Disseminated Histoplasmosis in Persons with Interferon-γ Receptor 1 Deficiency

Christa S. Zerbe and Steven M. Holland

1University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; and 2Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

(See the article by de Moraes-Vasconcelos et al. on pages e31–7)

Mutations in the interferon (IFN–γ) receptor predispose to infection with bacille Calmette-Guérin, nontuberculous mycobacteria, and Salmonella organisms. We identified a patient with recurrent disseminated Histoplasma capsulatum osteomyelitis who had an autosomal dominant form of IFN-γ receptor 1 deficiency (i.e., a 4-bp deletion at or near base 818). IFN-γ-mediated immunity is important in the control of histoplasmosis.

There are very few inherited syndromes involving susceptibility to fungal infection. Mucocutaneous candidiasis occurs in persons with autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia [1], several types of severe combined immunodeficiency [2], chronic mucocutaneous candidiasis [3], and hyperimmunoglobulinemia E recurrent infection (also known as "Job syndrome") [4]. In these diseases, Candida infections tend to be restricted to the mucous membranes or to the nails and do not usually cause systemic infection. In contrast, spontaneous invasive filamentous fungal infections, such as aspergillosis, occur almost exclusively in persons with chronic granulomatous disease [5]. In Job syndrome, there are case reports of invasive aspergillosis [4, 6], ileocecal histoplasmosis [7–9], and esophageal cryptococcosis [10].

Exposure to Histoplasma capsulatum is quite extensive, especially in the midwestern United States [11]. Goodwin et al. [11] reviewed cases of primary disseminated histoplasmosis at Vanderbilt University Medical College (Nashville, TN) between 1932 and 1978 and reported a rate ranging from 1 case/100,000 population to 1 case/500,000 population. In addition, higher rates among children and among 3 sibling pairs were identified in the 102 total cases they examined, suggesting that familial genetic factors might be involved [11]. More recently, disseminated histoplasmosis has been reported in CD40 ligand deficiency, one of the forms of X-linked hyperimmunoglobulin M syndrome (table 1) [12–14, 18]. There is 1 report of successful immune control of pulmonary histoplasmosis in an individual with hypogammaglobulinemia, indicating the superfluity of antibody production to Histoplasma containment and elimination [15]. To our knowledge, there are no reported cases of histoplasmosis in persons with agammaglobulinemia, severe combined immunodeficiency, or chronic granulomatous disease. Although Histoplasma organisms cause infection in persons with advanced HIV infection, most of these cases occurred during the era before adequate prophylaxis and potent antiretrovirals were available [19]. Of interest, among organ transplant recipients, Histoplasma infection is quite rare, even in areas of endemicity [20]. Therefore, the occurrence of a relatively rare disseminated infection in individuals with rare genetic syndromes suggests a causal link.

Case report. A white boy aged 3 years and 8 months who was native to Tennessee and the child of unrelated parents was admitted to the hospital in 1991 with recurrent fever, hepatosplenomegaly, and left cervical adenopathy unresponsive to empiric antibiotic therapy. There was no family history of infection or household illness. A chest radiograph showed large right paratracheal lymphadenopathy with right middle and lower lobe pneumonia. The erythrocyte sedimentation rate was 121 mm/h. Results of a purified protein derivative skin test were negative. Results of a fungal serological test were positive for H band; results of complement fixation test were positive for Histoplasma yeast, and mycelial forms of the organism were detected at a titer of 1:64. Bronchoscopic washings, a sputum specimen, and a bone marrow aspirate all grew H. capsulatum on pure culture. After a 6-day course of oral ketoconazole therapy to which there was no response, treatment was switched to amphotericin B for 10 days, followed by oral ketoconazole for 10 months. Of note, during this hospitalization episode and twice later, gastric aspirates (but no other specimens) tested positive for Mycobacterium avium complex (MAC), but these findings were not considered to be pathologic.

At the age of 4 years and 6 months, the patient was admitted for fever, night sweats, and hepatosplenomegaly. The erythrocyte sedimentation rate was 124 mm/h. Chest radiography revealed bilateral interstitial pulmonary infiltrates. CT showed...
Susceptibility to nontuberculous mycobacterial infections is linked to mutations in the genes encoding IFN-γR1, IFN-γ receptor 2 (IFN-γR2), IL-12–receptor subunit β1, IL-12 subunit p40, signal transduction and activator of transcription 1, and the NFκB essential modulator [23, 24]. Certain viral infections (e.g., those due to cytomegalovirus, varicella-zoster virus, and respiratory syncytial virus) have been reported to be more often disseminated and severe in cases of complete IFN-γ receptor deficiency. However, this is unlikely, because there were extensive samples taken from bone marrow and other sites that did not grow or show mycobacteria until much later during the course of illness, indicating that MAC was not yet disseminated at the time when histoplasmosis was initially identified.

In vitro study showed diminished, but not absent, IFN-γ–induced TNF-α upregulation. Subsequent genetic study showed the typical 818del4 deletion in IFNGR1, which leads to autosomal dominant IFN-γ receptor deficiency (case 38I in the study by Jouanguy et al. [21]). This mutation is characterized by the presence of a single normal allele of the IFN-γ receptor 1 (IFN-γR1) and a truncated mutant allele (818del4), which exerts a dominant negative effect on IFN-γ responsiveness but does not completely abrogate it [23].

Results and discussion. Several features indicate that the development of disseminated histoplasmosis in this patient was due to a defect in the IFN-γ immune response. His infection was disseminated at the outset and was treatment refractory, despite several episodes of definitive therapy, both of which are uncommon features in the immunocompetent host. The identification of MAC in the initial gastric aspirates raises the theoretical possibility that the mycobacterial infection was some sort of immunosuppressive event that facilitated disseminated histoplasmosis [22]. However, this is unlikely, because there were extensive samples taken from bone marrow and other sites that did not grow or show mycobacteria until much later during the course of illness, indicating that MAC was not yet disseminated at the time when histoplasmosis was initially identified.

Treatment with clarithromycin, clofazimine, ethambutol, and amikacin was restarted, and the patient was referred to the National Institutes of Health (Bethesda, MD). Closed needle biopsy of the left distal femur showed granulomatous inflammation and a single acid-fast rod. Subcutaneous treatment with IFN-γ (50 μg/m²) was given 3 times/week. After addition of IFN-γ, he had progressive clearing of all bone lesions, and normalization of the erythrocyte sedimentation rate. Maintenance therapy has consisted of prophylactic itraconazole, azithromycin, and IFN-γ, and mycobacterial or fungal disease has not recurred. Examination during a follow-up visit at 17 years of age revealed that he was healthy.

In Table 1, Characteristics of invasive histoplasmosis in persons with primary immunodeficiency.

<table>
<thead>
<tr>
<th>Immunodeficiency, site or type of infection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked hyperimmunoglobulin M syndrome (CD40L)</td>
<td>[12]</td>
</tr>
<tr>
<td>Esophagus</td>
<td>[13]</td>
</tr>
<tr>
<td>Systemic</td>
<td>[14]</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>[7]</td>
</tr>
<tr>
<td>Job syndrome</td>
<td>[8]</td>
</tr>
<tr>
<td>Ileocecal</td>
<td>[9]</td>
</tr>
<tr>
<td>Colon</td>
<td>[15]</td>
</tr>
<tr>
<td>Systemic</td>
<td>[16]</td>
</tr>
<tr>
<td>Hypogammaglobulinemia, lung (limited)</td>
<td>[17]</td>
</tr>
<tr>
<td>Common variable hypogammaglobulinemia, meningitis</td>
<td>[18]</td>
</tr>
<tr>
<td>Common variable immunodeficiency, colon</td>
<td>[19]</td>
</tr>
<tr>
<td>Disseminated histoplasmosis, multifocal osteomyelitis</td>
<td>PR</td>
</tr>
</tbody>
</table>

NOTE. PR, present report.
mosis in the mouse model has been shown to be IL-12 dependent and mediated by IFN-γ [27].

Mutations in the genes encoding IFN-γR1 and IFN-γR2 occur in both autosomal recessive (complete or partial) and dominant forms with distinct phenotypes [26]. Nontuberculous mycobacterial and bacille Calmette-Guérin osteomyelitis are common in patients with the dominant form of IFN-γR1 deficiency, as was found in this child [21, 26]. The reasons for the occurrence of mycobacterial osteomyelitis in the autosomal dominant form of IFN-γR1 deficiency are not known, but this child’s clinical presentation with multifocal recurrent Histoplasma osteomyelitis may be a reflection of this specific autosomal dominant mutation.

The absence of histoplasmosis in patients with X-linked agammaglobulinemia and chronic granulomatous disease indicates that neither antibody formation nor superoxide generation are important in the susceptibility to or control of histoplasmosis. In contrast, the occurrence of histoplasmosis in persons with CD40 ligand deficiency points to the functions of T cells, monocytes, and macrophages as the critical elements in control of this infection. Along these lines, CD4+ T lymphocytopenia may be risk factor as well, but this has not been well characterized. This is in accord with observations from transplant experiences, in which Histoplasma infections appear to be related to immune suppression involving steroids, which suppresses both T cell, monocyte, and macrophage function [28–32]. However, even transplant-related Histoplasma infection is a relatively uncommon event, because long-term follow-up analysis involving 1283 patient-years of data in an area of endemicity near Indianapolis, Indiana, did not show any infections [20]. A similar paucity of histoplasmosis infections is found in persons with advanced HIV infection [19, 33].

This case suggests that disseminated histoplasmosis should be added to the list of infections that prompt clinicians to consider additional investigation of the IFN-γ–IL-12 pathway, after HIV infection and CD40 ligand deficiency have been excluded. The accompanying report of disseminated paracoccidioidomycosis in a Brazilian patient with IL-12 receptor deficiency by de Moraes-Vasconcelos et al. [34] further indicates that this pathway is important in the control of invasive yeasts. The addition of these genetic defects to those few that are recognized to predispose to invasive infection with Histoplasma species and paracoccidioidomycosis indicates that the IFN-γ–IL-12 pathway is crucial in the control of these intracellular fungal infections. It is noteworthy that histoplasmosis and mycobacteria (i.e., bacille Calmette-Guérin and some of the nontuberculous mycobacteria) are similarly affected by mutations in these pathways: in the normal host, these infections are contained in the lung and are successfully controlled. In the immunocompromised host, such as those with defects in the IFN-γ–IL-12 axis, these infections cause disseminated or extrapulmonary presentations. The similar clinical picture caused by Histoplasma organisms and mycobacteria in these patients suggests a strong link in the control mechanisms.

This suggests that disseminated histoplasmosis may have been a presentation-associated finding for other patients with undiagnosed IFN-γ receptor defects. Most of these defects can be identified by flow cytometry for detection of the IFN-γR1 molecule: overaccumulation of the receptor on the cell surface is indicative of the dominant negative partial form of IFN-γR1 deficiency, whereas no detection of IFN-γR1 by flow cytometry is consistent with the complete recessive deficiency. In vitro studies can be performed in research laboratories to quantify the amount of TNF-α produced in response to IFN-γ stimulation, as well. Genetic sequencing of the gene encoding IFN-γR1 is also available in commercial and research centers.

As was recently well illustrated by Dorman et al. [26], the presence of even a small level of IFN-γ reactivity, as seen in persons with dominant negative IFN-γR1 defects, is a significant factor in the overall survival rate, the spectrum of infections, and the nature of the histopathologic findings. The occurrence of limited, granulomatous infection with osteomyelitis in individuals with disseminated histoplasmosis is extremely close in phenotype to that seen with nontuberculous mycobacteria. The fact that there is such a strong similarity in the clinical phenotype of infections in the dominant negative form of IFN-γR1 deficiency suggests that there may also be similarities to be found among patients with complete recessive defects in IFN-γR1, such as widespread, poorly controlled disease with high burden of organisms in the body. This disseminated phenotype was seen in some of the patients described in the first comprehensive compilation of disseminated histoplasmosis, but it preceded the age molecular diagnostic testing [11]. Therefore, we suggest that patients with severe, refractory, extrapulmonary, or disseminated presentations of H. capsulatum infection be considered for evaluation of the IFN-γ–IL-12 pathway.

Acknowledgments

We thank Susan Pilch for expert assistance with information technology. Potential conflicts of interest. C.S.Z. and S.M.H.: no conflicts.

References

5. Winkelstein JA, Marino MC, Johnston RB Jr, et al. Chronic granulo-