

Case report

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Synchronous primary malignancies in ovarian cancer and liver angiosarcoma

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1. Introduction

Ovarian cancer is one of the deadliest, most malignant gynecological tumors. The lack of a sensitive and efficient clinical screening methodology results in most diagnoses occurring at an advanced stage (Xie et al., 2021). The liver is one of the most common target organs for distant metastases occurring in ovarian cancer (Wang et al., 2019). Hepatic lesions suspected on imaging of ovarian cancer indicate the possibility of liver metastases.

Synchronous primary malignancies occur in 2–17% of patients with any history of cancer (Vogt et al., 2017). Liver angiosarcoma is an extremely rare disease, accounting for only 0.1–2% of all primary hepatic malignancies. Ovarian clear cell carcinoma is a rare tumor representing less than 5% of all malignant ovarian tumors (Soulé et al., 2021). Although extremely rare, the possibility of co-occurring primary ovarian and malignant liver tumors cannot be ruled out. To our knowledge, this is the first reported case of concurrent primary malignancies of ovarian clear cell carcinoma and liver angiosarcoma.

2. Case report

A 52-year-old G2P2 (gravida 2, para 2) woman with a body mass index of 21 who was menopausal at the age of 50 years reported right lower abdominal pain on presentation to her local gynecologist. The patient had no medical history of note and no history of exposure to vinyl chloride, iatrogenic exposure to thorotrast, use of androgenic steroids, and chronic arsenic ingestion. Her father had colorectal cancer, pancreatic cancer, and stomach cancer. Otherwise, her family history was unremarkable. She presented to her local obstetrics and gynecology department with right lower abdominal pain that had been present for two weeks, and an ovarian tumor was found on transvaginal ultrasonography. The mass was initially suspected to be ovarian cancer on magnetic resonance imaging (MRI), and she was referred to our medical center.

Pelvic examination revealed a 7-cm mass in the Douglas fossa. Transvaginal ultrasonography revealed a 7-cm right ovarian tumor, with blood flow inside the tumor and no ascites in the Douglas fossa. MRI revealed a 6-cm multilocular cystic mass with a stained-glass appearance in the right ovary (Fig. 1a). The solid part of the tumor showed high intensity on diffusion-weighted imaging and low intensity on apparent diffusion coefficient mapping. Contrast-enhanced computed tomography (CT) revealed a low-density area in both lobes of the liver (Fig. 1b). Five occupying lesions in the liver were visualized on abdominal ultrasonography; they were considered metastatic liver masses. Therefore, she was suspected of stage IVB ovarian cancer with liver metastases. Tumor markers indicated serum cancer antigen 125 (CA125; 28.7 U/mL) and cancer antigen 19-9 (CA19-9; 11.8 U/mL) levels in the normal range.

She underwent exploratory Laparoscopy, liver biopsy, and ovarian tumor biopsy for suspected stage IVB ovarian cancer (see Fig. 2). Macroscopically, we identified small ascites in the Douglas fossa and the normal uterus. The diameter of the right ovary was 7 cm, and the right

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Fig. 1. Magnetic resonance imaging (MRI) and computed tomography (CT) findings. (a) MRI (high intensity on T2-weight imaging [T2WI]) revealed a 6-cm multilocular cystic mass with a stained-glass appearance in the right ovary (white arrow). (b) Contrast-enhanced CT confirmed a 3-cm low-density area in segment 2 of the liver (white arrow).



Fig. 2. Intraoperative macroscopic image and macroscopic specimen findings. (a) Intraoperative macroscopic image of a tumor on the surface of the liver (white arrow). An egg-sized mass was found on the surface of the left outer lobe of the liver. A gastrointestinal surgeon performed three laparoscopic biopsies. (b) The uterus, left ovary, and left fallopian tube appeared normal. The right ovarian tumor contained a chocolate-like fluid. The cut surface was partially solid.

fallopian tube adhered to the small intestines. A 5-cm mass was found on the surface of the left outer lobe of the liver. No other suspected metastatic lesions were found macroscopically in the abdominal cavity.

We performed a laparoscopic biopsy of a tumor found on the surface of the liver. A laparoscopic biopsy of the right ovarian tumor was attempted. However, the tumor was broken down during adhesion detachment of the small intestine, and chocolate-like content spilled out during the attempted procedure. Considering that biopsy is difficult under laparoscopic surgery, there were no disseminated lesions (other than in the liver) within the abdominal cavity, and her abdominal pain was strong prior to surgery, we converted the procedure to a laparotomy and performed tumor resection. The right ovarian tumor was diagnosed as adenocarcinoma via rapid intraoperative diagnosis. Therefore, total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed (see Fig. 2).

The pathological evaluation was consistent with co-occurring primary clear cell carcinoma (pT1c1NxMx, ly(-), v(-), FIGO stage IC1) and primary angiosarcoma of the liver. The ascites were negative on cytological examination. The right ovarian tumor measured 5.2×3.2 cm in size. The cut surface was mainly solid with a yellowish-white appearance, cystic degeneration, and associated hemorrhage. Microscopically, the tumor showed a tubulocystic, papillary, and solid architecture. The tubulocystic lesion was lined with a single layer of cuboidal or hobnail cells, and the cysts occasionally contained dense eosinophilic secretions (Fig. 3a). Stromal hyalinization and myxoid stroma were also observed (Fig. 3b). consistent with clear cell carcinoma. Immunohistochemical studies revealed that the tumor cells were positive for HNF-1 β (hepatocyte nuclear factor-1 beta), partially positive for p53, and negative for ER (estrogen receptor).

The liver biopsy specimen contained atypical cells with large nuclei, eosinophilic cytoplasm forming solid sheets, and irregularly shaped vascular-like lumina and presented with partial necrosis (Fig. 3c). Immunohistochemically, the atypical cells were negative for HNF-1 β and PAX8 (paired box 8), and positive for CD31 (cluster of differentiation 31), ERG (erythroblast transformation-specific related gene) (Fig. 3d), and Factor VIII. The tumor showed endothelial differentiation. Based on these findings, we diagnosed the patient with a primary co-occurring liver angiosarcoma. Tiny clusters of similar atypical cells were observed on the serosal surface of the right ovary and uterus, suggesting possible dissemination of the angiosarcoma.

She reported right leg pain at the time of discharge. Three weeks after surgery, she was taken to positron emission tomography-computed tomography (PET/CT) to evaluate primary tumors of liver angiosarcoma. PET/CT confirmed the presence of enlargement of the liver tumor, increased multiple liver metastases, *para*-aortic lymph node metastases, and multiple bone metastases. One month after surgery, the patient was selected for palliative treatment because rapid disease progression was observed. She died five months after the surgery.

3. Discussion

The evaluated tumor cells had large nuclei and clear cytoplasm,

This case report presents synchronous primary malignancies in



Fig. 3. Histopathological findings (a, b) Ovarian tumor cells with large nuclei and clear cytoplasm infiltrated with tubulocystic, papillary, and solid patterns (a, b; hematoxylin and eosin staining with an original magnification of $\times 100$). (c) Atypical cells in the liver biopsy specimen proliferated with a solid and vascular-like luminal architecture (hematoxylin and eosin staining with an original magnification of $\times 200$). (d) Nuclear expression of ERG (erythroblast transformation-specific related gene) showed endothelial differentiation. dysfunction (original magnification $\times 200$).

ovarian cancer and liver angiosarcoma. The diagnostic criteria for synchronous primary malignancies: (1) the tumor must be clearly malignant on histological examination; (2) each tumor must be histologically different; and (3) the possibility that the second tumor represents a metastasis must be excluded (Warren, 1932). Synchronous primary malignancies occur in 2–17% of patients with any history of cancer (Vogt et al., 2017).

Angiosarcoma is a high-grade malignant neoplasm that arises from the endothelial cells of the blood or lymphatic vessels. Liver angiosarcoma is an extremely rare disease, accounting for only 0.1–2% of all primary hepatic malignancies. However, it is currently the third most commonly occurring primary hepatic malignancy. Primary liver angiosarcoma has an aggressive clinical course, and its prognosis is extremely poor in inoperable cases. The majority of patients die within six months of diagnosis. Even in treatable cases, only 3% of patients live longer than two years. The most effective treatment for single lesions of liver angiosarcoma is the complete hepatic resection or radical resection of the tumor. Unfortunately, no effective chemotherapy has been established. Transcatheter arterial chemoembolization (TACE) can also be used with palliative intention or to control bleeding. There are no established guidelines on optimal treatment modalities regarding surgery, chemotherapy, and radiation (Kumar et al., 2022).

Invasive epithelial ovarian cancer consists of five major histological subgroups—clear-cell, endometrioid, mucinous, high-grade serous, and low-grade serous. Recent work has shown that a subset of clear cell cancers evolve from endometriosis (Pearce et al., 2012). About half of the clear cell carcinomas are diagnosed with stage I, and there are fewer advanced cases. Conventional treatment for ovarian cancer involves two modalities of treatment: surgery and chemotherapy. The intention of surgery is to stage the disease and remove as much of the visible cancer as possible. The patient underwent exploratory laparoscopy, liver biopsy, and ovarian tumor biopsy for suspected stage IVB ovarian cancer. She was diagnosed with clear cell carcinoma stage IC1 and primary angiosarcoma of the liver. The therapies for clear cell carcinoma stage IC1 are primary debulking surgery and chemotherapy for ovarian cancer with platinum-based drugs after surgery (Guidelines for treatment of ovarian cancer, fallopian tube cancer and primary peritoneal cancer,

2020). Rose et al. (1989) previously reported autopsy findings in patients with ovarian cancer. Sixty-two patients with ovarian cancer (14.5% of 428 participants enrolled in the trial) had synchronous primary malignancies. Fifty-seven patients had two co-occurring primary cancers, and five patients had three co-occurring primary cancers. In 26 patients, the second primary cancer resulted in the patients' deaths. However, there were no cases of synchronous primary malignancies following an initial diagnosis of liver cancer in ovarian cancer patients (Rose et al., 1989). To the best of our knowledge, this is the first report of synchronous primary malignancies in ovarian cancer and liver angiosarcoma.

In the present patient, ovarian cancer was suspected on MRI prior to treatment, and CT and abdominal ultrasonography were suspicious for multiple liver metastases. Ovarian carcinoma metastasizes either by direct extension from the ovarian/fallopian tumor to neighboring organs (bladder/colon) or when cancer cells detach from the primary tumor. Exfoliated tumor cells are transported throughout the peritoneum via physiological peritoneal fluid and disseminate within the abdominal cavity, so extensive seeding of the peritoneal cavity is often associated with ascites (Ernst Lengyel, 2010). However, in this case, there was no evidence of ascites or dissemination of the malignancy other than in the liver, so we considered that exfoliated tumor cells were not yet transported. Moreover, MRI did not give the impression that the ovarian cancer was advanced enough to be accompanied by liver metastases, suggesting it was a primary tumor. Synchronous primary malignancies, including clear cell adenocarcinoma of the ovary and angiosarcoma of the liver, were diagnosed using biopsy. If a liver tumor is found together with ovarian cancer, it is necessary to determine whether this is a primary hepatic malignancy or metastatic liver cancer, as this knowledge informs appropriate clinical decision making. We considered that it is important to make a definitive diagnosis by performing a liver biopsy when appropriate (i.e., according to the imaging results of the suspected ovarian and liver tumors).

Declarations

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Tomomi Taguchi: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Tomomi Egawa-Takata:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Kimihiko Ito:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was generated with regard to this case report.

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