ABSTRACT

Antiretroviral therapy (ART) has precipitously decreased the morbidity associated with human immunodeficiency virus but can unmask and exacerbate opportunistic infections and autoimmune diseases. Various diseases have been reported in association with ART initiation, but there is scant literature describing inflammatory colitis in the setting of ART initiation. We present a 39-year-old man with chronic untreated human immunodeficiency virus and central nervous system toxoplasmosis who developed persistent diarrhea after initiation of ART. A comprehensive infectious workup was negative. Computed tomography demonstrated terminal ileum enteritis, which was confirmed by colonoscopy. Biopsy of the terminal ileum revealed fibrinous exudate and granulation tissue.

INTRODUCTION

Since its inception in 1980s, antiretroviral therapy (ART) has precipitously decreased the morbidity associated with human immunodeficiency virus (HIV). Early initiation of ART improves outcomes in newly diagnosed HIV-positive patients. However, early initiation of ART can lead to aberrant and dysregulated inflammatory responses, termed immune reconstitution inflammatory syndrome (IRIS). The recurrence, as well as unmasking of autoimmune conditions, after ART initiation has been described for Grave disease, sarcoidosis, Guillain-Barré syndrome, rheumatoid arthritis, polymyositis, systemic lupus erythematosus, autoimmune hepatitis, and inflammatory bowel disease (IBD). To our knowledge, only 2 cases have been published of ulcerative colitis (UC) being unmasked or paradoxically worsened in HIV patients after ART initiation. Idiopathic terminal ileal ulceration (ITIU) is a common finding in patients undergoing colonoscopy and can be asymptomatic or symptomatic with IBD-like complaints. Although asymptomatic ITIUs are generally benign and spontaneously resolve without treatment, Patients with symptomatic ITIU are occasionally diagnosed with IBD on follow-up colonoscopy and biopsy. Although there have been a few cases reports of IBD unmasked after ART initiation, this is the first case report of a symptomatic ITIU being unmasked in a HIV patient after ART initiation.

CASE REPORT

A 39-year-old man visiting New Jersey from the Dominican Republic with a 4-year history of untreated HIV presented to a primary clinic with a 3-week history of headaches, confusion, slowed mentation, and drooling. Cranial computed tomography (CT) revealed bilateral mass lesions, cranial magnetic resonance imaging revealed ring-enhancing lesions, HIV-1 was positive with a CD4 of 70 cells/μL and a viral load of 175,008 copies/mL, and toxoplasmosis IgG was positive. Thoracic, abdominal, and pelvic CTs revealed hepatic steatosis and splenomegaly with no evidence of enteritis or colitis.

On admission, intravenously sulfamethoxazole/trimethoprim (TMP/SMX) was started. After 2 weeks of therapy, a repeat magnetic resonance imaging brain demonstrated reduced size of the lesions, and the patient was transitioned to oral TMP/SMX. After initiation of oral therapy, the patient became leukopenic and developed mild abdominal pain, which was believed to be adverse effects of oral TMP/SMX; thus, treatment was switched to oral atovaquone, which led to the resolution of the leukopenia. Three weeks after
presentation, the patient was started on ART (bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate), after which he developed abdominal pain, diarrhea, and low-grade fevers. The patient did not receive any nonsteroidal anti-inflammatory drugs (NSAIDs) during hospitalization. A comprehensive infectious workup was negative (including Norovirus, Rotavirus, Adenovirus, Escherichia coli [0157, ETEC, and STEC], Salmonella, Shigella, Vibrio cholera, Yersinia, Cryptosporidium, Giardia, Entamoeba histolytica, acid-fast bacilli, and Clostridium difficile), as well as negative cytomegalovirus IgM and polymerase chain reaction, Epstein-Barr virus IgM, Helicobacter pylori stool antigen, fecal culture, stool O&P, RPR, and quantiFERON TB Gold. C-reactive protein was elevated (62 mg/L); however, there were no elevations in anti-deamidated gliadin or antitransglutaminase IgA. A flow cytometry lymphoma panel from peripheral blood was negative.

Repeat abdominal and pelvic CTs demonstrated small bowel enteritis with fat stranding and mesenteric edema and thickened/inflamed terminal ileum (Figure 1). Colonoscopy revealed ulcerated mucosa in the terminal ileum (Figure 2). A biopsy of which yielded ulcerated mucosa with fibrinous exudate and granulation tissue without granulomas nor viral cytopathic cells (Figure 3). Two weeks after initiation of ART, significant improvement in mental status and diarrhea occurred, and the patient was discharged home on ART, atovaquone, and valacyclovir for new-onset orolabial ulcers suspected to be due to herpes simplex virus. Outpatient infectious disease follow-up a week later revealed continued improvement in mental status and resolution of diarrhea; however, his orolabial ulcerations persisted. The patient did not follow-up.

**DISCUSSION**

As ileal intubations have become more common, the identification of terminal ileum ulceration has significantly increased. Terminal ileum ulcerations can be associated with NSAIDs, infections, IBD, and malignant disease or they can be idiopathic and found incidentally. ITIUs have been identified in patients with acute gastrointestinal symptomology and in patients without any symptomatology. When ITIUs are found incidentally in an asymptomatic patient, they generally resolve without any treatment and are unlikely to rapidly progress or cause any symptoms. The natural history of symptomatic ITIUs has not been well characterized. It has been suggested that the earliest lesion in CD may be a terminal ileal ulcer, which may potentially require months to years to definitively exhibit CD on biopsy. Courville et al reported the presence of symptoms to be the best predictor of progression to CD in patients with isolated terminal ileum ulceration; however, other authors have challenged this assertion and concluded no significant correlation between clinical symptoms, endoscopic features, or laboratory testing and progression of ITUI to CD. Mehta et al reported

![Figure 1. Coronal view of abdominal and pelvic computed tomographies revealed a long segment of thickened, inflamed terminal ileum with fat stranding along with mesenteric edema and mesenteric venous engorgement.](image1)

![Figure 2. (A) Ileoscopy revealing ulcerated and inflamed mucosa in the terminal ileum along with fibrinous exudates and (B) colonoscopy revealing ulcerated and inflamed mucosa at the base of the cecum along with fibrinous exudates.](image2)
that up to 25.7% of patients with symptomatic ITIU are later diagnosed with CD at the 3- to 6-month follow-ups.11

There is limited literature discussing ITIUs in HIV patients. A few case reports have described unmasked IBD in the setting of IRIS after initiation of ART.

1. Acosta et al described a patient with a 5-year history of untreated HIV who developed abdominal pain, hematochezia, and proctalgia on the initiation of ART. Colonoscopy and biopsy of the rectosigmoid was consistent with UC. The patient was started on steroid taper and follow-up colonoscopy at 6 months revealed resolution of UC.5

2. Fantauzzi et al described a patient with a 2-year history of clinically silent UC and untreated HIV, who developed fevers, abdominal pain, and later developed Guillain-Barré syndrome on the initiation of ART. The patient was given intravenous immunoglobulin for 5 days that lead to rapid resolution. Follow-up at 3 months revealed resolution of all symptoms.6

The case presented here is the first to describe a symptomatic idiopathic terminal ileum ulcer in a patient with untreated HIV after ART initiation. In any patient with terminal ileum ulceration, symptomatic or not, common culprits should be ruled out including NSAIDs, intestinal tuberculosis, eosinophilic enteritis, infections, and malignancy. Acute and chronic untreated HIV may cause enteropathy and gastrointestinal (GI) ulcerations. In our patient, however, HIV was diagnosed 4 years before, no GI symptoms were present on admission, and ART initiation did not lead to improvement of GI symptoms as would be expected in HIV enteropathy. HIV has been documented to cause idiopathic ulcerations in the upper GI tract and to a lesser extent in the lower GI tract.14–16

Idiopathic colonic ulcers secondary to HIV enteropathy resemble cytomegalovirus-induced ulcers endoscopically but are usually solitary and deep.17 Furthermore, HIV-induced ulcerations present with viral cytopathic effects on histopathology, none of which was noted in our patient.18 It is possible that ART initiation caused the GI symptomology in our patient and the terminal ileum ulceration was found incidentally. Close follow-up is advised for up to 6–8 months with repeat laboratory tests, imaging, and colonoscopy warranted based on clinical progression. Further studies are needed to assess whether the pathogenesis of ITIU has an autoimmune component and to elucidate the factors driving the development of autoimmune inflammatory diseases such as UC and CD in only a subset of patients with symptomatic ITIU.

DISCLOSURES

Author contributions: UM Nasir and J. Paer wrote the manuscript and revised the manuscript for intellectual content. Y. Jiang reviewed the literature. NM Mirani provided the histological images. S. Ahlawat provided the endoscopic images, wrote the manuscript, and revised the manuscript for intellectual content. KM Pergament wrote, edited, and revised the manuscript for intellectual content. UM Nasir is the guarantor of the article.

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