Merkel Cell Carcinoma with Gastric Metastasis, a Rare Presentation: Case Report and Literature Review

Vittorio Durastante1 · Antonello Conte1 · Pier Paolo Brollo2 · Carlo Biddau3 · Michele Graziano4 · Vittorio Bresadola2

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Abstract

Introduction Merkel cell carcinoma (MCC) is an infrequent, but highly aggressive neuroendocrine neoplasm of the skin with a propensity for recurrence and metastasis. We report a rare case of gastric metastatic localization of this cancer by focusing on the diagnostic, clinical, and surgical approach to the patient.

Case Report Clinical presentation begins with a peripheral lymphadenopathy whose immunohistochemical characterization identifies the lymphatic dissemination of the disease. Gradually, the patient develops a severe anaemic state which requires several blood transfusions and surgical gastric resection to remove a large bleeding lesion of the antral region. The histopathological analysis of the specimen confirms the metastatic origin from MCC, but the primitive lesion remains unknown.

Discussion Since this clinical situation is very rare, we conducted a review of the literature selecting the few cases reported, in order to evaluate the current knowledge on this topic. Metastatic involvement of the stomach from Merkel cell carcinoma is a rare presentation of this disease progression with a frequent delay in formulating the correct diagnosis and in further treatment which may be life-threatening for the patient. As regards the local treatment, there is no specific guideline, and the therapeutic indication should be tailored on the specific case.

Keywords Merkel cell carcinoma · Neuroendocrine tumors · Gastric surgery · Gastric metastasis · Immunotherapy for cancer

Introduction

Merkel cell carcinoma (MCC) is an infrequent, but highly aggressive neuroendocrine neoplasm of the skin with a propensity for recurrence and metastasis. There are very few epidemiological information regarding MCC. A recent analysis in the US population reports that the MCC incidence rate in 2013 was 0.7 cases/100.000 person-years, which increases exponentially with age from 0.1 to 1.0 to 9.8 (per 100.000 person-years) among age groups 40–44 years, 60–64 years, and ≥ 85 years, respectively [1]. Another epidemiological study conducted in Finland reports an incidence in 1989–2008 of 0.11/100.000 for men and 0.12/100.000 for women, with a mean age at diagnosis of 76 years (range 27–100) and 69% of the patients were women [2]. The 5-year survival ratio varies from up to 60–70% (stage I disease) to less than 15% (stage IV disease) depending on the considered population and it is strictly correlated with the stage at the diagnosis [3–5]. Ultraviolet (UV) radiation exposure, reduced skin pigmentation, history of other sun exposure linked skin cancer (melanoma in particular), Merkel cell polyomavirus infection (MCPyV +), immunosuppression (laeukemia or lymphoma, HIV infection, transplanted patient), and chronic inflammatory disorders are known risk factors for MCC development [6–12]. In up to 10% of patients, MCC is diagnosed after histopathological analysis of enlarged lymph nodes specimen with no evident primary cutaneous tumor and an improved prognosis.

1 General Surgery Department, Civil Hospital of Tolmezzo, Udine, Italy
2 General Surgery Department and Simulation Center, Department of Medicine, Academic Hospital of Udine, University of Udine, Udine, Italy
3 General Surgery Department, Hospital of Pordenone, Pordenone, Italy
4 General Surgery Department, Hospital of Latisana, Udine, Italy
than in cases of evident cutaneous MCC with lymph node metastasis. Besides regional lymph nodes, metastases are commonly found in the skin, distant lymph nodes, lungs, adrenal glands, liver, brain, and bones [13–15]. Metastatic spreading to the stomach is a very rare evolution of the disease [16]. Due to this infrequent presentation, there is often a delayed diagnosis and no unified consent about its treatment which, in the majority of the cases, aim to control the symptoms of the metastatic lesion as a bridge to systemic chemo-/immunotherapeutic treatment. In this context, we report our experience of a case of Merkel cell carcinoma with symptomatic gastric metastasis and a contextual review of the current literature.

**Methods**

After reporting our clinical case, we performed a review of the literature by searching the following terms on PubMed and Scopus databases: “Merkel cell carcinoma” AND “metastasis” AND (“gastric” OR “stomach”). Subsequently, a cross-check of the reference lists of selected articles was performed to find any missed papers. The research has been performed by three independent reviewers (P.P.B., C.B., and M.G.) and closed on the 30th September 2021. Only cases of gastric metastasis from MCC, in the absence of further confounding conditions, were selected. At the end, 20 publications have been considered relevant for the research query (Fig. 1) [16–35]. The information available for each clinical case (including the case report described herein) regarding the age, gender, ethnicity, primary site, therapy for primary site, time between initial diagnosis/therapy and metastasis presentation, management of metastasis, outcome at time of report, time between metastatic diagnosis and death have been collected and compared.

**Case Report**

A 61-year-old Caucasian man with no previous medical history presented to surgical evaluation with rapidly enlarging right inguinal lymph nodes. Surgical excisional biopsy of an inguinal lymph node confirmed the diagnosis of lymphatic metastasis from Merkel cell carcinoma by immunohistochemical assessment (IHC); no primitive skin lesion was found during dermatological evaluation. PET-CT scan (with 18F-deoxyglucose) showed suspicious tracer accumulations in the left colonic tract (benign tubular adenomas and a hyperplastic polyp confirmed at histological examination after endoscopic excision) and in some mediastinal lymph nodes. After the initial diagnosis and initial staging, a complete right inguinocrural lymphadenectomy was performed, followed by a cumulative 50 Gy radiant treatment of the region (2 Gy daily,
five days a week, 25 sessions). After two months, the follow-up abdominal MRI showed a highly vascularized lesion of the antral wall of the stomach (30 mm in diameter) which aroused the suspicion of a gastrointestinal stromal tumor (GIST). After one month, a total body CT scan showed no possible metastatic nodularity and confirmed the presence of the gastric lesion (47 mm in diameter) with perigastric lymph nodes enlargement (Fig. 2). Four months after inguinal radiotherapy, the patient started to develop increasing fatigue followed by emission of melena. The subsequent severe anaemia (Hb 7.6 g/dL) required urgent hospital admission and several blood transfusions were performed; the patient always remained hemodynamically stable with no cardiorespiratory symptoms. During gastric endoscopy, a bioptic specimen of the lesion was collected and the IHC analysis revealed a metastatic MCC localization. In order to control the chronic bleeding, the patient underwent an open gastric antral resection with Roux-en-Y gastro-jejunostomy (Fig. 3). Following the surgical procedure, no other blood transfusions were necessary with a rapid and spontaneous increasing in hemoglobin level (10.8 g/dL at hospital discharge); there were no post-operative complications and the patient was discharged on seventh post-operative day. IHC analysis of the surgical specimen confirmed the presence of a MCC metastatic localization on the antral wall of the stomach (positivity for CK20, chromogranin A and synaptophysin; negativity for TTF1 and CD20) with multiple lymph nodal involvements. The patient has been selected, after oncological evaluation, for a first-line immunotherapy with avelumab (Bavencio®, 800 mg iv every two weeks), an anti-PDL1 monoclonal antibody. Radiotherapy will be considered depending on the grade of disease control during follow-up.

Discussion

As emerged from our literature review, gastric metastasis from MCC are a very rare clinical presentation with only 21 cases reported so far, including this one (Table 1). With the limits of these small numbers, we noticed that the average age of presentation of the metastatic localization is 70.6-year-old (SD 11.7-year-old), ranging from 46- to 92-year-old; 5 cases are women (24%), while 16 are men (76%). With the same limitations, the average time from the initial diagnosis to gastric metastatic presentation is 22.3 months (SD 16.7 months), ranging from 2 to 72 months. The primary tumor site was unknown in only 2 cases (10%). In the other 19 cases with known primitive lesion, 12 (63%) were located to the lower part of the body (below the umbilical line); 4 (21%) were located to the head and neck region; 3 (16%) were located to the upper extremities. These lesions have been mainly treated at their primary site with surgical resection in variable combinations with chemotherapy and/or local radiotherapy; lymph node dissection has been reported in only 4 cases (19%). The signs and
| Case report       | Age (years) | Gender | Ethnicity | Site of primary MCC | Treatment of primary site lesion | Time between initial diagnosis or therapy and metastasis (months) | Clinical presentation | Treatment of metastasis | Outcome (at the time of report) | Time between metastatic disease and death |
|-------------------|-------------|--------|-----------|---------------------|----------------------------------|---------------------------------------------------------------|-----------------------|--------------------------|----------------------------------|------------------------------------------|
| Canales et al. (1992) [17] | 67          | M      | Unknown   | Right gluteal region | Surgical resection and local RT  | 11                                              | Generalized fatigue, orthostatic symptoms, melena | Total gastrectomy, CP, VCR, DOX | Receiving CT | NA                               |
| Krasagakis et al. (1997) [18] | 81          | M      | Unknown   | Right hand (5th finger) | Surgical resection, axillary lymph node dissection, RT, CT | 12                                              | GI bleeding                                  | Surgical resection of gastric mass | Deceased for metastatic disease | 3 weeks                            |
| Idowu et al. (2003) [19] | 79          | F      | Unknown   | Right inguinal     | Surgical resection, RT, CT      | 48                                              | Light-headedness, melena, 27.2-kg weight loss within 6 months | Not described                  | Deceased for metastatic disease | 4 months                           |
| Cubella et al. (2004)* [20] | 74          | M      | Unknown   | Right retroauricular | Surgical resection, CT          | 23                                              | Hematemesis, melena                             | Surgical resection of gastric mass | Deceased for metastatic disease | 2 months                           |
| Shalhub et al. (2004) [21] | 62          | M      | Unknown   | Right neck        | Surgical resection              | 72                                              | Persistent fevers, jaundice                      | CBDCA, EPEG                    | Deceased for metastatic disease | 1 month                            |
| Li and Liu (2004) [22] | 46          | M      | Caucasian | Left preauricular | Surgical resection, RT, CT      | 8                                               | Melena                                        | CDDP, DOX                       | Receiving CT | NA                               |
| Hizawa et al. (2007)* [23] | 85          | F      | Japanese  | Right eyelid      | Surgical resection, RT          | 20                                              | Vomit                                         | Palliative care                | Deceased for metastatic disease | 2 months                           |
| Wolov et al. (2009) [24] | 80          | M      | Unknown   | Right upper extremity | Surgical resection, RT          | 24                                              | Progressive fatigue, syncope, melena             | Combined CT-RT with 4 cycles of CBDCA | Deceased | Unknown                          |
| Rosa et al. (2010) [25] | 72          | F      | Unknown   | Right inguinal     | Surgical resection, RT, CT      | 24                                              | Light-headedness, epigastric pain, hematemesis, weight loss | Bilroth II resection, 2 cycles of adjuvant CT | Alive after 24 months of follow-up | NA                                 |
| Temiz et al. (2010) [26] | 75          | M      | Unknown   | Left thigh        | Surgical resection              | 10                                              | Perforated duodenal ulcer                       | Incidental resection of gastric mass | Deceased | 17 months                       |
| Syal et al. (2012) [27] | 68          | M      | Unknown   | Left leg          | Surgical resection, RT, CT      | Unknown                                        | Melena, fatigue, exertional dyspnea, epigastric pain | CT, RT                           | Receiving RT | NA                               |
| Parikh et al. (2014) [28] | 60          | M      | Hispanic  | Right inguinal    | CT, RT                          | 4                                               | Fatigue, weakness, black-colored stools         | 3 cycles of CT                  | Unknown | Unknown                          |
| Capella et al. (2014) [29] | 72          | M      | Unknown   | Unknown           | NA                              | 2                                               | Epigastric pain and 9-kg weight loss within 1 month | Total gastrectomy and splenectomy, EPEG, CDDP | Deceased for metastatic disease | 2 months                           |
| Santos-Juanes et al. (2016) [30] | 52          | M      | Unknown   | Right thigh       | Surgical resection, right inguinal lymph node dissection, RT, CBDCA, EPEG | 24                                              | Anemia                                       | CT                               | Deceased for metastatic disease | 6 months                           |
Table 1 (continued)

| Case report                  | Age (years) | Gender | Ethnicity | Site of primary MCC | Treatment of primary site lesion | Time between initial diagnosis or therapy and metastasis (months) | Clinical presentation | Treatment of metastasis | Outcome (at the time of report) | Time between metastatic disease and death |
|------------------------------|-------------|--------|-----------|---------------------|----------------------------------|------------------------------------------------------------------|-----------------------|--------------------------|----------------------------------|------------------------------------------|
| Pedrazzani et al. (2016) [31]| 70          | F      | Unknown   | Left knee           | Surgical resection               | 19                                                               | Asymptomatic          | No adjuvant therapy          | Alive after 12 months follow-up     | NA                                        |
| Hu et al. (2016) [16]        | 92          | M      | Caucasian | Left upper extremity| Surgical resection, RT           | 15                                                               | Fatigue, early satiety, syncope, melena, 9-kg weight loss within 1 month | Palliative care        | Deceased for metastatic disease    | 5 weeks                              |
| Hulstaert et al. (2016) [32] | 77          | M      | Caucasian | Abdominal wall (left sided paraumbilical) | Surgical resection               | 36                                                               | Melena                | CBDCA, EPEG (refused surgery)   | Receiving CT                       | NA                                        |
| Trivedi et al. (2017) [33]   | 52          | M      | Vietnamese| Left gluteal region | Biopsy, RT                       | 36                                                               | Ulcerated skin lesion, gastric perforation during CT              | CDDP, EPEG, emergency wedge gastrectomy | Alive after 18 months follow-up | NA                                        |
| Ha et al. (2018) [34]        | 82          | M      | Unknown   | Left gluteal region | Surgical resection, RT           | 36                                                               | Nausea, vomiting, 10-kg weight loss within 1 month               | CT, RT, immuno-therapy | Deceased for metastatic disease | Unknown                              |
| Kini et al. (2018) [35]      | 75          | F      | Unknown   | Left gluteal region | Surgical resection, left pelvic and inguinal lymph node dissection | 12                                                               | Recurrent vomiting and jaundice                                 | CT                      | Deceased for metastatic disease | 9 months                             |
| Durastante et al. (this case report) | 61          | M      | Caucasian | Unknown (right inguinal lymph nodes enlargement) | Right inguinal lymph node dissection, RT | 9                                                                | Fatigue, anaemia and melena                                        | Partial gastrectomy, immuno-therapy (anti-PDL1) | Receiving immuno-therapy (RT under evaluation) | NA                                        |

*M* male, *F* female, *RT* radiotherapy, *CT* chemotherapy, *CT-RT* chemo-radiotherapy, *GI* gastro-intestinal, *CP* cyclophosphamide, *VCR* vincristine, *DOX* doxorubicin, *CBDCA* carboplatin, *EPEG* etoposide, *CDDP* cisplatin, *NA* not applicable

*Publication not in English language*
symptoms related to gastric metastasis were aspecific and mainly related to gastrointestinal bleeding (melena, hematemesis, fatigue, anaemia, abdominal pain) and metastatic disease (fatigue, weight loss, persistent fever, abdominal pain); only one patient had an asymptomatic presentation. The gastric metastasis has been surgically treated in 8 cases (38%) in order to control the gastrointestinal bleeding and reduce the mass effect as a bridge to systemic therapy; in 2 cases, a perforation has occurred, one at presentation and one during chemotherapy. In 13 cases (62%) adjuvant chemotherapeutic treatment has been performed with various combinations of platinum-based (cisplatin, CDDP; carboplatin, CBDCA) regimens and the possible addition of etoposide (EPEG), taxanes and anthracyclines. Chemo-radiotherapy has been reported in one case (5%), while radiotherapy after chemotherapy has been adopted in 2 cases (10%). Of the 8 reported cases from 2016, only 2 (25%) have received immunotherapy for metastatic disease. At the time of case reporting, 8 patients were alive (38%), while 12 were deceased (57%); one was not declared. Of the 12 deceased patients, 10 had this negative outcome due to metastatic progression and in 9 cases the time between metastasis development and death has been reported. With the limits of these small numbers, the average time between gastric metastatic involvement and death is 3.1 months (SD 2.8 months), ranging from 3 weeks to 9 months. It is important to underline that each one of these 9 patients has been treated with standard chemotherapy and none of them has received immunotherapeutic drugs.

According to the most recent guidelines (National Comprehensive Cancer Network, NCCN [36] and European Dermatology Forum–European Association of Dermato-Oncology–European Organization for Research and Treatment of Cancer, EDF-EADO-EORTC [37]) on the management of Merkel cell carcinoma, a wide surgical resection (with 1 to 2 cm margins down to the muscle fascia or the pericranium, regardless of tumor size) of the primary lesion, if present, is the first step of treatment. Surgical biopsy of enlarged peripheral lymph nodes is always recommended. In patients with clinically negative lymph nodes, sentinel lymph node biopsy (SLNB) must be performed whenever possible, regardless of the size of the primary tumor. If lymphatic spreading is confirmed, a complete lymph nodal dissection and/or elective regional radiotherapy to the draining lymph node basin is the current standard of therapy, but none of these has been compared in a randomized setting. When the primary tumor site is known, an adjuvant wide-field radiotherapy might be considered to reduce the risk of nodal spread or recurrence [38, 39]. The most common chemotherapeutic treatments (adjuvant or for systemic disease) for MCC are platinum-based (cisplatin, CDDP; carboplatin, CBDCA) regimens, with the possible addition of etoposide (EPEG), taxanes and anthracyclines, but no standardized protocols have been released and their efficacy in advanced stage disease is poor [40]. After the introduction of immunotherapy in 2016, the PD1–PDL1 (programmed cell death-1 and programmed cell death ligand-1) immune-checkpoint pathway has become a key therapeutic target in reactivating immune responses against MCC. Today pembrolizumab [41] and avelumab [42] are indicated as first choice systemic therapy option for metastatic disease (for avelumab, regardless of the PDL1 expression status of the tumor).

Metastatic involvement of the stomach from Merkel cell carcinoma is a rare presentation of this disease progression. Due to its infrequency and later presentation after the primary site/lymph nodal involvement, there is a delay in correctly diagnosing the metastatic disease. This feature often causes a subsequent delay in further systemic treatment and may be life-threatening for the patient. As regards the local treatment of MCC-related gastric metastasis, there is no specific guideline, and the therapeutic indication should be tailored on the specific case.

**Declarations**

**Informed Consent** Informed consent was obtained from the patient to be included in the study.

**Human/Animal Rights** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

**Conflict of Interest** The authors declare no competing interests.

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