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CASE REPORT

Cutaneous Primary Cryptococcosis in an Immunocompetent Patient: Case Report

Criptococose Cutânea Primária em Paciente Imunocompetente: Um Relato de Caso

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ABSTRACT – Cryptococcosis is a systemic infection caused by *Cryptococcus neoformans*, an encapsulated opportunistic yeast. It primarily causes significant infections in immunocompromised individuals and the symptoms vary according to the integrity of the immune system. Cutaneous cryptococcosis affects about 20% of patients with disseminated cryptococcosis, but primary cutaneous cryptococcosis (PCC) without systemic infection is rare.

A 76-year-old male patient with chronic obstructive pulmonary disease, hypertension and dyslipidemia, presented with a violaceus inflammatory skin plaque with blisters that progressed despite intravenous ceftriaxone for 7 days. Histopathology of an incisional biopsy was compatible with the diagnosis of cutaneous cryptococcosis. There was a complete response to fluconazole 300 mg/day for 3 months. No systemic disease was detected and there was no evidence of immunosuppression.

The importance of including cutaneous cryptococcosis in the differential diagnosis of skin lesions in patients without immunosuppression or the use of immunosuppressive therapy is emphasized. The cutaneous manifestations of the infection can be the first indication for a disseminated disease, therefore, its early recognition is essential to obtain a good prognosis.

KEYWORDS – Cryptococcosis; Cryptococcus neoformans; Dermatomycoses; Immunocompetence.

RESUMO – *A criptococose é uma infecção sistémica causada por Cryptococcus neoformans, levedura oportunista encapsulada. Esta infeção ocorre principalmente em indivíduos imunocomprometidos e os sintomas variam de acordo com a integridade do sistema imunológico. A criptococose cutânea afeta aproximadamente 20% dos pacientes com criptococose disseminada, mas a criptococose cutânea primária (PCC) sem infecção sistémica é rara.*

Um paciente do sexo masculino de 76 anos, com doença pulmonar obstrutiva crónica, hipertensão arterial e dislipidemia, apresentou-se com placa cutânea inflamatória violácea com bolhas que progrediu apesar de ceftriaxone endovenoso por 7 dias, sem sucesso. A biópsia incisional revelou o diagnóstico histopatológico de criptococose cutânea. As lesões resolveram após tratamento com fluconazol 300 mg/dia durante 3 meses. Não se detectou doença sistémica e não havia qualquer evidência de imunossupressão.

Enfatiza-se a importância da inclusão da criptococose cutânea no diagnóstico diferencial das lesões cutâneas, mesmo em pacientes sem terapia imunossupressora. As manifestações cutâneas da infecção podem ser o primeiro indício para uma doença disseminada, pelo que o seu reconhecimento precoce é fundamental para um bom prognóstico.

PALAVRAS-CHAVE – *Criptococose; Cryptococcus neoformans; Dermatomicoses; Imunocompetência.*

INTRODUCTION

Cryptococcosis is a systemic infection caused by *Cryptococcus neoformans (C. neoformans)*, an opportunistic encapsulated yeast with worldwide distribution.[1,2] Infections occur mainly in immunocompromised individuals and symptoms vary according to the integrity of the immune system, ranging from asymptomatic respiratory infection to severe pneumonitis, which can spread to the central nervous system and other tissues, such as skin, prostate or bones.[3]

The authors report a case of extensive nonspecific cutaneous manifestations of cryptococcosis in a patient with chronic obstructive pulmonary disease, systemic arterial hypertension and dyslipidemia, without the use of immunosuppressants and without evidence suggesting immunosuppression.

CASE REPORT

A 76-year-old male patient was observed in November 12, 2020 at the medical outpatient clinic (AME) in the city of Peruíbe, São Paulo, Brazil, reporting intense pain, edema, erythema and heat, progressing for a week, located on the dorsum of his right

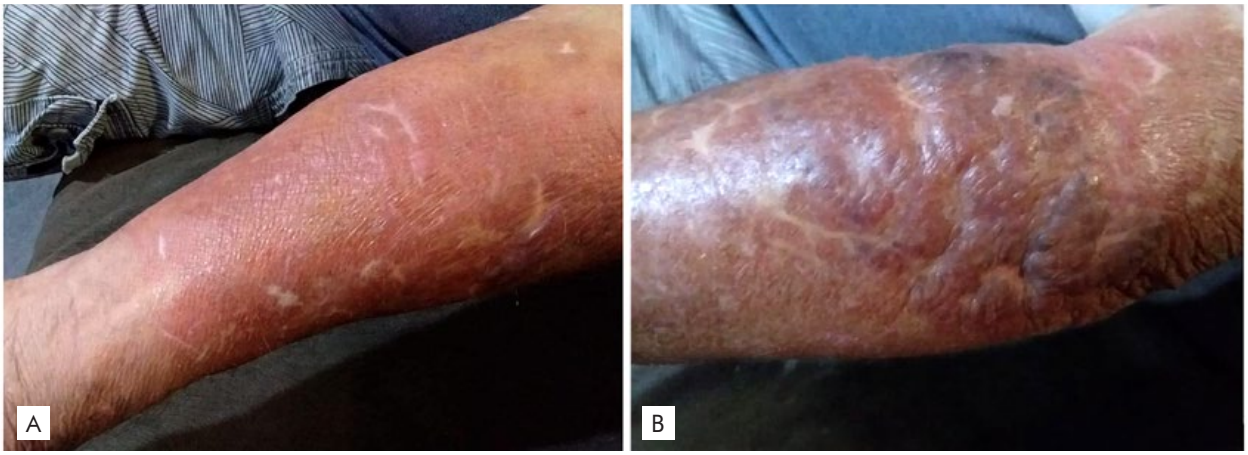

Figure 1 - Initial cutaneous lesions: erythematous plaque in the left forearm (A) with a more violaceous and infiltrated areas and a flaccid bullous appearance.

hand and all over the left forearm, with some tense blisters. He denied fever (Fig. 1).

In November 19, the initial erythematous plaque lesions on the hand and forearm worsened despite the administration of 1 g of intravenous ceftriaxone for 7 days and daily dressings with collagenase and chloramphenicol. The lesion extended to the elbow and arm, became more hyperpigmented with more bullae and excoriated/exulcerated areas with granulation tissue (Fig. 2). As lesions became more painful, oral gabapentin (300 mg of three times a day) was prescribed. During an incisional biopsy on the most flaccid bullous lesions, there was exudation of gelatinous and bloody material. Histology revealed epidermal acanthosis and foci of exulcerations, and, in the dermis and hypodermis, there was exuberant edema, vascular ectasias, recent hemorrhage and mixed interstitial infiltrate, rich in lymphocytes, histiocytes and neutrophils, surrounding numerous oval yeast structures with a thick capsule, measuring between 4 and 10 microns (Fig. 3). Mayer's Mucicarmine staining (Fig. 4) showed the presence of a thick mucoid capsule, confirming the histopathological diagnosis of cutaneous Cryptococcosis.

After etiological confirmation, the patient initiated oral fluconazole (300 mg/day). A previous contact with pigeon feces was confirmed and the authors confirmed once more, that the patient was not under treatment with immunosuppressive drugs and had no evidence of immunosuppression. Blood cultures for Cryptococci were negative

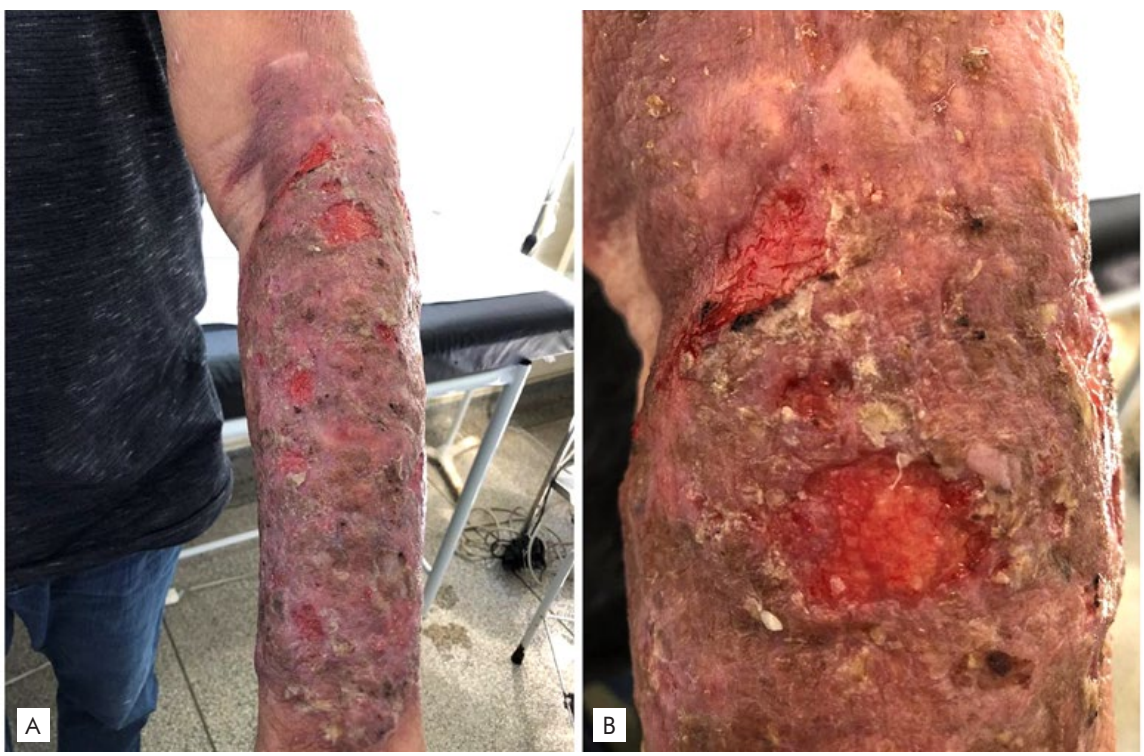

Figure 2 - Late lesions after two weeks of the initial lesions. a) after biopsy, forearm with erythema and skin hyperpigmentation, with excoriated and crusted areas; b) lesions with a reddish, granular and crusted bottom.

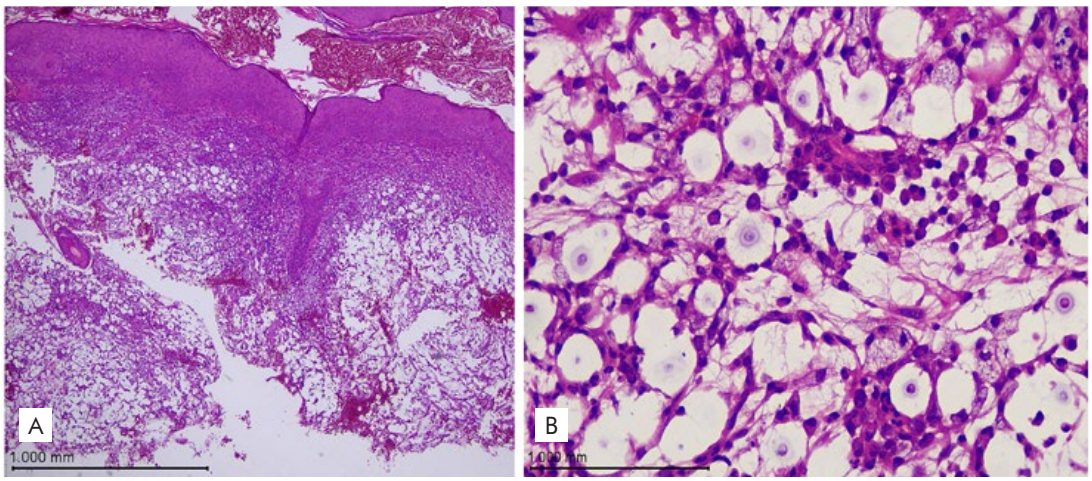

Figure 3 - Histopathology, H&E stain. A) Epidermis with acanthosis and dermis with edema, vascular ectasias and foci of recent hemorrhage (40x); B) On the right, mixed inflammatory infiltrate and edema, observing oval structures with a double oval capsule (400x)

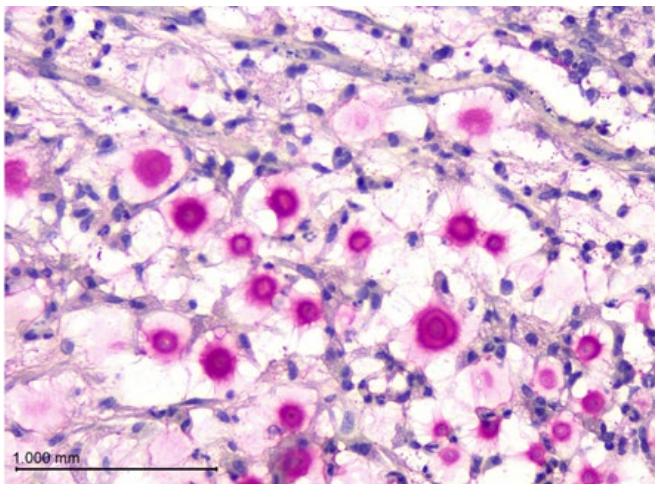

Figure 4 - Mayer's Mucicarmine staining. Yeast structures stained in magenta, showing thick double capsule rich in mucin (400x).

as well as serologies for HIV, hepatitis B and C and a complete blood count, coagulation tests, serum electrolytes, blood cultures, urinalysis, renal and hepatic function were normal. Nasopharyngeal swab for SARS-CoV-2 was negative.

Computed tomography of the chest without contrast showed traces of centrilobular and paraseptal emphysema in the upper fields, bronchial and bronchiolar inflammatory changes, related to chronic smoking. There was no mediastinal or hilar lymph node enlargement. Sparse calcified atheroma involved also the coronary (Fig. 5).

After one month of fluconazole therapy (300 mg/day), blisters and ulcers resolved with crusts, residual erythema and atrophy, still with diffuse infiltration (Fig. 6). A new biopsy performed on the forearm revealed still the presence of polymorphonuclear leukocytes, without observation of microorganisms. Culture was also already negative for aerobic, anaerobic bacteria, fungi, mycobacteria and acid-alcohol resistant bacillus.

Fluconazole therapy was kept for 3 months with full recovery of the lesions. After 4 months of the end of the treatment, the patient is still doing well and is under monthly surveillance, with no evidence of disease.

DISCUSSION

Epidemiology and Etiologic Agent

Cryptococcosis is a systemic fungal infection, caused mainly by *Cryptococcus neoformans* (*C. neoformans*), an encapsulated opportunistic yeast that has worldwide distribution, found mainly in soil, decomposing wood, pigeon feces, fruit and vegetables. After the

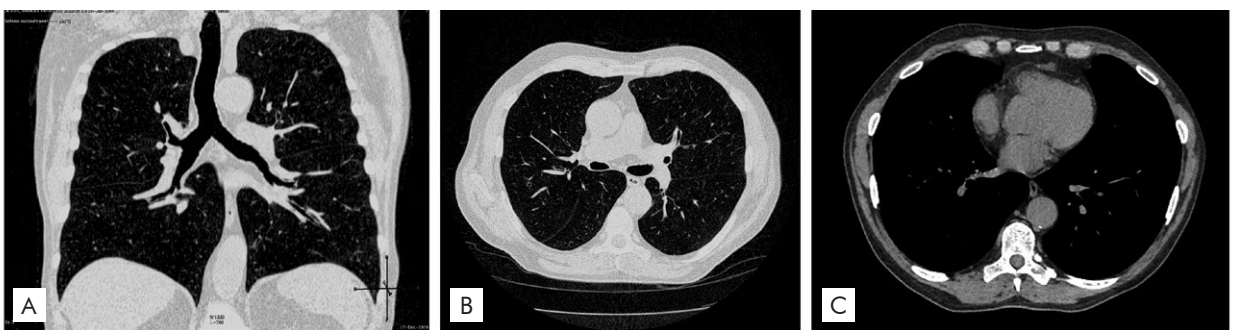

Figure 5 - Computed tomography of the chest with traces of centrilobular and parasseptal emphysema in the upper fields, without other specific alterations.

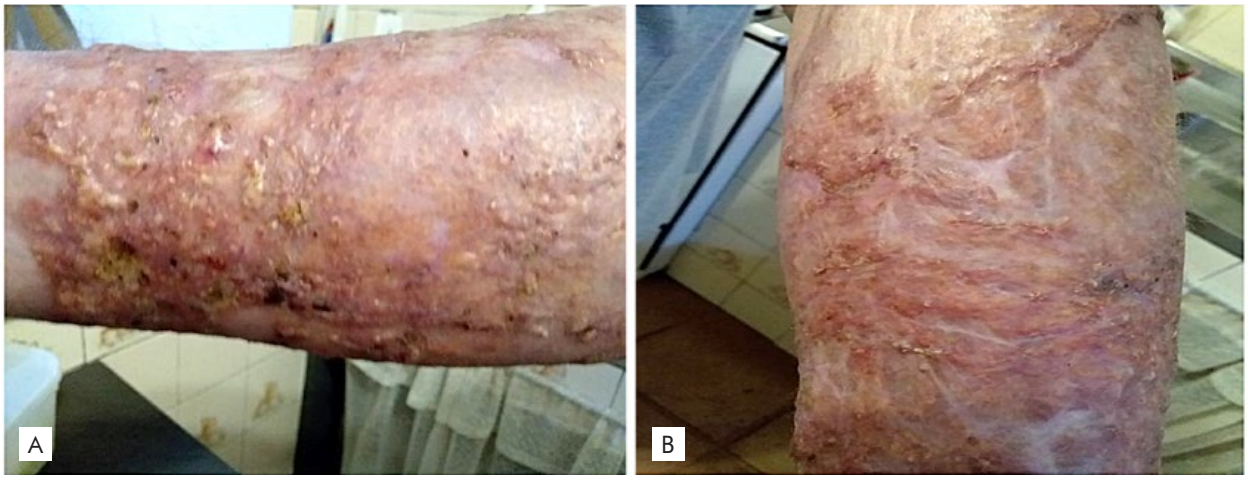

Figure 1 - Cutaneous lesions after one month treatment with fluconazol 300 mg/day. Regression of blisters and ulcers with residual erythema and atrophic surface.

diagnosis was confirmed, the patient reported previous contact with pigeon feces, which contributes to the recognition of a possible source of infection.[1,2]

The yeast has a polysaccharide capsule which is an important virulence factor, allowing its visualization with Indian ink, methylene blue and Mayer's mucicarmine.

There are four serotypes: serotype A, represented by *C. neoformans var. grubii*, with a global distribution. Serotypes B and C, represented by *C. neoformans var. gattii*, are limited to tropical and subtropical areas, and serotype D represented by *C. neoformans var. neoformans*, is found mainly in Europe.[1]

The pathogens *Cryptococcus neoformans* and *Cryptococcus gatti* currently represent the main worldwide cause of fungal meningitis.[1] *C. neoformans* mainly infects patients with low CD4+ T cell counts, while *C. gatti* also infects immunocompetent individuals.[4,5]

Cryptococcosis is rare in the population without HIV infection, or when there is no other state of immunocompromise, such organ transplantation, neoplasms or in chronic immunosuppressive treatment.[6]

Clinical features

Symptoms vary according to the functionality of the immune system. The pathogen, upon reaching the airways, can present as an asymptomatic respiratory infection to severe pneumonitis and acute respiratory failure. Chest radiographs can reveal unilateral, nodular or cavitary infiltrates.[8,9] From the lung infection it can spread to the central nervous system and other sites, such as skin, prostate or bones.[3] Central nervous system involvement is more common in immunocompromised patients, and symptoms are nonspecific, including headache, memory loss, tremor, muscle weakness, disorientation and confusion.

There are, in the literature, cases of familial cryptococcosis, related to inherited immunodeficiency diseases.[10,11] The disease is more frequent among men, which may suggest protective effects of estrogen.[7]

Cutaneous manifestations

Cutaneous cryptococcosis occurs mainly due to hematogenous dissemination. It affects about 20% of patients with disseminated cryptococcosis. *C. neoformans* serotype D, due to its dermatotropism, is associated with an increased risk of developing the cutaneous form.[12]

There is a wide spectrum of dermatological manifestations, including acneiform lesions, ulcerations, nodules, dome-shaped papules with central umbilication, and it may also present as bacterial cellulitis, as in the present case, as sarcoidosis-like or panniculitis.[13,14]

AIDS patients commonly present with molluscum contagiosum-like lesions, which may suggest one of the first clinical signs of infection spread.[7] Skin involvement in cryptococcosis also frequently occurs in liver transplant recipients using tacrolimus.[1]

The patient described did not have any evidence of immunosuppression, however he presented an extensive form of cutaneous involvement, without clinically or radiologically systemic signs, which demonstrates the importance of considering cryptococcosis as a differential diagnosis of skin lesions regardless of the immunological status of the patient.

Diagnosis

The diagnosis can be made by performing a skin biopsy with histopathological examination, microscopic evaluation and tissue culture. *C. neoformans* can be grown in various microbiological media with temperatures between 3°C and 30°C, with a maximum tolerance of 40° C.[15] Mucoid colonies and budding cells similar to encapsulated round yeasts with 5 μm to 10 μm in diameter can be found.[16] After staining with Hematoxylin and Eosin, a clear space can be observed around the cells, due to the capsule, which is stained with Alcian Blue or Mayer's Mucicarmine, the latter used in this patient's skin sample.

Infection can also be confirmed by biochemical tests such as the cryptococcal polysaccharide antigen and the fungus can be detected in the cerebrospinal fluid (CSF) and blood through the latex agglutination test or ELISA.[17]

Disseminated cryptococcosis is confirmed by a positive culture from at least two different sites or a positive blood culture.[18,19] Blood cultures of our patient were negative and the culture of the lesion after the treatment was also negative.

Treatment

Treatment depends on the patient's immune status and the location of the infection. It is important to rule out involvement of the central nervous system in disseminated cryptococcosis as, because of the risk of meningoencephalitis, the drugs used must penetrate the blood-brain barrier. [20]

In the guidelines for the management of disseminated cryptococcosis from the Infectious Diseases Society of America (IDSA), 2010,

induction therapy is performed for 2 weeks, using liposomal amphotericin B at a dose of 3-4 mg/kg/day intravenously or amphotericin B lipid complex 5 mg/kg/day in combination with flucytosine 100 mg/day followed by consolidation therapy using fluconazole at a dose of 400-800 mg daily for 8 weeks, which should be reduced to 200-400 mg/day and continued for 6 months to 1 year.[20]

Recent protocols describe the management for immunocompetent patients, but do not include a non-disseminated exclusive cutaneous form of the disease.[21]

Unfortunately, mortality in patients with cryptococcosis remains high, as patients are normally already in a deficient immune status, and drug resistance may occur due to changes in the target enzyme encoded by the *ERG11* gene, lanosterol 14α-demethylase, and the growth of biofilm. Research regarding new antifungal agents, immunomodulators, and other drugs that can be used as adjunct to the existing therapy is currently being carried out.[22,23]

A clinical improvement was noticed in the reported patient with the use of a intermediate dose of fluconazole, between 200-400 mg/day for 3 months, without the administration of amphotericin B because the patient had the non-disseminated form of the disease. A possible hypothesis for a good prognosis of this case may be attributed to a localized cutaneous form of the disease and the healthy immune status of the patient, which helped to control the infection.

CONCLUSION

Cryptococcosis is a fungal infection with a wide spectrum of clinical manifestations that can evolve to systemic involvement and death. Skin lesions are nonspecific and varied, occurring in approximately 20% of patients, but are usually indications of the disseminated form of the disease. Despite being an opportunistic infection, affecting more commonly immunocompromised patients, it is extremely important to consider this condition in the differential diagnosis of the most varied dermatological manifestations regardless of the patient's immunological status, thus avoiding a late diagnosis and progression to a poor prognosis.

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REFERENCES

1. Neuville S, Dromer F, Morin O, Dupont B, Ronin O, Lortholary O; French Cryptococcosis Study Group. Primary cutaneous cryptococcosis: a distinct clinical entity. Clin Infect Dis. 2003;36:337-47.
2. Chayakulkeeree M, Perfect JR. Cryptococcosis. Infect Dis Clin North Am. 2006;20:507-44, v-vi.
3. Negroni R. Cryptococcosis. Clin Dermatol. 2012;30:599-609. doi: 10.1016/j.clindermatol.2012.01.005.
4. Husain S, Wagener MM, Singh N. Cryptococcus neoformans infection in organ transplant recipients: variables influencing clinical characteristics and outcome. Emerg Infect Dis. 2001;7:375-81.
5. Singh N, Alexander BD, Lortholary O, Dromer F, Gupta KL, John GT, et al; Cryptococcal Collaborative Transplant Study Group. Cryptococcus neoformans in organ transplant recipients: impact of calcineurin-inhibitor agents on mortality. J Infect Dis. 2007;195:756-64.
6. Pappas PG. Cryptococcal infections in non-HIV-infected patients. Trans Am Clin Climatol Assoc. 2013;124:61-79.
7. Badreshia S, Klepeiss S, Ioffreda M, Miller J, Adams DR, Mackley C. Cutaneous cryptococcus in an elderly woman with chronic essential dermatitis. Cutis. 2006;78:53-6.
8. Schröter GP, Temple DR, Husberg BS, Weil R 3rd, Starzl TE. Cryptococcosis after renal transplantation: report of ten cases. Surgery. 1976;79:268-77.
9. Jarvis JN, Harrison TS. Pulmonary cryptococcosis. Semin Respir Crit Care Med. 2008;29:141-50.
10. Subramanian S, Mathai D. Clinical manifestations and management of cryptococcal infection. J Postgrad Med. 2005;51:S21-6.
11. Al-Akeel R, Ahmed M, Syed R. An overview of diagnostic criteria for identification of cryptococcal meningitis with special emphasis on AIDS. African J Biotechnol. 2012;11:11760-6.
12. Martinez LR, Garcia-Rivera J, Casadevall A. Cryptococcus neoformans var. neoformans (serotype D) strains are more susceptible to heat than C. neoformans var. grubii (serotype A) strains. J Clin Microbiol. 2001;39:3365-7.
13. Schupbach CW, Wheeler CE Jr, Briggaman RA, Warner NA, Kanof EP. Cutaneous manifestations of disseminated cryptococcosis. Arch Dermatol. 1976;112:1734-40.
14. Latino GA, Gago E, Vidau P, Vivanco B. Cutaneous cryptococcosis in a patient on chronic haemodialysis. Nefrologia. 2012;32:697-8. doi: 10.3265/Nefrologia.pre2012.Jun.11563.
15. Gazzoni AF, Severo CB, Salles EF, Severo LC. Histopathology, serology and cultures in the diagnosis of cryptococcosis. Rev Inst Med Trop Sao Paulo. 2009;51:255-9.
16. Odom A, Muir S, Lim E, Toffaletti DL, Perfect J, Heitman J. Calcineurin is required for virulence of Cryptococcus neoformans. EMBO J. 1997;16:2576-89.
17. Valente ES, Lazzarin MC, Koech BL, da Rosa RV, de Almeida R, de Oliveira UL, et al. Disseminated cryptococcosis presenting as cutaneous cellulitis in an adolescent with systemic lupus erythematosus. Infect Dis Rep. 2015;7:5743. doi: 10.4081/idr.2015.5743.
18. Mostafa WZ, Ishak EA, Ekladious EM, Arnaout HH. Disseminated cryptococcosis with cutaneous lesions. J Dermatol. 1996;23:209-13.
19. Chuang YM, Ho YC, Chang HT, Yu CJ, Yang PC, Hsueh PR. Disseminated cryptococcosis in HIV-uninfected patients. Eur J Clin Microbiol Infect Dis. 2008;27:307-10.
20. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2010;50:291-322.
21. Gilbert D, Eliopoulos G, Chambers H, Saag M, Pavia A. Guia Sanford para Terapia Antimicrobiana 2019. 49rd ed. São Paulo: Guanabara Koogan; 2019.
22. Mourad A, Perfect JR. Present and future therapy of cryptococcus infections. J Fungi. 2018;4:79. doi: 10.3390/jof4030079.
23. Gullo FP, Rossi SA, Sardi Jde C, Teodoro VL, Mendes-Giannini MJ, Fusco-Almeida AM. Cryptococcosis: epidemiology, fungal resistance, and new alternatives for treatment. Eur J Clin Microbiol Infect Dis. 2013;32:1377-91. doi: 10.1007/s10096-013-1915-8.