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Case Report

Diagnosis and therapy of chromoblastomycosis

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Abstract Chromoblastomycosis is a chronic deep mycosis of the skin and subcutaneous tissue. Clinical features are characterized by verrucous plaque lesions, especially in the lower extremities. The disease is difficult to cure and there is no gold standard therapy. A 72-year-old male farmer comes with thickened and bleeding skin on the left leg. For 10 years the thickened skin extends slowly from the back of the foot to the length of the left leg down to the bottom of the knee. A month earlier, the thickened skin becomes brittle and bleeding. hyperkeratotic plaques, verrucosa, multiple partial exudative, and hemorrhagic fissures. Scrapping skin lesions with 10% potassium hydroxide showing muriform cell (sclerotic bodies). Histopathological examination of granuloma inflammation composed of foamy macrophages, lymphocytes, histiocytes, multinucleated giant cells and many neutrophils, erythrocyte extravasation, and sclerotic bodies obtained in the brown dermis. Culture on Sabouraud dextrose agar media with chloramphenicol was not found in fungal colony growth. Patients have been treated with itraconazole 200 mg twice daily and showed clinical improvement after 3 weeks. Diagnosis of chromoblastomycosis is based on history, physical examination, histopathology, and culture. The risk factors for the disease including farmers who work barefoot. Further evaluation is still needed regarding the therapy and complications in this case.

Key words
Chromoblastomycosis, diagnosis, therapy.

Introduction

Chromoblastomycosis is a chronic fungal infection of the skin and subcutaneous tissue that results from the implantation of pigmented or dematiaceous fungi of environmental origin in the dermis.[1,2] Late diagnosis can lead to several problems, such as difficulty in managing therapy due to disease recurrences, low quality of life, and decreased ability to perform work activities. Clinical manifestations are nodular, verrucous lesions, and often on the lower extremities. The organisms that cause chromoblastomycosis are saprophytic fungi found in soil, wood, vegetative plants and mud.[3-5] The most common causative organisms include Fonsecaea pedrosoi, F. compacta, Phialophora verrucosa, Cladosporium carrionii, and Rhinocladiella aquaspersa.[6,7]

The disease is spread throughout the world but is mostly found in tropical and subtropical areas. The prevalence of the disease is highest in Central America and South America but also reported in Southern Africa, Asia, and Australia. Countries with the highest number of cases are Brazil, Costa Rica, and Madagascar.[8,9] Diagnostic techniques are based on clinical manifestations, the presence of muriform cells in the tissue, and the isolation and identification of the causative organism.[7] Lesions usually appear months or years before the patient seeks treatment and is diagnosed with the disease.[3,9]

Case Report

A 72-year-old man came to the hospital with the

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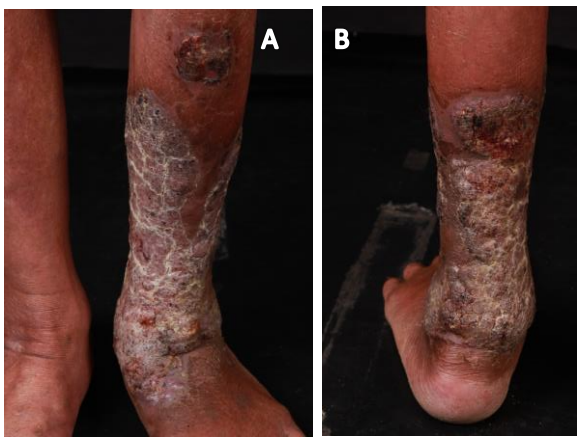

Figure 1 Verucous plaque on left low leg with pus and browny crusts (**A**) anterior aspect (**B**) anterior aspect.

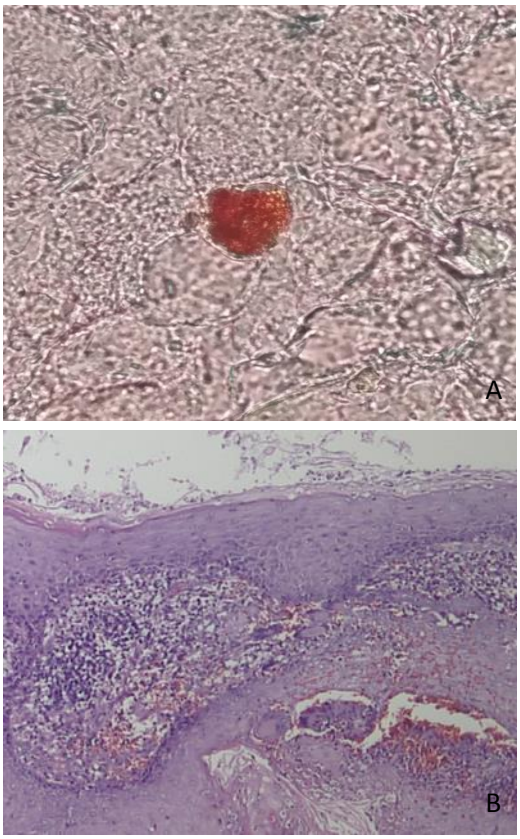

Figure 2 (**A**) muriform or sclerotic bodies in KOH 10% examination from lesion's scraped (**B**). Histopathological staining hematoxylin-eosin (HE) shows brown sclerotic bodies in the dermis.

chief complaint of thickened, and easily bleed skin over the left lower leg and left foot. The patient gave a history about 14 years ago, his left leg was scratched by a stone while harvesting, thus becoming injured and bleeding. The patient was immediately taken to the local health centre to clean the wound and received unknown oral and medical therapy. 10 years before coming to the hospital, he reported that the scars became thicker and expands slowly from the lower leg to the ankle and dorsal aspect of the left foot. According to the patient, sometimes warts feel painful, but not itchy.

A month before the referral, the thickened skin became more painful, as the lesions were bleeding and festering. The patient then came to a surgeon in Kulonprogo, was advised to remove the lesions by surgery, and sent the tissue sample for histopathological examinations. Later on, the lesions were concluded as granulomatous inflammation.

Following the surgery, the patient felt that his complaints had improved**.** However, after 3 weeks, the patient's skin began re-thicken at the site of the previous lesions. Therefore, the patient was referred to the dermatoveneorology division at Wates Hospital with a diagnosis of chronic granulomatous ulcer. Afterward, to confirm the diagnosis, the patient was referred to RSUP dr. Sardjito with a diagnosis of suspect chromoblastomycosis. During anamnesis, he denied any history of diabetes, hypertension, drug allergies, and previous similar diseases. He also denied any history of similar lesions in the family. Later, the patient was discovered a farmer by occupation who usually doesn't wear any footwear while working.

When first arrived at RSUP dr. Sardjito, the patient's general condition was good with the following vital signs: BP 120/80 mmHg, HR 84 times per minute, axillary body temperature 36.^{4} C, and RR 20 times per minute. There were no signs of anemia, cyanosis, jaundice, and dyspnea. No abnormalities were found on the examination of the heart, lungs, abdomen, and

genitalia. Dermatological examinations on the left cruris and left dorsal pedis revealed multiple hyperkeratotic plaques and verrucous, some with exudative and hemorrhagic fissures; an ulcer was also found on the tuberous region of the tibia cruris sinistra with a diameter of about 2x3x0.1cm, irregular edges, and covered with brown crusts.

Initially, the patient was differentially diagnosed with chromoblastomycosis, verrucous cuticular tuberculosis, and squamous cell carcinoma. Thus to establish the diagnosis, various supporting examinations are carried out. Routine blood examinations and urinalysis were within normal limits. Direct microscopic examination aided with 10% potassium hydroxide (KOH) on scraped materials from black dot lesions revealed muriform cells (sclerotic bodies), brown in color, and multiseptate. Gram examination of the lesions revealed polymorphonuclear cells with gram-positive cocci bacteria. Cultures of the skin biopsy samples on Sabouraud dextrose agar with chloramphenicol showed slow growth and dark colonies, appearing after 2 weeks of incubation.

Histopathological examination with hematoxylin-eosin (HE) staining showed hyperplastic pseudoepithelioma, parakeratosis, spongiosis with areas of suppuration containing neutrophils, neutrophil exocytosis in the epidermis and inflammatory granuloma composed of foamy macrophages, lymphocytes, histiocytes, multinucleated giant cells and neutrophils, extravasation erythrocytes, and brown sclerotic bodies in the dermis. Moreover, no fungal elements were found with periodic acid-Schiff staining, no acid-fast bacteria were found with Fite Faraco (FF) staining and no malignant cells were found. Hence, the result of the histopathological examination was concluded as a non-caseating suppurative granulomatous inflammation, where it was consistent with features typically found in chromoblastomycosis. The patient was treated with itraconazole 100mg PO two times a day, compression therapy with betadine 1% (15 minutes, twice a day) for ulcer wound care, and application of the mupirocin cream post-compression.

Discussion

Chromoblastomycosis (CBM) is a chronic fungal infection of the skin and subcutaneous tissue.[13] Most of the cases happen in men of age 30-60 yr., while children are rarely affected.[13] Men are affected four times more often than women, and 75% of CBM cases occur in farmers.[14] Thirteen cases of CBM in Nepal concluded that the ratio of occurrence in men to women was 6:1, of which the majority were aged 21-40 years (38.5%), and 41-60 years (38.5%).[15] Presumably, men are affected more often due to the large number of male workers who work in the open field, thus increasing the exposure of the microorganism.[3] In a case-series study of 325 chromoblastomycosis patients that took place in Amazon, Brazil, 86.1% of patients were agricultural workers and 93.2% of them were men.[16] Minotto *et al.* (2001) in their study conducted in Brazil, out of 100 patients with chromoblastomycosis, 72% of them were farmers and 78% of them were men.[17] In this case-report study, the patient was a 72-year-old male with complaints of thickened scars growing slowly over 10 years, where the patient works as a farmer who often works without using footwear, which is a predisposing factor for the occurrence of chromoblastomycosis.

Chromoblastomycosis is a slowly progressive disease.[3,13,14] Minotto *et al*. in their study found that the shortest period from onset to diagnosis of CBM was 2 months, while the longest was 40 years. The average time between the appearance of lesions and diagnosis was 14 years.[15,16]

Lesions occur at sites of minor trauma. The patient with CBM is usually someone who works in an open field or who rarely uses footwear. Trauma due to wood products and soil exposure leads to the implantation of organisms.[3,14] This is under the patient in this study, where the lesion occurs at the site of the stone-scratched when the patient is working barefoot in a rice field. Based on the epidemiology, history, and duration of the disease from the patient, he has a high risk and a strong suspicion of chromoblastomycosis.

In this patient, we found hyperkeratotic plaques and nodules, verrucous, multiple, only on the left leg. Chromoblastomycosis usually only affects one of the lower extremities, especially the leg, ankle and foot. The lesions appear as a result of direct inoculation of the microorganism into the skin.[3,14] Correia *et al.* (2010) in their study reported that of 27 chromoblastomycosis patients, most of the lesions were found on the leg (59.2%), followed by the thigh (29.6%). Pradhan *et al.* (2007) in their study also reported that 11 of 13 patients with chromoblastomycosis had lesions on the lower extremities.

Chromoblastomycosis lesions develop slowly and are asymptomatic in almost all cases. Symptoms like pruritus and pain can occur, but rarely.[3,17] Chandran *et al.* (2012) in their study reported that from a total of 35 cases, 21 cases manifested on the leg, 11 on the thigh, and 3 cases on the trunk. Out of 35 cases, 24 of them were asymptomatic, while the remainder developed symptoms of itching, pain, or both.

The clinical form of chromoblastomycosis lesions varies. There could be ≥2 of the 5 clinical forms of chromoblastomycosis lesions found in one person. 5 different forms include (1) nodular lesions with raised surfaces covered with scales (cauliflower-like scabs); (2) extensive tumor lesions; (3) extensive irregular hyperkeratotic verrucous lesions; (4) reddish, flat, scaly plaques; (5) atrophic and cicatricial lesions. The most common forms of lesions are nodular and hyperkeratotic verrucous.[14] Ulcers can also appear if there is a secondary infection or injury of the previous lesions.[7] In this case, the patient's lesions were plaques and nodules with hyperkeratotic and verrucous surfaces and exudative ulcers which partially were covered by brown crusts. Ulcers were caused by secondary infection, as evidenced by the findings of gram-positive cocci bacteria. Disease dissemination may arise from scratching autoinoculation and spread via the lymphatic system. Hematogenous spread is very rare.[3] Based on the clinical findings of this patient, this case corresponds to chromoblastomycosis of the nodular type and verrucous hyperkeratotic plaques.

The first differential diagnosis established was tuberculosis verrucosa cutis. The resemblance was based upon the clinical manifestation, which is a verrucous plaque with erythematous-based that grows slowly and chronically. However, from the area of lesion occurrence, it was not consistent with tuberculosis verrucosa cutis, as the common predilection area of the tuberculosis verrucosa cutis is the knee, elbow, hand, foot, and buttock, whereas, in this patient, the lesions were on the leg and foot. Moreover, from the histopathological findings, it was also not suitable for tuberculosis cutis verrucosa as the acid-fast bacteria were not found on Fite Faraco staining.

The second differential diagnosis was squamous cell carcinoma. Clinical features that resemble this diagnosis are ulcers that are painful and bleed easily, the chronic course of the disease, the predilection sites in the sun-exposed skin area, and higher incidence in elderly men. In addition, the risk factors are also under squamous cell carcinoma, which is being

exposed to UV light from the sun often due to the patient's occupation. However, the presence of verrucous plaques and nodules, non-elevating ulcer edges, and no regional lymph node enlargement on this patient were inconsistent with squamous cell carcinoma. Moreover, no malignant cells were found from the histopathological examination of this case.

In this patient, the diagnosis was based upon the patient's history, clinical findings, and results of the histopathological and culture examinations. Based on the prior literature, the diagnosis of chromoblastomycosis is made based on skin lesions characteristics and confirmed by the presence of muriform cells or sclerotic bodies on histopathological examination.[3] Microbiological diagnosis is very crucial. Microscopic examination with 10% KOH examination of the black dot lesion from this patient showed muriform cells (sclerotic bodies) in brown color. Chandran *et al.* (2012) in their case-series study found 42.8% of positive results with 10% KOH examination on muriform cells of 35 patients. The 10% KOH examination is an affordable and uncomplicated examination technique that does not require sophisticated equipment.[13] Histopathological examination performed on this patient revealed pseudoepitheliomatous hyperplasia with parakeratosis, spongiosis of the epidermis, and inflammatory granulomas consisting of foamy macrophages, lymphocytes, histiocytes, multinucleated giant cells, neutrophils, erythrocyte extravasation, and brown sclerotic bodies found in the dermis. In cases of chromoblastomycosis, histopathological examination of tissue biopsy will show pseudoepitheliomatous hyperplasia with parakeratosis, spongiosis, and sometimes abscess. Tuberculoid or suppurative granulomas with lymphocytes, plasma cells, neutrophils, eosinophils, macrophages, and multinucleated giant cells may also be found in the dermis. Fibrosis might appear in older cases.[15]

Proper identification of fungal growth is required to confirm the diagnosis of chromoblastomycosis. The culture of chromoblastomycosis requires media containing antibiotics, such as Sabouraud's dextrose agar with chloramphenicol and cycloheximide, because bacterial contamination is common.[3] Fungal cultures will show slow-growth dark colonies that accumulate.[14] The fungal culture in this patient did not reveal any fungal growth. In one case-report study, positive culture results were obtained in 88.5% of 31 cases of chromoblastomycosis.

The treatment used for the patient, in this case, was itraconazole 100mg PO twice a day. Chromoblastomycosis lesions are very difficult to cure, as it is still a therapeutic challenge.[11,14] Treatment is usually given for aesthetic or functional purposes, but it is also needed to prevent complications. The clinical response ranges from 10-80%, depending on the stage of the disease.

Extensive lesions of chromoblastomycosis are associated with low cure rates and high relapse rates.[3] In several case-series studies, only 30% of patients recovered and nearly 60% had improvement.[14] There is currently no gold standard therapy for chromoblastomycosis, but there are several options therapy: systemic anti-fungal drugs alone, or combined with physical treatments like surgery, cryotherapy, and thermotherapy.[11]

Treatment of chromoblastomycosis is difficult to evaluate due to lack of case reports, variations in disease stage, and shortfall in published randomized clinical trials on the treatment of chromoblastomycosis.[3] Azoles have both in vitro and in vivo action on dematiaceous fungi, including chromoblastomycosis. The principal mechanism of action is by inhibiting 14-demethylase and the formation of lanosterol into

ergosterol, a vital component of cell membranes.[11] A previously published literature stated that oral ketoconazole had no significant effect on the treatment for chromoblastomycosis. In this patient, his lesions were improved as some of the verrucous plaques began to thin, the ulcers began to close, and no exudation and hemorrhage were left found. Further therapy and observation are still needed to assess the success of therapy.

Conclusion

This study reports a case of chromoblastomycosis in a 72-year-old farmer male patient. The diagnosis was established based on the history, physical examination, and supporting examinations. Although chromoblastomycosis is a rare disease, it should be considered as a differential diagnosis of chronic skin lesions, especially in tropical countries. Further observations are still needed to evaluate the success of therapy on the patient.

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