Melanotic Macule

3.1 Introduction

Melanotic macules are well-demarcated, flat, pigmented lesions caused by a deposit of abundant melanin in the basal layer of the epidermis, accompanied by a slight or undetectable increase in the number of melanocytes. These deeply pigmented lesions contrast with those of actinic melanocytic hyperplasia in which no change in pigmentation or slight mottling is present. The lesions of lentigo simplex are smaller and histopathologically show a more significant increase in the number of melanocytes.

Melanotic macules are typically present on the lips, mouth, genitalia, and nail matrix or bed; on volar skin; and on the mammary areolae. They may be solitary or multiple and they are occasionally associated with a group of complex syndromes, either congenital or acquired. Some PU-VA-induced lesions have similar findings too.

Histologically, melanotic macules must be differentiated from an early stage of melanoma in situ. Genital melanotic macules can be clinically alarming and can resemble melanoma in situ to a greater extent than the other forms.

3.2 Orolabial Macules

These lesions were once called labial lentigo, a term that creates confusion with simple lentigo and that should be abandoned.

3.2.1 Clinical Features

Labial melanotic macules are flat and brownish black or black in color, with irregular but sharply demarcated margins.

They are typically situated on the center of the inferior lip (generally on the mucocutaneous edge). The vermilion border and upper gingiva are the most common sites. The lesions can be multiple, especially when they are associated with particular syndromes. Isolated congenital forms have been reported.

Lesions are also present on other parts of the oral mucosa and on the tongue. The site of the lesion is important in the differential diagnosis with melanoma which as favorite sites has palatal and upper gingival mucosa.

The lesions usually appear in women at the age of 30–40 years. Orolabial melanotic macules are common, being present in 3% of dark-skinned general population. They last for about 6–7 years and remain stable after their initial growth. The lesion does not change in color with exposure to sun.

In people with a dark complexion, they may be bilateral, symmetrical, and localized on the labial side of the gingiva. In these cases, the lesions may also be very widespread (Gondak et al. 2012).

Dermoscopy of orolabial macules usually shows a diffuse homogeneous “patternless pattern.”

3.2.2 Histological Features

Histologically (Fig. 3.1), lesions are characterized by the following features:

- The presence, along the basal layer, of rare melanocytes with thin elongated dendrites. Although the melanocytes can be double or triple the normal number, this increase is not readily appreciable in routinely stained sections (the increase is much more evident using immunostains). An obvious increase in the number of melanocytes is always against a simple melanocytic macule (and it favors early evolving oral melanoma). In some melanotic macules there is no increase in the number of melanocytes at all: these lesions are labeled as “melanocytic activation” or nonproliferative macules.
- Pigment is deposited in the keratinocytes of the basal layer. Usually only the basal layer is pigmented. Marked elongation of the rete ridges is lacking in oral lesions, but the involved epithelium is usually slightly hyperplastic.
- From a cytological point of view, the melanocytes are inconspicuous or epithelioid, often with a clear perinuclear halo. Cells may also be vertically oriented with an elongated nucleus and scant cytoplasm. Melanocytes are equidistant from each other and are separated by a constant number of keratinocytes. No melanocytes are scattered above the basal layer (a few suprabasilar melanocytes can however be seen with immunoperoxidase stains for melanocytes).
• There are fine dendrites that emanate from junctional melanocytes. These dendrites seem to trap the keratinocytes of the basal layer in a delicate meshwork. The dendrites reach half the thickness of the epithelium at most, and even this is exceptional; some immunoperoxidase stains, such as Melan-A or MART-1, stain these dendrites, and their presence can exaggerate the number of melanocytes.
• Melanocytes are clearly separated from each other by a number of normal keratinocytes; a lentiginous or nested pattern must be absent.
• Melanophages, vascular ectasia, and a few large fibroblasts are present in the dermis. Sometimes, a patchy lymphocytic infiltrate is present with some dermal melanophages, suggesting that oral melanotic macules can become inflamed. However, a dense lymphoplasmacytic infiltrate should make one suspect melanoma in situ.

The so-called smoker’s melanosis consists of poorly circumscribed macules affecting smokers, usually localized to the anterior mandibular gingiva. Histologically, they consist of hyperpigmentation of the epithelial basal layer without a detectable increase in the number of melanocytes (“melanocytic activation”).

3.2.3 Differential Diagnosis
The lesions sited on the lips are usually obviously benign, and a form of early evolving melanoma in situ is easily ruled out. Moreover, melanoma in situ on the lips is rare. Invasive melanomas on the lip are often desmoplastic or neurotropic and may rarely arise without an in situ component. Within the oral cavity, the differential diagnosis of a labial melanotic macule and melanoma in situ can be difficult, especially on the palate where both conditions occur. In the buccal mucosa, melanoma is much rarer. In this peculiar differential diagnosis, age is crucial: melanoma is very rare on the palate of youngsters.

From a histological point of view, the following considerations should be taken into due account:
• As a rule, an obvious increased number of melanocytes in a close lentiginous array is an indication of melanoma. Melanocytes are always separated by a constant numbers of keratinocytes in melanocytic macules. The aggregation of cells in lines, layers, or nests is always absent on melanocytic macules, even in the large ones.
• In the very early stage, melanoma can be characterized by a very slight increase in number of cells, but they are not regularly distributed (a detail that can be difficult to appreciate).
• On the edges of a melanoma of the oral cavity, the peripheral areas of the lesion can appear to be histologically similar to melanotic macules. One can distinguish a kind of gradient from the periphery of the lesion to the center: on the external edge of the lesion, the picture is indistinguishable from that of a melanotic macule. Proceeding toward the center of the lesion, the cells aggregate together with nuclei being more atypical. Even more centrally in the lesion, the nuclei become distinctly atypical, and the cells crowd around the junction in continuity (melanoma in situ). An invasive melanoma with the overt cytological aspects of malignancy is present in the center of the lesion.

In conclusion, even though, for epidemiologic and topographic reasons, we believe it is unlikely for a melanoma to arise within a mucosal or cutaneous melanocytic macule, we must admit that the initial evolving phases of melanoma of the oral cavity occasionally present with a histological picture indistinguishable from that of a melanotic macule.

3.3 Vulvar Melanotic Macules
Vulvar melanotic macule is frequent in the general population and is often biopsied to rule out melanoma in situ.

3.3.1 Clinical Features
The lesions are brown- or black-colored macules, with irregular margins that appear at the age of approximately 20–45 years, on the labia minora (but also on labia majora, introitus, and perineum); vaginal and cervical melanosis have also been described (Mannone et al. 2004). Data suggest that melanotic macules of the vulva are present in about 10% of the general female population. They usually are multiple (>50% of the cases) and may be extensive (as much as 5 cm in diameter). They remain stable after their initial growth.

Vulvar melanotic macules can be clinically indistinguishable from vulvar melanoma in situ. Even multicentricity cannot be taken as a sign of benignancy: in fact, multifocal vulvar melanomas very similar to vulvar melanotic macules are not exceptional.

Dermoscopic findings reported in the literature have described different appearances, but it seems that the structureless (homogeneous) and the ringlike patterns are both strong indications of vulvar melanosis (Ferrari et al. 2008). The ringlike pattern corresponds to the pigmentation of rete ridges combined with the absence of melanin above suprapapillary plates.

3.3.2 Histological Features
Histologically (Fig. 3.2), the picture is similar to that of an oral melanotic macule. Pigmentation is restricted to the keratinocytes of the basal layer, with roughly normal numbers of melanocytes at the junction. There are elongated and clubbed-shaped rete ridges.

The melanocytes are inconspicuous or rarely epithelioid with a clear perinuclear halo. Very rare enlarged nuclei can be seen. Dendrites are thin and short. Rare melanocytes above the junction are possible, but a disordered array is not a feature of a vulvar melanocytic macule. A sparse