48.1 Introduction

Ocular melanomas seen in dermatopathology or general pathology practice are mostly those on the palpebral or on the bulbar conjunctiva. The conjunctivae can be also secondarily involved by cutaneous melanoma of the eyelid. Cutaneous melanoma metastatic to the conjunctivae is known as well. The incidence of conjunctival melanoma is rising in the Western world (Triay et al. 2009; Shields et al. 2011), and this is probably related to sun exposure (as it is for lentigo maligna, an entity biologically and histologically related to conjunctival melanoma).

The literature on conjunctival melanoma has been plagued with decades-lasting controversy about the nomenclature of its early stages (Damato and Coupland 2008). Many ophthalmologists staunchly refuse to use the term melanoma in situ and instead prefer the descriptive term primary acquired melanosis (PAM). This clinical term encompasses both benign and potentially malignant proliferations and is histologically subdivided in PAM without atypia and PAM with mild or severe atypia. Only the latter forms are considered at risk of developing into an invasive melanoma (Shields et al. 2007).

This refusal to accept the term melanoma in situ was codified internationally and in the classification of World Health Organization, the conjunctiva is the only portion of human integument in which melanoma is situ is not allowed to develop.

As many dermatopathologists, we reject this scheme and prefer to classify conjunctival melanocytic proliferations into benign intraepithelial lesions and melanoma in situ. Trying to translate the terms of the two different points of view we could propose:

- PAM without atypia is conjunctival melanotic macule, solar lentigo, freckles, or racial melanosis; the risk of these lesions per se evolving into invasive melanoma is essentially nil.
- PAM with mild atypia is an early evolving form of melanoma in situ involving the basal layer of the epithelium, its cells are mostly small, the invasive melanoma risk is low, and invasive melanoma develops very late, if ever.
- PAM with severe atypia is melanoma in situ with large confluent nests and pagetoid spread; cells are mostly epithelioid. This form is at high risk of developing into an invasive melanoma in a short time.

We advocate the abandonment of the term PAM altogether, and in this chapter we only refer to melanoma in situ.

48.2 Clinical Features

Among ocular melanomas, conjunctival ones are rare, being much less prevalent than uveal and choroidal melanoma. They develop in patients after 50–60 years old and are very rare even in the third decade; less than 28 cases have been reported before 15 years of age. Melanomas in children are exceedingly rare and mostly reported as arising in a preexistent nevus. There is no gender preference among conjunctival melanomas in children.

Almost all patients are fair-skinned Caucasians, but conjunctival melanoma in Africans and Asians also occurs as well (Colby and Nagel 2005). In black patients, the diagnosis of melanoma is frequently hampered by the frequent presence of racial melanosis. Individuals with xeroderma pigmentosum have a disproportionate risk of developing this form of melanoma.

Melanoma can develop anywhere in the conjunctivae, being interpalpebral and limbal sites the most frequent. Tarsal conjunctiva is a rare localization, but this site is almost diagnostic of melanoma (nevi are very rare in this area). Nonlimbal localizations (Kaeser et al. 2006) are more prone to recurrence (extension of the lesion is another most crucial risk factor for recurrence as is the multifocality of the lesion).

Several clinical patterns of presentation have been described:
- Single macular lesion. This is by far the most common feature of presentation of all melanomas of the area. It histologically corresponds to a melanoma in situ. In this
in situ flat stage a conjunctival melanoma can remain stable for years and even for decades, and cases of lesions lasting 30 years are on record.

In its beginning, a melanoma in situ of conjunctiva is clinically indistinguishable from a melanotic macule; however, melanoma has a continuous slow growth which involves large areas of the conjunctiva (and cases with the black discoloration of an entire conjunctiva have been described). The cornea can also be involved. The macular stage of melanoma in situ is as a rule a monolateral neoplasia as is invasive melanoma. Bilateral lesions are usually due to racial melanosis.

Very large lesions situated on the nasal canthus (mediotarsal conjunctiva, plical, and caruncular conjunctiva) can spread to the nasal mucosa or to the paranasal sinus. Within these macular lesions, a nodule which represents the invasive stage of the melanoma may eventually develop (see below).

- Multiple macular lesions. As in other mucous membranes, melanoma on conjunctiva can also be multiple and it appears as irregular macules scattered all over the bulb and eyelid epithelium. The topographic relationship (is this multifocal or unitary disease?) is still not clear.

- Nodules on pigmented plaque in macular lesion. Over a greatly variable time period, a nodule or infiltrated plaque can develop in preexistent macular lesion. Up to 70% of all conjunctival melanomas have this clinical phenotype. Histologically, this lesion corresponds to an invasive potentially metastatic and lethal melanoma that developed within a previous melanoma in situ.

- De novo nodular or plaque-type melanoma. In about 12–37% of cases, conjunctival melanoma arises de novo on undamaged mucosa. Clinically, the lesion is a single nodule or plaque. The sclerocorneal limbus is the most common site. The growth pattern is exophytic in the limbus (it might be because the hardness of the connective tissue underneath is a barrier to neoplastic infiltration). An endophytic growth pattern resulting in a plaque is most probable on the fornix, caruncula, and palpebral conjunctiva. Many nodular or plaque-like lesions are connected with a large vessel (“feeder” vessel) that is very evident on examination of the sclera or on the conjunctiva.

De novo melanoma is reported as an unfavorable variant of conjunctival melanoma with high rate of metastases and death (Shields et al. 2011).

- Achromic lesions. Melanoma on the conjunctiva can be entirely devoid of visible pigment (Nabeshima et al. 2008). In these cases, they are pinkish, fleshy, or white lesions, occasionally multiple, which spread over the limbus and onto the conjunctival site of both eyelids (localization over the bulbar conjunctiva is rarer). Achromic melanoma can develop on a previous macular pigmented lesion (melanoma in situ) or de novo. This form of melanoma accounts for 19% of cases (Shildkrot and Wilson 2010) and is reputed as having a poorer prognosis. Another peculiar presentation is that of a hemorrhagic lesion, quite undetectable as a melanoma, on the clinical basis alone.

- Melanoma arising in a nevus. A few melanomas have been reported as developed in preexisting conjunctival nevus. The nevus occasionally appeared early in infancy and gave rise to melanoma late in adulthood. We have encountered only one case of this form of melanoma, which is quite rare indeed, although 5% of melanomas are reported as associated with nevus (Missotten et al. 2005); the prognostic outlook is estimated as more favorable than other form of conjunctival melanoma. Clinical hints of malignant evolution are as follows: change in size and color, rapid growth, and recurrence (Zembowicz et al. 2010).

- Melanoma on the cutaneous site of the eyelid. This form of melanoma is not frequent and, as a rule, develops with a lentigo maligna pattern (although cases in which a melanoma developed in a preexisting nevus are also reported). Rare amelanotic eyelid melanomas have also been seen.

- Cutaneous melanoma metastatic to the conjunctiva has been rarely described (Kiratli et al. 1996), occasionally with a striking endolymphatic pattern and nevoid features (Shields et al. 2009). They are frequently the first sign of the metastatic disease. The prognosis is very poor.

In all cases, clinical indications of melanoma are large size and plurifocality (in Caucasians) of the lesion, multicolored appearance, fixation to the sclera, corneal involvement, and “feeder vessels”; the location on the fornix and tarsal conjunctiva is a rare but important sign.

All forms of melanoma on the conjunctiva have a notorious tendency to recur after excision. Recurrences can be multiple and herald of a subsequent extraocular metastatic spread which can continue over a prolonged course. Clinical harbingers of an aggressive course are de novo subtype, localization on the fornix, and nodular growth.

**48.3 Histological Features**

**48.3.1 Melanoma In Situ of the Conjunctiva**

This represents an in situ stage of conjunctival melanoma, and it is morphologically similar to the equivalent forms on other mucous membranes or on acral skin or lentigo maligna.

At the beginning, the lesion consists in an inconspicuous proliferation of melanocytes along the epithelial basal layer. This alteration is closely similar (clinically and histologically) to some cases of conjunctival benign melanosis (conjunctival melanotic macule), with a barely appreciable increase of the number of melanocytes. A hint of the melanomatous nature of this deceptive lesion is the presence of