MUCOSAL MELANOMA AND PIGMENTED LESIONS OF MUCOSAL SURFACES

Adriano Piris, M.D.
Co-Director – Mihm Cutaneous Pathology Consultative Service (MCPCS)
Brigham and Women’s Hospital, Harvard Medical School
Stewart-Rahr-MRA Young Investigator: Melanoma Research Alliance, Washington, DC

Introduction
- Mucosal melanoma as different biological entity than cutaneous melanoma
- Rarity of disease and timing of diagnosis precludes significant studies to standardize staging and management

Mucosal melanoma diagnosis
- Mucosal lentigo (melanosis)
- Benign mucosal melanocytic proliferation: junctional or compound nevus, blue nevus
- Atypical melanocytic hyperplasia
- Melanoma in situ
- Invasive Melanoma

Diagnosis: Invasive mucosal melanoma
- Malignant “pigmented” nodule
- Rule out metastatic disease: Clinical history and identification of an in situ component
- Small samples: no obvious in situ component
- Examination of adjacent uninvolved mucosa is crucial

Diagnosis: Invasive mucosal melanoma
- Amelanotic nodule:
  - Undifferentiated or sarcomatoid proliferation
  - First: establish the melanocytic nature of the tumor (Immunohistochemistry)- S100, HMB45, Melan-A, Mart-1, and MitF
  - Second: Identify in situ component

Mucosal melanoma: in situ component
- Confluent growth of lentiginous and nested intraepidermal melanocytes with atypical features
- Emphasis of lentiginous growth with insidious and multifocal pattern, extending along underlying native glandular units
- These “precursor” lesions may be subtle and not readily visualized with H&E only
- Melanocytic markers are crucial to identify in situ/precursor lesions and extent of disease
Pathological Evaluation of the Tumor

- Tumor thickness correlates with survival
- 2.0 mm or less better prognosis
- Due to late diagnosis most lesions are usually thicker than 2.0 mm
- AJCC histomorphological criteria (from cutaneous melanoma) have not been validated

Evaluation of Local Disease

- A: Established primary mucosal melanoma
- B: Extent of local disease: CT or MRI
- C: Basic metastatic workup: serum lactate dehydrogenase, chest x-ray, combined PET/CT scanning of chest, abdomen, and pelvis

(Clinical) Evaluation of Extent of Disease

- Clinical staging system for cutaneous disease applied to mucosal melanomas
- Stage I: Localized disease
- Stage II: Regional lymph node disease
- Stage III: Disseminated disease

Sites of origin

- Respiratory mucosa
- Oral cavity
- Esophagus
- Genital mucosal surfaces
- Gastrointestinal mucosa
- Urinary tract
- Auditory canal
- Conjunctiva

Sinonasal mucosal melanoma

- Rare disease with poor survival
- Poorly characterized early/precursor lesions
- Retrospective analysis found 31 of 32 patients with associated intraepidermal melanocytic proliferations
Sinonasal mucosal melanoma

- Age: 30-90 years (median 71)
- M-F ratio 3:2
- Follow up (31 pts): 5 to 211 months (mean 42)
- 58% died of melanoma associated conditions
- 19% died of unknown causes
- 6% alive with metastatic disease
- 19% alive without melanoma

Characteristics of the invasive component

- Determination of accurate tumor thickness was not possible in the majority of cases due to fragmentation of the specimen
- In 7 specimens: 0.3 to 15.0 mm
- Morphology: epithelioid, spindled, and small cell morphology
- Presence of >3 mitoses/mm2 and necrosis correlated with tumor progression and overall survival

Sinonasal mucosal melanoma

- MMIS (confluent intraepithelial proliferation of cytologically atypical melanocytes): 67% of cases, confirmed by MITF
- Melanocytic hyperplasia (intraepithelial melanocytic proliferation without confluent growth or atypia): 16% (5 cases)
- Overall incidence of associated intraepidermal melanocytic proliferations: 83%

Single atypical melanocytes H&E

Atypical melanocytic hyperplasia
Hyperplasia and atypia, not MMIS

Mochel et al: Melanocytes within sinonasal mucosa
- Negative control: sinonasal mucosa removed for rhinosinusitis
- No intraepithelial melanocytes found in these negative controls
- Identification of melanocytic hyperplasia within the context of “melanosis” in sinonasal mucosa should raise the concern of a precursor lesion.

MMIS, resp. epithelium

Easy to miss MMIS
MITF extensive MMIS

MMIS in resp epithelium

MITF

Extensive gland involvement

Invasive component

Epithelioid cell with central necrosis
Small round cell

Spindle cell fascicular

Melanoma mimics in the mucosal surface
Freckles, Lentigines and Melanoses
The Freckles, lentigines, and melanoses

- Not classified as a form of **precancerous melanocytic proliferation**
- Their recognition is important because:
  - Clinical appearance resembles melanoma
  - **Multiple lentigines/ melanoses** may be a sign of a **systemic disease associated with non-melanocytic cancers**.

---

Labial melanotic macule

- **CLINICAL FEATURES**
  - Classically lower lip or just off midline
  - Similar lesions anywhere in oropharynx
  - Identical lesions in the genital mucosae are termed vulvar and penile melanosis
- **HISTOLOGY**
  - Slight epithelial hyperplasia; parakeratosis
  - Increased numbers of banal melanocytes with dendritic morphology; basilar hyperpigmentation
  - Melanophages in stroma
Atypical melanocytes in squamous mucosa: NOT melanosis

Vulvar Melanosis

- Clinically presents as a solitary (up to or several centimeters in size) or multiple intensely pigmented macule(s); similar phenomenon on penis is called penile melanosis.
- Clinical differential diagnosis: radial growth phase mucosal LMM, patch type Bowenoid papulosis, and pigmented Bowen's disease.

The genital melanocytic proliferations: main forms

- Mucosal lentigo
- Vulvar melanosis
- Common acquired nevus
- Dysplastic nevus
- Malignant melanoma

Vulvar Melanosis

- Clinically presents as a solitary (up to or several centimeters in size) or multiple intensely pigmented macule(s); similar phenomenon on penis is called penile melanosis.
- Clinical differential diagnosis: radial growth phase mucosal LMM, patch type Bowenoid papulosis, and pigmented Bowen's disease.
Vulvar Melanosis:
Histomorphology

- Hypermelanosis
- Mild increase in number of basilar melanocytes
- Acanthosis
- No melanocytic atypia
- Differential diagnosis: atypical lentiginous melanocytic hyperplasia (precursor lesion to melanoma)

Mucosal Lentigo From Simulators of Malignant Melanoma
Drs. Kerl and Cerroni, University of Graz

Atypical melanocytes in squamous mucosa: NOT melanosis

Cervico-vaginal invasive melanoma: Case 1
Vulvo-urethral invasive melanoma: Case 2

Malignant melanoma of anorectal region: a clinicopathologic study of 61 cases

Muhammad Usman Tariq, Nasir Ud Din, Nausheen Feroz Ud Din, Saira Fatima, and Zubair Ahmad

Annals of Diagnostic Pathology, 2014-10-01, Volume 18, Issue 5, Pages 275-281

Copyright © 2014 Elsevier Inc.
Ano-rectal Mucosal Melanoma

Anorectal melanoma

- Expression of vimentin, S-100, HMB-45, and Melan A in 100%, 100%, 94.4%, and 93.3% cases, respectively.
- Cytokeratins were positive in 9% and CD117 (c-kit) in 20% of cases in which they were performed.
- All cases were BRAF negative

Cutaneous Malignant Melanoma

- Superficial Spreading Melanoma
  - BRAF/NRAS
- Acral Lentigious Melanoma
  - CKIT
- Lentigo Maligna Melanoma
  - CKIT
- Chronic Sun Damage (CSD)
- Nodular Melanoma
  - ?BRAF/NRAS

Mucosal Malignant Melanoma: CKIT

Types of Non-Melanocytic Ocular Pigmentation

Scleral Diseases
- Blue Sclera
- Staphylooma
- Scleromalacia
- Senile hyaline plaque

Metabolic Disorders
- Ochronosis
- Gaucher’s disease
- Jaundice
Benign Epithelial Pigmented Tumors

- Pigmented seborrheic keratosis
- Benign squamous papilloma
- Verruca vulgaris
- Pigmented eccrine poroma

Ophthalmic Pathology Describes Melanocytic Lesions to Arise from 3 Types of Melanocytes

1. Intraepithelial melanocytes that lie among the basal epithelial cells and may show dendritic processes between keratinocytes
2. Nevius cells- oval cells that form nests and sheets at the epidermal-dermal or epithelial-subepithelial junction
3. Fusiform dendritic melanocytes that lie in the deeper mesenchymal or subepithelial tissue

Congenital Melanosis Benign Epithelial Melanosis - Clinical

1. Patchy flat brown pigmentation of conjunctival epithelium
2. Associated with skin color
3. Usually bilateral non-inflamed non-vascularized and stationary
4. Most common in limbal area and may advance to caruncle
5. May advance onto cornea after surgery or trauma-streaks and swirls
6. Usually congenital may be acquired in african-americans

Conjunctival Nevi

General Clinical Considerations

- Single most common site- juxta-limbal followed by epibulbar, the plica, and caruncle
- May be focal or diffuse but not multifocal
Nevi most unusual in palpebral or fornical conjunctiva, **suspect melanoma**

All bulbar nevi freely movable with Q tip traction unless hinged at limbus -if hinged and immovable, **suspect melanoma**

---

All palpebral nevus-like lesions should be biopsied

Conjunctival nevi do not extend onto the cornea - if observed probably melanoma

---

**Common Acquired Nevi**

1. Junctional - Type A cells in nests
2. Compound - Intraepithelial and substantia propria proliferation - subepithelial cells have a "lymphocytoid" appearance and are not melanized in deeper component
3. Subepithelial – May show type C cell proliferation
4. Blue nevi - Characteristic dendritic cells.
5. 40% of conjunctival nevi have a combined element, often very focal

---

6. Downward protrusion of small solid pegs of epithelium is typical for sub epithelial nevi
7. Epithelium- lined cysts multiple and diffuse are characteristic for benign sub epithelial nevi
8. Balloon cells and spindle cells may be found in conjunctival nevi
9. Blue nevi
   - Characteristic dendritic cells.
Junctional Nevus in a 7 year old boy

Courtesy of Dr. Frederick A. Jakobiec, 2014
Combined Nevi

- 40% of a series of 95 conjunctival nevi had a combined element (personal series)
- The combined component varied from a blue nevus to a deep penetrating nevus
- In most instances, the combined aspect was very small but rarely accounted for most of the nevus
- These lesions are benign
COMPOUND NEVUS OF SPITZ

Sub-epithelial Melanocytes and Associated Lesions - Scleral Dendritic

1. Blue nevus
2. Cellular blue nevus
3. Occulodermal melanocytosis

Blue Nevus
Oculodermal Melanocytes (Ota)

Clinical:
1. Ipsilateral pigmentation of periocular skin along with melanosis oculi
2. Periorbital skin may be brown, slate or bluish
3. Pigment deep to conjunctiva and doesn’t move with Q tip traction in contrast to benign epithelial melanosis
4. Most common in Blacks and Asians
5. Low risk of uveal or orbital melanoma

Acquired Melanosis of the Conjunctiva

1. Benign epithelial melanosis of conjunctiva
   - congenital
2. Primary acquired melanosis of conjunctiva
3. Secondary acquired melanosis of conjunctiva

PRIMARY ACQUIRED MELANOSIS

Definition accepted by World Health Organization (WHO)

1. Lesion is primary because not the result of racial, metabolic or local topical factors
2. Acquired – not congenital
3. Melanosis – due to melanin production

Primary Acquired Melanosis

Clinical
- Flat
- Brown (golden brown to chocolate)
- May involve cornea
- May involve any aspect of conjunctiva including tarsal conjunctiva, fornix and caruncle
- May be multiple
- Almost always unilateral.
- May extend across lid margin into epidermis.
- May “shrink”, progress or remain stable for prolonged periods.
- Occurs in middle-aged or elderly, usually white patients (rare in blacks).
PAM Histology

**PAM 1**
without atypia (overproduction of Melanin with hyperplasia)

Hyperplasia of benign melanocytes confined to basilar epithelium (not considered premalignant)

**PAM 2**
with atypia

Examine for epithelioid cells and pattern of growth

---

Normal Conjunctiva

Courtesy of Dr. Frederick A. Jakobiec. 2014

---

PAM without atypia – there is an increased number of melanocytes

Courtesy of Dr. Frederick A. Jakobiec. 2014

---

PAM with atypia – there is an increased number of basal melanocytes and some scattered higher level dendritic melanocytes

Courtesy of Dr. Frederick A. Jakobiec. 2014

---

Primary Acquired Melanosis with Moderate Atypia

PAM with moderate-to-severe atypia – there are large dendritic melanocytes

Courtesy of Dr. Frederick A. Jakobiec. 2014

---

Primary Acquired Melanosis with Severe Atypia

PAM with severe atypia – there are numerous large dendritic melanocytes

Courtesy of Dr. Frederick A. Jakobiec. 2014
**Malignant melanoma of the Conjunctiva**

1. Melanoma with PAM (75%)
2. Melanoma without PAM (25%)
   
   Note: 25% of all lesions have evidence of pre-existing nevus
3. Overall mortality – 25% of all types

**Malignant Melanoma of the Conjunctiva**

- **Risk Factors**
  - Predominantly caucasians
  - Older age (average age 52-53 years)
  - Pre-existing Primary Acquired Melanosis (PAM) give rise to 60% of conjunctival melanoma
  - Rarely associated with a pre-existing nevus
  - History of extensive sunlight exposure

**Malignant Melanoma of the Conjunctiva**

- **Symptoms and Clinical Features**
  - 5-10% of all ocular melanomas
  - Average age 52-53 years
  - Equal sex incidence
  - Most common complaint is a pigmented spot or nodule; irritation and pain less common
  - Location:
    - Bulbar conjunctiva (92%)
    - Temporal-quadrant (63%)
    - Touching limbus (61%)
  - Pigmented lesion in the palpebral, forniceal conjunctiva, plica semilunaris, and caruncula are prima facie melanoma

**Malignant Melanoma of the Conjunctiva**

- **Symptoms and Clinical Features**
  - Melanoma without PAM is solitary nodule
  - Early invasion in PAM may be associated with a plaque
  - Any pigmented lesion surrounded by numerous vessels should be biopsied
  - Rarely the lesion is non-pigmented and the multiple vessels are a clue
  - Multiple lesions common 33%
  - Local recurrence 26% at five years; 51% at 10 years
  - Mortality 38% at 10 years

---

Griewank KG et al. J Clin Cancer Res. 2013
Farber M. et al. JAAD. 1998
Malignant Melanoma of the Conjunctiva

• Histopathology
  – Most lesions exhibit radial growth extending beyond the invasive component.
  – Pattern most commonly pagetoid but lentiginous variants occur (lentigo maligna can extend into the epithelium)
  – Invasive component can be spindled, small cell, epithelioid or mixed.
  – Mitoses frequent; greater than 5 per 10 hpf associated with high risk of metastases.
  – Thickness > 2mm. High risk of metastasis.
  – Lymphatic invasion. High risk of metastases.
  – Tis. absence related to high risk of metastases.

Zembowicz, A. et al. Arch Pathol Lab Med. 2010

Clinical Pathologic Correlations of Mutations

• Location:
  – Caruncle – BRAF 66% ; NRAS 0% ; Wild Type 33%
• Pathology:
  – Pre-existing nevus – BRAF 65% ; NRAS 27% ; Wild Type 8%
• No other clinical pathologic correlations found, including relationship to mitoses, metastases, and disease free or overall survival.


Malignant Melanoma of the Conjunctiva

• Prognosis
  – Palpebral conjunctiva, fornices, plica, caruncula, and lid margins:
    • Higher mortality than episclera
    • Higher risk for local recurrence
    • Higher risk for distant metastasis
  – Thickness > 2 mm. associated with high risk of metastasis and death
  – Cell type:
    • Mixed type 3x higher mortality than spindle cells
    • Pure spindle cells excellent survival
  – Positive margins predict higher risk of recurrence
  – Lymphatic invasion: 4x higher mortality
  – De novo melanoma 35% mortality at 10 years
  – Melanoma in PAM 9% mortality at 10 years

Activating Mutations in Conjunctival Melanoma

- BRAF - 29% (V600E 21%)
- NRAS - 18%
- Wild Type - 53%
- c-Kit - 0% (15% showed non-activating mutations)

- PTEN (Chromosome 10) loss commonly found in association with BRAF and usually with NRAS – Activation of AKT pathway

Griewank KG et al. Clin Cancer Res. 2013

Treatment of Conjunctival Melanoma

- Melanoma with PAM easily confused with nevus. Any lesion that changes should be removed
- Any pigmented lesion extending onto the cornea should be excised
  - Primary: Wide local excision
    - Adjuvant Therapy: Brachytherapy, cryotherapy, mitomycin
  - Multiple lesions and/or multiple recurrences:
    - Mitomycin or brachytherapy primarily
  - Exenteration: Reserved for extensive wide-spread recurrences or invasion of sclera
- Sentinel Lymph Node Biopsy: (Preliminary Results)
  - Performed for tumors > 2mm. In thickness or with ulceration or mitoses >5 per 10 hpf

Griewank KG et al. Clin Cancer Res. 2013

Acknowledgments

Martin C. Mihm Jr., MD
Frederick A. Jakobiec, MD
Cynthia Magro, MD