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Research Letter

Disseminated granulosa cell tumor of pelvis

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Granulosa cell tumors (GCTs) of the ovary that arise from the sex cord stromal cells of the ovary accounts for 2–3% of all ovarian cancers [1,2]. GCTs are characterized by a low malignant potential, local spread, late recurrences (up to 20 years), and a high survival rate [3]. Two types of GCT have been noted, the adult type and the juvenile type [4]. GCT may be multicystic and contain serous fluid or blood. On histology, adult GCT shows an exclusive population of granulosa cells, an additional component of theca cells, fibroblasts, or both. Call-Exner bodies (grooved nuclei arranged in rosettes) form a microfollicular pattern resembling primodial follicles. GCT can recur or metastasize many years after initial treatment. Primary standard management of these tumors is surgery and consists of hysterectomy and bilateral salpingo-oophorectomy. For young patients with early Stage I disease who wish to maintain fertility, conservative management is reasonable and involves preservation of the uterus and the contralateral ovary [5]. Laparoscopic management of an adnexal mass is a common practice. A solid ovarian tumor requires clean and complete removal of the adnexa. Rupture of an ovary harboring the GCT may lead peritoneal implantation and lead to the need for chemotherapy to treat any more advanced disease.

We report herein a case with recurrent disseminated GCT of the pelvis previously identified as a fibroma (this was confirmed by reexamination to have contained a small amount of GCT) of the ovary and was treated by laparoscopic resectioning. The pathological diagnosis is discussed.

The patient is a 28-year-old female Gravida 0 Para 0 who presented with an irregular menstrual cycle for 1 year and infertility for 5 years. She had received laparoscopic right oophorectomy because of fibroma 4 years ago at another hospital. During the laparoscopic operation to treat the fibroma, there was no ascites in pelvic cavity. A benign tumor was impressed and the ovarian tumor was removed piece by piece through subumbilical port site. Pathology at the time confirmed that this was an ovarian fibroma.

After the initial surgery, her menstrual cycle became regular but then the amount of menstruation began to decrease again. Her menstrual cycle became irregular again 1 year ago. She sought medical help because of amenorrhea for 3 months and ultrasonogaphy revealed a hypoechoic mass of the left ovary. No endometrial lesion was noted on ultrasound examination. Because of an impression of a benign ovarian lesion, no tumor markers were examined preoperatively and she was admitted for laparoscopic surgery.

During laparoscopy, multiple reddish soft nodules ranging from 0.5 cm to 4 cm were found located in the parietal peritoneum area (Fig. 1A). The largest one, about 4 cm in diameter, was located at the left lateral abdominal wall and at the level of the umbilicus (Fig. 1B). The tumor was lipoma-like and rich in blood supply (Fig. 1C and D). All the disseminated tumors in the abdominal cavity were retrieved by endobag to prevent release of the tumor content into the pelvic cavity. The uterus and left adnexa were normal in appearance. The patient decided to receive conservative surgery based on consideration of her future fertility.

Microscopic examination of the multiple lesions showed that the tumors had cells with scanty cytoplasm with pale round to oval nuclei. Nuclear grooves were identified in many of the cells (Fig. 2A). The cells were arranged in microfollicular, trabecular, and diffuse patterns. Mitotic figures were rare. The tumor cells were found to stain positive using antibodies against smooth muscle actin, CD99, and inhibin (Fig. 2B–D). In view of the typical histological morphology and positive inhibin immunostaining, the lesion was diagnosed as a recurrent GCT, adult type. As a result of the diagnosis of GCT this time, we reviewed a previous surgical specimen from the fibroma and found that the previous fibroma contained a small amount of GCT. Thus, the final diagnosis is recurrent GCT.

GCT of the ovary represents a rare form of ovarian neoplasms and these can affect women at any age. In the

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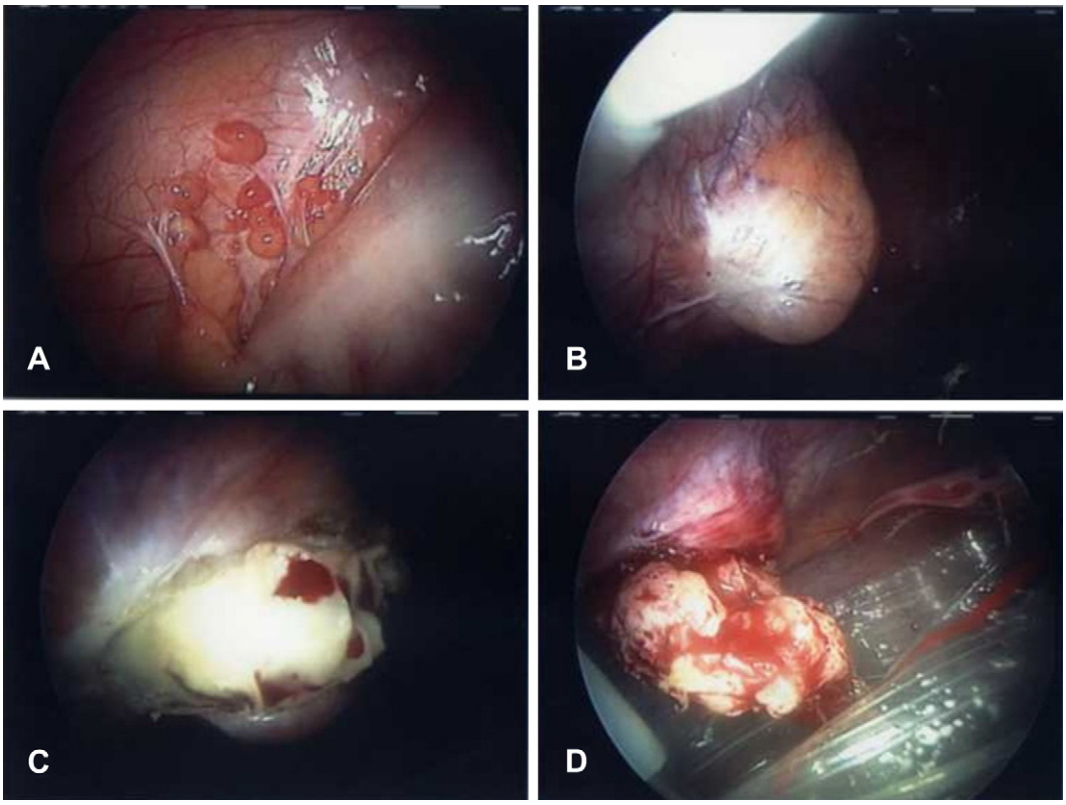

Fig. 1. (A) Multiple reddish soft nodules ranging from 0.5 cm to 4 cm were located in the region of the parietal peritoneum. (B) The largest nodule, about 4 cm in diameter, was located at the left lateral abdominal wall and at the level of the umbilicus. (C and D) The tumor was lipoma-like and rich in blood supply.

reproductive age group, most patients have menstrual irregularities or secondary amenorrhea, and cystic hyperplasia of the endometrium is frequently present. GCTs are usually Stage I at diagnosis but may recur 5–30 years after initial diagnosis. Most GCTs have an indolent growth pattern, and recurrence is not uncommon [6]. Patients with GCT require long-term follow-up with regular history taking, physical examination, and tumor marker studies because 17% of relapses can occur more than 10 years after diagnosis [7]. The most common site of recurrence is the pelvis.

Some patients have symptoms, such as abdominal pain and menstrual irregularities, but diagnosis of GCT is often elusive before surgery [8,9]. Complete surgical resectioning of the abnormal ovary is the mainstay of the management of early GCT. Young patients who desire future fertility may be managed conservatively with the preservation of the uterus and unaffected ovary [5]. Conservative surgery using laparoscopy has been reported to be a safe and effective method for the management of GCT [10]. For Stage IA disease, patients do not require further treatment. Close follow-up involving serial periodic measurements of the patient's inhibin level is recommended. More advanced cases of the disease should receive chemotherapy with the recommended regimen consisting of bleomycin, etoposide, and cisplatinum [11].

Typical histological findings of a GCT include small, pale, round to oval granulosa cells with characteristic "coffee-bean" nuclei. Call-Exner bodies are present in 30–60% of GCTs. Microfollicular, trabecular, insular, diffuse, or a mixture of these cell patterns are often found [12]. The differential diagnosis of GCT includes endometrial stromal sarcoma, undifferentiated carcinoma, and small cell carcinoma [9]. Immunostaining is also helpful with a definitive diagnosis. Inhibin is an important tumor marker for confirmation of a histological diagnosis of GCT [13].

Inhibin is a peptide hormone that participates in the regulation of the pituitary-gonadal feedback system and is selectively expressed by cells of sex cord-stromal derivation [14]. The ovary is the only source of inhibin secretion in nonpregnant women. The serum level of inhibin is often elevated in patients with granulose cell tumors [13]. It has been found to be a more reliable marker for GCT than estradiol [13]. Using immunohistological techniques, inhibin has been localized to the granulose cell layer, the surrounding theca cells of secondary follicles, and the hilar cells of the ovary [15]. The presence of moderate to strong staining for inhibin in a histologically indeterminate ovarian neoplasm provides strong support for sex cord-stromal differentiation and practically excludes a primary or metastatic carcinoma or a germ cell neoplasm [14]. In the present case, strong positivity for inhibin, smooth muscle actin, and CD99 confirmed the diagnosis of GCT.

The patient presented with multiple separate intrapelvic masses, which is unusual for a primary tumor. GCT is known to recur or metastasize years after initial diagnosis and treatment and therefore there is strong correlation between metastatic deposits in pelvic cavity and previous pathology.

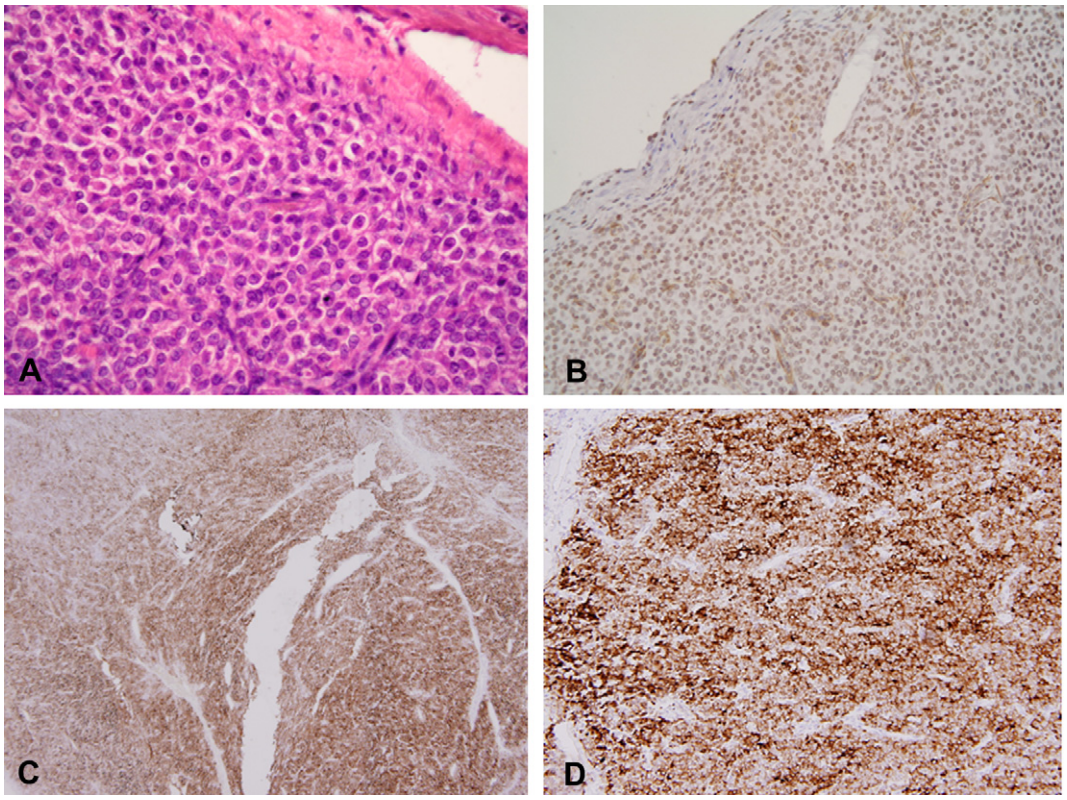

Fig. 2. Microscopic features and immunohistochemistry of the granulosa cell tumors. (A) Microscopic features of the GCT (H&E stain, 100×). (B) Microscopic immunohistochemistry showing that the tumor is positive for smooth muscle actin as well as (C) anti-cd99 and (D) anti-inhibin (50×). GCT = granulosa cell tumor; H&E = hematoxylin and eosin.

Diagnostic laparoscopy has been accepted as a standard for identifying the origin of a tumor, the extent of disease, and its respectability [9]. Therapeutic procedures for benign lesions, such as ovarian cysts or cystic teratomas, have been previously described. However, laparoscopic resection of ovarian malignancies has not yet been generally advocated. Nonetheless, this type of minimally invasive resectioning only means that there is a different type of access to the tumor and does not compromise surgical safety [10,16]. The use of an endoscopic retrieval bag into which the mass can be placed and reduced in size without spillage into the peritoneal cavity facilitates the safe removal of the mass. Frozen sectioning also can help with the diagnosis during the operation.

In conclusion, laparoscopic management of an unknown adnexal mass is acceptable and even preferable to laparotomy. Clean removal of the adnexal tumor without spillage of tumor contents needs to be emphasized. If the tumor is ruptured, then the patient should undergo an additional surgical procedure and receive adjuvant chemotherapy to treat any locally advanced disease. Immunostaining can help to differentiate GCTs from other neoplasms.

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