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ESCOLA DE MEDICINA
PUCRS

SCIENTIA MEDICA

Scientia Medica Porto Alegre, v. 34, p. 1-9, jan.-dez. 2024
e-ISSN: 1980-6108 | ISSN-L: 1806-5562

http://dx.doi.org/10.15448/1980-6108.2024.1.45917

SEÇÃO: CASE REPORT

Intestinal histoplasmosis and coinfections mimicking inflammatory bowel disease and neoplasia: a case series

Histoplasmose intestinal e coinfecções mimetizando doença inflamatória intestinal e neoplasia: uma série de casos

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Received on: Apr.10th, 2024.
Approved on: Oct. 03th, 2024.
Published on: Dec. 20th 2024.

Abstract

Objectives: to describe a case series of chronic diarrhea of infectious etiology previously identified as Inflammatory Bowel Diseases (IBD).

Case reports: we present four cases from a Brazilian tertiary hospital in which patients with HIV were initially treated for IBD or suspected neoplasia based on clinical presentation and colonoscopy findings. Late-stage HIV/AIDS diagnosis subsequently revealed disseminated histoplasmosis with intestinal involvement and coinfections, including cytomegalovirus colitis (n = 3) and tuberculosis (n = 1).

Conclusions: chronic diarrhea, particularly when accompanied by dysenteric symptoms, presents significant challenges in distinguishing between Inflammatory Bowel Disease (IBD), neoplasia, and infectious diseases. This case series highlights the importance of considering immunosuppression, especially HIV/AIDS and related opportunistic infections, in cases of chronic diarrhea. A comprehensive diagnostic approach incorporating microbiological, serological, molecular, and histopathological analyses is critical in identifying underlying etiologies, including coinfections. Early and accurate diagnosis facilitates appropriate treatment, reducing the morbidity and mortality associated with these conditions.

Keywords: cytomegalovirus, inflammatory bowel disease, histoplasmosis, HIV, gastrointestinal tuberculosis.

Resumo

Objetivos: descrever uma série de casos de diarreia crônica de etiologia infecciosa identificada previamente como doença inflamatória intestinal (DII).

Relatos de casos: apresentamos quatro casos de coinfecção intestinal em um hospital terciário brasileiro em que pacientes foram inicialmente tratados como DII ou suspeita de neoplasia, com base na apresentação clínica e nos achados da colonoscopia. O diagnóstico tardio da infecção HIV/AIDS levou à histoplasmose disseminada com envolvimento intestinal e coinfecção com colite por citomegalovirus (n = 3) ou tuberculose (n = 1).

Conclusões: a diarreia crônica, particularmente com características disentéricas, representa um desafio primordial na distinção entre DII, neoplasia e doenças infecciosas. Essa série ressalta a necessidade de considerar a imunossupressão, particularmente o HIV/AIDS, e as infecções oportunistas em casos de diarreia crônica. Uma abordagem diagnóstica abrangente que empregue análises micro-

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biológicas, sorológicas, moleculares e histopatológicas é fundamental para identificar etiologias, inclusive coinfecções. O diagnóstico precoce e preciso permite o tratamento adequado, reduzindo a morbidade e a mortalidade associadas a essas condições.

Palavras-chave: citomegalovírus, doenças inflamatórias intestinais, histoplasmose, HIV, tuberculose gastrointestinal.

Introduction

Chronic diarrhea is defined as a persistent alteration in stool consistency, typically softer or liquid, with an increased frequency of more than three evacuations per day, lasting for at least four weeks (1). Diarrheal cases with dysenteric features are often part of the differential diagnosis for inflammatory bowel disease (IBD), neoplasia, and infectious diseases, including human immunodeficiency virus (HIV) infection and its associated opportunistic coinfections (2).

Among infectious diseases, the main etiologies involve colitis or enteritis, which can be parasitic, viral, bacterial, fungal, or mycobacterial in nature (3). Severe immunosuppression related to HIV/AIDS (CD4 < 200 cells/mm^3) significantly increases the risk of gastrointestinal opportunistic infections. Achieving virological control and immune recovery through antiretroviral therapy is the most effective strategy for preventing and mitigating the severity of these infections (4).

This case series describes four patients admitted to a tertiary hospital in the Midwest region of Brazil between 2018 and 2022. Based on their clinical presentation and colonoscopy findings, these patients were initially diagnosed with IBD or suspected neoplasia. However, due to HIV-related immunosuppression, they developed intestinal histoplasmosis associated with other opportunistic infections, such as cytomegalovirus (CMV) and tuberculosis. This study adheres to Brazilian guidelines for human research and the Helsinki Declaration and was approved by the Institutional Ethics Committee (Ethics Approval Protocols numbers 4.654.234 and 6.317.632).

Case description

Patient 1

A 26-year-old female reported three years of watery diarrhea associated with abdominal pain, nausea, vomiting, asthenia, and a weight loss of 25 kg. On physical examination, she was alert, pallid, and dehydrated, with oral moniliasis and a distended, tender, and painful abdomen.

Abdominal computerized tomography (CT) revealed a small stenotic area in the distal ileum, with early contrast enhancement (**Figure 1**). A colonoscopy showed friable ulcers with raised edges and circumferential and constrictive lesions in the hepatic flexure and descending colon. The initial histopathological study (HPS) suggested Crohn's disease, and she started specific treatment with mesalamine and corticosteroids. When transferred to our service, a subsequent colonic biopsy highlighted viral inclusions compatible with cytomegalovirus (CMV) infection, and histiocytes filled with rounded structures, stained by periodic acid-Schiff (PAS) and Grocott (**Figure 2**).

The HIV 1 and 2 serology (Sg-HIV) was reactive, and the CD4 T lymphocyte count (LT-CD4+), HIV viral load (VL), and serum quantitative CMV polymerase chain reaction (PCR) were six cells/mm^3, 262,676 copies/mL, and 683,000 IU/mL, respectively. Additionally, serology by double radial immunodiffusion was positive for histo plasmosis.

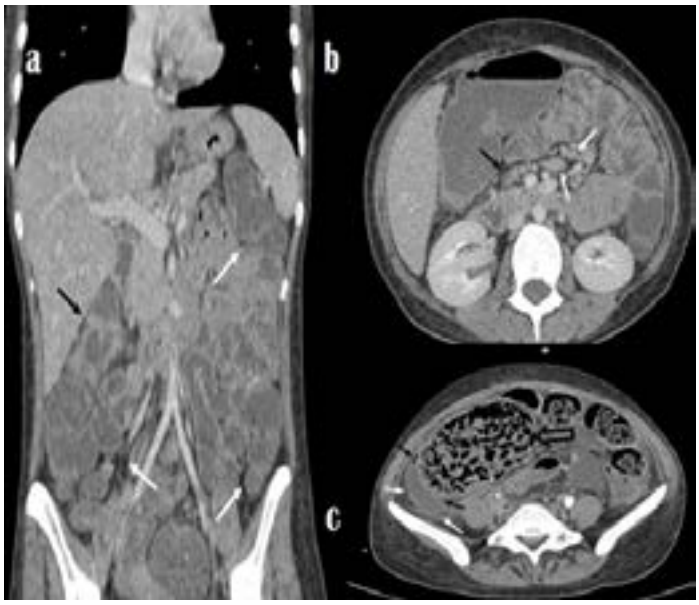

Figure 1 – a. Contrast-enhanced coronal CT scan of the abdomen in the portal phase: diffuse dilation of loops of the small intestine and colon (white arrow) and multiple points of intestinal parietal thickening (black arrow). **b.** Axial section: multiple lymphadenopathies at the root of the mesentery (white arrows) with central necrosis (black arrow). **c.** Axial view: significant dilation of the cecum (black open arrow), thickening and contrast enhancement - peritonitis (white arrow), and presence of free fluid with intermingled gas foci - pneumoperitoneum (black arrows).

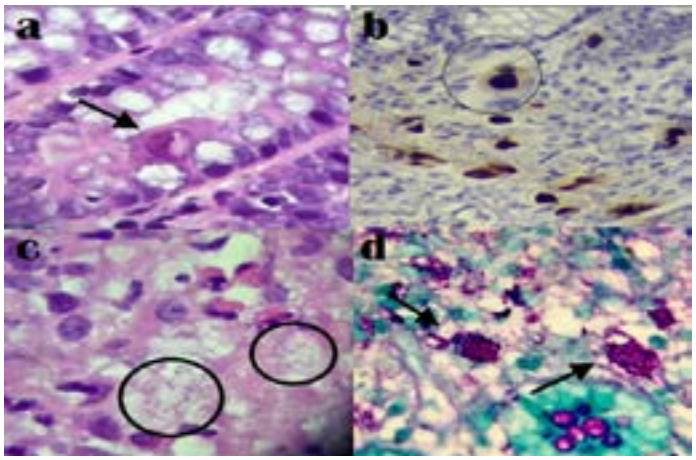

Figure 2 – **a.** Colonic mucosa showing cytomegalic viral inclusion, (black arrow); H&E – 100x.**b.** Positive immunohistochemistry for CMV, (black magnifying glass); 100X.**c.**Fungal structures within the cytoplasm of histiocytes, (black circle); H&E – 100x. **d.** Small"cluster" structures highlighted by PAS, (black arrow); 100X.

As a complication, the patient experienced intestinal perforation, requiring right colectomy and intensive care. She progressed with clinical and hemodynamic improvement. She received broad-spectrum antibiotics for septic shock, along with ganciclovir for disseminated CMV for 21 days, liposomal amphotericin B for disseminated histoplasmosis for 27 days, and itraconazole for 12 months. She remains well-adherent to antiretroviral therapy, with a CD4 T lymphocyte count

(LT-CD4+) of 356 cells/mm^3 and virologically controlled (HIV VL < 50 copies/mL).

Patient 2

A 58-year-old male reported daily fever over the past year, epigastric pain, night sweats, and profuse diarrhea, occasionally with hematochezia, along with a loss of approximately 13 kg. He was diagnosed with Crohn's disease and had been taking prednisone 40 mg/day and azathioprine 100 mg/day for one month. Upon hospital admission, Sg-HIV was reactive, LT-CD4+ = 41 cells/mm^3, and HIV-VL = 1,372,580 copies/mL. An abdominal CT scan showed diffuse colonic thickening, adjacent fat densification, dilation of the rectal ampulla, hepatosplenomegaly, and numerous retroperitoneal lymphadenopathies in the mesenteric region.

A colonoscopy revealed deep, friable ulcers with irregular edges, some of which were aphthous, covered by fibrin throughout the colon. HPS demonstrated an active chronic inflammatory process, ulcerations, an area with the outline of an epithelioid granuloma, and central suppurative necrosis. Grocott and PAS staining highlighted numerous ovoid intrahistiocytic, birefringent structures suggestive of *Histoplasma* spp (**Figure 3**). During the investigation, quantitative serum CMV PCR detected 360 IU/ml. The patient received intravenous liposomal amphotericin B and ganciclovir for 21 days. He remains under outpatient follow-up, asymptomatic, with good adherence to antiretroviral therapy, partial immune recovery (TL CD4+ = 265 cells/mm^3), and HIV-VL < 40 copies/mL.

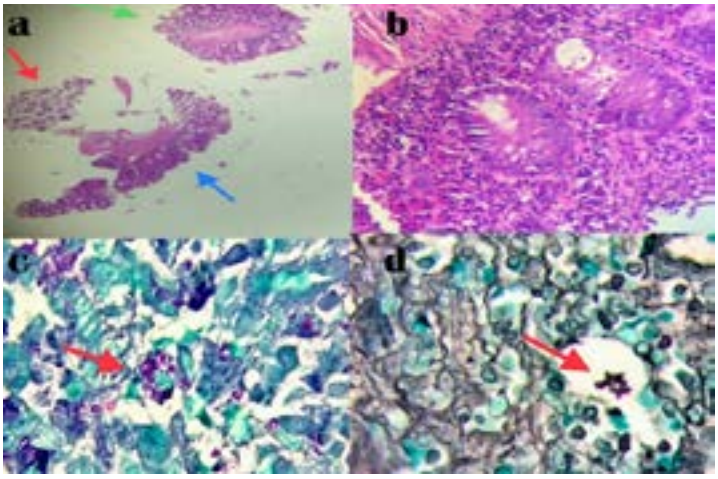

Figure 3 – a. Large intestine mucosa (H&E – 4x): preserved mucosa, with edema (green arrow); chronic inflammatory reaction (red arrow); inflammatory reaction and erosion (blue arrow).**b.** Large intestine mucosa (H&E – 40x): chronic diffuse inflammatory infiltrates and erosion foci.**c.** Intestinal mucosa (fungal PAS – 100x): intra-histiocytic yeast structures with clear perinuclear halo (red arrow). **d.** Clusters of budding yeast-like structures within histiocytes (red arrow) (Grocott silver methenamine staining – 100x).

Patient 3

A 24-year-old male complained of a dry cough, night sweats, persistent diarrhea, and a weight loss of approximately 8 kg in the last month. A colonoscopy showed deep ulcerated lesions with well-defined edges and a fibrinous base in the ileum and throughout the colon, raising suspicion for IBD. An abdominal CT scan revealed mild ascites, intraperitoneal adenopathy, and hepatosplenomegaly, which could correspond to lymphoproliferative or inflammatory-infectious disease. Sg-HIV was reactive, LT CD4+ = 69 cells/mm^3, and HIV-VL = 2,380,226 copies/mL.

Histopathology (HPS) of colon fragments

showed vascular congestion and mixed cellular infiltrate with a predominance of histiocytes, containing tiny, rounded structures with budding in "rows" and "grape clusters," stainable by Grocott and PAS, suggestive of yeasts. The blood culture was performed using Mycosel Agar and Sabouraud Agar with Chloramphenicol, and identification was done through microculture on potato dextrose agar slides, where typical tuberculate macroconidia of *Histoplasma capsulatum* were observed. Additionally, the rapid molecular test for *Mycobacterium tuberculosis* (Xpert TB/RIF, Cepheid, Sunnyvale, CA) was positive in intestinal fragments, showing sensitivity to rifampicin. The patient received liposomal amphotericin B for 17 days and a fixed-dose combination of antituberculosis agents for six months. He completed treatments and prophylaxis, remained virologically controlled, and achieved immune reconstitution with LT CD4+ = 431 cells/mm^3.

Patient 4

A 46-year-old male, recently diagnosed with HIV infection, LT CD4+ = 26 cells/mm^3 and HIV-VL = 577,785 copies/mL, was hospitalized due to a reduced level of consciousness. A head CT scan revealed extensive supra- and infratentorial lesions with an expansive effect. A chest CT scan showed parenchymal opacity with ground-glass attenuation in the right lower lobe and consolidations associated with a cavitary nodular formation in the left upper lobe. HPS of the brain lesion biopsy was positive for toxoplasmosis on immunohistochemistry, and the patient received treatment accordingly.

During hospitalization, he developed profuse diarrhea. An abdominal CT revealed multiple heterogeneous lymphadenopathies, parietal thickening, and cecal edema, with apparent ulcerations, reduced lumen, and partial intestinal obstruction. A colonoscopy identified an ulcerative-vegetative lesion in the distal transverse colon with complete circumferential involvement, raising suspicion of colon neoplasia. HPS demonstrated small viral inclusions in glandular cells, which were positive for anti-CMV antibodies on immunohistochemistry. Additionally, histiocytes containing tiny clustered yeasts were observed in their cytoplasm, highlighted by H&E and fungal stains (**Figure 4**). Despite improvement in the opportunistic infections, the patient died after an extended hospitalization due to healthcare-associated complications.

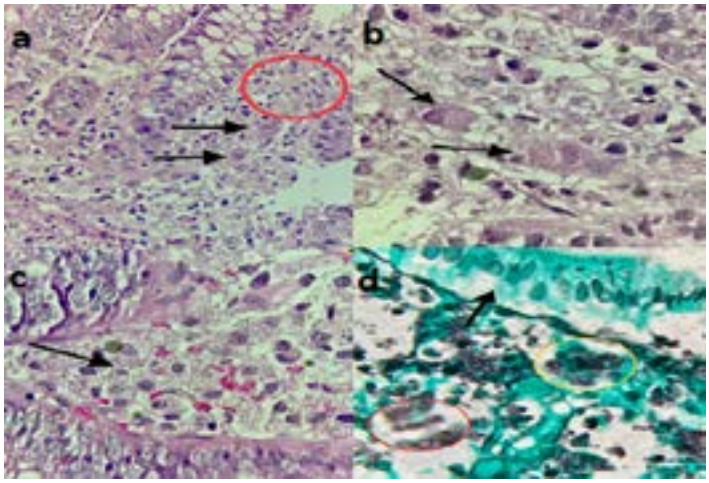

Figure 4 – a. Colonic mucosa showing mixed inflammatory infiltrate highlighting histiocytes containing fungal structures (red circle) and cells with cytomegalic inclusions (black arrow); HE – 40x. **b.** Details of CMV viral inclusions (intranuclear made up of viral proteins); HE – 100x. **c.** Details of histiocytes containing intracytoplasmic fungal structures (black arrow); HE – 100x. **d.** Colonic mucosa (black arrow), small rounded structures forming "bunches" (yellow magnifying glass) or "rows" (red magnifying glass); Grocott – 100x.

Discussion

In this case series, we present patients whose colonoscopy revealed ulcers or tumors that could easily be mistaken for IBD or neoplasms. All patients had a late HIV diagnosis, were in severe immunosuppression, and intestinal opportunistic coinfections, including histoplasmosis-CMV and histoplasmosis-tuberculosis, were confirmed by HPS using special stains and immunohistochemistry, in addition to specific microbiological, molecular, and serological methods.

Crohn's disease and ulcerative colitis are the main IBD. The pathogenesis of IBD is not entirely understood (5). Ulcerative colitis affects the mucosa and occasionally the submucosa of the colon and rectum, whereas Crohn's disease can occur in any part of the digestive tract, with a predilection for the ileal and ileocecal regions, often involving the entire thickness of the intestinal wall (6-7).Treatment depends on an accurate diagnosis for better disease control, often involving long-term combination therapies, including immunosuppressants (3).

The symptoms of IBD typically include fever, loss of appetite, weight loss, fatigue, and night sweats, associated with diarrheal stools. Rectal pain or bleeding, tenesmus, cramps, and abdominal pain may also occur, depending on the affected intestinal segment (8). Diagnosis requires a detailed anamnesis, physical examination, laboratory tests, stool analysis, radiological exams, endoscopy, colonoscopy, and biopsies followed by histopathological analysis.

Patients with HIV and CD4 count ≤ 150 cells/mm3 are at risk of developing systemic mycoses, such as histoplasmosis, including its disseminated form, characterized by fever, weight loss, pancytopenia, hepatosplenomegaly, and lymphadenopathy (9). Gastrointestinal histoplasmosis occurs in approximately 12% of disseminated cases, affecting mainly the colon, ileum, and ileocecal region, causing inflammatory diarrhea (10). In the Midwest region of Brazil, the estimated prevalence of histoplasmosis is 4.4%, and diarrhea, weight loss, and fever were reported in 44.8%, 63.1%, and 84.2%, respectively (11).

Endoscopic findings include ulcerations that resemble IBD or neoplasm-like polypoid masses (9). In case 3, due to wasting syndrome and intra-abdominal adenopathy, there was suspicion of hematologic malignancy. In case 4, the intestinal mass raised suspicion of adenocarcinoma as the primary hypothesis.

Gastrointestinal histoplasmosis is often considered a mimic of IBD; however, it is not commonly remembered as a differential diagnosis in these patients (9). Histological examination reveals macrophages infected with small yeast-like structures in their cytoplasm, especially in the lamina propria. HPS on its own presents challenges, as

identifying small intracellular budding yeasts using fungal stains can point to Histoplasma species, but may be mistaken for amastigotes of Trypanosoma or Leishmania species usingroutine staining alone (hematoxylin-eosin). Furthermore, the unavailability of urine antigen testing for *Histoplasma* species restricts our capacity to promptly confirm diagnoses and begin early treatment (12, 13, 14). Cases 1 and 2 were initially misdiagnosed as IBD and received immunosuppressants, which may have facilitated the progression of disseminated opportunistic infections. Patients presenting with fever and intestinal lesions on colonoscopy, particularly from endemic areas or with a history of potential environmental exposure, should be investigated, especially if they are immunosuppressed (10, 14).

Tuberculosis remains the infectious disease with the highest morbidity and mortality among people living with HIV/AIDS, even in the absence of advanced immunosuppression (15). The most common site of intestinal involvement is the ileocecal region, followed by the small intestines, colon, and gastroduodenal region (16). Intestinal obstruction is the most common complication due to progressive luminal stenosis or loop adhesions (17). Granulomas with caseous necrosis are important histopathological findings, and diagnosis can be confirmed by detecting alcohol-acid-resistant bacilli or positive cultures for *Mycobacterium tuberculosis* from fluids, lymph nodes, or tissues, though positivity rates are often

low (18). It is important to emphasize, however, that IBD can also present with granulomas, and that immunocompromised patients often do not demonstrate that histopathological pattern, which makes diagnosis even more challenging (18). Detection of *M. tuberculosis* through rapid molecular testing in tissue samples is highly specific for intestinal tuberculosis and may help differentiate it from Crohn's disease (19). The management of the coinfection presented significant challenges, as rifampin and isoniazid reduce itraconazole's effectiveness by altering CYP3A4 metabolism in the liver and intestines. Nonetheless, due to limited therapeutic options, the tuberculosis treatment continued with a combination of rifampin, isoniazid, ethambutol, and pyrazinamide, alongside itraconazole. The patient's clinical progress was closely monitored during outpatient follow-up, showing positive outcomes with a maintenance dose of itraconazole at 200 mg every 12 hours. Ideally, blood levels of itraconazole and concentrations of *Histoplasma* antigen (in serum or urine) should have been measured (20), but these resources were unavailable at our facility. Initial treatment with liposomal amphotericin B likely played a key role in the favorable outcome, as it enabled higher doses of amphotericin B with lower toxicity, as previously reported by Johnson PC et al. in cases of histoplasmosis in HIV-positive patients (21).

Most cases of disseminated CMV disease occur due to reactivation in the context of advanced immunosuppression, typically with a CD4 cell count < 50 cells/mm^3. CMV colitis occurs in approximately 17% of cases and mainly affects the distal segments of the colon (22). It is associated with low-grade fever, weight loss, anorexia, malaise, abdominal pain, and frequent watery diarrhea, sometimes of large volume, accompanied by tenesmus or hematochezia. Cytopenia may also be present (23).

CMV colitis in people living with HIV/AIDS can lead to complications such as perforation, intestinal obstruction, severe sepsis, and multiple organ failure. It is associated with high mortality rates due to postoperative complications. The pathogenesis involves submucosal vasculitis with thrombosis, leading to ischemia, ulcers, thinning of the intestinal wall, subsequent perforation, and gangrene (24), as seen in case 1, which presented with an acute perforated abdomen and peritonitis even during proper induction treatment.

Colonoscopy with biopsy is the preferred method for diagnosing suspected CMV colitis due to the presence of mucosal ulcerations. For confirmation, it is necessary to collect multiple biopsy samples for histopathological examination, as viral inclusions are often found in the endothelial cells of the deeper layers of the intestinal wall. Immunohistochemistry can be more sensitive than hematoxylin and eosin (H&E) stains (78-93%), although it is not routinely used. Another important diagnostic tool is quantitative PCR, which provides rapid results and compared to immunohistochemistry, is more sensitive and has a higher negative predictive value (25).

In our cases, these diagnostic resources were essential for determining the underlying etiologies. This study highlights gastrointestinal histoplasmosis coinfected with CMV in three cases and with tuberculosis in one. This type of coinfection is still underreported in the literature, making it difficult to establish the true incidence of such coinfections. The primary prevention of these severe opportunistic infections is the early initiation of antiretroviral therapy and the maintenance of high CD4+ T-cell counts (4).

This case series emphasizes the importance of establishing differential diagnoses in chronic diarrhea, especially ruling out immunosuppression, such as HIV/AIDS. A comprehensive laboratory investigation using microbiological, serological, molecular, and histopathological studies can help in the etiological identification, including coinfections, allowing for adequate treatment with lower morbidity.

Notes

Funding

This study did not receive financial support from external sources

Conflicts of interest disclosure

The authors declare no competing interests relevant to the content of this study.

Authors' contributions

All the authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve the version to be published.

Availability of data and responsibility for the results

All the authors declare to have had full access to the available data and they assume full responsibility for the integrity of these results.

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Os textos deste artigo foram revisados pela SK Revisões Acadêmicas e submetidos para validação do(s) autor(es) antes da publicação.