Classification of Melanocytic Conjunctival Lesions
and Emerging Entities

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Introduction
Conjunctival melanocytic lesions are some of the most diagnostically challenging specimens encountered by ophthalmic pathologists. They often contain features not seen in the skin, and for some lesions a variety of diagnostic designations have been proposed.

Melanosis (“Hypermelanosis”)

Racial Melanosis/Complexion Associated Pigmentation/Constitutional Melanosis – Epithelial pigmentation concentrated in the conjunctival base, but also often extending more superficially. It is seen most often in individuals with dark complexions.

Freckle/Ephelides – these are flat patches of epithelial pigmentation concentrated in the basal layer. Microscopically, they can appear essentially identical to racial/constitutional melanosis or primary acquired melanosis (PAM) without atypia.

Pigmentation secondary to systemic disease or drugs – conjunctival pigmentation can develop in patients with ochronosis or Addison disease, as well as those treated by systemic agents (phenothiazines, tetracycline) or topical epinephrine. Silver deposition (argyrosis) can also cause conjunctival pigmentation.

Melanocytic Proliferations

Junctional Conjunctival Nevi – the nevoid nests in epithelial base appear cytologically similar to those in skin nevi. Purely junctional nevi can be seen in children, but are almost never encountered in adults. In these older individuals, a diagnosis of PAM is more likely.

Compound Conjunctival Nevi – the subepithelial components of these lesions generally contain entrapped epithelial cysts and nests, and expansion of the cysts may account for rapid clinical growth of lesions in which the melanocytic component appears relatively quiescent. Hormone induced or inflammatory changes are often seen in adolescent junctional and compound conjunctival nevi.

Subepithelial Conjunctival Nevi – generally found in older individuals. The subepithelial component of conjunctival nevus is usually non-proliferative, and recent studies suggest that
HMB45 immunoreactivity is generally restricted to the junctional and superficial subepithelial regions as is true in the skin.

**Congenital oculodermal melanocytosis/Nevus of Ota** – bland spindled/dendritic melanocytes in the deep substantia propria and episcleral tissue. Patients are at increased risk for melanoma of the uveal tract and orbit.

**Conjunctival Blue Nevus** – appear microscopically similar to Nevus of Ota but are smaller and lack systemic associations.

**Primary Acquired Melanosis without Atypia** – in PAM without atypia, the lesion consists of increased epithelial pigmentation with either no melanocytic hyperplasia or a modest increase in cytologically bland melanocytes. These lesions can be microscopically indistinguishable from constitutional melanosis or lentigo.

**Primary Acquired Melanosis with Atypia** – a proliferation of atypical melanocytes in the epithelium. Most conjunctival melanoma develop from these lesions. PAM with mild atypia is often defined as a melanocytic proliferation restricted to single/lentiginous cells in the epithelial base, and is associated with low risk of progression to invasive melanoma. In moderate or severe atypia, abnormal melanocytes involve the more superficial epithelium singly or in nests. Epithelioid melanocytes also support the diagnosis of PAM with severe atypia or melanoma in situ.

**Melanoma in situ** – this diagnosis is used for extensive involvement of the epithelium by atypical melanocytes (generally including the full thickness). The distinction between PAM with severe atypia and MIS can be difficult, and some have argued that all PAM with severe atypia represents MIS.

**Conjunctival Melanoma** – is diagnosed when the basement membrane is breached and subepithelial tumor cells are present. Current AJCC clinical staging is based on tumor location and size, while pathological classification focuses on thickness of the lesion with cutoffs of \(<0.5\ mm, >0.5\ mm-1.5\ mm, and >0.5\ mm.\)

**Proposed Alterations to Nomenclature**

**Melanosis vs. Hypermelanosis** - It can be difficult to distinguish between the various clinical types of increased conjunctival epithelial pigmentation lacking melanocytic hyperplasia or cellular atypia. As noted above, many of these entities appear very similar or identical under the microscope, making accurate diagnosis difficult. In addition, some of the current designations (ie PAM without atypia) can be problematic in that clinicians are not always aware of the lack of malignant potential, potentially resulting in unnecessary therapy or patient concern. It has been suggested by some that the general designation “Conjunctival Benign Epithelial Melanosis” be used for this broad group. However, Coupland and Damato feel that “hypermelanosis” is a more accurate descriptor of the general phenomenon, and that the term “benign” is redundant.
PAM vs. C-MIN – Early designations of these lesions included “lentigo-melanosis” and “precancerous melanosis”, then “benign acquired melanosis” and “cancerous acquired melanosis”, and finally the WHO-sanctioned “primary acquired melanosis” with or without atypia. Coupland and Damato have suggested that “melanosis” is a poor descriptor of what it a proliferation of melanocytes. They further argue that these melanocytes are by definition neoplastic, and that these lesions should all be designated “conjunctival melanocytic intraepithelial neoplasia”. While the overall concept seems conceptually more accurate the historical designation PAM, one potential issue with their proposed classification scheme is that it includes PAM without atypia, which many would not be considered neoplastic.

Emerging Entities

Endocrine mucin producing sweat gland carcinoma – these are low grade tumors with a strong predilection for presenting on the eyelid. The lesions are often multinodular and can be solid, cribriform, papillary or cystic. The cells are round to oval and cytologically bland, with intracellular and/or extracellular mucin present. They tumors also contain varying numbers of cells expressing neuroendocrine markers such as synaptophysin and chromogranin. It has been suggested that these lesions represent a precursor to mucinous carcinoma of the eyelid.

Conjunctival Melanoacanthoma – we have recently encountered two cases of pigmented lesions on the conjunctiva with histopathological features highly similar to oral melanoacanthoma, a diagnosis which to our knowledge has not previously been used for lesions on the ocular surface.

Cystic Benign Melanosis of the Conjunctiva – Laird and colleagues recently reported 3 cases of a unique conjunctival lesion which they designated “cystic benign melanosis” and believe is distinct from cystic nevus and primary acquired melanosis. We recently encountered a similar case.