# 8.2

# Merkel Cell (Cutaneous Neuroendocrine) Carcinoma

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Merkel cell carcinoma (primary cutaneous neuroendocrine carcinoma, trabecular carcinoma) is a rare but often lethal tumor of uncertain histogenesis. Five cases were originally described by Toker[1] in 1972 as "trabecular carcinoma of the skin." This name was derived from the most characteristic (but least common) of three distinct histologic patterns for this tumor. Later electron microscopic analysis revealed cytoplasmic neurosecretory granules in the cells of this carcinoma and linked it to its most likely precursor, the Merkel cell. Pathologists suggest that this tumor should be called neuroendocrine carcinoma of the skin[2] because it is highly analogous to such tumors in the lung (small cell carcinoma) and other sites, likely sharing a similar precursor cell.

The Merkel cell was initially described as a "touch" cell ("tastzellen") by the German anatomist and histopathologist Friedrich Sigmund Merkel in 1875.[3] In early studies, he found a high density of these cells in pig snout skin, and their association with cutaneous nerves suggested a role in mediating the touch sensation (Figure 8.2–1). On light microscopy, Merkel cells are difficult to differentiate from melanocytes or Langerhans' cells; however, they can be readily identified by standard electron microscopy (Figure 8.2–2) or more routinely identi-

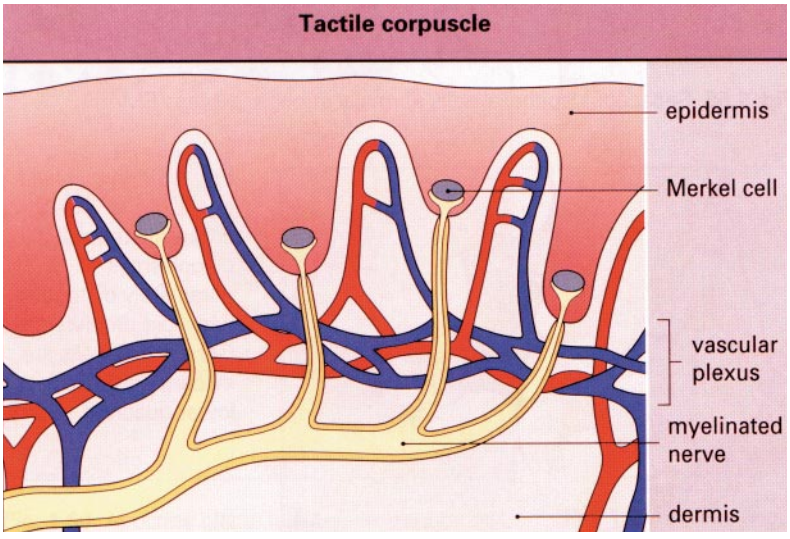



**Figure 8.2–1.** Schematic of the location of Merkel cells within the epidermis and association with cutaneous nerves. (Reprinted with permission from McKee. Pathology of the skin. 2nd ed. Mosby: London, 1996, pg 1.13)

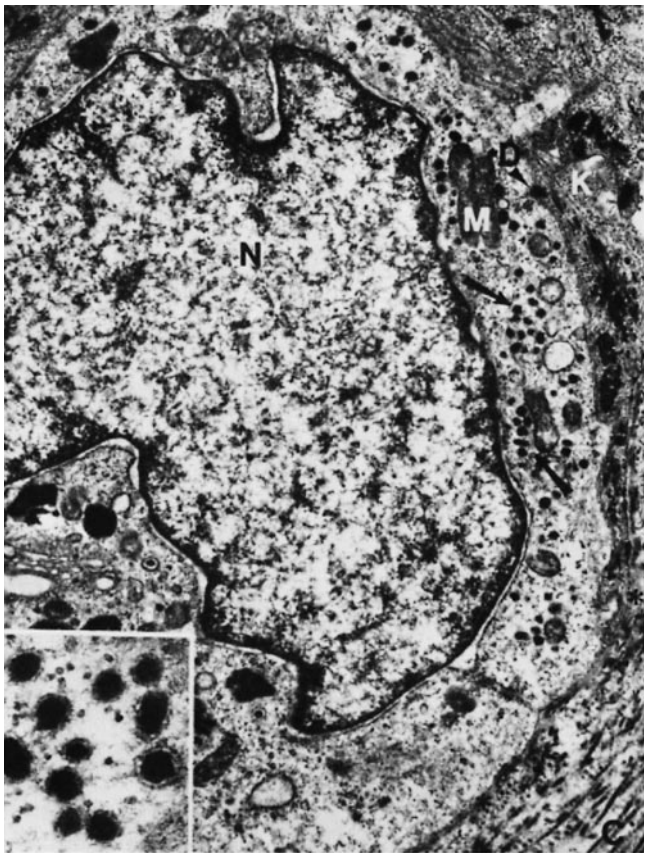



**Figure 8.2–2.** Electron micrograph of a Merkel cell. *Arrows* point to specific granules of the Merkel cell. (N = nucleus of Merkel cell; M = mitochondria; D with arrowhead = desmosome between Merkel cell and keratinocyte [K]; C = collagen with cross striation.) (x20,000 original magnification) (Reproduced with permission from Lever. Histopathology of the skin. 8th ed.) Inset shows characteristic cytoplasmic Merkel granules at high magnification (x75,000 original magnification).

fied by their immunocytochemical staining profile, as discussed in the pathology section below.

With only about 400 cases per year in the United States, Merkel cell carcinoma is at least 100 times more rare than melanoma,[4,5] and with a fatality rate of about 26 percent, it is the most lethal of the skin cancers (Table 8.2–1).[5,6] There has been considerable evolution in the treatment philosophy of Merkel cell carcinoma. As recently as 1987, it was suggested that this cancer should be treated "using the same rationale as applied for the treatment of squamous cell carcinoma."[2] It is increasingly apparent that the 10-fold greater fatality rate for Merkel cell carcinoma over squamous cell carcinoma can be significantly diminished through prompt aggressive treatment involving wide excision, lymph node biopsy, and adjuvant radiation therapy.

**Table 8.2–1. COMPARISON OF SKIN CANCERS: INCIDENCE AND MORTALITY IN THE UNITED STATES**

| Tumor | Annual US Incidence | Deaths | Fatality Rate |
|---|---|---|---|
| Merkel cell carcinoma* | 400 | 130 | 1 in 4 |
| Melanoma | 42,000 | 8,000 | 1 in 5 |
| Squamous cell carcinoma | 100,000 | 2,000 | 1 in 50 |
| Basal cell carcinoma | 850,000 | < 80 | < 1 in 10,000 |

*Figures are based on an estimated incidence of 0.16 per 100,000 and a 74 percent disease-specific survival.
Adapted from Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. CA Cancer J Clin 1998;48:6–29.

## CLINICAL PRESENTATION

Merkel cell carcinoma has a rather nonspecific appearance, usually developing on sun-exposed skin as a firm erythematous papule with occasional ulceration (Figure 8.2–3). Because of the rarity of this tumor and this nondistinctive appearance, the vast majority of these tumors are removed with a presumptive diagnosis of squamous cell carcinoma, basal cell carcinoma, keratoacanthoma, amelanotic melanoma, adnexal tumor, or lymphoma (Figures 8.2–4 to 8.2–6).[7]

The large role played by ultraviolet radiation in the development of this tumor is suggested by its presence in a sun-distribution on the body of older Caucasian individuals, many of whom already have other sun-induced skin cancers.[7] The most common primary site is the head and neck (40%), followed by the upper extremity (19%) (Figure 8.2–7).[8] In terms of gender, there is a slight male predominance (3:2). The median age for developing Merkel cell carcinoma is 66 years, with two-thirds of cases presenting in patients over 60 years of age.[8]

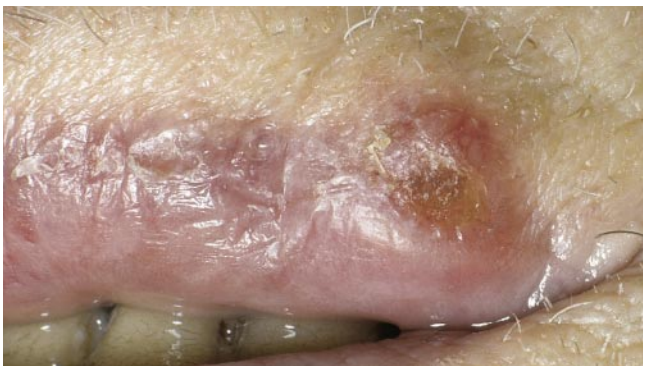


**Figure 8.2–3.** A Merkel cell carcinoma on the lip of a 92-year-old man.

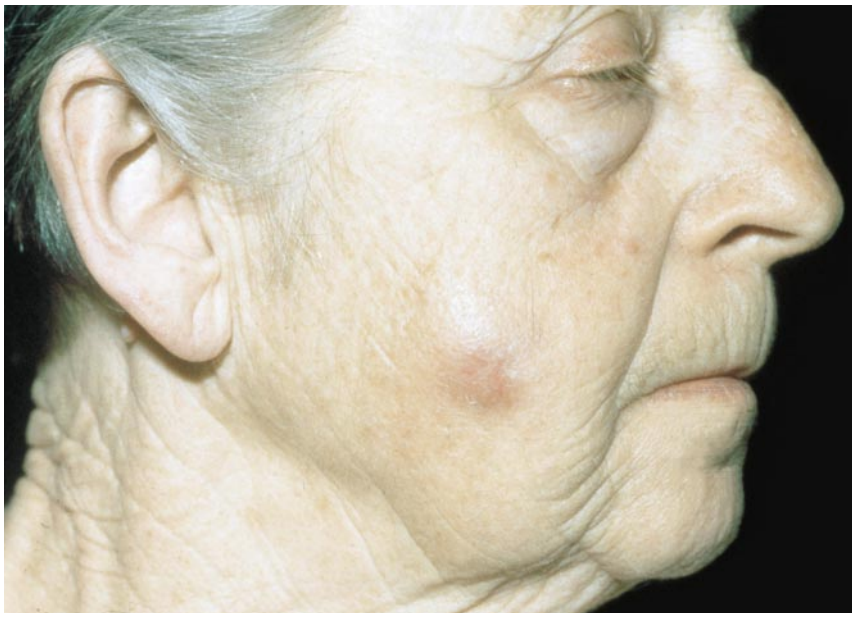


**Figure 8.2–4.** Merkel cell carcinoma arising on the face. (Courtesy of Dr. Helmut Kerl)

## PROGNOSIS

The outlook for patients with Merkel cell carcinoma (MCC) is partly dependent on the clinical stage of the disease although even the earliest lesion of MCC carries about a 10 percent chance of death within 2 years.[6] The staging system, the fraction of patients presenting with each stage, and survival is summarized in Figure 8.2–9. Larger primary tumors and the presence of disease in regional lymph nodes each diminish survival rates significantly. The most common sites for metastasis are listed in Table 8.2–2.[8] Several recent studies suggest that the outcomes depend on the optimal management of MCC with wide (2.5-cm margin) excision, lymphatic assessment, and radiation therapy.[9–12]

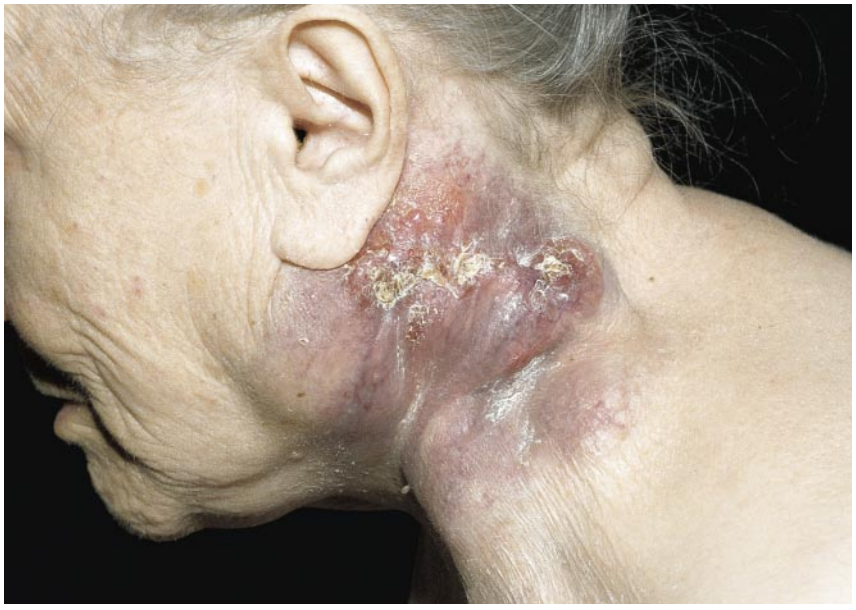


**Figure 8.2–5.** An advanced Merkel cell carcinoma involving the neck. (Courtesy of Dr. Helmut Kerl)

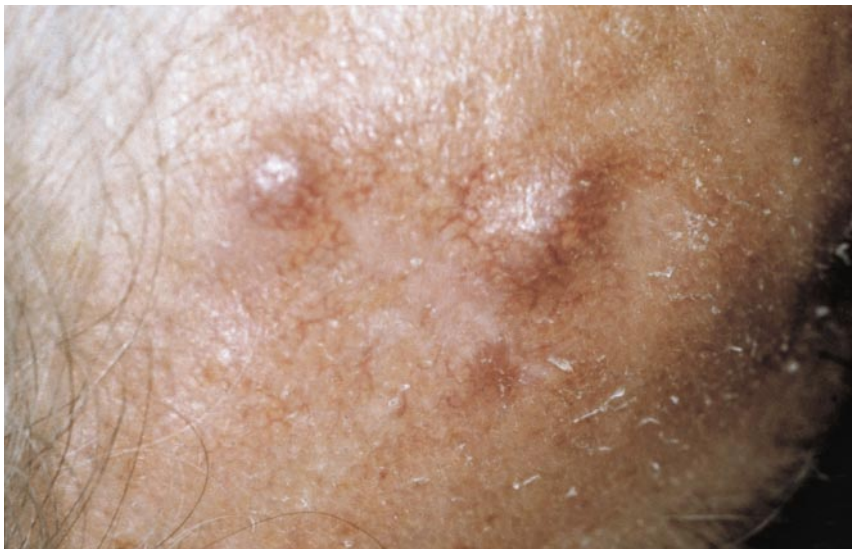


**Figure 8.2–6.** Multiple small tumor nodules of Merkel cell carcinoma on the forehead. (Courtesy of Dr. R.A. Johnson)

## RISK FACTORS AND ASSOCIATIONS

A history of prolonged sun exposure and age over 60 years are the major risks for MCC. Ultraviolet exposure in the form of psoralen plus ultraviolet A (PUVA) has also recently been associated with an approximately 100-fold increased MCC incidence.[13] Among 1,380 psoriasis patients treated with PUVA, 3 (0.2%) developed MCC. All 3 were elderly and had had between 4 and 60 prior non-melanoma skin cancers. In 2 patients, the MCC developed more than 20 years after PUVA therapy was initiated, and 2 patients had received more than 300 PUVA treatments.[13]

There are several recent reports of MCC associated with arsenic exposure (Figure 8.2–8).[14,15] Along the southwest coast of Taiwan prior to 1970, people drank artesian-well water containing high levels of arsenic. Elevated levels of squamous cell, basal cell, bladder, and lung carcinoma were encountered. More recently, six cases (higher than expected) of MCC were reported in this region.[15]

A role for immune surveillance in the control of MCC is suggested by several studies that document an

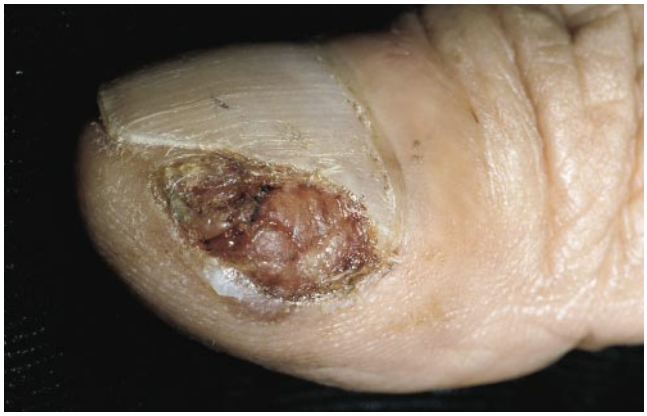


**Figure 8.2–7.** A rare subungual Merkel cell carcinoma (MCC): a small fraction of MCCs arise on relatively sun-protected sites. (Courtesy of Dr. R.A. Johnson)

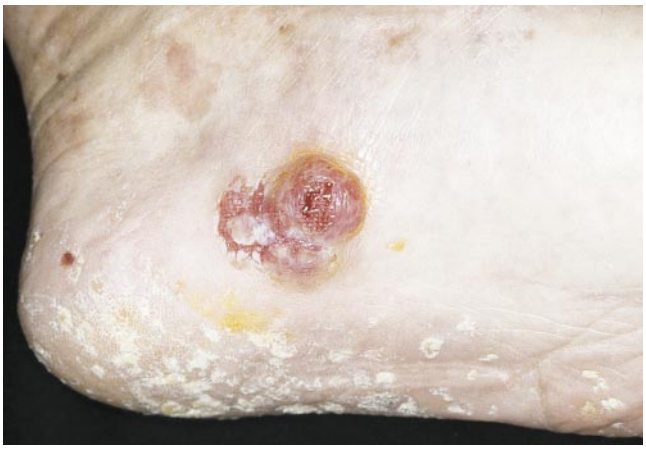
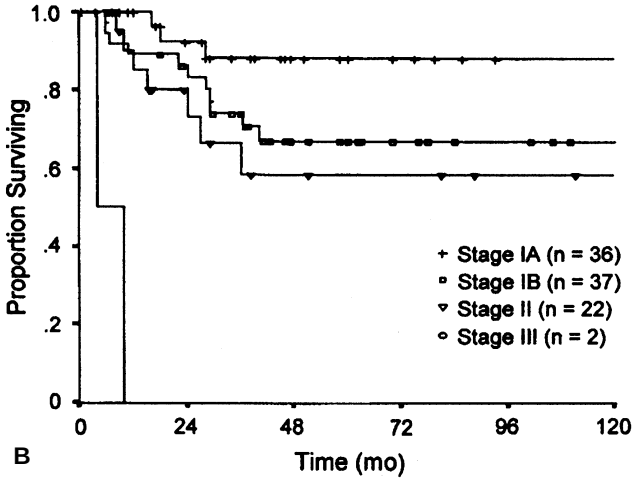


**Figure 8.2–8.** A Merkel cell carcinoma arising on the foot of a Japanese man exposed to arsenic. Multiple white arsenical keratoses can also be seen in addition to the red nodule of the Merkel cell carcinoma. (Reproduced with permission from Tsuruta D, Hamada T, Mochida K, et al. Merkel cell carcinoma, Bowen's disease and chronic occupational arsenic poisoning. Br J Dermatol 1999;41:641–3.)

A

| Stage | Presentation Characteristics | % of Cases |
|---|---|---|
| IA | Primary tumor < 2 cm | 37 |
| IB | Primary tumor > 2 cm | 38 |
| II | Spread to draining lymph nodes | 23 |
| III | Distant disease | 2 |




B

**Figure 8.2–9.** *A,* The staging classification for Merkel cell carcinoma is given with the frequency of patients presenting with each stage in 97 cases, the largest single series. *B,* Kaplan-Meier curves for 10-year disease-specific survival in patients with Merkel cell carcinoma, plotted by stage at presentation. (Reproduced with permission from Allen PJ, Zhang ZF, Coit DG. Surgical management of Merkel cell carcinoma. Ann Surg 1999;229:97–105.)

association with chronic immune suppression in organ transplant recipients. Some 52 Merkel cell carcinomas have been reported in organ transplant recipients.[16,17] Importantly, the mean age at diagnosis was younger (53 vs 66 years), and the MCC-associated death rate was more than double the death rate of MCC patients from the general population (68% vs 26%).[6,17]

A rare and welcome event in MCC management is spontaneous regression, of which 5 cases have been reported.[18] In one of these cases, a 65-year-old man was too ill to undergo treatment, and on follow-up 6 months later, the lesion had resolved.[18]

Virtually nothing is known of the molecular pathogenesis of MCC. The most commonly mutated gene in cancers in general, p53, was only targeted in a minority of MCCs (28%),[19] which suggests that it plays a minor and non-essential role in the development of this tumor. No association with clinical outcome was found after examining the expression level of proapoptotic (bax and wild-type p53) or antiapoptotic (bcl-2) genes in 25 MCCs.[20]

## HISTOLOGIC FEATURES

The Merkel cell tumor belongs to the group of small "blue" cell tumors, which also includes metastatic neuroendocrine carcinoma (usually of bronchial cell origin), lymphoma, primitive peripheral neuroectodermal tumor, and small cell melanoma.

Histologically, the tumor commonly involves the full thickness of the dermis (Figure 8.2–10) and frequently extends into the subcutaneous fat and adjacent skeletal muscle.[1,21–23] While a Grenz zone of dermal sparing often separates the tumor from the overlying epidermis, epidermal changes (including ulceration) are not uncommon. Occasionally, pagetoid spread may simulate melanoma or mycosis fungoides (Figure 8.2–11), and (exceptionally rarely) the tumor may appear to be wholly intraepidermal.[24,25] The majority of neuroendocrine carcinomas arise on the sun-exposed skin of elderly individuals, and severe actinic elastosis is therefore frequently present.

**Table 8.2–2. CHARACTERISTICS OF MERKEL CELL CARCINOMA IN 107 PATIENTS**

| Characteristics | % of Patients* |
|---|---|
| Gender | |
| Male | 59 |
| Female | 36 |
| Age (median = 66 yr) | |
| < 60 | 26 |
| ≥ 60 | 66 |
| Ethnicity | |
| White | 97 |
| Black | 1 |
| Primary site | |
| Head and neck | 37 |
| Upper extremity | 18 |
| Lower extremity | 17 |
| Trunk | 13 |
| Vulva | 3 |
| Metastatic site | |
| Skin | 28 |
| Lymph nodes | 27 |
| Liver | 13 |
| Lung | 10 |
| Bone | 10 |
| Brain | 6 |
| Bone marrow | 2 |
| Pleura | 2 |
| Pancreas | 1 |
| Testis | 1 |
| Small bowel | 1 |
| Stomach | 1 |

*In some cases, percentages were rounded to the nearest whole number. Reprinted with permission from Voog E, Biron P, Martin JP, Blay JY. Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma. Cancer 1999;85:2589–95.

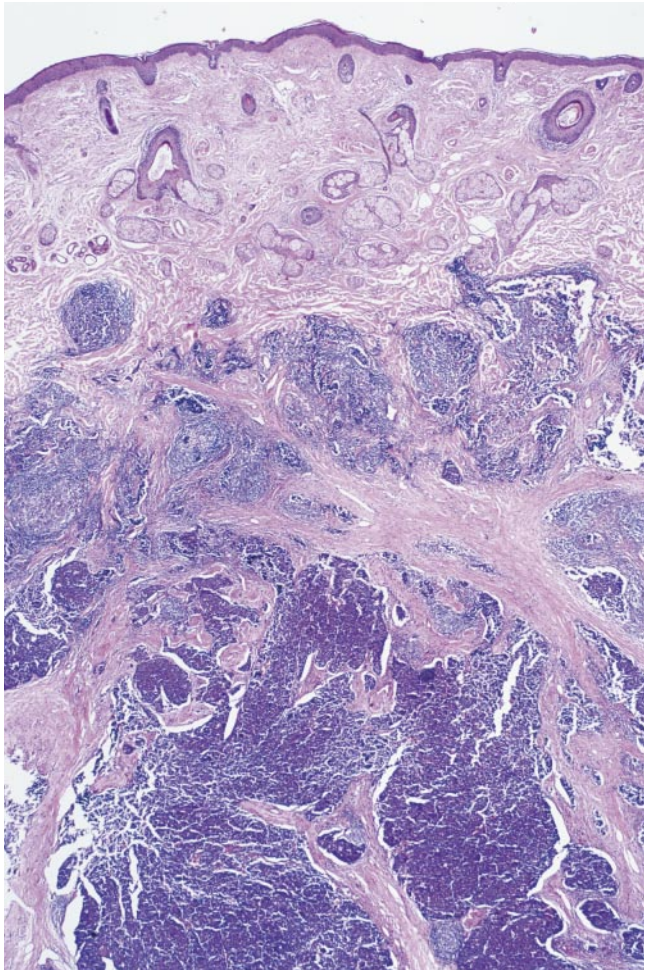


**Figure 8.2–10.** Scanning view shows extensive dermal infiltration by a small "blue" cell tumor.

A variety of histologic subtypes are recognized (Figures 8.2–12 to 8.2–16), including intermediate, small-cell, and trabecular.[21] Although the last conforms to the original description by Toker, it is in fact the least commonly encountered.[1] Mixed intermediate and small-cell variants are also not uncommon. Most often, the cells are present in diffuse sheets or nests sometimes showing regular borders but more often associated with an irregular infiltrating growth pattern dissecting between the collagen fibers of the adjacent dermis. In the trabecular subtype, the tumor cells are arranged in narrow strands or ribbons that are one or two cells thick, reminiscent of a carcinoid tumor.

The tumor cells have scanty indistinct amphophilic cytoplasm and generally have round or oval nuclei. The nuclei are characteristically vesicular, with pale-staining delicate chromatin (intermediate and trabecular types), although hyperchromatic and spindle forms (small-cell type) may also be encountered (Figure 8.2–17). The latter variant often shows nuclear molding. Nucleoli are commonly present but usually not prominent. Mitoses are typically numerous, and atypical forms are frequently seen. Apoptosis is often marked. Occasionally, geographic areas of necrosis are a feature, particularly in the small-cell variants, and cellular fragility may give rise to a conspicuous crush artifact, with encrustation of blood vessel walls and collagen fibers by nuclear debris. Additional features that may occasionally be encountered include small foci of squamous and/or ductal differentiation.[26] Lymphovascular invasion (Figure 8.2–18) is commonly present, but perineural infil-

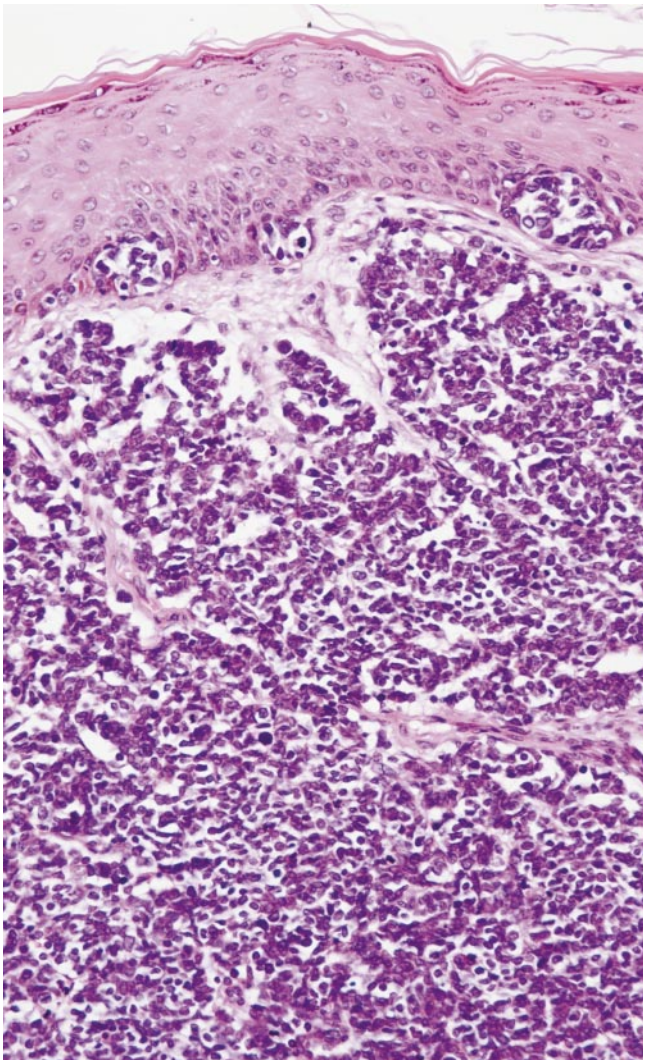


**Figure 8.2–11.** This view of a cutaneous neuroendocrine carcinoma shows intraepidermal involvement. The case was seen in consultation, with an initial diagnosis of cutaneous T-cell lymphoma.

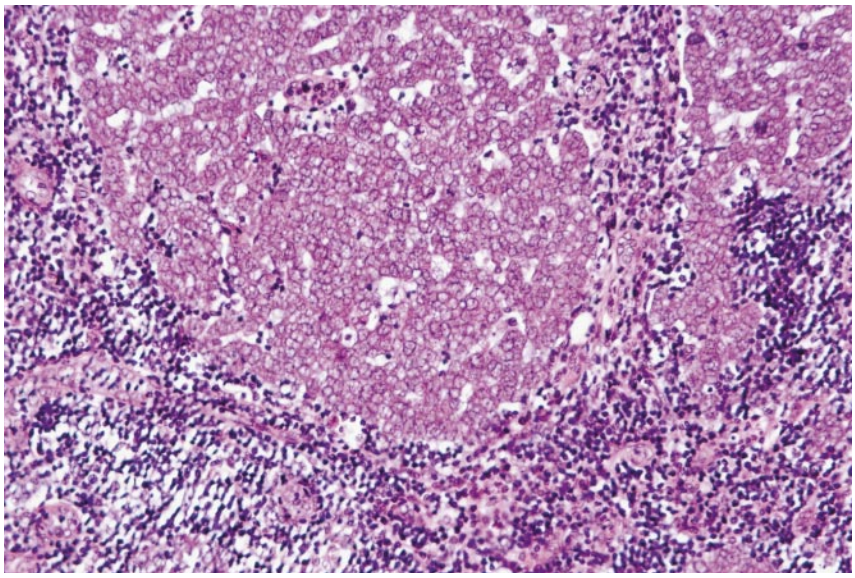


**Figure 8.2–12.** Intermediate neuroendocrine carcinoma. The tumor is composed of uniform small cells with minimal cytoplasm and round to oval palely staining nuclei. Lymphocytes are present in the background.

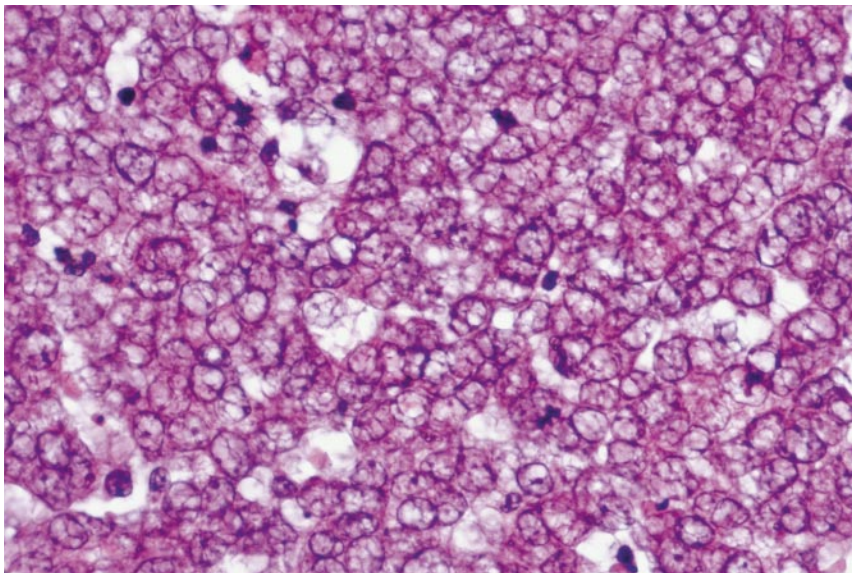


**Figure 8.2–13.** Intermediate neuroendocrine carcinoma; high-power view showing the characteristic nuclear morphology. There are numerous mitotic figures.

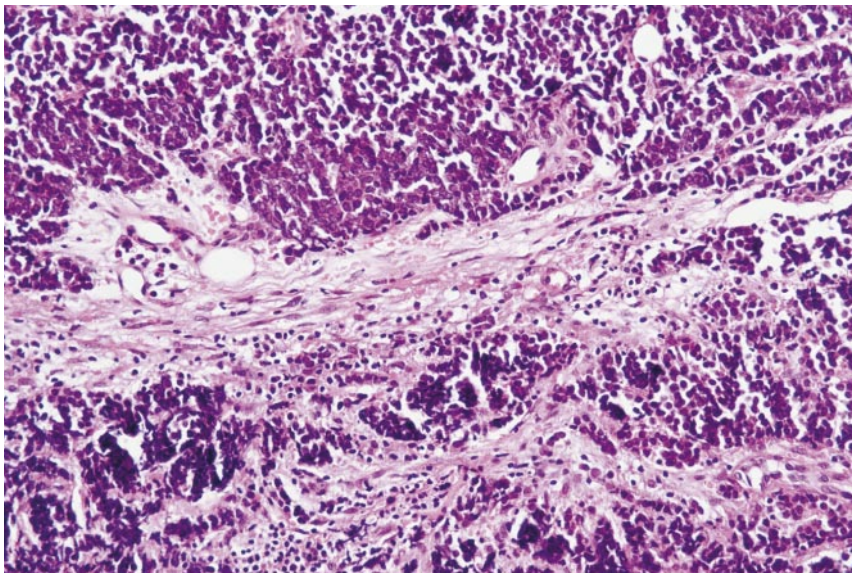


**Figure 8.2–14.** Small cell neuroendocrine carcinoma showing characteristic crushed nuclear debris in the lower half of the field. Such crush artifact is characteristic of neuroendocrine carcinomas, including Merkel cell carcinoma of the skin and small cell carcinoma of the bronchus.

**Figure 8.2–15.** Small cell neuroendocrine carcinoma composed of cells with hyperchromatic nuclei and minimal cytoplasm. An "Indian-file" distribution is seen in the center of the field. These features are indistinguishable from those of a bronchial small cell carcinoma.

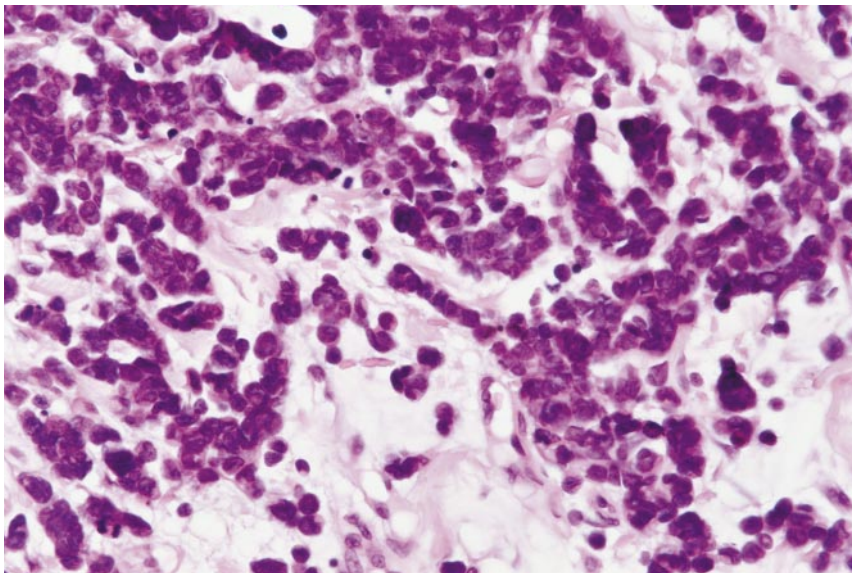


**Figure 8.2–16.** Primary cutaneous neuroendocrine carcinoma showing the typical appearances of the trabecular variant. This lesion may be confused with metastatic carcinoid tumor.

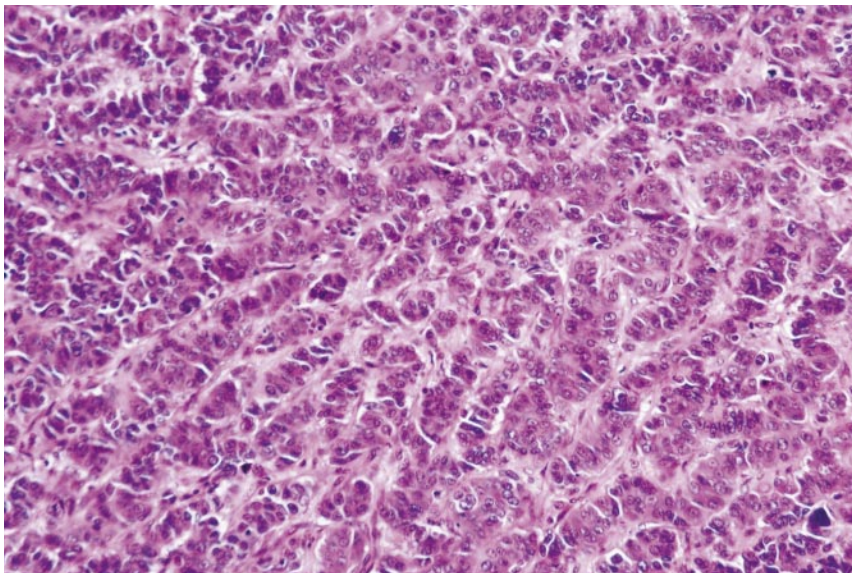
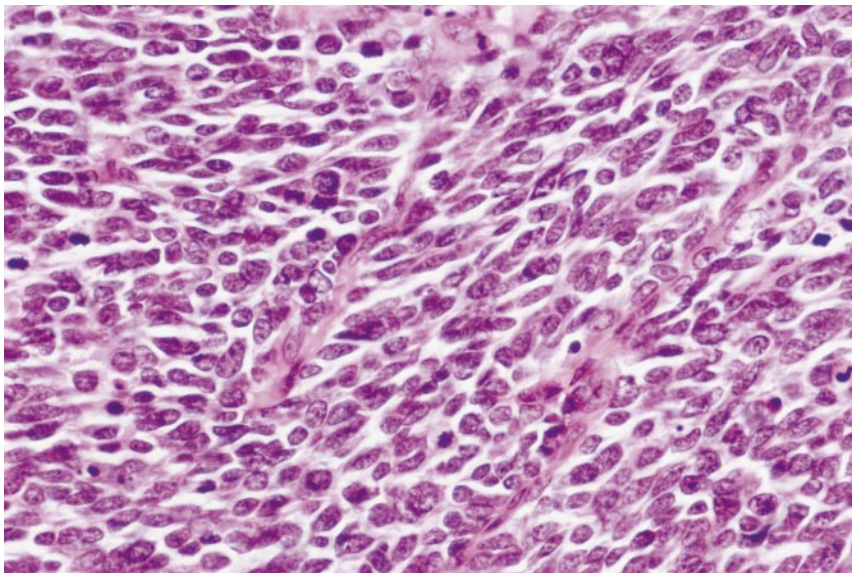


**Figure 8.2–17.** Small cell neuroendocrine carcinoma, showing spindle-shaped nuclei.



tration is rarely seen. The tumor infiltrate is usually accompanied by a lymphocytic infiltrate, and plasma cells are sometimes also present.

Occasionally, the overlying epidermis shows coexistent squamous cell carcinoma in situ although merging or continuity between the two populations is very rare. Primary cutaneous neuroendocrine carcinoma (notably the intermediate variant) may also coexist with invasive squamous cell carcinoma (Figure 8.2–19), and the two cell populations frequently appear to blend although they appear immunocytochemically distinct.[27–29] Whether this implies origin from a common stem cell is unknown. Neuroendocrine carcinoma rarely coexists with basal cell carcinoma (Figure 8.2–20) although this phenomenon likely represents a collision tumor.[30]

Immunocytochemistry (particularly in small-cell variants) plays an important role in the diagnosis of cutaneous neuroendocrine carcinoma, especially in the differentiation of cutaneous from bronchogenic neuroendocrine carcinoma (small cell carcinoma). The tumor cells express low-molecular-weight keratin (Cam 5.2, AE1/AE3, and cytokeratin 20) (Figure 8.2–21), frequently presenting as a paranuclear dot or crescent, neuron-specific enolase (Figure 8.2–22), epithelial-membrane antigen, chromogranin, synaptophysin, and PGP 9.5.[31–34] Merkel cell carcinoma is consistently negative for S-100 protein. The tumor

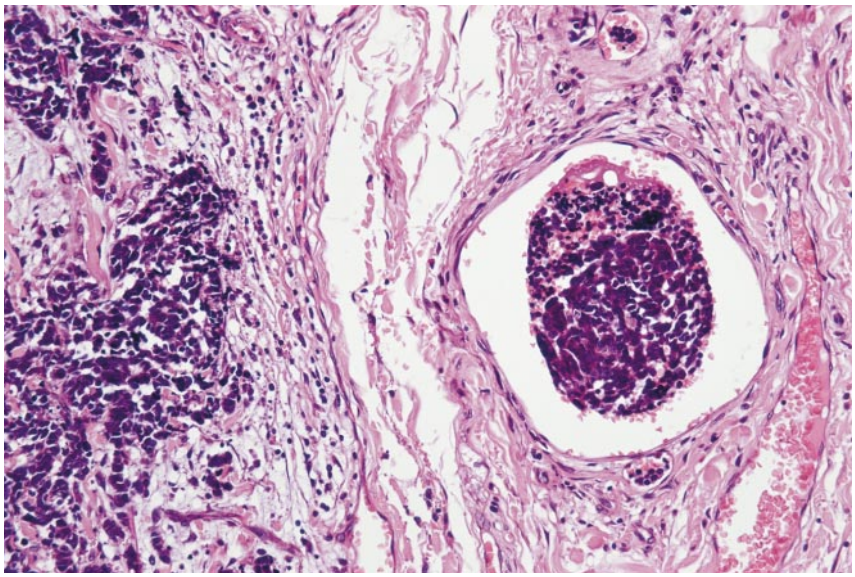


**Figure 8.2–18.** Lymphovascular invasion as shown in this field is an extremely common finding in cutaneous neuroendocrine carcinoma.

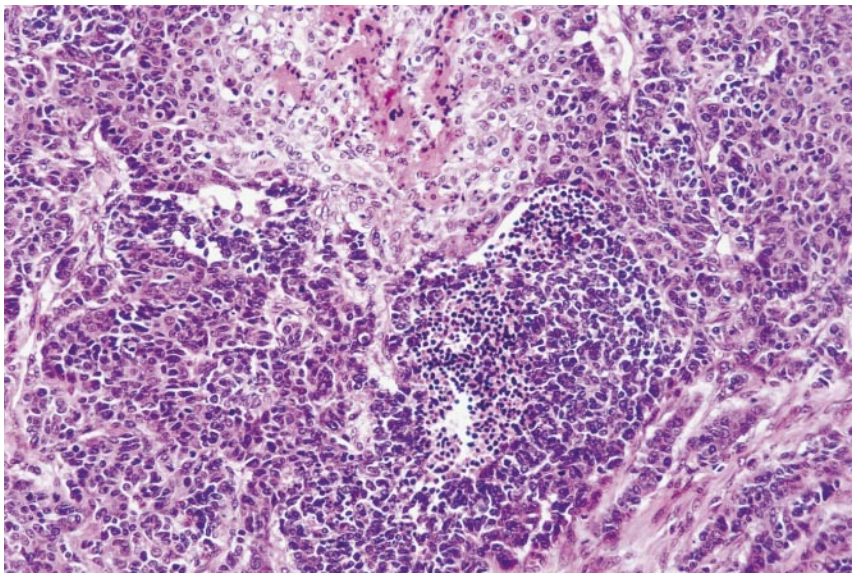


**Figure 8.2–19.** Occasionally, cutaneous neuroendocrine carcinoma coexists with invasive squamous cell carcinoma. This does not appear to be of any prognostic significance. Metastases are almost invariably restricted to the small-cell component.

**Figure 8.2–20.** Very occasionally, basal cell carcinoma (right) is seen adjacent to a neuroendocrine carcinoma. This is almost certainly coincidental.

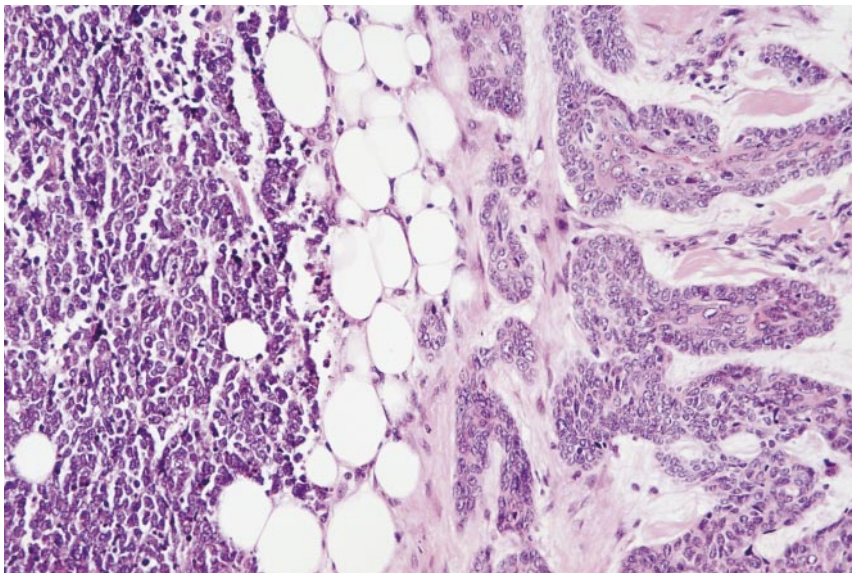


**Figure 8.2–21.** Cutaneous neuroendocrine carcinoma showing typical paranuclear-dot keratin positivity (Cam 5.2).

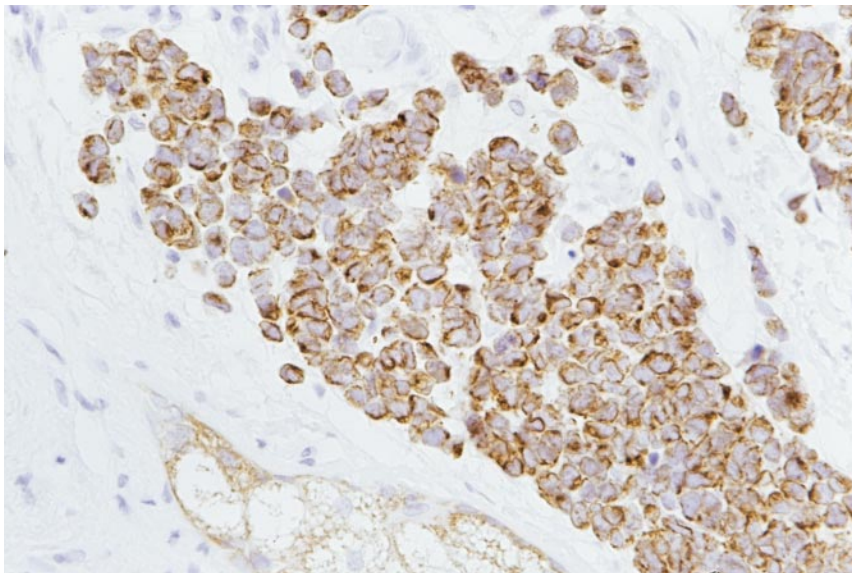
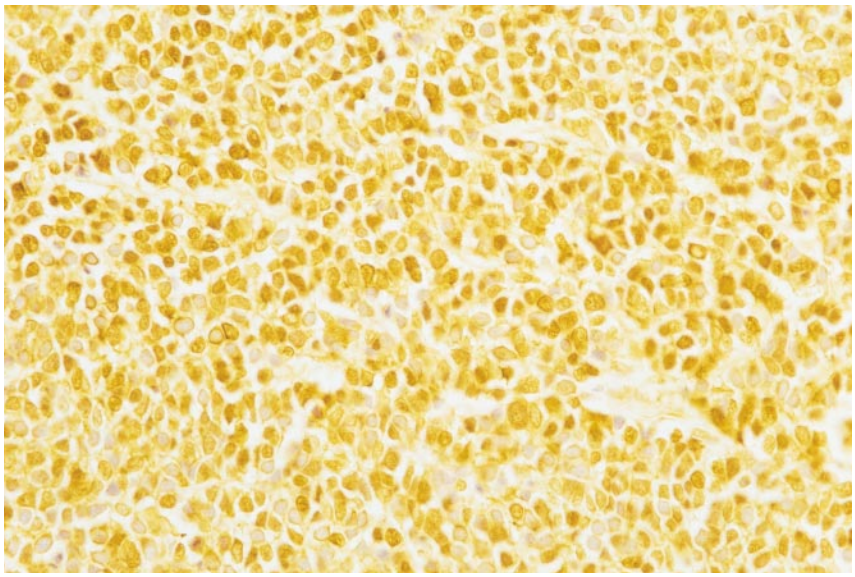


**Figure 8.2–22.** Cutaneous neuroendocrine carcinoma showing neuron-specific enolase expression.



may also contain a variety of neuropeptides, including calcitonin, bombesin, somatostatin, leu-enkephalin, adrenocorticotropic hormone (ACTH), and vasoactive intestinal polypeptide 2 (VIP 2).

Ultrastructurally, 100- to 250-nm membrane-bound neurosecretory granules are commonly seen in trabecular variants. They are sparser in intermediate variants and rare or absent in small-cell variants.[21] The presence of a paranuclear aggregate of intermediate filaments is a characteristic feature. Desmosomal cell junctions may be present in the trabecular variant.

## HISTOLOGIC DIFFERENTIAL DIAGNOSIS

Although the diagnosis may seem relatively straightforward in many cases, it is always important to exclude the possibility of metastasis, particularly from small cell carcinoma of bronchial derivation.[35,36] In addition, primary cutaneous neuroendocrine carcinoma may occasionally be confused with lymphoma, peripheral primitive neuroectodermal tumor, metastatic carcinoid tumor, or amelanotic small cell melanoma.[37,38] It is the small-cell variant of cutaneous neuroendocrine carcinoma, however, that causes the most diagnostic difficulty, particularly in distinguishing it from metastatic bronchial neuroendocrine tumors. The use of cytokeratins 7 and 20 with neurofilament immunocytochemistry affords the distinction in the vast majority of cases. Primary cutaneous lesions are positive for both cytokeratin 20 and neurofilament and negative for cytokeratin 7 whereas in the majority of cases, bronchial tumors are positive for cytokeratin 7 and negative for cytokeratin 20. In addition, the majority (although not all) of the latter are also neurofilament negative.[25,36] Neuroendocrine (small cell) carcinomas from other sites are also usually negative for cytokeratin 20, with the exception of salivary gland lesions, which have been shown to be positive in a significant proportion of cases.[36] The use of a battery of immunoreagents (Table 8.2–3) is recommended before a diagnosis of primary cutaneous neuroendocrine carcinoma is made.

## EVALUATION

This tumor's rarity and its relatively recent description (in 1972) have prevented the establishment of optimal treatment guidelines; there are only about 500 reported cases and no prospective trials of therapy. Several retrospective studies now shed light on the roles of surgery, radiation therapy, and chemotherapy in the adjuvant and recurrent-disease settings. Merkel cell carcinoma has a more aggressive behavior and different biologic responses to therapy than any of the other skin cancers. In terms

**Table 8.2–3. USE OF IMMUNOREAGENTS IN DIFFERENTIAL DIAGNOSIS OF MERKEL CELL (CUTANEOUS NEUROENDOCRINE) CARCINOMA**

| | Immunoreagent | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Tumor | CAM 5.2/ AE1/AE3 | CK 20 | Neurofilament Protein | NSE | EMA | CD99 | S-100 Protein | CK 7 | LCA |
| Merkel cell carcinoma | +ve; usually dotlike | +ve; usually dotlike | +ve; dotlike | +ve | +ve | May be +ve; cytoplasmic | –ve | –ve | –ve |
| Neuroendocrine carcinoma of lung | +ve; usually cytoplasmic | –ve | May be +ve | +ve | +ve | May be +ve; cytoplasmic | –ve | +ve | –ve |
| Lymphoma | –ve | –ve | –ve | –ve | Rarely +ve; Ki-1 lymphoma | Usually –ve | –ve | –ve | +ve |
| Peripheral primitive neuroectodermal tumor | 10% +ve | –ve | Rarely +ve | +ve | –ve | +ve; membranous | Rarely +ve | –ve | –ve |
| Metastatic carcinoid tumor | Often +ve | –ve | –ve | +ve | –ve | –ve | –ve | May be +ve | –ve |
| Small cell melanoma | 5% +ve | –ve | –ve | +ve | –ve | –ve | +ve | –ve | –ve |

CK = cytokeratin; NSE = neuron-specific enolase; EMA = epithelial-membrane antigen; LCA = leukocyte common antigen; +ve = positive; –ve = negative.

of its etiology and optimal management, it is not merely a variant of squamous cell carcinoma.

Upon making the diagnosis of Merkel cell carcinoma, a complete physical examination should be performed, evaluating the entire skin surface, lymph nodes, liver, and spleen. Liver function tests may help rule out spread to this organ (13% of metastatic disease is to liver). A baseline chest radiograph is important in excluding metastatic small cell carcinoma of the lung. Also useful is immunocytochemistry for cytokeratins 7 and 20, which differentiate neuroendocrine tumors of the lung from those of skin origin.[7] Computed tomography (CT) scans may be considered, especially if there is suspicion of a visceral origin of the skin lesion.

## MANAGEMENT

### Surgical Excision

Excision of the primary tumor mass of a Merkel cell carcinoma is essential, and several studies document the need for this excision to involve wider margins than those for squamous cell or basal cell carcinoma (Table 8.2–4). Among 38 Australian patients who had a simple excision (margins ≥ 0.5 cm), 100 percent experienced local recurrence of their Merkel cell cancers (Table 8.2–5).[11] Wide local excision with margins ≥ 2.5 cm yielded a local relapse rate of 49 percent among 41 patients in a Mayo Clinic series.[12]

The control of local recurrence is strongly linked to survival: among 35 patients in a St. Louis cohort, 2-year survival was 86 percent for those with no locoregional recurrence but only 35 percent for those with recurrence.[10] Thus, wide excision of the primary tumor with a 2.5-cm margin not only decreases the morbidity of locally recurrent MCC but also most likely improves survival.

Mohs' micrographic surgery is established for the treatment of several tumor types, including basal and squamous cell carcinoma, but its role in the treatment of Merkel cell carcinoma is unclear and doubtful. This technique has been evaluated in one small trial of 12 patients.[12] Among the patients who received Mohs' surgery alone, the local relapse rate was 50 percent, comparable to that for wide excision alone. Perhaps more important than the details of the surgical approach used to fully excise this tumor, is the concept that lymph node biopsy and radiation treatment are essential for optimal control of local disease.

### Surgical Treatment of the Draining Lymph Nodes

The critical role of adjuvant treatment with lymph node surgery is revealed by the largest cohort of MCC patients reported in the literature. Among these 102 MCC patients collected over 27 years in New York, elective lymph node dissection was the only parameter independently predictive of improved relapse-free survival.[6] This study also reported that the most common site of first recurrence is the draining lymph nodes. A separate study showed that a majority of patients with distant metastatic disease had had prior locoregional or nodal recurrence and that control of the lymph node involvement improves survival.[10]

Sentinel lymph node excision involves removing the one or two nodes shown to drain the tumor

**Table 8.2–4. MERKEL CELL CARCINOMA: FACTORS INFLUENCING SURVIVAL AMONG 35 PATIENTS**

| Characteristic | N | 2-Year Survival (%) | *p* Value |
|---|---|---|---|
| Stage | | | |
| I | 30 | 56 | |
| II | 3 | 33 | |
| III | 2 | 0 | < .01 |
| Age | | | |
| < 60 yr | 8 | 100 | |
| 60–70 yr | 8 | 86 | |
| >70 yr | 17 | 11 | < .01 |
| Surgical margin | | | |
| Wide (> 2.5 cm) | 15 | 86 | |
| Simple (0.5–2.5 cm) | 18 | 28 | .03 |
| Lymph node excision | | | |
| + | 11 | 100 | |
| – | 22 | 35 | <.01 |
| Radiotherapy (adjuvant) | | | |
| + | 13 | 77 | |
| – | 20 | 40 | .03 |
| Chemotherapy (adjuvant) | | | |
| + | 9 | 57 | |
| – | 24 | 51 | NS |
| Locoregional recurrence | | | |
| + | 20 | 35 | |
| – | 13 | 86 | <.01 |
| Distant recurrence | | | |
| + | 16 | 17 | |
| – | 17 | 100 | <.01 |

NS = not significant; N = population size.
Adapted from Kokoska ER, Kokoska MS, Collins BT, et al. Early aggressive treatment for Merkel cell carcinoma improves outcome. Am J Surg 1997;174:688–93.

**Table 8.2–5. IMPORTANCE OF COMBINED SURGERY AND RADIATION THERAPY TO PREVENT LOCAL RECURRENCE OF MERKEL CELL CARCINOMA**

| Treatment | Local Relapse (%) | Durability | Patients (n) | Reference |
|---|---|---|---|---|
| Excision (≥ 0.5 cm) | 100 | 6 mo to relapse | 38 | 11 |
| Excision (≥ 0.5 cm) + RT* | 30 | 17 mo to relapse | 34 | 11 |
| Wide excision (≥ 2.5 cm) | 49 | 60 mo F/U | 41 | 12 |
| Mohs' surgery† | 50 | 36 mo F/U | 8 | 12 |
| Mohs' surgery + RT* | 0 | 36 mo F/U | 4 | 12 |

F/U = follow-up; RT = radiation therapy.
*50 Gy of radiation delivered in 2-Gy fractions.
†Additional margins after Mohs' surgery: 0 mm in 7 cases, 5–10 mm in 6 cases. Average primary tumor size for Mohs' surgery was larger (2.98 cm) than that of the wide excision group (1.57 cm) although F/U interval was shorter for Mohs' surgery group (36 vs 60 mo).

site, using a combination of a radiotracer and a dye. This procedure is available at a growing number of centers around the country and is discussed in detail in a separate chapter in this volume. It involves much less morbidity than complete nodal dissection and has excellent sensitivity in melanoma, among other applications. Biopsy of sentinel nodes has now been investigated in two studies with Merkel cell carcinoma.[39,40] A total of 30 MCC patients were treated with the sentinel node procedure in the two studies. The 26 patients who had histologically negative sentinel nodes were followed up (mean periods of 7 or 10.5 months), and none of these patients developed recurrent disease. All four of the patients who had positive sentinel nodes had complete node excisions performed, two of which revealed additional positive nodes.[39,40] These studies suggest that the sentinel node procedure is a sensitive technique for detecting nodal involvement with MCC. With this technique, it should be possible to gain the survival benefit of lymph node dissection while sparing most patients the morbidity of a full elective lymph node dissection.

## Radiation Therapy

Whether patients have received simple, wide, or Mohs' excision of their Merkel cell carcinoma, studies suggest that adjuvant radiation therapy (XRT) has an impressive additional benefit. The addition of XRT to simple excision diminished the local recurrence rate from 100 percent (of 38 patients) to 30 percent (of 34 patients).[11] For Mohs' surgery, the addition of radiation therapy cut the local recurrence rate from 50 percent (of 8 patients) to 0 percent (of 4 patients).[12] In addition to decreasing the number of patients developing local recurrence, adjuvant XRT also increased the median time to recurrence from 5.5 months to 16.5 months.[11]

Importantly, the addition of XRT was associated with a statistically significant improvement in survival: among 35 patients, the 2-year survival for XRT-treated patients was 77 percent as compared to 40 percent for those who did not receive radiation.[10] In a Massachusetts General Hospital cohort, all 9 patients who received XRT survived whereas there were 7 deaths among the 22 patients who did not receive adequate (≥ 45 Gy) radiotherapy.[9] Multiple studies suggest that the proper dose of XRT is about 50 Gy, delivered in 2-Gy fractions to the primary tumor bed and the draining node basin.[9,11,41,42]

## Chemotherapy

Although Merkel cell carcinoma is partially sensitive to agents such as doxorubicin and cisplatin, there is no role for adjuvant chemotherapy in the management of Merkel cell carcinoma as multiple studies have shown that adjuvant chemotherapy has short-lived benefit,[42] does not improve survival,[8–10,42] and has significant mortality associated with its use.[8] Chemotherapy-associated deaths were significantly more common in patients over 65 years of age (16% of deaths were due to chemotoxicity) than in those less than 65 years old (3% of deaths were due to chemotoxicity).[8]

The story for chemotherapy in metastatic disease is quite different from its story in the adjuvant setting. An extensive analysis of 101 MCC patients who were treated with chemotherapy showed a response rate of 57 percent for patients with metas-

tases and 69 percent for those with locally advanced tumors.[8] There were no survivors among patients who had MCC metastases to viscera such as liver or lung.[8] Among those with metastases to skin, lymph nodes, or bone, however, the 2-year survival rate was ~15 percent after chemotherapy.[8]

Although the optimal chemotherapeutic agents and dosing regimen for MCC is unclear, polychemotherapy was associated with a better response rate than monochemotherapy (63% versus 43%).[8] Doxorubicin plus cisplatin showed a 100 percent response rate in 7 patients while polychemotherapy including 5-fluorouracil had a 92 percent response rate in 12 patients.[8]

## FOLLOW-UP

Close follow-up—every 3 months for at least a year—is warranted in monitoring Merkel cell carcinoma because most cases relapse within the 1st year.[7] This is significantly sooner on average than melanoma recurs, for example. Moreover, disease-specific survival with recurrent disease is 62 percent if recurrence is treated aggressively, so efforts to detect and treat recurrences promptly are likely to be beneficial.[6]

## SUMMARY

Merkel cell carcinoma is the highest-grade variant of skin cancer; fortunately, it is at least 100 times rarer than melanoma. Its clinical appearance is nonspecific, and it typically presents as a firm nodule on sun-exposed skin. Histologically, although the trabecular variant is rather characteristic, the more common small-cell variant can be distinguished from lymphoma and melanoma by a panel of antibodies that reveal its neuroendocrine and epithelial characteristics.

In terms of treatment, MCC is quite distinct from the other skin cancers, and it requires wide excision of the primary tumor, surgical biopsy of the draining lymph node bed, and adjuvant radiation therapy to the tumor bed and draining nodal basin (Figure 8.2–23). The role of chemotherapy is limited to metastatic disease or palliation of inoperable regional disease, because of high toxicity and the low durability of response. With optimal treatment such as this, up to 75 percent of patients can expect long-term survival.

**Surgery:**
- **Wide local excision (2.5 cm)**

**Node treatment:**
- **Sentinel node biopsy**
- **Completion adenectomy if sentinel node is positive**

**Radiation therapy:**
- **50 Gy in 2-Gy fractions to tumor bed and draining node bed**

**Chemotherapy:**
- **Not beneficial in adjuvant setting**
- **Metastatic disease:**
  - **Polychemotherapy including doxorubicin or 5-FU**

**Figure 8.2–23.** Treatment recommendations for Merkel cell carcinoma. Retrospective studies suggest that wide surgical excision, node biopsy, and radiation therapy each provide independent survival benefit in the adjuvant setting. (5-FU = fluorouracil)

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