CASE REPORT

Recurrent and fatal diarrhea caused by *Cystoisospora belli* in a man with HIV infection

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Abstract

Cystoisospora belli causes intestinal infection in immunocompromised hosts, including human immunodeficiency viruses (HIV)-positive patients, especially from tropical and sub-tropical areas, with watery and recurrent diarrhea, leading in advanced cases to malabsorption and death. Microbiological diagnosis is limited by intermittent or low shedding of oocysts in stool; therefore, endoscopy may be necessary to identify the pathogen in histological samples. Trimethoprim-sulfamethoxazole (TMP-SMX) represents the treatment of choice, and alternative agents are used in recurrences, but limited efficacy is described. Here, we present recently observed case of severe and fatal infection due to *C. belli* in a HIV-positive 40-year-old man from Brazil, revealing several limitations in diagnosis and therapy, which need to be investigated further. In particular, it is still not clear how the infection persisted over time leading to malabsorption, kidney injury, and subsequent death, even if a reasonable immune reconstitution was demonstrated. Additionally, we investigated what mechanisms might cause, whether failure of recovery of the immune response specifically to *C. belli*, drug malabsorption, resistance to TMP-SMX, sequestration into lymphoid tissue, or co-presence of visceral untreated Kaposi sarcoma. Also, the appropriate dosage and way of administration of the best therapeutic regimen were examined, since there is a lack of literature on these issues. Globalization and wider use of immunosuppressive therapies underline the importance of maintaining adequate awareness, also in HIV-negative and non-immigrant populations.

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Introduction

Cystoisospora belli, formerly known as *Isospora belli*, is a coccidia causing infection in immunocompromised hosts from tropical and sub-tropical areas. In subjects with human immunodeficiency viruses (HIV), a prevalence rate of 1-1.7% in non-endemic areas and 9.9-28% in endemic areas has been reported for this infection [1]. The transmission of infection occurs via oral-fecal route; oocysts are found in contaminated food, soil, water, and surfaces. Once ingested, multiplication occurs in the lamina propria of the enterocytes, lymph nodes, spleen, and liver. The disease manifests initially with intermittent watery diarrhea, abdominal discomfort, fever, nausea, anorexia, and weight loss, while in advanced stages, it leads to malabsorption and ultimate death. Relapses have been described in patients with HIV

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infection despite maintenance therapy with trimethoprim-sulfamethoxazole (TMP-SMX) and highly active antiretroviral therapy (HAART) [2]. *C. belli* infections have been reported in immunosuppressed patients with cancer, hypogammaglobulinemia, after organ transplant, and other disorders, in association with viral infections other than HIV [1].

The diagnosis is based on the direct detection of oocysts in fecal sample, but at times it is limited due to the intermittent or low level shedding. Repeated stool examinations with sensitive methods is therefore recommended. *C. belli* can also be detected in duodenal aspirates or biopsy tissues; more recently, PCR methods have been applied in research settings [1, 3]. The treatment of choice is TMP-SMX [3], and pyrimethamine may be used as alternative regimen in patients that do not respond or are intolerant [1, 3].

Case description

We reported a case of recurrent diarrhea and fatal outcome due to *C. belli* infection, recently observed in our institution. A Brazilian 40-year-old bisexual man was first seen in emergency room on March 8, 2019 due to intermittent diarrhea, weight loss, and diagnosed HIV. He was immediately referred to our infectious diseases outpatient service for follow-up. A workup screening revealed secondary syphilis, CMV-DNA of 866 copies/ml, HHV8-DNA of 1,667 copies/ml, CD4+ count of 70 cells/mmc, and HIV-RNA of 297.700 copies/ml. HIV-RNA sequencing did not reveal mutations of nucleoside reverse transcribed inhibitors, non-nucleoside reverse transcribed inhibitors, nor protease inhibitors. Fundus oculi examination was negative for CMV retinitis. On physical, the patient presented oral Kaposi sarcoma. He was started on HAART with emtricitabine/tenofovir alafenamide/dolutegravir, valganciclovir for CMV, primary prophylaxis with TMP-SMX, and diaminocillin for syphilis. On May 29, 2019, the patient was admitted to our Infectious Diseases Department due to watery diarrhea, acute renal failure, and severe metabolic acidosis. Microbiological examinations of stools were repeatedly negative for viruses, bacteria, and parasites. In addition, the presence of opportunistic infections, such as microsporidia, *Cryptosporidium parvum*, and acid fast bacilli were excluded. Abdominal CT scan revealed dolichocolon, whereas esophagogastroduodenoscopy and colonoscopy were normal. Abdominal MRI showed non-specific small thickening of the ileal loop. The patient was treated with intravenous hydration and bicarbonate infusion to correct metabolic acidosis and renal impairment. Empiric anti-infective therapy with azithromycin and albendazole was started, and HAART was stopped due to renal failure. After specialistic consultations, the patient underwent targeted diagnostic examinations to exclude lymphoma, coeliac disease, gastrinoma, VIPoma, and medullary thyroid cancer. During hospitalization, cyclical recurrent severe diarrhea continued, leading to prostration just in few hours, with acute renal failure and metabolic acidosis, which needed continuous liquid infusion and nephrologist consultations to manage metabolic derangement. Due to renal impairment, HAART regimen was changed to abacavir/emtricitabine/dolutegravir. After gastroenterological consultation to exclude inflammatory bowel disease, the patient underwent video capsule endoscopy, enteroscopy of the small intestine, and ileocolonoscopy. Histology revealed the presence of *C. belli* in the jejunum, ileum, and coecum as well as lesions due to Kaposi sarcoma (Figure 1). In addition to supportive therapy for metabolic acidosis, intravenous TMP-SMX was initiated and continued for 5 weeks, and then switched orally to a dose of 160/800 TID. Chemotherapy for Kaposi sarcoma was contraindicated due to persistent coccidian infection and worsened performance status. After few days, the patient presented

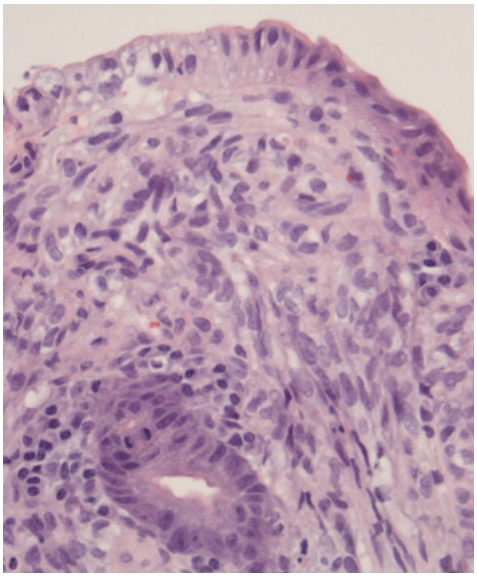

Figure 1. Histological section of jejunal biopsy (HE, 40×), co-presence of Kaposi sarcoma and *Cystoisospora belli* (courtesy of A. Pellegrinelli, Luigi Sacco University Hospital, Milan)

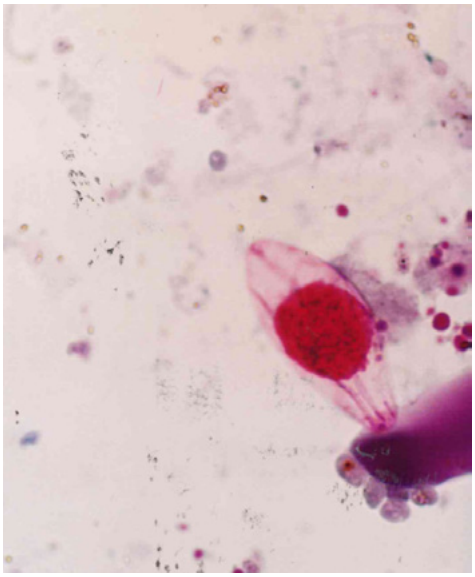

Figure 2. *Cystoisospora belli* oocysts, Kinyoun staining, 1,000× (courtesy of R. Grande, Luigi Sacco Universisty Hospital, Milan)

recurrence of symptoms, with stool examination showing *C. belli* (Figure 2). TMP-SMX was changed to intravenous with benefits. The patient was discharged on December 10, 2019 with higher dose of TMP-SMX (160/800 mg QID), in relation to CD4+ cell count below 200 mmc/ml. After one week only, he was admitted again for further recurrence. Stools examinations were repeatedly negative for *C. belli* and other pathogens. Therapeutic drug monitoring (TDM) of sulfamethoxazole plasma level was close to therapeutic range; therefore, underdosage was excluded. In order to augment the treatment, ciprofloxacine was added to TMP-SMX, and HAART was modified due to renal failure and to improve immune response with raltegravir/lamivudine/doravirine. CD4+ cell count increased to > 200 mmc/ml, and viral load was undetectable after six months of HAART. The patient was finally discharged. However, during next months, the patient was admitted either to our Department or Nephrology Department several times with similar symptoms. During these episodes, in addition to supportive care, alternative anti-infective therapies were attempted with pyrimethamine and combination of TMP-SMX, nitazoxanide, and metronidazole, without any modification of symptoms but progressive worsening of clinical condition. Once again, microbiological examinations excluded the presence of other pathogens. The patient underwent colonoscopy twice, with multiple biopsies to verify the presence of *C. belli*. Histological persistence of *C. belli* in different stages and bioptic sites was repeatedly found. Despite all our efforts, clinical condition continuously deteriorated, and the patient died after total of fifteen hospital admissions, two years since the first presentation.

Discussion

This case shows, even nowadays, several limitations in diagnosis and therapy of *C. belli* infection, and highlights the need of further research to understand its pathogenesis that might cause the persistence of the pathogen, leading in most cases to death. Diagnosis can be delayed by intermittent shedding of the parasite in stool. In our case, repeated stool specimens were analyzed by a skilled microbiologist, and were repeatedly negative, confirming limitations in detecting the parasite. Only histology allowed for demonstration of the infection. All these aspects together might have caused a delay in starting specific treatment and contributed to the negative outcome. Therefore, high microbiological and histopathological expertise are crucial.

The persistence of *C. belli* in our patient was probably due to several concomitant factors, which might explain how the infection persists despite immune reconstitution. Various hypotheses have been made [4, 5], such as failure of recovery of immune response specifically to *C. belli*, drug malabsorption, resistance to TMP-SMX, or sequestration of the parasite in lymphoid tissue. In our case, it is not clear whether the concomitant presence of visceral untreated Kaposi sarcoma might have played a potential role (Figure 1). On the other hand, the adherence and immune reconstitution inflammatory syndrome did not seem to be involved, because, respectively, undetectable HIV-RNA and slow increase of CD4+ were obtained with HAART.

Considering specific therapy, the appropriate dosage and way of administration of the best therapeutic regimen are not known, since literature remains scarce [6-8]. A recent review by Dubey *et al*. [1] investigated various therapeutic approaches to treat *C. belli*, and revealed a great heterogeneity of regimens used in different clinical settings. Here, we used high-dose of TMP-SMX as the first-line therapy, as suggested by guidelines [3], adapting the way of administration and dosage to the fragile patient's balance. TDM helped us to exclude malabsorption and consequently underdosage. In relation to the persistence of infection during TMP-SMX administration, we also tried second-line therapies, without clinical improvement or influence on the natural course of the disease.

Conclusions

C. belli must be included in the differential diagnosis of malabsorption and chronic diarrhea in HIV-infected patients, even with a reasonable immune reconstitution, especially in migrants from endemic countries, in order to start specific anti-infective therapy, potentially life-saving. Globalization and the wider use of immunosuppressive therapies underline the importance of maintaining adequate awareness also in HIV-negative populations through optimization of intervention strategies.

Conflict of interest

The authors declare no conflict of interest.

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