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SPECIAL ARTICLE

Merkel Cell Carcinoma: Recent Progress and Current Priorities on Etiology, Pathogenesis, and Clinical Management

The Rockville Merkel Cell Carcinoma Group

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ABSTRACT

Purpose
To expedite improved understanding, diagnosis, treatment, and prevention of Merkel cell carcinoma (MCC), a rare malignancy of cutaneous neuroendocrine cells that has a 28% 2-year mortality rate.

Methods
This article summarizes a workshop that discussed the state-of-the-art research and priorities for research on MCC and on a new human polyomavirus (ie, MCPyV) recently discovered in 80% of MCC tumors.

Results
Normal Merkel cells are widely distributed in the epidermis near the end of nerve axons and may function as mechanoreceptors or chemoreceptors. Malignant MCC cells typically stain for cytokeratin 20 as well as for other epithelial and neuroendocrine markers. MCC subtypes, which are based on histology, on cell line growth properties, and on gene expression profiles, have been reported but have not been linked to prognosis. Clinical management has been empiric. MCPyV is clonally integrated at various sites in the human genome of MCC tumors, with truncating mutations in the viral, large T antigen gene that interrupt viral replication. MCPyV seroprevalence may be high, as with previously known human polyomaviruses. MCC risk is increased 11-fold with AIDS and with other cell-mediated immune deficiencies, B-cell neoplasms, and ultraviolet radiation exposure.

Conclusion
Development and validation of a range quantitative polymerase chain reaction and serologic assays for detection of MCPyV, as well as an infectious clone of the virus, would clarify the fundamental biology, natural history, and epidemiology of the virus, of MCC, and of other diseases. Contingent on standardized histologic diagnosis and staging of MCC, consortia are needed to clarify the risks and benefits of sentinel lymph node biopsy, adjuvant radiation therapy, and salvage therapies; consortia are needed also for epidemiologic studies of MCC etiology.

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INTRODUCTION

Merkel cell carcinoma (MCC; formerly called trabecular carcinoma) was first described by Toker[1] in 1972. It is a rare, aggressive carcinoma of cutaneous neuroendocrine cells. The disease course is difficult to predict and ranges from relatively indolent to highly aggressive, often spreading to local, regional, and distant sites. Treatment options, which have not been rigorously evaluated, include surgery alone or with adjuvant radiation therapy, and systemic chemotherapy is reserved for recurrent or disseminated disease. After recognition that MCC incidence was increased 11-fold among those with the AIDS,[2] newly developed molecular and bioinformatics methods led to the discovery of a novel polyomavirus that may be an important etiologic agent.[3]

To identify opportunities and means for characterizing the etiology, pathogenesis, and clinical management of MCC, a workshop was held under the sponsorship of the National Institutes of Health Office of Rare Diseases, with additional support from the National Cancer Institute Division of Cancer Epidemiology and Genetics and Office of HIV and AIDS Malignancies. Participants (Data Supplement, online only) included epidemiologists, virologists, dermatologists, dermatopathologists, surgeons, and patient representatives. Lecturers reviewed and facilitated discussion of the state of knowledge, then subgroups identified priorities for future research. The presentations and discussions are summarized herein.

SUMMARY OF THE STATE OF KNOWLEDGE

MCC Epidemiology and Risk Factors

MCC is rare, with an estimated annual incidence of three occurrences per million people in the United States.[4] The mortality rate within 2 years of MCC diagnosis is 28%, largely because it often is metastatic at presentation. In a series of 251 patients from one institution, patients with stage IV (ie, distant metastatic) disease had a median survival time of 6.8 months.[5]

MCC is extremely rare before age 50 years, after which the incidence increases steeply with age, which suggests accumulation of oncogenic events. MCC incidence is increased approximately 11-fold for people with AIDS and five-fold for people who have undergone an organ transplantation.[2,6,7] The risk is much higher among people of European ancestry, and there is a small excess in men. The higher risk with European ancestry may relate to a deficiency of protective melanin, as the incidence is inversely related to latitude.[4] The majority of tumors present on the face and head, and many patients with MCC have other synchronous or metachronous, sun-associated, skin cancers. Thus, it appears likely that ultraviolet (UV) radiation contributes to the etiology of this malignancy. The risk of MCC may be particularly high with prior psoralen and UV-A (ie, PUVA) treatment, which reinforces the likely etiologic role of UV radiation.[8] In addition to skin cancers, patients with MCC have had increased risk for multiple myeloma, non-Hodgkin's lymphoma, and—in particular—chronic lymphocytic leukemia.[4,9]

MCC Polyomavirus

A team of scientists led by Yuan Chang, MD, and Patrick Moore, MD, MPH, at the University of Pittsburgh discovered a previously unknown polyomavirus, provisionally designated MCPyV, by the use of digital transcriptome subtraction and high throughput sequencing of cDNA libraries that they constructed from four MCC tumors.[3] Viral genome was detected eight of 10 MCC tumors, at low levels in 16% of unaffected skin tissues and 8% of tissues from other body sites of patients without MCC. In contrast to the four previously known human polyomaviruses, which belong to the simian virus 40 (SV40) subgroup, MCPyV is phylogenetically related to murine polyomaviruses. High levels of MCPyV DNA in MCC and low levels in some other tissues have been confirmed by other groups.[10-12] In MCC tumors, there is substantial variation in the relative abundance of MCPyV DNA. One study found that virus-positive MCCs contained between one viral DNA copy per 10,000 tumor cells to 10 viral DNA copies per tumor cell.[10]

MCPyV was integrated at various locations in the MCC tumor genome in a clonal pattern, which strongly implies that infection of the cells occurred before their clonal expansion. Additional evidence to suggest a direct mechanistic role for the virus is that the viral genome in MCC tumors is reported to have mutations that truncate the product of the large T antigen.[13] MCPyV large T protein is detected in virus-positive MCC tumors, and the genome mutations apparently do not affect binding of the retinoblastoma tumor suppressor protein (pRb) by large T protein. Rather, the mutations prevent complete replication of the viral genome.[13] A mutation in the *VP1* gene, possibly related to incomplete integration of the virus in MCC, also has been reported.[11] Such mutations have not been seen in viral genomes from nontumor cells, which supports the hypothesis that altered replication or integration of MCPyV may be involved in MCC tumorigenesis.

Epidemiology and Virology of Polyomaviruses

Polyomaviruses are small, double-stranded DNA viruses that have been found in many mammalian and nonmammalian species.[14] These viruses have exquisite species specificity, which appears to be largely dictated by intracellular host proteins or regulatory mechanisms that are required for establishment of infection or completion of the viral life cycle. Cell surface proteins that function as receptors or coreceptors also may contribute to species specificity.

The first two human polyomaviruses, designated BK virus (BKV) and JC virus (JCV), were discovered in 1971.[15-17] BKV is commonly acquired in early childhood, and JCV in later childhood; seroprevalence to BKV increases rapidly after birth and reaches 80% to 90% by the age of 10 years; it declines somewhat at older ages, for unknown reasons. Seroprevalence to JCV increases more slowly and reaches 60% to 70% by the age of 25 years. The modes of transmission of BKV and JCV have not been established, but they are often excreted in urine and detected in sewage. Virions can be shed with or without lysis of the infected cell. Among immunocompetent adults, the prevalence of virus in the urine (ie, viruria) is approximately 15% for BKV and is approximately 30% for JCV. Altered cellular immunity is associated with higher rates of viruria, especially for BKV. Approximately half of pregnant women shed BKV in their urine, whereas shedding of JCV does not appear elevated with pregnancy.

BKV replication causes nephropathy in immunosuppressed kidney transplantation recipients.[15] JCV is the cause of progressive multifocal leukoencephalopathy, a life-threatening disease of the central nervous system that occurs with AIDS and other severe immunodeficiency conditions.[16] The large T antigen of both BKV and JCV can bind to and inactivate p53 and pRb proteins, and both viruses have been shown to induce tumors in experimentally infected animals. However, no associations with human cancer have been clearly established, as there is inconsistency in the reported prevalence of BKV and JCV sequences in human cancer tissues, and epidemiologic cancer studies of BKV and JCV have been consistently negative.[18]

The third and fourth human polyomaviruses, designated KIV and WUV, were discovered in 2007 in nasal aspirates of children, which pointed to the possibility of respiratory transmission.[19-21] KIV and WUV have no known disease associations. Seroprevalence data on these newer viruses are sparse. Several unpublished reports suggest that seroprevalence of MCPyV is high, like BKV and JCV.

Microscopic and Molecular Features of Merkel Cells and MCC

In 1875, Friedrich Merkel described small, round or oval, basophilic cells that were located at the end of nerve axons, within the basal layer of the epidermis. Subsequently, Merkel cells were shown to be widely distributed throughout the skin, with high density on sensitive, hairless skin, particularly the fingers, palms, soles of the feet, and lips, as well as other parts of the face and ventral surface of the arms.[22] Merkel cells also may be dense around hair follicles, and they are found

in the oral mucus membranes. Proliferations of these cells in many skin conditions have been found,[23] and distinct populations have been identified.[24] They generally are thought, but not proven, to function as mechanoreceptors or chemoreceptors.[25] An epithelial origin is possible, but some data suggest that Merkel cells may have a neural-crest origin. Electron microscopy has vividly illustrated that Merkel cells contain whorls in the cytoplasm and dense granules at the cytoplasmic membrane.[26] Focal degranulation has been observed, but its significance is unknown. The granules label with antibodies to chromogranin and other neuroendocrine markers. Although the whorls were identified early as keratin intermediate filaments, it was not until 1992 that the characteristic, paranuclear, dot-like labeling of these whorls by antibodies to cytokeratin 20 (CK20) was observed. This particular feature has become pivotal in the distinction of MCC from histologically similar malignancies.[27]

MCC arises in the dermis but can involve deeper structures, as well as the epidermis. Mitotic figures and also apoptotic cells are observed frequently, and clusters of tumor cells often are seen in local and regional lymphatic vessels. There is often little or no reaction in the stroma or infiltration by inflammatory cells. Reported histologic variants include a large-cell type that often has a trabecular pattern and reportedly has the ultrastructural finding of a high density of granules, and a small-cell type that has an observed ultrastructural paucity of granules and a resemblance to skin metastases of small-cell lung carcinoma.[26,28] It is not clear whether prognosis differs for these histologic variants in comparison with the intermediate-cell type that accounts for the majority of MCC tumors.

The tumor cells possess ultrastructural and antigenic features in common with cells of epithelial and neuroendocrine origin, but whether MCC arises from normal Merkel cells is controversial.[23,26,28] Nonetheless, immunohistochemistry exploits these unusual properties to distinguish MCC from morphologically similar malignancies, including some lymphomas, Ewing sarcoma, and especially small-cell carcinoma of the lung. In particular, distinguishing MCC from small-cell lung carcinoma is based on MCC staining with CK20, often visualized as conspicuous paranuclear dots, and the absence of reactivity to thyroid transcription factor.[29] Useful criteria for confirmation of the diagnosis of MCC include CK20 reactivity along with reactivity to chromogranin, synaptophysin, neuron-specific enolase, and neural cell adhesion molecule. Some MCC have been described that express cytokeratin 7 without readily detected CK20.

Analyses of gene expression profiles of MCC cell lines have suggested the possibility of two subtypes that have distinct expression patterns and that correlate with the morphology, colony shape, and aggregation phenotypes of the cell lines.[30,31] Higher expression of genes involved in signal transduction pathways generally were found in classic MCC cell lines, whereas expression of genes related to cell cycle control and cell proliferation were associated with variant MCC cell lines. In one study that used high resolution, comparative genomic hybridization, MCC tumors frequently had lost regions of chromosomes 3p, 4, 5q, 7, 10, and 13, and many had extra copies of regions on chromosomes 1, 3q, 5p, and 6.[32] Loss of the *pRb1* gene region and amplification of the *L-Myc* gene region were common (26% and 31% of tumors, respectively) and were postulated to be functionally important. Less genomic aberration was associated with improved survival.[32]

Presentation, Staging, Management, and Prognosis of MCC

MCC is seldom suspected at presentation. The clinician's index of suspicion of MCC is increased with a lesion that is red but asymptomatic and that is expanding rapidly in a patient who is immune deficient, is old, or has UV-damaged skin.[33] Prognosis is poor with distant metastasis; otherwise, it is strongly related to the presence or absence of tumor in regional lymph nodes. A meta-analysis of data from 122 patients from several centers found that MCC recurred within 3 years in 60% of those with a positive sentinel lymph node biopsy (SLNB) versus 20% with a negative SLNB.[34] Spontaneous regression even in advanced stages has been reported.[35]

Five different staging systems have been proposed for MCC during the past 20 years, which results in confusion and inconsistency. In 2009, the American Joint Committee on Cancer is expected to publish a new consensus staging system for MCC on the basis of survival analysis of greater than 4,000 patients with MCC who had more than 5 years of follow-up data from the National Cancer Data Base. The major advantage of the new staging system will be the incorporation of MCC substages that are based on microscopic examination of regional lymph nodes. Recent work has shown significantly better survival for patients whose nodes were demonstrated microscopically to be negative for MCC compared with those whose nodes were negative only by clinical exam.[34]

Primary treatment of MCC typically has involved surgical excision with pathologic verification of complete removal of the tumor. The disease often recurs but is highly sensitive to ionizing radiation therapy.[36] For this reason, adjuvant radiotherapy generally is recommended, except for patients who have small tumors and no evidence of lymphatic or lymph node involvement. Chemotherapy often is used for palliation and provides overall response rates of approximately 70%[37]; however, the disease often recurs within a few months. Although no clinical trials have been conducted, a set of comprehensive, multidisciplinary treatment guidelines for MCC management is updated annually with input from more than a dozen institutions and is posted online by the National Comprehensive Cancer Network at http://www.nccn.org.

GAPS IN KNOWLEDGE AND PRIORITIES FOR RESEARCH

Virology and Epidemiology

The discovery of MCPyV presents many opportunities for insights on fundamental biology, as well as on the pathogenesis of MCC and, potentially, other conditions. Progress would be greatly advanced by the development of an infectious clone of MCPyV, which then could be used to dissect and define cellular tropism, the virus life cycle, interactions with host genomes and proteins, and immune responses. In the meantime, in vitro studies of the effects of expression of individual MCPyV genes in various cells and contexts would be helpful. In situ hybridization analysis would clarify the presence of MCPyV in individual malignant and nonmalignant cells. A formal catalogue of MCPyV sequences, episomes, and integration sites in MCC and various other tissues would be valuable.

The distribution, transmission dynamics, and natural history of MCPyV need to be characterized. This will require highly sensitive, specific, and reproducible assays for the detection and quantification of MCPyV genome and antibodies. Quantitative polymerase chain reaction (PCR) assays directed to various regions of the MCPyV genome should be developed. Sharing of reagents and DNA specimens to cross validate these assays should be performed, as this will facilitate standardization of results and interpretation of associations. Nested PCR generally should not be used to detect MCPyV DNA, as the virus may be an incidental bystander. Because so little is known about this virus and its natural history, various platforms and methods should be used to develop assays to detect and quantify MCPyV antibodies. Efforts should be made to detect and quantify immunoglobulin (Ig) A (IgA) as well as IgG antibodies against several viral proteins, including the large T and small T antigens. Sharing of serum or plasma specimens, as well as reagents, and cross validation of serologic assays will be important. Observations made on individuals who have discordant results may be highly informative. For example, MCC may prove to be associated with high viral load but low antibodies, but the reverse association or even a null association is possible and plausible. Because they would be costly and labor intensive, development of assays to assess cytotoxic T-lymphocyte activity and related responses is not an immediate priority.

With suitable assays, the distribution of MCPyV in body fluids, including plasma, blood cells, urine, stool, and oropharyngeal aspirates, will enable formal studies of the modes of viral transmission. Likewise, quantification of MCPyV genome in various tissues is needed to identify the in vivo reservoir. A wide range of sites, including bone marrow, brain, spinal cord, kidney, skin, and other organs, should be considered. Identification of differences in MCPyV seroprevalence and shedding, among and within populations, will establish the fundamental epidemiology of this virus. The possibility that MCPyV is associated with other diseases, especially malignancies of neuroendocrine or hematopoietic origin, should be evaluated rapidly and comprehensively by using immunohistochemistry to detect MCPyV large T protein, as well as by other methods. The possibility that MCPyV causes a rare disease other than MCC should be considered.

Because MCC risk varies with certain demographic and clinical variables, a uniform set of associated data should be obtained for all epidemiologic and translational investigations. Key variables should include age, sex, ethnicity, residential area, history of malignancy (including melanoma and nonmelanoma skin cancers), and conditions or treatments associated with immune deficiency or perturbation.

On the premise that MCPyV is highly prevalent among adults, epidemiologic study of MCC should focus on identification of major cofactors, including immune perturbations and UV-induced skin damage. A broad but careful study of cellular and humoral immunity could be done by using delayed-type hypersensitivity and quantification of immunoglobulin subclasses. An initial comparison of patients with MCPyV-positive versus MCPyV-negative MCC could be cost effective for elucidating major cofactors. A case-control study ultimately will be required, especially to understand the relationship of the virus to the malignancy. However, defining and recruiting suitable controls, as well as recruiting patients, will be challenging in view of the rarity of MCC. The possibility that MCC may arise from alternative pathways will need to be remembered.

Molecular Pathology and Clinical Management

Standardization of histologic criteria for defining and reporting MCC should be a high priority. To this end, the American Joint Committee on Cancer is adding relevant checklists for its staging systems, and use of these lists will be mandatory for accreditation by the Commission on Cancer of the American College of Surgeons. This is, however, only a first step. To advance from an empiric to an evidence-based process for clinical decision making and to define the standard of care, a consortium of centers with a strong interest in MCC is needed. Working together under a common research protocol; reviewed and approved ideally by a central institutional review board; and duly authorized with a Federal Wide Assurance from the Office of Protection from Research Risks, this consortium could rigorously assess patients with MCC who provide signed informed consent as research participants. Initially, such a protocol could define stages and rates of recurrence of MCC for histologic, anatomic, demographic, virologic, and other subgroups that have been uniformly defined. The uniform set of data described in Virology and Epidemiology for epidemiologic and translational studies will be equally important for clinical investigations.

The initial assessment and treatment of MCC are seriously hampered by a paucity of data on the risks and benefits of SLNB and adjuvant radiation therapy. SLNB is performed inconsistently on the basis of the size of the primary tumor, the detection of malignant cells in lymphatic vessels, and the lack of overt lymphadenopathy. Radiation therapy to the primary site and the draining nodes generally is performed, at least at referral centers, but it is deemed unnecessary for small, apparently early tumors. For carefully defined subgroups of patients in whom the risks and benefits of SLNB and adjuvant radiation therapy are ambiguous, a consortium could conduct randomized, clinical trials of these procedures that use recurrence rate as the outcome measure. A consortium also could develop and implement protocols to assess salvage therapies, with either conventional or investigational treatments, for patients with recurrent or disseminated MCC.

Development of novel, targeted therapies on the basis of comprehensive investigations of the molecular pathology of MCC and the potential effects of MCPyV should be a high priority. Differing patterns in the expression of genes across the spectrum of MCC must be borne in mind. Creation of an MCC tissue microarray (TMA) would facilitate this work. Additional insight likely would be obtained by identification of the transcriptome, including micro-RNAs, of MCC. Interpretation of molecular pathology studies, and their integration with virologic, epidemiologic, and therapeutic studies, will require the uniform data set mentioned in Virology and Epidemiology. If MCPyV is shown to play a causal role in MCC, pursuit of virus-specific therapies would be warranted. The most promising targets for antiviral drug development are the large and small T antigens. The development of high-throughput assays that are based on a functional activity of these proteins would facilitate drug screening. Vaccine development also would be a high priority. A vaccine would depend on a well-characterized, small-animal model for use in preclinical studies, as

well as on reagents and assays to measure cellular immune responses to the large and small T antigens.

To accelerate discoveries and the translation of those discoveries to improve diagnosis, staging, and treatments, better communication with and education of physicians and patients who are affected, directly or indirectly, by MCC is critically needed. The nascent MCC clinical referral and treatment group at http://www.merkelcell.org and the online patient discussion group at http://groups.google.com/group/merkelcell are useful and could be platforms to launch a consortium. However, technologies for communication and education evolve rapidly. To stay abreast and exploit this forward evolution, the MCC community should work closely with one or more large organizations, such as the American Society of Clinical Oncology, that are striving to improve communications and education related to cancer.

SUMMARY

MCC is lethal for about one third of patients. MCPyV is present in most MCC tumors and has characteristics that could contribute to neoplastic transformation. Although it is not yet clear if the virus contributes to the etiology of MCC, the discovery of the virus could be a major breakthrough. Translation of this discovery into prevention and treatment of MCC will require fundamental understanding of the virus, of normal and malignant Merkel cells, of the cell microenvironment, and of the interactions of these factors. Such research is always difficult, but it will be especially challenging, because MCC is rare and may be heterogeneous. The discovery of MCPyV should catalyze the establishment of multidisciplinary teams in an MCC consortium that would conduct institutional review board–approved research by using shared data and specimens from patient volunteers and appropriate controls.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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