Case Report

Candida parapsilosis meningitis as the first manifestation of AIDS: case report

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Candida meningitis is a rare condition that occurs more frequently in premature infants, immunocompromised patients or patients after neurosurgery. We describe a case of a previously healthy 41-year-old man with *Candida parapsilosis* meningitis associated with oropharyngeal candidiasis as the first manifestation of AIDS.

Introduction

Candida species represent the fourth most common cause of nosocomial bloodstream infections in Brazil (Colombo *et al.*, 2006), as well as the single most frequent cause of opportunistic fungal infections worldwide (Rueping *et al.*, 2009; Falagas *et al.*, 2010). The most frequently isolated pathogenic *Candida* species are *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. lusitaniae* and *C. glabrata* (Colombo *et al.*, 2006; Falagas *et al.*, 2010). Invasive candidiasis has a significant impact on patient outcome. In one study, it was estimated that the mortality attributable to invasive candidiasis is as high as 49 % (Gudlaugsson *et al.*, 2003).

The most frequently implicated risk factors for candidiasis include the use of broad-spectrum antibacterial agents, use of central venous catheters, receipt of parenteral nutrition, neutropenia, use of implantable prosthetic devices, receipt of immunosuppressive agents and AIDS (de Repentigny *et al.*, 2004; Pappas *et al.*, 2009). Candidiasis is the most frequent opportunistic fungal infection among patients infected with human immunodeficiency virus (HIV), and it has been estimated that more than 90 % of HIV-infected patients develop this often debilitating infection at some time during the progression of their disease, although the incidence of this disease in HIV infection has been significantly reduced since the introduction of highly active antiretroviral therapy (de Repentigny *et al.*, 2004).

In rare cases, *Candida* species infect parenchymal brain tissue or meninges, as a complication of haematogenously disseminated candidiasis, especially in immunocompromised patients (Scully *et al.*, 2008). Approximately 50 % of patients with *Candida* meningitis have had disseminated disease affecting other organs (Lipton *et al.*, 1984). *C. parapsilosis* can be part of the human microbiota and it is a very rare cause of meningitis, usually associated with previous neurosurgery or the presence of a central nervous system catheter (Bagheri *et al.*, 2010).

Despite the frequency of oesophageal candidiasis in AIDS patients as the first manifestation or as a complication during the clinical course of the disease, candidiasis of the central nervous system has not been described as the primary manifestation of the syndrome to our knowledge. This case report describes the occurrence of a *C. parapsilosis* infection in the central nervous system, an unusual opportunistic disease, at the onset of AIDS.

Case report

A 41-year-old man, previously healthy and without any prior history of hospitalization, was admitted with an intense holocranial headache, which began 15 days before his admission, associated with multiple episodes of vomiting during this period and recurrent high fever. One day before admission he noticed paresthesia in his right fingers. On physical examination, left facial palsy and neck stiffness with meningeal irritation signs (Kernig and

Abbreviation: CSF, cerebrospinal fluid.

Brudzinski) were noted. The patient also had several whitish plaques in the oral cavity, consistent with severe oropharyngeal candidiasis. Cardiopulmonary auscultation and abdominal examination were normal.

Complete blood count showed normal levels of haemoglobin and platelets. There was leukopenia with 2.930 cells (ml blood)$^{-1}$ (normal range: 4000–10 000), with a severe lymphopenia of 279 lymphocytes (ml blood)$^{-1}$ (normal range: 800–4500). Two blood samples for blood cultures were collected and tested negative. HIV serological tests (ELISA and Western blot) were positive. Because meningitis was suspected, the patient underwent lumbar puncture. The cerebrospinal fluid (CSF) was clear in appearance, with transparent supernatant and fast drip, which reflects increased intracranial pressure. There were 10 white blood cells ml^{-1} (43 % lymphocytes, 2 % monocytes and 55 % neutrophils), and only one red blood cell ml^{-1} was observed. The glucose concentration was 52 mg dl^{-1} (lower than normal) and protein levels were elevated at a concentration of 72 mg dl^{-1} (normal: 15–45 mg dl^{-1}). The search for acid–alcohol-resistant bacilli using the Ziehl–Neelsen method and the search for *Cryptococcus* species using China ink were negative. Under microscopic examination using Gram staining, oval yeast blastoconidia without capsules were found, many of which presented budding cells.

The treatment was initiated with amphotericin B (1 mg kg^{-1}), with a maximum dose of 50 mg per day. The patient's general condition worsened, with signs of respiratory failure, indicating the need for intensive care. Four days after admission and after a cumulative dose of 100 mg amphotericin B without improvement, the patient, while in the intensive care unit, developed irreversible cardiopulmonary arrest and died.

The CSF culture showed growth of creamy and smooth white colonies. Under microscopic examination, samples of colonies were characterized as oval blastoconidia, without capsules. Phenotypic tests were performed to identify the fungus, such as melanin production, urease production, growth on chromogenic medium (HiCrome *Candida* Differential Agar; HiMedia), sugar assimilation test and micromorphological analysis of fungal elements (Brito *et al.*, 2009; Sidrim *et al.*, 2010). The results for these tests were compatible with *C. parapsilosis*.

The confirmation of phenotypical identification was performed using PCR–agarose gel electrophoresis. The target for amplification was the 5.8S–28S rDNA region, by using the primers ITS3 (5′-GCATCGATGAAGAAC-GCAGC-3′) and ITS4 (5′-TCCTCCGCTTATTGATA-TGC-3′) (Fujita *et al.*, 2001; Brito *et al.*, 2009) (Fig. 1).

Finally, susceptibility of this isolate to classical antifungal drugs was determined through a broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI, 2002) and Sidrim *et al.* (2010). The MICs obtained for amphotericin B, fluconazole and caspofungin were 0.25, 1 and 0.5 µg ml^{-1}, respectively.
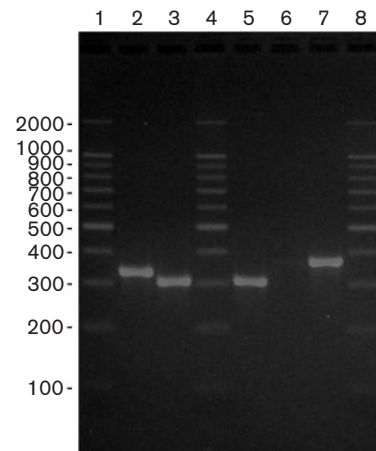

Fig. 1. Amplification of ITS3 and ITS4 regions by PCR–agarose gel electrophoresis. Lanes: 1, 4 and 8, 100 bp DNA ladder; 2, *Candida albicans* ATCC 10231; 3, *Candida parapsilosis* ATCC 22.019; 5, tested sample; 6, negative control; 7, *Cryptococcus neoformans* var. *grubii*.

Discussion

The increasing incidence of infection with HIV, the use of therapeutic modalities for advanced life support and certain surgical procedures, such as organ transplantation and the implantation of prosthetic devices, are important factors that have contributed to the expanding incidence of *Candida* infections (Pappas *et al.*, 2009). In recent decades, since the establishment of the AIDS epidemic, infections with *Candida* species have shown greater relevance and impact, especially in individuals with CD4 counts below 200 cells ml^{-1} (Chidzonga *et al.*, 2008).

The patient in this study presented with chronic meningitis caused by *C. parapsilosis*. This case report is justified by the rarity of this diagnosis. Meningitis caused by any *Candida* species had not been reported as the first manifestation of immunosuppression caused by HIV, despite the prevalence of oesophageal candidiasis in AIDS patients as a complication during the clinical course of the disease.

Certain infectious or non-infectious diseases (neoplasia, Behcet's disease, sarcoidosis, lupus erythematosus) can cause chronic meningitis. In any of the causes, signs and symptoms of meningoencephalitis are present, such as fever, headache, lethargy, confusion, nausea, vomiting and neck stiffness, usually with more than 2 weeks of evolution (Koski & Van Loo, 2010). These signs and symptoms were seen in the patient reported in this article.

Other causes of chronic infectious meningitis are much more common than candidiasis. *Mycobacterium tuberculosis* is a frequent infectious cause of chronic meningitis in immunocompetent patients, but in immunocompromised individuals, especially during the AIDS era, *Cryptococcus* species have been the most frequent cause. Other micro-organisms that cause chronic meningitis are

Treponema pallidum, *Coccidioides* species, *Histoplasma capsulatum* and *Sporothrix shenckii* (Scully *et al.*, 2008; Andreu-Ballester *et al.*, 2010).

Candida meningitis is rare and often associated with widely disseminated disease. It is related to a poor outcome and its risk factors are similar to those for candidaemia, such as prolonged antimicrobial therapy, indwelling venous catheters, parenteral nutrition, corticosteroid use, recent intra-abdominal surgery and intravenous drug abuse. Ventricular catheters have also been specifically associated with meningitis (Colombo *et al.*, 2006; Scully *et al.*, 2008). The patient in the study had signs of immunosuppression by HIV (severe lymphopenia), and lesions consistent with oropharyngeal candidiasis, a possible source of dissemination.

CSF findings were consistent with those reported in the literature. The CSF is frequently abnormal, usually showing pleocytosis, with a predominance of lymphocytes, along with hypoglycorrhachia and hyperproteinorrhachia. Gram staining frequently reveals yeast blastoconidia in smears, and CSF culture is usually diagnostic (Cohen-Wolkowiez *et al.*, 2007).

The patient reported in this study showed clinical signs of chronic meningitis. The first diagnostic hypotheses were cryptococcal meningitis or tuberculosis of the central nervous system because of the prevalence of these diseases. Positive serology for HIV increased the clinical suspicion of neural cryptococcosis. However, direct examination of the CSF, using China ink, was negative for the presence of fungal structures, and laboratory diagnosis depended on the microscopic evaluation of Gram-stained smears, when some structures seen were suggestive of the genus *Candida*. The culture for *Candida* was confirmed and subsequent species identification was performed.

The patient was healthy until the onset of symptoms consistent with meningitis and, after worsening of fever and headache and the appearance of whitish plaques in the oropharynx, he was taken to the hospital emergency room for investigation. The HIV test had strengthened the hypothesis of a fungal aetiology, and treatment with amphotericin B was started empirically for cryptococcosis. The isolated pathogen, however, was *C. parapsilosis*, and even with the use of an adequate therapeutic regimen, as the drug of choice for candidiasis of the central nervous system is also amphotericin B, the patient progressed to death, showing the gravity of such an opportunistic infection.

Although meningitis due to *C. parapsilosis* has been previously described in HIV infection (Baradkar *et al.*, 2008), this report demonstrates a primary mode of involvement of the central nervous system, since the patient had not shown any sign of prior opportunistic infection. This report describes a patient with a rare opportunistic disease during immunosuppression, which had not been described before to our knowledge. The appearance of meningeal candidiasis associated with oropharyngeal candi-

diasis in HIV-infected patients shows that the opportunistic nature of the pathogen allows a wide possibility of clinical manifestations, with increasing number of atypical cases. Although diagnostic hypotheses are an important tool for empirical treatment, it is important to confirm the specific aetiological agent. Thus, treatment can be more specific and directed to the disease and epidemiological characteristics can be better defined.

Acknowledgements

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