Lung cryptococcosis in a treated HIV-1-infected patient with suppressed viral load and past disseminated cryptococcosis: relapse or late IRIS?

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Sir,

Early initiation of combination antiretroviral therapy (cART) in AIDS presenters reduces mortality, but seems to worsen survival in cryptococcal meningitis, probably because of immune reconstitution inflammatory syndrome (IRIS), with fatal cerebral complications. Timing of cART initiation is not clearly defined, ranging from 2 to 10 weeks. Strategies aiming at reducing the risk of IRIS are lacking.

We report a case of pulmonary and mediastinal lymph node cryptococcosis occurring late after immune reconstitution and fluconazole prophylaxis discontinuation in a patient with previous AIDS-presenting disseminated/meningeal cryptococcosis.

A Pakistani man in his mid-forties presented with AIDS and disseminated/meningeal cryptococcosis (CD4 count 16 cells/mm³, plasma HIV-1 RNA 191 100 copies/mL and blood and CSF cultures positive for Cryptococcus neoformans). He was treated with a standard amphotericin B course, followed by secondary fluconazole prophylaxis; cART was introduced 1 month later with co-formulated zidovudine/lamivudine and lopinavir/ritonavir, achieving virological suppression and immune restoration (Figure 1). The nucleoside backbone was switched to tenofovir/emtricitabine after 1 month, because of bone marrow toxicity (haemoglobin 8.3 g/dL, white blood cells 1910/mm³ and neutrophils 390/mm³).

Lumbar puncture performed at baseline and after 3 months showed a decrease in HIV-1 RNA in the CSF, although the CSF/plasma viral load ratio did not decrease accordingly (2867/191 100 copies/mL = 0.02 at baseline versus 123/314 copies/mL = 0.39 at month 3). In the absence of new clinical symptoms, cryptococcal soluble antigen titre in the CSF increased from 1:512 at baseline to 1:2048 at month 3, but culture was negative; no other neurotropic viruses (herpes viruses 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein–Barr virus or JC virus) were detected by PCR.

A viral blip at month 5 (HIV-1 RNA 1170 copies/mL) was not confirmed (HIV-1 RNA <50 copies/mL after 2 weeks); lopinavir/ritonavir trough concentrations were adequate (5931 ng/dL/306 ng/dL).

Fluconazole prophylaxis was stopped after 8 months of cART and CD4 count >200 cells/mm³, according to guidelines.

Nine months later, the patient presented with cough, malaise, weight loss, anorexia and severe dysphagia. Endoscopy revealed extrinsic oesophageal compression. A whole-body CT scan showed enlargement of mediastinal lymph nodes and bilateral apical pulmonary solid infiltrations. Sputum smears were negative for acid-fast bacilli (even by PCR) and other microbes; T cell

Figure 1. Viral load (filled triangles) and CD4 T cell count (open squares) variation during patient treatment history. Grey-shaded boxes represent serum and CSF cryptococcal soluble antigen titres over time, expressed in weeks (W) after the start of cART. T0 corresponds to the first presentation, 1 month earlier.
interferon-γ release assay (Quantiferon®) was negative. Trans-branched fine-needle aspirate of the mediastinal lymph nodes and CT-guided fine-needle pulmonary aspirate, after routine Papanicolaou and May–Grünewald–Giemsa staining, surprisingly revealed the presence of yeast spores whose shapes were suggestive of cryptococci. *C. neoformans* was not detected in the CSF at ink coloration on a new lumbar puncture; the cryptococcal soluble antigen was negative in the CSF, although slightly positive (1:32) in the serum. CSF HIV-1 RNA was 585 copies/mL. Pending culture results, despite initial spontaneous clinical improvement without any added treatment (including steroids), fluconazole treatment of pulmonary cryptococcosis was started at 400 mg, and progressive clinical improvement was observed. Eventually, cultures of both fine-needle aspirate and CSF were negative.

This case raises several clinical management-related issues. Should it be considered relapse or late IRIS? Should fluconazole prophylaxis have been maintained for longer? Could a cART with a higher penetration coefficient have reduced the risk of persistent prophylaxis have been maintained for longer? Could a cART with a higher penetration coefficient 13 could have factors, clinicians should be aware of unusual cryptococcal finding, revealing a treatable condition. Lacking predictive work-up led to the discovery of an unexpected pathological presenting cryptococcal IRIS. The aggressive diagnostic result in better CSF viral control.

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