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CASE REPORT

Disseminated histoplasmosis in a late post-liver transplant recipient: a case report and literature review

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ABSTRACT

Histoplasmosis is an endemic mycosis in certain regions of Brazil and represents a rare opportunistic infection in solid organ transplant recipients. This report describes the case of a 68-year-old female liver transplant recipient (due to Caroli disease) who presented with abdominal pain, nausea, vomiting, and a distended, tender abdomen. Abdominal computed tomography revealed parietal thickening of the bowel wall, and colonoscopy identified polymorphic ulcers and ileocecal stenosis. Given the suspicion of tuberculosis, chest computed tomography was performed, which demonstrated pulmonary opacities. Although testing for acid-fast bacilli was negative, fungal staining was positive for *Histoplasma capsulatum*. Antifungal therapy with amphotericin B was initiated; however, due to clinical refractoriness, surgical intervention was required, including ileocecal resection with ileo-ascending anastomosis. A reoperation was performed due to postoperative complications, resulting in the creation of a terminal ileostomy. Following this intervention, the patient showed clinical improvement and tolerated an oral diet. This case highlights an atypical presentation of disseminated histoplasmosis with pulmonary and intestinal involvement, culminating in intestinal subocclusion in a late-stage liver transplant recipient. It underscores the importance of considering histoplasmosis in the differential diagnosis of immunosuppressed patients and the need for early investigation and treatment

Keywords: Histoplasmosis; Histoplasma; Immunosuppressive therapy; Liver transplantation

INTRODUCTION

Histoplasmosis is a fungal infection caused by the dimorphic organism *Histoplasma capsulatum*. Although rare, it is a recognized opportunistic infection in liver transplant recipients.[1,2] Its incidence among post-transplant patients is approximately 1 case per 1,000 person-years,[1] accounting for less than 1% of infections in solid organ transplant recipients.[2]

In immunocompetent individuals, approximately 95% of pulmonary infections caused by Histoplasma are asymptomatic. When symptoms do occur, they typically present as self-limited acute pulmonary infections.[3] However, in immunocompromised patients, histoplasmosis mayprogress to disseminated disease. Most cases occur within the first two years after transplantation and vary in severity, often presenting with nonspecific clinical features that may delay diagnosis and treatment.[4]

This case report describes an atypical presentation of disseminated histoplasmosis, manifesting as intestinal subocclusion in a late-stage liver

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transplant recipient. Despite the nonspecific nature of the symptoms, prompt investigation and early treatment are critical to achieving a favorable outcome, especially in immunosuppressed individuals.

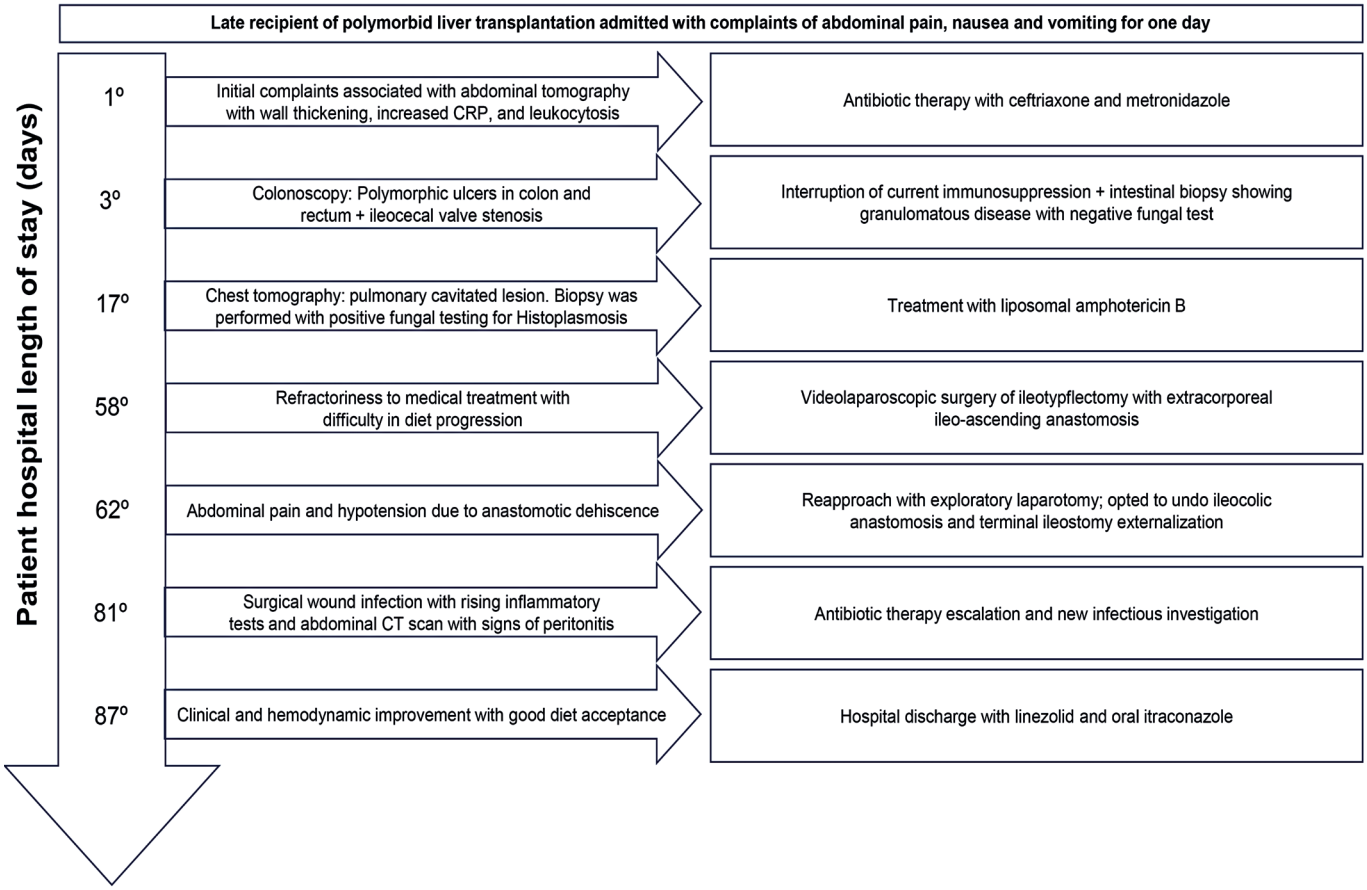
CASE REPORT

A 68-year-old female patient underwent liver transplantation in 2005 due to Caroli disease. Her medical history included insulin-treated type 2 *diabetes mellitus*, systemic arterial hypertension, non-dialysis- dependent chronic kidney disease, chronic anemia, gout, appendectomy, and pulmonary thromboembolism. After transplantation, she experienced recurrent episodes of acute cholangitis. However, investigations – including contrast-enhanced abdominal computed tomography (CT), percutaneous transhepatic cholangiography, and magnetic resonance cholangiopancreatography – revealed no evidence of biliodigestive anastomotic stenosis or other post-transplant biliary or arterial complications.

She was admitted to the hospital with a one-day history of abdominal pain, nausea, and vomiting. She also reported altered bowel habits and unintentional weight loss of 6kg over the preceding six months. She denied cough, dyspnea, chest pain, cutaneous changes, bleeding, or other systemic symptoms. Her immunosuppressive regimen included tacrolimus and mycophenolate sodium

On physical examination, the patient was afebrile and presented with abdominal distension and diffuse tenderness on palpation without visceromegaly. Bowel sounds were present, and there were no signs of peritoneal irritation or costovertebral angle tenderness. Laboratory tests and diagnostic imaging were requested. A summary of the key events is presented in figure 1.

Initial laboratory tests revealed elevated C-reactive protein (CRP) levels, leukocytosis, and acute kidney injury (KDIGO stage I). Contrast-enhanced abdominal CT (Figure 2) showed irregular thickening of the terminal ileum and ileocecal valve, with adjacent lymphadenopathy. Empirical antibiotic therapy was



Visual summary of the patient's clinical course during an 87-day hospitalization for disseminated histoplasmosis. Therapeutic milestones and outcomes are presented, culminating in hospital discharge with oral antifungal and antibiotic therapy.

Figure 1. Clinical timeline of hospitalization for disseminated histoplasmosis in a liver transplant recipient

initiated, and a colonoscopy was subsequently performed. The examination revealed extensive polymorphic ulcers throughout the colon and rectum, an ulcerated lesion in the cecum, and stenosis of the ileocecal valve which precluded passage of the endoscope (Figure 3).

Five biopsy samples demonstrated ulcerated chronic granulomatous colitis with epithelioid granulomas and multinucleated giant cells in the mucosa and submucosa, without central necrosis. Acid-fast bacilli (AFB) and fungal staining (Grocott) were negative. No samples were collected.

Given the endoscopic findings, immunosuppressive therapy was suspended, and the patient was started on a pureed diet and parenteral nutrition. A chest CT scan (Figure 4) was performed to investigate tuberculosis due to the granulomatous pattern. It

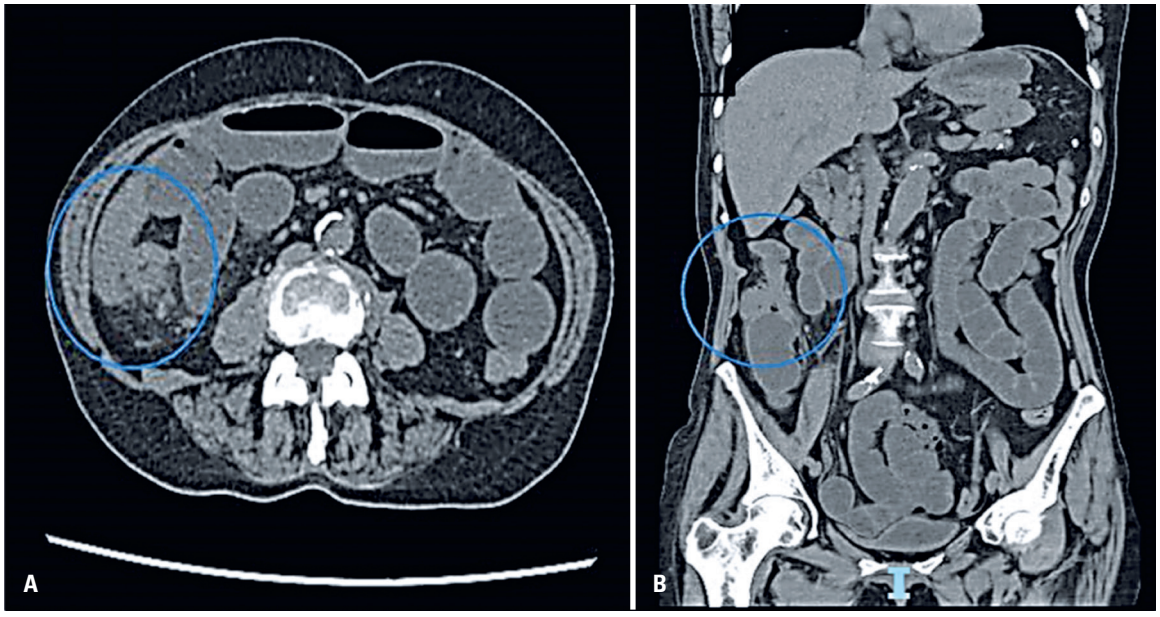


Figure 2. Contrast-enhanced abdominal computed tomography revealing ileocecal involvement. Axial (A) and coronal (B) images demonstrate irregular parietal thickening of the terminal ileum and ileocecal valve (blue circles). These findings were suggestive for an infectious or inflammatory etiology and prompted further investigation with colonoscopy and biopsy

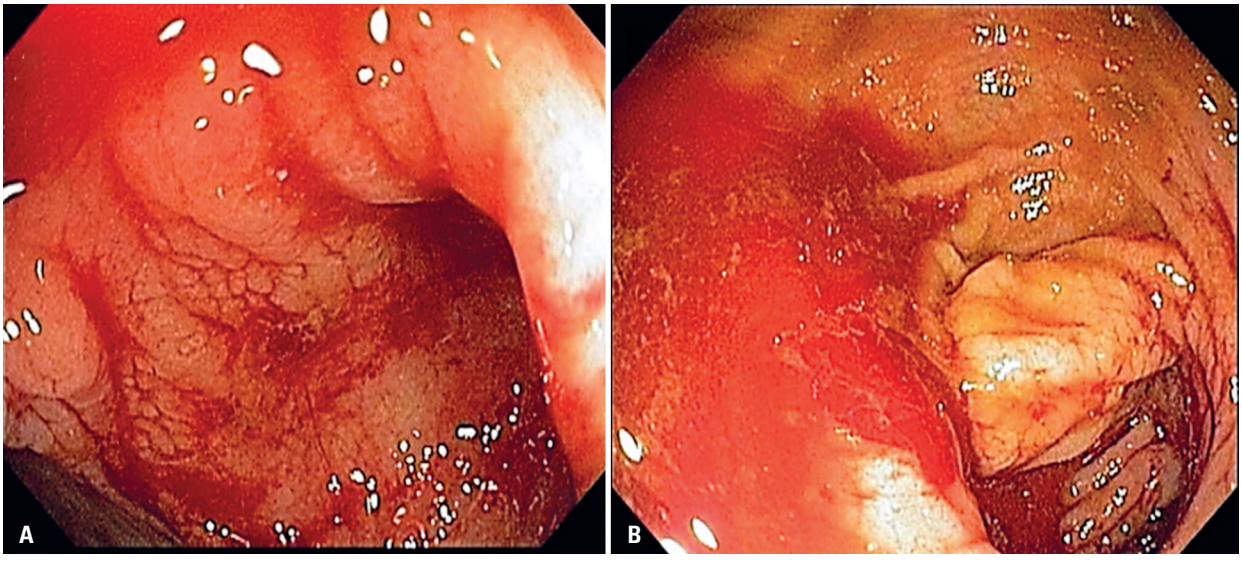


Figure 3. Colonoscopic findings of polymorphic ulcers and ileocecal valve stenosis. Colonoscopy showing mucosal ulcerations with polymorphic features. (A) Extensive ulceration in the colon with inflamed and friable mucosa. (B) Stenotic ileocecal valve with ulcerated mucosa and luminal narrowing. These findings, in conjunction with granulomatous inflammation on biopsy, were suggestive of an infectious etiology

revealed peripheral ground-glass opacities, scattered pulmonary micronodules, and a 2.8cm cavitary lesion in the right lower lobe. Biopsy of the pulmonary lesion showed well-formed epithelioid granulomas with multinucleated giant cells surrounding caseous necrosis. Acid-fast bacilli staining was negative, but fungal staining was positive for yeast-like cells suggestive of *Histoplasma* spp. The diagnosis was later confirmed by a positive serum histoplasmosis immunodiffusion test for the M band. Tests for urinary *Histoplasma* antigen, polymerase chain reaction for tuberculosis, and AFB in sputum were negative.

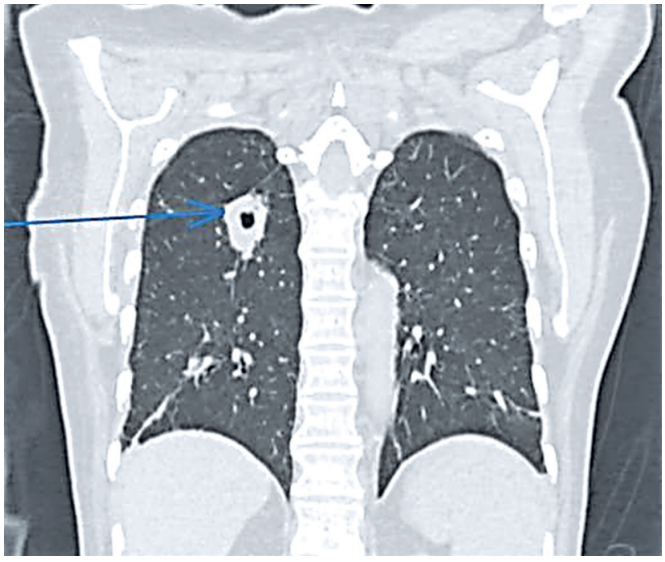


Figure 4. Chest computed tomography demonstrating a cavitary pulmonary lesion suggestive of fungal infection. Coronal chest computed tomography image showing a 2.8 cm cavitary lesion in the right lower lobe (arrow). This radiological finding, in the context of disseminated disease in an immunosuppressed patient, prompted biopsy. Histopathological analysis confirmed fungal infection consistent with *Histoplasma capsulatum*

Antifungal therapy with amphotericin B was initiated at 3mg/kg/day but was complicated by chest pain as an adverse reaction. After acute coronary syndrome was ruled out, treatment was switched to liposomal amphotericin B, administered over 8 hours, and titrated to a target dose of 5mg/kg/day. After 15 days, follow-up contrast-enhanced abdominal CT showed improvement in intestinal obstruction; however, the patient remained unable to tolerate oral intake due to persistent postprandial emesis.

Given the refractory clinical course, a laparoscopic ileocecal resection was performed. An extracorporeal ileo-ascending anastomosis was carried out intraoperatively due to the edematous and friable condition of the tissue. On postoperative day 2, the patient deteriorated, presenting with tachycardia, hypotension, abdominal pain, and distension. Contrast-enhanced abdominal CT revealed indirect signs of peritonitis and pneumoperitoneum, prompting exploratory laparotomy. Intraoperative findings confirmed anastomotic dehiscence, leading to resection of the anastomosis and the creation of a terminal ileostomy.

Histopathological examination of the surgical specimen confirmed ulcerated chronic granulomatous colitis with intense mixed inflammatory infiltrate and yeast-like structures positive on Grocott staining, suggestive of *Histoplasma* spp. The surgical margins were free of disease.

Ten days after reoperation, the patient was afebrile, with stable vital signs, and was tolerating a regular diet. However, laboratory results showed elevated CRP levels and leukocytosis despite 11 days of antibiotic therapy. Repeat 1 contrast-enhanced abdominal CT revealed increased intra-abdominal free fluid and more pronounced inflammatory changes compared with the pre-reoperation scan, suggestive of peritonitis. Ultrasound-guided percutaneous drainage was performed by interventional radiology, yielding 100mL of serous fluid.

Before culture results became available, the patient developed sepsis secondary to a surgical wound infection, requiring broad-spectrum antibiotics, further investigation for infectious complications, and liver biopsy to assess for possible rejection. All fluid and catheter tip cultures were negative for bacteria, fungi, and *Mycobacterium tuberculosis*. Follow-up imaging showed radiological improvement of the peritonitis. Liver biopsy revealed acute cellular rejection with a rejection activity index of 4 (portal inflammation 2, ductal injury 1, endothelial inflammation 1), prompting adjustment of the immunosuppressive therapy.

Five days later, the patient was hemodynamically stable, tolerating a full diet, and no longer required parenteral nutrition. Immunosuppression therapy was resumed due to rising liver enzyme levels. After 87 days of hospitalization, the patient was discharged with oral linezolid and itraconazole at a dose of 200mg three times daily for 1 week.

In the outpatient setting, she experienced episodes of acute kidney injury associated with dehydration and hyperkalemia, without electrocardiographic abnormalities. These episodes were managed with hydration and electrolyte correction. Itraconazole was continued at 200mg twice daily as secondary prophylaxis for 12 months. Seven months after hospital discharge, intestinal transit reconstruction was performed. The

patient remains under multidisciplinary outpatient follow-up without further surgical complications.

The study was approved by the Research Ethics Committee of *Hospital Israelita Albert Einstein* (CAAE: 93271025.2.0000.0071; #8.087.302

DISCUSSION

In immunosuppressed patients, histoplasmosis may progress to disseminated infection, with a reported mortality rate of 31%.[4] Intestinal involvement is identified by biopsy in up to 70% of cases, most commonly affecting the ileocecal region and colon; however, clinical presentation is nonspecific, and gastrointestinal symptoms are reported in fewer than 10% of cases.[5] Respiratory symptoms are often minimal in disseminated histoplasmosis: cough and dyspnea occur in only 10-30% of patients, and chest radiographs may appear normal in up to 50% of cases.[6] In severe untreated forms, mortality may reach 80%, with appropriate treatment, this rate can decreaseto 25%.[7] Residence in endemic areas combined with immunosuppression is a key risk factor for fungal infections such as histoplasmosis, underscoring the need for thorough investigation in high-risk patients.

This case illustrates an atypical manifestation of disseminated histoplasmosis in a late-stage liver transplant recipient, leading to intestinal subocclusion. The patient presented with extensive polymorphic ulcers throughout the colon and rectum, as well as a cavitary lesion in the right lung, with histopathological findings suggestive of *Histoplasma* infection. The therapeutic approach prioritized minimally invasive strategies while addressing both clinical and surgical complications. Following the initiation of amphotericin B – a drug known for its toxicity – the patient developed chest pain, prompting a switch to liposomal amphotericin B. This formulation offers equivalent antifungal efficacy with significantly reduced toxicity.[8] In addition, the infusion duration was extended to 8 hours to further reduce adverse effects, as recommended in the manufacturer's guidelines. These strategies enabled successful treatment initiation and subsequent dose escalation.

A delay in diagnosis occurred due to the disease's atypical presentation and the initial negative fungal staining (Grocott) results in the colonic biopsy samples.[2-4] While Grocott staining is a standard diagnostic method, its sensitivity depends on adequate tissue sampling, and false-negative results may occur. This highlights the importance of a broader diagnostic approach in patients with risk factors and granulomatous inflammation, even in the absence of positive fungal staining. Urinary antigen detection currently represents the most sensitive diagnostic tool for histoplasmosis[2] and should be considered in immunosuppressed patients from endemic areas presenting with nonspecific symptoms. However, a negative urinary antigen result does not exclude infection. In such cases, imaging studies – especially chest CT – may identify pulmonary lesions, as the lungs are the primary site of infection.[2] In the present case, the presence of a cavitary lesion facilitated biopsy and direct fungal identification, leading to diagnostic confirmation

Review of the literature reveals that gastrointestinal involvement in disseminated histoplasmosis occurs in approximately 11% of post-transplant patients.[2] Interestingly, Oh et al. described a 61-year-old liver transplant recipient who presented with abdominal cramping and non-bloody diarrhea, and was found to have colonic ulcerations due to histoplasmosis; the patient subsequently developed pericarditis and pleural effusions, which resolved following amphotericin B therapy.[9] In contrast to that case, our patient uniquely developed intestinal subocclusion – highlighting a rarer and more complex gastrointestinal complication in this population. While some case reports have described gastrointestinal ulcerations, to our Knowledge, none have documented intestinal subocclusion in solid organ transplant recipients.[10,11] Although rare cases of intestinal obstruction due to disseminated histoplasmosis have been reported in other immunocompromised individuals, none have involved patients with a history of solid organ transplantation.[12-14] Thus, this case represents an especially rare presentation, as the more typical gastrointestinal manifestations of disseminated histoplasmosis are diarrhea and bleeding.[12- 14]

The Infectious Diseases Society of America (IDSA) guidelines for the management of histoplasmosis recommend that, in immunosuppressed patients – particularly those with ongoing risk factors such as solid organ transplantation – prolonged antifungal therapy may be warranted to prevent relapse.[15] For severe disseminated disease, initial treatment with liposomal amphotericin B should be followed by oral itraconazole for at least 12 months.[15] Although these guidelines primarily address patients with human immunodeficiency virus (HIV), they acknowledge that individuals receiving chronic immunosuppression may similarly benefit from extended or indefinite secondary prophylaxis, depending on the degree and duration of immune compromise.[15] In non-HIV

solid organ transplant recipients, observational data and expert opinion presented at recent infectious diseases conferences support the use of secondary prophylaxis with itraconazole, particularly in cases of extensive disease, slow clinical resolution, or persistent immunosuppressive therapy.[16] The optimal duration remains uncertain, but many specialists advocate for at least 12 months of therapy, with some extending treatment indefinitely in high-risk scenarios. Close clinical and laboratory monitoring is essential to ensure therapeutic drug levels, prevent relapse, and minimize drug-related toxicity.

CONCLUSION

This case highlights the diverse clinical manifestations of histoplasmosis in immunocompromised patients. Early recognition and investigation are critical, particularly in transplant recipients. This report underscores the importance of including histoplasmosis in the differential diagnosis of solid organ transplant recipients presenting with nonspecific systemic or gastrointestinal symptoms, thereby facilitating timely diagnosis and appropriate management.

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DATA AVAILABILITY

The underlying content is contained within the manuscript.

AUTHORS' CONTRIBUTION

Yuri Longatto Boteon: was responsible for conceptualising the study. Fernando Camargo Fernandes, Pedro Cunha de Freitas Meirelles Meira, Amanda Pinter Carvalheiro da Silva Boteon, and Yuri Longatto Boteon: performed the formal analysis, investigation, methodology, and study visualization. Fernando Camargo Fernandes, Pedro Cunha de Freitas Meirelles Meira, and Yuri Longatto Boteon: drafted the manuscript. Amanda Pinter Carvalheiro da Silva Boteon, and Yuri Longatto Boteon: reviewed and edited the manuscript. All authors contributed to editing and approved the final version of the manuscript.

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