Histoplasmosis in Solid Organ Transplant Recipients

To the Editor—Cuellar-Rodriguez et al [1] present a review of their experience with the diagnosis and management of progressive disseminated histoplasmosis (PDH) in a large cohort of patients who had undergone solid organ transplantation. We comment upon some aspects of the observations and conclusions they have proposed in this important and timely report.

In their case definitions of clinical scenarios, the authors include as proven cases of active infection the coexistence of compatible clinical manifestations (undefined) and the histopathologic observation of yeast forms compatible with *Histoplasma capsulatum*. They report that yeast forms were observed in 9 explanted lung/lymph node specimens and in 4 donor lung specimens. In an additional patient, similar findings were present in the spleen removed during liver transplantation. Symptoms and laboratory examinations compatible with posttransplantation histoplasmosis were not identified in this group, prompting the authors to speculate that this may have resulted from the effectiveness of a standardized posttransplantation regimen of inhaled amphotericin B followed by an 18-month course of itraconazole (for lung transplant recipients) or fluconazole (for liver transplant recipients). This conclusion was based upon their presumption that these patients were at risk for “reactivation” of latent foci of viable *H. capsulatum*, which had been harbored within granulomas. However, there is no evidence that supports this premise. Convincing evidence to the contrary may be gleaned from an autopsy series [2] in which calcified granulomas were examined and 67% found to contain typical yeast forms. Fungal cultures of the contents of the granulomas were sterile and inoculation into experimental animals failed to cause infection; the investigators concluded that the yeast forms were not viable. In addition, reactivation did not occur in any of the 449 solid organ transplant recipients observed at Indiana University over a 3-year period (1283 patient-years), many of whom had serologic (24%) and radiographic (4%) evidence of old histoplasmosis and for whom antifungal prophylaxis was not used routinely [3].

The authors also speculate regarding the unanticipated presence of yeast-like forms in both explanted and donor organs, particularly in lung transplantation. The presence of asymptomatic granulomas within lung tissue and its adjacent lymph nodes, as well as the spleen, are reflective of the region’s endemicity for histoplasmosis [4], an infection which occurs asymptptomatically and/or is unrecognized in as many as 95% of affected individuals. In view of this, the opportunistic infections reported in the Cleveland Clinic series might be more likely attributable to environmental exposure [5] than to reactivation of latent foci of infection.

Lastly, our experience with the *Histoplasma* urine antigen assay (Table 1) performed on individuals with culture-proven PDH does not comport with that presented in the Cleveland Clinic series. In the latter, of 13 patients in whom antigen testing was performed, all of whom had *H. capsulatum* recovered from blood cultures, only 9 (69%) were antigen positive. This contrasts with our Indianapolis experience, in which urine antigen test results were positive for 100% of patients with PDH confirmed by culture and of those with negative culture results and for 92% of patients with PDH in whom cultures were not performed.

### Acknowledgments

**Potential conflicts of interest.** L.J.W. is an employee of MiraVista Diagnostics, the laboratory that performs the *Histoplasma* antigen test. C.H. and M.B.K.: no conflicts.

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### Table 1. Histoplasma Antigen Detection in Patients with Progressive Disseminated Histoplasmosis at Indiana University Medical Center

<table>
<thead>
<tr>
<th>Underlying condition</th>
<th>Culture-positive patients</th>
<th>Culture-negative patients</th>
<th>Culture not done</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ transplantation</td>
<td>19/10</td>
<td>3/3</td>
<td>5/5</td>
<td>18/18 (100)</td>
</tr>
<tr>
<td>Receipt of TNF blocker</td>
<td>3/3</td>
<td>9/9</td>
<td>6/7</td>
<td>18/19 (94.7)</td>
</tr>
<tr>
<td>Total</td>
<td>13/13 (100)</td>
<td>12/12 (100)</td>
<td>11/12 (91.7)</td>
<td>36/37 (97.2)</td>
</tr>
</tbody>
</table>

**NOTE.** TNF, tumor necrosis factor.
Organ of the Recipient or in Donor Tissue” [3].

Whether remote primary latent histoplasmosis represents a risk for reactivation is still controversial. As for many other diseases, the best evidence to support this possibility comes from published reports in which patients with different types of immunocompromise from endemic areas, develop active infection years after they move to areas where it is not endemic [4–8]. This scenario has been reported for patients with AIDS, solid organ transplant recipients, and recipients of tumor necrosis factor blockers. As mentioned in our study, it is routine practice in our hospital for lung transplant recipients to be provided with antifungal prophylaxis; therefore, we were unable to assess whether the group of patients with histologic evidence of histoplasmosis alone would or would not develop active disease absent this approach. The valuable incidence study by Vail et al [2] states that antifungal therapy courses were not recorded for solid organ transplant recipients, limiting conclusions regarding why no cases were seen. Ongoing concerns encouraging ongoing clinical evaluation include significant morbidity and mortality in cases of invasive fungal disease after lung transplantation [9, 10].

We agree with Hage and colleagues’ observation that the histologic finding of yeast-like forms compatible with histoplasmosis in lung, lymph nodes, and spleen are a reflection of regional endemcity or prior exposure to histoplasmosis. This is why we believe that physicians caring for lung transplant recipients in areas of endemicity and of nonendemicity (ie, unexpected histoplasmosis in donor tissue) may be confronted with this scenario. To our knowledge, there are no published reports on the specific management of these patients.

Lastly, regarding the Histoplasma urine antigen assay, we agree that the percentage of positive results in our study is lower than in some reports. As stated in our discussion, this was a 10-year review, so earlier patients were tested with previous versions of the assay. In addition, some of our patients started receiving antifungal empirical therapy before the assay specimens were collected. Finally, not all patients had positive blood culture results; some had positive bone marrow culture results or positive bronchoalveolar lavage fluid culture results (see Table 2 in the original publication) [3].

Fungal infections after solid organ transplantation remain a serious contributor to morbidity and mortality. Current guidelines suggest prophylaxis in some immunocompromise settings as a C-III recommendation [11]. As varied centers report data in this vulnerable patient population, our experience and understanding will progress, allowing more-informed diagnostic and tailored treatment approaches.

Acknowledgments

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Reply to Hage et al

To the Editor—We appreciate the interest shown by Hage et al [1] in our manuscript, and we would like to take the opportunity to clarify and reiterate some points.

Patients were only classified as having proven active histoplasmosis if there was a combination of clinical manifestations (eg, fever, cough, new lung infiltrates, and weight loss) and either microbiologic or histologic evidence of histoplasmosis, in similar method described in the histoplasmosis incidence survey among transplant recipients by Vail et al [2]. In our study, 14 patients fulfilled these criteria. Patients in whom yeast forms compatible with Histoplasma capsulatum were seen but who did not have clinical symptoms were not considered to have proven active histoplasmosis and were placed in a completely different scenario—namely, “Evidence of Histoplasmosis in the Explanted Organ of the Recipient or in Donor Tissue” [3].

Whether remote primary latent histoplasmosis represents a risk for reactivation is still controversial. As for many other diseases, the best evidence to support this possibility comes from published reports in which patients with different types of immunocompromise from endemic areas, develop active infection years after they move to areas where it is not endemic [4–8]. This scenario has been reported for patients with AIDS, solid organ transplant recipients, and recipients of tumor necrosis factor blockers. As mentioned in our study, it is routine practice in our hospital for lung transplant recipients to be provided with antifungal prophylaxis; therefore, we were unable to assess whether the group of patients with histologic evidence of histoplasmosis alone would or would not develop active disease absent this approach. The valuable incidence study by Vail et al [2] states that antifungal therapy courses were not recorded for solid organ transplant recipients, limiting conclusions regarding why no cases were seen. Ongoing concerns encouraging ongoing clinical evaluation include significant morbidity and mortality in cases of invasive fungal disease after lung transplantation [9, 10].

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