Oral medicine case book 63:
HIV-associated oral melanin hyperpigmentation

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INTRODUCTION

Oral melanin hyperpigmentation (OMH) is not uncommon in HIV+ persons.[1] In Venezuela (38%)[2] and in India (30%)[3] HIV-associated OMH (HIV-OMH) is quite common, but by contrast is substantially less common in Italy (6.4%)[4] and in sub-Saharan Africa (Tanzania, 4.7%, Kenya, 6%).[5,6] In South Africa, the national prevalence of HIV-OMH is unknown, but Arendorf *et al*., 1998, reported a prevalence of less than 1% in the population of greater Cape Town, although the authors could not differentiate with confidence between coloured and black South Africans, and they had not been able to exclude other causes for the melanin hyperpigmentation.[7]

HIV-OMH (Figure 1) may develop secondarily to HIV-induced upregulation of pro-inflammatory cytokines, to drugs used in treating HIV disease or concomitant associated diseases (zidovudine, clofazimine and ketoconazole), or to adrenocortical insufficiency, which frequently occurs in HIV+ persons with low CD4+ T cell counts. HIV-OMH may also be idiopathic. The increased melanin in HIV-OMH is located either in the epithelial basal cell layer, in melanophages in the lamina propria or at both sites.[1,8-10]

Both brown-black eumelanin and yellow-red pheomelanin are synthesized in melanosomes which are membrane-bound organelles within melanocytes. These melanosomes contain all the proteins and enzymes necessary for melanogenesis. Melanogenesis is a complex process controlled locally by multiple factors including alpha melanocyte stimulating hormone (αMSH) produced by keratinocytes and melanocytes, melanocytic melanocortin-1 receptors (MC1R), adrenergic and cholinergic agents, and cytokines in the microenvironment. The type and the amount of melanin produced is genetically determined.[11]

Oral mucosal and epidermal melanocytes are histologically and ultrastructurally identical, but it is recognised that oral melanocytes under physiological conditions are inherently less active metabolically.[13] Nevertheless, when stimulated by hormones, pro-inflammatory cytokines, tobacco smoke or infectious agents such as HIV, oral mucosal melanocytes may become active, producing melanin hyperpigmentation.[12,13]

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ACRONYMS

αMSH:	alpha melanocyte stimulating hormone
HAART:	highly active antiretroviral therapy
MC1R:	melanocortin 1 receptor
OMH:	Oral melanin hyperpigmentation
HIV-OMH:	HIV associated oral melanin hyperpigmentation

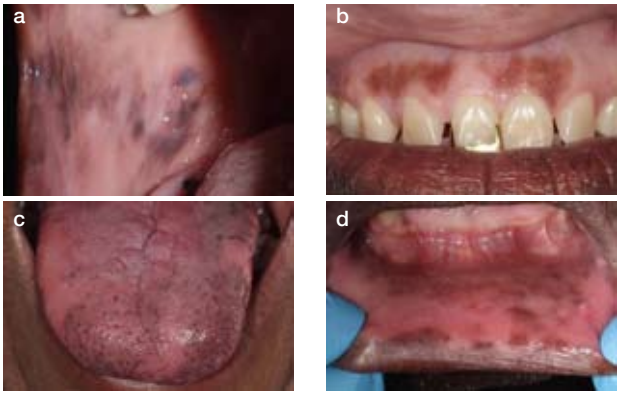

Figure 1a: Irregular, non-homogenous pigmented maculae on the buccal mucosa of a 68-year-old HIV-seropositive female on highly active antiretroviral therapy (HAART) with a CD4+ T cell count of 107 cells/mm^3. She had been diagnosed with HIV disease 7 years previously and HAART was started two years after the diagnosis. The hyperpigmentation appeared a year later.

Figure 1b: A light brown macule on the maxillary buccal gingiva of a 39-year-old HIV-seropositive female on HAART and with a CD4+ T cell count of 238 cells/mm^3. She had been diagnosed with HIV infection nine years previously and had started HAART a year later. The hyperpigmentation developed the following year.

Figure 1c: Multiple melanin pigmented fungiform papillae within macules of melanin hyperpigmentation, on the dorsum of the anterior tongue of a 37-year-old HIV-seropositive male on HAART, and with a CD4+T cell count of 63 cells/mm^3. He had been diagnosed with HIV infection and a HAART regime had been instituted nine years previously. The hyperpigmentation appeared a month thereafter.

Figure 1d: Multiple macules on the lower labial mucosa of a 43-year-old HIV-seropositive male on HAART with a CD4+ T cell count of 88 cells/mm^3. He had been diagnosed with HIV infection eight years previously and HAART had been started immediately. The hyperpigmentation appeared in the subsequent year.

None of these patients had any other oral soft tissue abnormalities or any apparent systemic disease apart from HIV infection.

DISCUSSION

Melanocytes originate from precursor cells which during development migrate from the neural crest, and ultimately differentiate into mature melanocytes that reside in the basal and suprabasal layers of the epidermis, and of the epithelium of mucous membranes.[14] Apart from their primary role in melanogenesis, melanocytes function as immune cells producing cytokines which modulate local immuno-inflammatory and antibacterial responses, and as neuroendocrine cells producing acetylcholine, catecholamines, opioids and

melanocortins, all of which contribute to tissue homeostasis.[11] Melanin plays an essential role in protection against ultraviolet radiation, and also provides protection against other environmental stressors such as reactive oxygen species, and is a main determinant of the colour of skin, hair and eyes.[12,15]

Melanocytes and their neighbouring keratinocytes form epithelial melanin units, each unit consisting of one melanocyte and a group of up to 36 keratinocytes.[16] The melanin-containing melanosomes produced by the melanocytes are transferred via the dendritic processes of the melanocytes to the keratinocytes within the unit.[16] Skin and oral mucosa owe their colour to the number and size of melanosomes, whether these contain eumelanin or pheomelanin, to the state of maturation of the network of melanocytic dendritic processes, and to the efficacy with which these dendritic processes distribute the melanosomes to neighbouring keratinocytes.[17,18]

Melanin biosynthesis is genetically determined and there are substantial differences in the degree of melanin pigmentation among racial/ethnic groups and between subjects of the same group. Both oral mucosal physiological/racial melanin hyperpigmentation[19] and HIV-OMH are more frequently seen in darker than in lighter skinned subjects.[20]

If it occurs, HIV-OMH usually appears within two years of the diagnosis of HIV infection, or after a month or more of antiretroviral medication with zidovudine,[21] and it is observed more frequently in HIV+ persons with a CD4+ T cell count of less than 200 cells/cubic mm.[22] It appears that HIV-OMH is brought about by upregulation of activation of normal oral melanocytes by HIV infection or by zidovudine with consequent increased production of melanin.[4] As it is ethically unjustifiable to biopsy HIV-OMH, it is not clear what role is played by an increase in the number of melanocytes, by an increase in the number of melanosomes, or by a shift in the type of melanin produced, in the pathogenesis of HIV-OMH.

It has been proposed that IL-1, IL-6 and TNF-α, which are upregulated during HIV infection, stimulate keratinocytes and melanocytes to produce αMSH, and stimulate melanocytes to express MC1R, thus resulting in increased melanogenesis by melanocytes, triggering the formation of HIV-OMH.[9] The fact that HIV-induced cytokine upregulation in HIV+ persons is inversely proportional to their CD4+ T cell counts may explain the observation that HIV-OMH occurs most frequently in HIV+ persons with low CD4+T cell counts.[22] HIV-OMH manifests clinically as single or as multiple brownish or brown-black macules or as ill-defined diffuse areas of melanin hyperpigmentation (Figure 1).

This hyperpigmentation may affect any part of the oral mucosa, but most frequently the buccal mucosa.[23] Although HIV-OMH does not have any clinical or pathological significance, it needs to be differentiated from similar pathologically hyperpigmented oral mucosal lesions or conditions including Addison's disease, Albright's syndrome, neurofibromatosis, smoker's melanosis, atypical melanocytic proliferations and melanomas.[23,24] These can usually be distinguished on the basis of a good medical history: but if hyperpigmentation follows a diagnosis of HIV infection or follows the initiation of HIV-related medication, then a diagnosis of HIV-OMH should be considered.[25]

Further research is needed in order to discover what mechanisms and environmental factors possibly play a role in the pathogenesis of HIV-OMH and whether HIV-OMH has any clinical significance in HIV disease.[25]

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