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Primary Ovarian Carcinosarcoma: Cytological, Pathological, Immunocytochemical, and Immunohistochemical Features

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Abstract

Ovarian carcinosarcoma composed of high-grade carcinoma and sarcoma is an extremely rare neoplasm and typically occurs in postmenopausal women aged over 60 years. A 73-year-old female, gravida three para three, presented to our hospital with right lower abdominal pain. Right pelvic solid tumor with ascites was detected on pelvic ultrasound examination. She underwent hysterectomy, bilateral salpingo-oophorectomy and partial omentectomy, but the tumor had invaded to the right ureter, and some fragile tumor could not be taken (sub-optimal surgery). On the imprint and ascitic cytology specimens during operation, atypical cells suggestive of adenocarcinoma and spindle atypical cells with immunocytochemically vimentin positive were found. The resected tumor was histopathologically carcinosarcoma consisted of serous adenocarcinoma, chondrosarcoma and fibrosarcoma. Immunohistochemical analysis revealed that adenocarcinoma cells were positive for AE1/AE3 and fibrosarcoma cells stained with vimentin. The final diagnosis was the right ovarian carcinosarcoma (stage pT3CNxMx). Microsatellite instability was stable and BRCA1/2 mutations could not be found in the carcinosarcoma cells. The patient was given four cycles of chemotherapy with paclitaxel, carboplatin and bevacizumab regimen, and thereafter she was treated with the ifosfamide and cisplatin because of slight elevation of serum CA125.

Keywords

Ovary, Carcinosarcoma, Immunocytochemistry, Immunohistochemistry, Ifosfamide, Cisplatin

1. Introduction

Ovarian carcinosarcoma (OCS) is an extremely rare type of gynecological malignancy accounting for 0.5% of all ovarian malignancies [1]. Histopathologically OCS is a mixed neoplasm composed of carcinomatous and sarcomatous components. The carcinomatous component often consists of serous or endometrioid carcinoma, meanwhile sarcomatous components include homologous stromal sarcoma, fibrosarcoma and leiomyosarcoma or heterologous rhabdomyosarcoma and chondrosarcoma etc. [2] [3].

OCS progresses rapidly, thus is typically diagnosed at an advanced stage. The prognosis is dismal and most patients relapse within one year after completion of initial treatment. Various prognostic factors of this malignancy have been reported. They include sarcomatous element more than 25%, expression of VEGF, mutation of *p53* [4] [5], Ki-67 overexpression [5], age under 65-year-old, disease stage, tumor grade [6] and residual tumor after surgery.

We herein report a case of OCS developed in the right ovary of an old Japanese woman. The OCS consisted of homologous fibrosarcoma, heterologous chondrosarcoma, and serous adenocarcinoma. Cytological and immunohistochemical features were also presented.

2. Case Presentation

A 73-year-old female, gravida three para three, presented to our hospital because of right lower abdominal pain. Right pelvic solid tumor with ascites was detected on pelvic ultrasound examination. MRI showed a pelvic mass, measuring 8.0 × 5.0 cm in diameter and arising from her right ovary, suggesting ovarian malignancy (**Figure 1**). Three weeks after her first visit to our hospital, she underwent an exploratory laparotomy in order to know the tumor. At the laparotomy, the right ovary was replaced by the tumor with partly bleeding that perforated at the back side of the serous side. After the right ovarian artery and vein were clamped, the very fragile tumor was possibly resected, and then the uterus,

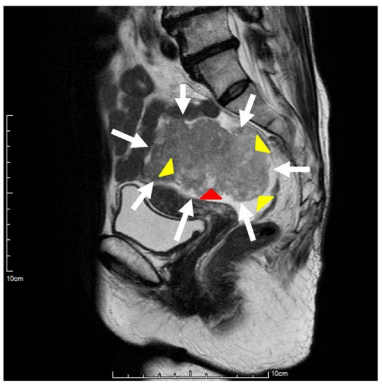

Figure 1. MRI findings. A multi-lobular and solid pelvic tumor of 8.0 × 5.0 cm in size (circled by arrows) is found at the back of uterus. Hemorrhage (red arrow head, high intensity in T2) and necrosis (yellow arrow heads, relatively high intensity in T2) within a tumor are suspected.

left ovary and tubes were resected. However, the tumor invaded to the right ureter, and some fragile tumor tissues could not be taken, thus the residual tumor was 1.5 cm, meaning so-called "sub-optimal surgery". The tumor containing bleeding and necrotic areas in parts was macroscopically yellowish and extremely fragile (Figure 2). Partial omentectomy was also performed. However, lymph node resections were not performed, because apparent tumor present in the pelvic cavity. We therefore indwelled subcutaneous reservoir for an intra-pelvic chemotherapy. A massive bloody ascites (approximate 800 ml) was aspirated and submitted to the cytology. On the imprint and ascitic cytology specimens, two different patterns of atypical cells suggestive of adenocarcinoma and spindle like atypical cells were found (Figure 3(a)). Immunocytochemistry with vimentin (Dako, 1:10 dilution) was performed. Vimentin was positive for spindle atypical cells, while negative for adenocarcinoma-like atypical glandular cells were (Figure 3(b)).

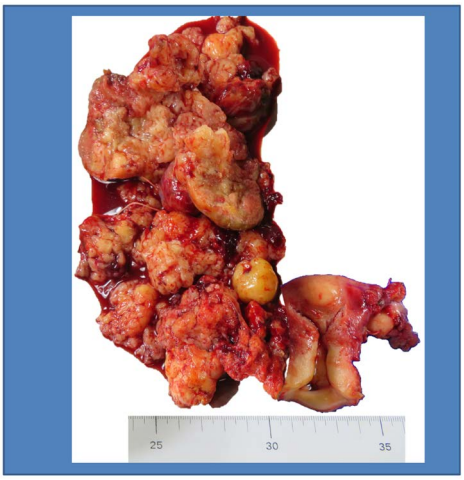

Figure 2. Resected tumor arising from the right adnexa. The tumor is highly fragile and hemorrhage and necrosis are observed.

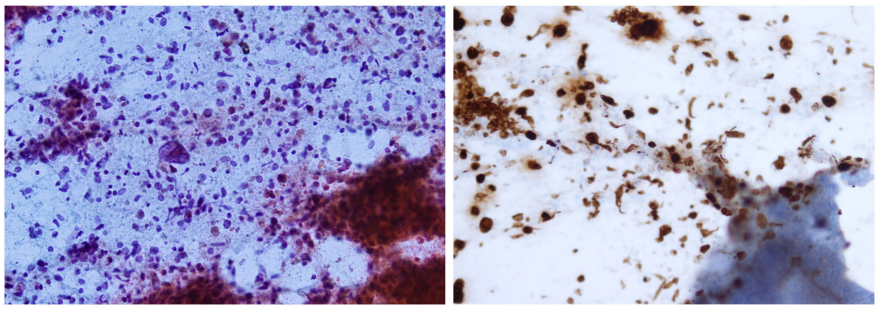

Figure 3. (a) Imprint cytology on the tumor. Small cell clusters consisted of neoplastic cells with dense and hyperchromatic nuclei are observed. Isolated and dispersal spindle cells with large nuclei are also noted (Papanicolaou stain, ×80); (b) Immunocytochemical staining with vimentin was positive for isolated spindle cells, suggesting sarcomatous cells, and negative for a glandular cell cluster (right lower), suggesting adenocarcinoma (×80).

The resected tumor was fixed in 10% neutral buffered formalin, routinely processed, and embedded in paraffin wax for histopathology and immunohistochemistry. Sections with 3 - 4 μm thickness were made and stained with hematoxylin and eosin (H & E) for histopathological diagnosis. Histopathological examination confirmed carcinosarcoma containing serous adenocarcinoma and chondrosarcoma (**Figure 4(a)**) and fibrosarcoma (**Figure 4(b)**). Immunohistochemistry using ten different antibodies, such as AE1/AE3 (Dako, 1:50 dilution, **Figure 4(c)**), CK7 (Dako, 1:50 dilution), CK20 (Dako, 1:250 dilution), vimentin (Dako, 1:10 dilution, **Figure 4(d)**), desmin (Dako, 1:100 dilution), EMA (Dako, 1:100 dilution), Sox9 (Atlas antibodies, 1:500), S100 (Dako, 1:3000 dilution), p53 (Dako, 1:100 dilution) and MIB-1 (Atlas antibodies, 1:50) was performed. Immunohistochemical stainability of the tumor cells was summarized in **Table 1**. Adenocarcinoma cells were positive for EMA, AE1/AE3 and CK7, but negative for CK20. On the other hand, chondrosarcoma cells were positive for vimentin, S100 and Sox9. Fibrosarcoma cells were positive for vimentin. The tumor cell nuclei of serous adenocarcinoma, fibrosarcoma and chondrosarcoma were partially positive for p53. We next determined DNA repair function of the tumor cells using the microsatellite instabilities (MSI)-IVD Kit (FALCO Biosystems,

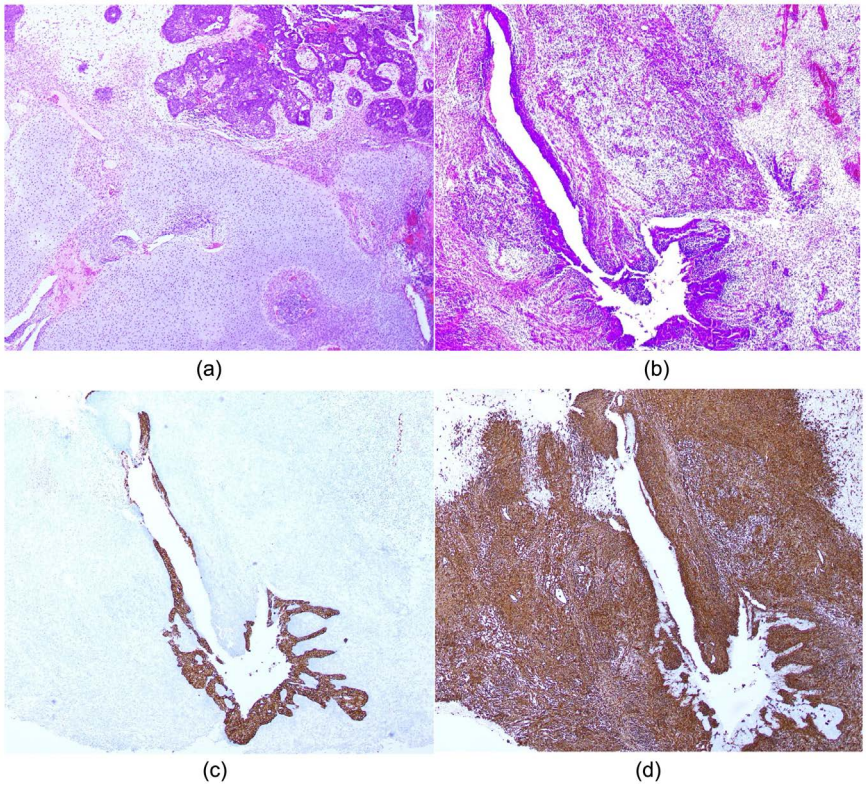

Figure 4. (a) Chondrosarcoma (left, lower side) and serous carcinoma (right, upper side) are observed (H & E stain, ×50); (b) Note: atypical glands of serous carcinoma (center) and fibrosarcoma surrounding the carcinoma element (H&E stain, ×50); (c) AE1/AE3 immunohistochemistry is positive in atypical glandular cells, but negative in atypical spindle cells (×80); (d) Immunohistochemical staining with vimentin was positive for spindle cells and negative for atypical glandular cells (×80).

Table 1. Results of immunohistochemical staining.

Neoplastic cells	Stainability against various antibodies								
	EMA	AE1/AE3	CK7	CK20	Vimentin	Desmin	Sox9	S100	p53
Adenocarcinoma cells	+	+	+	−	−	−	−	−	+/−
Chondrosarcoma cells	−	−	−	−	+	−	+	+	
Fibrosarcoma cells	−	−	−	−	+	−	−	−	

MIB-1 positive rates of adenocarcinoma, chondrosarcoma and fibrosarcoma cells were between 60% and 70%.

Kyoto, Japan), which is able to detect MSI-high status within tumor tissues [7], but no positive markers were detected, resulting in MSI stable. With the approval of the patient, we also examined BRCA1/2 mutations by BRACA-nalysis™ (Myriad Genetic Laboratories, Inc. Utah) [8], but no mutations were also detected. Thus, our final diagnosis was the right ovarian carcinosarcoma consisted of serous carcinoma (Grade 2), fibrosarcoma and chondrosarcoma; pT3CNxMx, (sub-optimal state, MSI not high and BRCA1/2 no mutations).

The patient showed uneventful clinical course after the operation. As the BRCA mutations were not detected, PARP inhibitors could not be administered. As the MSI was not high, we could not treat an immune checkpoint inhibitor, Pembrolizumab. Three weeks after the operation, she started the systemic chemotherapy with paclitaxel and carboplatin (TC) regimen for 3 weeks: the paclitaxel (175 mg/m^2), carboplatin (Auc = 5,350 mg/m^2, intra-peritoneal (i.p.) administration through the reservoir) for 3 weeks (1 cycle). Then, starting from the 2nd course of the TC regimen, bevacizumab (Bev, 15 mg/kg) was added every four weeks for 9 weeks (3 cycles). While the serum value of a tumor marker, CA125, was high before surgery and decreased by tumor resection and the TC-based chemotherapy until the 1st two courses (**Figure 5**). The normal range of CA125 is known to be under 35 U/ml, the value between 10 and 35 U/ml in the post-operative patients of ovarian cancer may suggest tumor recurrence or postoperative residual tumor [9]. The CA 125 value increased gradually during the TC-based chemotherapy (**Figure 5**). Therefore, the chemotherapy regimen was changed to ifosfamide (1.5 g/m^2, Day 1, 2 and 4) and cisplatin (15 mg/m^2, Day 1, 2 and 4, i.p. administration through the reservoir), IP regimen [3] [10] [11] for 6 weeks (2 cycles). Thereafter, CA125 value decreased and showed around 10 U/ml. The authors continued to administer the IP regimen chemotherapy under the close follow-up and monitoring the CA125 and neuron-specific enolase (NSE) values. Also, we should check the radiological examinations, including the PET-CT. At present, two tumor markers (CA125 and CEA) were within normal ranges for postoperative 7 months and the patient was free from tumor recurrence eight months after the first visit.

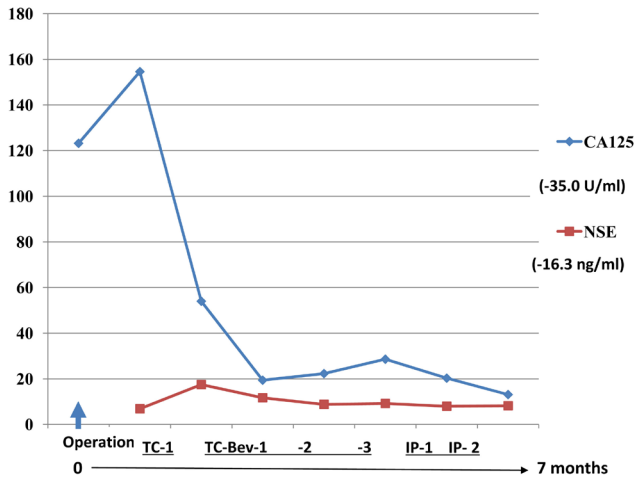

Figure 5. Changes of serum tumor markers, CA125 and neuron-specific enolase (NSE), after the operation. Parentheses are normal ranges. TC, paclitaxel and carboplatin; Bev, bevacizumab; IP, ifosfamide and cisplatin.

3. Discussion

We herein report an extremely rare case of OCS, accounting for 0.5% of all ovarian malignancies [1], with cytological and immunohistochemical findings. OCS was reported to be often found after menopause at a median age of 60 to 70 years old [12]. Our patient who is 73-year-old women is slightly older than the median age reported. Most OCS cases are diagnosed at an advanced age and advanced stage [12] [13]. OCS has a worse survival rate than high-grade ovarian cancer at the same FIGO stage, showing median overall survival ranging from 7 to 27 months [1].

There are a few cytological reports of OCS [14] [15]. Cytological diagnosis of effusion was useful for the differential diagnosis of carcinomatous and sarcomatous atypical cells from OCS [13] [16]. In this case, immunocytochemical staining for vimentin was positive in sarcomatous cells [15], while negative in carcinoma cells. The cytology and immunocytochemistry were thus useful for detecting sarcoma components, as experienced in the present case.

Histopathologically, OCS contains both carcinomatous and sarcomatous components. The carcinomatous component is usually endometrioid, clear-cell, serous, mucinous, squamous or undifferentiated [13]. The sarcomatous components are usually classified as homologous (fibrosarcoma, leiomyosarcoma, endometrial stromal sarcoma) or heterologous (rhabdomyosarcoma, chondrosarcoma, osteosarcoma or liposarcoma) [13]. In our case, carcinoma component was serous adenocarcinoma (high grade). The sarcomatous elements included homologous fibrosarcoma and heterologous chondrosarcoma.

As to pathogenesis of OCS, several theories have been proposed. They include the collision, combination and conversion theories. At present the last one postulating the sarcoma derives from carcinoma has been favored [17] [18]. Recent immunohistochemical and molecular findings support this hypothesis, which the OCS represent metaplastic carcinoma [19] [20]. Clonality studies pattern,

genomic analysis and loss of heterozygosity studies have shown that carcinomatous and sarcomatous components of OCS share common genetic alterations and are monoclonal [19]. In addition, carcinomatous component showed positive reaction for CK7 and negative for CK20, suggesting a Müllerian origin [21]. More recent molecular studies have shown four molecular subtypes: POLE-mutated, MSI, copy number high (CNH), and low (CNL) of gynecologic carcinosarcoma (uterus and ovary); most of the OCS cases were reported to belong to the CNH subtype and to show the worst prognosis [22]. The transformation of carcinoma to sarcoma might represent trans-differentiation, as found in epithelial to mesenchymal transition [23]. *TP53* mutations and/or protein overexpression are considered to be the most frequent events and might be related with poor prognosis [2] [4]. In our case we did not find immunohistochemical overexpression of p53 protein in both carcinomatous and sarcomatous elements. We consider that this may related to better prognosis of the patient.

In the present case, analyses of *MSI* and somatic *BRCA1/2* were negative. Clonal loss of the wild-type *BRCA2* allele as well as the same somatic mutation of the *TP53* gene showed an evidence for monoclonal origin [24]. *BRCA1/2* deficient tumor cells are sensitive to inhibitors of poly ADP ribose polymerase (PARP) [25]. In this case, *BRCA1/2* mutations could not be found, suggesting that OCS cells were not sensitive to PARP inhibitors. As the first line chemotherapy for OCS, IP regimen as well as TC and bevacizumab have been used, but the results remained controversial [10] [19]. In the present case, even though four courses of TC and bevacizumab were treated as the first line chemotherapy, serum CA125 increased. Although the normal range of CA125 is under 35 U/ml, the value between 10 and 35 U/ml measure in the post-operative patients with ovarian cancer is suggestive of recurrence or postoperative tumor retention [9]. Thus, we changed the chemotherapy regimen to the IP regimen, and clinical effects will be evaluated. For each OCS case, an effective treatment regimen, the TC-based, IP, or PARP inhibitor(s), must be chosen.

4. Conclusion

We report an extremely rare case of OCS with cytological and immunohistochemical findings. Vimentin immunohistochemistry and immunocytochemistry were useful for differential diagnosis of this case. As the MSI-high and *BRCA1/2* mutations could not be detected, the patient received chemotherapy with TC and IP regimens.

Acknowledgements

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Authors' Contributions

KenjiN designed and performed study, analyzed data and wrote the manuscript.

SM, KK, and YY performed immunocytochemistry, immunohistochemistry, and cytological diagnosis. KenjiN, KNa, MT, TS, and KentaroN are the obstetrician and gynaecologist who operated on the patient. MT, TS, and KentaroN collected the clinical data and wrote the manuscript. TT performed histopathological and cytological diagnosis and reviewed the article. All authors have read and approved the final manuscript.

Consent

Verbal consent was obtained from the patient before writing this case report.

Ethical Approval

This was obtained from the Ethical Committee of Gujo City Hospital before writing this case report.

Conflicts of Interest

The authors declare that they have no competing interests.

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