Case report

Two types of small cell carcinoma of the ovary: Two typical case reports

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1. Introduction

Small cell carcinoma of the ovary (SCO) was first reported in 1982 (Dickersin et al., 1982). The condition is rare, accounting for about 1% of all ovarian neoplasms. The entity of small cell carcinoma of the ovary is classified into the hypercalcemic type (SCOHT) and the pulmonary type (SCOPT) based on the pathologic findings and immunostaining profile of each tumor. There are only about 500 reported cases of SCOHT and 23 of SCOPT.

The clinical features of SCOHT and SCOPT differ. For example, SCOHT typically affects younger women (mean age, 22 years) than SCOPT (mean age, 51 years). Hypercalcemia is found in about 60% of patients with SCOHT (Young et al., 1994). Both are highly aggressive malignancies, but while SCOHT is resistant to chemotherapy and radiotherapy, progressing rapidly, SCOPT is sensitive to chemotherapy, although it also carries a poor prognosis. We present 2 patients who demonstrate the typical clinical course of each entity.

1.1. Patient 1

Six months after a cesarean delivery, a 33-year-old woman presented with lower abdominal pain and a sensation of abdominal fullness. Computed tomography (CT) showed ascites and multiple peritoneal lesions. Magnetic resonance imaging (MRI) revealed a 13-cm solid mass deriving from the right ovary (Fig. 1). The serum cancer antigen 125 (CA125) level was 120.5 U/mL, and the total serum calcium level was 16.0 mg/dL.

About 9 L of ascites was removed during laparotomy, during which many disseminated lesions and enlarged paraaortic lymph nodes were noted. We performed a right salpingo-oophorectomy and omental biopsy. The right ovary measured 15 cm and appeared ash gray and cystic. Histopathologic examination revealed follicle-like and sheet-like structures. The follicular lesions featured closely packed, small cells with scant cytoplasm and small nuclei, arranged in diffuse nests and around blood vessels. The sheet-like lesions featured large cells with abundant eosinophilic cytoplasm. Rhabdoid cells with eosinophilic cytoplasm were also noted. Immunohistochemistry showed a complete loss of SMARCA4 protein, but staining for SMARCB1 was positive (Fig. 2). The final pathologic diagnosis was SCOHT, and the patient was assigned an International Federation of Gynecology and Obstetrics (FIGO) ovarian cancer stage of IIIC.

After surgery, her serum calcium level decreased to 9.0 mg/dL. After 2 cycles of paclitaxel and carboplatin chemotherapy, follow-up CT revealed evidence of disease progression. Second-line chemotherapy with liposomal doxorubicin was also ineffective. As a third-line regimen, she received nedaplatin, irinotecan, and bevacizumab together with palliative radiation. However, the tumor progressed rapidly, and the patient died 7 months after her surgical diagnosis.

1.2. Patient 2

A 32-year-old woman experienced lower abdominal pain and diarrhea, followed a few days later by respiratory discomfort. A large amount of ascites and a right ovarian mass were noted on CT (Fig. 3).
Her serum CA125 level was elevated (50.5 U/mL). We diagnosed Meigs syndrome and performed an emergency laparotomy with right salpingo-oophorectomy. She had 7 L of ascites, and her spontaneous ruptured right ovary measured 8 cm in diameter. There were no disseminated lesions.

Histopathologic examination revealed small, round cells with scant cytoplasm, arranged in diffuse or insular patterns with slightly spindled, hyperchromatic nuclei. These findings were similar to those of small cell carcinoma of the lung. Immunohistochemistry staining for chromogranin A and synaptophysin was positive (Fig. 4). The pathologic diagnosis was SCOPT.

The patient underwent hysterectomy, left salpingo-oophorectomy, omentectomy, and pelvic and paraaortic lymphadenectomy. The right internal iliac node was enlarged to 2 cm. The final diagnosis was ovarian cancer, FIGO stage IIIA1(ii). She underwent 6 cycles of chemotherapy with etoposide and cisplatin. Two years after surgery, disease recurrence in the pelvis was detected. She underwent a further 3 cycles of paclitaxel-carboplatin (TC) and bevacizumab chemotherapy, with a partial response; she then underwent tumor resection and a further 3 cycles of TC chemotherapy and 9 cycles of bevacizumab monotherapy. One year later, a 2-cm mass in the right pelvis was detected on CT. She underwent 3 further cycles of TC chemotherapy. Unfortunately, a hypersensitivity reaction to platinum-containing drugs forced us to change to intensity modulated radiation therapy (54Gy/27Fr). After completing this treatment, she was noted to have a brain metastasis, for which she underwent craniotomy and stereotactic irradiation (30Gy/10Fr). Currently, she takes weekly paclitaxel and biweekly bevacizumab chemotherapy, targeting a recurrence at the vaginal cuff. She has had clinically stable disease for 12 months (Fig. 3) and is alive 6 years after her initial surgery.

2. Discussion

Both SCOHT and SCOPT are composed of small tumor cells, but their histological features differ somewhat. The tumors of SCOHT have focal, follicle-like spaces containing luminal eosinophilic fluid. A large cell component with eosinophilic cytoplasm is present in half of patients with SCOHT, often involving a rhabdoid appearance. In contrast, the lesions of SCOPT have a rosette-like appearance and are immunopositive for neuroendocrine markers, similar to small cell cancer.
carcinoma of other organs (Kurman et al., 2014). Most patients with SCOPT have the endometrioid and mucinous types of ovarian carcinoma (Eichhorn et al., 1992). Our 2 patients demonstrate the typical histological findings of SCOHT and SCOPT.

Some authors have recently reported that SCOHT is a monogenic disorder. Bailey et al. showed that 92.8% of patients with SCOHT exhibit immunohistochemical loss of the SMARCA4 protein, a key component of the switching/sucrose non-fermenting (SWI/SNF) chromatin remodeling complex (Bailey et al., 2015), which transforms the structure of chromatin by transferring and removing nucleosomes. The SMARCB1 gene mutation can be seen 95% of patients with rhabdoid tumor, and its protein forms SWI/SNF complexes with the protein SMARCA4. Hence, loss of the SMARCA4 protein may induce abnormal gene proliferation. Witkowski et al. identified a germline or somatic mutation of SMARCA4 in 30 of 32 SCOHT cases (Witkowski et al., 2014). Although we did not perform genetic analysis in our patient, immunostaining for SMARCA4 was negative. Elayne et al. recommended that SCOHT be reclassified as a malignant rhabdoid tumor of the ovary with SMARCA4 immunostaining and genetic testing as the diagnostic criteria (Elayne et al., 2017).

Hypercalcemia is a common finding in patients with SCOHT, but the mechanism is unknown. Stephens et al. found that the tissue vitamin D receptor is modestly downregulated, but it is not clear whether this is related to the hypercalcemia (Stephens et al., 2012).

Patients with SCOHT are usually treated with surgery, multiagent chemotherapy, and radiation. Harrison et al. studied 17 patients with SCOHT who underwent surgery and platinum-based chemotherapy. Stage I patients were alive without disease 10 to 60 months after surgery; however, patients with stage III disease showed rapid progression (Harrison et al., 2006). Young et al. found that 50% of 150 patients with SCOHT had stage I disease, and 33% of stage IA patients were alive and free of disease at 5 years, while only 10% of patients with stage Ic were alive (Young et al., 1994). Since neither chemotherapy nor radiation are effective for SCOHT, it is very difficult to treat advanced disease. The mechanism of its drug resistance is unknown. Our patient was resistant to all treatment. Based on our experience and on previous

Fig. 2. Histopathological findings. A: (HE) Follicle like space and sheet like space are seen. These are composed of small cell with scant cytoplasm. B: Tumor cells have activity for SMARCB1. C: This shows complete loss of tumoral SMARCA4 staining.
In contrast to SCOHT, the molecular biological background of SCOPT has not been elucidated. Most patients are treated with etoposide and cisplatin, the same treatment used for small cell lung carcinoma; however, some patients are treated with paclitaxel-carboplatin, the standard regimen for epithelial ovarian cancer. Kurasaki et al. reported that a patient with stage IIIa SCOPT who underwent paclitaxel-carboplatin chemotherapy had no disease recurrence at 22 months (Kurasaki et al., 2013). Suzuki et al. reported that a patient with stage Ic SCOPT was alive 36 months after paclitaxel-carboplatin chemotherapy (Suzuki et al., 2007). There is a case report that radiation therapy was effective for SCOPT (Terada et al., 2018). In our patient, chemotherapy and irradiation were effective: she has survived despite repeated recurrences. Even with disease recurrence, patients with SCOPT can expect relatively long-term survival. It is therefore important to proactively provide multiple chemotherapy and radiotherapy regimens.

Pressey et al. reported 2 patients with SCOHT who were treated with cisplatin and bevacizumab and experienced disease-free survival for 7 years (Pressey et al., 2013). However, bevacizumab was ineffective in our patient. This may be because we used it as third-line combination treatment, when the patient’s performance status was poor. There are preliminary reports that tazemetostat, a potent and selective EZH2 inhibitor (Chan-Penebre et al., 2017), and ponatinib, a tyrosine kinase receptor inhibitor (Lang et al., 2018) exhibit antitumor effects on SCOHT cell lines, and future clinical applications are expected.

There are no reports of molecular therapy for SCOPT, but bevacizumab was effective in our patient, both as combination and monotherapy. Bevacizumab may be useful for SCOPT, but as the number of case reports is small, more data are needed.

In conclusion, SCOHT and SCOPT share a category of ovarian cancer, but their clinical course differs dramatically. We expect that these disease states will be clarified by molecular or biological analysis and that novel therapeutic methods will be developed.

3. Consent

Written informed consent was obtained from both patients 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.
Conflict of interest

The authors have no conflicts of interest to declare.

Author’s contribution

MK, EK, SY, HY (Hiroshi Yagi), MY, TO, IO, KO and HY (Hideaki Yahata) took part in these cases. Especially, KO operated the patient of pulmonary type. KS and KK supervised this manuscript. KK made a decision of these cases, and proofread this manuscript. All authors have read and approved the submission of the manuscript.

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Fig. 4. Histopathological findings. A-B: (HE) Small round carcinoma cells with scant cytoplasm growth in diffuse or insular patterns. Chromatin aggregation is also seen. C-D: Chromogranin (C) and synaptophygin (D) are positive for immunohistochemical examination.
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