Primary Cutaneous Neuroendocrine Carcinoma with Diffuse Expression of Thyroid Transcription Factor-1: Report of Two Cases

José Maria Ortiz Salvador, Daniela Subiabre-Ferrer, Victor Alegre de Miquel

Abstract
Primary cutaneous neuroendocrine carcinoma (PCNC), previously known as Merkel cell carcinoma (MCC), is a rare tumor of the skin with aggressive behavior and poor prognosis. Typically, PCNC is positive for Cytokeratin-20 (CK20) and negative for Thyroid Transcription Factor-1 (TTF-1). Rarely, CK-20 negative and TTF-1 positive PCNCs have been described. We present the case of two patients with skin lesions histologically compatible with MCCs and a behavior characteristic of this disease, but with expression of TTF-1 instead of CK-20. In conclusion, there are increasing reports of TTF1+ CK20− skin lesions without signs of systemic disease which behave clinically and prognostically like a PCNC. The origin of these TTF1 tumors are, to date, unknown.

Key Words: Cytokeratin-20, immunohistochemistry, Merkel cell carcinoma, primary cutaneous neuroendocrine carcinoma, Thyroid Transcription Factor-1

Introduction
Primary cutaneous neuroendocrine carcinoma (PCNC), previously known as Merkel cell carcinoma (MCC), is a rare tumor of the skin with aggressive behavior and poor prognosis. Typically, PCNC is positive for Cytokeratin-20 (CK20) and negative for Thyroid Transcription Factor-1 (TTF-1). Rarely, CK-20 negative and TTF-1 positive PCNCs have been described. Here, we report two cases and discuss clinical presentation and outcome.

Case Report
Case 1
A 93-year-old man presented in 2015 with a rapidly growing red nodule on his upper lip [Figure 1a]. He was otherwise healthy and had no relevant antecedents. A skin biopsy was performed showing a poorly defined tumor with a dermal growth in a sheet pattern and infiltrating adipose tissue. The tumor was composed of small round blue cells with ovoid nuclei and finely dispersed chromatin. Immunohistochemistry was negative for CK-20 [Figure 1b] and positive for TTF-1 [Figure 1c]. Chromogranin and synaptophysin expression were positive. S100, HMB-45, and CD3 expressions were negative.

A total body computed tomography (CT) was performed showing no signs of noncutaneous neuroendocrine neoplasm.

Primary lesion was excised with wide margin. Sentinel node biopsy was negative for nodal metastasis. He was given adjuvant local radiotherapy to the primary tumor site. After 1-year of follow-up, no signs of internal neuroendocrine neoplasm developed. There was no recurrence of the primary lesion.

Case 2
An 88-year-old woman consulted in 2014 with a round lesion on her right inner canthus [Figure 2]. She had no known history of noncutaneous neuroendocrine neoplasm. The lesion was excised and the defect was covered with a skin graft. The biopsy showed a dermal nodule growing in a sheet pattern and trabecular infiltration in the tumor edge. It was composed of...
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Small cells 2–3 times bigger than a lymphocyte with amphophilic cytoplasm and round nucleus. Mitotic figures were abundant. IHC showed diffuse expression of TTF-1 and was negative for CK-20. The rest of the marker panel immunophenotype supported the diagnosis of neuroendocrine carcinoma, with no expression of melanocyte or lymphocyte markers. A pulmonary CT was performed with no signs of disease. Five months later the patient developed submandibular nodal lymphadenopathy. Fine needle aspiration was suggestive of MCC nodal metastasis. Regional radiotherapy was given to the patient, who was alive with the disease at the time of reporting.

Discussion

MCC or PCNC is a malignant proliferation of highly anaplastic cells with aggressive malignant course. Differential diagnosis must be made with metastatic noncutaneous neuroendocrine carcinoma, which shares with PCNC clinical and histopathological features. Among these neuroendocrine carcinomas, the most common by far is small cell carcinoma of the lung, however, other extrapulmonary sites such as bladder or stomach must be included in the differential diagnosis. TTF-1 and CK-20 are helpful tools in differentiating PCNC from noncutaneous neuroendocrine carcinoma. In one study, TTF-1 has been reported to have a specificity of 100% and a sensitivity of 85% for the diagnosis of small cell carcinoma of the lung.\(^1\) CK-20 was present in 95% of MCC and 33% of small cell carcinoma of the lung.\(^1\) Although TTF-1 is considered to be specific for small cell cancer of the lung, its positivity should not exclude neuroendocrine tumors of other sites or even PCNC. TTF-1 expression in PCNC is very uncommon and there have been very few reports of this phenomenon.\(^3\,4\)

Hanly et al.\(^5\) analyzed 21 cases of PCNC and found only one case of negative CK-20. Any of the 21 PCNC showed TTF-1 positivity. Iliadis et al.\(^3\) reported a case of PCNC with expression of TTF-1 and CK-20 behaving clinically as MCC without local or nodal recurrences over a 2-year period and without evidence of an extracutaneous neuroendocrine carcinoma.

Shalin et al.\(^4\) reported a case of MCC with lost expression of CK-20 and acquired expression of TTF-1 in subsequent metastases.

Our two patients presented with typical lesions of PCNC, with a red rapidly growing nodule appearing in the head of advanced age patients and with compatible histological findings with the only exception of the expression of TTF-1 instead of CK-20. No other internal findings suggestive of extracutaneous tumor were found in any of the patients. Control with other previously diagnosed PCNC was undertaken with clear expression of CK-20 and negative expression of TTF-1 in all cases.

In conclusion, TTF1 expression in conjunction with negativity for CK20 is highly suggestive of a noncutaneous neuroendocrine carcinoma, mostly small cell lung cancer. However, there are increasing reports of TTF1+ CK20– skin lesions without signs of systemic disease, which behave clinically and prognostically like a PCNC. The origin of these TTF1 tumors are, to date, unknown.

Abbreviations

PCNC = Primary cutaneous neuroendocrine carcinoma, MCC = Merkel Cell Carcinoma, CK20 = cytokeratin-20, TTF-1 = Thyroid Transcription Factor-1, FNA = Fine Needle Aspiration.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and
due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**
There are no conflicts of interest.

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