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CASE REPORT

Successful treatment of severe perianal Crohn's disease with infliximab in an HIV-positive patient

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Abstract
We present the case of a woman infected with the HIV type 1, controlled with highly active antiretroviral therapy. In the meantime, she developed a severe perianal disease, with complex fistulae and chronic anal fissures. After developing a severe chronic diarrhea, a total ileocolonoscopy with biopsies was performed, showing multiple ileal and segmental colonic erosions. Histology favoured a Crohn's disease diagnosis. Despite the limited experience of anti-tumour necrosis factor agents in the HIV-infected population, infliximab was started in this patient, due to her severe and symptomatic Crohn's disease, with a controlled HIV infection. No side effects were reported and her bowel movements and perianal disease improved right after induction regimen with infliximab. 1 year after starting this therapy she is in clinical and endoscopic remission. The CD4+ T-cell count remained stable, the HIV-RNA undetectable and no opportunistic infections were reported during follow-up period. Data concerning the use of anti-tumour necrosis factor drugs is limited in patients with both inflammatory bowel disease and HIV infection. Only three cases of Crohn's disease and concomitant HIV infection treated with infliximab were reported in the literature. This case report might help future decisions in patients with a similar clinical situation.

Keywords Human immunodeficiency virus · Inflammatory bowel disease · Tumour necrosis factor inhibitors

Introduction

Mortality as a result of human immunodeficiency virus (HIV) infection has declined with current highly active antiretroviral therapy (HAART). However, an effect of this therapy is its promotion of immune reconstitution, which leaves patients more vulnerable to develop immune related illnesses, such as Crohn's disease (CD) [1]. Therefore, more cases of HIV-infected patients with inflammatory bowel disease (IBD) candidates for biological treatment will emerge, leading to concerns regarding its safety in this particular subset of patients.

Case report

We present the case of a 47-years-old woman with the diagnosis of HIV type 1 (HIV-1) infection since 2003, without either episodes of opportunistic infections or a CD4+ T-cell count below 200 cells/μL. She had been on HAART therapy since 2008, with undetectable HIV-RNA and CD4+ T-cell count above 500 cells/μL.

Since 2013, she had multiple perianal surgical interventions, due to chronic anal fissures and complex intersphincteric perianal fistulae. Histology from anal canal biopsies revealed an intense chronic inflammation and mucosal ulceration, without dysplasia. Cytomegalovirus (CMV) immunohistochemistry, microbiological culture and staining for acid–alcohol resistant bacilli were negative. Between 2014 and 2016 she was submitted to multiple seton drainages, antibiotics and a fistulotomy.

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She developed diarrhea in 2015, first interpreted as a side effect of the protease inhibitors combination lopinavir/ritonavir (LPV/r). However, after replacing LPV/r with lamivudine/abacavir/efavirenz, her diarrhea got worse in 2016, with more than 6 bowel movements per day, with pus discharge, without blood. She also had an iron deficiency anemia, abdominal pain and fatigue. A total ileocolonoscopy (Fig. 1a, b) with biopsies was performed, showing multiple ileal and segmental colonic erosions, with histology favouring CD diagnosis, for which she was referred to Gastroenterology Outpatient Clinic.

Magnetic resonance enterography revealed wall thickening of the terminal ileum, sigmoid and rectum, without significant strictures or dilations. Pelvic magnetic resonance imaging revealed complex intersphincteric perianal fistulae (Fig. 2a, b), without perianal abscesses. Faecal calprotectin level was 554 mg/kg. Cultural stool tests, serologic tests for syphilis, chlamydia and herpes and cytology of the anal canal were negative.

Our patient had a moderate to severe disease, with a Montreal classification A2L3B1p, a Harvey-Bradshaw score of 13 (moderate disease) and a Crohn's Disease Activity Index (CDAI) of 333, for which glucocorticoids could have been used for the induction of remission. However, she had a severe perianal disease, with suppurative fistulae, despite treatment with ciprofloxacin and metronidazole. Because of this complex perianal disease, an anti-TNF drug was considered as the first-line therapy.

Before starting biological treatment, she had the following screening panel: negative Interferon-Gamma Release Assay (IGRA), negative anti-HCV, negative HBsAg and HBeAg, positive anti-HBc, negative anti-HBs and undetectable HBV-DNA. She also had positive IgG with negative IgM antibodies for CMV, herpes simplex virus, varicella zoster virus and Epstein–Barr virus.

Although our patient was chronically infected with HIV-1, the infection was under control for almost 10 years. Consequently, we decided to start infliximab (IFX) in 2017 at the standard dosages and frequency, while on HAART therapy with lamivudine/abacavir/efavirenz. There were no published data concerning the use of thiopurines in the HIV-infected population. Therefore, we decided that adding a thiopurine to IFX would further increase the risk of opportunistic infections. Immunization against Influenza virus and Pneumococci was prescribed during follow-up, according to standard protocol. No side effects were reported and her bowel movements and perianal disease improved right after induction regimen with infliximab. Six months after the first IFX infusion, she had 2 bowel movements per day; faecal calprotectin level at that time was 118 mg/kg.

A pelvic MRI performed 1 year after starting IFX revealed residual inflammatory signs, without abscesses or significant fistulous tracts (Fig. 3a, b). A total colonoscopy was performed 1 year after starting biological therapy (Fig. 4a, b), revealing endoscopic remission of the colon and proximal rectum, with mild distal proctitis, with histology revealing mucosal inflammation and ulceration, granulation tissue and lymphoid aggregates extending into the muscularis mucosae. CMV immunohistochemistry was negative.

After starting IFX, her HIV-RNA and CD4 cells count was measured every 3 months. After 1 year of IFX therapy, it was decided to increase interval to every 6 months, due to her persistently undetectable HIV-RNA.

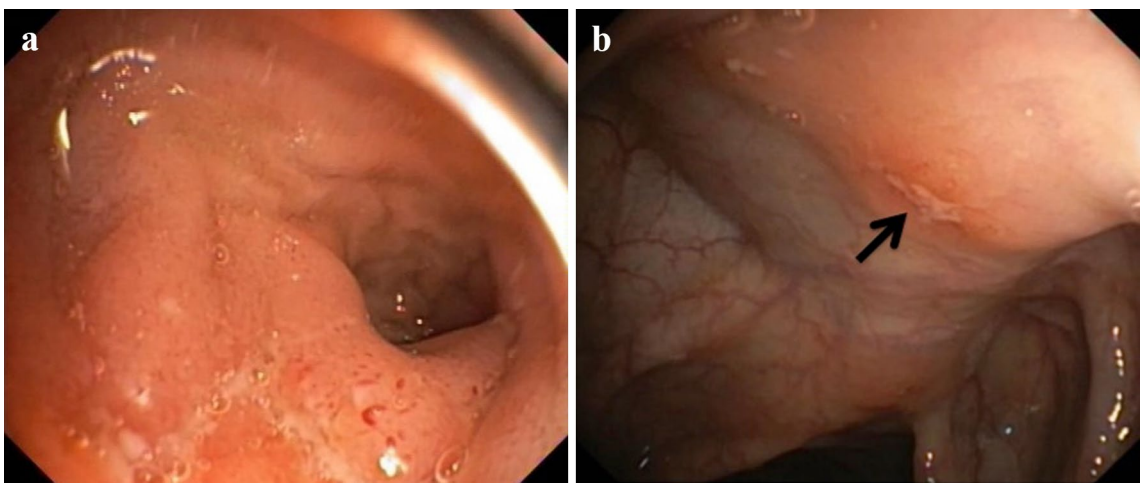

Fig. 1 **a** Terminal Ileitis from a colonoscopy preformed before starting IFX. **b** Ulcerative erosion (arrow) from a colonoscopy before starting IFX

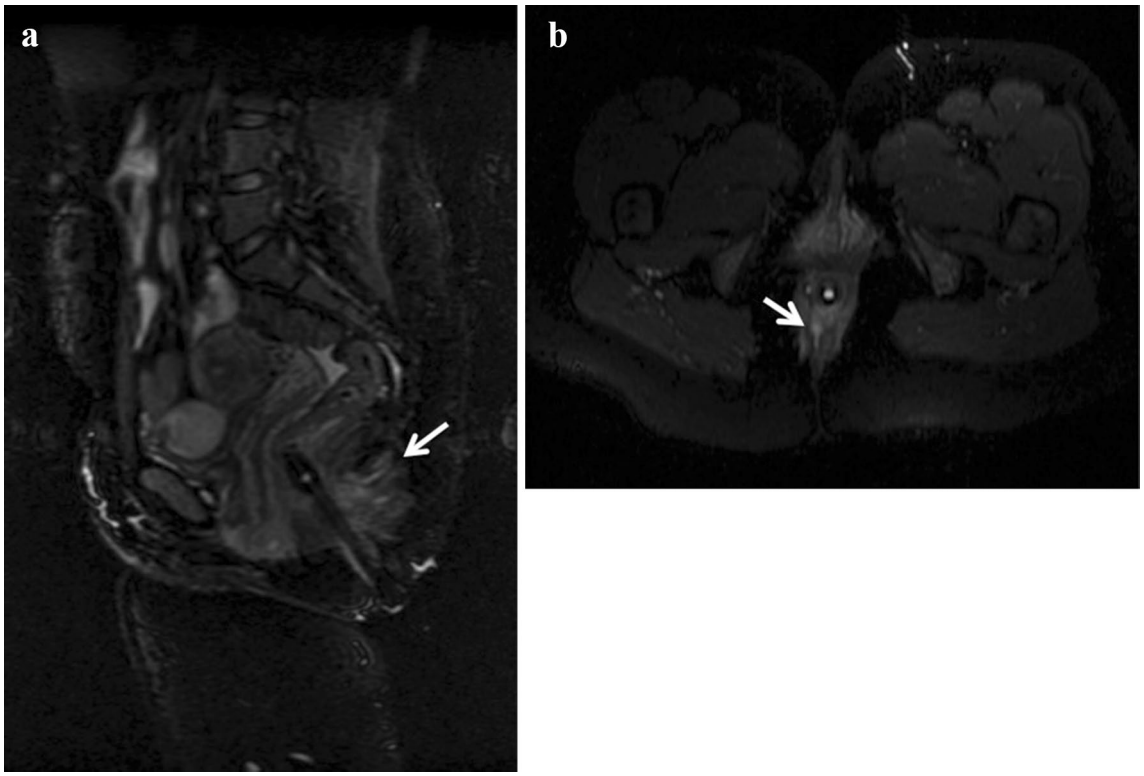

Fig. 2 **a** Sagittal section from a pelvic MRI previous to IFX, revealing complex intersphincteric perianal fistulae (arrow), with multiple fistulous tracts and inflammatory signs. **b** Axial section from a pelvic MRI previous to IFX, revealing an internal opening at 6 o'clock (arrow)

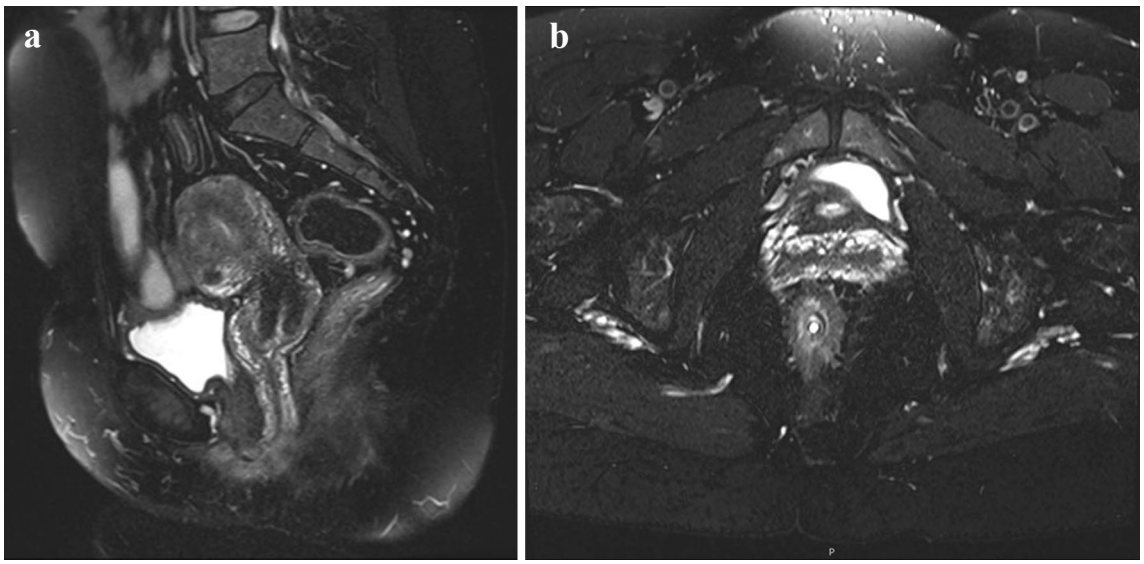

Fig. 3 **a** Sagittal section from a pelvic MRI 1 year after starting IFX, revealing residual inflammatory signs, with no fistulous tracts. **b** Axial section from a pelvic MRI 1 year after starting IFX, revealing residual inflammatory signs, with no significant fistulous tracts

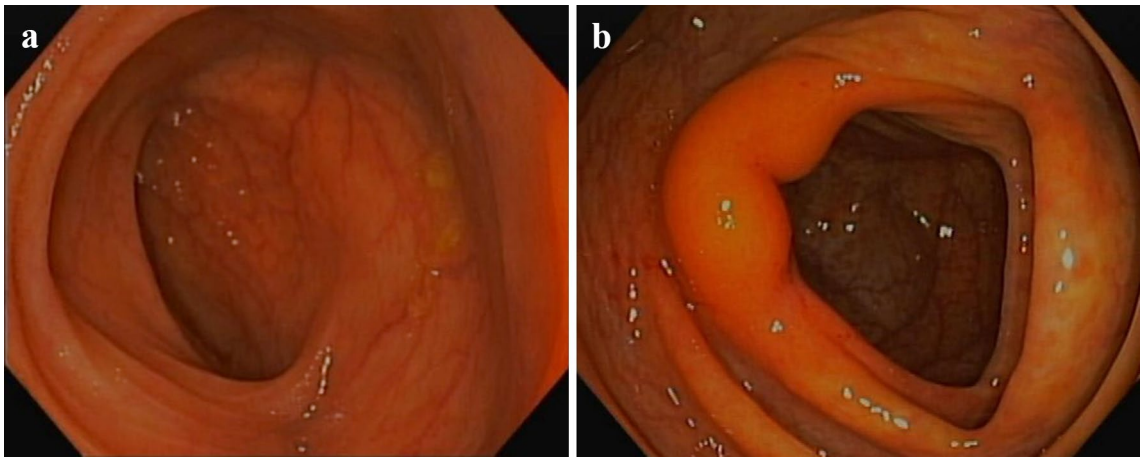

Fig. 4 **a** Terminal ileum, on a colonoscopy 1 year after starting IFX. **b** Ileocecal valve, on a colonoscopy 1 year after starting IFX

Discussion

Increased concentrations of tumour necrosis factor (TNF) can be shown in the mucosa of patients with active CD [2]. Raised plasma and tissue levels of TNF-alpha have also been observed in patients infected with HIV, with higher levels correlating with an increased severity of the disease. In vitro studies demonstrated that TNF-alpha promotes HIV expression via the nuclear factor kappa beta (NKkB) signaling pathway. HIV proteins Tat, Gp120, and Nef promote TNF-alpha expression via a common pathway that increases viral replication and causes apoptosis of uninfected bystander cells, leading to viral immune escape through lack of immunologic detection [3]. Although HIV-1 suppression has been demonstrated with anti-TNF-alpha agents, there is a minimal impact of anti-TNF-alpha therapy upon HIV load or CD4+ T-cell count [2, 4, 5]. TNF-alpha inhibitors, such as etanercept, adalimumab, and IFX, have been successfully used in patients with rheumatologic conditions with concomitant HIV infection [3, 5–8].

A review published in 2015 analysed the use of TNF-alpha inhibitors in patients with HIV/acquired immune deficiency syndrome, which included 27 patients. These patients were on etanercept, IFX or adalimumab, due to rheumatologic conditions, CD or hidradenitis suppurativa. Follow-up period ranged from 6 weeks to 11 years and 26 patients were on HAART. Infectious complications were reported in 4 of these patients (15%). Three patients had an infection resolved with antibiotics: 1 pulmonary and nodal tuberculosis, 1 facial abscess and 1 acute anterior uveitis. One patient had multiple bacterial infections leading to sepsis and death. However, this patient had CD4+ T-cell count of 20 cells/μL with a HIV load of 14.000 copies/mL. This review concluded that TNF-alpha inhibitors can be used in patients treated with HAART with stable CD4+ T-cell count at baseline. Physicians should work closely with infectious disease specialists for monitoring both CD4+ T-cell counts and viral load [3].

Data concerning the use of anti-TNF-alpha drugs is limited in patients with both IBD and HIV infection. Only 3 case reports of anti-TNF-alpha use in patients infected with HIV and concomitant CD were found. The first report was published in 2006 and concerns a woman already with HIV infection controlled with HAART, who first developed CD in the colon responsive to corticosteroids. Later, she developed another colonic flare and an intersphincteric fistulae. She was first treated with antibiotics and corticosteroids, but due to her perianal disease, IFX was latter started. Her CD4 counts were > 250 cells/μL before and during treatment, and HIV-RNA was always < 200 copies/μL. This patient experienced complete clinical and endoscopic remission, with closure of the fistulae. No adverse events from IFX were reported during the unspecified follow-up period [1]. Filippi et al. later published a second report of an HIV-positive patient with undetectable viral load while on antiretroviral agents. Due to flares of colonic CD unsuccessfully remitted with corticosteroids, IFX was started, resulting in clinical remission. This patient developed an allergic reaction during maintenance therapy, but no opportunistic infections were reported during this 15-week period. In fact, IFX infusions were followed by a dramatic decrease in both HIV viral load, but also in CD4 count [9]. The third case, published in 2009, reports a patient with small bowel and colonic CD, without an HIV status before starting corticosteroids. Due to a partial response to steroids and because he refused azathioprine, he was started on IFX. He was then lost to follow-up, but returned 3 years later with an acute exacerbation of his ileocolonic CD. Only then he was tested for HIV, which was positive, with low HIV-RNA load and a CD4 count of 290 cells/μL. He was started on IFX, with an increase in

Table 1 Case reports on HIV infected patients with CD treated with IFX

First author, year	CD location	HAART therapy	HIV-RNA before IFX (copies/mL)	CD4 cells count before IFX (cells/μL)	Side-effects
Beltrán B, 2006 [1]	Colon and perianal	Unknown	< 200	555	None
Filippi J, 2006 [9]	Colon	Unknown	~ 32.000	1000–1050	Allergic reaction
Habib SF, 2009 [2]	Ileum and colon	None	"Low"	290	Unknown (loss to follow-up)
Rafael MA, 2019	Ileum, colon and perianal	Lamivudine/abacavir/efavirenz	< 50	> 500	None

CD4 cell count after each infusion. However, he was not on antiretroviral therapy and he was lost to follow-up [2].

Therefore, our case is the second report of perianal CD in an HIV-positive patient treated with anti-TNF. It also differs from the first two reports as we decided to start an anti-TNF before a trial with corticosteroids, due to severe perianal disease. Secondly, the case report described by Fillipi et al. has a very short follow-up period, which cannot exclude infectious complications of immunosuppressive therapy. Additionally, in the last case, reported by Habib et al., the patient was not on antiretroviral therapy and it is not mentioned CD's response to therapy or infectious complications during follow-up (Table 1).

Finally, our report is the only one where HAART therapy was specified and the HIV follow-up (HIV-RNA and CD4 cell count) during IFX therapy was detailed. This case might contribute to help in future clinical decisions in patients with a similar situation. Therefore, based on our report and review of published data, IFX can be successfully used in patients with severe or refractory CD and concomitant HIV infection. However, clinicians must make sure that HIV suppression is sustained with HAART therapy before and during anti-TNF treatment. A close follow-up with stable numbers of CD4 cell count and undetectable HIV-RNA is fundamental for the safety of IFX use in these particular patients.

Although our patient follow-up period is still of 18 months, she significantly improved and showed no signs of opportunistic infections. However, longer follow-up periods have already been published in rheumatologic diseases, the longest being 11 years [10].

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Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest regarding this submission;

Informed consent Patient's informed written consent was obtained before submitting the paper.

References

1. Béltran B, Nos P, Bastida G, et al. Safe and effective application of anti-TNF-alpha in a patient infected with HIV and concomitant Crohn's disease. Gut. 2006;55:670–1.
2. Habib SF, Hasan MZ, Salam I. Infliximab therapy for HIV positive Crohn's disease: a case report. J Crohns Colitis. 2009;3:302–4.
3. Gallitano SM, McDermott L, Brar K, et al. Use of tumor necrosis factor (TNF) inhibitors in patients with HIV/AIDS. J Am Acad Dermatol. 2016;74:974–80.
4. Shale MJ, Seow CH, Coffin CS, et al. Review article: chronic viral infection in the anti-tumour necrosis factor therapy era in inflammatory bowel disease. Aliment Pharmacol Ther. 2010;31:20–34.
5. Cepeda EJ, Williams FM, Ishimori ML, et al. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. Annn Rheum Dis. 2008;67:710–2.
6. Nakamura M, Abrouk M, Farahnik B, et al. Psoriasis treatment in HIV-positive patients: a systematic review of systemic immunosuppressive therapies. Cutis. 2018;101:38–42.
7. Almoallim H, Jali I, Wali G. Successful use of antitumor necrosis factor-alpha biological therapy in managing human immunodeficiency virus-associated arthritis: three case studies from Saudi Arabia. Joint Bone Spine. 2013;80:426–8.
8. Sellam J, Bouvard B, Masson C, et al. Use of infliximab to treat psoriatic arthritis in HIV-positive patients. Joint Bone Spine. 2007;74:197–200.
9. Filippi J, Roger PM, Schneider SM, et al. Infliximab and human immunodeficiency virus infection: viral load reduction and CD4+ T-cell loss related to apoptosis. Arch Intern Med. 2006;166:1783–4.
10. Gaylis NB. Long term follow-up of an HIV-infected patient with reactive arthritis treated with infliximab. J Clin Rheumatol. 2012;18(3):153–4.