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Research Article

Chromoblastomycosis in Southern Madagascar: Our Experience

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Abstract

The authors present their experience in the detection, clinical diagnosis, treatment and outcomes of 20 subjects affected by chromoblastomycosis identified in two regions of Southern Madagascar over a long period (1990–2025). Mucocutaneous manifestations proved difficult to resolve therapeutically, not only in relation to the drugs used and the duration of treatment, but also because of patient compliance and the numerous logistical problems present in these regions. The proportion of clinically cured subjects was 30%, and this included only those with mild to moderate forms. The most frequently used drug was terbinafine.

Keywords: *Chromoblastomycosis; Neglected tropical diseases; Subcutaneous mycoses; Antifungal therapy; Terbinafine; Madagascar*

Introduction

Chromoblastomycosis is a chronic infection of the dermis and subcutaneous tissue caused by fungi largely belonging to the order *Chaetothyriales*, family *Herpotrichiellaceae*.

The fungal species most frequently identified are *Fonsecaea pedrosoi*, *Phialophora verrucosa* and *Cladophialophora carrionii*. These fungi are ubiquitously distributed worldwide, although their pathological manifestations are more frequent in tropical and subtropical regions [1,2,3,4,6,7,8,9,12,14,15,17,18,19,20] and only occasionally in other areas of the world.

These organisms are typically saprophytic fungi that can be isolated from soil, from the pulp and bark of both living and decomposing plants, from paper material and from any wooden product and/or tools used in its manufacture; under certain conditions they can infect humans with varying degrees of clinical manifestations. Madagascar represents the country with the highest number of reported cases worldwide, followed by Central and South American countries such as Brazil, Venezuela and Mexico; however, a significant frequency is also observed in China, the Indian subcontinent and Australia [1,2,3,4,6,7,8,9,12,14,15,18,19,20].

Operational Context

During the period 1990–1992, at the HCM of Sakalalina (a public hospital of the Malagasy State), district and region of Ihosy – Southern Madagascar, within a project managed by Italian Cooperation through the Italian NGO MSP with the Ministry of Health of Madagascar, and from 1998 to 2025 (with suspension from 2019 to the end of 2023) at the Antenne Chirurgicale St Croix (a private hospital of the Nazarene Sisters of Turin but recognised by the Malagasy State) of Isoanala Sud, district and region of Betroka – Southern Madagascar, within a cooperation between the ODV H&T (Italy) and the same Congregation of the Nazarene Sisters, we were present for extended periods on healthcare missions addressing both medical and surgical conditions. Both are small peripheral hospitals located in contexts not easily accessible by means of transport, both connected by difficult tracks often impassable during the rainy season (December–March) to the main centres (Ihosy, Betroka), and respectively about 55 and 80 km away from them. Better-equipped hospital facilities are located more than 150 km from the respective centres.

The climate is typical of the African bush, with reduced tree cover (Figure 1) and arable land mainly along the few watercourses, some of which are not perennial. Cactus vegetation and agave plants are present and particularly abundant in the territory of Isoanala and neighbouring areas.

The population lives mainly through field cultivation and the rearing of zebu cattle, a large bovine species common in Madagascar.

Figure 1. Landscape with vegetation in Southern Madagascar.

Although globally sedentary, the population shows considerable mobility between various villages located even at significant distances from one another; health education is limited and often difficult for the local population to understand, health centres are few and distant in relation to population needs, mostly poorly equipped medically and surgically for the diagnosis and treatment of the various pathologies encountered, and difficult for the population itself to access.

Materials and Methods

During the previously indicated periods, 20 cases (2 in Sakalalina and 18 in Isoanala) of subjects affected by chromoblastomycosis came to our attention: 16 men and 4 women, mean age 45.5 years, range 23–70. Eight subjects (1 woman and 7 men) did not possess identity documents indicating their date of birth, and therefore the calculation was made approximately based solely on their verbal declarations and on examination of their physical appearance.

Diagnosis was made through both direct clinical examination and complementary cyto-histological investigations. Mucocutaneous clinical manifestations were compatible with chromoblastomycosis lesions [1,2,4,5,6,7,14,15,16,17] in 17 cases, whereas 3 subjects did not have unequivocal characteristics of fungal infection.

Cyto-histological investigations were carried out in three different ways and in different locations:

1. Direct microscopic examination only of skin scales taken from the border and centre of lesions to search for the presence of sclerotic bodies (Figure 2), typical of the disease, after clarification treatment with 10% potassium hydroxide as internationally recommended (3 subjects). This examination was carried out directly by one of the authors at the hospital facilities.

2. Direct microscopic examination at our facilities, together with multiple biopsy sampling (from 1 to 3 fragments) for histopathological examination (sent to national or foreign institutes equipped with a Pathology Service) aimed at definitive diagnosis by searching for “fumagoid cells/bodies”, with preservation of biopsies in 10% formalin (12 subjects).

3. Only multiple biopsy sampling at our facility for histopathological examination to search for “fumagoid bodies”, with preservation of biopsies in 10% formalin (1 subject).

4. Direct microscopic examination at our facility associated with multiple biopsy sampling (with preservation of biopsies in 10% formalin) and with sampling of skin scales from the borders and centre of lesions and of exudate for culture examination to identify the responsible fungus (4 subjects). This latter group (three men and one woman, mean age 41.5 years, range 31–54) was studied during the same period (2003) in Isoanala and was the subject of a preliminary investigation aimed at identifying the fungal species. The samples were inoculated locally in Isoanala on Sabouraud agar with chloramphenicol and gentamicin and sent for further diagnostic investigations to the Institute Pasteur de Madagascar in Antananarivo. Culture examination gave a doubtful result in one case, but in 3 subjects it led to the isolation of *Cladophialophora carrionii*.

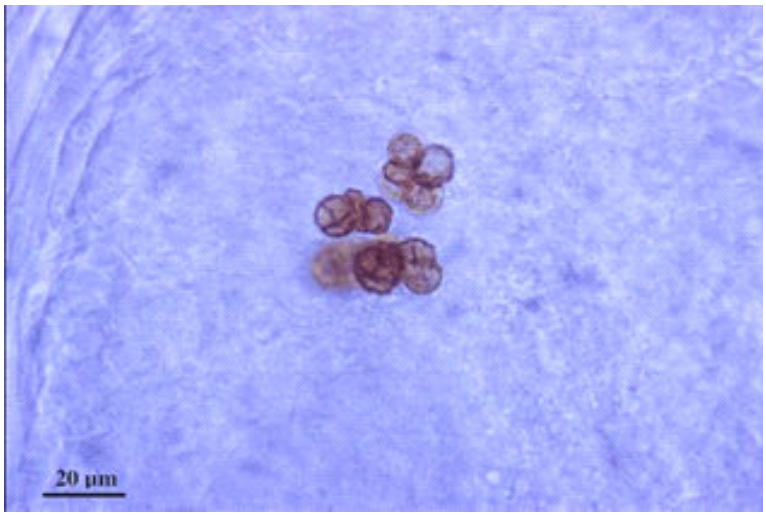

Figure 2. Sclerotic bodies under direct microscopic vision.

Mucocutaneous lesions (Table 1) were assessed morphologically, following the classification proposed by Carrion in 1950 [13], which uses the identification of five forms: nodular, tumoral or pseudotumoral characterised by large inflorescences or cauliflower-like masses, verrucous, cicatricial and plaque forms (Table 1). Severity of clinical manifestations was assessed according to what was proposed by Queiroz-Telles and de Andrade [17], i.e. mild, moderate and severe forms, retrospectively using photographic documentation and clinical data acquired for subjects identified before 2003, and subsequently we decided to use it systematically for all new cases through careful direct medical examination (Table 1).

Table 1. Clinical characteristics of the lesions.

	Location	Lesion number	Macroscopic appearance	Severity
1	Right lower limb	Single	Nodular	Mild
2	Right lower limb	Multiple	Plaque	Moderate
3	Buttocks + right lower limb	Multiple	Verrucous	Severe
4	Groin	Multiple	Nodular	Moderate
5	Right lower limb	Multiple	Verrucous	Moderate
6	Left lower limb	Multiple	Verrucous	Severe
7	Face + right lower limb	Multiple	Cicatricial–verrucous	Severe
8	Right lower limb	Multiple	Tumorous	Severe
9	Right lower limb	Multiple	Verrucous–tumorous	Severe
10	Left upper limb	Single	Cicatricial	Moderate
11	Left lower limb	Single	Plaque	Moderate
12	Left lower limb	Multiple	Verrucous	Severe
13	Right lower limb	Multiple	Verrucous–tumorous	Severe
14	Left lower limb	Single	Plaque	Moderate
15	Right lower limb	Single	Nodule	Mild
16	Right lower limb	Multiple	Tumorous	Severe
17	Right lower limb	Multiple	Verrucous	Severe
18	Right lower limb	Multiple	Plaque	Severe
19	Lower limbs bilaterally	Multiple	Verrucous-tumorous	Severe
20	Buttocks, right lower limb, hips, lower back bilaterally	Multiple	Plaque	Severe

All subjects reported having had cutaneous manifestations for a long time, which had evolved slowly, with a mean reported duration of 1–3 years for mild and moderate forms, whereas for severe forms it was 8–12 years. No patient reported having family members affected with similar lesions.

Table 2. Name of the drugs used and protocol**.**

Number of cases	Medical therapy	Treatment duration	Remarks
5	Terbinafine oral tablets 250mg	250 mg x 2/day for 2 months, followed by 250 mg/day for 6 months	
6	Terbinafine oral tablets 250 mg	250mg x 2/day for 2 months, followed by 250 mg/day for 3 months	
6	Terbinafine oral tablets 250 mg	250 mg x2/day for 3 months, followed by 250 mg/day for 3 months	A subject did not show up again, after the 5th month of therapy
1	Ketoconazole oral tablets 200 mg	200 mg/day for 3 months and after recurrence 250 mg/day for 3 months	Woman undergoing integrated surgical treatment after recurrence
1	Ketoconazole oral tablets 200 mg	200 mg/day for 6 months	
1	Itraconazole oral tablets 100 mg	200 mg/day for 8 months	Ongoing therapy

All subjects reported having had cutaneous manifestations for a long time, which had evolved slowly, with a mean reported duration of 1–3 years for mild and moderate forms, whereas for severe forms it was 8–12 years. No patient reported having family members affected by similar lesions.

Reported symptoms were classified into three categories:

A) Asymptomatic or paucisymptomatic: 2 cases of uninodular manifestation and the only case of multiple nodular lesions. These subjects underwent our evaluation for aesthetic reasons and for fear that the appearing nodule might further increase in size.

B) Symptomatic with intensely pruritic manifestations in subjects affected with the other forms (9 cases).

C) Symptomatic with diffuse pruritus and intense serohaemorrhagic exudate, sometimes purulent-like (Figure 3), with a nauseating odour such as to force the subject to isolate themselves from family/community or to be rejected by it (all remaining 8 cases).

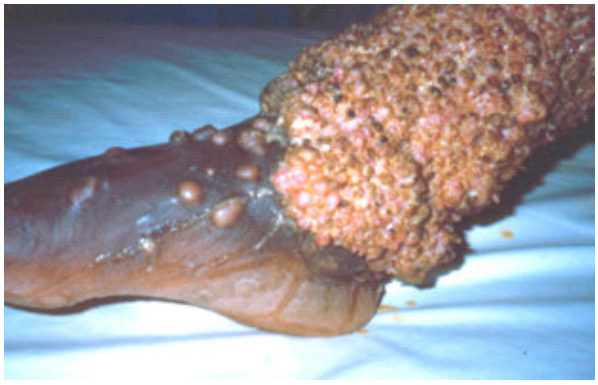

Figure 3. Purulent exudate from an active lesion.

As associated clinical manifestations, we observed associated lymphedema of the lower limbs affected by extensive multiple verrucous forms (2 cases), whereas in one case (tumoral form) there was also evident spread of infection to the subcutaneous tissue, muscle planes and bone tissue with osteolytic lesions. These lesions are particularly disabling and determine a significant degree of work disability, with impossibility of carrying out normal rural activities (cultivating fields, obtaining water supplies, etc.), and consequently it becomes very problematic to procure means of subsistence.

We note that 3 subjects, all identified in the period 1998–2000, had a history of positivity for Hansen's bacillus (2 paucibacillary forms and one multibacillary; only one individual (paucibacillary) was still taking specific therapy for this disease at the time of our evaluation).

Therapy and Results

Medical therapy (always administered exclusively orally) was indicated through an operational protocol (Table 2) with the administration of ketoconazole (2 cases), terbinafine (17 cases) and itraconazole (1 case). Dosage and duration of treatment were variable because no universally accepted standard therapy is reported in the literature. Treatment decisions also depended on patient compliance, geographic accessibility to our facilities, the monthly cost of therapy, and the feasibility of obtaining the drug locally in Madagascar for the full planned duration of treatment.

Drugs were initially administered at the hospital facilities to subjects daily for the first 10–15 days; subsequently, patients were given a quantity sufficient each time to cover a 30-day period to periodically monitor their health status and response to the instituted therapy. Only one subject (therapy still ongoing), domiciled in a remote location, was provided with sufficient therapy to cover a two-month period at a time.

Two subjects, both females, affected by nodular forms, underwent integrated medico-surgical treatment:

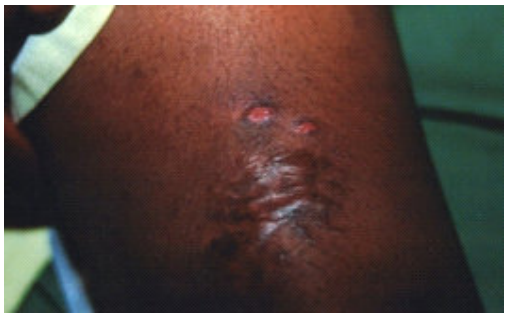

Figure 4. Satellite nodular lesions after the first surgical excision.

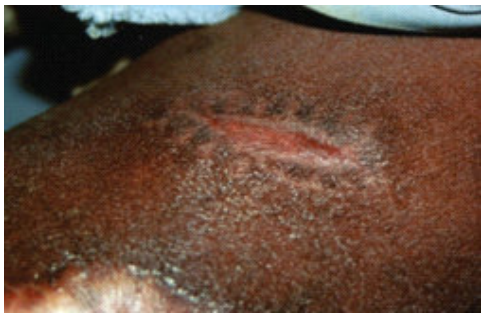

Figure 5. Previous case: result after surgical removal of the lesions and subsequent antifungal therapy.

In the first case, wide surgical excision of the single nodular lesion located in the lower third of the right thigh was performed, followed by ketoconazole 200 mg for 3 months; given the early recurrence with the appearance of small satellite nodules (Figure 4), it was decided to proceed with bulk removal of skin and subcutaneous tissue in the affected region and subsequent further 3 months of ketoconazole 200 mg/day, with excellent final results (Figure 5). In the second case, surgical removal of one of four nodular lesions at inguinal level was performed, one of which was located at the level of the labia majora (Figure 6), followed by administration of terbinafine 500 mg/day for one month followed by terbinafine 250 mg/day for a further five months.

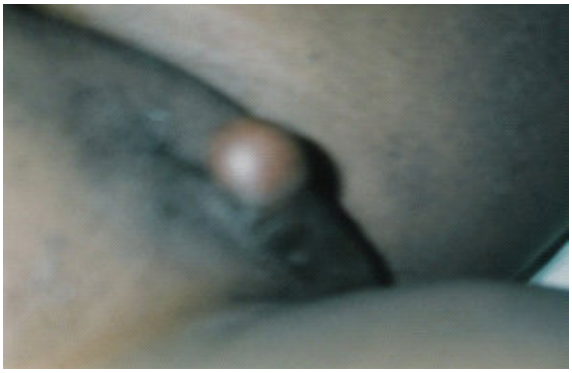

Figure 6. Nodular lesion on the labia majora.

The choice to use ketoconazole relates to the first two cases observed by us (1990–1992), when this drug was the most easily traceable and available in the country, just as the administration of terbinafine in the greater number of cases was based on data reported in the literature during the different time periods of our presence [5,10,11,14,16,17] and on the possibility of obtaining the drug locally.

For these reasons, we did not consider drugs reported to be more effective but much more expensive, or combined cryosurgical therapies [15,16,18], which we judged not feasible in our operational context.

Therapy was always provided free of charge, with the request for a symbolic contribution (the current equivalent of about €1) only for monthly follow-up visits, and the cost of therapy was borne entirely by our organisation; in this way we were able to achieve good adherence to the proposed therapeutic protocols.

During treatment, monthly monitoring of the most significant blood chemistry parameters did not show significant alterations in blood counts, liver or renal function, and no pharmacological intolerance phenomena were observed; in only one case treated with ketoconazole was a transient mild leukopenia found, which completely regressed three months after the end of therapy. The subject with ongoing therapy, due to the considerable distance (over 200 km) from our centre in Isoanala, is evaluated only clinically and with drug supply at a private dispensary located closer to their domicile.

Clinical response was assessed based on the reduction in the number and extent of lesions and their replacement mainly with depigmented spots, achromic or hypochromic areas, or, especially in severe plaque forms, also possibly with the appearance of hypopigmented fibrotic tissue in place of the previous mycotic lesions.

A clinical response with what can be defined as complete cure (total disappearance of the initial fungal lesions) was verified in only 6 subjects, presenting a mild (2 cases) or moderate (4 cases) degree of severity and with nodular (2 cases) and cicatricial or plaque (4 cases) macroscopic appearance. An important clinical response, i.e. reduction (assessed as greater than 80%) of the extent of the infected mucocutaneous surface and of the number of lesions, was verified in 2 cases affected by verrucous and plaque forms and in one case affected with tumoral form.

In all other cases (multiple verrucous lesions, extensive plaques, multiple tumoral/pseudotumor formations), a reduced therapeutic response was observed with persistence of mucocutaneous lesions in at least 50% of the initial extent, although there were depigmented spots/areas contiguous or discontinuous with the present mycotic lesions and a reduction in their volume as well as in the overall number of macroscopic lesions.

All subjects affected by severe forms with the presence of serohaemorrhagic secretions also showed a notable reduction or disappearance of such manifestations and cleansing of lesions after only two months of therapy.

Eighteen subjects completed the therapeutic protocol; one subject, after five months of therapy with terbinafine (proposed regimen 250 mg ×2/day for 3 months, then 250 mg/day for 3 months), did not return for follow-up, while another subject (the most recent one identified in 2025, case no. 20 in Table 1) has not yet completed the protocol (under treatment with itraconazole) and shows an excellent therapeutic response to this drug after the first 4 months of therapy (Figure 17, before the start of treatment; Figure 18, after 4 months of treatment), with the appearance of extensive depigmented areas replacing the mycotic lesions.

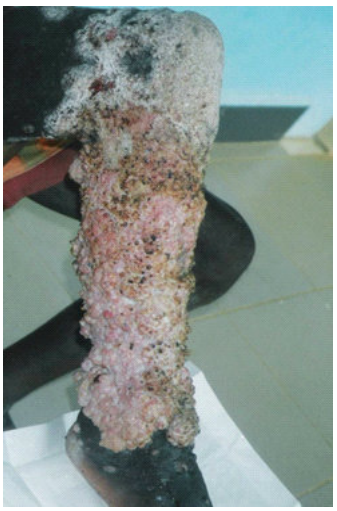

Figure 7. Extensive exudative pseudotumor lesions on the right lower limb.

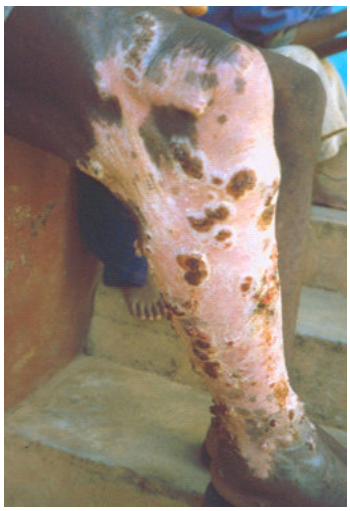

Figure 8. Previous case at the end of 6 months of antifungal treatment.

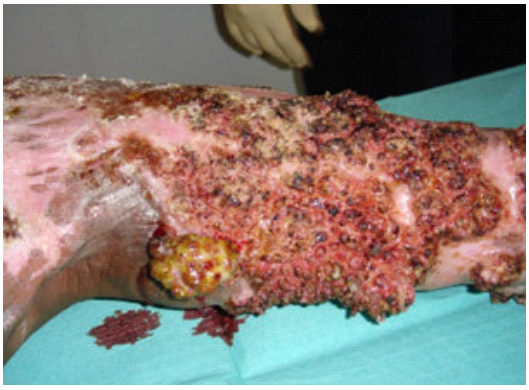

Figure 9. Previous case: at follow-up, after two years, extensive recurrences and new lesions on the previously achromic/ hypochromic areas.

Follow-up after the end of instituted therapy could be carried out in only 6 cases due to the distance of our centres from patients' domiciles, economic difficulties, health education and understanding of the importance of undergoing periodic follow-up.

The female subject affected by a nodular lesion, mild form, who underwent (as previously described) surgical intervention, therapy, re-intervention for recurrence and subsequent medical therapy, was still free from recurrence after 21 months of follow-up.

The female subject with multiple nodular lesions at inguinal level and labia majora was without signs of recurrence at the level of the previous surgical scar after two years of follow-up, but with the presence of the other previously reported lesions without apparent clinical response to therapy and the appearance of two new nodules at thigh level. The person declined to undertake a new therapeutic cycle.

A subject affected by extensive pseudotumor cauliflower-like lesions on the right lower limb, strongly exudative, severe clinical form (Figure 7), at the end of therapy presented an almost complete clinical remission (Figure 8), but after two years of follow-up new lesions developed on previously re-epithelialized areas in the form of pseudotumor inflorescences secreting a serohaemorrhagic liquid (Figure 9) and refused to undergo a new therapeutic cycle.

A subject with multiple verrucous lesions, partly pseudotumor, on the right lower limb (Figure 10), severe form, had a good therapeutic response with clear reduction of mycotic lesions at the end of five months of therapy (Figure 11), but after one year developed again new verrucous lesions along the inner surface of the right thigh (Figure 12) and refused to undergo a new therapeutic cycle.

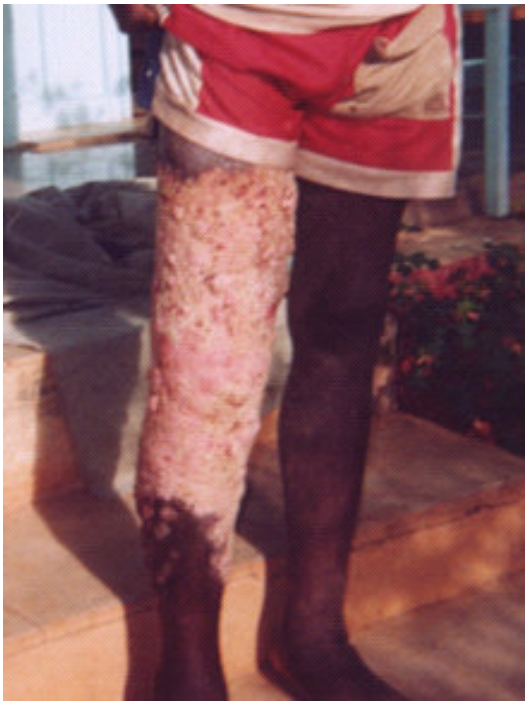

Figure 10. Multiple verrucous lesions and partly pseudotumor on the right lower limb.

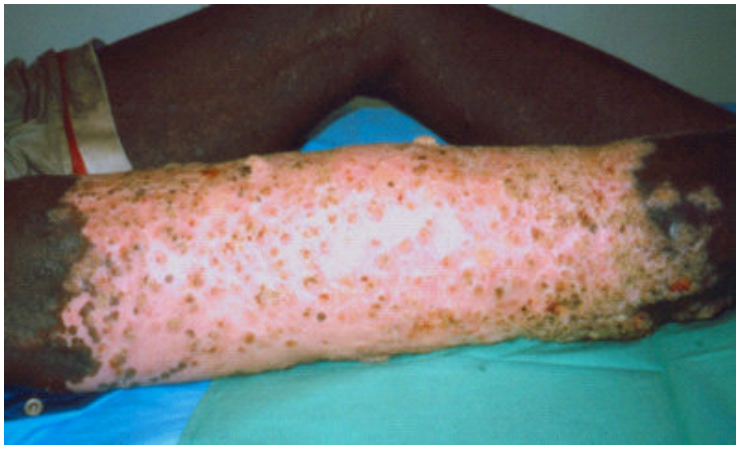

Figure 11. Previous case at the end of 5 months of antifungal therapy.

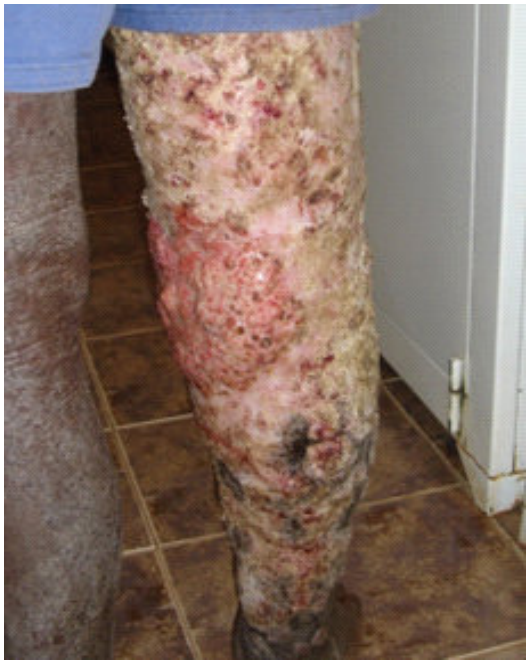

Figure 12. Previous case at follow-up, after one year, extensive recurrences of verrucous lesions were observed.

A subject affected by a single extensive plaque lesion, moderate form (Figure 13), eight months after the end of treatment showed complete cleansing and the presence of achromic areas, apparently free from recurrence (Figure 14).

A subject with significant involvement of the right lower limb, severe form, with limb lymphedema, extensive subcutaneous infiltration and osteolytic remodelling of the toes (Figure 15) presented at the end of treatment cleansing and clarification of lesions and a reduction in their volume and extent (Figure 16). The subject did not agree to undergo further treatment but returned for evaluation after two months with a clinical picture unchanged compared to the previous check.

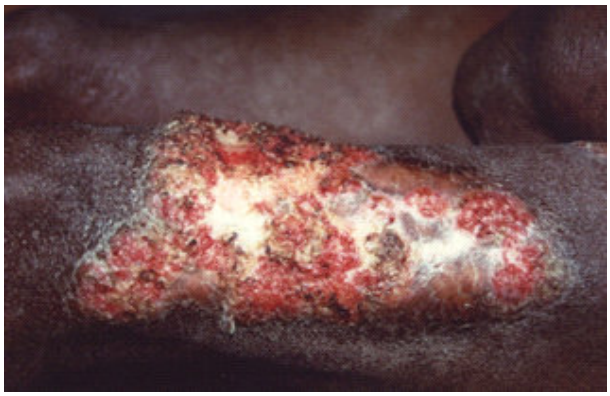

Figure 13. Extensive plaque lesion on the right lower limb.

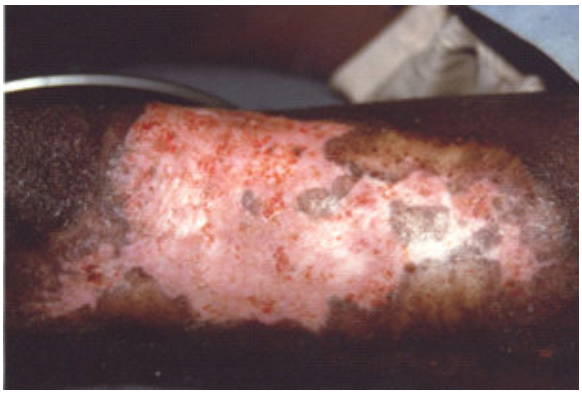

Figure 14. Previous case. At follow-up, after 8 months, apparent complete healing and the presence of an extensive achromic area.

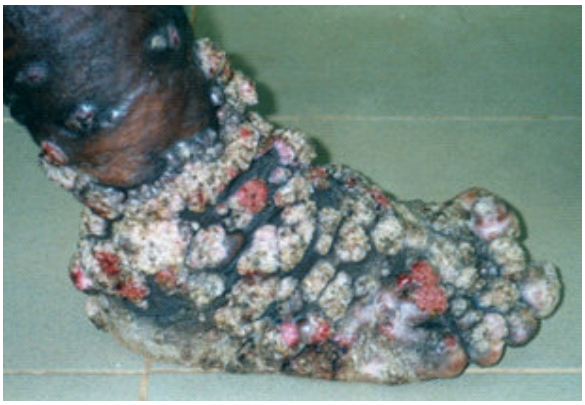

Figure 15. Multiple pseudotumor lesions with associated lymphedema and osteolytic lesions on the fingers.

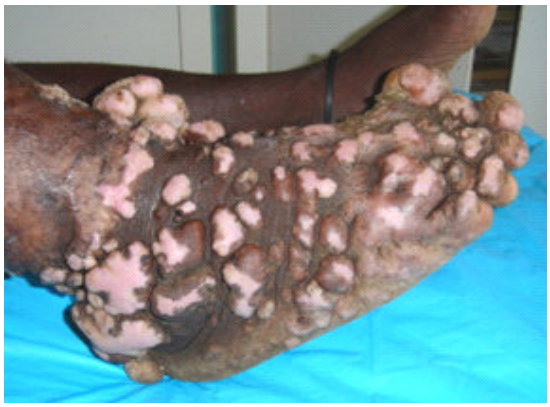

Figure 16. Previous case at the end of 8 months antifungal treatment.

All other subjects, once the proposed and instituted medical treatment had ended, no longer presented for follow-up visits and we subsequently had no further news of them.

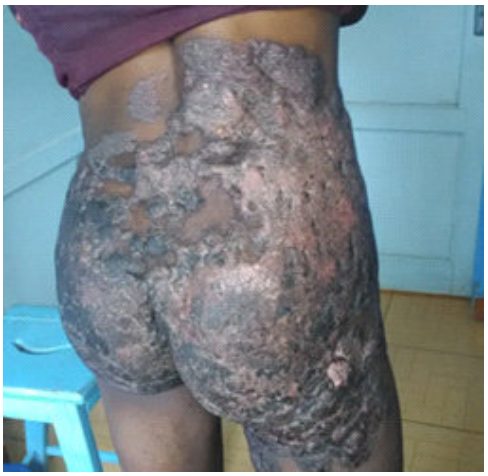

Figure 17. Extensive plaque lesions on the buttocks, back, hips, and lower right limb.

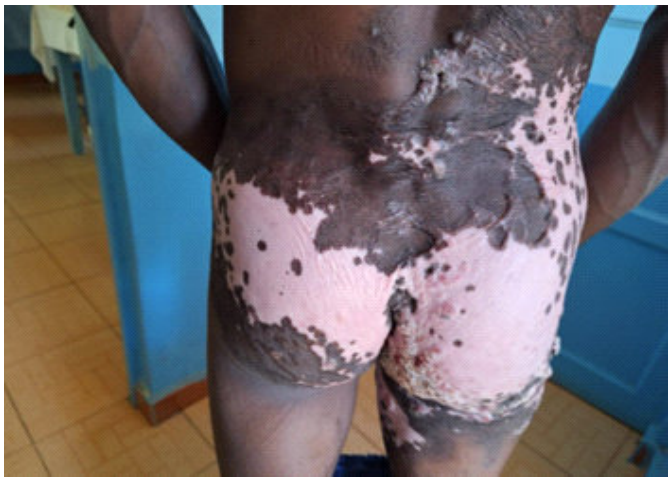

Figure 18. Previous case after 4 months of itraconazole treatment.

Conclusions

Chromoblastomycosis has shown an infrequent and sporadic occurrence in the two regions where we operated, but this could be due to underestimation of the problem and inadequate knowledge of this pathology by the public and private health and paramedical personnel present locally.

The choice to use the morphological classification proposed by Carrion [13] and the severity staging proposed by Queiroz-Telles [17] was dictated by the aim of applying simple, rapid evaluation schemes requiring minimal time for clinical assessment, in order to train the medical and paramedical staff present in the two facilities by suggesting practical clinical-diagnostic protocols in their application. For these reasons, we avoided using the classification with the applicative algorithm proposed by Castro [16], more complete but significantly more demanding, requiring suitable and specific training in its application to daily clinical practice by medical/paramedical staff in relatively isolated facilities such as those where we were present. In our case series, the clear prevalence of male subjects and a middle-adult age of cases confirms what is reported in the literature, where the incidence of the disease in youth or prepubertal age is low; likewise, the high number of subjects [17] with mycotic involvement of the lower limbs agrees with published data [1,2,3,4,6,8,9,15,16,17,18,19,20].

Culture findings in some subjects confirm, in our experience, what has long been reported by several groups and specialists [1,2,7,8,12], showing a distribution of the two most frequent species in Madagascar in more humid territories (*Fonsecaea pedrosoi* in the North and partly in the East) and in drier ones (*Cladophialophora carrionii* in the South of the island).

There are no shared guidelines regarding therapy to be instituted in subjects affected by chromoblastomycosis; clinical-diagnostic protocols differ among the various groups dealing with this disease; drugs and their dosages vary considerably; observed cases are not easily comparable due to different criteria relating to severity and stage of disease, and likewise for obtained results and follow-up, which are not easily comparable.

The different therapeutic protocols we applied using terbinafine, with different treatment durations and daily dosages due to our limited number of observed and treated cases, do not allow us to draw significant conclusions.

We note that all three protocols initially (in the first two months of therapy) proved effective in reducing the diameter and extent of lesions and in drastically and spectacularly reducing the nauseating secretions exuding from lesions. With continued therapy, results differed according to morphological form and degree of severity: we observed a better, albeit temporary, response in verrucous and tumoral forms, whereas plaque forms proved the most refractory.

Treatment duration in turn influenced obtained results: therapy should be continued indefinitely until complete resolution of pathology is observed or until evidence of lack of response, and therefore for an extremely long time [5,6,7,9,10,11,14,15,16,17,18,19,20], with problems related to patient compliance and logistical issues.

It also remains unclear how recurrence of the pathology should be managed: there are no shared guidelines for this problem, no uniformity of data published in the literature nor of criteria adopted regarding such situations.

We believe that training and sensitisation of the health and paramedical personnel present in facilities in the territory (clinics, dispensaries, health centres and maternal and child protection centres, both public and private), as well as those present in larger facilities (HMCs of various levels), is of fundamental importance for recognition, clinical diagnosis, therapy and periodic monitoring.

Such actions must be implemented with greater health education aimed at the population so that a greater number of cases is encouraged to present for clinical evaluation without waiting too long from the first appearance of cutaneous lesions.

A major problem is drug availability and cost; in low-income countries such as Madagascar, it is unthinkable to make affected subjects bear the cost of drugs for this pathology, but this requires economic support that must be provided by national/international bodies, and this problem must make us carefully reconsider the use of latest-generation drugs compared to older but certainly less expensive ones.

We believe that only when the above problems are addressed will chromoblastomycosis emerge from the long list of forgotten skin diseases [19] and Neglected Tropical Diseases, making it possible to provide an effective clinical and therapeutic response for subjects affected by this pathology.

Acknowledgement

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Conflict of Interest

The authors declare that they have no conflicts of interest with the pharmaceutical companies manufacturing the drugs mentioned in the text.

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