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Meningeal Cryptococcosis associated with Immune Reconstitution Inflammatory Syndrome (IRIS)

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Identification of authors' responsibility and contribution

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Abstract

Cryptococcosis in the context of HIV infection is a challenge for emergency healthcare staff receiving newly diagnosed patients with clinical debut of HIV infection or patients who may develop cryptococcosis due to immune reconstitution inflammatory syndrome (IRIS). A case of cryptococcal meningoencephalitis associated with IRIS in an HIV patient is presented, detailing the empirical management, diagnosis and evolution with targeted therapy.

Keywords: Cryptococcosis; Cryptococcus neoformans; HIV; AIDS;

Criptococosis meníngea asociada al síndrome inflamatorio de reconstitución inmunitaria (IRIS)

Resumen

La criptococosis en el contexto de la infección por el VIH es un reto para el personal sanitario de urgencias que recibe a pacientes recién diagnosticados con debut clínico de infección por el VIH o a pacientes que pueden desarrollar criptococosis debido al síndrome inflamatorio de reconstitución inmunitaria (SIRI). Se presenta un caso de meningoencefalitis criptocócica asociada a SIRI en un paciente con VIH, detallando el manejo empírico, el diagnóstico y la evolución con terapia dirigida.

Palabras clave: *Criptococosis; Cryptococcus neoformans; VIH; SIDA.*

Introducción

Opportunistic infections (OIs) are a challenge for physicians caring for HIV/AIDS patients. *Cryptococcus* species are characterised as mesophilic microorganisms (organisms whose optimum growth temperature is between 20-45°C), aerobes closely related to the yeast fungi used in bread making, found in trees and soil contaminated with bird faeces, growing as yeast-like cells of approximately 5 µm in diameter, characteristic of this genus is the polysaccharide capsule, which is produced by conditions that mimic human physiology (including high CO2 levels, low iron, neutral/alkaline pH and serum), as well as using phenolic substrates (dopamine) for melanin production that enhances the survival of these microorganisms in the host, which distinguishes it from other pathogenic yeasts (1).

Their main entry point is the airway by means of dried yeasts or spores, causing primary pulmonary infections, which can avoid the cough reflex and mucociliary clearance and penetrate deeply into the alveolar spaces thanks to their small size (1,2).

Cryptococcus neoformans is one of the members most commonly linked to meningoencephalitis in cases of immunosuppression, such as in HIV patients (3). Disseminated cryptococcosis (especially meningoencephalitis) has been associated with IRIS, at least 7 reports in the last 5 years and 14 in the last 10 years, according to a search in Pubmed with the terms mesh (Meningeal Cryptococcosis) and (Immune Reconstitution Inflammatory Syndrome) linked to the Boolean operator AND.

Case Report

History

Male patient aged 52 years with a history of HIV infection, cd4 count 59 cels/mL as of August 2019, viral load study could not be performed in the last control, so the treating physician started a scheme with AZT 300mg + ABC 600mg + EFV 600 mg in the last assessment in October 2019.

Current illness

The patient was admitted to the emergency department after presenting over a 2-week period with unquantified, intermittent thermal rise, high-intensity (10/10) holocranial headache that was unresponsive to analgesics, altered sensory function, irritability and agitation, associated with diarrheal stools that had spontaneously subsided, and bilaterally impaired hearing. A sample for bacterial and fungal culture was taken due to the patient's history of HIV.

Physical examination

On neurological examination, the patient was alert, confused, without involvement of cranial nerves, with no signs of motor or sensory focalization, with mild neck rigor (compatible with meningismus), with coordination and walking not evaluable. The rest of the physical examination revealed no remarkable alterations.

Complementary tests

With neurological authorisation, the patient underwent lumbar puncture with findings of hypoglycorrhachia 30 mg/dl, predominance of mononuclear cells 84%, hyperproteinorrachia 1575, LDH 28 U/ul, empirical treatment with Acyclovir was indicated while awaiting microbiological results.

The results on the 5th day after admission showed positive blood cultures of right and left arms, aerobes and fungi, *Cryptococcus neoformans* microorganism together with CSF. *Cryptococcus neoformans* with the fungigram (table 1).

Evolution

With CSF cytochemical results, empirical treatment with TMP/SMX was indicated at doses for meningeal toxoplasmosis, and Acyclovir; 48 hours later with preliminary results of encapsulated yeasts (highly compatible with *Cryptococcus* spp.), therefore a regimen with amphotericin B deoxycholate and TMP/SMX was added at a prophylaxis dose for pneumocystosis.

Once the patient completed the prescribed amphotericin B deoxycholate for a 10 days regimen, was re-evaluated, thus a rotation of the antifungal regimen to fluconazole. 48 hours after beginning the fluconazole regimen, the headache reappeared with moderate intensity, so it was indicated to maintain the fluconazole and restart amphotericin b for 7 more days. In the follow-up, once the 7-day scheme of amphotericin b combined with fluconazole was completed, in addition to the antituberculosis scheme, clinical improvement was observed in the patient, so it was indicated to maintain the prophylaxis of pneumocystis and the consolidation phase of cryptococcosis.

Diagnosis

After 24 days of hospitalization, the patient was released with the indication to maintain the antituberculosis regimen at the nearest clinic and was referred to the comprehensive care unit where he usually attends for the continuation of his HAART, with the diagnosis of Cryptococcosis due to IRIS.

Ethical aspects

For the presentation of this case, the patient's authorisation was sought through written informed consent for the use of data from the clinical history, laboratory results and radiological images.

Discussion and conclusion

C. neoformans differs from other yeasts by its ability to assimilate urea and by having phenoloxidase enzymes in its membrane, which allow it to transform phenolic compounds into melanin (4). Cryptococcosis as an OI has been linked to states of severe immunosuppression, usually evidencing CD4 counts <100 cells (5,6). Immune reconstitution inflammatory syndrome was first described in patients with Mycobacterium avium lymphadenitis concomitant with the recovery of the immune response associated with AIDS treatment (7). SIRI is more likely to occur in patients with CD4 <200 cells/mm^3 (8).

Cryptococcosis related to IRIS is found in 19.5% of HIV patients with OIs or who meet the definition of AIDS (9). It follows from the above that Cryptococcus screening is recommended for adolescents and adults, prior to the onset or resumption of HAART, or the change of scheme from first to second line (10), being complications of cryptococcosis, hydrocephalus, increased intracranial pressure, systemic inflammation, cerebral venous thrombosis or infectious vasculitis which can causes ischemic stroke, and lead to increase morbidity and mortality amongst HIV patients (8,11).

Differential diagnosis with tuberculosis and atypical mycobacteria (in the presence of cavitations) should be made in the initial pulmonary infection, which may manifest with cough and dyspnoea, the presence of pulmonary nodules (discard presence of colessional to Kaposi's sarcoma), pleural effusion, parenchymal infiltrates (alveolar occupation and patterned ground glass opacity) and hilary lymphadenopathies neumocistosis and histoplasmosis in HIV/AIDS patients (5,6,12).

However, asymptomatic cases may also exist, hence the importance of any case of BIH infection with subacute or chronic headache, with CD4 depletion should be investigated for cryptococcal meningitis (4). Cases of autopsies with evidence of dissemination to various organs by these micro-organisms have been mentioned (13). Cases of cryptococcosis in bone marrow have also been reported (14).

Microbiological isolation from bronchioalveolar lavage, antigen tests, blood cultures, Indian ink or negative stain form CSF or urine, fine-needle aspiration cytology of lymph node or next-generation sequencing (mNGS), can be employed to establish the diagnosis by the presence of *Cryptococcus* (12,15).

Liposomal amphotericin B is recommended for induction therapy, with deoxycholate as an alternative, followed by 10-12 weeks of maintenance therapy with fluconazole (4,5,12–14,16).

Cryptococcal meningitis is a common disease and cause of death among patients with HIV infection, which is why it is so important to diagnose and treat it promptly; there are case reports of this disease associated with immune reconstitution secondary to antiretroviral therapy (HAART), the most frequent associated symptoms are headache and thermal elevation, with its predominant

presentation in patients with CD4+ cell counts below 100 cells, although cases have also been documented with higher values, and even among immunocompetent patients (10,15,17). The most common species associated with AIDS is *C. neoformans* (1,10,12–14,17).

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