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Return of meningeal symptoms in a patient treated for cryptococcal meningitis

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Sirs: A 28-year-old Guinese man was admitted to our hospital with a 3-week history of severe headache, vomiting and fever. Ten months earlier he was diagnosed with AIDS. The presenting AIDS-defining illness then, was disseminated cryptococcosis: *Cryptococcus neoformans* had been recovered from CSF, bronchoalveolar washings, and blood. Standard treatment of CM with amphotericin B and flucytosine followed by fluconazole [1] resulted in clinical and microbiological cure. The patient had been taking fluconazole 200 mg QD PO as secondary prophylaxis since. After successful treatment of CM, HAART was initiated. This preceded admission by 320 days. The CD4 cell count rose from 0 to 120 cells/μl and HIV1-RNA to undetectable levels (<50 copies/ml). There was no reason to doubt compliance to fluconazole prophylaxis.

On examination an ill-looking man was seen, with low-grade pyrexia and stable haemodynamics. He was alert and cooperative, with no signs of meningism or mental confusion. Neurological examination and further physical examination revealed no abnormalities. Laboratory results were unremarkable. Brain CT-scan without contrast did not show any mass lesions, or hydrocephalus. Clear CSF was obtained, opening pressure was >50 cm H_2O. CSF contained 0.59 g/l protein, 3.0 mmol/l glucose (at a serum glucose concentration of 5.1 mmol/l) and 272×10^6/l leukocytes, mainly monocytic. It tested positive for cryptococcal antigen. Considering relapse CM, treatment appropriate to this diagnosis was initiated (amphotericin B 1 mg/kg intravenously per day and flucytosine 100 mg/kg/d PO).

After 1 week his headache and malaise had not improved. Both stain and culture were negative for *Cryptococcus neoformans*. Cryptococcal antigen titers were found to be low: 1:16 in serum and 1:4 in CSF. Therefore the diagnosis was revised to *Cryptococcus neoformans*-related immune reconstitution inflammatory syndrome (IRIS).

Antifungal treatment was discontinued and prednisone was prescribed (1 mg/kg/day IV).

One more lumbar puncture was needed for temporary relief of symptoms due to raised CSF pressure. Our patient made a dramatic recovery and was discharged from hospital 3 days later, symptom-free. Prednisone was tapered in 4 months.

IRIS can manifest itself as a latent infection unmasked by immune reconstitution, or as sterile inflammation in response to persisting antigens of an infection already treated. Therefore, latent infection should be ruled out in patients commencing antiretroviral therapy.

Key to the diagnosis of cryptococcal-related IRIS in patients treated with HAART is the absence of fungal cells in all cultures. Cryptococcal antigen in blood or CSF of HIV-infected patients previously treated for CM, is a poor marker of infection [2]. Shelburne et al. found low cryptococcal antigen titres of value in discriminating cryptococcal-related IRIS from CM in a retrospective cohort study [3]. Other factors predictive of cryptococcal-related IRIS are a higher white blood cell count in CSF, higher CSF glucose and a higher CD4 cell count. . Lumbar puncture opening pressure was significantly higher in the IRIS group. These findings reflect the inflammatory nature of the syndrome due to immune restoration. The presence of the following risk factors for IRIS support the diagnosis in this case: a rise in CD4 cell count, a decrease in viral load, and compliance with a secondary prophylactic treatment regime of fluconazole.

For treatment of the aseptic meningitis, anti-inflammatory drugs are a logical choice. Short-term corticosteroid administration was shown to be safe and well tolerated in patients who are receiving antiretroviral treatment [4]. It proved beneficial to prevent paradoxical reactions in tuberculous meningitis [5] and in other described cases of cryptococcal meningitis associated IRIS [6]. At a dose of 60 mg prednisone IV,

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our patient responded well. However, studies defining the role of corticosteroids in IRIS are urgently needed. The use of corticosteroids was demonstrated to be harmful in CM or cryptococcoma [7]. Therefore, exclusion of active cryptococcal disease remains the most important step in managing *Cryptococcus neoformans*—related IRIS.

Guidelines for the treatment of CM recommend daily lumbar punctures in all patients with initially elevated opening pressures (>25 cm H_2O) until the pressure is adequately controlled [1, 7]. Since the mechanism for increased intracranial pressure is thought to be the same in CM and cryptococcal IRIS, adherence to these guidelines seems prudent.

Concluding, the HIV-positive patient treated with highly active antiretroviral therapy and returning meningeal symptoms after treatment for cryptococcal meningitis is diagnostically challenging. Distinguishing between *Cryptococcus neoformans*—related IRIS and active cryptococcal disease as two different clinical entities is crucial.

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