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Case report

A case of pure-type ovarian squamous cell carcinoma producing granulocyte-colony stimulating factor

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1. Introduction

Squamous cell carcinoma of the ovary (OSCC) most commonly arises from the malignant transformation of a mature cystic teratoma. OSCC has also been reported to occur from a Brenner tumor, endometrioid adenocarcinoma, endometriosis, and a metastatic tumor (Jeffrey et al., 2011). However, pure-type ovarian squamous cell carcinoma (POSCC) not accompanied by a pre-existing ovarian lesion is extremely rare and has been reported to have a poor prognosis (Todo et al., 2005).

Granulocyte-colony stimulating factor (G-CSF)-producing tumors have been identified among malignant tumors at various sites, and 6 cases of G-CSF-producing tumors arising from the ovary have been reported to date (PubMed.https://www.ncbi.nlm.nih.gov/pubmed).

We herein present a case of G-CSF-producing POSCC. To the best of our knowledge, this is the first report of G-CSF-producing POSCC in the English literature.

2. Case report

A 39-year-old woman, gravida 5, para 2, visited our department with left lower abdominal pain. Her body temperature was higher than 38 °C. A pelvic examination and transvaginal ultrasonography revealed a 5-cm left adnexal mass containing a solid component with abundant blood flow. Magnetic resonance imaging (MRI) showed that the solid component with gadolinium enhancement presented high signal intensity in a diffusion-weighted image (DWI) and decreased intensity in the apparent diffusion coefficient (ADC) map (Fig. 1). These results strongly suggested that the tumor was malignant. The adhesion or invasion of the tumor to the sigmoid colon was also suspected. Furthermore, the signal intensity of bone marrow in T1- and T2-WI on MRI was markedly lower than that of an age-matched healthy woman. Contrast-enhanced CT showed swollen para-aortic lymph nodes, suggesting metastasis (Supplementary Fig. 1), whereas there was no evidence of other distant metastasis. Cervical cytology was negative, and upper gastrointestinal endoscopy and colonoscopy did not detect any tumors. Laboratory data (Table 1) indicated elevations in the white blood cell count (WBC) and C-reaction protein (CRP); however, there was no evidence of bacterial infection. ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) showed the elevated uptake of FDG in the left ovarian tumor and para-aortic and pelvic lymph nodes. In addition, increased uptake in systemic bone marrow, which indicated elevated bone marrow activity, was noted (Fig. 2). A serum sample showed elevations in G-CSF and IL-6 concentrations (Table 1). Therefore, our preoperative diagnosis was stage IIIA1, G-CSF-producing left ovarian carcinoma.

In laparotomy, there was no visible peritoneal dissemination, and peritoneal washing cytology was negative. The left ovarian tumor was 6 cm in diameter and strongly adhered to the uterus and sigmoid colon. Hysterectomy, bilateral salpingo-oophorectomy, partial sigmoidectomy, pelvic and para-aortic lymphadenectomy, and omentectomy were performed to achieve complete resection.

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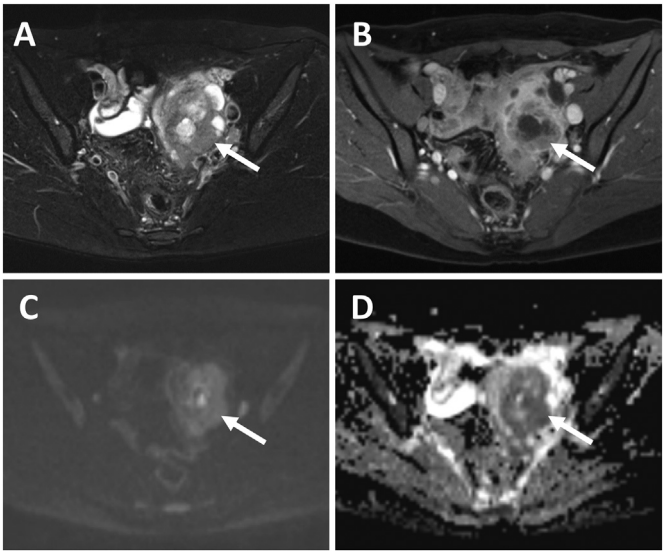

Fig. 1. Axial sections of pelvic MRI. A and B: T2-weighted image (WI) with Fat-saturation (Fat-Sat) (A) and gadolinium-enhanced T1-WI with Fat-Sat (B). A tumor that was 6 cm in diameter (white arrow) with solid and cystic components was detected on the left side of the pelvic cavity. No fat signal was indicated in this tumor. C and D: A diffusion-weighted image (DWI) (C) and apparent diffusion coefficient (ADC) map (D). The tumor (white arrow) showed reduced diffusion (high intensity of DWI) and low ADC, suggesting malignancy.

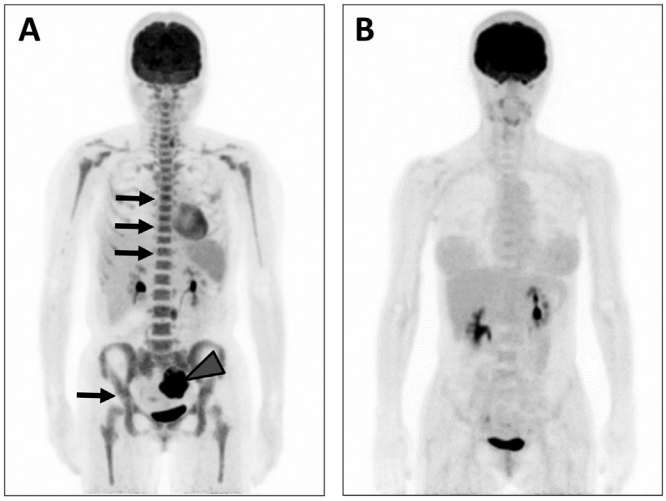

Fig. 2. Result of ^{18}F-FDG-PET/CT. A: The present case. B: An age-matched healthy female. The present case showed the strong accumulation of FDG in the left ovarian tumor (the gray arrowhead) and systemic bone marrow (black arrows).

Macroscopically, the left ovarian tumor was solid and invaded the uterus and sigmoid colon (Supplementary Fig. 2). Microscopically, the tumor was moderately differentiated squamous cell carcinoma (SCC) with marked neutrophilic infiltration (Fig. 3A, B). Other tumor components, such as a teratoma, Brenner tumor, endometrioid carcinoma, were not detected. A small lesion of endometriosis was detected at the uterine serosa near the OSCC lesions; however, the continuity of these lesions was not demonstrated. Hence, we judged that this tumor did not arise from endometriosis, and the diagnosis was POSCC. Furthermore, immunostaining revealed that tumor cells produced G-CSF (Fig. 3C). The tumor invaded the uterine myometrium and sigmoid colon, but not the right ovary, endometrium, uterine cervix, omentum, or lymph nodes. The postoperative diagnosis was G-CSF-producing POSCC, stage IIB.

WBC, CRP, G-CSF, and IL-6 decreased to within normal ranges approximately 1 to 2 weeks after surgery (Supplementary Table 1). The patient was successfully treated with six courses of adjuvant chemotherapy consisting of tri-weekly paclitaxel (175 mg/m^2) and carboplatin (AUC = 6) without G-CSF support. She has had no evidence of recurrence for 2 years after surgery.

3. Discussion

OSCC accounts for 0.5% of all ovarian carcinomas (Jeffrey et al., 2011). Among OSCC, POSCC is extremely rare, with only 30 cases being reported to date (Park and Bae, 2015). This case was examined pathologically in detail using 18 tissue sections excised from the ovarian tumor, which was 6 cm in size, and diagnosed as POSCC. POSCC cases have been reported to have a poorer prognosis than general epithelial ovarian carcinoma cases (Ohtani et al., 2000). Systemic combination chemotherapy with etoposide/cisplatin or paclitaxel/cisplatin and radiation therapy have been reported as adjuvant therapy for OSCC (Todo et al., 2005); however, the effectiveness of these adjuvant therapies has not yet been established. Therefore, this patient received adjuvant chemotherapy for general epithelial ovarian cancer with 6 courses of paclitaxel/carboplatin.

Although blood disorders were not present, this patient presented with enhanced inflammatory reactions, such as leukocytosis, fever, and elevated CRP. The diagnostic criteria of G-CSF-producing tumors are as

Table 1
Blood examination results before surgery.

Hematological test		Normal range	**Tumor markers**		Normal range
WBC	**21,260**	3040–8720/μL	**CA19–9**	**76.8**	< 37.0 U/mL
(SEG)	**80**	28.0–68.0%	**CA125**	**36.2**	< 35.0 U/mL
(BND)	1	< 10.0%	CEA	0.8	< 3.4 ng/mL
(MON)	5	< 10.0%	AFP	0.7	< 10.0 ng/mL
(EOS)	3	< 10.0%	**SCC**	**3.0**	0.1–1.5 ng/mL
(BAS)	0	< 2.0%	**LDH**	**254**	120–230 IU/L
(LYM)	9	17.0–57.0%	NSE	12.9	< 16.3 ng/mL
(ALY)	1	< 1.0%	HCG	< 0.5	< 5.0 IU/L
(PLM)	0	0.0%	E2	50.16	28.8–196.8 pg/mL
(MM)	1	< 1.0%	testosterone	0.22	0.15–0.44 ng/mL
(MY)	0	0.0%			
(PM)	0	0.0%	**Inflammatory markers and cytokines**		
(BLT)	0	0.0%			Normal range
RBC	3.84 × 10^6	2.92–3.73 × 10^6/μL	**CRP**	**11.07**	< 0.10 mg/dL
Hb	10.4	10.7–15.3 g/dL	Procalcitonin	0.06	< 0.50 ng/mL
HCT	32.5	33.6–45.1%	**G-CSF**	**420**	< 39 pg/mL
PLT	42.7 × 10^4	13.7–37.8 × 10^4/μL	**IL-6**	**22.3**	< 4 pg/mL

Bold and underline indicate the inspection items with abnormally high value.

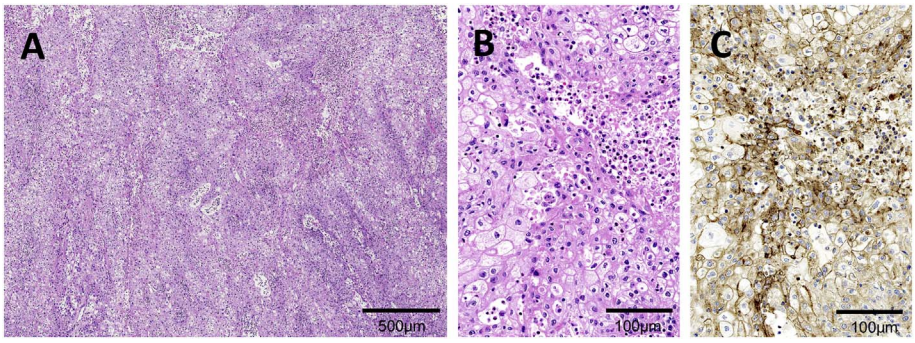

Fig. 3. Microscopic findings of the left ovarian tumor. A and B: Hematoxylin and Eosin staining (H & E) confirmed that the histological type was squamous cell carcinoma (SCC). C: Immunostaining for G-CSF revealed the production of G-CSF in this tumor.

follows (Futagami et al., 2010): 1) leukocytosis, 2) elevated G-CSF, 3) a rapid return to a normal leukocyte count following extirpation of the tumor, and 4) evidence of G-CSF production in the tumor. Since all 4 criteria were confirmed, the present case was diagnosed with a typical G-CSF-producing tumor. G-CSF-producing tumor cells frequently co-produce other cytokines such as IL-6, which causes a high fever and elevated CRP (Yoshimoto et al., 2005). The present case had an altered serum IL-6 level in parallel with G-CSF. Since no improvement was observed in fever or elevated CRP following the use of broad-spectrum antibiotics for 7 days, we considered this fever to be tumor-associated fever by tumor-produced IL-6. To date, six cases of G-CSF-producing ovarian cancer have been reported in the English literature, including clear cell carcinoma, undifferentiated carcinoma, and a mature cystic teratoma with malignant transformation (Futagami et al., 2010; Ichigo et al., 2013; Sudo et al., 1996). To the best of our knowledge, this is the first case of G-CSF-producing POSCC.

In MRI, T1- and T2-WI of the present case both showed lower signals in bone marrow than that of a healthy woman of the same age (Supplementary Fig. 3), suggesting a smaller amount of fatty marrow (Vogler and Murphy, 1988). In addition, the present case showed the elevated uptake of FDG into systemic bone marrow in ^{18}F-FDG-PET/CT. In the G-CSF-producing tumor, the strong accumulation of FDG was reported in systemic bone marrow, but not in the spleen (Morooka et al., 2008). These characteristic findings of MRI and ^{18}F-FDG-PET/CT suggested increased bone marrow activity and may be useful in the diagnosis of G-CSF-producing tumors.

G-CSF-producing tumors have been associated with a poor prognosis (Futagami et al., 2010). Regarding the underlying mechanisms, several studies reported that 1) G-CSF enhances the proliferation of carcinoma cells (Futagami et al., 2010), 2) G-CSF stimulates angiogenesis and promotes tumor growth (Natori et al., 2002), 3) the production of G-CSF by squamous cell carcinoma cell lines is closely associated with their *in vitro* invasiveness (Tsuruta et al., 1998), and 4) tumor-derived G-CSF induces an increase in the number of myeloid-derived suppressor cells (MDSC), which are involved in tumor growth and chemoresistance (Kawano et al., 2015).

Myelosuppression by anti-cancer drugs may be severe in patients with G-CSF-producing tumors because most hematopoietic cells are in the proliferating cell cycle stimulated by high serum G-CSF concentrations (Baer et al., 1996). However, chemotherapy-induced myelosuppression was not severe in the present case. This may be explained by chemotherapy being initiated after WBC and serum G-CSF decreased following complete resection of the G-CSF-producing tumor.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2017.11.001.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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