

CLINICAL VIGNETTE

Hold that Fluconazole: Cross-reactivity of *Coccidioides* and *Histoplasma* Testing After Spelunking in Puerto Rico

Hannah Shull, M.D., and Michael Cohen, M.D.

Introduction

Diagnosis of systemic infection with endemic mycoses is often acquired by serologic testing and the cross-reactivity of these tests to different fungi can sometimes make interpretation of results confusing. Through history, clinical awareness, and proper testing, one can abrogate diagnostic uncertainty and improve decisions in the treatment of these infections.

Case Presentation

A 23-year-old male with no prior medical history presented to his primary physician complaining of 10 days of chest pain that was pleuritic in nature, which he felt was due to a fall while playing soccer. A few weeks prior to this, he had an isolated fever with no other associated symptoms. A chest X-ray showed three small pulmonary nodules. A CT scan demonstrated mediastinal adenopathy with multiple, in excess of 100, sub centimeter bilateral pulmonary nodules with surrounding ground glass opacification. Concern was for lymphoma, vasculitis, sarcoidosis, or granulomatous infection with fungus or mycobacteria. The patient was referred to Pulmonary Clinic where it was elicited that he recently returned home from a vacation in Puerto Rico, but review of systems was negative for any other pulmonary or infectious symptoms. Consideration for biopsy of a nodule after multiple serologies were ordered. Additionally, a subsequent PET scan showed multiple hypermetabolic mediastinal and bilateral hilar lymph nodes, more consistent with an inflammatory process such as sarcoidosis or infection and with lymphoma being less likely.

Serologic testing was negative for tuberculosis, *Cryptococcus*, and anti-neutrophil cytoplasmic antibody, and his angiotensin converting enzyme level was normal. He was then found to have a positive *Coccidioides* complement fixation (CF) at a titer of 1:8, but EIA was negative for *Coccidioides* IgM and IgG. In consideration of the findings on chest CT, living in Southern California and a positive Cocci CF titer, the patient was felt to have pulmonary coccidioidomycosis and prescribed fluconazole. Afterward, his histoplasmosis urine antigen test resulted, which showed him to have a “positive result, below the limit of quantification”.

He was then referred to Infectious Diseases Clinic where a comprehensive travel history elicited that he had been only in the Los Angeles urban area and had not travelled to any of the

highly coccidioides endemic central valleys of California or Arizona. In addition, while in Puerto Rico he had gone spelunking in the *Aguas Buenas* caves, which are known for documented cases of histoplasmosis and high levels of *Histoplasma* carriage in the local cave bats.¹ At this time, he was now experiencing persistent night sweats and occasional non-productive cough despite 2 weeks of fluconazole. Given the additional travel history, concern was for pulmonary histoplasmosis and that fluconazole may not be effective. The patient was prescribed itraconazole and serology for histoplasmosis was shown to be Mycelial (M) band positive. He had rapid improvement and completed 3 months of itraconazole with resolution of all symptoms. Repeat CT of the chest at 3 months showed improved, calcified, sub centimeter nodules, much less in number than prior; it was considered consistent with resolved Histoplasmosis.

Discussion

The endemic mycoses such as *Histoplasma* and *Coccidioides* carry a significant disease burden in the specific localities where they are prevalent. Fortunately, they are generally well recognized and usually suspected due to clinical awareness by clinicians in these areas. Exposure during travel and then returning to a non-endemic area often results in diagnostic difficulty due to less clinical experience with these infections in non-endemic areas. Due to species specific differences in treatment recommendations and different anti-microbial sensitivities accurate diagnosis is essential for proper treatment. Considering there is significant overlap in clinical presentation, a thorough travel history and appropriate laboratory testing are key to extracting an exact diagnosis.

Coccidioidomycosis is endemic to the central valleys and deserts of California and Arizona and continues to have fluconazole utilized as a cornerstone of treatment. On the other hand, Histoplasmosis, which is another dimorphic fungus with a larger geographic spread, is relatively resistant to fluconazole and requires treatment with a broader anti-fungal possessing better mold activity, such as itraconazole. Therefore, it would seem crucial to carefully diagnose the correct fungi in cases of significant infection. Both these fungi can present similar clinical scenarios of granulomatous lung disease as was seen in our patient. Some clues that may help elicit the true pathogen

are travel and exposure history and subtle diagnostic differences such as less calcification or diffuse nodular disease with *Coccidioides* lung infection, although imaging is often indistinguishable.² This patient had possible risks for both *Coccidioides* and *Histoplasma* with confounding laboratory results initially showing positive *Coccidioides* complement fixation but negative EIA. There has been prior documented cross-reactivity between *Histoplasma* and *Coccidioides* testing, so the clinician must be aware of this for if risk for both pathogens exists. Extensive history, laboratory testing, and even tissue biopsy may be needed to ensure proper diagnosis and treatment.

Urine histoplasmosis antigen testing has significant false-positivity due to cross-reactivity with other fungal infections. This has been documented with coccidioidomycosis and thus there is always a consideration of false positivity in patients with risks for both organisms.³ Urine histoplasmosis antigen testing has an estimated up to a 90% cross-reactivity with blastomycosis and, to a much lesser extent, estimated 20% with *Coccidioides*. Antibody levels and EIA testing may be more sensitive than antigen testing in low level or subacute cases, and *Histoplasma* antibody positive M (mycelial) bands may be more specific.⁴ Even with *Coccidioides* testing using both EIA and complement fixation, there has been false positivity due to cross-reaction with histoplasmosis,⁵ and *Coccidioides* complement fixation testing has long been known to cross react with antigens of *Histoplasma* and *Blastomycosis*.⁶

Conclusion

Serologic testing for exposure to endemic mycoses can sometimes be difficult to interpret especially in patients with risk factors for exposure to different species. EIA methods may possibly be more reliable as there is significant cross-reactivity with complement fixation testing. In these cases, multiple serologic methods may need to be combined to help determine the likely pathogen and one can consider tissue biopsy when results seem confounding.

REFERENCES

1. **Ashford DA, Hajjeh RA, Kelley MF, Kaufman L, Hutwagner L, McNeil MM.** Outbreak of histoplasmosis among cavers attending the National Speleological Society Annual Convention, Texas, 1994. *Am J Trop Med Hyg.* 1999 Jun;60(6):899-903. PubMed PMID: 10403317.
2. **Gupta NA, Iv M, Pandit RP, Patel MR.** Imaging manifestations of primary and disseminated coccidioidomycosis. *Applied Radiology.* 2015; 9-21.
3. **Kauffman CA.** Histoplasmosis: a clinical and laboratory update. *Clin Microbiol Rev.* 2007 Jan;20(1):115-32. Review. PubMed PMID: 17223625; PubMed Central PMCID: PMC1797635.
4. **Hage CA, Ribes JA, Wengenack NL, Baddour LM, Assi M, McKinsey DS, Hammoud K, Alapat D, Babady NE, Parker M, Fuller D, Noor A, Davis TE, Rodgers M, Connolly PA, El Haddad B, Wheat LJ.** A multicenter evaluation of tests for diagnosis of histoplasmosis. *Clin Infect Dis.* 2011 Sep;53(5):448-54. doi: 10.1093/cid/cir435. Erratum in: *Clin Infect Dis.* 2012 Feb 1;54(3):454. PubMed PMID: 21810734.
5. **Kuberski T, Myers R, Wheat LJ, Durkin M, Connolly P, Kubak BM, Bruckner D, Pegues D.** Diagnosis of coccidioidomycosis by antigen detection using cross-reaction with a *Histoplasma* antigen. *Clin Infect Dis.* 2007 Mar 1;44(5):e50-4. PubMed PMID: 17278049.
6. **Kaufman L, Clark MJ.** Value of the concomitant use of complement fixation and immunodiffusion tests in the diagnosis of coccidioidomycosis. *Appl Microbiol.* 1974 Oct;28(4):641-3. PubMed PMID: 4213789; PubMed Central PMCID: PMC186788.

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