# 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 melanocytes 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 malignity 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 melanophagic component can be present in the dermis (Lenane et al. 2000).

In this case also, the main differential diagnosis is with an early form of melanoma in situ. In favor of a melanoma are the presence of crowded melanocytes along the junction, nuclear hyperchromasia and atypia, pagetoid spread, presence of elongated and thick dendrites, a dense inflammatory infiltrate in the submucosa, and a variably thick and thin epithelium. On occasion, very early melanoma in situ on vulva is indistinguishable from a melanotic macule. Clinical setting may be helpful: melanoma is much more frequent in elderly patients.

The melanotic macule of the vulva coincidental with lichen sclerosus and atrophicus deserves a special mention: in that case the inflammatory process can obscure the pigmentation and a Fontana-Masson stain for melanin could be necessary for highlighting the pigment.

# **3.4 Penile Melanotic Macules**

This form of macule is situated on the glans or on the shaft of the penis; rarely, macules are present in perineal area as well. This lesion seems much rarer than its vulvar counterpart.

#### **3.4.1 Clinical Features**

The lesions on the glans have irregular margins and may be quite large. The lesions may be multiple. Generally, penile macules have a history of being present for many years, they arise in adults or in the elderly (average is 40): in a few cases the lesion has been described in people under 20 years of age (Barnhill et al. 1990).

Genital macules can be part of hereditary conditions such as the Laugier-Hunziker, Peutz-Jegher, Carney, and the Riley-Bannayan-Ruvalcaba syndromes. Recently, the association of eruptive melanotic macules on male genital skin and malignant visceral neoplasms has been reported by different authors (Busam et al. 2003).

As in the case of vulvar melanotic macules, these lesions may be clinically indistinguishable from a melanoma (especially the lesions over the glans). A sign of benignity may be that lesion becomes stable after a phase of initial growth (although exceptions occur).

#### 3.4.2 Histological Features

Histologically (Fig. 3.3), lesions have the same appearance as their vulvar counterpart. However, it seems to us that in male genital skin the presence of alarming large epithelioid melanocytes is more frequent than in vulvar melanotic macules (Fig. 3.4). In these cases the small-size penile melanotic macules, the young age of the patient, the lack of pagetoid spread, and the absence of contiguity of cells help to rule out melanoma. Moreover, the atypical cells are randomly distributed along the junction, and the background is that of a melanotic macule. In one patient with multiple lesions of the penile shaft that we studied, only one had atypical epithelioid melanocytes, whereas the others were classic banal-looking melanotic macules.

# **3.5 Subungual Melanotic Macules**

Nail melanosis (nail bed melanotic macule) presents itself as a narrow, pigmented, and longitudinal stripe that usually originates from the matrix and involves the nail bed (Husain et al. 2006; Amin et al. 2008).

#### **3.5.1 Clinical Features**

These thin, elongated, elegant stripes have been named melanonychia striata in longitudinem. In contrast with a melanoma (which may also present itself as melanonychia striata), the longitudinal stripe due to a melanotic macule is clearly delineated with very sharp margins and is never thicker than 3 mm. The shape is rectangular, while a triangular shape suggests a melanoma. The reason for this is that the width of the distal part reflects how that of the proximal portion was months previously. Usually, Hutchinson sign is absent in melanonychia striata, namely, the pigmentation does not extend beyond the periungual skinfold (but exceptions exist, called pseudo-Hutchinson sign). Nail melanotic macules are often multiple, especially in dark-skinned people (melanoma of the nail bed is, as a rule, a single lesion). The site is important too: melanotic macules are randomly distributed, whereas 92% of subungual melanomas occur on the thumb or on the great toe (however, melanocytic macule can be situated on the big toe and thumb).

The lesion is very frequent among blacks (77% of the subjects above 20 years of age) and is uncommon but not exotically rare in Caucasians (1% of the population).

As we have said above, a melanotic macule is the most frequent cause of melanonychia striata. Nail matrix nevi and melanomas can also cause melanonychia striata (see Chaps. 19 and 45). In these cases, melanocytes are obviously increased in number and tend to aggregate in groups of single cells or in nests along the basal layer.

One can also see postinflammatory hyperplasia following a dermatosis involving the nails. Psoriasis, lichen planus, drug reaction, trauma, nail biting, infection, and other disparate conditions damaging the nail bed and matrix epithelium can leave nail pigmentation (also in the form of an elongated longitudinal stripe). In all these cases, only hyperpigmentation of the basal layer with no increase of the number of melanocytes is present (so-called melanocytic activation). Pigment is present in the dermis too.

#### **3.5.2 Histological Features**

Melanonychia striata due to melanotic macules histologically consists (Fig. 3.5) of a modest increase in the number of melanocytes (which are virtually undetectable in a routine hematoxylin and eosin stain in the normal ungual matrix). The melanocytes have thin cytoplasmic dendrites highlighted by melanin. These dendrites seem to trap keratinocytes, reaching half the thickness of the epithelium. Melanocytes are well separated from each other by basal layer keratinocytes, and they do not show any tendency to a lentiginous organization. In melanocytic activation, immunoperoxidase stains such as the cytoplasmic stains, Melan-A and MART-1, and the nuclear stains, micro-opthalmia transcription factor-1 and SOX-10, may be needed to reveal the number of melanocytes, which can be otherwise inconspicuous. The melanocytes in melanocytic activation can be situated well above the junction.

#### 3.5.3 Differential Diagnosis

In the distinction between a melanotic macule of the nail bed and an early evolving subungual melanoma in situ, it seems that dermoscopy could play an important role. Benign macules are gray, monochrome, with lightly colored parallel longitudinal lines. Brown to black lesions with unevenly pigmented, irregularly spaced, or confluent lines of different color along with nail plate dystrophy are a strong suggestion of melanoma. Dermoscopy also seems able to detect Hutchinson sign before its clinical appearance.

Dermoscopy (Thomas and Dalle 2007) of the nail plate edge is also used to better define the source of the pigmentation: pigmentation of the deep part of the nail plate is an indication of a distal matrix lesion, while pigmentation of the superficial portion of the nail plate indicates a proximal location of the pigment-synthesizing melanocytes within the matrix. The most frequent site of melanotic macules is the distal matrix.

The age of the patient has a crucial role in the diagnosis: melanoma in youngsters is exceedingly rare; reports on cases in children are not well documented.

Histologically, in melanotic macules the melanocytes are small and scattered among keratinocytes; dendrites are elongated but thin. Hyperchromatic elongated crescentshaped nuclei indicate melanoma, especially if aligned in a lentiginous row along the basal layer. Thick, heavily pigmented dendrites reaching the spinous layer suggest melanoma. Because dendrites eventually taper, cross sections will show a mixture of thin and thick dendrites in melanoma (which we term "anisodendrocytosis").

Some words of warning are necessary about the technical difficulties in performing and processing biopsies from the nail apparatus. The biopsy must include the nail matrix. This is where the cells of almost any prospective melanocytic lesion are situated. All too often, only the nail bed is sampled. In such cases, only the pigmented plate is present, without any discernible melanocytes. Moreover, the exact site within the matrix that is most likely to be involved (proximal or distal) must be correctly chosen.

Clinicians may be reluctant to biopsy the nail matrix at all because of resultant cosmetic deformities (e.g., pterygium). Hence, inadequate biopsies are common.

Correct orientation of the specimen in the paraffin block is crucial as well: marking the epithelial surface with ink is a suggested device for properly adjusting the specimen's position (George et al. 2008). Orienting the specimen with a suture is helpful in maintaining orientation, so that the sections can be taken longitudinally. This can be very helpful, as the cells of a melanoma in situ will often extend proximally along the eponychium and proximal nail fold or distally out into the nail bed, while melanotic macules do not do this. A histological section without any lesion sometimes is not the result of an improper biopsy but the consequence of a wrong orientation of the specimen. Specimens taken after nail avulsion can lack epithelium altogether, as it is sometimes ripped off when the nail plate is reflected.

#### **3.6 Acral Melanotic Macules**

These are brown macules with irregular margins situated on the volar side of the hands and feet in dark-skinned patients, especially of African ancestry. The lesions can be numerous and large. They are very frequent, especially in subjects over 30 years of age. Although less frequently, these lesions are possible among Caucasians with a dark complexion and in Asians. Pigment can be abundant and present in the spinous layer keratinocytes and corneocytes. Their differential diagnosis from melanoma on acral volar skin is treated in Chap. 45.

# 3.7 Reticulated Melanotic Macule (Ink Spot Solar Lentigo)

This lesion consists in small dark macules on the trunk (usually the upper back) of adults in sun-exposed areas (Bolognia 1992). The lesions are characteristically reticulated with jagged but sharp margins. They are relatively common. The histology (Fig. 3.6) of ink spot lentigo is that of a melanotic macule, namely, a barely detectable increase of finely dendritic melanocytes and a marked deposition of melanin in the basal layer. The epidermis is mildly hyperplastic.

The distinctive reticulated appearance is due to the pigment mostly involving the edges and bases of rete ridges, sparing the suprapapillary plate: as the pigmented keratinocytes situated along the sides of rete ridges are stacked on another when viewed from above, the intensity of pigmentation along the ridges is accentuated, especially in comparison to the less pigmented suprapapillary epidermis, explaining the reticulated appearance. Ink spot solar lentigines differ from conventional solar lentigines in these respects:

- More narrowly based
- More intense basilar hyperpigmentation
- Pigmentation more accentuated at the bases of rete ridges compared to the suprapapillary epidermis
- Melanocytic dendrites more apt to be visible (but are fine)

While the narrow lesion and intense pigmentation is similar to that of a simple lentigo, the increase in the number of melanocytes is far less.

## 3.8 Melanotic Macule of Conjunctiva

Melanosis of the conjunctiva is discussed in Chap. 23.

## **3.9 Areolar Melanotic Macules**

Melanotic macules are rarely reported on the areola of the breast (melanosis of the areola) with pigmentation of the basal layer and the presence of slight (or no) increase of the number of melanocytes. An increased in the size and pigmentation of the lesion can occur during pregnancy and become a source of clinical concern (Sceppa et al. 2008). The histology is quite banal and similar to that of melanotic macules on other parts of the body (Mikhail et al. 2008).

## **3.10 PUVA Induced Melanotic Macules**

As discussed in the previous chapter, prolonged PUVA therapy can induce a cohort of melanocytic lesions. Among them are melanotic macule-like lesions characterized by a subtly increased number of dendritic melanocytes at the junction (Fig. 3.7). Cells are enlarged but not atypical, there is no continuous or contiguous lentiginous array, and pagetoid spread is not present.

## **3.11 Simulators of Melanotic Macule**

Basal layer pigmentation with a slight increase in the number of melanocytes rarely occurs in fibrous papule and in condylomas but is more common in the epidermis above a dermatofibroma. The associated process indicates the correct diagnosis (Figs. 3.8 and 3.9). Dermatofibromas may induce a true melanocytic hyperplasia, and rarely, changes equivalent to those of simple lentigo or lentiginous junctional or even compound nevi are present above dermatofibromas.

# 3.12 Further Reading

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## 3.13 Summary

- Melanotic macules are small, flat, pigmented lesions localized on the oral and genital mucosae, on the nail matrix and bed, and on volar skin.
- The histological characteristics are:
  - Slight or no increase in the number of melanocytes
  - Melanin deposits in the basal layer
- The most important differential diagnosis is with early evolving melanoma in situ of volar skin or of orogenital mucosae. Occasionally this distinction can be exceedingly difficult.

# Fig. 3.1 Melanotic macule on the lip

The rete ridges of this melanotic macule are homogeneously pigmented (a), while pigment is diminished in the basal layer of the suprapapillary plates.

Melanocytes are barely distinguishable (b) and at high magnification can be discerned as small, round cells. Melanophages and a few lymphocytes are scattered in the upper dermis (c).

In cases like this, the diagnosis is straightforward and there is no differential diagnosis



# Fig. 3.2 Vulvar melanotic macule

Vulvar melanotic macules usually have similar features to their labial counterparts (a). Melanocytes are almost undetectable, whereas keratinocytes of the basal layer are deeply pigmented (b, c).

In cases like this the distinction from a vulvar melanoma is situ is easy, even if the macule is broad



# Fig. 3.3 Penile melanotic macule

Penile melanotic macule is much rarer than its oral and vulvar counterpart, but it is similar from a histological point of view: a slight or almost undetectable increase in the number of melanocytes along the basal layer and deposition of pigment in the same site (**a**, **b**). These cells are small and nuclei inconspicuous. A few melanophages are scattered among the collagen fibers of the superficial dermis.

In this case, melanocytes with a prominent nucleus and abundant epithelioid cytoplasm are visible at the junction among the basal layer keratinocytes and contrast with a population of much smaller melanocytes (c).

These epithelioid cells are sparse and they do not aggregate in a lentiginous pattern. It may be that melanotic macules are neoplasms in which there is minimal proliferation and that the larger cells are lesional and the smaller ones are those native to the site. The case illustrated in the next page (and composed of the larger type of cells) is much more complex.

In cases in which the differential diagnosis is challenging, the clinical setting can serve as a sort of mental status examination for the histopathologist. If a flat, pigmented lesion grows relentlessly, it should be looked at very carefully even if a partial biopsy seems to indicate benignancy







## Fig. 3.4 Penile melanotic macule with large cells

A 22-year-old man presented with a blackish macule on his penis.

Histologically part of the pigmented area has all the features of a melanotic macule: homogeneous basal layer pigmentation and rare benign-looking melanocytes (with nuclei of the same size or smaller than that of the keratinocytes).

In another part, a conspicuous number of large epithelioid melanocytes are present (a, b). Most of them are at the junction, but a few seem above it perhaps due to tangential sectioning (c). Cytologically, the cells are monomorphous in size and shape, nuclear content, and cytoplasm (which has ground glass feature).

An abundance of caution is mandatory in cases like this, but the lesion is most probably benign. This may be an analogue of a "spitzoid lentigo" seen on extragenital skin



Fig. 3.5 Nail bed and matrix melanotic macule (melanonychia striata in longitudinem)

This lesion was taken from the nail matrix, hence the basophilic hue of the epithelium (a).

The thin, elongated, elegant dendrites are more conspicuous than the nuclei of the melanocytes themselves (**b**).

In melanoma of the nail apparatus, dendrites are usually thick, and the nuclei are large and hyperchromatic. The density of melanocytes is generally greater than in this case.

Moreover, an inflammatory infiltrate is absent in the dermis (a frequent finding in the early melanoma in situ of the nail matrix and bed)



Melanonychia striata in longitudinem clinical features

(Courtesy of G. Fabrizi Parma, Italy)





# Fig. 3.6 "Ink spot lentigo" (reticulated melanotic macule of the trunk)

This zone of epidermis shows evenly elongated rete ridges that are heavily pigmented (**a**). Melanocytes are barely increased in number.

Note that the pigment distribution along the basal layer is not homogeneous: the suprapapillary plates are much less pigmented than the bases of the rete ridges; moreover, a few "skip areas" devoid of pigment are present (**b**).

In the dermis are a few elastotic fibers and a few melanophages (c). Even though "ink spot solar lentigo" may be actinically induced, it is generally present in sun-exposed but not necessarily severely sun-damaged skin.

The peculiar distribution of the pigment explains the reticulated pattern of the lesion from a clinical and dermoscopic point of view



# Chapter 3

# Melanotic Macule

## Fig. 3.7 "Melanotic macule" in PUVA-treated psoriasis

Patients treated for psoriasis with PUVA therapy sometimes develop lesions clinically and histologically similar to melanotic macules or simple lentigines.

In the case illustrated here (a) there is no significant increase in the number of melanocytes and they are inconspicuous (b). Hyperchromatic, enlarged nuclei are absent.

Despite these findings, the melanocytes that are here have elongated dendrites (c, d), some of them thick, a frequent sign in early evolving melanoma in sundamaged skin, the genitalia, and mucous membranes. The very even elongation of rete ridges and scarcity of melanocytes themselves would, however, be exceptional in melanoma in situ







# Fig. 3.8 Genital wart with dendritic melanocytic proliferation

This is not a melanotic macule or a melanoma is situ, but just a pigmented viral wart (a). A partially hidden melanocytic component is present with very elongated dendrites making a thick tangle around keratinocytes of the basal and spinous layer. Melanocytes are present at the junction or just above it (b). The dendrites herein are uniformly thin, a reassuring finding (c).

This lesion illustrates quite convincingly that an open mind (and clinical correlation) is necessary for a proper diagnosis. Attention to the surface configuration (see the lower left panel) is necessary to appreciate that this is a condyloma







# Fig. 3.9 Epidermal basal layer pigmentation due to a subjacent dermatofibroma

Epidermal, follicular, and melanocytic hyperplasias are frequent in the lesional skin of a dermatofibroma (**a**).

In this case the features seem very much like those of a melanotic macule with uniform pigmentation of the basal layer (b, c)



