Antibody testing to distinguish between histoplasmosis and blastomycosis

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DESCRIPTION

A 35-year-old man presented to the emergency department with headaches, productive cough and fevers to 39°C. Medical history was significant for chronic back pain. He lived in the Midwest USA, smoked 20 cigarettes a day, drank alcohol socially and did not use drugs. He worked in construction specifically doing demolitions work, including soil removal. Laboratory evaluation showed white cell count of 6.7x10^9/L (normal 3.7–10.5 x10^9/L) and C reactive protein of 6.6 mg/dL (normal <0.5 mg/dL). CT revealed numerous bilateral pulmonary nodules with hilar lymphadenopathy (figure 1).

Differential diagnosis included endemic mycoses, sarcoidosis and malignancy. Highest concern was for endemic mycosis since patient lived in the Midwest USA and worked in construction. He unfortunately could not provide sputum hence no sputum culture was sent. Serum antigen assays were obtained: serum histoplasma antigen level was 3.50 ng/mL (normal <0.4 ng/mL) and serum blastomyces antigen level was 5.00 ng/mL (normal <0.2 ng/mL). We were unable to determine which mycosis he had since the antigen assays are known to cross react. Given that both infections are treated identically, the patient was started on oral itraconazole therapy. In an attempt to determine the true aetiology of his infection, serum antibody testing was performed. Antibody testing is typically performed with immunodiffusion (ID) and/or complement fixation (CF) to maximise sensitivity and specificity. The ID test looks for H or M precipitins, while the CF test evaluates yeast or mycelial antibody titers.[1 2] In our patient, histoplasma M precipitin was detected while H precipitin was not detected and CF titers were negative (<1:8). The M band often appears earlier than the H band and is found in around 70% of histoplasmosis cases.[3] Given the presence of histoplasma M precipitin and the absence of blastomyces antibodies, we concluded that this patient's endemic mycosis was histoplasmosis. After 6 months of itraconazole therapy, his symptoms had completely resolved, repeat antigen testing was negative and a repeat CT scan showed near resolution of his numerous lung nodules (figure 2).

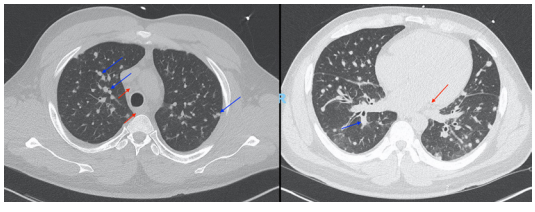

Figure 1 CT scan on initial presentation. Multiple bilateral pulmonary nodules (blue arrows) in a random distribution associated with mediastinal bilateral hilar lymphadenopathy (red arrows), favoured to represent either systemic granulomatous disease or metastatic disease with unknown primary.

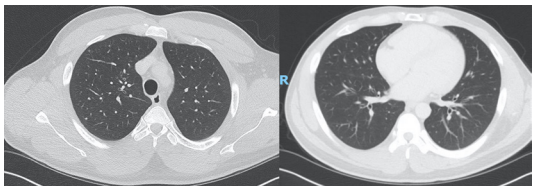

Figure 2 CT scan 6 months after initial presentation. Interval resolution of previously seen lymphadenopathy, and significant interval decreases in bilateral lung nodules.

Histoplasmosis is the most common endemic mycosis in the USA, with an estimated 60%–90% of individuals living in the Ohio and Mississippi River valleys exposed to the causative agent *Histoplasma capsulatum*.[4] Infection with *Histoplasma* is often asymptomatic or self-limited, but it can cause both local and disseminated disease.[5] Histoplasmosis is known to mimic malignancy, and it needs to be considered in the differential diagnosis of pulmonary malignancy.[6] When pulmonary mycosis is suspected, one of the challenges clinicians face is accurate diagnosis.[7] Culture and cytopathology are the gold standard for diagnosis. Obtaining an adequate specimen can be challenging due to need for invasive procedures (bronchoscopy), so serological testing is the preferred alternative.[5] Antigen testing for histoplasmosis has a sensitivity of 83% for detection of pulmonary histoplasmosis[8] whereas blastomyces antigen testing has 76% sensitivity for diagnosing pulmonary infection.[9] Antigen testing for disseminated disease is more sensitive from the urine (95% sensitivity in disseminated infection) than the serum (86% sensitivity in disseminated infection).[10] One diagnostic strategy for making an accurate diagnosis is to combine antigen and antibody testing, which can increase sensitivity to 96%.[8]

There is high cross-reactivity of the histoplasma and blastomyces antigen assays, with >60% of positive blastomyces urinary antigen assays cross reacting with histoplasmosis antigen assay,[11] and there is cross-reactivity between antibody assays for these two organisms as well. Another factor to consider when using antibody-based testing is that false negative testing may occur during early infection prior to antibody production.[2] In addition, the

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ordering provider should be aware of local prevalence of particular mycoses since this will affect positive and negative predictive values of testing assays.

If no suggestive extrapulmonary symptoms are present, one strategy to distinguish these two infections is simultaneous histoplasma and blastomyces antibody testing. If only one of these antibody markers is present it can guide the clinician to the true underlying pathology. In the above case, histoplasma antibody testing was positive while blastomyces antibody testing was negative, suggesting that histoplasma was the true disease process despite both antigen tests being positive. While antibody testing can be a useful diagnostic tool, results need to be interpreted in the context of the clinical scenario and should not be used as a stand-alone diagnostic tool.

Learning points

- Pulmonary histoplasmosis and blastomycosis present similarly with fever, lymphadenopathy and pulmonary nodules.
- Antigen testing of histoplasma and blastomyces is useful for initial diagnosis of mycoses, however, due to the high cross-reactivity of antigen assays, antibody testing can provide additional data for distinguishing between these mycoses.
- Pulmonary mycoses can masquerade as malignancy and providers should consider mycoses on the differential in patients with pulmonary nodules.

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