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Disseminated histoplasmosis and resistant tuberculosis in a patient with AIDS: A case report

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ABSTRACT

Histoplasmosis is a systemic mycosis with a wide global distribution, being more prevalent and endemic in the American Continent. Its progressive disseminated form primarily affects immunosuppressed individuals and plays a significant role as an AIDS-defining illness. The challenging aspect of differential diagnosis with tuberculosis lies in the clinical, radiological, and laboratory similarities between these two conditions, making the spectrum of co-infection even more complex. In this clinical study, we present the case of a 22-year-old Venezuelan patient with no prior comorbidities who was admitted with symptoms of diarrhea, fever, weight loss, and persistent cough over a 30-day period. Initially, he was diagnosed with acquired immunodeficiency syndrome (AIDS) and subsequently with pulmonary tuberculosis. However, due to the persistence of symptoms, the delayed diagnosis of disseminated histoplasmosis (DH) was also established through blood culture. Additionally, the patient exhibited resistance to rifampicin, a condition not previously documented in the literature. After treatment with amphotericin B, adjustment of the tuberculosis therapy, and initiation of antiretroviral therapy, the patient experienced a significant clinical improvement and currently remains asymptomatic. This case underscores the importance of raising clinical suspicion for disseminated histoplasmosis (DH) in HIV-infected patients and implementing enhanced diagnostic strategies, especially in regions with limited access to healthcare services and complementary examinations.

Introduction

Histoplasmosis is a systemic fungal disease caused by inhalation of the dimorphic fungus *Histoplasma capsulatum*. Its variants, *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii*, are responsible for human infections, with the former being the most prevalent in the Americas [1]. Histoplasmosis gained increased attention following the emergence of HIV, and since 1985, disseminated histoplasmosis has been recognized as an AIDS (Acquired Immune Deficiency Syndrome)-defining disease [2]. Histoplasmosis is often diagnosed alongside other opportunistic infections, particularly tuberculosis [3], presenting a global distribution, with endemic regions in the Americas. In Brazil, histoplasmosis has a high prevalence, especially in the central and northeastern regions of the country [4]. Despite being a well-described disease nationally, in the state of Roraima there are few reported cases of the disease, which makes it difficult to represent the real panorama of histoplasmosis in our country [5].

While the majority of those infected with histoplasmosis do not

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experience major clinical repercussions, symptomatic forms generally manifest with respiratory tract infections. The primary infection can progress with dissemination throughout the body, mainly in organs rich in macrophages such as the liver, spleen, lymph nodes, and bone marrow, thus being defined as disseminated histoplasmosis (DH). This form is rarely found in immunocompetent individuals and is associated with cellular immunity deficiencies, mainly AIDS patients [6]. Disseminated histoplasmosis (DH) in endemic places has an annual incidence of approximately 5 % in individuals with AIDS [7]. Co-infection is potentially fatal, especially if the CD4 T lymphocyte count is below 200 cells/mm3. It presents clinically in a non-specific way with high fever, significant anorexia, gastrointestinal changes, weight loss, generalized lymphadenopathy, polymorphic skin, and mucosal lesions, in addition to hepatosplenomegaly. Progression is generally rapid in these patients and peripheral pancytopenia can be seen in the laboratory when bone marrow involvement is present [6]. Pulmonary symptoms and imaging findings consistent with tuberculosis is also present in histoplasmosis [8]. In this context, diagnostic suspicion must consider the assessment of risk factors and the presence of signs and symptoms. Diagnostic confirmation can be obtained through specific laboratory tests, such as fungal cultures, serological tests, molecular analyses, or histopathological examinations. It is important to note that these tests often require a considerable amount of time to obtain results, which can compromise the agility of diagnosis and, consequently, the administration of timely treatment, which in turn is associated with an increase in the mortality rate [8].

The use of the ELISA urinary antigen test has proven to be more effective as a method of diagnosing disseminated histoplasmosis (DH) in patients with HIV. However, it is important to note that such assay kits associated with more robust evidence are widely available only through localized distribution of cutaneous lesions in the United States, resulting in limited availability in Latin American countries [9]. Moreover, it is important to note that although FDA-approved *Histoplasma* urinary antigen detection kits are available in several Latin American countries, their sensitivity is generally lower compared to the original MiraVista tests. MiraVista Diagnostics, a leading provider in fungal antigen detection, developed highly sensitive assays that are considered the gold standard due to their superior performance in detecting low levels of *Histoplasma* antigens, especially in immunosuppressed patients. Despite their accuracy, MiraVista kits are often costly and primarily distributed through private channels, particularly in the United States, making access difficult in low-resource settings. In addition to ELISA, the LFA (Lateral Flow Assay) has emerged as a promising alternative for the detection of Histoplasma antigens. LFA offers a rapid, user-friendly, and cost-effective diagnostic tool, making it particularly valuable in resource-limited settings where access to sophisticated laboratory infrastructure is restricted. Thus, expanding access to kits, the search for new methods, and raising awareness regarding the diagnosis of histoplasmosis become the challenges to be tackled to reduce patient morbidity and mortality, especially in the Americas [9].

In this study, we present an innovative case of a patient diagnosed with HIV, disseminated histoplasmosis, and rifampicin resistant tuberculosis, whose successful treatment occurred in the state of Roraima.

Case presentation

A 22-year-old man from Venezuela, had been in transit through Roraima for one month when he was admitted to the state's reference hospital (HGR – General Hospital of Roraima) on August 4, 2021. He presented with symptoms of diarrhea, persistent fever without formal temperature recordings, and significant weight loss of approximately 10 kg over the past 30 days. Additionally, over the preceding two weeks, he developed a cough that was initially productive but later became dry and worsened with exertion. The patient had no known comorbidities.

On physical examination, the patient appeared in stable general condition, afebrile, with normal skin coloration, well-hydrated, and breathing comfortably in room air. Vital signs included a blood pressure of 110/70 mmHg, heart rate of 64 bpm, and respiratory rate of 18 bpm. Examination of the oral cavity revealed whitish plaques consistent with oropharyngeal candidiasis. Abdominal evaluation demonstrated hepatomegaly and tenderness on deep palpation of the right iliac fossa, without evidence of peritoneal irritation.

On the skin, lesions were noted on the upper and lower limbs, with involvement of the palms of the hands and soles of the feet, in addition to an anorectal ulcer. No abnormalities were identified in cardiorespiratory evaluations, and the patient did not present enlarged lymph nodes. Laboratory tests showed the diagnosis of HIV and syphilis through a rapid test, in addition to pulmonary tuberculosis through sputum smear microscopy on August 6, 2021. Other routine exams were also requested (Table 1). It is noteworthy that during this period, there was no institutional availability of the rapid molecular test (RMT-TB) that analyzes sensitivity to rifampicin.

After admission to the infectious diseases' unit, the patient was diagnosed with tuberculosis and HIV co-infection. Treatment for tuberculosis was initiated on August 6, 2021, with a regimen including rifampicin, isoniazid, pyrazinamide, and ethambutol. Three weeks after initiating tuberculostatic treatment, antiretroviral therapy (ART) was started, consisting of tenofovir, lamivudine, and double dose dolutegravir. HIV genotypic resistance testing confirmed susceptibility to the prescribed regimen. During the first immunological assessment, conducted on October 11, 2021, the patient had a viral load of 18,171 copies/mL and a CD4 T count of 44 cells/mm^3 . However, the syphilis skin lesions disappeared.

About a week after the tuberculostatic treatment, the patient experienced clinical worsening, characterized by diffuse abdominal pain, vomiting, fever, considerably increased hepatosplenomegaly, and development of septic shock. This led to his transfer to an intensive care unit (ICU). Additional examinations revealed pancytopenia and a significant increase in lactate dehydrogenase (LDH) levels.

Given this clinical and laboratory picture, disseminated histoplasmosis was suspected, and treatment with liposomal amphotericin B was initiated empirically. Subsequently, the diagnosis was confirmed through blood culture (Fig. 1).

During this period, the patient received the results of the culture sensitivity test for *Mycobacterium tuberculosis* (MTB), which revealed monoresistance to rifampicin (sample collected on August 8, 2021, and confirmed resistance on October 22, 2021). Consequently, the treatment regimen was adjusted to include levofloxacin, ethambutol, isoniazid, pyrazinamide, and amikacin. Additionally, the antiretroviral therapy (ART) regimen was modified, replacing dolutegravir with efavirenz.

The patient showed satisfactory clinical progress, with significant clinical and laboratory improvements, which enabled his discharge from the hospital on December 1, 2021, after 120 days of hospitalization (Fig. 2). Following discharge, the patient was transferred to the state of Santa Catarina for continued treatment. No detailed follow-up information is available, but it is known that the patient remains alive, asymptomatic, and adherent to ART.

Discussion

It is well established that in developing countries, delays in HIV diagnosis and barriers to accessing ART represent significant risk factors for the development of opportunistic infections. In Brazil, among these opportunistic infections, tuberculosis is very prevalent [10]. When we consider the endemicity of histoplasmosis in the Americas, it is clear that the incidence of HIV-DH-TB co-infection has become a significant challenge in terms of public health in this region.

Migration from Venezuela to Brazil has been driven by the severe political and socioeconomic crisis affecting Venezuela, which has significantly worsened since 2015 (11). According to the International Organization for Migration, nearly one million Venezuelans have entered Brazil since 2017 [11]. This substantial migration flow

Table 1
Biochemical analysis during hospitalization.

Clinical test	Hospital Admission	ICU Admission	1 Day after ICU Discharge	2 Days before Hospital Discharge
Hemoglobin	**8.30 g/dL**	**10.20 g/dL**	**8.70 g/dL**	**10.40 g/dL**
Hematocrit	**24.80 %**	**30.50 %**	**26.30 %**	**31.00 %**
Leukocytes	**10.84 × 10 ^{3} /uL**	4.17 × 10 ^{3} /uL	4.97 × 10 ^{3} /uL	**1.93 × 10 ^{3} /uL**
Neutrophils	**91.30 %**	**89.50 %**	68.00 %	57.0 %
Platelets	200.00 × 10 ^{3} /uL	350.00 × 10 ^{3} /uL	**105.00 × 10 ^{3} /uL**	256.00 × 10 ^{3} /uL
Procalcitonin	**1.1 ng/mL**	-	**0.16 ng/mL**	-
C Reative protein	**145.79 mg/L**	**62.12 mg/L**	4.34 mg/L	7.27 mg/L
Lactate dehydrogenase	-	**2152.76 U/L**	**312.44 U/L**	**209.37 U/L**
BUN	**0.43 mg/dL**	35.91 mg/dL	25.51 mg/dL	**41.28 mg/dL**
CR	1.06 mg/dL	0.76 mg/dL	0.70 mg/dL	0.81 mg/dL
AST	**59.22 U/L**	**173.96 U/L**	**50.36 U/L**	**84.46 U/L**
ALT	**54.85 U/L**	**55.87 U/L**	26.69 U/L	**70.37 U/L**
ALP	-	-	**475.82 mg/dL**	**270.84 mg/dL**
GGT	**106.96 U/L**	**-**	**268.25 U/L**	**326.82 U/L**
TB	0.72 mg/dL	**4.33 mg/dL**	1.14 mg/dL	0.40 mg/dL
DB	**0.57 mg/dL**	**1.99 mg/dL**	**0.80 mg/dL**	0.27 mg/dL
IB	0.15 mg/dL	**2.34 mg/dL**	0.34 mg/dL	0.13 mg/dL
AMY	**153.79 U/L**	**-**	60.86 U/L	103.75 U/L
Lipase	**142.43 U/L**	-	34.45 U/L	-
PT	**16.6 seg**	**17.9 seg**	**15.9 seg**	-
INR	**1.22**	**1.33**	1.16	-

The values in bold are outside the reference values, according to the Laboratory Center of the General Hospital of Roraima (HGR). Hb (hemoglobin): 13.5–18 g/dL; Ht (hematocrit): 40–50 %; Leukocytes: 4–10 × 103/μL; Neutrophils: 50–70 %; Platelets: 150–400 × 103/μL; BUN (Blood Urea Nitrogen): 15–40 mg/dL; CR (Creatinine): 0.7–1.4 mg/dL; ALT (Alanine aminotransferase): 5–48 U/L; AST (Aspartate aminotransferase): 5–48 U/L; (ALP) Alkaline phosphatase: 27–100 mg/dL; GGT (Gamma-glutamyl transpeptidase): 12–45 U/L; TB (total bilirubin): 0.1–1.2 mg/dL; DB (direct bilirubin): 0–0.4 mg/dL; IB (indirect bilirubin): 0.1–0.8 mg/dL; AMY (amylase): 125–349 U/L; Lipase: 0–60 U/L; Procalcitonin: 0.01–0.12 ng/mL; PT (prothrombin time): 10–14 s; PTT (partial thromboplastin time): 25–39 s; INR (international normalized ratio): 0.8–1.2; LDH (lactate dehydrogenase): 200–480 U/L; CRP (C-reactive protein): 0–8 mg/dL.

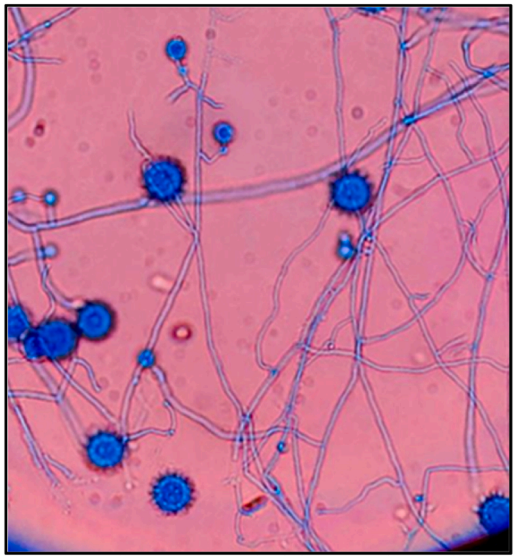

Fig. 1. Microscopic image of *Histoplasma capsulatum* isolated from the patient's blood sample, displaying the mycelial phase of the fungus. The image shows characteristic branching hyphae and round, spore-like macroconidia with a rough or spiked surface.

introduces new challenges for healthcare professionals, who must adapt their medical practices to account for the complexities of cross-border population movements and the unique health needs of migrant communities. The impacts of Venezuelan immigration on Brazilian public health are notable. Among these impacts, the resurgence of vaccine-preventable diseases in the country and the increase in imported cases of tuberculosis and HIV stand out. Many Venezuelans arrive in Brazil already carrying illnesses and, in many cases, without adequate treatment, which overloads public health services [12]. Immigration, although not the root cause of chronic health problems, ends up worsening them [12].

In this case, the epidemiological context is particularly significant, as the patient originates from Venezuela, a country with one of the highest rates of exposure to histoplasmosis in Latin America [13] (Figure 3). Conversely, the true incidence of histoplasmosis in Brazil remains underestimated due to the absence of mandatory reporting for the disease. Data is particularly limited in the North region, which includes states bordering countries with a high prevalence of histoplasmosis [5].

Due to the high burden of pulmonary tuberculosis (PTB) secondary to HIV, histoplasmosis in this population is commonly misdiagnosed as PTB, even in the presence of a negative microbiological test for MTB, due to similar clinical, radiological, and laboratory presentations [14]. This is also due, in part, to the lack of human and laboratory resources to make a definitive diagnosis of histoplasmosis [15].

Tuberculosis was diagnosed concomitantly in approximately 10 % of Brazilians with histoplasmosis [5]. Co-occurrence is known to represent an important challenge for diagnosis and treatment, especially in highly immunosuppressed individuals, due to common clinical findings, such as fever, night sweats, weight loss, lymphadenopathy, respiratory symptoms; image changes with lung lesions or miliary nodules; and laboratory tests, mainly pancytopenia, elevation of aminotransferases and acute phase reactants [3,16].

Multidrug-resistant tuberculosis (MDR-TB) is defined as tuberculosis that is resistant to both rifampin and isoniazid, two of the most effective first-line drugs. Extensively drug-resistant tuberculosis (XDR-TB) is an even more concerning form of the disease, characterized by additional resistance to a fluoroquinolone and at least one second-line injectable drug. Another concerning form of resistance is the monodrug rifampin-resistant tuberculosis (RR-TB), the case of our patient [17].

According to the World Health Organization (WHO), in 2023, the estimated proportion of people with TB who had MDR/RR-TB was 3.2 % among new cases and 16 % among those previously treated [18]. Monodrug-resistant tuberculosis arises from the selection of *M. tuberculosis* mutations during treatment with first-line antitubercular drugs. A key risk factor for this progression is the high prevalence of HIV infection, influenced by factors such as the impact of immunosuppression on mutation rates and decreased adherence to complex therapeutic regimens [19,20]. It is also noteworthy, as highlighted by genotyping

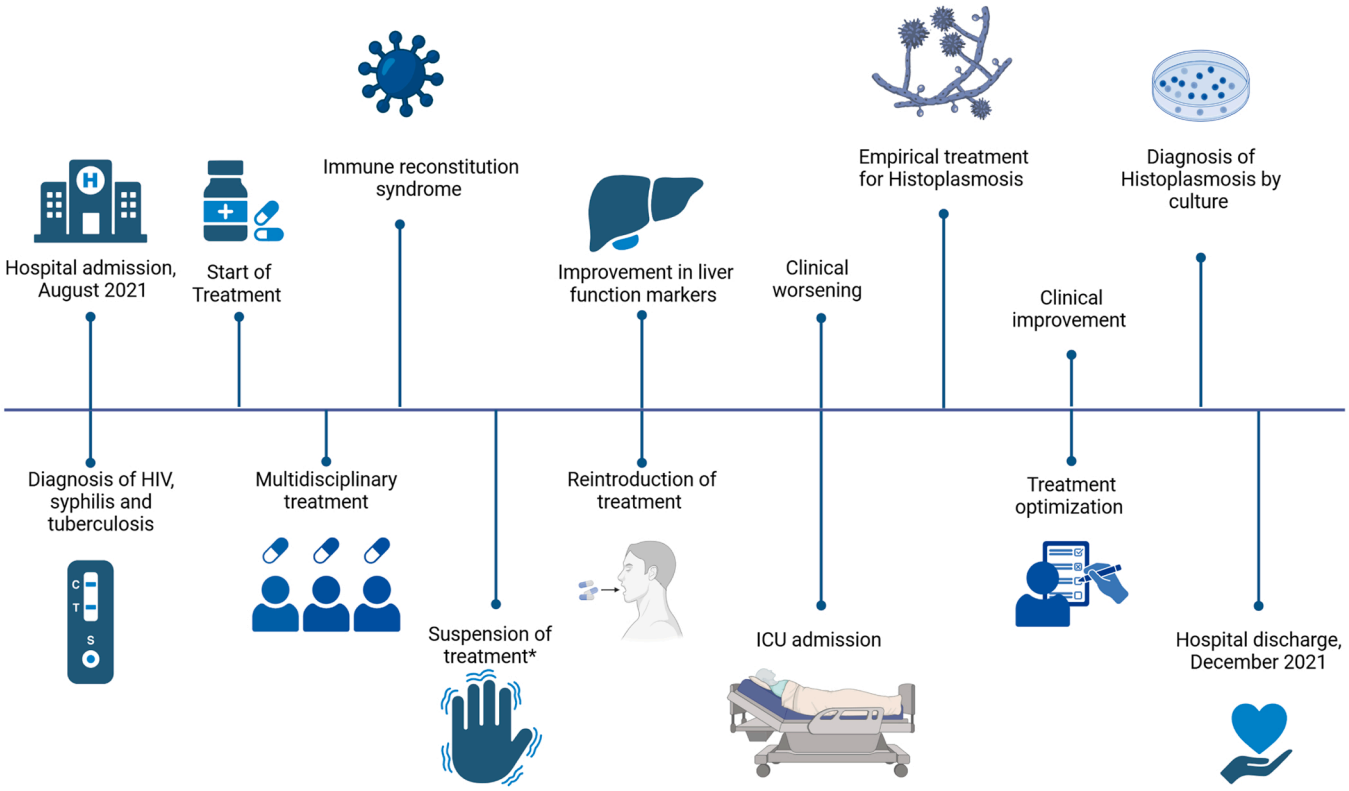

Fig. 2. Hospitalization timeline. Source: Own authorship (2024). Created with *Biorender.com.*

studies, the role of migration in the dissemination of resistant TB across borders, a fact coinciding with the case presented. Other factors associated with the development of multidrug resistance to TB are community transmission, nosocomial transmission, and non-standardization of treatment.

The patient in this study presented to the hospital with a clinical condition that included diarrhea, fever, weight loss, cough, and dyspnea on exertion. The presence of pancytopenia, high levels of C-reactive protein, and lactate dehydrogenase, in addition to the identification of consolidated opacities on admission tomography, raised the suspicion of a possible co-infection with resistant tuberculosis and histoplasmosis. Reports of this nature are scarce in the national context and are even rarer in the North region. During the clinical evolution, a crucial point was the identification of hepatotoxicity, initially attributed to tuberculosis treatment, but later confirmed as resulting from the double dose of dolutegravir. This finding reinforces the importance of carefully monitoring the use of high doses of antiretroviral drugs, especially in immunosuppressed patients, to prevent serious liver complications. The diagnosis was suspected based on clinical evidence, laboratory findings, epidemiological profile, and, mainly, due to the lack of clinical response to anti-tuberculous treatment, even with negative smear microscopy results, despite the inclusion of the basic scheme. It is worth mentioning that the rifampicin resistance test performed by GenXpert can detect early resistance if it had been performed at the time of tuberculosis diagnosis [21].

Confirmation of the diagnosis of DH was achieved through blood culture for fungi, considered the gold standard in the literature. Furthermore, histopathological analysis, targeting fungal elements and acid-fast organisms, together with microbiological confirmation, are preferred strategies to establish a definitive diagnosis, especially in cases of pulmonary co-infections [16]. However, it is important to note that culture sensitivity can vary, possibly due to differences in processing and sample type, and specificity can be difficult to measure due to methodological limitations [22]. The sensitivity of this method is greater in invasive samples, such as bone marrow, and studies have shown a blood culture positivity rate of only 36 % [23]. Furthermore, fungal growth can take 4–6 weeks, which means that waiting for culture results can expose the patient to empiric treatments that may be inappropriate and even toxic, especially in the case of tuberculosis. In addition to these methods, the buffy coat technique has been utilized in the northeast of Brazil for the diagnosis of disseminated histoplasmosis, particularly in AIDS patients. A study conducted at São José Hospital in Ceará demonstrated that stained smears of buffy coat had a very low sensitivity of 25.9 % but a high specificity of 100 % for detecting Histoplasma [24]. However, its very low sensitivity suggests that it should be used in conjunction with other diagnostic tests to improve accuracy, especially in endemic areas where timely diagnosis is crucial for reducing mortality.

On the other hand, circulating antigen detection assay proved to be superior to culture and serology, with high sensitivity and specificity, the latter being around 95 %. Although molecular tests perform well, there is still no consensus on laboratory protocols, which makes their reproducibility difficult [22]. Therefore, guidelines recommend the use of Histoplasma antigen testing as the preferred method in immunosuppressed individuals, due to the speed of diagnosis and its greater accuracy in the case of people living with HIV (PLHIV) [23]. However, it is important to note that these tests are not widely available, although there are kits that can be used at the bedside [25].

In the Brazilian context, these exams are generally limited and are not part of routines due to budget restrictions in the Unified Health System (SUS, from Portuguese *Sistema Único de Saúde*). This highlights the importance of immediate clinical and epidemiological suspicion, followed by the implementation of empirical treatment in cases of suspected disseminated fungal infection, in order to reduce morbidity and

mortality. It is worth mentioning that the patient described in this case was diagnosed with tuberculosis monoresistant to rifampicin and disseminated histoplasmosis, a case that, until now, had not been reported in the literature.

Conclusion

This case report underscores the critical importance of recognizing and managing histoplasmosis and tuberculosis co-infection, particularly in immunosuppressed individuals who fail to respond adequately to initial treatment. Prompt clinical suspicion of serious fungal infections and preparedness to initiate empiric antifungal therapy are essential to reduce the high mortality associated with these conditions. In this case, the rare coexistence of monodrug-resistant tuberculosis and disseminated histoplasmosis in a patient with AIDS highlights the complexities of diagnosing and treating co-infections in vulnerable populations.

Institutional review board statement

The study was approved by the Research Ethics Committee of the Federal University of Roraima, under protocol number CAAE 70320423.8.0000.5302 (approved on 4 August 2023).

Informed consent statement

Written informed consent has been obtained from the patient to publish this paper.

Presentation at a meeting

NA.

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CRediT authorship contribution statement

Galan Luis E. B.: Writing – review & editing, Supervision, Investigation, Conceptualization. **Pucca Manuela Berto:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Andrade Stephanye B.:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Honorato Dandara M.:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Paiva Artur D. P.:** Writing – review & editing, Investigation. **Neto Manoel M. S.:** Writing – review & editing, Investigation. **Romanazzi Marcela:** Writing – review & editing, Writing – original draft, Methodology. **Filardi Eloise T. M.:** Writing – review & editing, Writing – original draft, Methodology. **Carbonell Roberto C.:** Writing – review & editing, Investigation. **Dantas Domingos S. M.:** Writing – review & editing, Investigation. **Cerni Felipe A.:** Writing – review & editing, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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