Bone marrow metastasis of ovarian cancer: A two-center retrospective study and literature review

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Abstract. Bone marrow metastasis (BMM) causes pancytopenia and disseminated intravascular coagulation (DIC), resulting in rapid mortality. The incidence of this disease is likely underestimated, with confirmed BMM occurring at approximately twice the rates expected clinically. The present study describes two detailed cases and includes a literature review of BMM caused by ovarian cancer. The existing medical records of patients admitted to Oita University Hospital (Yufu, Japan) and Saitama Medical University International Medical Center (Hidaka, Japan) were retrospectively analyzed and a literature review regarding BMM associated with ovarian cancer was conducted. The literature review of BMM of ovarian cancer, including the present cases, revealed that patient ages ranged between 37 and 71 years, with tumor histology described in 5 out of 8 cases. Notably, 3 previous cases involved rare histological types (small cell carcinoma, carcinosarcoma and mucinous carcinoid), whereas the present identified cases involved common types. The first case involved a patient who developed isolated BMM/carcinomatosis during maintenance therapy with olaparib for recurrent high-grade ovarian serous carcinoma. The patient initially presented with elevated cancer antigen 125 levels and decreased blood counts. Following the onset of BMM, the patient's lactate dehydrogenase level was elevated to 2,712 U/l. The second patient was diagnosed with BMM/carcinomatosis, concurrent with an initial diagnosis of ovarian clear cell carcinoma. Both patients subsequently developed pancytopenia and DIC, resulting in mortality. To the best of our knowledge, the present study is the first retrospective study of BMM of ovarian cancer. For early diagnosis, BMM should be considered in the differential diagnosis when a reduction in blood counts is accompanied by an elevation in serum tumor markers, regardless of histological type.

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Abbreviations: BMM, bone marrow metastasis; DIC, disseminated intravascular coagulation; PARP, poly (adenosine diphosphate-ribose) polymerase; MRI, magnetic resonance imaging; CT, computed tomography; CA125, serum cancer antigen 125; AUC, area under the curve; CTCAE, Common Terminology Criteria for Adverse Events; CRP, C-reactive protein; WBC, white blood cell; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; PET, positron emission tomography; CEA, carcinoembryonic antigen

Key words: bone marrow carcinomatosis, BMM, ovarian cancer, serous carcinoma, clear cell carcinoma, isolated metastasis

Introduction

Ovarian cancer can metastasize to the peritoneum, omentum, lymph nodes, liver, lungs, and bones (1). However, reports on bone marrow metastasis (BMM) in ovarian cancer are rare (2-5). Most cancers that metastasize hematogenously are thought to have the potential to metastasize to the bone marrow; however, the frequency is low at approximately 1% (2,6,7). When cancers metastasize to the bone marrow, they rapidly progress to bone marrow carcinomatosis, a life-threatening condition characterized by disseminated intravascular coagulation (DIC) and microangiopathic hemolytic anemia. Although BMM generally has a poor prognosis, one prior study (8) revealed that appropriate supportive care and aggressive anti-tumor therapy tailored to the patient's condition might improve the prognosis. As such, early diagnosis is key in BMM. BMM is frequently detected late because clinicians have a poor understanding of the condition owing to its rarity, nonspecific symptoms, and blood test abnormalities, which can easily be mistaken for bone marrow suppression caused by chemotherapy. Herein, we present a two-center retrospective study and literature review of BMM caused by ovarian cancer.

Materials and methods

Retrospective analysis. We retrospectively analyzed the existing medical records of patients admitted to Oita University Hospital and Saitama Medical University International Medical Center between April 2014 and March 2023. We searched the medical records for cases that met both the criteria of 'ovarian cancer' and 'bone marrow metastasis.' One case was identified from each institution. The Institutional Review Board of the Ethics Committee of each institution approved this study (approval Code: 2586 and 16-257, approval Date: August 4, 2023 and September 5, 2018 respectively). Data were extracted from obstetric and gynecological records of patients diagnosed with BMM of ovarian cancer. This study adhered to the guidelines of the Declaration of Helsinki and was performed in conjunction with the prevailing ethical regulations. All patients provided written informed consent for publication. Patient information, including the age at diagnosis, chief complaint, history of pregnancy and delivery, past medical history, family history, clinical courses, treatment methods, blood tests, clinical imaging, pathological findings, and outcome, was collected.

Literature review. The PubMed® database was searched from inception until June 2024. The keywords used were 'ovarian cancer,' 'ovarian carcinoma,' 'bone marrow metastasis,' 'bone marrow carcinomatosis,' and 'disseminated carcinomatosis of bone marrow.' Junya Nakajima and Mitsutake Yano screened titles, abstracts, and full-text articles. Articles/case reports discussing BMM of ovarian cancer were included. The article also needed to be available in English, and either be open-access or available through the library of Oita University or Saitama Medical University International Medical Center. Articles with incomplete data, articles for which original data could not be obtained, conference abstracts, or animal/*in vitro* studies were excluded. Patient information, including the number of cases, age at diagnosis, chief complaint, clinical courses, treatment methods, blood tests, clinical imaging, pathological findings, and outcome, was collected.

Results

Patient characteristics. We identified two and six cases of BMM of ovarian cancer in our institutions and the literature review, respectively. Table I summarizes these cases (2-5). Eight cases have been reported; however, detailed pieces of information, such as blood tests, imaging tests, symptoms, and clinical courses, were only described in the present two cases. The patients' ages ranged from 37 to 71 years (median 51 years), while tumor histology was described in five of the eight cases. Notably, all three previous cases involved rare histological types (small cell carcinoma, carcinosarcoma, and mucinous carcinoid) of ovarian cancer, and only the present two cases involved the common histological types (high-grade serous carcinoma and clear cell carcinoma). Two of the three available cases had a history of chemotherapy; however, only case 1 received platinum-based chemotherapy and maintenance chemotherapy with poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors, which are the standard treatments for epithelial ovarian cancer. Detailed information regarding two cases in our institutes is provided below.

Case 1. A 64-year-old woman visited Oita University Hospital for evaluation of a pelvic mass. A summary of the patient's clinical course is illustrated in Fig. 1. The patient experienced frequent urination and constipation. Contrast-enhanced magnetic resonance imaging (MRI) and computed tomography (CT) revealed an 80 mm-sized pelvic tumor with peritoneal dissemination, enlarged pelvic lymph nodes, and ascites (Fig. 2A). The serum cancer antigen 125 (CA125) level was elevated (7,198 U/ml). Tumor biopsy revealed a high-grade serous carcinoma. The patient was diagnosed with stage IIIC ovarian cancer (cT3cN1M0). Debulking surgery (including hysterectomy and bilateral salpingo-oophorectomy), with each of three courses of neoadjuvant and adjuvant chemotherapy (paclitaxel: 80 mg/m^2 [weekly]; carboplatin: area under the blood concentration-time curve [AUC], 6 [tri-weekly]), was performed. All tumors were resected. Postoperative histological examination revealed stage IIIC ovarian cancer (ypT3cN1M0) (Fig. 2B). An isolated splenic metastasis was detected 43 months after the final round of chemotherapy. The patient subsequently underwent abdominal splenectomy and six courses of adjuvant chemotherapy (paclitaxel: 180 mg/m^2; carboplatin: AUC 6, tri-weekly). A complete response was obtained, and olaparib was initiated. Precisely 19 months after initiation, olaparib was withdrawn because of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 anemia. After 1 month, CTCAE grade 3 anemia and thrombocytopenia were diagnosed, and a blood transfusion was performed. This point was retrospectively considered to be the onset of BMM based on persistent cytopenia despite olaparib withdrawal and elevated CA125 levels. Exactly 1 month later, severe anemia and thrombocytopenia continued, and she had a fever of 38.7˚C. Her blood tests revealed the following levels: C-reactive protein (CRP), 11.11 mg/dl; white blood cell (WBC), 3.72x10^3 cells/μl; hemoglobin, 6.1 g/dl; platelet, 1.7x10^3 cells/μl; aspartate aminotransferase (AST), 74.6 U/l; lactate dehydrogenase (LDH), 2,712 U/l; and alkaline phosphatase (ALP), 81 U/l. The CA125 level was elevated to 117 U/ml. Contrast-enhanced CT revealed no obvious recurrence or focus of infection. Bone marrow biopsy revealed BMM/carcinomatosis of ovarian cancer (Fig. 2C). Immunohistochemically, the BMM tumor cells were positive for p53 and negative for AE1/AE3. The patient died owing to BMM of ovarian cancer and DIC 4 weeks following BMM onset and 1 week after admission/serum LDH elevation.

Case 2. A 51-year-old woman was admitted to Saitama Medical University International Medical Center owing to abdominal bloating, severe anemia, and elevated CA125 levels. Contrast-enhanced MRI and CT revealed bilateral ovarian tumors (Fig. 2D) and multiple bone masses (Fig. 2E). No peritoneal dissemination or lymph node metastasis were observed. Her blood tests revealed the following levels: CRP, 15.28 mg/dl; WBC, 12.11x10^3 cells/μl; hemoglobin, 3.3 g/dl; platelet, 426x10^3 cells/μl; AST, 22 U/l; LDH, 339 U/l; and ALP, 526 U/l. The CA125 level was elevated to 3,306 U/ml. The patient underwent abdominal total hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Intraoperative

Table I. Review of the present and previously published cases involving bone marrow metastases of ovarian cancer.

First author/s, year	Histological type	Patients, n	Age[a], years	Other lesions[a]	LDH[a], IU/l	ALP[a], U/l	Previous chemotherapy	Maintenance chemotherapy	Hematological abnormalities[a]	(Refs.)
Present case 1	High-grade serous carcinoma	1	71	None	2,712	81	TC, 12 courses	Olaparib for 18 months	Pancytopenia, DIC	-
Present case 2	Clear cell carcinoma	1	51	Only bones	712	526	No	No	Pancytopenia, DIC	-
Xiao *et al*, 2009	NA	3	NA	NA	NA	NA	NA	NA	NA	(2)
Saikia *et al*, 2005	Small cell carcinoma, hypercalcemic type	1	NA	NA	NA	NA	NA	NA	Hypercalcemia	(3)
Sreenan and Hart, 1995	Carcinosarcoma	1	NA	NA	NA	NA	NA	NA	NA	(4)
Alenghat *et al*, 1986	Mucinous carcinoid	1	37	NA	NA	NA	Cyclophosphamide, doxorubicin and 5-fluorouracil	NA	NA	(5)

[a]At diagnosis of bone marrow metastasis. ALP, alkaline phosphatase; DIC, disseminated intravascular coagulation; LDH, lactate dehydrogenase; TC, combination of paclitaxel and carboplatin; NA, not available.

Figure 1. Summary of the clinical course of case 1, including the (A) course of treatments, (B) blood cell counts, and (C) serum CA125 and LDH levels. CA125, cancer antigen 125; CR, complete response; Hb, hemoglobin; LDH, lactate dehydrogenase; PD, progressive disease; Plt, platelets; RECIST, Response Evaluation Criteria in Solid Tumors; SDS, secondary debulking surgery; TC, combination of paclitaxel and carboplatin; WBC, white blood cell.

findings revealed no peritoneal dissemination or ascites. Her peritoneal cytology results were negative for malignancy. On postoperative day 5, the patient experienced hemorrhagic shock caused by bleeding from the internal iliac artery, for which hemostasis was achieved using interventional radiology. Pathologically, the right and left ovarian tumors were clear cell carcinoma (Fig. 2F) and endometriotic cysts, respectively. On postoperative day 21, bone marrow biopsy revealed carcinomatous necrosis with immunohistochemical AE1/AE3 positivity (Fig. 2G and H). Subsequent positron emission tomography (PET)-CT confirmed the presence of multiple bone metastases without other metastases. The patient was diagnosed with stage IVB ovarian cancer (pT1aN0M1b, clear cell carcinoma) and BMM/carcinomatosis. She did not receive systemic chemotherapy because of her poor general health. She died of BMM and DIC 50 days postoperatively.

Discussion

This is the first retrospective study of BMM of ovarian cancer. To date, only eight cases of BMM of ovarian cancer have been reported. However, we believe that the frequency of BMM

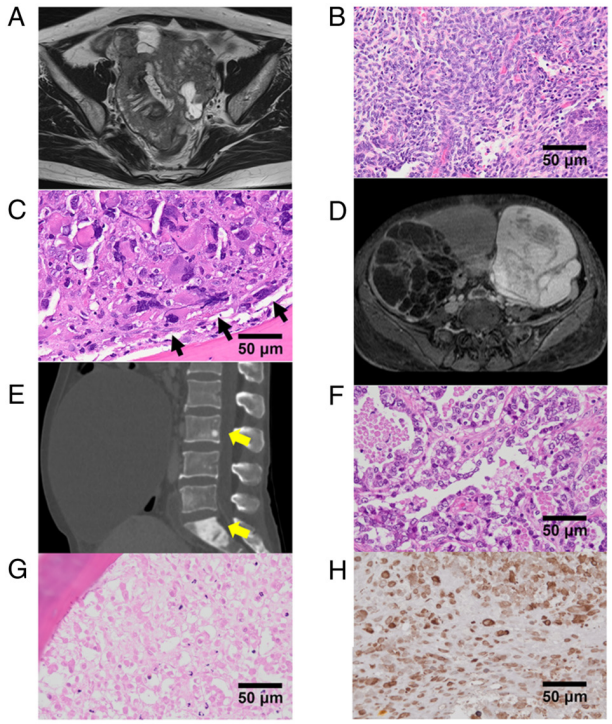

Figure 2. Clinical and pathological images of (A-C) case 1 and (D-H) case 2. (A) MRI of case 1 revealed that an ovarian tumor was occupying the pelvic cavity. (B) H&E staining (scale bar, 50 μm). The tumor exhibited papillary and solid growth of atypical glandular cells. (C) H&E staining (scale bar, 50 μm). The bone marrow tumor comprised a solid growth of pleomorphic atypical cells (arrows). (D) MRI of case 2 revealed a bilateral tumor. (E) Computed tomography revealed multiple bone mass (yellow arrows) in the spine, suggestive of metastasis. (F) H&E staining (scale bar, 50 μm). The tumor exhibited atypical tubular and papillary growth with a hobnail-like pattern. (G) H&E staining (scale bar, 50 μm). The necrotic epithelial cells were in the bone marrow. (H) AE1/AE3 staining (scale bar, 50 μm). The necrotic cell showed immunohistochemical positivity for AE1/AE3. MRI, magnetic resonance imaging.

of ovarian cancer has been underestimated. BMM has been observed in autopsies of 6-79% of patients with breast cancer; however, only 27% of cases were clinically diagnosed prior to autopsy (9). BMM is frequently accompanied by bone metastases (10). In stage IV ovarian cancer, bone metastasis accounts for 5% of cases and is the fourth most common site for distant metastasis (1). Among BMM cases, ovarian cancer accounts for 6% of cases and is the fifth most common cancer. As BMM of ovarian cancer is less rare than previously thought, clinicians should be aware of its characteristics and diagnostic markers. Additionally, BMM can occur not only in special cases, but also in common histological types treated with standard chemotherapy. To date, BMM of ovarian cancer has only been reported in cases involving rare histological subtypes, such as small cell carcinoma (hypercalcemic type), carcinosarcoma, and mucinous carcinoids, with frequencies of <1% (11), 2% (12), and <1% (13), respectively. The present study provided detailed clinical information regarding BMM of high-grade serous carcinoma (approximately 70%) (14), the most common histological type of ovarian cancer, and clear cell carcinoma (10-27%) (14,15), the second or third most common histological type, especially in East Asia. Furthermore, Case 1 is the first reported case of BMM occurring during standard chemotherapy for epithelial ovarian cancer (platinum-based chemotherapy and maintenance PARP inhibitor).

The difficulty in diagnosing BMM stems from a lack of established diagnostic markers. ALP and LDH are both considered useful diagnostic markers for BMM (8); however, these markers may not aid in early diagnosis. Al-Ibraheem *et al* (16) previously reported a case of laryngeal cancer with oligo-BMM without elevated ALP levels. In cases of isolated, few, or early BMM, these markers are not elevated, and may therefore not serve as diagnostic markers. In contrast, Chan *et al* (17) reported that serum carcinoembryonic antigen (CEA) is a potentially useful diagnostic marker of BMM in colorectal cancer. Wang *et al* (18) also showed that the serum CEA levels were more frequently elevated than the ALP or LDH levels in BMM of lung adenocarcinoma. In another study, the serum prostate-specific antigen level was correlated with the presence of micro-BMM in prostate cancer (19). In Case 1, elevated CA125 levels and decreased blood counts were detected earlier than LDH and ALP levels. These results indicate that a combination of serum tumor markers and blood counts could be useful in the early detection of BMM. PET-CT is useful for evaluating bone metastasis as a predictor of BMM (8); however, bone marrow biopsy should be considered because of isolated BMM without other lesions, including bone lesions, as seen in Case 1 and the study by Chan *et al* (17). Bone marrow biopsy is also useful for ruling out secondary leukemias. Additionally, poorly differentiated cancers have a higher occurrence of BMM and poorer prognosis than well-differentiated gastric (20,21) and breast cancers (22,23). In the present case 1, BMM after long-term chemotherapy became morphologically and immunohistochemically (AE1/AE3 became negative) poorly differentiated. Notably, some preclinical studies have demonstrated that long-term chemotherapy induces cancer stemness and tumor-promoting cytokines/chemokines (24,25). Clinicians should consider BMM during or after long-term chemotherapy.

BMM rapidly leads to death owing to severe blood cell depletion and DIC. Niu *et al* (26) and Hung *et al* (27) reported that vigorous anti-tumor therapy, including systemic chemotherapy and hormone therapy, led to longer survival in patients with BMM. The cornerstone of DIC management is specific and vigorous treatment of the underlying conditions (28). Systemic therapy, such as chemotherapy, requires a stable general condition and adequate bone marrow function. Early detection of BMM and treatment of the primary cancer can prevent severe thrombocytopenia and DIC (16). Blood transfusion, granulocyte colony-stimulating factor, erythropoietin, and thrombopoietin are also effective for BMM as supportive therapies in addition to anti-tumor medications (8). A combination of vigorous anti-tumor therapy and adequate supportive care is the key to the treatment of BMM. However, this study was limited by its small sample size, and further evidence is required before generalizing the management of BMM of ovarian cancer.

In conclusion, the frequency of BMM due to ovarian cancer may be underestimated. BMM progresses rapidly, leading to DIC and resulting in death; as such, early diagnosis is crucial. When decreasing blood counts are accompanied by elevated tumor marker levels, BMM should be considered in the differential diagnosis, regardless of the histological type.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TY, JN, YO and MiY conceived the study. TY, JN, YO, AY, YY, MasakY, MasanY, MiY and EK contributed to conception, design and acquisition of data. TY, JN, YO, AY, YY, MasakY, MasanY and MiY curated data. TY, JN, YO, MiY and EK analyzed and interpreted data. MiY acquired funding. TY, JN, YO, AY, YY, MasakY, MiY and EK contributed to the clinical management of the patients. MiY and EK supervised the study. JN, AY, MasakY, MasanY and MiY were involved in validation. TY, JN, YO, AY, YY, MasanY and MiY were involved in visualization. TY, JN and MiY wrote the original draft. MiY and EK reviewed and edited the manuscript. MiY and TY confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of the Ethics Committee of the Oita University and Saitama Medical University International Medical Centre (IRB nos. 2585 and 16-257; Hidaka, Japan), and was performed in accordance with the guidelines of the Helsinki Declaration of 1975, as revised in 1983. All study participants provided written informed consent to participate (or a formal waiver of consent).

Patient consent for publication

All study participants provided informed consent to publish medical records and images.

Competing interests

The authors declare that they have no competing interests.

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