Gynecologic Oncology Reports 28 (2019) 76–78

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

A rare case of Merkel cell carcinoma with ovarian metastasis

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ARTICLE INFO

Keywords:
Merkel cell carcinoma (MCC)
Ovarian metastases
Cutaneous malignancy
Gynecological malignancy

ABSTRACT

Introduction: Merkel cell carcinoma (MCC) is a rare cutaneous malignancy that normally occurs in sun-exposed areas of the skin. Risk factors are immundeficency and Merkel cell polyomavirus.

Treatment options are surgery, radiotherapy, chemotherapy and immunotherapy in clinical trials.

Case report: We describe a case of an 80-year-old woman with ovarian metastasis of MCC six years after excision of a cutaneous MCC on the cheek.

Discussion: To our knowledge only three cases with ovarian metastasis of MCC have been described so far. Our case is the second with distant metastasis to the ovary spreading from a primary tumor in the skin of the head, in the other two cases the primary tumor was in the inguinal skin.

Conclusion: MCC is a highly aggressive cutaneous and mucosal malignancy with frequent recurrence, lymph node and distant metastases. There is no clear consensus how to treat metastatic disease.

1. Introduction

The first description of Merkel Cell Carcinoma (MCC) was in 1972 by Toker explaining the tumor as a trabecular carcinoma of the skin (Toker, 1972). Today we know that MCC is a rare, highly aggressive neuroendocrine malignancy occurring mostly in elderly individuals. The etiology is not totally known, but general immunosuppression and ultraviolet light exposure seem to be risk factors and the Merkel cell polyomavirus, a DNA virus, seems to be a contributing factor of the occurrence of MCC. In nearly 80% of MCC cases the virus could be found. But depending on the different regions all over the world the incidence of virus positive compared with virus negative MCC differs (Feng et al., 2008). With 30% the mortality rate is higher than in malignant melanoma (Miller and Rabkin, 1999).

The incidence rate in the USA is about 0.44 cases per 100'000 and has increased for the last years (Miller and Rabkin, 1999; Hodgson, 2005). 50% of MMC occur in the head and neck region followed by trunk and extremities. The clinical appearance is a red-violet cutaneous nodule with a smooth surface, which is painless but rapidly growing (Schadendorf et al., 2017). Palpable regional lymphadenopathy with lymph node metastases are frequent. Distant metastases occur in the lungs, the liver, the bones and the brain. There are only a few case reports on metastases to the gastrointestinal system, the heart, the tonsil, the spinal cord, the testis, the orbita or the ovaries. Metastases of MCC have also been found in lymph nodes with unknown primary tumor (Llombart et al., 2017). To our knowledge just three cases with ovarian metastases of MCC have been described until now. In the first two cases the primary tumor was found in the inguinal skin, in the third case in the periauricular skin (George et al., 1985; Eichhorn et al., 1993; Acikalin et al., 2014). Metastases from MCC spreading to the ovaries are unusual. Common metastases in the ovaries descend from colon, stomach, appendix, breast and genitourinary tract (Acikalin et al., 2014). Metastatic MCC has poor prognosis. Two years after diagnosis the mortality rate is 30%, five years after 50% (Acikalin et al., 2014; Kouzmina et al., 2017).

2. Case report

We describe the case of an 80-year-old woman with complete resection of MCC on the cheek six years ago. It is unknown if there was a lymph node biopsy or a radiotherapy after the resection of the primary tumor. She reported in our outpatient clinic with increasing abdominal pain. In the preoperative examination a solid tumor of the left ovary was suspected (Fig. 1). The cancer-antigen 125 (CA-125) was normal. There was no indication of recurrence or other metastases of the resected MCC. The patient received abdominal hysterectomy and adnexectomy on both sides. The left ovary was an enlarged solid mass with a smooth, intact capsule. The tumor showed a torsion explaining the abdominal pain. There was no sign of other intraabdominal pathology. Histological findings showed a small-cell carcinoma with necrosis and intact capsule (Fig. 2). Immunohistochemically the tumor was positive for epithelial membrane antigen (EMA), cytokeratin 20

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https://doi.org/10.1016/j.gore.2019.03.011
Received 3 January 2019; Received in revised form 10 March 2019; Accepted 18 March 2019
Available online 20 March 2019

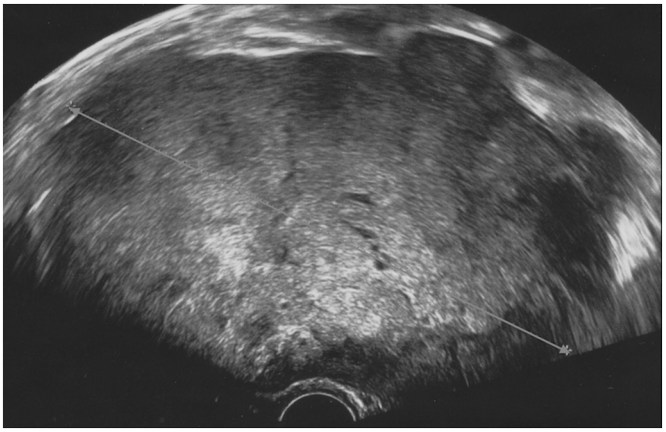

Fig. 1. Ultrasound image with the solid tumor of the left ovary (6 in. diameter).

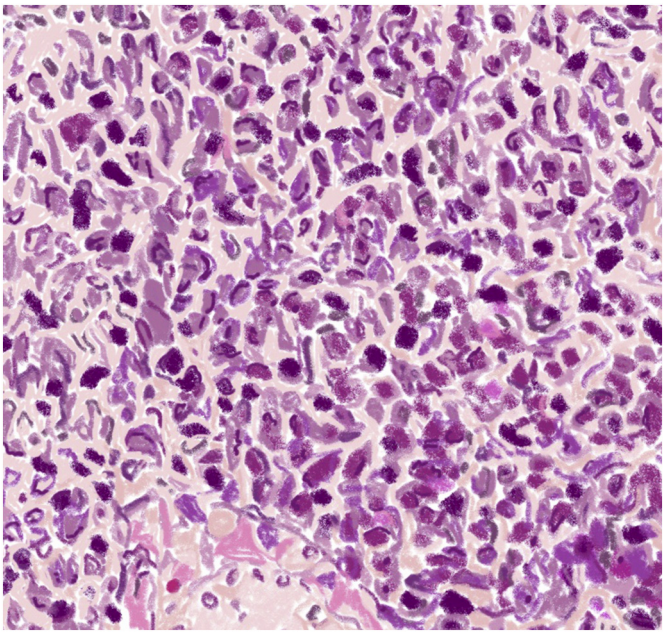

Fig. 2. Scheme of MCC with scant cytoplasm and round nuclei (hematoxylin and eosin stain) (Acikalin et al., 2014).

(CK20), chromogranin, synaptophysin and negative for thyroid transcription factor 1 (TTF-1). Diagnosis of MCC metastasis was indisputable. A virus test was not made. A few days after surgery the patient reported with new pain in her right femur, although she did not show any other symptoms before laparotomy except abdominal pain. Radiological examinations confirmed a pathological distal femur fracture due to metastatic bone infiltration. After osteosynthesis the follow-up was uneventful. In an additional computed tomography multiple lesions, likely to be metastases, were discovered. They were in the left suprarenal gland and outside of the pelvis in the left musculus piriformis. Nevertheless the patient refused radiation or chemotherapy. Six months later she reported again with discomfort because of multiple new cutaneous and subcutaneous metastases. Her quality of life was still good and so she decided to have the disturbing lesions on the thorax and supraclavicular removed. In a total body positron emission tomography-computed tomography (PET-CT) another metastasis in the heart was diagnosed. In the following months the patient agreed to the best supportive care.

3. Discussion

To our knowledge just three cases with ovarian metastasis of MCC have been described. In the first two cases the primary tumor was in the inguinal skin. In the third case it was periauricular. Our case is the second with distant metastasis in the ovary spreading of primary tumor from the skin of the head. In the three previously described cases the metastases were diagnosed within 15 months after the first treatment (George et al., 1985; Eichhorn et al., 1993; Acikalin et al., 2014). In our case the ovarian metastasis occurred astonishingly not earlier than six years after the primary disease. MCC often occurs in elderly patients on sun-exposed areas of the skin. Immunosuppression due to HIV-infection, chemotherapy, organ transplantation or malignant lymphoma increase the risk of MCC. Merkel cell polyomavirus seems to be a contributing factor of the occurrence of MCC (Acikalin et al., 2014). The origin of MCC is not exactly known. A neural crest origin of the Merkel cells is suspected. It would explain the neuro-endocrine and epithelial differentiation of the tumors (Wang et al., 2011).

After diagnosis of MCC a preoperative staging will be done by total body positron emission tomography-computed tomography (PET-CT) (Tothill et al., 2015).

Histopathological findings are a monotonous tumor cell population with large prominent nuclei and scant cytoplasma. Three histological subtypes exist: trabecular, intermediate and small cell MCC, but the utility of this classification is not clear (Schadendorf et al., 2017). Immunohistochemically MCC is positive for EMA, CK20 and neuroendocrine markers like synaptophysin and chromogranin. MCC is negative for TTF-1 to distinguish it from pulmonary small-cell carcinoma. With these markers a clear classification as MCC is possible (Schadendorf et al., 2017; Llombart et al., 2017; Acikalin et al., 2014; Uchi, 2018).

In our case the ovarian metastasis was positive for EMA, CK20, chromogranin, synaptophysin and negative for TTF-1.

The treatment of MCC depends on tumor size, localization and stage, but there is no consensus on the therapy of MCC. 2010 the first staging system for MCC was published and since then a few updates have been done. Carcinoma in situ is stage 0, a tumor ≤ 2 cm stage I and bigger tumor stage II. Stage III is reserved for nodal positive disease and stage IV for distant metastasis. The TNM classification exists too (Harms et al., 2016).

The primary treatment for early stages is surgery with sentinel node biopsy or complete lymph node dissection. Clinical nodal negative patient receive sentinel node biopsy and adjuvant radiation therapy. In clinical or histological node-positive disease complete lymph node dissection is recommended. If surgery of the primary tumor is not possible or the sentinel node is positive and complete lymph node dissection is not carried out, radiation therapy is also possible. Furthermore radiotherapy can be utilized as a palliative treatment (Schadendorf et al., 2017; Tothill et al., 2015). Because of the rarity of MCC there is a lack of experience of metastases, most publications are case reports and there are no controlled randomized trials about chemotherapy (Acikalin et al., 2014; Kouzmina et al., 2017; Tothill et al., 2015). Chemotherapy is reserved for metastatic disease and is similar to the treatment of small-cell lung carcinomata because of the same neuroendocrine origin of MCC. Common regimes include cisplatin or carboplatin, with etoposide and topotecan. (Schadendorf et al., 2017). Immunotherapy with e.g. immune checkpoint inhibitors or cytokines are used in clinical trials. Other immunotherapies are described but not yet established (Schadendorf et al., 2017; Tothill et al., 2015; Uchi, 2018; Nghiem et al., 2017). Potential therapeutic targets are currently under investigation. In clinical trials for the treatment of MCC tyrosine kinase inhibitors, somatostatin analogs and mammalian target of rapamycin inhibitors are being used. There is a case report of clinical response to idelalisib, a phosphoinositide 3-kinase inhibitor, in a patient with MCC. Gavvovidis et al. describe T-cell based immunotherapy. MCC cells can be targeted by Merkel Cell polyomavirus T antigen-specific T-cell receptors (Tello et al., 2018; Gavvovidis et al., 2018;

Shiver et al., 2015)

4. Conclusion

MCC is a rare tumor with an increasing incidence in the last years. It is a highly aggressive cutaneous and mucosal malignancy with frequent recurrence, lymph node and distant metastases. Each small, blue and round cell tumor could be an MCC. The histological and immunohistological examinations are very important to diagnose these metastases. Distant metastases of MCC to the ovaries are extremely rare (Acikalin et al., 2014).

In the described case the six-year-disease-free survival after the first tumor excision was extraordinarily long. In the previously published cases the first metastases were found 15 months after the diagnosis of MCC (Acikalin et al., 2014). The first sign of a disease recurrence with abdominal pain due to ovarian metastasis is astonishing. Even if the primary treatment is successful, regular follow-up examinations are important to recognize recurrence and metastases. There should be a clinical follow-up examination every 3 to 4 months for the first 2 to 3 years after treatment. After 3 years examinations can follow every 6 to 12 months. There are no guidelines for imaging frequency. Imaging depends on the patient's symptoms and risk factors, e.g. nodal disease or immunosupression. Positron emission tomography/computed tomography has the highest sensitivity for detecting subclinical disease (Tello et al., 2018). Our case is the second description of distant metastasis to the ovary spreading from a tumor in the skin of the head and neck.

There is little knowledge of treatments for metastatic MCC. Most recommendations result from case reports and it is unlikely that there will ever be a prospective trial because this is a very rare disease.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Author contribution section

S. Schmid was the responsible surgeon and all authors were involved in manuscript preparation.

Acknowledgments

None.

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