Case Report

Endometrioid endometrial carcinoma of no-specific-molecular-profile with multiple bone metastases and muscle involvement: Case report and review of the literature ☆

Martin Heidinger, MD[a,1,*], Mei Koh, MD[a], Mario Panzenboeck, MD[b], Thomas Lutz, MD[b], Kirsten D. Mertz, Prof. MD[c], Hansjoerg Huemer, MD[d], Marcus Vetter, PD MD[e], Frey Tirri Brigitte, MD[a]

[a] Women's Clinic, Cantonal Hospital Baselland, Liestal, Switzerland
[b] Institute for Radiology and Nuclear Medicine, Cantonal Hospital Baselland, Liestal, Switzerland
[c] Institute for Pathology, Cantonal Hospital Baselland, Liestal, Switzerland
[d] Women's Clinic, Bethesda Hospital Basel, Basel, Switzerland
[e] Department for Oncology, Cantonal Hospital Baselland, Liestal, Switzerland

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ABSTRACT

Bone metastasis and muscular involvement in endometrial carcinoma are rare, and information on molecular profiles of endometrial carcinoma with bone metastasis is scarce. We present a case of an 83-year old woman with a poorly differentiated endometrioid adenocarcinoma of no-specific-molecular-profile with para-aortic lymph node involvement, who underwent surgery, received adjuvant chemotherapy and vaginal brachytherapy but declined external beam radiotherapy. Fifteen months after the initial diagnosis she presented with pain in her right leg. Imaging showed an osteolytic lesion in the right femur with soft-tissue involvement. She underwent an open biopsy and protective osteosynthesis. Histologically, infiltrates of both bone and muscle were consistent with metastasis derived from endometrioid endometrial carcinoma. She received concomitant palliative chemotherapy and external beam radiotherapy to the right femur. Eleven months later, she presented with an acute hemiparesis caused by a right-sided subacute, superior frontal gyrus infarct, which

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also showed aggressive bone metastasis of the left sphenoid bone. She subsequently died 2 weeks later. This is a rare case of multiple bone metastases and muscle involvement in endometrial carcinoma. To our knowledge, this is the first reported such case in endometrial carcinoma showing no-specific-molecular-profile.

Introduction

Endometrial carcinoma (EC) is the sixth most common cancer in women worldwide and the most common gynaecologic malignancy in Europe and North America with an age-standardized incidence rate of 20.2 and 21.1 per 100 000 in 2020 respectively [1,2]. Clinically, EC typically presents with abnormal uterine bleeding, and most cases are diagnosed at an early stage. Metastasis typically occurs via direct extension, lymphatic spread or hematogenous dissemination. The commonest sites of distant metastasis are the lungs and liver [1]. Historically, ECs have been classified into 2 types, with Type I being estrogen-dependent endometrioid, and Type II estrogen-independent non-endometrioid carcinomas [3]. Recent molecular characterization of ECs in 4 subtypes, namely (i) DNA polymerase epsilon (POLE) ultramutated, (ii) Tumor protein 53 abnormal (TP53abn), (iii) microsatellite unstable and (iv) no-specific-molecular-profile (NSMP) represents enhanced prognostic profiles and potential for tailored therapy [4–6]. Bone involvement is generally considered rare in EC, with clinical incidence rates of <1% [7,8], whilst muscular involvement is considered extremely rare. Recently, a case-study by McEachron et al. reported a series of 7 EC patients with BM and available molecular profiling, of which all showed microsatellite instability (MSI) [8]. Here we report a rare case of multiple BM and muscle involvement in an endometrioid EC showing NSMP, with all previously reported cases being MSI. The article was written according to the CAse REport (CARE) guidelines, and the CARE checklist is provided in Supplementary Table 1.

Case Description

An 83-year old woman presented with postmenopausal bleeding and endometrial thickening on transvaginal ultrasound in September 2018. Endometrial pipelle sampling revealed an endometrial adenocarcinoma. She subsequently underwent a total laparoscopic hysterectomy, right-sided salpingo-oophorectomy as well as pelvic and para-aortic lymphadenectomy. The left tube and ovary were removed in 1963 following an ectopic pregnancy. Histology revealed a poorly differentiated endometrioid adenocarcinoma with uterine serosa penetration, infiltration of the parametrium, cervix, vessels, perineurium and para-aortic lymph node involvement.

The tumor was classified as pT3b, pN1(2/20), pL0, pV1, pPn1, cM0, G3, R0 (Stage FIGO IIIC2) [1,9]. Estrogen and progesterone receptors were positive; L1 Cell Adhesion Molecule (L1CAM) staining was negative. Mismatch-Repair-Proteins (MutL Homolog 1 - MLH1, PMS1 Homolog 2 - PMS2, MutS Homolog 2 - MSH2 and MutS homolog 6 - MSH6) were expressed. Next-Generation Sequencing (NGS, Oncomine Comprehensive Panel V3, 161 Gene, Thermo Fischer Scientific Inc., Waltham, Massachusetts, USA) showed mutations in the KRAS proto-oncogene (KRAS, Exon 2, Codon 12, p.Gly12Asp), catenin beta 1 (CTNNB1, Exon 3, Codon 33, p.Ser33Tyr), phosphatase and tensin homolog (PTEN, Exon 5, Codon 130, p.Arg130Gly), fibroblast growth factor receptor 2 (FGFR2, Exon 7, Codon 252, p.Ser252Leu) and retinoblastoma transcriptional corepressor 1 (RB1, Exon 18, Codon 567, p.Ser567Leu). Therefore, the tumor was classified as POLE-negative, microsatellite stable, TP53-normal and CTNNB1-mutated, which defined it as NSMP [4-6]. Histological findings are summarized in Figure 1.

Following discussion at the interdisciplinary tumor conference, a combined adjuvant radio-chemotherapy in "sandwich" method (ie, : chemotherapy – external beam radiotherapy – chemotherapy) was proposed to the patient. She consented to a course of 6 cycles of 3 weekly Carboplatin (AUC 5) and Taxol (175 mg/m2), which she received from November 2018 to February 2019. However, she declined external beam radiotherapy (EBRT). Vaginal brachytherapy was offered and accepted by the patient. She received 5 times 4 Gray (Gy) adjuvant vaginal brachytherapy in after loading technique in April 2019 after finishing chemotherapy. Two months after finishing the adjuvant therapy cycle a follow-up thoracic and abdominal computed tomography (CT) scan showed complete remission. The patient was subsequently scheduled to receive 3 monthly follow-up care.

Fifteen months after the initial diagnosis the patient presented to her general practitioner with atraumatic, progressive pain in the right hip and femur, with pain exacerbation on axial compression and rotation, and a reduced range-of-motion of the right hip joint. Pelvic magnetic resonance imaging (MRI) showed an oedematous lesion of 2 cm in the left os ilium, which was interpreted to be degenerative in a consecutive abdominal CT. Three months after the initial presentation to her general practitioner she presented to the orthopaedic department where a radiography of the right leg depicted an osteolytic lesion in the mid-shaft of the right femur suggestive of a metastatic lesion (Figs. 2A and B). A whole-body positron emission tomography-CT (PET-CT) confirmed a hypermetabolic, osteolytic lesion of the right femur with signs of extraosseus extension (Figs. 2C and D), and depicted multiple hypermetabolic peritoneal noduli in the small pelvis as well as in the left upper abdominal quadrant, suggesting intraperitoneal dissemination, as well as lymph node involvement in the right-sided common iliac region. Laboratory results showed an increased erythrocyte-sedimentation
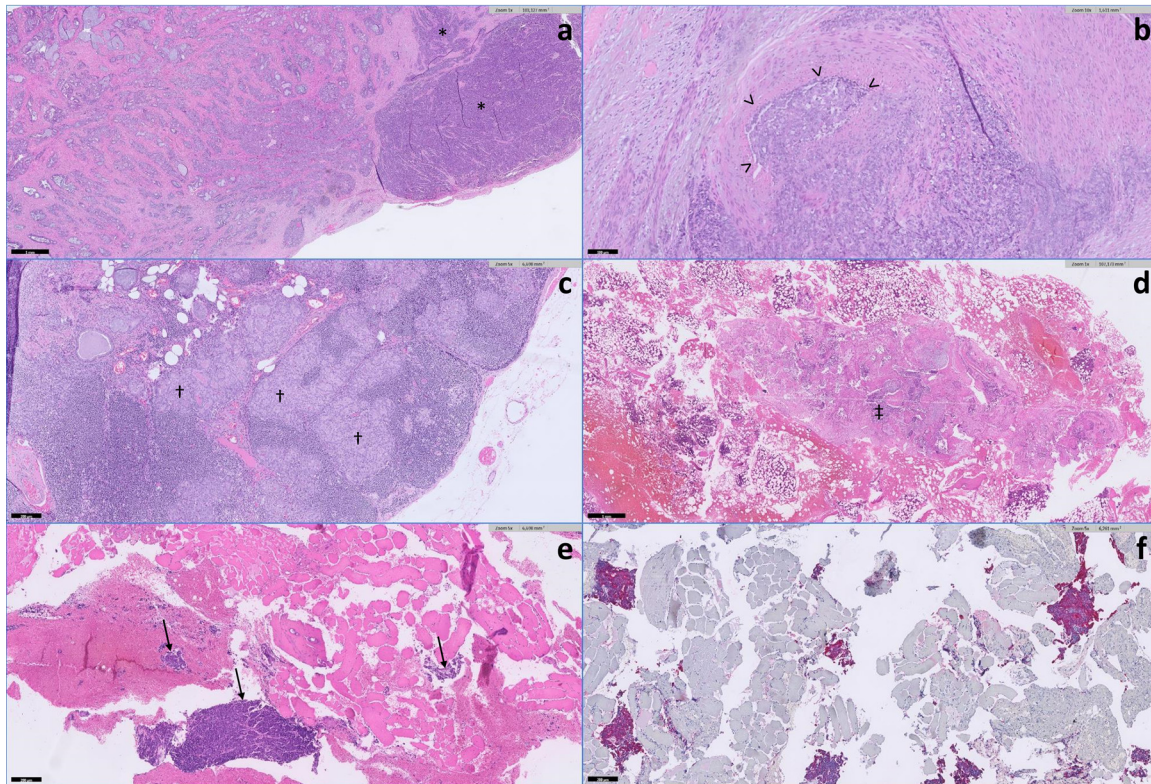
Fig. 1 – Histological findings of primary and secondary endometrial carcinoma. Primary histology revealed a poorly differentiated endometrioid adenocarcinoma of the endometrium (asterisk) with deep myometrial invasion as shown in H&E staining (A). Serosa penetration, bilateral parametrial as well as cervical stroma tumor-infiltration was identified. Vessel invasion (arrow-heads) (B) and perineural tumor-infiltration were present. Two para-aortic lymph nodes were found to be involved (dagger) (C). In samples obtained during open biopsy on the right femur 15 months after the initial diagnosis, histological workup of femur bone samples confirmed infiltrates of a poorly differentiated carcinoma with partial squamous differentiation (double dagger) (D), consistent with metastasis derived from poorly differentiated endometrioid adenocarcinoma. Furthermore, muscular tumor-invasion was present (arrows) (E), which is depicted with Pan-Cytokeratin staining (F).

rate (ESR = 24 mm/h; 42mm/2h) as well as increased CA15-3 (53 kU/L) and CA19-9 (27,9 kU/L). Both CEA (1,8 mcg/mL) and CA125 (8,1 kU/L) were within normal ranges.

The patient underwent an open biopsy as well as a protective osteosynthesis. Histologically, infiltrates of a poorly differentiated carcinoma with partial squamous differentiation, consistent with metastasis derived from poorly differentiated endometrioid adenocarcinoma were confirmed in bone (Fig. 1D) and muscle (Figs. 1E and F). The metastasis was shown to be estrogen- (70%) as well as progesterone-receptor (5%) positive. Mismatch-Repair-Proteins (*MLH1, PMS2, MSH2* and *MSH6*) were expressed. No gene-fusion was detected by NGS (Oncomine Comprehensive Assay, v3, 51 Gene, Thermo Fischer Scientific Inc., Waltham, Massachusetts, USA). Immunohistochemical testing for programmed cell death 1 ligand-1 (PD-L1) was performed on hysterectomy-tissue and showed negative tumor-cells (TC, <1%), yet positive immune-cells (IC, 5%) (Ventana PD-L1 (SP263), Roche, Basel, Switzerland).

A concomitant palliative chemotherapy with 6 cycles of 3 weekly dose-reduced Carboplatin (AUC 4) and Paclitaxel (70% of 175 mg/m2) and 5 fractions of EBRT to the right femur with a total dose of 20 Gy, starting in February 2020 was pro-

posed to the patient after discussion at the interdisciplinary tumor conference, to which she consented to. Dose-reduction of chemotherapy was carried out following apparent neurotoxicity (paraesthesia, ototoxicity) within the second half of the first chemotherapy cycle as well as due to the reduced general appearance of the patient (Eastern Cooperative Oncology Group - ECOG status 2-3). Follow-up thoracic and abdominal CT scans showed no new metastasis and regressive peritoneal lesions. Radiography of the right femur showed an intact osteosynthesis and a size-stable osteolytic lesion. Progressive osteopenia was detected on both CT scan and X-ray. Therefore, the patient was commenced on Calcium-D3 supplementation as well as monthly Denosumab therapy. An antihormonal endocrine therapy with aromatase-inhibitor was deferred due to the reduced general appearance and osteopenia.

In November 2020, the patient presented with a 2 week history of progressive, atraumatic lumbar pain without neurological symptoms. A spinal CT scan showed a stable fracture, highly suspicious for a pathological fracture as well as 4 quadrant ascites and multiple new peritoneal noduli, suspicious of progressive peritoneal dissemination. She was hos-
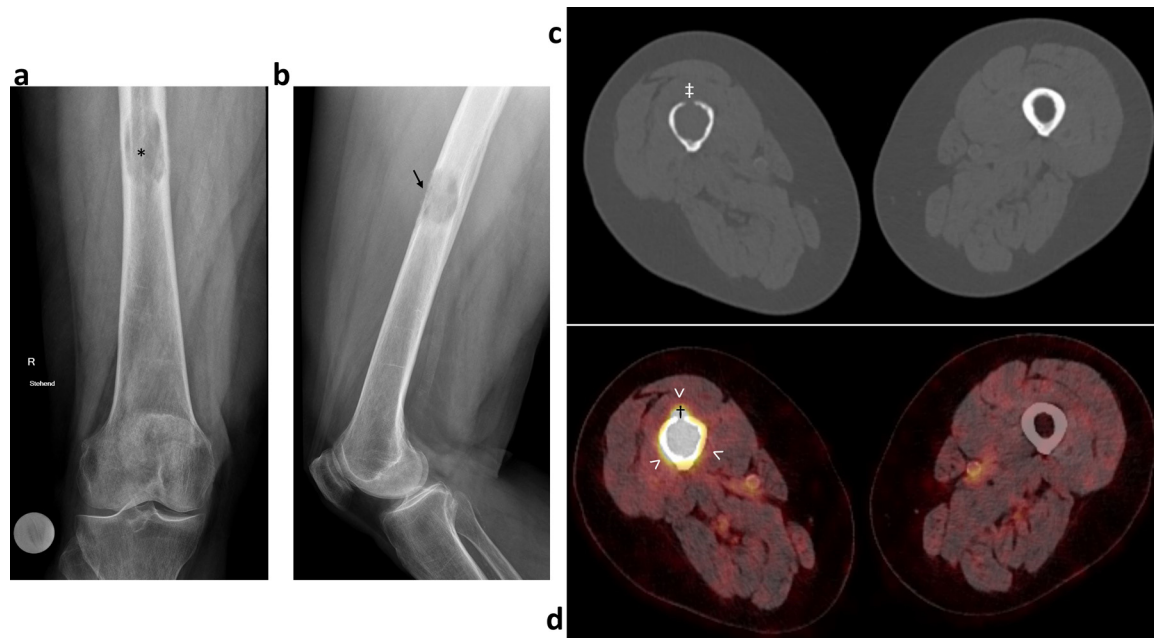
Fig. 2 – Imaging of femoral bone and soft-tissue involvement. X-ray of the right leg (anteroposterior view, standing) showing a 55 x 25,5 mm lesion (asterisk) in the mid-shaft of the right femur, suspicious of bone metastasis (A), showing an osteolytic lesion and cortical destruction (arrow) in the lateral view (B) in February, 2020. Clinical and imaging information resulted in a Mirel score of 11 points. A consecutive computed tomography (CT) scan of the lower extremities shows the right-sided femur with a thinned-out cortical bone, which in the anterior aspect shows complete destruction on axial imaging (double dagger) (C), as well as increased tracer-uptake (arrow-heads) and signs of extraosseus extension (dagger) on axial positron emission tomography – computed tomography (PET-CT) (D).

pitalised and conservatively managed with analgesia and a 3 point corset. During her admission, she developed an acute, left upper hemiparesis, which prompted a cranial CT scan. This showed a subacute infarction of the right-sided gyrus frontalis superior and a de-novo bone metastasis of the left sphenoidal bone as depicted in Figure 3. The patient subsequently died 2 weeks later.

The timeline of her episode of care is illustrated in Figure 4.

Discussion

Metastatic disease is a rare event in EC, with the majority of patients exhibiting a low risk of relapse. However, tumor size, histopathological and molecular characteristics of EC including *TP53abn* cancer and *L1CAM* positive cancer as well as tumor subtypes such as clear cell, serous, undifferentiated and mixed (>10%) cancers as well as carcinosarcomas are associated with poor prognosis and higher rate of relapse [10].

Bone metastases in EC are rare [7,8], whilst muscle involvement is extremely rare, with single case-reports describing such events [11-13]. Although to our knowledge no studies concerning direct risk factors for BM after EC have been conducted, our patient was considered high risk for recurrence of EC according to the ESMO-ESGO-ESTRO Consensus [10] due to multiple clinical, histopathological

and molecular features, namely (i) stage III endometrioid carcinoma [10], (ii) myometrial invasion >50% [6,10], (iii) grade 3 histology [6,14], (iv) substantial lymphovascular space invasion [6], (v) *CTNNB1* mutation[6,15], and (vi) *PTEN* mutation [6].

The molecular pattern of our patients EC confers a NSMP, originally named copy-number low cluster, generally showing an intermediate-low recurrence-free survival and overall survival prognosis [4,16]. In the original analysis by Kandoth et al. a *CTNNB1* mutation occurred in 52% of NSMP EC [4]. Furthermore, *CTNNB1* mutations in exon 3 have recently been shown to be a distinct prognostic marker for recurrence in NSMP EC, increasing the risk almost 3-fold [6,15]. *PTEN* mutations have been shown to increase the risk for distant recurrences in a univariable analysis of high-intermediate early-stage EC [6]. To date, 7 cases with BM after EC have been reported including a molecular analysis, whereas all 7 were shown to be MSI [8].

Additional biomarkers, as for example, the immunohistochemical marker *L1CAM* are continuously evaluated for their prognostic value [17], however our patients EC was shown to be *L1CAM* negative. Furthermore, for example, PD-L1 expression may confer to an augmented response to anti-programmed cell death protein 1 (PD1)/PD-L1 immunotherapy [18,19], whereas our patients EC showed PD-L1 negative TCs and 5% positive ICs.

Despite the fact that our patient declined combined treatment with chemotherapy and EBRT according to current treat-
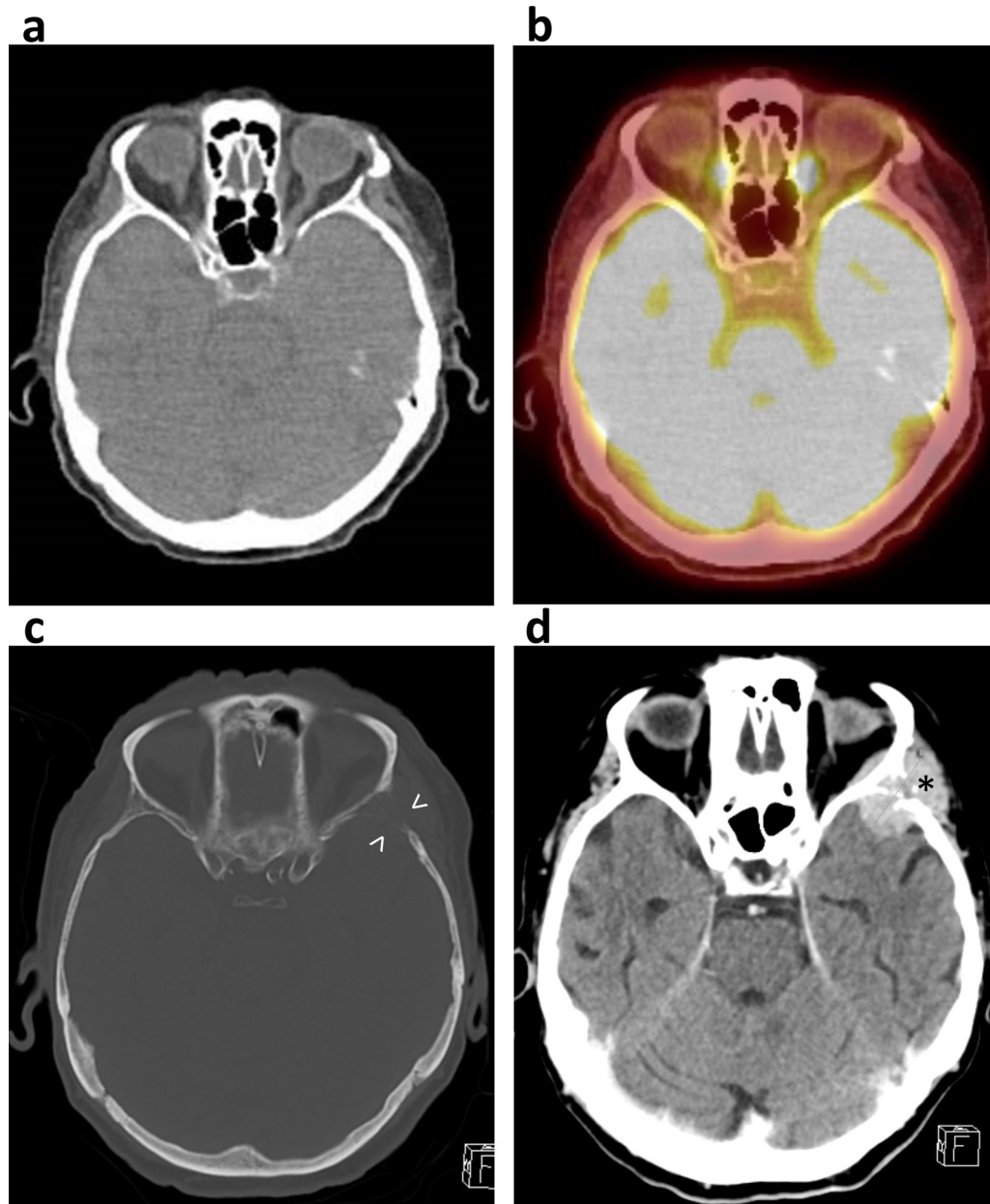
Fig. 3 – Imaging of cranial bone involvement. Top-row showing an axial non-enhanced computed tomography (NECT) cranium (A) as well as an axial positron emission tomography – computed tomography (PET-CT) of the cranium (B) in January, 2020 without signs of metastasis. Images in the bottom-row display cortical destruction of the left sphenoidal bone in the bone window of an axial NECT cranium (arrow-heads) (C), a 28 mm lesion in diameter infiltrating the left orbital region as well as the neurocranium via cortical destruction of the left sphenoidal bone in the soft-tissue window of the same NECT (asterisk) (D) in November, 2020.

ment recommendations [10] but consented to 6 cycles of Platinum- and Taxol-based chemotherapy, this has recently been reported to show no significant difference in relapse-free survival. This has also been noted in stage IIIC and IV patients in the GOG258 trial [20]. With regards to the significantly increased risk of vaginal recurrence in the chemotherapy-only group, it is of note that 58% of patients in the combined treatment group received vaginal brachytherapy [20]. The GOG249 trial showed similar recurrence-free and overall survival rates in patients with high-risk, early stage EC who received vagi-

nal brachytherapy with chemotherapy compared to patients who had only pelvic EBRT, but increased rates of pelvic and para-aortic nodal recurrence [21].

Our case report further demonstrates the rareness of this condition and its clinical presentation, thus substantiating the 3 month delay in diagnosis of the metastases.

The resection of bone metastasis has been shown to positively affect overall survival after BM in EC, whilst the presence of extraosseous metastasis together with BM negatively affect survival [22]. Concurrent BM and muscular metastases
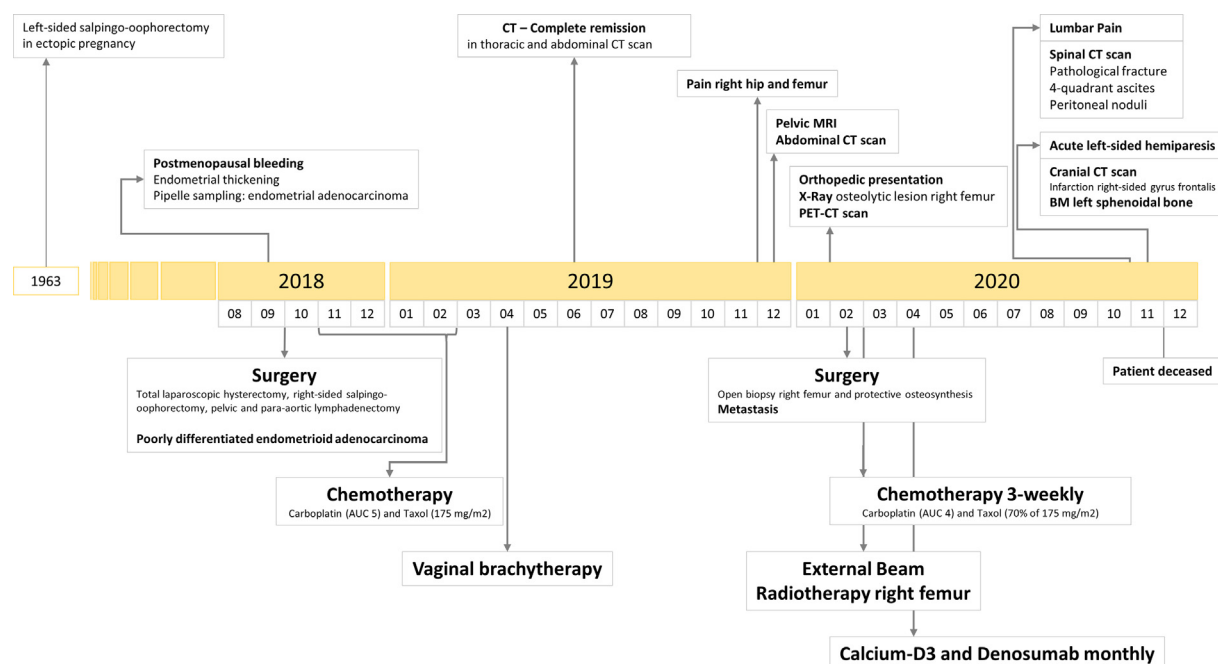
Fig. 4 – Timeline of episode of care. AUC – Area under the curve; CT – Computed tomography; MRI Magnetic resonance imaging; PET-CT – Positron emission tomography-CT; BM – Bone metastasis

in EC have been described by Oaknin et al. affecting the deltoid muscle and vertebral bones 7 years after the initial diagnosis of a low-risk EC, including a vaginal vault relapse 4 years after total abdominal hysterectomy and bilateral salpingo-oophorectomy, which was treated with adjuvant chemotherapy and pelvic EBRT. The bone and muscular metastases were initially treated with hormonal therapy (Progestin), which was eventually replaced by adjuvant chemotherapy due to disease progression and palliative EBRT to the spinal lesions due to pain. The patient died 6 months after diagnosis of the metastases [11]. Nguyen et al. reported a case of grade 1 EC, which was diagnosed with concurrent metastases to the right ischial bone and infiltration of the adjacent adductor musculature on magnetic resonance imaging. Adjuvant chemoradiotherapy was initiated and the patient survived up to 9 months after diagnosis [12]. In another case, infiltration of the right psoas muscle and bony involvement of the lumbar vertebra were reported as metastases of EC [13].

Recently, McEachron et al. reported BM in 7 cases of EC with MSI, which presented with stage III or IV disease [8]. In the general EC population, MSI occurs in about 26%-28% of cases and is associated with an intermediate prognosis and an increased risk for locoregional and distant recurrences [4,6]. However, MSI may be related to an enhanced immune-checkpoint blockade response [19,23]. To date no cases of BM and/or muscular metastasis in EC of NSMP have been reported.

Conclusion

This is a rare case of multiple BM and muscular involvement in EC. Information on molecular profiles of EC with BM is scarce.

To our knowledge, this is the first reported case of a patient with BM in EC showing NSMP, with all previously reported cases being MSI.

Funding statement

Data availability

All relevant data are reported within the manuscript.

Patient consent

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

CRediT authorship contribution statement

Martin Heidinger: Conceptualization, Writing – original draft. **Mei Koh:** Supervision, Writing – review & editing. **Mario Panzenboeck:** Visualization. **Thomas Lutz:** Supervision, Visualization, Writing – review & editing. **Kirsten D. Mertz:** Supervision, Visualization, Writing – review & editing. **Hansjoerg Huemer:** Supervision, Visualization, Writing – review & editing. **Marcus Vetter:** Supervision, Writing – review & editing.

Frey Tirri Brigitte: Conceptualization, Supervision, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.radcr.2022.03.096.

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