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CASE REPORT

DISSEMINATED CUTANEOUS CRYPTOCOCCOSIS IN A PATIENT WITH AIDS

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SUMMARY

The authors study a patient carrying Aids, with exuberant dermatological manifestations of cryptococcosis. They stress the therapeutic effectiveness of short-term amphotericin B. The authors reviewed cases of cutaneous infection with *Cryptococcus* reported in the national and international literature, verifying that the frequency has increased with the AIDS epidemic. Also, they discuss about the differential diagnosis with some cases of dermatosis, particularly with the disseminated giant molluscum contagiosum. In relation to the therapy, they affirm that the choice of drug depends on the organ involved, as well as the immune state of the patient.

KEYWORDS: Cryptococcosis; Cutaneous cryptococcosis; Disseminated cryptococcosis; Aids.

INTRODUCTION

Cryptococcosis, also known as torulosis, Busse - Buschke's disease and European blastomycosis is a cosmopolitan illness, with opportunist behavior[2,11,12,14,20,24,29].

It is a fungal systemic infection caused by *Cryptococcus neoformans*, characterized as a species of encapsulated yeasts which, based on the capsule structure, were grouped into two varieties that included five serotypes. *C. neoformans* var. *neoformans* including serotypes A, D and AD, and *C. neoformans* var. *gatti* contained strains with serotypes B and C. Based on DNA genotyping methods, several changes have been proposed. According to that, serotype A would be classified as a separate variety, *C. neoformans*, var. *grubii*. In AIDS patients, the vast majority of isolates are serotype A (var. *grubii*)[2,6,7,19,20,21].

Many cases described are associated to the immunosuppression, due to lymphoma[17], chronic leukemia[23,24], transplants of organs[11], use of corticosteroid[27,33], immunosuppressive drugs[14,27], systemic lupus erythematosus[28], diabetes mellitus[14,23], Cushing's syndrome[5] and, more recently, related with acquired immunodeficiency syndrome (Aids)[1,2,11,15,25,29].

With the advent of AIDS, the number of cases of cryptococcosis has increased: from 1982 to 1991, its incidence almost quadrupled in relation to the period from 1953 to 1981. In this syndrome, the incidence rates have reached 10% in the developed countries (USA, England, Italy, Australia and Germany), while in countries in development, they vary between 20-81%[16].

In Brazil, a study[9] of the illnesses associated to AIDS, from 1980 to 1999, in 157,775 sick people, showed a reduction in the incidence of all of them, compared to the initial period (1980-1988) and the final period (1998-1999). Candidiasis was found (59.2%), followed by tuberculosis (25.5%). In 4.5% of the cases, cryptococcosis had been detected, the majority being in men with more education, who are from the southeastern region and among men that had acquired the base illness by sanguineous transmission (heterosexual).

On the other hand, neurocryptococcosis, a fungal illness of high mortality[8], represents the second most common infection of the central nervous system in patients with AIDS. In Santos, during the period of 1/1/1984 to 9/30/2001, the Municipal Health Secretariat, registered 114 (2.6%) cases of cryptococcosis in the central nervous system in a total of 4,368 cases of AIDS in adults[31].

In relation to the cutaneous lesions of cryptococcosis, it can be confirmed that it is rare, occurring in only 5%-15% of the patients with systemic form of the illness[11,12]. In the two Brazilian studies cited above, there is no reference about the frequency of the cutaneous form of this deep fungal infection[8,9].

The objective of our study is to report on the exuberant dermatological manifestations of cryptococcosis in patient with AIDS, as well as the therapeutical effectiveness of short-term amphotericin B.

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CASE REPORT

RPS, 38 year-old, white male, single, autonomous worker, a native of Santos, São Paulo.

The patient sought the services of the Hospital Guilherme Álvaro (HGA) day clinic, complaining of about fifteen days of continuous headache, intermittent fever and lightly pruriginous injuries, which had begun in the face, with posterior centripetal evolution and spread to the entire tegument in a few days. Spontaneously, he informed us he has been carrying the virus of AIDS, without specific treatment for three months, because he gave up the treatment. Previously, he was treated for pulmonary tuberculosis.

During the dermatological examination, well-defined papules and nodules, erythematous, some with generalized centralis depression, were noticed, being more exuberant, however, in the face, anterior and posterior region of the trunk (Fig. 1,2,3).

During the physical examination, it was observed that the patient had lost weight, was in a poor general state, feverish, had slightly discoloured mucosa, generalized adenopathy, rigidity in the nape of the neck and hepatoesplenomegaly (palpable liver three cm below the right costal margin and palpable spleen four cm below the left costal margin).

On this occasion, he was hospitalized for some complementary examinations, for the purpose of diagnostic briefing, his initial hypotheses having had included cryptococcosis, histoplasmosis, paracoccidioidomycosis and disseminated giant molluscum contagiosum.

A biopsy of the cutaneous injury was made, and the histopathological examination, by optical microscopy with hematoxylin-eosin, revealed epidermis with acantholysis and dermis with agglomerate presence of vacuolized cells. The PAS and Grocott staining (Fig. 4, 5, 6) had been positive for encapsulated yeast cells,

Fig. 1 - Exuberant injury in the face, similar to giant molluscum contagiosum.

Fig. 2 - Injuries in the anterior region of the thorax.

Fig. 3 - Some injuries with centralis depression in the left shoulder.

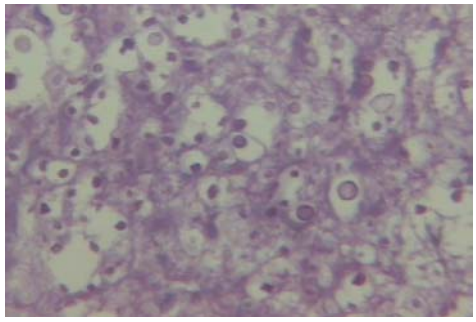

Fig. 4 - PAS 100x. Presence of innumerable encapsulated yeast cells.

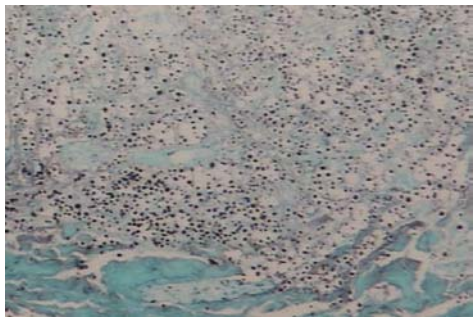

Fig. 5 - Grocott 40x. Presence of innumerable yeast cells of black color.

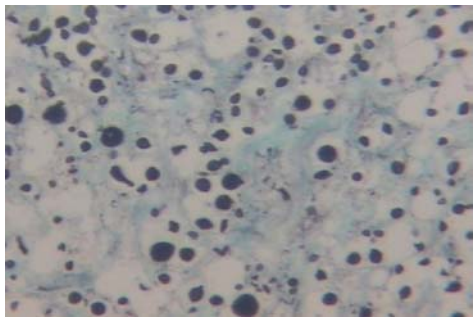

Fig. 6 - Grocott 100x. Yeast cells with multiple budding.

suggesting *Cryptococcus neoformans*. Also, other exams were performed: Hemoculture - positive for *Cryptococcus neoformans* and Culture of the cerebrospinal fluid - positive for *Cryptococcus neoformans* (Instituto Adolfo Lutz).

The initial hematological examinations had shown: Hb: 6.2 g/dL, Ht: 20 mL eritroc/dL, leukocytes: 1,800/mm^3, platelets: 200,000/mm^3, creatinine: 0.9 mg/dL and CD4: 2 cells/mm^3.

After the diagnostic confirmation, treatment for cryptococcosis with endovenous amphotericin B in increasing doses was initiated and the therapeutic schema for AIDS (3TC and d4T) restarted. During his hospitalization, the patient underwent a blood transfusion because of his anemic condition. Alteration of renal function (creatinine: 1.9 mg/dL) developed, after the beginning of the treatment with amphotericin B, a probable cause of this adverse effect, which was normalized later. Some common collateral effects of this drug, such as tremors and chills, also occurred with the patient. In relation to neurological and cutaneous forms, there was an improvement in the headache and development of injuries of the skin. He was released with accumulative dose of one g of amphotericin B, with fluconazole being prescribed for daily use, after release from the hospital. On that occasion he was reported to CRAIDS (AIDS Reference Center) where we found some examinations on his chart: 1) Direct mycological (liquor) - *Cryptococcus* spp. research - Positive; 2) Latex agglutination reaction for the *Cryptococcus neoformans* in liquor - Reagent (Instituto Adolfo Lutz). Also, we found a request for a new hospitalization, this time, to "Irmandade da Santa Casa de Misericórdia de Santos", due to the occurrence of headache, vomiting, right-side hemiparesis, dysphasia and mental confusion, with the diagnostic hypothesis of neurotoxoplasmosis. Consulting the chart from this hospital, we found a computerized tomography of the cranium whose contrast showed: slight dilatation of the infra and supratentorial ventricular system, with asymmetry of lateral ventricules, their being larger to the left, and in the left temporoparietal hipoattenuation zone, with effacement of cortical sulci; with diagnostic hypothesis of: Left temporofrontal ischemic focus? Infectious process? During this hospitalization period, the previous medicines were maintained and systemic corticosteroid, sulfadiazine and piremetamine introduced, the patient being released after 10 days, in a conscious state, although still having right-side hemiparesis. The patient was again sent to CRAIDS, when the clinical picture was much worse, requiring new hospitalization and returning to HGA 16 months after his first admittance into our service, with the same therapeutic procedure being maintained.

On that occasion, his relatives informed that the patient had not taken the prescribed medicine regularly.

Intercurrent ailments were the following: oral candidiasis, urinary infection, and B and C hepatitis. There was no reappearance of cutaneous lesions, and in the laboratory, the hemoculture and the liquor culture were negative for fungi.

He stayed in that hospital for 35 days until his death, always in grave condition, with right-side hemiparesis, dyslalia and prolonged periods of mental confusion. The causa-mortis was the multiple organ failure. Necropsy could not be performed, due to the unavailability, at that time, in the city.

In conclusion, the strict chart observation did not allowed us to make a definite neurological diagnosis. However, we point out that the purpose of this work was to describe an unusual form of skin manifestation of the disease, as well as its specific evolution.

DISCUSSION

The first case of cryptococcosis infection in human beings was reported in 1894, by Busse, in Germany. *Cryptococcus neoformans* was isolated for the first time by Sanfelice in this same year, from spoiled fruit juice[2,19,20]. In Brazil, the first publication was made by Almeida & Lacaz, in 1941[20].

Cryptococcus neoformans is a ubiquitous fungus, which belongs to the *Basidiomycota* Phylum and *Tremellomycetidae* Family. It is found in the ground and in tissues, secretions and excrements of animals and of the human beings. It is not contagious among humans[2,19,20]. Its transmission to humans occurs, mainly, by inhalation of non-encapsulated yeast forms or of those with thin capsules, transmitted, particularly, from contact with excrement of pigeons[12,26]. This patient reported the habit of going to caves, where conditions could be more compatible for histoplasmosis.

In the pulmonary parenchyma, the fungus can cause tissular and immune reactions, that normally block the infection. When it disseminates, this occurs through the hematogenic duct. It is important to note that, this fungus still has unexplained neurotropisms[12,29]. However, KUMAZAWA *et al.* (1998) observed, through serial magnetic resonance imaging, some radiological aspects in cryptococcosis of the central nervous system, that reflect the pathological mechanism of invasion by the fungi[18].

Two factors are basic in the pathogenesis of this deep mycosis: the virulence of fungus and the imunological response of the host. The resistence is so important that, many times, cryptococcosis can be the first sign of immunodepression, being one of the main illnesses associated to AIDS[8,9,31].

The incidence of the infection by *Cryptococcus* in patients with AIDS depends on determinative factors, particularly of CD4-cell counts below 100 cells/mL[32]. The patient in this study presented levels of CD4 of 2 cells/mL. It is important to remember that corticotherapy is essential for the treatment of certain illnesses associated to AIDS; however, it can predispose the infection of *Cryptococcus*[2].

The literature shows that cryptococcosis occurs more frequently in men (about 70% of the cases) and in adults (majority between 30 and 60 years)[2], data which corresponds to that of this patient (man of 38 years). The occurrence of cryptococcosis in children with AIDS corresponds 1%[1].

Cryptococcosis reaches several organs; when associated to AIDS, it appears in more than one location, in up to 50% of the cases[2], and this was also the case with the patient studied here.

Neurocryptococcosis represents the second most common infection in the central nervous system of patients with AIDS, a fact which has raised the mortality rate[8]. On the other hand, it is the most frequent

clinical manifestation of the illness (70 a 89.5%), mainly presenting chronic headache, fever, vomiting, rigidity in the nape of the neck and mental alterations, with torpor or coma[2] possibly developing. Some of these cited symptoms or signs had been observed in the patient studied here, who presented important neurological problems.

Also cases of pulmonary problems in AIDS are described, some with rapid deterioration followed by sudden death and others with spontaneous resolution. This patient did not present any pulmonary manifestations which are considered, together with the neurological ones, as the two principal forms of the disease[2,13,20,23].

It is important to point out the rarity and the polymorphism of the cutaneous picture. In its generalized forms, especially in patients who have AIDS, it presents acneiform injuries, papules, nodules, vesicles, ulcers, ecchymosis and rarely cellulitis[12,20,21,33]. It can appear similar to some dermatological diseases, among which are the following: basal cell carcinoma, disseminated giant molluscum contagiosum, paracoccidioidomycosis and histoplasmosis[11,20,21]. The patient in this study presented innumerable injuries mimicking molluscum contagiosum, characterizing a rare exuberant clinical manifestation.

To get a diagnostic of cryptococcosis, it is necessary to research the *Cryptococcus neoformans* in suspected organic material, on special stainings[2,20]. In the patient in question, this research was done in fragments of cutaneous injury, blood and cerebrospinal fluid, confirming the presence of fungus.

It is interesting to note that the positive culture not only serves for diagnostic purposes, but also as an important auxiliary method in the follow up of the patient, for evaluation of the viability of fungus, after the use of antifungal drugs[22].

Therefore, the presence of *Cryptococcus neoformans* in tests carried out with organic material is enough to determine the diagnosis of cryptococcosis, as was the case with this patient. However, diverse complementary methods still exist that can assist it, such as serological tests, antigen research of fungus and the techniques of polymerase chain reaction (PCR), intradermic reaction and imunohistochemistry[20].

In relation to the therapy, the choice of the drug depends on the organ involved, as well as on the immune state of the individual[30]. In the localized forms, fluconazole can be indicated; whereas in the most serious cases, amphotericin B must be initially used until there is clinical improvement and improvement in the cerebrospinal fluid parameters, including conversion for the negative culture and reduction of the cryptococcocical antigen headings. Many authors continue with amphotericin B until the end of the treatment; however, others complete it with fluconazole[30,32]. This latter option was chosen for this patient; however, it was not done regularly with him.

Another optional drug for cryptococcosis is the flucytosine, tested as monotherapy in patients of good prognosis by HOSPENTHAL & BENNETT, who demonstrated failure of the treatment in 57% of the cases; however it is affirmed that this fact would not be related to the development of resistance to the drug[10]. Some authors report that flucytosine does not contribute to the cure, but would only be efficient in the prevention of recurrences[30,32].

In positive HIV, PARISI *et al.* (1997) show the effectiveness of the use of amphotericin B together with flucytosin, until clinical improvement and cerebrospinal fluid complementing the treatment with itraconazole through the oral duct[25]. BROUWER *et al.* in 2004, also confirms the fast fungicidal action of the two first drugs in cryptococcical meningitis[4].

In negative HIV, BELLOSTA *et al.* (1999), LACAZ *et al.* (2002) and JOSHI *et al.* (2004) show the effectiveness of isolated fluconazole in the treatment of primary cutaneous cryptococcosis[3,12,21], while PINTADO *et al.* (1999) and MELZER *et al.* (1998) affirm that the association of amphotericin B and flucytosine generally induces a favorable reponse in cryptococcosis[24,27]. KORFEL *et al.*, in 1998, gave the first account of antimycotic treatment of cryptococcosis with liposome amphotericin B in patients with Hodgkin's disease. He affirms that this drug is less toxic and, perhaps, more effective than the conventional amphotericin B, especially when cytotoxic treatment is managed simultaneously[17].

On the other hand, it is opportune to make some comments about those prophylaxis[32]. Primary prophylaxis is not recommended, due to the rarity of the illness and the possibility of there occurring interactions with medicine, particularly in positive HIV patients, who take innumerable drugs. Secondary prophylaxis shows better results with fluconazol than that with itraconazol.

Finally, the prognosis of patients with cryptococcosis is poor, therefore this pathology is associated with immunosuppression. The evolution does not differ significantly between patients with disseminated or neurological cryptococcosis[22].

The patient in our study had an excellent therapeutic response to amphotericin B, having been released hospital for a period of time with important improvement of the neurological and cutaneous picture. However, this period was relatively short, as he died about 16 months afterwards, of multiple organ failure, due to probable neurotoxoplasmosis, without, however, a return of the cutaneous cryptococcosis. Secondary prophylaxis was not carried out.

CONCLUSION

Cryptococcosis is considered one of the main kinds of systemic mycosis in AIDS, being the second most common infection of central nervous system in these patients. The cutaneous form of this fungal infection is rare, and the differential diagnosis with the disseminated giant molluscum contagiosum[2,21] is particularly important.

Regarding therapy to treat AIDS, there are controversies over the isolated use of amphotericin B associated with the flucytosine, and also over whether or not it should be complemented by itraconazole or fluconazole. The advantages of the latter are its administration through the mouth and the lesser frequency of collateral effects[4,25,30,32].

Thus, early diagnosis and treatment is essential, in which there can be an improvement in the quality of life of these patients, and increase in the length of the life span, as well.

RESUMO

Criptococose cutânea disseminada em paciente com SIDA. Relato de caso

Os autores estudam um paciente portador de SIDA, com manifestações dermatológicas exuberantes de criptococose. Destacam a eficácia terapêutica da anfotericina B, a curto prazo. Revisam os casos de criptococose cutânea relatados na literatura nacional e internacional, ressaltando o aumento de sua freqüência com a epidemia da SIDA. Também discutem o diagnóstico diferencial com várias dermatoses, particularmente com o molusco contagioso gigante disseminado. Em relação à terapêutica, afirmam que a escolha da droga depende do órgão comprometido, assim como do estado imunológico do paciente.

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