Merkel cell carcinoma: an illustrative case and review

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Merkel cell carcinoma (MCC) was first described by Toker in 1972, as trabecular carcinoma [1, 2]. It is a primary cutaneous tumor of neuroendocrine origin characterized by aggressive course and poor prognosis [3–5]. Agelli and Clegg in 2007 showed that the incidence of MCC in the U.S. was 0.24/100000 per year [6]. Merkel cell carcinoma has a high propensity for local recurrence, lymphatic spread and distal metastases. Metastases are usually found in the skin (28%), liver (13%), bones (10%), and brain (6%). Typically, at the time of diagnosis, local or distant metastases are present. Merkel cell carcinoma affects mainly the elderly, more often men, usually between 65 and 85 years of age. Primary lesions are frequently localized in sun-exposed areas. In 29–40% of cases it is the head and neck region, followed by extremities (21–38%), trunk (7–23%), and other skin regions (3.4–12%) [7]. Merkel cell carcinoma often arises in the setting of immunodeficiency (post-transplant immunosuppression or HIV infection), autoimmune connective tissue diseases and neoplasm, particularly Hodgkin's disease, B-cell lymphoma, chronic lymphocytic leukemia, breast and ovary cancer [8, 9]. Established risk factors for MCC development are UV radiation, immunosuppression and Merkel cell polyomavirus infection [7, 10].

Clinically MCC appears as an indolent, rapidly growing blue-red nodule often with telangiectasias. Histological findings are: monomorphous indistinct bluish cells, often arranged in trabeculae or strands with numerous mitotic figures, apoptotic cells and occasionally necrosis. Lymphocyte intra- and peritumoral infiltration is common.

Routine histological examination may be of limited diagnostic value. Immunohistochemical staining, particularly against cytokeratin 20 (CK20) or chromogranin A, increase the effectiveness of MCC diagnosis [11].

Therapeutic management of choice is wide surgical excision or Mohs micrographic surgery of the tumor with sentinel lymph node biopsy. Adjuvant radiotherapy or chemotherapy is administered according to the clinical staging of disease. Metastases are treated with protocols similar to small-cell lung carcinoma management [12, 13].

A 74-year-old woman presented to our clinic with blue-red colored, well-demarcated skin tumors ranging from 0.5 cm to 2.0 cm in diameter located on the left lower extremity. Lesions were hard and painful on palpation (Figure 1). The enlarged inguinal lymph nodes were present bilaterally. Additionally the patient had a history of arterial hypertension, type 2 diabetes, rheumatoid arthritis and post-thrombotic syndrome.

Lesions appeared 2 years ago, initially they would remit spontaneously. One year after the first occurrence, a nodular, ulcerated lesion located in the proximity of the left medial malleolus was biopsied. Histopathological

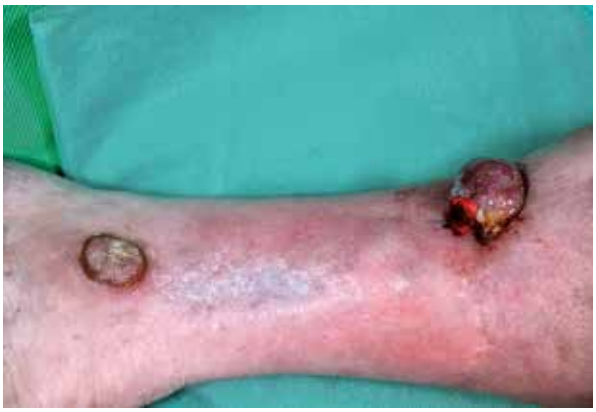

Figure 1. Blue-red colored, hard and painful to the touch skin tumors of the left lower leg diagnosed as MCC

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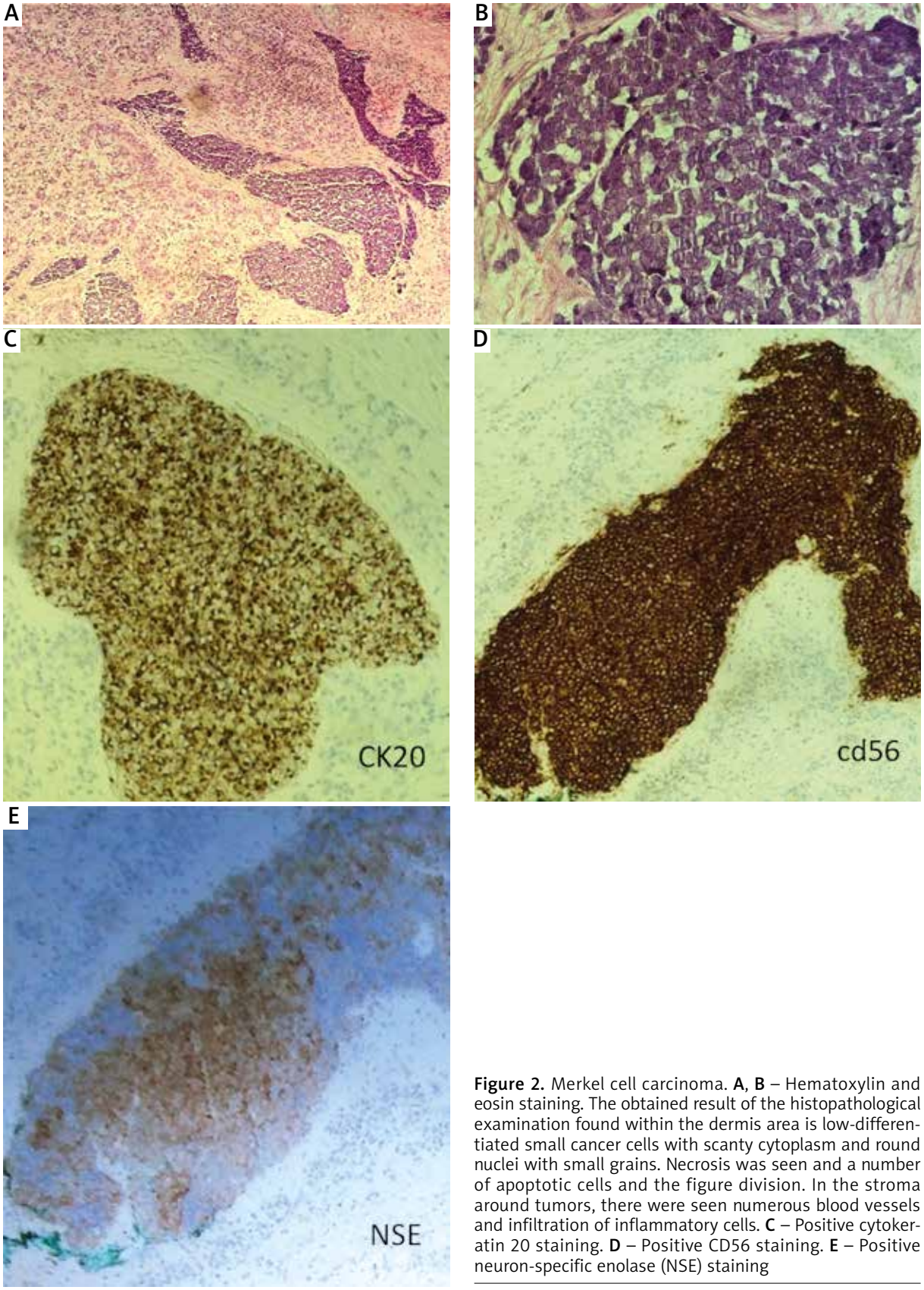

Figure 2. Merkel cell carcinoma. **A**, **B** – Hematoxylin and eosin staining. The obtained result of the histopathological examination found within the dermis area is low-differentiated small cancer cells with scanty cytoplasm and round nuclei with small grains. Necrosis was seen and a number of apoptotic cells and the figure division. In the stroma around tumors, there were seen numerous blood vessels and infiltration of inflammatory cells. **C** – Positive cytokeratin 20 staining. **D** – Positive CD56 staining. **E** – Positive neuron-specific enolase (NSE) staining

examination of skin biopsy revealed positive staining for chromogranin A and CD56 as well as positive staining for cytokeratin 7 and cytokeratin 20 with a dot-like pattern. Deep surgical margin was positive. During current hospitalization skin biopsy was repeated revealing nests of small undifferentiated cells with round nuclei and scant cytoplasm. Numerous mitotic figures and apoptotic cells were present with occasional necrosis. Abundant peritumoral lymphocyte infiltration was observed. Immunohistochemical stainings were positive for CK20 (with a characteristic dot-like pattern), CD56, epithelial membrane antigen (EMA, MUC1), neuron-specific enolase (NSE, focal expression). Leukocyte common antigen (LCA) expression was positive only in peritumoral infiltrate (Figure 2). Adjacent muscular tissue was infiltrated with tumor cells. Based on clinical appearance and histology, MCC was diagnosed.

Routine laboratory blood and urine tests, X-ray and computed tomography (CT) scans of the thorax, chest examination, USG of the abdomen and histology of enlarged inguinal lymph nodes were normal. The patient was staged IIC T4 N0 M0, where IIC is for primary tumors > 2 cm in size with extracutaneous invasion, T4 stands for primary tumor invading the bone, muscle, fascia, or cartilage; N0 – no regional lymph node metastasis and M0 – no distant metastases.

The patient has undergone two surgeries with skin grafting. Due to local spread of the tumor, the 2nd and 1st fingers with metatarsal head were amputated. Currently adjuvant chemotherapy is considered.

Merkel cell carcinoma is a rare neuroendocrine skin tumor occurring in the elderly, more often in men (70%). Common localization is the head and neck area and limbs, several cases of MCC in the anogenital area and on the mucosae have been reported [14]. Clinical appearance of MCC is heterogeneous. It frequently presents as an asymptomatic, reddish, bluish, or purple tumor of the skin. The size at the time of the first consultation is usually smaller than 2 cm, although rapid growth is characteristic [15, 16]. Merkel cell carcinoma pathogenesis remains largely unknown, but ultraviolet radiation and immunosuppression may play a significant role in the development of this cancer. In recent years, the relationship between Merkel cell polyomavirus infection and the development of the tumor was observed [17]. In the patient presented in this report, the incidence of tumors on both legs and the history of spontaneously resolving nodules may indicate MCC metastases without an apparent primary tumor. Spontaneous regression of the primary MCC tumor is not uncommon, with a dozen of cases described in medical literature [18]. Enlarged inguinal lymph nodes in our patient could indicate changes in tumor spread via lymphatic vessels. Cases of micro-metastases in the lymph nodes without clinical lymphadenopathy have been reported as well. Therefore, the sentinel lymph node biopsy and chest and abdomen imaging are necessary. Ulceration is uncommon in MCC. We believe that coexistence of MCC with post-thrombotic syndrome in our patient may explain ulceration of MCC tumor in this case.

Merkel cell carcinoma derives from neuroendocrine cells and typically has appearance of 'blue-cell tumor' comprised of small, monomorphous cells with scant cytoplasm. Cancer cells are usually restricted to the dermis and subcutaneous tissue with a little propensity to invade epidermis. Differential diagnosis should consider basal cell carcinoma, squamous cell carcinoma, lymphoma, melanoma, metastatic neuroblastoma and neuroendocrine carcinoma. Useful diagnostic features are a positive dot-like pattern of staining for CK20 and sometimes other cytokeratins as well as positive staining for chromogranin A, somatostatin, gastrin characteristic of cells of neuroendocrine origin. Merkel cell carcinoma cells also exhibit a positive reaction with CD117, CD99, but negative with LCA and S-100 protein and of TTF-1. In our case, MCC was positive for cytokeratin 7, CK20 chromogranin A and MUC1.

The prognosis in MCC is usually poor. The size of the primary tumor below 2.0 cm is associated with better prognosis, unfortunately, because of the very rapid proliferation of tumor cells, and diagnostic difficulties delaying diagnosis, in most cases, patients are diagnosed with MCC at the stage when the primary lesion exceeds 2.0 cm [19]. The classification of TMN American Joint Committee on Cancer (AJCC) proposed a clinical staging of MCC (0 to IV) [20]. According to this classification, the estimated 5-year survival rate for patients with stage IIC T4 N0 M0 is 50%.

Merkel cell carcinoma lesions are considered highly malignant, hence a combination of surgery, radiotherapy in stages IA to IIIB of the disease is recommended [21–24]. Because of a rapid progression of the disease, adjuvant chemotherapy is frequently administered [2]. One can consider both the chemotherapy and radiotherapy in order to reduce the tumor mass prior to surgery in stages IIC to IIIB. In our patient, due to the presence of coexisting diseases and general condition, only surgical treatment was applied. In the IV stage of disease, the treatment of choice is palliative chemotherapy with the assessment of response to therapy and toilet surgery or radiotherapy of the bone, central nervous system and extensive skin metastases. Because of its similarity to small lung cancer, recommended chemotherapy protocols are cisplatin with etoposide or doxorubicin and cyclophosphamide or ifosfamide. The value of adjuvant radiotherapy has been confirmed with meta-analysis [25–27].

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