ABSTRACT

Introduction: Chromomycosis is a localized chronic mycosis of skin and subcutaneous tissue caused by pigmented fungi. It is most common in tropical regions. Lesion usually presented with trauma history, and characterized by nodular verrucous that grow slowly on the lower extremities. The disease is difficult to treat. Case Report: A 33-year-old male gardener came with the main complaint multiple bumps accompanied with itchy and pain sensation on left leg that has become wider since 15 years before. There was a history of a thorn trauma in his left lower extremity and he used to contact with soil and plants. The patient was diagnosed as chromomycosis based on history, clinical features, and confirmed with potassium hydroxide 10% that showed muriform cell, and fungal culture revealed the species Fonsecaea pedrosoi. The patient has not improved significantly treated with ketoconazole 200 mg 2 times daily for 9 months. The treatment was replaced into itraconazole 100 mg 2 x 2 tablets combined with terbinafine 250 mg 2 x 1 tablets for 7 months and it gave a good result.

Discussion: Predisposing factors in this case were a history of thorn trauma and contact with soil and plants continuously. The lesions improved after 7 months treated with itraconazole and terbinafine. Chromomycosis is very difficult to treat and until now the gold standard treatment is not available yet. Combination therapy, itraconazole and terbinafine, could be considered for the therapy of chromomycosis with good result. Combination therapy can be continued until 2-4 weeks after no palpable nodules anymore.

Key words: chromomycosis, Fonsecaea pedrosoi, itraconazole, terbinafine.

INTRODUCTION

Chromomycosis (ICD 10 : B43.0 = the new name is Chromoblastomycosis), it is a chronic, progressive, subcutaneous mycosis caused by phoeid or dematiaceous fungi. It is a subcutaneous fungal infection, usually an occupational related disease, mainly affecting individuals in tropical and temperate regions. It is caused by a pigmented, so-called, dematiaceous fungus, with Fonsecaea pedrosoi being the etiological agent in 90% to 96% of cases. Although several species are etiologic agents, but Fonsecaea pedrosoi and Cladophialophora carrionii
are prevalent in the endemic areas. Chromomycosis lesions are polymorphic and must be differentiated from those associated with many clinical conditions. Diagnosis is confirmed by the observation of muriform cells (sclerotic or fumagoid cells or medlar bodies) in tissue and the isolation and the identification of the causal agent in culture. Chromomycosis is still a therapeutic challenge for clinicians due to the recalcitrant nature of the disease, especially in the severe clinical forms. There are three treatment modalities, i.e., physical treatment, chemotherapy and combination therapy but their success is related to the causative agent, the clinical form and severity of the chromomycosis lesions. There is no treatment of choice for this neglected mycosis, but rather several treatment options. Most of the patients can be treated with itraconazole, terbinafine or a combination of both. It is also important to evaluate the patient’s individual tolerance of the drugs and whether the antifungal will be provided for free or purchased, since antifungal therapy must be maintained in long regimens and the price are very expensive. In general, treatment should be guided according to clinical, mycological and histopathological criteria.

CASE REPORT

A 33-year-old man was admitted to Dermatovenerology Ward of Dr. Soetomo General Hospital, Surabaya, on February 15th 2015 with main complaint multiple bumps on his left leg. He presented with a 15 years long history and a verrucous nodules plaque cauliflower like lesion accompanied with itchy and pain sensation on the left leg (Figure 1). History revealed that it began with a small papular lesion on the knee and spreading to left thigh and calf. He claimed that the initial lesion had started on the left knee after a thorn trauma in his work place. This small papules enlarged became nodules and plaque over the years and spread to other parts of the left lower limb. During this time, he was also frequently in contact with soil and plants in his work place, without using any protective shoes.

No associated symptoms of fever, cough, joint pain, loss of appetite, loss of weight, or night sweats were present. He had no underlying risk factors for immunosuppression condition. No other family members had similar lesions.

General physical examination at first day of admission was within normal limit. Laboratory examination in the first admission revealed haemoglobin was 15.3 g/dL, white blood count was 11,4x10³/µL and platelets was 240x10³/µL. The result from urinary test was normal. From serum glutamic oxaloacetic transaminase (SGOT) was 24 U/L, serum glutamic pyruvate transaminase (SGPT) was 46 U/L and albumin was 3,2 g/dL. Direct examination of scales of the verrucous plaques in potassium hydroxide 10% supplemented with lactophenol demonstrated multiple dark brown muriform cells, approximately 4 µm in diameter, round to polyhedral (chestnut) in shape, thick-walled, and dark pigmented (Figure 2).

Culture of the tissue biopsy on Sabouraud’s dextrose agar with chloramphenicol revealed a slowly growing, velvety colony, dark brown which appeared after twenty days of incubation (Figure 3). Microscopic examination with lactophenol cotton blue staining showed dominant form of conidia, varying length, conidia closest to the conidiophore and short conidia chain branch, according to Fonsecaea pedrosai (Figure 4). Histopathological examination on Hematoxylin-eosin–stained (HE) and Periodic acid-schiff (PAS) staining revealed parakeratosis in the epidermis, acanthosis, inflammatory infiltration of lymphocytes, histiocytes, septate body arranged forming granulomas, while in dermis revealed inflammatory infiltration of lymphocytes, histiocytes, plasma cell, septate body between the fibrous connective tissue stroma, and it was also evident necrosis in accordance with chromomycosis (Figure 5).
Chromomycosis Treatment With Combination Of Itraconazole And Terbinafine

**Figure 2.** Potassium hydroxide 10% revealed muriform cells (+).

**Figure 3.** Sabouraud’s dextrose agar with chloramphenicol revealed black aerial hyphae.

**Figure 4.** Microscopic examination of the culture revealed *Fonsecaea pedrosoi*.

**Figure 5.** A. Histopathology examination with Hematoxylin and Eosin stain revealed granuloma and muriform cells and B. Periodic Acid-Schiff (PAS) stain revealed muriform cells. (100x magnification).
The patient was treated with oral ketoconazole 200 mg 2 times daily, he routinely control every one month. After 9 months of treatment there was no significant improvement (Figure 6), itchy and pain sensation still persisted, the lesion became hyperpigmented and there were new lesions. It was decided to change the therapy into combination oral antifungal itraconazole 400 mg/day and terbinafine 500 mg/day. In the 3.5 month there was improvement, itchy and pain sensation was decreased, the lesion became thinner, no new lesion on the left lower extremity was found (Figure 7). Patient felt satisfied after consuming combination therapy for 6 months (Figure 8) and completely healed within 7 months (Figure 9), the itchy and pain sensation has disappeared. The result of microscopic examination to detect the fungal from scrapings with potassium hydroxide 10% was not found after 7 months combination therapy. The combination therapy was still continued until one month to prevent relaps, after there was no palpable nodules anymore.

Figure 6. After 9 months treatment with ketoconazole, there were new lesions.

Figure 7. After 3.5 months combination therapy.

Figure 8. After 6 months combination therapy.

Figure 9. After 7 months combination therapy.

Figure 10. Potassium hydroxide 10% revealed no muriform cells after 7 months of combination therapy.
DISCUSSION

Chromomycosis (Chromoblastomycosis) is one of the most frequent infections caused by melanized fungi which can present as nodular, plaque like, verrucous, or cicatrical lesions. It was first described in 1914 by Max Rudolph in Brazil. Subsequently Medlar described the characteristic histological appearance of sclerotic bodies, which thereafter were named as ‘Medlar bodies’. Other synonyms are “copper-pennies” or “mauriform” cells (sclerotic or fumagoid cells or medlar bodies).1-4 Chromomycosis is belong to phaeohyphomycosis group and caused by dematiaceous (naturally pigmented) fungi (pheid fungi) such as Fonseccaea pedrosoi, Phialophora verrucosa, Fonseccaea compactum, Cladophialophora carrionii, Exophiala jeanesmei, Exophiala castellanii and Rhinocladiella aquaspersa.15,16 Fonseccaea pedrosoi is the most common causative agent. It is a subcutaneous fungal infection, usually an occupational related disease, mainly affecting individuals in tropical and temperate regions. The fungi are apparently introduced into host tissues through some minor injury where a contaminated splinter or thorn penetrates the skin.17,18 Chromomycosis affects mainly men aged between 30-60 years, uncommon in women or children aged younger than 15 years. There is a 4:1 male predominance, and farmers account for almost 75% of patients with the disease. Most patients have a history of trauma caused by wood or vegetation, and more than 80% are agricultural workers, who often go barefoot.7,8 In the 45 chromomycosis cases studied from Madagascar, 87% of the patients were males and 55% were agriculture workers. The male predominance probably represents increased exposure due to a preponderance of male outdoor workers in some countries.

The lesions are more frequent on the legs. The disease can also involve other exposed areas, such as hands, arms, trunk, buttocks, neck, forearms, and face. The autoinoculation spreading of the lesions is due to scratching and lymphatic spreading. Chromomycosis does not involve bone or muscle.10 Lesions are asymptomatic and growing slowly. The symptom noted is often pruritus and rarely pain. Early lesions begin as a small, erythematous papule. Lesions progress into an erythematous plaque with or without scales or ulceration, then the plaque develops into verrucous. Verrucous lesions look like a cauliflower. They can ulcerate and discharge pus due to secondary infection. Lesions may also heal leaving sclerotic plaques or keloids.18,19 In the advanced cases, more than one type of lesion can be observed in the same patient. In addition, lesions can be graded according to their severity. The mild form involves a solitary plaque or nodule measuring less than 5 cm in diameter. The moderate form consists of solitary or multiple lesions which may be nodular, verrucous or plaque types, existing alone or in combination, covering one or two adjacent cutaneous regions, measuring less than 15 cm in diameter. Finally the severe form includes any type of lesion alone or in combination, covering extensive cutaneous regions whether adjacent or non-adjacent, it was like this patient, severe lesions tend to respond slowly or even become non-responding to antifungal drugs.20,21

The diagnosis of chromomycosis is based on history, clinical finding, histopathology and culture. Direct microscopic examination using potassium hydroxide 10% of scraping lesion can reveal round, brown, thick-walled, multisepate sclerotic cells that are pathognomonic of chromomycosis.13,14 These are known as muriform cells (Medlar bodies, sclerotic bodies or fumagoid cells).13 Hematoxylin-eosin-stained biopsies will demonstrate inflammatory infiltrate characterized by mixed granulomatous response with small neutrophil abscesses, multinucleated cells, fibrosis, acanthosis, papillomatosis, hyperkeratosis, and pseudo-epitheliomatous hyperplasia. Round cooper-colored medlar bodies are often seen in groups within giant cells or suppurative foci.9 Culture of scraping must be performed on fungal media containing antibiotics, such as Saboraud’s dextrose agar with chloramphenicol. The microorganisms produce black and slowly growing appeared after 2 until 4 weeks incubation.14 The colony became heaped up, folded, with surface dark green, gray or black and velvety on further incubation, usually flat, then developing a convex, cone-shaped protrusion in the center. Colony becomes slightly embedded in the medium. The reverse side of the colony was black in colour. The microscopic examination showed species of Fonseccaea pedrosoi. This species was diagnosed by finding Cladosporium (Homodendrum) type which shows conidiophores vary in length and have tree-like branching, they bear ovoid, dark conidia in branching chain formation. When the conidia becomes detached, they have dark points on the ends where they had been joined together. This type of conidiation is sometimes the most prevalent. Rhinocladiella (Acrotheca) type was also found that showed conidiophores swollen, knotted, or club shaped, arising terminally or laterally on hyphae and bearing elongate conidia along the upper portion and the tips. In some instances, the primary conidia may produce secondary conidia, which may produce tertiary conidia, creating a Cladosporium-like formation.
other form that could not found was *Phialophora* type that showed vase- or urn-shaped conidiophores with terminal cup-like flares. Small, elliptic conidia are produced and accumulate at tip of the ‘vase’. This type of conidiation is often scant or lacking in this species.\(^\text{13}\)

Chromomycosis is difficult to eradicate. Patient with chromomycosis is a challenge to clinicians. Patients with extensive disease, the cure rates are low. In some cases, only 30% patients were cured, and almost 60% improved. \(^\text{15}\) There is no gold standard therapy for chromomycosis, but several treatment options are available including systemic antifungals used alone or combined with physical method such as surgery, local heat, or topical liquid nitrogen. \(^\text{8}\) For localized lesions, surgery is often a first line solution. Medical treatment options available are including: 5-flucytosine (50-150 mg/body weight per day in 4 divided doses), itraconazole (100-400 mg/day), thiabendazole (25 mg/body weight per day in 3 divided doses), ketoconazole (200-400 mg/day), terbinafine (250-500 mg/day), fluconazole (200-600 mg/day), and amphotericin B (up to 1 mg/body weight per day). Spontaneous resolution of the disease is rare. Amputation is hardly ever indicated because there is no dissemination into deep tissue. \(^\text{9}\) Treatment should be continued until one month after no palpable nodules available anymore. It is usually happened after several months or years of therapy. Relapse is common especially in the most extensive lesions. \(^\text{16}\)

Initial treatment in this case was ketoconazole 400 mg/daily with no significant improvement after 9 months of follow up. Then the treatment was switched into combination of itraconazole 400 mg/day and terbinafine 500mg/day. This combination therapy was giving a good results within 3,5 months and gave satisfactory result after 7 months of treatment. It was proven from potassium hydroxide 10% examination which revealed no muriform cells. There were no significant adverse effect noted of this combination treatment. Bloodwork (complete blood count [CBC], liver function tests, urea, and creatinine) was performed every 2 months and remained within normal limits. Chromomycosis develop slowly and difficult to treat with a high relapse rate, therefore early diagnosis, the selection of tretment and patient education is important.

REFERENCES