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Treatment of Severe Chromoblastomycosis Non Responsive with Itraconazole : A Case Report

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Abstract

Chromoblastomycosis is a chronic fungal infection of the skin and subcutaneous tissues caused by pigmented (dematiaceous) fungi. Itraconazole is widely used as a first-line antifungal therapy due to its availability and effectiveness. However, in certain cases, patients may not respond to itraconazole, necessitating alternative treatments. This research aimed to analyze the clinical response to alternative antifungal therapy in a case of chromoblastomycosis unresponsive to itraconazole. This case report involves a 52-year-old male patient presenting with progressively growing, itchy, blackened lesions on the plantar surface extending to the left ankle for 10 years. The condition was preceded by a history of untreated clavus and thorn trauma from sharp twigs or grass. Periodic Acid-Schiff (PAS) staining confirmed the presence of Medlar bodies, establishing the diagnosis of chromoblastomycosis. The patient received itraconazole 200 mg twice daily for 6 months without clinical improvement. Treatment was subsequently switched to fluconazole 150 mg once daily for 4 months, resulting in significant clinical improvement. This case demonstrates that while itraconazole is the standard treatment for chromoblastomycosis, alternative antifungal agents such as fluconazole can be effective in cases of itraconazole resistance or non-responsiveness. The findings emphasize the importance of tailored therapy based on clinical response and suggest that fluconazole may be considered as a viable alternative in such cases.

Keywords: Chromoblastomycosis, Case Report, Itraconazole, Fluconazole.

INTRODUCTION

Chromoblastomycosis is a chronic and progressive fungal infection of the skin and subcutaneous tissues, caused by pigmented (dematiaceous) fungi that are introduced into the dermis through minor trauma (Damayanti et al., 2022). This condition is particularly challenging to manage due to its chronicity, potential for severe complications, and resistance to conventional antifungal therapies. Globally, chromoblastomycosis is considered a neglected tropical disease, predominantly affecting individuals in tropical and subtropical regions. The disease's etiological agents, such as *Cladophialophora carrionii* and *Fonsecaea pedrosoi*, are saprophytic fungi commonly found in soil, decaying wood, and plant debris (Queiroz-Telles et al., 2017); (Queiroz-Telles & Santos, 2023).

While *C. carrionii* is more prevalent in arid climates and *F. pedrosoi* is predominant in humid forests, both fungi share the characteristic of infecting individuals through minor trauma, such as cuts or abrasions, often sustained during agricultural or gardening activities. The infection typically manifests as asymptomatic, erythematous nodules that

gradually develop into well-defined, verrucous, and scaly plaques over a period of months to years (Arguello-Guerra et al., 2016). These lesions are often localized to the lower limbs, correlating with the site of initial trauma. Despite being a chronic and localized disease, chromoblastomycosis can significantly impair quality of life, especially in advanced cases.

Effective management of chromoblastomycosis remains a global challenge due to the disease's chronic nature and resistance to standard therapies (Chowdhary et al., 2014). Current treatment modalities include antifungal agents, such as itraconazole and terbinafine, either alone or in combination. However, treatment outcomes are often suboptimal in moderate to severe cases. According to (Sanap et al., 2022), treatment success is hampered by factors such as delayed diagnosis, the presence of extensive lesions, and patient non-compliance. Furthermore, antifungal resistance, particularly to itraconazole—the most commonly prescribed first-line therapy—has been increasingly reported, necessitating the exploration of alternative therapeutic options (Logan et al., 2022).

In clinical practice, second-line therapies such as fluconazole have been evaluated, albeit rarely, in the context of chromoblastomycosis. Fluconazole, a triazole antifungal agent, is characterized by its excellent oral bioavailability, low protein-binding, and high tissue penetration. Despite its widespread use in other systemic fungal infections, the efficacy of fluconazole in treating chromoblastomycosis remains poorly documented, with only a handful of case reports highlighting its potential utility. This gap in knowledge underscores the urgency of systematically evaluating fluconazole as a viable alternative, particularly for patients who do not respond to itraconazole.

Several studies have highlighted the challenges and potential strategies in managing chromoblastomycosis. For instance, (Brandt & Warnock, 2023) reviewed the clinical presentations and therapeutic outcomes of patients with chromoblastomycosis, emphasizing the variability in response to itraconazole and terbinafine. Their findings suggested that combination therapies or adjunctive surgical interventions might be necessary for refractory cases. Similarly, a research by (Smith et al., 2024) discussed the global epidemiology and treatment approaches for chromoblastomycosis, advocating for the development of novel antifungal agents and personalized treatment regimens.

Case reports have also provided valuable insights into the potential use of fluconazole. One report documented a patient with moderate chromoblastomycosis who demonstrated significant clinical improvement following fluconazole therapy, despite initial resistance to itraconazole. These findings suggest that fluconazole may offer a promising alternative for managing refractory cases, warranting further investigation.

Case Illustration

A 52-years-old man from rural area came to the dermatovenereology polyclinic dr. Soeroto hospital with the main complaint of progressively growing, itchy, and blackened plantar to left ankle since 10 years ago. It started with clavus without adequate treatment then progressively widened. He complained painful (VAS 7/10) and itchy on his left foot. Previously, the patient likes gardening in the yard. The patient had a garden at home and when gardening he did not wear sandals. The patient was often scratched by sharp twigs or grass when gardening but never had serious injuries. Physical examination showed multiple verucous nodules and papules on the surface of hyperpigmented macules bases with medial diameter 41,5 cm on left plantar to dorsal pedis (Figure 1). Previously, he had been treated with itrakonazol 2 time daily for 6 months di another hospital but there were no clinical improvement. The patient first came dr. Soeroto Hospital in May 2024. Biopsy was performed and it showed atypic cells followed by histopathological examination which showed hyperkeratosis, acanthosis, and papillomatosis of epidermis and granulomatous reaction with mononuclear cells infiltration in brownish yellow pigment

at the dermis. Periodic Scid-Schiff (PAS) staining demonstrated Medlar bodies and no signs of malignancy were found (Figure 2). In conclusion, histopathology examination can support the diagnosis of chromoblastomycosis. The diagnosis was chromoblastomycosis. The patient was treated with fluconazole 1 time daily and he was educated to maintain foot hygiene. After 4 months follow up of treatment, the patient showed clinical improvement with reduced lesion size with medial diameter 37,5 cm on left plantar to dorsal pedis, reduced pain (VAS 3/10) and itchiness (Figure 3). Laboratory results over the last 4 months treatment follow up with fluconazole did not show any increase in urea, creatinine, SGOT, SGPT levels, and no side effects of the drug were reported by the patient.

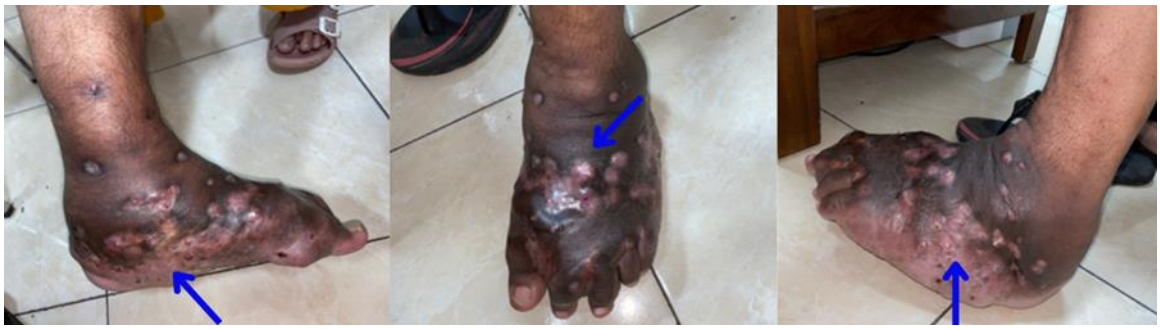

Figure 1. Multiple verucous nodules and papules on the surface of hyperpigmented macules bases on left plantar to dorsal pedis

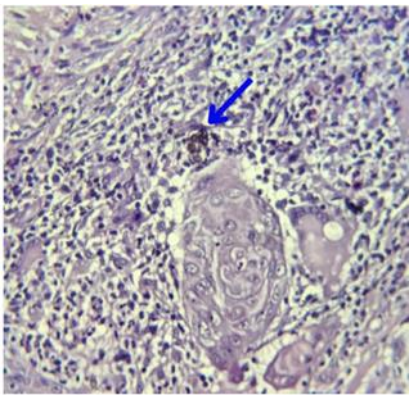

Figure 2. Periodic Scid-Schiff (PAS) staining demonstrated Medlar bodies and no signs of malignancy were found

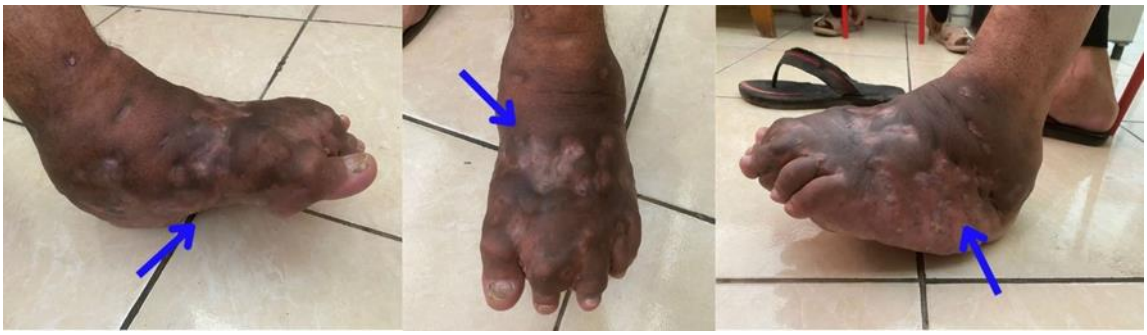

Figure 3. Skin lesion after 4 months treated with Fluconazole 150mg 1 time daily

The reported case underscores the urgent need to explore alternative treatment strategies for chromoblastomycosis, particularly in patients unresponsive to itraconazole. The successful use of fluconazole in this case highlights its potential as a safe and effective second-line therapy. Unlike itraconazole, which is associated with variable absorption and

significant drug-drug interactions, fluconazole offers a more predictable pharmacokinetic profile, making it an attractive option for managing refractory cases.

The novelty of this research lies in its systematic evaluation of fluconazole as a therapeutic alternative for chromoblastomycosis. By documenting the clinical response and safety profile of fluconazole in a patient with itraconazole-resistant chromoblastomycosis, this research contributes valuable data to the limited body of literature on this topic. Additionally, it provides a foundation for future research aimed at optimizing antifungal therapy for this challenging condition.

Based on the above background, this research aims to evaluate the clinical response to fluconazole as an alternative treatment for chromoblastomycosis in a patient unresponsive to itraconazole therapy, contributing to a better understanding of its efficacy and safety as a second-line treatment. So that the benefits in this research are to provide new insights related to the use of fluconazole as an alternative therapy in cases of chromoblastomycosis that does not respond to itraconazole therapy, especially in terms of its clinical effectiveness and safety profile. This research is expected to serve as a basis for the development of clinical guidelines in managing difficult-to-treat chromoblastomycosis, as well as assisting medical practitioners in choosing more appropriate antifungal therapy for patients with similar conditions.

RESEARCH METHOD

This research employed a case report design to examine the clinical management and treatment outcomes of a 52-year-old male patient diagnosed with chromoblastomycosis, unresponsive to standard itraconazole therapy. The subject was selected based on the inclusion criteria of being diagnosed with chromoblastomycosis and exhibiting resistance to itraconazole. Data collection involved clinical observations of lesion size, pain levels (using the Visual Analog Scale), and itching, along with histopathological examination using Periodic Acid-Schiff (PAS) staining to confirm the presence of Medlar bodies. Regular follow-up visits monitored the patient's clinical response to fluconazole therapy and any potential side effects, supported by laboratory tests measuring biochemical parameters such as urea, creatinine, SGOT, and SGPT levels to ensure safety. Data analysis consisted of descriptive assessments of clinical observations and laboratory results, comparative evaluation of outcomes with fluconazole versus prior itraconazole therapy, and interpretation of findings in the context of existing literature to highlight the potential of fluconazole as an alternative treatment for chromoblastomycosis.

RESULTS AND DISCUSSION

Chromoblastomycosis is a chronic fungal infection of the skin and subcutaneous tissues caused by pigmented (dematiaceous) fungi that are implanted into the dermis from the environment (Queiroz-Telles et al., 2017). The disease affects mostly laborers (farmers, wood cutters, latex gatherers) between 35 and 50 years of age in rural areas, and the infection is much more common in men. The lesions are usually on the lower limbs. Going barefoot or wearing sandals enhances the susceptibility, because the fungi enter hands or feet after local minor trauma. There is no ethnic predominance as all races seem to be susceptible. This demographic epidemiology correlates with our case where the patient are male in rural areas and he had history walking barefoot.

The human chronic infection begins with one or more nodules at the traumatized area. Many patients do not recall an injury. Chromoblastomycosis begins as small, asymptomatic erythematous nodules, with a slow growth over months to years (Yuliarto et al., 2023). The lesions gradually grow to form an erythematous plaque with a well-

defined border, which subsequently expands to form irregular verrucous or papillomatous lesions that are isolated or coalescent, often with superimposed ulceration. Multiple lesions may occur following lymphatic and perhaps hematogenous dissemination. The infection shows a greatly varied morphology of the lesions, among them keloid-like, cauliflower, pedunculated, ulcerated, and cicatricial, by expanding centrifugally. Chromoblastomycosis was classified by Carrión in 1950 into 5 type lesions : nodular, verrucous or warty, plaque (infiltrative or erythematous), tumoral, and cicatrical or atrophic. Complications of chromoblastomycosis are lymphadenopathy which is due to secondary bacterial infections and, in advanced disease, lymphostasis may resemble elephantiasis (Singh et al., 2024). Lesions are mostly seen on the lower extremities (feet, knee, legs), followed by those located on the upper extremities (hands, wrist, forearms). Other sites of lesions may include face, neck, dorsum, buttocks, and rarely, on mucous membranes. Some patients complain of pruritus and pain. Despite the protracted course of the disease, dissemination of the mycosis is rare. Occasionally, chronic disease leads to squamous cell carcinomas.

Chromoblastomycosis is caused by a group of genetically closely related dematiaceous fungi that have only one single-tissue form, characterized by round, thick-walled muriform cells - sclerotic bodies (Santos et al., 2021). Five principal etiologic agents have been recognized worldwide: Phialophora verrucosa, Fonsecaea pedrosoi, Fonsecaea compacta, Cladosporium carrionii, and Rhinocladiella aquaspersa (Brito & Bittencourt, 2018). Histopathology of chromoblastomycosis may show pseudoepitheliomatous hyperplasia of the epidermis, lymphohistiocytic infiltrates, and typical thick-walled dark-brown 'sclerotic' cells on skin biopsy confirming the presence of a dematiaceous fungus. It is dark coloured due to melanin in the walls of the organism. Gomori–Grocott Methenamine Silver (GMS) and PAS stains may be employed as it can highlight the fungal forms. These sclerotic cells, also known as Medlar bodies, are globe-shaped, cigar-colored, thick-walled structures that are 4-12 μm in diameter and these cells are pathognemonic finding in chromoblastomycosis. In this case, histopathological examination showed hyperkeratosis, acanthosis, and papillomatosis of epidermis and granulomatous reaction with mononuclear cells infiltration in brownish yellow pigment at the dermis. PAS staining examination demonstrated Medlar bodies which established chromoblastomycosis diagnosis.

Chromoblastomycosis is a disease that is often unresponsive to many antifungal and surgical procedures (da Silva Hellwig et al., 2019). In early localized lesions a wide and deep excision is recommended. Efficacious treatments include physical therapies such as cryotherapy (for lesions under 15 cm in diameter), photodynamic therapy, and laser treatment. The main treatments for chromoblastomycosis are itraconazole 200 mg daily, terbinafine 250 mg daily; and, in extensive cases, IV amphotericin B (up to 1 mg/kg daily).1–3 According to several open and noncomparative clinical trials, itraconazole is the standard therapy for chromoblastomycosis, and it is also the most commonly used antifungal drug. Itraconazole cure rates range from 15 to 80%.6 Fluconazole is another member of the triazole family and can be effective for chromoblastomycosis treatment.Fluconazole is a triazole antifungal agent for the treatment of systemic fungal infections active by both oral and intravenous routes. The drug is well absorbed, its plasma protein-binding is low (12%), and it penetrates well into tissues and body fluids. Reports of patients with chromoblastomycosis treated with fluconazole are rare. However, there are several case reports where fluconazole can be used effectively to treat chromobalstomycosis.

A serious case of chromoblastomycosis was resistant to any antifungal agents and was successfully treated with intravenous followed by oral fluconazole. Another case

reported the patient responded well to fluconazole after he was treated for 2 years and no side effects were observed. Fluconazole therapy can cause transient mild-to-moderate serum aminotransferase elevations and is a known cause of Drug-Induced Liver Injury (DILI). DILI occurs within the initial few weeks of therapy. Hepatotoxicity can be associated with hypersensitivity reactions, including eosinophilia, fever, and rash (De et al., 2018). In this case the patient was treated with Fluconazole 1 time daily for 4 months. After 4 months followed up, the patient showed clinical improvement with reduced pain and size of the lesion. He also didn't reported any side effects. Although treatable, there are many cases refractory to treatment; therefore, early intervention with regular follow-up is essential to reduce morbidity and mortality. Because there is rare internal organ involvement and the disease remains mostly cutaneous, there is less likely to be mortality due to the disease, except in certain cases, such as those with disseminated disease. Without treatment, complications are likely to occur, and with treatment, monitoring must be performed to observe patients for adverse effects of treatment (eg, hepatotoxicity).

CONCLUSION

In conclusion, chromoblastomycosis is a chronic fungal infection caused by pigmented fungi, commonly acquired through minor trauma in rural areas, as seen in the case of a 52-year-old man who contracted the disease after repeated barefoot trauma. Despite receiving itraconazole 200 mg twice daily for six months, the patient had no clinical improvement in lesion size, pain, or itching. However, treatment with fluconazole 150 mg once daily for four months resulted in significant clinical improvement. This case highlights the potential limitations of itraconazole as a standard first-line treatment for chromoblastomycosis and underscores the need for alternative therapeutic strategies in unresponsive cases. Successful results with fluconazole, a triazole class antifungal, demonstrate its efficacy as a second-line treatment option for chromoblastomycosis.

This research contributes to the growing body of evidence supporting fluconazole as a viable alternative for patients unresponsive to itraconazole. It underscores the importance of an individualized treatment approach and provides a basis for future research on the comparative efficacy of fluconazole in managing chromoblastomycosis. In addition, these findings encourage clinicians to consider flexible treatment strategies and emphasize the role of alternative antifungal agents in improving patient outcomes in challenging cases.

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