**Annals of Case Reports**
Javed N, et al. Ann Case Rep: 10: 102419
www.doi.org/10.29011/2574-7754.102419
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**Case Report**

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# Cryptosporidiosis in a Patient with Well-Controlled HIV Infection and Crohn's Disease Under Janus Kinase (JAK) Inhibitor and Corticosteroids Treatment: A Case Report

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**Citation**: Javed N, Agbebi A, Palagiri JL, Hou R. (2025). Cryptosporidiosis in a Patient with Well-Controlled HIV Infection and Crohn's Disease Under Janus Kinase (JAK) Inhibitor and Corticosteroids Treatment: A Case Report. 10: 2419. DOI: 10.29011/2574-7754.102419

**Received**: 20 September 2025; **Accepted**: 25 September 2025; **Published**: 29 September 2025

**Abstract**

Cryptosporidiosis is recognized as a cause of diarrheal illness with high prevalence among immunocompromised patients. We presented a case of a 61 year old male with well controlled HIV infection on highly active antiretroviral therapy (ART), who also has concurrent refractory ileocolic Crohn's disease with history of failure of multiple immunomodulatory therapies, most recently being on upadacitinib, a selective Janus kinase (JAK) Inhibitor, as well as an ongoing course of high dose of prednisone for treatment of possible flare of Crohn's disease. He was admitted to the hospital due to extreme malaise and fatigue, profound diarrhea, and hemoglobin of 5.9 g/dL. Laboratory examination also revealed lymphopenia with differentials of 4.5% and absolute lymphocytes of 0.59 × 1000 cells/μL, $CD4^+$ count of 120 cells/μL (30%), and HIV viral load undetectable. Stool studies including stool cultures as well as ova and parasites (O&P) test were negative. Gastrointestinal pathogen panel by multiplex PCR returned with detection of *Cryptosporidium*. He subsequently received oral nitazoxanide 500 mg twice daily for 14 days for treatment of gastrointestinal cryptosporidiosis, resulting in improvement of his symptoms. In patients with inflammatory bowel disease (IBD) under immunomodulatory therapies, cryptosporidiosis should be considered a possible cause of worsening gastrointestinal symptoms. As with all immunomodulatory therapies including JAK Inhibitors, corticosteroids, and others, careful assessment of any treatment-associated infection risk is essential to balance the potential risks of infection with the known benefits of the treatment.

**Keywords**: Cryptosporidiosis; HIV; Crohn's disease; Janus kinase (JAK) inhibitors; Corticosteroids, immunomodulatory therapies

## Introduction

Cryptosporidiosis is a parasitic infection caused by *Cryptosporidium* Spp, which infects the small bowel mucosa, and, if symptomatic, clinically characterized by watery diarrhea, often profuse and prolonged, with associated abdominal pain, nausea, vomiting, and fever. Infection with *Cryptosporidium* is highly prevalent among immunocompromised patients with acquired immunodeficiency syndrome, primary immunodeficiency, cancer, and organ transplant recipients [1]. Advanced immunosuppression, such as $CD4^+$ T lymphocyte ($CD4^+$) cell counts <100 cells/$mm^3$ is associated with the greatest risk for prolonged, severe, or

extraintestinal cryptosporidiosis. Diagnosis of cryptosporidiosis was traditionally made by microscopic identification of the oocysts in stool with acid-fast staining, direct fluorescent antibody (DFA), or enzyme immunoassay (EIA). Molecular methods, such as polymerase chain reaction (PCR), are increasingly favored over traditional methods like microscopy due to their higher sensitivity and specificity, and are now considered the gold standard for diagnosing cryptosporidiosis in many diagnostic laboratories [2].

Crohn's disease is a chronic inflammatory bowel disease of the gastrointestinal tract with symptoms evolving in a relapsing and remitting manner. It is also a progressive disease that leads to bowel damage and disability. All segments of the gastrointestinal tract can be affected, the most common being the terminal ileum and colon. The cardinal symptoms of Crohn's disease include abdominal pain, diarrhea (with or without gross bleeding), fatigue, and weight loss. The characteristic overlapping of the symptoms of *Cryptosporidium* infection and Crohn's disease flare can prove challenging and has a higher risk of misdiagnosis [3]. The concomitant occurrence in patients with HIV infection on immunomodulatory therapies for Crohn's disease makes it even more complicated to differentiate and manage the disease. Here we present a case of cryptosporidiosis in a patient living with well controlled HIV infection and refractory Crohn's disease with history of failure of multiple immunomodulatory therapies.

## Case Presentation

A 61 year old Caucasian male has been followed in the Infectious Diseases clinic for HIV care. He was diagnosed with HIV infection in July 2021 with $CD4^+$ count of 814 cells/μL (56%) at the time of diagnosis, and his HIV is well controlled on antiretroviral medication Biktarvy with the most recent with $CD4^+$ count of 605 cells/μL (56%) and HIV viral load of <20 copies/mL undetectable in May 2024. The risk factor for him to get HIV infection was primarily from male-to-male sexual contact. The patient has been strictly compliant with the antiretroviral medication with no history of AIDS.

His medical history is also notable for fistulizing Crohn's disease which was diagnosed in 1984, and the course was complicated by the stricture of the ileocolic region. He underwent ileocolonic resection with the most recent third surgery performed in February 2012, which included ileocolonic resection of his previous anastomosis with subtotal colectomy and ileosigmoid anastomosis. His prior treatment for Crohn's disease included infliximab, adalimumab, certolizumab pegol, methotrexate, and azathioprine. He had been on maintenance treatment with vedolizumab every 4 weeks for the last few years but treatment was changed to risankizumab in April 2023 due to ileitis on colonoscopy that was performed in March 2023. Given no improvement of his gastrointestinal symptoms, upadacitinib, a selective JAK inhibitor, was started in September 2023. He experienced ongoing symptoms including occasional abdominal pain, bloating, and diarrhea with frequency ranging from four to nine times daily, depending on the day. Colonoscopy was repeated in May 2024, showing active disease in the neo-terminal ileum (neo-TI). His gastroenterologist increased the dose of upadacitinib from 30 mg to 45 mg, and started ustekinumab, an antagonist against interleukin-12 (IL12) and interleukin-23 (IL23) for combo therapy. This caused significant arthralgias, fatigue, and psychological symptoms concerning for posterior reversible encephalopathy syndrome (PRES). Ustekinumab was discontinued after a dose. Prednisone 60 mg once daily for 14 days was started at the end of September 2024 followed by a taper protocol. Upadacitinib was continued.

On October 28, 2024, the patient presented to outpatient Infectious Diseases clinic for his routine HIV follow up. He experienced extreme malaise and fatigue, weakness, lightheadedness, and significant weight loss that started 1.5 months ago, and symptoms had been progressively worsening. He also reported a fever of 38.3°C a day prior. He complained of profound diarrhea with frequency ranging from ten to twelve times daily but denied any melena or hematochezia. He denied headache, confusion, respiratory symptoms, urinary symptoms, or rash. He was still undergoing prednisolone tapering, on 20 mg daily. Laboratory examination revealed leukocytosis of 13.3 × 1000 cells/μL, 88.2% neutrophils, lymphocytes of 4.5% with absolute lymphocytes of 0.59 × 1000 cells/μL (lymphopenia), anemia with a hemoglobin of 7.6 g/dL (was 12.9 g/dL on September 19, 2024), $CD4^+$ count of 120 cells/μL (30%), and HIV viral load of <20 copies/mL undetectable. Urinalysis was negative for nitrites, leukocytes, and bacteria. The patient was referred to the hospital for direct admission. He was noted further dopped hemoglobin to 5.9 g/d and required a unit of pRBC transfusion and iron infusion.

Further laboratory and image examination including blood culture and chest X-Ray were negative. CT angiography revealed right lower lobe subsegmental pulmonary embolism which was considered secondary to upadacitinib. Anticoagulation was started. CT of the abdomen and pelvis was performed following the uneventful administration of 100 mL of Isovue 370 intravenous contrast according to standard protocol, showing presence of right colonic wall thickening and fat stranding that was not seen on MRI enterography dated on October 5, 2024. Stool studies including stool cultures and ova and parasites test were negative. Gastrointestinal pathogen panel by multiplex PCR returned with detection of *Cryptosporidium*. Gastroenterology was consulted given suspension of active gastrointestinal bleeding and ongoing flare of Crohn's disease. Decision was made by gastroenterology to defer colonoscopy because his hemoglobin became stable after a unit of pRBC transfusion, and low suspicion of flare of Crohn's disease with ongoing prednisone tapering doses that was eventually

completed in the early of November, 2024. Upadacitinib was held off. Infectious Diseases was consulted and started oral nitazoxanide 500 mg twice daily for 14 days for treatment of cryptosporidiosis. With concern for his immunosuppressed status, further infectious workup was performed, fungal antigen testing for *Histoplasma, Blastomyces, Aspergillus,* and *Cryptococcus* were all negative, and cytomegalovirus DNA PCR in blood was not detected. He was also started on empiric intravenous piperacillin/ tazobactam, which was subsequently switched to oral ciprofloxacin and metronidazole for a total duration of 7 days for empirical treatment of possible bacterial colitis. Patient was discharged home on November 3, 2024 with gastroenterology and Infectious Diseases outpatient follow up.

During subsequent follow-up in 2 weeks, the patient exhibited notable clinical improvement, as evidenced by follow-up laboratory examination that revealed normalized absolute lymphocytes and recovered $CD4^+$ count above 700 cells/uL with a normal $CD4^+$/ $CD8^+$ ratio, and HIV viral load remaining undetectable. Infliximab was started by his gastroenterologist in December 2024, but has developed antibodies with zero drug level. Subsequently golimumab, another tumor necrosis factor (TNF) blocker, was started.

## Discussion

The incidence of cryptosporidiosis in people with HIV has decreased, particularly in high-income countries, due to low rates of environmental contamination and the widespread use of highly active ART. In the United States, the Centers for Disease Control and Prevention (CDC) monitors cryptosporidiosis through the National Notifiable Diseases Surveillance System (NNDSS), and the incidence of cryptosporidiosis in people with HIV is now below 1 case per 1,000 person-years [4]. Both innate and adaptive-mediated immunity play an important role in protecting the host from cryptosporidiosis and in clearance of the infection [5], particularly the pathway to induce a Th1 immune response with IFN-$\gamma$ production by $CD4^+$ T cells [6]. In those with advanced immunosuppression (typically $CD4^+$ counts below 100 cells/ $mm^3$), *Cryptosporidium* infection is more likely to be prolonged, severe, or involve extraintestinal sites [7]. Conversely, in individuals with $CD4^+$ counts above 150 cells/$mm^3$, the infection is often self-limiting and similar to that seen in immunocompetent individuals. In our case study, the patient has no previous history of AIDS with excellent compliance with ART. However, when he was diagnosed with gastrointestinal *Cryptosporidium* infection, he was noted dramatically decreased $CD4^+$ count to 120 cells/ µL from baseline $CD4^+$ count above 600 cells/µL, in the context of significant lymphopenia, lymphocytes of 4.5%, absolute count of 0.59 × 1000 cells/µL. The development of lymphopenia is caused by immune dysregulation of corticosteroids, a phenomenon that is one of the well-known side effects of corticosteroids use particularly with prolonged or high doses. The resultant low $CD4^+$ count made him more susceptible to opportunistic infections like *Cryptosporidium*.

The emergence of opportunistic infections like tuberculosis, multidermatomal herpes zoster, oral/esophageal candidiasis, and cryptococcosis associated with the use of JAK inhibitors has been reported [8, 9]. Janus kinases are members of the tyrosine kinase family that play a key role in transferring extracellular signals into the nucleus, altering DNA transcription, downstream translation, and effector protein manufacture. The JAK/STAT pathways down regulate more than 50 cytokines and growth factors and are considered a central communication node for the immune system [10, 11]. JAK inhibition has potential to suppress integral elements of the immune response. Across the selective JAK-1 clinical trials, absolute event rates for serious infections were found to be lower with smaller doses [12], and were comparable to non selective JAK inhibitors and biologics [13, 14]. An integrated analysis from upadacitinib **SELECT** trials including **SELECT-NEXT, SELECT-BEYOND, SELECT-EARLY, SELECT-MONO, SELECT-COMPARE** and **SELECT-SUNRISE** reported that event rates of serious infections were higher with the dose of 30 mg [14-19]. Whether the use of JAK inhibitors is associated to an increased risk of infection by *Cryptosporidium* Spp is not definitively established in the provided search results. Because JAK inhibitors target the JAK-STAT signaling pathway, which is involved in various immune responses including T cell function, particularly disruption of T cell-induced macrophage activation and reduction of downstream proinflammatory cytokine and chemokine responses, the resultant decreased production of TNF, IL-6, IL-15, IL-1RA and the chemokines IL-10, MIP1α, MIP1β, IP10 by Tck cell-activated macrophages may facilitate the infection with *Cryptosporidium* Spp. Continued monitoring and research are necessary to further assess the safety profile of JAK inhibitors, particularly regarding rare and opportunistic infections like *Cryptosporidium*.

Since cryptosporidiosis can mimic or even trigger relapses IBD, in some cases, cryptosporidiosis can be misdiagnosed as an IBD flare-up due to similar symptoms. It is crucial to consider cryptosporidiosis in IBD patients experiencing a worsening of symptoms, particularly if the patients are under immunomodulator treatment. Appropriate stool studies should be performed to identify the parasites. Diagnosis of cryptosporidiosis can be achieved through microscopic identification of oocysts in stool smears using acid-fast staining, direct immunofluorescence (DEA) and concentration methods (e.g., formalin-ethyl acetate). Antigen detection by enzyme-linked immunosorbent assay or immunochromatographic tests have sensitivities reportedly range from 66% to 100%. Multiplex PCR assay has become increasingly valuable and is now considered as a gold standard test in the

field of diagnosis of cryptosporidiosis, that can identify a greater number of cases than microscopic methods [20].

## Conclusion

*Cryptosporidium* infection is found to be highly prevalent among immunocompromised hosts with impaired innate and adaptive immunity. In patients with well controlled HIV infection on highly active ART, concomitant immunosuppressant use for treatment of concurrent medical conditions can predispose to the risk of *Cryptosporidium* infection. In patients with IBD under immunomodulatory therapies, cryptosporidiosis should be considered a possible cause of worsening gastrointestinal symptoms. As with all immunomodulatory therapies including JAK Inhibitors and corticosteroids, careful assessment of any treatment-associated infection risk is essential to balance the potential risks of infection with the known benefits of the treatment.

## Data availability

The data used to support the findings of this study are included within the article.

## Patient consent

Written informed consent was obtained from the patient. The design of the study conforms to the standards currently applied in the country.

## Conflicts of interest

NJ, AA, JLP, and RH: No reported conflicts of interest.

## Funding

There was no direct funding for this report.

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