Paradoxical immune reconstitution inflammatory syndrome associated with previous *Cryptococcus neoformans* infection in an HIV-positive patient requiring neurosurgical intervention

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SUMMARY

Immune reconstitution inflammatory syndrome (IRIS) in HIV-1-infected patients is associated with an exaggerated inflammatory response against an opportunistic infection during highly active antiretroviral therapy. The only review on IRIS associated with *Criptococcus neoformans* reported 21 episodes including lymphadenitis, necrotizing pneumonitis, breast and cutaneous abscess, and cryptococcomas. To our knowledge this is the first report of IRIS associated with previous meningeal criptococcal infection which required neurosurgical intervention with placement of a ventriculo-peritoneal shunt to drain a CSF cyst formed by exclusion of the temporal horn of the right lateral ventricle. We demonstrate that this procedure is possible without complications such as cryptococcal dissemination into the peritoneum.

KEY WORDS: Immune reconstitution inflammatory syndrome, *Criptococcus neoformans*

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The use of HAART for the treatment of HIV infection may be associated with the development of a marked inflammatory response against either previously identified or subclinical infections (Shelburne *et al.,* 2002). The occurrence of inflammatory signs and symptoms after starting HAART has been termed "immune restoration disease" and "immune reconstitution inflammatory syndrome" (IRIS) (DeSimone *et al.,* 2000; Shelburne *et al.,* 2003). Case reports of IRIS associated with *Cryptococcus neoformans* infection have mainly involved culture-negative meningitis but also included inflammatory lymphadenitis, necrotizing pneumonitis, breast and cutaneous abscess and cryptococcomas (Breton *et al.,* 2002; Blanche *et al.,* 1998; Skiest *et al.,* 2005; Haddow *et al.,* 2008). Furthermore an interesting paper published in 2008 by Shuli Bonham defined "Paradoxical IRIS" as: a clinical recrudescence of a successfully treated infection, with symptomatic relapse despite microbiologic treatment success, antigen driven immune activation and sterile cultures, typically". Cultures are often negative, but this depends on the nature of the infection and the timing of the event. Though cultures are negative, histopathology stains, antigen, or DNA based testing are frequently positive (Bonham *et al.,* 2008).

In the absence of secondary prophylaxis or a reconstitution of their immune systems, AIDS patients infected with *C. neoformans* have high rates of relapse (Bozzette *et al.,* 1991). We describe a patient presenting paradoxical IRIS associated with previous *Cryptococcus neoformans* infection.

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The patient required neurosurgical intervention with placement of a ventricular peritoneal shunt to drain a CSF cyst formed exclusion of the temporal horn of the right lateral ventricle from the CSF circulation.

A 49-year-old woman with HIV infection known since 1991 had never undergone laboratory or clinical monitoring. She was admitted to our hospital for the first time in December 2004 with complaints of fever, oral candidiasis, headache, altered mental status and neck rigidity. Brain CT scan with contrast medium administration was negative for injury, so lumbar puncture was performed. *Cryptococcus neoformans* grew in the CSF culture, CSF glucose level was 0.5 g/l (30% compared to blood glucose level), CSF albumin level was 0.74 g/l, WBC: 20/mm^3. The cryptococcal antigen was isolated in the CSF and blood and her CD4 cell count was 19 (4%) and HIV viral load was 200000 copies/ml. She was treated with fluconazole 800 mg iv q24h and two weeks later antiretroviral therapy was begun with AZT, 3TC and EFV. After 4 weeks of fluconazole treatment the CSF was sterile, the CD4 cell count was 98 (11%) and HIV viral load was <50 copies/ml; the patient was discharged from hospital with HAART, primary prophylaxis against opportunistic pathogens (cotrimoxazole 1 tab po q24h, azithromycin 1200 mg po weekly) and fluconazole (200 mg po 24h). In November 2005 (11 months later) she was again admitted to our hospital for headache and altered mental status. Brain CT with contrast medium administration disclosed an inhomogeneous hypodense area involving the right temporal region with perilesional oedema and significant mass effect on the midline structures (the temporal horn of the right lateral ventricle was excluded from the CSF circulation) and another hyperdense area at the head of the left caudate nucleus (Figure 1). The HIV viral load was <50 copies/ml and CD4 cell count was 148/mm^3 (11%). In agreement with our neurosurgery colleagues we performed lumbar puncture because there was no real risk of herniation. The cryptococcal antigen was isolated in the CSF and blood. *Cryptococcus neoformans* did not grow in the CSF culture, CSF glucose level was 0.4 g/l (50% compared to blood glucose level), CSF albumin level was 1.2 g/l, WBC: 1/mm^3. Additional laboratory tests excluded toxoplasmosis, tuberculosis, bacterial

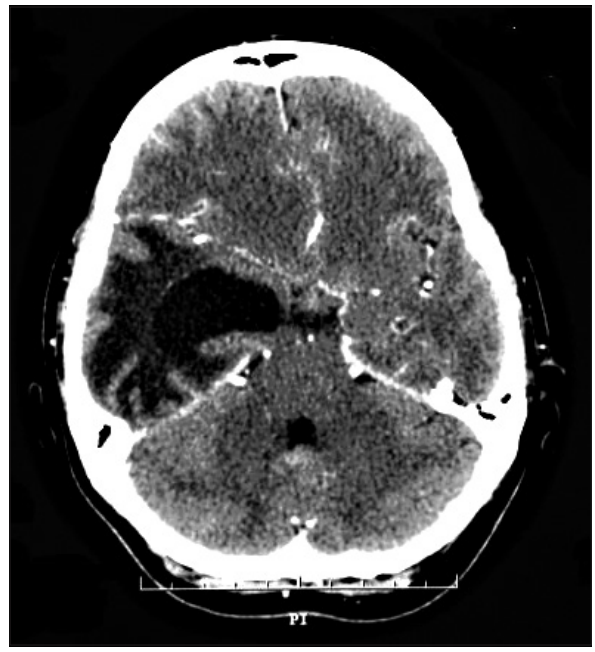

FIGURE 1

cerebral abscesses, syphilitic cerebral gummas and lymphoma. The patient underwent neurosurgical intervention positioning a Rickam intracavitary catheter with a subcutaneous reservoir in the temporal right region. The procedure was done using an intraoperative neuronavigator through a small temporal craniectomy. A ventriculo-peritoneal shunt was not inserted due to the danger of peritoneal cryptococcal dissemination. In the subsequent four weeks therapy liposomial amphotericin B (4mg/kg IV q24h), flucytosine (25 mg/kg po q6h), acetazolamide (2.5 mg/kg p.o q12h) and dexamethasone (0.15 mg/kg IV q6h) were administered. Because of intolerance HAART was changed to 3TC, ddI and ATV/r. During this period she received therapeutic Rickam subcutaneous reservoir punctures every three days with evacuation of 8-10 cc each time due to the high CSF opening pressures. After four weeks a new brain CT scan showed a worsening due to a further volumetric increase in the temporal horn of the right lateral ventricle and associated perilesional oedema. An obvious mass-effect on the brainstem was also noted, particularly in the right midbrain and ipsilateral subthalamic nucleus of the brain with evidence of subfalcine herniation caused by relocation of the midline structures which were displaced by

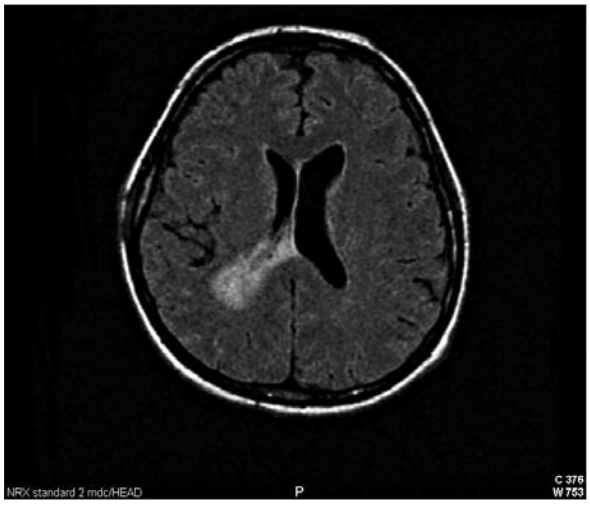

FIGURE 2

about 11 mm. Therefore the patient's endoventricular catheter was shortened and a medium pressure valve connected and positioned in the right temporal region, with placement of a peritoneal catheter type reflux control in the right paraumbilical region. The postoperative brain CT showed a complete reduction of the CSF fluid collection and better placement of the endoventricular catheter with no signs or symptoms of peritoneal cryptococcal dissemination. This improvement was confirmed by magnetic resonance imaging performed 10 days later (Figure 2). The patient was discharged with the same antiretroviral therapy and with antifungal therapy with fluconazole (200 mg po 24q). The HIV viral load remained <50 copies/ml and CD4 cell count was 182/mm^3 (10%). Thirty months have passed and the patient has remained in good health without requiring hospital admission. The HIV viral load remained <50 copies/ml and CD4 cell count was 503 mm^3 (20%).Our patient presented paradoxical IRIS associated with disseminated *Cryptococcus neoformans* infection arising 11 months after the beginning of HAART. Medical management with anti-inflammatory steroids and antifungal therapy failed so a neurosurgical procedure was performed with insertion of a Rickam intracavitary catheter with a subcutaneous reservoir in the temporal right region because of the danger of peritoneal cryptococcal dissemination. This procedure failed to reduce the intracranial hypertension even with therapeutic Rickam subcutaneous reservoir punctures every three days with evacuation of 8-10 cc each time. At this point the only way to resolve the serious cerebral complication was to position a ventriculo-peritoneal catheter type reflux control in the right paraumbilical region. There were no postoperative complications. Thirty months after the second intervention, the patient continues her HAART and fluconazole (100 mg) therapy. Her T CD4+ lymphocyte count was 503 mm^3 (20%) and HIV-RNA was <50 copies/ml. The last brain CT scan performed a few months ago showed a normal CSF circulation with the ventricular peritoneal shunt (VPS). This case report demonstrates that we should not be afraid to place a VPS in a patient with previous cryptococcal meningitis after 15 months of antifungal therapy and with sterile CSF.

Abbreviations
CT: computed tomography, CSF: cerebrospinal fluid, WBC: white blood cells, AZT: zidovudine, 3TC: lamivudine, EFV: efavirenz, ATV/r: atazanavir/ritonavir, ddI: didanosine, po: oral, iv: intravenous, VPS: ventriculo-peritoneal shunt

Consent
Written informed consent was obtained from the patient before publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests The authors declare they have no competing interests.

Authors' contributions
CB, MB, MP, LT, GV and FC made the diagnosis and were involved in subsequent management.
MN is the consultant neurosurgeon who performed the two operations.

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