Merkel Cell Carcinoma

—Associated with Squamous Cell Carcinoma—

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Merkel cell carcinoma (MCC) is an unusual primary cutaneous tumor, occasionally found concurrent with other malignancies. A case of MCC with coexisting squamous cell carcinoma (SCC) was studied histologically, immunohistochemically and ultrastructurally. The MCC and SCC occured at the same site, but each preserved its identity and transition between the two was not identified. (Ann Dermatol 4:(2) 133-138, 1992)

Key Words: Merkel cell carcinoma, Squamous cell carcinoma

Merkel cell carcinoma (MCC) is an unusual primary cutaneous tumor, first described in 1972 by Toker[1] as "trabecular carcinoma" of the skin, and has been reported under many different terms, including neuroendocrine carcinoma of the skin[2, 3], primary small cell carcinoma of the skin[4], and cutaneous APUDoma[5]. It has been believed that this tumor originated from Merkel cells (MC), as the ultrastructure of the tumor cells is strikingly similar to that of the MC[6]. An association of MCC with other malignancies has been documented. Some cases of MCC were found concurrent with squamous cell carcinoma (SCC) or basal cell carcinoma.

We report herein a case of MCC associated with SCC which we have lately experienced and studied, using the histopathological, immunohistochemical and electron microscopical techniques. The histogenesis of MCC with coexisting SCC is also discussed.

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REPORT OF A CASE

A 75-year-old female was referred to our outpatient department in February 1990 with a three-month history of an ulcerative nodular mass based on a dark reddish patch on the right buttock. Four years ago, she noticed an erythematous macule on the right buttock, which slowly enlarged. A small nodule developed over the patch and gradually grew to form a tumor in the preceding three months. The patient's past medical history was remarkable for facial palsy and senile cataracts. Physical examination revealed a dome shaped, fixed, nontender nodular mass based on a well-defined reddish patch on the right buttock with central ulcer and exudates (Fig. 1). There was no lymphadenopathy. The remainder of physical examination was unremarkable. Laboratory examinations including complete blood cell count, erythrocyte sedimentation rate, peripheral blood smear, urinalysis, renal function test, electrolytes, VDRL, pulmonary function test were normal. Result of liver function test showed mild hepatopathy. On routine chest roentgenogram, mild cardiomegaly was suspected. ECG showed coarse atrial fibrillation.

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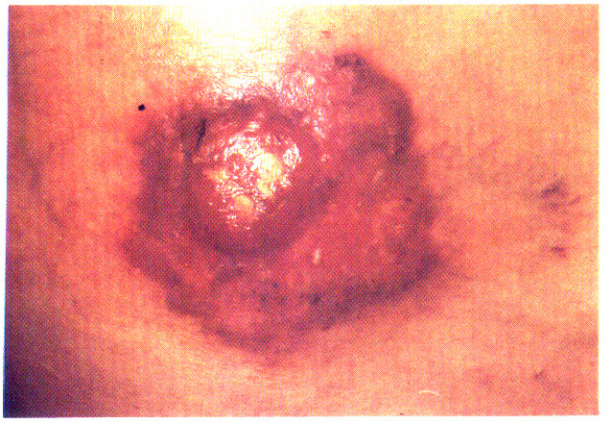

Fig. 1. A tumor based on a dark reddish patch on the right buttock.

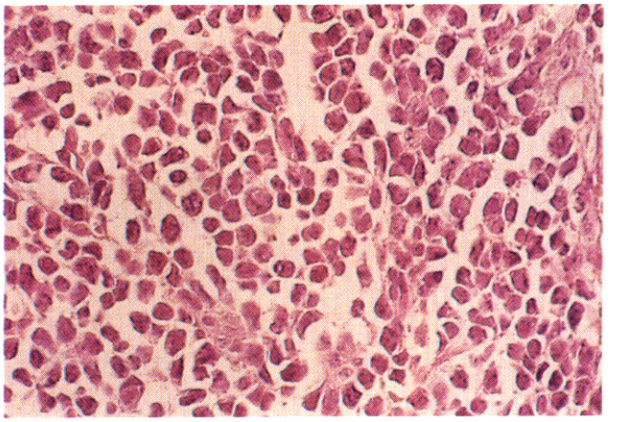

Fig. 2. The tumor cells of MCC contain round to polygonal nuclei and scanty cytoplasm (H&E stain, ×400).

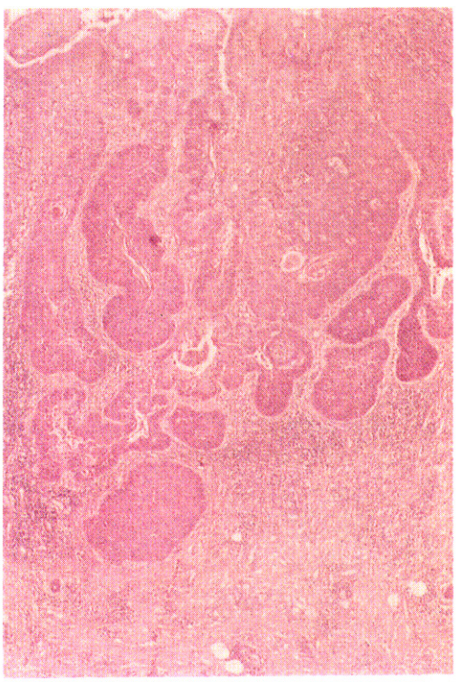

Fig. 3. SCC occurred immediately overlying the dermal MCC (H&E stain, ×40).

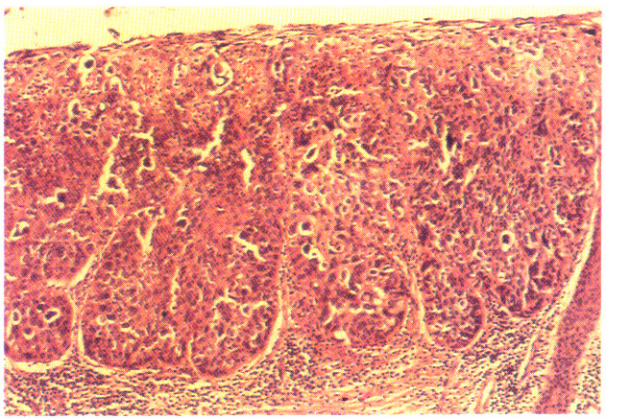

Fig. 4. Bowen's disease occurred on the peripheral patch (H&E stain, ×100).

The histology of biopsy specimen taken from the lesion was compatible with a diagnosis of MCC with SCC of the skin. A wide local excision with split-thickness skin graft was done under general anesthesia. Three months after operation, the enlargement of right inguinal lymph node was present, but she refused further evaluation. The patient died eight months after operation. Autopsy was not performed.

The specimen obtained from surgical excision was used for light and electron microscopic evaluations. Grossly, the tumor was a ulcerated and dome-shaped one and measured 10×8×3cm. On cut section, the tumor was a gray-white, solid mass with ill-defined margin. Microscopically the tumor was located mainly in the deep dermis, partly extending into subcutaneous tissue, with lack of any connection with epidermis. The tumor cells were arranged in dense cohesive sheets with a variable trabecular pattern. The individual cells showed uniform, round to polygonal with abundant poorly outlined cytoplasm and round to oval, centrally located vesicular nuclei with inconspicuous nucleoli (Fig. 2). Mitotic figures were easily seen. The epidermis overlying the tumor showed invasive squamous cell carcinoma (Fig. 3) and the patch area exhibited Bowen's disease (Fig. 4). But there were no admixture and no transition be-

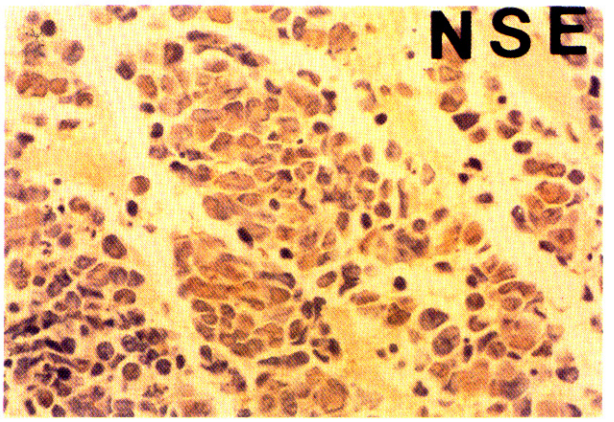

Fig. 5. Most cells of MCC show positive immunoreactivity for neuron-specific enolase (immunoperoxidase stain, ×400).

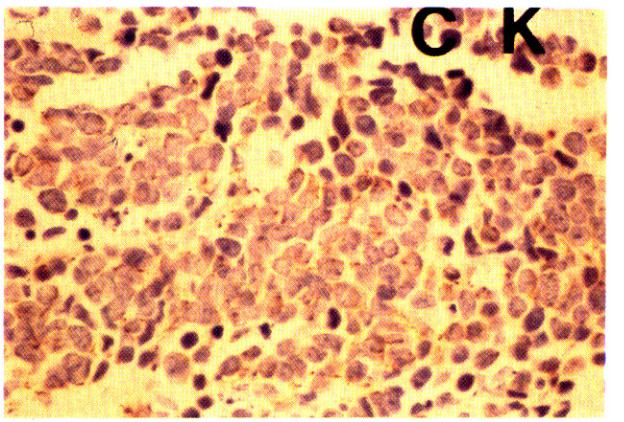

Fig. 6. Staining with low-molecular cytokeratin show paranuclear globules (immunoperoxidase stain, ×400).

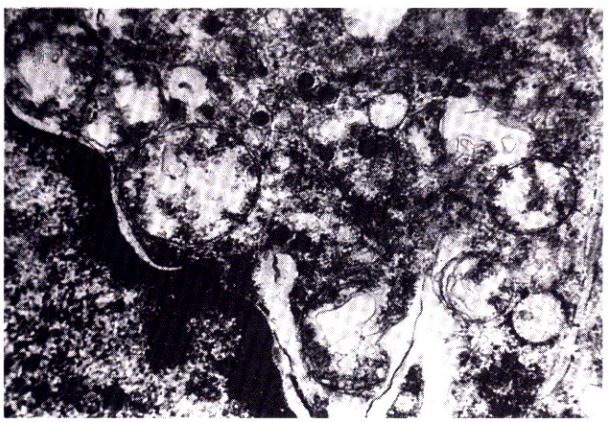

Fig. 7. Electron micrograph showing dense-core, membrane bound granules of a neurosecretory type and paranuclear whorl of intermediated filaments on the cytoplasm (MCC, EM, ×5,000).

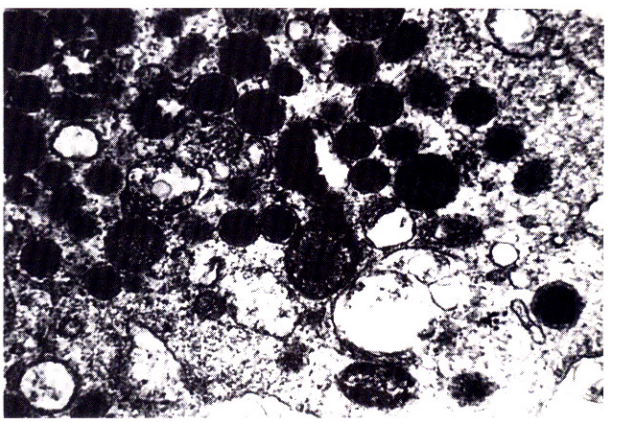

Fig. 8. Cytoplasmic processes containing aggregates of dense-core granules (MCC, EM, ×20,000).

Fig. 9. The tumor cells are connected by desmosome-like intercellular junctions (MCC, EM, ×20,000).

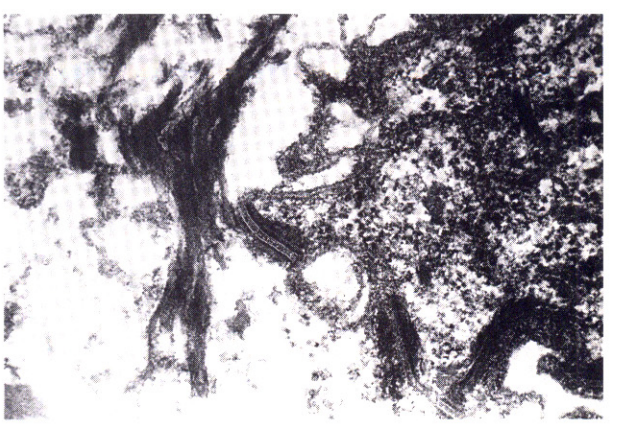

Fig. 10. Desmosome attached to tonofilaments on the cytoplasm (SCC, EM, ×20,000).

tween the elements of MCC and SCC. The tumor cells of MCC were negative for Grimelius and Fontana-Masson stains.

Immunohistochemical studies were carried out on formalin-fixed, paraffin-embedded tissue sections using immunoperoxidase technique with antibodies against neuron specific enolase (NSE), low-molecular weight cytokeratin, epithelial membrane antigen (EMA), Leu-7, leukocyte common antigen (LCA), chromogranin, carcinoembryonic antigen (CEA), S-100 protein, vimentin and muscle specific antigen (MSA). The cytoplasm of tumor cells was stained uniformly with anti-NSE antibody (Fig. 5) and discrete, round perinuclear globular form with anti-cytokeratin antibody (Fig. 6). EMA and Leu-7 were also stained positively but other markers, including LCA, chromogranin, CEA, S-100 protein, vimentin and MSA were unrewarded.

On ultrastructural examination, the tumor tissue of MCC consisted of compactly arranged electron-lucent, round to polygonal cells, which had a small amount of cytoplasm with some rough endoplasmic reticulum and mitochondria. A striking feature was the presence of spherical, membrane-bound, dense core granules (approximately 100nm in diameter) of neurosecretory type in the cytoplasm of most tumor cells (Fig. 7). Occasionally aggregates of granules were found in slender cytoplasmic projections extending into intracellular spaces (Fig. 8). The characteristic perinuclear whorls of intermediate filaments (approximately 10nm) were present in some cells (Fig. 7). Desmosome-like junctions were found joining adjacent cells (Fig. 9). The characteristic ultrastructural findings of MCC could not be found in the tumor tissue of SCC. Desmosomes attached to tonofilaments were seen within the cytoplasm (Fig. 10). The two tumors were well demarcated and transitional forms were not found.

DISCUSSION

Merkel cell carcinoma (MCC), as their name implies, is believed to originate from Merkel cells (MC) because of the ultrastructural similarities[6, 7]. The MC is a mechanoreceptor, situated in the basal layer of the epidermis[8-10] and the outer root sheath of hair follicles[7], and dermal stroma[11]. The embryologic origin of the MCC remains matters of dispute. The derivation from the neural crest or from the keratinocytes has been postulated.

MCC occurs in older adults with a mean age of 60 to 70 years. The tumor occurs almost exclusively in whites with an equal distribution between men and women. About 50 percent of the tumors arise in the head and neck region, 40 percent on the upper and lower extremities, and the rest in a random distribution, including trunk, palms and soles, and genitalia[12].

The usual clinical presentation is a rapidly growing, firm, intracutaneous non-tender nodule which measures up to several centimeters in diameter and is typically bluish red. They are usually soft with a white cut surface but may be red to violet, depending upon the vascularity of the lesions. The overlying skin is typically intact and shiny and rarely ulcerated. Satellite nodules may cluster around the primary lesion.

MCC is a highly aggresive, invasive, and potentially lethal tumor. Based on a study of 146 cases of MCC[13], it has been reported that local recurrence occured in 36%, regional lymph node metastasis occurred in 56%, distant metastasis occured in 28%, and death occured in 30%. Because of its aggressive nature, it is important that MCC be diagnosed rapidly and be treated early.

The histological appearances confirm the main features of nodular dermal growth of generally monomorphic cells with a mixture of growth patterns. The cells are usually round to polygonal with abundant poorly outlined cytoplasm. Nuclei are round to oval, with evenly dispersed chromatin, inconspicous nucleoli, and abundant mitoses. Numerous degenerating cells are seen.

The diagnostic electron microscopical findings are small dense-core membrane-bound secretory granules, perinuclear whorls of intermediate filaments, and desmosome-like structures. Our case presented similar histological and ultrastructural findings of MCC. But she developed a MCC on the right buttock which had been slowly growing uncommonly huge in size with the ulcerative surface.

Some monoclonal antibodies are very important in the investigation of MCC and in the differencial diagnosis from lymphoma, amelanotic mela-

noma, neuroblastoma, adnexal neoplasia, Ewing sarcoma, and other metastatic carcinoma. NSE positivity[14] and the presence of dense-core granules have repeatedly been demonstrated in MCC and interpreted as evidence of neuroendocrine differentiation. More recently, new markers of neuroendocrine differentiation such as chromogranin[15] and synaptophysin[16] have been used to immunostain a small number of MCC. Positive immunostaining for the lower molecular-weight cytokeratins has been found consistently in MCC[17]. The paranuclear globular pattern of staining has been described as a key point of distinction from metastatic small cell carcinoma of the lung[17]. In all likelihood, the globular staining of cytokeratin in MCC corresponds to the paranuclear filamentous aggregates seen ultrastructurally, however, these may also represent neurofilament protein. An additional evidence for epithelial differentiation is represented by immunopositivity for epithelial membrane antigen. Leu-7 and BA 1 are shared by several neuroendocrine cells and tumors, and are nonspecific for topographic origins. S-100 protein, CEA are consistently lacking in MCC. MCC also does not display LCA, as seen in malignant lymphoma. In our case, all immunohistochemical findings for MCC except chromogranin were compatible with the previous studies in the literature. Chromogranin is widely distributed in the secretory granules of most polypeptide-producing endocrine cells and the rate of its detection with immunohistochemical methods is closely proportional to the number of granules per cell[15]. However, such granules are often scant, and they are demonstrable only by examination of many fields.

Although the immunohistochemical and ultrastructural features of MCC indicate neuroendocrine differentiation, and some of these features are shared by MC, the origin of these tumors remains controversial. Suggested origin have included (1) the MC[6, 8, 18], (2) pluripotent basal cells[19], (3) pluripotent stems cells of adnexal epithelium[10], and (4) dermal neuroendocrine cells[11, 20].

Recently, epidermal epithelial derivation of MC has been supported by some evidences of Pasche[10] and Heenan[21]. Pasche et al[10] showed that MC were present in the epidermis and appendages before nerve ending reached the epithelium. Furthermore, they did not find any dermal MC on their electron micrscopic sections. Heenan et al[21] reported that morphological and immunohistochemical similarities between MCC and pulmonary small cell anaplastic carcinoma, now thought to be of bronchial basal cell origin, suggest that MCC was also derived from epithelium. When considered with the location of tumor in the dermis, MCC was more likely to be derived from the pluripotent stem cell of adnexal epithelium.

The most significant clinical features of MCC is its occurrence in elderly patients, mainly in exposed skin. The concurrence of solar keratosis, in situ SCC, and lentigo maligna are consistent with an etiological role of ultraviolet light of MC has been supported by some evidences. Concurrent SCC of the skin has been described in association with MCC with a frequency higher than could be attributed to chance association[12, 22, 23]. The concurrence of SCC with MCC has been interpreted, on the one hand, as a common response by different cells to the same carcinogenic stimuli[22], or, on the other hand, as supporting the theory of common ancestry of the two tumor types from a pluripotent basal cell[9].

In our case, invasive SCC occurred in the epidermis immediately overlying the dermal tumor, and Bowen's disease also occurred adjacent to the tumor. We did not find any continuity between the SCC of epidermal side and dermal MCC. They had their characteristic findings. A distinct demarcation between the two components was evident by light microscopy and electron microscopy, and transitional forms were not observed. Based on our case and previous reports, a possible process accounting for the histogenesis of MCC with SCC and Bowen's disease may be postulated: (1) SCC develops from Bowen's disease in the epidermis. (2) MCC develops from pluripotent stem cell of adnexal epithelium. (3) MCC and SCC independently derived from each different precursor cell and form one collision tumor.

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