A 74-year-old woman with diet-controlled diabetes mellitus type 2 (hemoglobin A1c level of 5.7%), gastroesophageal reflux disease, hypertension, and hyperlipidemia presented to an outside hospital with a 2-week history of severe fatigue, anorexia, left upper quadrant abdominal pain, and night sweats. She reported no fevers, respiratory or gastrointestinal complaints, sick contacts, recent travel, or illicit drug use. She was retired and lived on a farm with her husband, who was her only sexual partner. Medications on admission were amlodipine, aspirin, calcium carbonate—vitamin D, losartan, simvastatin, triamterene-hydrochlorothiazide, and omeprazole.

On arrival, vital signs were within normal limits: temperature of 36.8°C, blood pressure of 111/64 mm Hg, pulse rate of 79 beats/min, respiratory rate of 18 breaths/min, and oxygen saturation of 94% on pulse oximetry. The patient appeared fatigued but was nontoxic and in no acute distress. Examination was notable for abdominal distention with marked splenomegaly and left upper quadrant tenderness, nontender bilateral cervical lymphadenopathy, and stasis dermatitis in the lower extremities.

Initial laboratory work-up was as follows (reference ranges provided parenthetically): hemoglobin, 15.4 g/dL (11.6 to 15.0 g/dL); platelets 28 × 10^9/L (157 to 371 × 10^9/L); white blood cell count, 8.94 × 10^9/L (3.4 to 9.6 × 10^9/L); absolute neutrophil count, 0.55 × 10^9/L (>1.50 × 10^9/L); monocytes, 2.64 × 10^9/L (0.26 to 0.81 × 10^9/L); relative monocytes, 29.5% (2% to 11%); creatinine, 2.7 mg/dL (0.59 to 1.04 mg/dL); blood urea nitrogen, 49 mg/dL (6 to 21 mg/dL); alanine aminotransferase, 49 U/L (7 to 45 U/L); aspartate aminotransferase, 79 U/L (8 to 43 U/L); alkaline phosphatase, 86 U/L (35 to 104 U/L); total bilirubin 1.7 mg/dL (≤1.2 mg/dL); and calcium, 10.9 mg/dL (8.8 to 10.2 mg/dL). Peripheral blood smear was remarkable only for increased monocytes and decreased platelets. Protein electrophoresis revealed a small M-protein spike in the gamma region. Chest radiography showed a small right pleural effusion and right bibasilar atelectasis. A computed tomography scan of the abdomen was performed, which demonstrated marked splenomegaly and lymphadenopathy in the retroperitoneum, perihepatic region, and porta hepatis.

1. Given this patient’s history, laboratory findings, and imaging results at this time, which one of the following is the most likely diagnosis?
   a. Human immunodeficiency virus (HIV) infection
   b. Infectious mononucleosis
   c. Lymphoma
   d. Sarcoidosis
   e. Systemic lupus erythematosus

The differential diagnosis is broad in a patient presenting with fatigue, splenomegaly, diffuse lymphadenopathy, and cytopenias. Systemic infections, including those caused by HIV, Epstein-Barr virus (EBV), *Mycobacterium tuberculosis*, and dimorphic fungi, can cause this clinical picture and should be evaluated for. In this case, HIV infection is less likely as the patient has no known risk factors; she reports being in a monogamous relationship and denies illicit drug use. Infectious mononucleosis is also less likely, given the patient’s age and lack of fever or signs of pharyngitis. Atypical lym-
phocytes would also be expected on the peripheral blood smear, although their absence does not rule out the disease. A hematologic malignant neoplasm should be in the differential diagnosis and is the most likely diagnosis in a patient her age. The M-protein spike on protein electrophoresis and absolute monocytosis on complete blood count also favor this diagnosis. Autoimmune diseases should be considered but are less likely to be manifested initially at this patient’s age or to produce such profound cytopenias. Without respiratory symptoms, abnormalities on the chest radiograph, or evidence of other cutaneous, ocular, or musculoskeletal lesions, sarcoidosis is unlikely. Similarly, systemic lupus erythematosus is less likely, given the lack of other features such as rash, arthralgias, and chronic kidney disease. In this patient, both HIV screening and heterophil antibody test responses were negative. Serum complement levels were in the normal range.

Given the concern for a hematologic malignant neoplasm, a bone marrow biopsy was performed at the outside facility. The slides were sent to Mayo Clinic for initial interpretation. The pathologist noted a distinct population of atypical monocytes, most consistent with a myelomonocytic neoplasm, as well as an expanded population of NK cells. Flow cytometry of the aspirate confirmed an increased NK-cell population, although whether it was reactive or clonal was uncertain. She was transferred to Mayo Clinic for further work-up.

On arrival to Mayo Clinic, she continued to be hemodynamically stable. Findings on physical examination were unchanged. She continued to endorse significant fatigue and mild left upper quadrant abdominal pain, but her appetite had improved. Laboratory studies revealed persistent thrombocytopenia, neutropenia, and monocytosis. With fluid resuscitation at the outside facility, creatinine concentration had returned to baseline level. Bacterial and fungal blood culture specimens were obtained and subsequently returned negative.

With the uncertainty surrounding the expanded NK-cell population and ongoing concerns for chronic myelomonocytic leukemia, bone marrow biopsy was repeated. There were no diagnostic features of a myeloid leukemia on pathologic examination, and the distribution of the lymphoid infiltrate argued against a neoplastic NK-cell process; EBV-positive cells were seen, but no hemophagocytosis was noted. Grocott methenamine silver (GMS) staining revealed no organisms. Flow cytometry of the bone marrow demonstrated an abnormal NK-cell population but no definitive evidence of clonality. Flow cytometry of the blood was unremarkable.

2. Given the patient’s equivocal work-up so far, which of the following tests would be the next best diagnostic step?
   a. Lymph node fine-needle aspiration
   b. Excisional lymph node biopsy
   c. Repeated bone marrow biopsy
   d. Autoimmune serologies (antinuclear antibody, rheumatoid factor, extractable nuclear antigens)
   e. Bacterial or fungal cultures

Histopathologic examination of lymph node tissue can differentiate between malignant, infectious, and autoimmune conditions and in this instance provides the best chance for making a definitive diagnosis. Fine-needle aspiration of a lymph node, although less invasive than an excisional biopsy, is not the preferred method for obtaining tissue, given the potential for sampling error and the inability to assess tissue architecture, which is especially important for the purposes of diagnosing lymphoma. Excisional lymph node biopsy does not have these caveats and is therefore the best choice. A third bone marrow biopsy is of little utility as it would provide no additional information. As already discussed, an autoimmune condition is less likely in this case, given the patient’s age and lack of other organ system involvement. Furthermore, positive results on any serologic testing would not negate the need for lymph node biopsy to rule out other diagnoses. Last, the patient’s lack of fevers and hemodynamic stability argue against the presence of bacteremia or fungemia. A systemic bacterial or fungal infection...
could also be evaluated for with lymph node biopsy.

The decision was made to obtain an excisional lymph node biopsy specimen. A positron emission tomography—computed tomography scan was performed earlier and showed fluorodeoxyglucose uptake in the external iliac, inguinal, and cervical lymph nodes. The patient underwent surgical excision of a highly fluorodeoxyglucose avid and readily accessible left inguinal lymph node. Pathologic review found necrotizing granulomatous lymphadenitis; GMS stains revealed small, narrow budding yeast forms. An EBV-positive lymphoproliferation consistent with reactivation was also noted.

3. The results of the excisional lymph node biopsy are most consistent with infection with which of the following fungi?
   a. Histoplasma capsulatum
   b. Blastomyces dermatitidis
   c. Coccidioides immitis
   d. Candida species
   e. Aspergillus species

The GMS stain and periodic acid–Schiff stain are commonly used to visualize fungi. *Histoplasma capsulatum* is a small (2 to 4 μm), thin-walled, narrow budding yeast that is present within macrophages. It is the most likely diagnosis in this case. *Blastomyces dermatitidis* is a moderately sized, broad-based budding yeast. Both *H. capsulatum* and *B. dermatitidis* are endemic to the American Midwest. *Coccidioides immitis* presents as spherules of various sizes with multiple endospores on routine hematoxylin and eosin staining. It is ubiquitous in the American Southwest, to which the patient had no recent travel. *Candida* species are small yeasts with hyphae and pseudohyphae that exist in the extracellular environment. *Aspergillus* species present as thin hyphae with septa and acute-angle branching.

Shortly after discharge, the patient was seen in the hematology clinic, where it was thought that disseminated histoplasmosis provided sufficient explanation for the clinical picture. No further hematology work-up was suggested. Confirmatory histoplasmosis testing was ordered; urine and serum antigen test results was negative, whereas antibody testing was positive for an M band on immunodiffusion. The patient was subsequently seen by an infectious diseases specialist for treatment of disseminated histoplasmosis.

4. Which of the following is the most appropriate initial treatment of this patient’s condition?
   a. Caspofungin
   b. Anidulafungin
   c. Fluconazole
   d. Itraconazole
   e. Amphotericin B

There are conflicting data on the efficacy of echinocandins in treating *H capsulatum* infection, and therefore neither caspofungin nor anidulafungin is an acceptable choice. Fluconazole does demonstrate activity against *H capsulatum*, although it is less effective than itraconazole. Risk of relapse is also higher when fluconazole is used for maintenance therapy. Thus, it is reserved for patients who are unable to take itraconazole. Itraconazole is the preferred treatment of *H capsulatum* infection, with excellent efficacy in clearing infection and a minimal adverse effect profile. Amphotericin B is a first-line treatment of severe disseminated histoplasmosis and central nervous system (CNS) histoplasmosis; it may certainly have been considered while the patient was hospitalized. However, its adverse effect profile and intravenous route of administration make it unnecessary in an ambulatory patient without frank fungemia.

Itraconazole therapy was started with plans for completion of a 6-month course. Omeprazole had been discontinued during hospitalization, permitting the capsule form of itraconazole to be used. A 2-week follow-up was scheduled with determination of an itraconazole level beforehand as well as a complete blood count, electrocardiogram, and liver function tests (LFTs) to monitor for medication.
toxic effects. Repeated serum fungal culture specimens were obtained at the visit, and no growth was found.

5. Which of the following is this patient’s greatest risk factor for disseminated histoplasmosis?
   a. Diabetes mellitus type 2
   b. Medications
   c. EBV infection
   d. Place of residence
   e. Age

Most patients with disseminated histoplasmosis have an underlying cause of immunosuppression. Whereas type 2 diabetes mellitus and hyperglycemia have been shown to hinder the function of the innate immune system, diabetes has not been demonstrated to be a significant risk factor for disseminated histoplasmosis. In addition, this patient’s hemoglobin A1c level demonstrates good glycemic control. On review of the previously listed medications, none cause marked immunosuppression that would put the patient at risk for disseminated histoplasmosis. Infection with EBV does not increase one’s risk for disseminated histoplasmosis; rather, like disseminated histoplasmosis, reactivated EBV occurs in the context of immunosuppression. Residency on a farm does increase the risk for contracting histoplasmosis but does not itself augment the risk for disseminated disease. Most histoplasmosis infections remain either asymptomatic or confined to the lungs if no immunosuppression is present. In a patient with no obvious cause for immunosuppression, age is the most likely reason for her presentation. Increasing age is associated with cellular immune senescence, and extremes of age have been linked to disseminated histoplasmosis.²

Unfortunately, before the follow-up appointment, she was admitted to an outside hospital with neurologic deficits secondary to a subdural hematoma. Because of her thrombocytopenia, no surgical intervention was performed, but the neurologic examination findings remained unchanged and surveillance head imaging was stable. However, during her stay, copious pus developed at the site of the lymph node biopsy. Computed tomography of the abdomen and pelvis revealed an intra-abdominal abscess. Unfortunately, in this context, septic shock with multiorgan failure developed. Despite appropriate resuscitation measures, antibiotics, and amphotericin B, the patient died.

DISCUSSION

Histoplasma capsulatum is an opportunistic fungus found ubiquitously in the Ohio and Mississippi river valleys of the United States. Histoplasma infections are symptomatic in less than 1% of patients³; in those who do become symptomatic, a relatively mild, self-limited pulmonary infection with fevers, malaise, headache, and dry cough is the most typical presentation.⁴ In a small number of patients, disseminated infection occurs.

Progressive disseminated infection may be acute or chronic. Acute progressive disseminated histoplasmosis occurs in patients who are immunocompromised. Risk factors include AIDS, hematologic malignant disease, solid organ or hematopoietic stem cell transplant, congenital immunodeficiencies, and the use of immunosuppressive medications including corticosteroids and tumor necrosis factor inhibitors.⁵ Symptoms are manifested at the onset of fungal dissemination, and if it is left untreated, the disease is invariably fatal within 2 to 12 weeks.² Chronic progressive disseminated histoplasmosis generally occurs in older patients with no known cause of immunosuppression. It is thought that age-related cellular immune senescence plays a key role, with macrophages having an impaired ability to destroy the fungus.² Fungal dissemination is thought to be present months before the onset of symptoms, but without treatment, it is also thought to be invariably fatal.³ The patient in this case was elderly with no known cause of immunosuppression. Thus, chronic progressive disseminated histoplasmosis is more likely, permitted by age-related cellular immune senescence.
Regardless of disease chronicity, progressive disseminated histoplasmosis can be difficult to diagnose. It is manifested with a wide range of nonspecific findings that can be seen in other systemic infections, autoimmune diseases, and malignant neoplasms. Fever, malaise, hepatosplenomegaly, and pancytopenia are the most common presentations.² The gastrointestinal system and adrenal glands are involved in most cases on autopsy, but gastrointestinal symptoms or adrenal insufficiency is present in only 10% of cases.²,⁵ Gastrointestinal manifestations include abdominal pain, nausea, vomiting, and diarrhea but also ulcerations and polypoid lesions that may occur anywhere along the alimentary canal. Care must be taken not to misdiagnose such lesions as colitis or malignant disease, especially in cases in which the diagnosis would lead to immunosuppressive therapy.³ The skin and CNS are involved in approximately 10% of cases as well, usually in those with AIDS or other underlying immunosuppressive disorders.⁵⁻⁸ Skin manifestations are varied, ranging from nodules and papules to abscesses and dermatitis; CNS manifestations include meningitis, encephalitis, and focal lesions of the brain and spinal cord.⁷,⁸ More rare manifestations include endocarditis and hemophagocytic lymphohistiocytosis.³ In those with acute progressive disseminated disease, sepsis, disseminated intravascular coagulation, renal failure, and acute respiratory distress syndrome can develop.³

Given the varied clinical manifestations, patients from endemic areas presenting with nonspecific complaints should undergo testing for histoplasmosis, especially if they are elderly or immunocompromised. Culture of specimens from blood, bone marrow, skin, or another involved site remains the “gold standard” and returns with positive reactions in 75% to 85% of cases.⁶⁻⁹ Histopathologic evaluation can also provide a definitive diagnosis, with GMS staining showing the fungal organisms.⁹ Histoplasma antigen testing, by enzyme immunoassay, should be performed on the serum and urine. Urine antigen is more sensitive, although both tests can cross-react with other fungi, most notably Blastomyces and Paracoccidioides. Antigen testing can also be performed on bronchioalveolar lavage fluid and cerebrospinal fluid.⁹ Antibody testing is available and is most commonly done with complement fixation and immunodiffusion assays; the immunodiffusion assay is more sensitive. Antibody testing is less useful in those with acute progressive disseminated disease as they may not yet have antibodies and in those who are immunocompromised. Histoplasma polymerase chain reaction tests are still under investigation and have not been approved by the Food and Drug Administration.⁹

Treatment of disseminated histoplasmosis requires prolonged antifungal therapy. In ambulatory patients with mild to moderate symptoms, itraconazole therapy is preferred. The standard regimen is 200 mg 3 times daily for 3 days, followed by 200 mg twice daily for 6 to 12 months. The drug can be administered by a capsule or solution. The capsule is optimally absorbed in a highly acidic environment and thus should not be used in conjunction with proton pump inhibitors. During treatment, itraconazole levels and Histoplasma antigen concentrations in the urine and serum should be monitored to determine treatment efficacy.¹⁰ Other options for therapy include fluconazole, voriconazole, and posaconazole, although these are considered second-line therapies as primary response rates are lower and relapse rates are higher.¹¹ Echinocandins are not used for treating Histoplasma infection.¹⁰ In patients with severe symptoms or CNS involvement, liposomal amphotericin B is initially administered as it more rapidly eliminates fungemia. Dosing is 3 mg/kg per day for 1 to 2 weeks for patients with severe symptoms and 5 mg/kg per day for 4 to 6 weeks for CNS involvement. Regardless of symptom severity, lifelong itraconazole suppressive therapy...
should be considered in those with relapse, an irreversible cause of immunosuppression, and CD4 counts below 150 cells/mm³.¹⁰

Adverse effects of itraconazole include gastrointestinal distress, rash, and hepatotoxicity. The LFT results should be routinely monitored. The medication contains a black box warning for its negative ionotropic effects and should not be used in patients with heart failure. It is also a strong inhibitor of the CYP3A4 enzyme, which is responsible for the metabolism of a large number of medications. A thorough medication review should be performed and appropriate medication adjustments made before itraconazole therapy is initiated. Amphotericin B has numerous serious adverse effects including hypokalemia, hypomagnesemia, distal renal tubular acidosis, nephrotoxicity, agranulocytosis, and toxic epidermal necrolysis. Electrolyte values, creatinine concentration, complete blood count, and LFT results should be routinely monitored.¹²

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REFERENCES