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Case Report

# Patterns of spread of clear cell ovarian cancer: Case report and case series ☆

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## Case report

A 56 year old woman presented with pelvic discomfort. Ultrasound revealed a 10 cm complex right adnexal mass. The CA-125 was 134. Laparotomy revealed high grade clear cell carcinoma of the right ovary (OCCC) only, without surface involvement but with positive ascitic fluid and no extra-ovarian spread, FIGO stage IC (Fig. 1A).

Subsequent left lumbosacral pain developed, radiating to the left buttock, thigh and leg. A bone scan revealed a solitary focus of increased uptake in the intertrochanteric region of the proximal left femur (Fig. 2A), with metastasis suspected. Correlative poorly marginated osteosclerosis was subsequently identified on radiography. There was no osteolysis or fracture. These findings were confirmed on CT, with no evidence of cortical disruption. The lesion demonstrated medullary T1 hypointensity and STIR hyperintensity on MR, with no associated soft tissue mass. Maximal dimensions were 4.2 × 2.6 × 7.0 cm craniocaudal, with additional lobules of involvement extending into the metadiaphysis. These findings of infiltrative disease were consistent with metastasis, and less likely primary neoplasia. A core biopsy of the left proximal femur subsequently confirmed the presence of metastatic ovarian carcinoma of OCCC histology (Fig. 1B). This metastasis was also visualized on 18F-FDG PET/CT (Fig. 2B), which also revealed regions of increased activity in the left sacrum and right ilium.

The patient had received 3 cycles of carboplatin and paclitaxel by the time of the bone biopsy. The chemotherapy did not treat the bone involvement. Subsequent irradiation to the left hip and sacroiliac region

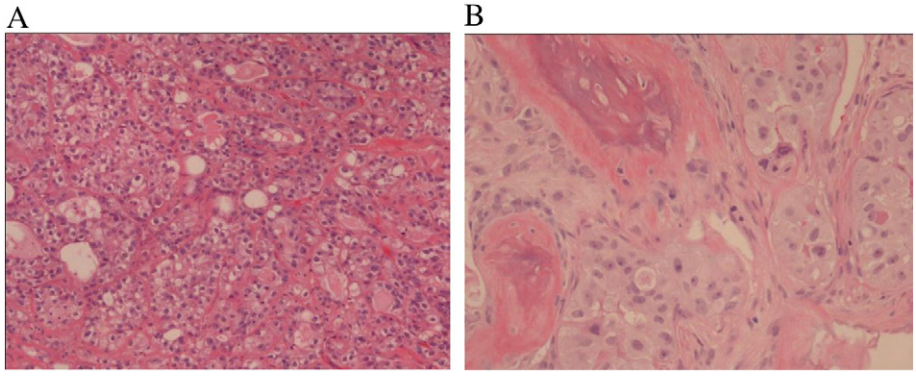


**Fig. 1.** A. The ovarian tumor, showing typical clear cell carcinoma, composed of an admixture of clear cells and cells with eosinophilic cytoplasm, with malignant cytological features. B. Bone biopsy, showing metastatic clear cell carcinoma, morphologically identical to that seen in the ovary.



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resulted in significant symptomatic benefit. The patient continued with 4 more cycles of carboplatinum and paclitaxel chemotherapy. A follow-up 18F-FDG-PET scan revealed progression with new areas of disease in the thoracic spine and right sacroiliac region. The previously irradiated area of the left femur however had "interval metabolic response to treatment with only minimal residual FDG accumulation persisting" (Fig. 2C).

## Case series

Our belief was that bone metastases are more commonly observed among OCCC than with the high grade serous histology (HGSC). To confirm this, institutional Research Ethics Board approval was obtained to review the initial metastatic pattern of all OCCC diagnosed and treated at one of the British Columbia Cancer Agency (BCCA) centers between 2000 and 2008 and to compare them to an equal number of randomly selected cases of HGSC, diagnosed during the same time period. The BCCA treats approximately 2/3 of all patients with a diagnosed malignancy in the province (population 4.5 million people). We identified 52 cases of OCCC with recurrence and matched them with 50 cases of HGSC. At diagnosis, 24 of 52 cases of OCCC had stages IA–IIC disease, and the remainder had stages IIIA–C (including residual positive disease). Thirty nine of 50 HGSC patients had FIGO stage IIIC, and 11 patients had stages IB to IIIB. Imaging was obtained on 49/50 and 50/52

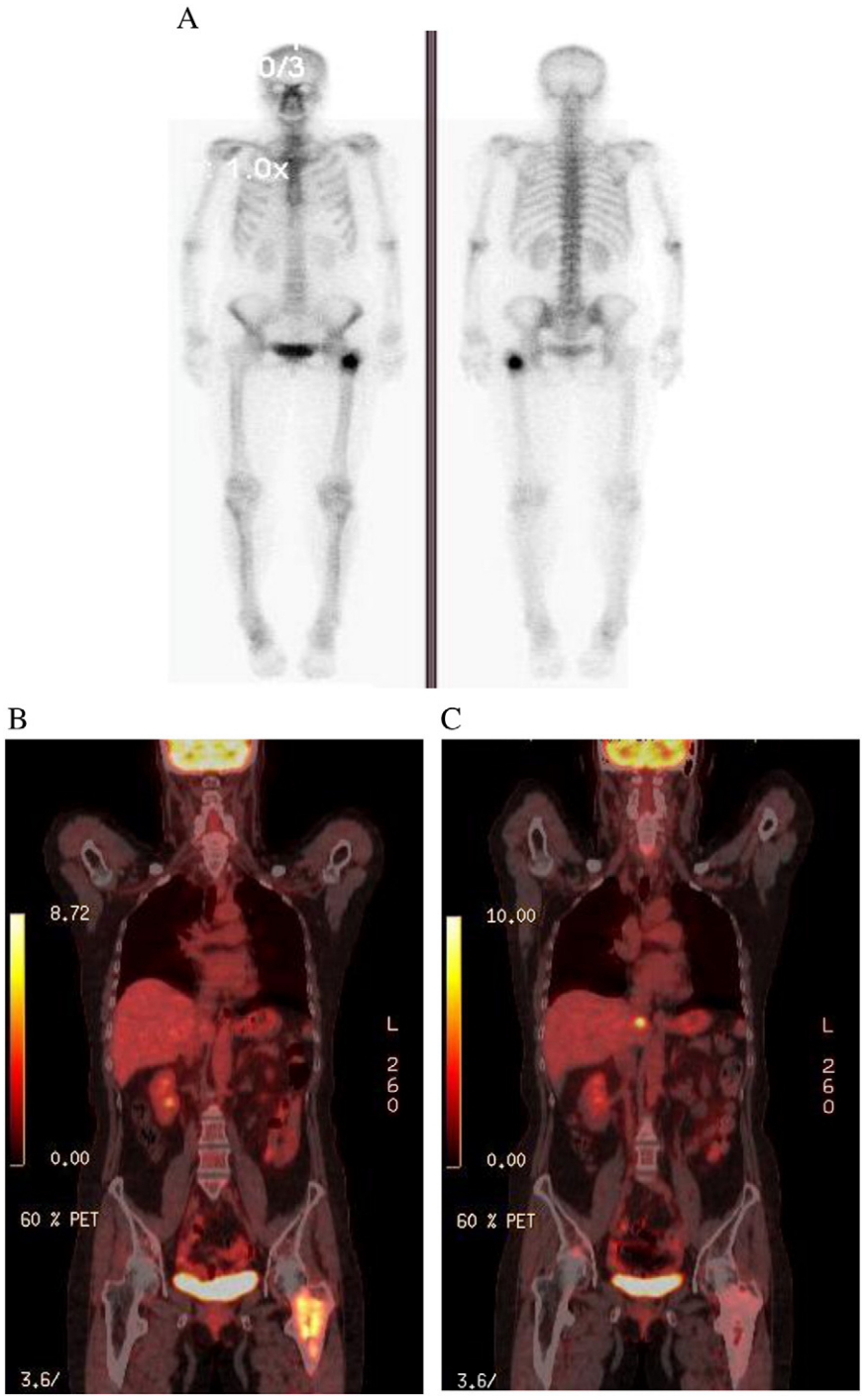


**Fig. 2.** A. Initial whole body bone scan demonstrating a single abnormality of the let proximal femur. B. Initial PET scan demonstrating cancer involvement of the left femur. C. PET scan post radiation demonstrating response.

cases of HGSC and OCCC respectively at the time of relapse and was primarily in the form of CT of the abdomen and pelvis. The median age at diagnosis was 53 years (range 24–88 years) and 64 years (range 36–84 years) for the OCCC and HGSC cases, respectively. The median time to relapse (from diagnosis to recurrence) was 12.7 months and 17.1 months for OCCC and HGCS, respectively.

Thirteen of 52 (25%) patients with recurrent OCCC had evidence of hematogenous metastases (i.e. visceral organ or bone disease). Three of these patients had distant bone metastases. Two of the patients with painful bone lesions required additional investigation with dedicated bone imaging. The third patient was found to have bone metastases incidentally at the time of relapse in other areas. Among the patients with recurrent high grade serous type, 8 of 54 (15%) had hematogenous metastatic disease, the majority to the liver (6 patients). One case of high grade serous cancer had vertebral bone involvement due to direct disease extension of a malignant retroperitoneal lymph node. No cases of brain metastases were recorded in either group (Table 1).

**Table 1**
Rate of hematogenous metastases among OCCC and HGSC of the ovary.

| Histology | Hematogenous only (% of total cases) | Bone metastases (% of total cases) | Other (% of total cases) |
|---|---|---|---|
| OCCC | 10 (25) | 3 (6) | 41 (79) |
| High grade serous | 8 (13) | 0 (0)[a] | 42 (78) |

[a] One case had vertebral bone involvement from direct extension of a metastatic lymph node.

## Discussion

The occurrence of bone metastases at any time is rare in ovarian cancers, reported in <2% of cases (Sugiyama et al., 2000), hence dedicated bone imaging is not routinely used. Our case report is interesting, as bone metastases at the time of OCCC diagnosis is rarely observed (Sugiyama et al., 2000). It was also interesting in that the classic findings of bone metastases (lytic lesions on X-ray or CT scan) were not apparent. Finally, despite apparent early stage disease, hematogenous spread had already occurred. Our patient may have been at risk for this given that cytologic positivity is known to be an adverse predictive factor for relapse (Hoskins et al., 2012).

Patterns of metastases in OCCC have not been well described. There is a single retrospective review of 44 cases of OCCC from the Brigham Hospital (spanning 1944 to 1981) in the literature. Of 25 patients who had recurrence, 40% had distant organ involvement which included bone, breast and brain (Montag et al., 1989). These were compared with a matched cohort of 55 patients with HGSC. Lymph node involvement was much more common among the patients with OCCC (40% vs. 7%) as was visceral organ involvement (40% vs. 13%). There were no cases of bone metastases among the HGSC patients compared to 16% among the clear cell cases (Jenison et al., 1989). This is in keeping with prior reports that bone metastases in HGSC are rare (Pectasides et al., 2006).

This observational case series suggests that bona fide hematogenous bone metastasis, while rare, is more likely to occur in OCCC than HGSC. Our analysis was not powered for statistical comparisons. While we did not record all sites of metastases throughout the full disease course, our initial observations are in keeping with clinical experience. Given that restaging with CT scans at the time of suspected relapse was the main imaging modality used in both the OCCC and HGSC patients, it is unlikely that a bias in detecting bone metastases exists. 2 of the 3 cases with bone metastases were investigated for pain as the presenting symptom while the other patient on staging CT was found to have a suspicious bone lesion prompting further investigations.

Our case is typical, in that the benefits of systemic therapy were minimal. However, the palliative benefit of radiation was both clinically and radiologically apparent. Advanced OCCC has a low response rate to standard cytotoxic regimens and a poorer prognosis than the HGSC counterpart (Recio et al., 1996). A series by Sugiyama et al. (2000) showed an 11.1% response rate with the use of platinum based regimens. Radiation therapy may have an under-recognized role in the management of OCCC (Nagai et al., 2007) (Swenerton et al., 2011). In a review of 158 women with advanced OCCC, 14 received radiation therapy alone for relapse. Treatment benefit was seen in 64% compared to 24% of the remainder receiving chemotherapy alone (Al-Barrak et al., 2011). The choice of chemotherapy administered did not have an impact. A beneficial impact of radiation on survival was also suggested in a large, population-based cohort of early stage patients with OCCC treated adjuvantly with chemotherapy and radiation (Hoskins et al., 2012).

Ovarian carcinomas are represented by a number of molecularly distinct diseases broadly defined by histotype, with different outcomes, patterns of relapse and response to therapy (Kobel et al., 2008). Clinicians treating patients with OCCC need to be aware of the metastatic potential of this disease and investigate symptomatic patients accordingly. Radiotherapy may be an effective treatment modality, even in the setting of otherwise chemotherapy refractory disease.

**Conflict of interest**
All authors declare no conflict of interest.

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