CASE IN POINT

Masquerading as Metastatic Carcinoma: A Diagnostic Challenge

Elaine M. Peplow, MD[a]

Background: Histoplasmosis and metastatic disease frequently share overlapping clinical features. It is important for clinicians to distinguish between these disease processes, as their treatment and prognosis significantly differ. The diagnostic challenge arises from overlapping imaging findings and nonspecific clinical symptoms.
Case Presentation: A 55-year-old male with a 35 pack-year smoking history presented with weight loss, drenching night sweats, and abdominal pain. Imaging revealed extensive peripancreatic, retroperitoneal, and pelvic lymphadenopathy, alongside a hypermetabolic 2.3-cm right lower lobe pulmonary nodule. Despite a high suspicion of metastatic cancer, initial esophagogastroduodenoscopy, colonoscopy, and endobronchial ultrasound-guided transbronchial needle aspiration were nondiagnostic. All fungal serologies and urine antigens were negative. A definitive diagnosis of necrotizing granulomatous inflammation consistent with *Histoplasma* was finally achieved following a surgical wedge resection. The patient showed clinical improvement following treatment with itraconazole 200 mg twice daily.
Conclusions: This case highlights the distinguishing features of histoplasmosis and metastatic disease, guiding clinicians toward accurate diagnosis and appropriate management, and ultimately improving patient outcomes.

CASE PRESENTATION

A 55-year-old White male Gulf War Marine veteran with a history of irritable bowel syndrome, chronic low back pain, anxiety, posttraumatic stress disorder (PTSD), and a 35 pack-year smoking history presented to the Edward Hines, Jr. Veterans Affairs Hospital primary care clinic with moderate abdominal pain for 1 week and altered bowel habits for several months. He reported mainly having diarrhea and more bloating than usual. The patient stated that he had experienced progressive fatigue over the past 6 months, along with new drenching night sweats and chills. He reported a 20-lb unintentional weight loss over the past 6 months. The patient noted no substance use or changes to his diet or exercise pattern. He had previously served in the US Marine Corps and was deployed to Okinawa, Camp Lejeune, Iraq, and Honduras during his 10-year military career.

This patient's initial abdominal computed tomography (CT) revealed multiple prominent lymph nodes in the peripancreatic, periportal, retroperitoneal, bilateral iliac, and inguinal regions. Due to substantial lymphadenopathy and gastrointestinal complaints, he was evaluated by gastroenterology and underwent both esophagogastroduodenoscopy and colonoscopy. Results were notable for gastric mucosal inflammation and intestinal metaplasia, as well as tubular adenomas throughout the colon; however, there was no evidence of mass lesions.

Due to ongoing systemic symptoms of unknown etiology, the patient underwent CT of the chest, revealing a 2.3-cm right lower lobe (RLL) pulmonary mass with right hilar lymphadenopathy. A positron emission tomography (PET) demonstrated hypermetabolic activity in the RLL nodule (standardized uptake value [SUV], 3.1) and adjacent lymph nodes (SUV, ≤ 5.8).

The patient was told that he likely had metastatic disease and was referred to the Hematology-Oncology service. He reported increased anxiety and insomnia. He also was referred to the Mental Health service, which started him on escitalopram 10 mg daily and hydroxyzine 25 mg daily as needed, and recommended therapy.

The Pulmonology service performed an endobronchial ultrasound (EBUS)-guided biopsy of mediastinal lymph nodes and the RLL nodule. Pathologic examination yielded necrotic debris and benign lymphoid tissue. All cultures and stains for fungal, mycobacterial, and bacterial organisms were negative.

The patient then underwent thoracic surgery for diagnostic wedge resection of the RLL. Histopathology revealed necrotizing granulomatous inflammation with fungal organisms morphologically consistent with *Histoplasma*. All microbiologic cultures remained negative. The patient's urine and serum histoplasma antigen, serum cryptococcal antigen, β-D-glucan, QuantiFERON-TB Gold, and blastomycosis tests

Author affiliations can be found at the end of this article.
Correspondence: Elaine Peplow (elaine.peplow@va.gov)

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were negative. The patient started itraconazole 200 mg twice daily and experienced slow improvements in his symptoms with follow-up by the Infectious Disease service and decreased anxiety.

DISCUSSION

This case highlights the diagnostic challenges associated with disseminated fungal infections, namely histoplasmosis, which can closely mimic malignancy in both clinical presentation and imaging.[1-3] The patient presented with classic B symptoms, diffuse lymphadenopathy, and a suspicious lung nodule, all features highly suggestive of malignancy.

Classic "B symptoms" (eg, fever, drenching night sweats, and unintentional weight loss) are constitutional manifestations that occur in association with lymphoid malignancies, particularly Hodgkin lymphoma and certain non-Hodgkin lymphomas. Their presence is central to disease staging, prognosis, and therapeutic decision-making.[4] The Ann Arbor staging system classifies systemic symptoms as B symptoms when any of the following are present: fever > 38 °C in the absence of infection, often intermittent; drenching night sweats requiring a change of bedclothes or sheets; or unintentional weight loss of > 10% of baseline body weight over 6 months.[5]

Although often associated with lymphomas, B symptoms are not pathognomonic. They may occur in chronic infections, such as tuberculosis and HIV infection, autoimmune diseases, and solid tumors.[5,6] Thorough evaluation, including infectious and inflammatory workups, is essential before attributing these systemic manifestations to a neoplasm.

Histoplasma capsulatum, the causative agent of histoplasmosis, is endemic in certain parts of the United States, including the Ohio and Mississippi River valleys. However, the fungus is also found in the Middle East, Asia, Africa, and Central and South America.[7] It is acquired via inhalation of soil contaminated with bird or bat droppings.[1] The patient's military service represents a potential environmental exposure risk. While immunocompetent individuals typically clear the infection, chronic progressive disseminated histoplasmosis can develop, particularly in patients with underlying pulmonary disease or subtle immunosuppression.[1,8]

Negative fungal serologies and antigen tests, as seen in this patient, are not uncommon in subacute or localized disease and should not delay further diagnostic interventions when clinical suspicion remains high.[2,9] Invasive procedures, including wedge resection, may be required to establish a definitive diagnosis.

EBUS-guided transbronchial needle aspiration (EBUS-TBNA) is a valuable minimally invasive technique for the evaluation of mediastinal and hilar lymphadenopathy. However, its diagnostic performance in cases of histoplasmosis is limited by several factors. First, low organism burden is a significant limitation. In immunocompetent individuals with subacute pulmonary histoplasmosis, the fungal load within lymph nodes or pulmonary tissue is often low, leading to negative fungal cultures specimens obtained using EBUS.[10] Second, the diagnostic yield of EBUS-TBNA for identifying *Histoplasma capsulatum* is variable. Detection of fungal elements or successful culture may be inconsistent and is influenced by operator expertise, needle size, number of passes, and specimen handling and processing techniques. Third, overlapping cytopathologic findings can complicate interpretation. The granulomatous inflammation characteristic of histoplasmosis is nonspecific and may also be observed in other conditions such as tuberculosis, sarcoidosis, and certain lymphoproliferative disorders. Therefore, clinical and radiologic correlation, as well as adjunctive testing, are essential for accurate diagnosis.[11] Fourth, sample quality poses additional challenges. Differentiating inflammatory cells from neoplastic elements, managing poorly preserved specimens, and avoiding contamination from bronchial wall tissue can all affect diagnostic accuracy.[12] Finally, inadequate or nondiagnostic sampling occurs in a subset of patients. Case series have reported nondiagnostic EBUS-TBNA results, necessitating reliance on complementary diagnostic modalities, including serologic assays, urine antigen testing, or surgical biopsy, to establish a definitive diagnosis.[9]

Necrotizing granulomas without confirmed microbiologic identification may still

justify antifungal treatment if histopathologic findings are consistent with fungal infection, as in this patient.[1,3] Itraconazole remains the first-line treatment, though adverse effects and treatment duration may impact adherence.[3]

The presentation of pulmonary nodules and diffuse lymphadenopathy in this patient was strongly suggestive of metastatic disease, especially given his smoking history. However, histoplasmosis can closely mimic metastatic cancer radiographically, leading to potential misdiagnosis.[13] In endemic areas, histoplasmosis should be included in the differential for any patient with suspicious thoracic imaging.

In this case, the diagnosis of malignancy was prematurely communicated to the patient based solely on imaging, prior to histologic confirmation. This approach carries significant risk, including psychological distress, initiation of inappropriate treatments, and delayed antifungal therapy. A similar diagnostic dilemma was described by Wheat et al, who emphasized the need for tissue sampling in distinguishing fungal infections from malignancy.[14] In the absence of tissue diagnosis, reliance on radiologic criteria alone can be misleading. PETs, which detect metabolic activity, are not specific and can show uptake in both neoplastic and inflammatory processes.[15]

This case reinforces the principle of diagnostic humility: no diagnosis, especially one as consequential as cancer, should be confirmed without histologic or microbiologic evidence. Multidisciplinary evaluation and appropriate use of tissue sampling are crucial to avoid harmful diagnostic errors.

CONCLUSIONS

In patients presenting with constitutional symptoms, diffuse lymphadenopathy, and pulmonary nodules, disseminated fungal infections such as histoplasmosis must remain in the differential diagnosis, even in the absence of positive fungal serologies.[1,2] Tissue diagnosis through invasive procedures may be necessary, particularly when initial biopsies and cultures are inconclusive.[1] Early recognition and treatment are critical to avoid complications from progressive disseminated infection.[3,8]

Author affiliations

[a]Edward Hines, Jr. Veterans Affairs Hospital, Illinois

Author disclosures

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Ethics and consent

The patient provided oral consent for this case report.

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