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Coexistence of neuroendocrine carcinoma and squamous cell carcinoma of the skin after kidney transplantation: a case report

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Neuroendocrine carcinoma (NEC) is a rare aggressive tumor of the skin with a shared phenotype of both endocrine and neuronal features. Its behavior includes rapid progression, common local recurrence, frequent metastasis to local lymph nodes, and occasional systematic involvement. The risk factors for NEC are similar to those for other skin cancers and mainly include ultraviolet light exposure, older age, T-cell immunosuppression, fair skin, and male sex. NEC is seen more frequently in the immunosuppressed population, and we report a rare case of NEC combined with squamous cell carcinoma (SCC) in a patient who underwent kidney transplantation. A 66-year-old man was referred with a brownish plaque on left cheek, and a punch biopsy result indicated SCC *in situ*. Wide excision was performed, and the defect was reconstructed using a bilobed flap. The final biopsy confirmed SCC combined with carcinoma with neuroendocrine differentiation, and positron emission tomography-computed tomography confirmed the absence of lymph node metastasis or systemic involvement. The patient showed no evidence of recurrence or other postoperative complications.

Abbreviations: MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; NEC, neuroendocrine carcinoma; PET-CT, positron emission tomography-computed tomography; SCC, squamous cell carcinoma

Keywords: Case reports / Neoplasms / Neuroendocrine carcinoma / Neuroendocrine differentiation / Kidney transplantation

Case Report

INTRODUCTION

Neuroendocrine carcinoma (NEC) of the skin is an uncommon aggressive tumor that presents both endocrine and neuronal phenotypic features. It is characterized by rapid progression, common local recurrence, frequent metastasis to local lymph nodes, and occasional systematic involvement [1]. The disease-specific mortality rate of NEC is estimated to be between 33% and 46%, which is three times higher than that of malignant melanoma. It is known to be more likely to develop in older individuals, and immunocompromised or immunosuppressed patients [2]. The pathogenesis of NEC is not yet fully understood; however, emerging evidence suggests Merkel cell polyomavirus (MCPyV)-associated and ultraviolet-mediated oncogenic pathways [3].

According to the fifth edition of the World Health Organization classification of non-melanocytic skin tumors, Merkel cell carcinoma (MCC) is currently classified as a primary NEC of the skin. Its subtype is divided into according to the following features: MCPyV-positive versus MCPyV-negative and pure MCC versus combined MCC [4]. NEC can exhibit aberrant immunohistochemical profiles that can lead to diagnostic diffi-

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culties. A consensus on the nomenclature of different subsets of NEC has yet to be reached. Some authors have suggested that combined squamous cell carcinoma (SCC) and NEC differ from pure MCC in terms of protein expression and genetics, in addition to morphology and the absence of MCPyV [5].

In our case, the coexistence of NEC and SCC was inadvertently discovered, and positron emission tomography-computed tomography (PET-CT) was performed postoperatively to check for locoregional and systemic involvement. To the best of our knowledge, this is the first report of NEC combined with SCC with a disparate immunohistochemistry profile from pure NEC in a Korean patient after kidney transplantation.

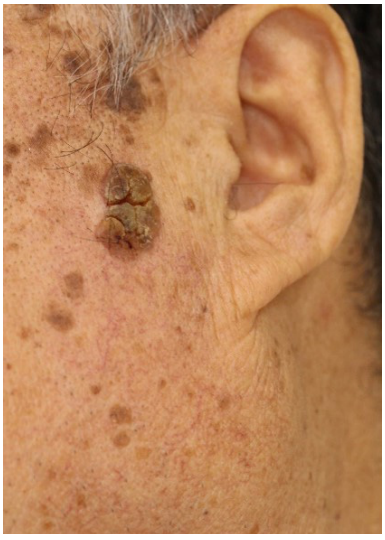

Fig. 1. A 66-year-old man with a 5-year history of a brownish pigmented plaque on the left cheek, was diagnosed as squamous cell carcinoma *in situ* via punch biopsy but later confirmed as combined neuroendocrine carcinoma with squamous cell carcinoma in surgical biopsy.

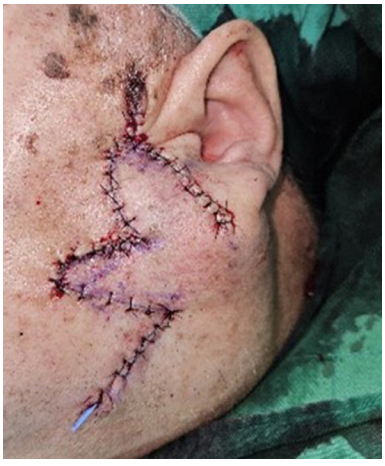

Fig. 2. In intraoperative photograph, bilobed transposition flap was performed to cover the skin defect after tumor excision.

CASE REPORT

A 66-year-old man presented with a 5-year history of a brownish pigmented plaque on his left cheek (Fig. 1). The patient had a personal history of chronic kidney disease and had undergone kidney transplantation 10 years ago. The patient had no family history of skin cancer, and his other comorbidities included hypertension, diabetes mellitus, hypothyroidism, and dyslipidemia. Punch biopsy performed by a dermatologist was positive for SCC *in situ*. However, a pathological correlation was recommended, as invasive SCC could not be completely excluded. In our patient, a wide excision with 5 mm safety margins was performed. The defective area of the left cheek was covered using a transposition flap (Fig. 2). Histological examination of the excised lesion under a microscope showed exophytic and verrucous tumors (Fig. 3). The majority of the tu-

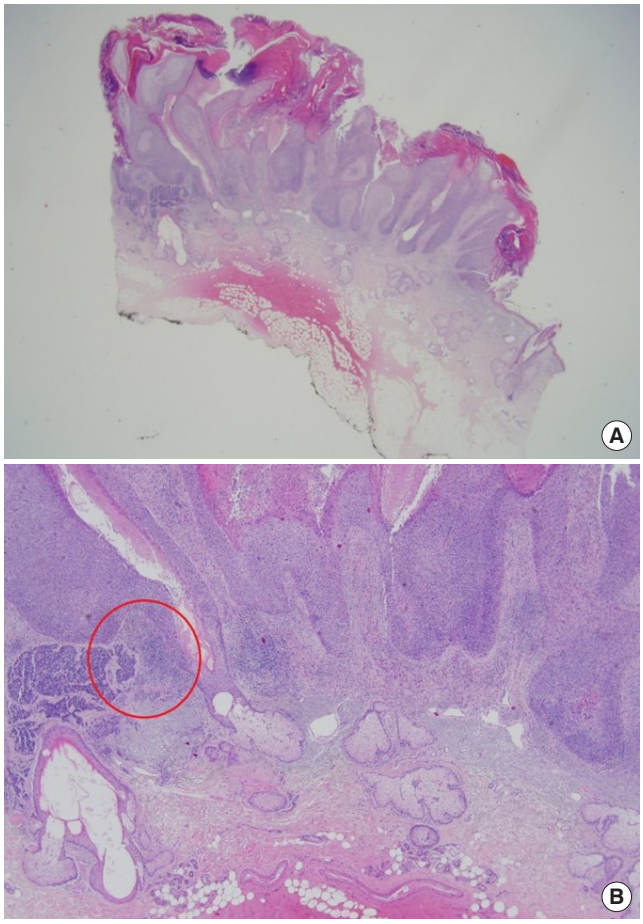

Fig. 3. A histopathologic examination of surgical specimen from a 66-year-old man with pre-diagnosed squamous cell carcinoma *in situ* lesion. (A) Histologic examination showing exophytic and verrucous tumor features (hematoxylin and eosin stain, ×15). (B) Red circle indicating an ill-defined aggregate of poorly differentiated tumor cells around squamous cell nests counting up to 1/10 of total tumor component (hematoxylin and eosin stain, ×100).

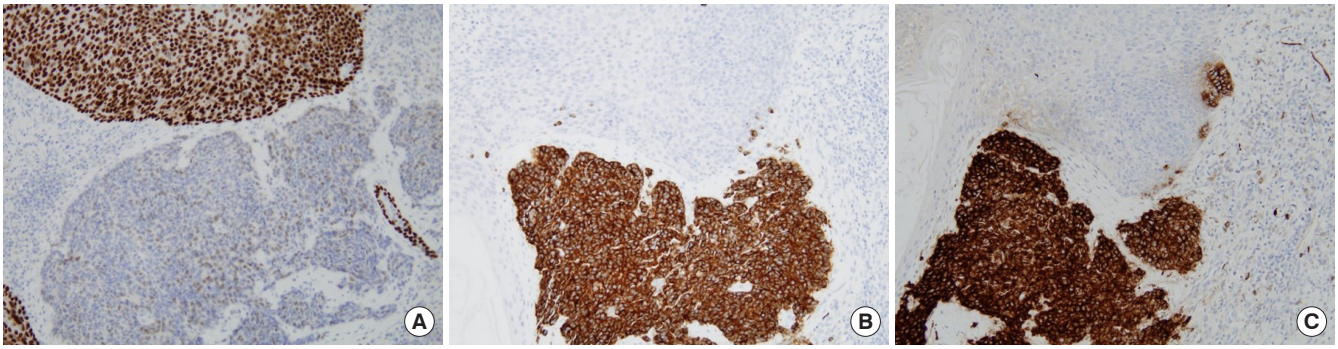

Fig. 4. An immunohistochemistry stain confirming primary cutaneous origin of the combined neuroendocrine tumor. (A) The upper part of the tumor cells showed positive reactivity to p63 supporting squamous cell differentiation. (B, C) Poorly differentiated tumor cells in the lower part showed positive reactivity to synaptophysin and CD56 indicating neuroendocrine differentiation (A-C, ×400).

mor was composed of SCC; however, an ill-defined aggregate of poorly differentiated tumor cells was noted around SCC nests. Immunohistochemical stain showed strong p63 positive reactivity in the upper part of the tumor, supporting squamous cell differentiation. Poorly differentiated tumor cells in the lower part showed strong synaptophysin and CD56 positive reactivity, but negative reactivity to p63, indicating neuroendocrine differentiation (Fig. 4). Both tumor components were positive for p53, but negative for CK20 and TTF-1. Due to limited resources and the unavailability of MCPyV large T-antigen immunohistochemistry, the existence of the polyomavirus was not confirmed. In conclusion, the pathologist confirmed this tumor as combined NEC rather than pure MCC, based on its histological and immunohistochemical profile. The ratio of neuroendocrine differentiation to total tumor component was 1/10. No evidence of lymph node metastasis or systemic involvement was discovered according to PET-CT. However, diffuse F-18 fluorodeoxyglucose uptake in the first part of the duodenum and the left peripheral zone of the prostate was noted. Prostate-specific antigen testing, ultrasonography, and endoscopy were performed during an annual health checkup; otherwise, no metastasis or systemic involvement was detected. Five months postoperatively, the patient showed no evidence of recurrence or other postoperative complications (Fig. 5).

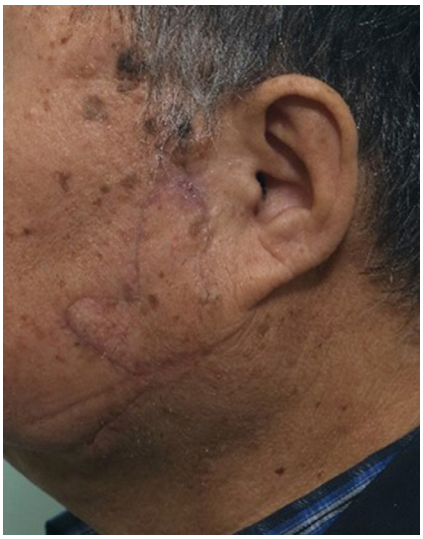

Fig. 5. Five-month postoperative photograph showing normotrophic scar with no tumor recurrence.

DISCUSSION

Advancements in kidney transplantation surgical techniques and the development of adjuvant drugs have led to an increasing number of patients undergoing kidney transplantation. After transplantation, immunosuppressive drugs must be administered to prevent organ rejection, balance immune response and enhance graft survival, which can lead to an increased risk of various skin cancers, such as SCC, basal cell carcinoma, malignant melanoma, and MCC.

The risk of MCC (primary cutaneous NEC) sharply increases after solid organ transplantation, likely due to long-term immunosuppression. Furthermore, immunosuppressive medications may act synergistically with ultraviolet radiation to increase the risk [6]. Multiple studies have reported the occurrence of pure MCC after kidney transplantation [7,8]. MCC are conventionally CK20-positive, making this feature useful for distinguishing MCC from other skin cancers; however, it is important to note that 10% of patients with MCC have been negative for CK20 expression [9]. Surgical management of both the primary site and sentinel lymph node is the standard treatment for MCC. The current National Comprehensive Cancer Network guidelines recommend wide local excision of the primary site with 1 to 2 cm margins to the investing fascia of muscle when clinically feasible. Additionally, the National Comprehen-

sive Cancer Network recommends lymph node dissection for clinically evident lymphadenopathy.

However, in our patient, the tumor cells were negative for CK20 and showed poor differentiation and a coexisting histological pattern combined with SCC, which differentiated the condition from pure MCC. Multiple studies have suggested that combined squamous cell and NECs differ from pure MCC [5]. In a large cohort study regarding pure MCC (MCPyV-positive and negative), MCPyV-negative MCC cases had a significantly increased risk of disease progression and mortality rate compared to MCPyV-positive MCC cases; the median overall survival of MCPyV-negative group and –positive groups were 3.3 year and 4.6 years, respectively [10]. However, contrary to conventional belief, a systematic review of 38 studies mentioned that the prognosis of combined SCC and MCC was comparable to that of pure, MCPyV-negative MCC [11].

In patients with NEC of the skin, an extensive workup is essential to rule out primary visceral involvement, and metastasis from carcinoid tumors of the bronchopulmonary or gastroenteropancreatic carcinoma [12]. In our patient, the tumor cells showed negative reactivity to TTF-1, gastrointestinal endoscopy showed no lesions, and postoperative PET-CT suggested no metastatic counterpart, thus favoring a primary cutaneous origin. Therefore, the tumor in this patient was confirmed to be a high-grade NEC of the skin combined with SCC.

Skin cancers such as basal cell carcinoma, SCC, melanoma and hematological malignances including chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, and salivary gland as well as biliary tract cancer, often co-occur in patients with NEC of the skin. The co-occurrence of these cancers in patients with NEC of the skin may be due to shared risk factors such as immunosuppression, ultraviolet exposure, and genetic predisposition. Additionally, the presence of MCPyV in most cases of NEC of the skin may contribute to the development of other malignancies [13,14]. Neuroendocrine and SCC could arise from pluripotent cells that differentiate along two distinct pathways, or NEC could have differentiated secondarily from cells arising in SCC. As NEC combined with SCC was confirmed postoperatively, we treated our patient following the MCC protocol. Although a 2 cm margin of wide excision was not performed because the extent of NEC was significantly smaller than that of SCC, vigilant investigation of systemic involvement and frequent clinical surveillance was performed to compensate for the absence of further resection. To the best of our knowledge, MCC and combined MCC have been reported in Caucasian patients after kidney transplantation; however, the ratio of neuroendocrine differentiation to total tumor components has not been reported in the literature. Notably, high-grade NEC of the skin combined SCC has not been reported. Although treatment for pure MCC has been well documented, the combined type of NEC with SCC has room for further research into the relationship between the ratio of NEC to total tumor components, prognosis, and treatment selection. Further research will also be required to confirm the efficacy of our treatment and prognosis.

In conclusion, this case report suggests that plastic surgeons should have increased vigilance during their evaluations of patients with skin cancer who underwent kidney transplantation and understand the different profiles of NECs that can differentiate the condition from pure MCC.

NOTES

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Ethical approval

The report was approved by the Institutional Review Board of Dongguk University Hospital (IRB approval No. 110757-202412-HR-03-02).

Patient consent

The patient provided written informed consent for the publication and the use of his images.

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