Merkel cell carcinoma: a review and update on current concepts

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Abstract

Merkel cell carcinoma (MCC) is a malignant, cutaneous neuroendocrine tumour of the elderly with an increasing worldwide incidence. Clinical presentation is generally characterized by a rapidly-evolving dermal tumour on sun-exposed skin of the head, neck or extremities. Histologically, there are sheets and cords of uniform, small cells with hyperchromatic nuclei and multiple small nucleoli. Mitoses and apoptotic bodies are widespread and lymphovascular involvement is commonly present. Aggressive surgical treatment of localized primary lesions followed by radiotherapy remains the mainstay of treatment. Lymph node metastases, local recurrences, and widespread dissemination are commonly seen. The 10-year survival rates for MCC are 71%, 48%, and 20% for localized, regional, and distant disease, respectively. Merkel cell polyomavirus (MCV) has been implicated as a contributing factor in the pathogenesis of MCC with approximately 80% of tumours showing positivity for the virus. This review provides an up-to-date overview of the clinicopathologic features, current knowledge of MCV, and recent advances in diagnosis, prognostication, and management of MCC.

Keywords cutaneous neuroendocrine carcinoma; Merkel cell; Merkel cell carcinoma; Merkel cell polyomavirus; trabecular carcinoma

Introduction

Merkel cell carcinoma (cutaneous neuroendocrine carcinoma, trabecular carcinoma) is a rare, highly malignant neuroendocrine skin tumour that was first described by Toker as trabecular carcinoma in 1972.[1] Six years later, ultrastructural studies revealed the presence of dense core granules in the cytoplasm of the tumour cells.[2] In 1980, the name "Merkel cell carcinoma" was proposed and adopted. Merkel cell carcinoma (MCC) typically presents in elderly, fair-skinned individuals as a rapidly growing dermal tumour, particularly on sun-exposed skin of the head, neck, and extremities. The male/female ratio varies among studies but there appears to be a slight male predominance. There is a 13-fold increase in patients with AIDS and a 10-fold greater incidence in patients with solid organ transplantation.[3,4] Immunosuppressed patients also tend to develop MCC at a younger age. The course of the disease is frequently characterized by lymph node metastases and local recurrences, even within the first year post removal of the primary tumour. Widespread dissemination is also quite common, often leading to a fatal outcome. Five-year overall survival rate is only about 40–50%.[5] The incidence of MCC in the United States is approximately 0.3–0.6/100,000 persons, which has been steadily increasing over the last few decades.[6–8] The SEER database indicates that, in 1986, the incidence was 0.15 cases per 100,000 in the United States. In 2001, the incidence had notably increased to 0.44 cases per 100,000, which represents an 8% increase. There are approximately 1500 new cases of MCC per year with a 33% annual mortality rate. Comparatively, malignant melanoma had a 3% age-adjusted increased annual incidence from 1986 to 2001, with approximately 74,000 new cases per year and an overall five year survival of 91.5%. The increasing incidence seen in both of these tumours may be attributable to an older age of the population, cumulative sun exposure, increased awareness of the disease, and improved diagnostic techniques. Merkel cells remain the sole neuroendocrine cells of the skin, with both neuroendocrine and epithelial profiles; however, it remains to be elucidated whether Merkel cells are the definitive precursor to MCC. Polyomavirus as a causative agent underlying MCC has recently gained attention, with the majority of tumours harbouring DNA derived from a relatively newly identified virus, the Merkel cell polyomavirus (MCV).[9] Progenitor seropositive tumour cells contain the same integrated polyomavirus genome suggesting an etiological role for the virus in tumourigenesis. The aim of this review is to provide an up-to-date overview of the clinical, pathological, and prognostic features of MCC, to present the current knowledge on MCV and its association with MCC development, and to describe recent advances in therapeutics and prognosis.

Cell of origin

Friedrich Sigmund Merkel, a leading German anatomist and histopathologist of the 19th century, was the first to describe cutaneous touch cells in 1875 and referred to them as "Tastzellen".[10] They later became known as "Merkel'sche Tastzellen" or "Merkel'sche Tastkorperchen" and ultimately the "Tast" was omitted and the cells were labelled as Merkel cells. Merkel cells are found in the skin and mucosa of all vertebrates. Specifically, they measure 10–15 microns in diameter and are located in the basal layer of the epidermis and interface with sensory (afferent) neurons at the dermal–epidermal junction. Merkel cells cannot be identified based solely on haematoxylin and eosin staining; however, the addition of immunohistochemistry and/or electron microscopy can aid in identification of individual Merkel cells. Merkel cells show immunoreactivity for low molecular weight cytokeratins CK8, 18, 19, and 20 as well as neuroendocrine markers neuron-specific enolase (NSE), chromogranin A, and synaptophysin.[11] Ultrastructurally, Merkel cells have peripheral spines and desmosomal attachments to adjacent keratinocytes. The cytoplasm has neurofilaments, intermediate keratin filaments, and dense-core granules. Dense core granules are 100–200 nm and contain a heterogeneous complement of neurosecretory substances. The cytoplasmic membrane, of most Merkel cells, is in close apposition to a nerve axon terminal in the underlying papillary dermis. In humans, Merkel cells are

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concentrated in specialized epithelial "touch domes" ("Haarscheiben") of hair-bearing skin, tactile areas of glabrous skin (e.g. fingertips), taste buds, labial epithelium, eccrine glands, anal canal, and the bulge area of hair follicles, the latter suggesting a possible role in adnexal development. In mammals, the highest density is found in whiskers and, in contrast to humans, some dermal Merkel cells have been reported, specifically associated with hair follicles.

Merkel cells have been postulated as having several functions including mechanoreception, endocrine, immunomodulation, and magnetoreception.[12,13] Although it was originally discovered over 50 years ago that Merkel cells are sensitive to touch, the mechanism was not well understood. Recent studies have shown that Merkel cells and afferent nerves serve as mechanoreceptors and that Merkel cell–neuron complexes mediate slowly-adapting responses to discern fine details of objects.[14] The dense core granules in the cytoplasm contain a variety of substances involved in the endocrine and immunomodulation functions.

There has been considerable controversy as to whether Merkel cells originate from neural crest or epidermal precursor cells. Recent studies, including lineage tracing and conditional knockout experiments with mice and immunohistochemical analysis in human tissue, have provided more compelling evidence of an epidermal origin of the Merkel cell.[15,16]

The role of the Merkel cell in human pathology is varied and reflects its heterogeneous functions.[17] Merkel cells are abundant in some adnexal neoplasms, especially trichoblastomas, and trichoepitheliomas. They are increased in processes associated with epidermal hyperplasia, such as psoriasis, prurigo nodularis, and neurodermatitis. They are also increased in skin with chronic ultraviolet radiation exposure. MCC has long been assumed to arise from Merkel cells although this theory has not been conclusively proven. In favour of a Merkel cell origin is that they are the only resident neuroendocrine cells in the skin and have similar cytokeratin and neuroendocrine profiles as the malignant cells of MCC. An alternate explanation is that MCC arises from pluripotent epidermal and/or dermal stem cells. This would account for the dermal location of MCC, relatively frequent coexistence of MCC with other skin epithelial malignancies, and the occasional presence of glandular differentiation (e.g. mixed sweat gland and neuroendocrine carcinoma).

Clinical features

Merkel cell carcinoma (MCC) typically presents as a rapidly evolving, asymptomatic, red to violaceous papule, nodule, or plaque, 2 cm in average diameter, on sun-exposed skin. Patients are usually elderly and many have a fair complexion. MCC is seen in men more often than women and Caucasians more often than other races. It affects older adults, with a median age at diagnosis of 70 years.[18] Less than 4% of affected patients are under 50 years of age and it is extremely rare in children. The most common site is the head and neck region. The extremities and trunk are less frequent sites of involvement. There is an increased incidence reported in patients with immunosuppression, chronic lymphocytic lymphoma (CLL), and organ transplantation. Further, MCC tends to present at an earlier age in patients with organ transplantation. There is strong evidence for UV light exposure as a risk factor for development of MCC although MCC in non-sun-exposed sites occurs and may be associated with a worse prognosis.[19] A proposed acronym that describes the clinical presentation of MCC is "AEIOU": asymptomatic, expanding rapidly, immunosuppressed, older than 50 years of age, and ultraviolet-exposed skin of a fair-skinned individual.[20] The clinical differential diagnosis is broad and MCC is rarely suspected at time of biopsy. The skin can have a subtle shine and overlying telangiectasia, features mimicking basal cell carcinoma or amelanotic melanoma. More often than not, lesions are favoured as benign before a microscopic diagnosis is rendered. Rarely, MCC can present initially in the lymph nodes or viscera. In these cases, regression of the primary cutaneous lesion, like that seen in melanoma, is postulated. MCC is an aggressive tumour frequently showing dissemination to regional lymph nodes at the time of diagnosis. Distant metastasis occurs in approximately 34% of cases. Common metastatic locations include liver, lung, bone and skin but there are reports of spread to other visceral organs.

Histopathology

Histologically, Merkel cell carcinoma is composed of uniform small round cells with a high nuclear-to-cytoplasmic ratio, finely granular chromatin, and numerous small inconspicuous nucleoli (Figure 1). They have a small amount of cytoplasm and vague cellular borders. The cells often show nuclear moulding. There may be areas of spindle cell, plasmacytoid, pseudorosette, or anaplastic morphology. Mitoses and apoptotic debris are generally widespread. MCC is primarily dermal but may have subcutaneous extension. Further, up to 10% of cases show epidermotropism.[21] Epidermal ulceration and reactive vascular proliferation can be seen in approximately 20% of cases. Tumour cells are arranged in sheets, cords, and solid nests/nodules. Three histologic patterns of MCC have been described: trabecular (10%), small cell (10%), and intermediate (80%).[22] Combined growth patterns are common and, if present, the trabecular pattern tends to be only at the periphery of the tumour. Cases with divergent differentiation have been described including glandular (eccrine), smooth muscle, and melanocytic differentiation. The associated stroma is vascular and delicate with desmoplasia only rarely identified. There may be an inflammatory infiltrate composed of lymphocytes and plasma cells. Like melanoma, MCC can undergo regression. Lymphovascular invasion is frequently present, both within and distant from the main tumour mass (Figure 2). MCC is often associated with other tumours, particularly other types of cutaneous malignancies and haematologic tumours (chronic lymphocytic leukaemia). Approximately 40% of MCC have overlying squamous cell carcinoma in situ/Bowen's disease. Less commonly, the tumours are associated with invasive squamous cell carcinoma, basal cell carcinoma, melanoma, and eccrine tumours.[23]

Immunophenotype

Immunohistochemistry can aid in confirmation of a diagnosis of MCC. The tumours characteristically show immunoreactivity for both epithelial and neuroendocrine markers. CK20 is predominately used by pathologists to confirm a diagnosis of MCC, as 80–90% of tumours show positivity in a distinctive paranuclear dot-like pattern.[24,25] This staining pattern is due to clumping of

