Decreased Merkel Cell Carcinoma Survival in Immune-Suppressed Individuals

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Merkel cell carcinoma (MCC) is an aggressive neuroendocrine skin cancer that is three times more likely to be lethal than a malignant melanoma. At least 75% of MCC tumors are associated with an oncogenic virus, Merkel cell polyomavirus (MCV). The incidence of MCC has tripled in the last 20 years. Furthermore, there is a 5-fold to 50-fold increase in incidence of this cancer in patients with chronic immune suppression, including HIV/AIDS, hematologic malignancies, autoimmune disease or solid organ transplantation. Since the majority of MCC tumors are associated with a virus, immunosuppression is hypothesized to worsen MCC-specific prognosis in addition to increasing risk for developing MCC. To determine if immunocompromised patients have worsened prognoses, researchers in the laboratory of Dr. Paul Nghiem of the Clinical Research Division and the Division of Dermatology at the University of Washington examined MCC-specific survival in a cohort of immune competent and suppressed patients.

MCC prognosis depends on the stage of disease presentation: 5-year relative survival decreases from 64% to 39% to 18% for local, nodal, and metastatic disease, respectively. Even with successful treatment, nearly 50% of MCC patients relapse. Led by co-authors Drs. Jayasri Iyer and Kelly Paulson, the current study examined 471 MCC patients, 41 of whom had systemic immune suppression and 430 of whom were not immune suppressed. Three-year overall survival was decreased in MCC patients with immune suppression to 33%, compared to patients without immune suppression at 59% (hazard ratio 2.1; $P < 0.01$). The small number of patients in this study prevented the researchers from determining the individual contributions of different forms of immune suppression to MCC outcomes.

To account for differences in death rates from causes other than MCC, the researchers also used competing risk regression analysis, where MCC-related deaths were considered events and non-related deaths were considered competing events. Using this analysis, immune suppression was a significant predictor of decreased MCC-specific survival (hazard ratio 3.0; 95% confidence interval 1.8-4.8; $P < 0.01$), with immunosuppressed patients having a three-year overall survival at half that of the comparison group (40% *vs*. 74%; $P < 0.05$). Multivariate competing risk regression analysis further confirmed that immunosuppression was an independent predictor of MCC-specific survival independent of cancer stage, age, or gender (hazard ratio 3.8; $P < 0.01$).

Previously, the Nghiem Laboratory investigated how the immune system controls MCC progression. MCV-specific antibodies increase with increased tumor burden in MCC patients but do not protect from disease progression, while the presence of infiltrating lymphocytes in MCC tumors is associated with markedly improved patient outcomes (Paulson *et al*., 2010, Paulson *et al*., 2011, Bhatia *et al*., 2011). Similar to other tumor viruses, most people infected with MCV do not develop MCC, emphasizing the importance of other co-factors involved in MCC development, including increased age, sun exposure, and immune dysregulation. These studies and others help explain why the incidence of MCC is increased in immunosuppressed patients, and why immunosuppression can lead to poorer MCC-specific outcomes. Harnessing the ability of the immune system to target MCV and control MCC development may lead to future treatments for MCC patients.

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Paulson K.G., Iyer J.G., Tegeder A.R., Thibodeau R., Schelter J., Koba S., Schrama D., Simonson W.T., Lemos B.D., Byrd D.R., Koelle D.M., Galloway D.A., Leonard J.H., Madeleine M.M., Argenyi Z.B., Disis M.L., Becker J.C., Cleary M.A., and Nghiem P. 2011. Transcriptome-wide studies of merkel cell carcinoma and validation of intratumoral CD8+ lymphocyte invasion as an independent predictor of survival. *Journal of Clinical Oncology*. 29:1539-46.

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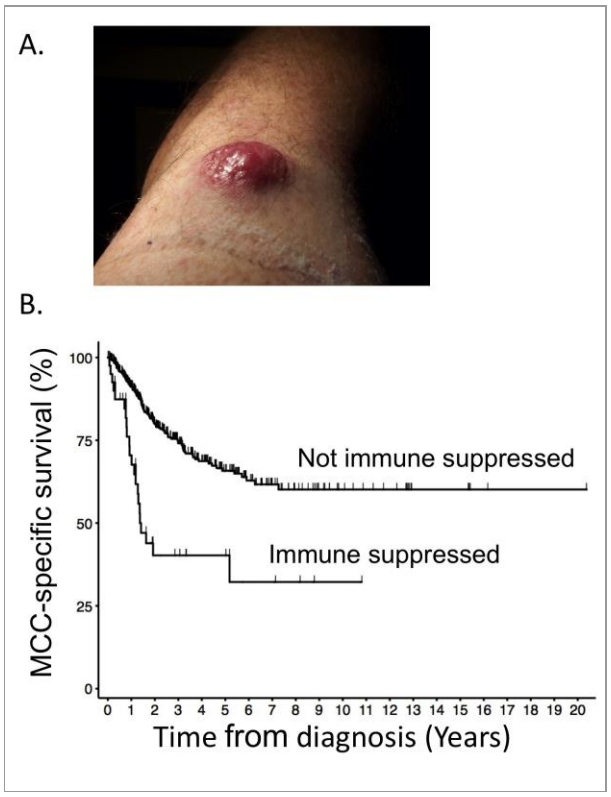

Images courtesy of Kelly Paulson and Paul Nghiem.

A) Image of Merkel cell carcinoma on the skin of a patient. B) Immune suppressed individuals (n=41) had significantly decreased MCC-specific survival as compared to patients without immune suppression (n=430) on univariate (hazard ratio 3.0; P <0.01) and multivariate (hazard ratio 3.8; P <0.01) competing risk regression analysis.