RELATO DE CASO

USE OF AMPHOTERICIN B IN THE SIMULTANEOUS TREATMENT OF CHROMOBLASTOMYCOSIS AND AMERICAN TEGUMENTARY LEISHMANIASIS: A CASE REPORT

ANFOTERICINA B NO TRATAMENTO SIMULTÂNEO DE CROMOBLASTOMICOSE E LEISHMANIOSE TEGUMENTAR: UM RELATO DE CASO

Gustavo Carneiro Resstel[1], Eduardo Bernardo Chaves Neto[1], Flávia Chaves Lacerda[1], Rafael Ramalho Vale Cavalcante[1], Carlos Alberto Rodrigues Junior[1], Fernanda José de Toledo Coelho[2], Fellipe Camargo Ferreira Dias[3], Olivia Maria Veloso Costa Coutinho[4].

ABSTRACT

Chromoblastomycosis (CMB) is a polymorphic fungal disease that usually affects the lower limbs and manifests as verrucous nodules or plaques that may ulcerate. American Tegumentary Leishmaniasis (ATL) is an infectious parasitic disease caused by digenetic protozoa of the genus Leishmania sp. which affects the skin and/or mucous membranes of man and various species of wild and domestic animals. Both are part of the World Health Organization (WHO) neglected tropical diseases portfolio, mostly affecting economically vulnerable populations without adequate sanitation and in close contact with infectious vectors. We present the report of a 59-year-old male patient, referred to the Hospital Geral Público de Palmas (HGPP) in December 2017, carrying a positive result from a direct parasitological detection test for Leishmania sp., in addition to multiple previously biopsied lesions caused by CMB. It was observed that the patient had an important improvement of the CMB lesions with the use of amphotericin B in combination with itraconazole, thus demonstrating the role that the former can play in the therapy of this fungal disease.

Keywords: Chromoblastomycosis; American Tegumentary leishmaniasis; Amphotericin B.

RESUMO

A cromoblastomicose (CBM) é uma doença fúngica polimórfica, que acomete normalmente os membros inferiores e que se manifesta como nódulos ou placas verrucosas que podem ulcerar. A leishmaniose tegumentar (LT) é uma doença infectoparasitária causada por protozoários digenéticos do gênero Leishmania sp. que acomete a pele e/ou mucosas do homem e de várias espécies de animais silvestres e domésticos. Ambas fazem parte do portfólio de doenças negligenciadas da Organização Mundial da Saúde (OMS), afetando em sua maioria pessoas economicamente vulneráveis, sem saneamento adequado e em contato próximo com vetores infecciosos. Apresentamos neste trabalho o relato de um paciente, masculino, 59 anos, encaminhado ao Hospital Geral Público de Palmas (HGPP) em dezembro de 2017, portando exame parasitológico direto positivo para Leishmania sp., além de múltiplas lesões causadas por CBM previamente biopsiadas. Foi observado que o paciente teve importante melhora das lesões de CBM com uso da anfotericina B em associação ao itraconazol, demonstrando o papel que essa droga pode exercer na terapêutica desta doença fúngica.

Palavras-chave: Cromoblastomicose; Leishmaniose Tegumentar; Anfotericina B.

ACESSO LIVRE

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Instituição: [1]Acadêmico(a) de Medicina, Universidade Federal do Tocantins, Tocantins, Brasil; [2]Médica, Especialista em Clínica Médica, Universidade Federal do Tocantins, Tocantins, Brasil. [2]Médico, Mestrando em Ensino em Ciências e Saúde, Universidade Federal do Tocantins, Tocantins, Brasil. [3]Docente, Médica infectologista, Universidade Federal do Tocantins, Tocantins, Brasil.

Autor correspondente: Gustavo Carneiro Resstel; gustavo.c.resstel@gmail.com

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INTRODUCTION

CHROMOBLASTOMYCOSIS

Chromoblastomycosis (CMB) is a polymorphic fungal disease that normally affects the lower limbs and manifests as verrucous nodules or plaques that may ulcerate.[1] The fungus's entrance through the skin is usually by traumatic implantation.[1]

A characteristic primary lesion is then formed at the inoculation site, followed by a chronic involvement of epidermis, dermis and subcutaneous tissue associated with a granulomatous, purulent and fibrotic reaction and a non-protective humoral immune response. It can evolve with secondary infection, leading to lymphedema and elephantiasis. In some rare cases, lymphatic and hematogenous dissemination has been observed. In general, CMB lesions are recalcitrant and extremely difficult to eradicate, and may undergo neoplastic changes that lead to skin cancer and constitute a true therapeutic challenge.[1-3]

The direct mycological test may find peculiar forms denominated shaped bodies, produced by the dematiaceous fungi. The most frequently isolated organisms are *Fonsecaea pedrosoi*, *Phialophora verrucosa*, *Cladosporium carrioni* and more rarely *Rhinocladiella aquaspersa.*[4]

CMB was added to the World Health Organization (WHO) portfolio of neglected diseases in 2017.[5] It is a disease of global impact, but more prevalent in tropical and subtropical regions, mainly in Brazil, Mexico, Cuba and the Dominican Republic. However, some cases in temperate regions have recently been reported.[2]

The first case of CMB was reported by Rudolph, in 1914, while describing the clinical findings of patients from Estrela do Sul, Minas Gerais.[3,6] Terra et al created the term chromoblastomycosis in 1922, to distinguish a fungal infection from a verrucous dermatitis.[6]

Because it is a mycosis of implantation, the host's occupation seems to play a significant role.[3] The fact that CMB is strongly associated with agricultural activities corroborates the occupational nature of this disease.[3] Because rural activities are more commonly performed by adult men, this disease rarely occurs before adolescence, with most patients in the 40-50 age group.[3] Adult male individuals are much more affected than women, in a proportion of 15:1.[7]

Since CMB is not a disease of compulsory notification, the epidemiological data are derived from published cases and surveys.[3] In Brazil, the Amazon region has been considered an endemic area and the estimated incidence rate is 3/100,000 inhabitants.[2,3] In the state of Tocantins, the occurance of 5,906 cases is estimated (0.68% of the estimate for Brazil).[7]

AMERICAN TEGUMENTARY LEISHMANIASIS

American Tegumentary Leishmaniasis (ATL) is an infectious parasitic disease caused by digenetic protozoa of the genus *Leishmania* sp., which affects the skin and/or mucous membranes of man and of various species of wild and domestic animals. Depending on the species of *Leishmania* and the relationship of the parasite with its host, the disease may present different clinical forms (cutaneous, mucosal or mucocutaneous).[8,9]

At least seven species of *Leishmania* sp. are responsible for causing human disease in Brazil. The tegumentary form is mainly caused by *L. (V.) braziliensis*, *L. (V.) guyanensis* and *L. (L.) amazonensis*. Rarely, it can be caused by *L. (V.) lainsoni*, *L. (V.) naiffi* and *L. (V.) shawi*. The visceral form of leishmaniasis is caused by *L. (L.) chagasi.*[10] In Central America, the cutaneous manifestations of *L. (L.) infantum chagasi* are quite common, while in Brazil they are extremely rare.[11]

The transmission of *Leishmania* sp. in the Americas occurs mainly through the bite of females of the genus *Lutzomyia* sp.. These females need blood for maturing their eggs, and suck many vertebrates, including amphibians, reptiles, birds and mammals, the latter reservoirs of *Leishmania* sp..[12]

ATL is still considered by WHO as a neglected disease, affecting mostly people living in poverty, without adequate sanitation and in close contact with infectious vectors[5], despite being estimated as the ninth largest cause of individual infectious disease.[13] According to WHO estimates, leishmaniasis occurs in 88 countries and notification is compulsory in only 30 of these. About 90% of all reported ATL cases have occurred in only six countries: Iran, Saudi Arabia, Syria and Afghanistan in the Old World; Brazil and Peru, in the New World.[9,14]

In the Americas, it occurs from the southern United States to northern Argentina, with important predominance in South America, where it comprises almost all countries except Uruguay and Chile.[5,8] In Brazil, ATL has been registered in all states, initially caused by the intrusion of man in the wild cycle, up to the 1950s, through deforestation for agriculture, construction of roads and hydroelectric dams, and the installation of population clusters. Since then, new outbreaks have occurred in several states.[10,15] In Tocantins, during the year of 2010, the incidence of ATL was 40.62/100,000 inhabitants, while the incidence rate in Brazil was 11.59/100,000 inhabitants.[16]

ATL is a public health problem, not only in Brazil, but also in other countries, due to its high incidence, wide geographical distribution and also the possibility of evolving to destructive, disfiguring and disabling forms. It is believed that the numbers of reported ATL cases do not reliably reflect the disease's evolution, either because of the patient's delay in searching for health care, the diagnostic difficulties or even failure in correctly reporting the cases. Still, the increasing number of new cases and the intensity with which the human being is reached is evident.[8,9]

We present here the case of a patient referred to the Hospital Geral Público de Palmas (HGPP) for ATL treatment, with a previous diagnosis of CMB from another service.

CASE

A. P. S., male, 59 years old, caucasian, married, rural worker, from the municipality of Abreulândia, Tocantins (TO). He was referred to the HGPP in December 2017, with a positive parasitological test for *Leishmania* sp.. He reported onset of a pustular lesion in the middle third of the left leg, 30

days prior to his arrival in the hospital, which progressed to two ulcerated lesions. The lesions were associated with pruritus, pain, purulent secretion and phlogistic signs. During this period, he reports apllying latex extracted from a sangra d'água plant (*Croton urucurama*) on the lesions, but no improvement was observed.

The patient reported a weight loss of 20kg in 3 months. In addition, he reported pain, crepitus and post-rest rigidity in the left knee joint. He referred as comorbidities: Systemic Arterial Hypertension (SAH) with a 10-year evolution; gouty arthritis, two years ago; obesity and dyslipidemia. He reported continued use of atenolol, acetylsalicylic acid, nifedipine, hydrochlorothiazide, losartan, allopurinol, and simvastatin. He also reported living in a masonry house, in the rural area, with untreated water supply. He is a farmer, with high exposure to sun light, without the use of sunscreen, only wearing physical barriers. He refers following a hyperlipidic and hyperproteic diet and sporadic ingestion of alcoholic beverages. He denies smoking and use of other drugs.

In the physical examination, at the time of hospital admission, the patient was in good general condition, with grade 2 obesity (BMI: 38.7 kg/m²). He presented gouty tophi located in the right metatarsophalangeal, ulnar-humeral and tibial-femoral joints. Crepitation was found in both knees, and he felt pain with mobilization of the left knee.

He had two blackened ulcerated lesions in the middle third of the left leg, measuring approximately 7cm and 3cm (figure 1).

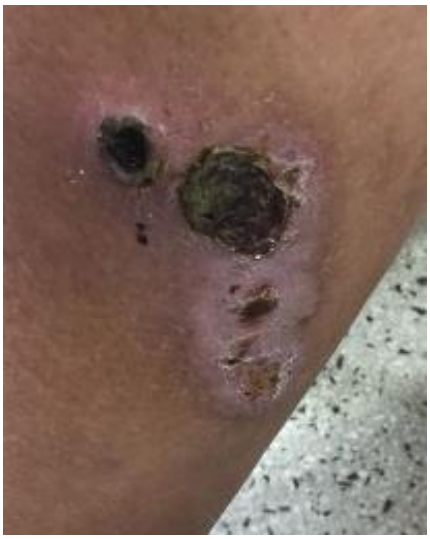

FIGURE 1 - Blackened ulcerated lesions in the left leg at hospital admission.

It was also observed that the patient had multiple verrucous-crustous, serpiginous, pruritic and desquamative lesions, with an erythematous base, distributed in the right lower limb (Figure 2). He also had a single lesion with the same pattern on the left arm. He reported that such lesions began about 20 years ago, with progressive evolution, being diagnosed as CMB three years ago, by means of a biopsy. He also reports that in the last 3 years he has undergone treatment for CMB, using itraconazole (100 mg twice daily), cryotherapy with liquid nitrogen and terbinafine, with stabilization of lesion growth. However, he says he has abandoned treatment due to lack of financial conditions.

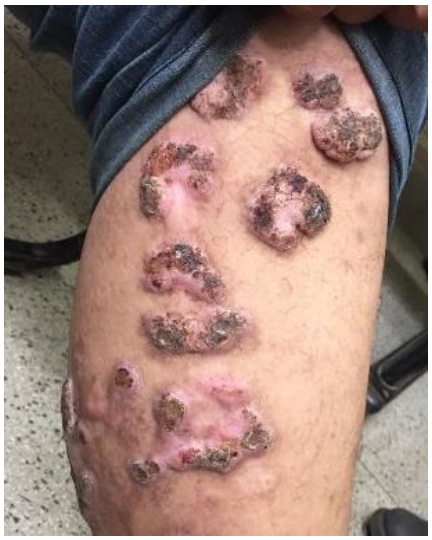

FIGURE 2 - Verrucous-crustous lesions (CMB) in right lower limb at hospital admission

Supplementary examinations at admission: hemoglobin: 14.3g/dL; hematocrit: 42%; platelets: 250,000/mm³; leukocytes: 7900/mm³; serum creatinine: 2.7 mg/dL; urea: 47.0 mg/dL; uric acid: 8.8 mg/dL; sodium: 128 mmol/L; potassium: 4.6 mmol/L; blood glucose: 145 mg/dL; and PCR: 13.14 mg/L. Rapid tests for HIV, hepatitis B and C, syphilis and chagas disease were nonreactive.

During hospitalization, ulnar thickening and sensitivity alteration was noted in the 4th finger bilaterally, with more pronounced involvement of the right side. Ultrasound examination showed bilateral ulnar thickening, with right joint effusion. A bacilloscopy (ZIEHL) was requested, which presented a negative result.

Treatment for ATL with liposomal amphotericin B was instituted because of the patient's age and his multiple comorbidities. The total dose initially programmed was 20 mg/kg, reaching a final dosage of 2.4 grams. The medication was initiated with a 300 mg dose, with adequate photoprotection and slow administration (1-2 hours).

After the third day of administration, the drug was discontinued due to worsening of the patient's renal function, despite the clinical improvement of both leishmaniasis and CMB lesions. Ultrasonography of the kidneys and urinary tracts demonstrated severe hydronephrosis on the right side. The patient was evaluated by the department of urology, which verified an irreversible loss of the right kidney, and decided to program a nephrectomy for another time and keep ambulatory monitoring until then. After the suspension of another nephrotoxic drug used by the patient, the allopurinol, the patient's renal function improved. Because there was no substitute for allopurinol available at the hospital, treatment for gout was discontinued. There was a follow-up by the department of nutrition/nutrology, in order to control uric acid levels through a specific diet.

The administration of liposomal amphotericin B was resumed 7 days after its suspension, at a dose of 250 mg/day. Four doses were administered, totaling 1900 mg. A new direct parasitological test for protozoa was performed after the

seventh dose of amphotericin B, demonstrating absence of the parasite, thus defining the end of treatment for the ATL. In addition to amphotericin B indicated for treatment of ATL, itraconazole at the dose of 200 mg twice daily for treatment of CMB was used.

The department of oncology surgery contraindicated debridement of the lesions. A new biopsy of fragments of all the lesions was carried out in order to rule out a possible spinocellular carcinoma. The results were negative for malignancy, ratifying previous biopsy for CMB.

He was discharged after 17 days of hospitalization with evident improvement in the appearance of both lesions (figures 3, 4 and 5) and programming for outpatient follow-up.

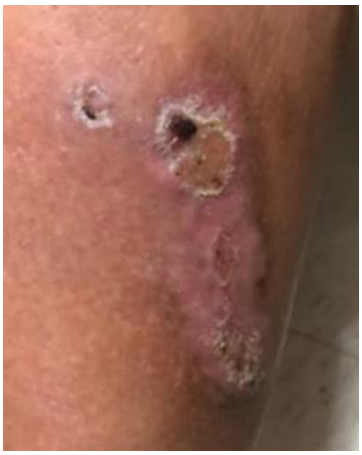

FIGURE 3 - Left Leg ATL Lesions at Hospital Discharge

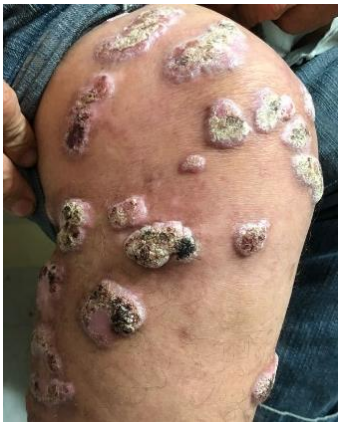

FIGURE 4 - CMB injury in right lower limb at hospital discharge

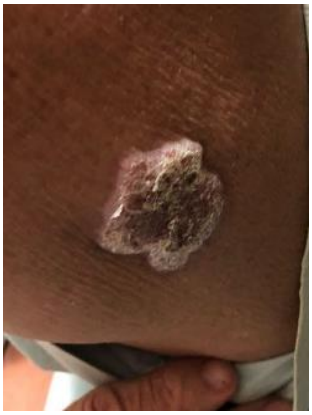

FIGURE 5 - CMB injury in left arm at hospital discharge

DISCUSSION

Chromoblastomycosis is characteristically a rare chronic skin disease that occurs due to a fungal infection. Its form of infection occurs, most of the times, due to a cutaneous trauma caused by an object contaminated by the fungus.

The diagnosis of CMB should be made as early as possible in order to begin treatment before there is dissemination and complications; and so that it can be rapidly differentiated from other diseases such as cutaneous leishmaniasis, sporotrichosis, cutaneous tuberculosis, leprosy and psoriasis.[17] In a study conducted by Correia et al[4], the time between the appearance of the lesions and the diagnosis ranged from one month to 25 years, and 29.6% of the cases had less than four years of evolution. The mean time between onset of a lesion and its diagnosis was 87.25 months, with standard deviation (SD) of 77.74 months. The analysis of this variable in rural workers shows that the average time between onset of the lesion and its diagnosis was 109.33 months, with SD of 93.23 months, while in other occupations, it was 69.18 months, with SD of 61.10 months.

The diagnosis is based on culture and direct microscopic examination with histopathological biopsy study. For a better accuracy, biopsy of the lesion with a large number of black spots is recommended.[18] In microscopy with 20% KOH, it is possible to observe multicellular microscopic structures (5 to 12 µm), with darkened and thickened walls, called medlar bodies (the fungal spores), which are pathognomonic of CMB. The finding of monoclonal infiltrates (macrophages and neutrophils) endorses the hypothesis.[17,19] The histopathological study is characterized by pseudoepitheliomatous hyperplasia with intraepidermal abscess and Medlar bodies.[20] Mycological culture is the diagnosis gold standard, since it is not only confirmatory, but also allows the isolation and study of the species of the infecting fungi.[18] More advanced tests may aid in diagnosis, like polymerase chain reaction (PCR) or serological tests (ELISA).

A long process that can be made by means of physical therapeutic methods, systemic therapy with antifungals or the combination of both characterizes the treatment of CMB. Itraconazole is the first-line therapy in systemic treatment, at a dose of 200-400 mg/day. Terbinafine is the second most frequently used antifungal agent, with a recommended dose of 250-500 mg/day. Both drugs may be used during a variable time. The response to terbinafine was similar to that of itraconazole.[21-23]

There are studies that reveal that amphotericin B used in combination with flucytosine and terbinafine in the treatment of the disease may lead to its cure.[24,25] However, due to the former's high nephrotoxicity, it is impossible to use it for long periods, and intravenous administration associated with intralesional injections is recommended.[24]

Physical methods include, mainly, surgery and cryotherapy. Conventional surgery (excisional biopsy) is the best among these treatments and is recommended in early stage lesions and when they are well delimited. Cryotherapy using liquid nitrogen is only recommended in cases of small lesions.[3]

In situations of refractoriness or advanced disease, the combination of systemic and physical therapies can be used. But there is no strong evidence of superiority of the combination of two types of systemic therapy.[3]

In this patient's case, the systemic therapy was previously associated with the physical therapy, by an irregular institution of itraconazole 200 mg/day associated with cryotherapy with liquid nitrogen and terbinafine, obtaining only stabilization of the lesions. But, due to difficulties of financial adherence to the scheme, the treatment was abandoned before its end.

During hospitalization, unlike what is reported as the recommended therapy in previous studies, a scheme that associated liposomal amphotericin B, totaling 1900 mg, with itraconazole 400 mg/day, was instituted. This strategy resulted in an evident clinical improvement of the lesions on the limbs, allowing an ambulatory follow-up.

The CMB cure criteria are based on clinical, mycological and histological criteria. In the presence of complete resolution of lesions, absence of fungal elements at microscopy and negative culture, the dermatosis is considered cured.

ATL is a complex disease transmitted by vectors and caused by protozoa of the genus *Leishmania* sp.. Its incubation period may take weeks to months. Asymptomatic infections can occur in 10% of cases, which is suggested through skin hypersensitivity tests.[27]

A wide variety of manifestations may occur, which can be attributed to variation in parasite virulence and host defense. Cutaneous manifestations associated with *Leishmania* may be:

Localized Cutaneous Leishmaniasis: Lesions usually occur on exposed areas of the skin and begin as a papule that becomes a lump, progressing to a painless ulcer with indentation at the edges and granulomatous fundus. Multiple lesions may be present and regional lymphadenopathy may occur. Secondary bacterial infections can be associated with the lesions. Their healing can take from months to years, depending on the size and the species involved, and this scar can become atrophic, with areas of hypo or hyperpigmentation or even keloid, in a patient with such predisposition.[28]

There are some clinical differences between species, but there may also be overlapping between them. The most common are: *L. infantum chagasi, L. braziliensis* and *L. guyanensis.*[29]

Diffuse or Disseminated Cutaneous Leishmaniasis: It is a rare form and usually occurs with the involvement of *L. amazonensis* and *L. Braziliensis.*[29] It begins with a lesion that does not ulcerate, and then amastigotes spread to macrophages in other regions, probably via blood or lymphatic vessels. Histologically, many parasites are visualized, but with little lymphocytic reaction. These patients often have a defect in cellular immunity, which makes treatment more difficult. Another important characteristic of this form is that it can occur concomitantly to mucosal involvement and systemic symptoms, such as fever and emaciation.[28]

Mucosal Leishmaniasis: It is characterized by mucosal destruction, deformities, pain and inflammation. Erosion can occur, most commonly in the mouth and nasal septum, and may involve other areas such as pharynx, ment and palate.

Recurrent form: The reactivation of the localized lesion occurs mainly in its borders.[29]

The definitive diagnosis can be made through direct investigation of the lesion through the scraping of the borders, culture of fragments obtained by biopsy, histopathology with visualization of amastigotes, PCR, serology and immunology (Intradermic Reaction of Montenegro) tests.[29]

Differential diagnosis includes bacterial infections, ecthyma, impetigo, sarcoidosis, lichen simplex, and fungal infections such as sporotrichosis, blastomycosis and chromoblastomycosis. Some characteristics that help differentiate it from other diseases are its chronicity, occurrence in exposed areas of the skin and ulcer with well-defined enduring edges.

Because of the rapid or late establishment of a specific immune response that leads to the parasite elimination, some individuals may have early lesion healing, sometimes without seeking medical attention, while others may remain for months with the lesion active and with a slow healing process.[29]

Pentavalent antimonials are the drugs of first choice in the treatment of cutaneous leishmaniasis. Meglumine antimonate is the formula available in Brazil. It should be administered at a dose of 10 to 20 mg Sb^{+5}/kg/day, with a maximum dose of 15 ml/day for 20 days. For the mucosal lesions, the treatment should last 30 days. It is contraindicated for pregnant women, patients with cardiac, kidney or liver disease and Chagas disease. If there is no satisfactory response or in the presence of contraindications, the second-choice drug is amphotericin B deoxycholate 0,7 to 1 mg/kg/day, with a total dose of 25 to 40 mg/kg, not exceeding the maximum daily dose of 50 mg in each application. It is contraindicated in patients with liver, renal or cardiac diseases. As a last resource, when attempts with other drugs have failed or there are contraindications, liposomal amphotericin B may be used, 2 to 5 mg/kg/day, depending on the clinical response, until reaching a total of 25 to 40 mg/kg.[29]

In the case presented, liposomal amphotericin B was the drug of choice for treatment due to the comorbidities presented by the patient, besides his age. The patient used 1900 mg of the medication, reaching a total of 15.8 mg/kg. The total dose was therefore below the goal recommended by the Health Ministry. However, due to a new direct parasitological test of the lesion with a negative result, and good cicatricial response, the patient was discharged.

The healing criterion of ATL is clinical, and regular follow-up during 12 months is indicated to verify the therapeutic response and the possibility of relapse after successful initial therapy. The case is considered as cured after complete epithelization of all lesions, which should occur within 90 days after the completion of the treatment regimen, and disappearance of crust, scaling, infiltration and erythema up to the 180th day.[29] Therefore, the patient still cannot be considered cured and, for this reason, outpatient follow-up will be necessary.

CONCLUSION

Amphotericin B is already a consolidated therapeutic alternative in cases of ATL, especially in patients who have restrictions concerning the use of pentavalent antimonials. However, CMB is still a therapeutic challenge and, in clinical practice, a great resistance to the most frequently used antifungal agents is observed. Therefore, the combined use of drugs is an effective alternative.

In the present case, although the patient was initially using the standard therapy for treatment of CMB, with itraconazole associated with terbinafine and cryotherapy, this strategy only achieved stabilization of the lesions, according to the report. Given the need to also treat ATL lesions, we could notice a significant improvement in CMB lesions with the use of amphotericin B in combination with itraconazole. However, despite the beneficial effect of the use of amphotericin B, the patient's renal status prevented the prolonged treatment with this drug.

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