

Summary of 7th Annual MMIG Meeting (2012)

(Merkel cell carcinoma Multi-center Interest Group)

Friday March 16th, 2012
American Academy of Dermatology Annual Meeting
San Diego, CA
Prepared by Drs. Paul Nghiem & Jayasri Iyer

Announcements:

- 1) If anyone is interested in presenting at next year's MMIG meeting in Miami Beach, (Friday March 1, 2013) please send Paul an email with proposed topic that is relevant to MCC patient care or translational research.
- 2) Preliminary data from Clifford Perlis at Fox Chase: Absolute lymphocyte count measured within one week of MCC surgery correlates with prognosis (while controlling for known factors associated with prognosis). If any centers have access to these data, Cliff's team would be happy to explore collaboration.
- 3) CT vs PET: Stay tuned next year for updates from Linda Wang, but this area remains controversial. We recently had an impressive false negative on PET (liver disease only visible on diagnostic CT). We also had a stunning false negative on CT (>20 bony mets only visible on PET and not CT).

Speakers/Topics (detailed in following pages):

- 1) **Update on the development and clinical validation of a serologic assay for tracking MCC disease burden**
Paul Nghiem, U Washington, Seattle
- 2) **Characterizing antigen-specific T cells in MCC & early forays into targeted immune therapy**
Jayasri Iyer, U Washington, Seattle
- 3) **The role of genetic analysis by comparative genomic hybridization of distinct MCC tumors from a single patient**
Siegrid Yu / Iris Ahronowitz (U California San Francisco)
- 4) **Dermoscopic features of Merkel cell carcinoma**
Chris Bichakjian / Marcus Frohm (U Michigan)
- 5) **Clinically relevant insights from a cohort of a 218 MCC patients from Northern California**
Maryam Asgari (Kaiser Permanente Northern California)

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 (~47%) as compared to control subjects (<1%) (Paulson 2010). These T-antigen antibodies are dynamic, often track with MCC tumor burden, and are not protective. To determine the T antigen seroreactivity in a newly diagnosed MCC patient, it is important to obtain the patient's serum sample near the time of diagnosis (preferably within 2 months of MCC diagnosis) as a positive serotiter rapidly falls to the baseline (within ~ 2 - 14 months) in the absence of any tumor (i.e following definitive treatment). This test has proven to be clinically useful in detecting disease recurrences before they are clinically apparent in several cases and appears to be very sensitive and specific for MCC. This test can be carried out at the University of Washington free of cost if a patient enrolls in MCC research (<http://www.merkelcell.org/help/participate.php>). We hope it will be a clinically available test by late 2012.

Reference:

[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
A PDF of this article can be downloaded from: <http://pnlab.org/clinical/MerkelCellCarcinoma.php>.

2) **Characterizing antigen-specific T cells in MCC & early forays into targeted immune therapy**

Jayasri Iyer, U Washington, Seattle

Dr. Iyer's talk focused on the T-cell immune response against MCPyV in MCC. Although a high intratumoral CD8-T-cell infiltration pattern within the MCC tumor is associated with 100% disease-specific survival, >80% MCC patients do not have significant CD8 infiltration. MCCs often evade the immune system by downregulating their MHC-I, however in many cases this phenomenon is reversible using intralesional interferon beta injection or XRT. Dr. Iyer briefly described the process by which 26 novel MCPyV epitopes were discovered (Iyer, Afanasiev et al, Clinical Cancer Research 2011), and how an HLA*A24 restricted MCPyV-specific tetramer was created. This tetramer allowed detection of MCPyV-specific T cells in HLA*A24 MCC patients (present in 5 of 8 MCC patients who were HLA*A24 positive). She further described a case in which several recent laboratory discoveries were translated into the early discovery and treatment of a low risk (stage IA) MCC patient who developed metastatic pancreatic MCC. T cells obtained from leukapheresis of this patient, were stimulated in the presence of the appropriate MCPyV peptide and autologous dendritic cells, cultured, and then enriched using HLAA*24 tetramer sorting and then further expanded in the presence of IL21 and IL2 to a final infusion product of 23 billion cells. The patient received three separate infusions (separated over several months). Since the patient's tumor had minimal HLA-I expression on his MCC tumors, in order to up-regulate MHC-I on his tumor (required for the tumor to be "visible" to T cells), prior to his first infusion the patient received IFN beta intralesional injection and prior to his second infusion he received 8 Gy RT treatment. The patient had complete resolution of one MCC lesion and significant shrinkage of other lesions. This case represents the first in human, T cell

therapy targeting a viral oncoprotein in a solid malignancy and presents an exciting new direction for treating MCC patients.

References:

[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

[Merkel cell polyomavirus-specific CD8+ and CD4+ T-cell responses identified in Merkel cell carcinomas and blood](#). Iyer JG, Afanasiev OK, et al. Clin Cancer Res. 2011 Nov 1;17(21):6671-80. Epub 2011 Sep 9. PMID: 21908576

3) **The role of genetic analysis by comparative genomic hybridization of distinct MCC tumors from a single patient**

Siegrid Yu/Iris Ahronowitz (U California San Francisco)

Iris Ahronowitz described a case of a 69-year-old female with a right cheek MCC s/p negative sentinel node and wide local excision. The patient developed another MCC lesion on her left ankle four months later. This lesion also had a negative SLNB, raising the possibility of two primary MCC tumors in this patient or of hematogenous metastasis. The patient further received adjuvant RT and remains disease-free 27 months after diagnosis.

To rule out the possibility of two primary MCCs, CGH analysis was carried out on three tumor tissue samples (initial right cheek biopsy, initial left ankle biopsy and re-excision of left ankle lesion, respectively). The data showed a narrow region of gain in chromosome 12p and whole arm losses in 8p and 17p that were identical across all three samples demonstrating that the two tumors arose from a common source, effectively ruling out multiple primary tumors for this case.

Two other case histories of patients who presented with synchronous tumors were also briefly described. A brief review of the literature (8 patients) for detecting whether synchronous tumors were identical/non identical tumors was discussed. Genetic analysis was carried out in 2 of 8 patients to clarify the relationship between tumors (The present study used aCGH and another study used Merkel polyomavirus LT antigen mutational analysis to determine that two MCC tumors had in fact arisen independently (Schrama D et al, 2010).

References:

[Distinction of 2 different primary Merkel cell carcinomas in 1 patient by Merkel cell polyomavirus genome analysis](#). Schrama D, et al. Arch Dermatol. 2010 Jun;146(6):687-9. PMID: 20566946

[Importance of Genetic Studies in Patients with Multiple Merkel Cell Carcinomas](#). Ahronowitz I, Nghiem P, Yu S. Acta Derm Venereol. 2012 Feb 15. doi: 10.2340/00015555-1303. [Epub ahead of print] PMID: 22334083

[An isolated Merkel cell carcinoma metastasis at a distant cutaneous site presenting as a second 'primary' tumor](#). Ahronowitz IZ, et al. J Cutan Pathol. 2011 Oct;38(10):801-7.

4) **Dermoscopic features of Merkel cell carcinoma**

Chris Bichakjian/Marcus Frohm (U Michigan)

Dr. Frohm's talk focused on the various dermoscopic features of MCC as evaluated in 10 primary MCC tumors from 10 patients. He also briefly summarized features of various dermatologic diseases (eg. comma vessels are seen in dermal nevi; dotted vessels are seen in Spitz nevi or very thin amelanotic melanoma (AMM); dotted vessels arranged as pearls on a line in clear cell acanthoma etc.). He described that: 1) 10/10 MCC tumors demonstrated milky-red areas/globules and numerous linear irregular vessels, 2) 6/10 tumors had out-of-focus small-diameter arborizing vessels, 3) 3/10 demonstrated small dotted vessels and or small glomerular vessels, 4) 2/10 had surface scale. None of the tumors demonstrated white structureless areas or a blue-white veil and there was no correlation between the dermoscopic features and histopathologic profile. Dr. Frohm concluded that clinicians should suspect a malignant diagnosis and biopsy a lesion if they find atypical vascular patterns such as milky-red areas/globules, polymorphous vessels, and linear-irregular vessels under dermatoscopy (Harting MS et al. J Am Acad Dermatol. 2011)

References:

[Dermoscopic vascular patterns in cutaneous Merkel cell carcinoma.](#) Harting MS, Ludgate MW, et al. J Am Acad Dermatol. 2011, Oct 4.

[Dermoscopy of Merkel Cell Carcinoma.](#) Dalle S, et al. Dermatology. 2012 Apr 6, PMID: 22487601

5) **Clinically relevant insights from a cohort of a 218 MCC patients from Northern California**

Maryam Asgari (Kaiser Permanente Northern California)

Dr. Asgari described the RC2 Challenge Grant collaboration on Merkel cell carcinoma between her research team at Kaiser Permanente Northern California (KPNC) and Dr. Nghiem's group. She described in brief the MCC demographic as well as survival analysis for the KP cohort. She described that the strengths of this cohort are that the KPNC dataset had similar age distribution as MCC patients in SEER and is thus more representative of the population than a database assembled at a tertiary care center (avoids ascertainment bias by age). Male gender was associated with increased MCC metastasis as well as MCC-specific mortality in this group. RT was associated with significantly lower locoregional recurrence rates (Hazard ratio = 0.2). A manuscript is in preparation.

In attendance at the San Diego 2012 MMIG meeting:

Ahronowitz, Iris
Asgari, Maryam
Bennet, Richard
Bichakjian, Chris
Boldrick, Jennifer
Brewer, Jerry
Brownell, Issac
Choi, Jaehyuk
Frohm, Marcus
Gao, Ling
Gharia, Manish J.
Hawryluk, Elena
Iyer, Jayasri
Knong, Bernice
Kruthen, Michael
Lai, Jennifer
Nghiem, Paul
Olerud, John
Otley, Clark
Parvathaneni, Upendra
Perlis, Cliff
Sober, Arthur
Stasko, Tom
Straswimmer, John
Swetter, Susan
Thakuria, Manisha
Wang, Linda
Wang, Richard
Wong, Mike
Yu, Siegrid
Zeitouni, Nathalie

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 donations from Merkel cell carcinoma patients.

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.

