Chromomycosis Treatment With Combination Of Itraconazole And Terbinafine

Amalia Rositawati, Sunarso Suyoso
Departemen/Staf Medik Fungsional Kesehatan Kulit dan Kelamin
Fakultas Kedokteran Universitas Airlangga/Rumah Sakit Umum Daerah Dr. Soetomo Surabaya

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 garderner came with the main complaint multiple bumps accompanied with itchy and pain sensation on left leg that has became wider since 15 years before. There was a history of a thorn trauma in his left lower extrimity 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 *Fonsacaea pedrosoi*. The patient has not improved significantly treated with ketoconazole 200 mg 2 times daily for 9 months. The treatment was replaced into itrakonazole 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 continously. 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, *Fonsacaea pedrosoi*, itrakonazole, terbinafine.

ABSTRAK
Latar Belakang: Kromomikosis adalah mikosis kronis lokal dari kulit dan jaringan subkutan yang disebabkan oleh jamur berpigmen. Infeksi ini paling sering terjadi di daerah tropis. Lesi biasanya diawali dengan riwayat trauma, dan ditandai dengan nodul verukosa yang tumbuh lambat pada ekstremitas bawah. Penyakit ini sulit diobati. **Kasus:** Seorang laki-laki 33 tahun bekerja sebagai tukang kebun datang dengan keluhan utama muncul benjolan-benjolan disertai dengan rasa gatal dan nyeri pada kaki kiri yang meluas sejak 15 tahun yang lalu. Terdapat riwayat trauma tertusuk duri pada ekstrimitas bawah sebelah kiri dan sering kontak dengan tanah dan tanaman. Diagnosis kromomikosis didasarkan pada anamnesis riwayat pasien serta gambaran klinis dan dikonfirmasi dengan pemeriksaan kalium hidroksida 10% yang menunjukkan sel muriform dan pada kultur jamur yaitu spesies *Fonsacaea pedrosoi*. Pasien belum membaik secara signifikan setelah diobati dengan ketokonasol 200 mg 2 kali sehari selama 9 bulan. Pengobatan kemudian diganti menjadi itrakonasol 100 mg 2 x 2 tablet dikombinasikan dengan terbinafin 250 mg 2 x 1 tablet selama 7 bulan dan memberikan hasil baik. **Diskusi:** Faktor predisposisi untuk kasus ini adalah riwayat trauma tertusuk duri dan riwayat kontak dengan tanah dan tanaman secara terus menerus. Lesi membaik setelah 7 bulan diterapi dengan itrakonasol, dan terbinafin. Kromomikosis sangat sulit untuk diobati dan sampai sekarang pengobatan standar baku belum tersedia. Terapi kombinasi, itrakonasol dan terbinafin, bisa dipertimbangkan untuk terapi kromomikosis dengan hasil yang baik. Pengobatan dengan terapi kombinasi dapat dilanjutkan sampai 2-4 minggu setelah tidak ada nodul yang teraba lagi.

Kata kunci: kromomikosis, *Fonsacaea pedrosoi*, itrakonasol, terbinafin.

Corespondence address: Amalia Rositawati, Departemen/Staf Medik Fungsional Kesehatan Kulit dan Kelamin Fakultas Kedokteran Universitas Airlangga, Rumah Sakit Umum Dr. Soetomo, Jl. Mayjen Prof. Dr. Moestopo No. 6-8 Surabaya 60131, Indonesia. Telepon: (031) 5501609, email: amaliawahdin@gmail.com.

INTRODUCTION

Chromomycosis (ICD 10 : B43.0 = the new name is Chromoblastomycosis), it is a chronic, progressive, subcutaneous mycosis caused by pheoid or dematiaceous fungi. It is a subcutaneous fungal infection, usually an occupational related disease, mainly affecting individuals in tropical and temperate regions.[1] It is caused by a pigmented, so-called, dematiaceous fungus, with *Fonsecaea pedrosoi* being the etiological agent in 90% to 96% of cases.[2] Although several species are etiologic agents, but *Fonsecaea pedrosoi* and *Cladophialophora carrionii*

are prevalent in the endemic areas.[3,4] 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[1]) in tissue and the isolation and the identification of the causal agent in culture.[5,6] Chromomycosis is still a therapeutic challenge for clinicians due to the recalcitrant nature of the disease, especially in the severe clinical forms.[7,8] 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.[9,10] 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-term regimens and the price are very expensive.[11,12,13] In general, treatment should be guided according to clinical, mycological and histopathological criteria.[14,15]

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 $11,4x10^3/\mu L$ and platelets was $240x10^3/\mu L$. 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).

Figure 1. Multiple verucous nodules and papules on the surface of hyperpigmented macules on the left leg of the patient on February 15th 2015.

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 pedrosoi* (Figure 4). Histopathological examination on Hematoxylin-eosin–stained (HE) and Periodic acid-schiff (PAS) staining revealed parakeratosis in the epidermis, acanthosis, inflamatory infiltration of lymphocytes, histiocytes, septate body arranged forming granulomas, while in dermis revealed inflamatory 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).

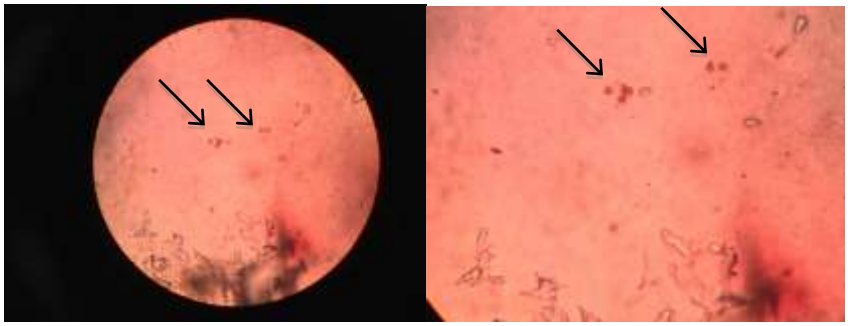

Figure 2. Potassium hydroxide 10% revealed muriform cells (+).

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

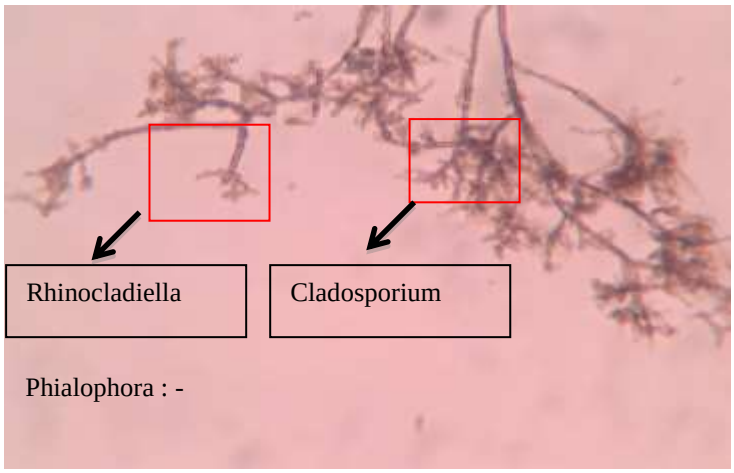

Figure 4. Microscopic examination of the culture revealed *Fonsecaea pedrosoi*.

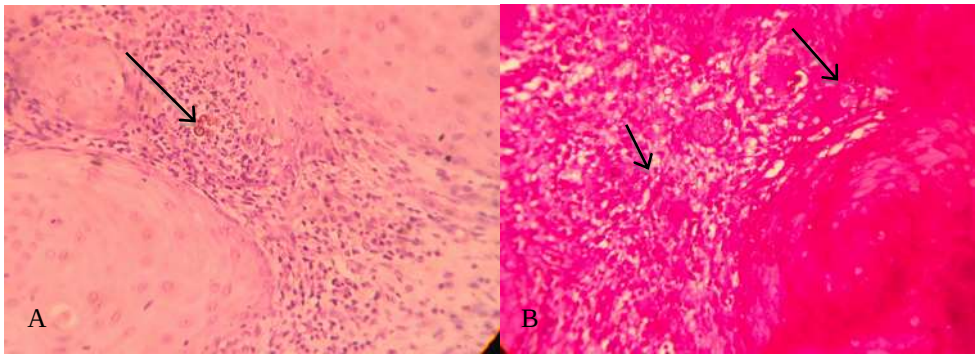

Figure 5. A. Histopatology examination with Hematoxylin and Eosin stain revealed granuloma and muriform cells and **B.** Periodic Acid-Schiff (PAS) stain revealed muriform cells. (100x magnification).

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 thiner, 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.

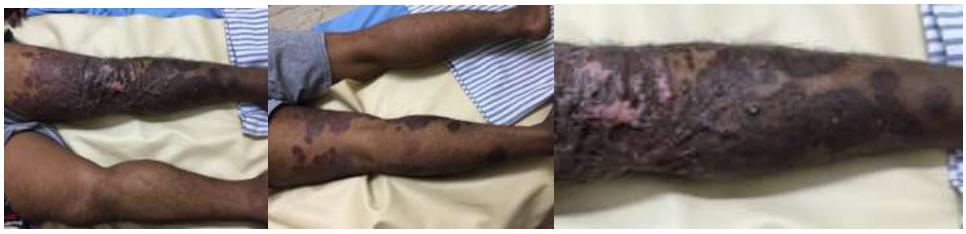

Figure 7. After 3,5 months combination therapy.

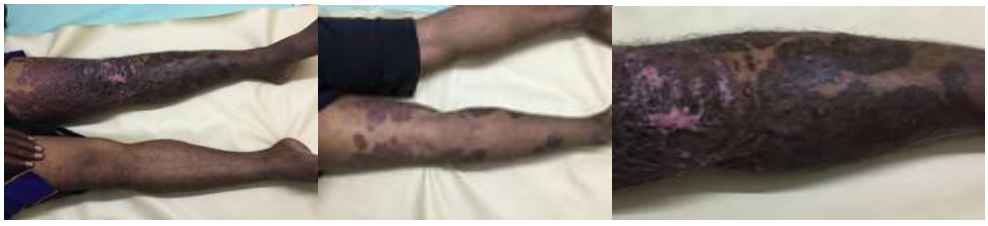

Figure 8. After 6 months combination therapy.

Figure 9. After 7 months combination therapy.

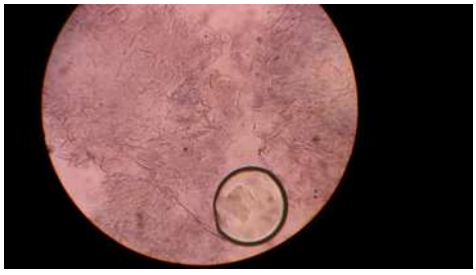

Figure 10. Potassium hydroxide 10% revealed no muriform cells after 7 months of combination therapy.

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 phaeohypomycosis group and caused by dematiaceous (naturally pigmented) fungi (pheoid fungi) such as *Fonsecaea pedrosoi, Phialophora verrucosa, Fonsecaea compactum, Cladophialophora carrionii, Exophiala jeanselmei, Exophiala castellanii* and *Rhinocladiella aquaspersa*.[15,16] *Fonsecaea 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, multiseptate 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 demostrate 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 *Fonsecaea pedrosoi*. This species was diagnosed by finding *Cladosporium (Homodendrum)* type which shows conidiophores vary in length and have treelike brancing, they bear ovoid, dark conidia in brancing 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. The

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.[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.[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.[8] For localized lesions, surgery is often a first line solution. Medical treatment options availabel 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.[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.[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

1. Guerrero TE, Isa-isa R, Isa M, Arenas R. Chromomycosis. Clin Dermatol J 2012; 30: 403-8.
2. Hay RJ. Deep Mycosis. In: Goldsmith LA, Katz SI, Gilcherst BA, Paller AS, Leffell DJ, Wolff K, editors. Fitzpatrick dermatology in general medicine. 8th ed. New York: Mc GrawHill; 2012. p.2315-6.
3. Baddley JW, Dismukes WE. Chromomycosis. In: Kauffman CA, Pappas PG, Sobel JD, Dismukes WE, editors. Essential of clinical mycology. 2nd ed. New York: Springer Science-Business Media; 2011. p. 427-31
4. Hay RJ and Ashbee HR. Mycology. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. Rook's textbook of dermatology. 8th ed. London Blackwell Publishing; 2010. p. 36.75-6.
5. Kalabhavi AS. Chromomycosis – Review Article. Int J Current Res 2013; 5(07): 1691-95.
6. Najafzadeh MJ, Sun J, Vicente VA, Klaasen CHW, Bonifaz A, van de Ende AHGG et al. Molecular epidemiology of *Fonsecaea* species. Emerging Infectious Disease 2011; 17 (3): 464-9.
7. Ameen M. Chromomycosis: clinical presentation and management. J Clin Exp Dermatol Res 2009; 34: 849–54.
8. Chunyang Li. Chromomycosis in China. Korean J Med Mycol 2011; 16 (4): 169-71.
9. Chandran V, Sadanandan SM, Sobhanakumari. Chromomycosis in Kerala, India. Indian J Dermatol Venereol Leprol 2012; 78: 728-33.
10. Correia RM, Valente NYS, Creado PR, Martins JE. Chromomycosis: study of 27 cases and review of medical literature. An Bras Dermatol 2010; 85 (4): 448-54.
11. Bobba S. Case study: chromomycosis. J Trop Dis 2014; 2 (4):1-2.
12. Slesak G, Inthaland S, Strobel M, Marschal M, Hall MJR, Newton PN. Chromomycosis after a leech bite complicated by miasis: a case report. BMC Diseases 2011; 11 (14): 1-8.
13. Jennis F. *Fonsecaea pedrosoi*. In: Frey D, Oldfield RJ, Bridger RC editors. A colour atlas of pathogenic fungi. London: Wolfe Medical Publication Ltd; 1985.p.106-7.
14. Al-Haqan E, Eassa B. Chromomycosis: a rare entity in Kuwait. Gulf J Dermatol Venereol 2010; 17 (1): 56-60.
15. Telles FQ, Santos DWCL. Chromomycosis in the clinical practice. Curr Fungal Infect Rep 2012; 6: 312-9.
16. Krzysciak PM, Piaszczynska MP, Piaszczynski M. Chromomycosis. Postep Derm Alergol 2014; 5: 310-21.
17. Telles QF, Santos DWCL. Challenges in therapy of chromomycosis. Mycopathologia 2013; 175: 477-88.

18. Gurumayum M, Okade R, Vidyavathi K, Prakruthi KN, Gowda T. Case report chromomycosis. Int J Biol Med Res 2014; 5: 4104-6.
19. Badali H, Gonzalez MF, Mousavi B, Zaragozi MT, Rodriquez JC, Hoog G, et al. Chromomycosis due to *Fonsecaea pedrosoi* and *F. Monophora* in Cuba. Mycopathologia 2013; 175: 439-44.
20. Hoz RM, Baddley JW. Subcutaneous fungal infections. Curr Infect Dis Rep 2012; 14: 530-9.
21. Hsu LY, Wijaya L, Shu-Ting E, Gotuzzo E. Tropical fungal infections. Infect Dis Clin N Am 2012; 26: 497-512.
22. Kusumaputra BH, Listiawan MY. Successful treatment of chromoblastomycosis with ketoconazole : a case report. Proceeding of the 12th APEODS in conjungtion with 13th PIT PERDOSKI; 2013 Oct 23-26; Yogyakarta, Indonesia.