Melanocytic lesions of the conjunctiva

Hardeep S Mudhar

Abstract

This article reviews the clinico-pathological details of common benign and malignant melanocytic lesions of the conjunctiva. Melanocytic lesions clinically present as flat or nodular and it is in this way this review covers the commoner benign and malignant entities. Several types of naevi can be identified in the conjunctiva, with some site-specific peculiarities, familiarisation with which will allow a correct interpretation. Benign and atypical, 'flat' intraepithelial melanocytic lesions are covered in detail as they constitute many cases of referred material to specialist ophthalmic pathologists. The various classification schemes for atypical intraepithelial melanocytes are covered. Common histological and prognostic details for invasive melanoma are mentioned. Ambiguous lesions are alluded to and how ancillary molecular investigations help in this regard, along with a brief summary of the recent advancements in the molecular biology for conjunctival melanoma.

Keywords blue naevus; combined naevus; conjunctiva; conjunctival melanocytic intraepithelial neoplasia; fluorescence in situ hybridisation; invasive melanoma; melanosis; naevus; primary acquired melanosis

Introduction

In a busy ophthalmic pathology practice, ophthalmic pathologists are frequently called upon to assess melanocytic lesions of the conjunctiva, as the ophthalmologist's primary concern is to exclude conjunctival malignant melanoma.

Like our dermatopathology colleagues, each conjunctival melanocytic lesion is assessed carefully for a variety of features before assigning it to a biological behaviour. There are some features of benign melanocytic conjunctival lesions that to a general pathologist or dermatopathologist would seem worrying, but to an ophthalmic pathologist, are permissible according to site-specific atypia. There is a range of non-neoplastic and neoplastic melanocytic lesions that affect the conjunctiva and this review will highlight the key histological features of each, difficult diagnostic areas and review some current diagnostic molecular trends that assist in challenging cases.

Basic conjunctival anatomy

The conjunctiva is a mucous membrane of columnar to stratified, non-keratinising, and goblet cell containing epithelium, lying on a substantia propria (Figure 1a and b). Its basic function is to attach the globe to the eyelids and to produce the mucous component of the tear-film. Melanocytes are present in the epithelium, usually along the basal layer and vary in number regionally per eye and between different races. They are highly dendritiform and pass on their melanosomes to the neighbouring epithelial cells.

There are three anatomical zones of conjunctiva. These zones are the palpebral conjunctiva (lining the inner surface of the eyelids), the forniceal conjunctiva (lining the superior and inferior cul-de-sacs where the palpebral conjunctiva is reflected onto the globe) and the bulbar conjunctiva (which clothes the sclera-the white part of the eye). Medially there are two specialised areas of the conjunctiva called the plica semilunaris (the equivalent of the nictitating membrane in cats) and the caruncle that comprises skin and conjunctival elements.

Basic clinico-pathological approach

Clinically, ophthalmologists see flat lesions or nodular melanocytic lesions. Flat lesions can be intra-epithelial or sub-epithelial. Nodular lesions can be epithelial but are mostly sub-epithelial. The pathology will be discussed according to flat and nodular with sub-categorisation. It is also critical to know whether the lesions are congenital or acquired, the age of the patient, the presence of pre-existing local or systemic disease and the race of the patient.

Flat intraepithelial melanocytic lesions

These can be divided into non-neoplastic and neoplastic lesions. It is important to know the race of the patient, the age and whether the lesions are newly acquired or longstanding or congenital and whether unilateral or bilateral.

Flat non-neoplastic melanocytic lesions

These reflect either an increase in melanin production or a hyperplasia of melanocytes, although often, these two processes coexist. The following conditions fit into this category: racial melanosis, primary melanosis without atypia, secondary melanosis, systemic conditions and paraneoplastic.

Racial melanosis[1–3]

Clinical: is bilateral and affects individuals with brown/black skin. The classical clinical presentation is with corneo-scleral limbal based, annular brown pigmentation, although the pigmentation can occur on the inter-palpebral bulbar conjunctiva and extend onto the peripheral cornea. The process is thought to be driven by ultraviolet light or inflammatory conditions.

Histopathology: there is an increase in melanin production with or without dendritic melanocyte hyperplasia along the basal layer, with some cases exhibiting upward drift of melanocytes (Figure 2a and b). The melanosomes are taken up by the neighbouring squamous epithelial cells at all layers that often form supranuclear caps. There is thought to be no malignant potential.

Primary melanosis without atypia[3,4]

Clinical: this is a unilateral acquired lesion, in the inter-palpebral, sun-exposed bulbar conjunctiva in adults and is the equivalent of an 'ephilis' of the skin, although it has been advocated that the dermatopathology terms are not applied to the conjunctiva. There should be no other underlying cause for the lesion.

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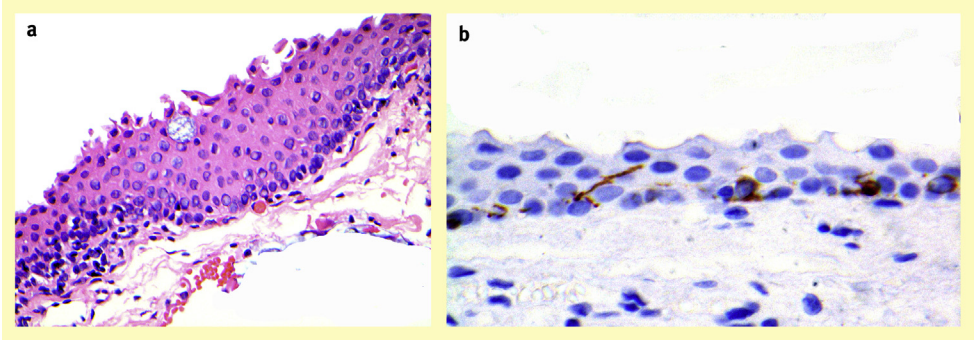

Figure 1 (**a**) Haematoxylin and Eosin (H&E) stained section showing normal conjunctiva with non-keratinising, goblet cell containing stratified squamous epithelium, resting on a substantia propria. (**b**) Melan A immunohistochemistry on normal conjunctiva showing very occasional melanocytes along the basal layer.

Histopathology: there are principally two patterns: The first pattern is an increase in melanin production (increased melanogenesis) without an increase in melanocyte numbers. The second pattern is a hyperplasia of non-atypical dendritic-shaped melanocytes, similar to that seen in racial melanosis with or without an increase in melanosome production. The exclusion of atypia can only be made histologically. Rarely does this condition progress to melanoma.

Secondary melanosis[4]

Clinical: this can be caused by a wide number of stimuli, including drugs (classically chlorpromazine — Figure 3), chronic conjunctival inflammation (classically due to trachoma and vernal (allergic seasonal) conjunctivitis) and secondary to benign and malignant ocular surface lesions such as viral papillomas, pinguecula and ptyrigium and within squamous dysplasia/in-situ squamous carcinoma affecting in patient's with black/brown skin. The latter can be clinically mistaken for melanoma rather than squamous neoplasia.

Histopathology: the histology of these cases is very similar to racial-type melanosis (see above).

Systemic conditions[4]

Clinical: neurofibromatosis, Peutz-Jeghers syndrome and Addison's disease can cause melanotic lesions of the conjunctiva.

Histopathology: this is very similar to what is observed in racial melanosis.

Paraneoplastic[5,6]

Clinical: Acanthosis nigricans has been documented to affect the conjunctiva. It tends to be papilleroid clinically and associated with varying degrees of melanin pigmentation.

Histopathology: the squamous epithelial cells are hyperplastic and heaped up into undulating mounds. The basal layer shows either an increase in melanin production with or without melanocytic hyperplasia.

Flat neoplastic melanocytic lesions[7–20]

PAM with atypia/CMIN/In-situ melanoma

Many terms have been applied to conjunctival atypical intraepithelial proliferations of melanocytes, such as precancerous melanosis, benign acquired melanosis, primary acquired melanosis (PAM) with atypia (a clinico-pathologic term), conjunctival melanocytic intra-epithelial neoplasia (CMIN) and in-situ melanoma. The terminology used has provided us with published intense debate between distinguished dermatopathologists and ophthalmic pathologists. The main terminology used by most ophthalmic pathologists is PAM with atypia, although some use the CMIN terminology alongside the PAM with atypia terminology. None of the devised morphological schemes devised for grading atypical intraepithelial melanocytic proliferations is perfect, so at present, ophthalmic pathologists are

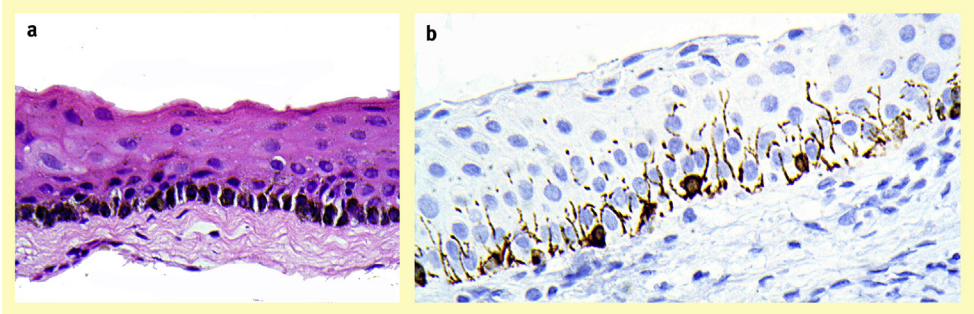

Figure 2 (**a**) H&E racial melanosis showing an increase in melanin pigment in the basal layer. (**b**) Melan A immunohistochemistry-racial melanosis showing melanocyte hyperplasia-note the very prominent dendritic melanocyte morphology.