

## Microsporidium Infection–Associated Acute Kidney Injury in a Patient With HIV



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Patients infected with HIV (human immunodeficiency virus) are at an increased risk of developing acute kidney injury (AKI) compared with patients without HIV infection. We report a rare case of disseminated *Microsporidium* infection–associated AKI affecting the native kidneys in a 30-year-old Asian woman with HIV infection. She initially presented to an outside institution with AKI after completing treatment with trimethoprim-sulfamethoxazole (Bactrim [Hoffmann-La Roche]) and prednisone for *Pneumocystis pneumonia*. She was empirically treated with prednisone for presumed acute interstitial nephritis due to Bactrim, and her serum creatinine concentration improved from 3.0 mg/dL to 1.8 mg/dL. She was subsequently initiated on antiretroviral therapy and was also treated with ganciclovir for cytomegalovirus viremia. Because of persistent fever, she was transferred to our institution and was diagnosed with a disseminated *Mycobacterium avium* complex infection and a disseminated *Microsporidium* infection. Her serum creatinine concentration increased to 4.2 mg/dL. A kidney biopsy was performed because of her worsening kidney function, which revealed plasma cell–rich acute interstitial nephritis associated with disseminated *Microsporidium* infection. She was maintained on antiretroviral therapy and was treated with albendazole. This case highlights the fact that there are various etiologies and kidney manifestations of AKI in patients infected with HIV with equally various implications for management; thus, performing a kidney biopsy is often crucial to help elucidate the underlying pathology and guide management.

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### INTRODUCTION

Patients with HIV (human immunodeficiency virus) infection are at an increased risk of developing acute kidney injury (AKI) compared with patients without HIV infection.<sup>1,2</sup> The etiologies and kidney manifestations of AKI in this patient population are diverse; thus, performing a kidney biopsy is often necessary for an accurate diagnosis and treatment.<sup>3</sup> Herein, we report a rare case of AKI secondary to acute plasma cell–rich interstitial nephritis associated with a disseminated *Microsporidium* infection affecting the native kidneys in a patient with HIV infection.

### CASE REPORT

Three months before presentation at our institution, a 30-year-old woman was diagnosed with HIV infection. During that time, her HIV viral load was 210,000 copies/mL, and her CD4 count was 13 cells/ $\mu$ L (range, 365–1,437 cells/ $\mu$ L). She was also diagnosed with *Pneumocystis pneumonia* and was treated with high-dose trimethoprim-sulfamethoxazole (Bactrim [Hoffmann-La Roche]) and prednisone. Two months later, she developed AKI with a peak creatinine concentration of 3.0 mg/dL (baseline creatinine concentration, 0.7 mg/dL) after completing treatment with Bactrim and prednisone taper. She was empirically treated with prednisone for presumed acute interstitial nephritis (AIN) attributed to Bactrim. Her serum creatinine concentration declined to 1.8 mg/dL, and she was initiated on antiretroviral therapy (ART) with Biktarvy [bictegravir + emtricitabine + tenofovir alafenamide

(Gilead)] that, after 2 doses, was switched to Juluca [dolutegravir + rilpivirine (ViiV Healthcare)] and emtricitabine. During admission, she was found to have cytomegalovirus viremia with retinitis treated with ganciclovir. At that point, she developed persistent fever and was transferred to our institution for further care. Her HIV viral load (10,500 copies/mL) and CD4 count (42 cells/ $\mu$ L) had improved. She was diagnosed with a disseminated *Mycobacterium avium* complex infection and disseminated *Microsporidium* infection with *Encephalitozoon* species growing in her urine and sputum. Her serum creatinine concentration increased to 4.2 mg/dL. A urinalysis showed pyuria (21–30 white blood cells/high-power field) without hematuria, and her 24-hour urine total protein output was 853 mg. A kidney ultrasound showed bilateral nephromegaly of 13 cm each (Fig 1). Because of the worsening kidney function, a kidney biopsy was performed.

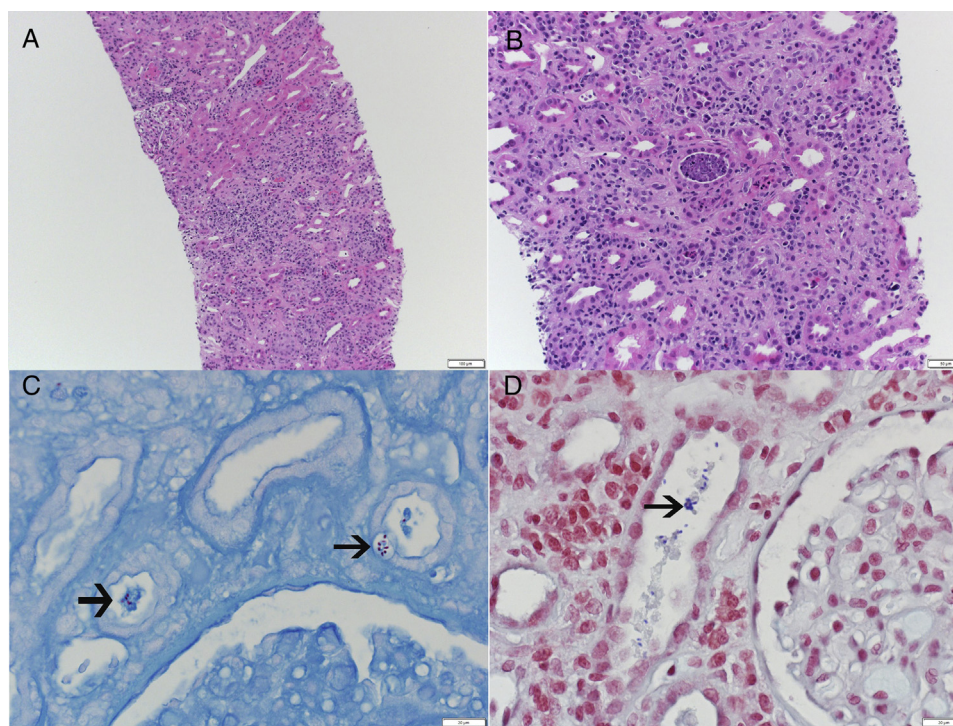
There were 8 glomeruli on the kidney biopsy, none of which was globally or segmentally sclerosed on light microscopy. The glomeruli did not show any evidence of crescents, fibrinoid necrosis, thrombosis, or endocapillary hypercellularity. The mesangium and glomerular capillary walls were unremarkable. Tubulitis and extensive interstitial inflammation containing both plasma cells and mononuclear cells were present. Viral cytopathic changes were not seen. Because of the extensive interstitial inflammation, it was difficult to estimate the extent of interstitial fibrosis and tubular atrophy, which was estimated to be mild at 10%–15%. The vessels were also unremarkable. On immunofluorescence, the glomeruli only showed mesangial staining for C3 (1 to 2+). On electron



**Figure 1.** (A and B) Kidney ultrasound showed bilateral nephromegaly with the left and right kidneys measuring 13.2 cm each.

microscopy, the glomeruli appeared normal; however, some of the tubular lumina contained small, encapsulated structures. These structures were found to be Gram-positive and acid-fast bacilli–positive microorganisms consistent with microsporidia. The final diagnosis was acute plasma cell–rich interstitial nephritis associated with disseminated *Microsporidium* infection (Fig 2).

The patient was maintained on ART and was initiated on treatment with albendazole at 400 mg administered orally twice daily, taken with fatty meals until the CD4 count increased to  $>200$  cells/ $\mu$ L and for at least 6 months after ART initiation. Her serum creatinine concentration initially improved to 2.8 mg/dL; however, 1 month later, she presented with uremic symptoms and worsening



**Figure 2.** (A) Low-power magnification (original magnification,  $\times 10$ ) and (B) high-power magnification (original magnification,  $\times 20$ ). On hematoxylin and eosin staining, the kidney biopsy contained 8 glomeruli, none of which was globally or segmentally sclerosed. In addition, glomeruli lacked proliferative features. The interstitium showed extensive inflammation with both plasma cells and mononuclear cells. (C and D) Original magnifications,  $\times 60$ . Acid-fast bacilli–positive and Gram-positive microorganisms (black arrows) consistent with microsporidia were identified in the tubular epithelium and lumen. Immunohistochemistry for Epstein-Barr virus was negative. Findings of immunofluorescence studies were negative for immune-complex glomerulonephritis, and electron microscopy showed normal-appearing glomeruli.

**Table 1.** Differential Diagnoses of Acute Kidney Injury in a Patient With HIV Infection

Disease	Causes and Examples
Prerenal	Volume depletion (eg, vomiting, diarrhea, and reduced oral intake)
Intrinsic renal	
• Glomerular	HIVAN, MCD, FSGS, IgA nephropathy, membranous nephropathy, MPGN, anti-GBM disease, and TMA
Mechanisms:	
○ HIV infection–related podocyte injury	HIVAN, MCD, and FSGS
○ Immune complex deposition	IgA nephropathy, membranous nephropathy, and MPGN
○ IRIS and autoantibody production	Anti-GBM disease
○ Unknown	TMA
• Tubular	Acute tubular injury, intratubular obstruction/crystalline nephropathy, Fanconi syndrome, and diabetes insipidus
○ Acute tubular injury	Sepsis, acute rhabdomyolysis, and medications (eg, acyclovir, aminoglycosides, amphotericin B, cidofovir, pentamidine, and tenofovir)
○ Intratubular obstruction/crystalline nephropathy	Acyclovir, foscarnet, protease inhibitors (atazanavir, indinavir, and darunavir), and sulfonamide antibiotics (sulfadiazine and trimethoprim-sulfamethoxazole)
○ Fanconi syndrome	Tenofovir
• Interstitial	Acute interstitial nephritis
○ Medications	ART, antibiotics, PPIs, NSAIDs, foscarnet, and allopurinol
○ Infections	Fungal, mycobacterial, and viral infections
• Postrenal	Urinary stone disease, malignancy, and mycobacterial and fungal infections
○ Urinary stone disease	Protease inhibitors (atazanavir, indinavir, and darunavir) and sulfonamide antibiotics (sulfadiazine and trimethoprim-sulfamethoxazole)

Abbreviations: ART, antiretroviral therapy; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; HIV, human immunodeficiency virus; HIVAN, human immunodeficiency virus–associated nephropathy; IgA, immunoglobulin A; IRIS, immune reconstitution inflammatory syndrome; MCD, minimal change disease; MPGN, membranoproliferative glomerulonephritis; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; TMA, thrombotic microangiopathy.

kidney function, with a serum creatinine concentration of 5.0 mg/dL. Findings of a repeat urine test for *Microsporidium* were negative, and repeat kidney ultrasound showed a significant decrease in the kidney size (10 cm bilaterally) and increased echogenicity, suggesting a chronic change and scarring. She thus started receiving maintenance hemodialysis. Both nephrology and infectious disease teams hypothesized that she might have had an underlying HIV-associated intrinsic kidney disease that was obscured by the

significant inflammation on the kidney biopsy. Immune reconstitution syndrome was considered but was believed to be unlikely as she had been on corticosteroid therapy.

## DISCUSSION

Although the overall incidence of AKI has decreased and stabilized since the advent of ART, it remains a common finding in patients with HIV infection.<sup>1,2</sup> HIV-dependent risk factors for AKI include a viral load of >10,000 copies/mL, a CD4 count of <200 cells/ $\mu$ L, a history of ART exposure, and an acquired immunodeficiency syndrome–defining illness. Aside from ART, other drugs used by patients with HIV infection, such as antibiotics for prophylaxis and/or treatment of opportunistic infections, are also associated with AKI in this patient population.<sup>1,2</sup> HIV-independent risk factors are similar to those of the general population, including advanced age, hypertension, diabetes, and pre-existing chronic kidney disease.<sup>1,2</sup> In addition, there are several different causes of AKI in patients with HIV infection (Table 1). The most common are prerenal causes, including volume depletion, and acute tubular necrosis due to sepsis and/or nephrotoxic drug exposure.<sup>1</sup> HIV is also associated with diseases of the glomeruli and interstitium. The primary examples are HIV-associated nephropathy, which is the most common glomerular lesion, and AIN. Immune-complex glomerulonephritis such as membranous nephropathy, focal segmental glomerulosclerosis, immunoglobulin A nephropathy, and thrombotic microangiopathy are the other glomerular lesions associated with HIV.<sup>3</sup>

AIN is a cause of AKI in up to 30% of patients with HIV infection. The majority of cases are associated with a drug hypersensitivity reaction; however, other etiologies include infection, systemic disease, and immunologic syndromes such as immune reconstitution syndrome and diffuse infiltrative lymphocytosis syndrome.<sup>4,5</sup> Nonsteroidal anti-inflammatory drugs and Bactrim are the most common culprit drugs.<sup>5</sup> Aside from clinical and laboratory features, these entities can be further differentiated histologically. The majority manifest lymphocyte-rich infiltrates, whereas tuberculosis and immune reconstitution syndrome have caseous and noncaseous granulomas, respectively.<sup>4,5</sup> HIV by itself can also cause AIN with a plasma cell–rich infiltrate. Other infections associated with AIN in patients with HIV infection are *Cryptococcus*, *Mycobacterium*, adenovirus, Epstein-Barr virus, polyomavirus, cytomegalovirus, *Candida*, and, as in our patient's case, *Microsporidium* infections.<sup>4,5</sup> Interestingly, in the series by Parkhie et al,<sup>5</sup> none of the patients presented with the classic clinical triad of fever, rash, and pyuria.

The role of corticosteroids in the treatment of AIN with and without infection remains debatable because of the lack of prospective randomized controlled trials and conflicting evidence from several retrospective studies.<sup>6,7</sup> Although some data suggest that corticosteroid therapy may result in kidney function improvement and/or

recovery, other studies have not shown any benefit.<sup>6-9</sup> There is currently an ongoing randomized controlled trial aiming to evaluate the effectiveness of prednisolone treatment in AIN (Prednisolone Treatment in Acute Interstitial Nephritis trial; NCT 04376216).<sup>10</sup>

Microsporidia are a diverse group of ubiquitous, spore-forming, obligate intracellular organisms that are related to parasitic fungi. They are an important group of opportunistic pathogens that seldom cause infections in immunocompetent hosts but can be a source of morbidity and mortality in immunocompromised hosts, including patients with HIV infection and malignancy, as well as those who are status post transplantation (both solid organ and hematopoietic stem cell). The *Encephalitozoon* species are most likely to cause disseminated disease.<sup>11-13</sup> The primary mechanism of transmission is the fecal-oral route.<sup>11-13</sup> The most common clinical manifestations are gastrointestinal in nature (eg, diarrhea); however, extra-intestinal manifestations involving the kidneys, lungs, and eyes have also been reported, particularly in kidney transplant recipients.<sup>11-13</sup> A diagnosis can be made microscopically by detecting spores in the stool, body fluids (including urine), or tissue specimens.<sup>11-13</sup>

Microsporidia can cause AKI since its spores are constantly shed into the tubular lumina where they incite inflammation. The spores can occasionally be identified within tubular epithelial cells; however, there is usually no glomerular involvement.<sup>11</sup> A recent literature review showed that a majority of the kidney transplant recipients presented with fever and allograft dysfunction and were treated for rejection before the diagnosis of *Microsporidium* infection, which occurred relatively early after the transplant (within 6 months).<sup>13</sup> In terms of management, albendazole is effective in most cases, especially those due to *Encephalitozoon* species; however, successful restoration of the immune system with ART is an important mainstay of treatment in patients with HIV infection.<sup>11</sup>

In our case, the differential diagnosis for the patient's AKI was broad. In brief, she had persistent decreased kidney function in the setting of multiple systemic infections after recent treatment with high-dose Bacrim, prednisone, and ART. A kidney biopsy was obtained to help elucidate the underlying pathology and guide management. She was found to have AKI secondary to *Microsporidium* infection-associated AIN and was appropriately treated. Unfortunately, however, her kidney function failed to recover, and she started receiving maintenance hemodialysis.

## ARTICLE INFORMATION

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## REFERENCES

1. Gameiro J, Agapito Fonseca J, Jorge S, Lopes JA. Acute kidney injury in HIV-infected patients: a critical review. *HIV Med*. 2019;20(2):77-87. doi:10.1111/hiv.12685
2. Li Y, Shlipak MG, Grunfeld C, Choi AI. Incidence and risk factors for acute kidney injury in HIV infection. *Am J Nephrol*. 2012;35(4):327-334. doi:10.1159/000337151
3. Hartle PM, Carlo ME, Dwyer JP, Fogo AB. AKI in an HIV patient. *J Am Soc Nephrol*. 2013;24(8):1204-1208. doi:10.1681/ASN.2012070665
4. Melica G, Matignon M, Desvieux D, et al. Acute interstitial nephritis with predominant plasmacytic infiltration in patients with HIV-1 infection. *Am J Kidney Dis*. 2012;59(5):711-714. doi:10.1053/j.ajkd.2011.12.017
5. Parkhie SM, Fine DM, Lucas GM, Atta MG. Characteristics of patients with HIV and biopsy-proven acute interstitial nephritis. *Clin J Am Soc Nephrol*. 2010;5(5):798-804. doi:10.2215/CJN.08211109
6. Predecki M, Tanna A, Salama AD, et al. Long-term outcome in biopsy-proven acute interstitial nephritis treated with steroids. *Clin Kidney J*. 2017;10(2):233-239. doi:10.1093/ckj/sfw116
7. Fernandez-Juarez G, Perez JV, Caravaca-Fontán F, et al. Duration of treatment with corticosteroids and recovery of kidney function in acute interstitial nephritis. *Clin J Am Soc Nephrol*. 2018;13(12):1851-1858. doi:10.2215/CJN.01390118
8. González E, Gutiérrez E, Galeano C, et al. Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. *Kidney Int*. 2008;73(8):940-946. doi:10.1038/sj.ki.5002776
9. Valluri A, Hetherington L, Mcquarrie E, et al. Acute tubulointerstitial nephritis in Scotland. *QJM*. 2015;108(7):527-532. doi:10.1093/qjmed/hcu236
10. Mose FH, Birn H, Hoffmann-Petersen N, Bech JN. Prednisolone treatment in acute interstitial nephritis (PRAISE)—protocol for the randomized controlled trial. *BMC Nephrol*. 2021;22(1):161. doi:10.1186/s12882-021-02372-4
11. Nagpal A, Pritt BS, Lorenz EC, et al. Disseminated microsporidiosis in a renal transplant recipient: case report and review of the literature. *Transpl Infect Dis*. 2013;15(5):526-532. doi:10.1111/tid.12119
12. Hernández-Rodríguez OX, Alvarez-Torres O, Ofelia Uribe-Uribe N. Microsporidia infection in a Mexican kidney transplant recipient. *Case Rep Nephrol*. 2012;2012:928083. doi:10.1155/2012/928083
13. Brown M, Longano A, Dendle C, Polkinghorne KR, Kanellis J. Confirmed microsporidial graft infection in a HIV-negative renal transplant recipient: a case report and review of the literature. *Transpl Infect Dis*. 2018;20(3):e12888 doi:10.1111/tid.12888