Melanocytic Lesions of the Conjunctiva

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● *Context.*—Melanocytic proliferations are among the most common neoplasms of the conjunctiva. They often represent challenging lesions for pathologists unfamiliar with unique histologic features of melanocytic proliferations in this location and with nomenclature used by ophthalmologists.

Objective.—To comprehensively review clinical aspects, pathologic features, and management of melanocytic proliferations of the conjunctiva.

Data Sources.—Review of the literature and personal experience of the authors.

Conclusions.—Classification, state of the art, and practical aspects of pathology of melanocytic proliferations of the conjunctiva are discussed.

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Melanocytic proliferations are the most common tumors of the conjunctiva, accounting for up to 53% of all conjunctival neoplasms.[1,2] These lesions can be a challenging diagnosis for general pathologists, as both benign and malignant melanocytic proliferations occurring in the anatomic context of the conjunctiva produce unique histologic patterns that are often different from those in the skin. Therefore, applying directly the histologic criteria developed for cutaneous melanocytic proliferations to these lesions may result in erroneous diagnoses. Moreover, proper communication with clinicians requires an understanding of the terminology for conjunctival melanocytic proliferations used by ophthalmologists.

This review aims to provide an update on the classification of melanocytic lesions of the conjunctiva for practicing general pathologists and dermatopathologists.

CLASSIFICATION OF CONJUNCTIVAL MELANOCYTIC PROLIFERATIONS

Classification of conjunctival melanocytic proliferations, as used by ophthalmologists, is unique to this anatomic location and has been a subject of ongoing debate and critique.[3–5] The 1980 World Health Organization classification is based on the ideas introduced by Zimmerman at the Armed Forces Institue of Pathology[6,7] and includes 3 categories: melanocytic nevus, conjunctival melanosis, and invasive melanoma. Conjunctival melanocytic nevi are similar to those occurring in the skin and are benign, acquired or congenital, circumscribed melanocyt-

ic proliferations. In contrast, the concept of conjunctival melanosis and the restricted use of the term *melanoma* to invasive tumors are unique to the conjunctiva. One of the peculiar aspects of this classification scheme is absence of the formal concept of melanoma in situ. All clinically macular intraepithelial melanocytic proliferations that are not nevi are included in a broad category of conjunctival melanosis. Melanosis can be primary or secondary (such as in Addison disease), and congenital (such as complexion-associated melanosis) or acquired. The most common form of melanosis is primary and acquired. It is further subdivided into primary acquired melanosis (PAM) without atypia and PAM with atypia. The concept of PAM with atypia is controversial, as it includes a spectrum of lesions showing only mild cytologic atypia to severely atypical lesions frequently associated with invasive melanoma.[8] Even though a strong argument can be made for using the term *melanoma in situ* for PAM with severe atypia, ophthalmic oncologists generally believe that "the term melanoma in situ could unnecessarily alarm both clinician and patients, particularly since many PAM lesions have little propensity to evolve into melanoma."[9] Historically, this attitude emerged as a reaction to overly aggressive management of cases that were diagnosed as melanoma in the past.

Conjunctival Nevus

Clinical Features.—Melanocytic nevi are the most common tumors of the conjunctiva, accounting for 28% of all tumors.[1,2] These lesions most commonly arise in the bulbar conjunctiva, caruncle, or plica semilunaris.[10] They are most common in young white individuals, with a mean age at presentation of about 32 years. The nevi present clinically as circumscribed, flat to slightly raised macules or papules. Nevi in children often lack pigmentation, but usually acquire pigmentation after puberty. However, up to 30% of nevi remain amelanotic.[11] Nevi on the bulbar conjunctiva move freely over the sclera and appear well circumscribed without extension into the cornea.[10,12–14] A common and characteristic feature of conjunctival nevi is the presence of intralesional cysts.[10,13]

A biopsy is usually performed when a pigmented nevus shows clinical characteristics of possible malignancy such as rapid growth, change in shape and/or color, recurrence after prior biopsy, and unusual location such as the palpebral conjunctiva or the fornix. Some lesions are removed for cosmetic reasons. Malignant melanoma will develop in less than 1% of conjunctival nevi.[10,13] Clinical features particularly suggestive of evolving melanoma include extension into the cornea, attachment to the sclera, and development of multiple ''feeder vessels'' seen by slit-lamp examination.[10–14] There are no specific clinical signs that can accurately predict malignant transformation in a conjunctival nevus.

Pathologic Features.—Histologically, conjunctival melanocytic nevi are classified similarly as in the skin, including junctional, compound, and subepithelial nevi. Nevomelanocytes can be organized into intraepithelial nests of oval cells (type A), sheets of oval to cuboidal cells (type B), and spindlelike cells in the subepithelium (type C) (Figure 1, A through D). About 5% of conjunctival nevi are junctional, characterized by nested but sometimes also lentiginous proliferations of type A or type B cells confined to the epithelium.[10] They may show occasional mitotic activity.[13] Junctional nevi with a prominent lentiginous growth pattern may be difficult to distinguish from PAM with atypia on a small biopsy specimen in the absence of clinical information.[13] Most junctional nevi are found in patients in the younger age groups. Therefore, they are believed to be at an early stage in the evolution of compound nevi.

Compound nevi are the most common type of conjunctival nevus, comprising about 70% to 78% of all nevi.[10] In adults, the intraepithelial component shows type A, or less commonly, type B melanocytes. As in the skin, most conjunctival nevi arising in adults show ''maturation'' with depth, that is, progressive evolution of the cell type from A to B to neurotized spindle C cells, with depth of the lesion into the superficial substantia propria.[11,13] A very characteristic and diagnostically useful feature of conjunctival nevi is induction of epithelial protrusions into the lamina propria and formation of intralesional epithelial cysts lined by conjunctival epithelium and goblet cells (Figure 1, B and C). These cysts are present in 50% of cases.[11] It seems that cyst formation is a function of time, as they are less frequent in early lesions. In rare, long-standing nevi, cysts may occupy most of the volume of the lesion and the melanocytic component may not be apparent. In contrast, conjunctival cysts are extremely rare in PAM and melanoma.[13]

Subepithelial nevi are the conjunctival counterpart of the dermal nevus and represent about 9% of all nevi.[10] These are more prevalent in the older age groups and have predominantly type B or C nevomelanocytes in the substantia propria, without an intraepithelial component.[13]

Juvenile Conjunctival Nevus.—In children and adolescents, rapidly growing conjunctival nevi can look very concerning clinically and are often biopsied.[15] Under the microscope, they also show concerning histologic patterns that, in the skin, usually raise a possibility of melanoma. As shown in our recent series,[16] juvenile conjunctival nevi often show confluent growth pattern in the junctional component and paradoxical ''reverse'' maturation, in which the nuclear and cytoplasmic size of melanocytes forming the subepithelial component is greater than that of the junctional component (Figure 1, E and F). In addition, a prominent inflammatory infiltrate may obscure the architecture of the nevus and foster misleading impression of cytologic atypia.[17]

Most variants of cutaneous nevi including combined nevus, balloon cell nevus, Spitz nevus, pigmented spindle cell nevus, and blue nevus have been reported in the conjunctiva.[18–25] Criteria for dysplastic or atypical nevi in the conjunctiva have not been established. It is not clear if patients with dysplastic nevus syndrome have higher incidence of conjunctival nevi. Earlier studies[26] suggested such a relationship, but a more recent case-control population study[27] has found no evidence for this claim.

Treatment.—Conjunctival nevi do not require treatment if clinically stable.[2,10] Excision or rebiopsy is recommended in lesions that change in size or color, recur, or show other clinical features of possible malignancy, or for cosmetic indications. There is no clinical benefit for reexcising conjunctival nevi showing focal cytologic atypia. Therefore, pathologists should refrain from making recommendation for reexcision in pathology reports without understanding the clinical context of the lesion and the risks of additional surgical intervention in this anatomically critical location.

Primary Acquired Melanosis

Clinical Features.—Primary acquired melanosis (PAM) comprises 11% of conjunctival melanocytic proliferations. It is clinically defined as an acquired, usually unilateral, flat, pigmented lesion most commonly occurring on the bulbar conjunctiva.[2] Primary acquired melanosis is most common in middle-aged or elderly white individuals. The melanosis can extend to the skin if the lesion involves the palpebral conjunctiva. The pigmentation in PAM may wax and wane and even disappear. A slit-lamp examination may reveal subclinical melanosis around the clinically visible lesion.[2] Primary acquired melanosis may also be amelanotic, and thus clinically indistinct.[12] By definition, PAM does not have an inciting event, is not congenital, and is not a secondary melanosis due to inflammation or a systemic disease. Primary acquired melanosis can be distinguished from complexion-associated melanosis because the latter is found commonly in dark-skinned individuals and shows bilateral involvement. In addition, pigmentation in complexion-associated melanosis usually does not change over time.[13]

Histologic Features.—Primary acquired melanosis with atypia and without atypia are clinically indistinct. Histologic examination is essential to determine the type of PAM and the risk of progression to melanoma.[28,29] Primary acquired melanosis with atypia has been associated with a 36% to 75% risk of progression to melanoma, whereas PAM without atypia is not believed to be a precursor lesion.[28,29] However, it is important to realize that a diagnosis of PAM without atypia does not entirely rule out progression to PAM with atypia, as patients with a history of melanoma often have features of PAM without atypia on biopsies of recurring pigmented lesions. Histologically, PAM is subclassified as without atypia if a biopsy shows no melanocytic proliferation or if melanocytic hyperplasia is only mildly cellular, limited to the basal layer, and if the cells do not exhibit any cytologic pleomorphism, nuclear hyperchromasia, or enlargement (Figure 2, A). Thus, PAM without atypia can be viewed as
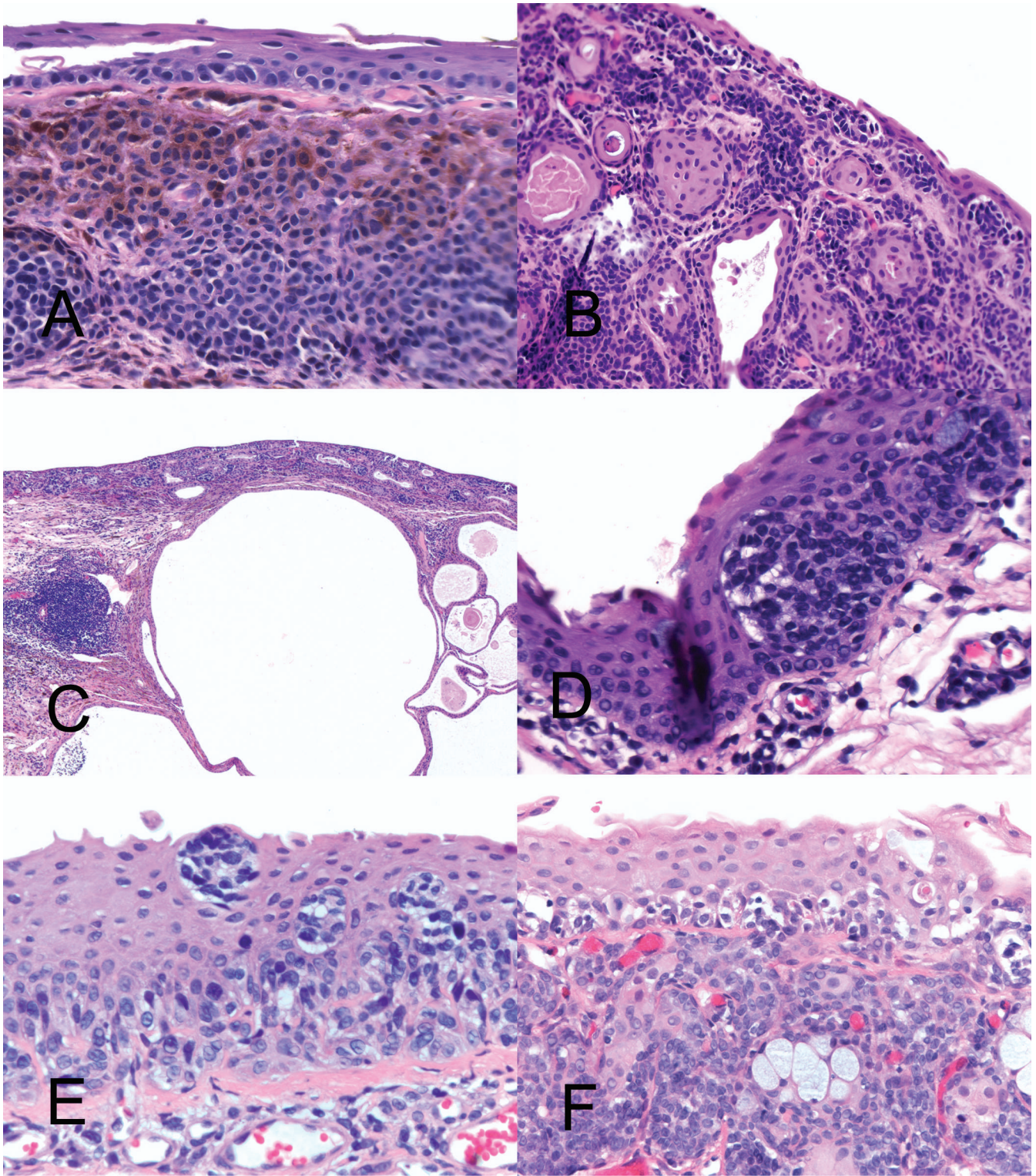
Figure 1. A, Subepidermal nevus. The lesion shows orderly maturation with depth. B, Compound nevus. Conjunctival cyst formation is a helpful diagnostic feature. Of note is the confluent growth pattern of junctional nests, which is not uncommon in conjunctival nevi. C, Cystic conjunctival nevus. In some long-standing lesions, conjunctival cysts can be very prominent. D, Intraepithelial nevus. The nevus cells have similar nuclei to those in the adjacent epithelium. E, Juvenile conjunctival nevus. Confluent growth of junctional nests or pagetoid spread is sometimes seen in rapidly growing nevi in children. F, Juvenile conjunctival nevus. The subepithelial epithelioid melanocytes are larger and have more abundant cytoplasm and larger nuclei than the junctional melanocytes ("reverse maturation") (hematoxylin-eosin, original magnifications ×200 [A], ×100 [B], ×20 [C], and ×400 [D through F]).
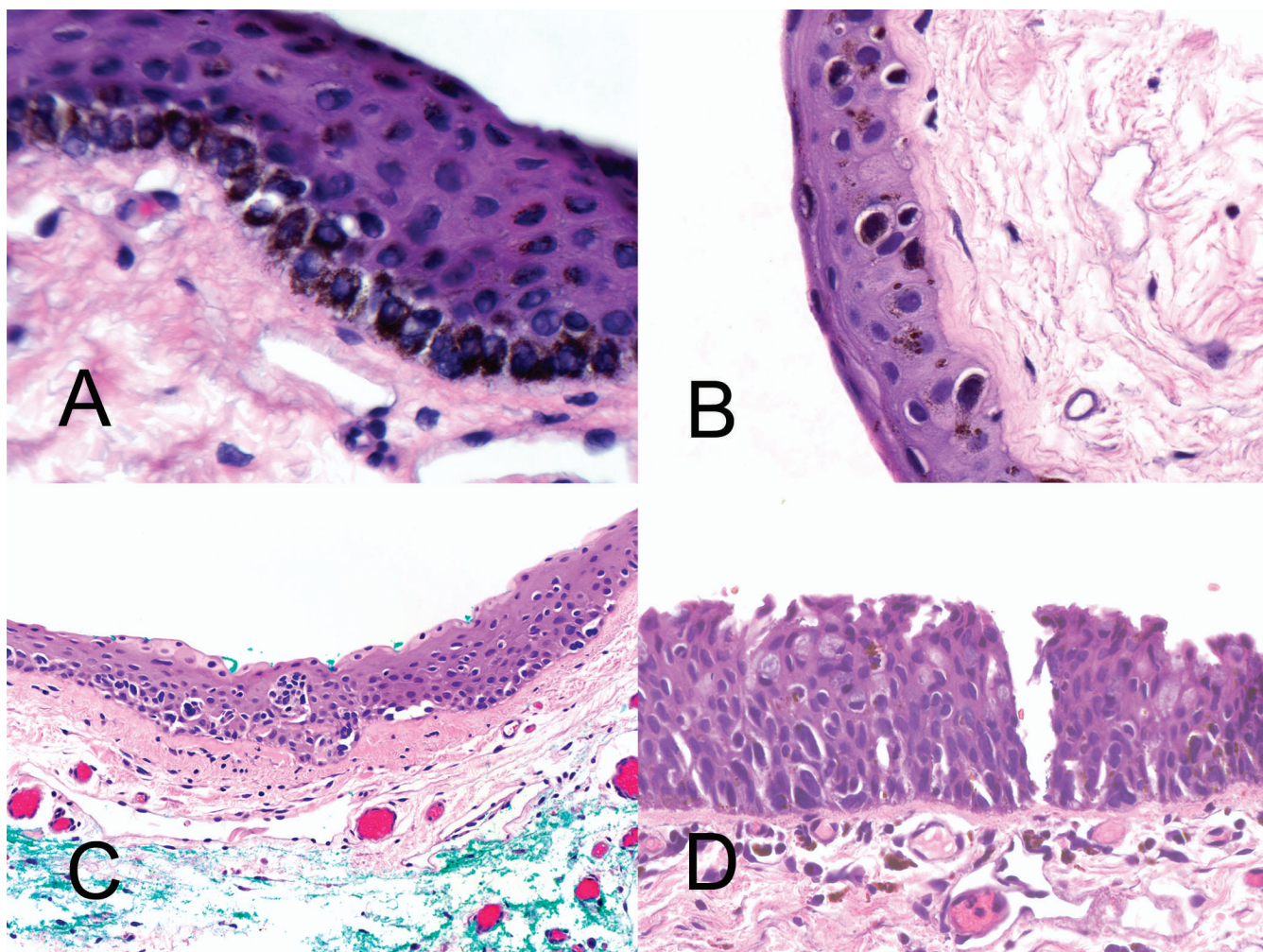
Figure 2. *A, Primary acquired melanosis without atypia. Melanocytic hyperplasia is minimal and pigmentation is due to increased melanization of basal layer epithelial cells. B, Primary acquired melanosis with atypia (low-risk pattern). The melanocytes feature hyperchromatic nuclei without nucleoli and scant cytoplasm. Such lesions have a lower risk of progression or association with invasive melanoma. C, Primary acquired melanosis with atypia (high-risk pattern). Note the single cell and nested growth pattern with pagetoid spread in the atypical conjunctival melanocytic proliferation. D, Primary acquired melanosis with atypia (high-risk pattern). Large cells with epithelioid features and abundant cytoplasm indicate a high probability of concurrent or subsequent invasive melanoma (hematoxylin-eosin, original magnifications ×400 [A and B], ×100 [C], and ×200 [D]).*

a conjunctival analog of cutaneous lentigo. Primary acquired melanosis with atypia is defined histologically as a diffuse intraepithelial melanocytic proliferation showing any degree of melanocytic atypia and/or increased cellularity. This broad definition results in a heterogeneous group of lesions with a varied degree of atypical melanocytic morphology and pattern of growth (Figure 2, B through D). The spectrum of cytologic features can range from small cells showing nuclear hyperchromasia and scant cytoplasm to severely atypical large pleomorphic epithelioid cells with ample cytoplasm and prominent nucleoli.[28] Architecturally, PAM with atypia can show different patterns ranging from the basilar single cell hyperplasia, basilar nesting, intraepithelial nests to pagetoid proliferation of single cells and complete replacement of the epithelial-stromal junction in some cases.[12] Given this histologic heterogeneity, it is not surprising that the term *primary acquired melanosis with atypia* imprecisely communicates the biologic potential of a lesion. At one end of the spectrum, PAM with atypia may have a low risk of progression to melanoma. At the other end, the term *primary acquired melanosis with atypia* will also be used for severely atypical melanocytic proliferations, which would most likely be classified as melanoma in situ at any other mucosal or cutaneous location. Folberg and McLean[28] were the first to observe that PAM with atypia, showing predominantly basilar hyperplasia, has an excellent prognosis, while 90% of the remaining lesions frequently progressed to melanoma. They also observed that the presence of any epithelioid cells was associated with a 75% chance of malignant transformation. We have recently reported a clinicopathologic correlation study of 29 cases of PAM with atypia,[8] which enabled us to formulate histologic criteria discriminating between lesions with a higher and lower risk for concurrent or subsequent melanoma. Our analysis showed that the cytologic rather than architectural features of PAM with atypia are more discriminatory for clinical risk. This is not surprising, as the assessment of the architectural aspects of the intraepithelial melanocytic proliferation, such as pagetoid spread, is very difficult in a thin conjunctival epithelium. Low-risk PAM with atypia is

composed of melanocytes with scant cytoplasm, high nuclear to cytoplasmic ratio, and hyperchromatic nuclei lacking nucleoli (Figure 2, B). Lesions with such features frequently recurred, but only 15% of patients had a concurrent or subsequent invasive melanoma.[8] High-risk PAM with atypia is characterized by epithelioid cell morphology, including oval vesicular or hyperchromatic nuclei, with or without prominent nucleoli; abundant cytoplasm; and a lower nuclear to cytoplasmic ratio (Figure 2, C and D). Ninety four percent of patients with high-risk PAM had concurrent or subsequent invasive melanoma, which metastasized in 25% of cases. All lesions showing a mixture of both low-risk and high-risk phenotypes progressed to invasive melanoma. The frequency of melanoma in high-risk PAM with atypia argues strongly for separating these lesions from the PAM showing low-risk features. In our reports, we refrain from using the outright term *melanoma in situ* for high-risk lesions in reverence to ophthalmic oncologists who are reluctant to use the term *melanoma* for noninvasive lesions. However, the ophthalmic oncology and pathology community should revisit the terminology related to PAM and seriously consider whether to adopt the term *melanoma in situ* for high-risk PAM. This would make this area less confusing for general pathologists and dermatopathologists who often offer consultation on these cases. Importantly, the term *melanoma in situ* appropriately communicates the substantial risk of invasion in the histologically recognizable high-risk subset of PAM with atypia.

The topic of terminology and classification of conjunctival melanosis was recently discussed by Damato and Coupland.[3] They proposed adopting the term *conjunctival melanocytic intraepithelial neoplasia without atypia* as a synonym for PAM without atypia (benign conjunctival melanosis) and *conjunctival melanocytic intraepithelial neoplasia with atypia* for PAM with atypia. They argue that such a diagnostic scheme would be in keeping with recent nomenclature trends and would be less likely to give false reassurance as does the ''benign-sounding'' PAM. The authors raised the issue of using the term *conjunctival melanoma in situ* for high-risk PAM but fell short of recommending it because of the general reluctance to do so in the ophthalmology community. Thus, the benefits of adopting this classification scheme are less compelling, as the classification does not address the most clinically relevant issue of terminology for high-risk lesions/melanoma in situ.

Treatment.—Small lesions of PAM are often managed initially by observation. Larger or changing lesions should be biopsied. At least 35% of PAM lesions will progress clinically and at least 11% will develop into a melanoma within 10 years.[29] The median interval between the time at biopsy and development into melanoma is 2.5 years, with a low risk of melanoma if no progression is seen after 10 years from diagnosis.[28] Primary acquired melanosis without atypia is not considered a premalignant lesion and does not require treatment. Primary acquired melanosis with atypia carries a risk of malignant transformation. The extent of PAM, measured in clock-hours, best correlates with the risk of transformation into melanoma.[29] Small lesions (less than 1 clock-hour) can be followed up with clinical observation. Larger lesions are usually treated by surgical excision and cryotherapy. Oral mucosal or amnitotic membrane grafting may be required

to fill defects after larger excisions. Unresectable or recurrent diffuse PAM with atypia is managed by mapping biopsies and cryotherapy or mitomycin C and close clinical follow-up.[29]

Malignant Melanoma

Clinical Features.—Conjunctival melanoma is rare and accounts for only 2% to 3% of ocular cancer, about 1% of noncutaneous malignant melanoma.[2,14,30–33] The incidence, which is increasing, is about 0.24 to 0.8 per million per year in the white population[30,32,34,35] and is epidemiologically associated with ultraviolet light exposure.[36–38] Conjunctival melanomas are more common in older individuals, with the mean age at presentation of 50 to 60 years. A recent review[39] found only 28 reported cases (only 8 with sufficient clinical detail) of conjunctival melanoma in children younger than 15 years. Conjunctival melanoma presents as an asymptomatic raised pigmented plaque, macule, or tumor ranging in size from millimeters to large tumor masses. This malignancy can occur in 3 clinical settings. Large population-based data indicate that about 53% to 75% of conjunctival malignant melanomas arise in the setting of PAM with atypia. About 5% of cases are associated with a nevus.[33,34,40] The remaining 18% to 30% of conjunctival malignant melanomas arise de novo. The presence or absence of a precursor lesion does not seem to affect the prognosis, but melanoma arising in PAM has a higher risk of local recurrence.[33]

The clinical features suggestive of melanoma include large size, variegated appearance, lack of mobility in relation to the sclera, extension onto cornea, presence of large feeder vessels, and evidence of canalicular obstruction. The color ranges from light to dark brown; rare cases are amelanotic. The most common location of the lesion is the bulbar conjunctiva close to the limbus. Melanoma involving the caruncle or the forniceal or palpebral conjunctiva is less common. However, any pigmented lesion in these locations must be biopsied, as malignant melanoma is the most likely diagnosis. Whether patients with a genetic predisposition for the development of cutaneous melanomas may also have an increased risk of conjunctival melanoma remains to be determined.

The survival rate for conjunctival melanoma ranges from 87% to 95% after 5 years and 70% to 86% after 10 years.[11,30–32,41] After 10 years, 50% of tumors will recur locally and about 25% will metastasize.[41] Adverse clinical prognostic indicators include nonbulbar (fornix, palpebral) location, involvement of the lymphatics-rich caruncle[42] and skin, invasion into the eye or brain, local recurrence, and large tumor size.[30–32,41,43,44] Melanomas occurring in the medial quadrants may also be more aggressive.[3] Corneal invasion does not affect prognosis.[45] Regional metastases usually involve preauricular and intraparotid lymph nodes. Fatal conjunctival melanoma is associated with metastasis to the liver, lung, brain, skin, and peritoneum.[33,34,45,46]

Histologic Features.—Histologic features of conjunctival melanoma are illustrated in Figure 3, A through F. Melanoma of the conjunctiva can be difficult to diagnose, even for experienced pathologists unfamiliar with this anatomic location. Direct application of criteria based on architectural patterns diagnostically helpful in cutaneous melanoma can be misleading in the context of the
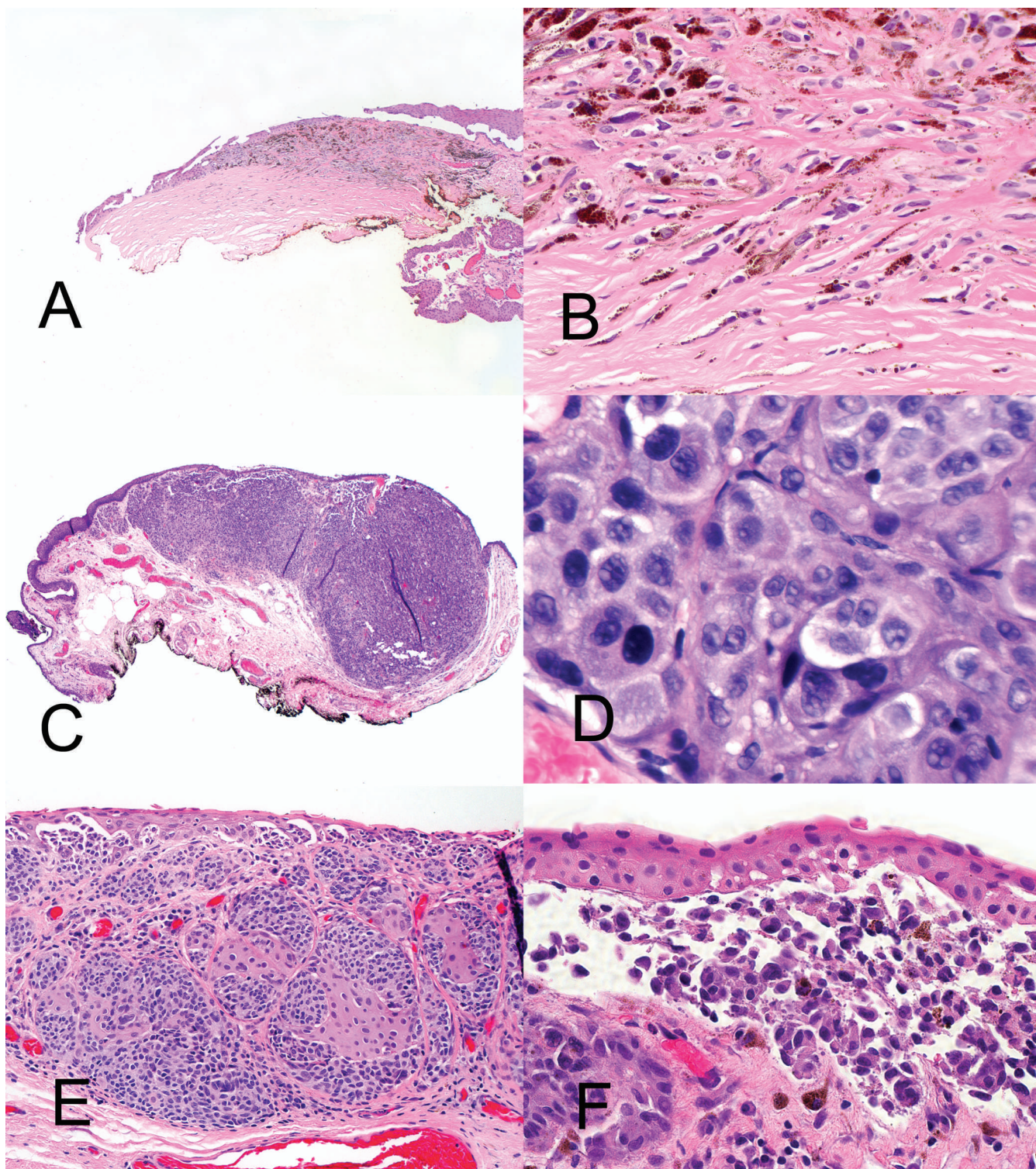
Figure 3. *A and B, Conjunctival melanoma. The tumor infiltrates corneal stroma and is composed of both spindled and epithelioid cells. C and D, Conjunctival melanoma, epithelioid cell type. Tumor cells feature prominent nucleoli, marked nuclear pleomorphism, and abundant cytoplasm. E, Conjunctival melanoma. The invasive component does not induce cyst formation and shows no maturation with depth. F, Early invasive melanoma. The intraepithelial component is highly atypical with discohesive nest formation. A focus of early invasion is seen in the left lower corner of the micrograph (hematoxylin-eosin, original magnifications ×40 [A and C], ×200 [B and F], ×600 [D], and ×100 [E]).*

conjunctiva. Thus, one must rely more on cytologic features and look for a different set of architectural clues. Conjunctival melanoma can be composed of 1 (or different proportions) of 4 different cell types: small polyhedral cells, epithelioid cells, balloon cells, and spindle cells.[33,47]

The latter 3 subtypes are easily recognized as malignant by observing significant cytologic atypia including large nuclear size, prominent nucleoli, or mitotic activity. Purely spindle cell melanomas have been found to be less aggressive.[48] Tumors composed of small polyhedral cells

can be very challenging diagnostically and may be mistaken for a nevus. In these lesions, architectural features can be a clue to the diagnosis. The most useful architectural patterns suggestive of conjunctival melanoma include (1) intraepithelial component showing pagetoid growth, which has to be interpreted with caution, as assessment of pagetoid spread is difficult in a thin conjunctival epithelium; (2) radial extension of the intraepithelial component beyond the lateral edge of subepithelial component, which can also be seen during the rapid growth phase of nevi, especially juvenile ones;[16] (3) patchy or bandlike inflammation at the base of the lesion, which is also not infrequent in juvenile nevi; (4) mitotic activity; (5) lack of maturation toward the base of the lesion, which in juvenile conjunctival nevi often shows paradoxical ''reverse'' maturation, with subepithelial cells larger than intraepithelial cells;[16] and (6) invasion of the sclera or cornea, which is virtually diagnostic if invasion is through the Bowman membrane or into the conjunctival stroma.

Several studies[32,33,48–52] have attempted to determine prognostic histopathologic features in conjunctival melanoma. Candidate prognostic indicators have included features found to be significant in cutaneous melanoma (eg, tumor thickness, histologic type, mitotic activity), or less frequently, in uveal melanoma (ie, cytologic type, the mean of the 10 largest nucleoli, extravascular matrix patterning, or microvascular density). However, the results were not consistent. This is in part because of small sample size and the fact that conjunctival melanoma is often biopsied early and because small size and often poor orientation preclude precise characterization.[51] Population-based series[34,35] have shown that tumor thickness of more than 2 mm is a statistically significant predictor of poor survival and may be a practical cutoff for consideration of sentinel lymph node sampling. However, conjunctival melanoma of any thickness can metastasize because of the close proximity of lymphatic channels to the superficial substantia propria.[53] Other series suggested that melanoma with a pagetoid growth pattern,[33] mitotic activity greater than 5 mitotic figures per 10 high-power fields, mixed cell type (other than spindle cell) morphology,[48] and the absence of an inflammatory response may have worse outcome.[54]

Immunohistochemical studies for melanocytic markers such as HMB-45, S100, and MART-1 may help in the differential diagnosis of small round blue cell tumors in the conjunctiva. A small series[55] has shown that S100A1 protein staining is increased in conjunctival melanomas compared to nevi. HMB-45 has also been shown to be increased in melanomas compared to PAM and complexion-associated melanosis, in another series.[56] However, immunohistochemistry plays a limited role in differential diagnosis between benign and malignant conjunctival lesions.

The molecular pathogenesis of conjunctival melanoma is poorly understood. Mutations in exon 15 of *BRAF*, commonly found in cutaneous melanoma, were identified in 3 of 21 and 5 of 22 conjunctival melanomas.[57,58] N-ras mutations appear to be rare.[59] Of 13 conjunctival melanomas, one was found to harbor *c-kit* mutation,[60] sometimes found in acral and mucosal melanoma, rendering them potentially susceptible to imatinib treatment. Cytogenetic analysis of conjunctival melanoma in a patient with dysplastic nevus syndrome revealed a clonal 1;14 translocation.[61]

Treatment.—All resectable conjunctival melanomas should be completely excised with ''tumor-free'' margins of at least 2 to 3 mm, with adjuvant cryotherapy or topical chemotherapy.[62] The risk of recurrence is reduced with adjuvant cryotherapy, irradiation, or topical chemotherapy.[62,63] Avoiding manipulation of the tumor during surgery, the ''no-touch technique'' is believed to reduce local recurrence rate and lymphatic spread.[64] Sentinel lymph node biopsy has been advocated in melanomas with a high risk for local metastases, such as those more than 10 mm in diameter and 2 mm in thickness and in nonlimbus locations.[34,43,46] Orbital exenteration does not improve outcome and is only indicated for advanced tumors invading into the orbit, or as palliative therapy.[42,62,63]

SUMMARY

Melanocytic lesions of the conjunctiva have a similar morphologic appearance to those of the skin. However, the classification scheme differs in the conjunctiva because of differences in anatomy, prognosis, and management. Nevi and PAM without atypia have a benign clinical course and are similar to nevi and lentigos in the skin. Primary acquired melanosis with atypia, although a controversial category, encompasses several morphologically similar lesions and has several features that can be used to stratify its risk toward the development of malignancy. Although melanomas in the conjunctiva appear similar to those in the skin, prognostic features and thus morphologic evaluation of these tumors is quite distinct. General pathologists and dermatopathologists should be familiar with the classification scheme of conjunctival melanocytic lesions in order to communicate relevant information to the ophthalmologist.

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