Successful treatment of extensive chromoblastomycosis with a combination of itraconazole and potassium Iodide.

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ABSTRACT:

KOOTIRATRAKARN T, UNGPAKORN R. SUCCESSFUL TREATMENT OF EXTENSIVE CHROMOBLASTOMYCOSIS WITH A COMBINATION OF ITRACONAZOLE AND POTASSIUM IODIDE. THAI J DERMATOL 2010; 26: 162-167.

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Chromoblastomycosis is a chronic cutaneous and subcutaneous fungal infection caused by a group of dematiaceous (black) fungi. The infection usually occurs through traumatic skin inoculation, with the majority of lesions occurring on the feet and legs of outdoor workers. Clinical features are papillomatous, verrucous and vegetating lesions. In general, a uniform, reliable treatment does not exist as one of the most common etiologic agents, *Fonsecaea pedrosoi* is difficult to manage from a therapeutic point of view. Even so, results are often unsatisfactory due to delayed treatment.

Key words: Chromoblastomycosis, itraconazole, potassium iodide

บทคัดย่อ:

ธนวัฒน์ คูถิรตระการ, รัฐภรณ์ อึ๊งภากรณ์ รายงานความสำเร็จในการรักษาผู้ป่วยโรค CHROMOBLASTOMYSIS ด้วย ITRACONAZOLE ร่วมกับ POTASSIUM IODIDE. วารสารโรคผิวหนัง 2553; 26: 162-167.

สถาบันโรคผิวหนัง กรมการแพทย์ กระทรวงสาธารณสุข

Chromoblastomycosis เป็นโรคเชื้อราเรื้อรังของหนังกำพร้าและหนังแท้ พบมากบริเวณแขนขา และบริเวณที่มีการบาดเจ็บของผิวหนัง โดยผิวหนังที่ติดเชื้อมีลักษณะหนา ด้านแข็งมีผิวที่หยาบขรุขระ และพบลักษณะของราดำฝังตัวเป็นจุดเล็กมองเห็นได้ด้วยตาเปล่า เชื้อที่ทำให้ก่อโรคได้ เช่น Fonsecaea pedrosoi, Phialophora verrucosa, Cladosporium carrionii, F. compacta และ Rhinocladiella cerphilum เป็นต้น ในการรักษาผู้ป่วยส่วนใหญ่ โดยเฉพาะในกลุ่มที่มีผื่นขนาดใหญ่ เรื้อรัง อาจจำเป็นต้องใช้ยาหลายตัวร่วมกัน รายงานฉบับนี้ขอนำเสนอการรักษาในผู้ป่วยชายที่มีประวัติการติดเชื้อ chromoblastomycosis เรื้อรังนานกว่า 30 ปี ด้วยยา itraconazole ร่วมกับ potassium iodide เป็นรายแรกและยังไม่เคยมีรายงานมาก่อน

คำสำคัญ: การติดเชื้อราในชั้นหนังแท้และหนังกำพร้า, itraconazole, potassium iodide

Chromoblastomycosis is truly a therapeutic challenge for clinicians due to recalcitrant nature, especially in the severe form[1]. Clinically, the disease is characterized by the development of verrucose, dyschromic, scaly plaques as well as atrophic patches and ulcerative lesions. Hyperkeratosis, fibrosis, and typical brown rounded structures known as muriform (fumagoid or sclerotic) cells (also known as Medlar bodies) are observed in tissue scrapings[2,3]. Five species of fungi are known generally to be the cause; they are classified according to specific morphological characteristics of sporulation that are evident on culture. *Fonsecaea pedrosoi* is the most prevalent of the five and *Phialophora verrucosa, Cladosporium carrionii, F. compacta* and *Rhinocladiella cerphilum* occur in descending order of frequency [4]. Chromoblastomycosis is associated with low cure rates and high relapse rates, particularly in chronic and extensive cases.

We report a healthy 63-year-old man with chromoblastomycosis caused by *F. pedrosoi* on the limbs complicated by disability. The successful treatment was achieved with itraconazole and potassium iodide, considered as only minimally effective when used as monotherapy. This is the first report of itraconazole and potassium iodide combination in the literature.



Fig. 1 (A) Typical extensive chromoblastomycosis involving the lower extremity, note the typical verrucous lesions intermingled with nonaffected skin areas.

(B) Improvement in the clinical appearance of the lesions

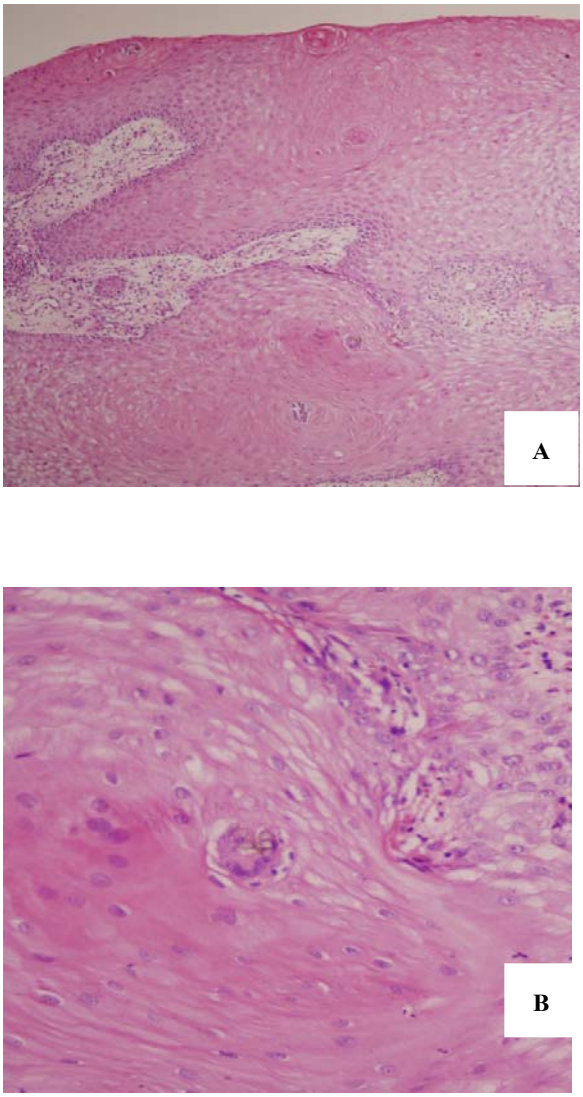


Fig 2. (A) showing hyperkeratosis, crusts, and pseudoepitheliomatous hyperplasia in the epidermis (haematoxylin and eosin).

(B) Mixed inflammatory cell infiltrate with sclerotic bodies (arrow) in the giant cell (haematoxylin and eosin)

Case report

The patient was a 63-year-old male agricultural worker. The infection started as a solitary nodule on his right ankle and over the next 30 years, multiple lesions formed at the site that expanded to confluent nodular groups of verrucous plaques with central clearance. In between the plaques were isles of uncompromised interlesional skin and atrophic areas. He discontinued the treatment with itraconazole 8 years previously due to financial problem and difficulty to seek medical attention. When the patient was evaluated, he was found to have an extensive plaque mainly compromising the dorsal area of his right foot and extending to the upper third of the thigh. There was concomitant stabbing pain, pruritus and joint anchilosis, all of which severely limited the functionality of the limb (Fig. 1A). Direct examination of the surface squamous-crusted lesions cleared with 10% potassium hydroxide (KOH) revealed the presence of pigmented fungal cells with thick walls. Biopsies taken from the periphery of the lesions showed slight laminar hyperkeratosis, as well as pseudocarcinomatous hyperplasia with microabscesses. At the dermal level there were granulomas with well-epithelioid differentiation, Langhans-type cells with a lymphohistiocytic inflammatory infiltrate, and polymorphonuclear neutrophils with presence of muriform cells (Fig. 2A-B). The tissue samples taken from the active border of the lesions were cut into thin slices and cultured in Sabouraud's dextrose agar. The colonies were identified as *F. pedrosoi*. Complete blood count (CBC), blood chemistry and anti-HIV antibody showed normal values. Radiological study of the affected limb did not reveal any alterations other than fibroid component restricted to soft tissues. Combined therapy with itraconazole and potassium iodide was implemented. Itraconazole was administered at 100 mg twice daily with Potassium iodide 900 micrograms/day for a full year after the patient's release from the hospital. Hepatic, renal, thyroid and cardiovascular functions were strictly monitored and no complications were noted. Electrolytic balance, liver, thyroid and renal abnormalities were monitored every 3 months during the study. Skin lesions were significantly improved from the 12th week of therapy. No new lesions developed and the fungus was no longer isolated from control skin biopsies after one year follow-up. The patient recovered the functionality of his leg and returned to his normal daily activities (Fig. 1B).

Discussion

Chromoblastomycosis is a disease difficult to treat due to the marked chronicity of lesions and the well-known resistance of many of its etiologic agents to monotherapy [5]. Response to treatment depends on the infective agent, the extent and chronicity of disease. Long-term courses of antifungals remain the cornerstone of treatment, enhancing compliance of the patient. It is well-known that there is no ideal effective therapy for chromoblastomycosis [6]. Treatment may be divided into three groups; physical treatment, chemotherapy and combination therapy. In early stages

of the disease, lesions respond to surgical resection but better results are achieved with systemic antifungals in more severe cases[7,8].

The main treatment involves the use of antifungal chemotherapy. In the management of extensive disease, the realistic goal may be to control disease activity and minimize risk of complication. Medical treatment options include 5-flucytosine, itraconazole, terbinafine, fluconazole, thiabendazole, ketoconazole, amphotericin-B and potassium iodide have been reported [2, 9, 10, 11]. All these agents are associated with significant adverse effects and require appropriate monitoring of liver and renal functions. Some of them are not available in endemic rural area. Concerning the extensive cutaneous lesion which is often present in infections due to *F. pedrosoi*, it is important to point out that the edema, dermal fibrosis, increased susceptibility to secondary infection, lead to impedance of lymphatic flow eventually causing lymphedema below the affected sites. Impairment of circulation caused by chronic lymphedema leads to skin and soft tissue atrophy, deformity, ankylosis of joints leading to permanent disability and carcinomatous transformation. Non-invasive squamous cell carcinoma may also arise from chronic lesion [2]. Imidazoles, mainly ketoconazole and itraconazole have been extensively used without satisfactory results [12]. Itraconazole is a fungistatic first-generation triazole, which inhibits the cell membrane ergosterol via 14-alpha-demethylase blockage. This compound is safe and useful for treating fungal infections requiring long-term therapy such as chromoblastomycosis. The trials using pulse itraconazole at 400 mg daily have demonstrated the effectiveness of this drug in treating cases caused *by F. pedrosoi* [2] and even at doses between 100 and 200 mg in long term therapy has been reported. On the other hand, resistance has been demonstrated in sequential isolates of *F. pedrosoi* from patients undergoing long-term therapy with this drug. The edema and dermal fibrosis can also reduce the tissue levels of antifungals which in turn diminishes the possibilities of successful therapy. For extensive lesions described in this case report, monotherapy may be ineffective, especially with infections caused by *F. pedrosoi*. Other combinations with 5-fluorocytosine and terbinafine for effective treatment in cases due to *F. pedrosoi* have been reported[13,14,15]. However, the cost and long duration of treatment are main issues leading to non-compliance in rural endemic areas.

Potassium iodide is an anti-fungal drug listed in the World Health Organization (WHO) essential drug list and generally thought to be the first choice for cutaneous sporotrichosis including fixed and lymphocutaneous types in developing countries. Potassium iodide is also effective in chromoblastomycosis[9,10]. The combination of itraconazole and potassium iodide remains economical, effective and well-tolerated initial treatment. The positive results may be the consequence of a possible synergism between both drugs on different anti-fungal

mechanisms of action. Treatment should be continued until there is clinical resolution, which is usually after several months of therapy. Relapse is, however, common especially in most extensive lesions.

For successful management of the patient with chromoblastomycosis, full assessment of the general health of the patient, their socioeconomic conditions, compliance to therapy, possible drug resistance, treatment of comorbidities and complications should be considered because none of the currently available treatments offer entirely satisfactory results in all cases. This is partly due to the diversity of etiologic agents, some of which may not be susceptible to the drugs used and partly due to the nature of the hyperkeratotic and nodular lesions that make it difficult for the pharmacologic agents to penetrate the tissue where the fungi are located. The most important factor, however, is extensive delay before patients started treatment. Most patients are agricultural workers in rural locales far from medical facilities. Furthermore, they are unable to afford the high cost, long duration of treatment or the time away from families that are dependent upon them.

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