INVESTIGATION

Chromoblastomycosis: study of 27 cases and review of medical literature

Cromoblastomicose: relato de 27 casos e revisão da literatura

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Abstract: BACKGROUND: Chromoblastomycosis is a subcutaneous mycosis that occurs mainly in rural workers although is being more commonly found among people working in other sectors. The fungus penetrates the skin after its inoculation and the most frequently isolated agent is the Fonsecaea pedrosoi.
OBJECTIVES: This study aims at evaluating patients suffering from chromoblastomycosis admitted into the Department of Dermatology of the University Hospital of the Faculty of Medicine of São Paulo State during the ten-year period from 1997 to 2007.
METHODS: It is a retrospective study and the medical report cards of 27 Brazilian patients diagnosed as suffering from Chromoblastomycosis from 1997 to 2007 at the Dermatology Department of the Medical School, University of Sao Paulo were reviewed. The following items were analyzed: previous therapeutic approaches; treatment implemented by the group; length of time between the appearing of the lesion and diagnosis; age; gender; profession; origin; site of lesions; isolated agents found in culture and histopathology.
RESULTS: Twenty two patients were from the state of Sao Paulo whereas the others came from the states of Bahia and Rondonia. 37% of them were rural workers. Men were more frequently infected (85%). Lesions were more commonly found on the lower limbs (59.2%). In 52% of the cases the isolated agent was the dematiaceous fungus Fonsecaea. pedrosoi. Biopsies showed sclerotic bodies in 92.5% of the cases.
CONCLUSION: Data found are in accordance with medical literature on the subject. The disease had been previously studied in our institution in 1983 by Cucé *et al*. This present study is the second retrospective one about the characteristics of patients suffering from chromoblastmycosis which has been published in indexed medical literature in the state of Sao Paulo.
Keywords: Chromoblastomycosis; Epidemiology; Fungi

Resumo: FUNDAMENTOS: A cromoblastomicose é uma micose subcutânea que acomete principalmente homens trabalhadores rurais, sendo cada vez mais observada em outras atividades profissionais. O fungo penetra na pele após inoculação, e o agente mais frequentemente isolado é a Fonsecaea pedrosoi.
OBJETIVOS: Este estudo visa a avaliar os pacientes com cromoblastomicose admitidos no departamento de dermatologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo no período de 1997 a 2007.
MÉTODOS: É um estudo retrospectivo, utilizando a revisão de prontuários, e inclui 27 pacientes. Analisaram-se os tratamentos prévios e os atuais instituídos, o tempo entre o aparecimento das lesões e o diagnóstico, a idade, o gênero, a profissão, a procedência, a localização das lesões e os agentes isolados em cultivo.
RESULTADOS: Vinte e dois pacientes eram procedentes do estado de São Paulo. Os demais eram procedentes da Bahia e Rondônia. A maioria dos pacientes estudados eram trabalhadores rurais (37%). Os homens foram os mais acometidos (85%). A maior parte dos pacientes apresentava lesões nos membros inferiores (59,2%). Em 52% dos casos foi isolado o fungo F. pedrosoi. O exame anatomopatológico mostrou corpos escleróticos em 92,5% dos casos.
CONCLUSÃO: Os dados encontrados estão concordantes com os da literatura, sendo este o segundo estudo retrospectivo sobre as características dos doentes portadores de cromoblastomicose no âmbito do estado de São Paulo publicado na literatura indexada.
Palavras-chave: Cromoblastomicose; Epidemiologia; Fungos

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INTRODUCTION

Chromomycosis is a fungal disease which is mainly located on the lower limbs presenting nodules and verrucose plaques that might ulcerate. It is a mycosis that occurs on the epidermis, dermis and subcutaneous tissue that might present secondary infection, leading to lymphedema and elephantiasis and occasionally to spinocellular carcinoma. Lymphatic and haematogenous dissemination have been observed in rare cases.[1]

The fungus penetrates the skin usually due to traumatic implantation. Especially in areas not protected by vestments, lesions develop on the site of the inoculation locating themselves on the skin and, sometimes, on the subcutaneous tissue.[1]

Originally described by Pedroso e Gomes, in 1914, in the city of São Paulo, chromomycosis is a worlwide distributed disease being more prevailing in tropical and subtropical countries, mainly in Brazil, Mexico, Cuba and the Dominican Republic. Climatic conditions associated with underdeveloped regions contribute to the maintenance of well characterized. endemic areas. It is produced by dematiaceous fungi that present in the direct micological exam singular shaped bodies. The most frequently isolated organisms are *Fonsecaea pedrosoi, Phialophora. verrucosa, Cladosporium carrioni*, and less frequently, *Rhinocladiella aquaspersa.*[2]

The Amazonian region, in Brazil, has been considered the main endemic area of chromomycosis.[2] There is only one study on chromomycosis epidemiologic data in the state of São Paulo, published in 1983 by Cucé *et al*[3] with patients from the University Hospital of the Faculty of Medicine of São Paulo state (HC-FMUSP). So, our study aims at gathering epidemiologic data; at analysing the anatomic distribution of lesions; at the identification of the etiological agents most involved; the histopathological findings discovered, time between the appearing of the disease and its diagnosis; the treatments and the therapeutic response of patients suffering from chromomycosis being treated in the University Hospital of the University of São Paulo (HC-FMUSP) in the ten-year period from 1997 to 2007. Apart from that, this study also aims at comparing the results found in this present study with the results previously found in this same institution by Cucé *et al*.[3]

MATERIALS AND METHODS

It is a retrospective study including 27 patients with a diagnosis of chromomycosis obtained by direct micological exam, histopathology or culture for fungi, admitted in the period between 1997 and 2007 and documented by the Departement of Dermatology of the Faculty of Medicine of the University of São Paulo, Brazil. Data were collected from the clinical reports of patients and the study was sanctioned by the ethical committee of the institution. Patients were grouped and analysed according to age, gender, profession, origins, location of lesions and agent isolated in cultivation. Previous and instituted treatments and the lengh of time between the appearing of the disease and diagnosis were also analysed.

RESULTS

Geographic disdribution

Twenty two patients were from the state of São Paulo, distributed among the following municipalities: two from Guaianases; one from Mogi das Cruzes, one from Suzano, one from Atibaia, one from Itaquacetuba, one from Juquitiba and one from Santos. Fourteen patients resided in the city of São Paulo; eight had been born in the state of São Paulo being four from the district of São Paulo; one from Juquitibá, one from Atibaia, one from Santos and one from Itaquacetuba. The remaining ones were from the following states: 5 (Bahia), 3 (Pernambuco), 2 (Minas Gerais), 2 (Paraná), 1 (Pará), 1 (Mato Grosso do Sul). Six affirmed they had been residing in the state of São Paulo longer than the period of time they have had the disease; two were ill before they moved to São Paulo and from five patients it was not possible to obtain this information. The others were from the states of Bahia(3) and Rondônia(2).

Patients profession

The majority of the studied patients were rural workers (37%). However, various other occupations were found associated with the disease as follows: maid (11%), locksmith (7,4%), civil construction workers (7,4%), lorry driver (3,7%), legal consultant (3,7%) and chapman (3,7%). The others were either retired (11%) or it was not known their professions (11%). The average age for the rural workers group was 64,20 years with a standard deviation (SD) of 14,18 years while for the other professions it was 59,07 years with a SD of 18,08 years. The average lengh of time between the apppearing of the disease and diagnosis concerning rural workers was around 109,33 months with a SD of 93,23 months, as for the others it was 69,18 months with a SD of 61,10 months.

Distribution according to gender and age

The disease was predominantly found in men (85%). The age group more affected by it was between 51 to 60 years of age. (29,6%), but the age of patients varied largely from 28 to 87 years of age (Table 1). The average age of patients was 60,85 years with a SD of 15,63 years, being for men 59,74 years and for women

Table 1: Distribution according to age and sex

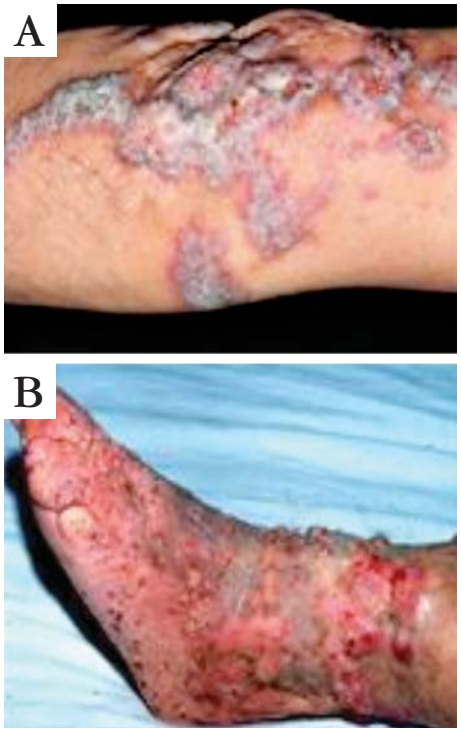
Age	Men	Women
21-30	1	0
31-40	1	1
41-50	4	0
51-60	8	0
61-70	3	1
71-80	3	1
>80	3	1
Total	**23**	**4**

Appearing of the disease average age (AA): 60,85 years; Standard deviation (SD):15,63 years.
Women:AA-67,25 years, SD-19,93 years.
Men:AA-59,74 years, SD-15,03 years.

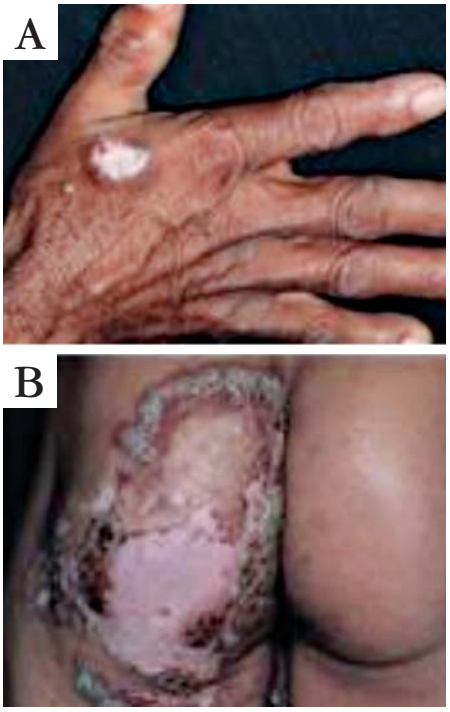
67,25 years with a standard deviation (SD) of 15,03 years and 19,93 anos, respectively. It is important to observe that the ages mentioned do not coincide with the begining of the infection, generally occured years before.

Anatomical distribution of the disease

Most patients presented lesions on the lower limbs (59,2%), followed by location on the upper limbs (29,6%). In 14,8% of the patients, lesions occured on the dorsum, from which 75% were also associated with lesions on the extremities and 25% of the cases showed lesions in only one anatomic site (Pictures 1 and 2). The average age of patients with lesions on the lower limbs was 63,53 years with SD of 14,10 years ,as for upper limbs it was 57,78 years with SD of 18,19 years.



Picture 1: A. Ulcerated verrucose plaque on the left elbow; **B.** Ulcerated verrucose plaque on the right foot



Picture 2: A. Verrucose nodule and infiltrate on the dorsum of the right hand **B.** Plaque with verrucose borders with atrophyc and sclerotic center on the left buttock

Etiological Agent

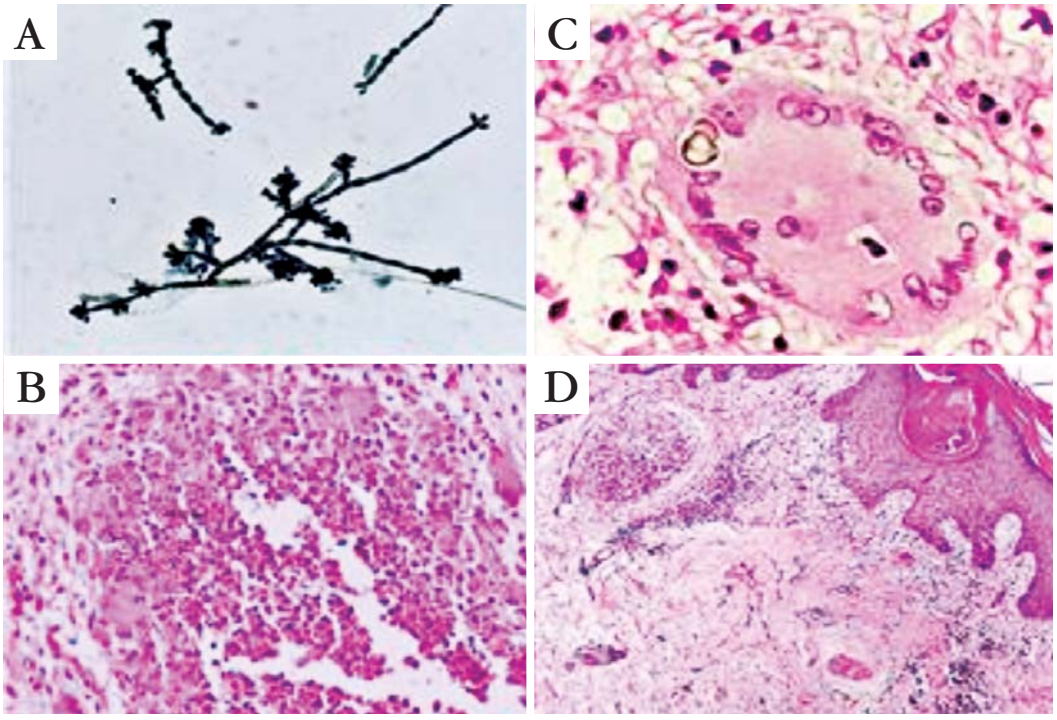
In all cases it was observed sclerotic or muriform bodies in direct micological exams with KOH of 10%. In 52% of the patients it was isolated the dematiaceous fungus *Fonsecae pedrosoi*, being negative for the others. In one culture F. pedrosoi and Cladosporium SP grew, being the latter one contaminative.

Histopathology

Chromoblastomycosis is a granulotomatosis disease which presents peculiar findings in a histopathologic exam. In our study we found sclerotic bodies in 92,5% of the cases. We observed the following histopathological findings in decrescent order: multinucleated giant cells (52%), lymphoplasmacytic infiltration (48%), pseudoepitheliomatous hyperplasia (33%), microabscesses on dermis (29,6%), epithelioid granuloma (26%), granuloma outline (22%) and microabscess on the epidermis (7%) (Picture 3).

Lengh of time to make the diagnosis

The lengh of time between the appearing of the disease and diagnosis varied from 1 month to 25 years, in 29,6% of the cases there was less than 4 years of evolution, from wich 25% needed seclusion from costumary activities (Table 2). The average lengh of time between appearing of the lesion and diagnosis



Picture 3: A. microcultivation of F. pedrosoi (blue cotton) culture; B. sclerotic bodies in the center of a suppurative area of a chromomycosis granuloma (hematoxylin-eosin, OM: X200); C. sclerotic bodies in a multinucleated giant cell (hematoxylin-eosin,OM: X400); D. Granulomas on the dermis and pseudoepitheliomatous hyperplasia (hematoxylin-eosin, OM: X100)

was 87,25 months with com SD of 77,74 months. This variable, when analysing rural workers, had an average lengh of time between appearing of the lesion to diagnosis of 109,33 months with SD of 93,23 months. In all other professions it was 69,18 months with SD of 61,10 months.

Treatment

From the patients studied 45% had already had some kind of treatment without therapeutic success. Among the treatments set up by us we could mention cryotherapy (isolated or associated with oral antifungal) surgical excision; and oral antifungal (itraconazole, terbinafine, ketoconazole and amphotericinB) isolated or associated, in different, therapeutic doses. From these 27 pacients, 10(37%) are still under treatment; 11(40,7%) presented clinical cure from which 8 (72,7%) in less than 2 1/2 years of treatment. As for the other patients -6(23%): 5 lost sequence and 1 died due Acute Myocardiual Infarction. Patients with clinical cure up-to-now have not presented recidivation. Clinical cure was considered when there was negativation of the direct micological. Further to that it was observed improvement in the lesions of patients which were situated and small in extension. Therapeutics set up for these patients varied from surgical excision (1 case), itraconazole and cryosurgery (5 cases), terbinafine and cryosurgery (1 case), and cryosurgery only (6 cases). The lengh of the treatment varied considerably (10 months to 6 years), being shorter for treatments with surgical excision or cryotherapy.

Table 2: Lengh of time between appearing of the disease and diagnosis of chromomycosis (years)

Lengh of time between appearing of the lesion and diagnosis (years)	number of cases
<4	8
4-8	5
8-12	5
12-16	4
24-28	1
Unknown	4

Average lengh of time between appearing of lesions and diagnosis.
TPtotal-87,25 months.
SD total-77,74.
TP in farmers-109,33.
SD in farmers -93,23.
TP in the other professions -69,18.
TP in the other professions -61,10.

DISCUSSION

Epidemiologic aspects were observed analysing the 27 patients with diagnosis of chromomycosis in our institution, from 1997 to 2007. Chromomycosis is found in all Brazilian geographic regions, calling the attention due to prevalence of cases, the southeast region. [4] It is a disease of cosmopolitan distribution with higher prevalence in tropical and subtropical regions of Latin America, Africa and Asia with hot and wet climate. In Brazil, Rio Grande do Sul, São Paulo, Rio de Janeiro, Minas Gerais, and states from the Amazonian region are endemic areas. [5] The majority of

cases reported here come from the district of São Paulo (44%) and the remaining ones either come from the interior of the state of São Paulo or from the other Brazilian states.The disease was prevalent among men (85%) and rural workers (37%), which is in accordance with previous data. [1, 2, 4, 6-11] This reality occurs because rural activities are mostly common carried out by men and because traumatisms related to the begining of this fungal disease have as main factor the manipulation of the rural vegetation, fact that was demonstrated by the isolation of *Fonsecaea pedrosoi* from thorns of the plant called *Mimosa pudica* indicating that it might be a natural source of infection of the *F. Pedrosoi* fungus. [4,12,13] Age related to the begining of the lesions in men was lower than in women. We inferred that this is due to the fact that the begining of professional activity for men, most of the time, is more precocious, exposing them to the etiologic agents. Following in much lesser percentages, although equalitarians, other rural activities stand out: the handling of agricultural tools and animals and other diverse causes. [4]. All women studied worked with domestic activities. It is possible that sexual hormones play an important role on the pathogenesis of this disease. [4,14] Studies suggest that the growth of *P. verrucosa* is regulated by steroid hormones and that the effect of progesterone could be mediated by intracellular receptors of the fungus. [14] It is important to point out that the other professions that deal with the industrialization of wood and civil construction have also constituted a significant number of patients presenting chromomycosis. It is important to remember that the age concerning the appearing of lesions in rural workers was higher than in other professions. We can assume that this might be due to the greater exposition of these professionals to the etiologic agent creating some resistance for the appearing of the clinical lesion, being necessary a greater lengh of contact time with it.

The lengh of time between the appearing of symptoms and definitive diagnosis varied a lot, being longer in rural workers patients. This fact may be explained by the difficulty these professionals have to access the health system. The evolution of the disease is slow and frequentely patients only seek for a doctor some years after the initial symptoms.[5]

The segment of the body mostly affected were the lower limbs which is in accordance with the bibliographical revision, [1, 2, 4,6,7,9,10,11] although in some works other sites are more prevailing. [5,16] In underdeveloped countries, people work without equipmentsfor protection, favouring the direct contact with the fungi habitat.[2] The predominant location of lesions on the lower limbs and history of previous local trauma is directly correlated with the type of activity performed and reinforces the hypothesis of traumatic implantation of the fungus in the tissues to produce such infection. These findings concur with the majority of the authors.[5]

The identification of *F. pedrosoi* as the main etiological agent in our cases concurs with other researches in tropical regions.[1, 2,8] In semiarid regions the C. carrioni can be found as main agent. [8]

There are three types of treatment, that is, physical treatment (cryotherapy and surgical excision), chemotherapeutic and combination of therapies. The success of the treatment is related to the causal agent, clinical form and extension of lesions.[17] Cryosurgery with liquid nitrogen is a surgical resource used to treat various cutaneous lesions, benign, pre-malignant and malignant. It promotes the destruction of the tissues affected through freezing and alteration of the immunologic response. Cryosurgery is used for the treatment of some infectious dermatoses, especially viral warts, leishmaniasis and chromoblasomycosis. [18] Cryosurgery with liquid nitrogen is an option of treatment for chromoblastomycosis and the results are more satisfying in localized and small lesions, being necessary an average of 6,7 sessions to cure, according to Pimentel *et al*.[19,20] It was previously believed that low temperatures could destroy the infective agent but it was demonstrated that the fungal cultures in temperatures as low as -196°C would not kill it. Although efficacy has been proved it is not clearly known the mechanism of cure. [21] The combination of itraconazole to reduce the size of the lesions with subsequent cryosurgery represents an alternative treatment for patients with large lesions.[22] The majority of antifungal medicines, systemic and oral, have been used and the best results are achieved with itraconazole and terbinafine in high doses , for at least 6 to 12months.[23]

This disease was previously studied in our institution. From 1971 to 1981, Cucé *et al* carried out a study based on the analysis of 37patients being 28 of them (75%), rural workers.[3] The majority of them was between 30 and 49 (51%) yearsof age. There were only 2 women. The main site of infection was the lower limb (89,1%), followed by the upper limb in 10,9% of the cases. None of them presented lesions on the face or dorsum.[3] Culture was positive in all cases.[3] The results described are similar to the results of our study. However, some different aspects were observed. Our study showed greater occurrence of other professional activities such as maid 3 (11%), carpenter 2 (7,4%), civil construction worker 2 (7,4%), lorry driver 1 (3,7%), consultant 1 (3,7%) and chapman 1 (3,7%); it was observed that other sites of the body presented the disease like the trunk and upper limbs which were infected in 8 patients (29,6%);

besides the fact of the cultures being positive in only 14(52%) of the cases. Progressive urbanization associated with the uprising of new professional activities linked to the civil construction, which involve manipulation of wood and greater manual skills might justify the decrease of occurrence among rural workers as well as the increase of occurrence in the upper extremities.

CONCLUSIONS

Chromycosis is not a disease of compulsory notification, being epidemiological data little known in the Brazilian territory.

In our study we could observe the epidemiologic variables involved with chromycosis, standing out the prevalence of the disease in the male sex, especially among rural workers, and its localization almost always on the lower limb.However, we also noticed a tendency of alteration of these aspects once we could observe a greater number of women with the disease and the occurrence of lesions in other sites. This can be explained by the economic and social consequences brought up by the industrial revolution, with a crescent insertion of women in the labour market.

Data found in our studies are concordant with medical literature, being this publication the second one about epidemiologic data on chromycosis in the state of São Paulo, within a bit more than three decades. ❑

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