Journal of Pharmacy and Pharmacology 6 (2018) 130-135
doi: 10.17265/2328-2150/2018.02.003

Colonic Bleeding Due to Histoplasma and Mycobacterium Coinfection in Renal Transplant Patient

Arthur Ivan Nobre Oliveira, Luiz Ricardo Pinheiro de Santana, Cicelys Andreina Malave, Flair Jose Carrilho and Andre Zonetti de Arruda Leite

Department of Gastroenterology, Division of Clinical Gastroenterology and Hepatology, Hospital das Clínicas - University of Sao Paulo School of Medicine, Sao Paulo 05403-010, Brazil

Abstract: Introduction: Histoplasmosis is a rare infectious condition caused by the fungus *Histoplasma capsulatum* that can be presented from asymptomatic to severe forms. Tuberculosis, still an endemic infection in some developing countries, can also have variable clinical presentations. Both diseases involve the lungs mostly, but in immunocompromised patients, especially those with advanced HIV infection and transplant patients, disseminated forms are more frequently found. Gastrointestinal involvement is unusual, and digestive bleeding is an even rarer complication. Case presentation: We report the case of a 39-year-old female who was diagnosed with a *Mycobacterium tuberculosis* and *Histoplasma capsulatum* coinfection occurring 11 years after a living-donor-related renal transplant. The patient presented a severe gastrointestinal bleeding caused by an ulcer in the ascending colon. She improved after a combined treatment with tuberculostatic and fungicidal drugs. Conclusions: Simultaneous gastrointestinal involvement by histoplasmosis and tuberculosis, presenting as severe digestive bleeding, with minimal respiratory symptoms associated, make this an extremely rare case and a diagnostic challenge. Therefore, it is important to keep a high clinical suspicion of opportunistic infection, especially in immunocompromised patient who presents with LGB.

Key words: Disseminated histoplasmosis, intestinal tuberculosis, colonic ulcer, lower gastrointestinal bleeding, renal transplant.

1. Introduction

LGB (lower gastrointestinal bleeding), currently defined as bleeding originating distal to the ileocecal valve, is a frequently self-limited condition, but it can be severe and require specific therapeutic intervention in up to 15-20% of times [1]. Diverticulosis is the leading cause of LGB, mainly among the elderly, followed by vasculopathies and then by inflammatory causes [2]. Infections are rarely related to clinically significant bleeding (less than 5%), being more relevant among immunocompromised patients [1].

Histoplasmosis is a rare infectious condition that usually affects immunocompromised patients, mostly with advanced HIV infection, and secondly transplants patients. It presents in variable forms, from asymptomatic to disseminated disease, and only a few cases reported as LGB [3]. On the other hand, tuberculosis is still an endemic disease in developing countries, which involve primarily the lung, but also can affect different organs, especially in immunocompromised patients, when it may be associated with a more severe disease. Even so, the bowels are rarely affected (less than 2%), mostly associated with the pulmonary form Ref. [4].

Intestinal coinfection by histoplasmosis and tuberculosis has been rarely reported, and it carries a significant prognostic and therapeutic burden. Intestinal bleeding caused by opportunistic infectious disease is even more unusual. The aim of this report is to reinforce the importance of systematic search for opportunistic infections in immunocompromised patients who present with an undetermined LGB associated with unusual acute lesion in the intestine.

Corresponding author: Arthur Ivan Nobre Oliveira, M.D., research fields: gastroenterology, hepatology and endoscopy.

2. Case Presentation

The patient is a 39-year-old female, from São Paulo—Brazil, who had long been diagnosed with SLE (systemic lupus erythematosus) and arterial hypertension. She had a renal transplant 11 years before from a living donor, but had developed chronic antibody mediated rejection and returned to hemodialysis eight years later. She was taking prednisone and everolimus as immunosuppressants.

She first presented with intermittent abdominal pain moderately severe four weeks before hospital admission, and a weight loss of about 10% of her usual body weight in the meantime. She was admitted after a sudden and massive lower intestinal bleeding, with hemodynamic instability. At admission, she looked severely ill, the heart rate was 110/min, respiration rate 24/min, temperature 37.1 °C, and blood pressure 80/54 mmHg. The patient looked emaciated; lung auscultation revealed bilateral fine crackles, and the abdomen was diffusely tender, but without any masses; no other abnormalities were found.

Laboratory investigations upon admission revealed severe anemia (hemoglobin 5.0 g/dL, hematocrit 0.16 L/L), platelet count 144,000/mm^3 and WBC (white blood cell) count was 8,100/μL with a neutrophil count of 82%. ESR (erythrocyte sedimentation rate) of 80 mm at the end of 1 h and CRP (C-reactive protein) was 57.2 mg/L. Serum albumin was 2.4 g/dL (3.5 to 5.5 g/dL), creatinine mildly increased, but a disproportionate raise in blood urea. Liver enzymes were normal. Immunodeficiency virus (HIV) test was negative. Other viral serologic tests for cytomegalovirus (IgG and IgM), hepatitis B and C virus were all negative.

Volemic resuscitation was promptly performed and four packed red cells were transfused. Spontaneous cessation of the intestinal bleeding happened still during her initial assessment.

Right after clinical improvement, upper endoscopy was performed, with no significant abnormalities found. Colonoscopy revealed a large single ulcerated lesion proximally in the ascending colon, which involved the ileocecal valve and over 1/3 of the mucosa round surface (Fig. 1). The ulcer had a hardened consistency and its bed was covered by fibrin and hematin. Numerous biopsies were taken from the edges and bed of the lesion.

An abdominal computed tomography (CT scan) revealed parietal thickening of the cecum and ascending colon, which were narrowed, and associated regional lymphadenomegaly up to 20 mm, a mild splenomegaly, a normal aspect graft kidney in the right pelvis, and minimal ascites (Fig. 2A). A chest CT scan revealed numerous centrilobular micronodules in the lower lobes, with a branching distribution and sequelae calcifications amidst (Fig. 2B).

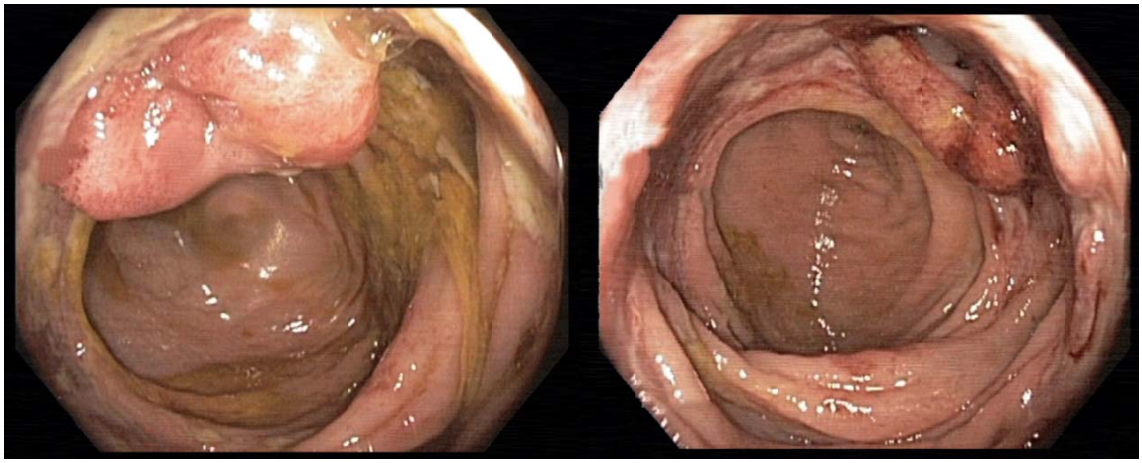

Fig. 1 Colonoscopy revealing an ulcerated lesion in the ascending colon, which involved the ileocecal valve.

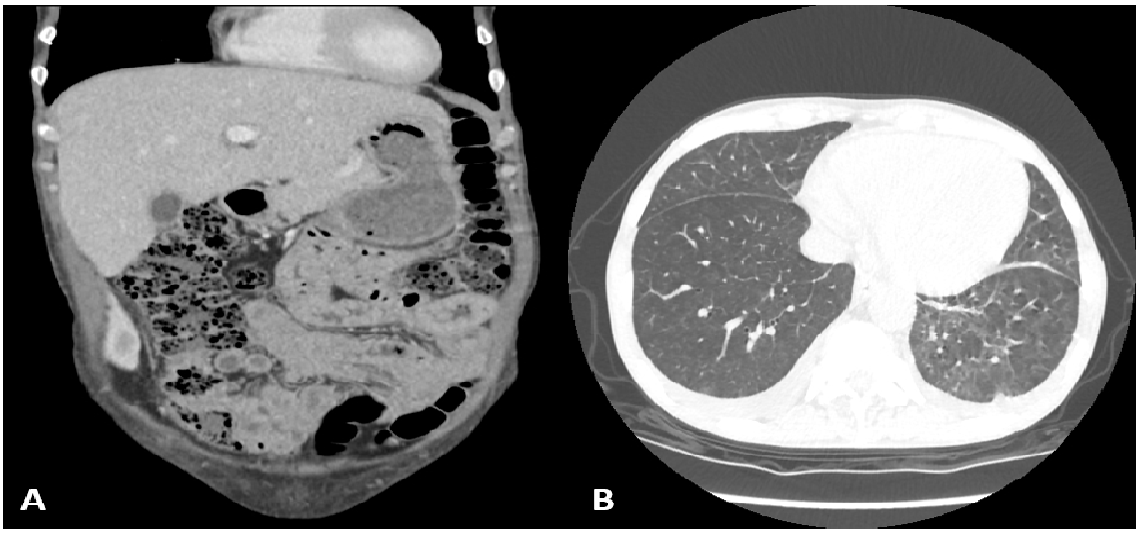

Fig. 2 (A) Coronal CT abdomen image demonstrates a sub-stenosing parietal thickening of the cecum. (B) Axial CT chest image revealing reticulonodular infiltrates with tree-in-bud (branching).

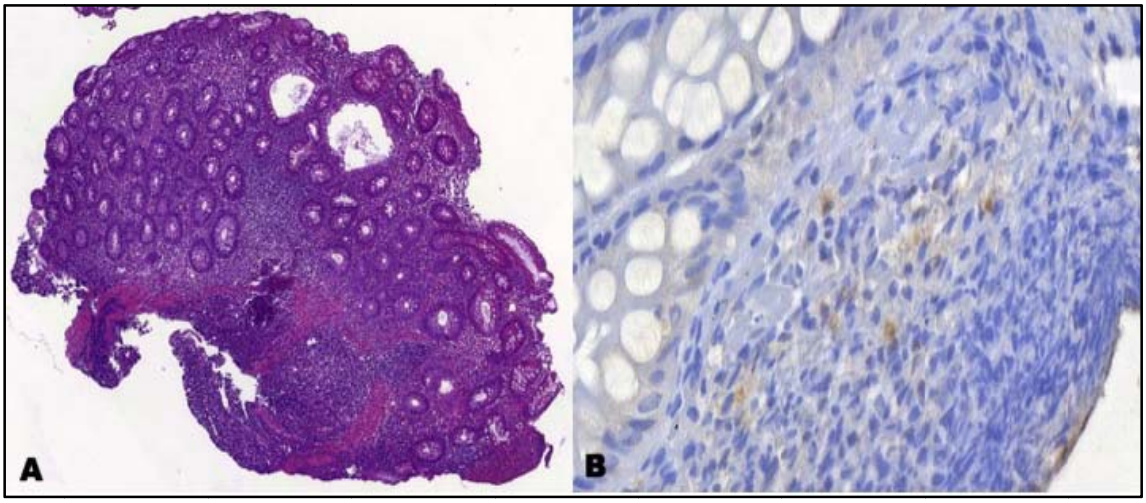

Fig. 3 (A) Biopsy of the colonic ulcerated lesion showing active granulomatous colitis, with fungal structures characteristic of *Histoplasma capsulatum* and also positive for acid-alcohol fast bacilli. (B) Immunohistochemistry for cytomegalovirus was negative and positive for anti-BCG in macrophages.

Acid-alcohol fast bacilli in the sputum were negative. Cultures taken from peripheral blood were also negative. However, the analysis of the biopsies taken from the colonic lesion revealed active granulomatous colitis, with fungal structures characteristic of *Histoplasma capsulatum*, and it was also positive for acid-alcohol fast bacilli (Fig. 3A). Immunohistochemistry for cytomegalovirus was negative; it turned out positive when tested for anti-BCG (*M. bovis*) in macrophages (Fig. 3B). A tissue PCR (polymerase chain reaction) was positive for *Mycobacterium tuberculosis*.

Thus, it was established a diagnosis of coinfection by *H. capsulatum* and *M. tuberculosis*, with disseminated disease (lung and GI tract) complicated by a colonic ulcer and severe intestinal bleeding.

The initial treatment was the quadruple drug regimen with rifampin, isoniazid, pyrazinamide and ethambutol for tuberculosis, lasting 8 weeks, and intravenous liposomal amphotericin B for histoplasmosis during 14 days. All drugs were well tolerated by the patient. Oral itraconazole was then started after the first 2 weeks in substitution for amphotericin, and rifampin with isoniazid were

maintained after 8 weeks. A close outpatient follow-up was done due the well-known interaction of rifampin with itraconazole. Triple immunosuppression was withdrawn, and monotherapy with prednisone 20 mg daily was kept. Tuberculostatic drugs were maintained for a total of 4 months after induction phase and itraconazole for a total of 12 months.

The patient greatly improved during the following weeks; the abdominal pain vanished and she gained weight; intestinal bleeding did not recur. Minor asymptomatic liver enzymes elevation occurred during treatment (AST and ALT up to twice the normal reference value), but resumed to their normal value afterwards. Repeated CT scans upon completion of treatment revealed significant reduction of the colonic thickening and of the lymphadenomegaly, as well as of the lung findings. She was enrolled again for a new renal transplant.

3. Discussion

Lower gastrointestinal bleeding is rarely associated to infectious causes, representing only a small fraction of cases in the general population [2]. Data about LGB in immunocompromised patients are not well reported, but opportunistic infections in the gastrointestinal tract certainly turn out to be more prevalent in this group.

Opportunistic infections are considerably common complications in immunosuppressed patients, such as those with advanced HIV infection and solid organ transplants. The patient in the current case was a renal transplant who had been taking several immunosuppressant drugs for over 10 years when the colonic bleeding occurred. Investigation revealed an ulcer as the source of bleeding, and its cause was a rare and unexpected coinfection by histoplasmosis and tuberculosis, making this a diagnostic and treatment challenge. The only well documented case that has been published up to now with a similar presentation was in an HIV patient with advanced disease [5]; to our knowledge, there are no reported cases in transplant patients.

Histoplasmosis is a systemic mycosis caused by the agent *Histoplasma capsulatum,* a dimorphic fungus that dwells as a mold in soils contaminated by feces of birds and bats. Its pathogenic mechanism involves the inhalation of propagules and initial lung infection, forming local granulomata, and also at distant sites after hematogenous dissemination [6, 7]. Immunocompetent hosts usually have asymptomatic or subclinical infection, recovering without medical intervention. Histoplasmosis as a syndrome is classically seen in immunocompromised patients and is likely to present as an acute or chronic pulmonary condition, in the form of pneumonia, pulmonary nodules or cavitary lung disease. Some patients, however, might develop extrapulmonary or disseminated disease, with a diversity of clinical forms involving mostly the liver, spleen, bone marrow, skin, adrenal glands, central nervous system, and the digestive tract [7].

Gastrointestinal clinically manifest disease is unusual and occurs in 3 to 12% of cases, usually in the disseminated form, even though necropsy series report it in up to 70%, which evidences subclinical involvement most at the times [8]. Chronic diarrhea associated to systemic symptoms, such as fever and weight loss, is the most common clinical manifestations, but severe complications might also occur, like obstruction, perforation and bleeding. Endoscopic findings vary from non-specific inflammatory signs to extensive ulcerated and stenosing lesions. The association of histoplasmosis and renal transplant is well reported and the peak incidence occurs in the first two years. Mortality rates reach up to 10% of cases [9]. Colonic involvement is rare and even more unusual presenting as a severe digestive bleeding [10].

Diagnosis can be established by means of specific serological tests, the finding of the fungus at histopathological examination or, in disseminated disease, on bone marrow examination or tissue culture, which could take, however, up to 4 to 6 weeks for the

final result [3]. On histological examination, the typical finding is a sarcoid-like epithelioid granuloma; yeasts can be observed inside phagocytic cells with special stains like Grocott (methenamine silver) and PAS (periodic acid Schiff) [11, 12]. Serologic tests for the histoplasmin antigen might yield false-negative results in disseminated disease in immunocompromised patients. The radioimmunoassay antigen detection is another widely used method, with a reported sensitivity of up to 85% in blood and 95% in urine [10].

TB (tuberculosis) has a pathogenic mechanism similar to histoplasmosis, affecting preferably immunocompromised patients. It is considered a major opportunistic infection in transplant patients, presenting in a diversity of forms. Most cases are originated from the reactivation of a latent infection by the agent *Mycobacterium tuberculosis*, but up to 5% of patients acquire it from an infected donor. Among solid-organ transplant patients, disseminated or extrapulmonary disease occurs in approximately one third to half of all cases [13]. Intestinal tuberculosis, a very rare form (less than 2% of cases), can be asymptomatic or presented as severe ulcerative colitis, complicating with intestinal obstruction or bleeding. In a Brazilian series with more than 7,000 renal transplant patients, eight developed intestinal tuberculosis, and three of them presented lower gastrointestinal bleeding, which demonstrates that this is an exceptional form of the disease [14].

Histoplasmosis treatment is done with antifungal agents like amphotericin B, preferably lipidic formulations because of their lower potential for causing renal damage, or azoles, itraconazole being more effective than fluconazole. In disseminated or severe forms of the disease, an initial course of amphotericin, lasting from 14 days to two months, is preferred, depending on the severity of the condition and tolerability of the patient. An oral course of itraconazole is carried out in the sequence, lasting at least 12 months; its total duration is to be individualized, though Refs. [9, 11]. Colonic tuberculosis is treated the same way as its pulmonary form, with 6 to 9 months (which can be extended) duration course of the quadruple drug regimen: rifampin and isoniazid throughout the entire treatment, and pyrazinamide and ethambutol in the first two months. It's advised that treatment in renal transplant patients be done likewise. Alternative regimens can be undertaken according to adverse effects of the drugs [13].

It is important to keep in mind that rifampin, in spite of being the preferred drug to treat tuberculosis, is a strong cytochrome P450 inducer, decreasing serum levels of itraconazole and interfering with its efficacy, as well as with some immunosuppressants like calcineurin inhibitors and sirolimus [15, 16]. An alternative regimen including quinolones, like levofloxacin, can be done with adequate efficacy, and there are some reports with favorable outcomes in renal transplants [17]. In our case, the patient had a satisfactory evolution with the four-drug anti-TB medication (rifampin, isoniazid, pyrazinamide and ethambutol), associated with amphotericin B followed by itraconazole, not developing any relevant side effects that caused further harm.

4. Conclusions

Colonic bleeding in immunosuppressed patients may be caused by much more diverse pathological conditions than in the rest of the population, and could be the first clue to search for an underlying opportunistic infection. Even though emergency therapy for the source of bleeding might not differ from the remaining situations, the delay to correctly diagnose and treating the causative agent can result in serious consequences and negative impacts on the prognosis of the patient. In the light of this, a high clinical suspicion and a systematic search for opportunistic infections in immunocompromised patients who present with an undetermined LGB are advised, even in cases of unusual presentations.

References

[1] Strate, L. L., and Gralnek, I. M. 2016. "ACG Clinical Guideline: Management of Patients with Acute Lower Gastrointestinal Bleeding." In: Am. J. Gastroenterol Advance Online Publication, March 2016.

[2] Gralnek, I. M., and Strate, L. L. 2017. "Acute Lower Gastrointestinal Bleeding." *N Engl. J. Med.* 376: 1054-63.

[3] Ayoub, F., et al. 2017. "Hematochezia: An Uncommon Presentation of Colonic Tuberculosis." *Case Rep. Gastrointest Med.* 2017: 7831907.

[4] Sharma, R, Lipi, L., et al. 2017. "Gastrointestinal Histoplasmosis: A Case Series." *International Journal of Surgical Pathology* 25 (7): 592-8.

[5] Rivera, Alejandro Piscoya, et al. 2005. "GI Tuberculosis and Histoplasmosis in an HIV (+) Patient Presenting with Lower GI Bleeding." *The American Journal of Gastroenterology* 100 (8): 1896.

[6] Bates, R., et al. 2015. "44-Year-Old Man with Abdominal Pain, Fever and Bloody Diarrhea." *Mayo Clin. Proc.* 90 (6): e59-6.

[7] Azar, M. M., and Hage, C. A. 2017. "Clinical Perspectives in the Diagnosis and Management of Histoplasmosis." *Clin. Chest Med.* 38 (3): 403-15.

[8] Psarros, G., and Kauffman, C. A. 2007. "Colonic Histoplasmosis: A Difficult Diagnostic Problem." *Gastroenterol Hepatol (N Y)* 3: 461-3.

[9] Gajurel Kiran, Dhakal Reshika, and Deresinski Stan. 2017. "Histoplasmosis in Transplant Recipients." *Clinical Transplantation*.

[10] Syed, T. A., Salem, G., and Kastens, D. J. 2017. "Lower Gastrointestinal Bleeding Secondary to Intestinal Histoplasmosis in a Renal Transplant Patient." *ACG Case Rep. J.* 4: e93.

[11] Ferreira, M. S., and Borges, A. S. 2009. "Histoplasmosis." *Revista da Sociedade Brasileira de Medicina Tropical* 42 (2): 192-8.

[12] Falci, D. R., Stadnik, C, M. B., and Pasqualotto, A. C. 2017. "A Review of Diagnostic Methods for Invasive Fungal Diseases: Challenges and Perspectives." *Infectious Diseases and Therapy*,1-11.

[13] Munoz, P., Rodriguez, C., and Bouza, E. 2005. "Mycobacterium Tuberculosis Infection in Recipients of Solid Organ Transplants." *Clin. Infect. Dis.* 40: 581.

[14] Rocha, A., et al. 2013. "Abdominal Tuberculosis Following Kidney Transplantation: Clinicopathologic Features and Follow-up in a Unique Case Series." *Clin. Transplant* 27: E591-6.

[15] Jaruratanasirikul, S., and Sriwiriyajan, S. 1998. "Effect of Rifampicin on the Pharmacokinetics of Itraconazole in Normal Volunteers and AIDS Patients." *Eur. J. Clin. Pharmacol* 54: 155-8.

[16] Agudelo, C. A., et al. 2012. "Tuberculosis and Histoplasmosis Co-infection in AIDS Patients." *The American Journal of Tropical Medicine and Hygiene* 87 (6): 1094-8.

[17] Munoz-Oca, J. E., et al. 2017. "Concomitant Disseminated Histoplasmosis and Disseminated Tuberculosis after Tumor Necrosis Factor Inhibitor Treatment: A Case Report." *BMC Infectious Diseases* 17 (1): 70.