Trichilemmal carcinoma with neuroendocrine differentiation

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Summary

We report a 12-mm nodular, cream-coloured skin lesion that appeared on the left nasal ala in an 81-year-old man. This trabecular infiltrative tumour showed keratin microcysts, stromal hyalization, cytoarchitectural malignancy features, colonizing melanocytes, and immunoexpression of epithelial membrane antigen, cytokeratin 15/20, chromogranin, synaptophysin and CD56. To our knowledge, this is the first documented case of a trichilemmal carcinoma with neuroendocrine differentiation and melanocyte colonization, which is suggested by the trabecular growth pattern and requires immunohistochemical confirmation. The colonization of the epithelial nests by nonatypical dendritic or spindle melanocytes is a clue to morphological recognition of pilar neoplasms, along with the presence of stromal induction (CD34-positive peritumoral spindle cells), catagen-like apoptotic bodies, calcifications, keratin microcysts and cell balls.

Skin adnexal tumours are rare entities causing diagnostic dilemmas in histopathological practice, for which the pattern recognition is diagnostically essential.1 Helpful clues include the presence of intracellular and intercellular lumina containing diastase-resistant, periodic-acid–Schiff (PAS)-positive material (ductal tumours), vacuolated epithelial cells with nuclear indentations (sebaceous tumours) and pilar elements (tumours with hair follicle differentiation). Adnexal neoplasms with pilar differentiation are the most elusive, often diagnosed as basal cell, squamous cell or undifferentiated carcinomas. The pilar differentiation is suggested by the presence of PAS-positive hyalinized stromal changes around the epithelial nests, keratinous microcysts and/or cell ‘balls’ with or without peripheral nuclear palisading, and changes in the eosinophils and clear cytoplasm.1,2 Features suggestive of pilar differentiation and malignancy criteria have been reviewed in detail elsewhere.3–6

The presence of melanocytes within various tumours has been reported, but they are almost always present in tumours with pilar differentiation.2 The terms ‘pigmented’ or ‘melanocyte-containing’ tumours have been used to describe ‘new’ entities or variants that occur when the number of melanocytes is increased in an otherwise conventional and well-recognized entity.7

We present a trichilemmal carcinoma with neuroendocrine differentiation and melanocyte colonization, discussing useful features to recognize its differentiation. Features helpful to diagnosis of skin adnexal tumours with epithelial pilar differentiation are outlined, in particular for cases with other lines of differentiation that may cause further diagnostic difficulties.

Report

The patient was an 81–year old man, who presented with a 12-mm nodular, cream-coloured skin lesion on the left ala of nose of unknown duration. The clinical diagnosis was of basal cell carcinoma. The specimen was routinely processed, inking the margins and serially sectioning the 20-mm area containing the lesion, which was 5 mm from the closest lateral margin.

The tumour showed infiltrative growth in trabeculae and strands, and contained keratin cysts and hyalinized...
stroma (Fig. 1). Cytologically, there was marked nuclear pleomorphism, small but distinct nucleoli and focal clear-cell changes. Numerous mitotic figures including abnormal forms were evident as were focal areas of necrosis. Another sparse population of spindle-shaped melanocytes was also noted within the tumour islands.

Sections were mounted on positively charged microscope slides (Superfrost Plus, Fisher Scientific, NJ, USA) and baked at 60 °C for 2 h. After routine dewaxing, rehydration and endogenous peroxidase quenching, the sections were sequentially incubated with polyclonal horse serum (1 : 100 dilution; Dako, Glostrup, Denmark), the corresponding primary antibody (4 μg/mL for all monoclonal antibodies; Dako) overnight at 4 °C, biotinylated antimouse antibody (1 : 200 dilution; Dako) and peroxidase-labelled avidin–biotin complex (1 : 100 dilution, Dako). All incubations were performed in a moist chamber at room temperature. The reaction was developed under microscopical control, using 3,3′-diaminobenzidine tetrahydrochloride as chromogen (Sigma, St. Louis, MO, USA), and the sections counterstained with haematoxylin. Both positive (reactive lymph node) and negative (omission of primary antibody) controls were simultaneously run.

Tumour cells were positive for epithelial membrane antigen (EMA) (75–80%); CD56, synaptophysin, chromogranin (25–30%); and cytokeratins 15 and 20 (80%+, paranuclear dot pattern) (Fig. 2). The spindle melanocytes showed positive staining with S100, HMB45, and melanA (5%); a small number of CD1a-positive dendritic Langerhans’ cells (1–3%) were present. The peritumoral stroma was CD34-positive.

The tumour had an infiltrative pattern with foci of necrosis, pleomorphic cells and atypical mitoses, suggesting a malignant neoplasm, and showed evidence of pilar differentiation, i.e. keratin cysts, peritumoral hyalinized stroma with CD34+ spindle cells, and tumour cells positive for CK15, CK20 and EMA (the latter previously reported occurring focally). Tumour cells were focally positive for neuroendocrine markers (chromogranin, synaptophysin and CD56). The diagnosis was trichilemmal carcinoma with neuroendocrine differentiation.

Neuroendocrine differentiation has not previously been reported in pilar neoplasms, with the exception of trichogerminoma. This neuroendocrine differentiation has been correlated with vascular endothelial growth factor and transforming growth factor-α immunexpression in carcinomas. These two angiogenic factors may aid the neovascularization of carcinomas, and their increased expression in tumour-associated neuroendocrine cells may contribute to a more aggressive phenotype in several types of tumour.

Primary cutaneous neuroendocrine (Merkel cell) carcinomas mainly present as dermal and subcutaneous masses in the sun-exposed skin of elderly patients. They show generally monomorphic cells with foci of pronounced pleomorphism. These tumours are heterogeneous and can occur in intimate association with carcinomas (particularly squamous and eccrine types).
Merkel cell carcinomas have also been reported associated with a trichilemmal cyst, showing pagetoid spread into the trichilemmal epithelium and other cutaneous malignancies. The association of Merkel cell carcinomas with other adnexal lesions and their dermal location strengthen the hypothesis of an origin.

**Table 1** Differential diagnosis of trichilemmal carcinomas with divergent differentiation.

| Categories                              | Conditions                                      | Key diagnostic features                                                                 |
|-----------------------------------------|------------------------------------------------|-----------------------------------------------------------------------------------------|
| With neuroendocrine differentiation     | Merkel cell carcinoma                          | Infiltrative trabecular growth                                                         |
|                                         |                                                 | Differentiated and intraepithelial malignant components can be present                  |
|                                         |                                                 | Irregularly distributed chromatin, no nucleolus                                         |
|                                         |                                                 | Diffuse expression of neuroendocrine and neuronal markers                               |
|                                         |                                                 | Occasionally, expression of divergent differentiation markers in malignant cells (e.g. melanocytic, glandular) |
| Metastatic neuroendocrine carcinoma     | Infiltrative growth                             | No connections with superficial or adnexal epithelia                                    |
|                                         |                                                 | Irregularly distributed chromatin, no nucleolus                                         |
|                                         |                                                 | Frequent lymphovascular invasion                                                       |
|                                         |                                                 | Diffuse expression of neuroendocrine markers                                            |
|                                         |                                                 | Expression of tissue-specific markers (e.g. TTF1, PSA)                                  |
| With melanocytic component              | Pigmented pilar-type basal cell carcinoma       | Infiltrative growth pattern, deep                                                      |
|                                         |                                                 | Connections with superficial epithelium                                                 |
|                                         |                                                 | Basaloid cells with focal evidence of pilar differentiation (hyaline cytoplasms, 'cell balls', catagen-like apoptotic bodies, calcification, D-PAS-positive stromal induction, peritumoral CD34-positive spindle cells). |
|                                         |                                                 | Retraction artifact at epithelial-stromal junction                                       |
|                                         |                                                 | Pigmentation/colonization by non-tumoral melanocytes                                   |

D-PAS, diastase-resistant periodic-acid–Schiff; PSA, prostate-specific antigen; TTF1, thyroid transcription factor 1.

Merkel cell carcinomas have also been reported associated with a trichilemmal cyst, showing pagetoid spread into the trichilemmal epithelium and other cutaneous malignancies. The association of Merkel cell carcinomas with other adnexal lesions and their dermal location strengthen the hypothesis of an origin.
from pluripotent stem cells of adnexal epithelium. In
the case reported here, malignant cells showed a
predominant pilar differentiation with only focal neuro-
endocrine features (Table 1). Abnormal differentiation
has been inversely correlated with malignancy and
precancerous lesions; progressive undifferentiation
is often associated with advanced tumour stages and
divergent differentiation is not unusual in a variety of
poorly differentiated malignant tumours (e.g. breast
ductal carcinoma, gastrointestinal adenocarcinomas or
desmoplastic small round cell tumour). The neuroen-
docrine differentiation is important, because these
tumours have been reported to be resistant to chemo-
therapy.

The presence of melanocytes in epithelial tumours is
relatively rare in cutaneous or extracutaneous neo-
plasms. The systematic presence of nonatypical spindle
melanocytes in pilar neoplasms questions the separation
of pigmented pilar neoplasms as independent entities.2,7
These conditions probably represent extreme forms of
melanocyte colonization of epithelial pilar tumours and
do not merit creation of ‘new’ entities such as ‘pig-
mented’ or ‘melanocyte-containing’ tumours.2 The
most important issue is to determine if the melanocytic
component shows evidence of dysplasia or malignancy
using standard criteria.12,13 Dysplastic and malignant
changes may occur in the melanocytic component of
epithelial pilar neoplasms and would explain the descrip-
tion ‘biphasic neoplasms’ .7,14 Melanocytes are
found within the epithelial nests of epithelial pilar
tumours (both benign and malignant),2 and can be used
as a clue to the recognition of this differentiation in the
absence of clinical pigmentation or epithelial cell
melanin during histological examination.2 Melanocytes
are rarely identified in other cutaneous epithelial
tumours, and are normally associated with clinical
and/or histological pigmentation.

In conclusion, neuroendocrine differentiation in
trichilemmal carcinomas is suggested by a trabecular
growth pattern and requires immunohistochemical
confirmation. The colonization of the epithelial nests
by nonatypical dendritic/spindle melanocytes is a clue
to the morphological recognition of pilar neoplasms,
along with the presence of stromal induction, catagen-
like apoptotic bodies, calcification, keratin microcysts
and cell balls. This feature lends the tumours a
heterogeneous appearance, containing tumour cells
and dendritic cells that may be pigmented.

References
1 Ackerman AB, De Viragh P A, Chongchitnant N. Neoplasms
with Follicular Differentiation (Ackerman’s Histologic Diag-
osis of Neoplastic Skin Diseases: a Method by Pattern Anal-
ysis). 1st edn. Philadelphia: Lea & Febiger, 1993.
2 Aly Z, Pozo L, Díaz-Cano SJ. Colonization of epithelial pilar
neoplasms by melanocytes. Histopathology 2006; 48: 213–
17.
3 Boscaino A, Terracciano LM, Donofrio V et al. Tricho-
lemmal carcinoma: a study of seven cases. J Cutan Pathol
1992; 19: 94–9.
4 Reis JP, Tellechea O, Cunha MF, Baptista AP. Trichilemmal
carcinoma: review of 8 cases. J Cutan Pathol 1993; 20: 44–9.
5 Swanson PE, Marrogi AJ, Williams DJ, et al. Tricho-
lemmal carcinoma: clinicopathologic study of 10 cases. J Cutan
Pathol 1992; 19: 100–9.
6 Wong TY, Suster S. Tricholemmal carcinoma. A clinic-
opathologic study of 13 cases. Am J Dermatopathol 1994; 16:
463–73.
7 Kanitakis J, Brutzkus A, Butnaru AC, Claudy A. Melano-
trichoblastoma. Immunohistochemical study of a variant of
pigmented trichoblastoma. Am J Dermatopathol 2002; 24:
498–501.
8 Kazakov DV, Kutzner H, Rutten A et al. Tricho-
germinoma: a rare cutaneous adnexal tumor with differentia-
tion toward the hair germ epithelium. Dermatology 2002;
205: 405–8.
9 Harper ME, Glynne-Jones E, Goddard L et al. Vascular
endothelial growth factor (VEGF) expression in prostatic
tumours and its relationship to neuroendocrine cells. Br J
Cancer 1996; 74: 910–16.
10 Pozo L, Sanchez-Carrillo JJ, Martinez et al. Differential
kinetic features by tumor topography in cutaneous small
cell neuroendocrine (Merkel cell) carcinomas. J Eur Acad
Dermatol Venereol 2007; DOI: 10.1111/j.1468-3083.2007.02236.x.
11 Heenan PJ, Cole JM, Spagnolo DV. Primary cutaneous
neuroendocrine carcinoma (Merkel cell tumor). An ad-
nexal epithelial neoplasm. Am J Dermatopathol 1990; 12:
7–16.
12 Gonzalez-Campora R, Galera-Davidson H, Vazquez-Ra-
mirez PJ, Diaz-Cano S. Blue nevus: classical types and new
related entities. A differential diagnostic review. Pathol Res
Pract 1994; 190: 627–35.
13 Pozo L, Díaz-Cano SJ. Malignant deep sclerosing blue
naevus presenting as a subcutaneous soft tissue mass. Br J
Dermatol 2004; 151: 508–11.
14 Rizzardi C, Brollo A, Colonna A et al. A tumor with com-
posite pilo-folliculosebaceous differentiation harboring a
recently described new entity – melanocytic matricoma.
Am J Dermatopathol 2002; 24: 493–7.