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ORIGINAL ARTICLE

Treatment of chromoblastomycosis with terbinafine: Experience with four cases

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Abstract

Background: Chromoblastomycosis is a chronic subcutaneous mycosis that occurs more frequently in tropical and subtropical areas and is caused by a group of dematiaceous fungi. It is a difficult-to-treat mycosis with low cure rates and a high rate of relapses. *Objective:* The objective of this trial is to prove the efficacy and tolerance of oral terbinafine in four cases of chromoblastomycosis. *Methods and results:* We included four cases of chromoblastomycosis, proved clinically and mycologically, that are presented herein; three of them caused by *Fonsecaea pedrosoi* and one by *Phialophora verrucosa*. Two had a small extension and the other two were of medium and large extension. Oral terbinafine was administered at a dose of 500 mg/day, which was reduced to half in two of the cases once an 80% improvement had been reached; in the third case the initial dose was maintained, and in the fourth case the dose was increased to 750 mg/day. Three cases reached clinical and mycological cure in a mean treatment period of 7 months, the fourth case reached a significant improvement only after 1.2 years of treatment. The medication was well tolerated; no liver alterations occurred; only one patient suffered mild dyspepsia. *Conclusion:* Terbinafine at 500 mg/day doses represents one of the best treatments for chromoblastomycosis due to its efficacy and excellent tolerability.

Key Words: *Chromoblastomycosis, Chromomycosis, Fonsecaea pedrosoi, Phialophora verrucosa, Terbinafine*

Introduction

Chromoblastomycosis, also called chromomycosis, is a subcutaneous chronic mycosis that occurs in tropical and subtropical areas. It is caused by a series of dematiaceous (black) fungi, predominantly by *Fonsecaea pedrosoi*, that live in soil, wood and decaying plants. It begins after trauma which results in inoculation of the fungus through contact with contaminated objects. It is one of the few mycoses for which there is no treatment of choice, but rather a series of therapeutic options [1–7].

The therapeutic success rate is usually low and relapses are frequent. Cure rates range from 15% to 75% and are determined by a series of factors such as: the causal agent, location of disease, clinical variety and, mainly, the extension of the lesions [8–11]. The aim of this paper is to present our experience with a series of clinical cases in which oral terbinafine was given as first-line treatment, at variable doses and treatment periods.

Patients and methods

Clinical case 1

A 78-year-old male farmer presented with a lesion in the right upper limb, involving the medial aspect of the forearm, presenting as erythemato-squamous plaques, with a verrucous appearance, irregular in shape and well delimited, with areas of residual scarring. Symptoms included moderate itching. Of chronic course, it started 6 years before as a 'spot' that gradually extended to its current shape. Prior therapies included topical myconazole and penicillin at unspecified doses and periods. Based on the clinical aspects, the presumptive diagnoses of chromoblastomycosis and verrucous tuberculosis were made.

The following mycological work-up was done: KOH (20%) direct examination that showed multiple clusters of fumagoid cells (muriform cells). In Sabouraud's dextrose agar medium *F. pedrosoi* was

isolated and identified. The biopsy showed a lymphohistiocytic inflammatory infiltrate with fumagoid cells, some of them inside giant cells, a process that confirmed chromoblastomycosis. Blood count, liver function tests and blood chemistry were also performed and their results were within normal ranges.

Once the diagnosis was confirmed, treatment with terbinafine 500 mg/day was instituted; topical 5% salicylic acid was added, applied twice daily. After 5 months of treatment, an 80% reduction of lesions was achieved and the dose was decreased to 250 mg/day until 9 months of treatment were completed. Clinical and mycological cure had occurred by the end of treatment. Liver function was monitored during the treatment period, without any reports of alterations. In the 1.5-year follow-up no clinical activity has occurred (Figure 1).

Clinical case 2

A 65-year-old male farmer presented with a dermatosis in the right upper limb, affecting the distal third region of the forearm dorsum. The lesion consisted of a warty, rounded, well-delimited erythematosquamous plaque, with hematic and meliceric scabs and an atrophic center, with gradual growth. Symptomatology included mild itching and tenderness. Of chronic course, it had started 2 years prior to consultation with a 'small bump' that spread gradually. Prior treatments were multiple topical home remedies. Medical history revealed untreated systemic arterial hypertension. Based on the clinical picture the presumptive diagnosis of chromoblastomycosis was made.

Direct examination with KOH (20%) showed clusters of fumagoid cells. In the culture with Sabouraud's dextrose agar medium and Sabouraud + antibiotics agar (Mycosel), *F. pedrosoi* was isolated

and identified. The biopsy reported a dense, lymphohistiocytic inflammatory infiltrate, with a few epithelioid histiocytes, neutrophils and foreign body types of multinucleated giant cells, some of which contained fumagoid cells. The diagnosis was compatible with chromoblastomycosis.

Treatment with terbinafine 500 mg/day was prescribed; after 4 months of therapy an 85% reduction of the lesion size had occurred. The dose was then decreased to 250 mg/day and given for another 4 months. Clinical and mycological cure was achieved upon completion of treatment. During the treatment (month 4), the patient developed peptic ulcer disease and was treated with ranitidine at 300 mg/day given in two doses for 1 month. The patient has been followed-up for 1 year with no evidence of disease activity (Figure 2).

Clinical case 3

A 38-year-old female patient, devoted to housework and farming activities, presented with a dermatosis involving the right lower limb that affected the medial malleolus of the foot and was composed of a nodular-verrucous, erythemato-squamous plaque, approximately 6 cm in diameter, with blood scabs and well-defined borders. The referred symptom was mild itching. The patient reported that the lesion had appeared 1 year before after trauma with wood. Prior treatment was not specified. Based on the clinical picture, the presumptive diagnoses of verrucous tuberculosis, fixed-cutaneous sporotrichosis and chromoblastomycosis were made.

The following mycological tests were performed: 20% KOH direct examination, which showed multiple clusters of fumagoid cells (muriform cells). In the culture with Sabouraud's dextrose agar, *Phialophora verrucosa* was isolated and identified. No skin biopsy was performed. Blood count, liver function tests and
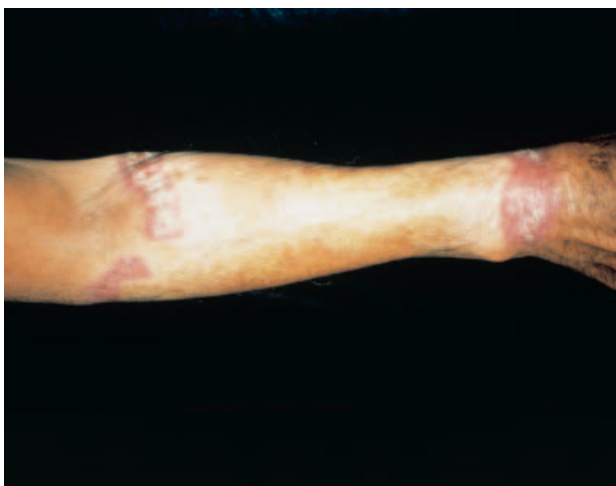
(A)

(B)

Figure 1. (A) Chromoblastomycosis baseline (Case 1); (B) clinical and mycological cure (1.5-year follow-up).
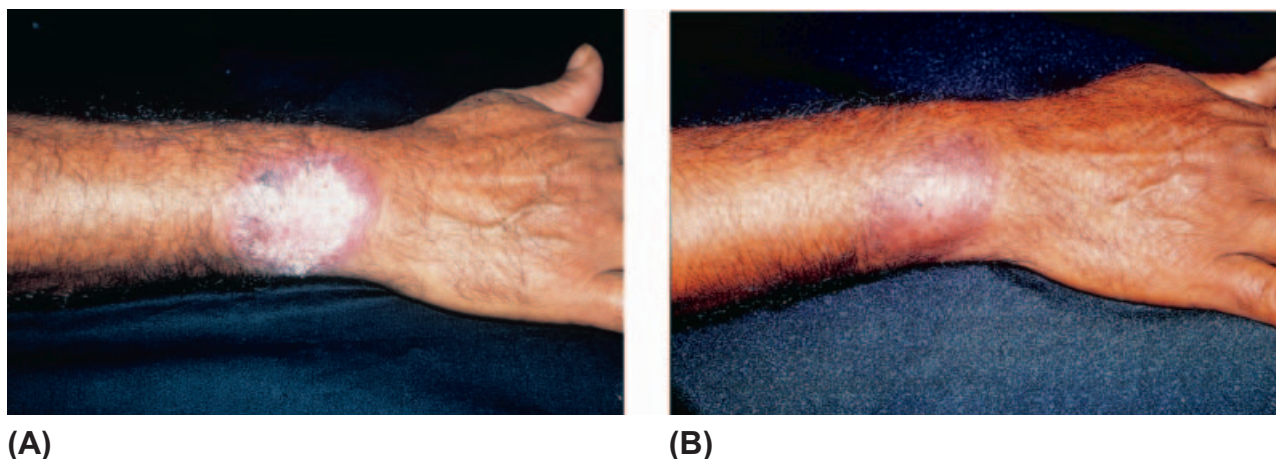
(A)   **(B)**

Figure 2. (A) Chromoblastomycosis baseline (Case 2); (B) clinical and mycological cure (1-year follow-up).

blood chemistry results were all within normal ranges.

Treatment with terbinafine 500 mg/day was instituted. At 2 months, a significant reduction of lesions occurred; the dose was then decreased to 250 mg/day and given for another 2 months. Clinical and mycological cure were achieved. The patient has been followed-up for 1.2 years without evidence of disease activity. Liver function tests were performed during the treatment period and no alterations were reported.

Clinical case 4

A 58-year-old male farmer presented with a dermatosis in the right lower limb, involving the dorsum and distal aspect of the right foot, the lower third and medial aspect of the leg. The lesion was composed of several nodular and verrucous, vegetating plaques, with erythemato-squamous areas that followed the lymphatic tract. Symptoms included mild itching and tenderness. The lesion had appeared 7 years prior to consultation, after trauma with wood splinters. Prior treatments included multiple home remedies and oral ketoconazole, at unspecified dose and duration. Based on the clinical picture, the presumptive diagnoses of verrucous tuberculosis, lympho-cutaneous sporotrichosis and chromoblastomycosis was made.

Direct examination with 20% KOH showed clusters of fumagoid cells. In the culture with Sabouraud's dextrose agar and Sabouraud + antibiotics agar, *F. pedrosoi* was isolated and identified. No biopsy was taken. Treatment with terbinafine at doses of 500 mg/day was given for 8 months. A significant reduction of the lesions had occurred after this period. The dose was increased to 750 mg/day for 3 more months, and then decreased to 500 mg/day for another 3 months. Currently the patient has a 70% reduction, but continues to have areas of clinical and mycological activity. The decision was made to combine this treatment with cryosurgery and the patient has undergone six sessions with the open-spray freezing method.

Discussion

The treatment of chromoblastomycosis has been quite variable and may be divided into two groups: physical therapy using various methods such as: standard surgery, electrodesiccation and curettage, Mohs' surgery and thermotherapy (local heat and cryosurgery) [7,9,12–16]. In general, this kind of therapy is recommended for small, early cases; surgical procedures may result in lymphatic spread of the disease. The best results have been achieved with cryosurgery, which may involve one or several sessions. It is currently recommended to combine physical therapies with chemotherapy.

Chemical treatment has involved a series of drugs that include the following major ones: 5-fluorocytosine, amphotericin B (systemic, intralesional and intra-arterial), tiabendazole, ketoconazole and fluconazole [7,9,16–18]. Cure rates with most of them are variable, some cause early resistance and others are very toxic. The triazole derivative that has recently produced the best results is itraconazole, given at doses of 200–400 mg/day; it may be given as monotherapy or combined with cryotherapy [16,19,20]. The major problem in the treatment of chromoblastomycosis is that this condition tends to form a dense dermal fibrosis that spreads and causes the large verrucous areas (cauliflower-like) that hinder the penetration of medications.

Terbinafine is an orally administered alilamine with a broad spectrum in vitro against dermatophytes, yeasts and some dimorphic fungi. Its primary mechanism of action is fungicidal and it acts in first steps of ergosterol synthesis, thus causing blockade at the level of squalene-epoxidase. Unlike azole derivatives, it does not rely on the cytochrome P-450 pathway (CYP3A4), which is involved in the metabolism of most drugs, and thus has minimal
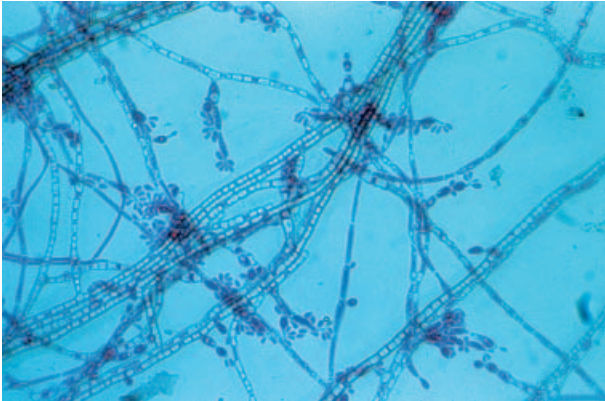
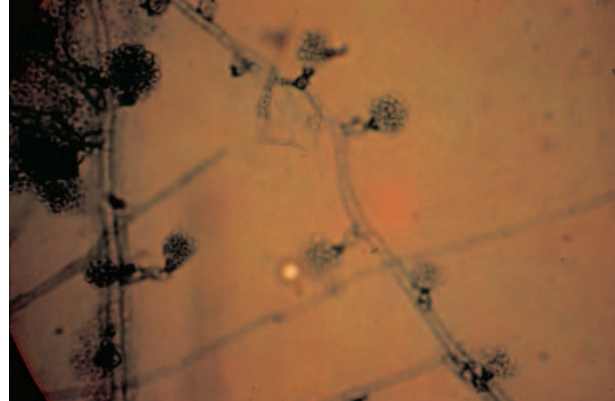Figure 3. *Fonsecaea pedrosoi* (microculture, erythrosine, 40 ×).

Figure 4. *Phialophora verrucosa* (direct exam, cotton-blue stain, 60 ×).

drug–drug interactions. It is a well-tolerated drug with a low side effect rate of 2–10% [21–24].

Esterre et al. [25] published in 1996 the first experience with terbinafine for chromoblastomycosis and this is still the largest case series published so far. It was an open-label trial with 43 patients, some of them previously treated (tiabendazole). Terbinafine was given at doses of 500 mg/day for 6–12 months. In most cases the causal agent was *F. pedrosoi* (Figure 3) and in others, *Cladophialophora carrionii*. Clinical and mycological cure was obtained in 74.2%. In other cases reported after this publication, low doses (250 mg/day) were used and cure was achieved, taking longer [26–29].

After the clinical use of terbinafine, McGinnis and Pasarell [30] conducted an extensive in vitro study with 203 strains of dematiaceous fungi exposed to itraconazole and terbinafine to determine the minimum inhibitory concentrations (MICs) and the geometric MICs (Table I). In general, the geometric MICs for both drugs are low, especially in cases involving *F. pedrosoi*: 0.07 μg/ml for itraconazole and

0.03 μg/ml for terbinafine. This may be related to the good response to both drugs, with terbinafine being slightly more sensitive. There are several studies that also show the different in vitro response to the various drugs used [31,32].

Concerning the cases presented in this paper, three reached clinical and mycological cure and the fourth case had a significant improvement, but with areas of clinical activity and muriform cells. With regard to the etiology, most cases were caused by *F. pedrosoi* and one by *P. verrucosa* (Figure 4); the latter is the first case reported that was treated and cured with terbinafine, in only 4 months (Table II). This may be due to the fact that this species is similar to *C. carrionii*, which is considered to be more sensitive to various therapies [7–9,16].

One of the most important variables to attain therapeutic success is the extension of lesions. Of the four cases treated, two had a small extension and were cured at 4 and 8 months; the third one had a medium extension involving almost all of the forearm and part of the arm, and achieved cure by 9 months. In the fourth case, improvement was all that could be achieved; however, the fact that this was the most chronic case should be stressed (7 years). Recently, Gupta et al. [33] reported a study that consisted of providing alternate and combined treatment with itraconazole and terbinafine, with good results; most cases had been refractory to other therapies. The good response rates of this regimen stem form the possibility of a synergistic effect of the two drugs, since they both act on ergosterol synthesis, but at different levels.

Table I. In vitro comparison of itraconazole and terbinafine MIC levels (principal etiologic agents of chromoblastomycosis)[30].

Etiologic agent	Itraconazole	Terbinafine
Fonsecaea pedrosoi (17[a])	0.03–1[b] (0.07)[c]	0.03–0.06[b] (0.03)[c]
Cladophialophora carrionii (21)	0.03–0.06 (0.03)	0.03–0.125 (0.03)
Phialophora verrucosa (17)	0.03–0.125 (0.07)	0.03–0.06 (0.03)

[a]Number of strains tested. [b]MIC (μg ml^{-1}): read at 72 h incubation. [c]MIC geometric mean (μg ml^{-1}).

Table II. Response and dosing of terbinafine in the cases presented.

Case	Causal agent	Terbinafine 750 mg/day	Terbinafine 500 mg/day	Terbinafine 250 mg/day	Outcome (Time)
1	*F. pedrosoi*	–	5 months	4 months	Cure (9 months)
2	*F. pedrosoi*	–	4 months	4 months	Cure (8 months)
3	*P. verrucosa*	–	2 months	2 months	Cure (4 months)
4	*F. pedrosoi*	3 months	11 months	–	Improvement (1.2 years)

Conclusion

Terbinafine is an effective drug in the treatment of chromoblastomycosis; it is well tolerated and has minimum side effects. It is therefore considered as one of the most effective drugs to treat this mycosis.

Acknowledgements

References

[1] McGinnis MR, Hill CH. Chromoblastomycosis and phaeohyphomycosis: new concepts, diagnosis, and mycology. J Am Acad Dermatol 1983;8:1–16.

[2] Rippon JW. Chromoblastomycosis. In: Medical Mycology. The Pathogenic Fungi and the Pathogenic Actinomycetes. Philadelphia: WB Saunders, 1988. p 276–96.

[3] Lavalle P. Chromomycosis. In: Cañizares O, editor. Clinical Tropical Dermatology. London: Blackwell Scientific Publications, 1975. p 36–41.

[4] Arenas R. Chromoblastomycosis. In: Jacobs PH, Nall L, editors. Antifungal Drug Therapy: A Complete Guide for the Practitioner. New York: Marcel-Dekker, 1990. p 43–50.

[5] Elgart GW. Chromoblastomycosis. Dermatol Clin 1996; 14:77–83.

[6] Bonifaz A. Chromoblastomycosis. In: Arenas R, Estrada R, editors. Tropical Dermatology. Georgetown, TX: Landes Bioscience, 2001. p 68–71.

[7] Sanche SE, Sutton DA, Rinaldi MG. Dematiaceous fungi. In: Anaissie EJ, McGinnis MR, Pfaller MA, editors. Clinical Mycology. New York: Churchill-Livingstone, 2003. p 325–51.

[8] Bonifaz A, Carrasco-Gerard E, Saúl A. Chromoblastomycosis: a clinical and mycological experience of 51 cases. Mycoses 2001;44:1–7.

[9] Restrepo A. Treatment of tropical mycoses. J Am Acad Dermatol 1994;31(suppl 1):S91–102.

[10] Esterre P, Andriantsimahavandy A, Raharisolo C. Natural history of chromoblastomycosis in Madagascar and the Indian Ocean. Bull Soc Pathol Exot 1997;90:312–17.

[11] Attapattu MC. Chromoblastomycosis: a clinical and mycological study of 71 cases from Sri Lanka. Mycopathologia 1997;137:145–51.

[12] Castro LG, Pimentel ER, Lacaz CS. Treatment of chromomycosis by cryosurgery with liquid nitrogen: 15 years' experience. Int J Dermatol 2003;42:408–12.

[13] Hiruma M, Kawada A, Yoshida M, Kouya M. Hyperthermic treatment of chromomycosis with disposable chemical pocket warmers. Report of a successfully treated case, with a review of the literature. Mycopathologia 1993;122:107–14.

[14] Kuttner BJ, Siegle RJ. Treatment of chromomycosis with a CO_2 laser. J Dermatol Surg Oncol 1986;12:965–8.

[15] Tagami H, Ginoza M, Imaizumi S, et al. Successful treatment of chromoblastomycosis with topical heat therapy. J Am Acad Dermatol 1984;10:615–19.

[16] Bonifaz A, Paredes-Solís V, Saúl A. Treating chromoblastomycosis with systemic antifungals. Expert Opin Pharmacother 2004;5:247–54.

[17] Diaz M, Negroni R, Montero-Gei F, et al. A Pan-American 5-year study of fluconazole therapy for deep mycoses in the immunocompetent host. Pan-American Study Group. Clin Infect Dis 1992;14(suppl 1):S68–76.

[18] Tilnelnot K. Therapy of infections caused by dematiaceous fungi. Mycoses 1997;40:91–6.

[19] Queiroz-Tellez F, Purim K, Fillus JN, et al. Itraconazole in the treatment of chromoblastomycosis due to *Fonsecaea pedrosoi*. Int J Dermatol 1992;31:805–12.

[20] Bonifaz A, Martínez-Soto E, Carrasco-Gerard E, Peniche J. Treatment of chromoblastomycosis with itraconazole, cryosurgery and combination of both. Int J Dermatol 1997;36:542–7.

[21] Ryder NS, Favre B. Antifungal activity and mechanism of action of terbinafine. Rev Contemp Pharmacother 1997;8:275–87.

[22] Hall M, Monka C, Krupp P, O'Sullivan D. Safety of oral terbinafine. Results of a postmarketing surveillance study in 25 884 patients. Arch Dermatol 1997;133:1213–19.

[23] Pérez A. Terbinafine: broad new spectrum of indications in several subcutaneous and systemic and parasitic diseases. Mycoses 1999;42(suppl 2):111–14.

[24] Hay RJ. Therapeutic potential of terbinafine in subcutaneous and systemic mycoses. Br J Dermatol 1999;141(suppl 56):36–40.

[25] Esterre P, Inzan CK, Ramarcel ER, et al. Treatment of chromomycosis with terbinafine: preliminary results of an open pilot study. Br J Dermatol 1996;134(suppl 46):33–6.

[26] Esterre P, Ratsioharama M, Roig P. Potential use of terbinafine in the treatment of chromoblastomycosis. Rev Contemp Pharmacother 1997;8:357–61.

[27] Sevigny GM, Ramos-Caro FA. Treatment of chromoblastomycosis due to *Fonsecaea pedrosoi* with low-dose terbinafine. Cutis 2000;66:45–6.

[28] Tanuma H, Hiratsu M, Mukai H, et al. A case of chromoblastomycosis effectively treated with terbinafine. Characteristics of chromoblastomycosis in the Kitasato region, Japan. Mycoses 2000;43:79–83.

[29] Hussain I, Rashid T, Haroon TS. Parenteral vitamin D(3) and oral terbinafine for refractory chromoblastomycosis. Br J Dermatol 2002;146:704.

[30] McGinnis MR, Pasarell L. In vitro evaluation of terbinafine and itraconazole against dematiaceous fungi. Med Mycol 1998;36:243–6.

[31] Caligiorne RB, Resende MA, Melillo PH, et al. In vitro susceptibility of chromoblastomycosis and phaeohyphomycosis agents to antifungal drugs. Med Mycol 1999;37:405–9.

[32] Bedout C, Gómez BL, Restrepo A. In vitro susceptibility testing of *Fonsecaea pedrosoi* to antifungals. Rev Inst Med Trop Sao Paulo 1997;39:145–8.

[33] Gupta AK, Taborda PR, Sanzovo AD. Alternate week and combination itraconazole and terbinafine therapy for chromoblastomycosis caused by *Fonsecaea pedrosoi* in Brazil. Med Mycol 2002;40:529–34.