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What's New in Dermatopathology: News in Nonmelanocytic Neoplasia

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KEYWORDS

• Nonmelanocytic neoplasia • Dermatopathology • Merkel cell carcinoma • Squamous cell carcinoma • Muir-Torre syndrome • Sebaceous

KEY POINTS

- The proposed oncogenic role of Merkel cell polyomavirus in Merkel cell carcinoma has prompted researchers to explore its role in several human cancers, including non-Merkel skin cancers, neuroblastoma, and lung cancer.
- In the seventh edition of the American Joint Committee of Cancer's recommended staging criteria manual, new staging systems for Merkel cell carcinoma and squamous cell carcinoma (with the exception of those affecting the eyelid, vulva, or penis) were introduced, which separated these entities from the existing nonmelanoma skin cancer staging system because of their increased metastatic potential.
- The entity known as reticulated acanthoma/epithelioma with sebaceous differentiation is controversial and there is a need to develop clear-cut diagnostic criteria. A possibility of association of this entity with Muir-Torre syndrome (MTS) has been raised.
- Sebaceous neoplasms, including sebaceous adenomas, sebaceomas and sebaceous carcinomas, and multiple keratoacanthomas, may occur sporadically or can be seen as a manifestation of MTS. It is important to differentiate between sporadic sebaceous tumors and sebaceous neoplasms arising in association with MTS, because the skin findings may be the primary presentation and lead to the diagnosis of MTS.

This article reviews the recent dermatopathology literature involving nonmelanocytic neoplasia, with a focus on important work done over the last 5 years. The discussion includes advances in the understanding of Merkel cell carcinoma (MCC) pathogenesis and prognosis; changes in the seventh edition of the American Joint Committee of Cancer staging manual in reference to staging of squamous cell carcinoma (SCC) and MCC; newly described or rare histopathologic patterns and entities including squamoid eccrine ductal carcinoma (SEDC), rippled-pattern adnexal neoplasms (RPAN), onychomatricoma (OM), spindle cell–predominant trichodiscoma (SCPT) and neurofollicular hamartoma, and myoepithelioma; and microsatellite instability (MSI) in sebaceous neoplasms of Muir-Torre syndrome (MTS) and other tumors.

MCC AND MERKEL CELL POLYOMAVIRUS

MCC of the skin is a rare, aggressive cutaneous malignancy that predominantly affects elderly white

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men. MCC has a tendency for local recurrence and regional lymph node metastasis. Factors associated with development of MCC include ultraviolet radiation exposure, immunosuppression, and Merkel cell polyomavirus (MCPyV). MCPyV represents the first polyomavirus linked to human cancer.[1]

Feng and colleagues used a methodology known as digital transcriptome subtraction to first identify this virus. The group then confirmed the presence of MCPyV in 8 of 10 MCC tumors. Additionally, in 6 of the 10 samples, the viral genome was clonally integrated into the human genome. This integration of the viral genome not only refutes the possibility that MCpyV is merely a coincidental, passenger infection in MCC but also supports the contention that virus-associated tumors are "biologic accidents."[2] It is also important to note that this identified pattern of integration also suggests that MCPyV infection and integration occurs before the replication of tumor cells.[3]

Other researchers have identified MCPyV in MCC. In the largest retrospective case series, DNA from MCPyV was detected in 91 of 114 patients diagnosed over a 25-year period in Finland. Additionally, there was no evidence of MCPyV in 22 control samples from other tumors (glioblastoma or melanoma) or normal tissues.[4] MCPyV has also been identified in nonlesional skin of those diagnosed with MCC.[5,6]

The high incidence of MCC in the immunocompromized population first suggested the possibility of an infectious cause of MCC.[7] This tumor has an aggressive course in immunosuppressed patients with a reported mortality rate of up to 56% in this group. The mean age of diagnosis is about 10 years earlier than immunocompetent patients.[8] Chronically immunosuppressed patients are more than 15 times more likely to be diagnosed with MCC than age-matched immunocompetent individuals, especially in those who are HIV-positive.[9]

Direct causality, however, still remains a highly debated topic. Factors supporting this infectious cause include increased tumor incidence and high mortality in the immunosuppressed population, presence of viral DNA in most MCCs, large T antigen transcript presence in MCC tumor cells, and the clonal integration of MCPyV DNA in tumors. In contrast, features that argue against a viral cause of MCC include the presence of MCPyV-negative tumors, predilection for fair-skinned individuals, and lack of tumors among close contacts, all of which would be suspected with a viral infection.[3,5,7]

Thus far, only one study has explored prognosis of MCpyV presence and survival. In a Finnish study, DNA-positive MCCs were located on the extremities more frequently than those that were DNA-negative, had less frequent regional lymph node involvement, and better overall survival rates.[4] Further research is necessary to fully support this finding.[10]

MERKEL CELL POLYOMAVIRUS IN OTHER NEOPLASIA

The proposed oncogenic role of MCPyV in MCC has prompted researchers to explore its role in several human cancers, including non-Merkel skin cancers, neuroblastoma, and lung cancer. For instance, Mertz and colleagues[11] were able to establish a link between epidermodysplasia verruciformis, a rare genodermatosis in which patients are particularly susceptible to infection with specific human papillomavirus subtypes. In this study, several skin neoplasms (carcinomas in situ, invasive SCCs, and common warts) were biopsied from six patients with congenital epidermodysplasia verruciformis and one subject with acquired epidermodysplasia verruciformis secondary to immunosuppression. All specimens were found to have MCPyV DNA. In contrast, all seven normal skin samples from these subjects tested negative for MCPyV DNA. It is suggested by the authors that MCPyV and epidermodysplasia verruciformis and human papillomavirus may act as synergistic oncogenic cofactors in development of epidermodysplasia verruciformis neoplasms.[11]

Results from a recent study evaluating 72 tumors, other than MCC, have questioned an MCPyV association with other types of cancer. A study published by Ly and colleagues[12] examined 57 such lesions, consisting of 15 melanomas, 5 in situ melanomas, 15 invasive SCC, 4 basal cell carcinomas (BCC), 3 actinic keratoses, 2 seborrheic keratosis, 1 common wart, 1 verruca plana–like lesion, 1 virus-associated trichodysplasia spinulosa, and 10 benign follicular lesions. Also, 15 cases each of pulmonary and gastrointestinal neuroendocrine tumors were included in the study. All 72 tumors tested negative for MCPyV irrespective of any known MCC diagnosis or immune status. Rollison and colleagues[13] recently released the first serologic case-control study relating MCPyV and SCC. Data showed that MCPyV DNA was found in 38% of SCC cases (55 of 145). A statistically significant association was even observed between MCPyV seropositivity and MCC DNA-positive SCC (odds ratio, 2.49; 95% confidence interval, 1.03–6.04). Future research into the mechanism of the immune evasion used by MCPyV will help to establish whether causality exists among this proposed human cancer-causing virus and other tumors.