

Merkel cell carcinoma with an unusual immunohistochemical profile

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The clinical and morphological picture of Merkel cell carcinoma (MCC) may be rather challenging; therefore, the immunohistochemical profile plays a relevant role in confirming the microscopic diagnosis. A panel of antibodies including cytokeratins 20, 7 and epithelial membrane antigen, and neuron-specific enolase is used in confirming the morphological diagnosis of MCC. The majority of MCCs express CK20 and are CK7-negative. Herein, we present a case of primary cutaneous neuroendocrine carcinoma with an atypical immunohistochemical pattern. An 83-year-old woman presented with a painless plaque, red to violaceous in colour, located in the leg. The skin tumor was excised, formalin-fixed and paraffin-embedded. Tissue sections were immunostained with a panel of antibodies routinely utilized in complex primary skin tumors for evidencing epithelial and neuroendocrine differentiation of tumor cells. The neuroendocrine differentiation of tumor cells was evidenced by their immunoreactivity for synaptophysin, chromogranin A and neuron-specific enolase. Tumor cells also showed diffuse cytoplasmic staining for CK7. No immunoreactivity was detected for CK20 and thyroid transcription factor-1. Our data, together with previous rare reports of CK20-/CK7+ MCCs, lay stress on the importance of routinely utilizing a panel of antibodies in the differential diagnosis of complex primary carcinomas of the skin and may have important implications in expanding the differential diagnosis of skin tumors. In particular, caution should be taken in excluding the diagnosis of MCC only on the basis of the absence of reactivity of tumor cells for CK20, favouring the wrong diagnosis of less aggressive skin tumors.

Key words: Merkel cell carcinoma, immunohistochemical profile, CK20 negative, CK7 positive.

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Merkel cell carcinoma (MCC), also known as trabecular carcinoma or primary cutaneous neuroendocrine carcinoma, is a rare and very aggressive skin cancer. MCC is thought to be derived from pressure-sensing Merkel cells (Goessling *et al.*, 2002; Schwartz *et al.*, 2005); it is most commonly found in head and neck and in the upper extremities of individuals over 65. The clinical presentation of MCC is non-specific, presenting as a painless, rapidly growing (Silva *et al.*, 1984), red to violaceous plaque or nodule, usually less than 2 cm in diameter. MCC often recurs locally and has a propensity for both local and distant metastases via hematogenous and lymphatic routes. Locoregional recurrence rates range from 20% to 80% (Tai *et al.*, 2000; Goessling *et al.*, 2002); metastasis occurs approximately in 50% of cases, the skin being the main site of metastatic spread (28%), followed by lymph nodes (27%), liver (14%) and lung (10%) (Voog *et al.*, 1999). The diagnosis of MCC is based upon the clinical presentation and on the histological picture, confirmed by immunohistochemical data. Microscopically, MCC appears as a blue cell tumor with small, round, monomorphic cells, with scant cytoplasm and a "salt and pepper" chromatin pattern. The cells may be arranged in a variety of patterns including solid, diffuse or trabecular structures. Defined by both neuroendocrine and epithelial differentiation, MCC displays immunoreactivity for epithelial membrane antigen (EMA) (Sibley *et al.*, 1985), neurofilaments (Fantini *et al.*, 1995), neuron-specific enolase (NSE) (Gould *et al.*, 1985), synaptophysin (Ortonne *et al.*, 1988), chromogranin, neural cell adhesion molecule (NCAM/CD56) and cytokeratin (CK) 20 (Moll *et al.*, 1995). Immunohistochemistry is essential in the diagnosis of MCC and in differentiating it from other tumors including:

small cell carcinoma of the lung (SCCL), lymphoma, Ewing's sarcoma and salivary gland small cell carcinoma. Most MCCs stain positively for CK20 and are not reactive for CK7 (Jensen *et al.*, 2000). At the best of our knowledge, just seven cases of CK20-negative and CK7 positive MCCs have been reported (Kenneth *et al.*, 2007). Here we report a case of this rare variant of primary neuroendocrine CK20-/CK7+ carcinoma.

A 83-years old woman was admitted to our hospital (San Giovanni di Dio, Cagliari) for a painless, red to violaceous plaque, located in the leg. There was no previous history of irradiation. A wide excision of the lesion, including grossly free margins, was performed.

The lesion measured 5 mm in its greatest diameter and extended in depth up to 8 mm. Microscopically, the tumor was superficially locat-

ed but not connected to the epidermis. It showed a trabecular dermal population of epithelioid cells with enlarged nuclei characterized by a "salt and pepper" chromatin pattern (Figure 1a), and a brisk mitotic rate, in the absence of necrosis. Neuroendocrine differentiation was evidenced by immunoreactivity of tumor cells for synaptophysin, chromograninA and NSE (Figure 1b). In addition, cancer cells showed diffuse cytoplasmic staining for CK7 (Figure 1c). CK20 (Figure 1d) and TTF-1 staining were negative. Clinical work up for metastatic disease including CT scan of the thorax was negative. No evidence of metastatic disease was present at a 6 months follow up.

Primary cutaneous neuroendocrine carcinoma was initially described as a distinct entity by Toker in 1982 (Toker, 1982). Thirty seven years later, the origin and histogenesis of MCC remains contro-

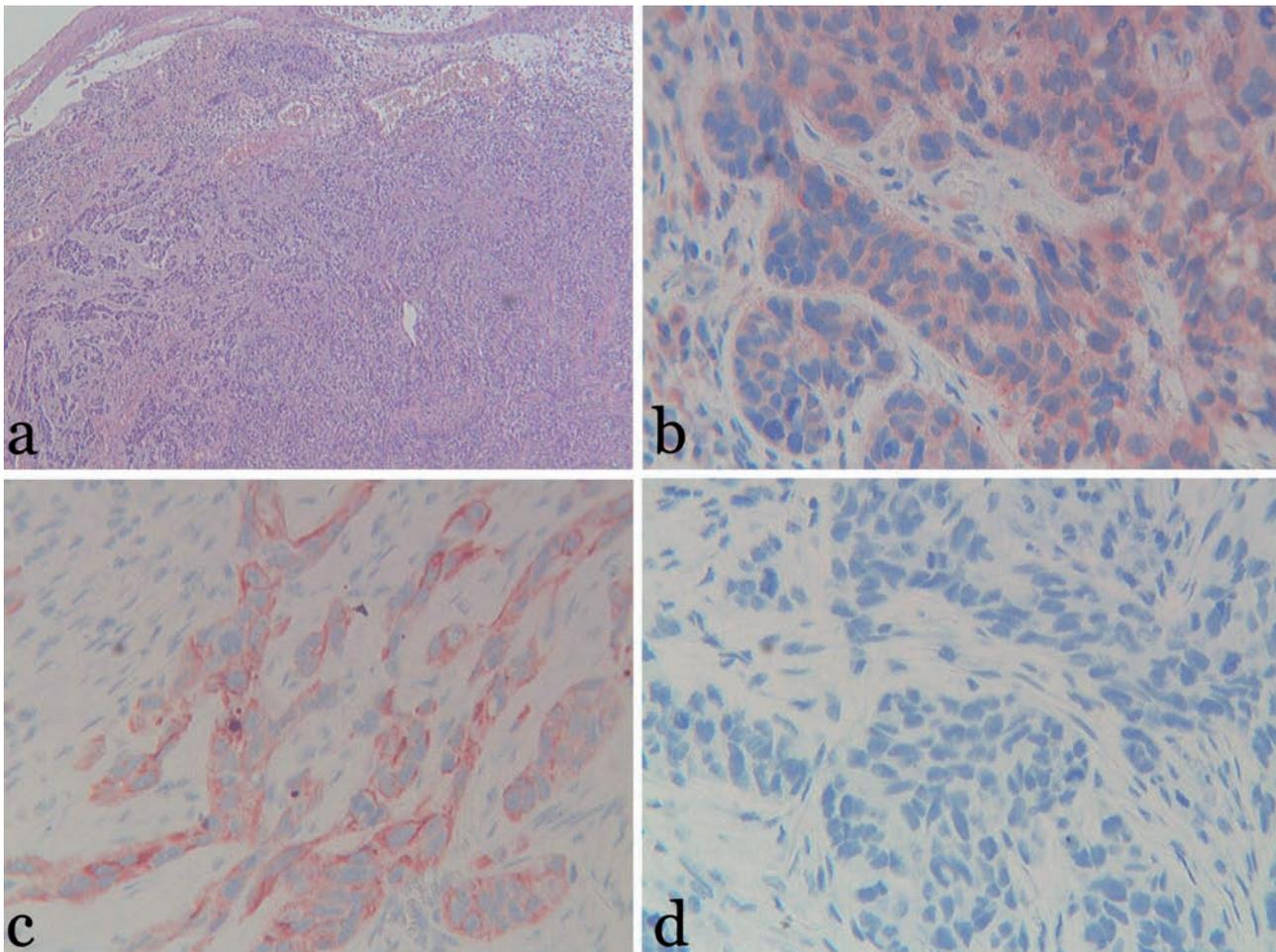


Figure 1. Merkel cell carcinoma: (a) MCC showing nests of deeply basophilic proliferating cells within the papillary and reticular dermis. (hematoxylin and eosin; 4x, original magnification); (b) a ribbon-like (trabecular) growth pattern cells positive for NSE (25x, original magnification); (c) cells diffusely positive for Ck7 (25x, original magnification); (d) absent immunoreactivity for Ck 20 (25x, original magnification).

versial. Suggested origins of MCC include sweat gland epithelium, Merkel cell and pluripotent cells in the epidermis and/or dermis (Brwon *et al.*, 2000). The description of granules in MCC has been described as indistinguishable from those seen in cells of neural crest derivation, suggesting the origin of MCC from Merkel cells (Silva *et al.*, 1984). Merkel cells are known to be CK20-positive; only in a subset of MCC CK7 immunoreactivity has also been described (Yao *et al.*, 2002). The diagnosis of MCC can be both clinically and histologically challenging. The clinical presentation is rather non-specific and lesions initially interpreted as basal cell carcinoma or squamous cell carcinoma (SCC) can be later diagnosed as MCC, based upon the immunohistochemical findings. Immunohistochemistry focused upon both the epithelial and neuroendocrine differentiation of MCC, has now become essential in confirming the diagnosis of this tumor. CK20 positivity and CK7 negativity is considered the typical immunohistochemical profile useful in confirming the diagnosis of MCC. CK20 is an intermediate filament protein whose expression is primarily restricted to gastric and intestinal epithelium (Botta *et al.*, 2001), urothelium, taste buds of the tongue and Merkel cells (Moll and Franke, 1985; Moll *et al.*, 1995). CK20 staining in MCC is described as having a characteristic perinuclear punctuate staining pattern. Cutaneous SCC, basal cell carcinoma and melanoma have been shown to be negative for CK20 (Moll and Franke, 1985). Bobos *et al.* reported that CK20 was expressed in 87% of MCCs (339/391), while in SCCL CK20 immunoreactivity was showed only in 14 of 302 cases (4.6%) (Bobos *et al.*, 2006).

Our case showed a peculiar immunohistochemical profile: synaptophysin, chromogranin, NSE positivity, CK20 negativity and immunoreactivity for CK7. CK7, a member of the basic type II CKs, is mainly found in glandular epithelia and in transitional epithelia (Kenneth *et al.*, 2007). CK7 has been reported to be expressed in association with CK20 in 23-31% of MCCs (Bobos *et al.*, 2006). In a review of the literature, there are documented cases of CK20+/CK7+, CK20+/CK7-CK20-/CK7- MCCs (Jensen *et al.*, 2000). Only seven cases, at the best of our knowledge, with the CK20-/CK7+ profile have been described (Kenneth *et al.*, 2007). The significance of the immunophenotype CK20-/CK7+ in a primary neu-

roendocrine carcinoma is yet to be determined. Merkel cells are known to be CK20+ and in a review of the literature CK7 immunoreactivity has also been described in a subset of Merkel cells (Yao *et al.*, 2002).

The absence of reactivity for CK20 and the aberrant expression of CK7, absent in normal Merkel cells, could identify a subset of MCCs originating from dedifferentiated Merkel cells. According to Kenneth *et al.* (2007), the findings of positive CK7 staining in MCC carcinoma may further define/expand the immunohistochemical profile of this neoplasm while supporting a possible derivation from Merkel cells. Finally, from a practical point of view, our case underlines that caution should be taken in excluding the diagnosis of MCC only on the basis of the absence of immunoreactivity for CK20, favoring the wrong diagnosis of less aggressive skin tumors.

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