Mucosal Melanoma

Naren Venkatesan, MD
Mentor: Amy Hessel, MD
The University of Texas Medical Branch (UTMB Health)
Department of Otolaryngology – Head & Neck Surgery
Grand Rounds Presentation
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Case Presentation

- MC is a 49 yo female presented to an outside ENT with complaints of hoarseness
- Patient underwent an MSDL demonstrating mucosal melanoma of right arytenoid and right base of tongue
- Interval History:
  - Increasing Hoarseness
  - No dysphagia or odynophagia
  - No SOB, hemoptysis, dyspnea, fevers, chills, or weight loss
  - No skin lesions on recent dermatological exam
  - No history of skin lesions excised
Case Presentation

- ROS: + anxiety
- Family Hx: Negative for cutaneous malignancies or head and neck cancers
- PMH: UC, Hay fever, Asthma, Migraines
- PSH: Tubal Ligation
- Social History:
  - Alcohol: 2 glasses of wine per week
  - Smoking: 9 pack years (quit 12 years prior)
  - No illicit drug use
Physical Exam:
  - Vitals: AF VSS
  - Gen: NAD
  - Skin: No visible lesions or prior excision scars
  - Ears, Nose/Nasal Mucosa, and Oral Cavity – no gross lesions and no pertinent findings
  - Neck: No cervical lymphadenopathy

  - Fiberoptic Laryngoscopy was performed
CT Neck with contrast – two foci of enhancement (1.5 cm) in the right base of tongue with no adenopathy noted

CT Thorax with contrast – No metastatic disease

CT Abdomen and Pelvis with contrast – No evidence of metastatic disease in the abdomen or pelvis

Outside PET/CT – Negative for metastasis
Case Presentation
Case Presentation

- Outside Pathology
  - Right Arytenoid Biopsy:
    - Ulcerated melanoma, involving submucosa and focally mucosa, present at tissue edges
  - Right Base of Tongue Biopsy:
    - Melanoma involving mucosa and submucosa, present at tissue edges
Mucosal Melanoma

Brief Background
Mucosal melanoma is a rare disease, accounting for less than 1% of all melanoma cases in the US

0.8 – 1.8 % of all melanomas and 6.3 – 8% of head and neck melanomas


Characteristics of Patients with Mucosal Melanoma

- Equal male and female preponderance
- Mean age of 60-69 years
- > 50% located in head and neck
- Sinonasal is most common site
Characteristics of Patients with Mucosal Melanoma

- Rare cancer with very poor prognosis
- Oral mucosal melanoma presents earlier than sinonasal mucosal melanoma
- Decreased nodal metastasis in comparison to cutaneous melanoma
- High rate of distant metastasis
60% typically in the nasal and paranasal sinus region
- Nasal septum
- Lateral Nasal wall
- Turbinates
- Nasal vestibule
- Of the sinuses, maxillary is most common at 6% then ethmoid, frontal, and sphenoid
Oral Mucosa is second most common site
- 70% in the upper alveolus and hard palate

Oropharyngeal and Laryngeal Mucosa
- Exceedingly Rare
- Only case reports

Presentations of Mucosal Melanoma

- Sinonasal mucosal melanoma
  - Epistaxis, Nasal Obstruction, Facial deformity, facial pain, proptosis/diplopia
  - Typically bulky or polypoid in appearance and more likely not pigmented

- Oral
  - More often flat and pigmented
  - Most often asymptomatic
Mucosal Melanoma Staging

- Ballantyne Staging System
  - Stage I – Limited to Localized Disease
  - Stage II – Presence of Nodal Involvement
  - Stage III – Presence of Distant Metastasis
Updated Staging of Local Disease

### TABLE 1.


<table>
<thead>
<tr>
<th>Staging group</th>
<th>Tumor</th>
<th>Node</th>
<th>Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td></td>
</tr>
<tr>
<td>IVA</td>
<td>T4a</td>
<td>N0</td>
<td></td>
</tr>
<tr>
<td>IVB</td>
<td>T3-T4a</td>
<td>N1</td>
<td></td>
</tr>
<tr>
<td>IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
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Epithelium/submucosa (mucosal disease)

Deep soft tissue, cartilage, bone, or overlying skin

Brain, dura, skull base, lower cranial nerves, masticator space, carotid artery, prevertebral space, mediastinal structures, cartilage, skeletal muscle, or bone

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Koivunen P et al. Accuracy of the current TNM Classification in Predicting Survival in Patients with sinonasal mucosal melanoma. Laryngoscope 2012; 122: 1734-1738
Treatment
Work-Up

- Metastatic disease should be evaluated for at onset – including CT Chest and PET/CT
- Unlike cutaneous melanoma, mucosal melanoma should be considered for multimodality therapy regardless of stage
  - Surgery
  - Melanoma Medical Oncology
  - Melanoma Radiation Therapy
Work-Up

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**Mucosal Melanoma**

**PRESENTATION**

- Biopsy confirms diagnosis of mucosal malignant melanoma

**WORKUP**

- H&P including complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- Verification of pathology using appropriate staining (HMB-45, S-100, Melan-A)
- CT and/or MRI to determine anatomic extent of disease, particularly for sinus disease
- Chest imaging as indicated
- Consider PET-CT scan to rule out metastatic disease

**TREATMENT**

- Sinus or nasal cavity mucosal melanoma
  - See Primary Treatment (MM-2)

- Oral cavity, oropharynx, larynx, or hypopharynx mucosal melanoma
  - See Primary Treatment (MM-3)

**Note:** All recommendations are category 2A unless otherwise specified. Clinical Trials: NCCN believes that all patients should be offered the opportunity to participate in a clinical trial if one is available and appropriate. For more information about NCCN Trials, visit www.NCCN.org/trials.
Treatment of Mucosal Melanoma

- Primary Site: Surgical Resection with clear margins is a minimum

- Treatment of the Neck
  - Sentinel Lymph Node Biopsy
  - Prophylactic Neck Dissection

- Role of Radiation Therapy

- Role of Chemotherapy
Initial presentation with neck metastasis

- 25% for oral mucosal melanoma
- 6% for sinonasal melanoma

Role of Sentinel Lymph Node Biopsy

- Not as efficacious as in cutaneous melanoma
  - Low reported rate of nodal metastasis
  - Delayed presentation of neck metastasis

Role of Sentinel Lymph Node Biopsy

- Sentinel Lymph Node Biopsy
  - Evaluated in limited studies demonstrating no clear benefit
  - Deemed not beneficial in preventing locoregional or distant metastasis
  - Still remains an area for future evaluation

Sinonasal Mucosal Melanoma

- Not advocated
- Typically not identified on initial presentation
- Recurrence is often either local or distant rather than regional
- Highest reported percent of patients with regional recurrence - ~ 25%

## Work-Up

### NCCN Guidelines Version 1.2012

#### Mucosal Melanoma

<table>
<thead>
<tr>
<th>PRIMARY TREATMENT</th>
<th>ADJUVANT TREATMENT</th>
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</thead>
<tbody>
<tr>
<td>Stage III</td>
<td>Strongly consider postoperative RT to primary site&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>T4a, N0</td>
<td>Postoperative RT to primary site&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sinus or nasal cavity mucosal melanoma</td>
<td>Follow-up&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>T3-T4a, N1</td>
<td>Postoperative RT to primary site and neck&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Clinical trial (preferred) or Primary RT&lt;sup&gt;b&lt;/sup&gt; or Systemic therapy&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Clinical trial (preferred) or Best supportive care or Primary RT&lt;sup&gt;b&lt;/sup&gt; or Systemic therapy&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
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<sup>a</sup>See *Principles of Surgery (Surg.-A)*

<sup>b</sup>See *Principles of Radiation Therapy (MM.-A)*

<sup>c</sup>See *Principles of Systemic Therapy for Advanced or Metastatic Melanoma* page ME-D from the NCCN Melanoma Guidelines.

*Note: All recommendations are category 2A unless otherwise indicated.*

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Role of Prophylactic Neck Dissection

- **Oral Mucosal Melanoma**
  - Debated but more encouraged
  - Greater relative frequency of neck involvement at initial presentation
  - Increased rate of regional relapse at nearly 70%

Work-Up

Mucosal Melanoma

**PRIMARY TREATMENT**

- Stage III
  - Wide surgical resection
  - Elective neck dissection
  - Strongly consider postoperative RT

**ADJUVANT TREATMENT**

- Stage IVA
  - Wide surgical resection
  - Neck dissection
  - Postoperative RT

**FOLLOW-UP**

- Stage IVB
  - Clinical trial (preferred)
  - Primary RT and/or Systemic therapy

- Stage IVC
  - Clinical trial (preferred)
  - Best supportive care
  - Primary RT or Systemic therapy

**Follow-up**

- Recurrent or Persistent Disease
  - See NCCN Melanoma Guidelines

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*See Principles of Surgery (SURG-A)*

*See Principles of Radiation Therapy (MM-A)*

*See Principles of Systemic Therapy for Advanced or Metastatic Melanoma page ME-D from the NCCN Melanoma Guidelines*

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Radiation Therapy
Primary Radiation Therapy

- Only small case series and case reports in literature
- Gaze et al – 8/13 patients with complete clinical response to XRT alone
- Remainder of studies advocate radiotherapy for inoperable tumors or recurrence

Greatly improved local control

- Temam et al (2005) – 69 patients:
  - Surgery alone (26%) vs Surgery + Post-op XRT (62%)

- Owens et al (2003) – 48 patients:
  - Surgery alone (55%) vs Surgery + Post-op XRT (83%)
Radiation Therapy

Mucosal Melanoma

PRINCIPLES OF RADIATION THERAPY

RT for Unresectable Locally Advanced Melanoma:
- 66-74 Gy
- Palliative RT dose and schedule may be considered

Postoperative RT:
- Primary site resection:
  - Parameningeal sites:
  - RT to primary site + 2-3 cm margins or to anatomic compartment
  - Oral cavity, oropharynx, and hypopharynx sites:
  - RT to primary site (+ 2-3 cm margins or anatomic zone) and elective treatment to neck
    (unless negative pathology findings of neck dissection)
  - Also strongly consider radiation to primary site for any locally recurrent disease after
    previous resection.

  - Neck/nodal basin dissection:
  - High-risk features:
  - >2 nodes
  - Single node >3 cm
  - Extracapsular nodal disease
  - Node resection (alone) with no further basin dissection
  - Recurrence in nodal basin after previous surgery.

  - Dose and fractionation:
  - Primary and neck (high-risk sites): 60-66 Gy (2.0 Gy/fraction) or 70 Gy for gross disease
  - Lower-risk, undissected, or uninvolved portions of neck: 50-60 Gy (2.0 Gy/fraction)

1 See Radiation Techniques (RAD-A) and (Discussion).

Note: All recommendations are category 2A unless otherwise stated. Clinical Trials: NCCN believes that the best treatment for any patient with cancer is in a clinical trial. The patient and physician are strongly encouraged to discuss participation in a clinical trial at the first possible opportunity.
Role of Systemic Therapy

- Uncertain and Unproven but with promise
  - Imatinib, Nilotinib, Masitinib, and other KIT inhibitors
  - Dacarbazine – current standard
  - Interferon – Alpha
  - Interleukin – 2

Role of Systemic Therapy

- **B-RAF**
  - Targeted therapies for this oncogene used for cutaneous melanoma
  - Data suggests decreased frequency of this mutation in mucosal melanoma

- **KIT**
  - Identified in nearly 15-30% of cases of MM
  - Can lead to nearly 1 further year of survival
Back to our case
Case Presentation

- Surgery – 12/14/12
  - Oropharynx – Trans-Oral Robotic Resection
  - Larynx – Right Arytenoid Mucosal excision from prior site of excisional biopsy
    - Procedure: Uncomplicated course
    - Discharged home
    - Post-operative course: Uneventful
Pathology

- Right Base of Tongue – Mucosal Malignant Melanoma
  - Melanoma 5.0 mm, ulcerated
  - Thickness 2.3 mm
  - Margins: Negative

- Right Base of Tongue – further Anterior Margin – Negative

- Right Arytenoid Resection – Squamous Mucosa
Case Presentation

- Genetic Testing
  - BRAF – no mutation detected
  - KIT – variant detected, possible germline polymorphisms
  - NRAS – no mutation detected
Case Presentation

- Post-Operative Radiation Course
  - IMRT with 6 MV photons selected for minimized field
  - 3000 cGy delivered over 5 fractions
  - Treatment from 1/18 – 1/31

- Patient to return for follow up next month with videotroscopy
Phenomenon of Satelittosis
- Seen in cutaneous melanoma but not described for mucosal melanoma

Multiple mucosal melanomas
- Two lesions may be in close proximity but typically in same site – reported in oral cavity and nasal cavity

Treatments from literature
- Laryngectomy with neck dissection and Radiation therapy

- Wenig BM. Laryngeal mucosal malignant melanoma. A clinicopathologic, immunohistochemical, and ultrastructural study of four patients and review of literature. Cancer 1995 Apr; 75(7):1568-1577