A Rare Presentation of Endometrial Cancer recurrence with Scapular metastasis: A Case Report and Review of the Literature

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Abstract
Bone metastasis from endometrial cancer is rare. Most of the early stage endometrial cancers with endometrioid histology are confined to the uterus at the time of diagnosis and confer a good prognosis. Endometrial metastases to the bone are generally restricted to the axial skeleton, including the pelvis and thoracolumbar vertebrae. Skeletal metastases in the appendicular skeleton such as scapula, clavicle and extremities to tibia, and tarsus are rarely reported. We present the case of a 50-year-old woman with diagnosis of endometrioid adenocarcinoma of the endometrium, FIGO stage IB, grade 2, with lympho-vascular space invasion who developed recurrence within 10 months with bone metastasis to left scapula and extraosseous soft tissue mass over left shoulder. There are very few cases reported in literature of scapular metastases in an early-stage endometrial carcinoma. We discuss evaluation, treatment options, overall survival rates and provide a literature review of prior published reports.

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Introduction
Endometrial cancer is among the most common gynaecologic malignancy accounting for 6% of all cancers in women globally (1). Majority of cases are diagnosed in early stage, endometrioid subtypes with favourable prognosis. The risk of recurrence is 10-15% and majority of recurrence are estimated to occur in three years from primary diagnosis (2). The most common sites of recurrence include pelvic, para-aortic lymph nodes, vagina, peritoneum, and lungs. These are considered as typical sites of recurrence in 80-90% of cases (3). However, the atypical sites of recurrence include bones, brain, intra-abdominal organs, abdominal wall, and muscle (4). The prevalence of osseous metastases in endometrial carcinoma ranges from 4 to 7% (5), whereas the muscular and soft tissue metastases is 2 to 6% (6). Due to its atypical site, we report this case of endometrioid adenocarcinoma of the endometrium with bone metastasis to scapula and extraosseous soft tissue mass. As to date, there is only one case that has been reported in the literature (7).
Case report
A 50-year-old woman para 3 presented with abnormal uterine bleeding and endometrial sampling revealed a complex endometrial hyperplasia with atypia. Computed tomography of thorax, abdomen, and pelvis (CT TAP) was suggestive of endometrial mass with no locoregional extension. Following that, she underwent total abdominal hysterectomy, bilateral salpingooophorectomy with pelvic and para-aortic lymphadenectomy. The histopathological examination showed moderately differentiated endometroid adenocarcinoma with tumour invading more than half of the myometrium, FIGO stage 1B with lymphovascular space invasion. According to ESMO-ESGO-ESTRO consensus on endometrial cancer 2016, the tumour was in the category of high intermediate-risk hence it was decided by a multidisciplinary team of gynecologic surgeons, pathologists, and oncologists to proceed with adjuvant radiotherapy. The patient received brachytherapy to the vaginal cuff with total dose of 24 Gray (Gy) (4 fractions of 6 Gy) which was completed 4 weeks following surgery. However, five months after the completion of radiotherapy, she presented with left shoulder swelling and pain and limited restricted of movements. A magnetic resonance imaging (MRI) of left shoulder revealed a 3x5x6 cm bony mass, suggestive of metastases (Figure 1).

![Figure 1. A magnetic resonance imaging (MRI) of left shoulder revealing a 3x5x6 cm bony mass, suggestive of metastases](image)

Additional computed tomography showed an ill-defined lytic lesion at the left scapula, multiple lung metastasis, enlarged left supraclavicular, left axillary and abdominal lymph nodes. Positron emission tomography (PET)/CT of the whole body demonstrated an ill-defined lytic lesion with extensive soft tissue component seen in superior aspect of the left scapula with increased FDG uptake (SUV max 15.9) and multiple liver metastasis (Figure 2).

![Figure 2. Positron emission tomography (PET)/CT of the whole body demonstrating an ill-defined lytic lesion with extensive soft tissue component seen in superior aspect of the left scapula with increased FDG uptake (SUV max 15.9) and multiple liver metastasis](image)

There were also hypermetabolic paraaortic, aortocaval lymph nodes and left supraclavicular and axillary lymph nodes. Based on the clinical, radiological, and histological examination via core biopsy, a diagnosis of recurrent endometrioid adenocarcinoma of endometrium with nodal recurrence and scapular metastasis was confirmed. She was reviewed by medical oncologist to receive palliative chemoradiation. She underwent 5 fractions of 20 Gy radiation therapy at her left shoulder and started on chemotherapy of carboplatin AUC 4 and paclitaxel 175 mg/m2 for six cycles. Upon follow-up, her neuropathic pain was much improved, and she was scheduled for a regular, 3-monthly follow-up. At 6 months, the shoulder swelling resolved, with
complete range of movement. A repeat CT revealed a complete remission of distant metastasis.

Discussion
This case report describes an atypical site of metastasis of endometrioid adenocarcinoma of endometrium. A review of literature revealed only one reported case so far of endometrial carcinoma metastatic to the scapula wherein bony metastases was the primary presentation (7). This case adds to literature of bone metastases to the scapula at early stage with endometrioid histology with moderately differentiated tumour.

The overall incidence of bony metastasis is 0–15% of all metastatic endometrial cancers (8). The most common sites of bony metastases include the axial skeleton (vertebrae and pelvis) in the presence of advanced disease and poorly differentiated tumors (9). Recurrent endometrial carcinoma with metastatic lesions are found predominantly in the lymph nodes, omentum, lungs, and liver (10). The mode of spread is either by direct invasion or via the lympho-vascular pathway (11). The mechanism of spread is thought to be related to the tumor behavior, vascular supply, immune system, and bone environment (12). Albaredo et al postulated that the venous backflow in the tumor spread that can result in greater propensity to lower extremity involvement (13). It has been identified that one of the important factors for skeletal involvement is the histological type whereby high-grade lesions have been associated with an increase in bony metastasis (14). This is further supported by recent study by Hong L et al, that serous histology is strongly associated with developing bone metastasis (15). Abdul-Karim et al. determined that bone metastasis was related to moderately or poorly differentiated EC (16). Although it is rare, there are few reports of bone metastases in well-differentiated endometrial carcinoma (17).

In our case, the patient presented with symptoms of bone pain which prompted further evaluation. Presence of soft tissue mass in the MRI of shoulder prompted further assessment with CT TAP which revealed lytic tissue of left scapula. PET/CT of whole body provides an added advantage of assisting in the differentiating between benign and malignant disease (18). It is essential to ascertain the pathological diagnosis of any bony lesions by a biopsy. A percutaneous method of biopsy via fine needle aspiration and core biopsy has been proven effective for pathological evaluation of bone lesions especially in the presence of soft tissue component as illustrated by this case (19).

Currently there are no recommendations for screening for bone metastases upon initial diagnosis of endometrial carcinoma or as post-treatment surveillance. However, targeted screening can be considered for development of bone metastasis in the presence of serous and type II endometrial cancer histology. Furthermore, PET/CT should be considered in symptomatic patients in type I histology as the diagnosis can be missed by conventional CT imaging (14). Most patients present with pain (81%) or fracture (9.5%) at the time of diagnosis of bone metastasis (20). There is no protocol or standard recommendation in the management of bone metastasis. Based on the literature, the most common treatment includes multimodality approach such as surgical excision of the lesion, site-directed radiation therapy, and chemotherapy (21). Treatment modality depends on the number of sites of metastasis, concomitant extraosseous metastasis, response to previous therapy and performance status of the patient (20). Our patient received directed radiation followed by chemotherapy. It has been postulated that the indication for systemic chemotherapy is an extrapolation from the management of recurrent endometrial carcinoma with locoregional metastasis where a combination of paclitaxel and carboplatin is the standard of practice (11). There are case reports on the benefit of zoledronic acid for bone metastasis of endometrial cancer. The evidence stemmed from other solid tumors such as prostate and breast, bisphosphonates could be considered as the treatment modality (22).

Based on the case series by Yoon et al., the median overall survival (OS) and progression free survival following bone metastasis was 33 months (range 9–57 months) and 15 months (range 12–17 months), respectively (20). It has been determined that the patients with bone metastasis at recurrence had significantly longer OS as opposed to those patients with
bone metastasis at the diagnosis of endometrial carcinoma (36 vs. 13 months; \( P = 0.042 \)) (20). This is further supported in series by Uccella et al highlighting that isolated bone metastasis with no extraosseous spread is associated with longer survival (26 vs. 6 months; \( P = 0.008 \)) (10). In our patient, bone metastasis occurred 10 months after the primary diagnosis. There is also extraosseous spread at lung and caval lymph nodes. At this point we are unable to determine the survival chances of this patient and only time will answer this question.

Molecular signature and clinical applications
With the new genomic era, there has been a call for integration of molecular features in the risk stratification of endometrial carcinomas (23). This will contribute towards better assessment of biological behavior of individual patient’s treatment decisions and outcomes (24). So far, the most comprehensive molecular study of endometrial carcinoma has emerged from the data from The Cancer Genome Atlas (TCGA) project, which has classified the endometrial cancer molecular information into four groups - POLE ultramutated, MSI hypermutated, copy-number (CN) low, and CN high which all correlates with the disease progression and overall survival rate (25,26).

Endometrial cancers with POLE mutations are observed in younger, thinner women who show favorable prognosis regardless of grade, myometrial invasion and LVS I status (27). It is observed that patients belonging to the POLE and the MSI subgroups emerged as tumors with much better survival outcomes as compared to comparison to the p53 mutant group and the NSMP group which are associated with poor prognosis and early recurrence, despite an endometrioid histology (28). It is plausible that our patient would have belonged to p53 mutant group or the NSMP group of molecular characterization that would have possibly contributed to aggressive disease progression. However, integrating molecular classification as standard care will require more prospective clinical trial determining the survival rates, quality of life and health economic implications at local context (29) Currently, several different targeted therapies are undergoing clinical evaluation. In particular, EGFR, human epidermal growth factor receptor-2 (HER2), mTOR and VEGFR inhibitors that have been tested in phase I and II trials, with modest response rates (30). The present literature provides some promising findings with PI3Kinase, mTOR and angiogenesis inhibitors (31,32). However more evidence is required in this area with studies which should be biomarkers driven.

Conclusion
Scapular metastasis in early stage of endometrial carcinoma with endometrioid histology and moderately differentiated tumor is a rare entity. Till date, only one such case is reported with advanced stage. Although bone metastasis is a rare occurrence in endometrial carcinoma especially in early stage, due attention to bone pain or joint swelling will assist in timely diagnosis and targeted treatment that will enable good palliation and prolong survival. Given the increasing incidence of endometrial cancer and the overall cost implications, there is a role of integrating molecular information on the hysterectomy specimens as value added tool for better prognostication of these tumors. Evidences are promising for targeted therapy but need validation with clinical trials essentially biomarker driven.

Declaration of interests
The authors declare no conflict of interest.

Author contributions
VK conceptualized the idea behind this manuscript. All other authors contributed equally in writing and editing it.

Consent
Written informed consent was obtained from the patient described for publication of the images and case detail.

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