

Acute Liver Failure and Fever of Unknown Origin

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We describe a case of acute liver failure in a woman in whom a diagnosis was initially unable to be established. The patient rapidly deteriorated, requiring admission to the intensive care unit, and was placed under consideration for liver transplantation. On consultation with the infectious disease service, thorough history taking was performed that uncovered salient epidemiologic information pointing toward the eventual diagnosis of disseminated histoplasmosis. We discuss aspects of diagnosis and management, including the management of immune reconstitution syndrome which complicated treatment.

Keywords. histoplasmosis; immune deficiency; immune reconstitution syndrome; TNF- α inhibitor.

CASE REPORT

A 70-year-old woman presented to her primary care doctor for 2 weeks of diarrhea, generalized malaise, worsening fatigue, and decreased appetite. For several months before this, she experienced fatigue, night sweats, intermittent diarrhea, and unintentional weight loss. She denied oral ulcerations, cough, or new rashes. She was jaundiced on evaluation. Laboratory work revealed deranged liver chemistries in a cholestatic pattern. She was referred to the emergency room for concern for potential acute liver failure.

On presentation to the emergency room, the patient's temperature was 38.7°C (101.7°F), she was tachycardic to 104 beats per minute, blood pressure was 100/56 mm Hg, respiratory rate was 20 breaths per minute, and her oxygen saturation was 94% on ambient air. She was somnolent and confused during the examination, with grade 3 encephalopathy by West Haven criteria. She was jaundiced with scleral and integumentary icterus. Her abdomen was distended with a positive fluid wave, though soft. She had right upper quadrant abdominal tenderness and palpable hepatosplenomegaly. Asterixis was absent.

The patient's medical history was remarkable for psoriatic arthritis. For treatment of her psoriasis, she received monthly infliximab infusions. She was not receiving other

immunosuppressing medications. Her medications also included over-the-counter acetaminophen and naproxen, as well as numerous herbal supplements. She was not receiving anticoagulants.

Her complete blood count showed a white blood cell count of 8.19 K/ μ L (reference range: 4.00–11.00 K/ μ L). Liver chemistries were deranged with a total bilirubin of 10.9 mg/dL (reference range: 0.0–1.2 mg/dL), direct bilirubin of 8.0 mg/dL (reference range: 0.1–0.5 mg/dL), alanine aminotransferase to 65 IU/L (reference range: 4–35 IU/L), aspartate aminotransferase to 181 IU/L (reference range: 11–40 IU/L) and alkaline phosphatase to 509 IU/L (reference range: 30–115 IU/L). Her coagulation studies were also abnormal, with an international normalized ratio of 1.9 (reference range: <1.3). C-reactive protein was 62 mg/L (reference range: <5 mg/L). Ferritin was 10 142 ng/mL (reference range: 30–202 ng/mL). Albumin was 2.1 g/dL (reference range: 3.2–5.4 g/dL). Acetaminophen level was <10 μ g/mL (reference range: 10–30 μ g/mL). Anti-smooth muscle antibody was 72 U (reference range: <20 U) and antinuclear antibodies were positive (reference range: negative).

She underwent magnetic resonance cholangiopancreatography, which revealed a mild, diffuse T2 hyperintense signal throughout the liver with periportal and gallbladder wall edema, concerning for acute hepatitis. There were no visualized focal liver lesions nor any evidence of biliary ductal dilation. There were no noted bile plugs nor evidence of duct paucity. A computed tomography scan of the abdomen and pelvis with intravenous contrast additionally showed numerous splenic lesions with associated splenomegaly (Figure 1).

A liver biopsy demonstrated severe portal and pan-lobular inflammation, as well as balloon degeneration, bridging necrosis, and confluent necrosis involving 40% of the sample, as well as infiltrates with predominantly lymphocytes, some plasma cells, neutrophils, and scattered eosinophils.

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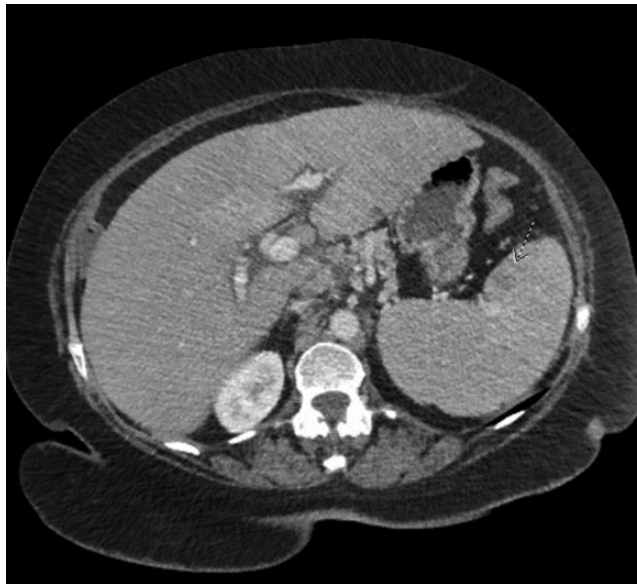


Figure 1. Contrast-enhanced computed tomography scan of the abdomen and pelvis. Numerous hypointense splenic lesions with associated splenomegaly.

She continued to deteriorate, becoming increasingly more encephalopathic, requiring transfer to the intensive care unit. She continued to experience daily fevers as high as 40.4°C (104.7°F). Due to worsening liver synthetic function she was evaluated for liver transplantation, at which time infectious diseases was consulted for pretransplant evaluation. Additional epidemiologic history was obtained on infectious disease consultation. She was born and raised in New England, United States. She had a declawed pet kitten at home. She had worked as a housewife all her adult life. The patient reported regular use of marijuana and denied alcohol or tobacco use. Her travel history included internationally to Mexico, 5 years prior to presentation. Domestically, travel history included to various states including New York, Pennsylvania, Indiana, Ohio, Minnesota,

California, Virginia, and North Carolina. Several months prior to presentation, she went on a road trip for 3 weeks down the Eastern seaboard, stopping at North Carolina and Virginia, then traveling inland up to Ohio to visit relatives.

Additional laboratory investigations were requested. Hepatitis A immunoglobulin M (IgM) was negative and immunoglobulin G (IgG) was positive. Hepatitis B surface antibody, surface antigen, and core IgG and IgM antibodies were nonreactive. Hepatitis C antibody was nonreactive. Herpes simplex virus 1 and 2 serum IgG and viral polymerase chain reaction (PCR) were negative. Varicella zoster serum IgG was positive and serum PCR was negative. Epstein-Barr virus IgG was positive, and serum PCR was negative. CMV IgG was positive and PCR was negative.

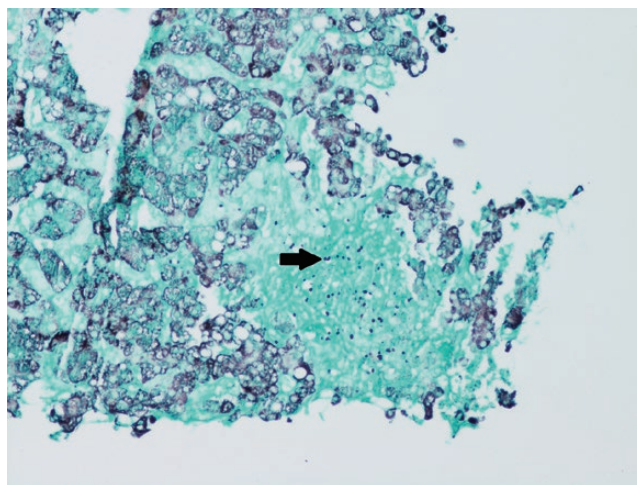


Figure 2. Grocott methenamine silver–stained liver biopsy specimen, 200× magnification. Multiple *Histoplasma* yeast forms are present (arrow).

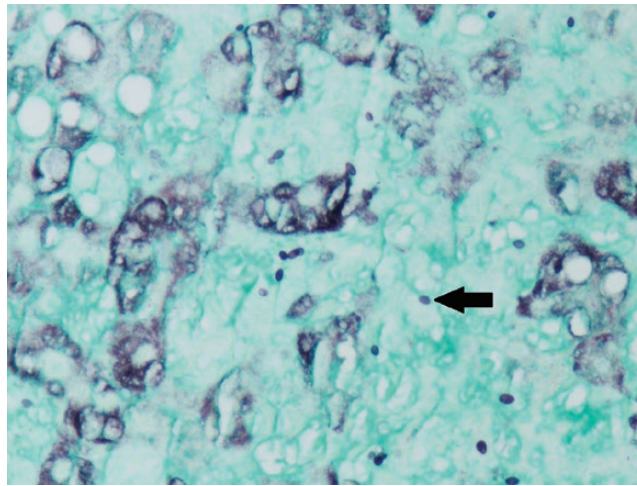


Figure 3. Grocott methenamine silver–stained liver biopsy specimen, 400× magnification. Multiple *Histoplasma* yeast forms are present (arrow).

With her history of infliximab use, recent travel history, several months of preceding symptoms including diarrhea, and subtle splenic changes noted on imaging, endemic fungal etiologies were considered. Periodic acid–Schiff (PAS) and Grocott methenamine silver stains were recommended to be performed on the liver biopsy specimen, which returned positive for many fungal yeast elements (Figure 2 and Figure 3).

Serum β -D-glucan was recommended, which returned strongly positive at >500 pg/mL (reference range: negative). *Histoplasma* urinary antigen returned positive at >20 ng/mL (reference range: undetectable).

Fungal isolator blood cultures were obtained thereafter, which returned positive for *Histoplasma capsulatum*.

To further assess the extent of disease severity and guide treatment agents and duration, she underwent a lumbar puncture due to her lethargy and confusion. While there was no cerebrospinal fluid (CSF) pleocytosis, yeast forms consistent with *Histoplasma* were visualized on culture, consistent with central nervous system (CNS) involvement. *Histoplasma* antigen levels on CSF returned positive, below the limits of quantification (reference range: undetectable).

The patient was started on combined intravenous liposomal amphotericin B as well as intravenous voriconazole. Her fevers resolved, and she had rapid improvement of mental status. She continued amphotericin B and transitioned to oral voriconazole; however, due to gastrointestinal side effects of voriconazole, she switched to itraconazole solution.

After 2 weeks of therapy, her fevers returned. Repeat computed tomography of her chest, abdomen, and pelvis noted increased thoracic lymphadenopathy without other focal infectious findings. The timing of fever onset, 8 weeks after cessation of her immunomodulator therapy, in the setting of improving disseminated disease, raised clinical concern

for immune reconstitution syndrome (IRIS). She initiated treatment with systemic corticosteroids with rapid improvement. She completed a total 6 weeks of combined intravenous amphotericin B and oral itraconazole, then switched to itraconazole alone with a plan for 1 additional year of treatment thereafter. The patient showed remarkable clinical improvement, and at 9-month follow-up was completely symptom free and had returned to all prior activities. She had followed with her rheumatologist, and decision was made not to resume infliximab.

DISCUSSION

Histoplasma capsulatum is a dimorphic fungus, a member of the Ascomycetes family. It is found in 2 phases, the mycelial and yeast phases. At temperatures of $\geq 37^{\circ}\text{C}$, the yeast phase is activated, which has increased infectivity [1]. *Histoplasma* is usually found in soil, as well as in guano of birds and bats. It is endemic in various parts of the United States, particularly within the central and eastern states, especially the Mississippi and Ohio River valleys.

Histoplasma conidia are usually taken up via the inhaled route. Conidia are inhaled and deposited into alveoli where they are endocytosed by resident alveolar macrophages and neutrophils. These conidia transform into yeast phase in the lungs, and then migrate and disseminate intracellularly via lymphatic drainage into lymphoid-rich organs such as the liver and spleen.

Histoplasmosis can remain dormant and reactivate from an endogenous focus [1]. For this reason, in evaluation of a patient with suspected histoplasmosis, it is important to obtain a detailed travel history that includes even remote travel. Review of our patient's prior travel uncovered visits to endemic regions that may have been potential places of the initial inoculating event.

Disseminated histoplasmosis can occur in patients with underlying immunocompromising conditions. In the case of our patient, her primary risk factor was exposure to the tumor necrosis factor alpha (TNF- α) inhibitor infliximab, leading to impaired cellular immunity, the primary host defense against *Histoplasma capsulatum* [2]. The US Food and Drug Administration has issued a black box warning stating that infliximab increases the risk for opportunistic infections, including invasive fungal diseases [14]. Histoplasmosis occurs in as many as 18.78 of 100 000 people treated with infliximab [3].

Laboratory derangements typical of disseminated histoplasmosis include signs of bone marrow suppression with cytopenia of multiple lines [5]. Patients may also have markedly elevated lactate dehydrogenase and ferritin levels. With liver involvement, there may be elevated liver enzymes with varying patterns of elevation, commonly cholestatic with an elevated alkaline phosphatase [5, 6].

Histopathology of involved organs usually reveals formation of granulomas in deposited tissues [4]. Notably in our case, liver biopsy did not show visible granulomas. Only specific fungal staining delineated invasive disease when added later. This led to a delay in diagnosis—pathology supported necrotizing hepatitis initially attributed to hepatotoxins from ingesting numerous herbal supplements.

Most cases of hepatic histoplasmosis in the literature report the finding of granulomas on liver biopsy [4, 6, 10–12]. However, a retrospective study performed by Lamps et al found that while portal lymphohistiocytic inflammation was common in hepatic specimens, granulomas were found in only 20% of patients discovered to have *Histoplasma* hepatitis [13]. For this reason, even in the absence of granulomas, it is salient to perform fungal staining on pathologic samples when investigating liver failure of uncertain etiology.

In addition to tissue diagnosis, *Histoplasma* urinary antigen is a useful diagnostic tool. Antigen levels correlate with severity of disease and can be utilized to follow the clinical course [3]. Serum *Histoplasma* antigen, by contrast, has poor correlation with disease severity [3].

There is often a delay in diagnosis of CNS histoplasmosis, usually due to a low index of suspicion [9]. Classically, the CSF profile will show a lymphocytic pleocytosis; however, this is only present in approximately 50% of cases. Furthermore, CSF glucose and protein levels are often within normal limits [9]. Diagnosis can be made with positive CSF *Histoplasma* antigen levels, as well as positive CSF *Histoplasma* antibodies [9]. Furthermore, CSF fungal cultures may also directly isolate the organism. Imaging via computed tomography or magnetic resonance imaging may occasionally reveal mass lesions [9].

The treatment for disseminated histoplasmosis, including with CNS involvement, involves initial therapy with

amphotericin B for 4–6 weeks followed by 1 year of oral itraconazole. With disseminated disease not involving the CNS, intravenous amphotericin B is usually given for up to 2 weeks before de-escalating to oral therapy [7]. It is recommended to check itraconazole levels during treatment to ensure they reach therapeutic range [7]. We opted to overlap treatment of amphotericin and itraconazole to ensure maintenance of therapeutic itraconazole levels prior to transitioning to monotherapy; however, there are no specific data to support this practice, and thus we do not specifically recommend it.

In cases of CNS histoplasmosis, it is recommended to ensure undetectable CSF antigen levels and resolution of all CSF derangements prior to discontinuing itraconazole therapy [7]. For all cases of histoplasmosis, it is recommended to follow urine *Histoplasma* antigen levels for at least 1 year after completion of itraconazole therapy to monitor for signs of relapse. Low-level urinary antigen level alone is not reason to continue therapy [7].

Generally, TNF- α inhibitor therapy is discontinued on diagnosis of histoplasmosis. However, as in the case of our patient, this may increase risk for paradoxical IRIS. There is controversy regarding the ideal management of immunosuppression in this setting, as TNF- α inhibitors can serve as treatment for paradoxical IRIS. There are case reports describing successful combinations of antifungal therapy with continuation of TNF- α blocker therapy [8]. In cases where TNF- α inhibitor therapy is elected to be discontinued, IRIS is usually responsive to corticosteroid therapy [8].

There are no specific guidelines regarding the safest timing for reintroduction of TNF- α blocker therapy after completing therapy for histoplasmosis. In a case series involving 98 patients, 24 of 25 patients safely resumed TNF- α blocker therapy after 12 months of azole treatment *and* resolution of clinical disease [3].

This case illustrates the importance of considering epidemiologic exposures and host factors such as underlying immunodeficiencies to generate an infectious disease differential in patients with acute liver failure. Though the patient's liver biopsy did not show evidence of granulomas that would typically point toward a fungal pathogen, we considered her relevant epidemiologic exposures to direct diagnostic techniques including serologic testing, pathologic special stains, and standard microbiologic diagnostic methods to define the etiology, extent, and severity of disease and guide appropriate management.

Notes

Patient consent statement. Written informed consent was obtained from the patient for publication of this case report and all accompanying images.

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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