Basal cell carcinoma with progression to metastatic neuroendocrine carcinoma

Raj Patel,[1] Volkan Adsay,[2] Aleodor Andea[1]

[1]Department of Pathology and Dermatology, University of Alabama at Birmingham, Birmingham, AL; [2]Department of Pathology, Emory University, Atlanta, GA, USA

Abstract

Merkel cell carcinoma (MCC) or primary cutaneous neuroendocrine carcinoma is a malignant tumor considered to demonstrate differentiation towards Merkel cells that are present at the base of the epidermis or around the apical end of some hair follicles and are thought to play a yet uncertain role in sensory transduction. Here we present the case of a 54-year old female with a basal cell carcinoma (BCC) of the skin with neuroendocrine features (positivity for chromogranin) that has evolved during multiple recurrences and radiotherapy into a high-grade neuroendocrine carcinoma with morphological and immunohistochemical features of MCC (trabecular and nesting arrangement, positivity for chromogranin, cytokeratin 20, neuron specific enolase, and also neurosecretory granules on electron microscopy). The progression from a chromogranin positive basal cell carcinoma of the skin, to a high-grade neuroendocrine carcinoma demonstrates the potential for cross differentiation among skin tumors.

Introduction

Primary cutaneous neuroendocrine carcinoma is a malignant skin neoplasm considered to exhibit differentiation towards Merkel cells on the basis of structural similarities, hence the designation of Merkel cell carcinoma (MCC).[1] Merkel cells have neuroendocrine properties and are thought to function as a neurosecretory transmitter. These cells are present at the base of epidermis or around the apical end of some developing hair follicles, usually protruding into the dermis in direct contact with mechanoreceptive cutaneous nerve endings.[2] Their location near the hair follicles led to the hypothesis that Merkel cells may play a role in the formation and proliferation of hair follicles in the developing skin[2] and also may participate in the induction and alignment of arrector pili muscles at fetal stage.[3]

The initial report on MCC appeared in 1972 by Toker *et al.*[4] under the heading of trabecular carcinoma. It was later noticed that the trabecular pattern was outnumbered by other patterns displayed by this tumor and, therefore, MCC has gradually replaced the original name and established its place in the neuroendocrine family of tumors. There is, however, some controversy regarding the Merkel cell "origin" of MCC. Although Merkel cells are abundant in areas of skin involved in touch perception, such as finger tips, this location is uncommon for MCC.[5] Also, the cells of MCC do not express the opioid peptides identified in normal Merkel cells.[6] For these reasons, some authors advocate the term primary cutaneous neuroendocrine carcinoma which lacks the implication of a Merkel cell differentiation.

Several studies have described the presence of tumors with variable differentiation such as squamous, eccrine, apocrine, pillar and melanocytic associated with MCC.[7-12] In addition, some MCCs have histological features that resemble a basal cell carcinoma (BCC) such as mucinous stroma or stromal artifactual retraction.[13] While some of these observations possibly represent random collision tumors, they also raise the possibility that a totipotent stem cell is at the origin of tumors with variable phenotypic expression.[14] In addition, the recent discovery of Merkel cell polyoma virus not only in MCC but also in BCC tumors from immunocompromised patients raises another question regarding a common etiology.[15] In this study, we present a patient with a BCC with neuroendocrine properties that during multiple recurrences has transformed into a high-grade neuroendocrine carcinoma with features of MCC. This observation seems to support the existence of totipotential stem cells with initial basal cell and later neuroendocrine differentiation.

Materials and Methods

All specimens studied from this patient were surgically removed, fixed in formalin and embedded in paraffin according to routine procedures. Sections were stained with hematoxylin and eosin and/or hematoxylin-phloxine-saffron.

For immunohistochemical studies, an antigen retrieval method was used: sections in citrate buffer were heated in the microwave 2 times for five minutes each. The antibodies used in this study are listed in Table 1.

Electron microscopy was performed using paraffin embedded tissue. The thin section was stained with 1% uranyl acetate and examined under a Zeiss 109 electron microscope.

Correspondence: Aleodor Andea, University of Alabama at Birmingham, 619 19th St S PD6A Room 149, Birmingham, AL 35249, USA.
E-mail: aandea@uab.edu

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Case Report

The patient was a 54-year old female who presented originally with a BCC on skin of the right thigh which was surgically removed. Six years after the initial diagnosis, at the age of 60 years, the patient presented with right inguinal lymphadenopathy that upon biopsy was diagnosed as metastatic carcinoma. She subsequently received radiation therapy to the right inguinal area. Extensive clinical work-up revealed no primary carcinoma lesion other than the previously excised BCC. After another three years, the patient underwent a right nephrectomy for hydronephrosis due to obstruction by metastatic carcinoma of the right ureter. She was given additional radiotherapy. Finally, after another four years, at the age of 67, the patient presented with recurrent hip pain and multiple episodes of rectal bleeding with negative endoscopic and radiological work-up. At surgical exploration, a right common iliac artery-appendiceal peritoneal fistula and a large infected retroperitoneal hematoma were found. The patient underwent ileo-cecal resection and right ooforectomy with surgical repair of the right common iliac artery. Examination of the appendix and right ovary showed a diffusely infiltrating, poorly differentiating carcinoma with basaloid and trabecular features, with vascular and perineural invasion. There was extensive involvement of the appendiceal wall by tumor producing an arterial-appendiceal fistula. There was also acute appendicitis, peri-appendicitis and fibrinopurulent peritonitis of a large bowel segment.

Pathological findings

The initial excised tumor was a classical example of a superficial BCC (Figure 1). Although there was not any particular feature to announce a more aggressive behavior, retrospective immunohistochemical analysis

demonstrated granular positivity for chromogranin in many of the tumor cells. The metastatic BCC in the lymph node showed only partial peripheral palisading; a trabecular pattern was identified, the nuclei were round to ovoid, larger than in the primary tumor, and with an open chromatin pattern (Figure 2). The right ureteral metastasis showed a prominent trabecular pattern (Figure 3). Elsewhere, areas of squamous differentiation were also noted. The last specimen, appendix and ovary, had many histological features of a neuroendocrine carcinoma. In many areas, cells were arranged in nests, having round nuclei with open, finely granular chromatin pattern and little cytoplasm (Figure 4). Some areas showed a suggestion of peripheral palisading of nuclei (Figure 5). Squamous differentiation in the form of keratin pearls was noted focally.

The immunohistochemical profile of the last metastasis is summarized in Table 1. Notable is the positivity for keratin 20 (Figure 6). The tumor also showed positivity for AE1, chromogranin (Figure 7) and neuron specific enolase. The stains for keratin 7, synaptophysin and neurofilament were negative.

Electron microscopic studies performed on the paraffin block from the ovary specimen, revealed cells with very smooth nuclear contours, with multiple nucleoli and scattered dense-core, membrane bound neurosecretory granules, consistent with a neuroendocrine origin (Figure 8). In addition, perinuclear bundles of microfilaments and cell junctions (desmosomes) were identified.

Discussion

This case demonstrates a clinical evolution and a histophenotypic transformation, during multiple recurrences and radiotherapy treatment from a classical BCC of the skin, into a high-grade neuroendocrine carcinoma with morphological and immunophenotypic features of MCC. The progression was rather smooth, with each recurrence over the years, the tumor developing gradually more pronounced features of a neuroendocrine carcinoma. The cells became larger, round to oval in shape, with very scanty cytoplasm, arranged as a rim around the washed-out nucleus. The nuclei showed clearing of the chromatin, a high proliferative rate and usually multiple, inconspicuous nucleoli.

Many cutaneous neoplasms arise from uncommitted totipotential cells, which, under various oncogenic stimuli, may differentiate to one or more cellular lines to varying extents.[16] Several investigators have reported the association of MCC with tumors of various other differentiations, either as separate masses or intimately admixed. The most common tumor

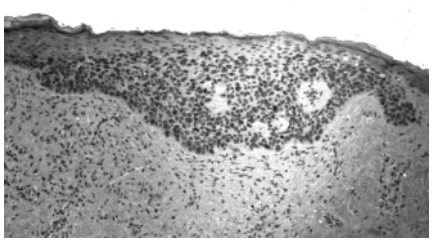

Figure 1. Low power view of the initial basal cell carcinoma of the skin (x20).

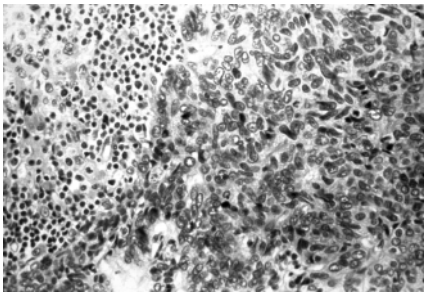

Figure 2. Metastatic BCC in the inguinal lymph node showing partial peripheral palisading, clearing and enlargement of the nuclei (hematoxylin-eosin, original magnification, x20).

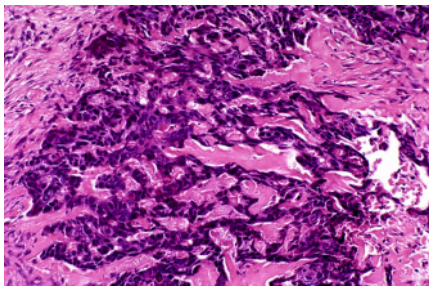

Figure 3. Metastasis around the urethra showing a prominent trabecular pattern (hematoxylin-eosin, original magnification x20).

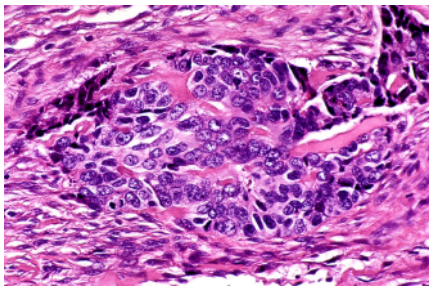

Figure 4. Ovarian metastasis exhibiting histological features of a neuroendocrine carcinoma. In many areas cells were arranged in nests, having round nuclei with open, finely granular chromatin pattern and little cytoplasm (hematoxylin-eosin, original magnification x40).

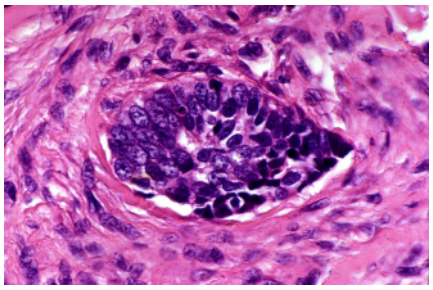

Figure 5. Ovarian metastasis with peripheral palisading of the nuclei (hematoxylin-eosin, original magnification, x40).

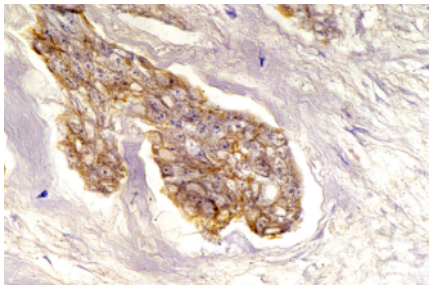

Figure 6. Immunohistochemical staining for cytokeratin 20 showing diffuse positivity.

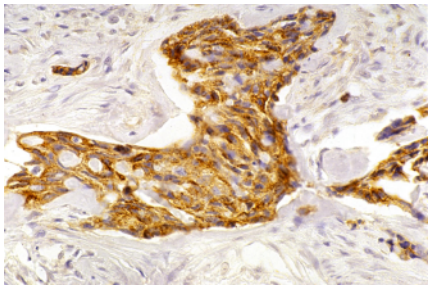

Figure 7. Immunohistochemical staining for chromogranin showing intense positivity (hematoxylin-eosin, original magnification x40).

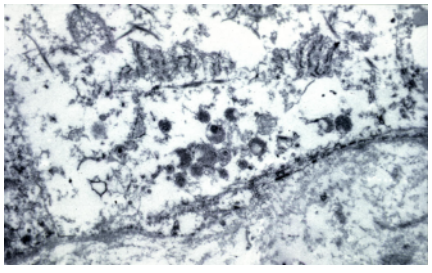

Figure 8. Electron microscopy revealing dense-core, membrane bound neurosecretory granules (original magnification x30000).

Table 1. Immunohistochemical stains performed on the ovarian metastasis.

Antibody	Dilution	Digestion cocktail	Source	Results
CK 903	1:100	Citrate Buffer	Enzo	Positive
AE1	1:100	Pepsin	Boehringer	Positive
Chromogranin	1:1k/2k	Citrate Buffer	Dako	Positive
CK 7	1:200	Pepsin	Dako	Negative
CK 20	1:50	Pepsin	Dako	Positive
NSE	1:500	Citrate Buffer	Dako	Positive
Synaptophysin	1:250	Citrate Buffer	Dako	Negative
Neurofilament	1:2k	Citrate Buffer	Dako	Negative

CK: Cytokeratin, NSE: Neuron specific enolase.

associated with MCC is squamous cell carcinoma which is encountered in about 10% of cases.[8,9,14,17-20] This association was either in the form of squamous cell carcinoma *in situ* overlying the MCC[8] or in the form of infiltrating squamous cell carcinoma admixed with the MCC.[9,14,17,18] The association of BCC with MCC is a rarer occurrence; however, it is documented.[14,17-19,21,22] Cerroni *et al.*[18] reported a case presenting with MCC, SCC and BCC arising at the same site. Another case report[22] noted the combination of MCC with BCC in a young patient diagnosed with hypohidrotic ectodermal dysplasia that is known to predispose towards actinic alterations. The patient developed multiple neuroendocrine tumors in the sun-damaged skin, concomitantly with multiple BCC of the face.

As opposed to the previously reported cases, the present case is unique in that it shows not just a static association of BCC and MCC but progression from one tumor to another through transitional forms. The only other case that is similar to ours is a study by Rocamora *et al.*[21] in which the authors reported a case of BCC of the skin of the dorsum of the nose that recurred and later metastasized as a neuroendocrine carcinoma of the skin.

The presence of areas with squamous differentiation in MCC seems to question the neural crest origin of Merkel cells. In fact, the study of Ochiai *et al.*[23] on fine ultrastructural and morphometric aspects of Merkel cell during fetal and postnatal development supports the idea that Merkel cells may be keratinocytic in origin. In conclusion, although the embryologic origin of Merkel cell is not definitively determined, an epidermal, rather than neural crest origin, is plausible.

The presence of neuroendocrine features in BCC tumors is not an uncommon occurrence and has been previously reported.[14] However, the neuroendocrine cells present in BCCs failed to show all the histological characteristics of classical Merkel cells and are negative for keratin.[14,20]

It may be significant to note the recently discovered role of Merkel cell polyomavirus (MCV) in MCC and BCC tumors in immunocompromised patients. Kassem *et al.* suggest that there is some potential linkage between non-melanoma skin tumors including BCC and MCV.[15] If this is true, one can speculate that MCV could facilitate the transformation of BCC into MCC. Supporting the link between these tumors is also the observation that some MCCs contain areas that demonstrate histological similarities to BCC and may lead in fact to misdiagnosis.[13]

Our case supports the existence of some degree of "plasticity" in epidermal tumors that allows for the observed evolution from a classical BCC with neuroendocrine properties to a poorly differentiated neuroendocrine carcinoma. It is possible that a subclone of basal cells, exhibiting neuroendocrine differentiation and more aggressive behavior, metastasized as a high-grade neuroendocrine carcinoma. This may represent an example of the so-called "dedifferentiation" process, similar to the dedifferentiation observed in liposarcomas or chondrosarcomas. This transformation suggests that there is a link between epithelial and Merkel cells in the epidermis. Further studies are, however, warranted to establish if a common totipotential progenitor cell for both epithelial and neuroendocrine carcinomas of the skin does in fact exist.

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