Pigmented corneal nerves in leprosy patients treated with clofazimine+

Nervos corneanos pigmentados em hansenianos tratados com clofazimine

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SUMMARY

Clofazimine is a valuable drug for treatment of bacillary infection and for reactional states in leprosy. Side effects include redbrown skin pigmentation, darkening of the skin lesions; red coloration of urine, stools, sputum and sweat; and dryness of the skin and gastro-intestinal symptoms. Conjunctival pigmentation is the most common ocular side effect. Corneal and retinal changes have also been reported. We describe, for the first time, pigmentation of corneal nerves occuring in two patients, with the diagnosis of lepromatous leprosy, treated with clofazimine.

Key-words: Leprosy; Corneal nerves; Pigmentation; Clofazimine.

INTRODUCTION

Clofazimine is phenazine derivative that has been used in the treatment of leprosy for more than 20 years. It is valuable for the treatment of the bacillary infection, and for the immunological reaction in lepromatous leprosy, such as erythema nodosum leprosum (ENL) [1]. The side effects include red-brown skin pigmentation, darkening of the skin lesions; red coloration of urine, stools, sputum and sweat; dryness of the skin, particularly of forearms and lower legs, and gastro-intestinal symptoms especially abdominal pain [2,3,7]. Conjunctival pigmentation is the most common ocular side effect [2, 3, 4, 5], but brownish colored subepithelial corneal lines [1, 4, 6], crystals in the conjunctiva and cornea [13], macular pigmentary changes [6, 14], dimness of vision and dryness have been reported [3].

Herein we describe 2 lepromatous leprosy patients, treated with clofazimine, that developed pigmentation of the corneal nerves.

CASE REPORT

Case 1:

A 28 years old Filipino man with a diagnosis of lepromatous leprosy, gave a history of progressive nodular skin lesions over his arms and ear lobes for 1 and a half years. He had been treated with triple therapy (Dapsone-Rifampin and Clofazimine (100mg/day) for 6 months. His skin had a bronzed appearance with numerous, small, hyperpigmented patches over the brows and cheeks; the lesions were flat and the skin was diffusely thickened. He was found to have bilateral enlargement of the ulnar nerves and weak orbicularis oculi muscles. His ocular examination at that time revealed diffuse episclerites in both eyes, superficial keratitis, interstitial avascular keratitis and beaded nerves. In September 1989, several corneal nerves had brown pigment, specially in the areas of beading.

Case 2:

A 38 years old, Cambodian male, had a 22 years history of lepromatous

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leprosy. The evolution of his clinical picture was marked by the appearance of several cutaneous lesions, partial or total absorption of the fingers and collapse of this nasal bridge. In 1985, after being treated with Dapsone and Rifampin for 5 years, he was also started on Clofazimine 100 mg a day. At the time of our examination he was found to have blue hyperpigmentation of the skin of his face, total body surface anesthesia, enlargement of both ulnar nerves, and moderate bilateral enlargement of the radial cutaneous nerves. The ocular examination showed bilateral trichiasis of the upper lids, loss of the lateral aspects of the eyebrows, superficial keratitis and beaded nerves. Several corneal nerves contained diffuse brown pigment mostly concentrated in the beaded areas, extending to the center of the cornea.

DISCUSSION

Mycobacterium leprae has an affinity for small unmyelinated nerve fibers, it flourisches best in the cooler areas of the body, and its growth is encouraged by the presence of dihydroxyphenylalanine (DOPA) in the surrounding tissues [8]. In this respect, the anterior segment of the eye serves as a fertile soil where the organisms easily multiply. Corneal involvement in leprosy consists of transitory corneal nerve opacification, avascular keratitis, pannus, interstitial keratitis and corneal lepromata [8]. Opacification of the corneal nerves is due to edema secondary to the multiplication of bacilli in or adjacent to the nerves, and cellular infiltration [9]. Aggregation of inflammatory cells gives the appearance of beading [9].

Clofazimine (Lamprene-Geigy, G 30320) is a phenothiazine derivative that has been used in the treatment of leprosy since 1962. It has a bacteriostatic action equal to that of dapsone and produces a comparable fall in the morphological index. The drug also has an anti-inflammatory effect which is of value in reactional states, but possibly only in high doses which causes side-effects that most patients will not accept [7,10]. It is a red crystalline substance, soluble in lipids, and is suspended in an oil/wax base. The drug is phagocytosed into cells containing the bacilli [7,10]. The ocular side effects of the drug include conjunctival pigmentation, pigmentary changes of the cornea described as brownish, sub-epithelial lines, resembling in some cases the Hudson-Staehli line [4,5,6], polychromatic corneal and conjunctival crystals [13], and pigmentary changes in the macula [6,14]. Walinder et al [4], reported on 2 patients treated for psoriasis, who developed subepithelial brown lines which in one case had a branching pattern, but the deeper corneal layers were normal. Withdrawal of the drug resulted in regression of the corneal changes [6].

Font and co-workers found polychromatic crystals in the anterior stroma of the cornea and conjunctiva of a patient receiving an estimated cumulative dosage of 219g over a three year period. The crystalline changes resolved in several weeks after discontinuation of the drug but rapidly reaccumulated when the drug was reinstituted.

In our two cases the patients received daily clofazimine (100mg) for at least 1 year when the corneal changes were observed. They had evident skin pigmentary changes. The corneal pigment was located in mid stroma and its association with the corneal nerves was evident, especially in areas of beading. They did not resemble the crystals described by Font and no conjunctival pigmentation was present. The fact that both patients are from the Far East might raise the possibility of a racial variation explaining the pigmentary changes found in the corneal nerves, but in this case the pigments would not be found as far from the limbus as in the cases reported and also they would not have a preference for areas of corneal beading.

Our two patients have a diagnosis of lepromatous leprosy and we believe that the pigment seen in the cornea may represent macrophages which have phagocytosed Clofazimine. This concept correlates with the findings by Sakurai and Skinsnes who showed brown pigmentation due to a ceroid-like substance in macrophages in a series of three cases of lepromatous leprosy treated with clofazimine [11,12]. Our findings suggest that corneal nerve involvement in leprosy may be due, in part, to the presence of active bacilli in phagocytic cells in or around the nerves.

RESUMO

Clofazimine (Lamprene®) é uma droga utilizada no tratamento da infecção bacilar e nos estados reacionais da hanseníase. Seus efeitos colaterais incluem pigmentação marrom-avermelhada da pele; escurecimento das lesões cutâneas; coloração vermelha da urina, fezes, escarro e suor; pele seca e sintomas gastro-intestinais. Pigmentação da conjuntiva é o efeito colateral ocular mais comum. Alterações da córnea e retina também já foram descritas. Relatamos, pela primeira vez, pigmentação de nervos corneanos em dois pacientes com o diagnóstico de lepra lepromatosa, que foram tratados com Clofazimine.

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