Case Report: Treatment of Chromoblastomycosis with Combinations including Acitretin: A Report of Two Cases

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Abstract. Chromoblastomycosis is a cutaneous fungal infection caused by dematiaceous fungi that belong to the order *Chaetothyriales* and family *Herpotrichiellaceae*. This infection is prevalent in tropical and subtropical areas and has been designated as a neglected tropical disease according to the WHO. Chromoblastomycosis infection is difficult to treat, and there are limited therapeutic options, making urgent the characterization of new medicines or approaches to treat such infection. In the present case report, two patients with extensive chromoblastomycosis lesions were treated with the combination of itraconazole, acitretin, and imiquimod. In the fourth month of treatment, both patients showed improvement of verrucous plates, suggesting that acitretin combined with drugs already used in chromoblastomycosis therapy can decrease the time of treatment, improving patient's quality of life.

CASE REPORT

Patient 1 is a 55-year-old man, farmer, had lesions in the left leg for 35 years. He sought healthcare services 1 year after the appearance of the skin lesion. He was subjected to physical and chemotherapeutic approaches, such as itraconazole, fluconazole, ketoconazole, terbinafine, and cryotherapy and phototherapy were attempted with limited success. Medical records detailing these previous treatments, including dose, duration, and comorbidities over a period of more than 30 years could not be found. He was admitted to the dermatology outpatient service of the "Hospital das Clínicas da Universidade de São Paulo." He presented numerous skin lesions, characterized by erythematous, infiltrated, circumscribed, irregular plaques with hyperkeratotic verrucous surface (Figure 1A). In addition, crusted and healed areas completely covered the left inferior member, and in the dorsal area of the foot, verrucous plates with sclerotic bodies were observed (Figure 1B). Histopathological study performed in the section collected in the medial face of the thigh showed an intense inflammatory infiltrate, characterized by the presence of lymphocytes, macrophages, and multinucleated giant cell (Figure 1C), and muriform cells surrounded by granulomas were identified (Figure 1C, inset). Culture of the smears was performed in Sabouraud dextrose agar medium, which led to the morphological identification of *Fonsecaea* species as the etiological agent after the 15th day of culture (Figure 1D). Hepatic and renal parameters were normal, and the treatment with the drug combination was initiated with itraconazole (200 mg/day) and acitretin (50 mg/kg),¹ as well as topical imiquimod (Modik[®] 50 mg/g, Germed, Campinas, SP, Brazil) once a day, five times per week. A significant reduction of hyperkeratotic and verrucous plates was observed in the affected area after 4 months of treatment. The reduction in the size of lesions revealed a verrucous white plate with thick and irregular borders in the ankle (Figure 1E), which was behind the numerous verrucous plates observed before treatment. Histopathology

study of this plate showed the presence of spinocellular carcinoma; moreover, nuclear magnetic resonance exhibited a diffuse thickness of the skin and subcutaneous tissue. In addition, a neoplastic expansive lesion was observed in the lateral and dorsal areas of the left feet, with bone infiltration (data not shown). Besides the aforementioned treatment, the patient was subjected to 13 cycles of carboplatin and paclitaxel therapy, which was ineffective at controlling neoplastic lesion. Despite that, significant improvement of verrucous plates and hyperkeratosis was observed (Figure 1F). The affected leg was amputated, and relapses have not been observed. In addition, fungal infection is controlled, and the patient has been followed up periodically.

Patient 2 is a 46-year-old farmer presenting with lesions in the right leg for 22 years (Figure 1G). During this time, itraconazole (200 mg/day), terbinafine (250 mg/day), and cryotherapy (one session per month) were used. This association was used during 3 years when he gave up the treatment because of the limited success. There is no history of other comorbidities. All macroscopic features and histopathological changes were similar to those found in patient 1. Culture of the smears led to the morphological identification of *Fonsecaea* species as the etiological agent after the 15th day of culture in Sabouraud dextrose agar medium. All biochemical parameters were normal, and thus, the same therapeutic scheme was used: itraconazole (200 mg/day) and acitretin (50 mg/kg) by oral route, as well as topical imiquimod once a day, five times per week. Four months after treatment commenced, significant reduction of verrucous plates and hyperkeratosis was observed; macroscopically, all lesions were flatter and less crusty (Figure 1H and details in Figure 1I) than those before treatment. Despite the successful therapy combination, the use of acitretin was interrupted on the fourth month because of the increase in cholesterol, hepatic transaminases, and gamma-glutamyl transferase levels. The treatment is still ongoing with oral itraconazole and topical imiquimod.

DISCUSSION

Chromoblastomycosis is difficult to treat and has low cure rate, and relapses have been documented. Classical treatment is performed with antifungal drugs over long periods and can be combined with physical approaches, such as surgery,

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FIGURE 1. (A, B, and G) Patient 1 presented lesions in the skin characterized by erythematous, infiltrated, circumscribed, irregular plaques with hyperkeratosis in the inferior members. (C) Histological section of the skin lesions from patient 1 showed an intense inflammatory infiltrate with the presence of giant and muriform cells (inset). (D) Culture of the smears led to the identification of *Fonsecaea* genus as the main etiological agent in both cases (stained by lactophenol cotton blue). (F) Despite the chemotherapy failure during the treatment of spinocellular carcinoma, skin lesions of patient 1 caused by *Fonsecaea* sp. significantly improved. (E, H, and I) Patient 2 treated with the combination of itraconazole, imiquimod, and acitretin showed improvement of the skin lesions during 4 months. This figure appears in color at www.ajtmh.org.

cryotherapy, and thermotherapy.² Available antifungal agents are limited, making extremely important to characterize and standardize new therapeutic options directed to this neglected fungal disease.^{3,4} Previously, our group studied the efficacy of imiquimod alone or in combination with antifungal drug in the treatment of chromoblastomycosis.^{5,6} Although imiquimod was effective, it is also a consensus that the treatment depends on the etiological agent, size, and extension of the lesions, as well as comorbidities.⁷ Thus, it is still important to characterize new drugs or approaches directed to this disease. Recently, Bao et al.¹ showed the efficacy of acitretin combined with tioconazole in patients with chromoblastomycosis; treated patients lesions completely healed after the first month of treatment. The rationale for the application of acitretin was based on the mechanism of this drug in psoriasis. In such condition, acitretin inhibits the excessive cell growth and keratinization, thus reducing the thickening of the skin plaque formation and scaling.⁸ Similarly, in chromoblastomycosis, hyperkeratosis can be observed in affected areas; thus, the use of acitretin could aid the healing process in studied patients.

In the present study, the combination of itraconazole, an antifungal drug; imiquimod, an immunomodulating agent; and acitretin improved the skin lesions in patient 1 with only minor side effects, such as mucosa and skin dryness. Moreover, blood biochemical parameters were normal, suggesting that acitretin may be a promising adjuvant in the treatment of chromoblastomycosis. After improvement of lesions, it was possible to detect a spinocellular carcinoma hidden behind verrucous plates. It is well established that neoplastic transformation can occur in chronic lesions, and it is associated with an abnormal proliferation of chronically activated keratinocytes. Despite being a rare disease, reports have shown malignant transformation even for other histological subtypes of cancers, such as melanoma.^{9–11} Patient 2 showed a significant reduction in the skin lesions during the treatment with the drug combination studied herein which became flatter and less crusty than the lesions before treatment.

It has been documented that patients treated with antifungal drugs can take long period of time for the lesions to improve or heal. Recently, it was demonstrated that itraconazole was used during 24 months in a case of chromoblastomycosis caused by *Rhinocladiella aquaspersa*¹²; furthermore, a patient's cutaneous lesions caused by *Fonsecaea pedrosoi* healed after 7 months of treatment with a regimen of oral itraconazole and terbinafine.¹³ By comparison, in patients treated with the combination of acitretin, imiquimod, and itraconazole the size of lesions decreased after the fourth month; thus, acitretin can be considered an important adjuvant in the treatment of chromoblastomycosis. Despite the efficacy of the combination, changes in the blood biochemical parameters were observed in patient 2, leading to the suspension of acitretin during the treatment. Previous studies showed that chronic use of acitretin can alter blood biochemical parameters and thus should be prescribed with caution.¹⁴

Taken together, data showed herein suggest that acitretin and imiquimod may be therapeutic adjuvants in cases of

chromoblastomycosis and may decrease the time of the treatment compared with antifungal monotherapy. Further studies are necessary to comprehend the role of acitretin and imiquimod in the treatment of chromoblastomycosis.

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