The Pathologic Spectrum of Gastrointestinal and Hepatic Histoplasmosis

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Abstract

We characterized the pathologic spectrum of lesions in gastrointestinal and hepatic histoplasmosis by studying cases of disseminated disease in immunocompromised and immunocompetent patients from endemic and nonendemic areas. We evaluated 56 specimens from 52 patients with H&E and silver stains. Of these patients, 43% presented with gastrointestinal rather than pulmonary symptoms. Thirty-one percent had gastrointestinal lesions, 10% had liver lesions, and 43% had both. Gross gastrointestinal features included ulcers (49% of patients), nodules (21%), hemorrhage (13%), obstructive masses (6%) and normal mucosa (23%). Microscopic gastrointestinal findings included diffuse lymphohistiocytic infiltration (83%), ulceration (45%), lymphohistiocytic nodules (25%), or minimal inflammatory reaction (15%) but only rare well-formed granulomas (8.5%). The most common hepatic finding was portal lymphohistiocytic inflammation; discrete hepatic granulomas were seen in less than 20% of involved livers. The pathologist must be aware of the broad range of gastrointestinal and hepatic lesions produced by histoplasmosis and, in particular, that well-formed granulomas are rare. Given the appropriate clinical context, histoplasmosis should be considered in both immunocompetent and immunocompromised patients, regardless of pulmonary symptoms, in nonendemic as well as endemic areas.

Histoplasma capsulatum, initially described in 1905 by Samuel Darling, MD,1 is endemic to the central United States, especially within the Ohio, Missouri, and Mississippi River valleys.2,3 Histoplasma organisms are dimorphic, existing in the mycelial form at room temperature, but transforming to the yeast form at the body temperature of mammals.2 This saprophytic soil fungus is most plentiful in soil enriched by avian or bat guano, the growth-promoting effects of which have been observed repeatedly.2,4-6

Infection occurs almost exclusively by inhalation of airborne conidia, although rare instances of transcutaneous and conjugal infection have been reported, and primary gastrointestinal infection by contaminated drinking water has been suggested.2-3,7-9 Once inhaled, the organism is ingested by tissue macrophages. Histoplasma capsulatum may proliferate within macrophages, spread to regional lymph nodes, and disseminate via hematogenous or lymphatic routes until the development of specific cell-mediated immunity occurs.2,3,10

The majority of human infections with Histoplasma organisms are asymptomatic pulmonary infections. In endemic areas, the population is infected and probably re-infected multiple times; the vast majority of both primary infections and reinfections are clinically silent.11 However, Histoplasma organisms may cause serious and potentially fatal disease, including severe chronic cavitary pulmonary disease, fibrosing mediastinitis, and disseminated disease involving multiple organ systems.2 In years before AIDS, the prevalence of dissemination was estimated as 1 per 100,000 to 500,000 cases of histoplasmosis.2 More recent estimates show that disseminated histoplasmosis occurs in approximately 55% of infected immunocompromised patients and 4% of infected immunocompetent patients.12-14 These statistics emphasize the higher probability of dissemination in the AIDS era. Moreover, they show that although dissemination...
is much more common in immunocompromised patients, it also occurs in apparently normal hosts.

Gastrointestinal and hepatic involvement are frequent in disseminated histoplasmosis. Gastrointestinal involvement occurs in 70% to 90% of patients with disseminated histoplasmosis, while the liver is involved in approximately 90%. However, the pathologic spectrum of lesions in these sites, both gross and microscopic, has not been investigated thoroughly or well characterized. We studied cases from immunocompetent and immunocompromised children and adults with *H capsulatum* infection from both endemic and nonendemic areas. To our knowledge, this is the largest, most diverse group of gastrointestinal and hepatic cases of histoplasmosis to be reported.

**Materials and Methods**

We searched for cases with a confirmed diagnosis of histoplasmosis from the surgical pathology and autopsy files of Vanderbilt University Medical Center (Nashville, TN), the University of Arkansas for Medical Sciences (Little Rock), the University of Texas Medical Branch (Galveston), the University of Michigan Hospitals (Ann Arbor), the Carle Clinic (Urbana, IL), and the University of Washington Medical Center (Seattle). Fifty-six specimens from 52 patients with gastrointestinal and hepatic histoplasmosis, between the years of 1946 and 1998, were retrieved. The cases came from multiple states including Tennessee (32 cases), Arkansas (2 cases), Michigan (1 case), Texas (19 cases), and Illinois (2 cases), representing endemic and nonendemic areas. Specimens included 6 from resections, 14 from biopsies, and 36 from autopsies. Some of the autopsy cases from Vanderbilt University Medical Center have been reported previously. Specimens were stained with H&E and Gomori methenamine silver, periodic acid–Schiff with diastase, or methenamine silver with H&E counterstain for detection of fungi. All cases were reviewed by at least 2 pathologists (L.W.L. and M.A.S.). Criteria for inclusion were demonstration of typical *Histoplasma* organisms (ovoid, 2-5 μm, usually intracellular yeast forms with small buds forming at the more pointed pole) in gastrointestinal or hepatic tissue, and/or a positive culture directly from the liver or gastrointestinal tract. In autopsy cases in which *Histoplasma* organisms had been identified in extraintestinal or extrahepatic sites but the gastrointestinal tract and liver were reportedly normal, available gastrointestinal and hepatic tissues were retrieved and evaluated. Medical records and autopsy reports were reviewed for multiple variables, including age, sex, clinical immune status, history and presentation, patterns of organ involvement, and fungal culture, histoplasmin skin test, and serologic test results.

Chi-square analysis was used to determine the statistical significance of clinical and pathologic features when comparing different patient groups.

**Results**

**Clinical, Demographic, and Laboratory Findings**

Clinical, demographic, and laboratory findings are given in Table 1. Age ranged from 3 months to 69 years (median, 30.5 years). Immunocompromised patients included 20 HIV-positive patients and 5 with other reasons for immunocompromise, including diabetes, renal transplantation, use of corticosteroids, Whipple disease, and systemic chemotherapy. Thirty-six cases were from endemic areas (Tennessee, Illinois, and Arkansas), and 20 cases were from areas in which histoplasmosis is not considered endemic (Texas and Michigan).

The majority of patients had fever at the time of presentation. Notable gastrointestinal and hepatic presenting symptoms and signs included diarrhea, hemorrhage, abdominal pain, dysphagia, nausea and vomiting, small bowel obstruction, hepatomegaly, jaundice, and elevated serum transaminase.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>37 (71)</td>
</tr>
<tr>
<td>Females</td>
<td>13 (25)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (4)</td>
</tr>
<tr>
<td><strong>Immune status</strong></td>
<td></td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>25 (48)</td>
</tr>
<tr>
<td>No known immunodeficiency</td>
<td>25 (48)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (4)</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>35 (67)</td>
</tr>
<tr>
<td>Child younger than 18 mo</td>
<td>17 (33)</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Predominantly gastrointestinal and/or hepatic</td>
<td>23 (44)</td>
</tr>
<tr>
<td>Predominantly pulmonary</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Both gastrointestinal/hepatic and pulmonary</td>
<td>16 (31)</td>
</tr>
<tr>
<td>Neither gastrointestinal/hepatic nor pulmonary</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Unknown clinical presentation</td>
<td>2 (4)</td>
</tr>
<tr>
<td><strong>Culture results for Histoplasma organisms (n = 28)</strong></td>
<td></td>
</tr>
<tr>
<td>Positive*</td>
<td>26 (93)</td>
</tr>
<tr>
<td>Negative</td>
<td>2 (7)</td>
</tr>
<tr>
<td><strong>Culture results unavailable or culture not performed (n = 9)</strong></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Negative</td>
<td>8 (88)</td>
</tr>
<tr>
<td><strong>Serologic test results (n = 10)</strong></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Negative</td>
<td>4 (40)</td>
</tr>
</tbody>
</table>

*Unless otherwise noted.

1 Sites yielding positive cultures included bowel, blood, bone marrow, liver, lung, sputum, tonsil, and spleen.
levels. Patients with neither gastrointestinal nor pulmonary symptoms presented with fever of unknown origin, weight loss, anemia, or thrombocytopenia.

Patterns of Organ Involvement

Thirty-one (60%) of 52 patients had both hepatic and gastrointestinal involvement. Sixteen patients (31%) had lesions limited to the gastrointestinal tract; in 3 of these, the liver was examined and found to be negative for *Histoplasma* organisms, and in the remainder, hepatic tissue was unavailable for evaluation. Five patients (10%) had only hepatic involvement (4 with intestinal biopsy specimens that were negative for fungi, and 1 who did not undergo intestinal biopsy). The specific locations of gastrointestinal lesions are given in Table 2. Fifteen cases (29%) showed prominent involvement of mesenteric, peripancreatic, periesophageal, and/or periluminal lymph nodes. Thirty-eight patients had histologically documented evidence of multisystem organ involvement, including 33 patients with pulmonary involvement. Only a single case had gastrointestinal involvement but lung tissue that was negative for fungi. In the remainder of cases without documented pulmonary involvement, the lungs were not available for examination. Other affected sites included spleen, adrenal, prostate, kidney, bladder, heart, tongue, testis, ovary, skin, brain, and bone marrow.

Gastrointestinal Pathologic Findings

A combination of different types of lesions, both gross and microscopic, was seen in virtually all cases. Ulcers were the most common gross lesion (23 [49%] of 47 patients with gastrointestinal lesions) and were identified most frequently in the ileum but also were seen in the jejunum, colon, esophagus, and stomach. Typically, the ulcers ranged from 0.2 to 4.0 cm in greatest dimension, were multiple, and consisted of annular lesions with raised borders, associated hyperemia and/or hemorrhage, and necrotic gray material at the base. Mucosal nodules (10 [21%] of 47 patients), hemorrhage or petechiae (6/47 [13%]), lymphoid hyperplasia (7/47 [15%]), and large, obstructive masses (3/47 [6%]) also were seen. The spectrum of microscopic gastrointestinal lesions included diffuse lymphohistiocytic infiltration (39 [83%] of 47 patients), ulceration (21/47 [45%]), and lymphohistiocytic nodules (12/47 [26%]). The lymphohistiocytic infiltrate and nodules usually involved both the submucosa and the mucosa but rarely extended into the muscularis propria, serosa, and mesentery. These lesions contained numerous eosinophils, neutrophils, and plasma cells, in addition to macrophages and lymphocytes; giant cells were noted only rarely. Superficial mucosal ulceration often was present overlying lymphohistiocytic nodules. Both ulcers and nodules often overlaid Peyer patches. Organisms usually were present within macrophages in the inflammatory infiltrate; rarely, in cases of severe infection, extracellular organisms also were seen. Only rare patients (4/47 [8%]) had gastrointestinal lesions containing discrete, well-formed granulomas; these were seen primarily in large lesions of the small bowel that involved the full thickness of the bowel wall.

Hepatic Pathologic Findings

Of the 36 patients with hepatic involvement, 17 (47%) had grossly enlarged livers; 14 (39%) had mottled or markedly
congested livers, most likely due to the prominence of yeast-laden macrophages within the distended sinusoids. Only 6 (17%) of the patients with liver involvement had discrete, grossly apparent hepatic lesions. Gross lesions most often were nodules ranging from 0.2 cm to more than 1.0 cm in greatest dimension and were parenchymal and capsular in location. Large areas of centrilobular necrosis were seen in 1 case. Microscopically, affected livers most often contained portal lymphohistiocytic inflammation (14 [39%] of patients with liver involvement) Image 6 and sinusoidal Kupffer cell hyperplasia (12 [33%]). Fungal organisms were present in portal and sinusoidal macrophages, and the majority of livers contained large numbers of organisms. Discrete granulomas were seen in 7 (19%) of patients with liver involvement. When present, granulomas usually were multiple and were seen in both portal and lobular regions. Hyalinized or calcified nodules consistent with remote healed granulomas were seen only rarely. Approximately 22% (8/36) of the patients with liver involvement had hepatic sinusoidal congestion and organisms within macrophages but only a minimal associated

Image 2 A, Colonic biopsy specimen showing diffuse lymphohistiocytic infiltration in the lamina propria and fungi within distended macrophages (H&E, ×40; inset, ×170). B, Numerous Histoplasma organisms (Gomori methenamine silver, ×40).

Image 3 Ulcerated lymphohistiocytic nodule in the small bowel of an infant (H&E, ×5) containing innumerable Histoplasma organisms (inset, Gomori methenamine silver, ×200).

Image 4 Well-formed epithelioid granulomas within an ulcerated ileal lesion (H&E/methenamine silver, ×25). Rare organisms are identified within granulomas (inset, H&E/methenamine silver, ×200).
inflammatory reaction Image 7. In both affected livers and gastrointestinal tract lesions, organisms occasionally were visible with H&E staining when numerous fungi were present; however, special stains usually were required for detection of Histoplasma organisms.

Pancreatobiliary Pathologic Findings

Involved pancreata showed lymphohistiocytic inflammation and macrophages laden with Histoplasma organisms within the fibrous septa of the pancreas Image 8. Affected gallbladders showed mucosal and submucosal lymphohistiocytic infiltration similar to that seen in the bowel.

Abdominal Lymph Node Findings

The majority of involved abdominal lymph nodes showed necrotizizing granulomas containing large numbers of Histoplasma-laden macrophages. However, rare nodes showed only a minimal reaction to intracellular organisms present within them.

Several features of gastrointestinal and hepatic histoplasmosis were noted to be different when the immunocompromised adult, children younger than 18 months of age, and apparently immunocompetent adult patient groups were compared and analyzed statistically Table 3. Immunocompromised adults and young children were more likely to have large numbers of organisms (P < .03). Young children were more likely to have grossly visible lymphoid hyperplasia of the bowel (P < .01). Immunocompromised adults were more likely to have grossly normal mucosa in bowel involved by Histoplasma organisms (P < .05).

Although immunocompromised adults and young children had more large obstructive masses in the intestine (histoplasmosas) and grossly apparent liver lesions, these numbers were not statistically significant; however, this may be because the numbers in the groups were small. Well-formed granulomas were present in immunocompromised adults and those adults without known immunodeficiency, but not in young children; this association also was not statistically significant. In all 3 groups, many patients presented with predominantly gastrointestinal or hepatic, rather than pulmonary, symptoms.

Twenty (80%) of the 25 immunocompromised patients and 9 (33%) of the 27 patients with no known immunodeficiency had concomitant infections. Coinfections in the immunocompromised group included strongyloidiasis, cytomegalovirus infection, candidiasis, herpes simplex virus infection, Mycobacterium avium-intracellularure infection, toxoplasmosis, hepatitis B, hepatitis C, hookworm infection, Pneumocystis carinii pneumonia, aspergillosis, and Whipple disease. Concomitant infections in the group with no known immunodeficiency were predominantly bacterial and included staphylococcal sepsis, Escherichia coli sepsis, Pneumocystis pneumonia due to Pseudomonas organisms, and sepsis due to Klebsiella organisms; 1 case of measles and 1 case of cytomegalovirus esophagitis also were present in this group.

Discussion

Our findings emphasize that although histoplasmosis generally is regarded as a “granulomatous” disease, a wide
spectrum of gross and microscopic lesions may be seen when infection occurs in the gastrointestinal tract and liver. Discrete well-formed granulomas are uncommon, while lymphohistiocytic nodules or infiltrates, ulceration, and hepatic Kupffer cell hyperplasia are much more common histologic findings. When well-formed granulomas were found, they were not predictive of immune status, as they were seen in immunocompromised patients and in patients without known immunodeficiency. Another important observation is that histoplasmosis may be present even though the gastrointestinal mucosa or hepatic parenchyma appear entirely unremarkable (both grossly and microscopically) or with only minimal inflammatory reaction, especially in immunocompromised adults and young children.

Although several previous reports have described cases of hepatic and gastrointestinal histoplasmosis,\textsuperscript{2,11,16-23} we believe that ours is the largest, most diverse group of cases to be reported to date. In contrast with the findings of some previous studies, the majority of our patients were febrile at presentation.\textsuperscript{18} We found that gastrointestinal and/or hepatic signs and symptoms may predominate and that patients with disseminated disease may have no pulmonary symptoms. Sathapatayavongs and colleagues\textsuperscript{14} also noted in their large series of disseminated histoplasmosis that 28.8% of patients had normal chest radiograph findings, emphasizing the importance of considering the diagnosis of histoplasmosis even when pulmonary symptoms or radiographic evidence of pulmonary involvement are lacking.

Before the AIDS epidemic, the prevalence of dissemination was estimated as 1 per 100,000 to 500,000 (0.0002%-0.001%) cases of histoplasmosis, with approximately one third of these occurring in infants.\textsuperscript{2} Since the advent of the

\begin{table}[h]
\centering
\caption{Selected Features of Gastrointestinal and Hepatic Histoplasmosis in Immunocompetent and Immunocompromised Patients*}
\begin{tabular}{lcccc}
\hline
& \multicolumn{2}{c}{Immunocompetent Adults (Older Than 10 y; n = 10)} & \multicolumn{2}{c}{Younger Than 18 mo (n = 17)} & \multicolumn{2}{c}{Immunocompromised Adults (n = 25)} & \multicolumn{2}{c}{Total (n = 52)} \\
\hline
Obstructive intestinal mass & 0 (0) & 1 (6) & 2 (8) & 3 \\
Gross intestinal ulceration & 5 (50) & 8 (47) & 10 (40) & 23 \\
Grossly normal gut mucosa\textsuperscript{†} & 1 (10) & 1 (6) & 9 (36) & P < .05 & 11 \\
Lymphoid hyperplasia\textsuperscript{‡} & 0 (0) & 7 (41) & 0 (0) & 7 \\
Well-formed gut granulomas & 2 (20) & 2 (12) & 3 (12) & 5 \\
Gross liver lesions & 0 (0) & 0 (0) & 2 (8) & 4 \\
Well-formed hepatic granulomas & 1 (10) & 1 (6) & 5 (20) & 7 \\
Gastrointestinal or hepatic presenting symptoms & 3 (30) & 8 (47) & 12 (48) & 23 \\
Large no. of organisms\textsuperscript{‡} & 0 (0) & 8 (47) & 16 (64) & P < .03 & 24 \\
\hline
\end{tabular}
\footnotesize{\textsuperscript{*} Data are given as number (percentage) of patients with feature. \\
\textsuperscript{†} These categories were associated with the patient groups noted at the given P values.}
\end{table}
AIDS epidemic, disseminated histoplasmosis has become much more prevalent and now is reported to occur in 4% of immunocompetent persons with histoplasmosis and 55% of immunosuppressed patients. Since histoplasmosis initially was reported in patients with AIDS in 1982, the case definition of AIDS has been expanded to include extrapulmonary histoplasmosis as an AIDS-defining illness, and infection in this population often is virulent with a high mortality rate. Elderly persons and infants are also at increased risk of disseminated disease.

The mechanism by which Histoplasma organisms disseminate, especially in immunocompetent patients, remains unclear. Some have postulated that a few histiocytes may fail to kill the organisms, yielding a “carrier” state that eventually leads to proliferation of organisms within macrophages and subsequent dissemination. Another theory is that dissemination occurs during a transient immune deficiency, such as a concomitant viral infection. Regardless of the mechanism, there are numerous patients in the present study and described in the literature who have disseminated histoplasmosis but no demonstrable defect in cellular immunity. Dissemination to the gastrointestinal tract and liver occurs via the reticuloendothelial system, including the Kupffer cells in the liver and tissue macrophages in the gastrointestinal tract. This affinity for the reticuloendothelial system probably explains why the ulcers and nodules characteristic of gastrointestinal histoplasmosis often are associated with Peyer patches and mucosal lymphoid aggregates and also may explain why the ileum, with its rich lymphatic network and numerous Peyer patches, is one of the most common sites of gastrointestinal involvement by histoplasmosis.

Several additional laboratory methods are available for the diagnosis of histoplasmosis. Fungal cultures take several weeks and, although definitive, are not useful for rapid diagnosis; in addition, negative culture results do not exclude the possibility of infection. The histoplasmin skin test result often is falsely negative in infants, elderly patients, and patients with disseminated disease; in addition, a positive test result cannot distinguish active disease from previous infection. Serologic tests, including complement fixation tests and immunodiffusion assays, also are unreliable for use in patients with disseminated disease. Of our patients with negative skin test results or negative serologic test results, 42% (5/12) were children younger than 18 months of age; the remainder were adults with no known immunodeficiency. As cultures are lengthy and difficult, and many ancillary laboratory tests are unreliable (especially in the context of disseminated disease), morphologic examination of a tissue biopsy specimen with appropriate special stains remains one of the more rapid and reliable methods for the diagnosis of histoplasmosis. An expeditious diagnosis is essential in this disease, particularly when it has disseminated, as antifungal therapy must be instituted quickly.

The differential diagnosis for the inflammatory lesions of gastrointestinal histoplasmosis includes idiopathic inflammatory bowel disease (ulcerative colitis and Crohn disease), sarcoidosis, and other infections. The differential diagnosis for the hepatic lymphohistiocytic lesions predominantly includes other fungal and bacterial infections. Histoplasma organisms may be identified easily on special stains by their characteristic morphologic features. Differentiation from...
carinii is based on the lack of budding, extracellular location, characteristic internal structure, and the different inflammatory reaction usually seen in infection with *P. carinii*. In addition, intestinal and hepatic infections with *P. carinii* are exceedingly rare. *Candida* (or *Torulopsis*) *glabrata*, a similarly sized yeast, is slightly larger, has more frequent buds, and more often is extracellular. In addition, *C. glabrata* is amphophilic and stains entirely with H&E, without the pseudocapsular or “halo” effect that is often seen with *Histoplasma* organisms.27 *Histoplasma* organisms may be distinguished from *Cryptococcus* and *Blastomyces* organisms morphologically; cryptococci also have a mucicarmine-positive capsule. Visceral leishmaniasis also is included in the differential diagnosis; however, *Leishmania* organisms have a characteristic kinetoplast and are Gomori positive.

Clinically, patients with predominantly gastrointestinal and/or hepatic symptoms may seem to have idiopathic inflammatory bowel disease or another form of infectious enteritis or hepatitis. Patients may have symptoms that mimic other systemic febrile illnesses, including disseminated malignant neoplasm, systemic infection, and autoimmune disease. Rarely, patients may present with bowel obstruction mimicking a neoplasm and requiring surgical intervention.10,21

Gastrointestinal and hepatic histoplasmosis occurs in both immunocompetent and immunocompromised patients, in children and adults, and in endemic and nonendemic areas. Pathologists must be aware of the wide range of patients in whom histoplasmosis may occur, as well as the spectrum of gross and microscopic lesions the fascinating *Histoplasma* organism can produce. In many of our patients in whom cultures, serologic tests, and skin tests for *Histoplasma* were performed, results were negative. This observation emphasizes the necessity for having a high index of suspicion of histoplasmosis in the appropriate clinical context. The pathologist should consider this diagnosis for any patient with unexplained inflammatory hepatic or gastrointestinal lesions and should have a low threshold for ordering appropriate special stains. In addition, the diagnosis of histoplasmosis should be considered for patients with appropriate gastrointestinal and hepatic signs or symptoms even if the tissue is essentially normal, as immunocompromised patients and infants may harbor numerous organisms but have minimal tissue reaction.

As Goodwin et al3 stated in 1981, “The diagnosis of histoplasmosis begins with thinking of it.”

References

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