,11,16]	3	
AMB + IVIG + anakinra[7]	1	
No AMB[7]		3
Other antifungal (FCZ, KCZ, VCZ)[7]	3	2
IVIG × 1[17]		1

AMB: Amphotericin B, ICZ: Itraconazole, IVIG: Intravenous immunoglobulin, FCZ: Fluconazole, KCZ: Ketoconazole, VCZ: Voriconazole

We performed a review of the literature and found 69 cases of HLH due to histoplasmosis in AIDS [Supplementary Table 1]; six cases were excluded for incomplete reporting of data or unconfirmed histoplasmosis. Most patients received AMB (54/63) and 75% of those who received it alone survived – comparable to prior estimates. Use of AMB showed a tendency toward improved survival (39 survived, 15 died) when compared to alternative antifungals (3 survived, 2 died). Many of the cases which utilized steroids did not specify dosing. The few reports of combination therapy using AMB with etoposide or anakinra, which are HLH-directed therapeutics, had 100% survival rate (4/4 patients). The potential benefit of these agents must be weighed against the risk of further bone marrow suppression which can cause bleeding and other infections. It is difficult to make conclusions about the effectiveness of the various therapies given the small number of patients in each treatment group and the noncontrolled nature of this review [Table 1]. Use of these targeted therapies should be considered in discussion with specialists in infectious diseases and hematology/oncology.

Research quality and ethics statement

The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines, notably the CARE guideline, during the conduct of this report.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Cases of hemophagocytic lymphohistiocytosis-associated disseminated histoplasmosis in HIV/AIDS

Case report/series	Age/sex	CD4 count	Histoplasmosis treatment	HLH Tx	Outcome
Majluf-Cruz *et al*., 1993[7]	37 male	NR	FCZ		Survived
	49 male	NR	AMB		Survived
	36 male	NR	None		Died
Koduri *et al*., 1995[7]	NR	36	AMB	IVIG × 2 days	Died
	NR	4	AMB	IVIG × 2 days	Died (day 6)
	NR	6	AMB	IVIG × 2 days	Died
	NR	22	AMB	IVIG × 2 days	Survived
	NR	32	AMB		Survived
	NR	44	AMB		Survived
Chemlal *et al*., 1997 (omitted)[7]	50	34	NR		NR
Kumar *et al*., 2000[7]	40 male	NR	None		Died (within 48 h)
Gil-Brusola *et al*., 2007[7]	33 male	39	None		Died (day 18)
Guiot *et al*., 2007[7]	43 male	66	LAMB × 3 weeks, ICZ		Survived
Sanchez *et al*., 2007[7]	61 male	4	AMB		Survived
Chandra *et al*., 2012[7]	38 female	NR	KCZ		Survived
De Lavaissiere *et al*., 2009[7]	33 male	NR	AMB, ICZ	IVIG	Survived
Vaid and Patel, 2011[7]	25 male	153	Antifungal		Died
Chandra *et al*., 2012[7]	38 female	NR	KCZ		Survived
Telfer and Gulati, 2012[7]	28 male	12	VCZ		Died
Huang, 2014[7]	25 male	4	Antifungals (assumed AMB)	Dex	Survived
Subedee and van Sickels, 2015[7]	42 female	40	LAMB, ICZ		Survived
Castelli *et al*., 2015[7]	32 male	3	LAMB × 2 weeks, itra	Etoposide, dex	Survived
Townsend *et al*., 2015 (omitted)[7]	31 female	1	LAMB		Died (day 16)
	53 male	6	LAMB × 2 weeks, itra		Survived
	33 female	1	LAMB × 3 weeks, itra		Survived
	28 male	NR	NR		Survived
	44 male	2	LAMB × 16 days, itra		Survived
	52 male	16	LAMB × 6 days, itra	IVIG, steroids	Died (day 9)
	52 male	16	LAMB × 3 days, itra	IVIG	Died (day 9)
	32 male	50	LAMB × 18 days, itra		Survived
	51 male	9	LAMB	Steroids	Died (day 13)
Nieto *et al*., 2016[7]	33 male	NR	AMB	Steroids	Survived
Gómez-Espejo *et al*., 2017[7]	23 male	7	LAMB	IVIG, dex	Survived
Ocon *et al*., 2017[7]	49 male	7	LAMB	Anakinra, IVIG	Survived
Loganantharaj *et al*., 2017[7]	46 male	54	LAMB		Survived
Asanad *et al*., 2018[7]	48 male	20	LAMB × 2 weeks, ICZ		Survived
Tsuboi *et al*., 2019[7]	56 female	13	LAMB × 2 weeks, ICZ		Survived
Jabr *et al*., 2019[7]	48 male	50	LAMB × 2 weeks, intra × 12 months	None	Survived
	41 male	10	LAMB × 2 weeks, oral azoles	None	Died (day 43)
Gonzalez-Hernandez *et al*., 2020[11]	21 male	6	LAMB × 2 weeks, itra	IVIG, pred	Survived
Montenegro-Idrogo *et al*., 2020[8]	33 female	188	AMB, ICZ		Survived
	35 female	2	AMB		Died (day 2)
	36 male	156	AMB, ICZ		Survived
	45 male	29	AMB		Died (day 7)
	33 male	99	AMB, ICZ		Died
	32 female	31	AMB, ICZ		Died (day 13)
	30 male	16	AMB, ICZ		Survived
	26 male	63	AMB, ICZ		Survived
Atiyat *et al*., 2021[17]	55 male	44		IVIG × 1	Died
Castejón-Hernández *et al*., 2021[9]	46 male	10	AMB		Died
Tomaino *et al*., 2022[14]	32 male	11	AMB	IVIG, methylpred	Died (day 14)
Lage *et al*., 2022[10]	44 female	16	LAMB × 2 weeks		Survived
Nguyen *et al*., 2020[11]	30–40	15	LAMB, itra		Died (day 20)
	50–60	4	LAMB, itra		Survived

Contd...

Supplementary Table 1: Contd...

Case report/series	Age/sex	CD4 count	Histoplasmosis treatment	HLH Tx	Outcome
	30–40	25	LAMB, itra		Survived
	40–50	14	LAMB	IVIG, steroids	Survived
	40–50	166	LAMB, itra		Survived
	60–70	9	LAMB, itra		Survived
Omitted	50–60	22		Steroids	Survived
Omitted	40–50	20	LAMB, itra		Survived
Omitted	40–50	837	None		Survived
	40–50	25	LAMB, itra		Survived
	40–50	25	LAMB, itra	Etoposide	Survived
Omitted	40–50	36	LAMB, itra		Died (day 30)
	40–50	25	LAMB, itra	Steroids	Survived
	50–60	25	LAMB		Survived
Warren *et al*., 2022[12]	42 female	NR	AMB	Dex	Survived
Fogelson *et al*., 2022[16]	30 male	19	LAMB × 2 weeks, ICZ	Etoposide × 10 doses, dex	Survived
Pipito *et al*., 2023[15]	54 female	25	LAMB, ICZ	IVIG, steroids	Survived

NR: Not reported, AMB: Amphotericin B, ICZ: Itraconazole, IVIG: Intravenous immunoglobulin, FCZ: Fluconazole, KCZ: Ketoconazole, VCZ: Voriconazole, HLH: Hemophagocytic lymphohistiocytosis, LAMB: Liposomal AMB