**ABSTRACT**

**Introduction:** Histoplasmosis is an infection caused by dimorphic fungus, *Histoplasma capsulatum*, and it has not been reported in juvenile systemic lupus erythematosus (JSLE) patients, particularly progressive disseminated histoplasmosis (PDH) subtype.

**Case report:** We reported herein a 14-year old girl who was diagnosed with JSLE. Six months later, she had abdominal distension and received prednisone, hydroxychloroquine and azathioprine. Computer tomography evidenced hepatosplenomegaly and multiple mesenteric, mediastinal and retroperitoneal enlarged lymph nodes, forming large conglomerates at the mesentery, suggestive of lymphoproliferative disorder. After 10 days, she had acute surgical abdominal, and underwent a laparotomy and intestinal perforation and conglomerates of lymph nodes were observed. The jejunum biopsy showed perforated acute enteritis with hemorrhage and necrosis, and Grocott staining identified *Histoplasma* sp. and the culture showed a heavy growth of *Histoplasma capsulatum*. At that moment liposomal amphotericin B (1.0 mg/Kg/day) was introduced. Despite this treatment she died due to septic shock eight days later. Diffuse *Histoplasma capsulatum* was evidenced at autopsy.

**Conclusion:** We reported a severe opportunistic infection in JSLE patient with adenopathy and multiple intestinal perforations. This study reinforces the importance of early diagnosis and antifungal therapy, especially in patients with these uncommon clinical manifestations.

**Keywords:** Histoplasmosis; Juvenile systemic lupus erythematosus; Children; Opportunistic infection.

**INTRODUCTION**

Systemic lupus erythematosus (SLE) is clearly associated with infection, generally caused by virus and bacteria, and rarely by opportunistic agents, such as fungi. Histoplasmosis is an infection caused by thermal dimorphic fungus, *Histoplasma capsulatum*, with three major clinical presentations: progressive disseminated histoplasmosis (PDH), pulmonary and primary cutaneous. The PDH is the rarest and severe subtype of histoplasmosis, affecting mainly immunocompromised patients.

A recent review reported the association of SLE and histoplasmosis in 14 adult patients, eight of them had PDH. However to our knowledge, no cases of histoplasmosis were described in lupus pediatric population. Therefore, we reported herein a juvenile SLE (JSLE) patient that presented PDH with fever, hepatosplenomegaly and large conglomerate adenopathy.

**CASE REPORT**

A 14-year old girl was diagnosed with JSLE according to American College of Rheumatology classification criteria, based on hematological disorder (hemolytic anemia, leucopenia, lymphopenia and thrombocytopenia), serositis (pleuritis and pericarditis), antinuclear antibodies (ANA) 1/320 (dense fine speckled pattern) and proteinuria of 1.1 g/24 hours. At that moment, the SLE Disease Activity Index 2000 (SLEDAI-2K) was 10 and she was treated with prednisone (60 mg/day) and hydroxychloroquine (150 mg/day). One month later, she presented arterial hypertension, thrombocytopenia...
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Camila M. P. França e Col (52,000/mm³), C 3 13 mg/dL (normal 16-38) and C 4 139 mg/dL (normal 79-152), urinalysis (64,000 leukocytes/mL, 112,000 erythrocytes/mL), proteinuria 0.53 g/24 hours and renal biopsy showed mesangial proliferative nephritis (class II of World Health Organization – WHO classification) with SLEDAI-2K of 15. Azathioprine (100 mg/day) and enalapril were introduced, and the prednisone dose was progressively reduced. Five months later, she was hospitalized due to cough and sputum for 15 days. She also had abdominal pain in left flank for one week with fever, bilious vomiting and acute diarrhea. On physical examination, she had abdominal distension with pain at palpation in the left flank and impetigo in hands and buttocks, and ceftriaxone and clindamycin were promptly administered. At that moment she received prednisone (10 mg/day), azathioprine (100 mg/day) and hydroxychloroquine (150 mg/day). Her laboratory exams revealed hemoglobin 9.2 g/dL, hematocrit 29.2%, white blood cell count 3,430/mm³ (98% neutrophils, 1% lymphocytes, 1% monocytes), platelets 222,000/mm³, C-reactive protein 78.5 mg/dL (normal < 5), urea 25 mg/dL (normal 10-42), creatinine 0.6 mg/dL (normal 0.6-0.9), C 3 20 mg/dL, C 4 80 mg/dL, urinalysis (17,000 leukocytes/mL, 16,000 erythrocytes/mL and granular casts) and 24 hours proteinuria 0.868 g/24h. The IgM and IgG antiphospholipid antibodies and lupus anticoagulant testing were normal. Abdominal computer tomography (CT) evidenced hepatosplenomegaly and multiple mesenteric and retroperitoneal enlarged lymph nodes, forming large conglomerates at the mesentry, suggestive of lymphoproliferative disorder (Figure 1). The thoracic CT also found diffuse mediastinal enlargement of lymph nodes, forming conglomerates, measuring up to 2.3 cm in diameter. After 10 days of hospitalization, she developed severe abdominal pain and distension, rebound tenderness and abdominal muscle guarding compatible with acute surgical abdomen. She underwent a laparotomy and intestinal perforation and conglomerates of lymph nodes were observed, and intestinal resection was performed. The jejunum biopsy showed perforated acute enteritis with hemorrhage and necrosis, and Grocott staining identified Histoplasma sp. The jejunum tissue culture showed a heavy growth of Histoplasma capsulatum. The abdominal lymph nodes also isolated Histoplasma sp. in Grocott staining (Figure 2) and the culture showed Histoplasma capsulatum. The double agar gel immunodiffusion was positive for Histoplasma capsulatum. The serologies and DNA of cytomegalovirus, Paracoccidioides brasiliensis and Aspergillus fumigatus in serum samples, using the polymerase chain reaction (PCR), were negative. After 22 days of hospitalization, liposomal amphotericin B (1.0 mg/Kg/day) was associated and doppler echocardiography showed pulmonary arterial pressure of 60 mmHg without systolic and diastolic dysfunctions. Despite this treatment she died due to septic shock eight days later. At autopsy, signs of septic shock, multiple intestinal perforations in jejunum, serositis, acute renal tubular necrosis and areas of hemorrhage in lungs, trachea and bladder were observed. No pulmonary thrombosis and vasculitis were detected. Histoplasma capsulatum was evidenced in bone marrow, lungs, lymph nodes (mediastinal, pa-
raaortic and abdominal) and in multiple mural nodules in mesocolon.

DISCUSSION

To our knowledge, we described the first JSLE patient with fatal disseminated histoplasmosis, mainly with retroperitoneal and mediastinal mass, and multiple intestinal perforations.

*Histoplasma capsulatum* is a dimorphic fungus of Ascomycetes class. Histoplasmosis is common systemic mycosis in patients suffering from immunodeficiency syndrome (AIDS) and may affect in other immunocompromised subjects, such as immunodeficiency disorders that involve macrophage, monocyte and T cells.

Approximately 10% of patients with histoplasmosis had a disseminated subtype. Symptoms of PDH are nonspecific and include chills, fever, malaise, anorexia, weight loss, cough, dyspnea and diarrhea, as observed in our patient. Of note, gastrointestinal involvement is a rare manifestation of histoplasmosis. The ileum and cecum are the most common sites affected. Depending on the layer of bowel wall involvement and the extent of the disease, the manifestations of histoplasmosis differ widely and can include perforation, gastrointestinal bleeding and peritonitis. Perforation most commonly occurs in the small gut, as also observed herein.

The PDH diagnosis is suggestive as the presence of clinical manifestations that do not improve after at least 3 weeks of acute infection, associated with physical or radiographic findings and/or laboratory evidence of involvement of extrapulmonary tissues. Importantly, the gold standard to histoplasmosis diagnosis is to identify *Histoplasma capsulatum* in culture or histology. Additionally, the serologic test, as immunodiffusion assay, has sensitivity to this diagnosis of approximately 80%.

This diffuse or localized histoplasmosis infection was rarely reported in SLE, mainly in adult population. In the disseminated form associated with lupus, the most affected tissues are bone marrow and lungs, as evidenced in this case. To the best of our knowledge, large retroperitoneal and mediastinal adenopathies and severe intestinal abnormalities were not reported in adult and pediatric SLE.

In addition, the main differential diagnosis of patient with large adenopathy with intestinal perforation in immunocompromised patients include mainly: histoplasmosis, lymphoproliferative disease, cytomegalovirus, Epstein-barr infection, aspergillosis and tuberculosis.

One of relevant clinical manifestations of our patient was the presence of pulmonary hypertension. The main causes of pulmonary hypertension in SLE patients are lung disease (generally related to disease activity and/or infections, as pulmonary vasculitis and alveolar hemorrhage), antiphospholipid syndrome, left heart disease and non cirrhotic portal hypertension. Alveolar hemorrhage possible due to histoplasmosis was the only factor associated to pulmonary hypertension observed in our lupus patient. Interestingly, we recently evidenced that this severe manifestation had a significant mortality in JSLE patients compared to adult SLE.

Histoplasmosis in lupus patients is associated with immunosuppressive drugs use, especially corticosteroid, azathioprine, cyclophosphamide and rituximab, as also observed in our case.

The treatment of PDH includes amphotericin B (1.0 mg/kg daily for 4-6 weeks) or liposomal amphotericin B (1.0 mg/kg daily for 2-4 weeks) followed by itraconazole (5-10.0 mg/kg daily in 2 doses) to complete 3 months of therapy. In spite of antifungal therapy, three of eight patients with SLE and PDH died, as observed in our JSLE patient. Furthermore, untreated disseminated histoplasmosis is considered to be fatal for most patients, with mortality rate from 83 to 93%.

The most important risk factors associated to fatal outcome of our JSLE patient were related to disease itself (activity, lymphopenia and leucopenia), treatments (corticosteroid and immunosuppressive drug), and delay of histoplasmosis diagnosis and antifungal therapy.

In conclusion, we reported a severe opportunistic infection in active JSLE patient with diffuse and large adenopathy, and multiple intestinal perforations. This study reinforces the importance of early suspicious diagnosis and the prompt use of antifungal therapy, especially in patients with these uncommon clinical manifestations.

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