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Recent advances in the biology of Merkel cell carcinoma☆

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Summary Recent outstanding research has rapidly revealed new aspects of the biology, etiology, and clinicopathology of Merkel cell carcinoma, a rare but highly aggressive neuroendocrine skin malignancy that affects the elderly and immunosuppressed patients. Molecular biological studies, especially the discovery of Merkel cell polyomavirus, have shed new light on the pathogenesis of the disease. Increasing evidence strongly suggests that this virus is causally related to the development of Merkel cell carcinoma. On the other hand, many studies have also indicated that a subset (approximately 20%) of Merkel cell carcinomas are not likely to be associated with the virus. Tumors with and without the virus have been shown to be significantly different in prognosis, oncogene expression, and histologic appearance, suggesting that they have different etiologies. Moreover, studies on the histopathology, immunohistochemistry, and cytogenetics have revealed several biological factors that are related to the clinical behavior and prognosis of the disease. This review summarizes the advances in the molecular biology of Merkel cell carcinoma based on recent study results. Although the exact molecular pathway of the pathogenesis of Merkel cell carcinoma remains unclear, further understanding of the pathophysiology of this tumor is expected to result in novel therapeutic approaches for management of the disease and contribute to better patient outcomes.

1. Introduction

Merkel cell carcinoma (MCC) is a rare but aggressive and frequently lethal human skin malignancy with neuroendocrine differentiation. This tumor predominantly affects the elderly and immunocompromised individuals and mostly occurs in sun-exposed areas of the skin, particularly the head and neck regions. From this evidence, it was long thought that immunosuppression and ultraviolet (UV) irradiation are the main etiological factors of the disease; but little was known about the molecular mechanisms directly involved in the tumorigenesis. In 2008, a surprising discovery was reported by Feng et al [1] in *Science* that a previously unidentified polyomavirus was found in 8 (80%) of 10 MCC tumors, which aroused interest in researchers around the world including pathologists and oncologists as well as virologists. This virus, named Merkel cell polyomavirus (MCPyV), was also detected in human tissues other than MCC but much less frequently. Moreover, MCPyV was demonstrated to be monoclonally integrated into the host genome in MCC, suggesting that viral infection preceded clonal expansion of the tumor [1]. Polyomaviruses generally have genes coding large and small T antigens (LT and ST, respectively) that are capable of inducing tumors in animals and transforming mammalian cultured cells. Moreover, viral genome integration is one of the typical features of virus-mediated oncogenesis, such as rodent tumors with simian virus 40 and human cervical cancers with human papillomavirus [2]. Therefore, MCPyV in MCC is thought not to be a passenger

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virus but to play a causative role in tumorigenesis and has drawn the attention of researchers as the first model of polyomavirus-mediated human neoplasm.

MCC was first reported in 1972 by Cyril Toker [3] as "trabecular carcinoma of the skin." He described 5 cases of tumors located in the dermis or in the immediate subcutis composed of solid anastomosing trabeculae, cords, or nests of cells with large, vesicular nuclei and scanty cytoplasm arising in elderly patients that were sometimes recurrent and life-threatening. Based on the histological features and tumor location, he first postulated that the tumor was derived from immature cells capable of reproducing primitive sudoriferous structures; however, subsequent ultrastructural study by Tang and Toker [4] revealed that all 3 trabecular carcinomas examined contained varying numbers of dense core granules that were thought to be identical to those seen in cells differentiating from the neurocrest. From the close similarity at the ultrastructural level, they proposed that Merkel cells, which were considered to be neurocrest derivatives and to function as mechanoreceptors, were the origin of the tumor. In addition, subsequent studies including immunohistochemistry confirmed that this tumor and normal Merkel cells share some neuroendocrine features [5-7] and commonly express simple epithelium-type cytokeratins (CKs), most importantly, CK20 [8,9]. At present, this tumor is thought to be most closely associated with Merkel cells and is therefore referred to as MCC in general; however, because the theory that this tumor originates from Merkel cells has never been established beyond doubt, some prefer the designation "neuroendocrine carcinoma of the skin" for this entity [10]. An alternative theory is that this tumor arises from a pluripotent stem cell in the dermis [11], but the exact origin of the tumor remains unknown.

The discovery of MCPyV in MCC by Feng et al [1] has added another dimension to the investigation into the molecular pathogenesis of MCC. Currently, increasing evidence suggests a causative role for the virus in MCC tumor development, although the exact tumorigenic pathway has not yet been elucidated. In this review, the author presents a brief description of the general features of MCC and summarizes the results of recent research into the biology of MCC, mainly based on immunohistochemistry, molecular genetics, and virology.

2. General features of MCC

Recent large-scale epidemiological studies based on the Surveillance Epidemiology and End Results Program of the National Cancer Institute found that the estimated overall age-adjusted (to the 2000 US standard population) incidence rate of first primary MCC in the United States was 0.6 per 100 000 in 2006 and has quadrupled during the past 2 decades [12,13]. The incidence of MCC is highest in whites, extremely low in black people, and intermediate in other ethnic groups [14]. According to a research conducted by Ono et al [15] in 1995, the estimated prevalence in Japan was 1.45 per million, much less than in whites. MCC occurs in both sexes, but there is a slight male predominance (2:1 in whites and blacks and 1.5:1 in other ethnic groups) [14]. It mostly occurs in the elderly aged 60 years or older, and its incidence increases sharply with age. Immunosuppressed patients such as organ transplant recipients and patients with AIDS have an increased risk of MCC, and it tends to develop at a younger age [14].

Clinically, MCC typically presents as a rapidly growing, nontender, red to violaceous papule or nodule on sun-exposed areas of the skin, especially in the head and neck regions (Fig. 1). It also arises commonly on the extremities and less frequently on the trunk. Epidermis overlying the lesion is usually intact; but in a few cases, ulceration or crusting may be seen. Because such a clinical appearance is nonspecific, MCC is rarely suspected clinically at the time of initial presentation. Differential clinical diagnoses frequently include basal cell carcinoma (BCC), squamous cell carcinoma (SCC), pyogenic granuloma, keratoacanthoma, amelanotic melanoma, benign cyst, adnexal tumors, lymphoma cutis, and other metastatic neoplasms [16]. For diagnostic confirmation, histological examination of biopsy specimens is usually required. Treatment is essentially total excision with a wide surgical margin, but radiation therapy is also effective. On rare occasions, MCC regresses completely without any treatment. Patients with regional or distant

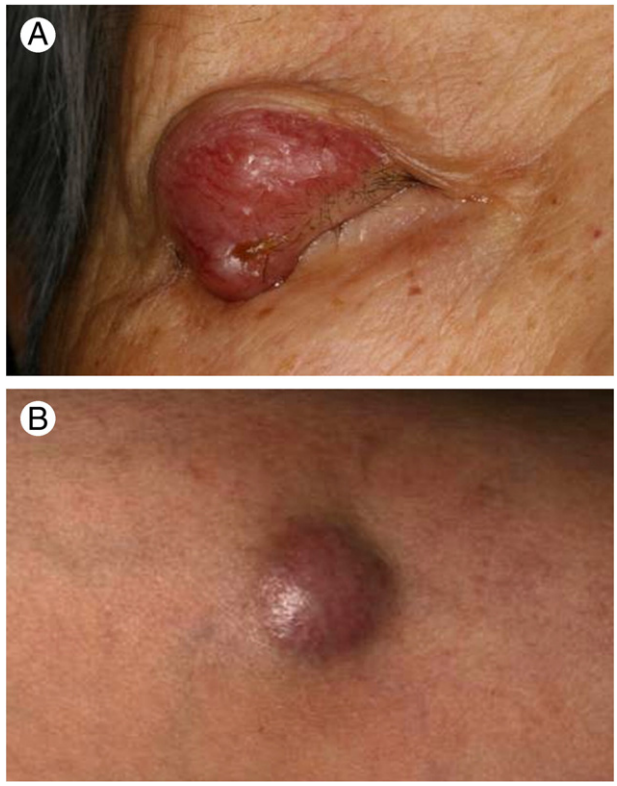

Fig. 1 Clinical pictures of MCC arising in the right upper eyelid (A) and in the thigh (B).