

Summary of 2011 MMIG Meeting
(Merkel cell carcinoma Multi-center Interest Group)

Friday February 4th, 2011
American Academy of Dermatology Annual Meeting
New Orleans, LA

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Speakers/Topics (detailed in following pages):

- 1) **Antibodies, CD8 T cells, and Prognosis in MCC.**
Paul Nghiem, U Washington, Seattle
- 2) **Immune Evasion Mechanisms in HPV & MCC.**
Rachael Clark, Brigham Women's Hospital/Harvard, Boston
- 3) **MCC Pathology Interesting Case & Update.**
Melissa Pulitzer, Memorial Sloan Kettering Cancer Center, New York
- 4) **Non-MCPyV polyomavirus infection in the skin & clinical associations.**
Richard Wang, U Texas Southwestern, Dallas
- 5) **A small lacrimal MCC: When is adjuvant radiation not indicated?**
Sherrif Ibrahim, U Rochester, NY

- 1) **Antibodies, CD8 T cells, and Prognosis in MCC.**
Paul Nghiem, U Washington, Seattle

MCC is associated with Merkel cell polyomavirus in ~80% of cases. T antigen oncoproteins are persistently expressed in MCC tumors. Antibodies against these oncoproteins are often detected in MCC patients (~41%) as compared to control subjects (<1%) (Paulson, 2010 Cancer Research). These T-antigen antibodies are dynamic, often track with MCC tumor burden, and are not protective. This test has already proven to be clinically useful in detecting disease recurrences before they are clinically apparent in several cases.

Dr. Nghiem described how CD8-T-cell infiltration within the MCC tumor is an important determinant in MCC patient survival. He noted that there were two types of CD8 infiltration, peritumoral (that appeared stalled at the tumor edges) and intratumoral infiltration. Of these two types, only intratumoral CD8 cell infiltration within the MCC tumor was associated with improved survival for MCC patients. Patients with robust intratumoral CD8 infiltration had 100% MCC-specific survival regardless of whether they presented with local, nodal or distant metastatic MCC.

References:

[Antibodies to Merkel cell polyomavirus T antigen oncoproteins reflect tumor burden in merkel cell carcinoma patients.](#) Paulson KG et al. Cancer Res. 2010 Nov 1;70(21):8388-97. PMID: 20959478

[Transcriptome-Wide Studies of Merkel Cell Carcinoma and Validation of Intratumoral CD8+ Lymphocyte Invasion as an Independent Predictor of Survival.](#) Paulson KG et al. J Clin Oncol. 2011 Mar 21. [Epub ahead of print], PMID: 21422430

PDFs of these articles can be downloaded from: <http://pnlab.org/clinical/MerkelCellCarcinoma.php>

2) Immune Evasion Mechanisms in HPV & MCC.

Rachael Clark, Brigham Women's Hospital/Harvard, Boston

Why can CD8 T-cells penetrate some tumors but not others?

Dr. Clark's study (Trimble 2010) of HPV-16 associated high-grade cervical dysplasia showed that there were two types of CD8 T cell infiltration: intraepithelial CD8 T-cell infiltration or CD8 T cells restricted to mucosal stroma. CD8 T cell recruitment to the dysplastic epithelium was associated with regression of the dysplastic lesion, while lesions without CD8 T-cell infiltration did not regress over time. **This finding is clearly highly analogous to the CD8 / MCC relationship discussed above.** A potential mechanism of this finding was that dysplastic epithelium that contained CD8-T cell infiltrates had increased expression of "MAdCAM-1" (mucosal addressin cell adhesion molecule-1; a molecule that mediates homing of T cells in mucosal sites). Upon comparing multiple high power fields, CD8 infiltration and MAdCAM-1 expression correlated very strongly to one another. Thus, variable expression of vascular adhesion molecules appears to play a role in immune evasion in several cancers and this should be investigated in MCC.

T-cells infiltrating MCC are functionally deficient

Dr. Clark noted several immune evasion mechanisms that are at play in MCC. These include: 1) defective homing (decreased cutaneous lymphocyte antigen, CLA), 2) increased CD25+ FoxP3 T-regulatory cells and 3) defective T-cell activation (decreased CD25 and CD69 expression in T-cells isolated from MCC as compared to those isolated from normal skin, suggesting suppression of T-cell activation).

T cells that infiltrate MCC tumors are suppressed but can be reactivated

Dr. Clark noted that addition of cytokines (IL2 and IL15) to the MCC tumor cultures likely result in proliferation of antigen-specific (MCC specific) T cells as noted by expression of CD137 (antigen-specific T cell activation marker) on these T cells and selective loss of viable tumor cells following co-culture. MCC tumors transplanted into immunodeficient mice failed to grow, unless tumor associated T cells were depleted using Ontak (denileukin diftitox – kills IL2-receptor positive cells). This finding suggests that T cells within the transplanted tumor were suppressing tumor growth. T- cells derived from such xenografts were similarly cultured/expanded using IL2 and IL15. Analysis of these expanded T cells showed that these cells produced IFN- γ upon exposure to MCC tumor suggesting that these T cells were likely MCC-specific.

These data suggest a possible role for intralesional administration of T-cell activating agents for MCC therapy. Future directions include studies of exhaustion (PD1 pathway) and generation of peptide-MHC tetramers that would allow staining and tracking of MCPyV specific T cells.

Reference:

[Human squamous cell carcinomas evade the immune response by down-regulation of vascular E-selectin and recruitment of regulatory T cells.](#) Clark RA et al. J Exp Med. 2008 Sep 29;205(10):2221-34. PMID: 18794336

[Human papillomavirus 16-associated cervical intraepithelial neoplasia in humans excludes CD8 T cells from dysplastic epithelium.](#) Trimble CL, et al. J Immunol. 2010 Dec 1;185(11):7107-14. PMID: 21037100

3) MCC Pathology Interesting Case & Update.

Melissa Pulitzer, Memorial Sloan Kettering Cancer Center, New York

Dr. Pulitzer described a case in which squamous cell carcinoma arose in conjunction with Merkel cell carcinoma of skin. She showed data that MCC tumors arising in combination with squamous cell carcinoma are likely to be MCPyV negative. She also described histologic differences between MCPyV-positive and negative MCC tumors (MCPyV negative tumors tend to have less round nuclei and greater cytoplasmic area than MCPyV positive tumors). Dr. Pulitzer also reviewed data that lymphovascular invasion is an important pathologic parameter for MCC. A recent study by Fields et al also suggest that presence of lymphovascular invasion (LVI) is strongly associated with MCC recurrence and poor prognosis. (This point has clinical significance in that pathology reports of MCC commonly do not comment on LVI and a quick phone call to the pathologist can remedy this in an addendum.)

Reference:

[Merkel cell polyomavirus expression in Merkel cell carcinomas and its absence in combined tumors and pulmonary neuroendocrine carcinomas.](#) Busam KJ et al. Am J Surg Pathol. 2009 Sep;33(9):1378-85. PMID: 19609205

[Association of Merkel cell polyomavirus infection with morphologic differences in Merkel cell carcinoma.](#) Kuwamoto S et al. Hum Pathol. 2011 May;42(5):632-40. Epub 2011 Jan 31. PMID: 21277612

[Vascular invasion is an early event in pathogenesis of Merkel cell carcinoma.](#) Kukko HM et al. Mod Pathol. 2010 Aug;23(8):1151-6. Epub 2010 May 14. PMID: 20473275

[Recurrence and Survival in Patients Undergoing Sentinel Lymph Node Biopsy for Merkel Cell Carcinoma: Analysis of 153 Patients from a Single Institution.](#) Fields RC et al. Ann Surg Oncol. 2011 Mar 24.

4) Non-MCPyV polyomavirus infection in the skin & clinical associations.

Dr. Richard Wang, U Texas Southwestern, Dallas

A new polyomavirus named Trichodysplasia spinulosa associated virus (TSPyV or TSV) was discovered in 2010. Dr. Wang described a Trichodysplasia spinulosa case. Histologic features of

Trichodysplasia spinulosa include distorted anagen follicles with absence of hair papillae, abnormal proliferation of inner root sheath cells, and abnormally large “trichohyaline” granules and gray-blue cytoplasmic material. There are now 11 cases of Trichodysplasia spinulosa, all of which have been found to have TSPyV sequences present (Feltkamp MC, unpublished)

Reference:

[Discovery of a new human polyomavirus associated with trichodysplasia spinulosa in an immunocompromized patient.](#) Van der Meijden E, et al. PLoS Pathog. 2010 Jul 29;6(7):e1001024. PMID: 20686659

[Viral-associated trichodysplasia spinulosa: a case with electron microscopic and molecular detection of the trichodysplasia spinulosa-associated human polyomavirus.](#) Matthews MR, Wang RC, et al. J Cutan Pathol. 2011 May;38(5):420-31. PMID: 21251037

5) A small lacrimal MCC: When is adjuvant radiation not indicated?

Dr. Sherrif Ibrahim, U Rochester, NY

Dr. Ibrahim discussed a challenging case of a small MCC in the lacrimal gland in a 52-year-old woman (currently there are no reported cases of MCC arising in the lacrimal gland). SLNB is not established for lacrimal gland tumors and in part due to this, no lymphatic mapping was carried out for this patient. The patient refused any further treatment and has been disease free for seven months.

Dr. Ibrahim discussed various treatment options for eyelid MCCs (surgery with/without radiation, radiation of primary and node bed, etc.), and their drawbacks. Dr. Ibrahim described various situations wherein radiation therapy may not necessarily be indicated. These include small tumors, pathologically node negative disease, no concerning histologic features (such as lymphovascular invasion), wide excision with negative margins, poor patient performance, etc. Location of the MCC tumor and high risk of complications should be taken into consideration while considering radiation therapy.

Discussion of this case was extremely lively. Most audience members felt that the patient had insisted on a risky course in not opting for wide excision or radiation.

In attendance at the New Orleans 2011 MMIG meeting:

Murad Alam (Northwestern, Chicago, IL)
 Yevgeniy Balagula (MSKCC, NY)
 Dan Berg (UW, Seattle, WA)
 Jeremy Bordeaux (Case Western Reserve University)
 Jerry Brewer (Mayo Clinic, Rochester, MN)
 John Carucci (NYU, NY, NY)
 Rachael Clark (BWH, Boston, MA)
 Clara Curiel (Arizona Cancer Center, Tucson, AZ)
 Harley Haynes (BWH, Boston, MA)
 Sherrif Ibrahim (U Rochester, NY)
 Natalia Jaimes (Colombia, South America)
 Bianca Lemos (Emory University, Atlanta, GA)
 Stuart Lessin (FCCC, Philadelphia, PA)
 Juan Carlos Martinez (Mayo Clinic, Jacksonville, FL)
 Natalia Mendoza (Colombia & NY)
 Brent Moody (Skin Cancer & Surgery Center, Nashville, TN)
 Paul Nghiem (UW & Fred Hutchinson CRC, Seattle, WA)
 Clark Otley (Mayo Clinic, Rochester, MN)
 Cliff Perlis (FCCC, Philadelphia, PA)
 Melissa Pulitzer (MSKCC, NY)
 Henry Randle (Mayo Clinic, Jacksonville, FL)
 Faramarz Samir (TJU/PMA, Philadelphia, PA)
 Arthur Sober (MGH, MA)
 Tom Stasko (Vanderbilt, Nashville, TN)
 John Strasswimmer (Palm Beach, FL)
 Linda Wang (DF/BWCC, Boston, MA)
 Richard Wang (UTSW, Dallas, TX)
 Matt Zook (FCCC, Philadelphia, PA)

Goals of the Merkel cell carcinoma Multi-center Interest Group (MMIG)

- Promote communication and collaborative studies on MCC
- Enhance access to patient data and specimens
- Expand evidence-based care for MCC

The homepage for MMIG contains photos, meeting summaries and more at:
<http://merkelcell.org/MMIG.html>

MMIG is funded in part by a grant from the Jerry Wachter Fund of the American Cancer Society (www.jw.org).

Please note that in some cases these summaries reflect unpublished data and are provided to help MMIG members manage their patients and give an overview of what is being done at different centers for care and research.