CASE REPORT

Early-onset primary peritoneal carcinoma from atypical cells after risk-reducing salpingo-oophorectomy for *BRCA2* mutation carrier: a case report

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Abstract Risk-reducing salpingo-oophorectomy (RRSO) in *BRCA* mutation carriers is performed to reduce carcinogenesis. It decreases the ovarian, tubal, and peritoneal cancer risk to 3.5–4.3% and breast cancer risk to 30–40%. According to a previous study, despite RRSO, 3.4% of patients develop breast cancer and 0.8% develop peritoneal cancer. However, the long-term risk of recurrence and appropriate treatment for patients with unsuspected neoplasia after RRSO are unclear. Case: A 61-year-old woman who had a *BRCA2* mutation underwent RRSO. Her pelvic washing cytology showed atypical cells, and similar atypical cells were identified on her fimbria. She underwent strict surveillance. Elevated CA125 levels and increased ascites in the pelvic cavity were detected by routine surveillance at 18 months after RRSO. She underwent staging laparotomy and was diagnosed with primary peritoneal carcinoma stage IIIC. It is helpful to perform surveillance by transvaginal ultrasound and serum CA125 analyses in cases that require strict management. The appropriate intervention should be considered for cases in which atypical cells or non-invasive carcinoma are detected after RRSO.

Keywords Primary peritoneal carcinoma · Risk-reducing oophorectomy · Laparoscopy · *BRCA* mutation · Pelvic washing cytology

Introduction

Mutations in *BRCA* genes are correlated with increased risks of breast, ovarian, tubal, and peritoneal cancers. Genetic counseling and risk-reducing surgery, including risk-reducing bilateral salpingo-oophorectomy (RRSO) and mastectomy, are often recommended for *BRCA* carriers. RRSO is recommended in *BRCA* carriers at between 35 and 40 years and upon the completion of child bearing [1].

The breast cancer risk in *BRCA1* carriers up to 70 years is 55–70% and that for *BRCA2* carriers is 45–70%. The ovarian cancer risk is approximately 40% in *BRCA1* carriers and 15% in *BRCA2* carriers [2]. RRSO reduces cancer risk in *BRCA* carriers and leads to decreases in the ovarian, tubal, and peritoneal cancer risk to 3.5–4.3% and breast cancer risk to 30–40% [3, 4]. According to another study, 3.4% of patients develop breast cancer and 0.8% develop peritoneal cancer after RRSO [5].

After RRSO, the incidence of unsuspected neoplasia on the fallopian tube [including serous tubal intraepithelial carcinoma (STIC)] and/or abnormal cytological findings in peritoneal washings is 4–12% [6]. Some studies have reported the uncommon recurrence of unsuspected neoplasia and primary peritoneal carcinoma in 1–4% of patients after RRSO. However, few studies have examined the long-term risk of recurrence in patients with unsuspected neoplasia [7–12]. Accordingly, the appropriate measures for patients with these unsuspected neoplasia after RRSO are controversial.

In the present report, we describe a case of primary peritoneal carcinoma after RRSO. The patient had an unsuspected neoplasia on the tube without malignant findings and her pelvic washing cytology showed atypical cells at the time of RRSO. During surveillance at 13 months after

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RRSO, we suspected primary peritoneal carcinoma on the basis of elevated CA125 levels and increased ascites.

Case report

A 61-year-old woman (gravida 2, para 2) was diagnosed with breast cancer at 59 years of age. We suspected hereditary breast and ovarian cancer syndrome (HBOC) on the basis of her family history (one case of ovarian cancer, two breast cancer, and two pancreatic cancer) (Fig. 1). We, therefore, recommended genetic counseling, after which she received a genetic test for HBOC syndrome. She had the *BRCA2* mutation and elected to undergo RRSO after her breast cancer operation. She underwent laparoscopic RRSO at 59 years of age. Her abdominal cavity findings included no adhesion and small ascites. We performed RRSO according to our protocol. We obtained a pelvic washing and removed 2 cm of the proximal ovarian vasculature/IP ligament; this protocol is similar to the NCCN guideline established in 2015, with some modifications. This operation was her first abdominal operation.

Her initial pathological report indicated no malignancy on the tube, fimbria, or ovary, but the pelvic washing cytology showed atypical cells (Fig. 2a). We re-evaluated the samples to clarify the pathological differences among RRSO samples (fimbria, tube, and ovary) and the washing cytology. The final pathological report showed atypical cells on the intraepithelial fimbria. However, p53 immunostaining of the lesion was negative, so we could not conclude that it was a carcinoma (Fig. 3). We recommended

Fig. 2 Pelvic washing cytology findings. 2a: Ascites smear in RRSO. The smear is composed of clusters, including atypical cells showing high an N/C ratio and nuclear shape irregularities, but not carcinoma. 2b: Ascites smear in PPC. The smear shows a cluster with anisocytosis, nuclear enlargement, a high N/C ratio, and prominent nucleoli

that the patient undergo strict surveillance. She underwent surveillance by transvaginal ultrasound and serum CA125 analyses at short intervals (every 1 month for the first half year and every 3 months thereafter). At 6 months after RRSO, screening by computed tomography scan showed no evidence of disease. The serum CA125 level was 6.4 U/ml at 13 months after RRSO, 111 U/ml at 16 months, and 1368 U/ml at 18 months. The ascites in the pelvic cavity were first detected at 18 months after RRSO. The cytology of ascites collected by transvaginal puncture showed

Fig. 1 Family history

Fig. 3 Fimbria findings at RRSO. There was no strong heteromorphism to morphologically up to cancer in HE staining. CA125 and ki67 immunostaining were positive, but p53 staining was negative

adenocarcinoma (Fig. 2b). A computed tomography scan showed omental metastasis. She was treated by surgical cytoreduction and hysterectomy. The omental metastasis was minor, but there was extensive dissemination on the Douglas' pouch and the inferior surface of the diaphragm.

Peritoneal excision and omentectomy samples contained high-grade serous adenocarcinoma, although the uterus was intact. In the omentum sample, p53 immunostaining was negative, similar to atypical cells on fimbriae at RRSO (Fig. 4). She was diagnosed with primary peritoneal

Fig. 4 Primary peritoneal carcinoma findings of omentum. Carcinoma with anisokaryosis, prominent nucleoli, and solid growth was observed as an indicator of malignancy. p53 immunostaining was negative, similar to the RRSO samples

carcinoma stage IIIC, and started chemotherapy, including carboplatin (AUC 6), paclitaxel (175 mg/m²), and bevacizumab (15 mg/body), administered every 3 weeks.

Discussion

We performed RRSO for *BRCA1/2* mutation carriers after obtaining approval from the Ethics Committee of our hospital in 2011. We adopted a SEE-FIM protocol to evaluate the fallopian tube constantly from the time of RRSO. Twenty mutation carriers underwent RRSO to date. One patient was diagnosed with STIC. Another patient (this case) had atypical cells on the fimbria at the time of RRSO. The frequency of pathological abnormalities in our RRSO cases was similar to that of previous reports.

Pelvic washing cytology at RRSO is recommended according to the NCCN guidelines [13]. However, whether or not pelvic washing cytology should be performed at RRSO is controversial. Blok et al. reported that malignant washing cytology samples fail to add value to histopathological examinations for the detection of ovarian and/or fallopian tube cancer using the SEE-FIM protocol [14].

In our case, pelvic washing cytology showed atypical cells and the initial pathological report for RRSO samples did not indicate malignancy. It was difficult to detect abnormalities following the SEE-FIM protocol. We re-evaluated RRSO samples in more detail. The findings of the final pathological report were atypical cells on the fimbria. Accordingly, pelvic washing cytology facilitates diagnosis.

NCCN guidelines for HBOC do not recommend surveillance for ovarian cancer by transvaginal ultrasound and serum CA125 levels owing to a lack of evidence supporting the detection of early-stage carcinoma, but may be considered at the clinician's discretion [1]. We performed postoperative surveillance for all cases by transvaginal ultrasound and monitored serum CA125 levels every half year since the time of RRSO. Primary peritoneal carcinoma (PPC) onset was not observed, with the exception of this case, to date. In this case, we checked for the presence of ascites and dissemination to the Douglas' pouch by transvaginal ultrasound and serum CA125 levels every month owing to the atypical cells in ascites and fimbria of the RRSO sample. As a result of this strict surveillance, we were able to detect PPC before the onset of symptoms. Depending on the case, our experience suggests that transvaginal ultrasound and serum CA125 levels can be useful tools for detecting early-stage PPC after RRSO.

In a study by Powell et al. [8], patients with *BRCA1/2* mutations underwent staging laparotomy and platinum-based chemotherapy after abnormal findings were obtained in RRSO. The patients did not experience relapse. However, other patients with *BRCA1/2* mutations

only received RRSO, and increased recurrence was confirmed by positive washing cytology results compared with that by STIC alone. The authors strongly suggest staging laparotomy and chemotherapy if pathological findings are abnormal [8]. There is no protocol for patients diagnosed with STIC or atypical lesion at the time of RRSO. In our patient, we decided not to perform staging laparotomy and platinum-based chemotherapy, because the abnormalities were non-invasive carcinomas; instead, patients underwent strict surveillance.

Murray et al. [15] reported a 3.5% cumulative risk of PPC for all *BRCA* mutation carriers and a 3.9% cumulative risk for *BRCA1* mutation carriers in 20 years of follow-up after prophylactic oophorectomy. A review of the English-language literature published from 2006 to 2015 related to salpingo-oophorectomy, including RRSO, or benign indications revealed 67 total patients with isolated STIC at RRSO. Three patients with *BRCA* mutations were diagnosed with PPC during follow-up at 43, 48, and 72 months after RRSO, and the duration from RRSO to diagnosis with PPC was longer than 3 years in all cases. Two of the PPC patients underwent washing cytology at the time of RRSO, and the results were negative [16].

In our case, the period from RRSO to the diagnosis of PPC was 18 months, which was shorter than that of previous reports. It is possible that treatment for patients with atypical cells in peritoneal washing cytology should be the same as that for patients with confirmed malignancy. NCCN guidelines clearly include the RRSO protocol in the principles of surgery for ovarian cancer. They also indicate that if occult malignancy or STIC is identified, a gynecologic oncologist should be consulted. However, the guidelines do not include a protocol for management or treatment [13].

Conclusions

It is helpful to perform surveillance by transvaginal ultrasound and serum CA125 analyses in cases that require strict management. The appropriate intervention should be considered for cases in which atypical cells or non-invasive carcinoma are detected after RRSO. However, the appropriate treatment for these cases has not been established. We should consider treatment in each case. In the future, it is desirable to establish a case management strategy.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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