Merkel Cell Carcinoma: Diagnosis, Management and Controversies

Forum 542
Sunday, February 3, 2008, 3:00-5:00 PM
American Academy of Dermatology Annual Meeting
San Antonio, TX

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Kevan Lewis, MD, Mayo Clinic, Rochester, MN
Tara Miller, MD, UCSF, San Francisco, CA

DESCRIPTION
Merkel cell carcinoma (MCC) is a frequently lethal skin cancer with a higher mortality (33%) than melanoma (15%) and evidence of rapidly increasing incidence. Management of MCC is challenging, as therapy is different in nature than for other skin malignancies and is controversial within the literature. Proper care requires coordination between dermatologists, radiation and medical oncologists, and surgeons. In this session, speakers will present the most current data on the clinical presentation, staging, pathology, and management of MCC. Representative and challenging cases will be presented to highlight treatment options and relevant data.

LEARNING OBJECTIVES
Following this forum, the attendee will be able to:
1. Define the risk factors, incidence, clinical, pathologic, and prognostic characteristics of Merkel cell carcinoma.
2. Examine data on wide versus Mohs excision, sentinel lymph node biopsy, radiation and chemotherapy.
3. Utilize this information to guide management of representative cases.

OUTLINE OF SESSION
1. Merkel Cell Carcinoma Overview and Clinical Presentation - Paul Nghiem, MD, PhD
2. Pathologic Features - Klaus Busam, MD
3. Staging & Prognosis - Bianca Lemos, MD
4. Role of Radiation Therapy - Kevan Lewis, MD
5. Multidisciplinary Management - Christopher Bichakjian, MD
6. Challenging Cases & Discussion - Tara Miller, MD
Merkel Cell Carcinoma: Overview and Key Issues
(Revised 11/19/2007)

Prepared by: Paul Nghiem, MD, PhD, and Bianca Lemos, MD, University of Washington, Seattle, WA

OUTLINE OF HANDOUT

1. Impact of Merkel Cell Carcinoma (MCC)
2. Clinical presentation & pathology
3. Staging & Prognosis
4. Treatment
5. Summary
6. Annotated References

See www.merkelcell.org for more info or for a pdf of this handout.
PART 1: IMPACT OF MERKEL CELL CARCINOMA (MCC)

Fatality Rates:

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Fatality Rate</th>
</tr>
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<tbody>
<tr>
<td>MCC</td>
<td>1 in 3</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1 in 6</td>
</tr>
<tr>
<td>Sq Cell CA</td>
<td>1 in 50</td>
</tr>
<tr>
<td>Basal Cell CA</td>
<td>&lt;1 in 10,000</td>
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</tbody>
</table>

(Nghiem & Jaimes, 2207) (Agelli et al., JAAD, 2003)

Incidence has tripled since 1986:

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence Rate</th>
</tr>
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<tbody>
<tr>
<td>1986</td>
<td>0.15 per 100,000</td>
</tr>
<tr>
<td>2001</td>
<td>0.44 per 100,000</td>
</tr>
</tbody>
</table>

(Hodgson et al., J Surg Oncol, 2005)

Estimates of 600-1500 cases/year in US:

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases/Year</th>
</tr>
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<tbody>
<tr>
<td>1999</td>
<td>~600</td>
</tr>
<tr>
<td>1997</td>
<td>~950</td>
</tr>
<tr>
<td>2007</td>
<td>~1500</td>
</tr>
</tbody>
</table>

(Agelli et al, JAAD, 2003, SEER data)

Risk factors will translate to increasing incidence in future:

- Age > 65 yr
- Fair skin / prolonged sun exposure / PUVA therapy
- Profound immune suppression (HIV, solid organ transplant, CLL)
  - 13.4-fold increase among HIV+ pts
  (Engels et al., Lancet, 2002)
  - ~10 fold increase after solid organ transplantation
  (Miller et al., Cancer Epidemiol Biomarkers Prev, 1999, using SEER)

7.8% of 195 MCC pts had HIV, CLL, Organ Transplant (at DFCI/MGH/UW/SCCA)

Controversy & bias is abundant

- Lack of balanced information due to no "owner" of MCC
- "Narrow" literatures are field/expertise biased:
  Derm/Mohs, Surg, Med Oncol, Rad Tx
- Few MDs are familiar with this disease or its management

MCC management is often not optimal

Underused therapies:
- Sentinel lymph node biopsy
- Radiation therapy

Overused therapies:
- Over-aggressive surgery/amputation
- Scans (CT/MR/PET)
- Chemotherapy

These issues will be detailed below
**PART 2: CLINICAL PRESENTATION AND PATHOLOGY**

### Clinical Presentation

**Non-specific clinical presentation of MCC**

- Firm, red to purple non-tender papule/nodule
- Rapid growth within prior 1-3 months
- Usually on a sun-exposed location (but not always)
- May rarely ulcerate

At biopsy, most common presumed diagnosis was cyst/acneiform lesion

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Benign</td>
<td>57%</td>
</tr>
<tr>
<td>Cyst/acneiform lesion</td>
<td>36%</td>
</tr>
<tr>
<td>Lipoma</td>
<td>6%</td>
</tr>
<tr>
<td>Dermatofibroma</td>
<td>5%</td>
</tr>
<tr>
<td>Malignant</td>
<td>34%</td>
</tr>
<tr>
<td>Non-melanoma skin CA</td>
<td>14%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>9%</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>8%</td>
</tr>
<tr>
<td>&quot;Nodule/mass&quot;</td>
<td>6%</td>
</tr>
</tbody>
</table>

All others had 3 or fewer presumptive diagnoses: insect bite, abscess, chalazion, melanoma, neural tumor, appendage tumor. 72 of 138 cases stated a presumed diagnosis at biopsy. Total presumed diagnoses = 100

12 pts had 2 presumed dx, 5 pts had 3 presumed dx, 2 pt had 4 dx. Our unpublished data.

### Pathology

Merkel cells are mechanoreceptors (fine touch) within basal epidermis

Three histologic patterns (all with similar prognosis):

- **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

**Immunohistochemistry panel:**

<table>
<thead>
<tr>
<th></th>
<th>CK20*</th>
<th>CK7</th>
<th>LCA</th>
<th>S100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merkel cell carcinoma</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Melanoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

*87% of MCC vs. 4.6% of SCLC are CK20 positive (Bobos et al., Am J Dermatopathal, 2006)

**Pathology Summary:**

*"Peri-nuclear dot pattern of cytokeratin" is pathognomonic*

**Favorite boards question!**

Prior to CK20/CK7 (early 1990s) many cases were misdiagnosed as lymphoma, SCLC etc.

If immunohistochemistry is done properly, diagnosis is definitive.
Merkel Cell Carcinoma, Paul Nghiem, MD, PhD

PART 3: STAGING & PROGNOSIS

MCC Stages at Diagnosis (Allen/Coit/Busam/MSKCC, 2005):

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>% Pts</th>
<th>3 yr survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Localized disease, primary &lt; 2 cm</td>
<td>~30%</td>
<td>~90%</td>
</tr>
<tr>
<td>Stage II</td>
<td>Localized disease, primary ≥ 2 cm</td>
<td>~30%</td>
<td>~70%</td>
</tr>
<tr>
<td>Stage III</td>
<td>Nodal disease</td>
<td>~30%</td>
<td>~60%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Metastatic disease</td>
<td>~10%</td>
<td>&lt;20%</td>
</tr>
</tbody>
</table>

*Essentially all MCC-specific deaths occur by 3 yr after dx*

- A new staging system is currently being updated for 7th edition of the AJCC staging manual. The new system will be very similar to Allen, et al. (2005) system (above) but will differentiate microscopic (pathologic) vs macroscopic (clinical) method of node staging for stages I-III in the form of substages. This system will be adopted by the AJCC for the 7th Ed. of the staging manual, expected to be published in 2009.

Sentinel lymph node biopsy should be performed routinely in MCC

MCC has much higher LN involvement (~30%) than melanoma (~5%)

Among 122 patients without palpable lymph nodes, 39 (32%) had a positive SLNB
SLNB-positive patients benefited from adjuvant nodal therapy:
- 0% disease-free survival if no adjuvant tx (n=3)
- ~60% if adj XRT or Surg given (n=26); (p<0.01)

(Gupta et al., Arch Dermatol, 2006)

CT Scans: Data from Gupta, et al., Arch Dermatol, 2006. CT scans in 34 cases, PET scan in 1 case; Gold Standard for presence of disease was pathologic dx within 6 months of CT/PET Scan

- 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)

CT Scan Summary

CT Scans failed to detect nodal disease in all 7 pts with positive SLNB
(who also received scans)
No true disease detected by scans in SLNB-negative patients.
14 false positive nodal scans per one unique* true positive scan
(*identified by scan only and not by exam/history)
True negative scan for distant spread : 100% (16 of 16 pts)

Bottom line on CT Scans:
For detecting nodal disease: SLNB sensitivity >> CT Scan sensitivity
Scans not very useful if small primary or if SLNB is negative
Scans useful for SLNB-positive patients to rule out distant spread
PART 4: TREATMENT

Can MCC be treated like BCC? (no)
Simple excision with 0.5 cm margins:
100% recurrence in 38 pts (Meeuwissen, et al 1995)

Can MCC be treated like SCC/Melanoma? (no)
Wide local excision >2.5 cm margins:
49% regional recurrence/persistence
41 pts (O'Connor, et al 1997)

Is Mohs excision alone sufficient? (no)
Mohs excision +/- "safety margin" of 1 cm:
16% recurrence in 25 patients (Boyer et al., JAAD, 2002)
Mohs + XRT:
0% recurrence in 20 patients (Boyer et al., JAAD, 2002)

Can MCC be treated by XRT only? (maybe)
60 Gray (6000 cG) to primary site +/- node bed:
0% recurrence in 9 patients with 3 yr follow-up (Mortier et al., Arch Dermatol, 2003)

Effect of adding XRT to surgery:

<table>
<thead>
<tr>
<th></th>
<th>Event-Free Survival rate</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>1 yr</td>
<td>5 yrs</td>
<td>HR</td>
</tr>
<tr>
<td>Local recurrence</td>
<td></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>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgery + RT</td>
<td>169</td>
<td>90%</td>
<td>88%</td>
<td>0.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regional recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery only</td>
<td>373</td>
<td>63%</td>
<td>44%</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Surgery + RT</td>
<td>125</td>
<td>85%</td>
<td>77%</td>
<td>0.34</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

• HR=Hazard Ratio, the relative likelihood of experiencing a particular event
• Local recurrences at 5 years were diminished by 3.7-fold with the addition of XRT (40% to 13%)
  (Lewis et al., Arch Dermatol, 2006)

Is XRT indicated in most cases? YES!
XRT markedly decreases local recurrence and thus morbidity
XRT link to survival is less strong, but trend found in many studies.
XRT side effects are usually minimal:
  Mild-moderate fatigue, acute erythema, chronic radiation skin changes
  Risk of SCCs in those with life expectancy > 20 years
  Nead/Neck: ulcers, pain (acute), dry mouth/taste changes (chronic)

XRT as monotherapy
Some patients may have inoperable disease.
XRT monotherapy effective at controlling/curing extensive local disease
  (Multiple examples in our series and in the literature: Mortier et al., Arch Dermatol, 2003)
Adjuvant nodal therapy benefit depends on SLNB status

Among **SLNB-positive** patients:
- Improved disease-free survival (p<0.01)
  - Adjuvant XRT: 0% (n=3)
  - + Adjuvant XRT: 60% (n=26)

Among **SLNB-negative** patients:
- Non-significant trend for improved disease-free survival
  - Adjuvant XRT: 70% (n=19)
  - + Adjuvant XRT: 90% (n=24)

(Gupta et al., *Arch Dermatol*, 2006)

**Adjuvant nodal therapy: XRT or surgery?**

We typically use nodal XRT rather than surgery
(We believe side effects are less and efficacy is better)

Frequency of lymphedema after adjuvant nodal XRT or Surg:
- inguinal > axillary > head/neck

**Chemotherapy**

Most commonly used agents: Carboplatin + Etoposide (VP-16)
Useful in palliative setting for symptomatic disease:
- Most patients will have a response

6 reasons we do not recommend **adjuvant chemotherapy** (Garneski & Nghiem):
- Mortality: 4-7% deaths due to adjuvant chemo in MCC
- Morbidity: neutropenia (60% of pts) fever and sepsis (40%)
  (Poulsen et al., *Int J Radiat Oncol Biol Phys*, 2001)
- Decreased quality of life: fatigue, hair loss, nausea/vomiting
- MCC that recurs after chemo is less responsive to later palliative chemo
- Chemo suppresses immune function (important in fight against MCC)
- Trend toward decreased survival among patients with nodal disease:

<table>
<thead>
<tr>
<th>Node Positive pts tx with</th>
<th>MCC-specific survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adjuvant Chemo (n=53)</td>
<td>60%</td>
</tr>
<tr>
<td>Adjuvant Chemo (n=23)</td>
<td>40%</td>
</tr>
</tbody>
</table>

(Allen et al., *J Clin Oncol*, 2005; p=0.08, not a randomized trial, but certainly does not suggest a survival benefit!)
Treatment bottom line:
Current management of Merkel cell carcinoma tends to
Underuse:
Sentinel lymph node biopsy
Radiation therapy
Overuse:
Over-aggressive surgery/amputation
Scans (CT/MR/PET)
Chemotherapy

*Schematic of our recommended management:

* Recommended Radiation Therapy dose (NCCN Guidelines for MCC, 2006)
  45-50 Gy for: Primary site with negative excision margins
  Node bed with no palpable disease
  55-60 Gy for: Primary site with positive excision margins
  Node bed with palpable disease
  (XRT given in 2 Gy fractions, 5 times/week over 4-6 weeks)
PART 5: SUMMARY

- MCC incidence is rising and it has a higher mortality than melanoma.
- SLN bx, surgery and radiation are indicated in almost all cases.
- CT Scans have poor sensitivity for nodal disease (20%) and poor specificity for distant disease (48%).
- Over-aggressive surgery and adjuvant chemotherapy have high morbidity and no proven benefits.
- The [www.merkelcell.org](http://www.merkelcell.org) website is a practical reference for patients & MDs in determining therapy and prognosis.
  (Easy to find via Google search of *Merkel cell carcinoma*).

PART 6: ANNOTATED REFERENCES

(Most can be downloaded via [www.merkelcell.org](http://www.merkelcell.org))

- **Largest study (1034 pts) of survival after MCC diagnosis via SEER data. Essentially all deaths due to MCC occur within three years of dx. No data on treatments included.**

- **Study of 251 patients from Memorial Sloan-Kettering Cancer Center’s MCC database, between 1970-2002. Conclusions: 1) Pathologic nodal staging identifies a group of patients with excellent long-term survival. 2) After margin-negative excision and pathologic nodal staging, local and nodal recurrence rates are low. 3) Adjuvant chemo for Stage III patients showed a trend (p=0.08) to decreased survival compared with Stage II patients that did not receive chemo.**

- **A comprehensive overview of the surgical approach to primary MCC and the use of adjuvant XRT and chemotherapy. Treatment guidelines based on multidisciplinary experience and evidence in the literature are provided.**

- **Review and discussion of literature on adjuvant chemotherapy and radiation in MCC showing a reduction in recurrence with radiation therapy but no survival benefit with chemotherapy.**

- **A website dedicated to providing easily understood information on MCC causes, prognosis and therapy. 20 page color pdf can be downloaded from the site.**

- **Evaluation of 122 MCC patients (61 from the Dana-Farber and 92 from the literature).** Findings: 32% of patients with clinically local-only disease clinically were found to have microscopic nodal disease by SLNB. Three-year recurrence rate was 3 times higher in this group (+SLNB vs - SLNB). **Relapse free survival was improved with the use of adjuvant XRT in patients with a positive SLNB. CT scans had a low sensitivity and poor specificity for detecting nodal disease that was not readily clinically apparent.**


- **Meta-analysis demonstrating reductions in local and regional MCC recurrence in patients treated with surgery plus XRT as compared to those treated with surgery alone.**


- **Retrospective analysis of SEER (1,487 patients) found improved survival in patients treated with adjuvant radiation therapy, particularly in larger tumors (>1 cm).**


- **French study of stage I MCC that found no difference in overall survival in treatment with radiation therapy alone (9 patients) compared with surgery and radiation therapy (17 patients).**


- **Consensus recommendations for MCC management from 20 different cancer centers in the US.**


- **Comprehensive chapter on MCC in a multiauthored textbook of dermatology.**