

## CLINICAL REPORT

# Metachronous Merkel Cell Carcinoma on Both Cheeks

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**Merkel cell carcinoma (MCC), an aggressive skin cancer with neuroendocrine features, has been found to be associated with a new type of human polyomavirus called Merkel cell polyomavirus (MCV). Patients diagnosed with MCC have a significantly increased risk of a second primary cancer. We report here the first case of two primary MCCs arising on the face at different times, associated with MCV infection. The tumour on the patient's right cheek was surgically removed, followed by chemotherapy. After a 10-year tumour-free period, a new tumour developed on the patient's left cheek. Histological and immunohistochemical findings were consistent with MCC. The tumours had high MCV copy numbers and expressed large T antigen, which may play a major role in MCV-mediated carcinogenesis. This case highlights the close links between MCC and MCV. Key words: Merkel cell carcinoma; Merkel cell polyomavirus; metachronous; face.**

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Merkel cell carcinoma (MCC) is a highly aggressive neuroectodermal carcinoma arising from mechanoreceptor Merkel cells (1). It was first described by Toker in 1972 (2). In the USA its incidence has increased sharply, tripling over the past two decades, to 1,500 cases per year (3). The results of several studies suggest that multiple factors contribute to the pathogenesis of MCC. For instance, MCC occurs more frequently in immunocompromised patients (4–9). Exposure to ultraviolet (UV) radiation also increases the risk of MCC (5, 10). Furthermore, the newly identified Merkel cell polyomavirus (MCV) is closely associated with the pathogenesis of MCC (11–15). Epidemiological studies indicate that patients diagnosed with MCC have a significantly increased risk of a second primary cancer (9, 16). However, an increased risk of a subsequent primary MCC has not been reported. We report here the first case of two primary MCCs arising on the face at different times, which were associated with MCV infection.

## CASE REPORT

A 78-year-old Japanese woman initially presented with a 2-month history of a tumour on her right cheek, which had rapidly increased in size. Physical examination revealed a round, 7-mm diameter, reddish, firm, painless mass on her right cheek. Regional lymphadenopathy was not detected. Excisional biopsy showed that the tumour was located entirely in the dermis. The tumour cells were arranged in nests and sheets. Cytologically, the tumour cells were monomorphic with scanty cytoplasm (Fig. 1a). The nuclei were round and had fine granular or dusty chromatin with small nucleoli. The mitotic rate was high, with 10 mitoses per high-power field. The results of immunostaining are summarized in Table I. Histological and immunohistochemical findings were consistent with MCC of the cheek.

Two months after the initial surgery, there was tumour recurrence on her right cheek and a wide resection of the tumour was performed. Under general anaesthesia, the tumour was excised with a 3-cm margin of surrounding tissue, excluding the facial nerve. The cheek defect was covered by a split-skin graft harvested from the patient's right thigh. Light microscopy revealed that the MCC had a positive deep margin. There was no evidence of distant metastases to the lungs, bones or lymph nodes. Following the second surgery, one course of adjuvant chemotherapy (DAV: dacarbazine, nimustine, vincristine) and radiation therapy (total 20 Gy, 10 fractions) were administered.

Although there had been no tumour recurrence on long-term follow-up, she re-presented with a 3-month history of a painless, rapidly enlarged mass on her left cheek approximately 10 years after the initial appearance of the MCC. Physical examination revealed an 18 × 12-mm, reddish, firm mass on her left cheek (Fig. 2). Regional lymphadenopathy was not detected. The tumour was surgically removed and the defect was closed with a cutaneous flap. Histologically, the tumour displayed features of MCC (Fig. 1b). The results of immunostaining are summarized in Table I. The histological and immunohistochemical findings of the tumour were consistent with a MCC, and were essentially the same as those observed 10 years previously. The patient had a local recurrence of the tumour 6 weeks later, and, taking into account her age and general condition, the tumour was resected with a narrow margin, followed

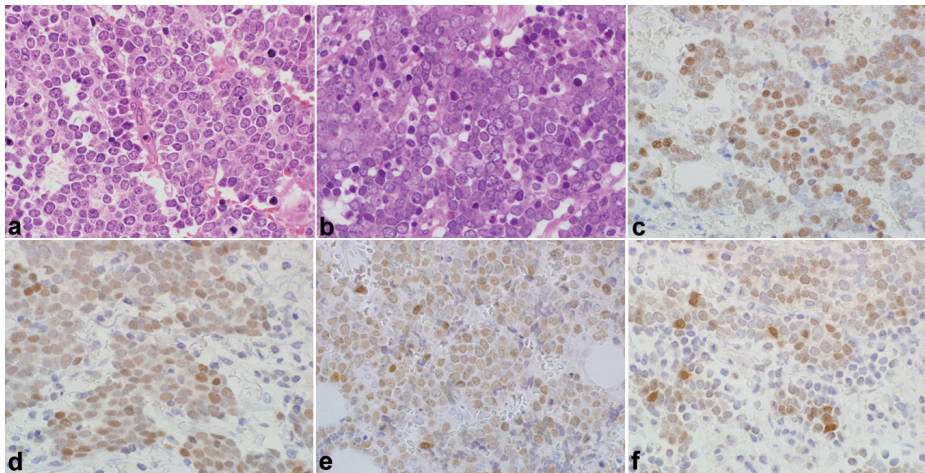


Fig. 1. Histopathological analysis of the first and second tumour in the (a, c, e) right and (b, d, f) left cheek, respectively. (a, b) The tumour cells had scanty cytoplasm and round nuclei with fine granular chromatin and small nucleoli (haematoxylin and eosin, original magnification  $\times 400$ ). (c, d) Merkel cell polyomavirus large T antigen was detected in the nuclei of the tumour cells with a rabbit polyclonal antibody (original magnification  $\times 400$ ) and (e, f) a mouse monoclonal antibody (original magnification  $\times 400$ ).

by radiation therapy (total 50 Gy, 25 fractions). However, the patient required six further operations for the local recurrence. There was no evidence of recurrence 3 months after the final surgery.

MCV DNA was detected in the samples of the first and second primary MCC by nested PCR (17). Real-time PCR revealed that the samples had high viral copy numbers (2.5 and 326 MCV copies/cell, respectively). Immunohistochemistry using a rabbit polyclonal antibody against MCV large T (LT) antigen (National Institute of Infectious Diseases, Tokyo, Japan) and a mouse monoclonal antibody (CM2B4, sc-136172, Santa Cruz Biotechnology, Santa Cruz, CA, USA) showed that LT antigen was expressed in the nuclei of MCC cells in the samples (Fig. 1c–f).

DISCUSSION

To the best of our knowledge, this is the first case report of a metachronous MCC of the skin. Howard et al. (9) reported a significantly increased risk of subsequent cancers of the salivary gland, biliary sites other than the liver and gallbladder, and non-Hodgkin’s lymphoma after a primary MCC. Kaae et al. (16) reported a statistically significant increased risk of squamous cell carcinoma of the skin and chronic lymphocytic leukaemia after a diagnosis of MCC. As MCC is a rare tumour, it is unknown whether there is an increased

risk of MCC following another MCC. The occurrence of two primary MCCs is very rare and it has been described only once, involving the lip and palatine tonsil within a 7-year interval (18). Our patient represents the first case of a metachronous MCC arising in the same organ (facial skin).

MCC tends to recur locally and give rise to regional nodal and distant metastases. In our case, it was very unlikely that the tumour in the left cheek was a result of metastasis from the right cheek because there was no local recurrence, regional lymph node metastasis or distant metastasis in the 10-year follow-up period. Given that MCC usually exhibits rapid growth, the possibility of a metastasis could be rejected.

There are two main aetiological factors associated with increased risk of MCC, namely UV radiation and immunosuppression. Regional incidence of MCC increased with increasing sun exposure as measured by the UVB solar index (5). The head, which is the most sun-exposed anatomical site, was the location of 44.5–48.3% of MCC (5, 9, 16, 19). In addition, many individuals who were diagnosed with MCC had a history of other sun-induced skin cancers (9, 16). Indeed, UV-induced

Table I. Immunohistochemical findings

Immunohistochemical markers	First tumour in the right cheek	Second tumour in the left cheek
Cytokeratin 20	+	++
Neuron specific enolase	++	+
Synaptophysin	++	++
Chromogranin A	+	+
Epithelial membrane antigen	+	+
CD56	++	++
CD117 (c-kit)	+	+
S-100 protein	-	-

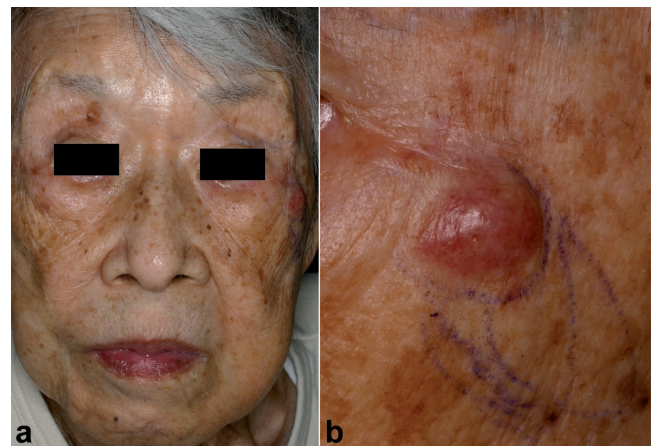


Fig. 2. Clinical appearance of (a) the skin-grafted area on the right cheek, and (b) the erythematous nodule on the left cheek.

mutations are observed in most Merkel and skin squamous cell carcinomas (10). A higher incidence of MCC is also seen in patients with conditions of suppressed or disordered immunity, including those on immunosuppressive therapy for organ transplantation (4–6), those with HIV infection (7, 8) or B-cell malignancies such as multiple myeloma, non-Hodgkin's lymphoma and chronic lymphocytic leukaemia (5, 9). Our patient did not have a history of malignancy or HIV infection, although the anatomical distribution and the age of the patient were typical of MCC.

A new type of human polyomavirus has been identified in MCC and called MCV (11). MCV has a double-stranded circular DNA composed of 5387 base pairs. This genome encodes the three structural proteins that constitute the viral particle (VP1, 2, 3) and two early tumour antigens, called small T and LT. The presence of MCV DNA sequences in MCC has been confirmed in several case series (12, 14). Clonal integration of MCV DNA sequences was observed in MCC, suggesting that viral infection may be an early event in the pathogenesis of MCC (11, 14). In addition, analysis of MCV DNA sequences derived from MCC revealed mutations that inactivated the helicase domain but preserved the Rb binding domain of LT, which eliminated viral DNA replication capacity, and this may play a major role in MCV-mediated carcinogenesis (13). In our case, the specimens from the first and second primary MCC had high viral copy numbers and expressed LT antigen. Thus, it seems likely that the occurrence of the MCC was caused by MCV infection. Mogha et al. (15) demonstrated that solar radiation has an impact on MCV mRNA levels that may explain the association between MCC and sun exposure. This study supports the idea that the two primary MCC of the cheeks in our case were caused by MCV.

*The authors declare no conflicts of interest.*

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