CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 31-2013: A 29-Year-Old Man with Abdominal Pain, Fever, and Weight Loss

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PRESENTATION OF CASE

Dr. Nosheen Reza (Medicine): A 29-year-old man was seen in an outpatient clinic affiliated with this hospital because of abdominal pain, fever, and weight loss.

The patient was reportedly well until unintentional weight loss occurred approximately 6 weeks before presentation. Three weeks before presentation, upper abdominal pain developed that the patient rated at 8 on a scale of 0 to 10, with 10 indicating the most severe pain. The pain radiated to his throat, increased after eating and drinking, and did not diminish with ibuprofen.

At the outpatient clinic, the patient reported nausea, occasional vomiting, decreased food intake, and a loss of 10 kg from his usual weight of 64.4 kg. He reported no headaches, visual changes, neck stiffness, dyspnea, substernal chest pain, lower abdominal pain, diarrhea, back pain, dysuria, rashes, or joint pain. He had had a respiratory illness approximately 2 years before this evaluation. He had no known allergies. He was born in Central America and had been living in the United States for 4 years. He worked in agriculture and did not speak English. He smoked cigars occasionally, drank alcohol infrequently, and did not use illicit drugs.

On examination, the patient appeared cachectic. The temperature was 37.3°C, the blood pressure 101/68 mm Hg, the pulse 114 beats per minute, the respiratory rate 20 breaths per minute, and the oxygen saturation 100% while he was breathing ambient air. The abdomen was soft, with normal bowel sounds and without tenderness or distention. There was macular hyperpigmentation of the feet and legs that reportedly had not changed for 10 years. The remainder of the examination was normal. Urinalysis revealed 1+ protein and was otherwise normal. Ranitidine was prescribed, and the patient returned home with instructions to follow up the next day when test results were available. Blood levels of glucose, calcium, phosphorus, lipase, and amylase were normal, as were the results of tests of liver and renal function. Testing for antibodies to hepatitis C virus was negative; other test results are shown in Table 1.

Dr. Carol C. Wu: A frontal chest radiograph showed subtle, tiny nodules throughout both lungs, without focal consolidation (Fig. 1A). There was no evidence of mediastinal or hilar lymphadenopathy.

Dr. Reza: Two days later, the patient returned to the outpatient clinic. He reported

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	Outpatient Clinic	On Admission
Hematocrit (%)	41.0–53.0	33.2	26.7
Hemoglobin (g/dl)	13.5–17.5	10.7	8.6
White-cell count (per mm³)	4500–11,000	3100	4100
Differential count (%)			
Neutrophils	40–70	79.2	88.8
Lymphocytes	22–44	11.4	5.6
Monocytes	4–11	7.2	3.4
Eosinophils	0–8	0.3	1.0
Basophils	0–3	0.3	0.2
Platelet count (per mm³)	150,000–400,000	345,000	279,000
Mean corpuscular volume (μm³)	80–100	79	79
Erythrocyte count (per mm³)	4,500,000–5,900,000	4,220,000	3,400,000
Mean corpuscular hemoglobin (pg/red cell)	26.0–34.0	25.4	25.3
Mean corpuscular hemoglobin concentration (g/dl)	31.0–37.0	32.2	32.2
Sodium (mmol/liter)	135–145	131	133
Potassium (mmol/liter)	3.4–4.8	3.5	3.1
Chloride (mmol/liter)	100–108	96	103
Carbon dioxide (mmol/liter)	23.0–31.9	19.8	19.9
Protein (g/dl)			
Total	6.0–8.3	8.4	6.6
Albumin	3.3–5.0	3.2	2.3
Globulin	2.3–4.1	5.2	4.3
Helicobacter pylori immune ratio	Negative at 0.00–0.88; equivocal at 0.89–0.99; positive at >0.99	1.56	
HIV-1 and HIV-2 antibodies and p24 antigen	Nonreactive	Reactive	
HIV-1 antibodies, by Western blot analysis	Negative	Positive (bands p18, p24, p31, p40, gp41, p51/p55, p65, and gp120/gp160 were detected)	
HIV-1 RNA, by PCR (copies per ml)	<20 (assay range, 20–10,000,000)		172,000
Lactate dehydrogenase (U/liter)	110–210		283
T-lymphocyte subsets			
Absolute lymphocyte count (per mm³)	950–2967		190
CD4 count (per mm³)	348–1456		10
CD4 (% of total lymphocytes)	21–64		5.4
CD8 count (per mm³)	148–1173		114
CD8 (% of total lymphocytes)	9–48		59.8
CD4:CD8 ratio			0.09

* HIV-1 denotes human immunodeficiency virus type 1, HIV-2 HIV type 2, and PCR polymerase chain reaction.
† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

persistent abdominal pain that he rated at 8 on a scale of 0 to 10, as well as sore throat, fever, and one episode of hematemesis that had occurred the day before. He reported no cough, congestion, or improvement with ranitidine. The temperature was 38.3°C, the blood pressure 105/65 mm Hg,

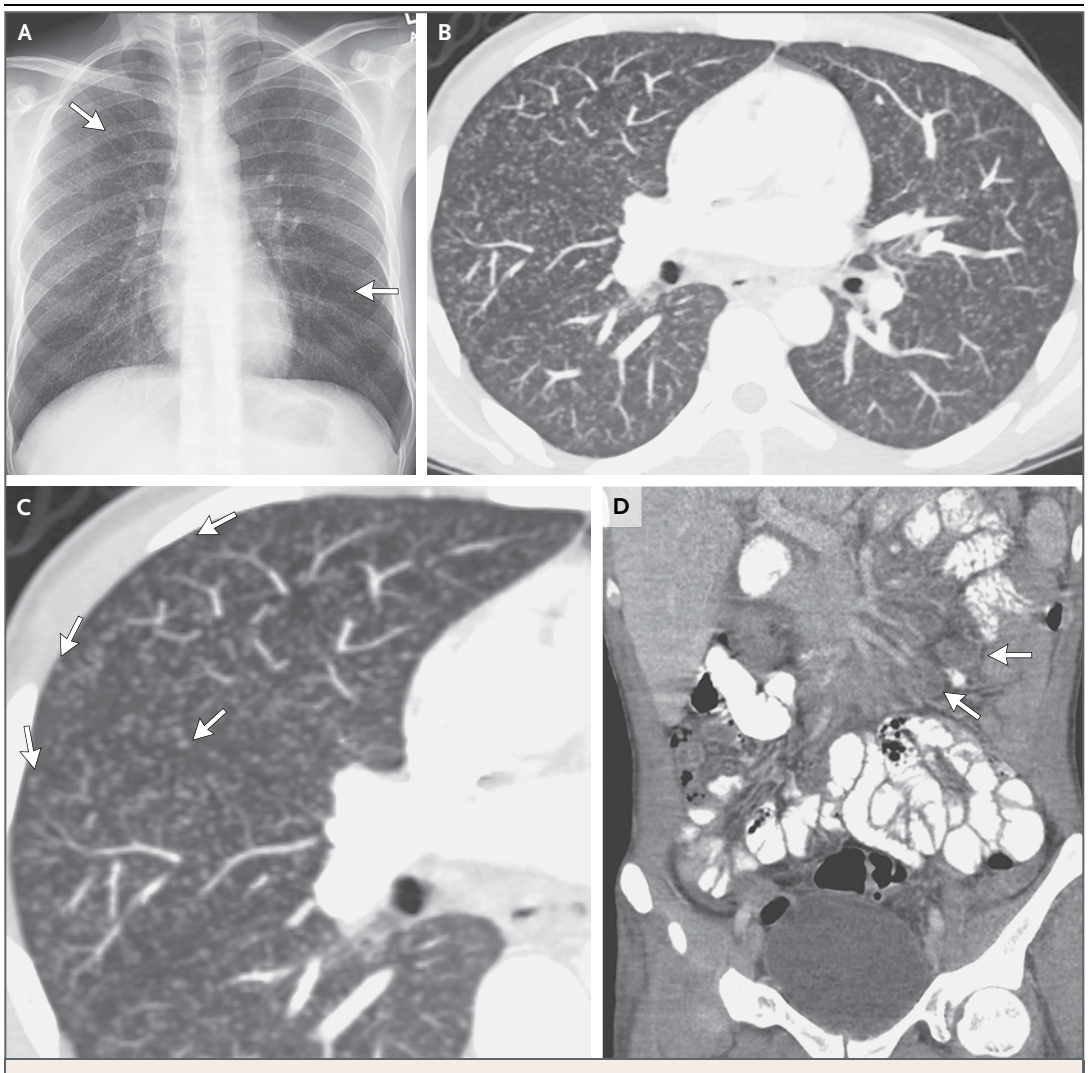

Figure 1. Images of the Chest, Abdomen, and Pelvis.

A frontal chest radiograph shows multiple tiny nodules throughout both lungs (Panel A, arrows). An axial image from a CT scan of the chest shows numerous nodules, 1 to 3 mm in diameter, randomly distributed in a miliary pattern in both lungs (Panel B). Magnification of the same axial image shows the miliary nodules (Panel C, arrows). A contrast-enhanced, coronal reformation of a CT scan of the abdomen and pelvis shows multiple enlarged mesenteric lymph nodes with low-attenuation centers (Panel D, arrows).

the pulse 119 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 99% while he was breathing ambient air. There were coarse breath sounds at both lung bases. The abdomen was firm, without distention, masses, guarding, or rebound; the remainder of the examination was unchanged. Airborne precautions were instituted, and a face mask was placed. Acetaminophen was administered, and a tuberculin skin test was performed. The patient was transported to the emergency department of this hospital. He was heterosexual and reported having no more than eight partners in his lifetime and consistently using condoms. There was no known history of exposure to tuberculosis.

On examination, the temperature was 35.9°C, the blood pressure 100/65 mm Hg, the pulse 68 beats per minute, the respiratory rate 24 breaths per minute, and the oxygen saturation 99% while the patient was breathing ambient air. The weight was 47.6 kg, the height 160 cm, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 18.6. A white

Figure 2. Millet Seeds.

exudate was present on the underside of the tongue. A nontender, mobile lymph node, 1 to 2 cm in diameter, was present in the left submandibular chain, and additional nontender, mobile lymph nodes were present in the right submental region and the right cervical region. Fine rales were scattered throughout both lungs, and the abdomen was soft; the remainder of the examination was unchanged. Blood levels of glucose, calcium, phosphorus, magnesium, lipase, and amylase were normal, as were the results of tests of liver and renal function; other test results are shown in Table 1.

Dr. Wu: Computed tomography (CT) of the chest performed after the intravenous administration of contrast material revealed numerous nodules, 1 to 3 mm in diameter, randomly distributed in a miliary pattern (i.e., having an appearance that is similar to millet seeds [Fig. 2]) in both lungs, without mediastinal, hilar, or axillary lymphadenopathy (Fig. 1B and 1C). To help evaluate the patient's abdominal pain, a contrast-enhanced CT scan of the abdomen and pelvis was obtained that showed multiple enlarged mesenteric lymph nodes and new, small bilateral pleural effusions. The mesenteric lymph nodes had low-attenuation centers that were suggestive of central necrosis (Fig. 1D). There was no evidence of bowel dilatation or bowel-wall thickening.

Dr. Reza: Specimens of blood, sputum, and urine were obtained. Intravenous saline and one dose of ceftriaxone and azithromycin were administered, followed by fluconazole, omeprazole, and nystatin suspension. Results of coagulation tests were normal. The patient was admitted to the hospital.

During the first day, the temperature rose to 39.7°C. Acetaminophen was administered.

Diagnostic tests and procedures were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Howard M. Heller: The patient was a 29-year-old man from Central America presenting with weight loss and progressively worsening upper abdominal pain that was exacerbated by eating. He had nausea and vomiting, and then hematemesis developed. Examination was clinically significant for cachexia, fever, probable oral thrush, and lymphadenopathy, without hepatosplenomegaly. The patient had rales on examination and was tachypneic but not hypoxemic. The chest radiograph showed diffuse small nodules. Laboratory results were notable for anemia that worsened in the few days before admission to this hospital and for hypergammaglobulinemia. Blood levels of amylase and lipase were normal. Testing for human immunodeficiency virus (HIV) was positive, and the CD4 T-lymphocyte count was 10 per cubic millimeter.

HIV TESTING

The patient did not present with identifiable risk factors for HIV infection, but it was still appropriate to perform HIV testing in light of the weight loss, oral thrush, hypergammaglobulinemia, and lymphopenia. It is not unusual for patients to disclose risk factors only after receiving a diagnosis of HIV or after presenting with acquired immunodeficiency syndrome (AIDS)–defining illnesses. This case illustrates the importance of offering routine HIV testing to all persons presenting for medical care, even those who do not appear to be at high risk for infection.

ILLNESSES ASSOCIATED WITH HEMATEMESIS

Although this patient received a diagnosis of HIV–AIDS, diseases not related to HIV can also develop, and it is important not to assume that all the patient's illnesses are manifestations of HIV infection. In addition, patients with AIDS often present with more than one opportunistic infection, so even when an opportunistic infection has been identified, other possible diagnoses must still be considered. In this patient, possible diagnoses that are unrelated to HIV include gastritis and peptic ulcer disease.[1] Serologic testing for *Helicobacter pylori* was positive, so we must consider the possibility that he has an *H. pylori*–related ulcer or gastric carcinoma; either of these diagnoses could explain his abdominal pain and hematemesis. The nausea and vomiting could have led to a Mallory–Weiss tear. The weight loss

could have been due to decreased food intake during the weeks before admission, since eating appeared to exacerbate the abdominal pain. These conditions may adequately explain many features of this patient's presentation, but we need to account for the fever and the nodular infiltrate on the chest radiograph to arrive at a unifying diagnosis.

Tuberculosis is a possible diagnosis in this case because it typically causes fever and is a common opportunistic infection in patients with AIDS who are from areas where tuberculosis is endemic. There is no evidence on the patient's chest radiograph of calcified granulomas. Tuberculosis can be manifested by an infiltrate of small nodular lesions that are usually characterized as miliary (Fig. 2). We do not know the result of the tuberculin skin test, but given the patient's degree of immunosuppression, a negative result is unreliable. Gastrointestinal tuberculosis can occur, but if it leads to gastrointestinal bleeding, the source of the bleeding is usually in the lower gastrointestinal tract; since this patient's bleeding manifested as hematemesis and was clearly from the upper gastrointestinal tract, tuberculosis is unlikely to be the cause. However, tuberculosis should remain in the differential diagnosis while we consider the possibility of multiple opportunistic infections.

Gastrointestinal Kaposi's sarcoma due to human herpesvirus 8 can cause bleeding from both the upper and the lower gastrointestinal tracts, but bleeding is an unusual manifestation of Kaposi's sarcoma. Furthermore, there was no evidence of Kaposi's sarcoma on the patient's skin or oral mucosa, so gastrointestinal or other visceral Kaposi's sarcoma is unlikely. Gastric lymphoma with hemorrhage has been reported in patients with AIDS but does not explain this patient's pulmonary findings. Herpes simplex virus type 1 can cause esophageal ulceration with bleeding, but the patient's pain seems to be localized more to the gastric area than to the esophagus. Visceral leishmaniasis is an AIDS-related parasitic infection and has been reported to cause gastrointestinal hemorrhage[2]; it is commonly seen in the Mediterranean region, South Asia, and the Middle East but not in Central America. Cytomegalovirus can cause gastritis as well as esophageal or gastric ulceration. Thus, it should be included in the differential diagnosis even though it cannot explain the pulmonary findings in this case.

NODULAR LUNG DISEASE AND AIDS

Diffuse reticulonodular infiltrates in patients with AIDS can be due to several pathogens.[3] Patients with *Pneumocystis jirovecii* pneumonia typically present with diffuse interstitial infiltrates, but they can also present with reticulonodular disease, although this is usually related to granuloma formation in persons who have higher CD4 T-lymphocyte counts than this patient had. Kaposi's sarcoma can cause a reticulonodular pattern but is more commonly associated with bulky nodular disease. Pulmonary disease is nearly always preceded by cutaneous or oral mucosal involvement. Viral pathogens (e.g., cytomegalovirus), cancers (including lymphoma), and lymphoproliferative disorders do not cause reticulonodular disease. Fungal infection with cryptococcosis, coccidioidomycosis, penicilliosis, or histoplasmosis may cause disseminated disease in patients with AIDS and can manifest with a reticulonodular infiltrate.

The opportunistic infection that could provide a unifying diagnosis is histoplasmosis. In areas where histoplasma is endemic, disseminated histoplasmosis occurs in up to 30% of patients with AIDS and is the AIDS-defining illness in up to 50% of those patients.[4] In the United States, histoplasma is endemic in the Ohio and Mississippi River Valleys; it is also endemic in Central America, South America, and the Caribbean. It causes a latent infection that can reactivate years after the patient has left the endemic area, especially when CD4 T-lymphocyte counts fall below 100 per cubic millimeter. Patients typically present with indolent fever and weight loss,[5-7] and diarrhea is common. Lymphadenopathy or hepatosplenomegaly may be present on examination, as well as mucosal involvement, with ulcerations in the oropharynx or anal area. Skin lesions similar to those seen in persons infected with other dimorphic fungi can be present but are much more common in persons in South America than in North America or Central America. Results of chest radiographs are abnormal in up to 70% of patients with disseminated disease and may show interstitial or reticulonodular infiltrates, even in patients who have no pulmonary symptoms. Up to 12% of patients with AIDS and disseminated histoplasmosis have gastrointestinal involvement, most commonly in the colon or cecum.[7-9] Small-bowel involvement[10] and upper gastrointestinal bleeding have also been reported in these patients.

Pancytopenia may occur because of bone marrow infiltration. Esophageal involvement is rare.

In conclusion, disseminated histoplasmosis could be a unifying diagnosis that explains this patient's symptoms and findings, and it is a highly possible diagnosis given his geographic history. In some countries in Central America, 15% of patients with AIDS and disseminated histoplasmosis also have tuberculosis,[11] so it would not be surprising if this patient had both opportunistic infections. The diagnostic test was probably an upper endoscopy to identify the source of the bleeding. If he has gastrointestinal histoplasmosis, we would expect to see ulcerations, probably in the duodenum, and the yeast would be easy to identify on histopathological examination. The urinary histoplasma antigen test is highly sensitive in the detection of disseminated disease, even more so than the serum antigen test.

Dr. Eric S. Rosenberg (Pathology): Dr. Reza, what was your impression when you first evaluated this patient?

Dr. Reza: We thought reactivation tuberculosis or miliary tuberculosis was the most likely diagnosis. We also considered endemic fungi such as histoplasmosis or blastomycosis, which could be related to the patient's occupation as an agricultural worker.

CLINICAL DIAGNOSES

Miliary tuberculosis and advanced HIV–AIDS.

DR. HOWARD M. HELLER'S DIAGNOSES

Gastrointestinal and disseminated histoplasmosis. The acquired immunodeficiency syndrome.

PATHOLOGICAL DISCUSSION

Dr. Virginia M. Pierce: Because the initial clinical and radiologic differential diagnoses included tuberculosis, multiple respiratory specimens were submitted to the microbiology laboratory for acid-fast smears and mycobacterial cultures, all of which were negative.

The first diagnostic test, an enzyme immunoassay for urinary *Histoplasma capsulatum* antigen, was positive. The antigen-detection test is important in the diagnosis of histoplasmosis, but it has limitations. Cross-reactivity occurs in patients infected with other fungal pathogens, especially other agents of endemic mycoses (e.g., *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Penicillium marneffei*, and *Coccidioides immitis*); therefore, positive results must be considered in the context of a patient's epidemiologic history. In turn, negative results do not rule out the diagnosis of histoplasmosis; the sensitivity of the assay varies with the clinical syndrome, disease severity, tempo of disease progression, and immune status.[12]

In this case, multiple sputum specimens, as well as samples obtained by bronchoalveolar lavage and transbronchial biopsy, were submitted for fungal culture; all these specimens grew a mold after approximately 2 weeks of incubation at 30°C. The mold colonies initially appeared buff-colored and waxy but became white, with a delicate, cottony texture, after additional incubation (Fig. 3A). On microscopical examination, the mature mold had septate hyphae and large, round, thick-walled macroconidia, with cylindrical surface projections, features morphologically consistent with *H. capsulatum* (Fig. 3B).[13]

H. capsulatum is a dimorphic fungus that grows as a mold in the environment and as a yeast at body temperature. In the environment, mold spores are dispersed by activities that disrupt the soil, and the spores can then be inhaled by humans. After the fungus has been inhaled and has reached lung temperature, it converts into a small, round or oval budding yeast. Historically, this property of thermal dimorphism was exploited in the laboratory as a way to verify the identity of the isolate as *H. capsulatum*. Currently, we use a commercially available DNA probe to rapidly confirm the identity of the mold. In this case, we performed a nucleic acid hybridization test 1 day after the first observation of a suspicious colony, and it confirmed the identity of the isolate as *H. capsulatum*.

Dr. Richard L. Kradin: The bronchoalveolar-lavage specimen showed multiple dust-laden macrophages. A few macrophages appeared to contain yeast, 2 to 4 μm in diameter (Fig. 4A). At low magnification, several non-necrotizing granulomas were identified (Fig. 4B). Examination at high magnification showed a granuloma with multinucleated giant cells and lymphocytes at its periphery (Fig. 4C). A Gomori methenamine silver stain showed yeast, 2 to 4 μm in diameter, that were undergoing narrow-neck

budding (Fig. 4D) and that were consistent with *H. capsulatum*.

Dr. Pierce: Taken together, the results of the urinary antigen test and cultures and the biopsy findings confirm the diagnosis of histoplasmosis in this patient. However, Dr. Heller's point about considering the possibility of more than one pathogen when caring for immunocompromised patients is important. The respiratory cultures also grew small amounts of *Candida albicans*, *Pseudomonas aeruginosa*, alpha-hemolytic streptococcus, and a mycoplasma species. Tests for *P. jirovecii*, influenza virus types A and B, respiratory syncytial virus, adenovirus, and parainfluenza virus types 1, 2, and 3 were all negative.

Dr. Rosenberg: Dr. Reza, what happened with this patient?

Dr. Reza: The patient completed a 2-week induction course of amphotericin B and was then transitioned to itraconazole. Two separate induced-sputum specimens were cultured and grew mucoid pseudomonas, for which the patient was treated with a 10-day course of cefepime. He was also treated with a 5-day course of azithromycin for mycoplasma.

After determining the diagnosis of HIV–AIDS, we discussed options for when to initiate antiretroviral therapy. Given that the patient's initial CD4 T-lymphocyte count was 10 per cubic millimeter and the HIV RNA level was 172,000 copies per milliliter, we elected to initiate antiretroviral therapy with emtricitabine, tenofovir disoproxil fumarate, and raltegravir. We also started trimethoprim–sulfamethoxazole and azithromycin prophylaxis. He was seen at a follow-up visit 3 weeks after discharge and felt well. He had gained 9.1 kg and reported having no fever, chills, cough, dysphagia, odynophagia, diarrhea, or skin changes. Two months after discharge, the CD4 T-lymphocyte count was 116 per cubic millimeter and the viral load was 62 copies per milliliter. The complete blood count was notable for peripheral-blood eosinophilia of 42.8%, with an absolute eosinophil count of 2700 per cubic millimeter. His primary care physician and infectious-disease specialist decided to treat him with empirical ivermectin for strongyloides. At his most recent follow-up visit, the peripheral-blood eosinophilia was diminished but remained elevated at 13.8%.

Dr. Heller: Was the patient evaluated by endoscopy?

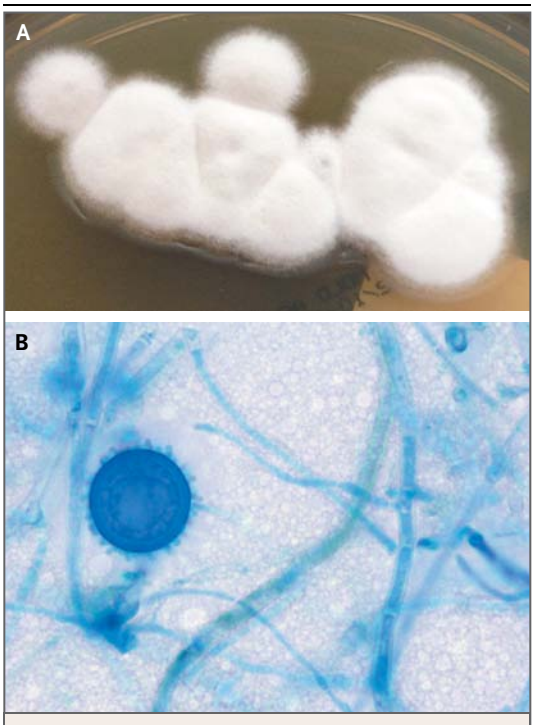

Figure 3. Microbiologic Findings.
A mold was isolated from the initial sputum specimen. The mature mold was white and had a delicate, cottony texture (Panel A). On microscopical examination of a lactophenol cotton-blue tease-mount preparation, the mold had septate hyphae and large, round, thick-walled macroconidia, with cylindrical surface projections (Panel B). These features are morphologically consistent with *Histoplasma capsulatum*.

Dr. Emma Kaplan-Lewis (Medicine): After initiation of antifungal therapy, the patient did not have further episodes of abdominal pain or recurrent hematemesis, so endoscopy was not performed. The *H. pylori* antibody positivity was noted; however, when I saw him as an outpatient, he was having difficulty with the complexity of his medication regimens for HIV and histoplasmosis. We decided that, until he was very clear about his antifungal medication and antiretroviral therapy, we were not going to treat the *H. pylori*. He is aware that this will need to be treated eventually, but he has not had a recurrence of abdominal symptoms, and his most recent rectal examination showed guaiac-negative stool.

A Physician: In patients with disseminated histoplasmosis, is there a risk of acquiring the immune reconstitution inflammatory syndrome (IRIS)?

Dr. Heller: Yes. In this patient, the infection is now controlled with amphotericin B and itracon-

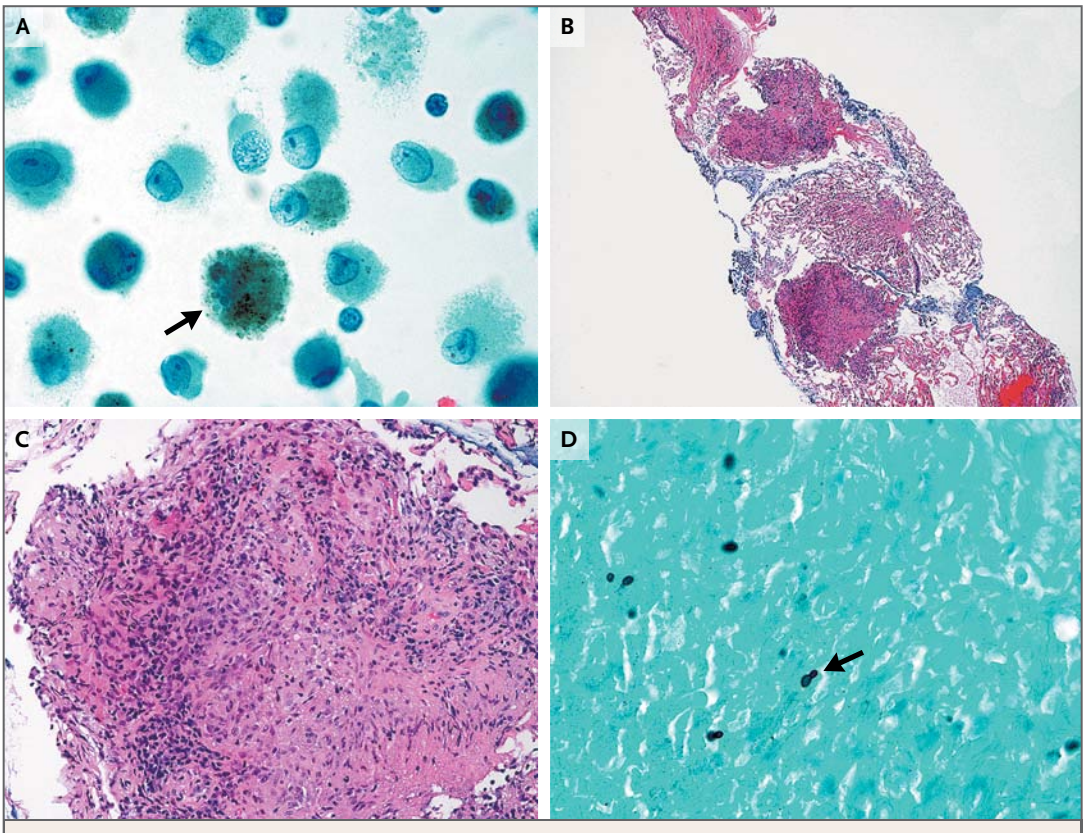

Figure 4. Bronchoscopy Specimens.

A bronchoalveolar-lavage specimen shows a few macrophages containing intracellular, yeastlike structures surrounded by clear halos (Panel A, arrow; Papanicolaou stain). At low magnification, several non-necrotizing granulomas are present (Panel B, hematoxylin and eosin). Examination at high magnification shows a granuloma with multinucleated giant cells and lymphocytes at its periphery (Panel C, hematoxylin and eosin). A Gomori methenamine silver stain reveals yeast, 2 to 4 μm in diameter, that are undergoing narrow-neck budding and that are consistent with histoplasma species (Panel D, arrow).

azole, but as his immune system is reconstituted and the CD4 T-lymphocyte count rises, there is a chance that the abdominal symptoms, lung symptoms, and fever will recur. If this happens, we usually stay the course, and a patient's condition typically improves. IRIS has definitely been reported in patients with histoplasmosis.

A Physician: How do you time the initiation of antiretroviral treatment in a patient with an opportunistic infection?

Dr. Heller: Several studies have compared the value of deferring antiretroviral treatment with starting it immediately, and most of the data suggest starting HIV treatment immediately. For patients with HIV infection and tuberculosis, it has been shown that better outcomes are achieved if HIV treatment is started concurrently with tuberculosis treatment.[14]

Dr. Hasan Bazari (Medicine): Why do we use glucocorticoids as an adjunct to antimicrobial therapy in patients with *P. jirovecii* pneumonia, and is that treatment generalizable to other opportunistic infections?

Dr. Heller: The use of adjunctive glucocorticoids for *P. jirovecii* pneumonia became the standard of care more than 20 years ago. When they are used for treating severe *P. jirovecii* pneumonia, survival rates improve. Most of the patients we treat have moderate disease, and glucocorticoids are used to decrease morbidity; they do nothing to prevent death in these patients, but exercise tolerance improves more quickly and fibrotic disease is less likely to develop. We do not use glucocorticoids in mild cases. In the United States and western Europe, the use of glucocorticoids is standard but also determined

in the context of a patient's overall risk for tuberculosis. If glucocorticoids are administered to a patient with latent tuberculosis, the disease is likely to reactivate. The World Health Organization guidelines and national guidelines in most other countries where tuberculosis is endemic do not recommend the liberal use of glucocorticoids. Several years ago, I spent some time in a resource-limited country where tuberculosis is endemic. Some physicians advocated the use of adjunctive glucocorticoids, but the head of the tuberculosis hospital said, "Whenever we use steroids, we have steroids in one hand and isoniazid in the other."

ANATOMICAL DIAGNOSIS

Histoplasma capsulatum infection.

This case was presented at the Medical Case Conference.

Dr. Wu reports receiving royalties from Amirsys. Dr. Kradin reports providing expert testimony on behalf of patients in cases involving asbestos and lung disease. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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