Bilateral femur metastases in low-grade endometrial carcinoma

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Key Clinical Message
Lower-limb bone metastases are uncommon in low-grade endometrial carcinoma, and are mostly located on the axial skeleton. Here, we present a rare case of bilateral femur metastases in low-grade endometrial carcinoma and performed a review of the current literature.

Keywords
Bone metastasis, bone scan, endometrial carcinoma, gynae-oncology, low grade.

Introduction
Endometrial carcinoma is the most common gynaecologic malignancy of postmenopausal women, usually revealed by vaginal bleeding. Most patients are diagnosed at an early stage, the disease being limited to the uterus. Overall 5-years survival rate is 80–90%. For patients with stage III and IV disease, it decreases markedly and ranges from 30% to 90% and 0% to 18%, respectively [1]. Factors which typically confer a better prognosis and outcome are surgical stage I, low-histologic grade, nonserous or nonclear cell morphology, and superficial or no invasion of the myometrium [2]. The majority of patients with early stage endometrial cancer are treated with primary surgical resection. Patients with advanced stage disease are treated with additional treatment after surgical resection because of a relatively high rate of recurrence. Most of these recurrences occur locally within the pelvis. Distant metastases may occur and are associated with more aggressive histological subtypes, including high-grade endometrioid, papillary serous or clear cell carcinoma [3]. In the largest series to date on grade 1 endometrioid endometrial cancers, the incidence of pelvic lymph node involvement, pelvic metastasis, and distant metastasis specific to grade 1 tumors is estimated at 3.3%, 4.6%, and 2.4%, respectively [4]. Endometrial carcinoma is likely to metastasize to lymph nodes, pelvic soft tissues, peritoneal surfaces, lung, and liver [5]. Bone metastasis is very uncommon with a frequency of 0–8%, and axial skeleton remains the most frequent site. Bone metastasis is presumably due to hematologic dissemination rather than the more typical route of endometrial cancer metastasis, which is by direct extension or by lymphatic spread [6, 7].

We reviewed the literature and found 32 cases of bone metastases, 18 of which involved the lower limbs [6–33]. We describe the case of synchronous metastases at both distal femurs from a low-grade endometrial carcinoma.

Case Report
A 63-year-old woman was referred to our hospital for vaginal bleeding. She was menopausd, multiparous, and took no medication. She had no contributory factors. No family history of cancer was noticed.
Hysteroscopy with biopsies was performed. Pathology revealed International Federation of Gynaecology and Obstetrics (FIGO) grade I endometrioid endometrial adenocarcinoma from all biopsy sites. Immunohistochemical staining revealed tumor cells positive for estrogen receptor and progesterone receptor and scatteredly positive for p53. Pelvic ultrasonography and Magnetic Resonance Imaging (MRI) were performed, revealing a large process tissue involving the entire uterine cavity and infiltrating more than 50% of the myometrium. The lesion was limited to the uterus. Clinical and imaging stage was Ib.

The patient underwent laparoscopic radical hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymphadenectomy. Histological evaluation revealed a 6.5 cm low-grade endometrial carcinoma (endometrioid type grade 1), infiltrating into more than 50% of the myometrium with vascular emboli. Serosa, ovaries, and cervix were normal and peritoneal cytology was negative. Pelvic lymphadenectomy revealed one left node involved amongst the eleven removed, classifying the disease as FIGO stage IIIC. Consequently, it was decided to perform postoperative pelvic external radiotherapy (45 Gray) and vaginal brachytherapy (25 Gray).

Before this treatment and due to an injury of the knee, imaging assessment of the right patella femoral dislocation with X-rays and MRI revealed a soft-tissue lesion onto the anterior aspect of the distal right femur (Fig. 1A). Surgical biopsy confirmed bone metastasis of the primary endometrial carcinoma. A bone scan was then performed and found an increased uptake on the contralateral distal femur. MRI confirmed a second bone metastasis to the left distal femur (Fig. 1B). Metastatic workup including body CT scan did not show any other lesion, routine biochemistry, and blood count were normal. Disease was thus eventually classified as FIGO stage IVB.

Orthopedic management consisted of surgical excision of the right distal femur with prosthetic reconstruction of the right knee and preventive intramedullary nailing of the left femur (Fig. 2) followed by external radiotherapy to both metastases sites and adjuvant chemotherapy (Carbo-platin/Taxol). Pelvic radiotherapy and brachytherapy were dismissed because of the presence of metastases.

The patient did not suffer any major side effects from the treatment, and complete pain relief was achieved with normal walking. At 2 years follow-up, the patient did not show any relapse, progression of the lesion to the left femur, or new metastasis.

Discussion

This report describes an unusual case of synchronous bilateral bone metastasis of a grade 1 endometrioid endometrial adenocarcinoma, which is usually associated with a good prognosis. In endometrial cancer, distant metastases are most frequently in the lungs and liver [24]. Endometrial cancer with metastasis to bone has been reported to occur in 2–6% of all metastatic endometrial cancers [25].

Endometrial carcinoma typically disseminates by direct invasion or via the lymphatic route whereas bone metastases are usually the consequence of blood stream invasion. It has also been suggested that the spread to lower limb bones occurs by venous retrograde flow of tumour emboli [7, 24]. Such an event appears to be very uncommon, as only 32 cases of endometrial adenocarcinoma metastatic to bone were previously reported.

In 10 cases, the metastasis was the presenting manifestation of cancer, while in the remaining cases the mean...
interval from initial diagnosis to bone metastasis was about 3 years (6 months to 5 years) [7, 29, 34].

Our case is the second one reporting bilateral metastases to the femurs. The first one dealt with a 48-year-old patient presenting a high-grade stage IIB endometrial adenocarcinoma treated by curative radical hysterectomy, bilateral salpingo-oophorectomy, pelvic, and para-aortic lymphadenectomy, followed by radiotherapy and chemotherapy. Bilateral femur metastases were diagnosed 22 months after surgery. She underwent surgical excision of bone metastasis and adjuvant treatment including chemotherapy, palliative radiation, and hormone therapy. Three and a half years after treatment of bone metastases, no relapse had been observed [21].

Amongst the 32 previously reported cases, most of the tumors were intermediate or high-grade endometrial carcinomas and only 11 were low grade. The characteristics of these patients are shown in Table 1.

In our case, endometrial carcinoma was initially rated as a clinical early stage, and then reclassified after pathological examination as stage IIIC. No specific bone metastatic workup was performed despite a positive pelvic lymph node, and femoral lesions were secondarily diagnosed because of knee symptoms. After the finding of the right distal femoral metastasis, bone scan was performed and demonstrated the contralateral lesion.

As suggested in previous studies, endometrial carcinomas with isolated and asymptomatic bone metastases may represent an unusual entity with better prognosis than other stage IV [15, 18]. As recently shown in a randomized clinical trial, node negative patients <65 years have 94.4% 5-year overall survival and 96.3% 5-year cancer-specific survival, while among patients with positive lymph nodes up to 74% 5-year overall and cancer-specific survival has been described [35]. Optimal control of the disease requires complete surgery with pelvic lymph node staging, which can safely be performed by laparoscopy [36, 37]. Furthermore, we recommend that bone scan be included in systematic metastatic workup of endometrial cancer, particularly when the tumor presents high risk of distant dissemination such as grades 2 and 3, locally advanced stages and in case of nodal involvement. Multimodal therapies are usually advocated for such lesions (surgery, radiotherapy, chemotherapy, and hormone therapy...) and seem to be efficient, with a long disease-free period after treatment. However, there is no consensus on the standard treatment of stage IVB endometrioid endometrial carcinoma.

In conclusion, the present case report is unusual for the following reasons: metastases were bilateral, symmetrical, synchronous, and located on the femurs; The primary tumor histological grade suggested a good prognosis and finally the diagnosis of metastases was concomitant with endometrial cancer upon clinical signs. Femoral metastasis in endometrial cancer is a rare entity but its early diagnosis allows adapted treatment.

## Conflict of Interest

Authors declare no conflicts of interest.

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