Case report

Coexistence of head and face Merkel cell and squamous cell carcinomas in the elderly population – a case report and literature review

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Merkel cell carcinoma (MCC) is a rare and highly aggressive neuroendocrine cancer type that predominantly impacts sun-exposed skin areas in the elderly, particularly the head and neck (41–50%), followed by the limbs (32–38%). There is likely an association between MCC and other cutaneous malignancies, such as cutaneous squamous cell carcinoma (CSCC), Bowen's disease, and basal cell carcinoma. Cutaneous squamous cell carcinoma is the most common concurrent tumor with MCC, especially in sun-exposed regions of the skin. Herein, we present a case of coexistence of MCC and CSCC in the craniofacial region, accompanied by an extensive review of relevant literature on this topic.

Key words: Merkel cell carcinoma, cutaneous squamous cell carcinoma, coexistence.

Introduction

Merkel cell carcinoma (MCC) is a rare and aggressive skin tumour characterised by neuroendocrine features. It often presents as rapidly growing, asymptomatic patches or nodules. This carcinoma predominantly affects elderly individuals in sun-exposed areas of the skin and has a high propensity for metastasis, potentially leading to death.

Cutaneous squamous cell carcinoma (CSCC) also frequently occurs in sun-exposed regions of the skin and typically exhibits a lower degree of malignancy compared to MCC. However, when metastasis occurs, patients may experience a poor prognosis. Cutaneous squamous cell carcinoma is one of the most commonly diagnosed forms of non-melanoma skin cancer, with its global incidence rising steadily in recent years. Cutaneous squamous cell carcinoma is caused by the uncontrolled proliferation of abnormal epidermal keratinocytes, which may result from prolonged dysplasia in the epidermis [1].

Case report

In June 2022, the general surgery department of our hospital admitted an 84-year-old female patient for the evaluation of a right facial mass that had been detected 3 years prior. The right side of her face exhibited a solid, well-defined mass measuring 25 × 30 × 30 mm, which had limited mobility, local tenderness, and erythema, accompanied by ulceration. Following the patient's admission, examinations were conducted, and there were no contraindications to surgery. The patient underwent the procedure under local anaesthesia, performed by the head of our department. Postoperatively, the patient did not receive any specialised oncological treatment; instead, she was prescribed a traditional Chinese medicine for the management of her condition.

From a pathological perspective, microscopic examination revealed that the tumour was situated within both the epidermis and dermis of the skin. Merkel cell carcinoma was confined solely to the dermis, with no

involvement of the epidermis. It exhibited a diffuse, nest-like, and infiltrative growth pattern, with indistinct borders relative to the SCC region. The cancerous cells displayed blue-staining characteristics, had a round and uniform shape, a loosely structured cellular arrangement, and scant cytoplasm. The nuclei appeared vacuolated, with indistinct nucleoli and numerous mitotic figures. The squamous cell carcinoma region was positioned in both the epidermis and dermis, with neoplastic components adhering to the epidermis, showcasing a nest-like and invasive growth pattern. The cells exhibited marked atypia, and localised areas demonstrated tumour necrosis (Fig. 1).

Immunohistochemically, the MCC area was positive for synaptophysin and CD56, and negative for p63 and p40. CK20 cytokeratin exhibited characteristic perinuclear dot-like stained areas. The cutaneous squamous cell carcinoma area was positive for p63 and p40, and negative for synaptophysin, CD56, and CK20. The infiltration of CD20- and CD3-positive lymphocytes among cancer tissues was sporadically distributed. The Ki-67-LI levels differed between the 2 tumour types: 80% for MCC and 50% for CSCC (Fig. 2).

Patient outcome

Two months post-surgery, the patient observed the re-emergence of tumour growth on the right side of her face. The mass gradually increased in size, leading to discomfort and swelling. It measured approximately 40 × 30 × 30 mm, felt firm upon palpation, was immobile under pressure, had poorly defined borders, and exhibited no signs of tenderness or visible redness/ulceration on its surface. Upon readmission, the patient underwent ultrasound and CT scans, which revealed multiple solid masses in the liver, suggestive of metastatic tumours. Regrettably, the patient passed away 6 months later due to tumour progression.

Discussion

In 1972, pathologist Toker first described MCC as a dermal trabecular carcinoma [2]. It is now understood that the tumour originates from Merkel cells located in the basal layer of the epidermis. As research has advanced, and based on the analysis of tumour tissue morphology, gene expression, and molecular levels, there is growing evidence suggesting that both ultraviolet- and virus-related MCCs originate from basal keratinocytes in the ear and hair follicle elevations [3]. Merkel cell carcinoma, also referred to as primary cutaneous neuroendocrine carcinoma, is a seldom seen and fast-growing tumour type of the nervous system, with an estimated yearly occurrence of around 0.23/100,000 [4]. The mechanisms underlying the cause and development of MCC are not completely understood. It is likely that the integration of the Merkel cell polyomavirus (MCPyV) genome (or frequent DNA mutations caused by long-term

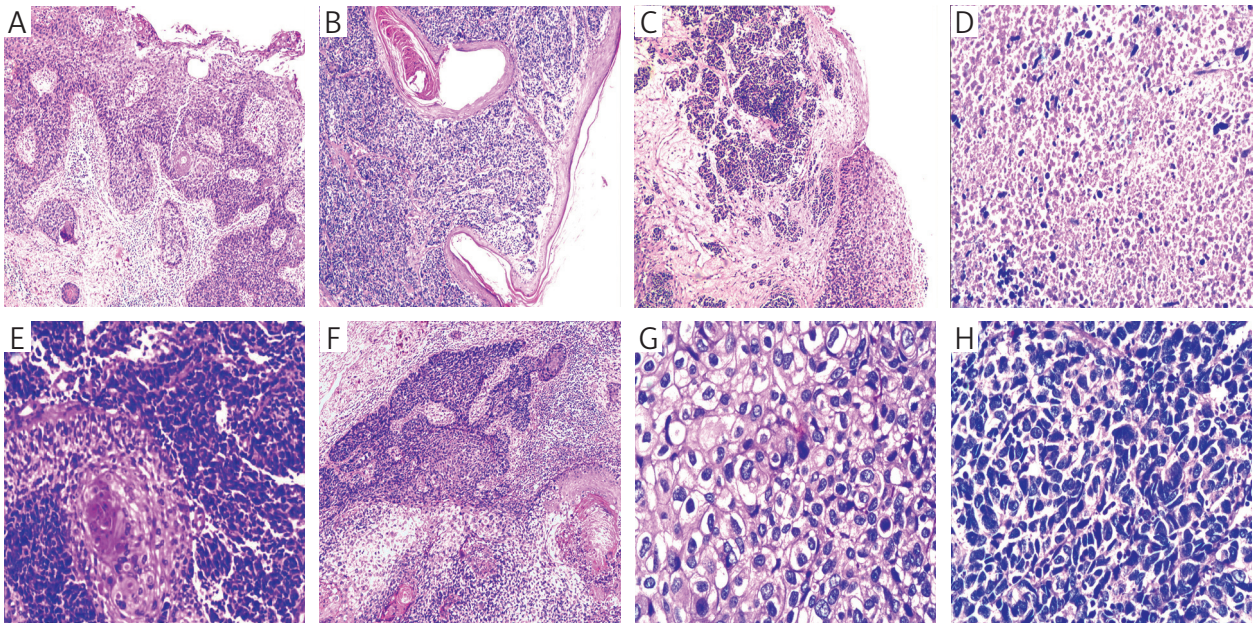

Fig. 1. Histopathological findings. A) Squamous cell carcinoma associated with the epidermis (100×). B) Merkel cell carcinoma not associated with the epidermal layer (100×). C) Merkel cell carcinoma coexisting with squamous cell carcinoma, showing a relationship with the epidermis (100×). D) Necrotic region within the tumour (100×). E) Squamous cell carcinoma observed forming keratin pearls (200×). F) Merkel cell carcinoma coexisting with squamous cell carcinoma, exhibiting indistinct boundaries (200×). G) Cellular features of squamous cell carcinoma, including enlarged cell nuclei and significant atypia (400×). H) Cytological characteristic of Merkel cell carcinoma, showing finely granular chromatin in the nucleus (400×)

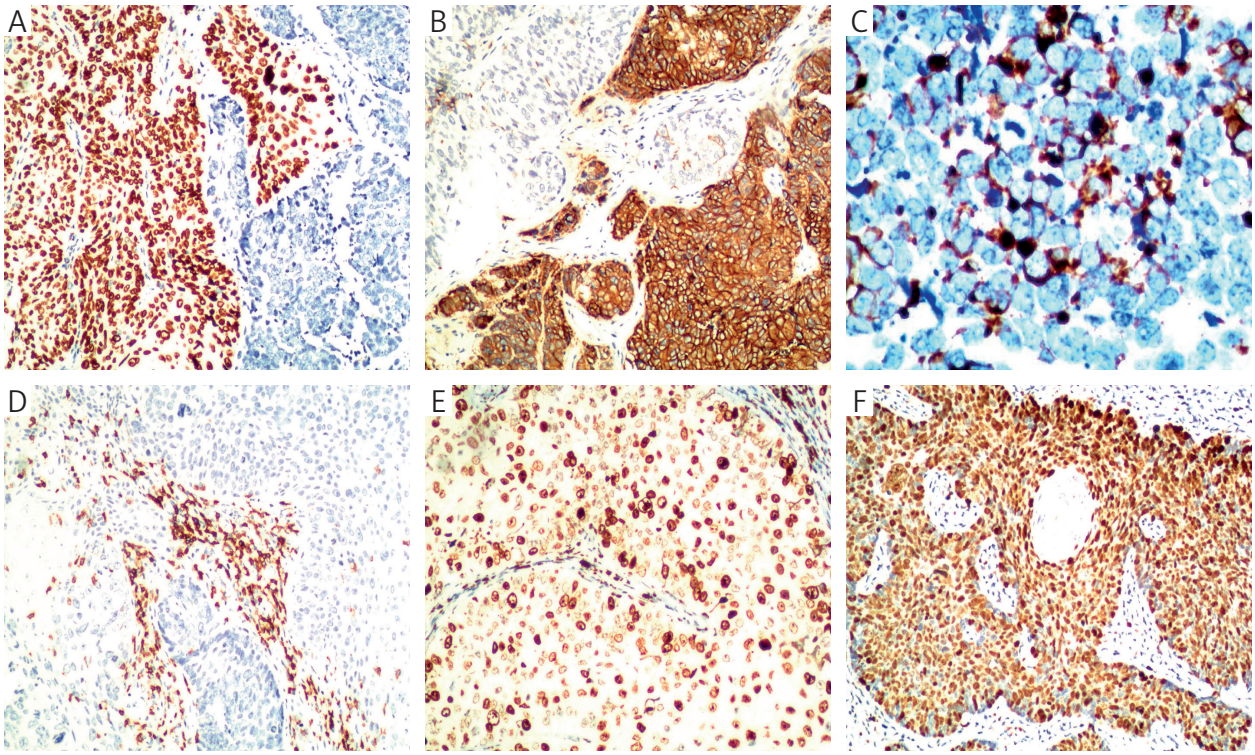

Fig. 2. Immunohistochemical findings. A) Squamous cell carcinoma area showing positive staining for p63, while Merkel cell carcinoma area showing negative staining for p63 (200×). B Merkel cell carcinoma area showing positive staining for synaptophysin, while squamous cell carcinoma area showing negative staining for synaptophysin (200×). C) Merkel cell carcinoma area with CK20 cytokeratin exhibiting characteristic perinuclear dot-like staining (400×). D) Infiltration of CD20 positive lymphocytes among cancer tissues distributed sporadically (200×). E) Ki-67-LI levels in squamous cell carcinoma at 50% (200×). F) Ki-67-LI levels in Merkel cell carcinoma at 80% (200×)

exposure to ultraviolet radiation) plays a significant role in its formation. Consistently, MCPyV has been detected in up to 80% of pure MCC cases [5]. The findings by Paik *et al*. support the concept that the carcinogenesis of Merkel cell carcinoma has both Merkel cell polyomavirus-driven and non-Merkel cell polyomavirus-driven (primarily sun-dependent) pathways, with the latter being significantly more frequent in Australia and in mixed squamous-Merkel cell carcinomas (which are also more frequent in Australia) [6].

Risk factors contributing to MCC include exposure to sunlight or other forms of ultraviolet radiation, a compromised immune system, and a previous history of cancer. The mortality rate for MCC is alarmingly high, with 33% of patients succumbing within 3 years of diagnosis. Alvarez-Coronel *et al*. did not identify clinical or pathological characteristics associated with the various degrees of tumour budding (TB). Likewise, TB did not influence survival [7]. The histological characteristics of MCC primarily manifest as skin lesions that exhibit various patterns, including intermediate-sized cell, small cell, and trabecular variants. These cells typically possess minimal cytoplasm, with round to oval nuclei that contain punctate to fine granular and dusty chromatin. The nucleoli are inconspicuous, and numerous mitotic figures are observed. Immunohistochemical analysis usually reveals a distinct perinuclear dot-like pattern and demonstrates positive staining for cytokeratin CK20, epithelial membrane antigen, synaptophysin, neuron-specific enolase, chromogranin A, and CD56. Additionally, positivity for B-cell lymphoma 2 has been detected in 85% of all MCC cases and is associated with more favourable clinical outcomes [8].

Among non-melanoma skin cancers, CSCC ranks second in prevalence, with basal cell carcinoma being its most common subtype [9]. The excessive growth of abnormal keratinocytes is a contributing factor to the onset of CSCC [10]. Risk factors associated with squamous cell carcinoma include a weakened immune system, older age, being male, having fair skin, a background of actinic keratosis, and extended periods of sun exposure [11]. High-risk clinical and pathological characteristics linked to CSCC spread include a compromised immune system, inadequate histological differentiation, invasion of nerves, invasion of lymphatic vessels, tumour size exceeding 2 cm, and penetration depth surpassing 6 mm. The most common metastasis sites are typically the scalp, ears, or lips [12]. Cutaneous squamous cell carcinoma is usually locally invasive and can spread to other parts of the body, frequently leading to high recurrence

rates [13]. The incidence of CSCC is 3 times higher in men than in women [14].

Merkel cell carcinoma has been linked to skin growth pathologies such as squamous cell carcinoma, Bowen's disease, and basal cell carcinoma. Of these conditions, squamous cell carcinoma is the most frequently occurring concurrent tumour, constituting 5–34% of all MCC cases [15, 16]. The development of simultaneous MCC and CSCC could be attributed to 2 factors:

- the origin from a mutual multipotent stem cell precursor (such as hair follicle multipotent stem cells),
- or a collective reaction to the same risk factor, such as ultraviolet radiation [17, 18].

In concurrent MCC and CSCC cases, MCPyV is generally not present, in contrast to CSCC-free MCC, which suggests potential variations in the fundamental pathogenic mechanisms of MCC-combined tumours [19]. Combined squamous and Merkel cell tumours represent an immunophenotypically and genetically distinct variant of primary cutaneous neuroendocrine carcinomas. They stand out for their highly mutated genetic profile, significant p53 expression and/or mutation, absent RB1 expression (in the context of increased incidence of RB1 mutations), and minimal neurofilament expression [20]. Patients with the combination of CSCC and MCC exhibit a later age of onset, increased invasiveness, higher metastasis rates (40% and 77%, respectively), and poorer prognosis (with survival periods of 54 and 41 months, respectively) than patients suffering only from MCC [21, 22].

Multiple primary malignant tumours (also known as multiple primary cancers) refer to the occurrence of 2 or more primary malignant tumours in single or multiple organs and tissues of the same patient, at the same time or successively. Multiple primary malignant tumours were first reported by Warren *et al*. in the 19th century [23]. The intimate admixture of the 2 antigenically different neoplastic cell types, and a common aetiological role of ultraviolet light (and possibly infrared damage), support the theory that some Merkel cell and squamous cell carcinomas may arise from a pluripotent epidermal stem cell [24]. The combination of MCC and CSCC typically manifests as a rapidly expanding, solitary purplish-red patch or nodule, often without obvious symptoms. Surface ulceration may also occur. This presentation commonly arises in sun-exposed areas of the skin, particularly on the head and neck. On dermoscopy, lesions caused by the coexistence of MCC and CSCC appear as nodules or patches with minimal scaling. Surrounding these lesions, small dot-like and short irregular linear blood vessels are usually observed, while larger branching blood vessels may be prominent in the central pink area [25]. Iwasaki *et al*. analysed the morphologic properties of MCC cells obtained from 26 cases and demonstrated that MCPyV-negative MCC cells had more irregular nuclei and more abundant cytoplasm compared with MCPyV-positive MCC cells. Pathologists can predict the absence of MCPyV infection using H&E staining and our morphologic criteria, especially when the tumour has an SCC component or shows typical MCPyV-negative morphology [26]. Sirikanjanapong *et al*. reported a unique case of MCC that showed both intraepidermal and dermal components admixed with SCC *in situ*. To our knowledge, 20 cases of coexisting MCC and squamous cell carcinoma, both invasive and *in situ*, have been previously reported. However, none had simultaneous intraepidermal and dermal components of MCC. Additionally, based on differences in the immunohistochemical expression levels between the epidermal and dermal components, they were able to support the theory that MCC originates from stem cells located in the hair follicles of the dermis [27].

The outlook for this illness is currently not promising, with around 40% of the patients experiencing the spread of the disease to distant parts of the body. The 5-year survival rates of patients with tumours confined to one area, patients with cancer that has spread to nearby lymph nodes, and those with cancer that has spread to distant parts of the body are 51%, 35%, and 14%, respectively [28, 29]. Prognosis worsens with advancing age. Elderly patients exhibit a significant decline in their tolerance to radiotherapy and chemotherapy, resulting in a progression-free survival rate of only 3–8 months following treatment. However, immune checkpoint inhibitors (ICIs) have recently emerged as a promising option for first-line therapy.

Conclusions

Merkel cell carcinoma combined with CSCC is a rare and aggressive cancer that carries a high risk of invasiveness and metastasis, leading to a poor prognosis for patients. Consequently, accurate and timely pathological diagnosis is crucial for managing these cases. The present case has improved our understanding of this uncommon type of solid skin tumour, which may help prevent future misdiagnoses and ensure appropriate treatment.

Disclosures

1. All authors can attest that the submitted case report does not contain any identifiable information or patient health information. Only unidentifiable images are described. Approval has been obtained from the Institutional Review Board of Hubei Provincial Hospital of Integrated Chinese and Western Medicine (2024081). The patient provided written consent for the publication of this report.

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