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Immune readouts may have prognostic value for the course of Merkel cell carcinoma, a virally-associated disease

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Merkel cell carcinoma (MCC) is an unusual form of skin cancer that disproportionately strikes elderly or immunocompromised individuals. The tumor typically presents as a fast growing, violet colored skin nodule, often on a sun-exposed site such as the face or an extremity. Although MCC is relatively uncommon, it has high reported disease-specific mortality rates of 28% by two years and 46% by five years after initial diagnosis^{1,2}. In 2008, it was discovered that a great majority of MCC tumors harbor a previously unknown species of polyomavirus³. Current evidence supports the view that this virus, called Merkel cell polyomavirus (MCPyV or MCV), is a causal factor underlying most cases of MCC.

In the current issue of *JCO*, two papers offer new findings that could, at a minimum, provide additional prognostic indicators for the likely outcome of an MCC diagnosis. In one report, a group led by Pierre Coursaget (Touzé et al.) show that MCC patients with high levels of serum antibodies against the VP1 major capsid protein of MCPyV tend to enjoy better disease outcomes⁴. The second report, from a group led by Paul Nghiem (Paulson et al.), shows that MCC tumors that have been infiltrated by CD8+ T cells are dramatically less likely to recur or metastasize after treatment⁵. Both papers support the conclusion that signs of stronger immune function correlate with better outcomes for MCC patients.

The pathogenesis of virally-induced cancers can be broadly divided into two categories: indirect and direct.⁶ With indirect viral carcinogenesis, the effects of the virus, such as inflammation triggered by chronic infection, lead to the malignant transformation of “bystander” cells that are not themselves infected. Liver cancer induced by hepatitis C virus is an example of such indirect viral carcinogenesis. In the direct mechanism, the malignant tumor is derived from progeny of a chronically infected cell. The induction of cervical cancer by human papillomaviruses (HPVs) is a clear example of direct viral carcinogenesis, with chronic HPV infection resulting in a series of cellular changes in the target cell that cooperate with the viral oncogenes to give rise to malignancy.⁷ In well-studied examples, such as HPV-induced cervical cancer, the directly-induced tumor cells remain dependent on the ongoing expression of the viral oncogenes for maintenance of the tumorigenic phenotype.

Several lines of evidence suggest that MCPyV plays a direct oncogenic role in most cases of MCC and that viral gene expression generally helps to maintain the oncogenicity of the tumor. First, MCPyV DNA is often found clonally integrated into the cellular genome of

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MCC tumor cells and their metastases, suggesting that the virus often plays an early role in tumorigenesis³, reviewed in⁸. The proposed direct link between MCPyV and MCC is also supported by the observation that most MCC tumors express detectable amounts of the MCPyV tumor (T) antigens, which are believed to be the primary viral oncogenes⁹. Furthermore, cultured cell lines derived from MCPyV-positive MCC tumors typically remain dependent on expression of the MCPyV T antigens for maintenance of the transformed phenotype in vitro¹⁰. In addition, most MCC patients display unusually high titer serum antibody responses against various MCPyV proteins^{4,11–14}.

In general, patients with impaired immune function are at increased risk of developing virally-associated cancers⁽⁶⁾. A likely explanation for this observation is that viral proteins, being foreign, but also being present in the tumor cells, can serve as targets for immune-mediated clearance of virally-induced cancers and their precursor lesions, and that immune dysfunction can attenuate this protective response. Epidemiological evidence supports the conclusion that immunosuppressed patients have an increased risk of developing MCC^{15,16}. The current results from the Nghiem and Coursaget groups support the additional notion that, even among MCC patients, there may be different degrees of immunological impairment and that immunological surveillance remains a clinically important factor in the control of frank MCC. Thus, immune function may influence both the induction of MCC and, importantly, its clinical outcome.

In Paulson et al., both univariate and multivariate analyses indicated that the presence of large numbers of CD8+ T cells in MCC tumors was strongly associated with longer disease-free survival. It is tempting to speculate that these T cells specifically recognize epitopes of the MCPyV T antigens. One potential caveat, however, is that Paulson et al. note that there was no relationship between intratumoral CD8+ T cell infiltration and the abundance of MCPyV DNA, which was detected in 75% of the tumors analyzed. The idea that CD8+ T cells specific for MCPyV antigens might facilitate tumor clearance is consistent with prior observations showing that patients whose MCC tumors carry greater amounts of MCPyV DNA (which appears to correlate with more uniform expression of MCPyV T antigens) have a better prognosis^{17,18}. It is conceivable that immunotherapy against such viral determinants might eventually be able to improve the outcome of some MCPyV-positive MCC patients whose immune system does not by itself adequately control the tumor.

A variety of studies have found that, in addition to the roughly 20% of MCC tumors without detectable levels of MCPyV DNA, a substantial fraction of MCPyV DNA-positive MCC tumors carry less than one copy of the viral genome per tumor cell. The simplest interpretation of this finding is that MCC has two etiologies: most cases are caused by MCPyV, but some cases have a different, MCPyV-independent etiology that remains undefined. This would be reminiscent of oropharyngeal cancer, where some cases are believed to be caused by HPV, while others are not. Analogous to MCC, HPV-positive oropharyngeal cancers also have a better prognosis than HPV-negative tumors.¹⁹ Touzé et al. also suggest an alternative, but more speculative, possibility: that virtually all cases of MCC are attributable to MCPyV infection, but that, in a minority of MCC cases, a “hit-and-run” mechanism allows for gradual loss of MCPyV oncogene expression. In this scenario, MCPyV infection would induce the initial pre-malignant lesion, but subsequent cellular

changes would render ongoing expression of the MCPyV oncogenes unnecessary for continued tumor cell growth and metastasis, perhaps explaining some of the MCC tumors with low numbers of copies of MCPyV DNA. Although such viral hit-and-run mechanisms have not been clearly documented in human cancers, a precedent for the effect has been observed for gastrointestinal cancers induced by bovine papillomavirus type 4²⁰. The possibility that some MCC tumors might evolve to escape immune responses targeting MCPyV antigens suggests that a subset of MCPyV-induced MCC tumors might not be suitable candidates for immunotherapeutic approaches to treatment of this lethal form of cancer.

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