

## LETTER TO THE EDITOR

**DIFFUSE TTF-1 EXPRESSION IN A CASE OF MERKEL CELL CARCINOMA**

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Dear Editor,

We herein report an unusual case of a cytokeratin-20 positive/cytokeratin-7 negative (CK20+/CK7-) Merkel cell carcinoma (MCC) that also showed immunoreactivity to two different thyroid transcription factor-1 (TTF-1) clones. An 88-year-old woman with no known history of a non-cutaneous neuroendocrine neoplasm presented with a 1.1 cm tumour located in the upper lip, allegedly having noticed it 2 months previously. The lesion was excised with negative margins. Lymph nodes were negative according to clinical examination (no pathological node examination was performed).

Histologically, the presence of a fairly circumscribed neoplasm was observed with neuroendocrine cell tumour morphology, compatible with MCC. It consisted of intermediate size, roundish cells, in groups or trabeculae, with minimal cytoplasm, a coarse chromatin pattern and increased mitotic activity (Fig. 1A). In between neoplastic buds extending to the subcutaneous fatty tissue, multiple vessels and areas of necrosis were observed, but no lymphovascular invasion and no skin ulceration. Immunohistochemically, nuclear TTF-1 positivity was observed in a substantial amount of tumour cells. Two different clones raised against TTF-1 were used, namely SPT24 [Novocastra, UK, 1/80 dilution] (Fig. 1B) and 8G7G1/1 [DAKO, Denmark, 1/50 dilution] (Fig. 1C). The rest of the marker panel immunophenotype, namely chromogranin A+, CD56+, NF+, CK20+ (dot-like/crescentic) (Fig. 1D), and CK7- confirmed initial histological diagnosis of MCC. MCC polyomavirus antigen presence could not be investigated.

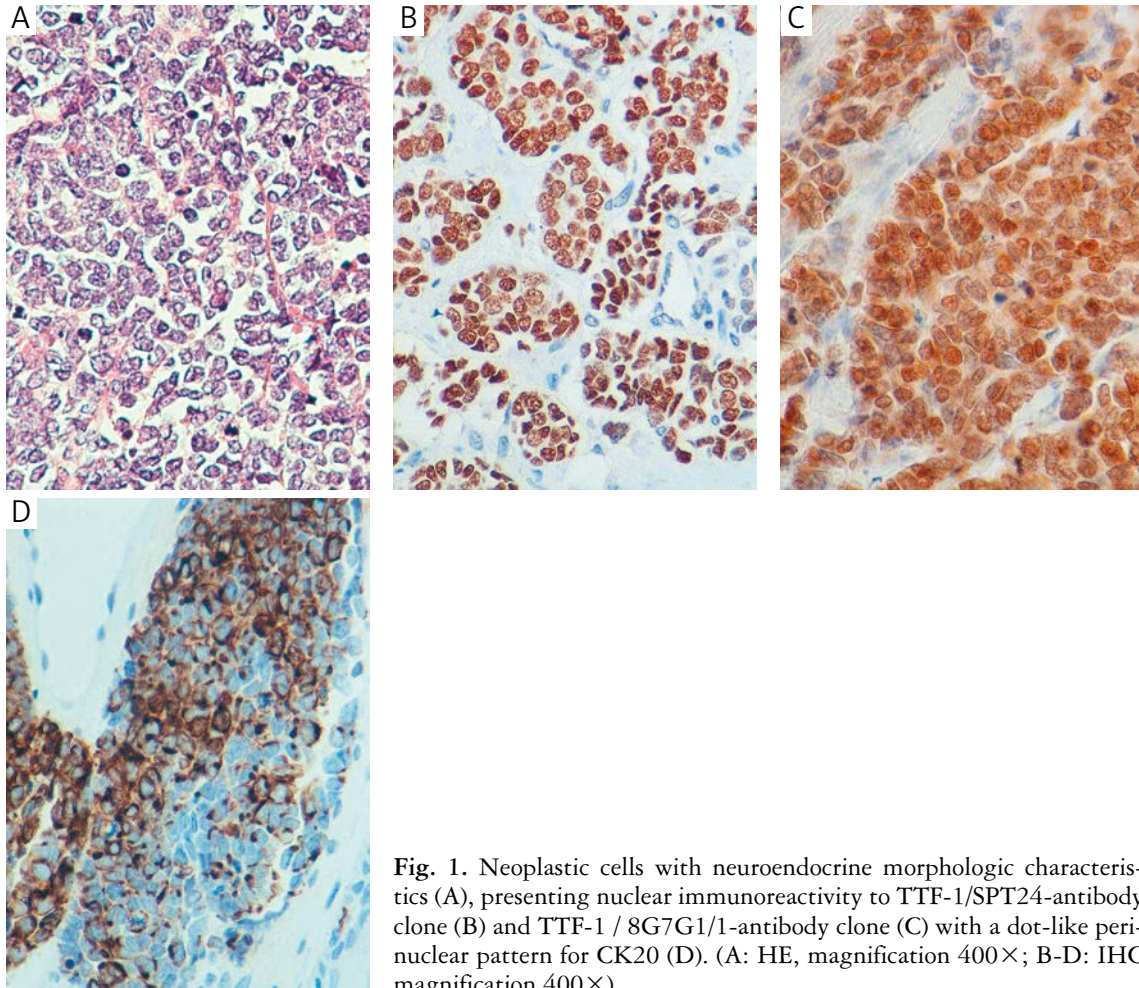
The neoplasm was staged as IB (T1cN0M0). The patient was clinically evaluated with no other relevant finding. The presence of a primary extra-cutaneous neuroendocrine carcinoma was excluded. During a 2-year follow-up period the patient did not show recurrence.

Merkel cell carcinoma is a rare, clinically aggressive, primary neuroendocrine skin neoplasm with variable prognosis. Adverse histopathological prognostic factors include lymphovascular invasion, large tumour size, small cell size and high mitotic rate [1]. Merkel cell carcinoma should be distinguished from a metastatic small cell carcinoma (SCC), mostly of the lung. Expression of TTF-1, especially when combined with immunostaining with CK20 and certain neuroendocrine markers, holds great differential-diagnostic value in the distinction between an MCC and a skin metastasis of an SCC (pulmonary or extra-pulmonary). Although TTF-1 is considered a sensitive and specific marker for SCCs of the lung, positivity should not exclude neuroendocrine tumours of other sites, not even an MCC, as of late. Thyroid transcription factor-1 positivity in MCCs is highly unusual, and there are, to our knowledge, only eight reported cases in the English medical literature [1-6]. Its significance remains to be elucidated through further studies. Only two of the reports referred to the clones used [5, 6], and those were different. It is of note that Buresh et al. described weak positivity to clone SPT24.

In our case TTF-1 nuclear immunopositivity was observed for both available and widely used antibody clones (SPT24 and 8G7G1/1). This is of certain significance, since it has been observed that SPT24 has a higher affinity but lower specificity in comparison to 8G7G1/1, due to a shorter amino acid chain, amongst other findings [7, 8].

Even though the unexpected TTF-1 positivity in carcinomas arising in organs other than lung and thyroid has been reported more frequently with the recently available SPT24 anti-TTF-1 monoclonal antibody, it has also been shown to occur with the commonly used 8G7G3/1 clone, albeit in a lower percentage of cases [9].

In our opinion, if it is possible, both clones should be used when investigating TTF-1 expression in an MCC, in view of a possible cross-reaction manifested in positive staining with the one, after a negative result with the other, an issue mentioned in other tumours as well. In addition, it could be of some interest for future studies to examine whether TTF-1 positive MCC cases would show a statistically significant preference either for one clone or the other and investigate the clinicopathological correlation.



**Fig. 1.** Neoplastic cells with neuroendocrine morphologic characteristics (A), presenting nuclear immunoreactivity to TTF-1/SPT24-antibody clone (B) and TTF-1 / 8G7G1/1-antibody clone (C) with a dot-like perinuclear pattern for CK20 (D). (A: HE, magnification 400×; B-D: IHC magnification 400×)

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