CASE REPORT
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Chromoblastomycosis: a tropical – subtropical fungal disease with pathognomonic features not to be neglected in a global health scenario

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Larissa de Andrade Defendi and Marcelo Balancin were responsible for the written commination of the manuscript. Giuliano Ferreira Morgantetti and Guilherme Alencar de Medeiros collected clinical information. All authors contributed equally to the revision of the manuscript.

Competing interests
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Abbreviations
CBM, chromoblastomycosis; SCC, squamous cell carcinoma; IRD, immunosuppressive related diseases.

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Abstract
Chromoblastomycosis (CBM) is a fungal disease, distributed in tropical and subtropical regions, affecting mainly rural workers. It is characterized by chronic skin lesions that may vary from nodular, tumorous, verrucous or plaque type. Associated constitutional symptoms are rarely found. The histological presentation may yield a pathognomonic feature, the Medlar (sclerotic) bodies, in which a typical brown to black pigment is depicted, explaining "copper pennies" as its alias. In this article, the case of a 56-year-old woman in the countryside of Brazil is reported, whose main complaint was a chronic leg ulcer for the past 8 years. The left leg had a large, partially ulcerated plaque lesion was found. Microbiological cultures were positive for the pathogen. Histological analysis demonstrated pseudoepitheliomatous hyperplasia, lymphohistiocytic infiltrate and sclerotic bodies ("copper pennies"). CBM's epidemiological panorama, once established uniquely by geographical distribution, is transitioning to a global health issue, influenced by immunosuppressive conditions, global warming and migration. This scenario demands CBM to be widely considered as a differential diagnosis and may represent a clinical challenge in regions whose professionals have little expertise in infectious tropical diseases.

Keywords: chromoblastomycosis; fungal infection; histopathology; global health

Introduction

Chromoblastomycosis (CBM) is a chronic fungal infection of the skin and subcutaneous tissues that often results from direct inoculation, such as from a wood splinter [1]. It emerges as one of the most prevalent transcutaneous traumatic implantation mycoses in individuals living in tropical and subtropical zones around the world [2]. Pedroso and Gomes were the first to observe the disease in 1910 [3], in Sao Paulo, Brazil, reporting it only in 1920 [4]. The first description of CBM is attributed to Max Rudolph, a German physician who published the first cases from the city of Estrela do Sul (Minas Gerais – Brazil), in 1914 [5].

Epidemiological 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 [6]. In Brazil, the estimate incidence rate is 3/100,000. Most of the cases in literature 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 [1, 7, 8].

Several dematiaceous fungi cause chromoblastomycosis, including *Fonsecaea compacta, Rhinocladiella aquaspersa, Phialophora verrucosa, Fonsecaea pedrosoi* (humid areas) and *Cladophialophora carrionii* (semiarid regions) [9, 10]. Cellular division occurs by internal septation rather than budding. These agents are soil and/or plant saprobes with typical mycelia in environmental samples, changing morphology to the muriform (sclerotic) form when they are in contact with human tissues.

The histological presentation may yield a pathognomonic feature in up to 93% of cases: the Medlar (sclerotic) bodies [11]. Also known as muriform cells, these 9-10 microns thick-walled oval structures may be found in the stratum corneum (or other layers of epidermis) and in granulomas / giant cells. A typical brown to black pigment is depicted, sparing the need of additional stain for identification [12] and explaining “copper pennies” as its alias. The biology of muriform cells is poorly understood, likely representing the adaptive form of these dematiaceous fungi when surviving for prolonged periods in hostile environments [13].

Lymphoplasmacytic infiltration and pseudoepitheliomatous hyperplasia of the *stratum corneum* are the main histological features related to CBM infection. Their presence is estimated in 50% and up to 3%, respectively. Chronic involvement of cutaneous and subcutaneous tissues, associated with a granulomatous, purulent or fibrotic tissue formation, are due to non-protective humoral immune response [9, 14].

CBM, as most of the neglected tropical diseases, imposes a clinical challenge. The recalcitrant nature of chronic and severe late-stage disease and the lack of clinical trials pave grounds for a mostly treat-and-test therapeutic basis [15]. Options are separated into three categories: physical treatment (surgical excision, thermotherapy, cryosurgery and local heat); chemotherapy (calciferol, 5fluorocytosine, thiabendazole, amphotericin B, ketoconazole, fluconazole, itraconazole, posaconazole and terbinafine); and combination therapy [2]. Failure may be associated to the host’s underlying conditions such as: undernourishment leading to inadequate immune response; the multitude of etiologic agents; and inadequate chemotherapy [2].

Case presentation

A 56-year-old woman was admitted to the dermatology clinic in the countryside of northern Brazil (Maranhão state region) with a chronic leg ulcer for 8 years. No other symptoms were reported. At physical examination, a large, partially ulcerated plaque lesion was found in the anterior side of the left leg. Microbiological cultures and a biopsy were performed in its borders. Histological analysis demonstrated intense pseudoepitheliomatous hyperplasia with dense lymphohistiocytic infiltrate (Figure 1). On high power, pathognomonic sclerotic bodies (“copper pennies”, Figure 2) were depicted, leading to the diagnosis of Chromoblastomycosis. Cultures were positive for this pathogen. Chemotherapy treatment was introduced, and the patient remained with no evidence of disease progression until the conclusion of this article.

Informed consent was obtained directly from the patient before the study and the presented data is anonymized and deidentified to restrict identification.

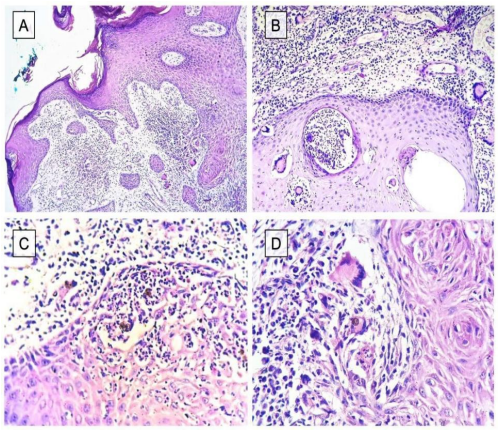

Figure 1 Histological presentation of CBM. (A) Panoramic view of skin biopsy depicting pseudoepitheliomatous hyperplasia with marked proliferation of *stratum corneum*, disposed in an infiltrative-like fashion in dermal compartment. (B) Dense inflammatory infiltrate and epidermal micro-abscess areas with notable multinucleated giant cells. (C) Dark structures in the micro-abscess area. (D) Multinucleated giant cell with intracytoplasmic minute dark-tinged structures (H&E, ×40, ×100, ×400, ×400).

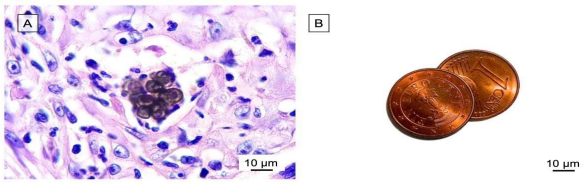

Figure 2 Pathognomonic features of CBM. (A) Sclerotic bodies with its characteristic 9-12 micrometer dimensions, ovoid and pigmented, amidst a dense inflammatory infiltrate. (B) Resemblance to “copper pennies” is evident, even considering contemporary Euro pennies (author photograph) (H&E, ×630).

Discussion

CBM is an occupational disease. The lesions are observed on the extremities of outdoor rural workers, with most patients in the age group between 40 to 50 years old, similarly to our reported case. The main associated risk factors are lack of protective shoes, gloves or garments; poor nutrition and hygienic habits [9].

Skin lesions are the most common clinical presentation. The primary lesion (at the site of inoculation) is a pink papule, and it further progresses to a verrucous plaque. Skin forms may vary from nodular, tumorous, verrucous and plaque type [2], sometimes imposing a diagnostic challenge. Usually, there are no associated constitutional symptoms.

Cases of squamous cell carcinoma (SCC) arising from a chronic inflammatory microenvironment (Marjolin ulcer phenomenon) with CBM as the underlying etiologic agent have been widely reported [16–19]. A Brazilian series of 100 cases with a 14-year follow-up period found an incidence of SCC around 2% [19]. CMB and SCC are differential diagnosis that should be mutually excluded, especially in broad and chronic limb lesions [16].

In terms of histological evaluation, the differential are fungal infection (Paracoccidioidomycosis) and fungal mimickers as Phaeohyphomycosis with “copper penny” spore-like organisms [20,

21], commonly seen as a dermal-based pseudocyst, an abscess or ulcerated necrotic granulomas. Anecdotal reports have also described melanoma as a mimicker [12].

In 2018, as it might be starting a third wave of non-desired immunosuppressive related diseases (IRD) due to global warming, CBM should be considered a differential diagnosis in a multitude of clinical scenarios. In the 1980s, when HIV infection emerged [22], the first wave of IRD was reported, varying from opportunistic co-infections to increased cancer risk [23]. Organ transplantation fostered the second wave of IRD due to immunosuppressive therapy [24]. Global warming, in a similar fashion, tends to swift the epidemiological profile of many infectious diseases. The expected thermal increases up to 5.8°C by the end of this century might cause tropical / subtropical conditions to appear in temperate climates. The West Nile Virus, for example, previously restricted to the southern and southwestern regions of the United States, has been already notified in eastern states [25]. Similarly, the risk of Lyme disease has significantly increased in northern states from 1993 to 2007 [26].

In a global health scenario, other factors to be considered are the heterogeneous populations and their transit. Migration and asylum seeking can lead to unexpected diagnoses, determining the need to adapt the approach to public health issues in some countries [27–29]. Consequently, an increased awareness of tropical / subtropical infectious diseases features, as provided by this report, is mandatory for accurate diagnosis and treatment.

Conclusion

Ulcerative skin lesion, a common scenario in developing countries, may present a wide range of differential diagnoses, from fungal infections to squamous cell carcinoma. In this report, we have illustrated a classical histopathological case of Chromoblastomycosis. In clinical terms, the suspicion should be followed by a biopsy of the lesion; in pathological terms, findings such as granulomatous response, the presence of giant cells, pseudoepitheliomatous hyperplasia and diffuse lymphohistiocytic infiltrate should warrant the search for epidermal or dermal sclerotic (Medlar) bodies. Their identification should spare the need of additional stains. Treatment imposes a clinical challenge due to a myriad of facts: the chronicity, the difficulty in identifying of correct pathogen and the accompanying social panorama. Once restricted to specific climates, Chromoblastomycosis might face an epidemiological swift in a globalized scenario; therefore, the knowledge of its clinical and pathological features is of utmost importance for pathologists.

References

1. Queiroz-Telles F. Chromoblastomycosis: a neglected tropical disease. *Rev Inst Med trop S Paulo* 2015;57(suppl 19):46–50. http://doi.org/10.1590/S0036-46652015000700009
2. Queiroz-Telles F, Esterre P, Perez-Blanco M, Vitale RG, Salgado CG, Bonifaz A. Chromoblastomycosis: an overview of clinical manifestations, diagnosis and treatment. *Med Mycol* 2009;47(1):3–15. http://doi.org/10.1080/13693780802538001
3. Criado PR, Valente NYS, Brandt HRC, Belda Junior W, Halpern I. Dermatite verrucosa de Pedroso e Gomes (Cromomicose): 90 anos depois, ainda entre nós. *An Bras Dermatol* 2010;85(1):104–105. http://doi.org/10.1590/S0365-05962010000100018
4. Pedroso A, Gomes JM. Sobre quatro casos de dermatite verrucosa produzida por Phialophora verrucosa. *An Paul Med Cir* 1920;11:53–61.
5. Rudolph M. Über die brasilianische "Figueira" (Vorläufige Mitteilung). *Arch Schiffs und Tropen-Hyg* 1914;18:498–499.
6. Marques GF, Masuda PY, Sousa JMP, Barreto JA, Wachholz PA. Clinical and demographic profile of chromoblastomycosis in a referral service in the midwest of São Paulo state (Brazil). *An Bras Dermatol* 2015;90(1):140–142. http://doi.org/10.1590/abd1806-4841.20153252
7. Lu S, Lu CM, Zhang JM, Hu YX, Li XQ, Xi LY. Chromoblastomycosis in mainland China: a systematic review on clinical characteristics. *Mycopathologia* 2013;175(5-6):489–495. https://link.springer.com/article/10.1007/s11046-012-9586-z
8. Yap FBB. Chromoblastomycosis. *Int J Infect Dis* 2010;14(6):e543–e544. http://doi.org/10.1016/j.ijid.2009.07.005
9. Avelar-Pires C, Simoes-Quaresma JA, Moraes-de Macedo GM, Brasil-Xavier M, Cardoso-de Brito A. Revisiting the clinical and histopathological aspects of patients with chromoblastomycosis from the brazilian amazon region. *Arch Med Res* 2013;44(4):302–306. http://doi.org/10.1016/j.arcmed.2013.04.008
10. Gomes RR, Vicente VA, Azevedo CMPS de, et al. Molecular epidemiology of agents of human chromoblastomycosis in brazil with the description of two novel species. *PLoS Negl Trop Dis* 2016;10(11):e0005102. http://doi.org/10.1371/journal.pntd.0005102
11. Correia RTM, Criado PR, Valente NYS, Martins JEDC. Chromoblastomycosis: study of 27 cases and review of medical literature. *An Bras Dermatol* 2010;85(4):448–454. http://doi.org/10.1590/S0365-05962010000400005
12. Deb Roy A, Das D, Deka M. Chromobalstomycosis - a clinical mimic of squamous carcinoma. *Australas Med J* 2013;6(9):458–460. http://doi.org/10.21767/AMJ.2013.1806
13. Bui AQ, Espana EM, Margo CE. Chromoblastomycosis of the conjunctiva mimicking melanoma of the ciliary body. *Arch Ophthalmol* 2012;130(12):1615–1617. http://doi.org/10.1001/archophthalmol.2012.1573
14. Queiroz-Telles F, De C L Santos DW. Challenges in the therapy of chromoblastomycosis. *Mycopathologia* 2013;175(5-6):477–488. http://doi.org/10.1007/s11046-013-9648-x
15. Queiroz-Telles F, Fahal AH, Falci DR, Caceres DH, Chiller T, Pasqualotto AC. Neglected endemic mycoses. *Lancet Infect Dis* 2017;17(11):e367–e377. http://doi.org/10.1016/S1473-3099(17)30306-7
16. Bazaliński D, Przybek-Mita J, Barańska B, Więch P. Marjolin's ulcer in chronic wounds - review of available literature. *Contemp Oncol* 2017;21(3):197–202. http://doi.org/10.5114/wo.2017.70109
17. Azevedo CMPS, Marques SG, Santos DWCL, et al. Squamous cell carcinoma derived from chronic chromoblastomycosis in Brazil. *Clin Infect Dis* 2015;60(10):1500–1504. http://doi.org/10.1093/cid/civ104
18. Torres E, Beristain JG, Lievanos Z, Arenas R. Chromoblastomycosis associated with a lethal squamous cell carcinoma. *An Bras Dermatol* 2010;85(2):267–270. http://doi.org/10.1590/s0365-05962010000200025
19. Minotto R, Bernardi CDV, Mallmann LF, Edelweiss MIA, Scroferneker ML. Chromoblastomycosis: a review of 100 cases in the state of Rio Grande do Sul, Brazil. *J Am Acad Dermatol* 2001;44(4):585–592. http://doi.org/10.1067/mjd.2001.112220
20. Skupsky H, Junkins-Hopkins J. Counterfeit pennies: distinguishing chromoblastomycosis from phaeohyphomycotic infections. *Am J Dermatopathol* 2017;39(6):485–487. http://doi.org/10.1097/DAD.0000000000000679
21. Krzyściak PM, Pindycka-Piaszczyńska M, Piaszczyński M.Krzyściak PM, Pindycka-Piaszczyńska M, Piaszczyński M. Chromoblastomycosis. *Adv Dermatology Allergol* 2014;5:310–321. http://doi.org/10.5114/pdia.2014.40949
22. Chang CC, Crane M, Zhou J, et al. HIV and co-infections. *Immunol Rev* 2013;254(1):114–142. http://doi.org/10.1111/imr.12063

23. J Silverberg M, Chao C, A Leyden W, et al. Hiv infection and the risk of cancers with and without a known infectious cause. *Aids* 2009;23(17):2337–2345. http://doi.org/10.1097/QAD.0b013e3283319184
24. George MP, Masur H, Norris KA, Palmer SM, Clancy CJ, McDyer JF. Infections in the immunosuppressed host. *Ann Am Thorac Soc* 2014;11:S211–S220. http://doi.org/10.1513/AnnalsATS.201401-038PL
25. Soverow JE, Wellenius GA, Fisman DN, Mittleman MA. Infectious disease in a warming world: how weather influenced west nile virus in the United States (2001–2005). *Environ Health Perspect* 2009;117(7):1049–1052. http://doi.org/10.1289/ehp.0800487
26. Tuite AR, Greer AL, Fisman DN. Effect of latitude on the rate of change in incidence of Lyme disease in the United States. *CMAJ Open* 2013;1(1):E43–E47. http://doi.org/10.9778/cmajo.20120002
27. López-vélez R, Turrientes MC, Huerga H. Infectious diseases in immigrants from the perspective of a tropical medicine referral unit. *Am J Trop Med Hyg* 2003;69(1):115–112. http://doi.org/10.4269/ajtmh.2003.69.115
28. Castelli F, Sulis G. Migration and infectious diseases. *Clin Microbiol Infect* 2017;23(5):283–289. http://doi.org/10.1016/j.cmi.2017.03.012
29. Eiset AH, Wejse C. Review of infectious diseases in refugees and asylum seekers-current status and going forward. *Public Health Rev* 2017;38(1):1–16. http://doi.org/10.1186/s40985-017-0065-4