

Merkel Cell Carcinoma of the Head and Neck and Associated Second Primary Cancers: Report of Three Cases

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ABSTRACT

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin carcinoma¹. The purpose of this study is to describe clinical and pathological characteristics, diagnostic procedure and treatment outcomes of the patients with MCC of the head and neck treated in Otorhinolaryngology, Head and Neck Surgery Department of the University Hospital Center Zagreb between the years 2007 and 2011. Three patients with MCC of the head and neck were treated during this period. First patient was diagnosed with MCC of the left retroauricular region with metastases in the lymph nodes of the left side of the neck, pT2N2M0 Stage IIIB. Second patient was diagnosed with anaplastic carcinoma of the lower lip, pT1N1bM0 Stage IIIB and third patient was diagnosed with MCC of the face which was previously treated as benign lesion, cT1N1bM0 Stage IIIB. Two of the patients had second primary tumor of different histology. All of the patients were treated with wide surgical excision of the tumor and neck dissection combined with adjuvant radiotherapy. Treatment outcome was poor and reason for this was late detection of disease. Management of the MCC patients requires multidisciplinary approach with high clinical suspicion of the treating specialist and pathologist due to immunohistochemical techniques required for diagnosis. Detection of the MCC in earlier stages is necessary for the better survival rate.

Key words: *Merkel cell carcinoma, second primary tumor, wide surgical excision, treatment outcome, immunohistochemical techniques*

Introduction

Merkel cell carcinoma (MCC) is a rare neuroendocrine carcinoma of the skin which was first described by Toker in 1972¹⁻⁴. Incidence ranges from 0.24 to 0.44 per 100 000 people per year¹. Mostly, these tumors appear in the 7th and 8th decade of life². Risk factors are sun exposure and immune suppression, including chronic lymphocytic leukemia (CLL) and HIV^{1,3,4}. The risk of second primary cancer following the diagnosis of MCC and the risk of second primary MCC following other first primary cancers was quantified in research of Howard et al. from 2006⁵. They identified an increased risk for developing Non-Hodgkin lymphoma (NHL) after MCC, but the risk for developing CLL after MCC was not seen as statistically significant. In contrary, in research made by Koljonen et al.³ from 2009 was reported significantly increa-

sed risk for developing CLL in patients diagnosed with MCC. Also, in research from 2010 Koljonen et al.⁴ reported that patients diagnosed with MCC have significantly elevated risk for basal cell carcinoma of the skin and CLL. This was explained as a consequence from shared etiological factors between MCC and other tumor types, such as immunosuppression or possibly Merkel cell polyomavirus infection^{3,4,6}. Human polyomavirus discovery is helping to understand pathogenesis of MCC and to develop a new approach to the treatment of the disease⁶. MCC is also known as apudoma of the skin, trabecular cancer or small-cell neuroepithelial tumor of the skin. When discovered was termed »trabecular carcinoma of the skin« because of histopathologically described anastomosing trabeculae and cell nests in the dermis⁶. No-

menklature was changed to MCC after the tumor cells were characterised by the presence of electron-dense neurosecretory granules and Merkel cells are the only type of cutaneous cells expressing such granules^{2,6}. Three histopathologic types are described- a trabecular form, an intermediate one and the small cell type. Definitive diagnosis is established by positive staining for chromogranin, synpatophysin, neuron-specific enolase and the neural cell adhesion molecule, which represents both epi-

thelial and neuroendocrine antigens present in normal Merkel cells⁶. The expression of cytokeratin 20, found in the tumor cells in a dot-like paranuclear pattern and along the cytoskeleton, is the most characteristic sign for the identification⁶. The most difficult differentiation is often between primary MCC and metastatic small cell of the lung⁷. CK-20 is very sensitive marker for MCC and TTF-1 is positive in small cell lung cancer but is consistently absent in MCC⁷ (Figure 1).

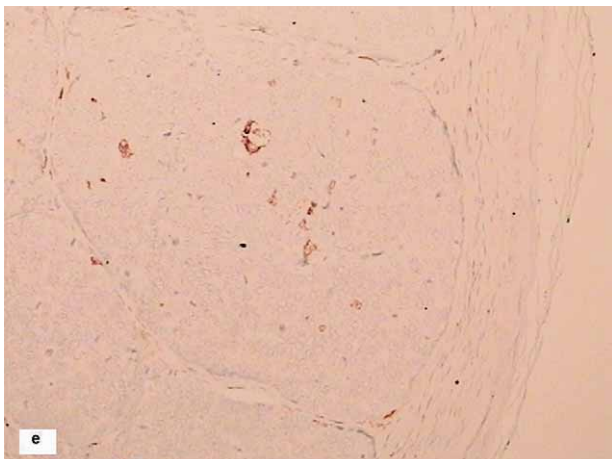
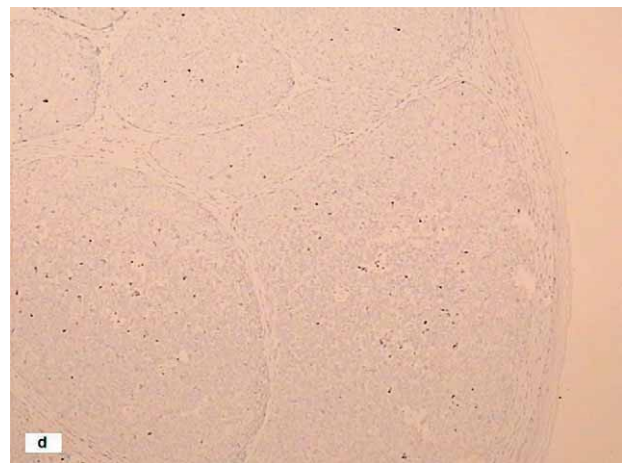
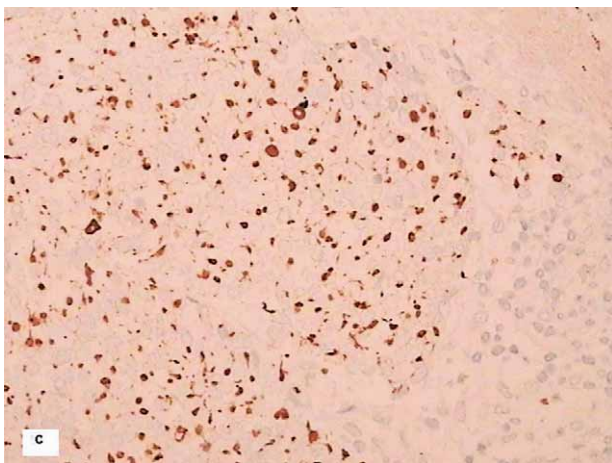
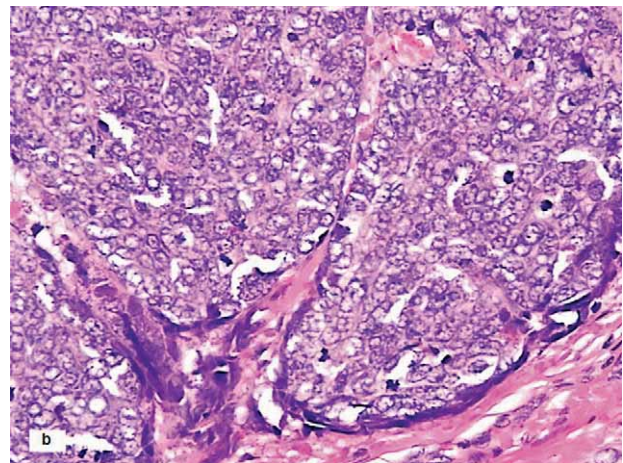
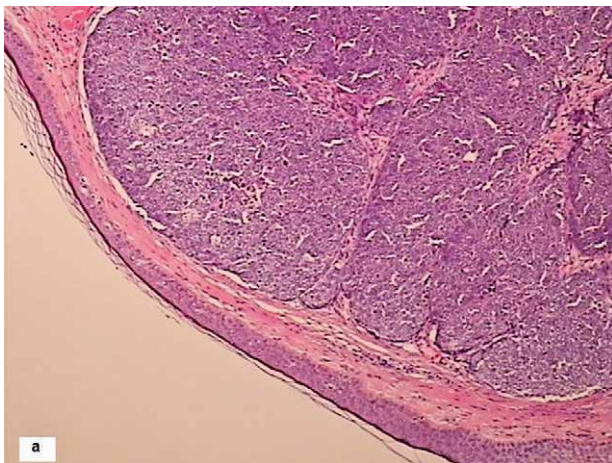


Fig. 1. is showing pathohistological characteristics of MCC: a) HE 100x: In the dermis under the intact epidermis the lobular tumor is formed. b) HE 400x: tumor is composed of atypical tumor cells with ambiguous cytoplasmic membranes and bright large nucleus. c) AE1/3 400x: inside of the tumor pan-cytokeratin positivity in a dot-like appearance of cytoplasmic stain. d) TTF 200x: negative TTF is excluding lung cancer. e) LCA 400x: negative LCA in tumor cells, positive in a few inflammatory cells of the stroma is excluding lymphoma. HE-Hematoxylin-eosin, AE1/3- Anti-Keratin AE1 and AE3, TTF-Thyroid Transcription Factor 1, LCA-Leukocyte Common Antigen.

In most of the cases (81%) MCC appears in the sun-exposed skin such as head and neck area and extremities⁶. Clinical presentation is not specific, but usually presents as firm red-violet cutaneous tumor nodule^{1,6}. In 56% of the cases the lesion is thought to be benign before biopsy¹. In contrary to the clinical presentation, MCC is very aggressive tumor presenting with high grade local recurrence and regional lymph node metastases.

Treatment options include wide surgical excision with or without regional lymph node dissection, radiotherapy and chemotherapy. The purpose of this article is to discuss diagnostic procedure and treatment outcomes of three different patients treated in our institution.

Case Reports

From the year 2007 to 2011 three different patients were treated in Otrhinolaryngology, Head and Neck Surgery Department of the Zagreb University Hospital Center. Tumor staging system described by the American Joint Committee on Cancer, 7th ed., 2010 was used.

First patient, 87 years old, male, was diagnosed with MCC of the left retroauricular area with the metastases in the cervical lymphnodes of the left side, pT2N2M0 Stage IIIB. The patient noticed a tumor behind left auricle 4 months before the check up and swelling on the left side of the neck in the last 2 months. From the history of disease there were no other malignances reported. In the local status an exofitic lesion, size 3x3 cm with the areas of ulcerations and necrosis. On the left side of the neck in level V appears conglomerate of lymphnodes, size 4x4 cm, hard and fixed to the surrounding area. Preoperative ultrasonography and fine needle aspiration biopsy of the conglomerate with immunocytochemistry showed CK 20 positive, chromogranin positive and LCA negative malignant cells highly specific for Merkel cell carcinoma. Preoperative CT scan was also performed. The treatment was wide local excision of the tumor and left auricle *en bloc*, left radical neck dissection and total left parotidectomy. Pathohistological analysis showed a tumor 4,5x3 cm infiltrating retroauricular area and fat tissue of the parotid area. In total were 17 lymphnodes with conglomerate removed among which were 13 lymphnodes with conglomerate infiltrated with the tumor. Adjuvant radiotherapy was performed. The patient died 6 months after the surgery from cardiac failure.

Second patient, 64 years old, female, with a tumor of the lower lip. She was operated under the local anesthesia in the other institution. Pathohistological analysis showed anaplastic carcinoma with free margins. Three weeks after she palpated enlarged lymphnodes of the right side of the neck and she was recieved in our Department with the tumor pT1N1bM0 Stage IIIB. From the history of disease: thirteen years ago she was operated because of the breast cancer and recieved adjuvant chemoradiotherapy. Two years ago she was diagnosed with NHL, she recieved chemotherapy. Preoperative CT scan showed two enlarged lymphnodes in the right submandi-

bular region and fine needle aspiration biopsy confirmed metastases of poorly differentiated carcinoma.

The treatment was right radical neck dissection. Pathohistological analysis showed 28 lymphnodes and conglomerate in total and 11 lymphnodes from the levels I-V with the conglomerate were infiltrated with Merkel cell carcinoma. Postoperative chemoradiotherapy was planned.

One month after the right radical neck dissection the patient discovered enlarged lymphnodes of the left submandibular area. Fine needle aspiration biopsy showed metastases of the poorly differentiated carcinoma. The treatment was left extended supraomohyoid neck dissection. Pathohistological analysis of the neck levels I-IV showed 20 lymphnodes in total and 3 lymphnodes were infiltrated with Merkel cell carcinoma. Postoperative chemoradiotherapy was performed. Patient died 5 months after the second surgery.

Third patient, 77 years old, female, with a small yellowish lesion on the right cheek at first was treated as benign lesion suspected to atheroma. Under the local anesthesia excision of the lesion was performed, pathohistological analysis showed cutaneous Merkel cell carcinoma with positive margins. One month later she was recieved in our Department for the surgical reexcision (Figure 2). In the physical status of the neck there were enlarged lymphnodes in the level V bilaterally and in the level I on the left side of the neck enlarged one lymphnode, cT1N1bM0 Stage IIIB.



Fig. 2. Third patient: After the surgical excision in the right cheek

Preoperative CT scan (Figure 3 and 4) was performed.

Fine needle aspiration biopsy discovered metastases of the MCC in the right submandibular lymphnodes and hyperplasia of the lymphocytes in the neck lymphnodes bilaterally. During the hospitalisation leukocytosis was discovered and NHL was diagnosed. The treatment included wide surgical reexcision and right radical neck dissection (Figure 5 and 6). Pathohistological analysis showed tumor size 1 cm which is infiltrating subcutaneous fat tissue and skeletal musculature, the base of the

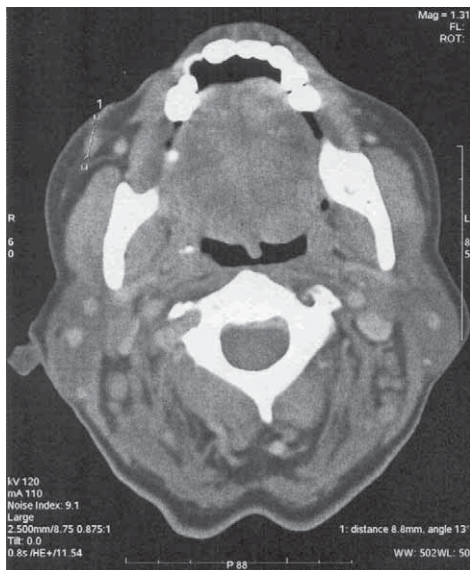


Fig. 3. Third patient: CT scan showing in the right cheek area postoperative irregularities and oval solid mass size 8 mm in diameter which represents residual tumor tissue



Fig. 5. Third patient: Wide surgical reexcision

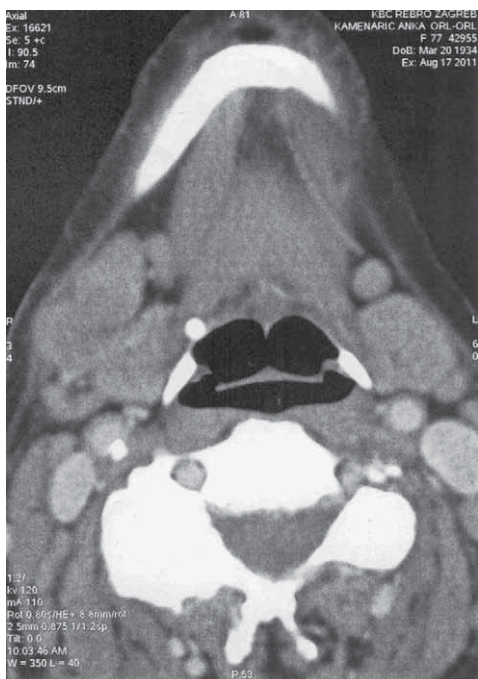


Fig. 4. Third patient: CT scan showing enlarged lymph nodes bilaterally.



Fig. 6. Third patient: Radical neck dissection.

preparation was positive with tumor tissue. MCC was also found in the fat tissue of the right submandibular area. Lymphnodes from the level 1 to V were free from MCC, but were infiltrated with tumor tissue described as NHL, B-small lymphocytic lymphoma. After the surgical treatment, radiotherapy is planned. Patient was transferred to Hematology Department for the further treatment which is still on.

Discussion

There is no well defined management for the patients with cutaneous MCC. The patients treated in our institution were very different in the clinical presentation of the disease, comorbidities and the presence of the second primary tumor. None of them at the beginning of the treatment was suspected to be diagnosed with MCC and all of them were recieved in our institution in Stage III of the disease. The rarity of the disease, aggressive nature and it's pathohistological characteristics are the reasons why the diagnosis is confirmed in the later stages. The complete examination of the suspicious lesion of the skin and high awareness of the specialist together with pathologist should be the initial work up. The primary treatment was surgical. We performed local wide excision with clear lateral surgical margins. In preoperative management we were using CT scan and ultrasonography with

fine needle biopsy of the suspicious lymph nodes which resulted to be very specific in detection of positive regional lymph nodes metastases. The neck dissection was performed due to the results of biopsy. Many authors suggest sentinel lymph node biopsy as important in staging and treatment of the MCC⁹. Also, Mohs surgery is advisable to reduce local persistence of the disease⁸.

Adjuvant radiotherapy was carried out in all our patients and is mostly used to minimize a locoregional recurrence¹⁰. Chemotherapy doesn't improve overall survival¹¹. Tumor staging is the most important prognostic factor¹². The patients treated in our institution were all Stage III of the disease with poor prognosis and outcome.

Associated second primary cancers such as NHL in our two patients, one diagnosed before MCC and the other simultaneously with MCC supports research results from Howard et al.⁵ from 2006.

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Conclusion

MCC is aggressive neuroendocrine skin tumor closely associated with the other cancers, mainly squamous skin carcinoma, NHL and CLL. Two of our patients support this association. Recognition of connection between MCC and other malignancies should be included in diagnostic protocol of MCC management.

Patients treated in our institution had bad outcome in spite of wide surgical excision, radical neck dissection and adjuvant radiotherapy. The reason for that is detection of the disease in Stage III. Detection of the MCC in earlier stages is necessary for the better survival rate. The treatment requires multidisciplinary approach with high clinical suspicion of the treating specialist and pathologist due to immunohistochemical techniques required for diagnosis.

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KARCINOM MERKELOVIH STANICA GLAVE I VRATA I PRIDRUŽENI SEKUNDARNI PRIMARNI KARCINOMI: PRIKAZ TRI SLUČAJA

SAŽETAK

Karcinom Merkelovih stanica (KMS) je rijedak i agresivan neuroendokrini karcinom kože¹. Cilj ove studije je opisati kliničke i patohistološke karakteristike kao i dijagnostički protokol i ishod liječenja pacijenata sa KMS glave i vrata liječenih na Odjelu za otorinolaringologiju i kirurgiju glave i vrata Kliničkog bolničkog centra Zagreb u periodu od 2007. do 2011. godine. Tri pacijenta sa KMS glave i vrata liječeno je u ovom periodu. Prvom pacijentu je dijagnosticiran KMS lijeve retroaurikularne regije sa metastazama u limfne čvorove lijeve strane vrata, pT2N2M0 Stadij IIIB. Drugom pacijentu je dijagnosticiran anaplastični karcinom donje usne, pT1N1bM0 Stadij IIIB, a trećem pacijentu je dijagnosticiran KMS na licu koji je prethodno tretiran kao benigna lezija, cT1N1bM0 Stadij IIIB. Dva pacijenta su imala drugi primarni tumor različite histologije. Svi pacijenti su bili liječeni kirurški. Učinjena je široka ekscizija tumora i disekcija vrata u kombinaciji s adjuvantnom radioterapijom. Ishod liječenja je bio loš, a razlog tome je kasno otkrivanje bolesti. Liječenje pacijenata sa KMS zahtijeva multidisciplinarni pristup sa visokom kliničkom sumnjom specijaliste odgovornog za liječenje i patologa vezano za imunohistokemijske tehnike potrebne za dijagnozu. Otkrivanje KMS u ranijim stadijima je nužno kako bi se postigla bolja stopa preživljenja.