



# Merkel Cell Carcinoma

## Merkel Hücreli Karsinom

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### ABSTRACT

Merkel cell carcinoma (MCC) is a rare tumor that arises from mechanoreceptor Merkel cells. Ultraviolet exposure, immunosuppression and Merkel cell polyoma virus play a significant role in tumor pathogenesis. Although it typically presents as an initially indolent growing, painless solitary lesion, the course of MCC may be aggressive due to the nodal invasion, distant metastasis and high recurrence rates. We presented a case of MCC with a background history of rheumatoid arthritis treated with immunosuppressive therapy for many years who had necrotizing granulomatous lymphadenitis.

**Keywords:** Merkel cell carcinoma, immunosuppression, therapy

### ÖZ

Merkel hücreli karsinom (MKK), mekanoreseptör Merkel hücrelerinden kaynaklanan nadir bir tümördür. Ultraviyole maruziyeti, immünosupresyon ve Merkel hücreli polyoma virüsü, tümör patogeneğinde önemli bir rol oynamaktadır. Tipik olarak başlangıçta yavaş büyüyen, ağrısız soliter bir lezyon olarak ortaya çıkmasına rağmen, MKK'nin seyri nodal invazyon, uzak metastaz ve yüksek nüks oranları nedeniyle agresif olabilir. Geçmişinde romatoid artrit öyküsü bulunan, uzun yıllardır immünosupresif tedavi gören ve nekrotizan granüloamatöz lenfadeniti olan bir MKK olgusunu sunuyoruz.

**Anahtar Sözcükler:** Merkel hücreli karsinom, immünosupresyon, tedavi

### Introduction

Merkel cell carcinoma (MCC) is an aggressive primary neuroendocrine cutaneous tumor that arises from mechanoreceptor Merkel cells (1).

Although MCC is a rare tumor, incidence of MCC has tended to increase in seniors in the last two decades. This higher prevalence of MCC seen in seniors may be explained with immunosenescence. Because, immune system plays a key role in tumorigenesis of MCC (2).

Due to the local recurrence and early regional and distant metastasis tendencies of MCC, early diagnosis and treatment

may increase survival rates (3). We presented a 65-year-old female immunosuppressed patient who was treated with wide excision, regional lymph dissection, radiotherapy and chemotherapy.

### Case Report

A 65-year-old female patient was admitted to the dermatology clinic with a non-tender, solitary and fast-growing lesion which was reddish purple in color and 3x4 cm in size on her right malar region that had been present for 4 months (Figure 1 a, b). The result of a punch biopsy was reported as a neuroendocrine tumor and the patient was referred to our clinic.

The initial neck examination was negative for lymphadenopathy.

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She reported that she had been diagnosed as having rheumatoid arthritis (RA) in 1999, and treated with 30 mg/day prednisolone. Routine abdominal ultrasonography which had been performed in 2009 revealed the growth of lymph nodes, hence prednisolone's dose was reduced from 30 mg/day to 15 mg/day and hydroxychloroquine sulphate was added with a dose of 400 mg/day with a suspicion of sarcoidosis. She has used prednisolone 7.5 mg/day since 2015 and the dosage has been increased due to the attacks.

Biopsy of the tumoral mass revealed that the number of mitosis was 52/mm<sup>2</sup>, there were widespread lymphovascular invasion and slight lymphocyte infiltration. Nodular and infiltrative tumor growth pattern was observed, and the depth of the tumor was extended to the subcutaneous adipose tissue. Lastly, MCC was diagnosed following the exclusion of other neuroendocrine tumors, radiologically.

A positron emission tomography (PET) scan was performed to rule out a metastasis of a neuroendocrine tumor, and a lymphadenopathy in the posterior pectoral muscle area was revealed.

Under the general anesthesia, the tumor mass on the right malar region was excised with 1.5 cm surgical margin and a skin substitute patch (Epigard®, Biovision) was applied to the excised area. The lymph node was removed by a thoracic surgeon. The pathology of the tumor was reported as MCC, and the biopsy of the removed lymph node was reported as a necrotizing granulomatous lymphadenitis (Figure 1 c,d,e). The surgical margin of the tumor base was found to be closer than 0.1 cm and re-excision was performed. The defect area was repaired with a Mustardé flap and a full-thickness graft which was harvested from the left supraclavicular region. After the wound healing process, the patient was treated with quadruple anti-tuberculosis (TB) therapy regimen (ethambutol 1.5 g/day, rifampicin 600 mg/day, pyrazinamide 2 g/day, isoniazide (INH) 300 mg/day) for two months. Subsequently, double anti-TB treatment regimen (rifampicin 600 mg/day and INH 300 mg/day) was applied and the treatment period was completed to a year and successful result was obtained from the specified treatment.

One week after the initiation of anti-TB treatment, 5,400 cGy radiotherapy was applied in 30 fractions.

One week after the onset of radiotherapy regimen, chemotherapy was started and performed on the 1<sup>st</sup>, 8<sup>th</sup> and 15<sup>th</sup> days of every 21-day periods, cisplatin 40 mg/m<sup>2</sup> was applied for 3 courses and etoposide 100 mg/m<sup>2</sup> was applied for 3 courses.

There was no recurrence and local-distant metastasis at 60-month follow-up (Figure 1 f, g).

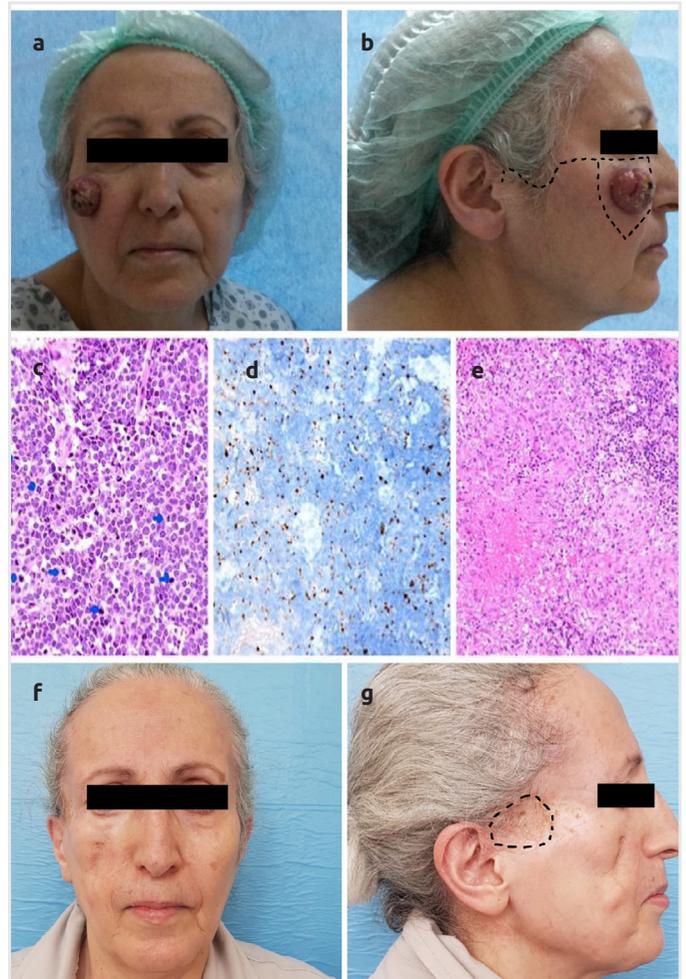
**Discussion**

The MCC is more common in white race and males over 65 years of age. Ultraviolet exposure, immunosuppression and Merkel cell polyoma virus (MCPyV) play a significant role in tumor pathogenesis (4,5).

Immunosuppression is thought to be an important risk factor for MCC. Immunosuppressed patients; especially those with hematological malignancy, HIV, autoimmune disease and organ transplants, are at high risk for developing MCC (6,7).

Our patient had RA and sarcoidosis. She received systemic steroid treatments because of these diseases. In our patient, we think that both autoimmune diseases and their treatments play a role in the development of MCC by causing immunosuppression.

The MCCs are located in the head and neck region, extremities and trunk. As in our case, there is a painless, firm, pinkish purple, solitary, and glossy nodule which is rapidly growing in a



**Figure 1 a, b.** (upper row). Preoperative frontal and lateral views of the patient. Note the resection borders and the Mustardé flep design on the lateral view

**Figure 1 c, d, e, (middle row).** c) Merkel Cell Carcinoma: Increased nucleus/cytoplasm ratio in basophilic tumoral cells with dispersed mitotic figures (HE X200); d) Merkel Cell Carcinoma: Diffuse paranuclear CK20 positivity in tumor cells (x200) e) Necrotizing granulomatous lymphadenitis: Granuloma formation with central necrosis surrounded by epitheloid histiocytes, multinuclear giant cells surrounded by lymphocytes (HE x100)

**Figure 1 f, g.** Late postoperative frontal and lateral views of the patient. Note the grafted area on the lateral view (lower row)

short period of 1-3 months. The differential diagnosis includes keratoacanthoma, seborrheic keratosis, actinic keratosis, Bowen's disease, squamous cell carcinoma, morpheiform basal cell carcinoma, pyogenic granuloma, nevi, amelanotic melanoma, Kaposi's sarcoma, lymphomas, angiocarcinomas, and skin metastases of tumors (8,9).

Merkel cells are dermal sensory neuroendocrine cells which serve as mechanoreceptors in the basal layer of the epidermis. MCCs originate from the dermoepidermal junction. Diagnosis is made with an incisional biopsy (4,8). A small cell blue tumor pattern is seen in the light microscope. These cells have high mitotic activity as it is seen in our case. MCCs are distinguished from other small cell blue tumors such as melanoma, lymphoma, small cell carcinoma, metastatic carcinoid tumor, neuroblastoma and sweat gland tumors by the perinuclear globule staining with low molecular weight cytokeratins such as cytokeratin-20. MCC also reacts to the neuroendocrine markers such as chromogranin, somatophysin, calcitonin and vasoactive intestinal peptide. MCC also reacts to the other neuroendocrine markers such as chromogranin, somatophysin, calcitonin and vasoactive intestinal peptide. MCC is distinguished from the melanoma by negative reaction to S100 and HMB45, from cutaneous metastases of small cell carcinomas by negative reaction to Thyroid transcription factor-1 (T), and from lymphoma by negative reaction to leukocyte common antigen and vimentin (10,11).

The MCCs develop regional metastases in a short period of time. At the time of the diagnosis, 73% of the patients have local lesions, 23% regional lymph node metastasis and 4% distant metastasis. The MCCs often metastasize to the dermis, liver, bones, brain and lymph nodes (3,12). Metastases can be detected by CT, magnetic resonance imaging, PET or octreotide scintigraphy (3).

Wide excision, regional lymph dissection (if there is metastasis) and adjuvant RT can be used in the regional control of the disease. Curative treatment of metastatic MCCs has not been established yet (3,13,14).

While the response rate to cyclophosphamide/adriamycin/vincristine treatment is 75.7%, the response rate to etoposide/cisplatin (EP) is reported to be 55-60% in the case of locally advanced tumor or metastasis in the literature (15). A mortality rate of 3.4% due to the chemotherapy is also reported in the literature. Considering that immunosuppression caused by adjuvant chemotherapy may affect the defense of the patients against the tumor, newly developed immunotherapeutic agents such as avelumab, pembrolizumab, ipilimumab and nivolumab have recently been used (15,16).

The 5-year survival rate varies from 18% to 80% depending on the stage of the MCC disease (17). Therefore, early diagnosis and treatment may improve the survival rates.

Our patient was successfully treated with quadruple anti-TB therapy, 5,400 cGy radiotherapy and chemotherapy (cisplatin and etoposide).”There was no recurrence in the 5-year follow-up. As a result, MCC is a rare, aggressive carcinoma that usually

arises in the sun-exposed regions. Physicians should consider MCC in the differential diagnosis when they encounter with a rapidly growing, painless lesion especially in individuals with high ultraviolet exposure and immunosuppression or who are under immunosuppressive therapy. Patients with MCC should be checked up at the short intervals during the first 2 years due to the local recurrences which are frequently seen in this period.

## Ethics

**Informed Consent:** Obtained.

**Peer-review:** Externally peer reviewed.

## Authorship Contributions

Surgical and Medical Practices: S.S.E., A.K., O.C.A., Ö.S.K., P.A., P.Y., Concept: S.S.E., A.K., O.C.A., Ö.S.K., P.A., P.Y., Design: S.E.E., A.K., O.C.A., Ö.S.K., P.A., P.Y., Data Collection or Processing: S.S.E., A.K., O.C.A., Ö.S.K., P.A., P.Y., Analysis or Interpretation: S.S.E., A.K., O.C.A., Ö.S.K., P.A., P.Y., Literature Search: S.S.E., A.K., O.C.A., Ö.S.K., P.A., P.Y., Writing: S.S.E., A.K., O.C.A., Ö.S.K., P.A., P.Y.

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