To the Editor:

Merkel cell carcinoma (MCC) is a rare primary cutaneous neoplasm characterized by neuroendocrine differentiation. Histopathologically, MCC belongs to the category of “small blue cell neoplasms,” being characterized by monomorphic cells with round-to-oval nuclei, finely dispersed chromatin, and scant cytoplasm. MCC cells express a combination of low molecular weight cytokeratins (CK20 and/or CK7) and neuroendocrine markers. A significant breakthrough in understanding the molecular pathogenesis of MCC occurred in 2008, when a novel human polyomavirus (Merkel cell polyomavirus, MCPyV) was shown to be clonally integrated in the host genome of approximately 80% of MCC cases.1,2

Most of MCC cases are dermal-based lesions, showing variable extension into the subcutis and/or the epidermis. Although epidermotropism is a well-known histological scenario, only 10 cases of MCC confined to the subcutis ("panniculitic MCC") have been reported in the available literature (Table 1).3–10 Here, we report the first case of panniculitic MCC with an indistinguishable positivity for MCPyV, as established by immunohistochemistry. We believe that our findings raise further questions regarding MCC cell of origin.

A 75-year-old man with no significant medical history presented to our clinic with a 1-year history of a painless, growing subcutaneous mass localized to the right gluteal region. On physical examination, the subcutaneous tumor appeared as a mobile mass with normal overlying skin, measuring 4 cm in diameter. Punch biopsy of the gluteal mass revealed a deep, sheet-like proliferation of primitive round blue cells almost filling the subcutaneous layer (Fig. 1A); tumoral cells exhibited finely granular chromatin, indistinct nucleoli, and scant cytoplasm (Fig. 2A). The neoplastic growth, which was consistent with neuroendocrine carcinoma, was entirely confined to the hypodermis. Mitotic rate was high, and necrotic cells were frequent. By immunohistochemistry, most neoplastic cells expressed CK20 in a paranuclear dot-like configuration (Fig. 2B); staining for CK7 was negative. The tumor was diffusely positive for synaptophysin and NSE, whereas TTF-1 and S100 were not expressed. Immunohistochemistry for MCPyV large T-antigen (LTA) with CM2B4 antibody was diffusely positive in the sheet-like proliferation but not surrounding tissues (Fig. 1B), with predominantly nuclear labeling of neoplastic cells (Fig. 2C). A final diagnosis of panniculitic MCPyV-positive MCC was rendered. Treatment consisted of surgical excision of the tumoral mass down to the fascia followed by adjuvant radiotherapy. The patient responded to treatment and was disease-free after a 12-month follow-up.

Subcutaneous involvement by MCC is a fairly common occurrence; extension into the subcutis, however, typically follows the growth of primarily dermal-based lesions.1 Among the only 11 reported cases of panniculitic MCC, 8 tumors, including the present case, were assessed for immunohistochemical expression of CK20 and CK7: 7 cases showed the conventional CK20(+) phenotype, whereas only 1 case stained positive for CK7 and negative for CK20.3–10 In addition, none of reported cases of panniculitic MCC showed evidence of divergent differentiation. Importantly, our case is the first panniculitic MCC to be assessed for

---

**TABLE 1. Summary of Reported Cases of Panniculitic Merkel Cell Carcinoma**

<table>
<thead>
<tr>
<th>Case</th>
<th>Ref</th>
<th>Age, Sex</th>
<th>Anatomical Site</th>
<th>Immunodef</th>
<th>IHC Phenotype</th>
<th>MCPyV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Balaton et al2</td>
<td>78, F</td>
<td>Groin, Pelvis</td>
<td>No</td>
<td>panCK+, NF+</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>Balaton et al2</td>
<td>81, F</td>
<td>Groin</td>
<td>No</td>
<td>panCK+, NF+</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>Balaton et al2</td>
<td>60, M</td>
<td>Groin</td>
<td>No</td>
<td>panCK+, NF+</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>Huang et al4</td>
<td>63, F</td>
<td>Arm</td>
<td>No</td>
<td>CK20+, CroA+, Syn+</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>Sama et al5</td>
<td>83, F</td>
<td>Cheek</td>
<td>No</td>
<td>CK20+, CroA+, Syn+</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>Gambichler et al6</td>
<td>59, F</td>
<td>Groin</td>
<td>No</td>
<td>CK20+, CK7−, CD56+, TTF1− (+PCR)</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>Tsai et al7</td>
<td>77, M</td>
<td>Groin</td>
<td>No</td>
<td>CK20−, CK7+, CroA+, Syn+, TTF1−</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>Garcia-Rabasco et al8</td>
<td>60, F</td>
<td>Arm</td>
<td>Yes (long-term anti-TNF-alpha therapy)</td>
<td>panCK+, CK20+, TTF1−</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>Nambudiri et al9</td>
<td>76, F</td>
<td>Breast</td>
<td>No</td>
<td>panCK+, CAM5.2+, CK20+, NF+, Syn+, TTF1−</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>Davenport et al10</td>
<td>51, F</td>
<td>Leg</td>
<td>Yes (long-term anti-TNF-alpha therapy)</td>
<td>CK20+, Syn+, TTF1−</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>present case</td>
<td>75, M</td>
<td>Buttock</td>
<td>No</td>
<td>CK20+, CK7−, Syn+, TTF1− (+IHC)</td>
<td>NA</td>
</tr>
</tbody>
</table>

CroA, choromargin A; F, female; IHC, immunohistochemistry; Immunodef, presence of immunodeficiency; M, male; MCPyV, Merkel cell polyomavirus; NA, not assessed; NF, neurofilament protein; PCR, polymerase chain reaction; REF, reference; Syn, synaptophysin.

The authors declare no conflicts of interest.
MCPyV infection with the CM2B4 immunostaining.

MCC shows a typical predilection for chronically sun-exposed areas, suggesting a major role of ultraviolet radiation exposure in its pathogenesis.\(^1\) UV-induced carcinogenesis, however, is unlikely to be involved in development of panniculitic MCC. Available evidence suggests that MCPyV-positive and MCPyV-negative MCC subsets develop through different molecular pathways, respectively, thus representing distinct clinicopathological entities.\(^1,2\) The clinicopathological characteristics of reported cases of panniculitic MCC (i.e., expression of a CK7\(^{−/−}\)/CK20\(^{+}\) phenotype, absence of divergent differentiation, and lack of association with chronic sun damage), including our case, seem to suggest that panniculitic MCC mostly belongs to the MCPyV-positive MCC subset; further data, however, are needed to confirm this conclusion.

Panniculitic MCC is indistinguishable from metastases of extracutaneous neuroendocrine carcinomas on morphological grounds alone.\(^8\) Importantly, the immunohistochemical expression of LTA using the CM2B4 antibody has been shown to be highly specific for MCC; therefore, positive staining for LTA may provide unquestionable aid in the distinction between MCC and non-MCC small round cell neoplasms.

Ultrastructural as well as immunophenotypical features suggest that MCC cells differentiate toward cutaneous Merkel cells (MCs).\(^1\) Whether MC should be regarded as MCC cell of origin, however, is a subject of controversy. Recent evidence supports the view that most skin epithelial neoplasms derive from stem cells located in the basal layer of the interfollicular epidermis or in the bulge area of hair follicles.\(^1,11\) These epithelial stem cells could also account for the genesis of MC and MCC, respectively. Indeed, MCs seem to derive from epidermal stem cells, through a stepwise maturation process featuring the sequential activation of a MC-specific set of genes, including Atoh1, Sox2, and Isl1.\(^12\) The occurrence of panniculitic MCC, however, seems to be hardly justified by the existence of epidermal or

**FIGURE 1.** A, Scanning magnification view demonstrating sheet-like growth of primitive round blue cells confined to the subcutis. B, Strong and diffuse expression of MCPyV LTA labeling neoplastic cells but sparing surrounding tissues (A, hematoxylin and eosin, original magnification ×20; B, original magnification ×20).

**FIGURE 2.** A, High-power view revealing diffuse proliferation of small round blue cells with finely granular chromatin, indistinct nucleoli, and scant cytoplasm. B, Expression of CK20 in a paranuclear dot-like pattern. C, Strong, diffuse, predominantly nuclear expression of MCPyV LTA in neoplastic cells (A, hematoxylin and eosin, original magnification ×200; B, original magnification ×400; C, original magnification ×400).
bulge region hair follicle stem cells. A complementary explanation may lie in the identification of label-retaining cells with myoepithelial features and stem cell behavior, localized in the basal layer of the secretory acinar region of sweat glands, lying at the border of the dermis and subcutis; accordingly, secretory coil-derived stem cells might serve as cells of origin of deep-seated neoplasms with adnexal differentiation, including MCC. Such a scenario, however, remains highly speculative; further research is needed to test this hypothesis.

**Andrea Saggini, MD*  
Viviana Lora, MD†  
Roberto Baldelli, MD‡  
Augusto Orlandi, MD*  
Carlo Cota, MD§**  
*Anatomic Pathology, Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy  
†Clinical Dermatology, Department of Clinical Dermatology, San Gallicano Dermatological Institute, IRCCS, Rome, Italy  
‡Endocrinology Unit, AO San Camillo, Forlanini, Rome, Italy  
§Dermatopathology Unit, San Gallicano Dermatological Institute, IRCCS, Rome, Italy

**REFERENCES**


**Endocrine Mucin-Producing Sweat Gland Carcinoma in an Elderly Man**

**INTRODUCTION**

Endocrine mucin-producing sweat gland carcinoma (EMPSGC) is an uncommon low-grade adnexal neoplasm that most often occurs on the eyelid of elderly women. First reported over 20 years ago, EMPSGC exists on a spectrum that begins with eccrine cysts and ends with invasive mucinous carcinoma. It is analogous to solid papillary carcinoma of the breast. More than 70 cases of this entity have been reported in the literature, with most cases being reported in the last 5 years. This is likely due to an increase in diagnosis, not necessarily an increase in incidence. EMPSGC can be locally aggressive and can recur, but it is not known to metastasize. Treatment options include excision with wide margins or Mohs micrographic surgery. We present the case of a 70-year-old white man who had a biopsy of an eyelid lesion clinically concerning for basal cell carcinoma (BCC).

**CASE**

A 70-year-old white man presented to his ophthalmologist for a 6-week follow-up after having cataract surgery. He complained of a slowly enlarging bump on his left upper eyelid. Physical examination revealed a firm, 4-mm skin-colored papule on the left lateral upper eyelid on a background of extensive photodamage. An excisional biopsy with margins was performed to rule out BCC. Histopathological examination revealed a well-circumscribed dermal tumor comprising round to oval cells with round, central nuclei and prominent nucleoli with scattered atypical mitoses and lakes of mucin (Figs. 1A–D). Immunostains were positive for chromogranin, synaptophysin, cytokeratin 7 (CK7), estrogen receptor, and GATA3 (Figs. 2A–E). Calponin and p63 stains highlighted stromal myofibroblasts around the tumor, rendering a diagnosis of EMPSGC. Since the excision, patient has been doing well, with no evidence of tumor recurrence.

**REFERENCES**


