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An Immunosuppressed Woman with Diverse Symptoms and Bicytopenia

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Keywords

Syncopal episode, Urinary tract infection, Disseminated Histoplasmosis.

Introduction

A 67-year-old woman presented to the emergency department after a ground level fall due to a syncopal episode. She complained of increased weakness over the past several weeks, presyncope, and fatigue. Additional symptoms included chills, fever, abdominal pain, diarrhea, nausea, vomiting, arthralgias, and myalgias. She reported a recent urinary tract infection that continued to cause dark, strong-smelling urine, dysuria, and frequency despite treatment with Macrobid. She denied congestion, rhinorrhea, shortness of breath, chest pain, and skin changes. Her past medical history was significant for rheumatoid arthritis, for which she had been on etanercept for 6 years followed by methotrexate and adalimumab for some time. On presentation, heart rate was 85 beats per minute, and she was afebrile. Her body mass index was 20.4 kg/m^2. Physical exam showed dry mucous membranes and left CVA tenderness. Initial investigations revealed sodium of 124 mmol/L (normal, 137-145 mmol/L). Hemoglobin concentration was 9.3 g/dL (normal, 12.4-15.2 g/dL), mean corpuscular volume 88.2 fL (normal, 80.0-100.0 fL), hematocrit 27.6% (normal, 36.0-46.0%), platelet count 134 K/uL (normal, 150-450 K/uL), and red blood cell count 3.13 M/uL (normal, 3.90-5.10 M/uL). White blood cell count was normal. The patient was admitted to the hospital for management of hyponatremia. Subsequent investigations revealed iron level of 21 ug/dL (normal, 37-170 ug/dL), ferritin of 3,120 ng/mL (normal, 11.1-264.0 ng/mL), and normal TIBC and fibrinogen. Platelet count trended downward over the next couple of days reaching a low of 50 K/uL. Additional pertinent laboratory studies revealed triglyceride level to be 234 mg/dL (normal, 0-149 mg/dL), D-Dimer 1,950 ng/mL (normal, 0-230 ng/mL), C-Reactive Protein 76.8 mg/L (normal, 1.0-10.0 mg/L), absolute CD4+ cell count 418 cells/ul (normal, 575-1,070 cells/ul), kappa free light chain 53.25 mg/L (normal, 3.30-19.40 mg/L), lambda free light chain 75.81 mg/L (normal, 5.71-26.30 mg/L), and beta-2 microglobulin 9.7 mg/L (normal, <=3.0 mg/L). Immunoglobulin levels were normal. Computed tomography scans showed significant findings in the duodenum (Figure 1) and spleen (Figure 2). Bone marrow biopsy revealed a key finding for diagnosis (Figure 3).

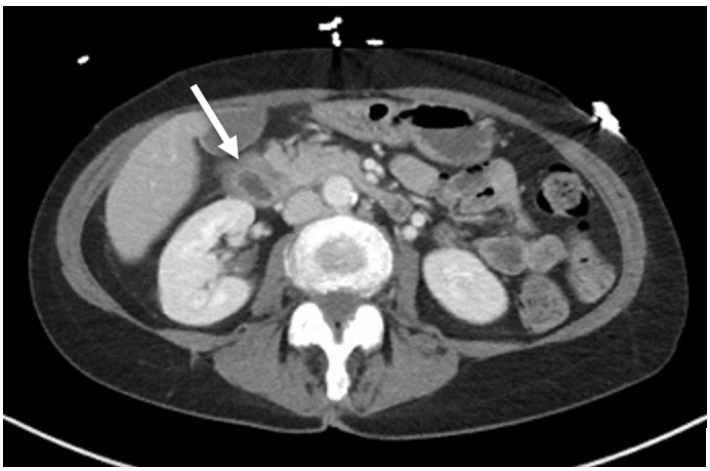

Figure 1: CT scan of the abdomen and pelvis showing mild thickening of the proximal duodenum and minimal adjacent fatty stranding suggestive of duodenitis.

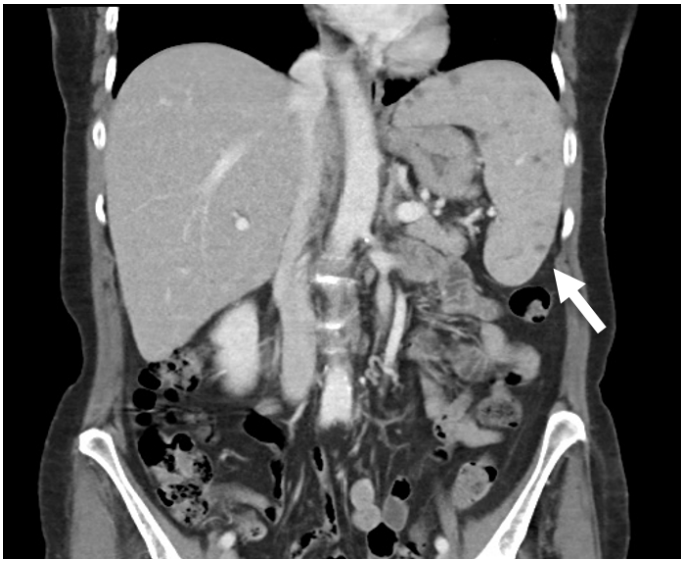

Figure 2: CT scan of the abdomen showing a mildly enlarged spleen containing several hypodense probable complex cysts or hemangiomas.

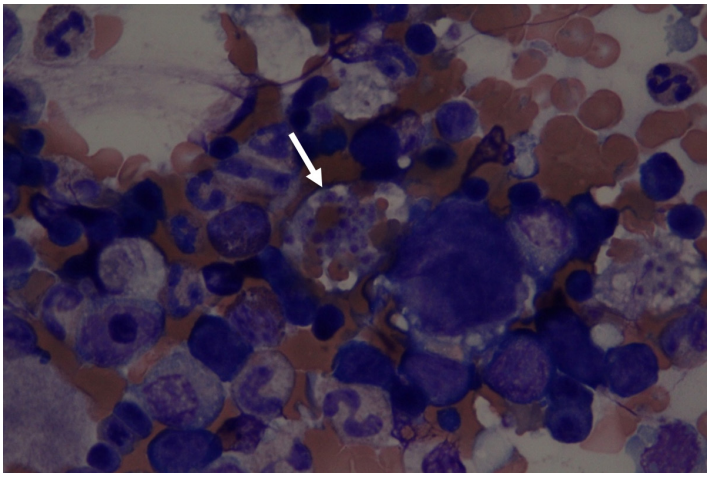

Figure 3: Bone marrow biopsy with findings that led to diagnosis.

Diagnosis: Disseminated Histoplasmosis

The patient was diagnosed with disseminated histoplasmosis. Although the presence of bicytopenia with normocytic anemia and thrombocytopenia in the setting of Rheumatoid Arthritis raised concerns for Hemophagocytic Lymphohistiocytosis (HLH), bone marrow biopsy revealed non-necrotizing granulomas with yeast forms consistent with Histoplasmosis. The bone marrow biopsy additionally revealed hypercellular marrow for patient age with mildly increased erythroid precursors and mildly increased megakaryocytes with mild atypia, which were favored to be reactive. Morphologic evidence of HLH was not seen.

Upon further workup, Fungitell test was greater than 500 pg/mL, fungal cultures grew *Histoplasma capsulatum*, antibodies against Histoplasma were detected, and Histoplasma antigen was detected in both urine and serum. It was also discovered that the patient maintains a chicken coop at home. The patient was started on liposomal amphotericin B (Ambisome) at 3mg/kg every 24 hours. Before and after each infusion of Ambisome, she was given a bolus of saline. She remained on IV Ambisome for one week after which she was switched to oral itraconazole therapy because of elevated liver transaminases. She started at 200 mg itraconazole 3 times/day for 3 days followed by 200 mg 2 times/day for one year. After one year, she will continue oral itraconazole 200 mg once daily for prophylaxis in case she continues to be on immunosuppressive medications for rheumatoid arthritis.

Histoplasma capsulatum is a dimorphic fungus found in bat and bird droppings throughout the United States [1], but especially in the Mississippi and Ohio River Valley regions where it is estimated that 60-90% of people have been exposed [2]. It infects human hosts through inhalation of aerosolized microconidia. Once inside the host, microconidia convert to the yeast form inside macrophages. Activated macrophages and CD4 T lymphocytes produce IFN-γ to induce granuloma formation and wall-off infection. Immunosuppressants such as TNF-blockers, methotrexate, and glucocorticoids can increase the risk of disseminated histoplasmosis. Pulmonary symptoms such as cough, shortness of breath, and chest pain are common, and radiology findings may include pulmonary nodules or lesions and mediastinal and hilar lymphadenopathy. Gastrointestinal and central nervous system involvement is less common but can be seen in disseminated infections. Immunocompromised patients are more likely to suffer from progressive disseminated histoplasmosis. Disseminated infection may present with fever, lymphadenopathy, hepatosplenomegaly, pancytopenia, transaminitis, and elevated lactate dehydrogenase. Cytology shows ovoid intracellular yeasts with narrow-based budding visualized on PAS or GMS stain [3]. Urine antigen testing is the most sensitive and rapid method of detection although the gold standard is a fungal culture that may take several weeks [4]. Treatment varies based on severity [3]. For a case of severe disseminated histoplasmosis such as this one, treatment consists of 1-2 weeks of IV liposomal Amphotericin B followed by oral itraconazole 200 mg three times a day for three days and then two times a day for at least one year [1].

Disseminated histoplasmosis can present similarly to HLH, which is a serious and often fatal condition associated with neoplastic, infectious, and autoimmune diseases [5]. It consists of widespread multiorgan inflammation due to deficient NK cells that allow prolonged activation of antigen presenting cells and CD8+ T cells that release excessive cytokines [6]. It is often undiagnosed and should be considered for patients with unexplained fevers and cytopenia. Several infections are associated with HLH including viral, bacterial, and fungal organisms, most notably *Histoplasma*

capsulatum. Bone marrow biopsy reveals accumulation of lymphocytes and macrophages that may demonstrate hemophagocytosis. HLH can be diagnosed by five out of eight criteria: fever; splenomegaly; cytopenias affecting at least 2 of 3 lineages in the peripheral blood; hyperferritinemia greater than 10,000 μg/L; hypertriglyceridemia and/or hypofibrinogenemia; hemophagocytosis in the bone marrow, spleen, or lymph nodes; low or absent NK-cell activity; and high levels of soluble CD25 [5].

There have been several cases where patients met the diagnostic criteria for HLH and were found to have disseminated histoplasmosis [4,6-8]. Three of these cases are reported on patients who were taking immunosuppressants for rheumatoid arthritis and presented with vague symptoms including fever, fatigue, and upper respiratory symptoms [4,6,7]. One case was reported in an immunocompetent patient [8].

This case shows that disseminated histoplasmosis may present with vague symptoms and lab results resembling HLH. Exposure history may be key to diagnosis as in this patient who maintained a chicken coop. Delayed diagnosis may increase mortality, morbidity, and length of hospitalization. A high index of suspicion should be maintained in immunosuppressed patients presenting with unexplained fever and fatigue who reside in or have recently traveled to the Mississippi and Ohio River Valley regions.

References

1. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007 Update by the Infectious Diseases Society of America. CID. 2007; 45: 807-825.
2. Centers for Disease Control and Prevention. Histoplasma Statistics, US Department of Health and Human Services. 2020. https://www.cdc.gov/fungal/diseases/histoplasmosis/statistics.html
3. Araúz AB, Papineni P. Histoplasmosis. Infect Dis Clin North Am. 2021; 35: 471-491.
4. Swaminathan N, Vinicius JM, Serrins J. Hemophagocytic Lymphohistiocytosis (HLH) in a Patient with Disseminated Histoplasmosis. Case Rep Hematol. 2020.
5. Rosado FG, Kim AS. Hemophagocytic Lymphohistiocytosis: An Update on Diagnosis and Pathogenesis. Am J Clin Pathol. 2013; 139: 713-727.
6. Suman S, Lenert A. Diagnostic Dilemma of Disseminated Histoplasmosis Mimicking Hemophagocytosis Lympho-histiocytosis in Patient with Rheumatoid Arthritis on Anti-TNF Therapy: Case Report and Review of the Literature. Case Reports in Rheumatology. 2019.
7. Hofmann E, Mühlethaler K, Pollak M, et al. Travel related histoplasmosis – a diagnostic challenge in a patient with tumor necrosis factor alpha (TNF-α) inhibitor therapy. Trop Dis Travel Med Vaccines. 2022; 8: 21.
8. Chen H, Yuan Q, Hu H, et al. Hemophagocytic Lympho-histiocytosis Secondary to Disseminated Histoplasmosis in HIV Seronegative Patients: A Case Report and Review of the Literature. Front Cell Infect Microbiol. 2022; 12.