Effective multidisciplinary treatment for ovarian granulosa cell tumor with multiple metastases - a case report

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Summary

Ovarian granulosa cell tumor (GCT) is among the ovarian sex-cord stromal tumors that are classified as borderline malignancies. We report a case of GCT with multiple metastases for which multidisciplinary treatment including surgery, chemotherapy and radiotherapy was effective. A 41-year-old woman underwent left salpingo-oophorectomy because of an ovarian tumor in 2004. Final pathology confirmed a granulosa cell tumor adult type, FIGO Stage IC. In 2008, tumorectomy of the lower abdominal wall metastases was also performed. After three cycles of BEP chemotherapy for metastases of the right lung, liver, paraaortic lymph node and rectus, surgical resection was performed in 2009. In 2010, local radiation was performed for the first lumbar vertebral metastasis. Ovarian GCTs exhibit slow growth but if the surgical stage is IC or higher, there is the possibility of recurrence. It is important to treat recurrent tumors with the combination of surgery, chemotherapy, and radiation therapy.

Key words: Ovarian granulosa cell tumor; Recurrence; BEP.

Introduction

Ovarian granulosa cell tumors (GCT) are among the ovarian sex-cord stromal tumors that constitute nearly 2-3% of all ovarian neoplasms [1, 2]. They are often estrogen-producing tumors and are seen in women of all ages. Although they are classified as borderline malignancies, the prognosis is relatively good. They often have late recurrence after ten years or more. As such, 10-year survival rates of almost 90% have been reported, with 20-year survival rates dropping to 75% [3]. The tumors may spread hematogenously, but most recurrences often remain in the abdominopelvic cavity. However, metastases to the abdominal wall, muscle and bone are rare [3-5].

We report a case of GCT with subcutaneous metastases and metastases to the lung, liver, paraaortic lymph node, rectus, and lumbar spine, in which multidisciplinary treatment including surgery, chemotherapy, and radiotherapy was effective.

Case Report

A 41-year-old (gravid 0, para 0) woman underwent an emergency laparotomy with left salpingo-oophorectomy for a left ovarian tumor with abdominal pain in 2004. Final pathology confirmed a granulosa cell tumor adult type, FIGO Stage IC (pT1cNXM0) (Figure 1). The results of the immunohistochemical study are summarized in Table 1.

Ascitic fluid cytology from the first operation was positive. As the patient wanted to preserve fertility, no additional surgery was performed. Although we explained the need for regular follow-up to her, she suspended follow-up, of her own accord.

The patient underwent a medical examination at our hospital after having had a subcutaneous tumor in the lower abdominal wall in 2008. Since abdominal magnetic resonance (MR) identified subcutaneous tumors in the lower abdominal wall, tumorectomy was performed by a dermatologist in our hospital. The final pathology confirmed metastases of the granulosa cell tumor and surgical margins were negative. No additional treatment was administered, and she was subsequently followed up in our hospital.

In 2009, although she had no complaints, a follow-up thoracoabdominal computed tomography (CT) (Figure 2) scan was performed which indicated metastatic tumors in the right lung, liver, paraaortic lymph node, and rectus. Since multiple lesions were observed at that time it was considered that surgical resection would be difficult. Thereby we determined that chemotherapy was appropriate, with a dose schedule of bleomycin 30 mg/patient (day 2, 9, 16), etoposide 100 mg/m^2 (day 1-5), cisplatin 20 mg/m^2 (day 1-5) every three weeks. She received three cycles of BEP therapy.

After three cycles of BEP the thoracoabdominal CT scan (Figure 3) indicated that the liver tumor had disappeared, and that the other metastatic lesions were reduced. After the chemotherapy, the patient went into partial remission. Thereafter, she underwent total abdominal hysterectomy, right salpingo-oophorectomy, pelvic lymphadenctomy, paraaortic lymphadenctomy, partial omentectomy, partial rectus resection, and thoracoscopic partial right lung resection.

Lesions were found in the paraaortic lymph node, rectus, and right lung. Final pathology confirmed metastases of GCT in all sites. Since the microscopic finding of these lesions demonstrated that the there were viable cells, but that they were part of tumors with necrotic changes, the BEP therapy was effective pathologically (Figure 4). The results of the immunohistochemical study are summarized in Table 1.

In 2010, abdominal CT and MR imaging indicated a metastatic tumor in the first lumbar vertebra (L1), and positron emission tomography (PET)-CT indicated accumulation in L1 (Figure 5a, b). The orthopedist and radiologist in our hospital diagnosed the GCT metastases in L1, and local radiation 40Gy was administered to L1. Seven years have passed since the initial treatment, with no recurrence to date.

Revised manuscript accepted for publication September 1, 2011

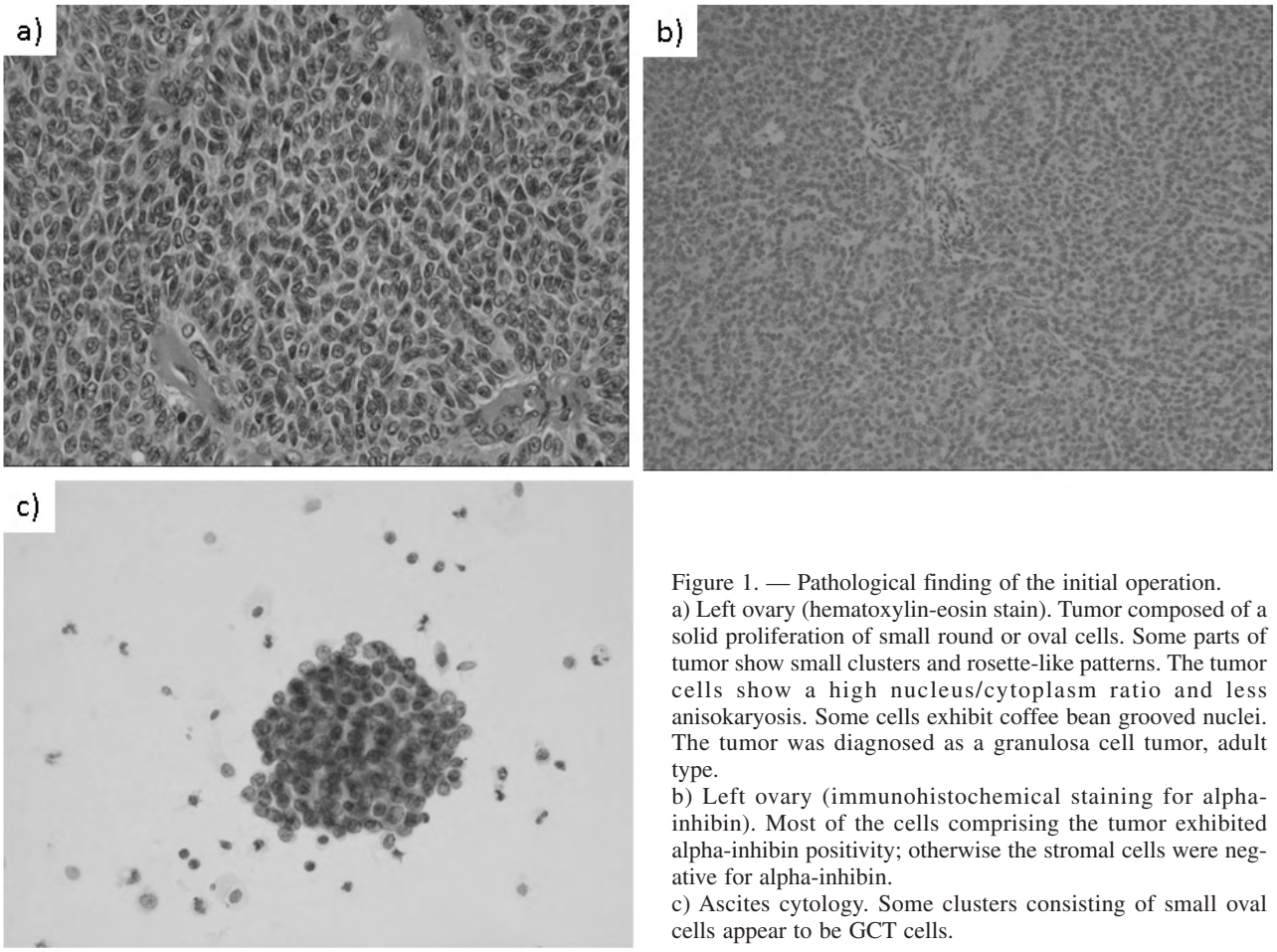

Figure 1. — Pathological finding of the initial operation.
a) Left ovary (hematoxylin-eosin stain). Tumor composed of a solid proliferation of small round or oval cells. Some parts of tumor show small clusters and rosette-like patterns. The tumor cells show a high nucleus/cytoplasm ratio and less anisokaryosis. Some cells exhibit coffee bean grooved nuclei. The tumor was diagnosed as a granulosa cell tumor, adult type.
b) Left ovary (immunohistochemical staining for alpha-inhibin). Most of the cells comprising the tumor exhibited alpha-inhibin positivity; otherwise the stromal cells were negative for alpha-inhibin.
c) Ascites cytology. Some clusters consisting of small oval cells appear to be GCT cells.

Table 1. — *Immunohistochemical finding and mitotic index in the primary lesion and metastatic lesion*.

	Primary lesion	Metastatic lesion
α-Inhibin	+	+
Mitotic index	1-2/10 HPF	10-20/HPF
Ki67 index	a few	10%

Discussion

Ovarian GCTs are borderline malignancies, because they are relatively slow growing tumors and often have a good prognosis. However, due to their slow growth, late recurrence, after ten years or more, has often been reported. After initial treatment in this case, the patient developed multiple metastases to the abdominal wall within four years, to the lung, the liver, the paraaortic lymph node, and the rectus muscle within five years, and to the bone within six years. The initial treatment for ovarian GCTs is surgical resection if the patient does not wish to preserve fertility, and the standard operative procedures are recommended, i.e., hysterectomy, bilateral salpingo-oophorectomy, and partial omentectomy.

If the patient hopes to preserve fertility, unilateral salpingo-oophorectomy should be performed after adequate examination of the abdominal cavity [3]. However, if the clinical stage is IC or higher, careful consideration regarding preservation of the adnexa should be made, since some recurrences have been reported [6]. In advanced cases, additional chemotherapy or radiation therapy should be considered after surgery because surgical resection alone is not expected to be able to remove all microlesions. Since this case was FIGO Stage IC, and cytology of the ascites was positive, we had to consider the indication for surgery that would preserve the patient's fertility. Even though her ovaries were preserved, adjuvant chemotherapy had to be added. However, adjuvant chemotherapy and radiation for ovarian GCTs have not been investigated in a phase III study, but only in small-scale studies. Therefore, sufficient evidence for adjuvant therapy does not exist. While ovarian GCTs often recur in the pelvis, distant metastases are very rare. However, lung metastases, liver metastases, lymph node metastases and bone metastases have been reported, as observed in this case [4, 7-9].

The treatment for recurrent tumor of ovarian GCTs includes surgery, chemotherapy, radiation, and hormone

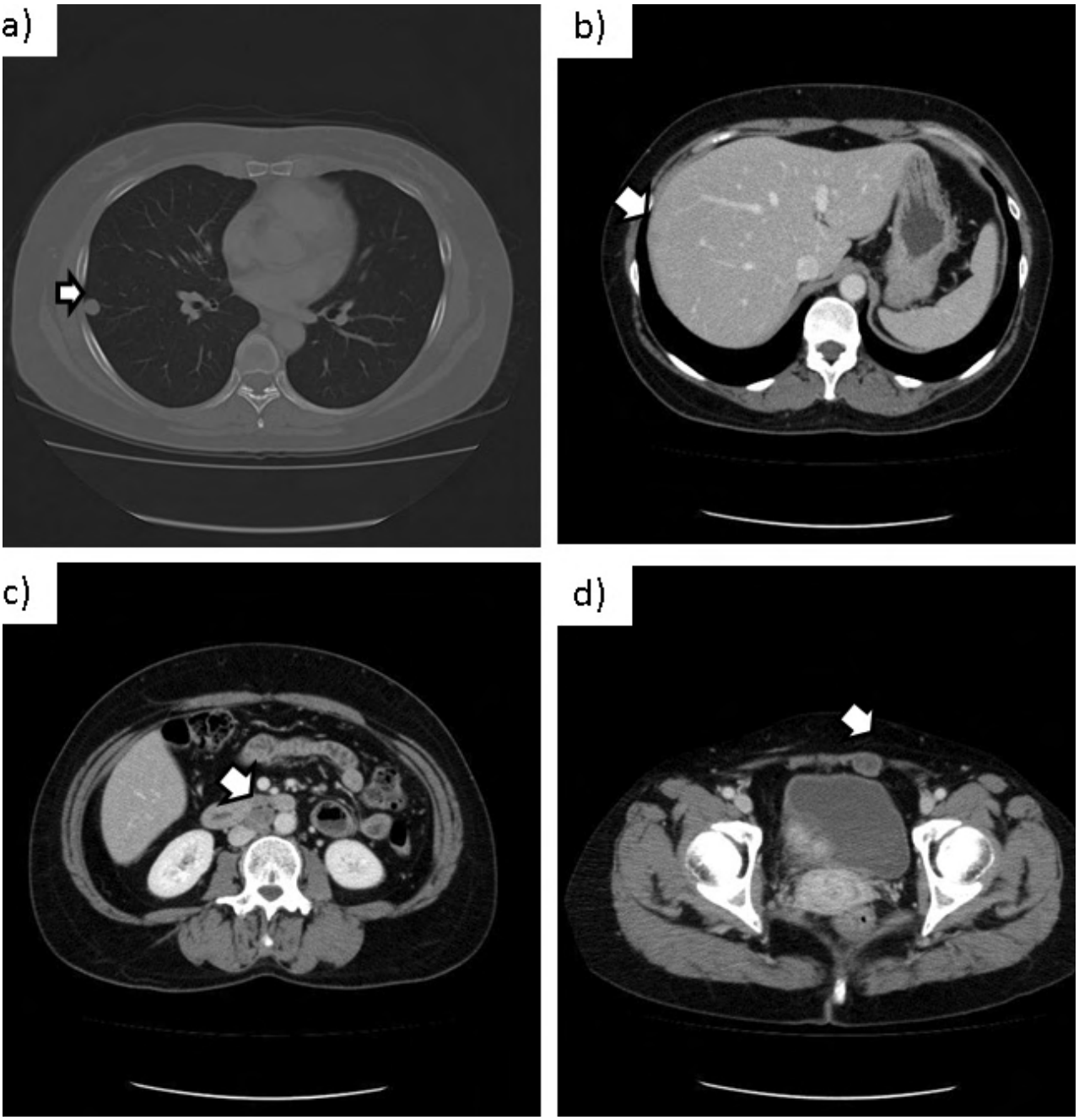

Figure 2. — Lung, liver, paraaortic lymph node (PAN), rectus metastases before the chemotherapy.
a) Lung, b) Liver, c) PAN, d) rectus.
Each arrow indicates a metastatic lesion of the lung, liver, PAN, and rectus.

therapy. Diagnostic imaging, such as CT and MR imaging, is useful for the diagnosis of recurrent GCTs. On the other hand, PET scan has been reported to be less helpful in the diagnosis of recurrence [10]. Since ovarian GCTs are borderline malignancies, their cell growth is slower than cancer cells. Furthermore, due to the lower 18F-fluorodeoxyglucose (18F-FDG) uptake, tumor cells are considered to be false negative in a PET scan. While the lumbar spine metastasis was positive in a PET scan in this case, the standard uptake value (SUV) was slightly high, 3.60, and the diagnostic sensitivity of recurrence and metastases was not considered to be higher with a PET scan compared to CT or MR imaging.

GCTs are estrogen-producing tumors and estradiol is known to be one of the tumor markers of GCTs. Inhibin and anti mullerian hormone (AMH) have been reported to be useful as tumor markers of GCTs but they are off-label examinations in Japan [6, 11]. In this case estradiol did not increase during the recurrence and inhibin and AMH were not examined.

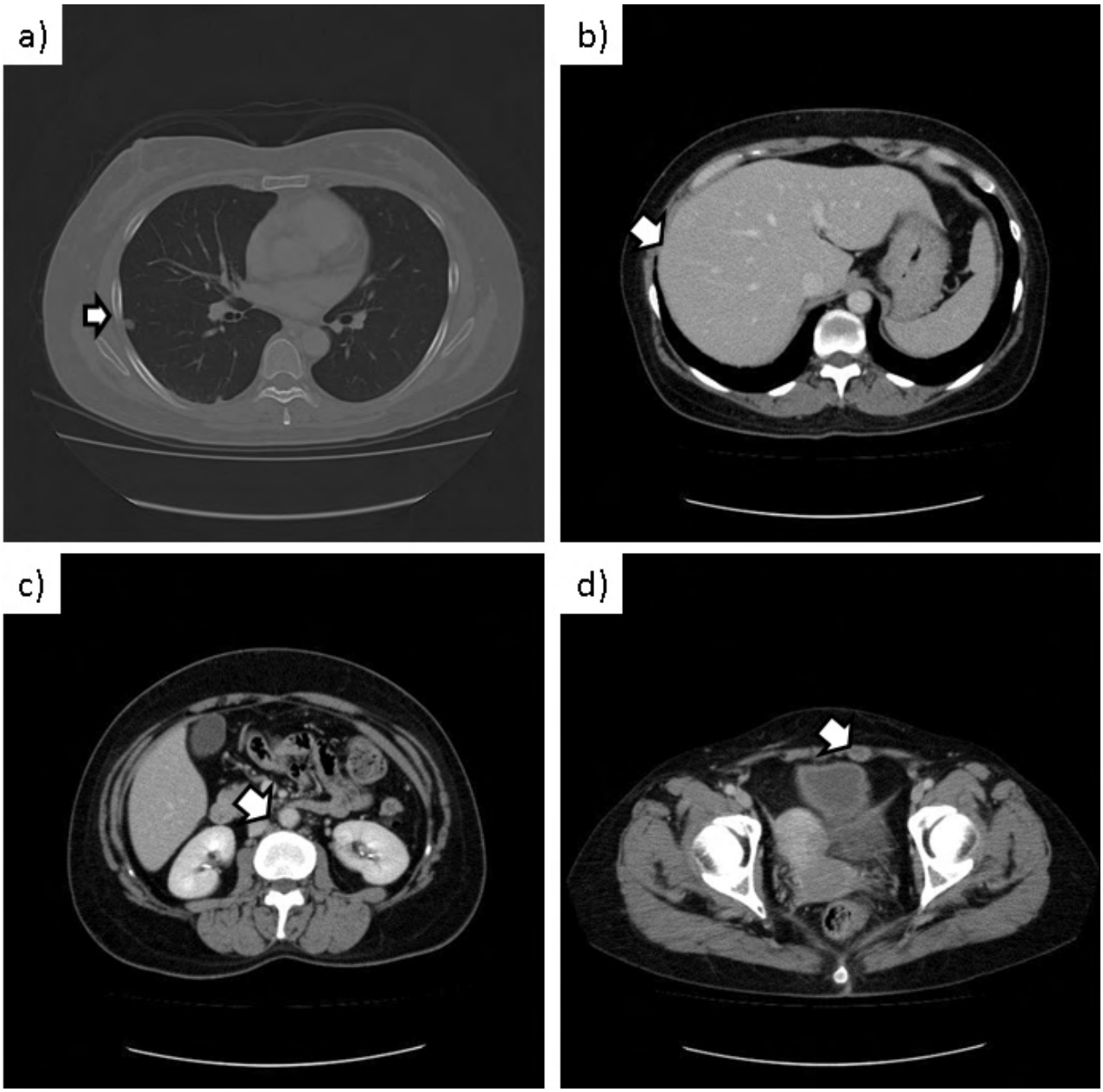

Figure 3. — Lung, liver, paraaortic lymph node (PAN), rectus metastases after three cycles of BEP therapy.
a) Lung, b) Liver, c) PAN, d) rectus.
Each arrow indicates a metastatic lesion of the lung, liver, PAN, and rectus. All lesions are smaller than before the chemotherapy (Figure 2).

In chemotherapy, small-scale clinical studies of BEP and PVB for ovarian GCTs have been performed, and the responsiveness for BEP and PVB has been reported to be 37% and 60.5%, respectively [12, 13]. These regimens are performed for ovarian GCTs in Japan. Since these regimens contained bleomyocin, which has toxicity for the lungs, they are limited to three or four cycles. As in this case, if multiple metastatic lesions are detected, chemotherapy is recommended alone, but if few recurrent lesions are detected, and they are operable, it is desirable to add the appropriate surgery and radiation therapy.

Radiation therapy is performed when the lesion is localized. In a retrospective study, the lesions disappeared in 43% of cases [14]. It is also useful as a treatment for palliative care [15]. Dubuc-Lissoir et al. reported that radiation therapy was effective for vertebral metastases [4]. Since recurrence of the lesion after chemotherapy was solely within the lumbar spine, which was difficult to remove surgically, radiation therapy was performed.

Hormone therapy, as a gonadotropin releasing hormone analog or aromatase inhibitor, has been reported

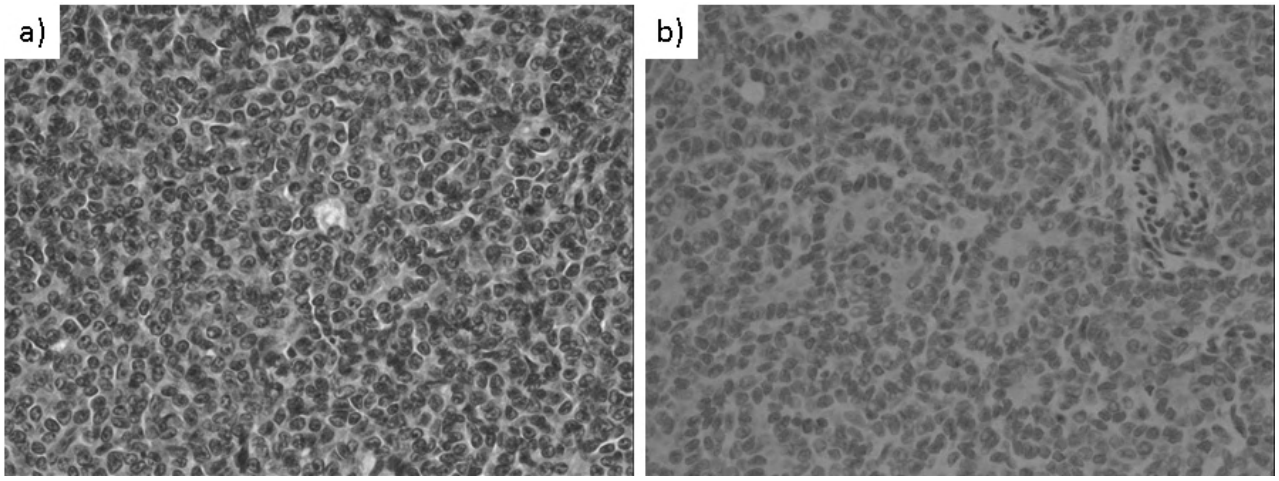

Figure 4. — Pathological findings of the metastatic lesion.
a) Left ovary (hematoxylin-eosin stain). Tumor cells are similar to Figure 1. This tumor was diagnosed as a recurrence of the granulosa cell tumor, adult type.
b) Left ovary (immunohistochemical staining for alpha-inhibin). Most of the cells comprising this tumor exhibited alpha-inhibin positivity.

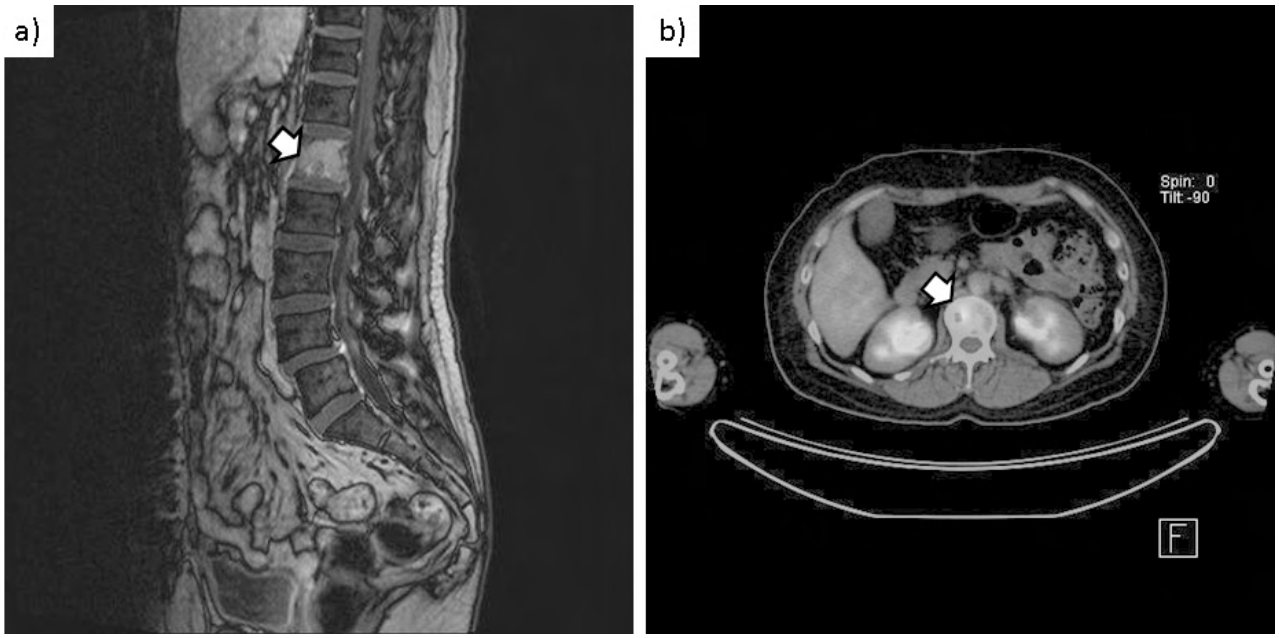

Figure 5. — First lumbar vertebra (L1) metastasis.
a) MR finding.
b) PET-CT scan finding.
Each arrow indicates a metastatic lesion of the L1; SUV is 3.60.

to be effective for GCTs. However, hormone therapy for GCTs has not often been administered in Japan [16, 17].

The clinical risk factors that predict the recurrence of ovarian GCTs have been reported to be age, surgical stage, the presence of residual tumor, and additional treatment. The pathological risk factors that predict the recurrence of ovarian GCTs have been reported to be tumor size, nuclear atypia, mitotic index, Ki-67 index and positivity for alpha-inhibin, but this remains debatable [6, 18-20]. In this case the surgical stage was I, and the mitotic and Ki-67 indexes were not high. However, since the peritoneal cytology was positive, it is suspected that there was a residual tumor in the body at the cellular level.

In conclusion, ovarian GCTs exhibit slow growth, but if surgical stage is IC or higher, there is the possibility of recurrence. We need more careful follow-up after the initial treatment. It is important to treat recurrent tumors with such combination of surgery, chemotherapy, and radiation therapy.

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