

CLINICAL MYCOLOGY COURSE

A MAN IN HIS 40S PRESENTING WITH FATIGUE AFTER TRAVEL TO GUATEMALA PRESENTED BY ILAN S. SCHWARTZ, MD, PHD



Initial Presentation

A man in his 40s who had no known medical conditions presented for evaluation because of a 1-week history of fatigue soon after travel to Latin America. The patient had engaged in sexual relations with men, although he had been celibate for several years. His travels in the past 5 years included trips to Central America, South Africa, and China. He most recently returned several weeks ago from Guatemala. He denies contact with animals, including bats or birds.

In the past 6 weeks, the patient has lost 20 pounds. He also had diarrhea with up to 5 loose bowel movements a day, although this improved a week prior to presentation when he received a course of metronidazole for traveler's diarrhea. He also has had a mild, non-productive cough for one year. He had no headache or altered sensorium reported.

Case Work-up

On examination, his vital signs were blood pressure 117/80 mm Hg, heart rate 90 beats per minute, 16 respirations per minute, and 96% oxygen saturation level on room air. His temperature was 36.1°C (97.0°F), and he appeared slightly hypovolemic. Central nervous system examination was normal. Thoracic examination was unremarkable. The spleen appeared enlarged based on a positive Castell's sign, though it was not felt by palpation.

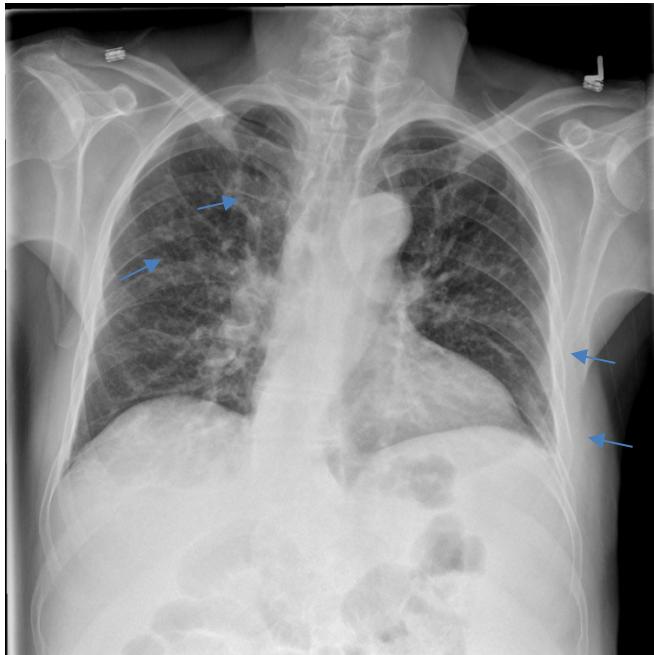
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Investigations:

- Hemoglobin 101 g/L
- Mean corpuscular volume 82 μm^3
- White blood count 1.4 (neutrophils 1.2, lymphocytes 0.1) $\times 10^9/\text{L}$
- Platelets $45 \times 10^9/\text{L}$
- Reticulocyte count 1.1%
- B12 and folate were normal
- Electrolytes showed slight hypokalemia (3.1 mmol/L) but were otherwise unremarkable
- Aspartate aminotransferase 84 IU/L, alanine transaminase (ALT) normal
- Bilirubin 19 $\mu\text{mol}/\text{L}$
- Alkaline phosphatase normal
- Lactate dehydrogenase was 600 U/L (reference range: 140-280 U/L).

Ultrasound confirmed the finding of an enlarged spleen. A chest X-ray is shown below (Figure 1).

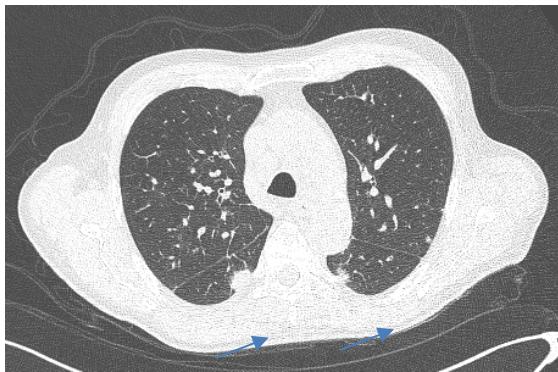
Figure 1. Chest X-ray showing numerous nodules (arrows). Courtesy of Ilan Schwartz MD, PhD.



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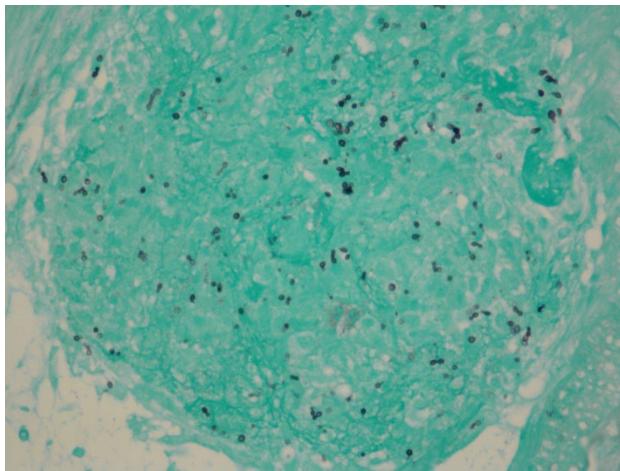
A computerized tomography (CT) scan was performed (see Figure 2), which showed numerous small nodules similar to those seen on the following representative axial view.

Figure 2. CT scan, axial view, showing numerous small nodules (arrows). Courtesy of Ilan Schwartz MD, PhD.



An HIV test was reactive. CD4 lymphocyte count was 10 cells/mm³. An endobronchial ultrasound-guided lymph node biopsy is performed. The histopathology is shown below in Figure 3.

Figure 3. Grocott methenamine silver (GMS) stain, x200. Note the small oval to round yeast-like cells with narrow based budding. Image courtesy of Lakshmi Puttagunta, MD.



Challenge Question 1. The exposure history, clinical presentation, and histopathology is most consistent with which of the following diagnoses?

- A. *Emergomyces africanus*
- B. *Histoplasma capsulatum*
- C. *Sporothrix schenckii*
- D. *Talaromyces marneffei*
- E. Consistent with all of the above

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Discussion

- A. ***Emergomyces africanus*.** *Emergomyces* species are dimorphic fungi that cause opportunistic infections in patients with advanced HIV disease and other immune compromised states. *Emergomyces africanus* is endemic to southern Africa, with most reports from South Africa. The disease, termed emergomycosis, is usually disseminated¹. Pulmonary involvement occurs in the majority of cases, and cutaneous disease is present at diagnosis in 95% of patients^{1,2}. In tissue, the yeast phase of *Emergomyces* appears similar to *Histoplasma capsulatum*, from which it cannot be reliably discerned³. Other species of *Emergomyces* include *E pasteurianus*, which has been reported from Europe, Asia, and Africa; *E. canadensis*, reported from Canada and the United States; and *E. orientalis* and *E. europaeus* from Asia and Europe, respectively¹.
- B. ***Histoplasma capsulatum*.** *Histoplasma capsulatum* is a true pathogen in the sense that it can cause disease in immune competent hosts⁴. However, in immunocompromised patients like those with advanced HIV disease, it more frequently causes disseminated (rather than localized) disease called progressive disseminated histoplasmosis. Infection can involve the blood, lymph nodes, lungs, and virtually any other body site⁵. The true geographic range of *H. capsulatum* is poorly understood, and this fungus can be found to greater or lesser degrees worldwide⁶. Nonetheless, the areas of highest incidence are Latin America and parts of the US and Canada adjacent to the St Lawrence, Ohio, and Mississippi riverways.
- C. ***Sporothrix schenckii*.** *Sporothrix schenckii* can be found worldwide on plant matter, most notably sphagnum (peat) moss, and is associated with saprotic transmission (ie, from plants to humans)⁷. In contrast, *S brasiliensis* is found only in Brazil and is associated primarily with zoonotic transmission (i.e., from animals to humans) involving cats⁸. In immunocompetent patients, sporotrichosis most commonly occurs after transcutaneous inoculation and spreads via the lymphatics, resulting in lymphocutaneous nodules that ascend the limb—a pattern sometimes known as “sporotrichoid” given the classic association with *Sporothrix*. In immunocompromised patients, however, sporotrichosis can be disseminated and clinically resembles histoplasmosis⁹. Given the degree of dissemination and the absence of association with a primary lesion (or histories of trauma), these infections may be acquired through inhalational inoculation. In tissue, *Sporothrix* yeasts may be more elongated, like cigars, but in practice it is not always easy to distinguish from the other fungi on this list³.
- D. ***Talaromyces marneffei*.** *Talaromyces marneffei* (formerly *Penicillium marneffei*) is a dimorphic fungus found in Southeast Asia that causes talaromycosis (penicilliosis), an opportunistic infection of patients with advanced HIV and other immunocompromising conditions¹⁰. Talaromycosis is typically a disseminated disease. Skin lesions are present in most patients at diagnosis. However, similar to emergomycosis, the absence of skin lesions cannot exclude the diagnosis. In tissue, the yeast-like cells of *T. marneffei* replicate by binary fission rather than by budding¹¹. Because the yeast-like cells seen in tissue in this case demonstrate budding, it cannot be talaromycosis.
- E. **Consistent with any of A-C.** The clinical syndrome described is consistent with disseminated fungal disease caused by several dimorphic fungi, including emergomycosis, histoplasmosis, and sporotrichosis.
- F. **Consistent with all the above.** The answer cannot include talaromycosis because *T. marneffei* does not bud; it replicates by binary fission.

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Correct answer: E. Given the recent travel to Latin America, histoplasmosis is suspected.

Challenge Question 2. Which test has the best sensitivity in progressive disseminated histoplasmosis?

- A. Urinary *Histoplasma* antigen
- B. Serum *Histoplasma* antibody
- C. Fungal blood culture
- D. Bronchoalveolar lavage (BAL) for fungal culture

Discussion

A. Urinary *Histoplasma* antigen.

Urinary *Histoplasma* antigen measurement is a sensitive test for progressive disseminated histoplasmosis. There are a number of different assays, but collectively their overall sensitivity in patients with progressive disseminated histoplasmosis was 95% (95% confidence interval 94-97%) in a meta-analysis¹².

B. Serum *Histoplasma* antibody.

Histoplasma antibody tests have poor sensitivity for progressive disseminated histoplasmosis. In a meta-analysis, the combined sensitivity of these tests for progressive disseminated histoplasmosis was 58% (95% confidence interval 53-62%), although individual studies of different assays have reported sensitivities of up to 90%¹².

C. Fungal blood culture.

Progressive disseminated histoplasmosis may be diagnosed by growth of *H capsulatum* from blood, bone marrow, or other affected tissue (eg, lymph node, skin, lung, etc.). However, sensitivity of culture is variable, depending on specimen type and processing¹². The specimens for which culture is the most sensitive in progressive disseminated histoplasmosis are blood, especially with lysis centrifugation, and bone marrow, ranging from 60-90%^{12,13}.

D. Bronchoalveolar lavage (BAL) for fungal culture.

In general, the yield of BAL or respiratory sample culture in patients with progressive disseminated histoplasmosis is lower than blood and bone marrow or tissues rich in immune cells (eg, lymph nodes, liver, spleen). Couppie et al¹³ reported BAL culture was positive in 45% of tested patients in a large cohort of patients with advanced HIV disease in French Guiana, compared to culture of liver (87%), lymph node (80%), bone marrow (78%), skin and oral mucosa (55%), lower digestive tract (74%), and blood (61%).

Correct answer A. Urinary *Histoplasma* antigen.

Challenge Question 3. What is the best initial treatment for progressive disseminated histoplasmosis?

- A. Liposomal amphotericin B
- B. Itraconazole
- C. Isavuconazole
- D. Liposomal amphotericin B plus micafungin

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Discussion

- A. **Liposomal amphotericin B.** Initial treatment of moderate or severe progressive disseminated histoplasmosis should include liposomal amphotericin B (3-5 mg/kg intravenously daily) for 14 days. Subsequently, treatment should include a triazole (preferably itraconazole in the absence of contraindications) for 12 months pending immune reconstitution^{14,15}.
- B. **Itraconazole.** Itraconazole is an appropriate initial treatment in patients with mild histoplasmosis^{14,15}. The patient described has severe disseminated disease, and thus itraconazole monotherapy would not be an appropriate initial treatment choice.
- C. **Isavuconazole.** Isavuconazole has been used in the treatment of histoplasmosis¹⁶, but there is substantially less experience with this drug than with itraconazole (which is substantially less expensive), and neither would be the initial treatment of choice in an immunocompromised patient with severe disease^{14,15}.
- D. **Liposomal amphotericin B plus micafungin.** In general, echinocandins are not active in vivo against *H. capsulatum*¹⁷ or other dimorphic fungi, and they would be of no added benefit over amphotericin B alone.

Correct answer: A.

Challenge Question 3. When should antiretroviral therapy (ART) be started?

- A. **5 to 7 days before starting antifungal therapy**
- B. **At the time of starting antifungal therapy**
- C. **3 to 5 days after starting antifungal therapy**
- D. **4 weeks after starting antifungals**

Discussion

- A. **5 to 7 days before starting antifungal therapy.** In general, superimposed infections complicating advanced HIV disease should be treated before starting ART¹⁵. Initiating ART prior to antifungals will result in a dangerous delay of treatment and could result in clinical worsening due to immune reconstitution inflammatory syndrome (IRIS).
- B. **At the time of starting antifungal therapy.** Initiating ART at the time of antifungal therapy is reasonable, but based on the occasional occurrence of IRIS¹⁸, concerns about drug-drug interactions and possible intolerances, it is preferred to first introduce the antifungal and then introduce ART thereafter.
- C. **3 to 5 days after starting antifungal therapy.** In the *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV*, the Centers for Disease Control and Prevention, National Institute of Health, and HIV Medical Association recommend starting ART as soon as possible *after* antifungals are initiated¹⁵. Alternatively, some experts recommend waiting at least 2 weeks after antifungals are started to initiate ART because of concerns about IRIS¹⁸.
- D. **4 weeks after starting antifungals.** Delaying ART initiation for 4 weeks is not required, and improved immune function is imperative for successful treatment of progressive disseminated histoplasmosis^{14,15}.

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Correct answer: C is the correct answer, albeit without prospective data to support it. There is limited data to guide the initiation of ART in persons living with HIV and diagnosed with histoplasmosis or other endemic mycoses. Paradoxical IRIS is uncommon in patients with histoplasmosis who are initiated on ART, but it can occur¹⁸. For this reason, some experts recommend delaying ART by several days or even weeks after antifungals are initiated^{15,18}.

Challenge Question 4. In addition to symptom review and clinical examinations, how should the patient be monitored?

- A. Serial urinary *Histoplasma* antigen
- B. Serial *Histoplasma* antibodies
- C. Serial chest CT
- D. All of the above

Discussion

- A. **Serial urinary *Histoplasma* antigen.** Serial measurement of *Histoplasma* antigen in urine can help evaluate response to therapy and can predict relapse^{15,19}. The IDSA histoplasmosis guidelines, published in 2007, recommend measuring *Histoplasma* antigen during therapy and for up to 12 months after treatment cessation¹⁴.
- B. **Serial *Histoplasma* antibodies.** Antibodies to *Histoplasma* generally decrease with clinical recovery but following these levels has not been validated to guide treatment decisions and is not recommended¹⁴.
- C. **Serial chest CT.** Serial chest imaging to evaluate response of nodules to therapy is reasonable but for the most part, X-ray should be sufficient¹⁴. The persistence of small nodules, which may or may not be calcified, does not necessitate continuation of therapy.
- D. **All of the above.** This is not the correct answer because only A is correct.

Correct answer: A.

Case Follow-up

Five months into treatment with itraconazole (capsules), the patient returns for a follow-up visit. He is short of breath, and he is noted to have pitting edema to his knees. Chest examination reveals fine basilar crepitations, and a chest X-ray confirms pulmonary edema. His CD4 count is now 250 cells/mm³.

Challenge Question 5. What is the most appropriate next step in management?

- A. Continue itraconazole capsules
- B. Switch to another formulation of itraconazole
- C. Switch to another triazole
- D. Switch to liposomal amphotericin B
- E. Stop treatment as he has likely had enough

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Discussion

- A. **Continue itraconazole capsules.** Given that the clinical presentation is likely congestive heart failure secondary to (or worse because of) itraconazole, this drug should be stopped. Itraconazole is a negative inotrope and can worsen congestive heart failure²⁰. This is true irrespective of the formulation.
- B. **Switch to another formulation of itraconazole.** Changing to another formulation of itraconazole would not help because itraconazole itself is a negative inotrope.
- C. **Switch to another triazole.** Other triazoles do not share the adverse effect of acting as negative inotropes. Unacceptably high rates of relapse were observed in patients with HIV-associated histoplasmosis treated with fluconazole in the era before ART was widely available²¹. Newer triazoles like voriconazole²², posaconazole²³, and isavuconazole¹⁶ are reasonable second-line options for patients with histoplasmosis.
- D. **Switch to liposomal amphotericin B.** Weekly amphotericin B is an option. However, given the potential toxicities associated, including nephrotoxicity and line-related complications, an oral triazole would be preferred.
- E. **Stop treatment as he has likely had enough.** Patients with progressive disseminated histoplasmosis should be treated for at least 12 months pending immune reconstitution¹⁴. Earlier treatment discontinuation may increase the risk of a relapse, although the absolute risk is unknown.

Correct answer: C.

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References

1. Schwartz IS, Govender NP, Sigler L, et al. *Emergomyces*: the global rise of new dimorphic fungal pathogens. *PLoS Pathog.* 2019; 15(9): e1007977. doi:10.1371/journal.ppat.1007977
2. Schwartz IS, Govender NP, Corcoran C, et al. Clinical characteristics, diagnosis, management and outcomes of disseminated emmonsiosis: a retrospective case series. *Clin Infect Dis.* 2015;61(6):1004-12. doi:10.1093/cid/civ439
3. Schwartz IS, Kenyon C, Lehloenya R, et al. AIDS-related endemic mycoses in Western Cape, South Africa, and clinical mimics: a cross-sectional study of adults with advanced HIV and recent-onset, widespread skin lesions. *Open Forum Infect Dis.* 2017;4(4):ofx186. doi:10.1093/ofid/ofx186
4. Wheat LJ, Azar MM, Bahr NC, Spec A, Relich RF, Hage C. Histoplasmosis. *Infect Dis Clin North Am.* 2016;30(1):207-27. doi:10.1016/j.idc.2015.10.009
5. Franklin AD, Larson L, Rauseo AM, et al. A comparison of presentations and outcomes of histoplasmosis across patients with varying immune status [published online ahead of print, 2021 Jan 13]. *Med Mycol.* 2021;myaa112. doi:10.1093/mmy/myaa112
6. Bahr NC, Antinori S, Wheat LJ, Sarosi GA. Histoplasmosis infections worldwide: thinking outside of the Ohio River valley. *Curr Trop Med Rep.* 2015;2(2):70-80. doi:10.1007/s40475-015-0044-0
7. Barros MB, de Almeida Paes R, Schubach AO. *Sporothrix schenckii* and Sporotrichosis. *Clin Microbiol Rev.* 2011;24(4):633-654. doi:10.1128/CMR.00007-11
8. Friedman DZP, Schwartz IS. Emerging fungal infections: new patients, new patterns, and new pathogens. *J Fungi (Basel).* 2019;5(3):67. doi:10.3390/jof5030067
9. Queiroz-Telles F, Buccheri R, Benard G. Sporotrichosis in immunocompromised hosts. *J Fungi (Basel).* 2019;5(1):8. doi:10.3390/jof5010008
10. Limper AH, Adenis A, Le T, Harrison TS. Fungal infections in HIV/AIDS. *Lancet Infect Dis.* 2017;17(11):e334-e343. doi:10.1016/S1473-3099(17)30303-1
11. Salzer HJF, Burchard G, Cornely OA, et al. Diagnosis and management of systemic endemic mycoses causing pulmonary disease. *Respiration.* 2018;96(3):283-301. doi:10.1159/000489501
12. Caceres DH, Knuth M, Derado G, Lindsley MD. Diagnosis of progressive disseminated histoplasmosis in advanced HIV: a meta-analysis of assay analytical performance. *J Fungi (Basel).* 2019;5(3):76. doi:10.3390/jof5030076
13. Coupié P, Herceg K, Bourne-Watrin M, et al. The broad clinical spectrum of disseminated histoplasmosis in HIV-infected patients: a 30 years' experience in French Guiana. *J Fungi (Basel).* 2019;5(4):115. doi:10.3390/jof5040115
14. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2007;45(7):807-25. doi:10.1086/521259
15. Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. . 2019.
16. Thompson GR 3rd, Rendon A, Ribeiro Dos Santos R, et al. Isavuconazole treatment of cryptococcosis and

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dimorphic mycoses. *Clin Infect Dis.* 2016;63(3):356-62. doi:10.1093/cid/ciw305

17. Hage CA, Connolly P, Horan D, et al. Investigation of the efficacy of micafungin in the treatment of histoplasmosis using two North American strains of *Histoplasma capsulatum*. *Antimicrob Agents Chemother.* 2011;55(9):4447-50. doi:10.1128/AAC.01681-10
18. Melzani A, De Reynal De Saint Michel R, Ntab B, et al. Incidence and trends in immune reconstitution inflammatory syndrome associated with *Histoplasma capsulatum* among people living with HIV: a 20-year case series and literature review. *Clin Infect Dis.* 2020;70(4):643-65. doi:10.1093/cid/ciz247
19. Hage CA, Kirsch EJ, Stump TE, et al. *Histoplasma* antigen clearance during treatment of histoplasmosis in patients with AIDS determined by a quantitative antigen enzyme immunoassay. *Clin Vaccine Immunol.* 2011;18(4):661-666. doi:10.1128/CVI.00389-10
20. Ahmad SR, Singer SJ, Leissa BG. Congestive heart failure associated with itraconazole. *Lancet.* 2001;357(9270):1766-7. doi:10.1016/S0140-6736(00)04891-1
21. Wheat J, MaWhinney S, Hafner R, et al. Treatment of histoplasmosis with fluconazole in patients with acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Acquired Immunodeficiency Syndrome Clinical Trials Group and Mycoses Study Group. *Am J Med.* 1997;103(3):223-32. doi:10.1016/s0002-9343(97)00151-4
22. Freifeld A, Proia L, Andes D, et al. Voriconazole use for endemic fungal infections. *Antimicrob Agents Chemother.* 2009;53(4):1648-51. doi:10.1128/AAC.01148-07
23. Restrepo A, Tobón A, Clark B, et al. Salvage treatment of histoplasmosis with posaconazole. *J Infect.* 2007;54(4):319-27. doi:10.1016/j.jinf.2006.05.006