

## Case report

# Cave diving for a diagnosis: Disseminated histoplasmosis in the immunocompromised

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## ABSTRACT

Tumor necrosis factor (TNF) inhibitors are widely used in the treatment of inflammatory conditions and are associated with risks of invasive infections. We present a diagnostically challenging patient with unique comorbidities and travel history. A 53-year-old man with a history of polysubstance abuse and psoriasis on adalimumab presented to our hospital directly from the airport with fever, dyspnea, and cough. He had been living in Costa Rica and engaged in many outdoor activities. Within 6 h and a limited history, he was intubated; vasopressors and antimicrobials were promptly administered. An extensive infectious disease investigation was undertaken, considering potential travel-related exposures and his immunosuppressive state. However, multi-organ failure with worsening disseminated intravascular coagulation ensued, and within four days of admission, the patient passed away. Five days after his death, the urine *Histoplasma* antigen resulted positive. Disseminated histoplasmosis should be suspected in a patient on anti-TNF therapy, with a severe febrile illness and pneumonia refractory to antibacterial therapy. A high index of suspicion is necessary to make the diagnosis and initiate prompt treatment.

## Case

A 53-year-old man with a history of psoriatic arthritis, chronic back pain, and polysubstance abuse presented to our hospital directly from the airport with progressive fever, dyspnea, and cough. Within 6 h of admission, the patient was intubated; vasopressors, vancomycin, and zosyn were promptly administered.

He had been living in Costa Rica for the past few years. Three months prior to presentation, he was arrested and admitted to a substance detoxification facility. One month prior to presentation, he was treated with levofloxacin for “pneumonia.” Routine bloodwork was remarkable for thrombocytopenia. Thereafter, he developed progressive dyspnea, cough, malaise, fevers, and night sweats prompting his return to the U.S.

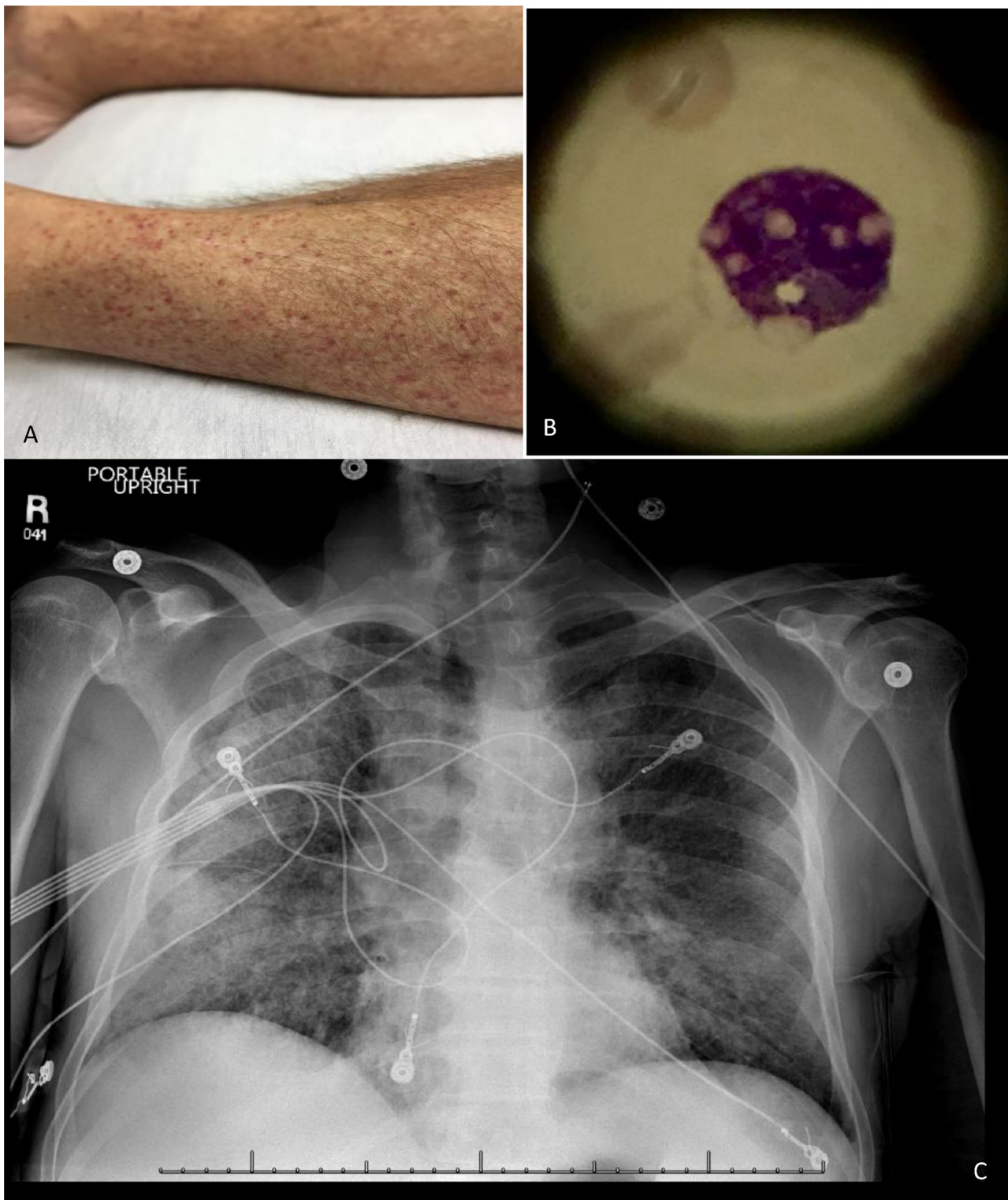
Given his rapid decompensation, further history was obtained from chart review and family members. He suffered from chronic back pain after an occupational injury. Subsequently, he developed mood and substance abuse disorders. For psoriatic arthritis, he was on adalimumab and methotrexate, which he continued in Costa Rica. While there, he became involved with the illicit drug trade, often traveled by boat and actively pursued inexpensive fentanyl patches among other opiates and benzodiazepines throughout the region.

On physical examination, he was febrile (101.8 °F), tachycardic (120 beats per minute), hypotensive (99/61 mmHg), tachypneic (30 breaths per minute), and hypoxic with 80% oxygen saturation on room air. He was diaphoretic and distressed. Mild scleral icterus and non-blanching petechiae on his lower extremities and torso were present (Fig. 1A). The abdomen was diffusely tender to palpation with hepatosplenomegaly. The remaining physical exam was unremarkable. He was evaluated by the Infectious Disease service and intravenous doxycycline was added given the risk for leptospirosis, rickettsial infections, and Q fever.

Urine drug screen was negative. Respiratory viral panel PCR, Influenza A, B and H1N1, Streptococcal pneumonia and Legionella urine antigens, as well as HIV antigen/antibody screen and viral load, were all negative. Blood and urine cultures were negative. Chikungunya and Zika PCR were negative. Coxiella, Rickettsia, *Histoplasma* urine antigen and *Leptospira* serology were collected as send-out tests. Dengue PCR was consistently negative on serial checks. Malaria antigen test was weakly positive. Quantiferon test returned unequivocal. Three sputum AFB smears and cultures were negative.

The initial blood smear was negative for malaria but revealed possible intracellular yeast without any characteristic morphology; Micafungin was added (Fig. 1B). This was not seen on subsequent

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**Fig. 1.** A: Non-blanching petechia on lower extremities: The *clinical exam within hours of admission*. B: Peripheral Blood Smear: A phagocytic histiocyte engulfing Histoplasma yeast on day 3. C: Chest radiograph on admission: Bilateral ground glass reticulo-nodular infiltrates that eventually progressed to acute respiratory distress syndrome.

smears. Hepatitis A IgM resulted positive (IgG was negative). Abdominal imaging revealed hepatosplenomegaly and biliary sludge. Serial chest radiography revealed worsening diffuse bilateral alveolar infiltrates (Fig. 1C). Given worsening bilateral alveolar infiltrates (Fig. 1C), ARDS protocol was initiated.

His condition continued to worsen over the next few days. Multi-

organ failure with worsening disseminated intravascular coagulation (DIC) ensued. He received serial transfusions of platelets, plasma, cryoprecipitate, and red blood cells in the setting of DIC. He continued to deteriorate despite the escalation of vasopressors. Family members later confirmed the patient's exotic lifestyle included recreational cave diving and spelunking. He passed away 4 days into his hospital course.

A few days after his death, dengue and all other serology was confirmed negative, *Leptospira* IgM was equivocal and the urine *Histoplasma* antigen returned positive at greater than 25 ng/ml, indicating a diagnosis of disseminated histoplasmosis, as suggested by the initial blood smear.

## Discussion

The clinical syndrome of histoplasmosis usually begins with low-grade fevers and cough and is easily mistaken for community-acquired pneumonia [1–3]. When limited to the lungs, pulmonary histoplasmosis can be non-specific both clinically and on imaging. Lung tissue biopsy and respiratory cultures may show visible *Histoplasma* within histiocytes on hematoxylin and eosin stain (Fig. 1B) [2,4]. Positive urine and serum antigens meet diagnostic criteria; biopsy is not required in such cases. The urine antigen is often detected at higher concentrations in immunocompromised patients with severe disseminated disease [5]. Unfortunately, not all institutions offer these assays and results can be delayed several days [3]. Therefore, a high index of suspicion is necessary for prompt diagnosis and management. This case was further complicated by a broad differential diagnosis of fever in a traveler.

Because of scleral icterus, abdominal pain, and rash with shock, multi-organ failure, thrombocytopenia, coagulation abnormalities, and transaminase elevations, both dengue hemorrhagic fever and leptospirosis (Weil's disease) were high on the differential diagnosis. Though the endemic burden is low, severe malaria was also considered a possibility, especially when the malaria antigen test returned weakly positive early in the hospital course [6]. Several thick and thin smears, which were all negative, confirmed the absence of malaria.

With a history of autoimmune disease, he likely had the autoantibody called Rheumatoid Factor (RF) which led to a false positive malaria antigen test [7]. Similar to how RF binds to IgG molecules, it weakly binds to the trapping antibody of the malaria testing strip [8]. Another confounder was a positive Hepatitis A IgM test in the setting of elevated transaminases and liver failure, though the patient's presentation was not characteristic of fulminant hepatitis.

Given the context of possible substance abuse and homelessness, disseminated tuberculosis was considered as well. It is clinically difficult to distinguish between disseminated infections of histoplasmosis and tuberculosis given the initial symptoms, pulmonary involvement (cavitation and infiltration) and progression to pancytopenia and transaminitis [3]. Studies have suggested that tuberculosis presents less frequently than histoplasmosis in the setting of Tumor Necrosis Factor (TNF) inhibitors [9].

Histoplasmosis can become life-threatening (20% mortality) when it presents as an opportunistic infection in patients receiving anti-TNF therapy [10]. Adalimumab is a monoclonal antibody that inhibits TNF, a cytokine involved in the pathogenesis of many inflammatory disease states including the activation of macrophages [11]. Consequently, the patient's phagocytic macrophages were unable to eliminate the yeast or create a barrier of granulomas to prevent spreading via the lymphatic system [3]. Lungs are uniquely susceptible to the immunosuppression of anti-TNF therapy because alveolar macrophages are more affected than peripheral monocytes [12].

Several studies have demonstrated patients from endemic regions, with evidence of past histoplasmosis, largely did not develop histoplasmosis despite undergoing varying immunocompromising regimens: chemotherapy, anti-TNF therapy, or transplant therapy [10]. Therefore, we conclude this patient likely suffered a primary infection rather than a reactivation.

## Conclusion

This case emphasizes the importance of a high index of suspicion in the diagnosis and management of a severely ill patient on TNF blockers. The patient's history of travel and substance abuse confounded the diagnosis. Since there was limited history due to the rapid respiratory collapse, an extensive infectious evaluation was performed to account for fever in the returning traveler. Prompt administration of anti-fungal therapy targeted at disseminated histoplasmosis, such as liposomal amphotericin b, may or may not have altered the course of this patient's illness. Travel associated infections that can present in a similar fashion as well as false-positives from confirmatory lab testing, unfortunately, delayed the diagnosis beyond the patient's prognosis. The history of anti-TNF immunosuppression was key to the diagnosis of this opportunistic infection.

## Conflicts of interest statement

We have no financial or personal relationships to disclose.

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