Merkel Cell Carcinoma of the Extremity

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Patient Presentation

80 year old man: noted a new skin lesion on his right forearm

- It was removed by his dermatologist without pathologic analysis.
- The lesion returned within 1 month, growing to 1-2cm in size.
- Biopsy showed Merkel cell carcinoma.
Physical Exam

- Physical exam: Right dorsal forearm has 3x3 cm round erythematous papule, bleeding with bandage removal, on a background of diffuse erythema & induration ~16cm proximal to distal and 5-7cm medial to lateral, extending to the ventral surface of the forearm.
Workup

- Consider MRI of the primary site to assess for deep invasion
- PET/CT for regional and distant staging
- Biopsy of primary and sentinel node biopsy
Imaging

• PET/CT showed FDG-avid disease in the right forearm and right axilla.

• Note: diffuse lymphadenopathy elsewhere from advanced Mantle Zone lymphoma
Pathology

• Right axillary LN biopsy/ excision in which multiple matted nodes are removed:
  – Metastatic Merkel cell carcinoma with ECE, largest focus 21mm.

• Punch biopsies around the lesion in the area of erythema & induration:
  – All consistent with Merkel cell carcinoma.
General Principals

Merkel cell is a primary neuroendocrine malignancy of the skin, which is typically rapidly progressive with marginal, regional, and distant recurrence.
General Principals: Surgery

Primary management consists of wide local excision (1-2cm margin) and sentinel node biopsy ± adjuvant radiation

- Best in cN0 patients
- Relative indications for adjuvant primary irradiation: LVSI, immune suppression, positive margin
- If cN+: lymph node dissection or FNA bx + RT
- Relative indications for adjuvant nodal irradiation: multiple positive nodes, ECE, SLNBx +, high risk of false SLNBx (H&N regions have multiple basins or aberrant drainage, risk of false neg up to 20% [Tai 2013, Ridge 2007])
  - No RT after full node dissection without adverse features
- Observation after complete resection for <1cm and N0
General Principals: Adjuvant RT

Evidence for adjuvant radiation

• Large population databases:
  – NCDB: Bhatia JNCI 2016, Vargo 2016 JNCI

• Meta-analysis:
  – Pooled 1254 patients from non-randomized studies: Lewis Arch Derm 2006
General Principals: Definitive RT

- Definitive radiation can be used for unresectable disease
  - Doses > 50Gy indicated, consider 60-66Gy
  - Margins 3-4cm around the primary to account for lymphovascular spread and in-transit metastases
  - Treat primary and lymph nodes in continuous field if possible (defined as less than 20cm by TROG 9607)
# Dosing Summary

<table>
<thead>
<tr>
<th>Primary</th>
<th>Regional Nodes</th>
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<tr>
<td><strong>R0</strong></td>
<td>50-56Gy/25-28fx SLN Bx negative</td>
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<tr>
<td><strong>R1</strong></td>
<td>56-60Gy/28-30fx cN+, no dissection</td>
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<td><strong>R2 or definitive</strong></td>
<td>60-66Gy/30-33fx Microscopic pN+</td>
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<td>ECE</td>
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Definitive Therapy

• Wide margins around the tumor bed are recommended, 3-4cm if possible, to account for in-transit metastases and lymphovascular spread
Our Patient

• Definitive primary radiation
• Adjuvant axillary radiation indicated for multiple nodes with ECE
Radiation Plan

• Setup: supine, arm slightly akimbo, stabilized in a cast, wire induration, BB sites of biopsy, wire scar (if present), margin ≥4cm around induration, 0.5cm superflab bolus

• 50Gy/25fx to arm and axilla, 6MV AP/PA
  – Arm (64Gy): 14Gy/7fx boost, 12MeV enface
  – Axilla (60Gy): 10Gy/5fx boost, 6MV AP/PA
Our Patient

1 week post-RT:
• Radiation resolved pain at the primary site
• Expected skin desquamation
• New area of erythema at the distal field margin (wrist) at 1 month after treatment: *treatment related versus marginal failure?*
Our Patient

4 weeks post-RT:
• Worsening erythema and developed discrete nodule
• Biopsy proven MCC
Radiation Plan 2

- 30Gy/5fx to right wrist
Our Patient

4 months after initial radiation course:

• Increasing pain in the right axilla, imaging showed increased right axillary and supraclavicular adenopathy
Radiation Plan 3

- 30Gy/10fx to right axilla/ supraclav regions
Systemic Therapy

• Currently reserved for the metastatic setting with checkpoint immunotherapy showing promise
  – Avelumab is approved for patients with metastatic MCC irrespective of prior therapy based on the results of the JAVELIN study (Kaufman J Immunother Cancer, 2018)
  – Pembrolizumab and Nivolumab also show antitumor activity in metastatic disease

• Adjuvant and neoadjuvant immunotherapy with checkpoint inhibitors is currently being studied
  – ADMEC-O (NCT02196961) is studying adjuvant Nivolumab (previously had Ipilimumab arm, now closed) in completely resected MCC
  – ADAM (NCT03271372) is studying adjuvant Avelumab for patients with nodal disease from MCC after surgery +/- RT
  – CheckMate 358 looked at neoadjuvant Nivolumab, preliminary results at ASCO 2018 showed major pathologic response in 65% of patients
Conclusions

• This case illustrates the **high risk of marginal and regional failures** in Merkel cell carcinoma.

• Adjuvant or definitive radiation is an important tool in the management of MCC.

• Immunotherapy (avelumab, pembrolizumab) are emerging systemic therapies.
Another Case

• See experts weigh in on another case featured in “The Gray Zone,”
  – Int J Radiation Oncol Biol Phys, Vol. 100, No. 1, pp. 12e13, 2018
References

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• Checkmate 358 https://clinicaltrials.gov/ct2/show/NCT02488759

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