Overview

- History
- Brief Facts
- Typical Presentation
- Cytopathology
- Neuroendocrine Tumor
- Staging
- Treatment
History

- 1875 – Friedrich Merkel describes the Merkel cell in the skin of ducks and geese
- 1972 – Cyril Toker writes of the first case of Merkel Cell Carcinoma
Aliases

- Trabecular carcinoma of the skin
- Neuroendocrine cancer of the skin
- Small Cell carcinoma of the skin
BRIEF FACTS OF
MERKEL CELL CARCINOMA
Why worry about Merkel Cell Carcinoma?

- Age-adjusted Incidence in the US:
  - 0.15 per 100,000 in 1986
  - 0.44 per 100,000 in 2001

- US Incidence:
  - 0.23 per 100,000 among whites\(^1\)
  - 0.01 per 100,000 among African Americans\(^1\)
Why worry about Merkel Cell Carcinoma?

- Fatality Rates
  - Merkel Cell Carcinoma – 1 in 3
  - Melanoma – 1 in 6
  - Squamous Cell Carcinoma – 1 in 50
  - Basal Cell Carcinoma – < 1 in 10,000
Why worry about Merkel Cell Carcinoma?

- Most common site of primary MCC is the head and neck region – nearly 47%³
- In Head and Neck, most common sites are:
  - Perioral
  - Periocular
- Mucosal presentations are rare – 4.5%⁴
Who gets Merkel Cell Carcinoma?

- Presents in patients > 65 years of age
- Significant Male Predilection
  - Studies place the ratio from 1.5 – 2.5 : 1
- Risk Factors:
  - Fair Skin
  - Prolonged Sun Exposure
  - UVA therapy
  - Immunosuppression
Who gets Merkel Cell Carcinoma?

- Immunosuppressed patients have a significantly increased risk
  - HIV - 13.4-fold increase
  - Organ Transplant – 10-fold increase
  - Chronic Lymphocytic Leukemia
What are Merkel Cells?

- Type I Mechanoreceptors – provide the sense of fine touch and hair movement
- May operate independently or in conjunction with a tactile hair disc
- Typically located in the basal layer of the epidermis, at the dermal–epidermal junction
- Arise from neural crest cells which then form cells capable of Amine Precursor Uptake and Decarboxylation
Neural Crest Cells

- Odontoblasts
- Enterochromaffin
- Parafollicular thyroid cells
- Carotid body/Glomus cells
- Adrenal medulla
- **Merkel cells**
- Satellite glial cells
- Schwann cells
- **Melanocytes – Key differential of Merkel Cell Carcinoma**
- Iris pigment cells
TYPICAL PRESENTATION
HPI: A 70 yo male patient presents to the clinic with rapidly enlarging mass near the upper lip. He is a fair-skinned individual who lives on a farm. When asked about skin protection, he denies use of a hat or sunscreen. He notes that the mass has been increasing in size since first noted 2 months prior. It is not painful. It has not bled at any point.

PMH: None

PSH: Cholecystectomy

Social History: Smokes one pack per day x 30 yrs; No alcohol use
Typical Presentation

PE:

- Firm, red non-tender papule in the upper lip
- Measures 1-1.5 cm
- No ulceration noted
- No cervical lymphadenopathy palpable
- No other lesions are present
Typical Presentation
Presentation
CYTOPATHOLOGY/HISTOLOGY
Cytopathology – Skin
Figure. Hematoxylin-eosin staining and cytokeratin 20 immunostaining of a positive sentinel lymph node in Merkel cell carcinoma. A, Initial hematoxylin-eosin staining failed to identify micrometastatic Merkel cell carcinoma cells despite the presence of occult disease. B, Micrometastatic disease (arrows) was identified only after cytokeratin 20 immunostaining.
Cytopathology

- Predominantly single cells
- Round, vesicular nuclei; scant cytoplasm
- Scant to absent molding
- Numerous mitoses
- “Perinuclear button-like inclusions”
- Positive cytokeratin, neurofilament, and neuron-specific enolase
Cytopathology

- Electron Microscopy
In a series by Dr. Paul Nghiem of a 100 patients, initial biopsy results are as follows:

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<tr>
<th>Category</th>
<th>Percentage</th>
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Histologic Patterns

- Three main histologic patterns seen:
  - Intermediate type
    - most common type
    - ddx: small blue cell tumors/melanoma/lymphoma
  - Small cell type
    - ddx: small cell lung CA (SCLC)
  - Trabecular type
    - ddx: metastatic carcinoid

- Regardless of type, the prognosis remains the same
NEUROENDOCRINE ROLE
Role as Neuroendocrine Tumor

- Rarely secretes a hormone
- Case reports show an association with Adreno-Cortico Tropic Hormone (ACTH) or Anti-diuretic Hormone (ADH)
  - Postoperative hyponatremia in a patient with ACTH-producing Merkel cell carcinoma by Anzai S et al.\(^7\)
  - Paraneoplastic syndrome of inappropriate antidiuretic hormone mimicking limbic encephalitis by Blondin NA et al.\(^8\)
Role as Neuroendocrine Tumor

- Adreno-Cortico Tropic Hormone
  - Secreted by the anterior pituitary gland
  - Principal effects are increased production and release of cortisol
  - Acts on the adrenal cortex
  - Often secreted in paraneoplastic syndromes, especially Small Cell Lung Cancer
Role as Neuroendocrine Tumor

- Excess Adreno-corticotropic Hormone (ACTH), aka Cushing’s disease
  - Weight gain with central obesity and moon facies
  - Hirsutism
  - Purple Striae – thinning of skin
  - Polyuria
  - Hypertension
  - Hyperpigmentation
Role as Neuroendocrine Tumor

- **Anti-Diuretic Hormone**
  - Typically made in the posterior pituitary gland
  - Acts on the distal renal tubule and collecting duct in the nephron
  - Results in water retention without retaining solute
  - Often secreted in paraneoplastic syndromes, especially Small Cell Lung Cancer
Role as Neuroendocrine Tumor

- Excess Anti-diuretic Hormone (ADH)
  - Symptoms
    - Early findings: Headache + Nausea + Vomiting
    - Irritability
    - Confusion
    - Seizures
    - Coma
  - Signs/Findings
    - Hyponatremia – severe if <120
    - Concentrated Urine – urine osm >300
STAGING
# Staging

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</tr>
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<td>Any tumor size with nodal involvement, but no metastases</td>
</tr>
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Table 2. The 2002 AJCC staging categories for MCC$^6$
## Primary Tumor (T)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor (e.g., nodal/metastatic presentation without associated primary)</td>
</tr>
<tr>
<td>Tis</td>
<td>In situ primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Less than or equal to 2 cm maximum tumor dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Greater than 2 cm but not more than 5 cm maximum tumor dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Over 5 cm maximum tumor dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Primary tumor invades bone, muscle, fascia, or cartilage</td>
</tr>
<tr>
<td>Regional Lymph Nodes (N)</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td></td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>cN0</td>
<td>Nodes negative by clinical exam* (no pathologic node exam performed)</td>
</tr>
<tr>
<td>pN0</td>
<td>Nodes negative by pathologic exam</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in regional lymph node(s)</td>
</tr>
<tr>
<td>N1a</td>
<td>Micrometastasis**</td>
</tr>
<tr>
<td>N1b</td>
<td>Macrometastasis***</td>
</tr>
<tr>
<td>N2</td>
<td>In transit metastasis****</td>
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AJCC Staging Manual 2009

Differentiates between pathologic negative neck, clinically negative neck, and extracutaneous involvement.
Staging Updated

- AJCC Staging Manual 2009

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<th>M0</th>
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<tr>
<td>Stage IA</td>
<td>T1</td>
<td>pN0</td>
<td>M0</td>
</tr>
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<td>T1</td>
<td>cN0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2/T3</td>
<td>pN0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2/T3</td>
<td>cN0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>Any T</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Any T</td>
<td>N1b/N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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Differentiates between microscopic vs macroscopic/occult lymph node metastasis
Stage = Survival

- Disease stage was the only independent predictor of survival ($p = 0.001$)
  - Stage I, 81%
  - Stage II, 67%
  - Stage III, 52%
  - Stage IV, 11%
Survival
Most common stage on Initial Presentation

- Average size of a Head and Neck tumor is $1.59 \text{ cm}^{10}$
- So often at onset is stage I by size with a negative neck
- However, survival rates are not that high
Role of CT for Nodal Disease and Metastasis

- CT is poor for evaluating neck disease but good for distant mets – Gupta et al.\textsuperscript{15}

- **CT Scans for NODAL DISEASE**
  - Sensitivity (of scans for nodal disease) \(20\%\)
    - (4 of 20 pts with nodal disease called positive by scans)
  - Specificity (of scans for nodal disease) \(87\%\)
    - (13 of 15 pts without nodal disease called negative by scans)

- **CT Scans for DISTANT SPREAD**
  - Sensitivity (of scans for distant sites) \(100\%\)
    - (4 of 4 pts with distant disease called positive by scans)
  - Specificity (of scans for distant sites) \(48\%\)
    - (16 of 33 pts without distant disease called negative by scans)
What prevents better outcome?

- Pathologic Diagnosis is tough

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What prevents better outcome?

- Pathologic Diagnosis is tough
- Uncertainty regarding treatment of the clinically negative neck
  - Nearly 50% of patients in one series had microscopic evidence of disease in a clinically negative neck$^{11}$
What prevents better outcomes?

- Pathologic Diagnosis is tough
- Uncertainty regarding treatment of the clinically negative neck
- Early Spread / Late Presentation
  - 10-30% present with nodal involvement\textsuperscript{12,13,14}
  - 6% present with metastasis\textsuperscript{12,13,14}
TREATMENT
Treatment options

- Wide Local Excision
- Selective Lymph Node Biopsy
- Regional Lymph Node Dissection
- Radiation Therapy
- Chemotherapy
- Combined Modality
Treatment

- Surgical Treatment is Wide Local Excision
  - Exact margins – Uncertain – Preferred is $> 3$ cm

- Unlike other non-melanotic skin cancers, Merkel cell has a high propensity for nodal metastasis
  - Merkel Cell Carcinoma tends to have nearly 30% lymph node involvement – greatest among skin cancer (Melanoma only has 5%)\(^{15}\)
Selective/Sentinel Lymph Node Biopsy

Approximately 75% of patients present without evidence of nodal metastasis.

Schmalbach et al.\textsuperscript{16} performed SLNB in 10 patients with Stage I MCC showing 2 with nodal metastasis and literature review showed 12% false-negative rate when finding negative SLNB.

Current MCC practice guidelines\textsuperscript{17} by the National Comprehensive Cancer Network recommend SLNB for untreated, localized, Stage I disease.
Need for Cytokeratin 20 Stain

- Even tougher to ID Merkel cells in Lymph node
Radiation Therapy

- Remains controversial
- Currently, the National Comprehensive Cancer Network recommends radiation therapy for:
  - Primary Tumor Site
  - In-Transit Lymphatics
  - Draining Nodal Basins in patients only undergoing a WLE
Role of Post-Operative XRT

- Arguments for Surgery alone:
  - Allen et al.\textsuperscript{9} showed that the combination of wide local excision with negative margins and a selective neck dissection results in a 8% local recurrence rate.

- Arguments for XRT:
  - Medina-Franco et al. – Review of 11 case series (1024 patients) where local recurrence rate was decreased from 52.6 % to 10.5 % with use of XRT ($p = 0.00001$)\textsuperscript{14}
## Role of Post-Operative XRT

<table>
<thead>
<tr>
<th>Event-Free Survival rate</th>
<th>N</th>
<th>1 yr</th>
<th>5 yrs</th>
<th>HR</th>
</tr>
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<tbody>
<tr>
<td><strong>Local recurrence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery only</td>
<td>418</td>
<td>71%</td>
<td>61%</td>
<td>1.00</td>
</tr>
<tr>
<td>Surgery + RT</td>
<td>169</td>
<td>90%</td>
<td>88%</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Regional recurrence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>373</td>
<td>63%</td>
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<tr>
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<td>125</td>
<td>85%</td>
<td>77%</td>
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- Local Recurrence is decreased nearly 4 fold by post-op XRT\(^1^8\)
Role of Primary XRT

- Use 60 Gray to Primary Site

- Arguments for XRT:
  - Pape et al.$^{18}$ compared treatment of patients with Stage I MCC with primary radiation therapy versus wide local excision with radiation therapy with comparable rates of regional recurrence
  - Mortier et al.$^{19}$ treated a small patient group with primary XRT with 0% recurrence in 3 years
Summary of Role of XRT

Best Summary:

- XRT as primary treatment may be considered in elderly who cannot tolerate surgery or have disease in an area that does not allow wide local excision.

- In a clinically positive neck, XRT increases disease-free survival but not overall survival\(^20\).

- The role of XRT in a clinically negative neck is the toughest area to assess but such patients should likely undergo a selective lymph node biopsy and post-operative XRT.
Can Chemotherapy play a Role?

- Currently, not often employed for the following reasons:
  - Chemotherapy suppresses immune function
  - Decreased quality of life in elderly: fatigue, hair loss, nausea/vomiting
  - Associated neutropenic fever and sepsis
Suggested Treatment Protocol

1. Biopsy of Primary Lesion Shows MCC
   - Nodes Not Palpable
     - Sentinel Lymph Node Biopsy (SLNB) & excision with negative margins
       - SLNB Negative
         - Radiotherapy* to Primary Site ± Draining Lymph Node Basin
       - SLNB Positive
   - Nodes Palpable
     - Biopsy of Palpable Nodes
       - Biopsy shows MCC
         - CT Scan of Chest, Abdomen & Pelvis
       - Biopsy does not show MCC
         - Excision with negative margins + Radiotherapy* to Primary Site ± Draining Lymph Node Basin

2. CT Scan Negative
   - Excision with negative margins + Radiotherapy* to Primary Site & Draining Lymph Node Basin
3. CT Scan Positive
   - Further Evaluation and Palliative Surgery, Radiotherapy &/or Chemotherapy
HIGHLIGHTS
Clinical Presentation

- Summarized by the acronym “AEIOU”:
  - Asymptomatic or nontender
  - Expanding rapidly
  - Immune suppressed
  - Older than 65 years
  - Ultraviolet exposure or Fair skin
Pathology - Bottomline

- Peri-nuclear inclusions on H&E staining
- Cytokeratin (20) staining differentiates from small cell lung cancer, melanoma, and lymphoma
- Small Blue Cells are noted under H&E stain
  - First – Rule out Lymphoma and Rule in Carcinoma
  - Second – Rule out Basal Cell and Squamous Cell Carcinomas
  - Third – Rule out Metastatic neuroendocrine tumors – particularly small cell lung cancer
  - Finally – confirm Merkel cell with Cytokeratin 20 stain
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Bibliography

6. Miller et al., Cancer Epidemiol Biomarkers Prev, 1999, using SEER.
17. AJCC 2009 Cancer Staging Guidelines.