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Case Report: A Case of Severe Cryptococcal Immune Reconstitution Inflammatory Syndrome Presenting with Brain and Intradural Abscesses in an HIV Patient

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Abstract. Clinical worsening or new manifestation of cryptococcal disease following initiation of anti-retroviral therapy (ART) in an HIV patient is a hallmark of cryptococcal immune reconstitution inflammatory syndrome (C-IRIS). However, it can be difficult to distinguish IRIS from worsening or new infection. Here, we present a case of severe C-IRIS involving multiple cerebellar, spinal, and intradural abscesses and spinal arachnoiditis 7 months after ART initiation in an AIDS patient with uncertain prior ART compliance. He had multiple prior episodes of cryptococcal meningitis with complications necessitating ventriculoperitoneal shunt placement and was on suppressive fluconazole when he developed worsening brain manifestations. He received empiric anti-cryptococcal re-induction without improvement. All cerebrospinal fluid cultures remained sterile, with negative *Cryptococcus* PCR testing, and his condition continued to worsen prior to corticosteroid initiation. Ultimately, C-IRIS was diagnosed by brain biopsy. This case demonstrates an extreme in severity of C-IRIS and in the timeline of presentation after ART initiation.

INTRODUCTION

Immune reconstitution inflammatory syndrome due to *Cryptococcus* cryptococcal immune reconstitution inflammatory syndrome (C-IRIS) occurs in 19.5% of HIV patients with prior-documented AIDS-defining conditions starting anti-retroviral therapy (ART)[1] and remains a significant cause of morbidity and mortality in this population. Cryptococcal immune reconstitution inflammatory syndrome presents after beginning ART as either worsening of previously diagnosed cryptococcal meningitis or as an "unmasking" of previously unknown cryptococcal disease.[2] Cryptococcal immune reconstitution inflammatory syndrome normally presents as meningitis, but other central nervous system (CNS) manifestations include intracranial cryptococcomas, cysts, abscesses, hydrocephalus, and raised intracranial pressure, cranial nerve lesions, dysarthria, and paresis.[2–14] Immune reconstitution inflammatory syndrome may present similarly to disease relapse, which can make diagnosis challenging.[15] We describe a case of an AIDS patient with recurrent cryptococcal meningitis who developed CNS C-IRIS after ART initiation, the severity and extent of which has not been previously reported.

CASE REPORT

A 48-year-old man with HIV/AIDS and recurrent *Cryptococcus neoformans* meningitis with obstructive hydrocephalus requiring ventriculoperitoneal shunt (VPS) on maintenance fluconazole and ART presented with 4 months of progressive confusion, photophobia, and weakness. The patient had five prior episodes of cryptococcal meningitis, most recently 8 months prior (CD4 < 20 cells/μL at that time) in the setting of poor medication compliance, and multiple social barriers to routine follow-up care. He had been treated with amphotericin B and flucytosine for 2 weeks, and then continued on fluconazole for consolidative therapy. Anti-retroviral therapy was started 24 days after antifungal initiation.

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At the time of presentation, 7 months after ART initiation, he was started on amphotericin B plus flucytosine. His ART was continued, as CD4 had improved to 35 cells/μL and HIV viral load was undetectable. Lumbar cerebrospinal fluid (CSF) studies revealed white blood cells count (WBC) 72 cells/cumm, total protein 620 mg/dL, glucose 35 mg/dL, and CrAg titer > 1:2,560. Fungal culture and *Cryptococcus* PCR were negative. Magnetic resonance imaging (MRI) of the brain showed leptomeningeal enhancement and micro-abscesses (Figure 1).

After 2 weeks of induction therapy, repeat CSF studies showed opening pressure 32 cmH_2O, WBCs 127 cumm, total protein 620 mg/dL, and glucose 39 mg/dL; fungal culture remained negative. A second MRI showed new ring-enhancing abscesses in the cerebellum, worsening leptomeningeal enhancement with occlusion of the fourth ventricle, and new vasogenic edema in the temporal lobe (Figure 2).

The diagnoses considered included refractory *Cryptococcus*, C-IRIS, tuberculous (TB) meningitis, or bacterial VPS infection. He was started on empiric TB therapy (rifampin/isoniazid/pyrazinamide/ethambutol or RIPE) plus dexamethasone while CSF AFB cultures were pending, and also placed on meropenem and vancomycin. He continued to decline neurologically, prompting neurosurgery consultation for brain biopsy. All bacterial, fungal, and acid fast bacilli (AFB) cultures of the left frontal bone, dura, arachnoid, and brain were negative. Pathology showed numerous yeast consistent with *Cryptococcus* (Figure 3). Given the presence of yeast and negative cultures, C-IRIS was considered the most likely diagnosis. The lack of response to antifungal, anti–TB, and antibiotic therapy supported this. Prednisone 40 mg daily was started, and fluconazole and RIPE were continued.

At his follow-up visit, he was neurologically stable, and prednisone was decreased to 35 mg daily. Three weeks later, fevers, headaches, weakness, and bowel/bladder incontinence recurred. CD4 count was 46 cells/μL (6%). Cerebrospinal fluid showed WBCs 1900 cells/cumm, total protein 620 mg/dL, and glucose 10 mg/dL; all cultures remained negative (Table 1). MRI of thoracic and lumbar spine showed dural thickening and enhancement throughout the spine (Figure 4). This included areas of dorsal phlegmon in the thoracic region and a complex abscess surrounding the thecal sac, compressing the S1 nerve root. CT-guided aspiration of this abscess revealed 1+ yeast and 1+ PMNs

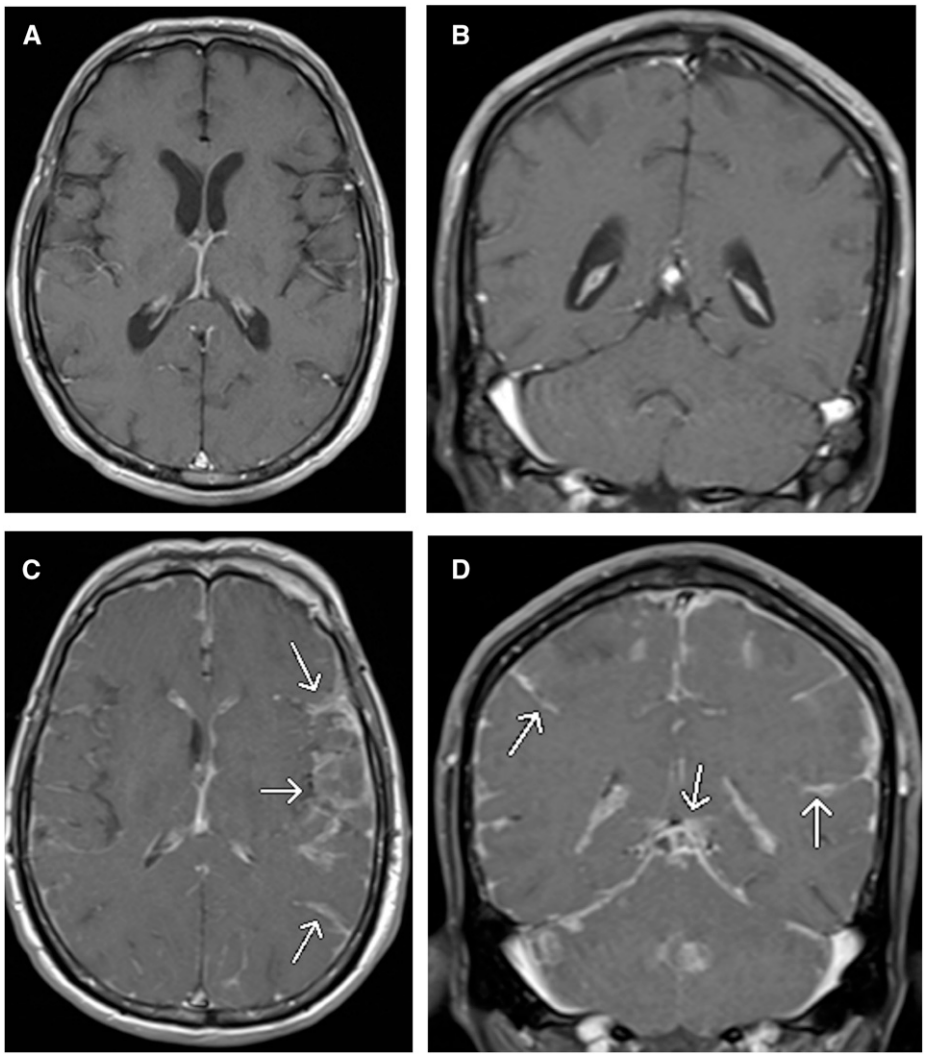

FIGURE 1. Initial axial (**A**) and coronal (**B**) contrast-enhanced T1-weighted MRI images show no abnormal enhancement. Subsequent axial (**C**) and coronal (**D**) contrast-enhanced T1-weighted MRI images show new diffuse leptomeningeal enhancement (arrows).

on Gram stain but no growth in cultures. With multiple negative cultures, yet still a moderate burden of yeast on staining, the suspicion for C-IRIS further increased, and we concluded that his clinical deterioration likely correlated with tapering his corticosteroid dosing. Thus, his prednisone was increased to 60 mg daily. Because of remaining uncertainty regarding occult, active cryptococcal disease, the patient was restarted on flucytosine for 2 weeks, while continuing on maintenance fluconazole (400 mg daily). His RIPE therapy was discontinued after the AFB cultures of CSF demonstrated no growth at 6 weeks.

With the increased corticosteroid dosing, he exhibited sustained clinical improvement over time. He was maintained on prednisone 60 mg daily for 3 weeks and 55 mg daily for 6 weeks, which was reduced to 50 mg daily at his most recent follow-up. At this appointment, 2 months following his hospital course, he continued to have significant improvement in his neurological status.

DISCUSSION

Cryptococcal meningitis remains among the most common causes of AIDS-related mortality, estimated to be 15–20%.[16] Cryptococcal immune reconstitution inflammatory syndrome is a common complication of cryptococcal meningitis following ART initiation, and the two disorders can be difficult to distinguish. This case was particularly challenging because of extensive brain and spinal disease, which is more often seen with severe TB or *Coccidioides* CNS infections. Chronic hydrocephalus and a VPS further complicated the possible diagnosis.

Cerebrospinal fluid inflammation is nonspecific in this setting and is consistent with *Cryptococcus* meningitis, C-IRIS, cytomegalovirus polyradiculopathy, or another infection, such as tuberculosis, bacterial, or rarer forms of meningitis. The patient's CrAg titer remained high in all CSF samples, but these levels can remain elevated despite resolving or resolved infection, and serial monitoring has a limited diagnostic value.[17] The multiple negative CSF cultures and *Cryptococcus* PCR assays support an inflammatory disease process rather than active infection. The brain biopsy strongly supported diagnosis of C-IRIS, with pathology showing *Cryptococcus* yeast with negative cultures, leading to the initiation of corticosteroids.

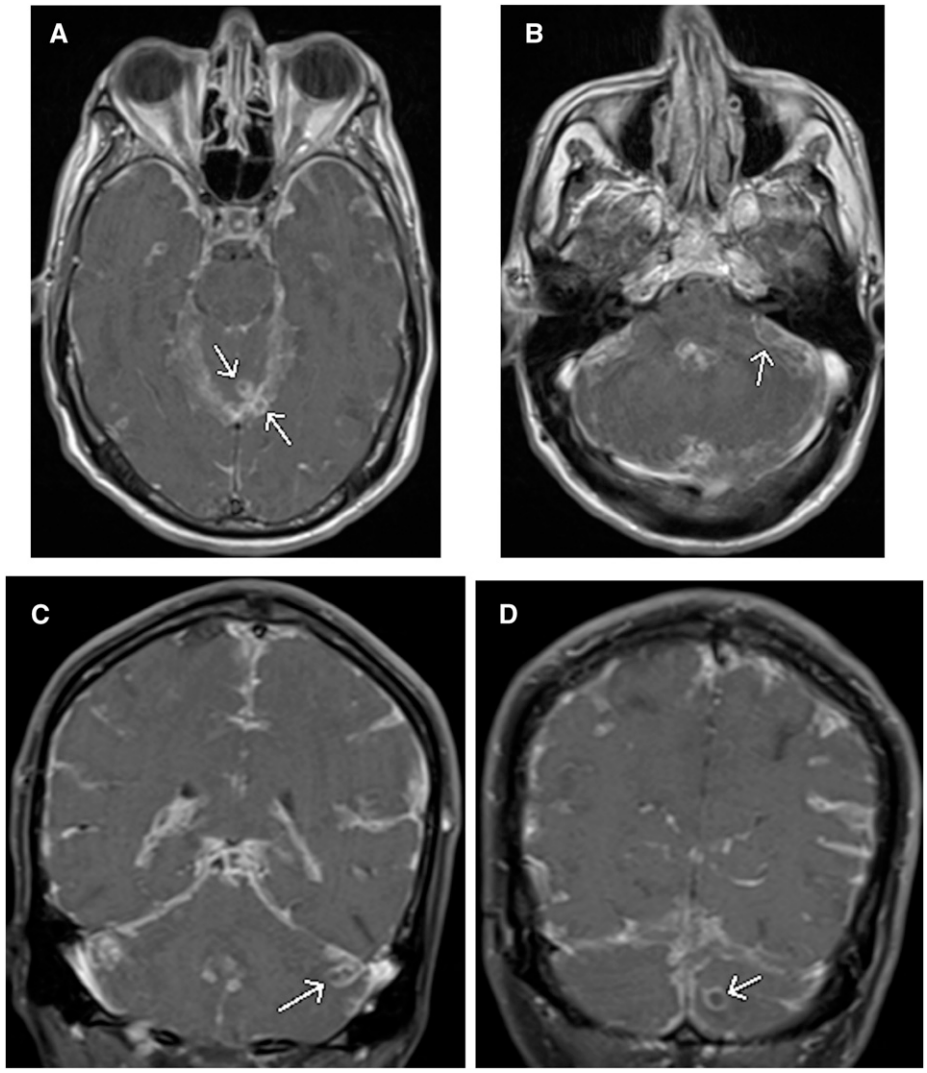

FIGURE 2. Follow-up axial (**A** and **B**) and coronal (**C** and **D**) contrast-enhanced T1-weighted MRI images show worsened leptomeningeal enhancement and new ring-enhancing parenchymal abscesses abutting the tentorium and within the left cerebellar hemisphere (arrows).

A limited number of cases of isolated infratentorial or spinal cryptococcal infection have been reported. The cerebellar cases were in immunocompetent patients.[18,19] Spinal cases range from epidural involvement to intramedullary abscess.[20–32] To our knowledge, only one case of spinal-cerebral infection due to *C. neoformans*, which was in an HIV-negative, immunocompetent patient, has been reported.[33] Ours is the first known case of C-IRIS with these widespread and specific manifestations. Prior cases of C-IRIS involving the spine may have been undiagnosed because it was asymptomatic. Indeed, even with extensive spinal involvement, our patient did not have significant back pain. Thus, we advise a low threshold for spine imaging when severe C-IRIS is suspected, especially if the CSF profile continues to be markedly abnormal.

Although the current standard is to start patients on ART as early as possible, even with ongoing opportunistic infection, delay is advised with certain infections. Studies on tuberculous meningitis have shown significantly higher severe adverse events with early ART.[34] In cryptococcal meningitis, one study showed that early ART (within 72 hours of cryptococcal meningitis diagnosis) in patients with AIDS resulted in significantly higher mortality than delayed (after 10 weeks of fluconazole) ART (88% versus 54%).[35] A subsequent similar study found higher mortality in early (1–2 weeks) than in delayed (5 weeks after diagnosis) ART cohorts (45% versus 30%).[36]

Current U.S. guidelines recommend ART be initiated 2–10 weeks after the start of antifungal therapy in HIV patients with cryptococcal meningitis.[37,38] Given that studies have looked at only two intervals (5 and 10 weeks) for "delayed" therapy, the optimal time for ART initiation may be even longer, especially in cases of severe cryptococcal meningitis. Our patient was initiated on ART 24 days after starting antifungal therapy. We suspect he used ART only sporadically in the prior 7 months given his high levels of HIV viremia and low CD4 count. This case illustrates that even with successful treatment of cryptococcal meningitis and a delay in starting ART, patients may have life-threatening C-IRIS.

Patients with advanced AIDS remain at high risk for C-IRIS after the initiation of ART. It can be difficult to predict which of these patients may develop severe C-IRIS, even in instances

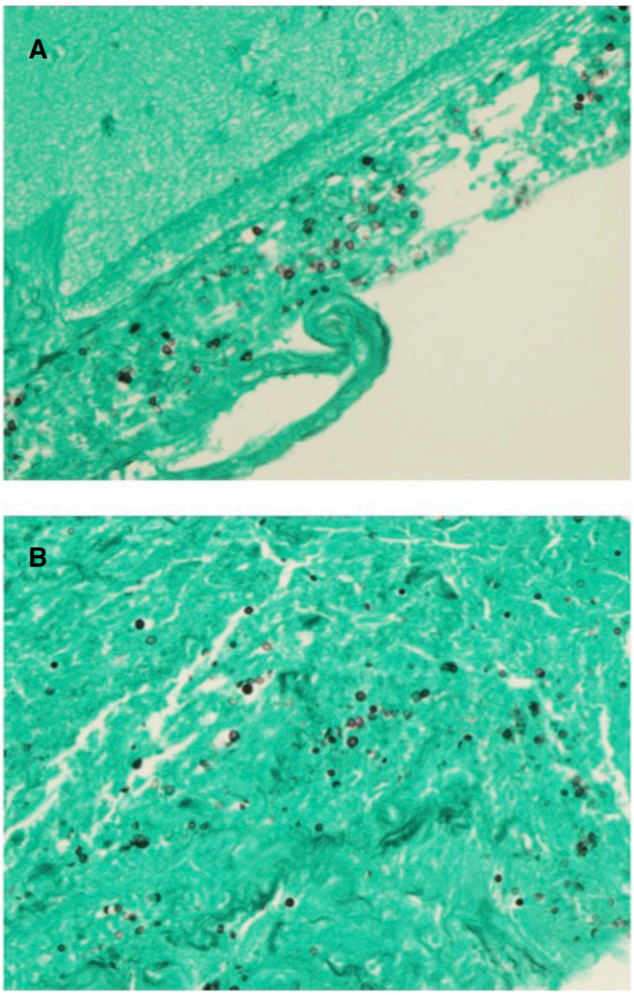

FIGURE 3. Grocott's methenamine silver (GMS)-stained pathology specimens of the brain (**A**) and arachnoid (**B**) tissues revealing numerous yeast forms. This figure appears in color at www.ajtmh.org.

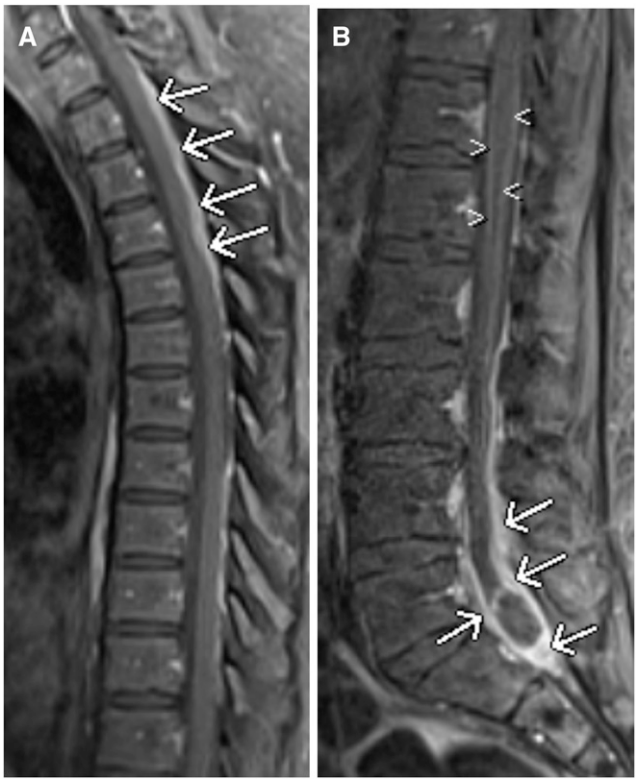

FIGURE 4. Sagittal contrast-enhanced T1-weighted MRI image through the thoracic spine (**A**) shows dorsal dural thickening and enhancement (arrows). Sagittal contrast-enhanced T1-weighted MRI image through the lumbar spine (**B**) shows leptomeningeal enhancement around the conus (arrowheads) and dural thickening and enhancement around the distal thecal sac (arrows).

of delaying ART initiation appropriately. Our patient had known risk factors associated with poorer outcomes in cryptococcal meningitis, such as high pre-ART CrAg and lower levels of CSF inflammation.[39–42] However, this pattern is not uncommon in patients with cryptococcal meningitis in advanced AIDS. His absolute CD4 count did not appreciably increase after ART initiation (Table 1), which may give a false impression that IRIS was not occurring. However, his CD4% did markedly increase from 1% to 6–7%, making the percentage, perhaps, a more sensitive marker for IRIS, as shown in prior studies.[43,44]

TABLE 1

Serum and CSF parameters at indicated time points before and after ART initiation

	Pre-ART initiation*					Post-ART initiation				
Date	October 15, 2017	October 21, 2017	October 24, 2017	October 26, 2017	October 28, 2017	February 9, 2018	June 11, 2018	June 22, 2018	June 27, 2018	August 29, 2018
CD4 (cells/μL)			< 20			40		35		46
CD4 (%)			1			6		7		6
LP OP (cm H_2O)	24	50	36	47	39	–	–	29	32	–
CSF WBC (per cumm)	2	5	3	0	12	96	72	187	127	1900
CSF neut (%)	3	12	5	–	0	21	25	65	52	74
CSF lymph (%)	61	65	39	–	43	70	67	25	34	16
CSF total protein (mg/dL)	36	34	27	33	28	620	620	620	620	620
CSF glucose (mg/dL)	13	17	20	19	24	10	35	41	39	10
CSF CrAg titer	1:2,560	1:2,560	1:2,560	1:2,560	1:2,560	1:2,560	1:2,560	1:2,560	–	1:2,560
C. neo. PCR	Positive	–	–	–	–	Negative	Negative	–	–	Negative
CSF Gram stain	Moderate *C. neo.*	Moderate *C. neo.*	Moderate *C. neo.*	Moderate *C. neo.*	Rare *C. neo.*	Moderate *C. neo.*	Negative	Negative	Negative	Negative
CSF fungal culture	*C. neo.*	Negative	*C. neo.*	–	*C. neo*	Negative	Negative	Negative	Negative	Negative

ART = anti-retroviral therapy; *C. neo* = *Cryptococcus neoformans*; CSF = cerebrospinal fluid; OP = opening pressure.
* Anti-retroviral therapy initiation November 9, 2017.

This case demonstrates that complications of C-IRIS can include cerebellar abscess and spinal involvement, the latter of which may occur without significant localizing symptoms. Distinguishing such manifestations from worsening cryptococcal infection or coinfection can be challenging, and biopsies of the affected areas may be warranted for definitive determination. The extremes in severity and time course of this case reinforces previous research on the benefit of delayed ART initiation for cryptococcal IRIS up to 10 weeks from the time of antifungal initiation, especially for patients with certain predictive factors of IRIS as mentioned earlier. An individual risk/benefit profile should be considered by the treating clinician, further adding to the complexity in caring for these often-challenging and gravely ill patients.

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