GAFFI Fact Sheet

Chromoblastomycosis

Chromoblastomycosis (CBM) or chromomycosis is one of the most prevalent implantation or subcutaneous mycosis in individuals living in tropical and subtropical zones around the world. Dr Max Rudolph, a German Doctor working in Brazil, first described it a century ago in 1914 [1,2]. 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 and fibrotic tissue response and a nonprotective humoral immune reaction. [3, 4] Lesions related to this disease are usually recalcitrant and extremely difficult to eradicate. Due to its chronicity the CBM lesions may undergo neoplastic transformation leading to skin cancer. [5, 6] Except for small initial lesions, which should be surgically removed for cure, CBM lesions constitute a true therapeutic challenge for clinicians and patients (figure 1).[7]

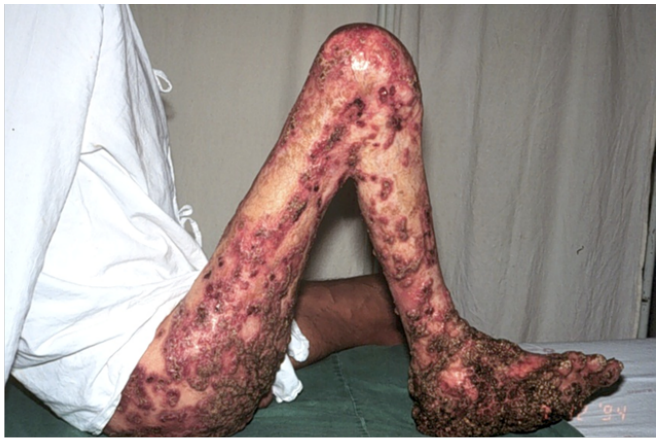

Figure 1. Severe and recalcitrant clinical form of chromoblastomycosis

Eco-epidemiology

Chromoblastomycosis is the most common of several mycoses caused by melanized or black fungi. Agents of CBM are found on plants thorns or debris.[8,9] They mainly belong to *Fonsecaea* and *Cladophialophora* and to a less extent to *Rhinocladiella* genera, while scattered cases have been reported in *Phialophora* and *Exophiala. F. pedrosoi* and *C. carrionii* are usually found in tropical and subtropical regions; *F. pedrosoi* primarily in humid areas, whereas *C. carrionii* is prevalent in semiarid climates.[10-13,14] *C. carrionii* isolates from different continents are clonally distinct.[15] As with other members of the Herpotrichiellaceae family, these agents have melanin in their cell wall, an important pathogenicity factor.[16] It is believed that the CBM etiologic agents are soil and/or plant saprobes with typical mycelia in environmental samples, changing morphology to muriform (sclerotic) form in tissue (Figure 2). [17, 18]

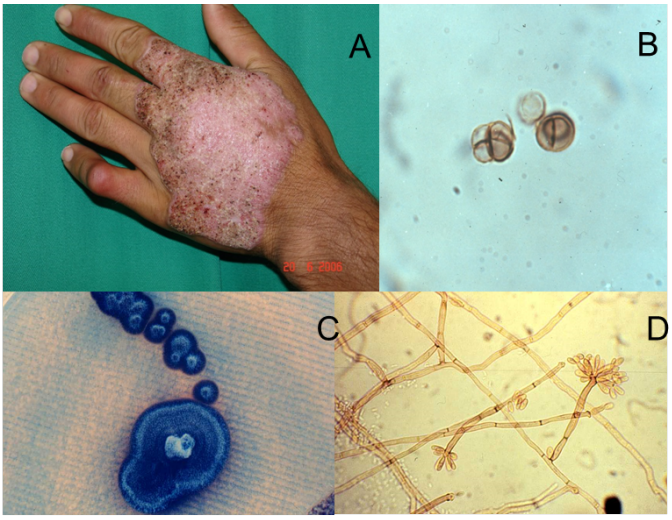

Figure 2. Clinical and microbiological aspects of chromoblastomycosis: The etiologic agent is easily found in the "black dot" lesion covered area (circled) A. Muriform cells are pathognomonic for this disease. They are observed either on wet mount (B) or in histologic sections. *Fonsecaea pedrosoi* is 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 climates. CBM has no compulsory notification and so all epidemiology data is derived from published case reports and surveys. Incidence rates range from 1:6,800 (14/100,000) (Madagascar) to 1/ 8,625,000 (0.012/100,000) (USA). In Brazil the estimate incidence rate for this disease is 3/100,000. [2] Most of the reported cases occur in Latin America, the Caribbean, Asia, Africa and Australia. Madagascar, Brazil, Mexico, Dominican Republic, Venezuela, India, Taiwan and Southern China contribute with the majority of cases (Figure 3). [2, 3. 11-14, 19 -25]

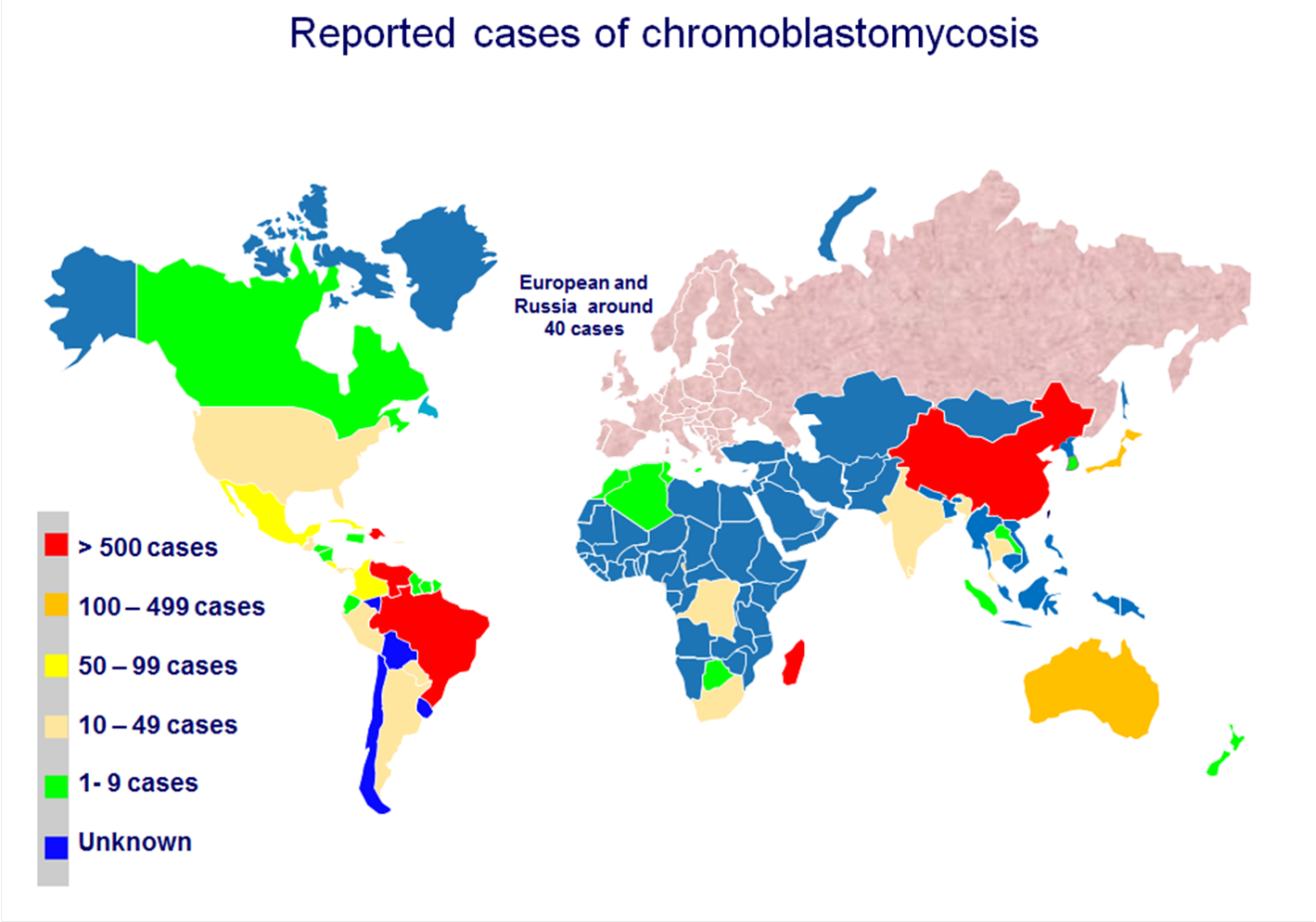

Figure 3. Geographic distribution of chromoblastomycosis according to case reports

Chromoblastomycosis-causing fungi are found worldwide in soil and decaying plant materials, including wood. Because CBM is an implantation mycosis, occupation seems to play an important role on the occurrence of this disease. [23] This disease rarely occurs before adolescence with most of patients being 40 to 50-year-old men, with male-to-female ratios of 5:1 and 9:1. [2,3,12,14,18] The majority of lesions are observed on the extremities of outdoor rural workers. The main risk factors associated with CBM infection are: lack of protective shoes, gloves or garments, and poor nutrition and hygienic habits. [2, 10, 14, 26] CBM is considered an occupational disease, occurring in farm laborers, lumberjacks, or vendors of farm products. A potentially important source of infection was reported in an endemic area located in the of the State of Maranhao, on the fringes of the Amazon rainforest in Brazil, where thousands of families are involved in harvest of babassu (*Orbignya phalerata*), a wild palm tree. 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 developing CBM after trauma sustained at work (Figure 4). [27,28] Other occupational hazards are likely in other environment (see Table 1).

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

Table 1. Details of subcutaneous traumas leading to chromoblastomycosis in 32 Brazilian patients adapted from ref [2]

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

Clinical Manifestations

Following transcutaneous traumatic implantation, and after an uncertain incubation period, the initial CBM lesion appears at the site of infection. 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. [4, 10] The initial skin lesion may progress and evolve with diverse clinical types including nodular, tumoral (cauliflower-like), verrucous and cicatritial appearances (Figure 5). [4, 10. 18, 26] In advanced and more severe cases, more than one type of lesion can be observed in the same patient. The clinical polymorphism of the CBM lesions elicits multiple differential diagnoses including infectious and non-infectious possibilities. This may cause diagnosis delay, lack of therapeutic response and mobility. [4, 10]

At the beginning the initial lesions are asymptomatic, and usually do not interfere with a 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 the 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 bring generalized ill health, and scarring. In the most severe cases, chronic lymphedema and ankylosis develop and non-invasive squamous cell carcinomas may arise. All these complications do lead to definite disability (Figure 1). [4, 10]

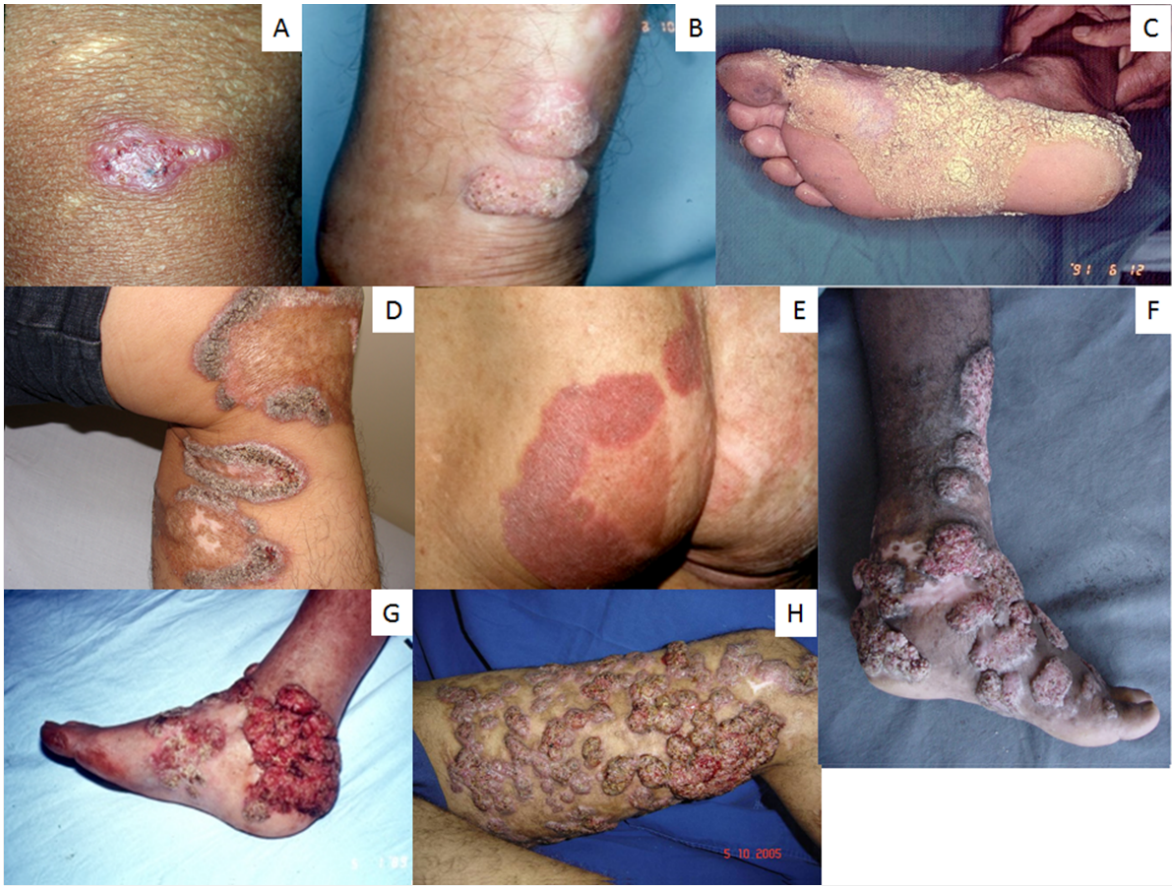

Figure 5. Lesions of chromoblastomycosis may depict clinical polymorphism end elicit several differential diagnosis. The Initial lesion of chromoblastomycosis (1 A), may evolve to five main clinical types: Nodular lesions on the lower leg (1 B), verrucous lesion of the foot (1 C), cicatritial lesions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

Diagnosis

Diagnosis of CMB 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 surface of the lesion where "black dots" may be visible. When examined under light microscopy the pathognomonic "muriform cells" are depicted. These chestnut to rounded brown pigmented and cross septated structures are distinctive and have been referred to as "sclerotic bodies, fumagoid cells" cooper pennies". [4, 10, 16, 19] Muriform cells are considered as a biological adaptation leading the etiologic agents to survive in the hostility of the tissue host environment. [18] Histologically, CBM typically reveals pseudoepitheliomatous 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. [30] When cultivated, all the CBM agents grow slowly in culture. Initially the colonies are deep green, depicting a velvety dark aspect with time. Presumptive species identification may be achieved by mycologic morphologic methods but molecular techniques are suggested for definitive identification. [31]

Therapy

If not discovered early when the initial CBM lesions may be surgically removed, these implantation mycoses are usually recalcitrant and very difficult to treat. [32] 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. [3, 4, 7]

Table 2. Treatment options for chromoblastomycosis.

Physical methods	Chemotherapy	Combination therapy
Surgical resection*		Itraconazole + cryotherapy
Cryotherapy**		Terbinafine + cryotherapy
Local heat (dry)**	Itraconazole ***	Itraconazole + terbinafine ¶
Photodynamic therapy**	Terbinafine ***	Itraconazole + photodynamic therapy
	Posaconazole ¶	Itraconazole + 5-fluorocytosine ¶

* For initial lesions only
** Used only in association with systemic antifungals
*** Most used therapy -
¶ Used for refractory forms

Almost a century has passed since Max Rudolph first reported the disease in 1914. Since then, several therapeutic regimens have been proposed, including physical therapeutic methods and chemotherapy with antifungals Nowadays itraconazole is the most used therapeutic regimen in doses from 200 to 400 mg per day. [7, 33, 34] The higher dose of 400mg daily is much more effective than lower doses. As a second option, terbinafine, 500 mg per day has been used. [35, 36] The possibility of cure depends on the etiologic agent, severity of the disease and criteria of cure used for therapy evaluation. As severity increases, cure rate decreases and relapses are frequent with both itraconazole and terbinafine, ranging from 15 to 80 %. [3, 33-35] For refractory cases, the combination of itraconazole and terbinafine or itraconazole and flucytosine may bring some relief to un-responsive patients. [35, 36] Among the recently licensed antifungals, posaconazole is an attractive option for severe or refractory forms of CBM. [37] For limited disease the topical application of the TH7 agonist imiquimod may be helpful, but data are limited to 4 patients.[38]

Neglected Tropical Disease

The **Neglected Tropical Diseases** (NTDs) constitute a group of tropical infections, which are especially endemic in low-income populations in developing regions of Africa, Asia, and the Americas[39]. The World Health Organization (WHO) acknowledges them as a symptom of poverty and disadvantage. Those most affected by the neglected diseases are typically the poorest populations often living in remote, rural areas, urban slums or in conflict zones. With little political voice, the NTDs had a low profile and status in public health priorities, until the individual diseases were collectively labeled as NTDs and collective actions were initiated. In 2017, the WHO accepted chromoblastomycosis as an NTD, [40] alongside the previously designated mycetoma.

A consensus definition for public health purposes of chromblastomycosis was agreed at the 2017 ISHAM Working Group meeting in Havana: "Chromoblastomycosis is a chronic (>3 months) cutaneous and subcutaneous fungal infection manifesting with mostly verrucous, nodular and plaque lesions, depicting muriform fungal cells on microscopy."[41]

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