Case Report

P16 Expression of Merkel cell carcinoma in a Mixed Squamous Cell Carcinoma: A Case Report

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Received Date: 31 March 2017; Accepted Date: 18 July, 2017; Publication Date: 14 August, 2017

Abstract

Merkel cell carcinoma (MCC) is an uncommon, aggressive neuroendocrine skin cancer. Ever since the Merkel cell polyomavirus (MCPyV) was first isolated in 2008, the relationship between MCPyV and MCC has been studied. Reported herein is a case of a 92 year-old Asian woman admitted for a skin tumor consisting of both Merkel cell and squamous cell carcinomas in the cheek. The two carcinomas are different not only in morphology but also in their immunohistochemical profiles. p16, a well-known marker of human papilloma virus (HPV) related tumorigenesis, was very highly expressed in these patients with MCCs, which could explain the pathogenesis of MCPyV-negative MCC. High expression of p16 can be a useful diagnostic marker of primary cutaneous neuroendocrine carcinoma.

Keywords:
Merkel cell carcinoma; Squamous cell carcinoma; p16

Introduction

Merkel cell carcinoma (MCC) is a rare type of aggressive skin cancer [1]. Because MCC favors ultraviolet-damaged skin of elderly patients with immunosuppressive or inflammatory comorbidities, the risk of developing this tumor has increased, especially combined squamous cell carcinoma (SCC) [2]. Meanwhile, Merkel cell polyomavirus (MCPyV) was isolated from a specimen obtained from a MCC patient in 2008 [3]. Although MCPyV is usually the cause of MCCs, the molecular mechanisms remain inadequately understood. Polyomavirus-encoded T antigens target several tumor suppressor proteins, including the retinoblastoma protein (RB) and the p53 protein [4]. This pathway is almost similar to the effect of p16 in human-papilloma- virus (HPV)-related tumorigenesis of squamous cell neoplasms. We describe a case of squamous cell carcinoma (SCC) and MCC in the skin tumor of a 92 year old Asian woman. The histomorphology and immunohistochemical profiles of the two tumors were different. In addition, p16 overexpression was mainly observed in MCC.

Case Presentation

A 92 year old Asian woman presented with a nodular mass of the left cheek, which had been rapidly growing for one year (Figure 1A). It was a 2.2 cm sized, scaly nodule, which was brownish-colored. Head and neck CT revealed a cutaneous mass, partially involving the subcutis, but not showing any bone destruction (Figure 1B).
A wide excision was made, including a safety margin.

**Figure 1:** (A) A crusted, scaly, brownish nodular mass was present at the left cheek. (B) The head and neck computed tomography (CT) showed a cutaneous mass partly involving subcutaneous soft tissue and not bone destruction. The sections showed a nodular tumor growth consisting of two different tumors: SCC and MCC. The surface epidermis was thickened by atypical keratinocytes due to diffuse actinic keratosis, which invaded the dermal stroma. MCC was mainly located at the dermo-epidermal junction to the deep dermis (Figure 2). The tumor cells of MCC revealed finely stippled chromatin with scanty cytoplasm (Figure 2).

**Figure 2:** The sections show a nodular protruding tumor consisting of two different tumors: SCC and MCC. The overlying epidermis was thickened by atypical keratinocytes due to diffuse actinic keratosis. MCC was mainly located at the dermo-epidermal junction to the deep dermis (hematoxylin-eosin [H&E], x 10). The tumor cells of MCC revealed finely stippled chromatin with scanty cytoplasm (insert) (H&E, x 400).

The immunohistochemical studies (Figure 3) of the two tumors were quite different. MCC showed neuroendocrine differentiation [synaptophysin (Figure 3A), CD56 (Figure 3B)] and was positive for cytokeratin 20 in the paranuclear dot-like immunostaining (Figure 3C); p16 (Figure 3D) expression was diffusely high in MCC, but focally positive in SCC. The p63 (Figure 3E) immunohistochemical staining was only positive for the SCC. Staining for SV40 (polyomavirus) (Figure 3F) was negative in both tumors. The patient had been stable for two months after the excision, following which she was lost to follow-up.

**Figure 3:** The immunohistochemical panel of scanning power view (x10) revealed two distinctly different profiles: the MCC expressed in synaptophysin (A), CD56 (B), CK20 (C) and p16 (D); and the SCC showed focal expression in only p16 (D) and diffuse expression in p63 (E); SV40 for polyomavirus was not detected (F).

**Discussion**

MCC is a rare cutaneous neuroendocrine carcinoma (0.6 per 100,000 persons) that has an aggressive course with the 5 year disease-specific survival rate estimated at 30-64% [1]. MCC co-occurring with non-MCC tumors, particularly SCC, accounts for 5-14% of all MCC cases. Combined tumors are thought to be more aggressive than MCC alone. Suarez et al. summarized 26 cases of mixed MCC and SCC and compared these to 20 cases of MCC alone [5]. They reported more frequent metastasis and death than in MCC alone. The combination of SCC and MCC presents on the actinically damaged skin of elderly patients, most frequently in the head and neck. The patient reported herein had actinic keratosis, which...
suggested a potential etiology of exposure to ultraviolet light.

MCPyV is a recently discovered virus linked to MCCs that contains clonally integrated viral DNA, expresses viral T antigen transcript and protein, and is an addition to the large and small viral T antigen oncoproteins [6]. The patient reported herein had negative result for SV40 (polyomavirus antigen); Thus, MCC in this patient was not caused by polyomavirus infection.

Some studies suggest that MCPyV-positive MCC differs from MCPyV-negative cancers in terms of several clinical and molecular features. The former shows female predominance, an intermediate-type histology, and location in the limb. Moreover, the tumor expresses RB and patients with these tumors do not have the TP53 mutation, but TP53 mutations were detected in MCPyV-negative MCCs [7]. The genetic profile of MCPyV-negative MCCs showed up regulation of MMP-10 and CDKN2A, which mediate apoptosis and are members of protease related families. Non-existent role in carcinogenesis had been mentioned as 'hit-and-run' phenomenon [8]. High expression of p16 has been found in HPV-associated lower anogenital squamous tumor (LAST) [9], which supports the assertion that pRB/E2F-p16 and p21 are the main oncogenic proteins. This cascade of oncogenic proteins is very similar to the tumorigenesis of MCCs.

A case report of combined SCC and MCC of the vulva showed the roles of HPV and MCPyV; additionally, p16 was expressed in both tumor types unlike the case report in the study [10]. In the case reported by Chen et al., MCC tumor cells expressed a synaptophysin ~p16+/chromogranin+/CK+/~CK20+/CD56+/CK5+/+P63-/P16+ immunoprofile, whereas the SCC part was synaptophysin ~p16/chromogranin-/CK+/~CK20+/CD56-/CK5+/P63+/P16+.

The identification of the virus showed type 16-HPV and E6/E7 messenger RNA expression in both tumors. Another case report of anal-canai neuroendocrine carcinoma associated with squamous intraepithelial neoplasm demonstrated the positivity of p16 in the two tumor components [11]. The co-expression of p16 in both MCC and SCC might be related with the increased presence of HPV in the vulva and anus compared to the other site of the skin.

The p16 positivity in MCC has been intermittently described in an aspect of MCPyV associated tumorigenesis. However, virus negative MCC also expresses for p16, which can be is diagnostically useful for differential diagnosis of MCC in a group of neuroendocrine carcinomas. Therefore, measuring p16 in the immunohistochemical panel for small, round cell tumors, the p16 expression can be helpful, especially for cutaneous tumor.

Acknowledgement

The authors thank Ms SW Chun for skillful technical assistance in immunohistochemistry.

Conflicts of Interest

The authors declare that they have no competing interests.

References


JAAD Case Reports; 1: 196-199.