

Case Report

Chromoblastomycosis in children and adolescents in the endemic area of the Falcón State, Venezuela

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The present paper describes 22 cases of chromoblastomycosis (CBM) caused by *Cladophialophora carrionii* in children and adolescents (2–19 years old). The patients were seen between 1992 and 2004 and all resided in a CBM endemic area in the semi-arid zone of the Falcón state, Venezuela. Twelve of the 22 patients (54.55%) had close relatives who also had CBM and 19 (86.36%) were male. Lesions consisted of erythematous papules with desquamation or squamous plaques (0.12–14.19cm in diameter), located primarily on the upper limbs (77.27% of patients). Thirteen of the patients were treated with topical 5-fluorouracil (5-FU; 1% cream), seven with topical ajoene (0.5% gel) and two had electrodesiccation and/or fulguration. Two patients who did not respond to 5-FU were treated with oral itraconazole (100 mg/day for 1 month). Complete clinical and mycological remission was achieved in 17/20 (85%) of the patients treated with 5-FU, ajoene and electrodesiccation and/or fulguration. In addition, similar results were obtained with the two patients who received itraconazole therapy. These cases emphasize the importance of early diagnosis in mycotic diseases difficult-to-treat such as CBM. By early intervention we were able to employ topical treatment with a minimum of adverse effects to achieve a high percentage of favorable therapeutic responses. The patients were thus able to avoid the evolution of the chronic, deforming and incapacitation clinical manifestations associated with CBM.

Keywords Chromoblastomycosis, children, adolescents, Venezuela

Introduction

Chromoblastomycosis (CBM) is a chronic granulomatous disease of the skin caused by dematiaceous fungi, frequently found in men, especially those from rural areas and/or those working in the field. This mycosis is generally seen in subjects above 20 years of age but a few cases have been described in patients below the age

of 20. At present, little information is available on the natural history of the disease in children and adolescents [1–12].

The endemic area of CBM caused by *Cladophialophora carrionii*, in Venezuela, is located in the north-western region of the country, with more than 50% of the cases reported from the semi-arid zone of the Falcón state. Some authors have shown an association of *C. carrionii* with several species of xerophilous plants, as well as various occupations of those living in the state. Both of these are considered as being important risk factors in acquiring the disease [2,4,13]. Moreover, it has been suggested that susceptibility to CBM may be inheritable in this endemic area, involving 47–65% of the cases. These results suggest an impor-

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tant role of genetic factors in the pathogenesis of the disease (according to model of threshold for multifactorial characters of the native population) [14,15].

In the present study we report 22 cases of CBM in young subjects (2–19 years old). This figure represents 2.6% of the national registry (844 cases) and 4.16% of the 529 cases diagnosed in the semi-arid zone of the Falcón state, until 2004 [13,16].

Cases

Twenty-two cases of CBM in children and adolescents were diagnosed between 1992 and 2004. All patients were resident of an endemic area in the semi-arid zone of the Falcón state, Venezuela. Clinical diagnosis was confirmed by direct microscopic examination of 10% KOH mounts of scales from lesions. Inoculation of other portions of the lesions in Lactrimel supplemented with chloramphenicol (250 mg/l) allowed the identification of *Cladophialophora carrionii*, as the causal agent in all cases.

The family history of the patients revealed that 54.55% had close relatives with CBM. These patients comprised five non-related families in which family 1 (Siblings: 0014-93, 0018-93, 0020-93, Cousins: 0002-97, 0005-97), family 2 (0005-99) and family 3 (Siblings: 0010-94, 0017-94) had ascending grandparents with CBM. Family 4 (Siblings: 0004-94, 0005-94, 0012-97) and family 5 (0010-93) were the product of parents with consanguineous unions and CBM.

The demographic and pathological characteristics of the patients were (Table 1): age range, 2–19 years (Mean \pm SD: 11.14 \pm 4.82); sex: male, 86.36% (19/22) and female: 13.64% (3/22), ratio: 6:1; duration of the disease was from 3 months to 6 years (Mean \pm SD: 1.7 years \pm 1.47); lesions primarily located on the upper limbs (17/22, 77.27%). Lesions on other body areas were much less frequent as they involved the back (3/22, 13.64%), lower limbs (1/22, 4.55%), and buttocks (1/22, 4.55%). The lesions consisted of erythematous papules with desquamation or squamous plaques (0.12–14.19 cm in diameter, Mean \pm SD: 2.34 \pm 3.61) (Figs. 1 and 2), accompanied in some cases by itching of low to moderate intensity.

Thirteen patients received topical treatment with 5-fluorouracil (5-FU, 1% cream), an antineoplastic drug, while seven other patients received ajoene 0.5% gel (a compound originally isolated from alcoholic extracts of garlic, *Allium sativum*), applied on the lesions once a day with occlusive cures, for a period of 21 days to three months [17]. Two patients had electrodesiccation and/or fulguration of the lesions (2 to 3 sessions with intervals of 21 days between each session) (Table 1). 3

patients under 5-FU treatment abandoned the therapy. One of these patients (0005-94) was evaluated three years later and it was found that there had been an increase in the diameter of the lesion from 0.49 to 6.25 cm. At this time, the patient was treated with topical ajoene which resulted in remission of symptoms after 3 months of therapy. Two patients who did not respond to 5-FU therapy were treated with oral itraconazole (100 mg/day for 1 month) [18] and one who did not respond to ajoene, is presently being treated with topical 5-FU (Table 1 and Fig. 2). Topical treatment resulted in complete clinical and mycological remission in 85% (17/20) of the patients. Treatment with itraconazole (two patients) resulted in complete cure of both individuals. Follow-up during a period of four years showed absence of relapses.

Discussion

Although CBM is rarely described in children and adolescents, the present report confirms the presence of the disease in these two age groups [1,3–6,8,11,12]. The shorter time of exposure to the pathogen and the fact that the initial symptoms do not constitute reasons for medical consultation may help to explain the limited number of cases of CBM in children described in the literature. The prolonged evolution time of CBM (10 years or more) suggests that disease in adults could have been acquired in childhood. CBM infection was detected in 30% of inhabitants of the endemic area between 5 and 14 years old by means of the application of intradermal test with *C. carrionii* antigens [19]. Besides the clinical expression of the CBM other aspects of the host-fungus relationship have to be determined.

The higher incidence of CBM in males may be the result of their early work as goat herders and to their outdoor recreational activities. Both of these would bring them into greater contact with the natural vegetative reservoir of the etiologic agent in the endemic area of the Falcón state [4,13].

In contrast with other geographical areas of the world in which CBM is predominantly associated with the lower limbs, in Venezuela the lesions are more frequent on upper limbs (77.27% of present cases) [5,7–10]. This fact could be explained by greater contact with *Cactaceae* and fences composed of tree trunks in the vicinity to the patient's houses, as well as the work of the affected children that includes the daily practice of withdrawing plant thorns from the goat hides [1–4].

Twelve of the 22 patients (54.55%) had close relatives who also had CBM (several affected siblings in a single family). These 'clusters' may be explained by families

Table 1 Chromoblastomycosis in children and adolescents: Demographic and pathological characteristics of the patients, Falcón-Venezuela

Patients N°/UNEFM	Age (years)	Sex	Disease duration (years)	Lesion location	Lesion diameter (cm)	Treatment*	Remission of the disease
0024-98	2	M	<1 (3 months)	Buttock	0.25	Electrosurgery	Yes
0005-97	3	M	1	Arm/Elbow	1	Ajoene for 1 month	Yes
0004-94	5	M	<1 (6 months)	Forearm	0.12	5-FU for 1 month	Yes
0010-94	5	F	<1 (6 months)	Arm	0.25	5-FU for 1 month	Yes
0005-94	7	F	1	Forearm	0.49	5-FU	Unevaluable, discontinued therapy
0005-99	7	M	<1 (3 months)	Leg	0.25	5-FU	Unevaluable, discontinued therapy
0002-97	8	M	3	Back	1	Ajoene for 2 months	Yes
0009-00	9	M	1	Hand	4	5-FU for 3 months	Yes
0018-98	11	M	<1 (8 months)	Back	0.25	Electrosurgery	Yes
0005-04	11	M	3	Forearm	4	Ajoene for 21 days	Yes
0013-04	11	M	6	Shoulder	14.19	Ajoene 5-FU	No In treatment at the moment
0020-93	12	F	3	Hand	0.75	5-FU for 3 months	Yes
0014-93	13	M	<1 (6 months)	Hand	1.5	5-FU for 3 months	Yes
0002-01	13	M	2	Arm	1.5	Ajoene for 3 months	Yes
0013-97	14	M	3	Hand	7	Ajoene for 1 month	Yes
0022-92	15	M	3	Forearm	1	5-FU for 2 months	Yes
0023-92	15	M	<1 (6 months)	Forearm	0.25	5-FU	Unevaluable, discontinued therapy
0018-93	15	M	3	Hand	10	5-FU for 3 months Itraconazole for 1 month	No Yes
0002-95	16	M	1	Hand	1.5	5-FU for 3 months Itraconazole for 1 month	No Yes
0010-93	17	M	3	Forearm	1	5-FU for 1 month	Yes
0017-94	17	M	<1 (6 months)	Back	0.25	5-FU for 1 month	Yes
0012-97	19	M	1	Hand	0.48	Ajoene for 2 months	Yes

*Treatment: topical 5-Fluorouracil 1% cream (5-FU) and topical ajoene 0.5% gel.



Fig. 1 CBM in arm: squamous plaque, two years of evolution (0002-01 patient).



Fig. 2 CBM in shoulder, erythematous squamous plaque, six years of evolution (0013-04 patient).

long residence in the semi-arid area which is the natural reservoir for *C. carrionii* and their daily farming activities. Nevertheless, studies carried out on family groups of the region have shown that the incidence of the illness amounts to 8.79% among relatives of patients as compared to 1.6% in the general population. The risk of developing CBM is 3.5 times higher among members of common ancestry. It has been estimated that there is a 47–65% risk of inheritable susceptibility to CBM, suggesting that genetic factors may play an important role in the development of the disease [4,14,15].

Other studies have shown that the susceptibility to illness may be influenced by a gene located on chromosome 6, in the region of the major histocompatibility complex. This would suggest that individuals carrying HLA-A29 have a 10-fold increased risk of developing CBM than those lacking the antigen [20]. These reports highlight the need to carry out immunogenetic investigations to clarify the genetic aspects involved in the development of the CBM.

CBM is generally considered to be a difficult to treat mycotic infection, but we were able in the present cases to achieve a high percentage of clinical and mycological remission (86,36%). These results confirm data from previous studies that indicate the effectiveness of ajoene and 5-FU in the treatment of CBM caused by *C. carrionii* (localized lesions) [17,21,22]. Two patients who received 5-FU and who did not experience clinical or mycological remission were treated with itraconazole for 1 month (Table 1), resulting in remission of the disease. Similar responses have been reported in 90 other patients from the semi-arid zone of the Falcón state, treated with itraconazole, i.e., 96.25% clinical and mycological remission in patients with localized and extensive/disseminated lesions at 1.55 ± 0.28 and 2.18 ± 0.71 months, respectively [18,21,22]. Therapeutic success may be related to the etiological agent (*C. carrionii* is more sensitive than *Fonsecaea pedrosoi*), to the severity of disease and to the choice of the antifungal drug [23,24].

These cases emphasize the importance of early diagnosis in mycotic diseases difficult to treat such as CBM (Table 1). By early intervention we were able to employ topical treatment with a minimum of adverse effects to achieve a high percentage of favorable therapeutic responses. The patients were thus able to avoid the evolution of the chronic, deforming and incapacitation clinical manifestations associated with CBM.

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