Case Report

Combination Treatment of Itraconazole and Terbinafine for Chromoblastomycosis Caused by Fonsecaea Pedrosoi

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Abstract

Chromoblastomycosis is a chronic subcutaneous fungal infection mainly caused by *Fonsecaea pedrosoi*. This report describes a 42-year-old man with a verrucous plaque on the right ankle, initially presenting as small papules ten years ago, progressively enlarging. The patient, an oil palm worker, had a history of recurrent trauma and inadequate antifungal treatment. Diagnosis was confirmed by KOH, histopathology, and culture showing *Fonsecaea pedrosoi*. Combination therapy with itraconazole 100 mg twice daily and terbinafine 250 mg once daily for six months led to complete clinical and mycological cure. This case emphasizes the role of combined antifungal therapy in neglected chromoblastomycosis and the importance of early diagnosis and adherence to treatment.

Keywords: Chromoblastomycosis, combination treatment, Fonsecaea pedrosoi, itraconazole, terbinafine

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Introduction

Chromoblastomycosis is a chronic granulomatous fungal infection of the skin and tissues caused by inoculation with pigmented (dematiaceous) fungi of the order *Chaetothyriales* and family *Herpotrichiellaceae*.[1] Chromoblastomycosis is caused by penetration of wood, plants, or soil contaminated with fungi.[2] *Fonsecaea pedrosoi* is a species that causes chromoblastomycosis that is commonly found, which is around 90%.[1] Chromoblastomycosis is more common in men aged 30-50 years, mostly related to agricultural professions which related to trauma. Chromoblastomycosis is recalcitrant and very difficult to treat. There is no gold standard for chromoblastomycosis treatment, but treatment options vary from systemic antifungals, physical methods, and combination therapy. Various combination therapies can be used, ranging from the combination of itraconazole/terbinafine and cryotherapy, itraconazole with photodynamic therapy (PDT), itraconazole with 5-fluorocytosine, and combination therapy of itraconazole and terbinafine.[1,3] Combination therapy of itraconazole and terbinafine has been shown to be effective in chromoblastomycosis because both drugs have synergistic effects.[3] This case is presented because chromoblastomycosis caused by *Fonsecaea pedrosoi* remains a therapeutic challenge, especially in neglected or chronic cases. The report highlights the successful outcome of combined itraconazole and terbinafine therapy, which may serve as a valuable reference for clinicians managing similar difficult cases in resource-limited or tropical settings.

Case Report

A 42-year-old male oil palm plantation worker presented with a reddish, verrucous lump on his right ankle that had gradually enlarged over ten years. He often worked barefoot and experienced repeated minor injuries to his feet due to wooden

splinters. The lesion began as small itchy papules, which later thickened and coalesced into a plaque.

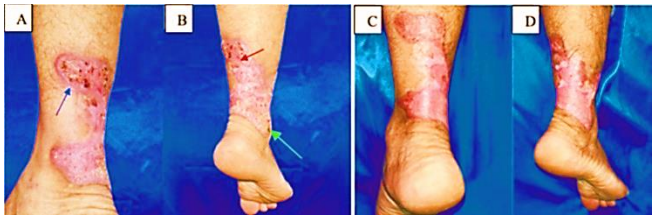

Figure 1: *Skin lesion: Before therapy (A) Verucous erythematous plaque (blue sign), with irregular edges, (B) erosion (red sign), partially covered with brownish crusts (green sign), After 6 months of combination therapy (C,D).*

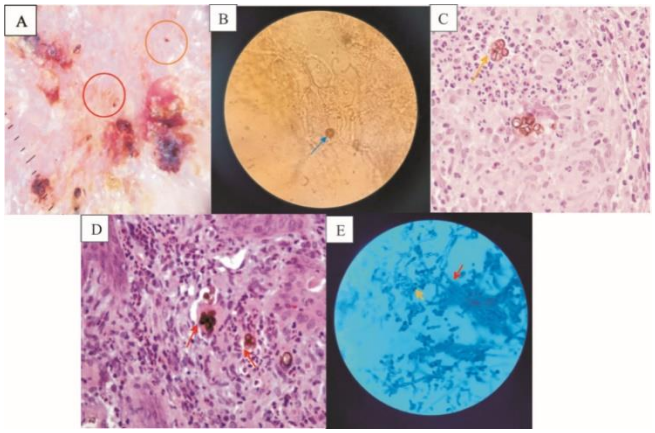

Figure 2: Summarizing the combined diagnostic images (A) Dermoscopy: Reddish-black dot (orange circle), with yellowish-orange ovoid structures over yellow (red circle). (B) KOH 10%: muriform cell. (C) Histopathology: medlar bodies (yellow arrow, X400) (D) Histochemistry: medlar bodies (red arrow, X400) and (E) Fungal Culture: dark brown hyphae (red arrow), skeletal, with conidiospores (yellow arrow), microscopically, characteristic of *Fonsecaea pedrosoi*.

Four years prior, the lesion had reached the size of a coin. The patient received oral ketoconazole 200 mg once daily for about one year without improvement and discontinued the medication on his own. Six weeks before presentation, the lesion had rapidly expanded to palm size and developed crusts, blisters, and intense pruritus.

On examination, a verrucous erythematous plaque with irregular borders, partial erosion, and brownish crusts was noted on the right ankle (Figure 1A, B). Dermoscopic examination showed multiple reddish-black dots with yellowish-orange ovoid structures over yellow, pink, and white areas, with scales and crusts (Figure 2A). Direct microscopy of skin scrapings with 10% KOH revealed muriform (Medlar) cells (Figure 2B). Histopathological examination demonstrated hyperkeratotic and parakeratotic squamous epithelium with fibrocollagenous connective tissue and suppurative granulomas composed of epithelioid cells, multinucleated Langhans giant cells, lymphocytes, plasma cells, neutrophils, and eosinophils. Medlar bodies were visible within and between granulomas (Figure 2C). PAS staining confirmed the presence of pigmented fungal elements (Figure 2D). Fungal culture on Sabouraud Dextrose Agar grew blackish-brown, velvety colonies microscopically identified as Fonsecaea pedrosoi (Figure 2E). GeneXpert testing for Mycobacterium tuberculosis was negative.

The patient was treated with a combination of itraconazole 100 mg twice daily and terbinafine 250 mg once daily for six months. Monthly follow-ups included clinical assessment, mycological examination, and monitoring of liver and renal function, which remained within normal limits. Noticeable clinical improvement was observed after eight weeks, with progressive flattening of the plaque, reduction in crusting, and cessation of itching. By the end of six months, the lesion had completely healed, leaving post-inflammatory hyperpigmentation and hypopigmentation with irregular edges (Figure 1C, D). The patient remained disease-free after one year of follow-up.

Discussion

The diagnosis of chromoblastomycosis is made based on history, clinical findings, histopathologic biopsy, and fungal culture.[4] Chromoblastomycosis is associated with agricultural professions with 70% cases associated with trauma.[1] The initial infection is usually found on the legs, arms, and upper body, as a verucous papule that spreads slowly over months or years, accompanied by a thickening lesion of 2-3 cm.[5,6] The patient works as an oil palm worker, did not use footwear when working with chief complaints of verucous papules felt about 10 years ago and developed into verucous plaques on the right ankle.

The typical dermoscopic examination in chromoblastomycosis is multiple scattered reddish black dots, due to transepidermal elimination process of inflammatory cells, fungal elements, and hemorrhage. Other dermoscopic features that can be found are yellowish orange ovoid areas over a pinkish white background, scales, crusts, and polymorphic vessels can also be seen.[7] Examination of skin scrapings with potassium hydroxide (KOH) 10-20% shows muriform (sclerotic) cells and dematiaceous hyphae can be found.[1,5] This is a pathognomonic sign of chromoblastomycosis as found in the case.

Fungal culture of chromoblastomycosis can be performed on Saboraud Dextrose Agar, growing in the range of 2-4 weeks.[1,4] In this case, we found that fungal culture grew in 3 weeks as a dark brown colony, with a velvety structure, and can be identified as *Fonsecaea pedrosoi*. Histopathologic examination with hematoxylin-eosin staining revealed pseudoepitheliomatous hyperplasia in the epidermis, suppurative granulomas without mucosa/caseous consisting of epithelioid cells and Langhans giant cells, accompanied by a collection of eosinophils, lymphocytes, and plasma cells forming isolated microabscesses in the dermis.[1,5] Muriform bodies can be found alone or clustered, inside and outside multinucleated giant cells, with a diameter of 5-12 µm.[5] Other stains such as PAS and silver methenamine can clarify fungal cells.[8]

Combination therapy in chromoblastomycosis is considered effective. Gupta *et al,* reported 4 cases of chromoblastomycosis caused by *Fonsecaea pedrosoi*, which were given alternate week therapy or combination of itraconazole and terbinafine.[3] The synergistic effect between itraconazole and terbinafine is because terbinafine inhibits the enzyme squalene epoxidase (the first stage of ergosterol biosynthesis), while itraconazole inhibits 14-alpha-sterol demethylase (the middle stage of ergosterol biosynthesis). This is favorable pharmacokinetically and pharmacodynamically because at the hepatic level, the two drugs are on different pathways, so there is no negative interaction, thereby reducing the hepatic accumulation of both drugs and the risk of hepatocellular damage is reduced. The conclusion that can be drawn from the synergistic effect of these two drugs is that itraconazole and terbinafine inhibit two stages in ergosterol biosynthesis, a weakness in the fungal membrane, so the drug can enter the fungal cells better and increase the work of leukocytes in the immune system.[9]

In this case, the patient had a history of using ketoconazole 200 mg per day for two months, but the patient discontinued the treatment on his own. The patient was given combination therapy of itraconazole 100 mg tablets and terbinafine 250 mg tablets every 12 hours orally for 6 months. Complete blood tests, liver function, and renal function were performed monthly. Side effects of itraconazole may include gastrointestinal disorders, edema, hypertension, hyperkalemia, negative inotropic effects, hepatitis, jaundice, Steven-Johnson syndrome, peripheral neuropathy, and adrenal suppression. Meanwhile, terbinafine can cause minimal gastrointestinal disturbances (abdominal pain, nausea, vomitus, diarrhea), changes in appetite, impaired taste, hepatotoxic symptoms and skin hypersensitivity eruptions.[10] In our case, the side effect was nausea. Blood laboratory tests were normal.

Evaluation of the chromoblastomycosis therapy response was based on clinical and mycological examination in this case. The clinical picture of the patient after itraconazole and terbinafine combination therapy showed thinning verucous plaques, leaving post-inflammatory hyperpigmented and hypopigmented patch. On mycological examination, no fungal elements were found in the skin scraping examination with 10% KOH. Patient is also advised to use protection while working, such as shoes, clothes, gloves, thus reducing the risk of chromoblastomycosis infection.

Conclusion

This case report discusses the diagnosis of chromoblastomycosis caused by *Fonsecaea pedrosoi*, which was treated with itraconazole and terbinafine combination therapy. In this case, there was clinical improvement of the patient's lesion within 6 months of combination therapy. Combination therapy has a favorable synergistic effect in the management of chromoblastomycosis. Close mon-

itoring of complete hematology, renal and hepatic function was performed in the patient. In our case, no serious adverse drug effects were reported. Further research is needed in the future on the use of itraconazole and terbinafine combination therapy for long-term therapy of chromoblastomycosis.

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Author's Contribution

FA: Conceived, designed, edited the manuscript, given final approval of the version to be published, critical revisions.

ELY: Manuscript writing, final approval of the version to be published, agree to be accountable for all aspect of the work.

R: Manuscript writing, final approval of the version to be published, agree to be accountable for all aspect of the work.

RP: Manuscript writing, final approval of the version to be published.

SAN: Conceived, designed, edited the manuscript, given final approval of the version to be published, critical revisions.

SD: Manuscript writing, final approval of the version to be published, agree to be accountable for all aspect of the work.

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