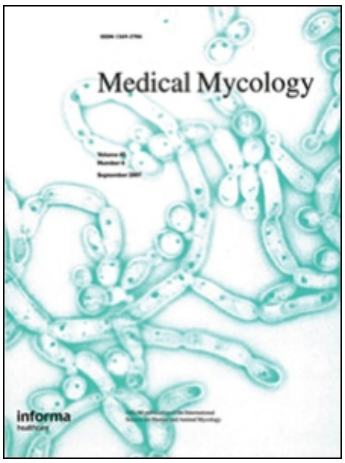

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Chromoblastomycosis: an overview of clinical manifestations, diagnosis and treatment

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Review Article

Chromoblastomycosis: an overview of clinical manifestations, diagnosis and treatment

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Chromoblastomycosis is one of the most frequent infections caused by melanized fungi. It is a subcutaneous fungal infection, usually an occupational related disease, mainly affecting individuals in tropical and temperate regions. Although several species are etiologic agents, *Fonsecaea pedrosoi* and *Cladophialophora carrionii* are prevalent in the endemic areas. Chromoblastomycosis lesions are polymorphic and must be differentiated from those associated with many clinical conditions. Diagnosis is confirmed by the observation of muriform cells in tissue and the isolation and the identification of the causal agent in culture. Chromoblastomycosis still is 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 chromoblastomycosis 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-term regimens. In general, treatment should be guided according to clinical, mycological and histopathological criteria.

Keywords Chromoblastomycosis, chromomycosis, clinical, diagnosis, treatment

Introduction

The clinical spectrum of human infections caused by melanized fungi is wide and may affect any organic site. Etiologic agents, as well as diseases caused by them are heterogeneous in nature, including superficial, cutaneous, subcutaneous and systemic phaeohyphomycosis, fungemia, sinusitis, mycetoma and chromoblastomycosis (CBM) [1–4]. Together with sporotrichosis and

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mycetoma, CBM is one of the most frequently encountered subcutaneous mycosis [2,5]. The first published cases of CBM date back to 1914 and are credited to Rudolph, who described an exotic disease called 'figueira' (fig tree) in rural workers living in the hinterland of the State of Minas Gerais, Brazil [6,7] Although Pedroso had observed early cases in Sao Paulo, his article was not published until 1920 [8]. The term 'chromoblastomycosis' was introduced by Terra *et al*. in 1922 [9] and validated in 1992 [10].

Chromoblastomycosis refers to chronic cutaneous and subcutaneous lesions, developing at the site of a previous transcutaneous trauma. The disease hallmark is the presence of muriform cells, embedded in the granulomatous and suppurative tissue reaction [1,2,11]. Muriform cells have been referred to as sclerotic cells, copper pennies, or as fumagoid, chromo or Medlar bodies. According to Matsumoto, the term 'muriform' should predominate over 'sclerotic' [12]. The latter refers to 'sclerotia', which are compact masses of dormant hyphae [13]. The disease is more common among males, possibly due to occupational reasons; however, certain hormonal and genetic factors may play a role in fungal adaptation to host tissues [2,14–16]. It is usually found in tropical and subtropical regions with higher prevalence in Africa (Madagascar and South Africa) [17,18] and Latin America (Mexico, Central America, Brazil and Venezuela) [2,19–22]. It has also been reported from other countries from Asia (India, China, Japan and Malaysia) and Australia [23–25]. Rarely are CBM patients observed in northern Europe and the USA [11,26,27].

Several dematiaceous fungi are involved with the disease etiology. The most common agents are *Fonsecaea pedrosoi* and *Cladophialophora carrionii*. Both are usually found in tropical and subtropical regions although *F. pedrosoi* is seen in humid areas, whereas *C. carrionii* is prevalent in semiarid climates [18–22,24,28]. Less frequently, the disease is caused by *Phialophora verrucosa*, *Rhinocladiella aquaspersa* or *Exophiala dermatitidis* [1,11,12,29]. In recent years, *Exophiala jeanselmei* and *E. spinifera* have also been observed forming muriform cells in typical CBM lesions; thus they are also considered etiologic agents [2,30–32]. All these agents belong to a single order of ascomycetous fungi, the *Chaetothyriales.* Recently some unexpected agents (*Aureobasidium pullulans, Rhytidhysteron* sp., *Chaetomium funicola* and *Catenulostroma chromoblastomycosum)* were associated with CBM-type skin lesions [33–35], but primarily in immunocompromised hosts, and without evidence of the presence of muriform cells. In contrast, CBM is usually observed in otherwise healthy individuals. The reports of cutaneous, subcutaneous and systemic infections in immunocompromised hosts are better referred to as phaeohyphomycotic infections, because only hyphae, yeasts or vesicular cells are observed in tissue [1,2,12,36–39]. Chromoblastomycosis and phaeohyphomycosis represent two poles of a spectrum of diseases caused by melanized fungi. Clinically its boundaries are unclear and both infections may be caused by the same etiologic agents. Although either immunocompetent and immunosuppressed hosts may present both types of infections, CBM usually is observed in immunocompetent hosts and phaeohyphomycosis is not. So the host immune status may play an important hole in the clinical evolution of these diseases [40,41]. The taxonomy of the genus *Fonsecaea* have been reviewed on the basis of ribosomal DNA internal transcribed spacer (ITS) sequence data. According to De Hoog *et al*., the traditional distinction between *F. pedrosoi* and *F. compacta* is not valid today and the latter seems to be no more than a morphological variant from *F. pedrosoi*. On the other hand, another species was recognized, i.e., *F monophora*. This new Fonsecaea species shows an opportunistic profile and it is related to phaeohyphomycosis [42–44].

Clinical features

Infection starts after the etiologic agents gain entrance through puncture wounds [45,46]. Most of the initial lesions are observed in the lower limbs, especially with respect to rural host populations that do not routinely wear shoes. In areas where *C. carrionii* is prevalent, the initial lesions may occur in the upper limbs [2,15,21]. Less frequently, CBM lesions are reported in different sites, like the buttocks, trunk and face [2,47–49]. The initial lesion is usually solitary and unilateral, presenting as a small, pink smooth-surface, papular skin lesion. The papules gradually increase over a few weeks and may havet a scaly surface (Fig. 1). With time, the initial lesion may evolve into several types of skin lesions leading to a polymorphic clinical appearance. Itching is an important symptom of the disease, and is generally hypothesized to lead to dissemination by autoinoculation and contiguous spread [17]. Lymphatic dissemination to remote sites has also been reported in a small number of cases [50,51]. To better describe the CBM clinical aspects, several classifications were proposed by many authors during the last century [52–54]. Among these, the classification introduced by Carrión in 1950, characterized five different types, viz. nodular, plaque-type, tumoral, cicatricial and verrucous lesions (Table 1, Fig. 2) [54]. Nodular, tumoral and verrucous types are more frequent then the cicatricial and plaque-type

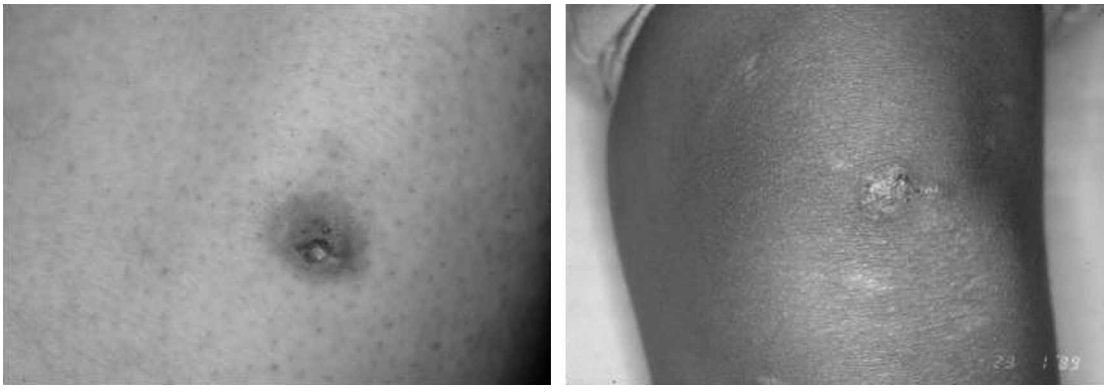

Fig. 1 Initial lesions of chromoblastomycosis. A biopsied ertitematous papular skin lesion on the thigh, three months after a thorn trauma (left). A scaly papulous ulcerative lesion on the knee, after six months evolution (right).

lesions [1,52]. 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 (Fig. 3) [2,55,56]. Severe lesions tend to respond slowly or even become non-responding to antifungal drugs.

Table 1 Classification of chromoblastomycosis lesions.

Nodular type	Moderately elevated, fairly soft, dull to pink violaceous growth. Surface smooth, verrucous or scaly. With time lesions may gradually become tumorous.
Tumorous type	Tumour like masses, prominent, papillomatous, sometimes lobulated; 'cauliflower like'. Surface partly or entirely covered with epidermal debris and crusts. More exuberant on lower extremities.
Verrucous type	Hyperkeratosis is the outstanding feature. Warty dry lesions. Frequently encountered along the border of the foot.
Cicatricial type	Non-elevated lesions that enlarge by peripheral extension with atrophic scarring, while healing takes place at the centre. Usually with annular, arciform or serpiginous outline. Tends to cover extensive areas of the body.
Plaque type	Slightly elevated, with variously sized and shaped areas of infiltration. Reddish to violaceous in colour presenting a scaly surface, sometimes shows marked lines of cleavage. Generally found on the higher portions of the limbs.

Adapted from references [2,49,50].

Initially, CBM lesions are oligosymptomatic and do not interfere with patient's activities. In moderate forms, local pain and intense itching predominate as symptoms. With time as the severity increases, edema and secondary bacterial infections may bring significant limitation to labor activities. In the most severe cases, chronic lymphoedema and ankylosis develop and non-invasive squamous cell carcinomas may arise from chronic lesions [57,58]. All these complications may lead to the definite disablement of the patients, as illustrated in the following example:

A 66-year-old white male presented with a history of chronic CBM lesions affecting his left lower limb. The disease started 36 years earlier, after a knife wound, when he worked as a farmer in the hinterland of Brazil south region. At diagnosis, he was treated with itraconazole and after 80 months of therapy, most of the lesions had scarred with dense fibrosis and lymphoedema. At this time, a small ulcerated skin lesion was noted on his left foot lateral face. After six months the lesion became invasive, with a vegetant and papilomatous aspect. Almost his entire podal region became affected. An escamous cell carcinoma was diagnosed in a skin biopsy and the patient was submitted to a limb amputation (Fig. 4).

Correct diagnosis of CBM is based on clinical and pathological data and confirmed by microbiological documentation of the causative agent. Lesions are clinically polymorphic and may simulate several infectious and non-infectious diseases. The differential diagnosis of the several types of the CBM lesions is therefore broad and includes many infectious and non-infectious possibilities (Fig. 5, Table 2).

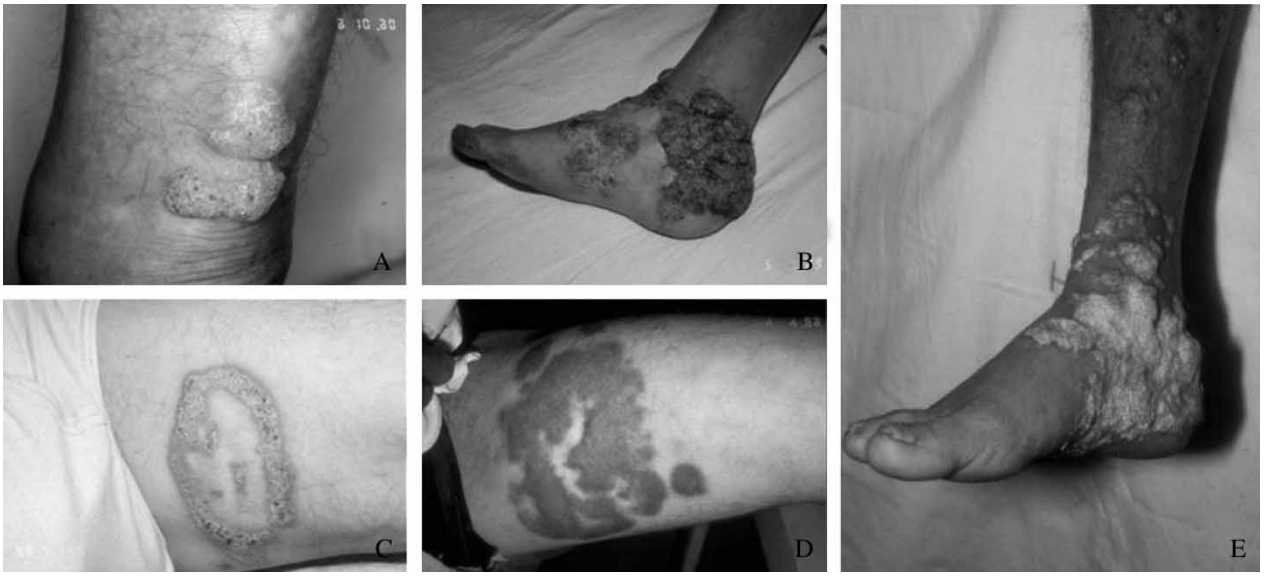

Fig. 2 The five types of chromoblastomycosis lesions, according to Carrion, 1950. (A) Nodular, (B) tumoral, (C) cicatritial, (D) plaque, and (E) verrucous.

Laboratory diagnosis

Diagnosis of CBM is routinely based on direct examination and culture. Special attention should be given to skin lesions covered with 'black dots'. These are small hematic crusts containing cellular debris and fungal structures, resulting from their transepithelial elimination [11,17,59]. The area with 'black dots' should be preferably selected for sample collection [60]. All suspicious material, including skin scrapings, crusts, aspirated debris and tissue fragments can be analyzed. Although direct microscopic wet mount examination (KOH 20–40%) is a fast diagnostic method, biopsy is preferred for two reasons, i.e., (1) to enhance positive culture results due to decrease of bacterial contamination, and (2) to help to evaluate criteria for interruption of treatment [2,17,55,56,60] (Table 3). The observation of muriform cells in clinical

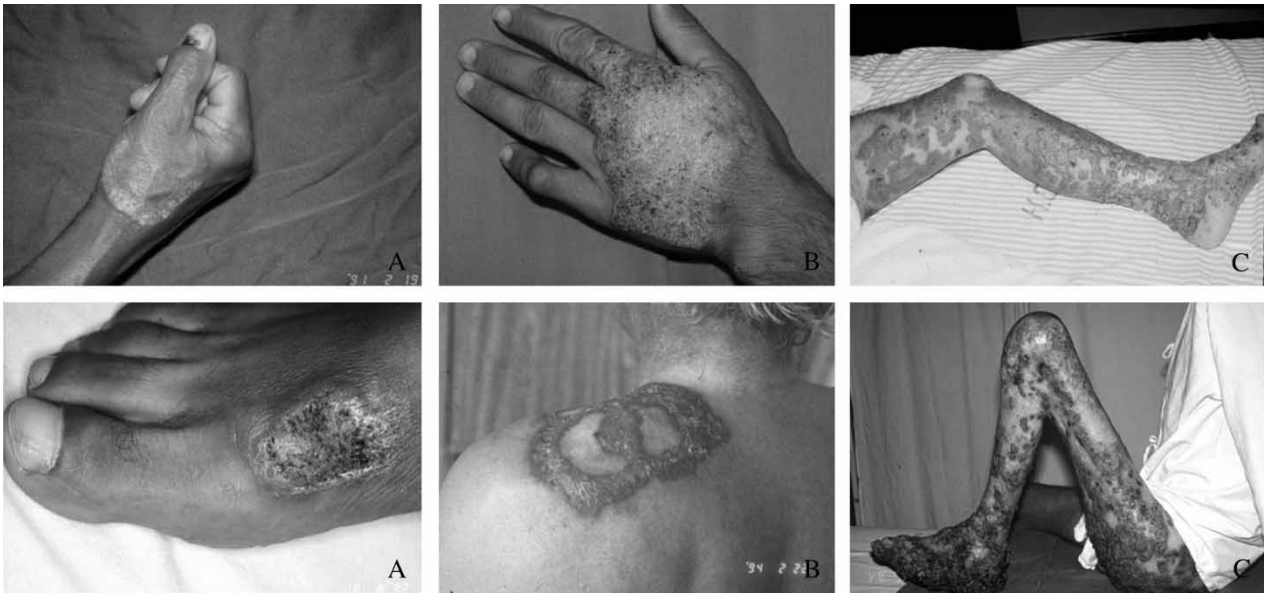

Fig. 3 Lesions of chromoblastomycosis showing different grades of severity. (A) Mild lesions, (B) moderate lesions, and (C) severe lesions.

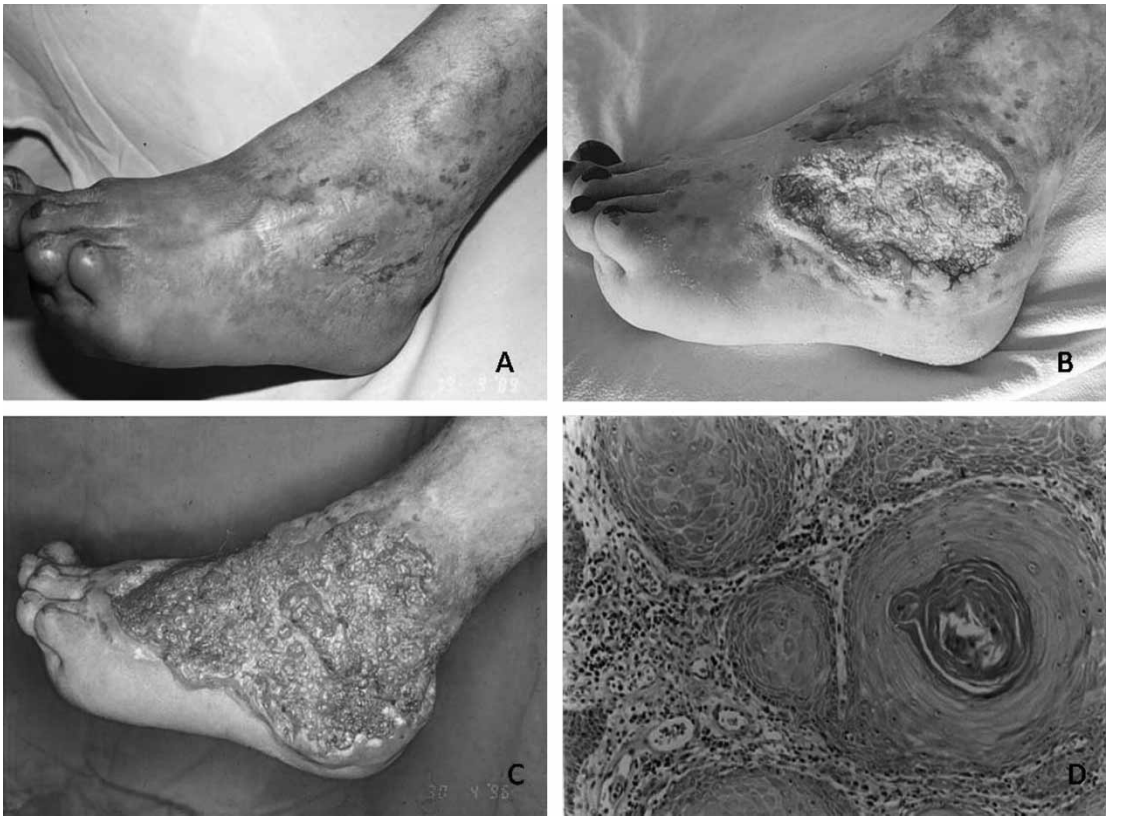

Fig. 4 Malignization of a foot lesion of chromoblastomycosis. During therapy the podal lesions scarried with fibrosis, but an ulcerated lesion can be observed in the foot lateral face (A). With time, the small lesion evolved to an extensive and ulcerative lesion with secondary bacterial infection (B). 80 months later, the lesion evolved with vegetant and papilomatous masses (C). A skin biopsy depicted a well differentiated epidermoid carcinoma with typical 'corn pearls' with nuclear atypies in the middle of neoplasia cell blocks. HE $\times 400$.

samples is mandatory for confirmation of CBM. Single or clustered muriform cells may be present. They are 5 to 12 μm in diameter, round to polyhedral (chestnut) in shape, thick-walled, dark pigmented and having both transverse and longitudinal cross-walls resembling a brick wall (Fig. 6). The melanized fungus cells are easily discovered in hematoxilin-eosin tissue sections. There is no need for special staining. The addition of calcofluor white may be helpful when fungal cells are scarce. This fluorescent reagent was demonstrated to increase the sensitivity of the detection of many fungi, but the utility in the case of pigmented fungi remains unclear.

Histologically, the tissue response in CBM is not specific and may be similar to deep mycoses. Hyperkeratosis and pseudoepitheliomatous hyperplasia are the main features observed in the stratum corneum and epidermis. Several micro-abscesses, with or without pigmented fungal elements may be observed in the epidermis. Although muriform cells are usually observed in the micro-abscesses, sometimes they undergo dimorphic transformation and display hyphal forms near the cutaneous surface, especially in the crusty material covering the lesions [61]. Deeper in the dermis and subcutis, a non-specific and diffuse infiltrate is observed. The tissue response to the fungi is typically mixed, consisting of micro abscesses and granulomatous response, with giant cells [11,17,62]. There is some evidence linking CBM lesions to cellular immune response. In patients with verrucous lesions, the histopathogical analysis shows a granulomatous reaction with suppurative granulomata containing several fungal cells, suggesting a Th2 immunological response. On another hand, in skin biopsies from patients with erythematous plaque lesions, the granulomatous reaction presents a tuberculoid granulomata pattern with reduced number of fungal elements, pointing to a Th1 immune response [63].

All agents of CBM form slow growing dark pigmented colonies on mycology routine culture media. As

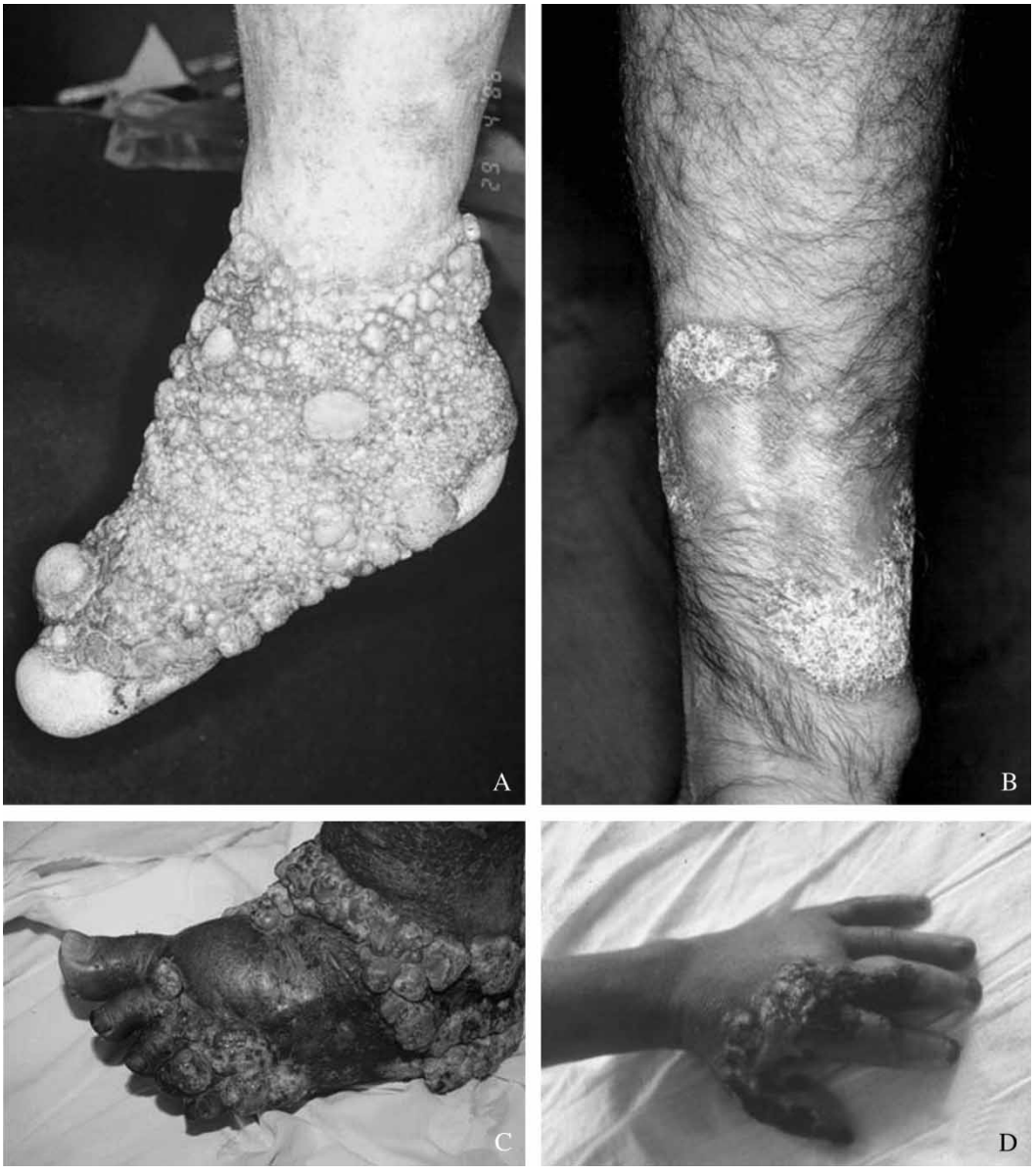

Fig. 5 Differential diagnosis of the chomoblastomycosis lesions. (A) Nodulo-papilomatous foot after repetitive episodes of erisipela. (B) Verrucous skin lesions in a disseminated form of paracoccidioidomycosis. (C) Tumoral and nodular lesions in a patient with cutaneous disseminated sporotrichosis. (D)Verrucous leishmaniasis.

species produce the same type of pigmented cells in their pathogenic stage, the isolation of the etiologic agent in culture is needed for identification [29–31,64]. The use of conventional mycological methods, like morphology and physiology, may be inadequate and as a result, molecular identification may be indicated. Two recent articles describe non-cultural methods for the identification of CBM agents, i.e., a duplex PCR targeting the ribosomal DNA for *Fonsecaea* spp. [65], and a specific oligonucleotide primer for identification of *C. carrionii* [66].

Regarding the immune response, as in other chronic fungal infections, the humoral immune system does not seem to be protective in comparison with cell-mediated immunity. Serological intradermal tests have not been standardized for this disease. Antibodies have been detected in patients and host responses to fungal antigens occur at both cellular and humoral levels [67–69]. One study employed an ELISA assay using *C. carrionii* antigen AgSPP. Serum from patients with CBM was positive and was useful in some cases for analyzing the evolution pre and post treatment.

Table 2 Differential diagnosis of chromoblastomycosis lesions.

Infectious diseases	Fungi	Paracoccidioidomycosis,
		Blastomycosis,
		Fixed sporothrichosis,
		Coccidioidomycosis,
		Phaeohyphomycosis,
		Granulomatous candidiasis and trichophytosis, etc.
	Bacteria	Cutaneous tuberculosis,
		Leprosy
		Tertiary syphilis
		Syphilis, nocardiosis,
		Ecthyma
		Mycobacteriosis (*M. marinum, M. fortuitum*)
	Protozoa	Leishmaniasis
		Rhinosporidiosis
Non-infectious diseases		Escamous carcinoma
		Psoriasis
		Sarcoidosis,
		Lupus, erythematosus, etc.

Besides, healthy patients were all negative. It was concluded that this assay could be recommended for establishing remission criteria [70].

Treatment

Patients with CBM still are a true therapeutic challenge for clinicians due to the recalcitrant nature of the disease especially in the severe clinical forms [2,18,19,55,72,73]. As in other endemic mycoses, comparative clinical trials are lacking in CBM. Hence, there is no treatment of choice for this mycosis, but rather a series of therapeutic options. Treatment may be divided into three groups; physical treatment, chemotherapy and combination therapy (Table 4). In early stages of the disease, lesions respond to surgical resection, but later, as severity increases, better results are achieved with systemic antifungals. In contrast to yeasts, no standard methods to test *in vitro* susceptibility are available for melanized fungi [73,74]. Determination of *in vitro* susceptibility profiles may be useful to indentify intrinsic microbiologic resistance to antifungal drugs, but does not predict clinical response [75].

Table 3 Treatment options for chromoblastomycosis.

Physical methods	Chemotherapy	Combination therapy
Standard surgery	Calciferol (Vit D3)*	Itraconazole + cryosurgery
Moh's surgery	5-fluorocytosine*	Terbinafin + cryosurgery
CO_2 laser*	5-fluorouracil*	Itraconazole + terbinafin
Thermotherapy	Thiabendazole*	Itraconazole and/or terbinafin + dry heat
Cryosurgery	Amphotericin B*	
Local heat (dry)	Ketoconazole*	
	Fluconazole*	
	Itraconazole	
	Posaconazole	
	Terbinafine	

*Not used or not a first line therapy.

Several treatment regimens have been evaluated in the past, using an open non-comparative clinical trials design. In most of them, the authors do not employ standardized parameters to grade the lesions according to severity, nor do they use objective criteria to terminate therapy [76,77]. Today, regimens using calciferol, flucytosine monotherapy, thiabendazole, fluconazole and ketoconazole are not frequently employed. Amphotericin B is not considered a first line therapy due to its significant nephro and cardiotoxicity, a principal contraindication of long-term therapy. Moreover this polyenic compound is less active *in vitro* against melanized fungi than triazoles and terbinafin [78]. At present, the most useful antifungals against CBM include itraconazole and terbinafine [40,55,56,79–81]. These drugs can be used alone, or in combination in more severe and recalcitrant cases [82]. Similarly flucytosine may be associated with itraconazole [83]. Itraconazole is a fungistatic first generation triazole, which inhibits the cell membrane ergosterol via 14-alpha-demetilase blockage [84]. This compound is safe and useful for treating fungal infections requiring long-term therapy such as CBM [85]. On the other hand, resistance has been demonstrated in sequential isolates of *F. pedrosoi* from patients undergoing long-term therapy with this drug [75]. This may be linked to local dense fibrosis which reduces itraconazole tissue levels [41]. The mode of action of terbinafin, which is fungicidal rather than fungistatic to melanized fungi, is related to its blocking of squalene epoxidase, an early ergosterol synthesis precursor [73]. In addition, this allylamine may present an antifibrotic effect on CBM lesions, as was demonstrated experimentally [86].

In general CBM is very difficult to treat and prone to recurrence. Treatment success is driven by three critical factors. First, is the causative agent as it is known that *C. carrionii* and *Phialophora verrucosa* are less sensitive *in vitro* to antifungal drugs than *F. pedrosoi*. Second, is the clinical form and its severity, e.g., time of evolution, lesions localization and extension and co-morbidities such as grade of edema, fibrosis, lymphostasis, associated bacterial infection, malignization, etc. (Tables 1 and 2). Third, is the choice of antifungal drugs, e.g., fungicidal *versus* fungistatic, drug-to-drug interactions,

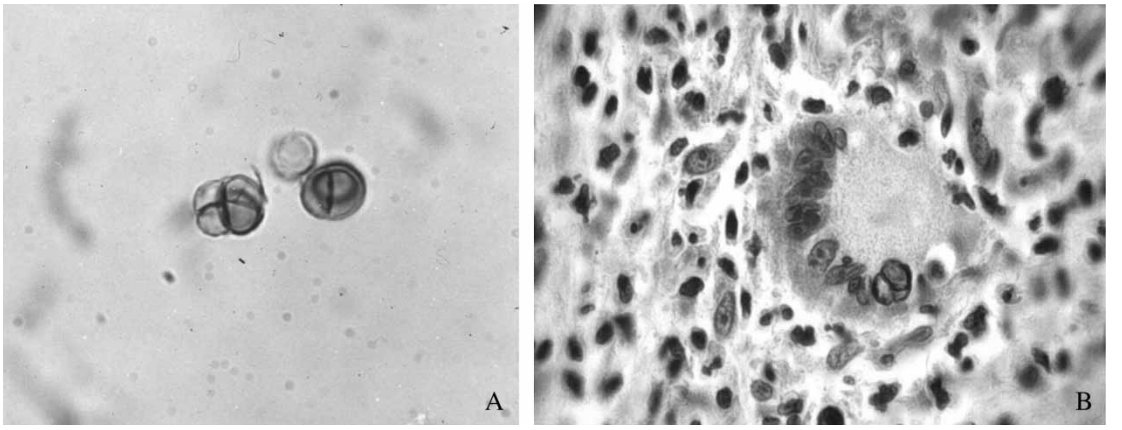

Fig. 6 Muriform cells of chromoblastomycosis as observed in KOH wet mount (A) and in HE sections (B).

gut absorption. It is also important to evaluate the patient's individual tolerability and if the treatment will be provided for free or purchased, since antifungal therapy must be maintained in long-term regimens. In general, treatment should be guided according to clinical, mycological and histopathological criteria [2,17,19,41,55,87] (Table 4).

According to published data, cure rates observed with antifungal drugs vary from 15 to 80%. In severe forms cure rates are particularly low and relapse rates are high [41,87]. Physical methods are usually indicated to support chemotherapy.

Physical treatment

Surgery

Standard surgery with appropriate margins and curettage with electrodessication may be recommended for small and well-circumscribed lesions. The latter has been used in only a few cases and is thought to result in lymphatic spread of the disease [19,88]. There are some case reports using Moh's micrographic surgery, particularly in patients' with limited lesions, with the capability of performing histopathologic monitoring until absence of fungal activity (muriform cells) is proven [89]. CO_2 laser photocoagulation is among other methods that have been used, but, as with other modalities, the number of cases reported is small [90,91].

Table 4 Criteria for the interruption of treatment in chromoblastomycosis.

Clinical
Complete healing of all lesions with athrophic scarring
Disappearance of pain and itching
Follow-up observation period of at least two years without recurrence
Mycological
Absence of fungal elements on direct examination
Failure to isolate the etiologic agent from biopsied tissues
Persistence of these findings in three consecutive monthly biopsies
Histologic
Absence of muriform cells and microabscesses
Replacement of active granulomatous infiltrate in the dermis by a chronic inflammation and dense fibrosis
Atrophy of the epidermis
Persistence of all these findings in three consecutive monthly biopsies.

Adapted from reference [17].

Local heat therapy

The rationale of this type of treatment is that fungi such as *F. pedrosoi* are susceptible to high temperatures. The absence of growth of this fungus in culture media at a temperatures above 40°C has been shown *in vitro* and clinical and mycological cure has been demonstrated in several cases [19,92]. The skin tolerates temperatures up to 43°C for long periods of time without being harmed. The source of heat can be any device that releases heat constantly [93]. In a series of four cases treated successfully with local heat therapy, Tagami *et al*. reported using two heat sources (benzene pocket warmer, Hakuukin-Kairo Ltd, Osaka and pocket handkerchief-type warmers, manufactured by various Japanese companies) [94]. In one of the cases reported, involving patients with extensive CBM, a standard electric blanket was used. The authors reported good results after a 2–12 month treatment period (mean of 3 months). The advantages of this type of therapy include its low cost and the possibility of using it for both limited and extended cases, particularly in the limbs where heat sources can be easily applied [19,90,92–95]. It is important to emphasize that humid heat (water baths), as used for sporotrichosis, are not useful to treat CBM, since this method not only

works inappropriately, but may also lead to dissemination of the disease.

Local cold therapy (cryosurgery)

Cryosurgery is undoubtedly the physical therapy with the best reported results, particularly when used in combination with systemic antifungal agents [96,97]. Earlier case series involved topical application of liquid nitrogen by means of cotton swabs [97]. Currently liquid nitrogen spray devices (open technique with tissue temperature measurement) facilitate application and yield better results [96]. Castro *et al*. reported the results of 15-years experience with 22 cases achieving a mycological and clinical cure rate of 40.9% [98]. Cryosurgery is the kind of treatment that must be individualized based on the clinical location and extension of the lesions. It is recommended to treat small lesions located far from large skin folds to avoid secondary fibrosis and to reduce chances of retractile scars. The main side effects of liquid nitrogen include pain, edema at the treatment site and the formation of blisters, scabs and crusts, as well as bacterial superinfection. Residual postinflammatory hypopigmentation during the healing phase occurs secondary to melanocyte destruction during the freezing process [19,96,97]. It is important to emphasize that cryosurgery must be combined with chemotherapy, as dissemination of the infection has been reported with cryosurgery alone. Therefore, even with small lesions a loading dose of systemic antifungals (e.g., itraconazole or terbinafin) is recommended at least one month prior to the cryosurgical procedure [19].

Chemotherapy

Patients with CBM are still a true therapeutic challenge for clinicians due to the recalcitrant nature of the disease especially in the severe clinical forms [2,5,40,41,71,72]. Various drug therapies have been tried throughout time; some of them proved initially effective improving early infection or even achieving permanent cure, nevertheless breakthrough relapse or relapse after completion of treatment has been reported.

5-Fluorocytosine (5-FC)

The use of 5-FC, a derivative of the pyrimidine base cytosine, in the mid-1960s marked an important development in the chemotherapy for CBM. Up to the 1980s it was one of the drugs of choice, but its use in both mono and combination therapy has provided variable results [87]. Recommended doses range from 100–150 mg/kg/day, divided into four dosages, for 6–12 months. The 10% 5-FC solution may be applied topically twice a day followed by an occlusive bandage. Doses exceeding 10 g/day resulted in marked clinical improvement and in some cases in total cure within a few months. However, it was later found that, particularly in patients with long standing disease, the activity of the drug seemed to stop suddenly after a few months, with no significant improvement despite increased dosage [87]. Moreover, *F. pedrosoi*, in particular, is able to develop *in vitro* resistance to 5-FC quite easily. 5-FC has been combined with other drugs like potassium iodide or amphotericin B, which constitutes a preferred option given the increased resistance that occurs when it is used alone [11,23,72,87,99]. The best results of combination therapy was reported by Pradinaud in a small patient group receiving itraconazole in addition to 5-FC [83].

Itraconazole

Itraconazole is recommended at a daily dose of 200–400 mg, according to the severity of the lesions (Table 2). In a series of 30 Brazilian patients treated with itraconazole, 200–400 mg/day (Table 4), it was shown that eight patients with mild forms of the disease achieved clinical and mycological cure after 10.9 months (range 7.0–17.6 months). Similar response was noted in 11 (91%) of the 12 patients with moderate forms after 12.9 months (range 5–31 months) of continuous treatment. Among the nine patients with severe lesions, four (44%) had clinical and mycological response after a mean treatment duration of 30 months (range 10–51 months), and the remaining patients showed significant improvement [2,55]. The use of itraconazole in pulse therapy regimens (400 mg/day during one week in a month), was successful in a few cases [100]. Although attractive, its use may induce resistance. Itraconazole was also evaluated in combination therapy, either with cryosurgery or with 5-fluorocytosine [82,83,97,98].

Terbinafin

This is an allylamine derivative used at 250–500 mg/day doses. As with itraconazole, it shows good *in vitro* activity against melanized fungi [78]. There are few reports of successful treatment at low dosage (250 mg/day) [101,102], nevertheless, 500 mg/day is considered to be more appropriate. Esterre *et al*. [80] achieved a 74.2% clinical and mycological cure rate after 12 months, with good patient tolerance. It is one of the drugs with the best reported efficacy and safety results, mainly due to its fungicidal activity and to the fact that

it does not involve the cytochrome P-450 oxidase resulting in minimal drug-drug interactions [79–81,100,102–104].

Combination of physical methods and chemotherapy

Surgical methods may lead to cure, but may also lead to spread of the disease. It is therefore important to apply additional chemotherapy, specifically itraconazole or terbinafine. Reports combining heat therapy with itraconazole were outstanding [41,87], but cryosurgery plus itraconazole may even be better, especially in extensive cases. Itraconazole is applied until maximal reduction of lesions is achieved, which occurs after 8–12 months of treatment, and subsequently surgery is performed in several sessions [96,97].

Systemic combination therapy

Given the high relapse rate of the disease, chemotherapeutic combinations may increase the cure rate, but also produce more side effects. The most widely used combinations in the past have been 5-FC+amphotericin B, and 5-FC+itraconazole [41,83,87]. Recently, Gupta *et al*. reported their experience with itraconazole and terbinafin with chronic cases of CBM that had been unresponsive to amphotericin B, oral antifungals (including itraconazole) or heat therapy [82]. The study involved two treatment modalities, i.e., alternate and concomitant combinations. The former consisted of alternate weeks of itraconazole 200–400 mg/day and terbinafin 500–750 mg/day. The latter involved giving itraconazole 200–400 mg/day plus terbinafin 250–1000 mg/day concomitantly [82]. The results from this study were probably due to synergistic effects of ergosterol synthesis as a mechanism of action shared by the two drugs, although operating at different levels in the pathway.

Future therapeutic trends

In a recent comparative clinical trial, Perez-Blanco reported that topical ajoene resulted in a response similar to that of topical 5-flucytosine in patients with mild forms of CBM caused by *C. carrionii* [105]. Although this garlic active substance is not commercially available, it may be helpful in combination therapy with chemotherapy and or physical methods.

Conclusion

Among the second generation triazole derivatives, voriconazole and posaconazole have a potential for use in CBM, despite high costs in long-term therapy. Voriconazole has not yet been evaluated in CBM, but posaconazole proved to be effective in a few *F. pedrosoi* cases that were previously refractory to various treatment regimens [106].

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