Cutaneous manifestation of cryptococcosis in a patient with acquired immunodeficiency syndrome (AIDS) - a case report

Manifestação cutânea da criptococose em paciente com síndrome da imunodeficiência adquirida (SIDA) - relato de caso

Amanda Almeida Albuquerque [1], Vitor Laerte Pinto Júnior [2], Márcia dos Santos Lazéra [3]

Resumo

A criptococose é uma infecção fúngica causada pelo agente encapsulado C*ryptococcus neoformans*, sendo a variante *gattii* responsável pela infecção em imunocompetentes e a variante *grubii* pela infecção em imunodeprimidos. Infecções por *C. neoformans* têm sido cada vez mais reconhecidas como uma ameaça significativa para a saúde das populações imunocomprometidas em todo o mundo, especialmente em indivíduos com AIDS. O agente é adquirido por inalação e dissemina-se por via hematogênica atingindo o sistema nervoso central (SNC), a pele, entre outros sistemas. Manifestações cutâneas ocorrem em 10% a 15% de todos os casos de criptococose sistêmica e é frequentemente associada com infecção sistêmica. Nesse relato, descrevemos um caso de um paciente de 28 anos, soropositivo para vírus da imunodeficiência humana (HIV), em que o acentuado envolvimento cutâneo fornece a suspeita clínica de criptococose disseminada, confirmada pelas análises do líquido cefalorraquidiano e do histopatológico da lesão. Apesar do reconhecimento e tratamento correto da micose, o paciente morreu após três dias de permanência no hospital, o que reforça a gravidade dessa condição e a necessidade da suspeita clínica na presença de lesões cutâneas típicas.

Palavras chave: Criptococose, AIDS, Anfotericina B.

Abstract

Cryptococcosis is a fungal infection caused by *Cryptococcus neoformans* encapsulated agent, being the variant *gattii* responsible for infection in immunocompetents and the variants *grubii* for infection in immunodeficients. *C. neoformans* infection have been increasingly recognized as a significant threat to the health of immune compromised populations throughout the world, especially in individuals with AIDS. The agent is acquired by inhalation the disease spreads through the hematogenic way affecting the central nervous system (CNS), skin, among other systems. Cutaneous manifestations occur in 10-15% of all cases of systemic cryptococcosis and is often associated with systemic infection. In this report we describe a case of a patient of 28 years, with human immunodeficiency virus (HIV) positive, in which markedly cutaneous involvement provided the clinical suspicious of disseminated cryptococcosis, confirmed with analysis cerebrospinal fluid (CSF) and lesion histopathology analysis. Despite the recognition and correct treatment of the mycosis, the patient died after three days of hospital stay, reinforcing the severity of this condition and the need of clinical suspicious in the presence of typical cutaneous lesions.

Key words: Cryptococcosis, AIDS, Amphotericin B.

1. Acadêmica do Curso de Medicina da Universidade Católica de Brasília
2. Médico, doutor, docente do Curso de Medicina da Universidade Católica de Brasília.
3. Médica, doutora, pesquisadora do Instituto de Pesquisa Clínica Evandro Chagas - FIOCRUZ-RJ
E-mail do primeiro autor: amanda.al.alb@gmail.com
Recebido em 07/10/2012 Aceito, após revisão, em 19/10/2012

Introduction

Cryptococcosis (torulose, blastomycosis European or disease Busse-Buschke) is a systemic mycosis caused by an encapsulated cosmopolitan fungi from the *Cryptococcus neoformans* complex.[1,2,3] This complex is represented by two species: *Cryptococcus neoformans*, causing cryptococcosis, an opportunistic condition related to cell immunosuppression, especially in patients infected with human immunodeficiency virus (HIV) and *Cryptococcus gattii*, causing primary cryptococcosis in apparently immunocompetent hosts.[1,3] Both can cause meningoencephalitis with a severe and fatal evolution accompanied or not of apparent lung injury, fungemia and dissemination to multiple organs and systems.[1]

The *C. neoformans* complex includes two sibling species: *C. neoformans* (serotypes A, D and hybrid AD) and *C. gattii* (serotypes B and C).[1-4] Global molecular epidemiological studies of the agents of cryptococcosis identified eight major molecular types. Thus, *C. neoformans* was grouped into the types VNI (serotype A), VNII (serotype A), VNIII (serotype AD), and VNIV (serotype D); *C. gattii* was grouped into the types VGI, VGII, VGIII and VGIV.[5] Studies related to genotyping of DNA suggested that serotype A is a new separate species, called *C. neoformans grubii* variant, with a worldwide distribution and sharp dermotropism, affecting immunocompromised individuals, especially those infected with human immunodeficiency virus, being the most frequent variant in Brazil.[1,2,3]

The disease is acquired by inhalation of infectious propagules resistant to environmental conditions, determining the pulmonary primary infection, symptomatic or asymptomatic, with the possibility of further hematogenous spread.[1,3] Cutaneous manifestations occur in 10-15% of all cases of systemic cryptococcosis.[3,6] Rarely, there may be traumatic inoculation through the skin, causing the primary cutaneous cryptococcosis.[3] The skin lesions are extremely polymorphic, which makes the diagnosis difficult. However, there are some good laboratory test that can be associated with the clinical history and physical examination for the diagnosis of cryptococcosis[3].

This report describes a case of disseminated cryptococcosis by *C.neoformans* as the first opportunistic infection associated to AIDS in which cutaneous manifestations were very pronounced and helped in the diagnosis of this disease. The principal aim is to highlight the importance of the suspicious of *C.neoformans* involvement in critically ill patients with cutaneous eruption.

Case report

A 28 years old male patient, born in Rio de Janeiro, Brazil, was admitted in a reference hospital of infectious diseases in May of 2001 complaining of fever, headache, progressive dyspnea and loss of weight beginning one month before. During the clinical examination, the patient had an ill appearance with pronounced dyspnea denounced by the utilization of accessory respiratory muscles. He presented popular

skin eruptions with central umbilication varying in size from few millimeters to ten centimeters of diameter (figure 1). Neurological examination was normal (absence of motor deficits, nerve palsies or nuchal rigidity), abdominal examination demonstrated liver and spleen enlargement. A discrete wheezing was detected in pulmonary auscultation. The patient was asked about sexual behavior but he denied any sexual intercourse during his life, although he had pronounced genital warts (figure 2); at the second day of hospital stay he informed that he had a few active and passive homosexual relations without protection.

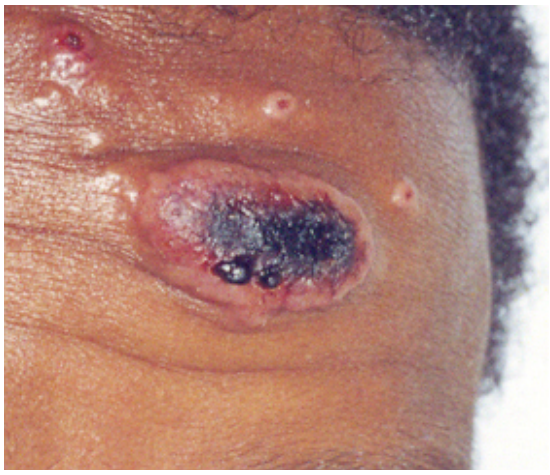

Figure 1 - Polymorphic cutaneous lesions on the face caused by disseminated *Cryptococcus neoformans* infection in a 28 years old male patient with HIV/aids.

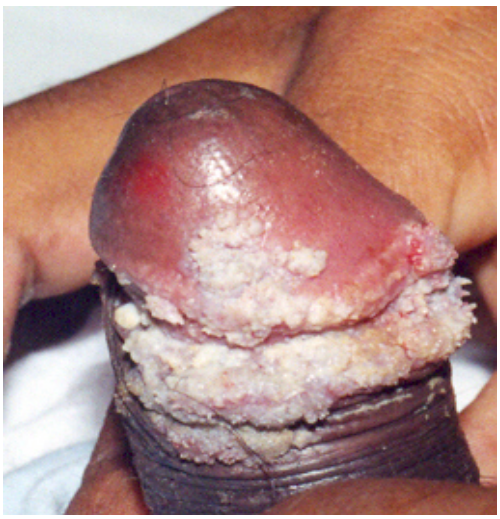

Figure 2 - *Condiloma acuminada* in genital area of 28 years old male patient with HIV/aids and disseminated criptococcosis co infection.

An arterial blood gas analysis evidenced a pH of 7.40, a pO2 below 70 mmHg, a pCO2 of 30 mmHg and a negative base excess suggesting metabolic acidosis compensated by a respiratory alkalosis. Blood cells counts were abnormal, with anemia and leukopenia. Blood urea was 136 mg/dl, potassium was 5.8 mg/dL and creatinine was 1.0 mg/dl (prerenal insufficiency). Lactic dehydrogenase was 499 mg/dL, marginally above the normal limit of 480 mg/dL. Chest x-ray showed a fine granular bilateral infiltration and cranial computed tomography showed diffuse enlargement of the ventricular system as consequence of cranial hypertension, without focal lesions. It was performed a lumbar puncture, which demonstrated a high pressure limpid cerebrospinal fluid (CSF), with two mononuclear leukocytes, protein of 43 mg/dL and glicose of 84 mg/dL. The direct microscopy with India ink evidenced numerous yeasts of *C.neoformans* and the latex agglutination test of for the fungus was also positive in CSF and in serum. Pathology study of the skin lesion with Mayer mucicarmin stain evidenced numerous fungal yeasts exhibiting great polysaccharide capsules stained in magenta color surrounded by a weak inflammatory reaction. Cultures of the skin, CSF and urine specimens demonstrated growth of *C. neoformans*. A rapid HIV test was positive.

The treatment for cryptococcosis was started with 50 mg/day intravenous infusion of amphotericin B deoxycholate; intravenous co-trimoxazole was also introduced with corticosteroids in order to treat a possible pneumocystosis. Despite this, his neurological condition deteriorated, in the second day of admission the patient needed respiratory assistance and in the third day he died.

Discussion

Currently, AIDS is the predisposing factor in approximately 80-90% of cryptococcal infections[7]. The vast majority of infections in these patients are caused by the serotype A, also identified as *grubii* variant, whose dermatotropism is responsible for variable cutaneous manifestation.[3] Some studies show that cryptococcosis occurs in about 6-13% of patients with AIDS, and is the most frequent cause of meningitis in these patients. Skin lesions, usually secondary to systemic involvement, occur in about 10% of individuals with AIDS.[2]

In immunocompromised individuals, after the primary infection, the agent spreads by blood affecting other organs, especially the Central Nervous System (CNS) (manifesting as meningoencephalitis) and other sites such as skin, lymph nodes, bones / joints, eyes, heart, liver, spleen, kidney, thyroid, adrenals, and even the prostate - being considered as a reservoir for disease recurrence.[3,8] Usually this situation does not respond satisfactorily to conventional treatment and develop into a fatal course.[3]

Cryptococcosis can be the first opportunistic infection in AIDS, but it may be associated with other infections, especially esophageal and oral candidiasis, pneumocystosis, tuberculosis and histoplasmosis.[4] This patient had also genital warts, which reinforces the obligatory investigation of genital and perianal region in situations in which sexually transmitted infections and AIDS are suspected.

Cutaneous cryptococcosis involves a broad spectrum of clinical manifestations, especially in AIDS patients, and in general, are markers of disseminated cryptococcal infection.[1,3] The lesions may include papules, infiltrated plaques, pustules, herpetiform

vesicles, nodules, edema / subcutaneous masses, umbilicated papules, cellulitis / abscesses (refractory to conventional antibiotics), ulcers or nodules in the oral mucosa.[3,9] According to some authors, the disseminated cutaneous form have a predilection for head and neck skin, however, any area of skin or mucosa can be infected.[3] Very often in disseminated cryptococcosis cutaneous lesions occur as papules with central umbilication very similar to *molluscum contagiosum* lesions, which can be also disseminated, like in our case.[2,3,9]

Clinical history and physical examination can suggest the diagnosis, although very often the patient does not present the typical complaints of meningoencephalitis like headache or meningeal signs, in our case these manifestations were also not identified at admission. Therefore, laboratory isolation of the fungus is the only definitive criterion for the diagnosis establishment. The performance of lumbar puncture is mandatory, alterations in CSF biochemistry and cellularity in immunosuppressed patients with aids are generally unremarkable, but may show an increase in initial CSF pressure, mild pleocytosis with lymphocytes, protein and moderate hypoglycorrachia.[3,10] Direct examination with India ink and culture of CSF have high yields. Pathological analysis of skin lesions of AIDS patients shows uniformly the presence of the fungus with absence of immune response.[10]

An important diagnostic tool is the direct agglutination with latex particles performed in the CSF or sera, with a sensitivity of 97% and 87% respectively.[11] Other corporal fluids are also useful to establish the diagnosis in disseminated disease, like the isolation of the fungus in urine, a noninvasive method which is also costless.[12]

Compromised mental status at admission represents a risk factor for a poor prognosis in patients with cryptococcosis, but other variables are also relevant as determinants of a poor prognosis, such as the age inferior of 35 years, extraneural cryptococcosis, hypernatremia and high burden of fungal cells in CSF direct examnination.[4]

The recommended therapeutic regimen for individuals with AIDS and cryptococcal disseminated infection with involvement of the CNS is the use of amphotericin B deoxycholate (0.7 to 1 mg / kg / day) with or without 5-flucytosine (100-150mg/kg quid), by two to three weeks, followed by consolidation with fluconazole (200-400 mg / day orally or intravenously) for 10-12 weeks. Following the attack phase, maintenance with fluconazole (200 mg / day orally) is recommended until immunosuppression persists (in AIDS patients, a T cell CD4 count less than 200 cells in serum), in order to prevent relapses[3]. Lipid formulations of amphotericin B are also recommended as first line agents for treatment of this mycosis, presenting less renal toxicity and permitting the infusion of higher doses, but it is costs are still very elevated for use in low and middle income countries[3].

In the present case we were not able to perform the CD4 T cell count and the HIV viral load and the patient died before the clinical response to the therapy, nevertheless aids associated cryptococcosis affects individuals with very low CD4 T cell count, bellow 50 cells, which predisposes to others opportunistic infections and is also associated with the severity of the case.[3]

Conclusion

Clinical suspicious of cryptococosis in immunocompromised individuals, especially with AIDS, is of uttermost importance to

guide laboratory investigation. The presence of skin lesions in this scenario, which usually represent a marker of disseminated cryptococcosis, can aid in this suspicious.[2,3,13] Thus, whenever the hypothesis of cutaneous cryptococcosis is suggested, there is the need of a proper and detailed investigation for extracutaneous disease, including others opportunistic infections, in order to establish the diagnosis and treatment as early as possible aiming a better prognosis.[2,3,14]

References

1. Kon AS, Grumach AS, Colombo AL, Penalva ACO, Wanke B, Teller FQ, et al. Consenso em criptococose 2008. Rev Soc Bras Med Trop. 2008; 41(5):524-44.

2. Dinato SLM, Dinato MM, Nakanishi CP, Almeida JRP, Romiti N. Disseminated cutaneous cryptococcosis in a patient with AIDS. Rev Inst Med trop S.Paulo. 2006; 48(6):353-8.

3. Bivanco FC, Machado CAS, Martins EL. Criptococose cutânea. Arq Med ABC. 2006; 31(2):102-9.

4. Pappalardo MCSM, Melhem MSC. Cryptococcosis: a review of the brazilian experience for the disease. 2003; 45(6):299-305.

5. Meyer W, Marszewska K, Amirmostofina M, Igreja RP, Hardtke C, Methling K, et al. Molecular typing of global isolates of *Cryptococcus neoformans* var. *neoformans* by PCR-fingerprinting and RAPD. A pilot study to standardize techniques on which to base a detailed epidemiological survey. Electrophoresis. 1999; 20(8):1790-9.

6. Ministério da Saúde. Doenças Infecciosas e Parasitárias [acesso em 09 jul 2012]. Disponível em: http://bvsms.saude.gov.br/bvs/publicacoes/doencas_infecciosas_parasitaria_guia_bolso.pdf

7. Levitz SM. The ecology of Cryptococcus neoformans and the epidemiology of cryptococcosis. Rev Infect Dis. 1991; 13(6):1163-1169.

8. Rodrigues FB, Baciotti M, Zanatto MP, Silva JO, Martins MA, Martinez R. Cutaneous cryptococcosis due to *Cryptococcus gattii* in a patient on chronic corticotherapy. Rev Soc Bras Med Trop. 2010; 43(2):211-2.

9. Lacaz CS, Heins-Vaccari EM, Hernández-Arriagada GL, Martins EL, Prearo CAL, Corim SM, et.al. Primary cutaneous Cryptococcosis due to *Cryptococcus neoformans* var. g*attii* serotype B, in an immunocompetent patient. Rev Inst Med trop S.Paulo. 2002; 44(4):225-8.

10.Ramdial PK, Calonje E, Sing Y, Chotey NA, Aboobaker J. Molluscum-like cutaneous cryptococcosis: a histopathological and pathogenetic appraisal. J Cutan Pathol. 2008; 35(11):1007-13.

11. Warkentien T, Cianflone NFC. An Update on Cryptococcosis Among HIV-Infected Persons. Int J STD AIDS. 2010; 21(10):679–84.

12. Pinto Junior VL, Galhardo MCG, Lazéra M, Wanke B, Reis RS, Perez M. Criptococose associada à AIDS. A importância do cultivo da urina no seu diagnóstico. Rev Soc Bras Med Trop. 2006; 39(2):230-2.

13. Vandersmissen G, Meuleman L, Tits G, Verhaeghe A, Peetermans WE. Cutaneous cryptococcosis in corticosteroid-treated patients without AIDS. Acta Clin Belg. 1996; 51(2):111-7.

14. Ribeiro GP, Soares DAS, Pereira LMD, Bastos LIS, Pena SS, Miranda DC. Criptococose articular: Relato de caso. Rev Para Med. 2007; 21(4):69-72.