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Case Report

A complex case of disseminated histoplasmosis triggering hemophagocytic lymphohistiocytosis in a patient with lupus ☆

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ABSTRACT

Disseminated histoplasmosis is a rare yet serious fungal infection that primarily affects individuals with compromised immune systems. While it is widely known for its endemicity in the Midwest region of the USA, recent studies have indicated a noteworthy increase in sporadic cases, suggesting a widening of the endemic region for the pathology. This report describes a case of disseminated histoplasmosis in a 39-year-old female with a history of lupus, hypertension, anxiety, asthma, idiopathic edema, and fibromyalgia from a nonendemic region, who presented with cyclic fevers of unknown origin, peripheral edema, and oral sores. On admission, she was diagnosed with acute pyelonephritis and started on levofloxacin. She continued to develop worsening leukopenia and thrombocytopenia in addition to bone and joint pain. Bone marrow biopsy results were consistent with hemophagocytic lymphohistiocytosis (HLH) triggered by histoplasmosis confirmed by PCR. Despite an initial negative urine antigen test for Histoplasma, subsequent tests showed rising levels. The patient's clinical course was marked by a protracted hospital stay, multiple systems involvement, severe de-conditioning, drug side effects requiring adjustments in anti-fungal medications, and interdisciplinary care. The patient gradually improved and was discharged home with follow-ups. This study underscores the role of timely diagnosis of disseminated histoplasmosis in patients with underlying autoimmune diseases for favorable outcomes, thereby emphasizing the necessity of heightened clinical suspicion. By addressing the nuanced challenges that arise in managing multiple complications in the domain of disseminated histoplasmosis, advocates a comprehensive interdisciplinary approach to optimize patient care.

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Introduction

Histoplasmosis, caused by dimorphic fungi, mainly Histoplasma capsulatum, is a leading cause of endemic mycosis in the United States that predominantly affects the lungs [1]. Although it has been predominantly endemic to the Midwest region of the USA, recent studies show an increase in sporadic cases, implying the expansion of the endemic area [2]. However, in patients with immune compromise, progressive disseminated histoplasmosis (PDH), a form of histoplasmosis affecting nearly any organ with affinity to those rich in macrophages, such as lymph nodes, liver, spleen, bone marrow, and the gastrointestinal system is commonly reported. Despite its rarity, the diagnostic landscape can be further complicated by the emergence of HLH, presenting formidable challenges in diagnosis, effective treatment, and prognosis [3].

Systemic lupus erythematosus (SLE) is an autoimmune disorder that can alter an individual's immune state. Combined with steroids and immunosuppressants usually prescribed in these patients, lupus can predispose a patient to severe fungal infection. Furthermore, the overlapping nature of symptoms observed during increased lupus activity, including drug side effects such as persistent fever, fatigue, arthralgia, hematologic abnormalities, mucocutaneous lesions, and multiple organ involvement, can mask or delay the diagnosis of disseminated histoplasmosis [4].

We present a case of disseminated histoplasmosis in a patient with a history of lupus on prednisolone, who presented to a hospital complaining of cyclic fever, peripheral edema, and oral ulcers like her usual lupus flare symptoms. After comprehensive evaluation and the involvement of different specialties, a diagnosis of disseminated histoplasmosis complicated by HLH was made, leading to a protracted hospital course marked by multiple complications and medical interventions.

Case presentation

A 39-year-old female from a suburban area in a northeastern state in the United States, an area not typically endemic to Histoplasmosis, with a history of lupus on prednisone and hydroxychloroquine presented to a hospital with a cyclic fever of unknown origin, peripheral edema, oral sores, and ulcers typical of her usual lupus flares. Her medical history was remarkable for hypertension, asthma, anxiety, and fibromyalgia. Her medications included losartan, torsemide, buspirone, and albuterol as needed. Initial physical exam was significant for mouth sores, and bilateral costovertebral tenderness consistent with her presentation the day prior, during her office encounter complaining of bilateral flank and suprapubic pain with dysuria, for which she was started on oral levofloxacin. Upon rheumatology consultation, initial treatment with an escalated dose of prednisolone and IV levofloxacin for lupus flare and pyelonephritis was initiated. Subsequently, a negative urine culture led to discontinuation of levofloxacin.

However, her clinical course deviated from worsening leukopenia, thrombocytopenia (Table 1), and persistent fever. On the fifth hospital day, the infectious disease team was consulted, she was worked up for tick-related infections, and empiric doxycycline was initiated for 7 days. However, a fever of 102°F (38.9°C) was recorded overnight, which persisted despite nonrevealing culture and workups and with increased arthralgia and generalized pancytopenia (Table 1). Despite low serum complement levels (C3: 62.9 mg/dL, reference range: 90-180 mg/dL; C4: 2 mg/dL, reference range: 10-40 mg/dL), ANA and Anti-dsDNA were negative. On the 14th day of admission, a hematology-oncology team was consulted, and her ferritin level was elevated, consistently above 7500 ng/mL (reference range: 12-150 ng/mL), which was presumed to be due to an active reactive phase; bone marrow biopsy (BMB) was performed, and she was started on G-CSF injections with intermittent platelet transfusion. By this time, her fever was responsive to steroids, and analgesics were administered as needed. In the subsequent week, hypotension (BP 90/55) and tachycardia (PR 116) with a fever of 103.7°F(39.67°C) associated with rigors were documented, inciting initiation of IV cefepime and vancomycin. Bolus IV fluid was administered and home antihypertensives were put on hold. At the time, she had pancytopenia (Table 1), blood cultures were negative, CT of the abdomen and pelvis showed hepatosplenomegaly, and CT angiography revealed the absence of pulmonary embolism.

An elevation in T-cell levels was observed, raising concerns for HLH with macrophage activation syndrome, given her history of lupus, pancytopenia, and elevated ferritin levels. BM biopsy revealed hypercellular marrow (70%-80%) with left-shifted myeloid maturation, atypical erythroid maturation, megakaryocytic hyperplasia, and no increase in blasts. Histiocytic aggregates, cellular debris, and increased hemosiderin disposition were suggestive of BM injury. GMS and PAS staining showed spherules and PCR confirmed histoplasmosis. A urine antigen test for histoplasmosis initially yielded negative results, however, repeat Histoplasma antigen was positive with a value >15 ng/mL (reference: <0.2 ng/mL) for which IV Liposomal amphotericin B 250 mg every 24 h with chemotherapy containing etoposide and dexamethasone at 10 mg/m^2 daily with a taper was initiated according to the HLH-94 protocol [5]. The following day, a rapid response was called for atrial fibrillation with a rapid ventricular response (rate of 150-160). She was transferred to the ICU and started on metoprolol, diltiazem, and amiodarone drips and later transitioned to oral amiodarone. A second rapid response was called for recurrent fever 102.2°F (39°C), anemia, thrombocytopenia (Table 1), and bilateral leg pain a week later. The patient was transferred back to the ICU, and blood culture grew Staphylococcus aureus and Serratia marcescens, prompting re-initiation of IV vancomycin and cefepime. Chemotherapy was held and the patient was intubated for severe respiratory distress and transfused with packed red blood cells and platelets. Subsequently, thoracocentesis revealed Histoplasma spherules in pleural fluid, following moderate left basilar pleural effusion (Fig. 1). A left-side chest tube was placed and maintained for 5 days with a persistent output of a serous fluid negative for empyema. Furthermore, new hyperkalemia (k 6.1 mmol/L, reference: 3.5-5.0 mmol/L), and persistent acidosis (lactate 4.1 mmol/L, reference: 0.5-2.2 mmol/L) with worsening renal functions (Cr 1.7 mg/dL, reference: 0.6-1.2 mg/dL) were noted eventually requiring hemodialysis.

Table 1 – Results of complete blood count.

CBC indices	Initial	Day 5 (persistent fever)	Day 27 (hypotension)	Day 37 (second rapid response)	Day 79 (vaginal bleeding)	Unit	Reference range
WBC	**2.69**	**3.46**	**3.93**	**0.11**	10	Thousands/μL	4.31-10.16
HGB	14.2	14.1	**9.9**	**5.7**	**7.6**	g/dL	11.5-15.4
HCT	47.3	46.6	**33.3**	**17.6**	**25.8**	%	34.8-46.1
MCV	**79**	**78**	**76**	**78**	**100**	fL	80-98
MCHC	**30**	**30.3**	**29.7**	32.4	**29.5**	g/dL	31.4-37.4
RDW	**18.9**	**18.1**	**16.8**	**19.7**	**22.8**	%	11.6-15.1
PLT	**80**	**43**	**26**	**13**	**20**	Thousands/μL	149-350

CBC, complete blood count; WBC, white blood cells, HGB, hemoglobin; HCT, hematocrit, MCV, mean cell volume; MCHC, mean corpuscular hemoglobin concentration, RDW, red cell distribution width; PLT, platelet.

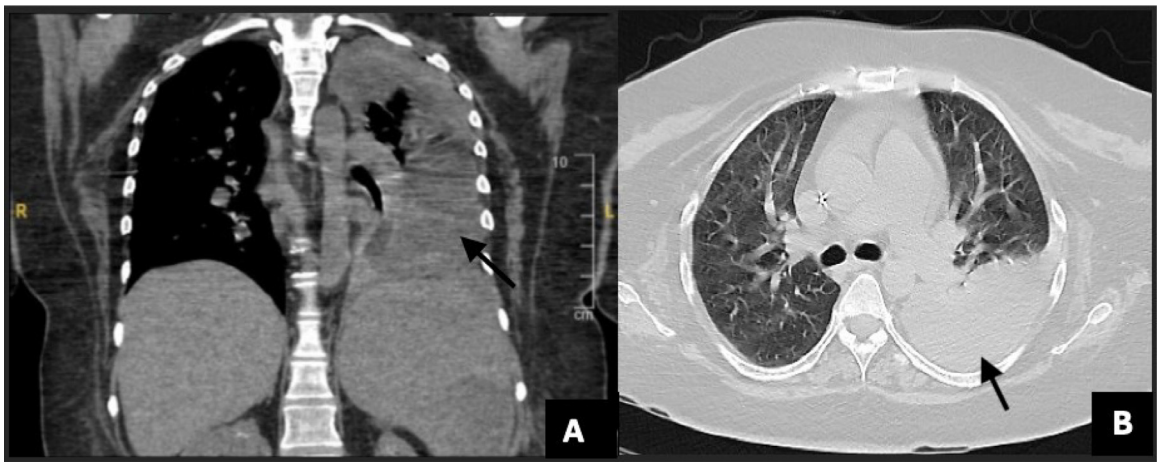

Fig. 1 – CT of the chest in coronal (A) and axial (B) views: Shows a large left pleural effusion (arrow) with adjacent compressive atelectasis. Axial view also shows several ground glass opacities in the right lung. Notable cardiomegaly is also observed.

The following week, gastroenterology (GI) consultation was sought for raised liver enzymes (Aspartate transaminase 742 U/L, reference: 10-40 U/L; alanine transaminase 196 U/L, reference: 7-56 U/L; alkaline phosphatase 1055 u/L, reference: 44-147 U/L; total protein 6.1 g/dL, reference: 6.4-8.3 g/dL; albumin 2.4 g/dL, reference: 3.5-5.0 g/dL; and total bilirubin 6.62 mg/dL, reference: 0.1-1.2 mg/dL). CT of the abdomen revealed hepatosplenomegaly with splenic infarcts (Fig. 2). Multifocal etiologies were entertained, including infiltrative processes from HLH and histoplasmosis or drug-induced liver injury from antifungals, antibiotics, amiodarone, and/or etoposide. Heparin drip was initiated, followed by Apixaban. Amid the changes in the liver enzyme tests, a recurring transition between amphotericin and itraconazole 200 mg every 8 hours has been documented. A positive anticardiolipin antibody along with new-onset vaginal bleeding and hemolysis suggested a possibility of thrombotic microangiopathy or autoimmune hemolytic anemia/thrombotic thrombocytopenic purpura as potential causes of pancytopenia (Table 1). Gynecological evaluation did not identify a specific cause. After serologic tests, including ceruloplasmin levels, and viral and autoimmune screening to rule out etiologies of hepatitis, the GI team performed a liver biopsy in the third month of admission. Pathology results from the biopsy showed histoplasmosis involving hepatocytes, portal tracts, and vessels, noncaseating granulomas, reactive bile ductular proliferation with peri cholangitis, PAS-D positive globules, and perisinusoidal and portal fibrosis. Following the liver biopsy, a decision was made to switch her antifungal medication to posaconazole 300 mg twice daily.

Follow-up and outcome

After 5 months of hospitalization, marked by severe deconditioning, proximal muscle weakness, and presumed critical illness myopathy, requiring intensive therapy for a month, the patient's symptoms gradually resolved, and she was discharged with GI, rheumatology, hematology and oncology, psychiatry, and primary care physician follow-up. She is on Eliquis for atrial fibrillation and posaconazole 300 mg twice daily, and the plan is to continue antifungal medication for a minimum of 12 months given her immune state. Subsequent urine antigen for histoplasmosis was low and was continued to be followed monthly until it remained undetectable. She continued to be on buspirone for her anxiety. Otherwise, the patient remained asymptomatic.

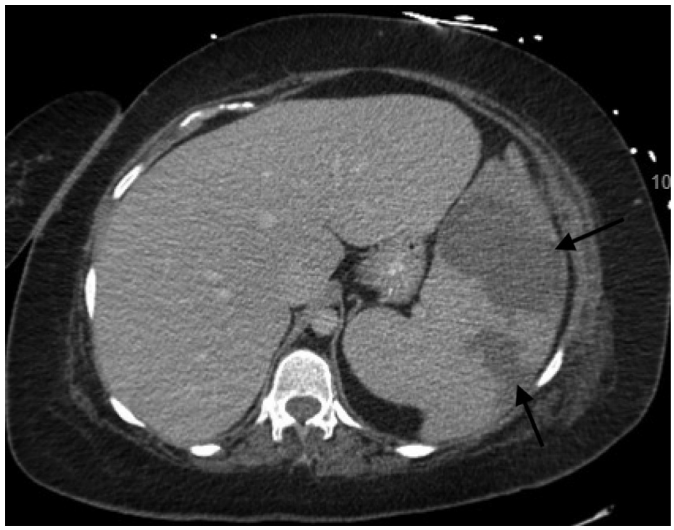

Fig. 2 – CT of the abdomen shows hepatosplenomegaly with splenic hypodense lesions (arrows).

Discussion

Histoplasmosis infection is acquired through inhalation of spores of Histoplasma fungi present in contaminated soil. Once inhaled, spores can transform into yeasts, and they can infect alveolar macrophages through phagocytosis. Cytotoxic T lymphocytes (CTL) play a crucial role in controlling this infection. Individuals with impaired CTL, such as those with SLE, HIV, and chemotherapy, have difficulty mounting an effective response against fungi, leading to the development of PDH. PDH is characterized by symptoms such as high-grade fever, fatigue, weight loss, malaise, generalized lymphadenopathy, hepatosplenomegaly, and oral ulcers. Along with GI, pulmonary, and adrenal involvement, PDH can result in deranged laboratory values, such as elevated ferritin and LDH, pancytopenia due to bone marrow involvement, elevated liver enzymes, and low albumin due to liver dysfunction. PDH can also trigger HLH, a rare but fatal complication associated with poor prognosis [3].

In patients with lupus, fever should be attributed to lupus after an exhaustive search for infection. In addition, low serum complement levels, high disease activity scores, and response to steroids favored high lupus activity in the early course of our case [6], which is in line with previous reports [4,7]. Studies have shown that there is a delay in the diagnosis of histoplasmosis in patients with lupus, averaging around 6 months [7]. While the gold standard for diagnosing histoplasmosis is to visualize the fungus in pathological examination of tissues, antigen testing from body fluids, especially urine, has a sensitivity of more than 95% and is a rapid and convenient screening and diagnostic tool. Some diagnostic tests for PDH may yield false-negative results depending on the disease stage or immune status [3]. The stepwise approach used in our case, with repeated tests following radiological and laboratory clues such as pancytopenia, elevated ferritin levels, and abnormal liver enzymes, has been proven beneficial in facilitating early detection [2,4]. This is crucial for immunocompromised individuals who fail to respond to conventional treatments like steroids [7].

HLH is a rare, potentially life-threatening syndrome characterized by exaggerated activation of T cells, leading to systemic inflammation and a cytokine storm. The secondary or acquired form of HLH can be triggered by infections (viral, bacterial, and fungal) and immune suppressants such as steroids, autoimmune disorders, and malignancies. Its clinical manifestations overlap with those of PDH, encompassing fever, weight loss, fatigue, cytopenia, raised inflammatory markers, and multiple organ involvement. Elevated ferritin levels, particularly when ranging from thousands, should raise suspicion of HLH [5,8]. Diagnosis should adhere to the HLH-2004 diagnostic criteria, of which our case displayed 5 features [9]. While the core treatment for HLH according to the HLH-94 protocol remains immune suppression via chemotherapy and steroids to address the hyperinflammatory state, secondary HLH warrants emphasis on the management of the triggering condition [5,8]. In our case, despite the observed intermittent resolution of fever, the progressive decline in her physical condition, regardless of escalation in steroid doses, shifted the clinical suspicion to histoplasmosis as the likely trigger. Consequently, antifungal therapy was initiated despite the initial absence of a positive urine antigen test, leading to gradual remission.

The decision to choose an antifungal agent for histoplasmosis should depend on the immune status of the patient, severity, and localization of the disease, and tolerance of the antifungal agent. In moderate to severe PDH in the context of immune compromise, such as in this case, the recommended first-line treatment is IV liposomal amphotericin B followed by step-down itraconazole for 12 months [10]. Although amphotericin is considered an effective antifungal agent for systemic mycosis, leading to comparably rapid clearing of fungemia, it is poorly tolerated in many patients and is associated with fever, hypotension, anemia, arrhythmias, raised liver enzymes, and liver failure, ultimately requiring dose reduction and discontinuation [11]. In the occurrence

of such adverse events, as in our case, treatment can be changed to second-line antifungals such as voriconazole and posaconazole. Fluconazole is the least preferred alternative because of its low efficacy and high relapse rate [10]. Because patients with impaired CTL are at high risk of relapse, ongoing surveillance for response to treatment, recurrence of the disease via quantified urine antigen test, monitoring for drug concentration and side effects, ensuring adherence to maintenance therapy, and addressing patients' immune state are pivotal to minimize complications and improve their quality of life [3].

Conclusion

A high level of suspicion of PDH in patients with an altered immune state due to autoimmune disorders and immunosuppressants is pivotal to facilitate early diagnosis and improve prognosis. While studies on autoimmune disorders are wide-ranging, the effects of chemotherapy, immune suppressants, and antifungals in the context of autoimmune diseases bring with them a potential area of research targeting the development of tailored therapeutic approaches. Moreover, the challenges encountered in addressing adverse effects, disease complications, and the transition between antifungals require further investigation. Given the intricate nature of such cases, a large emphasis should be placed on interdisciplinary collaboration, which is crucial in navigating challenges in diagnosis and treatment, decision-making, and better patient outcomes.

Author contributions

All authors contributed to the writing and revision of the manuscript. All authors have approved the final manuscript for submission.

Patient consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. The patient was informed that all personal information would be removed to ensure anonymity.

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