

Dermatophytosis caused by *Trichophyton rubrum* as an opportunistic infection in patients with Cushing disease*

Dermatofitose por *Trichophyton rubrum* como infecção oportunistica em pacientes com doença de Cushing

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Abstract: *Trichophyton rubrum* is a common agent found in superficial mycoses, which present ample non-inflammatory lesions, with chronic evolution, especially in immunocompromised patients. The hypercortisolism in Cushing's syndrome increases the risk of infections as a result of the immunosuppressive effect of glucocorticoids. The reported cases here refer to two different types of dermatophytosis caused by *Trichophyton rubrum* in patients with Cushing's disease, resistant to antifungal treatment. The disease remitted after the levels of cortisol went back to normal.

Keywords: Cushing's syndrome; Dermatomycoses; Immunosuppression; Onychomycosis

Resumo: O dermatófito *Trichophyton rubrum* é um agente comum nas micoses superficiais, podendo apresentar lesões extensas pauci-inflamatórias de evolução crônica, especialmente em imunocomprometidos. O hipercortisolismo, na síndrome de Cushing, aumenta o risco de infecções, resultado do efeito imunossupressor dos glicocorticóides. Os casos relatados apresentam duas formas distintas de dermatofitose, em pacientes com doença de Cushing, causadas por *Trichophyton rubrum* e posterior remissão após normalização da cortisolemia.

Palavras-chave: Dermatomicoses; Imunossupressão; Onicomicose; Síndrome de Cushing

INTRODUCTION

Cushing's syndrome (CS) occurs due to prolonged exposure to high levels of glucocorticoids. The most common cause of CS results from exogenous administration of this hormone. The exogenous production might be high either because of an adrenal tumor or because of an adrenocorticotrophic secretory tumor (ACTH) that might have a hypophyseal origin. Cushing's disease (CD), that is caused by hypophyseal adenoma, is responsible for the largest number of endogenous CS cases.^{1,2}

In the natural history of CD some infectious complications might attack 42% of the non-treated patients.³ High levels of circulating glucocorticoids influence the immune system, reducing, mainly, cellular immunity. The relative risk of acquiring an infection is 1,5 times higher in patients with this

syndrome.^{3,4} Cortisol level impacts the immune system in a dose-dependent way, with higher chances of serious and opportunistic infections in cases with higher values of plasmatic cortisol.⁵

With the deficit of cellular immunity associated with the deficient function of macrophages and neutrophils there is a high risk of infections, by opportunistic fungi, in the hypercortisolism conditions, in the same way it occurs in dermatophyte fungal infections.⁶ Invasive fungal infections are the most studied ones but there are a few reports, with emphasis in the relation between superficial mycoses and hypercortisolism.⁷

The authors of this study present two cases of opportunistic infection via *Trichophyton rubrum*, with distinct clinical presentations in carriers of

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Cushing's disease with spontaneous remission of dermatophytosis, after normalization of the plasmatic cortisol level.

CASE REPORTS

Case 1

Man, mulatto, aged 22 was admitted into the emergency service with diabetic ketoacidosis, serious hypertension and atrial fibrillation. Dermatological exam revealed moon face, plethoric, nuchal gibbus, wide, purplish abdominal striae, acne on the chest and hematomas in areas of trauma. He also presented non-pruritic plaques, erythematous-brownish, desquamative, more intense at the edges, situated on the axillary and inguinal folds expanding to the chest, abdomen, thighs and knees (Figure 1) – mycological exam revealed *T. rubrum*. The diagnosis of hypercortisolism via Cushing's disease was confirmed after clinical investigation.

Oral ketoconazole (600mg/day) was used due to its action on steroidogenesis, to control hypercortisolism, with partial resolution of dermatophytosis. The ketoconazole was suspended due to the progressive elevation of hepatic transaminases, with worsening of the dermatophytosis condition. After specific treatment of the disease, with recession of the hypophyseal adenoma, there was normalization of the cortisol levels and total regression of the infection by *T. rubrum*.

Case 2

Woman, white, aged 26, sought the endocrinology service due to weight gain of 40 kg and secondary amenorrhea. Dermatological exam

revealed moon face, plethoric, wide, purplish abdominal striae on the arms and abdomen, haematomas and hirsutism. The patient also presented whitish plaques on the nail of the left thumb (Figure 2) After mycological exam the clinical hypothesis of superficial white onychomycosis caused by *T. rubrum* was confirmed.

After clinical investigation it was diagnosed hypercortisolism caused by Cushion's disease. The patient had a transsphenoidal surgery for resection of the hypophyseal lesion, the levels of cortisol normalized and there was also spontaneous remission of the fungal nail lesion accompanied by mycological cure.

DISCUSSION

The predisposition for infections, observed in patients with hypercortisolism is a consequence of the complex effects of glucocorticoids on cellular and humoral immunity. Cellular immunity is particularly affected by the hormonal action on neutrophils, macrophages and lymphocytes Th1, with significant increase on the susceptibility to opportunistic infections, especially the fungal ones.^{7,8} The hyperglycemic state found in patients with CD, resulting from the increase of insulin resistance on tissues also contributes to immunosuppression.⁸

Inflammatory lesions, with little or no symptom and extense distribution on tegument combined with resistance to conventional antifungal treatment are characteristic of lesions caused by dermatophytosis in patients with Cushing's syndrome. Cremer G. was one of the first authors to study the influence of Cushing's syndrome on the development of dermatophytoses.⁹ Further to describing the clinical characteristics of the



FIGURE 1: Extense dermatophytosis in patient with Cushing's disease



FIGURE 2: White superficial onychomycosis in patient with Cushing's disease

lesions the author also evidenced that these patients presented cutaneous reaction negative to trychophytin, proof of a deficit on the specific cellular immunity presented by these patients.

However, there are other works that demonstrate, in a more incisively way, the relation between hypercortisolism and the clinical evolution of superficial mycoses, that can present a total or partial clinical resolution after normalization of cortisol levels.^{10,11}

The first case of this report shows well the influence of hypercortisolism on the development of the infection. It was initiated the use of ketoconazole, 600mg/day to control hypercortisolism. There was improvement on the dermatological condition, with partial resolution of the dermatophytosis condition. After discontinuation of medication due to increase in the hepatic transaminases levels the dermatophytosis returned. It presented spontaneous resolution, with confirmation of mycological cure only after specific treatment for CS and normalization of cortisolemia. In the second case, there was also resolution of the infection after normalization of the cortisol levels.

Further to the influence of cortisolemia on the

development of the disease, the clinical presentation of dermatophytoses also changes. Typically, the cases are extense and pauci-inflammatory. In the first case, the absence of pruritus and extense onset were the clinical aspects that attracted the most attention. The second case presents a condition of white superficial onychomycosis by *T. rubrum*, opportunistic infection typical of HIV positive patients.

The cases of dermatophytosis associated with CS previously reported were caused by fungi of the Trichophyton sp types, being the *T. rubrum* the most frequent one. The origin of superficial mycosis, in these cases, seems to be due to dissemination of indolent infections, localized or by contamination after home contact⁹⁻¹¹

The authors consider that the dermatophytosis associated to CS should be defined as an opportunistic infection. Atypical clinical condition, little response to conventional antifungal therapy and resolution of dermatophytosis after the normalization of cortisol levels justify this statement.^{9,11,12} New studies on the prevalence and clinical characteristics of dermatophytoses in patients with CS should be carried out to consolidate this concept. □

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