



## Disseminated histoplasmosis in an immunocompetent pediatric patient

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### ABSTRACT

*Histoplasmosis is an endemic fungal infection caused by the fungus Histoplasma capsulatum. The disseminated form is associated with a high morbidity and mortality in pediatrics.*

*Here we report the case of an immunocompetent female patient diagnosed with disseminated histoplasmosis.*

*She was 3 years old and presented with protracted febrile syndrome and hepatosplenomegaly confirmed by ultrasound. Lab tests showed normocytic anemia and leukopenia. Diagnosis was made by periportal and perisplenic lymph node biopsy. The culture was positive for Histoplasma capsulatum and histopathological studies showed granulomatous lymphadenitis with intracellular yeast-like elements. Amphotericin B was administered at 1 mg/kg/day for 6 weeks, with a favorable clinical course.*

*Disseminated histoplasmosis should be considered in patients from endemic areas who present the triad of fever, hepatosplenomegaly, and cytopenias so as to provide a timely treatment, improve prognosis, and reduce the mortality from this disease.*

**Key words:** Histoplasma capsulatum; histoplasmosis; child.

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## INTRODUCTION

Histoplasmosis is an endemic fungal infection caused by the dimorphic fungus *Histoplasma capsulatum*. Its actual incidence is unknown because it is not a notifiable disease.<sup>1</sup> Most knowledge about pediatric histoplasmosis is derived from case series and case reports; its clinical management is based on data and experience on adult patients.<sup>2</sup> In Argentina, different epidemic outbreaks have been documented, and only one case series has been reported in children.<sup>3-5</sup> The disseminated form is associated with a high morbidity and mortality and often occurs in hosts with cell-mediated immunity and children younger than 2 years.<sup>6</sup> Signs and symptoms include fever, malaise, anorexia, hepatosplenomegaly, and hematologic

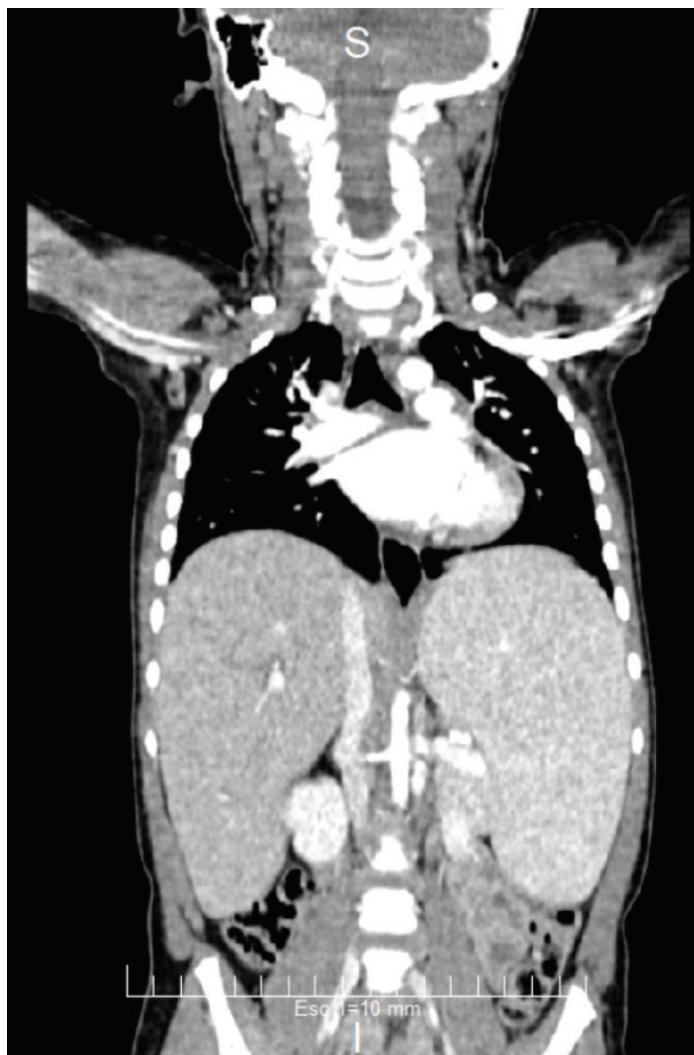
abnormalities.<sup>7</sup>

We report a case of disseminated histoplasmosis in an apparently immunocompetent 3-year-old girl from an endemic area of histoplasmosis.

## CASE REPORT

A 3-year-old previously healthy girl from the rural region of James Craik in the province of Córdoba, presented with fever and hepatosplenomegaly confirmed by ultrasound. Lab tests showed normocytic normochromic anemia (hemoglobin 9.1 g/dL) and leukopenia (leukocytes 2000/mm<sup>3</sup>), aspartate aminotransferase 63 U/L, gamma-glutamyltransferase 51 U/L, elevated alkaline phosphatase (214 U/L), lactate dehydrogenase (LDH) 407 U/L, erythrocyte sedimentation rate > 120 mm/h, and normal

**FIGURE 1. Computed tomography of the abdomen with contrast: marked homogeneous splenomegaly. Spleen 16 cm. Homogeneous hepatomegaly. Liver 14 cm**



kidney function tests, ionogram, and urinalysis. Serological testing for human immunodeficiency virus, human T-lymphotropic virus type 1, human T-lymphotropic virus type 2, VDRL, hepatitis C virus, Huddleson, Rose Bengal test, cytomegalovirus, *Toxocara canis-catis*, *Mycoplasma pneumoniae*, parvovirus, and *Brucella abortus* were negative; Epstein-Barr virus and toxoplasmosis: positive for immunoglobulin G (IgG) and negative for immunoglobulin M (IgM), and positive for *Bartonella henselae* IgM and IgG. The blood and urine cultures were negative; the echocardiogram and fundus examination were normal. The Mantoux test showed a 3-mm induration. The computed tomography (CT) of the abdomen with contrast revealed homogeneous hepatosplenomegaly (spleen 16 cm, liver 14 cm) (Figure 1). The chest CT was normal. In the bone marrow aspiration, cellularity was slightly decreased, and the bone marrow biopsy showed granulomas made up of epithelial cells in the interstitium.

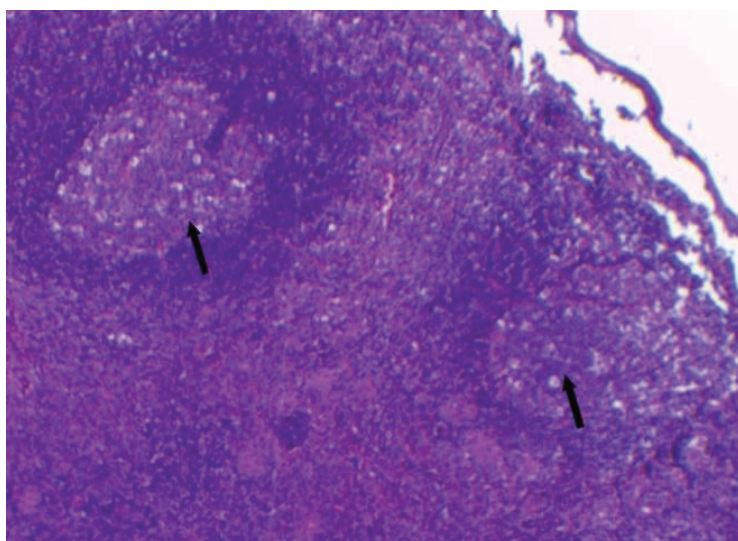
Treatment with azithromycin at 10 mg/kg/day was started for probable cat scratch disease; fever went down after 48 hours. The patient completed 5 days of treatment, and fever returned at the end of it. IgM and IgG serology for *Bartonella henselae* was repeated and results were negative. A new abdominal ultrasound showed persistent hepatosplenomegaly and enlarged lymph node at

the hepatic and splenic hilum, which had not been previously observed. The patient continued with bicytopenia, increased acute phase reactants, and elevated LDH. In addition, she developed a coagulation disorder with reduced plasma prothrombin activity (PPA) (54%).

Other studies were performed: vanillylmandelic and homovanillic acid measurements in urine, gastric lavage for culture of *Mycobacterium tuberculosis* and detection of serum antibodies for *Coccidioides* spp., *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, and antigen for *Cryptococcus neoformans* complex, which were all negative. Laparoscopic periportal and perisplenic lymph node biopsy was done. The samples were sent for culture of fungi, common germs, mycobacteria, *Brucella* spp., and for histopathological studies.

Seven days after the biopsy, the culture developed yeast-like fungi. We started treatment with deoxycholate amphotericin B (1 mg/kg/day). The cultures showed growth on Sabouraud agar at 2 temperatures: yeast-like fungus at 37 °C and mycelial fungus at 28 °C, with macro- and micromorphological characteristics compatible with *Histoplasma capsulatum*, which confirmed the diagnosis of disseminated histoplasmosis. Histopathological studies showed granulomatous lymphadenitis with intracellular yeast-like elements (Figures 2, 3, and 4).

**FIGURE 2. Lymph node biopsy: 4x panoramic view, hematoxylin and eosin staining. Distended sinusoids and histiocyte infiltration (black arrows)**

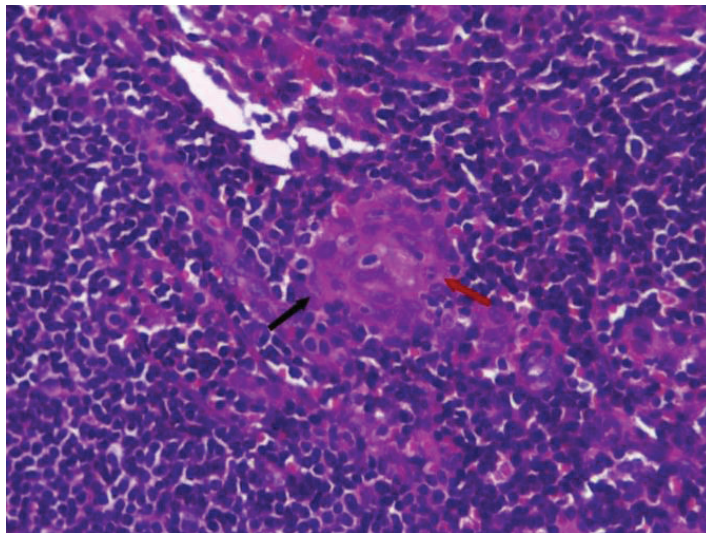


The patient had a favorable clinical course, with resolution of febrile symptoms 72 hours after starting the antifungal treatment and normalization of lab test values. She completed a total of 6 weeks of intravenous treatment. At hospital discharge, she continued with itraconazole (10 mg/kg/day) orally for 6 months.

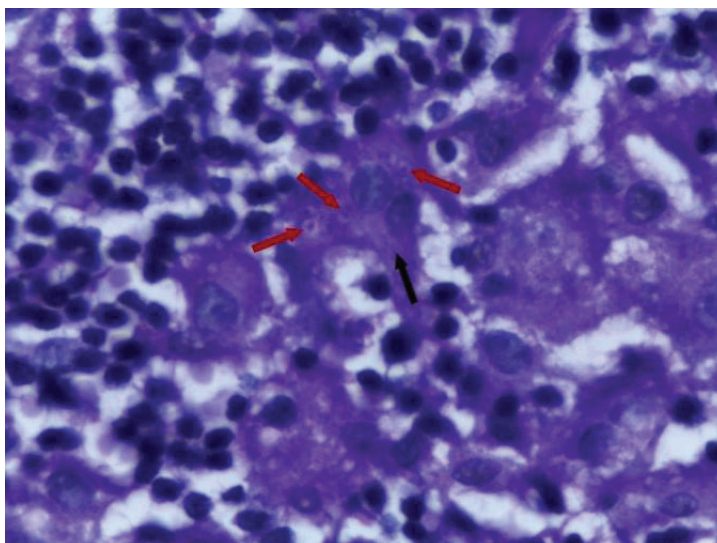
Inborn errors of immunity were ruled out. Complement components (C3 and C4) were normal. Humoral immunity: hypergammaglobulinemia with high IgG and IgM

levels. IgA and IgE levels were normal. Antibody response for viruses (hepatitis A, hepatitis B, and rubella), polysaccharides (pneumococcus), and protein antigens (tetanus toxoid) was normal. The phagocytosis assay, nitroblue tetrazolium test (NBT) and lymphocyte populations showed normal results. Autoantibodies (antinuclear antibody [ANA], anti-neutrophil cytoplasmic antibody [ANCA], anti-cyclic citrullinated peptides [anti-CCP]) were negative. A whole exome sequencing of genes involved

**FIGURE 3. Lymph node biopsy 40x, hematoxylin and eosin staining: small granuloma without central necrosis (black arrow) with intracellular yeast-like elements compatible with *Histoplasma capsulatum* (red arrow)**



**FIGURE 4. Lymph node biopsy: 100x, PAS staining: intracellular yeasts (red arrows) compatible with *Histoplasma capsulatum* in the cytoplasm of histiocytes (black arrows)**





in Mendelian susceptibility to mycobacterial diseases (MSMD) was done: *IL12RB1*, *IL12RB2*, *IL12B*, *IL23R*, *ISG15*, *USP18*, *IFNGR1*, *IFNGR2*, *IFNG*, *STAT1*, *JAK1*, *TYK2*, *IKBKG*, *TBX21*, *ZNFX1*, *CYBB*, *ISG15*, *IRF8*, *SPPL2A*, and other genes, *CYBB*, *CYBA*, *CYBC1*, *NCF1*, *NCF2*, *NCF4*, *IL17RA*, *IL17RC*, *IL17F*, *CARD9*; no mutation was identified.

At 2 years of follow-up, her evolution was favorable without relapse of disease.

## DISCUSSION

Here we report the case of a 3-year-old immunocompetent female patient from an endemic area of Argentina diagnosed with disseminated histoplasmosis. The diagnosis was established after 40 days of hospitalization. Diagnostic delay is frequent; therefore, it is necessary to establish a high index of suspicion in endemic areas. A case study published by Hospital de Pediatría Prof. Dr. Juan P. Garrahan reported that the median time from symptom onset to diagnosis was 2 months.<sup>5</sup>

The main symptom in our patient was fever, in agreement with what has been published in the bibliography, where fever was the most prevalent symptom in 62% and 76% of the patients according to the different series.<sup>5,8</sup>

Hematologic alterations are present in most patients with disseminated histoplasmosis.<sup>5,7</sup> Ávila et al. reported that 60–85% of infants with disseminated histoplasmosis had bone marrow abnormalities,<sup>9</sup> which is consistent with that reported by Odio et al. and Tobón et al., where 100% of patients studied had disseminated histoplasmosis with evident bone marrow abnormalities.<sup>7,10</sup> Increased LDH levels were observed in 25% of patients.<sup>11</sup>

The definitive diagnosis is established when the fungus is isolated in cultures at 2 temperatures (28 °C and 37 °C) or observed by direct microscopy with different staining techniques. *Histoplasma capsulatum* can be seen in biopsy sections of infected tissues when stained with hematoxylin and eosin, periodic acid Schiff (PAS), Grocott-Gomori methenamine silver, and the Wright-Giemsa method. In our patient, *H. capsulatum* was isolated in an intra-abdominal lymph node biopsy. A limitation of using a culture as a diagnostic method is the slow growth and that, in approximately 20% of cases of disseminated disease, results may be false negative.<sup>12</sup>

Other diagnostic methods available include

antigen detection in blood and urine, with a sensitivity of more than 80% in pulmonary histoplasmosis and 90% in disseminated histoplasmosis.<sup>13</sup> The sensitivity of antibody detection by immunodiffusion, complete fixation, or immunoassay is variable; in patients with disseminated histoplasmosis, it has been described in 75%.<sup>14</sup>

The first-line treatment for disseminated histoplasmosis is amphotericin B for 4–6 weeks. In pediatrics, the conventional form (sodium deoxycholate) is generally well tolerated and is preferred over the liposomal form. Itraconazole is recommended in the consolidation phase at doses of 50 to 100 mg/kg/day.<sup>2</sup>

As part of the diagnostic algorithm to rule out inborn errors of immunity, we performed a basic panel of immunological tests; then we assessed genetic defects in interferon gamma (IFN- $\gamma$ )-dependent immunity, known as Mendelian susceptibility to mycobacterial diseases (MSMD). This is a rare primary immunodeficiency, and the clinical disease caused by mycobacteria is the only manifestation in some of these disorders, while others have increased susceptibility to a broader range of pathogens, including *Histoplasma* spp. Endemic fungal infections have been reported in AR *IL12R $\beta$ 1*, AR *IFN- $\gamma$ R1*, and autosomal dominant gain-of-function *STAT1* defects.<sup>6,15</sup>

Lee et al., have proposed an algorithm to study inborn errors of immunity in patients with endemic mycoses, starting by taking the patient's history, including previous infections, chronic mucocutaneous candidiasis, autoimmune manifestations, and family history. The study establishes a basic panel of immunologic tests, including the measurement of immunoglobulins (IgG, IgA, IgM, and IgE), and lymphocyte populations, a nitro blue tetrazolium (NBT) or dihydrorhodamine tests to assess oxidative burst activity, and the examination by an immunologist to determine the presence of IL-12/IFN- $\gamma$  axis and anti-IFN- $\gamma$  autoantibodies.<sup>6</sup>

## CONCLUSION

Although the pathogenic role of *Histoplasma capsulatum* as an opportunistic microorganism in immunocompromised patients is well known, we report the case of an immunocompetent patient. Disseminated histoplasmosis should be considered in the diagnostic algorithm of patients from endemic areas who present the triad of

fever, hepatosplenomegaly, and cytopenias so as to provide a timely treatment, improve prognosis, and reduce the mortality from this disease. ■

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