Concurrent high-grade serous carcinoma and borderline tumor demonstrating different chemo-sensitivity

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Abstract Ovarian high-grade serous adenocarcinoma responds well to regular platinum/taxane chemotherapy, while borderline tumor survives and demonstrates persistent disease. A 69-year-old Japanese woman was suspected for having advanced ovarian carcinoma. MRI showed cystic tumor containing solid component of the right adnexal region with massive ascites and peritoneal dissemination. Serum CA125 was elevated to 203 µ/ml; however, no remote metastases were detected. Laparotomy revealed that peritoneal carcinomatosis spreads out to omentum and subphrenic area. Omentum was partially removed with big tumor nodules that histologically demonstrated the high-grade serous adenocarcinoma with positive ascites cytology. After 6 cycles of postoperative chemotherapy with docetaxel and carboplatin, she received second surgery where the known residual bilateral adnexa and all of the persistent tumors were perfectly resected. Pathological examination of the tumor revealed serous borderline tumor with microinvasion and no evidence of residual high-grade serous carcinoma with negative ascites cytology. This is the extremely rare case of concurrent high-grade serous carcinoma and borderline tumor demonstrating differential chemo-sensitivity.

Keywords High-grade serous carcinoma · Serous borderline tumor · Chemo-sensitivity

Introduction

Recent molecular analysis has suggested a dual pathway of serous carcinogenesis; low-grade serous neoplasms (low-grade serous carcinoma and serous borderline tumor) and high-grade serous carcinoma. These are not two grades of the same neoplasm but considered to represent two independent tumor types, with different underlying pathogenesis, molecular events, clinical behavior, and drug sensitivity [1–5]. It is expected that the coexistence of low-grade and high-grade serous carcinoma would be rare or may even be mutually exclusive. There are only a small number of reported cases in which low-grade serous carcinoma or serous borderline tumor coexists with a high-grade serous carcinoma [6–8]. However, some studies have reported that the high-grade component was present only in recurrence.

Although platinum-based chemotherapy has improved the prognosis of patients with advanced mullerian adenocarcinoma, the significance of chemotherapy for low-grade serous neoplasms has yet to be evaluated. This finding highlighted the need for investigation to determine the role of other chemotherapeutic agents, hormonal therapies, and targeted biologic agents in the treatment of low-grade serous ovarian carcinoma. Schlumbrecht et al. showed that consolidation treatment with hormone antagonists demonstrated a protective associative trend with survival [9]. Because of differential chemo-sensitivity of low-grade and high-grade serous neoplasms, the correct diagnosis of grading for serous neoplasms is crucial when considering chemotherapy for the patient. We report here an extremely rare case in which the low-grade and high-grade components coexisted in the original neoplasm, demonstrating differential chemo-sensitivity.

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Case report

A 69-year-old 2 para 2 gravida postmenopausal Japanese woman presented hip pain. She had a history of colon cancer for which she had received left hemicolectomy. Magnetic resonance imaging (MRI) showed double cystic masses in the pelvic cavity, containing solid component and presenting high intensity on T2-weighted imaging (T2WI) (Fig. 1a, b) and diffusion weighted imaging (DWI). They were low on apparent diffusion coefficients (ADC). Serum CA125 was elevated to 203 U/ml. Systemic computed tomography (CT) revealed extensive peritoneal dissemination with huge omentum metastasis and massive ascites. She received partial omentectomy for the large tumor mass, but leaving the small measurable tumors behind on the peritoneum, bladder, diaphragm, liver, and intestines with multiple disseminations where the ovaries couldn't be identified and the complete cytoreductive surgery couldn't be performed. At this point, the whole treatment plan was made out for

neoadjuvant chemotherapy followed by second surgical attempt when a good response is noted.

Pathological examination of the specimen presented high-grade serous adenocarcinoma invading into the surrounding fibro-adipose tissue (Fig. 2a) with positive ascites cytology. p53 immunohistochemical staining exhibited diffuse intense nuclear immunoreactivity, with most of the tumor cell nuclei being positive (Fig. 3a). MIB-1 index of this tumor was about 75% (Fig. 3d). The patient was diagnosed with stage IIIC, (pT3cNXMX) mullerian high-grade serous adenocarcinoma. She received postoperative chemotherapy with docetaxel 70 mg/m² combined with carboplatin AUC 6.

After 6-cycles of chemotherapy, she showed partial response (PR) on RECIST standard with the normalization of CA125 level to 15 U/ml. CT imaging demonstrated the disappearance of solid components in the pelvic cavity, while the persisting subphrenic cystic component existing since before the initial chemotherapy did not show any change in diameter (Fig. 1c).

Fig. 1 Sagittal (a) and axial (b) MR image of the pelvis showed double cystic masses in the pelvic cavity containing solid component with high intensity. c Post-chemotherapy CAT scan revealed persisting small cystic mass in subphrenic area (arrow)

Fig. 2 **a** Primary tumor shows high-grade serous carcinoma composed of cells with enlarged atypical nuclei and abundant mitotic figures. **b** The persistent tumor shows serous borderline tumor composed of uniform small tumor cells without mitotic figure

On the second surgery, the persisting subphrenic tumor, bilateral adnexa, residual omentum, and intestinal surface including small tumor nodules were resected without any further residual tumor. Pathological examination of all the surgical specimens, including bilateral adnexa, presented serous borderline tumor with microinvasion but negative for peritoneal washing cytology (Fig. 2b). P53 immunohistochemical staining exhibited focal (approximately 50% nuclei showed strong positivity), weak, and heterogeneous staining (Fig. 3b); this has been referred to as wild-type staining as was reported by Clinton et al. [10]. MIB-1 index of this tumor was just about <20% (Fig. 3e).

The data suggested that all of the high-grade serous carcinoma was eradicated by chemotherapy, while the resected persistent tumors were chemotherapy-survived borderline tumors. Considering that borderline tumor is chemo-refractory and that chemotherapy provides no survival benefit for the patient, additional chemotherapy was discontinued.

However, 9 months after the second surgery, a whole body CT image showed lymph node metastasis in the mediastinum and external iliac region with peritoneal dissemination. Serum CA125 had risen to 78 U/ml, suggesting the relapse of high-grade serous carcinoma. Despite the recommendation for as much as tumor biopsy or resection followed by a second line chemotherapy, the patient would not consent to any further examination or therapy. She died of her diseases two years after the first surgery.

Discussion

It is believed that low-grade serous neoplasms (low-grade serous carcinoma and serous borderline tumor) and high-grade ovarian serous carcinomas represent two distinct

tumor types rather than a spectrum of a single neoplastic process [1–5].

This might explain why it is unusual to find the coexistence of low-grade and high-grade serous carcinoma. Some studies have suggested that the majority of high-grade and low-grade serous carcinomas develop independently, but in rare cases, a high-grade serous carcinoma may arise from an atypical proliferative serous (borderline) tumor [6]. Other studies indicate that the high-grade serous carcinoma develops from low-grade serous neoplasms through a process of dedifferentiation [10]. Some case reports have also presented the recurrence of serous borderline tumor with or without microinvasion as high-grade serous carcinoma, and such reports argue that serous borderline tumor may have the potential to transform into high-grade carcinoma [7, 11].

The case described herein demonstrated two distinctive tumor components confirmed before treatment; a solid tumor in the omentum and a cystic tumor in the subphrenic area. Removal of the solid component revealed high-grade serous carcinoma. Based on this pathological diagnosis, the patient received chemotherapy that eradicated all solid components leaving behind the known cystic tumor, resulting in PR on RECIST evaluation.

Afterwards, the persistent cystic tumor was removed, but a serous borderline tumor with microinvasion was histologically revealed. This is an extremely rare case, presenting the coexistence of high-grade serous carcinoma and serous borderline tumor. More interestingly, the case apparently indicates differential chemo-sensitivity. This case presents and confirms traditional evidence that high-grade serous carcinoma is chemo-sensitive, while the serous borderline tumor is apparently chemo-refractory. This is substantially important case to demonstrate concurrent, as opposed to

Fig. 3 Immunohistochemical staining. P53 staining was shown in primary tumor (a), persistent tumor (b), and p53 negative control (c). MIB-1 staining was shown in primary tumor (d) and persistent tumor (e)

sequential, existence of high-grade serous carcinoma and serous borderline tumor associated with chemo-sensitivity.

This case study highlighted three important issues. First, the detection order of these two types of tumor in

our patient was notable; high-grade serous carcinoma was found on primary surgery, and then borderline tumor on secondary surgery. The evidence seems to support the fact that the borderline tumor had been present in the original

neoplasm, but was only manifest in the second surgery. Despite the rarity of such cases, previous studies documented high-grade serous carcinomas have been detected in the recurrent setting following the primary borderline tumor.

Second, the tubal fimbria was not examined histologically during primary surgery, while most studies reported that high-grade serous carcinomas arise from the fimbria of fallopian tubes. In our case, a bilateral adnexal tissue was only available during second surgery after the preceding chemotherapy had eradicated the high-grade carcinoma. Histologically, the right fallopian tube revealed the existence of borderline tumor without any evidence of disease on the left fallopian tube. It is not clear whether the high-grade serous carcinoma had arisen from the fallopian tube nor is it clear whether the borderline tumor in fimbria show the peritoneal invasive implant, given the strong impact of chemotherapy against the high-grade carcinoma.

The findings from our case as well as existing literature indicate that the clinical behavior of serous borderline tumor or low-grade serous carcinoma is distinct from high-grade serous tumors. Our study is limited by ambiguity of the exact origin of the tumor (ovary, fallopian tube, or peritoneum) and possible missing of the minor remaining high-grade serous tumor at the second surgery. In this regard, meticulous tissue sampling from several parts in exploratory laparotomy should be recommended. Despite these limitations, our case provided valuable data of concurrent existence of high-grade serous carcinoma and borderline tumor with differential chemo-sensitivity, which might be beneficial for constructing future treatment design for this entity of patients.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

Informed consent This patient has already died of disease more than a year ago. At this moment, we could not keep track of the patient's

guardian or next of kin and the written consent could not be available. In the report described here, all personal details of the patient were removed from the case report to ensure that the patient cannot be identified.

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