Merkel Cell Tumor of the Thigh

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Abstract. This case of a Merkel cell carcinoma is unusual due to the occurrence of the tumor on the thigh; most Merkel cell tumors have been found on the sun-exposed region of the head and neck. Histologically, the nodule was composed of sheets of uniform, poorly differentiated cells with a high nuclear to cytoplasmic ratio. Electron microscopy revealed perinuclear filaments, scattered dense core granules, and complex, interdigitating processes within cytoplasmic membranes. Treatment consisted of surgical excision of the tumor with a wide margin.

INTRODUCTION

We report a case of Merkel cell carcinoma, also known as primary neuroendocrine carcinoma of the skin, located on a nonsun-exposed area of the thigh. Treatment consisted of surgical excision with a wide margin. After 3 years of follow-up, there is no evidence of tumor recurrence.

CASE REPORT

A 71-year-old Latin American man presented with a 2-month history of a nodule on the left medial thigh, first noted as a “purple spot” which soon enlarged and became intermittently painful when exposed to cold. There was no history of previous skin conditions. Past medical history was remarkable for noninsulin-dependent diabetes mellitus, hypertension, and a history of smoking (100 packs per year).

Physical examination of the skin revealed a solitary, firm, shiny, violaceous, dome-shaped nodule measuring 2.6 x 2.3 cm on a papillomatous base, surrounded by a poorly demarcated, mottled, brownish-red patch measuring 8.0 x 8.5 cm representing an area of contact irritant dermatitis due to a previous dressing (Fig. 1). No lymphadenopathy was detected, and the remainder of the physical examination was unremarkable. Clinical differential diagnoses included adnexal tumors, melanoma, lymphoma, and metastatic carcinoma.

Laboratory and radiologic evaluation showed no evidence of metastatic disease. Chest x-ray revealed two areas of increased density in the left upper lung field, clinically unchanged from previous studies and believed to represent stable granulomatous change.

Histopathologic evaluation of the skin showed focal hyperpigmentation of the basal layer but otherwise a normal epidermis. The superficial and deep dermis contained a diffuse infiltrate composed of uniform, round atypical cells with enlarged nuclei (Figs. 2 and 3). In some areas, the atypical cells formed cohesive nests, whereas in other areas, they were prominently discohesive. Focally, there was a...
suggestion of trabecular formation. Mitoses were not conspicuous (Fig. 4). The histologic differential diagnoses included malignant melanoma, adnexal tumors, neuroblastoma, lymphoma, and metastatic oat cell carcinoma. Special stains for chloracetate esterase, metachromatic granules, and pan leukocyte antigen were all negative. Tests for neuron-specific enolase and monoclonal antibodies for cytokeratin were not performed.

Ultrastructural analysis of the lesion revealed atypical cells with oval nuclei showing focal indentations and evenly dispersed chromatin. Of note, there were perinuclear filaments with focal aggregation (Fig. 5). Within the cytoplasm one found, in addition to mitochondria and golgi, scattered dense core granules. Cytoplasmic membranes showed complex interdigitating processes (Fig. 6). There were no myeloid or Birbeck granules, melanosomes, or mast cell granules seen. These findings were determined to be compatible with Merkel cell carcinoma, also known as primary neuroendocrine carcinoma of the skin.

FIGURE 1. Dome-shaped nodule on left medial thigh.

FIGURE 2. Dense diffuse dermal infiltrate of clusters and cords of round uniform cells.

FIGURE 3. (Mid power) dense deeply invasive cords and nests of cells with hyperchromatic rounded nuclei with scant cytoplasm.
DISCUSSION

Because of the similarities both histologically and ultrastructurally between Merkel cell tumors and metastatic oat cell carcinoma, several authors emphasize that all three features, namely, dense core granules, perinuclear filaments, and interdigitating processes be present before making the diagnosis of Merkel cell carcinoma. Other authors have been unable to find consistent, reliable, distinguishing features ultrastructurally between Merkel cell and oat cell carcinoma and stress the importance of thorough evaluation for occult malignancy before making the diagnosis of Merkel cell carcinoma. Ultrastructural analysis is also necessary to separate Merkel cell tumor from squamous cell carcinoma (poorly differentiated), malignant melanoma, histiocytosis X, and adnexal tumors (Table 1).

Treatment of the tumor consisted of surgical excision with a wide margin. After 3 years of follow-up, there is no evidence of tumor recurrence. Had examination of the patient revealed lymphadenopathy, local nodal resection and postoperative radiation therapy would have been considered.

Treatment of Merkel cell carcinoma is controversial and published studies are difficult to interpret because of the limited follow-up and variation in the modes of treatment used. Postexcision, approximately 25–65% of patients develop local or lymphatic metastases, depending on the series, and 20% die as a result of their disease. Recurrences are felt to be related to the presence of tumor close to the surgical margin. Thus, several authors emphasize the need for at least a 2 mm microscopic tumor-free margin in the primary excision.

Stawowy proposes the following guidelines in the management of Merkel cell carcinoma: thorough clinical evaluation to detect the presence of
Merkel cell tumor

metastatic disease, wide excision of tumor, postoperative local radiation therapy in selected cases, and regular follow-up. In the absence of lymphadenopathy, the pathological examination of the primary tumor serves as parameter for the need for lymph node biopsy. If the primary tumor is larger than 2 cm, contains 10 or greater mitoses per high-power-field, demonstrates evidence of lymphatic invasion or is composed of the small cell variant, a partial regional node dissection is recommended. The presence of lymphadenopathy makes lymph node biopsy mandatory. Should nodes prove to be positive, a radical lymph node dissection followed by radiotherapy and/or chemotherapy is recommended. In general, chemotherapy, consisting of Doxorubicin alone or in combination with cyclophosphamide or imidazole carboxamide, is recommended if the tumor is not resectable, is metastatic, is of the small cell variant, or if greater than 30% of the node is replaced by tumor.

Roenigk et al. emphasize the need for preoperative diagnosis using both formalin-fixed and electron microscopic techniques before proceeding with definitive excision. Frozen tissue technique, employed in microscopically controlled excisional surgery, was considered inadequate for the diagnosis of Merkel cell carcinoma and thereby also in the evaluation of surgical margins.

Of the over 100 cases of Merkel cell tumor described so far, the case presented here is moderately unusual as far as its location on the body. Whereas most Merkel cell tumors have been found on the head and neck in sun-exposed areas, this patient's tumor was located on the thigh in a non-sun-exposed site. In one series, 3 of 37 cases presented on the thigh. In all other respects, this patient's profile reflects that found in the literature for Merkel cell carcinoma, namely, late age of onset, rapid growth rate, and the histologic and ultrastructural features described above. Risk factors for this tumor have included sun exposure and advanced age. Males have an increased risk of developing this tumor.

O'Rourke recently reported a case of Merkel cell carcinoma that, after undergoing local metastasis, regressed spontaneously. This was felt to be the result of a cell-mediated immune phenomenon.

Hoefler et al. demonstrated the presence in Merkel cell tumors of neuron specific enolase, cytokeratin, and neurofilament protein by immunohistochemical techniques. Not only may these techniques aid in the differential diagnosis (Table 2), but they may also point to the cell origin for these tumors. Based on early studies using these techniques, the Merkel cell tumors may be more closely related to neuroendocrine cells than to epidermal Merkel cells because of their resemblance morphologically to enteroendocrine cells of the small intestine, their location in the dermis and subcutis, and the absence in these tumors of vasoactive intestinal polypeptide (VIP) and meten...

| TABLE 1 | Ultrastructural Features Important in the Diagnosis of Merkel Cell Tumors |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Squamous Cell Carcinoma | + | + | - | - | - | - |
| Malignant Melanoma | - | - | + | - | - | - |
| Histiocytosis X | - | - | - | + | - | - |
| Adnexal Tumor | - | + | - | - | + | - |
| Lymphoma | - | - | - | - | - | - |
| Oat Cell Carcinoma | - | - | - | - | - | rare |
| Merkel Cell Tumor | - | - | - | - | - | + |

| TABLE 2 | Immunohistochemical Features Important in the Diagnosis of Merkel Cell Tumors |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Neuron Specific Enolase | Neurofilament Protein | Keratin Antigens | S 100 Protein |
| Malignant Melanoma | - | - | - | + |
| Lymphoma | - | - | - | - |
| Neuroblastoma | + | - | - | - |
| Adnexal Tumor | - | - | + | - |
| Merkel Cell Tumor | + | + | + | - |

(From Hoefler et al., 1984)

cephalon, two markers for Merkel cells. In summary, Merkel cell tumor of the skin is a relatively rare neoplasm with a potentially aggressive behavior. Early diagnosis using electron microscopy, light microscopy, and immunohistochemical techniques are useful in establishing a diagnosis of Merkel cell tumor. Merkel cell tumor should be considered in the differential diagnosis of all solitary tumor nodules of the skin, whether or not they appear on sun-exposed surfaces.

REFERENCES


Eight patients were treated as outpatients under local anesthesia. Previous treatment with continuous wave CO<sub>2</sub> lasers had been unsuccessful. A vaporizing mode was used. Once the overlying epidermis was removed, fine forceps were used to extricate the underlying cyst. The wounds usually healed in 7-10 days although fading required 6-8 weeks. Five of six patients had good to excellent results; the remaining patient did not improve. Recurrences were uncommon. Although previous authors have reported good results with the continuous wave CO<sub>2</sub> laser, these authors suggest that the superpulsed CO<sub>2</sub> laser may be more effective and may cause less scarring because of the tissue vibration it creates and because less thermal damage occurs.
**EXTENDING YOUR LIMITS IN HIGH-POTENCY CORTICOSTEROID THERAPY**

For Dermatologic Use Only—Not for Ophthalmic Use

Summary of Important Information

**INDICATIONS AND USAGE** DIPROLENE AF Cream is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatitis.

**CONTRAINDICATIONS** DIPROLENE AF Cream should not be used in patients who are hypersensitive to betamethasone dipropionate or to any ingredient in this preparation.

**PRECAUTIONS** General: Systemic absorption of topical corticosteroids has not been adequately controlled. Therefore, patients receiving a large dose of a potent topical corticosteroid applied to a large surface area should be evaluated periodically for evidence of evidence of HPA axis suppression. To evaluate this, the 24-hour urinary free cortisol level and ACTH stimulation test should be performed. If HPA axis suppression is noted, an attempt should be made to withdraw the drug or reduce the frequency of application to the skin. Because of the high potency of DIPROLENE AF Cream, systemic absorption of this product is an important consideration.

**Pediatric Use** Use of DIPROLENE AF Cream in children under 12 years is not recommended.

**HISTORY OF CORTICOSTEROID USE** Topically applied corticosteroids can be absorbed in sufficient quantities to produce systemic effects. See PRECAUTIONS—Pediatric Use.

**TOXICITY** Systemic absorption of topical corticosteroids has not been adequately controlled. Therefore, patients receiving a large dose of a potent topical corticosteroid applied to a large surface area should be evaluated periodically for evidence of evidence of HPA axis suppression. To evaluate this, the 24-hour urinary free cortisol level and ACTH stimulation test should be performed. If HPA axis suppression is noted, an attempt should be made to withdraw the drug or reduce the frequency of application to the skin. Because of the high potency of DIPROLENE AF Cream, systemic absorption of this product is an important consideration.

**Metabolism** Topically applied corticosteroids are absorbed in sufficient amounts to produce systemic effects. See PRECAUTIONS—Pediatric Use.

**DOSAGE AND ADMINISTRATION** Apply a thin film of DIPROLENE AF Cream to the skin. Use twice daily. Treatment with DIPROLENE AF Cream should be limited to 45 g per week.

**ADVERSE REACTIONS** Adverse reactions to corticosteroids are readily controlled by stopping the drug or reducing the frequency of application to the skin. Because of the high potency of DIPROLENE AF Cream, systemic absorption of this product is an important consideration. Adverse reactions of topical corticosteroids are usually classified as local or systemic. Local adverse reactions include skin atrophy, striae, and secondary infection. Systemic adverse reactions include suppression of the adrenal cortex.

**OVERDOSE** Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. See PRECAUTIONS—Pediatric Use. DIPROLENE AF Cream is not to be used with occlusive dressings. See DOSAGE AND ADMINISTRATION for appropriate use of DIPROLENE AF Cream.

**EFFECTS OF OVERDOSE** Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. See PRECAUTIONS—Pediatric Use. DIPROLENE AF Cream is not to be used with occlusive dressings. See DOSAGE AND ADMINISTRATION for appropriate use of DIPROLENE AF Cream.

**Drug Interactions** None known.

**Pregnancy** Category C

**Lactation** Approximately 5% of the dose is excreted in breast milk.

**Laboratory Tests** The following tests may be helpful in evaluating HPA axis suppression: Urinary free cortisol, ACTH stimulation test.

**THERAPY EXTENDING YOUR LIMITS IN ADVANCED THERAPY**

**REFERENCES**


