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Case Report

PROGRESSIVE DISSEMINATED HISTOPLASMOSIS WITH HEMOPHAGOCYTIC LYMPHOHISTOCYTOSIS IN IMMUNOCOMPETENT PATIENT: A CASE REPORT AND REVIEW OF THE LITERATURES

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) secondary to Histoplasma capsulatum infection is a rare disorder a life-threatening hyperinflammatory syndrome [1]. Here, we present a rare case of disseminated histoplasmosis in a non-HIV patient, whose disease course was complicated by HLH with a full recovery after appropriate therapy. Although cases of patients with human immunodeficiency virus (HIV) infection have been well documented, little study has reported in the setting of HIV seronegative. In this study, we report a case of HLH secondary to histoplasmosis in an immunocompetent patient in Rural tertiary care hospital Dr.RPGMC Tanda H.P. and review all cases on this situation.

Objective:-The objective is to study their epidemiology, clinical characteristics, diagnostic approaches, and therapeutic response. A 31year-old male presented with fever, fatigue, anorexia, and weight loss. Bone marrow examination suggest fungus organism and hemophagocytosis, and bone marrow culture confirmed Histoplasma capsulatum, as the etiology of HLH. The patient was successfully treated.

Review of Literature: -We reviewed a total of the 13 cases (including our patient) of HLH with histoplasmosis in immunocompetent patients. Twelve of the 13 patients are from endemic areas, and nine of the 12 cases are from emerging endemic areas, India and China. Three patients had sojourn history may related to the disease onset. Twelve of the 13 cases fulfilled HLH-2004 criteria. The diagnosis of Histoplasma capsulatum infection was established by histological examination (13 of 13), culture (4 of 13), molecular method (2 of 13), and antigen or serological assays (2 of 13). Amphotericin B, posaconazole, and itraconazole show favorable activity against the fungus, seven patients used specific treatment for HLH. For analysis of outcomes, two of the 13 patients died. Our present case report and literature review show that disseminated Histoplasma capsulatum infection with HLH in the immunocompetent population becomes increasingly common in emerging endemic areas and have high mortality. It is essential for clinicians to be highly skeptical of such disease diagnosis due to the non-typical population and disease presentation. Timely diagnosis and early use of antifungal agents will lead to favorable prognosis.

Keywords: HIV seronegative, immunocompetence, histoplasmosis, hemophagocytic lymphohistiocytosis, liposomal amphotericin B.

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Introduction

Histoplasmosis is infection caused by fungus histoplasma capsulatum. Fungus lives preferably in humid and acidic soil in the endemic areas. Soil enriched with birds or bat dropping promotes the growth and sporulation's of histoplasma. It is dimorphic fungus that causes histoplasmosis[2]. With a worldwide incidence, epidemic distribution mainly in North America and Latin American countries[3]. Many areas of Asia, including India, Southeast Asia, and China along Yangtze River, are also endemic [4]. Infection occurs when inhalation of fungal spores or hyphae from the environment soil and the lung is the primary organ of infection. H. capsulatum can disseminate throughout the body in immunocompromised persons [3,5] who are at least 10 times more likely to develop progressive disseminated histoplasmosis (PDH) than the general individuals [6] without timely diagnosis and treatment can lead to fatal illness. In immunocompetent and non-respiratory patients, they are usually clinically silent or mild manifestations, and diagnosis is often so challenging that the rate of underdiagnosis is high. Acquired HLH is association with systemic infections, malignant diseases, or autoimmune disorders, cases onset mainly in adults[7]. Most cases of HLH secondary to Histoplasma capsulatum infection present in immunocompromised patients[8] and clinicians are vigilant in diagnosing the disease in endemic areas. we present a rare case of an immunocompetent patient who was 31 years old and driver by profession and residing in Dehi, diagnosed as Histoplasma infection and secondary HLH, which was successfully treated by Liposomal Amphotericin B (3mg/kg/day) 150 mg /day for 14 weeks followed by Itraconazole 200 mg BD for next 12 months. A review of literature on this situation is also performed.

Case Presentation

A 31year-old male was admitted to medicine department of Tertiary care hospital Dr. RPGMC Tanda H.P. with complaints of intermittent fever associated with fatigue and anorexia for 3 months. He also given h/o loss of 6 kg weight for last 3 months. History of pain abdomen (epigastrium) was there for which he took treatment from private hospital where he was diagnosed with chronic calcified pancreatitis and main pancreatic duct stone for which patient undergone ERCP on 7th FEB 2023 but fever persisted. The patient visited our hospital for persistent fever. On physical examination patient was conscious, cooperative well oriented to time, place and person. His vitals were within normal at the time of presentation. Temp. recorded 101^{o}F , pulse rate of 97 /min, respiratory rate of 18/min, and blood pressure of 98/60 mm of hg and has normal oxygen saturation. He had pallor and hepatosplenomegaly. CVS and Respiratory systems were within normal limit. The laboratory examination indicated pancytopenia at admission: hemoglobin, 8.4 mg/dL; platelet, 90× 109 /L; leucocytes, 2.7 × 109 /L; neutrophils, 1.4 × 109 /L. The C-reactive protein (CRP) level was 35 (normal < 8) mg/L and procalcitonin (PCT) level was 1.23 (normal < 60) pg/ml and the GM (galactomannan) level was not elevated. Epstein–Barr virus, cytomegalovirus, hepatitis virus B and C, COVID-19 and Serological results for human immunodeficiency virus (HIV), HCV, HBS ag, scrub typhus, leptospirosis, brucellosis, enteric fever were negative, chronic malaria and tuberculosis is ruled out. His blood and urine cultures were sterile. We had kept possibility of Pyrexia with Hepatosplenomegaly with pancytopenia. Possibility of HLH syndrome secondary to

(1) Infection: - Leishmaniasis and Tuberculosis.

(2) Hematological malignancy /lymphoma was kept.

To fulfill HLH - (2004) Criteria and to make diagnosis bone marrow aspiration and bone marrow biopsy was done. Bone marrow biopsy revealed hemophagocytosis and negative result for bacterial culture. Hematoxylin and eosin (HE)-stained bone marrow demonstrated oval or

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round organisms with amaranth nuclei and capsule-like unstained halos around these organisms observed in the cytoplasm of phagocytes s/o histoplasmosis.

Table 1 shows the results of relevant blood investigations. Chest x rays and Computed tomography (CT) of the chest was normal but the abdominal CT showed hepatosplenomegaly and chronic calcified pancreatitis. Figure 2-4 showing CT finding. 2D Echography normal study with EF 55-60%. Final diagnosis made was Pyrexia with hepatosplenomegaly with pancytopenia: -HLH syndrome secondary to progressive disseminated histoplasmosis. The patient received Liposomal Amphotericin B 3 mg /kg /day for 14 days. Monitoring of RFT and Electrolytes were done regularly. At day 4 after treatment, the body temperature settled and general condition of patient improved, followed by tab. Itraconazole 200 mg twice a day for a total of at least 12 months. During follow up patient was afebrile, had gained weight and regression of hepatospenomaly was there.

Cell count, CRP, and serum ferritin improved substantially after a week. In this case, the patient presented with HLH with fever, splenomegaly, elevated ferritin, hyperfibrinogenemia, blood cell abnormalities, and hemophagocytosis. Although he had no immunocompromised disease and never went to epidemic area instead of that he had invasive fungal infection like progressive disseminated histoplasmosis.

Table 1: Blood investigations of patient.

Hb	6.1
TLC	3200
RBC	2.48
PLATELETS	105
C-reactive protein	18.9
procalcitonin	3
Fibrinogen	370
Prothrombin time/INR	14/1.2
D-dimer	Normal
S.ferritin	1030
ANA/RA factor	Negative
Serum urea	53
Creatinine	1.18
Serum Na+	137
TG	182
LFT SGOT/SGPT	34 30

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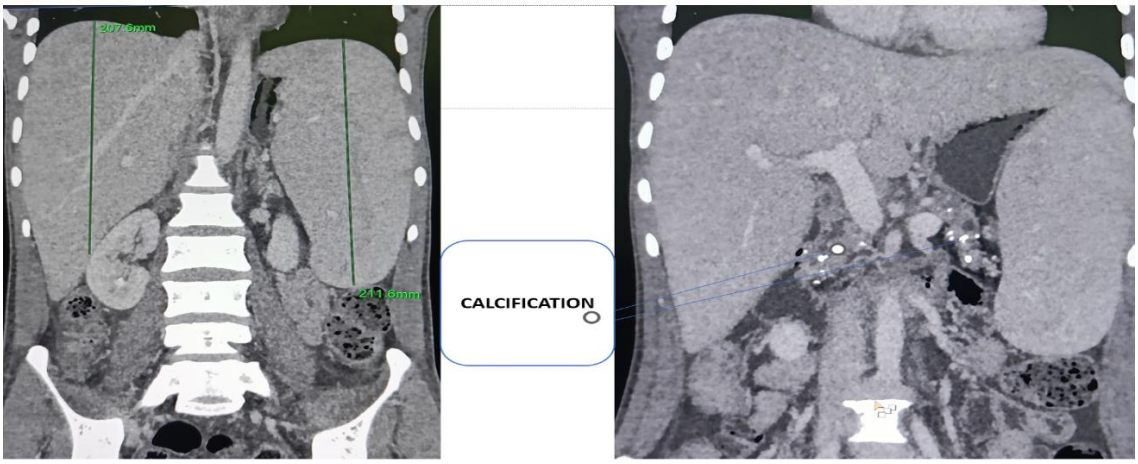

Figure 3: CT Abdomen showing hepatosplenomegaly and pancreatic calcification.

Figure 4: Abdominal CT scan showed splenomegaly and hepatomegaly with pancreatic calcification.

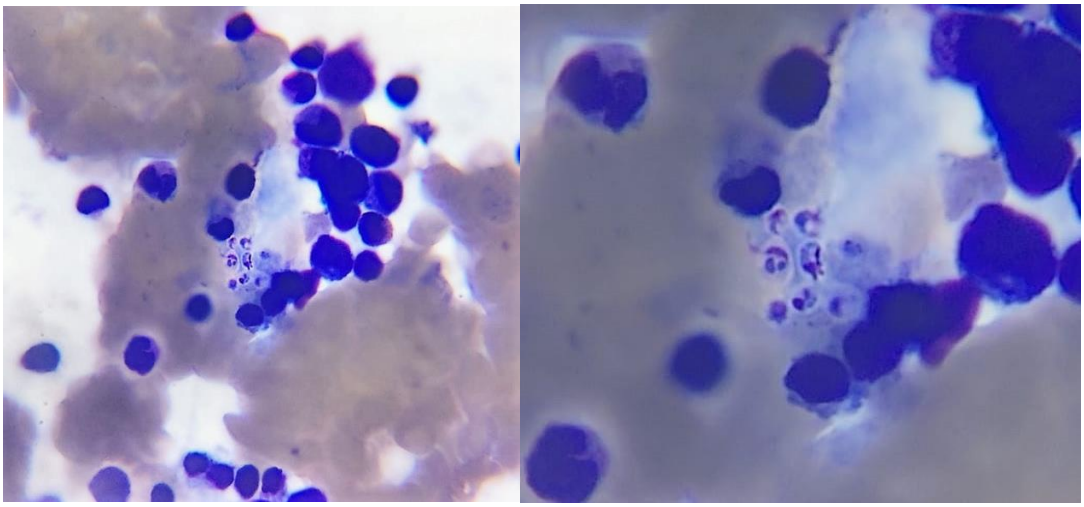

Figure 5: H-E stain of bone marrow puncture images showing these oval or round organisms with amaranth nuclei and capsule-like unstained halos around observed in the cytoplasm of phagocytes and few extracellular. Intensely PASS +VE

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LITERATURE OF REVIEW

A total of 90 articles were retrieved from the databases without time limit, including 77 papers in English, 8 in Spanish, and 2 in Chinese. Total of 128 cases has been reported till 2022 all over world. Case report and case series for HLH and histoplasmosis were identified in the five databases (PubMed, Embase, Web of science, China National Knowledge Infrastructure, and Wan fang Data) by using search criteria ("lymph histiocytosis, hemophagocytic" [MeSH Terms] and "Histoplasmosis" [MeSH Terms]). This review of literature identified 13 cases (9.4%), presenting a confirmed HLH with histoplasmosis of intact immunology. 65 of 128 (50.8%) patients were infected with HIV; 20 of 128 (15.6%) had rheumatic disease; 15 of 128 (11.7%) had organ transplant history (14 cases with renal transplant, and one case with heart transplant) and 3 of 128 (2.3%) had hematologic malignancy. In India total of 6 cases has been reported so far. Out of that 4 people were HIV negative and 2 were HIV positive and 7th one is our patient. In Himachal Pradesh HLH secondary to histoplasmosis has not been reported, this is the first case of disseminated histoplasmosis with HLH in immunocompetent patient.

TABLE 2 | Case reports on HLH due to histoplasmosis in HIV seronegative patients.

Reference	(Kashif et al., 2015)	(Mukherjee and Basu, 2015)	(Sonavane et al., 2016)	(Ferguson-Paul et al., 2016)	(Schulze et al., 2017)	(Bommanan et al., 2017)
Published year	2015	2015	2016	2016	2017	2017
Number of cases	1	1	1	1	1	1
Home country	USA	India	India	USA	Germany	India
Age/Gender	34y/M	52y/M	43y/F	6m/F	59y/F	32y/M
Occupation	/	/	Homemaker	NA	/	/
History of sojourn	Nigeria	/	/	–	Thailand/ Costa Rica	–
Clinical manifestation						
Fever	+	+	+	+	+	+
Fatigue	–	–	+	–	–	–
Rash	–	+	–	–	–	–
Weight loss	+	–	+	–	+	+
Anorexia	+	–	+	–	–	–
Cough	–	–	+	–	–	–
Foot edema	–	+	+	–	–	–
Co-infections	–	–	M.TB	–	EBV/Hafnia alvei	–
Underlying disease	Sickle cell disease	COPD/DM/EN	TB	–	breast cancer	–
Leucocytes (k/ml)	10	4.2	2.6	/	12.37	1.4
Neutrophils (k/ml)	/	/	/	1.5	/	1.2
Hemoglobin (g/dl)	4.9	6	7	5.9	5.8	7.9
Platelet (k/ml)	48	/	91	11	128	40
Triglycerides (mg/dl)	135	/	NR	378	270	/
fibrinogen (g/L)	0.69	/	0.53	0.78	/	/
NK cell activity	/	/	/	NR	/	/
Serum ferritin (mg/L)	7,493	3.06	891.7	1,218	99,919	3,339
Soluble CD25 (U/ml)	/	/	/	21,530	4,445	/
ALT (U/L)	5,058	/	23	/	44	62
AST (U/L)	16,637	/	28	/	39	52
LDH	1,466	/	296	/	306	/
Hepatomegaly	+	+	+	+	–	+
Splenomegaly	+	+	+	+	–	+
Lymphadenopathy	+	+	–	–	+	–
Pulmonary disorders	+	/	+	+	+	–
Number of HLH-2004 Criteria	6	3	6	7	5	5
Hemophagocytosis	BM Bx	BM Bx	BM Path	BM Path	BM Path	BM Path
Diagnosis of Histoplasmosis						
Path	LN Bx	liver/spleen Bx	BM Path	BM Path	colon/liver/LN/ lung Bx	BM Path
Culture	/	/	/	/	/	/
Antigen assays	–	/	/	Serum/urine/CSF	/	/
Antibody assays	/	/	/	+	/	/
Molecular method	/	/	/	/	+	/
Antifungal treatment	AmB/Itra	AmB	AmB/Itra	AmB/Itra	AmB/Posa	AmB
HLH-specific Treatment	DE	–	–	DE	–	–
Outcomes	Died	Died	Recovery	Recovery	Recovery	Recovery

Reference	(Xiong et al., 2017)	(Pancoast et al., 2019)	(Gupta et al., 2019)	(L Xiaolin et al., 2021)	(Song et al., 2021)	(Sijie et al., 2022)	PS
Published year	2017	2019	2019	2020	2021	2022	–
Number of cases	1	1	1	1	1	1	1
Home country	China	USA	India	China	China	China	China
Age/Gender	37y/M	3m/M	29y/M	27y/M	16y/M	44y/M	46y/M
Occupation	blood bank worker	NA	/	/	NA	/	Cooker
History of sojourn	–	/	/	/	/	Kenya	–
Clinical manifestation							
Fever	+	+	+	+	+	+	+
Fatigue	–	–	–	+	–	+	+
Rash	–	–	–	–	–	–	–

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Reference	(Kashif et al., 2015)	(Mukherjee and Basu, 2015)	(Sonavane et al., 2016)	(Ferguson-Paul et al., 2016)	(Schulze et al., 2017)	(Bommanan	et al., 2017)
Weight loss	+	–	+	–	–	+	+
Anorexia	–	–	+	–	–	+	+
Cough	+	–	+	–	–	+	–
Foot edema	–	–	–	–	–	+	–
Co-infections	CMV HSV	–	–	HBV	–	–	–
Underlying disease	–	–	–	Hepatitis	–	–	–
Leucocytes (k/ml)	1.86	/	3.9	3.45	2.35	2.2	1.6
Neutrophils (k/ml)	1.23	/	/	/	0.84	1.63	1.3
Hemoglobin (g/dl)	8.6	/	8.4	8.7	11.8	6.3	6.3
Platelet (k/ml)	2	/	79	32	62	4	44
Triglycerides (mg/dl)	/	213	304	/	1.44	/	NR
Fibrinogen (g/L)	/	1.32	<1.5	3.6	1.6	/	1
NK cell activity	/	/	/	/	NR	Below NR	/
Serum ferritin (mg/L)	543.3	830	>2,000	1,900	403.8	2,545	2775
Soluble CD25 (U/ml)	/	9,560	/	>7,500	>44,000	35,854	/
ALT (U/L)	82	/	/	98.6	32	40	53
AST (U/L)	70	/	/	32.3	45	49	81
LDH	352	/	579	468	/	/	122
Hepatomegaly	+	+	+	+	+	+	+
Splenomegaly	+	+	+	+	+	–	+
Lymphadenopathy	+	–	–	+	+	–	+
Pulmonary disorders	+	–	–	+	–	+	–
Number of HLH-2004 Criteria	5	6	5	6	5	6	6
Hemophagocytosis	BM Path	BM Path	–	BM Path	BM Path	BM Path	BM Path
Diagnosis of histoplasmosis							
Path	BM Path	BM Path	BM Path	BM Path	BM Path	BM Path	BM Path
Culture	blood	/	/	/	BM	BM	BM
Antigen assays	/	serum/urine	/	/	/	/	/
Antibody assays	/	/	–	/	/	/	/
Molecular method	/	/	/	/	/	+	/
Antifungal treatment	AmB	AmB/Itra	AmB/Itra	AmB	AmB	AmB/Itra	AmB/Itra
HLH-specific Treatment	IVIG	–	–	DEP	DEP	IVIG	IVIG/ Prednisone
Outcomes	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery

HLH : SECONDARY TO HISTOPLASMOSIS (INDIA)

AUTHOR	YEAR	AGE	UNDERLYING DISEASE	DIAGNOSIS	TREATMENT	OUTCOME
Kumar et al.	2000	50	None	SPLENIC ASPIRATE	NONE	DIED
	2000	40	HIV	BONE MARROW Bx	NONE	DIED
Chandra et al.	2012	38	HIV	NOT REPORTED	KETOCONAZOLE	SURVIVED
Mukherjee and basu	2015	52	IMMUNOCOMPETENT	AUTOPSY	AMP B	DIED
Sonavane et al	2016	43	IMMUNOCOMPETENT	BONE MARROW BIOPSY	AMP B / ITRACONAZOLE	SURVIVED
Karthik bommanan et al	2017	32	IMMUNOCOMPETENT	BONE MARROW BIOPSYIN INDIA TOTAL OF 7 CASES HAS BEEN REPORTED SO FAR . OUT OF THAT 4 PEOPLE WERE HIV NEGATIVE AND 2 WERE HAVING HIV. IN HIMACHAL PRADESH HLH SECONADARY TO HISTOPLASMOSIS HAS NOT BEEN REPORTED YET.	AMP B / ITRACONAZOLE	SURVIVED

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The features of the 12 patients and our case with competent immunology are summarized in the Table 2. Two of them were infants, and the others were all older than 16 years. Among the 13 cases whose sex was mentioned, 10 were male patients, including our patient. Four patients were China born, two of them had a sojourn history in Africa, five patients were India born (including one case of us), three patients were America born, and one patient was Germany born but had a visiting of a bat cave when she had traveling in Thailand 8 months before onset. Three patients had job as cook, blood bank worker, and homemaker; occupations of other seven patients were unknown.

The nonspecific clinical syndrome consists of fever (13 of 13), weight loss (8 of 13), anorexia (5 of 13), fatigue (4 of 13), and cough (4 of 13). Among 13 patients whose laboratory tests were mentioned, significant cytopenia involving at least two cell lines, elevated ferritin, hypertriglyceridemia, elevated LDH, elevated hepatobiliary enzymes, and organomegaly (hepatomegaly, splenomegaly, and lymphadenopathy) are common symptoms. NK cell activity was detected in three study, In the cases reviewed, histological and cytological examinations in bone marrow (10 cases) and colon/liver/lymph node/lung/spleen (three cases) lead to fast diagnosis of Histoplasma capsulatum. The fungal was culture in three cases in bone marrow and one case in blood. The etiology was identified by molecular methods in two patients. Antigen and serological assays of histoplasma capsulatum were less used in clinical practice, only detected in two patients.

All patients are treated with first line systemic antifungal formulation with liposomal amphotericin B, and eight disseminated infection patients received step down to azoles as recommended by the Infectious Diseases Society of America [10] Condition was improved in 11 patients after antifungal and HLH-specific treatment.

Discussion

Environmental soil is the reservoir of Histoplasma capsulatum [11]. Contaminated soil of bird or bat cave, especially that found beside chicken coops or under blackbird roosts, provides a luxuriant condition for mold growth[12]. Histoplasmosis is endemic worldwide; in our literature review, five cases were from China and four cases were from Africa, and two Chinese patients had a history of sojourn in Africa. This suggests that clinicians need to raise awareness of the diagnosis of Histoplasma capsulatum infection in both areas. From its discovery in the United States, a century ago to now its spread around the world, there are three main reasons: convenient travel and enhanced connectivity increases imported and exported cases of histoplasmosis; climate change and anthropogenic land utilization creates conditions that are more conducive to fungi [6] and the HIV pandemic and the widely use of immunosuppressive agents results in more cases of histoplasmosis[4]. Our case report and literature reviews are of great value in the context of a worldwide epidemic. Furthermore, after retrieving data of literatures from five databases, we found that the HLH with histoplasmosis in immunocompetent patient is extremely rare but had high mortality. Therefore, it is necessary for clinicians to understand and recognize the disease. Given what we already know, histoplasmosis endemic is highly associated with AIDS [12].

The HLH-2004 criteria are used for diagnosis. Family history or molecular diagnosis is accord with HLH, or five of these eight criteria must be present (fever, splenomegaly, bicytopenia, hypertriglyceridemia and hypofibrinogenemia, hemophagocytosis, low/absent NK cell activity, hyperferritinemia, and high-soluble interleukin-2 receptor levels)[13]. In our review of the

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literature, 12 patients with disseminated histoplasmosis meet the above five of the eight criteria. The standard diagnosis methods of histoplasmosis include growth of mold in culture and confirmation of yeast on cytopathology or histopathology of clinical specimens. Histoplasmosis mold form requires 6 weeks to grow in culture and may lead to delays in patient treatment. By contrast, histopathology and cytology have faster diagnosis process but lower sensitivity and specificity. Antigen detection represents a valuable diagnostic tool and a useful measure of treatment response, Serum antibodies have limited diagnosis utility for produced 4 to 8 weeks after acute histoplasmosis infection and can yield false-negative and false-positive results[8]. Molecular diagnosis is used for the identification of suspected histoplasma capsulatum isolated from culture and it characterized by rapid turnaround times, less susceptibility to host factors and high sensitivity and specificity.

It is worth noting that 11 patients experienced clinical improvement and survived. Two of these patients had been deteriorating and died. Previous literature reviews suggest that the mortality rate of HIV-infected patients with HLH caused by disseminated histoplasmosis is 10%–44%[10] . H. capsulatum infections as a trigger for secondary HLH are primarily consider in our study, but exon detection of HLH mutated genes, NK cell activity, soluble interleukin-2 receptor (sIL2R), and interferon (IFN)-g should be tested to support our speculation. Unfortunately, we did not verify it further. The presence of other hidden immunodeficiency disorders is also uncertain.

Conclusion:

The purpose of this case report is to give an insight into a case of disseminated histoplasmosis with HLH in an immunocompetent male, a differential to be considered in future in a patient presenting with prolonged fever as infections are an important group of etiologies in the Indian scenario. Histoplasmosis-associated HLH is a life-threatening complication. Early diagnosis and management can be life-saving. It is necessary for clinicians to improve the awareness of disease diagnosis due to atypical population and disease presentation. Timely diagnosis and early use of antifungal agents will lead to favorable prognosis.

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