CASE REPORT

A paradoxical decline: intracranial lesions in two HIV-positive patients recovering from cryptococcal meningitis

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SUMMARY

Cryptococcal immune reconstitution inflammatory syndrome (C-IRIS) is an increasingly important manifestation among patients with HIV/AIDS, especially as the use of antiretroviral therapy (ART) is expanding worldwide. *Cryptococcus* and associated C-IRIS are common causes of meningitis. While intracranial lesions are common in HIV/AIDS, they are rarely due to cryptococcosis or C-IRIS. We describe two cases of paradoxical C-IRIS associated with the development of intracranial cryptococcomas in HIV/AIDS. Both patients had an initial episode of cryptococcal meningitis treated with antifungal therapy. At the time, they had initiated or modified ART with subsequent evidence of immune reconstitution. Two months later, they developed aseptic meningitis with intracranial lesions. After exhaustive work ups, both patients were diagnosed with paradoxical C-IRIS and biopsy confirmed intracranial cryptococcomas. We review the important clinical, diagnostic and therapeutic features of cryptococcomas associated with C-IRIS in HIV/AIDS.

BACKGROUND

In 2007, cryptococcal meningitis was estimated to annually affect nearly 1 million people with HIV, resulting in approximately 600 000 deaths.¹ With the advent of antiretroviral therapy (ART), cryptococcal immune reconstitution inflammatory syndrome (C-IRIS) is an increasingly recognised phenomenon manifested by either paradoxical or ART-associated C-IRIS.^{2–5}

In paradoxical C-IRIS, the most common subtype, antifungal therapy and initiation or modification of ART leads to improvement of cryptococcosis; immune reconstitution follows and is associated with clinical deterioration.^{2 6 7} ART-associated C-IRIS is a phenomenon among individuals who initiate ART, which subsequently reconstitutes the immune system and unmasks sub-clinical cryptococcosis.⁶

Aseptic meningitis is the most common central nervous system (CNS) manifestation of C-IRIS.⁶ Although intracranial cryptococcal abscesses (cryptococcomas) are occasionally observed among immunocompetent individuals with cryptococcal meningitis,⁸ case reports and small observational studies suggest that they are a very rare finding in HIV.^{6 7} Owing to this, and since there are many potential causes of intracranial lesions in individuals with AIDS,^{9–12} the diagnosis of cryptococcomas associated with C-IRIS is elusive.

In this report, we describe two cases of paradoxical C-IRIS associated with intracranial cryptococcomas in persons living with HIV, followed by a review of the most recent literature on the epidemiology, pathophysiology, diagnosis and treatment of cryptococcomas in HIV-positive individuals with C-IRIS.

CASE PRESENTATION

Patient 1

A 30-year-old man living with HIV presented with 2 weeks of headache, fever and neck stiffness. Four months earlier, he had been admitted to an outside hospital with cryptococcal meningitis confirmed by cerebrospinal fluid (CSF) cultures. His CD4 cell count was 6 cells/mm³ (1% of peripheral white cell counts (WCCs)). He had been diagnosed with HIV 3 years earlier in the setting of *Pneumocystis jirovecii* pneumonia. His CD4 cell count was 4 cells/mm³ and he was started on first-line ART. Owing to virological failure, he had been recently transitioned to second-line therapy. He was treated with amphotericin B and flucytosine and ultimately discharged on ART and oral fluconazole (400 mg daily).

He remained asymptomatic until 2 months later, when he represented with recurrence of cryptococcal meningitis confirmed by positive CSF cultures. His plasma CD4 cell count had increased to 79 cells/mm³ (4% of WCCs) with a now undetectable HIV viral load. He received fluconazole (400 mg daily) for cryptococcal meningitis and continued ART with resolution of symptoms.

Two months later, he presented to the university medical centre with 2 weeks of fever, night sweats, headache and increasing neck stiffness. He reported consistent use of fluconazole and ART. Additional medical history was significant for bipolar affective disorder, high-risk sexual behaviour and a remote history of injection drug use. On presentation, he was febrile with a temperature of 38.5°C, with otherwise normal vital signs. He was thin appearing with normal mental status. Neurological examination revealed meningismus, but the remainder of the physical examination was normal.

Patient 2

A 40-year-old man living with HIV was transferred to the university medical centre for evaluation and management of left frontotemporal lesions. He had been well until 3 months prior when he presented to an outside hospital with cryptococcal meningitis (CSF CrAg titre 1:320). Further work up revealed

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that he was HIV positive with a CD4 cell count of 18 cells/mm³ (5% of peripheral WCCs) and HIV viral load of 401 000 copies/mL. He was treated with liposomal amphotericin B (4 mg/kg intravenous daily) and flucytosine (25 mg/kg by mouth four times per day) for 4 weeks followed by fluconazole (800 mg daily). He was discharged on first-line ART.

He improved and was otherwise well until 2 weeks prior, when he experienced expressive aphasia followed by headache and right facial weakness. MRI of the head with contrast showed two rim-enhancing lesions of the left frontotemporal regions (figure 1B). He endorsed significant weight loss, but denied other constitutional symptoms. He reported adherence to fluconazole, ART and chemoprophylaxis with azithromycin and dapsone. He had a history of remote cocaine and methamphetamine use and was sexually active with women only.

INVESTIGATIONS

Patient 1

Head CT scan with contrast demonstrated multiple rim-enhancing lesions. CSF studies showed 64 white blood cells (WBCs) per mm³ (73% lymphocytes) and CrAg titre was 1:4. Plasma CD4 cell count was 157 cells/mm³ (7% of WCCs) and HIV viral load was undetectable. MRI of the brain revealed diffuse meningoencephalitis and multiple ring-enhancing lesions (figure 1A).

Serum Venereal Disease Research Laboratory test and toxoplasma immunoglobulins were negative. CSF *Coccidioides* serologies and toxoplasma PCR were also negative. All bacterial, fungal and mycobacterial cultures of the CSF and blood were sterile. Cytology markers for leukaemia and lymphoma were negative.

The patient experienced multiple seizures and underwent right temporal craniotomy with biopsy for definitive diagnosis. Bacterial, fungal and mycobacterial cultures of the specimen as well as Gram stain and acid-fast bacilli stain were negative. Pathology, however, revealed chronic vascular and perivascular inflammation of the pia and parenchyma with cryptococcal organisms, consistent with the diagnosis of a cryptococcoma (figure 2).

Patient 2

Lumbar puncture (LP) showed an opening pressure of 38 cm H₂O. CSF had 2 WBCs per mm³ with a CrAg titre of 1:64. Plasma CD4 cell count and viral load were 84 cells/mm³ (9% of peripheral WCCs) and 745 copies/mL, respectively.

Figure 1 (A) T2-weighted brain MRI of patient 1 with contrast demonstrating diffuse meningoencephalitis of the right caudate head and right temporal lobe with a central punctate focus of enhancement of the right caudate head (arrow), consistent with a 'target sign'. (B) T1-weighted brain MRI of patient 2 with contrast demonstrating two rim-enhancing lesions of the left frontotemporal regions with cystic, necrotic changes (arrows).

Serum toxoplasma immunoglobulins were negative as were CSF studies for JC virus PCR, toxoplasma IgG and PCR, Epstein-Barr virus PCR and flow cytometry for markers of leukaemia and lymphoma. Bacterial, fungal and mycobacterial cultures of the CSF were sterile. Chest CT scan identified three non-calcified pulmonary nodules up to 1.1 cm in the right upper lobe, consistent with possible pulmonary infection (figure 3).

The patient underwent craniotomy with biopsy of the left frontal lesions due to worsening headache and focal weakness. Bacterial and fungal cultures were negative. Pathology revealed marked acute and chronic inflammation of the brain parenchyma with rare, degenerated fragments resembling fungal forms consistent with a cryptococcoma.

DIFFERENTIAL DIAGNOSIS

Both patients had a history of AIDS-associated cryptococcal meningitis with initiation or modification of ART and presented with subacute meningeal inflammation associated with new intraparenchymal CNS lesions. The differential diagnosis included infectious aetiologies, such as toxoplasmosis, coccidioidomycosis, histoplasmosis, *Mycobacterium tuberculosis*, syphilis and, less likely, cytomegalovirus and JC virus. The recent history of cryptococcal infection was concerning for relapse. Non-infectious aetiologies, such as primary CNS lymphoma, were also considered. The initial work up failed to reveal a culpable infectious or malignant cause. Paradoxical C-IRIS, therefore, was thought to best explain the constellation of findings in the setting of recent cryptococcal meningitis treated with anti-fungal therapy and initiation or modification of ART. This suspicion was ultimately confirmed by biopsy and sterile cultures in both cases.

TREATMENT

Patient 1

The patient initially underwent re-induction with liposomal amphotericin B (3 mg/kg intravenous daily) and flucytosine (21 mg/kg by mouth four times per day) for a total 14-day course. He was ultimately transitioned to fluconazole (1200 mg daily) after induction resulted in flucytosine-associated

Figure 2 Biopsy of the pia mater revealing chronic vascular and perivascular inflammation as well as cryptococcal organisms (arrows).

Figure 3 CT of the chest of patient 2 revealing 1.1 cm non-calcified pulmonary nodule in the right upper lobe, suggestive of pulmonary infection (1 nodule marked by arrow).

transaminitis. Levetiracetam and fosphenytoin were started in the setting of seizures, and an external ventricular drain was placed due to evidence of hydrocephalus on repeat head CT scan. Prednisone (60 mg by mouth) was also initiated after completion of brain biopsy.

Patient 2

This patient initially underwent re-induction with liposomal amphotericin B (5 mg/kg intravenously daily) and flucytosine (25 mg/kg by mouth four times per day) for 6 weeks. Owing to elevated intracranial pressure, serial LPs were performed for pressure management and the patient was started on dexamethasone (4 mg by mouth three times per day). Levetiracetam was initiated in the setting of intermittent seizures.

OUTCOME AND FOLLOW-UP

Patient 1

The patient was discharged on a prednisone taper, phenytoin, fluconazole (1200 mg daily) and ART. Two weeks after discharge, his CD4 cell count was 71 cells/mm³ with an HIV viral load of 160 498 copies/mL in the setting of suspected medication non-adherence. He underwent head CT scan with contrast for recurrent headaches, which revealed calcification of the caudate head without evidence of ongoing cryptococcomas or other intracranial processes. LP was negative. Unfortunately, the patient was lost to follow-up and ultimately died in hospice care per his preference and that of his family.

Patient 2

The patient was continued on ART and completed 6 weeks of liposomal amphotericin B and flucytosine with improvement of symptoms. He subsequently transitioned to fluconazole consolidation therapy (800 mg daily) for a 6–18 month course. Two months after discharge, repeat LP, head MRI, plasma CD4 cell count and HIV viral load were significantly improved. He has since had no known recurrence of disease.

DISCUSSION

Cryptococcal meningitis is estimated to affect nearly 1 million persons living with HIV/AIDS annually and is responsible for over 600 000 deaths/year.¹ The incidence may be declining, however, as ART is scaled worldwide. C-IRIS is an increasingly common phenomenon that clinically manifests as either paradoxical or ART-associated C-IRIS.

A review of six studies (approximately 2000 patients) found that the incidence of ART-associated C-IRIS among people living with HIV (varying CD4 counts) was 0.2–1.6%. The same review, however, revealed that 8–49% of 598 patients with cryptococcosis developed paradoxical C-IRIS after starting ART. The most common manifestations were aseptic meningitis (74%), lymphadenopathy (11%) and pneumonitis (5%). Other manifestations of CNS disease included intracranial or spinal cryptococcomas. Overall mortality varies, with reports of 27–84% in parts of Africa to <20% in most of North America,⁶ though this is likely dependent on the availability of diagnostics, antifungal therapy and management of intracranial pressure.

The prevalence of intracranial cryptococcomas is largely unknown, but it is very infrequent in HIV-associated cryptococcal meningitis and C-IRIS. A retrospective Italian study examined 40 HIV patients and found one intracranial cryptococcoma in a total of five patients with C-IRIS.¹³ Other examples of intracranial cryptococcomas associated with C-IRIS are limited to only a few case reports.^{7 14 15} Cryptococcomas are better reported in the setting of cryptococcal meningitis, though wide variation in reported prevalence exists. Of patients with cryptococcal meningitis and HIV, 4.6–21% had intracranial lesions suggestive of cryptococcomas.^{8 16–18} However, since histological correlation was not made, these are likely overestimates, given the broad differential of intracranial lesions associated with HIV. Cryptococcomas may be more prevalent among immunocompetent hosts with cryptococcal meningitis,⁸ though further data are limited. Multiple studies suggest *Cryptococcus gattii* may cause a disproportionate number of pulmonary and CNS cryptococcomas, but the majority of lesions are still due to *C. neoformans*, given the much higher prevalence of this species.^{8 19 20}

In paradoxical C-IRIS, cryptococcal organisms are destroyed in the setting of antifungal therapy.^{6 7} In treatment-naïve individuals, initiation of ART leads to immune reconstitution, allowing immune cells to respond to antigens of inactivated cryptococcal organisms, resulting in the clinical manifestations of C-IRIS. A similar process also occurs in ART-associated C-IRIS,⁶ though cryptococcal species may still be alive since they have not been exposed to antifungal therapy.²¹ Thus, C-IRIS is likely the result of poor antigen clearance and lack of inflammation that subsequently recovers following ART.^{6 22} This may be further exacerbated by a predisposition to a dysregulated proinflammatory response.^{6 21 23} Restoration of CD4 cells may also trigger a reverse in the predominantly Th2 response towards a Th1 proinflammatory response.^{6 24–26} In C-IRIS, cryptococcomas may represent recovery of immune function at specific sites of infection, such as brain parenchyma, lymph nodes or lungs,¹⁴ as was suggested by the chest CT scan of patient 2 (figure 2).

A major challenge in establishing the diagnosis of cryptococcomas is distinguishing it from other intracranial lesions. Studies suggest that toxoplasmosis is the most common intracranial pathology in HIV, followed by primary CNS lymphoma.^{9–12} Other causes include coccidioidomycosis, histoplasmosis, *M. tuberculosis*, syphilis, cytomegalovirus and JC virus.

After non-cryptococcal infectious aetiologies and malignancy are excluded, it remains difficult to distinguish between paradoxical C-IRIS versus relapse of cryptococcal meningitis from suboptimal fungal therapy or low adherence.⁶ *C. neoformans* resistance must also be considered, though it is exceedingly rare.^{27–29} Of note, a higher proportion of *C. gattii*, an emerging cryptococcal infectious species, may be associated with antifungal resistance,³⁰ and should be considered in endemic areas.

Figure 4 Timeline of paradoxical C-IRIS after initial episode of cryptococcal meningitis followed by recovery of immune function (ART, antiretroviral therapy; CSF, cerebrospinal fluid; ICP, intracranial pressure; C-IRIS, cryptococcal immune reconstitution inflammatory syndrome).

In paradoxical C-IRIS, symptoms recur within 12 months of cryptococcosis treated with antifungal therapy and ART (either initiation or regime modification) (figure 4). Adherence to ART and antifungal therapy is essential, and virological response to ART is suggestive of the diagnosis. Common pathogens and malignancy must be excluded. CSF cultures should be negative for potential causative organisms, though cultures may occasionally remain positive for *Cryptococcus*. Culture positivity for *Cryptococcus* after 3 months, however, is more likely to reflect treatment failure. CSF CrAg titre and peripheral CD4 cell count are not particularly useful as a diagnostic criteria for C-IRIS. Other characteristic but non-diagnostic features include opening pressure ≥ 25 cm H₂O and elevated CSF WCCs.⁶

There are no definitive criteria for the diagnosis of intracranial cryptococcomas. Currently, available evidence is derived from case studies and expert opinion. Imaging may reveal small, ring-enhancing lesions,²⁵ though larger lesions (≥ 3 cm) are occasionally seen with or without evidence of hydrocephalus.^{31–32} Clinical and radiographic improvement occurs following antifungal therapy.^{7–15} In paradoxical C-IRIS, specimen cultures are classically sterile,^{6–7–13–15–25–33–34} but in cryptococcal meningitis, they frequently reveal viable organisms.^{31–35–37} Histological findings in paradoxical C-IRIS include the presence of inactive cryptococcal species or fungal elements, inflammation, granulomas and necrotic material.^{6–7–33–38–39}

A lack of data limits the therapeutic approach to treating C-IRIS and intracranial cryptococcomas.²⁵ Since the underlying pathology of C-IRIS is inflammatory, the primary aim is to minimise inflammation and alleviate intracranial pressure. According to Infectious Disease Society of America guidelines, 6 weeks of induction therapy is recommended with amphotericin B (0.7–1 mg/kg intravenous per day) or liposomal amphotericin B (3–4 mg/kg intravenous per day) plus flucytosine (25 mg/kg by mouth four times per day). Following induction therapy, consolidation and maintenance therapy with fluconazole (400–800 mg by mouth daily) is recommended for a minimum of 6 months, though 12–18 months is preferred and lifetime treatment may be indicated. Given the lack of evidence to support this practice and the potential toxicity associated with amphotericin, this practice is controversial. Mass effect and oedema should be treated with corticosteroids and a gradual taper. Larger, accessible lesions (≥ 3 cm) with mass effect may undergo open versus stereotactic debulking, which may also aid in tissue diagnosis. Elevated intracranial pressure should be relieved with serial therapeutic LP or the placement of a ventriculoperitoneal shunt.²⁵ There are no recommendations regarding whether

ART should be continued after the diagnosis of intracranial cryptococcomas in the setting of C-IRIS. Data regarding prevention of paradoxical C-IRIS are conflicting,^{2–4–25–40–44} but recent data have suggested delaying the initiation of ART until approximately 5 weeks after initial treatment for cryptococcal meningitis, particularly for those with low CSF WCCs.⁴⁵

Learning points

- ▶ Cryptococcal meningitis is estimated to affect nearly 1 million patients with HIV/AIDS annually and is responsible for up to 25% of all deaths in Africa due to AIDS.
- ▶ Paradoxical cryptococcal immune reconstitution inflammatory syndrome (C-IRIS) is an important and common occurrence following the initiation of ART in individuals with recent or subclinical cryptococcal meningitis, and may become increasingly common as the use of ART is expanding worldwide.
- ▶ Cryptococcomas are rare in persons living with HIV, but difficult to diagnosis due to challenges in distinguishing between it and more common intracranial lesions in the setting of AIDS.
- ▶ Therapy for cryptococcomas associated with cryptococcal meningitis or C-IRIS is similar to treatment for cryptococcal meningitis, but consists of a much longer duration and focuses extensively on minimising intracranial pressure through anti-inflammatory management, cerebrospinal fluid drainage and, occasionally, surgical intervention.

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