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CHROMOBLASTOMYCOSIS: A NEGLECTED TROPICAL DISEASE

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SUMMARY

Chromoblastomycosis (CMB) is a chronic fungal infection of the skin and the subcutaneous tissue caused by a transcutaneous traumatic inoculation of a specific group of dematiaceous fungi occurring mainly in tropical and subtropical zones worldwide. If not diagnosed at early stages, patients with CBM require long term therapy with systemic antifungals, sometimes associated with physical methods. Unlike other neglected endemic mycoses, comparative clinical trials have not been performed for this disease. Nowadays, therapy is based on a few open trials and on expert opinion. Itraconazole either as monotherapy or associated with other drugs, or with physical methods, is widely used. Recently, photodynamic therapy has been successfully employed in combination with antifungals in patients presenting with CBM. In the present revision the most used therapeutic options against CBM are reviewed as well as the several factors that may have impact on the patient's outcome.

KEYWORDS: Chromoblastomycosis; Dematiaceous fungi; Fungal infections; Antifungal treatment.

INTRODUCTION

Neglected diseases constitute a group of tropical and subtropical infections which are endemic in low-income populations in developing regions of Africa, Asia, and Latin America. The World Health Organization (WHO) acknowledges the neglected diseases as a symptom of poverty and disadvantage. The most affected by the neglected diseases are the poorest populations often living in remote, rural areas, urban slums or in conflict zones. With little political support, neglected tropical diseases are not on the priority list of public health systems[37]. A series of endemic diseases including helminths, protozoa, bacterial and viral infections, but not fungal diseases other than mycetoma are considered neglected diseases by WHO[36]. Its global burden should be even greater than mycetoma and CBM can lead to potential incapacity for labor. The aim of this review is to update the main clinical, epidemiological and therapeutic topics on CBM, a typical orphan disease.

CHROMOBLASTOMYCOSIS

Chromoblastomycosis or chromomycosis is one of the most prevalent transcutaneous traumatic implantation or subcutaneous mycosis in individuals living in tropical and subtropical zones around the world. Although PEDROSO & GOMES observed some patients in 1910 in Sao Paulo, Brazil, the scientific report of these observations appeared only in 1920[20]. This is the reason why the first description of CBM is actually attributed to Max RUDOLPH, a German doctor who published the first cases of CBM from the city of Estrela do Sul, Minas Gerais, Brazil, in 1914[9,32]. This disease presents the following characteristics: primary lesion beginning at the site of inoculation; chronic involvement of cutaneous and subcutaneous tissues associated with a granulomatous, purulent, fibrotic tissue formation and a non-protective humoral immune response[24]. CBM lesions are usually recalcitrant and extremely difficult to eradicate. Due to its chronicity, CBM lesions may undergo neoplastic transformation leading to skin cancer[24,27]. Except for small initial lesions that can be cured by surgical removal, CBM lesions constitute a true therapeutic challenge for clinicians and patients (Fig. 1).

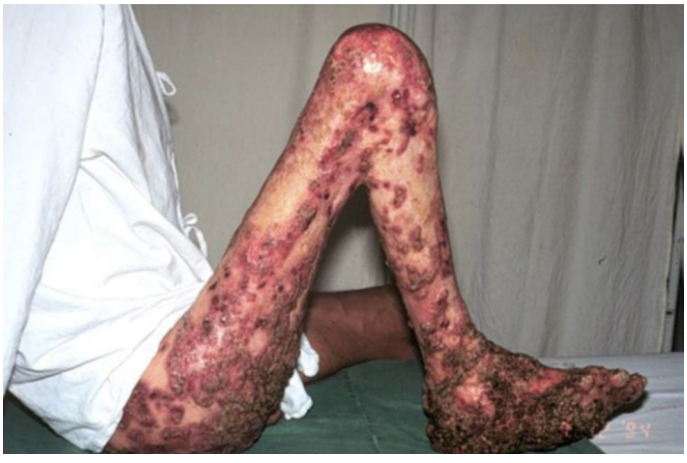

Fig. 1 - Severe and recalcitrant clinical form of chromoblastomycosis.

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ECO-EPIDEMIOLOGY

Chromoblastomycosis is the most common of several mycoses caused by melanized or black fungi. CBM agents are found on soil, plant thorns and debris[15,35]. These fungi belong mainly to *Fonsecaea* and *Cladophialophora* genus and, while scattered cases have been reported in *Phialophora, Rhinocladiella* and *Exophiala* genus. *F. pedrosoi* and *C. carrionii* are usually found in tropical and subtropical regions. *F. pedrosoi* is primarily found in humid areas, whereas *C. carrionii* is prevalent in semiarid climates[11,23,24,34,38]. As with other members of the Herpotrichiellaceae family, these agents have melanin in their cell wall, an important pathogenicity factor[31]. It is believed that CBM etiologic agents are soil and/or plant saprobes with typical mycelia in environmental samples, changing morphology to the muriform (sclerotic) form in tissue (Fig. 2)[13,19].

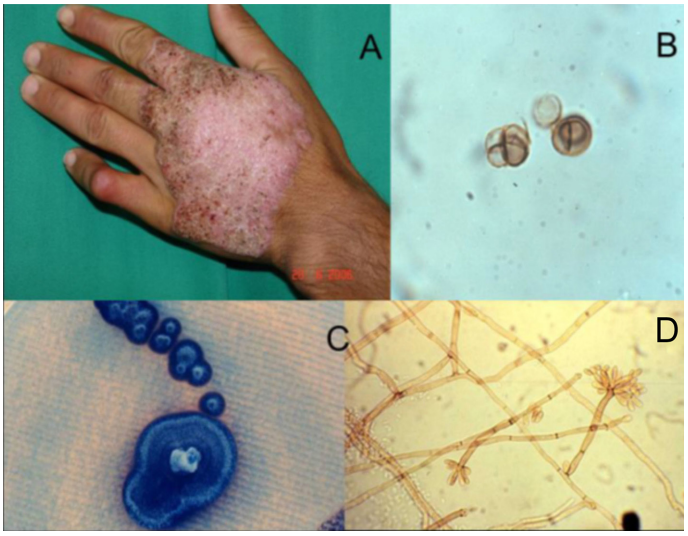

Fig. 2 - Clinical and microbiological aspects of chromoblastomycosis: The etiologic agent is easily found in the "black dot" lesion covered area (circled) A. Muriform cells are pathognomonic for this disease. They are observed either on wet mount (B) or in histologic sections. *Fonsecaea pedrosoi* is one of the prevalent agents in humid areas. Figures C and D depicts its macro and micromorphology aspects.

The highest prevalence of the disease is within a zone between 30° latitude North and 30° latitude South, coinciding with most of the tropical and subtropical zones. CBM is not a compulsory reportable disease so that all epidemiology data is derived from published case reports and surveys. Incidence rates range from 1: 6,800 (14/100,000) in Madagascar to 1: 8,625,000 (0.012/100,000) in USA. In Brazil the estimate incidence rate of CBM is 3/100,000[25]. Most of the reported cases occur in Latin America, the Caribbean, Asia, Africa and Australia. Madagascar, Brazil, Mexico, Dominican Republic, Venezuela, India and Southern China contribute with the majority of cases (Fig. 3)[3,11,16,17,23,25,29,34,38].

Chromoblastomycosis-causing fungi are found worldwide in soil and decaying plant debris, including wood. Because CBM is an implantation mycosis, occupation seems to play an important role[1,24,25]. This disease rarely occurs before adolescence with most patients in the age group between 40 to 50-years old, with a male-to-female ratio of 5:1 and 9:1.[1,24,25]. The majority of lesions are observed on the extremities of outdoor rural workers. The main risk factors associated with CBM infection are: lack of

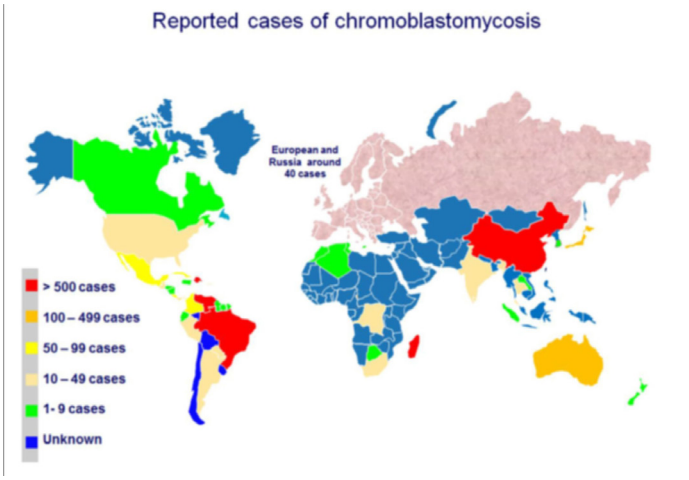

Fig. 3 - Geographic distribution of chromoblastomycosis according to reported cases. (Courtesy of Dr Daniel Wagner dos Santos, University of Sao Paulo, Brazil).

protective shoes, gloves or garments, poor nutrition and hygienic habits[1]. CBM is considered an occupational disease, occurring in farm workers, lumberjacks, or vendors of farm products. A potentially important source of infection was reported in an endemic area located in the Maranhao State, on the fringes of the Amazon rainforest in Brazil, where thousands of families are involved in babassu (*Orbignya phalerata*) a wild palm tree, harvesting. The local population collects babassu nuts to extract the babassu oil, an important component for local and international beauty product manufacturers. Because melanized fungi have been isolated from babassu shield fragments, this may be a risk factor for hundreds of people developing CBM after trauma that occurred at work (Fig. 4)[18,33]. Other occupational hazards are likely in other environments (Table 1).

Fig. 4 - Babassu (*Orbignya phalerata)* nutcracker woman in the State of Maranhao, Brazil. (Courtesy of Professor Conceição Pedroso, Federal University of Maranhao, Brazil).

CLINICAL MANIFESTATIONS

Following a transcutaneous traumatic implantation, and after an uncertain incubation period, the initial CBM lesion appears at

Table 1
Details of subcutaneous traumas leading to chromoblastomycosis in 32 Brazilian patients adapted from reference[18]

Type of trauma		Number of cases
Plant	Wood	9
	Straw	2
	Grass	2
	Thorn	2
	Palm tree	1
	Bamboo	1
	Spiny seed	1
Animal	Insect sting	2
	Buck rear	1
	Cock spine	1
	Caterpillar	1
Agricultural tool	Hoe	2
	Axe	1
	Knife	1
	Mill	1
Other	Fall	2
	Brick	1
	Shoes	1

the inoculation place. It may start as a solitary macular lesion, later progressing to a raised papule with a pink smooth surface that gradually increases over a few weeks before becoming scaly[6,24,28]. The initial skin lesion may progress and evolve with diverse clinical types including nodular, tumoral (cauliflower-like), verrucous or a scar-like appearance (Fig. 5)[6,8,20,24,28]. In advanced and severe cases, more than one type of lesion can be observed in the same patient. The clinical polymorphism of CBM lesions elicits multiple differential diagnoses including infectious and non-infectious possibilities. This may cause diagnosis delay, lack of therapeutic response and loss of mobility[6,24,28]. At the beginning, the initial lesions are asymptomatic, and usually do not interfere with the patient's activities. Over time, itching becomes the predominant symptom of the disease, which in the moderate forms is intense and may be accompanied by local pain. Because CBM lesions are very pruritic, it is accepted that the disease dissemination to other skin sites usually occurs by autoinoculation and/or contiguous lymphatic spread. As severity increases, edema and bacterial secondary infections affect the health of the patient as a whole, modifying the appearance of the skin and causing scars. In the most severe cases, chronic lymphedema and ankylosis develop and non-invasive squamous cell carcinomas may arise. All these complications can lead to definite disability (Fig. 1)[6,24,28].

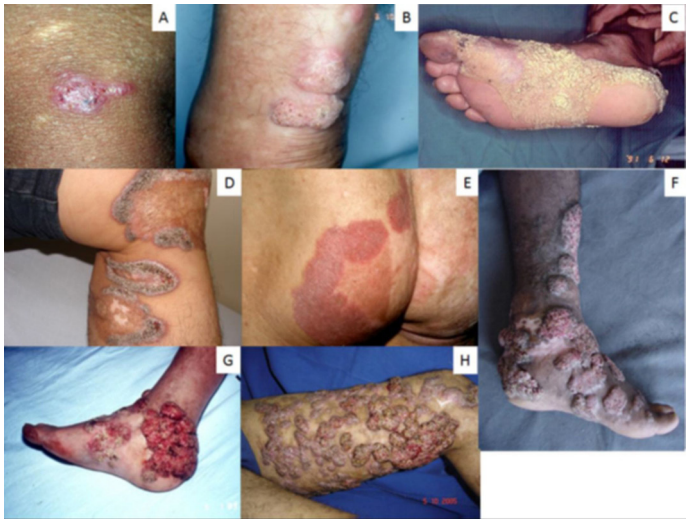

Fig. 5 - Lesions of chromoblastomycosis may depict clinical polymorphism end elicit several differential diagnoses. The initial lesion of chromoblastomycosis **(1A),** may evolve to five main clinical types: nodular lesions on the lower leg **(1B),** verrucous lesion of the foot **(1C),** scar lesions on the knee and lower leg **(1D),** plaque lesion on the buttocks **(1E),** tumoral (cauliflower) lesions on the foot **(1G)** and mixed lesions composed by plaque, nodular and verrucous lesions involving the lower limb **(1H).**

DIAGNOSIS

Diagnosis of CBM is mainly based on clinical and epidemiological suspicion in endemic areas but it must be confirmed by microbiological demonstration of the etiologic agents in clinical samples. Skin biopsies or scrapings should be taken from the surface of the lesion where "black dots" may be visible. When examined under light microscopy the pathognomonic "muriform cells" are depicted. These chestnut, rounded brown pigmented and cross chambered structures are distinctive and have been referred to as "sclerotic bodies, fumagoid cells" cooper pennies"[1,24,25]. Muriform cells are considered as a biological adaptation allowing the etiologic agent to survive in the hostile host tissue environment[19] Histologically, CBM typically reveals pseudo epitheliomatous epidermal hyperplasia, hyperkeratosis, irregular acanthosis, alternating with areas of atrophy and collection of inflammatory cells forming epidermic abscesses. Granulomatous reaction with different grades of fibrosis can be found at the dermal level. Muriform cells may be observed among these structures or inside Langerhans giant cells[4]. When cultivated, all CBM agents grow slowly in culture. Initially, colonies are deep green, depicting a velvet dark aspect with time. Presumptive species identification may be achieved by mycological morphologic methods, but molecular techniques are suggested for definitive identification[10].

THERAPY

Chromoblastomycosis lesions are recalcitrant and very difficult to treat. If not discovered early when the initial CBM lesions may be surgically removed, long periods of systemic antifungal therapy alone or in combination with several physical methods is the rule for many patients. The efficacy of therapy may be related to the severity and duration of the disease, to the etiologic agent and to the patient's compliance. As comparative trials on this disease are lacking, evidence that helps to select optimal therapy is based on a few open clinical studies and expert opinion. No ''gold standard'' therapy for CBM is available, but treatment options include systemic antifungals, as monotherapy or combined, physical methods and immune adjuvants (Table 2)[6,27,28].

Over time, several therapeutic regimens have been tried, including physical methods such as surgery, thermo, laser and photodynamic therapies[6,24,27,28]. These therapeutic modalities are only indicated at the early stages of the disease. They can also be associated with systemic antifungal therapy. Initially, mild CBM lesions can be treated by surgical excision but unfortunately most of the patients present with moderate

Table 2
Treatment options for chromoblastomycosis

Physical methods	Chemotherapy	Combination therapy
Standard surgery *	Calciferol (Vit D3) §	Itraconazole + cryotherapy ¶¶
Iontophoresis §	5-fluorocytosine §	Terbinafin + cryotherapy ¶¶
Moh's surgery §	5-fluorouracil §	Itraconazole + terbinafin ¶¶
CO_2 laser §	Thiabendazole §	Itraconazole + photodynamic therapy ¶¶¶
Cryotherapy **	Amphotericin B §	Itraconazole + 5-fluorocytosine ¶¶
Local heat (dry) §	Ketoconazole §	
Photodynamic therapy **	Fluconazole §	
	Itraconazole ¶	
	Terbinafin ¶	
	Posaconazole ¶¶	
	Isavuconazole ¶¶¶	

* For initial lesions only; **Used only in association to systemic antifungals; ¶ Most used therapy; ¶¶ Use for refractory forms; ¶¶¶ Potential use; § Not used or not a first line therapy or abandoned therapy.

to severe forms, leading to long-term courses of systemic antifungal drugs. In addition, neither *in vitro* sensitivity tests are standard for the filamentous and the parasitic (muriform), nor experimental therapy models have been successfully developed[31]. Thus, it is accepted that the most used drugs are itraconazole and terbinafine at daily doses of 200-400 mg and 250-500 mg, respectively[7,12,26,27,28,30]. In refractory cases, the combination of these two drugs can be tempted[27]. Other effective treatments include posaconazole, 800 mg per day and the combination of itraconazole with 5-flucytosine[2,5,14,21]. The association of the latter with posaconazole may play an important role in the therapy of CBM. The duration of therapy must be based on clinical, mycological and histopathological criteria (Table 2). According to published data, cure rates with terbinafine or itraconazole vary from 15 to 80%, depending on the severity of the disease. As expected, in severe forms cure rates are lower and relapses are more common[14,26,27].

RESUMO

Cromoblastomicose: doença tropical negligenciada

Cromoblastomicose (CMB) é uma infecção fúngica crônica da pele e tecido subcutâneo causada pela inoculação transcutânea traumática de um grupo específico de fungos dermatiáceos que ocorrem principalmente em zonas tropicais e subtropicais do mundo. Quando não são diagnosticados nas fases iniciais, pacientes com CBM necessitam de tratamentos prolongados com antifúngicos sistêmicos, por vezes associados a métodos físicos. Diferentemente de outras micoses endêmicas negligenciadas, não foram realizados ensaios clínicos comparativos para esta doença. Atualmente a terapia é baseada em alguns poucos ensaios abertos e em opiniões de especialistas. Itraconazol é amplamente utilizado como monoterapia ou em associação com outras drogas, ou com métodos físicos. Recentemente, a terapia fotodinâmica foi empregada com sucesso combinada a antifúngicos em pacientes com CBM. Neste manuscrito as opções terapêuticas mais utilizadas contra CBM foram revistas, assim como os diversos fatores que podem influenciar a evolução dos pacientes.

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