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Merkel Cell Carcinoma

■ Synonyms:	Trabecular carcinoma of skin, primary small cell carcinoma of skin, cutaneous APUDoma
■ Etiology:	Ultraviolet light, chromosome 1 abnormalities, p53, bcl-2, c-kit receptor
■ Associations:	Aging, immunosuppression, other cutaneous and visceral malignancies
■ Clinical:	Painless, solitary rapidly growing nodule on exposed cutaneous site
■ Histology:	Diffuse or aggregated dermal nests of small blue cells, numerous mitoses
■ IHC repertoire:	CK-20(+), synaptophysin (+), S-100 (+/−), Melan-A (−), CK-7 (−), CD-45 (−)
■ Staging:	I = localized disease, II = I and regional node(s) (+), III = extranodal metastases
■ Prognosis:	Overall 5-year ~60% survival
■ Adverse variables:	Male, head location, mitoses >10/HPF, vascular permeation, (+) lymph nodes
■ Treatment:	I = WLE/XRT, II = WLE/XRT/ELND, III = XRT/?CTX/?ABMT/limb perf HPF = high power fields, WLE = wide local excision, XRT = X-ray radiotherapy, CTX = chemotherapy, ABMT = autologous bone marrow transplantation

Merkel cell carcinoma, as first described by Toker, et al. (1) in 1972, and otherwise known as trabecular carcinoma of the skin, neuroendocrine carcinoma of the skin, cutaneous APUDoma, primary small cell carcinoma of the skin with endocrine differentiation, is an uncommon, aggressive cutaneous neoplasm. Friederich Merkel first discovered the Merkel cell in 1875. It is a large, clear, usually round or oval cell found in the basal layer of the epidermis. It is found in close association with terminal axons, and is joined to keratinocytes. They are found in highest concentrations in acral skin, namely the fingertips and nasal tip, as well as glabrous skin, hairy skin, and mucous membranes. The exact function of Merkel cells is unclear, but it is generally thought that they are a form of touch receptor (2–4). The origin of Merkel cell carcinoma is controversial as well. It may arise from epidermal Merkel cells, dermal neuroendocrine cells, or poorly differentiated epidermal stem cells.

The etiology of this tumor is unknown, although it is likely that a number of different factors play a role in its development. Merkel cell carcinoma is located primarily on the head and neck, areas that commonly receive actinic damage. Hence, it is thought that UV radiation may play a role in the development of these tumors. However, there have been many reports of tumors arising in non-sun-exposed regions as well, and thus other factors must play a role. Changes in chromosome 1 have been frequently identified in MCC, thus lending to the hypothesis that there may be a genetic predisposition in certain individuals to develop this tumor (5). More recent data have examined the role of bcl-2 and p53 genes in Merkel cell carcinoma. P53 and bcl-2 expression in MCC is variable, and either loss of function or excess function of either bcl-2 and/or p53 may promote tumor development (6). In one study by Su, et al., CD117 (KIT receptor) was found to be expressed in 95% of tumors (7). Merkel cell carci-

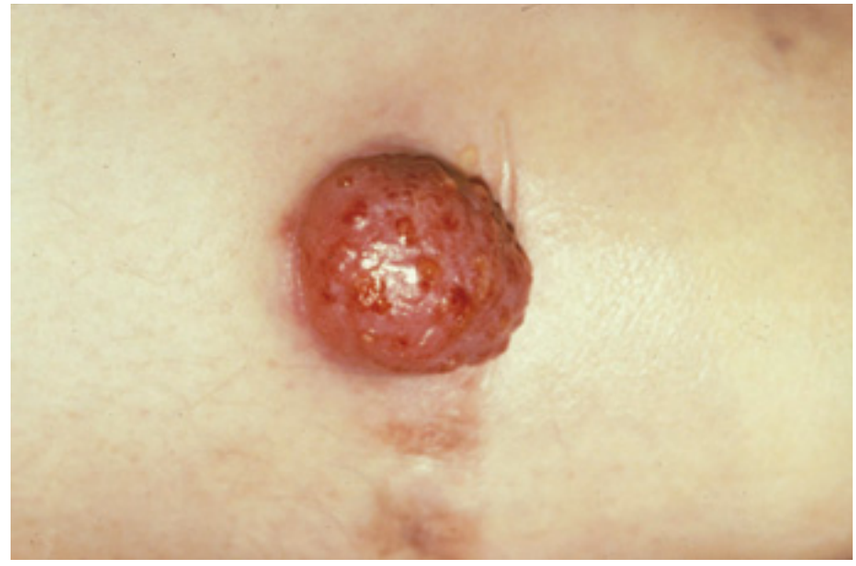

FIGURE 7.1. Erythematous glistening papule of merkel cell carcinoma.

noma is a very rare neuroendocrine cutaneous neoplasm, and as of the year 2000, approximately 1100 cases have been reported in the literature since first noted by Toker in 1972 (4). Herbst, et al. reported that approximately 400 new cases are diagnosed in the United States each year. It is most common in elderly individuals, primarily on the head and neck (44%–50%, 20% of which arise in the periocular region), followed by the extremities (40%–44%), the trunk (8%), and the buttocks (9%) (1–4). This tumor occurs primarily in Caucasians, with a few case reports in African Americans and Polynesians. Most patients are in their 60 s and 70 s at the time of diagnosis, with the average age being 65, but the literature cites cases documented on patients as young as 7 years of age and up to 97 years of age. The ratio of men to women varies among different reports, with some citing equal incidence of occurrence among both sexes, some reporting a slightly higher incidence in men (1.5 : 1), and others finding a slightly higher incidence in women. Merkel cell carcinoma has also been reported to arise in patients with other neoplasms, at a frequency higher than expected by chance alone (4). These include squamous cell carcinoma, basal cell carcinoma, and lentigo maligna. Other internal malignancies that have been documented to be associated with MCC are Hodgkin's lymphoma, breast carcinoma, endometrial carcinoma, colon carcinoma, prostate cancer, ovarian cancer, bladder transitional cell carcinoma, squamous cell carcinoma of the larynx, B-cell lymphoma, and chronic lymphocytic leukemia (CLL). Merkel cell carcinoma has also been reported to arise in sites of previous radiation therapy (2–4). Immunosuppressed patients have been found to be at an increased risk for many malignancies, including Merkel cell carcinoma. Immunosuppressed individuals tend to have tumors that behave more aggressively than those seen in the general population.

Merkel cell carcinoma can present in many different ways, but is most often a solitary, painless, pink to reddish-blue or brown dome-shaped nodule or plaque on sun-exposed skin of elderly individuals (Figure 7.1). The lesion may sometimes ulcerate, and can range in size from 0.2 cm to 5.0 cm, with the largest lesion reported as 23.0 cm in greatest diameter (2–4).

Merkel cell carcinoma is composed of small, monomorphic, basophilic tumor cells with round to oval-shaped nuclei and scanty cytoplasm. The nuclei have finely granular dispersed chromatin, and nucleoli are absent or few in number. The nuclear-to-cytoplasmic ratio is high, as is as the mitotic rate, and pyknotic nuclei and apoptotic bodies may be present. The tumor cells occupy the dermis, and may extend into the subcutaneous fat (Figures 7.2 and 7.3). The epidermis is generally spared, but there are reports of epidermotropism or "pagetoid" spread. In these instances, MCC may mimic melanoma, mammary and extramammary Paget's disease, mycosis fungoides, pagetoid Bowen's disease, and intraepidermal epithelioma (8–9). The association of Merkel cell carcinoma with the aforementioned tumors, and its propensity to develop both squamous and eccrine differentiation, support a link between MCC and the epithelium. A dense lymphocytic infiltrate is typically present within and surrounding the tumor. There may be involvement of the dermal lymphatics and blood vessels. Merkel cell carcinoma has been classified into 3 histologic subtypes. The intermediate cell type is considered the most common variant of MCC,

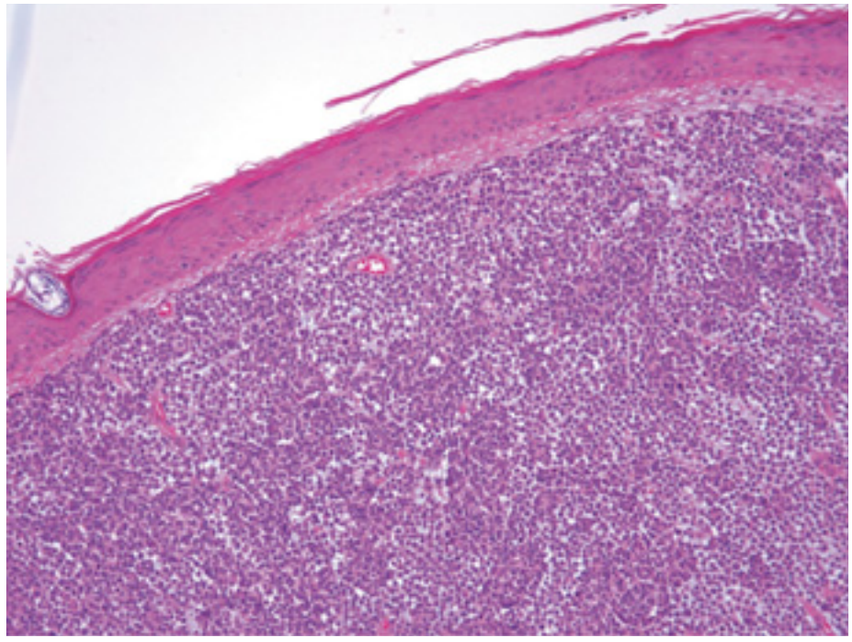

Figure 7.2. Low power photomicrograph depicting diffuse dermal permeation by neoplastic cells.

seen in approximately 50% of all Merkel cell carcinomas. It displays a solid, diffuse pattern made up of cells that are less compact, with focal areas of necrosis. Mitotic figures are conspicuous. There is a lymphocytic infiltrate within and around the tumor. The second histologic variant described by Gould, et al., the small cell variant, is composed of solid sheets and clusters of cells in the dermis, lacks glandular differentiation, and often has areas of necrosis. The trabecular pattern, considered to be the least common pattern, is characterized by round to polygonal cells arranged in organoid clusters and trabeculae, which may occasionally exhibit gland-like formations. This clas-

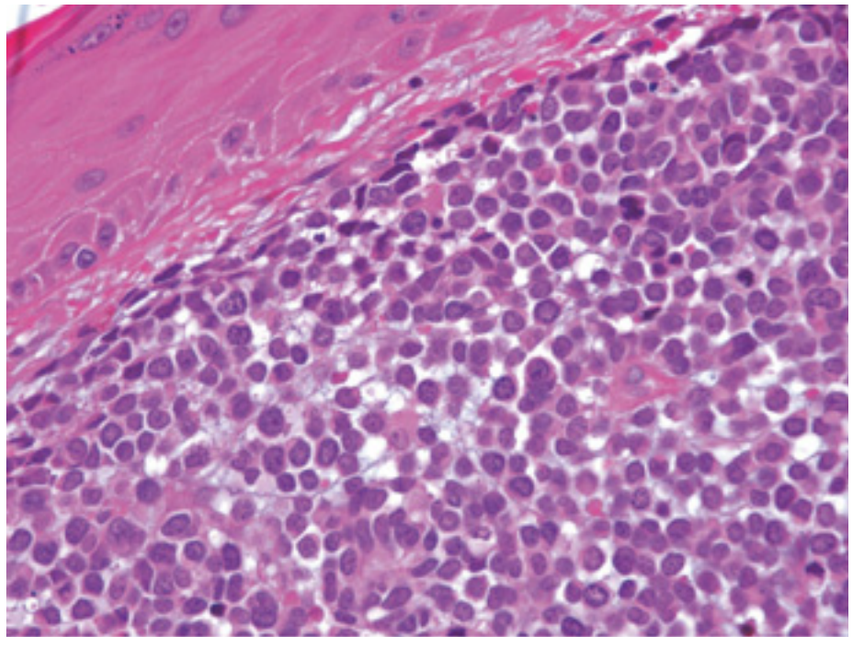

Figure 7.3. High power photomicrograph depicting small blue cells containing speckled nuclear chromatin. Note scattered mitotic figures.

sification scheme arranged by Gould, et al., is comprehensive; however, many tumors are composed of cells of different sizes and patterns, and not all tumors will fit exactly into one subtype. A triad of findings suggested to be virtually pathognomonic of MCC includes vesicular nuclei with small nucleoli, abundant mitoses, and apoptosis. The differential diagnosis includes other poorly differentiated small cell tumors. These include small cell carcinoma of the lung (oat cell carcinoma), cutaneous large cell lymphomas, neuroblastoma, metastatic carcinoid, amelanotic melanoma, sweat gland carcinoma, medullary carcinoma of the thyroid, Langerhans cell histiocytoses, plasmacytoma, Ewing's sarcoma, leukemias, and anaplastic carcinoma.

The definitive diagnosis of Merkel cell carcinoma requires the use of immunohistochemistry. The armamentarium of immunohistochemical stains that may be useful in diagnosing MCC is vast, and controversy exists as to which markers are best suited for this purpose. Anticytokeratin antibodies are the most sensitive markers for MCC, with various studies citing up to 100% positive reactivity to anti-keratin antibodies to low molecular weight cytokeratins (Figure 7.4). A perinuclear dot-like pattern of positivity is characteristic for MCC, and is a feature generally not observed in SCC (10–12). Keratin reactivity favors the diagnosis of MCC, and excludes melanoma and lymphoma. Diagnoses that MCC cannot be differentiated from with these markers include carcinoid and metastatic small cell lung cancer. Positive reactivity with anti-CK 8, 18, 19, and 20 also support an epithelial derived component of MCC. Among the anti-cytokeratin markers, most studies suggest than anti-CK 20 is highly specific for MCC, and is thought to be a strong predictor of MCC when determining the diagnosis of small cell carcinomas. The newest marker being investigated for use in identifying Merkel cell carcinomas is thyroid transcription factor 1 (TTF-1). It is a nuclear transcription factor expressed in thyroid and lung epithelial cells. TTF-1 belongs to a family of transcription factors that are expressed in the thyroid, lung, and certain regions of the brain. This marker is also found in pulmonary carcinomas, reacting with 72.5% of adenocarcinomas, 83%–100% of small cell carcinomas, 100% of atypical carcinoid tumors, and 75% of neuroendocrine carcinomas. It is not, however, expressed at all in MCC. TTF-1 is a sensitive and specific marker for small cell lung carcinoma, and CK 20 is a sensitive but not 100% specific marker for MCC. Thus, with the above information, it appears that a combination of TTF-1 and anti-CK 20 should provide the best sensitivity and specificity when needing to distinguish MCC from other small cell carcinomas.

Staging, based on the extent of local and systemic disease, is important in guiding treatment as well as determining prognosis. Stage I disease is local disease without lymph node or systemic involvement. Stage II disease refers to regional lymph node disease without evidence of systemic spread. Stage III refers to metastatic disease.

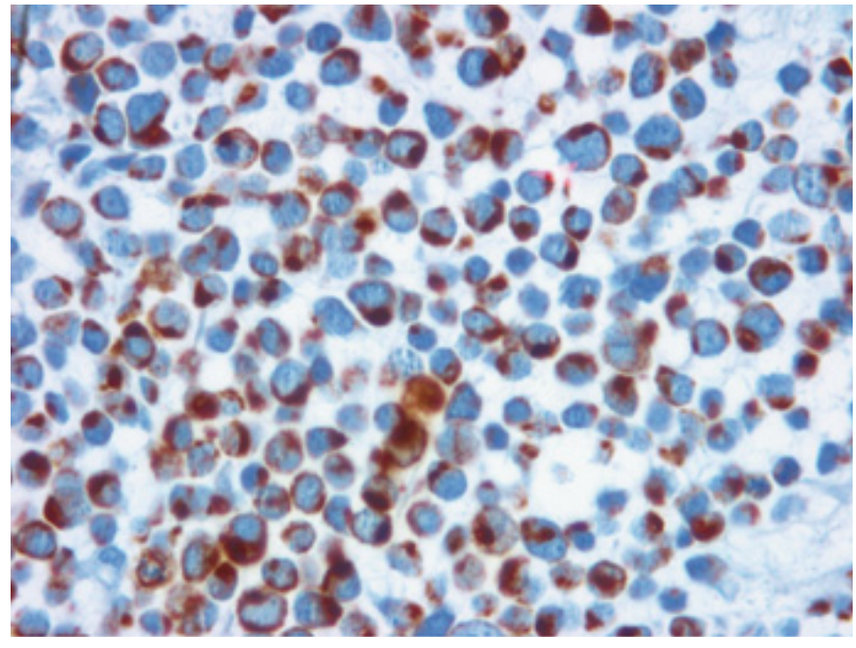

FIGURE 7.4. Dot-like paranuclear immunostaining with cytokeratin 20 in Merkel cell carcinoma.

Merkel cell carcinoma is a very aggressive malignancy in which metastatic disease is not uncommon. Survival rates vary, but the overall survival rate has been reported to range from 58% to 79% (13–27). It is considered to be the deadliest skin cancer, with a higher fatality rate than melanoma. Factors that have been found to be relevant to prognosis include tumor size and location, the sex and age of the patient, the stage of disease, and histologic characteristics. Tumors on the head and neck generally have the worst prognosis, followed by lesions on the trunk and extremities. Male sex has been reported to portend a worse prognosis, while age at diagnosis has been controversial. Histologic features associated with a poor prognosis include a mitotic rate of >10 per high power field, and evidence of vascular or lymphatic involvement.

Merkel cell carcinoma has been considered to follow a course similar to that of an intermediate or thick melanoma, but with a worse prognosis. Local recurrence usually occurs within 4 months of excision of the primary tumor, and is not uncommon, occurring in 20% to 44% of cases, with few reports citing up to 70%. Regional nodal metastases have been reported to occur in 31% to 80% of MCC; however, only 12% to 31% of these cases are present at the initial presentation. They are more common in tumors of the head and neck, and most nodal metastases are discovered within 7–24 months of initial treatment. Nodal involvement is a significant prognostic indicator, with a 5-year survival rate of 48% for patients with nodal disease, as compared to 88% for those without nodal involvement. Distant metastases indicate a very poor prognosis, and are the most important predictor of survival. They are found in 1/3 to 2/3 of patients with MCC, but are rarely present at initial presentation. The most common sites are lymph nodes, followed by liver, bone, brain, lung, skin, and GI tract. Distant metastases are diagnosed at a mean time of 18 months after initial diagnosis. The mortality rate of patients with systemic metastases ranges from 67% to 74%, with death usually occurring within 6 months of detection of the metastases. Spontaneous regression is a rare phenomenon that has been noted to occur in some cases of Merkel cell carcinoma. As of 2002, 10 cases in the literature have been reported.

Due to the rarity of this tumor, there are no widely adopted, standard treatment regimens. Early diagnosis and treatment are essential due to the aggressiveness of MCC and its propensity for local recurrence and metastases. Multimodality treatment is thought to offer the best overall survival rates, but specific treatments are controversial and their benefits debatable. The following are recommendations based on each stage of disease. Stage I disease should be treated with surgical excision, using wide local excision with 2–3-cm margins, dissecting to fascia. Excision may be followed by elective lymph node dissection or lymphoscintigraphy and sentinel node biopsy. Postoperative radiation may also be considered. The use of chemotherapy at this stage is not well defined and requires further investigation. Stage II disease requires re-excision of local recurrences, followed by postoperative radiation to the primary and regional nodal basins. Elective lymph node dissection or sentinel node biopsy should be considered. If regional nodal metastases have been detected, total lymphadenectomy and postoperative radiation provides the best management. Stage III disease most often requires systemic chemotherapy. Other investigational treatments, including bone marrow transplant, local hyperthermia, and hyperthermic limb perfusion therapy, have rarely been used, with disappointing results.

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