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Ophthalmic Pathology: Pigmented Conjunctival Lesions

By Yeni H. Yücel, MD, PhD, FRCPC

The richness and diversity of ophthalmic pathology has served as a platform for the clinical practice of ophthalmology. Its application to ophthalmology has had a phenomenal impact on our understanding of the natural history of eye disease and the response of tissues to treatment modalities. Furthermore, ophthalmic pathology, as a discipline concerned with how and why ocular cells break away from normal physiological roles and relationships, remains at the interface between experimental and clinical ophthalmology. This issue of *Ophthalmology Rounds* will illustrate this interface by examining three cases of conjunctival melanocytic lesions.

Because the eye can be examined and imaged directly, ophthalmology has been able to extensively exploit the correlation between the clinical manifestations of disease and its pathological findings. Whether in the form of a fine needle aspirate, biopsy, evisceration, enucleation, or exenteration, the pathological examination of an eye tissue sample plays an important role in the decision-making tree for the diagnosis and management of a patient. Providing relevant clinical information to the pathologist can give added value to the pathological studies. Clinicopathological correlation continues to be fundamental to the clinical practice of ophthalmology and is highly relevant to the study of new emerging diseases and treatment modalities.

Nowhere is the role of ophthalmic pathology more obvious than in the management of the patient with a suspected or confirmed primary or secondary tumour. Pathological examination is fundamental to differentiate between benign, precancerous, and cancerous lesions. This information is relevant to ensure the adequate treatment of malignancies, while avoiding overly aggressive treatment for benign or precancerous lesions. The management of epibulbar lesions is a classic example in which collaboration between the surgeon and the pathologist can provide the optimum patient outcome.

Epibulbar conjunctival lesions

In the case of non-pigmented epibulbar conjunctival lesions, the diagnosis is usually based on the clinical features of these lesions. The differential diagnosis

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includes inflamed pinguecula, episcleritis, conjunctival cyst, allergic conjunctivitis, foreign body granuloma, lymphangioma, and squamous epithelial neoplasia.[1]

When dealing with pigmented epibulbar conjunctival lesions, information that is helpful in differentiating benign pigmented lesions from malignant lesions and those with malignant potential include age, skin pigmentation of the patient, location, colour, size, and elevation of the lesion. A number of conditions can be considered, including conjunctival racial melanosis, primary acquired melanosis, secondary melanosis, nevus, melanoma, ocular melanocytosis, and extraocular extension of an uveal melanoma.[1] A diagnosis based solely on the clinical features of a lesion may not be possible and a biopsy for histopathological examination can help to formulate the diagnosis and a prognosis for the patient. To illustrate some of these points, 3 cases of conjunctival melanocytic lesions are described.

CASE 1 – A pigmented conjunctival nevus

A 45-year-old Caucasian male presented with an enlarging cystic pigmented lesion in the temporal bulbar conjunctiva of the right eye (Figure 1). The brown lesion measured 3.5 × 3 mm. Surgical excision was performed and the specimen was submitted for pathological examination.

This hematoxylin and eosin (H & E) stained section (Figure 2) shows conjunctival epithelium (arrow) and substantia propria. Pigmented nevus cells are noted in the epithelium and additional nests of nevus cells are noted in the substantia propria. Numerous epithelial cysts (C) are also present. The resection margins (not shown) are free of nevus cells. The pathological diagnosis is a completely resected pigmented conjunctival nevus.

Comment: In this case of pigmented conjunctival nevus, the change in apparent size of the lesion is most likely due to enlargement of intrinsic cysts. The involvement of epithelial cysts in the enlargement of these lesions has been frequently described.[2-4] Other causes of enlargement are inflammation within the nevus, increased pigmentation in previously amelanotic regions of the nevus, or neoplastic growth. These features can best be evaluated with histopathological examination.

Figure 1: Cystic pigmented lesion in the temporal bulbar conjunctiva

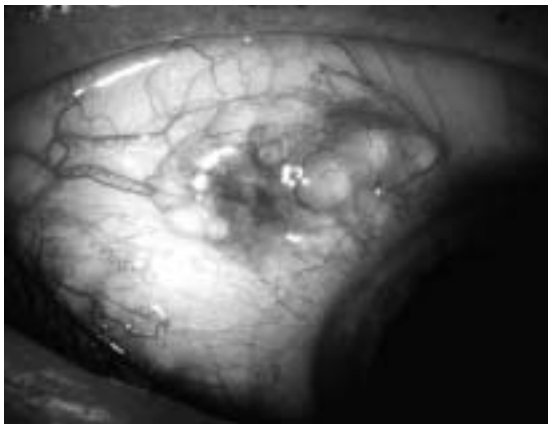
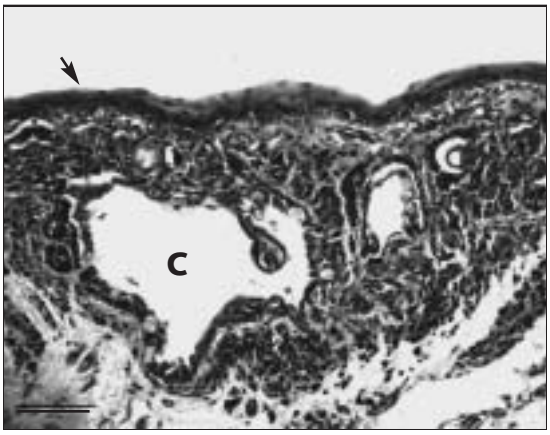


Figure 2: H & E stained section showing conjunctival epithelium (arrow) and substantia propria



c = cyst
The bar indicates 250 µm.

CASE 2 – Primary acquired melanosis (PAM) with atypia

A 37-year-old Caucasian woman presented with 4 golden-brown lesions in the bulbar conjunctiva of the left eye, suspicious because of changes over a period of several years. Multiple excisional biopsies were taken, and the specimens were submitted for pathological examination. Figure 3 shows the pigmented lesion located in the 12 o'clock position.

The section (Figure 4) shows an H&E stained excisional biopsy of a limbus lesion in the 12 o'clock position, showing conjunctival epithelium (arrow) and substantia propria. The conjunctival epithelium shows basilar hyperplasia and nests of atypical melanocytes (under arrow), with features of high nuclear/cytoplasmic ratio and lack of cohesiveness (high power insert). No frank invasion of the substantia propria is observed. Similar findings were noted for all other excised lesions and resection margins showed normal conjunctiva. The pathological diagnosis is completely excised primary acquired melanosis (PAM) with atypia.

Comment: PAM with atypia has the potential for malignancy and usually presents as a flat and variably brown unilateral lesion, in middle-aged or elderly white patients. It must be distinguished from PAM without atypia and histopathological examination is required.[5] PAM without atypia is a benign condition characterized by melanin pigmentation of the conjunctiva with or without hyperplasia of cytologically benign melanocytes. Lesions designated as PAM without atypia showed no progression to melanoma.[5] PAM with atypia features cytologically atypical conjunctival melanocytes. A study of lesions classified as PAM with atypia demonstrated that 46% progressed to melanoma.[5] The presence of atypical melanocytes within the epithelium in any location other than the basal layer of the epithelium was associated with progression to melanoma in 90% of cases, and the presence of intraepithelial atypical melanocytes with abundant cytoplasm (epithelioid cells) was associated with progression to melanoma in 75% of cases.[5] The rate of recurrence in PAM with atypia is approximately 60% and is associated with incomplete excision or corneal involvement.[5]

Figure 3: Pigmented lesion in the 12 o'clock position

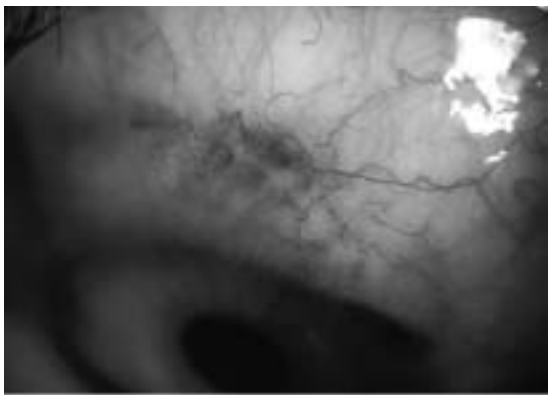
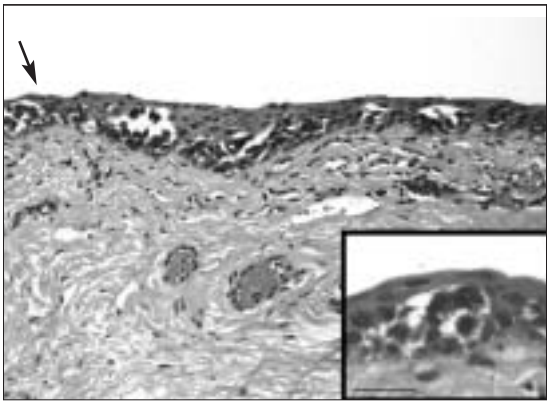


Figure 4: H & E stained excisional biopsy of a limbus lesion



Arrow points to atypical melanocytes (insert)
The bar indicates 125 µm.

CASE 3 – Conjunctival malignant melanoma

A 70-year-old female presented with a recurrent pigmented temporal bulbar conjunctival lesion of the right eye. The lesion had been previously resected from the infero-temporal limbus 11-months earlier, with a pathological diagnosis of nodular melanoma. The recurrent lesion now extended into the cornea from the limbus and measured 3 × 2.5 mm (Figure 5). Exenteration of the right eye was performed and the specimen sent for pathological examination.

The H & E stained section (Figure 6) shows the limbus on the left and central cornea on the right. The limbal tumour (T) invades the peripheral cornea involving the superficial and mid-stroma. A scarred area (S) corresponds to the previous resection site and disrupted Bowman's layer (arrowhead). Descemet's membrane is noted indicating a full thickness cornea section (arrow). No tumour cells are noted in the epithelium. The pathological diagnosis is recurrent malignant melanoma of the conjunctiva invading the cornea.

The higher power microphotograph (Figure 7) shows malignant melanoma cells arranged in sheets. Ovoid nuclei with eosinophilic cytoplasm can be seen and many of the tumour cells show prominent nucleolus. Rare melanin pigment deposits are also noted (arrowheads).

Comment: Conjunctival melanoma, while uncommon, carries an overall mortality rate of approximately 30%. Based on Western population-based studies, the annual incidence of conjunctival melanoma ranges from 0.02 to 0.05 cases per 100,000, with similar numbers in men and women.[6] Up to 75% of conjunctival melanomas are associated with PAM, while up to 20% of melanomas are associated with conjunctival nevi.[7] Conjunctival melanoma often spreads via the lymphatics to regional lymph nodes where histopathological examination often reveals metastatic tumour.[8-12] This is in contrast to uveal tract melanomas that spread hematogenously with a preference for the liver.

When monitoring the patient with conjunctival melanoma after primary treatment,

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Figure 5: Pigmented temporal bulbar lesion extending into the cornea

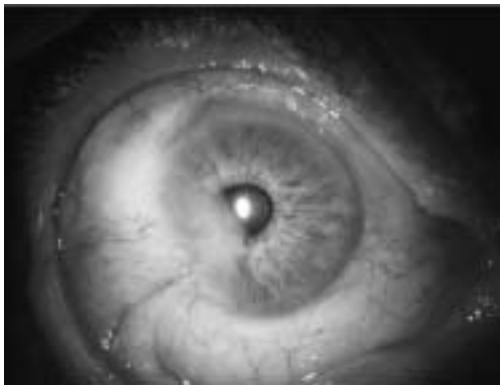
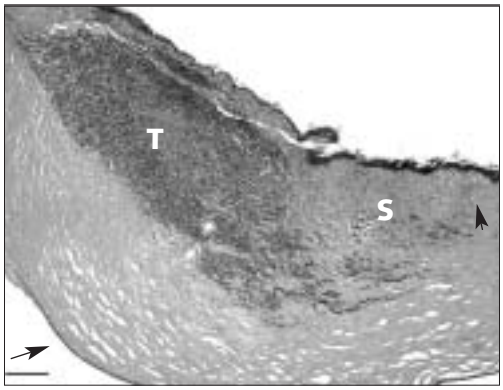


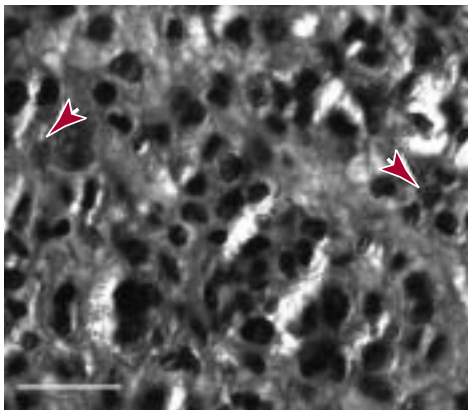
Figure 6: H & E stained section of limbus and cornea



T = limbal tumour S = scarred area
Arrowhead = Disrupted Bowman's layer
Arrow = Descemet's membrane
The bar indicates 250 µm.

CASE 3 *(continued)*

Figure 7: Microphotograph of malignant melanoma cells



Arrowheads = rare melanin pigment deposits
The bar indicates 25 µm.

it is important to consider that local recurrences are common and occur in more than 50% of patients. The recurrences are usually evident within the first 5 years after initial presentation.[13] Close follow-up of the patient is warranted, since approximately 30% of patients will develop a metastatic spread to the lymph nodes.[10]

Clinical predictors of adverse prognosis include conjunctival involvement at the lid margins, palpebrae, fornices, plica, and caruncle, in addition to a multifocal distribution pattern. Pathological predictors of a worsened prognosis include the presence of atypical melanocytes within the epithelium (pagetoid spread),[7] or a diagnosis of mixed cell type tumour (epithelioid and spindle cells).[8] Histological evidence of lymphatic invasion carries a 4-fold higher death rate compared to those without lymphatic involvement.[8] Increased tumour thickness[7,8] and mitotic figures[7,10,14-16] are also predictive of a less favourable prognosis.

Conclusion

Relevant clinical information regarding the lesions, such as number, location, pre-existence size, colour, and any documented changes, is useful to the pathologist in formulating a pathological diagnosis. These cases of conjunctival lesions illustrate the important relationship between the pathologist and eye surgeon for managing patients with seemingly innocuous lesions, to prevent consequences that may be devastating.

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Abstracts of Interest

Tumours of the conjunctiva and cornea

SHIELDS CL, SHIELDS JA; PHILADELPHIA, PA

The authors review in this article the tumors of the conjunctiva and cornea comprising a large and varied spectrum of conditions. These tumors are grouped into two major categories of congenital and acquired lesions. The acquired lesions are further subdivided based on origin of the mass into surface epithelial, melanocytic, vascular, fibrous, neural, histiocytic, myxoid, myogenic, lipomatous, lymphoid, leukemic, metastatic and secondary tumors. Melanocytic lesions include nevus, racial melanosis, primary acquired melanosis, melanoma, and other ocular surface conditions like ocular melanocytosis and secondary pigmentary deposition. The most frequent non-melanocytic neoplastic lesions include squamous cell carcinoma and lymphoma, both of which have typical features appreciated on clinical examination. The caruncle displays a slightly different array of tumors compared to those elsewhere on the conjunctiva, as nevus and papilloma are most common, but oncocytoma and sebaceous gland hyperplasia, adenoma, and carcinoma can be found. In this review, they provide clinical description and illustration of the many conjunctival and corneal tumors and they discuss tumor management.

Surv Ophthalmol 2004; 49:3-24.

Conjunctival nevi: clinical features and natural course in 410 consecutive patients

SHIELDS CL, FASIUDDEN A, MASHAYEKHI A, SHIELDS, JA; PHILADELPHIA, PA

This retrospective study describes the clinical features of a conjunctival nevus and to evaluate the lesion for changes in colour and size over time. The 2 main outcome measures were changes in tumor colour and size. The nevus was brown in 65%, tan in 19%, and completely nonpigmented in 16%. The anatomical location of the nevus was the bulbar conjunctiva (72%), caruncle (15%), plica semilunaris (11%), fornix (1%), tarsus (1%), and cornea (<1%). The bulbar conjunctival lesions most commonly abutted the corneoscleral limbus. The nevus quadrant was temporal (46%), nasal (44%), superior (6%), and inferior (5%). Additional features included intralesional cysts (65%), feeder vessels (33%), and visible intrinsic vessels (38%). Cysts were clinically detected in 70% of histopathologically confirmed compound nevi, 58% of the subepithelial nevi, 40% of the junctional nevi, and 0% of the blue nevi.

Of the 149 patients who returned for periodic observation for a mean of 11 years, the lesion colour gradually became darker in 5% (7 patients), lighter in 8% (12 patients), and was stable in 87% (130 patients). The lesion size was larger in 7% (10 patients), appeared smaller in 1% (1 patient), and was stable in 92% (137 patients). There were 3 patients who developed malignant melanoma from a preexisting compound nevus (2 cases) or blue nevus (1 case) over a mean interval of 7 years. The authors conclude that conjunctival nevus is a benign tumor most often located at the nasal or temporal limbus and rarely in the fornix, tarsus, or cornea. Over time, a change in tumor colour was detected in 13% (20/149) and a change in tumor size was detected in 8% (12/149).

Arch Ophthalmol 2004;122:167-175.

Upcoming Department Events

April 22, 2004
VPP – Dr. Donald Fletcher, Birmingham, Alabama
Advances in Low Vision Rehabilitation

Aprill 29, 2004
VPP – Dr. Douglas Coster, Australia
Development in corneal therapeutics

May 6, 2004
VPP – Dr. Kathleen Digre, Salt Lake City, Utah
Neuro-ophthalmic changes in pregnancy

May 13, 2004
VPP – Dr. Shaun Singer, Toronto, ON
Quality Assurance Rounds

May 20, 2004
VPP – Dr. David Apple, Charleston, North Carolina
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Note: Visiting Professors Programme (VPP) site address: Toronto Western Hospital, West Wing, Room 2 - 401, 399 Bathurst Street, Toronto.

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