Colite inespecífica - de que devemos suspeitar?

Unspecific colitis - What should we suspect?

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RESUMO

A amebíase intestinal pode ser assintomática ou apresentar-se com múltiplos sintomas inespecíficos. Os achados endoscópicos de amebíase intestinal podem mimetizar os de outras entidades, como a doença inflamatória intestinal. Descrevemos um caso de colite por *Entamoeba histolytica* num doente sem fatores de risco à exceção de uma viagem de duas semanas ao Brasil treze anos antes da deteção de úlceras no cego. O diagnóstico de amebíase intestinal só foi efetuado após sete anos de seguimento.

Palavras-chave: colite; *Entamoeba histolytica*; úlcera

ABSTRACT

Intestinal amebiasis may manifest as an asymptomatic or symptomatic disease. Endoscopic findings of intestinal amebiasis may mimic other entities, like inflammatory bowel disease. Hereby we present a case of a misdiagnosed Entamoeba histolytica colitis in a patient without risk factors apart from a two-weeks uneventful trip to Brazil thirteen years before the detection of cecal ulcers. The diagnosis of intestinal amebiasis was only made after seven years of follow-up.

Keywords: *colitis; Entamoeba histolytica; ulcer*

CLINICAL CASE

The authors present a case of a 58 years-old Caucasian male with a background history of type 2 diabetes mellitus, hypertension and dyslipidemia who was referred to our department after findings of clean-based ulcers in the cecum with normal intervening mucosa during a colonoscopy performed in March 2014, within the context of the population-based colorectal cancer screening. Histology revealed an inflammatory infiltrate containing lymphocytes, eosinophils, and plasma cells, with mucous secretory activity. Colonic biopsies were negative for cytomegalovirus and tuberculosis. At that time, the patient was asymptomatic. Six months later, the patient started to present mild abdominal pain, in the inferior quadrants of the abdomen, without alarm symptoms. This pain lasted less than 30 minutes, occurred up to three times a week, and was commonly associated with bowel movements. Considering prior findings and the new onset of symptoms, ileocolonoscopy was repeated in July 2015, which was unremarkable, and no biopsies were taken. Stool studies, including bacteria and parasites' culture, microscopic examination for ova, cysts and parasites, antigen tests for *Salmonella*, *Yersinia*, *Shigella*, *Cryptosporidium* and *Campylobacter*, and search for *Clostridium difficile* were negative. Small-bowel capsule endoscopy was performed to search for lesions that could aid diagnosis, including erosions that could suggest inflammatory bowel disease; however, this exam was also unremarkable. Therefore, the patient was discharged from our Gastroenterology consultation,

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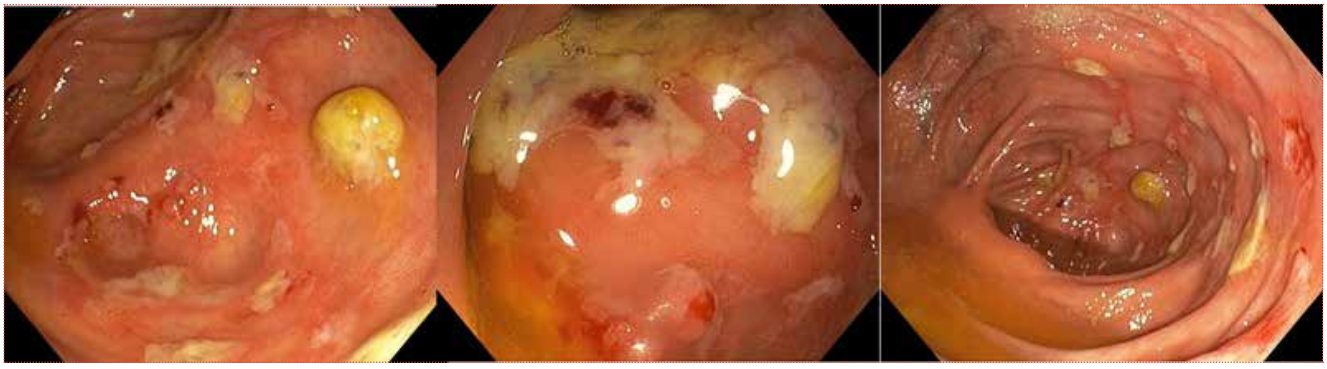

FIGURE 1 Colonoscopy findings with skip lesions of superficial ulcers around 5-20 mm covered with exudate were present at the cecum and proximal ascending colon.

with the diagnosis of unspecific transient colitis; no treatment was started. Lately, in October 2019, in routine assessments, a discrete normocytic normochromic iron-deficiency anaemia was detected (haemoglobin 12.8 g/dL [reference range 13.0-18.0], with red blood cell mean corpuscular volume 86.3 fL [reference 80.0-10.0], besides ferritin 20.0 ng/mL [reference 39.0-439.0], and transferrin saturation 12% [reference 20.0-50.0]). Also, the patient had mild leucocytosis 11.6x10^3/uL (reference 3.8-10.6) and monocytosis (7% of white blood cells [reference 0.1-0.8]); neutrophils, basophils and eosinophils were within the normal range as well as C-reactive protein (0.31 mg/dL [reference 0.0-0.5]). At this time, along with his usual abdominal pain pattern, he also reported alternating bowel habits (periods of diarrhoea [up to four times a day] alternating with constipation) without fever, anorexia, weight loss or visible blood loss. Endoscopic studies were repeated and ileocolonoscopy again revealed several clean-based ulcers in the cecum. Biopsies suggested acute unspecific colitis. In this context, the patient was again referred to our Unit. Regarding travelling outside Europe, the patient had a two-weeks trip to Brazil in 2001, although he reported to have followed the recommended sanitary precautions and the stay was uneventful). He denied gastroenteritis contacts, taking non-steroid anti-inflammatory drugs, contact with unvaccinated or wild animals, consumption of non-pasteurized milk products or raw water. Faecal calprotectin was elevated (522 µg/g) and stool studies were again negative. Computed tomography angiography was also unremarkable. Colonoscopy was repeated at our facility, and skip lesions of superficial ulcers around 5-20 mm covered with exudate were detected in the cecum and proximal ascending colon (Figure 1). Histopathologic evaluation with haematoxylin and eosin staining exhibited polymorphonuclear inflammation and the presence of microorganisms, with morphological features strongly suggestive of *Entamoeba histolytica*, features that were better appreciated with periodic acid-Shiff (PAS) staining. The immunostaining for CD68 was negative, allowing distinction, in this inflammatory setting, between macrophages (CD68 positive), and pathogenic microorganisms (Figure 2).

The patient was subsequently treated with systemic and endoluminal antiprotozoal therapy - metronidazole 500 mg three times a day for 10 days, plus paromomycin 600 mg three times a day for 7 days (25mg/Kg per day). One month later the patient was asymptomatic - no abdominal pain in the previous two weeks, with five to six bowel movements per week, types 3-4 (Bristol stool scale). The colonoscopy performed after three months revealed no lesions (Figure 3). The patient remained asymptomatic during the following 18 months of follow-up.

Infection with *Entamoeba histolytica* is distributed worldwide, especially in the tropical areas with poor sanitary conditions.[1] The presentation of intestinal amebiasis is widely variable. Even though around 90% of the patients are asymptomatic *E. histolytica* carriers (luminal amebiasis)[1],

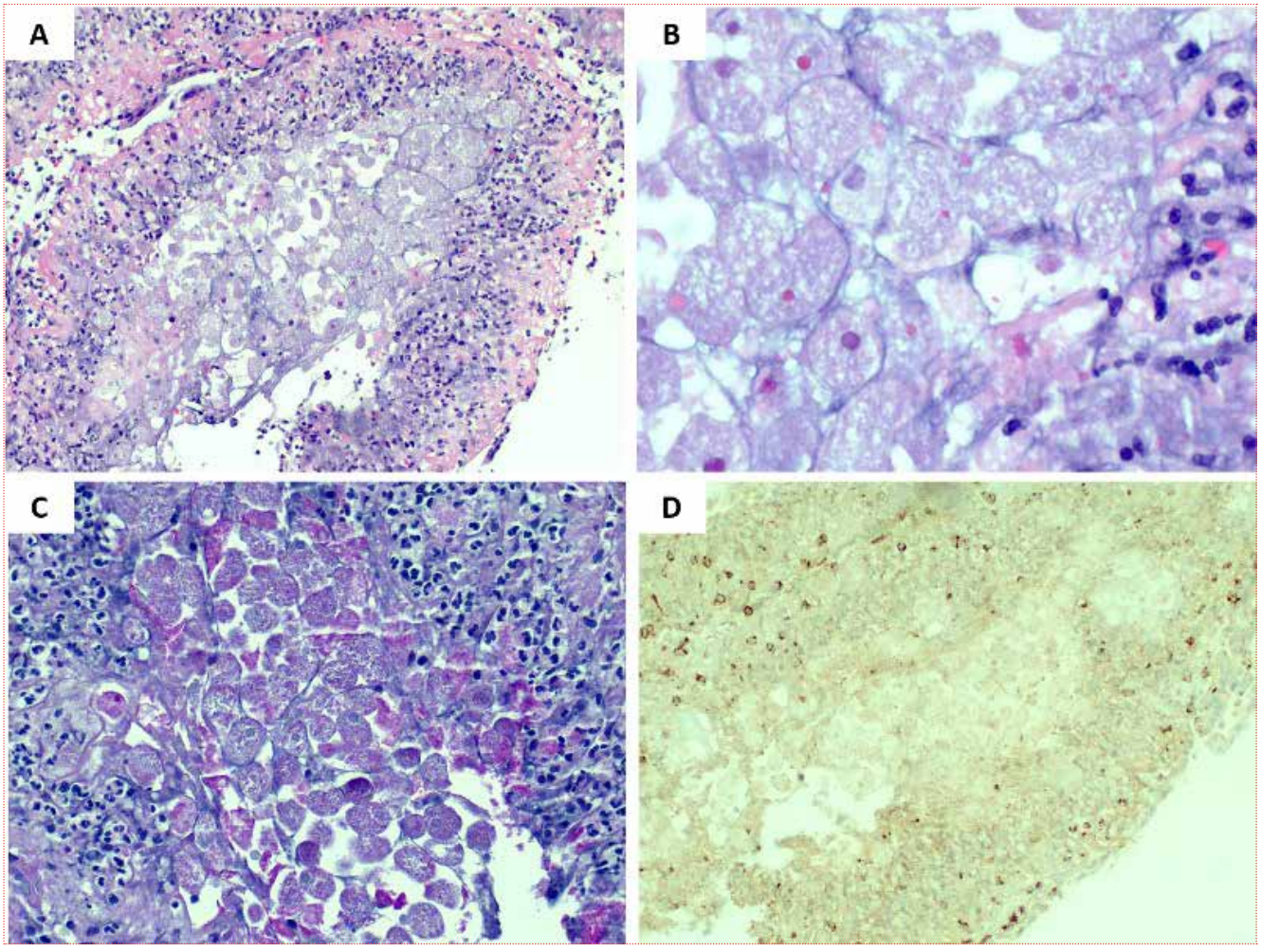

FIGURE 2 Pathological findings of colon biopsy. On haematoxylin and eosin staining, (H&E, 100X), several microorganisms were found, in association with granulation tissue and leukocytic exudate of the colonic mucosa (A). On higher power (H&E, 400X), the microorganisms were morphologically compatible with *Entamoeba histolytica*, displaying a small, round, and central nucleus with a microvesiculous cytoplasm (B). The histochemical study was positive for periodic acid–Schiff stain (200X) (C) and immunostaining was negative for CD68 (100X) (D).

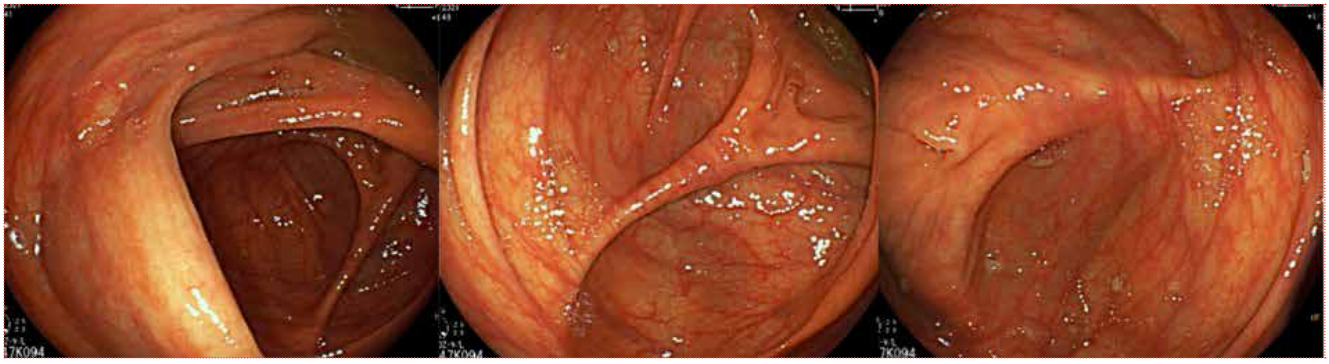

FIGURE 3 Colonoscopy findings three months after treatment with metronidazole and paromomycin.

some develop elusive long-standing symptoms, including abdominal pain, diarrhoea, and weight loss. This symptomatic prolonged infection classically presents as chronic colitis, with cumulative bowel damage, yet some present symptoms of acute colitis even years after acquiring the pathogen. In some patients, extraintestinal

dissemination may occur (invasive amebiasis)[2]. Endoscopic findings of amoebic colitis include multiple discrete small ulcers usually involving the cecum, ascending colon, and rectum.[3,4] The diagnosis of intestinal amebiasis may be done by stool microscopy, polymerase chain reaction (PCR), antigen detection (serum or stool), serology, and histologic examination of colonic biopsy specimens. The microscopic detection of *E. histolytica* cysts and/or trophozoites is frequently the first-line investigation; however, it has low sensitivity and specificity (as *E. histolytica* and non-pathogenic *E. dispar* may be morphologically very similar), both ranging from 20 to 65%.[5] The sensitivity of antigen detection in serum and stool samples has been reported to be 65% and 90%, respectively. Serum antibodies are detected in 70–90% of individuals, however it is not possible to differentiate acute from past infections. Molecular assays have sensitivity and specificity above 99% and are currently the gold standard for diagnosis; these tests have also the advantage of allowing the simultaneous detection of multiple pathogens.[6] Finally, the visualization of amoeba in colonic biopsy specimens is rare and is not considered a routine diagnostic tool.[6]

Our patient had a seven-year history of colitis which could be misdiagnosed with other entities that share some clinical features and whose endoscopic findings may be similar. First, other infectious colitis, including *Salmonella*, *Shigella*, *Escherichia coli*, *Campylobacter*, *cytomegalovirus*, histoplasmosis, or intestinal tuberculosis. Second, post-infectious irritable bowel syndrome. Third, inflammatory bowel disease, even more considering its increasing incidence. Fourth, drug-induced colitis, yet the medication history of our patient appeared innocent. Fifth, lymphoma or adenocarcinoma, even though the clinical setting and disease course was not typical. Pathological findings were of vital importance to solve the case. Despite previous unspecific histological examinations, the use of the right staining during the microscopic evaluation was important to display trophozoites of *Entamoeba histolytica* and allowed adequate treatment.

This clinical case reminds the importance of infectious agents in chronic diarrhoea aetiology and highlights the diagnostic challenge, especially when recent epidemiological risk factors and clinical characteristics are unhelpful and stool studies are negative. Also, it reinforces the relevance of past exposures and trips, as the incubation period of some infections may range from few days to some years.

Conflicts of interest: None to declare.

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