A recurrent granulosa cell tumor of the ovary 25 years after the initial diagnosis: A case report

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ABSTRACT
INTRODUCTION: Granulosa cell tumors (GCTs) are rare functional sex-cord-stromal ovarian neoplasms characterized by low malignancy potential and late relapse, which rarely metastasize to the liver. PRESENTATION OF CASE: A 43-year-old female, who had undergone surgery to treat a GCT of the left ovary in 1976, complained of abdominal distention in May 2001. Imaging studies demonstrated masses in the right lobe of the liver, together with massive ascites. The patient’s bloody ascites showed no cytological evidence of malignancy. A diagnostic laparoscopy was performed, and the biopsy specimen was histologically proven to be a recurrent granulosa cell tumor. The patient was successfully treated surgery followed by systemic chemotherapy. Her postoperative course was uneventful and systemic chemotherapy was repeated due to the suspicion of a recurrence in the pelvic cavity. DISCUSSION: GCTs which are rare malignant tumors of the ovary, tend to be associated with late recurrence. Although most recurrences occur within 10 years after the initial diagnosis, there are occasional reports of recurrences after 10 years have been. We experienced the rare case of a patient who relapsed 25 years after the initial diagnosis. CONCLUSION: The long natural history of this disease highlights the importance of extended follow up for GCT patients. In addition, aggressive therapy including surgery and chemotherapy may contribute to a patient’s long-term prognosis.

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1. Introduction
Granulosa cell tumors (GCTs) are rare functional sex-cord-stromal ovarian neoplasms characterized by low malignancy potential and late relapse, which rarely metastasize to the liver [1]. We describe a patient with a recurrent ovarian GCT with extensive liver metastasis 25 years after her initial diagnosis, for which diagnostic laparoscopy and biopsy were useful.

2. Case presentation
A 43-year-old female, gravida 2, para 2, with a history of left salpingo-oophorectomy in 1976 for GCT, underwent an examination after presenting with abdominal distention in May 2001. Massive ascites and multilocular masses were observed in the right lobe of the liver on ultrasound (US) and computed tomography (CT). Paracentesis revealed bloody ascites with a class II cytology. The diagnosis on referral to our hospital, was a possible cystadenocarcinoma of the liver.

On physical examination, the patient’s abdomen was distended with massive ascites. The laboratory examinations revealed no abnormalities: the level of estradiol and tumor markers including CA546, CA125, CEA, C19-9, and DUPAN-2 were all normal. A US revealed massive ascites. Repeated paracentesis of the abdomen failed to demonstrate malignant cells. An abdominal US and CT demonstrated multilocular cystic masses in the right lobe of the liver measuring 10 cm in diameter, while a 2 cm cyst was detected in the right ovary. On magnetic resonance imaging (MRI), the liver masses were found to have extended superiorly and invaded the diaphragm (Fig. 1). Angiography demonstrated the encasement of the right hepatic artery and the inferior phrenic artery branches and tumor neovascularity (Fig. 2A and B). Although the imaging studies were highly suggestive of cystadenocarcinoma of the liver, the diagnosis of recurrent GCT could not be ruled out.
A diagnostic laparoscopy was performed in May 2001. After the aspiration of 3400 ml of bloody ascites, multilocular masses were observed in the right lobe of the liver, which had ruptured, resulting in local peritoneal dissemination. A small cyst was also present in the right ovary. Biopsies of the liver, the right ovarian cyst and the areas of peritoneal dissemination revealed a GCT that resembled the previous pathology of the left ovary (Fig. 3).

Because of the favorable outcomes associated with platinum-based chemotherapy in patients with recurrent GCTs, we speculated that a mass reduction and postoperative chemotherapy could give her the best chance of cure. We performed an extended right hepatic lobectomy with the combined resection of the diaphragm, cholecystectomy, omentectomy, right salpingo-oophorectomy, and hysterectomy. The final pathologic examination showed metastatic recurrent granulosa cell tumors of the liver and invasion into the diaphragm. A microscopic examination revealed a mostly macrofollicular pattern of growth with Call–Exner bodies and occasional macrofollicular pattern areas (Fig. 4A). The nuclei of the tumor cells also showed mitotic figures and grooves resulting in a characteristic “coffee-bean-like” appearance (Fig. 4B). An immunohistochemical staining was performed and was positive for inhibin (Fig. 4C and D).

The patient’s postoperative course was uneventful. After being discharged from the hospital, systemic chemotherapy was administered consisting of carboplatin and cyclophosphamide. The systemic chemotherapy was repeated again due to a suspected tumor recurrence in the pelvic space and liver. She remains alive at 14 years after the surgery.

3. Discussion

GCTs are rare tumors which account for approximately 2–3% of all ovarian malignancies. They are associated with a favorable prognosis, especially when they are detected in the early stages.
[2–4]. Björkholm and Silfversward reported in 1981 that the 5-year survival rates were over 95% for stage I, 55% for stage II, and 25% for stage III tumors [3]. Lauszus et al., reported that the survival rates for stage I at 5, 10 and 20 years were 94%, 82%, and 62%, respectively [4]. These data suggest that GCTs tend to be associated with late recurrence.

Several series have shown the recurrence rates range between 9 and 35% [3,4]. The recurrence of GCTs is associated with a poor prognosis. Although most recurrences are within 10 years after the initial diagnosis [4,5], there are reports of recurrence after 10 years. In our case, the patient relapsed 25 years after the initial diagnosis.

Table 1 shows the reported cases of GCT recurrence after 20 years.

GCTs are associated with a low incidence of hepatic metastasis(<5–6%) [6]. On imaging studies, the liver metastases of GCTs are characterized by thickened walls with hypervascularity and nodular excrescences. Our case was initially suspected of having a suspicious cystadenocarcinoma of the liver based on the CT findings, while angiography showed neovascularity of the tumor. However, because we could not rule out recurrent GCTs because of the patient’s past history, we performed a laparoscopic examination. We found the laparoscopic examination to be a safe and useful diagnostic technique.

Case of advanced metastatic GCTs, are typically treated, as our patient was treated, with aggressive surgical resection (when possible), followed by postoperative systemic chemotherapy. Radiation therapy may have some effect in cases with minimal residual disease. Systemic chemotherapy should be prescribed to obtain better tumor control and an improved long-term survival rate. Although our patient experienced another recurrence at 2 years

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Disease-free interval (years)</th>
<th>Site of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shimizu et al. [7]</td>
<td>1999</td>
<td>20</td>
<td>Lung</td>
</tr>
<tr>
<td>Spencer et al. [8]</td>
<td>1999</td>
<td>21</td>
<td>Lung</td>
</tr>
<tr>
<td>Stenwig et al. [5]</td>
<td>1979</td>
<td>22</td>
<td>Not specified</td>
</tr>
<tr>
<td>Li and van der Walt [9]</td>
<td>1984</td>
<td>22</td>
<td>Paraaortic, extending to kidney</td>
</tr>
<tr>
<td>Chen et al. [10]</td>
<td>2012</td>
<td>22</td>
<td>Peritoneum</td>
</tr>
<tr>
<td>Evans et al. [2]</td>
<td>1980</td>
<td>23</td>
<td>Not specified</td>
</tr>
<tr>
<td>Hasilakos et al. [15]</td>
<td>2008</td>
<td>25</td>
<td>Pelvis</td>
</tr>
<tr>
<td>Hitchcock et al. [16]</td>
<td>1989</td>
<td>26</td>
<td>Peritoneum</td>
</tr>
<tr>
<td>Sommers et al. [17]</td>
<td>1955</td>
<td>26</td>
<td>Omentum</td>
</tr>
<tr>
<td>Chew et al. [18]</td>
<td>2003</td>
<td>29</td>
<td>Spleen</td>
</tr>
<tr>
<td>Singh-Ranger et al. [19]</td>
<td>2004</td>
<td>30</td>
<td>Pelvis</td>
</tr>
<tr>
<td>Hines et al. [1]</td>
<td>1996</td>
<td>37</td>
<td>Not specified</td>
</tr>
<tr>
<td>East et al. [20]</td>
<td>2005</td>
<td>40</td>
<td>Liver, peritoneum, other ovary</td>
</tr>
<tr>
<td>(Present report)</td>
<td>2001</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>
after the second surgery, her prognosis improved by combination chemotherapy and she remains alive after 14 years.

4. Conclusions

The long natural history of this disease highlights the importance of extended follow-up for GCT patients. In addition, aggressive therapy including surgery and chemotherapy may contribute to a favorable long-term prognosis.

Conflicts of interest

None.

Funding

None.

Ethical approval

Not applicable.

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.

Author contributions

Fumihiko Fujita contributed reports retrieval and drafting of this manuscript. Eguchi Susumu and Mitsuhiro Takatsuki contributed surgical procedures of this case report. Kazuma Kobayashi and Kengo Kanetaka contributed acquisition of clinical data. Masahiro Ito and Kuniko Abe contributed pathological analysis. Tamotsu Kuroki contributed critical revision of this manuscript.

Guarantor

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