Case report

MERKEL CELL (NEUROENDOCRINE) CARCINOMA OF THE SKIN

G. Torlone, I. D'Alessandro, A. Rossodivita, K. Peris and S. Chimenti

ABSTRACT

An 81-year-old woman presented with a 3 months history of an erythematous indurated plaque, with isolated and confluent nodules, located on the right leg. The lesion measured 8 x 12 cm and was asymptomatic. Histologic examination of a skin biopsy specimen showed a diffuse, dense infiltrate through the whole dermis to the subcutis, composed of medium-small cells, with round or oval nucleus and ill-defined cytoplasm. A focal trabecular pattern was also seen. Immunohistochemical positive reactions for anti-cytokeratins (CK), neurofilaments (NF) and neuron specific enolase (NSE) antibodies were detected. Electron microscopy revealed membrane-bound, dense-core neurosecretory granules, paranuclear whorls of intermediate filaments, and poorly formed desmosomes. Routine laboratory examinations were within normal limits. Esophagogastroscopy and computed tomographic (CT) scans of the chest and abdomen showed no abnormalities. On the basis of clinicopathologic and ultrastructural findings, a diagnosis of Merkel cell carcinoma was established. The patient was treated with radiotherapy on the right leg and inguinal lymph nodes (50 Gy total dose in 25 fractions over 5 weeks). Complete regression of cutaneous lesion was achieved, and after a follow-up period of 1 year no recurrence has been observed.

KEY WORDS

Merkel cell carcinoma, radiotherapy

INTRODUCTION

Merkel cell carcinoma (MCC) is an uncommon cutaneous tumor first reported by Toker in 1972 as "trabecular carcinoma of the skin" (1). Tang and Toker, in 1978, demonstrated by electron microscopy the presence of cytoplasmic neurosecretory granules (2). By analogy with the Merkel cell, different terms have been used to identify this tumor, including "malignant Merkel cell tumor", "cutaneous APUDoma", and "neuroendocrine carcinoma of the skin" (3-6). The histogenetic relationship between MCC and the normal Merkel cell, however, is still debated.

MCC usually occurs in the elderly, but patients ranging in age from 7 to 95 years have been reported (7). MCC has also been described in young adults with congenital ectodermal dysplasia syndrome (8,9). There is no sex predilection (10,

11). Caucasians are most commonly affected. Occasional reports in blacks (12) and Polynesians (13) have been published.

Most frequently, MCC arises on sun-exposed skin. 50% of cases affect the head and neck, and approximately 40% the extremities, whereas the trunk and mucous membranes are affected in less than 10% of cases (7). A previous history of concomitant squamous cell carcinoma has been found in one third of patients with MCC, suggesting that a common carcinogen such as ultraviolet light may have a role in the development of these tumors (14, 15). Further support for this hypothesis is the finding that the majority of MCC on lower extremities occur in females (12).

We described a case of MCC in a female patient with a primary lesion unusually large on the right leg.

CASE REPORT

An 81-year-old, diabetic woman presented with an erythematous plaque, with single and confluent, non ulcerated, reddish nodules on the right leg, which had developed approximately three months earlier. The lesion was firm and measured 8 x 12 cm (Fig. 1). On physical examination palpable lymph nodes were not detected.

Histologic examination of a skin biopsy specimen showed a diffuse, dense dermal infiltrate of neoplastic cells extending into the subcutaneous tissue (Fig 2). A focal trabecular pattern was also seen. Individual cells were round, of medium-small size, and have a round or oval nucleus, with inconspicuous nucleoli and evenly dispersed chromatin. The cytoplasm was scanty and ill-defined. Necrotic cells and mitotic figures were frequent (Fig. 3). The periodic acid-Schiff stain was negative. Immunohistochemical investigation, performed with a standard 3-step immunoperoxidase technique on routinely fixed paraffin embedded tissue sections, showed the tumor cells to be diffusely positive for anti-neuron specific enolase (NSE) antibody (Fig. 4). They also stained in a paranuclear pattern with anti-cytokeratins (CK) and neurofilaments (NF) antibodies (Fig. 5). Protein S-100 (S-100), leukocyte common antigen (LCA) and chromogranin A (CGA) were negative. Electron microscopy revealed round, membrane-bound neurosecretory granules, with a dense core and submembranous halo, in the periphery of the tumor cell cytoplasms. Paranuclear whorls of intermediate filaments and poorly formed desmosomes were also found (Fig. 6) Routine laboratory examinations were within normal limits. Esophagogastroscopy and computed tomographic (CT) scans of the chest and abdomen showed no abnormalities. Based on clinico-

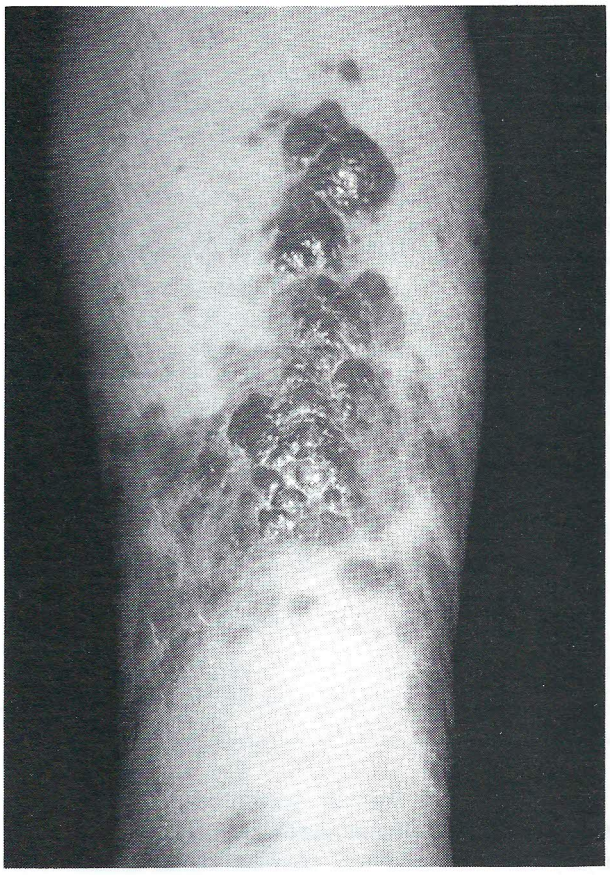

Fig. 1. Erythematous plaque, with single and confluent nodules, located on the right leg.

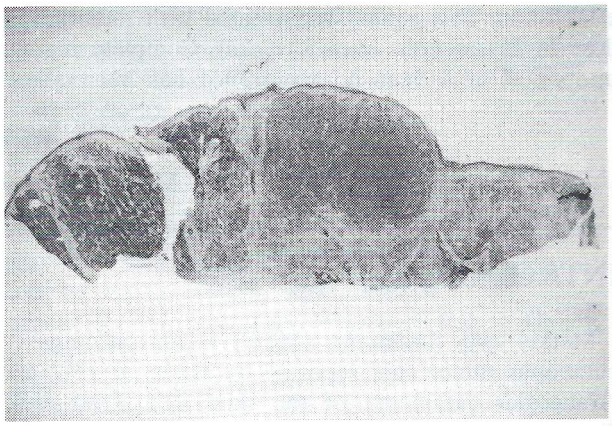

Fig. 2. Scanning magnification shows a diffuse, dense infiltrate through the whole dermis to the subcutis (H&E 25x).

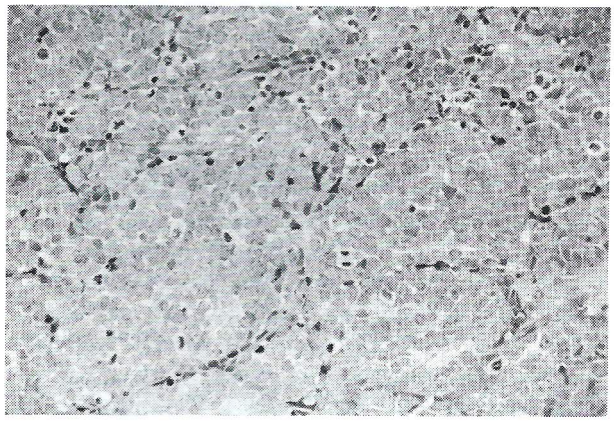

Fig. 3. Higher magnification shows medium-small cells with round or oval nucleous and incospicuous nucleoli (H&E 400x).

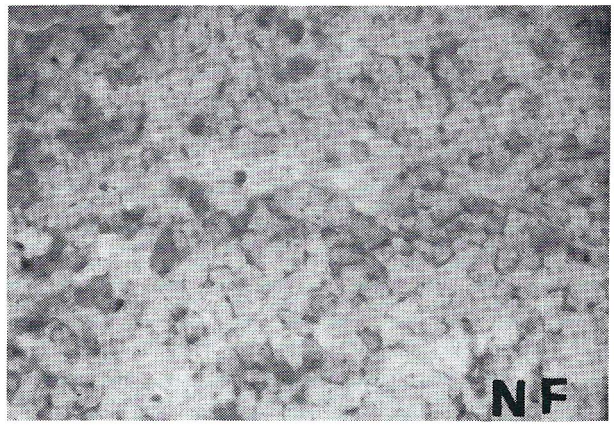

Fig. 5. Positive reaction of tumor cells for neurofilaments.

pathologic and ultrastructural findings, a diagnosis of MCC was made. The patient was treated with radiotherapy on the right leg and inguinal lymph nodes (50 Gy total dose in 25 fractions over 5 weeks). A complete regression of cutaneous lesion was achieved and after a follow-up period of 1 year no recurrence has been observed.

DISCUSSION

MCC is clinically characterized by a solitary, dome-shaped nodule or indurated plaque. It is red or violaceous, and tends to have a shiny surface, often with overlying teleangectasies. The epidermis may be ulcerated or intact. Multiple lesions have been rarely reported. Most tumors measure less than 2 cm in diameter (7). Our patient had a tumor unusually large (8 x 12 cm), but other cases of MCC as large as 12 to 15 cm have been occasionally documented (16, 17).

Diagnosis of MCC by clinical features alone is usually very difficult. Entities that may mimic this tumor may be confused, and include lymphoma, malignant melanoma, and cutaneous metastases of oat cell carcinoma.

MCC originates in the dermis and may extend to the subcutaneous tissue. Epidermal involvement has been rarely observed (18). Three histologic patterns of MCC have been described: 1) trabecular type; 2) intermediate-cell type; 3) small-cell type (19, 20). The trabecular type, which is the most clearly

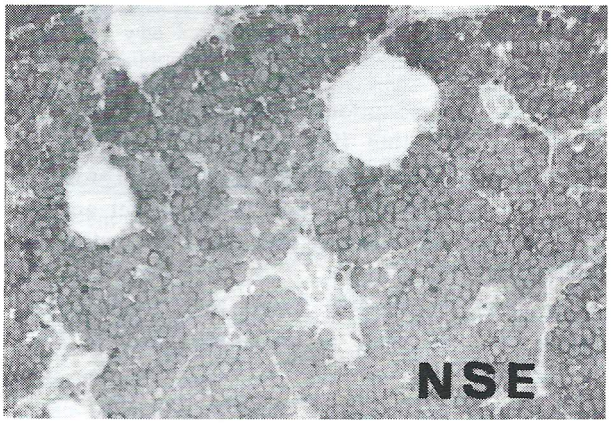

Fig. 4. Positive reaction of tumor cells for neuron specific enolase.

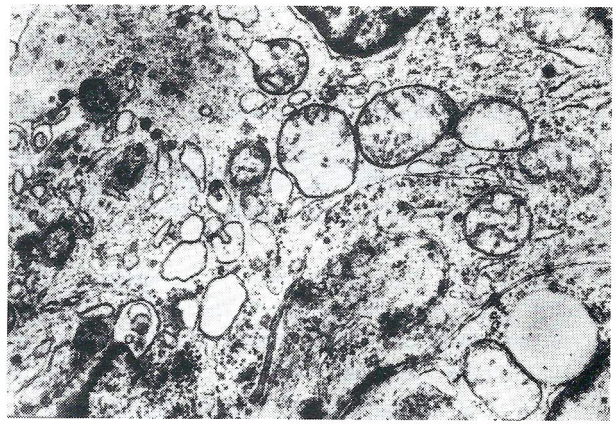

Fig. 6. Electron micrograph shows neurosecretory granules (Pb+Ur 45000x).

differentiated, is characterized by uniform tumor cells with a round or oval nucleus, inconspicuous nucleoli, evenly dispersed chromatin, and ill-defined cytoplasm that are arranged in anastomosing trabeculae separated by strands of connective tissue. Most MCC are of the intermediate-cell type consisting of large solid nests of cells of intermediate size, with a trabecular pattern peripherally. Cell necrosis and apoptosis are common. The small-cell variant, with an estimated lower incidence, consists of diffusely infiltrating sheets of small cells, and suggests a more aggressive subtype compared with the trabecular pattern. The histologic findings in our patient were that of intermediate-cell type.

Although light microscopy may be suggestive of the diagnosis, immunohistochemical and ultrastructural analysis are often required to distinguish MCC from other poorly differentiated tumors. MCC stains with anti-cytokeratins and neurofilaments antibodies in a paranuclear pattern, and diffusely with anti-neuron specific enolase antibody (21-22). Furthermore, positive reactions for chromogranin A and synaptophysin may be observed in some cases (23-24). Coexpression of both epithelial and neuroendocrine markers has also been described in small-cell carcinoma of the lung, but paranuclear cytokeratin and neurofilament staining is rarely present and may be useful in differential diagnosis. Lymphoma may bear a considerable resemblance both clinically and histologically with MCC, but lacks epithelial and neuroendocrine markers, while stains positively for leukocyte common antigen which is consistently absent in MCC. S100 protein nearly always shows a negative reaction in MCC (25). Ultrastructurally, neurosecretory granules and poorly formed desmosomes are usually found. Intermediate filaments are seen as paranuclear whorls in more than 90% of primary MCC of the skin. This disagrees with their presence in less than 10% of neuroendocrine, tumors from other sites (10). However, an accurate systemic evaluation should be done to exclude a cutaneous metastasis from a visceral neuroendocrine tumor. MCC may be biologically aggressive. Approximately one third of patients develop local recurrence within 1 year. Regional lymph node metastases occur in one half to two third of cases; most of these are palpable at presentation. Hematogenous and distant lymphatic metastases occur in more than one third of patients and most commonly involve liver, bone, brain, lung and skin (7).

Long-term prognosis of patients with MCC is relatively poor. 1-, 2- and 3-year survival rates have been estimated at 88%, 72%, and 55%, respectively. Females have a significantly better prognosis than males, with survival at 2 years of 79% versus 58% and of 68% versus 36% at 3 years respectively (11).

Surgical excision is the treatment of choice. An adequate margin of clearance (2.5-3 cm) must be obtained to minimize the risk of local recurrence. Prophylactic nodal dissection is not recommended in the absence of palpable lymph nodes (26). Radiation therapy may be used as an adjunct to surgery for the prevention of locoregional disease (27). In patients with recurrent or metastatic MCC various chemotherapeutic regimens have been used with variable success. A multimodality treatment approach, chemotherapy followed by radiotherapy, is indicated in some cases (28, 29). in our patient we used radiotherapy alone because of her advanced age and the size of the tumor.

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