The Surgical Pathology of Pigmented Conjunctival Melanocytic Lesions

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1. Background  
   a. In ophthalmic surgical practice, there is a compelling conflict between the need to eradicate cancer and the desire to preserve vision  
      i. Consequences and example:  
         1. It is not possible to excise pigmented conjunctival lesions with “adequate margins” because the sacrifice of conjunctival goblet cells and accessory lacrimal gland tissue may result in a painful dry eye that compromises vision  
      ii. Fear of darkness – blindness – is a primal fear. Children are afraid of the dark. Adults are afraid of losing their independence.  
         1. Most ophthalmologist have heard patients exclaim, “Doctor, I'd rather be dead than blind!”  
   b. Before the public awareness of AIDS and Alzheimer's disease as major public health issues, the Gallup Organization polled Americans asking the following question: What disease do you fear most?  
      i. In both the 1960s and 1970s, the most feared disease was cancer. The second most feared disease was blindness.  
      ii. Therefore, a patient who is confronted with a diagnosis of ocular cancer, is confronted with two terrible fears. The surgeons who care for these patients must balance two compelling needs.  
      iii. And therefore, the surgical pathologist must be sensitive to the patient's perspective and the therapeutic options.  

2. Challenges to the Surgical Pathologist  
   a. Understanding the unique microanatomy of the conjunctiva  
   b. Appreciating and using the clinician's terminology  
   c. Knowing the surgical and medical treatment of these disorders  

3. Microanatomy of the Conjunctiva  
   a. Bulbar conjunctiva  
   b. Palpebral conjunctiva  
      i. Tightly tethered to the underlying tarsus  
      1. Therefore, even invasive lesions in this area appear clinically flat  
   c. Fornix  
      i. A pseudostratified columnar epithelium with goblet cells. Do not mistake the normal histology for dysplasia!  
   d. Caruncle  
      i. Conjunctival mucosa with pilar units, sebaceous glands, and eccrine glands in the submucosa  
   e. The Limbus  
      i. The importance of Bowman's layer as a surgical pathology landmark  
      ii. Most surface neoplasms of the conjunctiva that extend into the cornea remain superficial to Bowman's layer  

4. Handling the conjunctival resection at the limbus: be certain to take histological sections that run perpendicular to the limbus (bottom panel, right)
5. Conjunctival Nevi: Key teaching points
   a. Junctional nevi are seldom encountered and should only be diagnosed in young children
      i. Pathologists who are tempted to render a diagnosis of junctional nevus should consider the possibility of *primary acquired melanosis with atypia*, a melanoma precursor
   b. Nevi only seldom encroach upon the cornea
      i. Pigmented lesions that invade the cornea are not likely to be benign
   c. Be aware of the inflamed conjunctival nevus of childhood, a compound nevus with chronic inflammation populated by variable numbers of eosinophils
      i. There is no counterpart to this lesion in cutaneous pathology as this is not a halo nevus and bears no relation to vitiligo

6. Conjunctival melanoma and its precursors
   a. The overall mortality of conjunctival melanoma is 25%
   b. Clinical Terminology
      i. Congenital melanosis oculi (also known as congenital ocular melanocytosis)
         1. Conceptually, this is a congenital nevus of the uvea
         2. There may be an increased risk of uveal melanoma in the Caucasian population with this disorder (but not in Asians or African-Americans)
         3. The sclera appears to be blue clinically because of the deep uveal pigmentation (the Tyndall effect renders the melanin blue clinically)
         4. The pigmentation is not in the conjunctiva
      ii. Secondary acquired melanosis
         1. No risk of developing melanoma
         2. Examples:
            a. Complexion-associated pigmentation: bilateral conjunctival pigmentation in individuals with dark skin tone
            b. Secondary to systemic disease (e.g., Addison's disease)
            c. Secondary to topical medications (silver nitrate, epinephrine)
            d. Other pigmentations (e.g., mascara)
      iii. Primary acquired melanosis
         1. Meeting the following diagnosis criteria
            a. unilateral
            b. acquired
            c. flat
            d. brown pigmentation in a fair-complexioned individual
        iv. Very Important - Key conceptual point
           1. There are no clinical criteria to that permit the prediction of the histology of conjunctival pigmented lesions that meet these five criteria!
           2. Therefore, ophthalmologists have been taught to take biopsies from every patient with a lesion that does meet these criteria.
   c. Pathology terminology
      i. Primary acquired melanosis
         1. Without atypia: hyperpigmentation of the conjunctiva with or without melanocytic hyperplasia but without atypia
            a. No likelihood of progression to melanoma
            b. Cannot be called "lentigo" histologically – the conjunctiva lacks rete
         2. With atypia: atypical intraepithelial melanocytic hyperplasia, with or without pigmentation
            a. 50-90% likelihood of progression to melanoma if not completely extirpated
   d. Questions for discussion
      i. Primary acquired melanosis without atypia: *Why isn't this called lentigo or ephelis?*
      ii. Primary acquired melanosis with atypia: *Why isn't this called “melanoma in situ”?*
iii. Answers
1. Because there are no clinical criteria to allow for the separation of melanoma precursors from completely benign lesions,
2. Because the nomenclature is shared between clinician and pathologist, and
3. Because the nomenclature guides therapy
7. ADASP Recommendations for Reporting Conjunctival Melanoma
   a. Indicate the location of the lesion
      i. Melanomas arising in the fornix, palpebral conjunctiva, plica semilunaris, and
         caruncle, tend to follow a more aggressive course than melanomas affecting and
         confined to the bulbar conjunctiva and limbus
   b. Indicate the procedure undertaken to obtain tissue
      i. Incisional biopsy (including "map" biopsy – the procurement of multiple small
         biopsies from the conjunctiva)
      ii. Excisional biopsy
      iii. Debridement of the corneal epithelium
   c. When present, indicate involvement of the
      i. Episclera
      ii. Corneal stroma
      iii. Orbital fat
   d. Thickness (depth)
      i. Measured from the top of the epithelium to the deepest tumor cell in the
         substantia propria
         1. recall that the conjunctiva is not normally keratinized and a granular layer
            is absent
   e. Measure of proliferation
      i. Mitoses
      ii. Proliferation index
   f. Margins
      i. Completely removed
      ii. Lateral margins involved but deep margin uninvolved
      iii. Deep margins involved but lateral margins uninvolved
      iv. Not complete either laterally or in depth
   g. Vascular invasion
      i. None
      ii. Lymphatics
      iii. Vascularity
      iv. Lymphatics and vascular

8. Treatment options
   a. Excisional biopsy (compare with "map biopsy")
   b. Cryotherapy
   c. Topical chemotherapy (mitomycin-C)
      i. role of post-treatment biopsy
      ii. mitomycin-C effects within the epithelium

9. Final points
   a. The best treatment of conjunctival melanoma is its prevention through the appropriate
      treatment of conjunctival primary acquired melanosis with atypia, and
   b. The best treatment requires a partnership between the surgeon and the pathologist.

Suggested Additional Readings:

The General Surgical Pathology of Pigmented Conjunctival Lesions
1. Jakobiec FA, Folberg R, Iwamoto T: Clinicopathologic characteristics of premalignant and
2. Folberg R, Jakobiec FA, Bernardino VB, Iwamoto T: Benign conjunctival melanocytic lesions:


*Hum Pathol* 2003;34:114-118.  


**Conjunctival Nevi**


**Primary acquired melanosis with and without atypia and conjunctival melanoma**


**The Nomenclature Debate**


**Topics in Management**


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Summary Points:

1. The surgical pathologist must be aware of the surgeon’s goal to preserve vision in addition to the extirpation of melanomas and their precursors,
2. Therefore, the surgical pathologist must be aware of variations in the conjunctival microanatomy, the terminology shared by the surgeon and the pathologist, and, of course, the microscopic appearances of the spectrum of conjunctival pigmented lesions.
3. Conjunctival melanoma is associated with a 25% mortality, and the best treatment of conjunctival melanoma is its prevention through extirpation of its precursor lesion – primary acquired melanosis with atypia.
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Background

Inherent conflicts of interest:
Balancing the need to eradicate cancer
with the desire to preserve vision

– The Gallup Polls
– “Doctor, I’d rather be dead than blind!”
Challenges to the Surgical Pathologist

Understanding …

– The conjunctival microanatomy
– The ophthalmologist’s terminology
– Surgical and medical approaches to treatment
Microanatomy of the Conjunctiva

Bulbar Conjunctiva

Palpebral Conjunctiva

Fornix
The Ocular Caruncle
Microanatomy of the Limbus

Importance of Identifying Bowman’s Layer
Partnering with the Surgeon

Surgical Techniques to Obtain Optimal Biopsy Material
http://eyepath.comd.uic.edu
Click on Practical Tips
Conjunctival Nevi
Conjunctival Nevi: Clinicopathological Features
Conjunctival Nevi: Histopathological Features

Subepithelial Nevus, Conjunctiva

Subepithelial Nevus, Caruncle
Conjunctival Nevi: Variants

Blue Nevus, Bulbar Conjunctiva
Inflamed Juvenile Nevus
Conjunctival Nevi: Teaching Points

Junctional nevi are seldom if ever encountered
  Suspect melanoma precursor if melanocytes are confined to the epithelium

Nevi only very rarely encroach upon the cornea are almost never encountered in the palpebral conjunctiva
  Suspect melanoma in these topological contexts

Inflamed juvenile nevi are common
  Clinically present with growth which may reflect acquisition of the inflammatory component
  Not associated with halo nevus or vitiligo – entirely benign
Conjunctival Melanoma, Melanoma Precursors, and the Pretenders

The mortality of conjunctival melanoma is 25%
Conjunctival Melanoma and Precursors

Primary Acquired Melanosis

Malignant melanoma

Overall mortality: 25%
Primary Acquired Melanosis

Secondary Acquired Melanosis

Complexion-associated pigmentation
Addison’s disease
Peutz-Jegher’s Disease
Topical Medications
Others

Congenital Melanosis
The Dilemma

Unilateral flat conjunctival pigmentation in a fair-complexioned adult

There are no clinical criteria that allow separation of PAM without atypia
Primary Acquired Melanosis

- Hyperpigmentation without melanocytic hyperplasia or atypia
- Hyperpigmentation with hyperplasia or atypia

Primary Acquired Melanosis without atypia

Primary Acquired Melanosis with atypia
**Terminology**

Primary acquired melanosis without atypia

*Why don’t we call this “ephelis” or “lentigo”?*

Primary acquired melanosis with atypia

*Why isn’t this called “melanoma in situ”?*

**Why?**

*Because there are no clinical criteria to allow for the separation of melanoma precursors from completely benign lesions,*

*Because the nomenclature is shared between clinician and pathologist, and*

*Because the nomenclature guides therapy.*
Unilateral, flat pigmented conjunctival lesion

Clinical Diagnosis

PAM

Biopsy

PAM without atypia  PAM with atypia

Histological Diagnosis
PAM without atypia

No progression to melanoma

PAM with atypia

50-90% progression to melanoma

Malignant Melanoma

25% mortality
Primary Acquired Melanosis

Hyperpigmentation without melanocytic hyperplasia or atypia

Primary Acquired Melanosis without atypia

Hyperpigmentation with hyperplasia or atypia

Primary Acquired Melanosis with atypia
ADASP Protocol: Conjunctival Melanoma

### Checklist for Conjunctival Melanoma

**Site (circle all affected)**
- Conjunctiva
- Bulbar, palpebral, fornix
- Caruncle
- Plica semilunaris
- Limbus
- Cornea

**Procedure**
- [ ] Excisional biopsy
- [ ] Incisional biopsy
- [ ] Debridement of corneal epithelium

**Involvement of the (circle all that apply)**
- Corneal stroma
- Episclera
- Orbital fat

**Thickness**
- ____.____ mm

**Mitotic Rate**
- ____.____/mm²

**Excision (circle one)**
- Complete
  - Not complete laterally (indicate affected margins)
    - but complete in depth
  - Not complete in depth but complete laterally
  - Not complete either laterally or in depth

**Vascular Invasion (circle one)**
- Absent
- Blood vessels
- Lymphatics
- Blood vessels and lymphatics
Treatment Options

Excision
   *Limited option*

Cryotherapy

Topical Chemotherapy
   *Mitomycin-c eyedrops*
   *Role of post-treatment biopsy*
      *Histological mitomycin effect*
The best treatment of conjunctival melanoma is its prevention through treatment of PAM with atypia.
The best treatment requires a partnership between the surgeon and the pathologist.
Many of the clinical photographs used in this presentation first appeared in the following articles:


Many of the photomicrographs used in this presentation originate from the following source: