

# Papulosquamous rash in a man with HIV disease

Treatment of this infection is often not necessary—except when the patient is both symptomatic and immunosuppressed, like the one in this case.

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## CASE

A 41-year-old Colombian male visited an urgent care facility complaining of a chronic, nonproductive cough. The physician, noting that the patient had mild oropharyngeal thrush and a low WBC count, suggested HIV testing. The results were positive. A chest film showed no acute disease. A lower respiratory infection was diagnosed and treated with moxifloxacin.

One month later, the patient came to the emergency department (ED) with a cough, a fever of 100.7°F, chills, confusion, and malaise. He was noted to have a generalized papulosquamous rash over most of his body (see Figure 1). The patient denied having any other chronic medical problems. There was no history of household contacts having tuberculosis, and the family history was significant only for MI in a brother at age 50 years. The patient reported that he had arrived from Colombia approximately 6 months earlier and was living with his sister and brother-in-law. He had not traveled outside of New York State since his arrival. He was currently working in a local Mexican restaurant but had previously worked as a landscaper in Colombia. His stated risk factor for acquiring HIV was multiple female sexual partners.

In the ED, he reported a 10-lb weight loss over the past month and mild nausea with occasional acid reflux, but he denied headaches, visual changes, meningismus, difficulty breathing, chest pain, or urinary complaints. His physical examination was significant for fever, oral thrush, inguinal lymphadenopathy, and the aforementioned rash; all other findings were unremarkable.

The patient was hospitalized for 6 days, and during this time he underwent lumbar puncture. The results included 43.5 mg/dL of protein, 51 mg/dL of glucose, and 2 WBCs/mm<sup>3</sup> in the CSF. CT of the head, abdomen, and pelvis showed no abnormalities, but chest CT demonstrated multiple bilateral hilar and mediastinal lymph nodes. The chest film revealed no acute disease. Testing for cryptococcal antigen (serum and CSF) and acid-fast bacilli smears were negative.

The patient became afebrile on day 3 of admission and symptomatically improved. His discharge diagnoses included oropharyngeal candidiasis, possible HIV-related lymphoma, rash of unknown origin, and AIDS. Discharge medications included pantoprazole, 40 mg daily for acid reflux; nystatin oral suspension for thrush; metoclopramide, 5 mg three times daily as needed for nausea; and trimethoprim/sulfamethoxazole DS daily for prophylaxis against *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia (PCP). The results of skin biopsy, polymerase chain reaction of the CSF for toxoplasmosis, and VDRL of the CSF were pending at discharge.



FIGURE 1. Generalized papulosquamous rash

One day after being discharged from the hospital, the patient presented to our office to begin highly active anti-retroviral therapy (HAART). He complained of shortness of breath, fever, rash, and joint pain. The review of systems was positive for fever, night sweats, rash, dysphagia, gum pain, nonproductive cough, shortness of breath, diarrhea, and muscle weakness. His temperature was 102.9°F; BP, 93/56 mm Hg; pulse, 134 beats per minute; and oxygen saturation, 96%. The patient was thin and in obvious distress. Oropharyngeal thrush and ulcers were noted. The neck was supple with no meningismus. The lungs were clear to auscultation bilaterally, without wheezes, rhonchi, or rales. Tachycardia was present, but the heart rhythm was regular, and there were no murmurs, gallops, or rubs. The abdominal, genital, and rectal examinations were unremarkable. Strength was 5/5 throughout. The patient's gait was unsteady, with dragging of the left leg. Cranial nerves II through XII were intact; reflexes were +2/4; and there was stocking-and-glove distribution of paresthesia of the hands and feet bilaterally. A diffuse papulosquamous rash with some crusting covered his entire body.

The patient was admitted to the university hospital. The results of laboratory studies are shown in Table 1 (page 28). Bone marrow aspirates and biopsy and tests for rapid plasma reagin (RPR) and serum cryptococcal antigen were ordered as well. The differential diagnosis included secondary syphilis, cryptococcal disease, histoplasmosis, lymphoma, and psoriasis with a secondary infection.

## DISCUSSION

The RPR was nonreactive, as was the VDRL of the CSF that was pending from the patient's previous hospital admission, thus ruling out syphilis. The serum cryptococcal antigen test was negative, which ruled out cryptococcal disease. The skin biopsy report indicated leukocytoclastic vasculitis associated with dermal histoplasmosis, with the diagnosis being supported by Grocott methenamine silver (GMS) and periodic acid-Schiff stains. The bone marrow aspirate stained with GMS also revealed fungal organisms consistent with *Histoplasma capsulatum*.

**Histoplasmosis** is caused by *H capsulatum var capsulatum* and *H capsulatum var duboisii*. The former is found more

frequently in North, Central, and South America, and the latter is seen in Africa. Within the United States, histoplasmosis is most common in the Ohio and Mississippi River Valleys. Given that our patient had arrived in New York only 6 months before his symptoms began, his infection was probably a reactivation of an endogenous infection acquired in Colombia. There is controversy in the medical community regarding reactivation of endogenous latent foci versus exogenously acquired infection in HIV-infected patients, as data support both mechanisms of infection.<sup>1</sup> The skin lesions

## “Extrapulmonary, disseminated histoplasmosis is an AIDS-defining illness, according to the CDC.”

suggest that this patient was infected in Colombia, as skin lesions are more common in strains of *H capsulatum* from South America.<sup>2,3</sup>

Most often the fungus is found in soil, particularly in areas containing bird or bat droppings. These enhance the nitrogen content of the soil, providing a more suitable environment for the fungus to thrive. Outbreaks have occurred around dilapidated buildings, urban renewal projects, and construction in general, where the fungus in the soil is aerosolized and then inhaled.<sup>4</sup> Children and the immunosuppressed are at increased risk of developing symptomatic histoplasmosis.

Typically, infection begins when spores are inhaled. Macrophages ingest the fungus but do not immediately kill it. Approximately two weeks lapse before the cellular immunity required to kill the fungus develops. During this period, the macrophages may disseminate the fungus hematogenously. Subsequently, sensitized T-lymphocytes activate macrophages to develop fungicidal properties.<sup>5</sup>

Histoplasmosis may have an asymptomatic, acute, chronic, or disseminated course. Clinically, about 90% of immunocompetent patients exposed to *Histoplasma* are asymptomatic; when symptoms do develop, the illness is typically flulike and self-limited. Hilar and mediastinal lymphadenopathy can

### TEACHING POINTS

- Histoplasmosis is caused by *Histoplasma capsulatum*, a fungus found in soil. Outbreaks have occurred around dilapidated buildings, urban renewal projects, and construction in general, where the fungus in the soil is aerosolized and then inhaled.
- Histoplasmosis may have an asymptomatic, acute, chronic, or disseminated course.
- Clinically, about 90% of immunocompetent patients exposed to *Histoplasma* are asymptomatic. Children and the immunosuppressed are at increased risk of developing symptomatic histoplasmosis, and extrapulmonary, disseminated histoplasmosis is an AIDS-defining illness, according to the CDC.
- Treatment may not be required for immunocompetent patients with mild acute histoplasmosis. In the setting of HIV disease and immune suppression, however, therapy is recommended and includes amphotericin B followed by itraconazole.

### COMPETENCIES

●●●● Medical knowledge

● Interpersonal & communication skills

●● Patient care

● Professionalism

● Practice-based learning and improvement

● Systems-based practice

## CASE REPORT | Histoplasmosis

**TABLE 1. Laboratory results**

Cell immunology	
Absolute CD4+	54 cells/mm <sup>3</sup>
Absolute CD8+	346 cells/mm <sup>3</sup>
CD4+%	6.8
CD8+%	43.3
CD4+/CD8+ ratio	0.16
Viral load	3,600,000 copies/mL
Hematology	
Hematocrit	25.5%
Hemoglobin	9.1 g/dL
International normalized ratio	1.2
Platelets	500 × 10 <sup>3</sup> /μL
RBC count	3.03 × 10 <sup>6</sup> /μL
WBC count	12,200/μL
Metabolic panel	
Alkaline phosphatase:	388 IU/L
ALT	Hemolyzed
AST	Hemolyzed
BUN	30 mg/dL
Chloride	92 mEq/L
Creatinine	2.0 mg/dL
Glucose	84 mg/dL
Lactate dehydrogenase	5,089 IU/L
Potassium	5.7 mEq/L
Sodium	120 mEq/L
Urinalysis	
Glucose	Negative
Hemoglobin	2+
Ketones	Negative
Leukocyte esterase	Trace
Nitrites	Negative
pH	5.5
Protein	2+
Specific gravity	1.021

be seen on CT, as was the case in this patient. In immunocompetent patients, symptomatic infections usually resolve with supportive care alone. Ten percent of patients may develop arthritides, pericarditis, or mediastinal fibrosis, a rare complication that results in constriction of the structures and vessels surrounding the heart.<sup>6</sup>

**Disseminated disease** is more likely to occur in immunosuppressed patients. This patient's papular rash suggests progressive disseminated histoplasmosis (PDH). When there is bone marrow involvement, as the aspirate staining revealed in this patient, anemia, leukopenia, and/or thrombocytopenia may be present. This patient also had a marked elevation of his alkaline phosphatase level—a common finding with this infection, as the fungus invades the liver in up to 90% of cases of PDH. The liver is thought to bear a high burden of yeast-laden macrophages because this organ contains a great number of mononuclear phagocytes.<sup>7</sup> An elevated creatinine level and a decreased sodium level were noted but were rapidly corrected with hydration.

Another clue to the diagnosis in this patient was the extremely elevated lactate dehydrogenase (LDH) level. Corcoran and colleagues found that 73% of their patients with disseminated histoplasmosis had an LDH greater than 600 IU/L;<sup>8</sup> LDH is often used as a clinical marker for the severity of PCP. As the treatments for PCP and histoplasmosis differ, it is important to distinguish between the two and initiate the correct treatment as quickly as possible. Butt and colleagues compared AIDS patients with a diagnosis of PCP (n=120) and those with a diagnosis of histoplasmosis (n=30) and found that median LDH levels were 319 IU/L and 619 IU/L, respectively. If a patient with AIDS presents with an LDH greater than 650 IU/L, a diagnosis other than PCP should be considered—and if the clinical picture is compatible with histoplasmosis, it should be included in the differential. Note also that elevated LDH levels can be seen with lymphoma, tuberculosis, and toxoplasmosis, so such elevations should not be the sole criterion for a diagnosis of histoplasmosis.<sup>9</sup>

Diagnostic antigen testing should be performed on both urine and serum. Blood cultures for fungus should also be obtained. Specimens may also be obtained from skin or other tissue for histopathologic examination.

**Treatment** may not be required for immunocompetent patients with mild acute histoplasmosis. In the setting of HIV disease and immune suppression, however, therapy is recommended. Note also that extrapulmonary, disseminated histoplasmosis is an AIDS-defining illness according to the CDC HIV classification system.<sup>10</sup>

Treatment for disseminated histoplasmosis is amphotericin B, followed by itraconazole; dosages and length of treatment depend on the severity of the infection.<sup>11</sup> In our patient, the liposomal form of amphotericin B was used for induction therapy; this agent is less toxic and is associated with improved survival when used as induction therapy for histoplasmosis in patients with AIDS.<sup>12</sup>

When hospitalization is no longer needed, therapy can be switched to itraconazole, 200 mg twice daily, for the remain-

der of the induction period, which is 12 weeks.<sup>12</sup> In patients with HIV infection, potential drug-drug interactions with itraconazole are important to consider. For example, ritonavir, a protease inhibitor used in antiretroviral treatment, is an inhibitor of the cytochrome P-450 (CYP3A4) enzyme, as is itraconazole. Caution is necessary when using itraconazole with other pharmacologic agents, and potential drug interactions should be identified before prescribing. In patients taking multiple agents that affect CYP3A4, the dosage of itraconazole may require adjustment based on the choice of antiretroviral agent and therapeutic drug monitoring (TDM) may be required.

Our patient was treated with atazanavir, 300 mg daily; ritonavir, 100 mg daily; and a fixed-dose combination of tenofovir and emtricitabine. The inhibitory effect of ritonavir on CYP3A4 allowed the patient to take 200 mg of itraconazole once daily instead of 200 mg twice daily, as determined by TDM of the itraconazole serum concentrations.<sup>13</sup>

Authorities disagree on when treatment may be discontinued. Some argue that itraconazole may be halted once the patient's CD4+ cell count climbs above 200/mm<sup>3</sup> and one year of antifungal therapy has been completed; however, the CDC and the Infectious Diseases Society of America recommend lifelong treatment.<sup>11</sup>

A major side effect of this medication is GI upset. It also carries a black box warning that it has been associated with heart failure (HF) and should not be given to patients with cardiac dysfunction, such as HF or a history of HF; the warning is based on 58 reports of adverse event where itraconazole contributed to, or may have caused, HF. Animal studies have also demonstrated the negative inotropic effect of itraconazole. Finally, cases of hepatitis associated with this

agent have been reported, so patients should be warned of signs of hepatitis.<sup>14</sup>

When immunocompromised patients with HIV infection present with illness suggestive of fungal infection, including fever, night sweats, weight loss, and rash, the clinician should consider fungal disease, especially in endemic areas. The CDC has issued an informational bulletin on protecting workers at risk for histoplasmosis. Patients who report an occupation or hobby listed in Table 2 may be at an increased risk for acquiring histoplasmosis.<sup>15</sup>

Early, appropriate intervention can improve the success of therapy for histoplasmosis. The patient in this case has improved greatly with HAART, and his dermal lesions and other symptoms have resolved. **JAAPA**

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#### DRUGS MENTIONED

Amphotericin B (Amphocin, Fungizone Intravenous)  
Amphotericin B lipid complex injection (Abelcet)  
Atazanavir (Reyataz)  
Emtricitabine and tenofovir (Truvada)  
Itraconazole (Sporanox)  
Metoclopramide (Reglan, Reglan Syrup)  
Moxifloxacin (Avelox)  
Nystatin (Mycostatin Suspension)  
Pantoprazole (Protonix)  
Ritonavir (Novir, Novir Softgel)  
Trimethoprim/sulfamethoxazole DS (Bactrim DS, Septra DS)

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**TABLE 2. Persons at risk for exposure to *H capsulatum***

Bridge inspector or painter
Chimney cleaner
Construction worker
Demolition worker
Farmer
Gardener
Heating and air-conditioning system installer or service person
Microbiology laboratory worker
Pest control worker
Restorer of historic or abandoned buildings
Roofer
Spelunker (cave explorer)
Data from Lenhart SW et al. <sup>15</sup>