Case Reports

Recurrence of granulosa cell tumor 25 years after initial diagnosis. Report of a case and review of the literature

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Summary

Granulosa cell tumors (GCTs) are rare functional sex cord-stromal ovarian tumors constituting approximately 2-3% of all ovarian malignancies. They are characterized by low malignant potential, local spread, late recurrence and high survival rates. We report a case of recurrent ovarian GCT in a 60-year-old woman 25 years after the initial diagnosis. The patient underwent surgical resection of the pelvic masses and refused to receive any adjuvant treatment, considering the late recurrence and high survival rates of this tumor. This case illustrates an example of a very late recurrence and emphasizes the importance of the extended follow-up required for these patients.

Key words: Adult granulosa cell tumor; Recurrence.

Introduction

Granulosa cell tumors (GCTs) are rare functional sex cord-stromal ovarian tumors constituting approximately 2-3% of all ovarian malignancies. Two distinct types exist, known respectively as adult and junenile. The adult granulosa cell tumors (AGCTs) account for 95% of all granulosa cell tumors [1]. They are characterized by low malignant potential, local spread, late recurrence and high survival rates [2]. Recurrences as late as 20 or more years after the initial diagnosis have been reported [3, 4].

We report a case of recurrent ovarian GCT 25 years after the initial diagnosis together with a review the literature.

Case Report

A 60-year-old, para 2 woman presented with abdominal and pelvic discomfort. Physical and pelvic examination revealed a right lower quandrant mass. Her past medical history was significant for a total abdominal hysterectomy and bilateral salpingo-oophorectomy in 1982 for a solid left ovarian mass. Pathologic evaluation revealed a GCT of the ovary and no significant abnormality of the uterus, tubes or contralateral ovary. No additional therapy was prescribed.

Transvaginal pelvic sonography (TVS) confirmed a tumor in the anatomical location of the right ovary measuring 52 x 40 mm in diameter, with both solid and cystic components (Figure 1). Doppler examination showed a normal vascular pattern. Magnetic resonance imaging (MRI) of the abdomen revealed a right-sided solid and cystic pelvic mass, 45 mm in diameter, adherent to the right rectus abdominal muscle. Another complex cystic lesion 25 mm in diameter was also detected below the previous one in the lower pelvic wall. Laboratory work-up revealed normal levels of CA-125 (15.35 U/ml), CEA (1.7 ng/ml), inhibin-B (8.9 pg/ml) and 17β-estradiol (30.6 pg/ml).

At laparotomy, a 4 x 5 cm mass, partially solid and cystic, adherent to the right rectus abdominal muscle and above the pubic symphysis was found. Another solid mass 3 cm in diameter was found in the lower pelvic wall, adhering to the rectum. The liver, hemidiaphragms, intestines, abdomen and pelvis were all normal, with the exception of dense pelvic adhesions. Peritoneal lavage for cytology, extensive adhesiolysis and resection of the pelvic masses were performed.

The specimen that was attached to the rectus abdominal muscle consisted of fibrofatty tissue with an attached fragment of skeletal muscle and measured 10 x 6 x 3.5 cm. On sectioning, a cyst measuring 4 cm in diameter was identified. Its lining consisted of hemorrhagic friable tissue, which microscopically was fibrin and focally a recurrent granulosa cell tumor (Figure 2). Focal involvement of the striated muscle by granulosa cells was also identified (Figure 3). The specimen that was excised from the lower abdominal wall was well circumscribed and measured 3.5 x 2.5 x 2 cm. The cut surface was solid and focally cystic. Microscopically it was a recurrent granulosa cell tumor growing in a diffuse and trabecular pattern with rare Call-Exner bodies. The neoplastic cells had low mitotic activity (< 1 mitotic figure/10 HPF) and were positive for inhibin and vimentin by immunohistochemistry. Cytopathologic examination of the peritoneal washings was negative.

Postoperative recovery was uncomplicated. Adjuvant chemotherapy and radiotherapy were recommended. However, despite the consultation from her doctors, the patient refused to follow any adjuvant treatment, keeping in mind the late recurrence and high survival rates of this tumor. The patient has been followed-up regularly for one year without any signs of recurrence.

Discussion

GCTs of the ovary are hormonally active tumors which account for a small percentage of ovarian malignancies. They occur more often in posmenopausal women, with a

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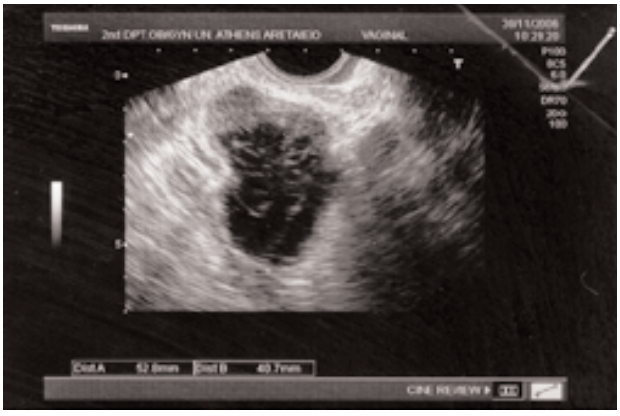

Figure 1. — Transvaginal ultrasonogram demonstrating a tumor measuring 52 x 40 mm in diameter with both solid and cystic components.

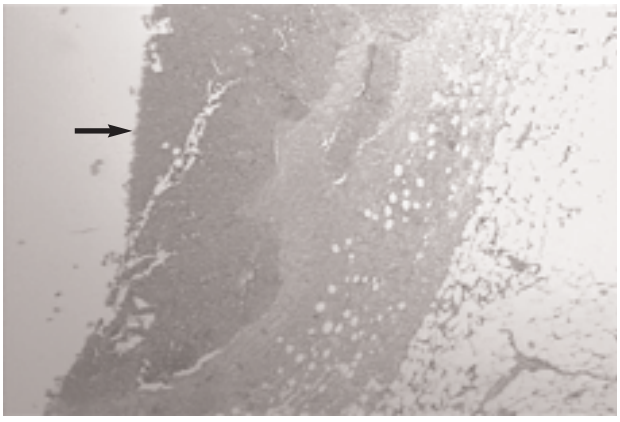

Figure 2. — Low power view of the cystic granulosa cell tumor. Fibrofatty tissue, cyst wall and granulosa cell tumor (arrow) (H&E x 25).

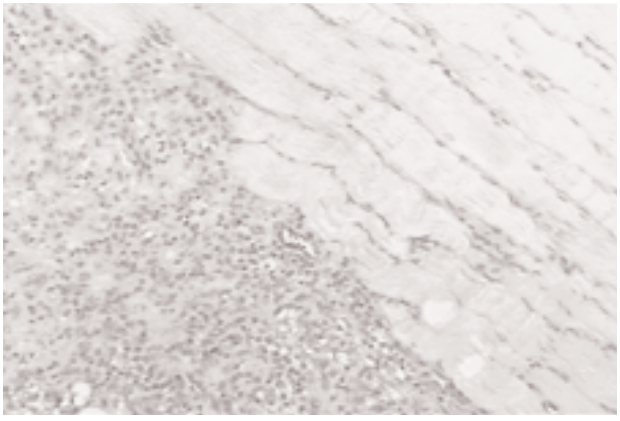

Figure 3. — Granulosa cells involving skeletal muscle (H&E x 160).

peak incidence between 50 and 55 years of age. Patients with GCTs often present with nonspecific symptoms of abdominal pain or distension due to large tumor size [5]. Also, about 10% of patients present with acute abdominal pain and hemoperitoneum due to torsion or rupture of the tumor [2]. About two-thirds of patients have endocrine manifestations due to hormone secretion by the tumor, leading to early diagnosis. The majority of these neoplasms are estrogenic [6]. Rarely, are they androgenic and cause virilization [7]. The consequences of estrogen production depend on the age of the patient. The most common symptom in postmenopausal women is vaginal bleeding. Due to prolonged exposure to tumor-derived estrogen, about 50-60% of patients develop endometrial hyperplasia and 5-10% have concomitant uterine cancer [2]. Occasionally, swelling and tenderness of the breast are prominent symptoms. In contrast, premenopausal women may develop irregular menses or less often, amenorrhea. A juvenile form of GCT in prepubertal girls is associated with isosexual precocious puberty. Elevated levels of estrogens and inhibin have been reported and vaginal cytologic smears typically show increased maturation of squamous epithelial cells [1].

Stage of disease at presentation is the most important prognostic factor. About 85-90% of patients present with Stage I disease, which is associated with a greater than 90% 5-year survival rate. Bilateral tumors are uncommon, accounting for 2-8% of cases. Poor prognostic factors include tumor size greater than 10-15 cm, high mitotic index, tumor rupture and lymphatic invasion [2].

Treatment for GCTs is primarily surgical. The extent of initial surgery is somewhat controversial. During the reproductive years, conservative surgery with unilateral salpingo-oophorectomy with careful staging and endometrial biopsy (to exclude a concomitant uterine cancer) appears to be adequate for Stage I disease. Radical surgery with total abdominal hysterectomy, bilateral salpingo-oophorectomy and complete tumor debulking is preferable for patients with greater than Stage IA disease or if infertility in not an issue. Adjuvant chemotherapy or radiation therapy in the setting of completely resected Stage I tumors does not appear to reduce the risk of recurrence. Advanced metastatic GCTs are typically treated with aggressive surgical resection, followed by postoperative radiation therapy or systemic chemotherapy. Radiation therapy may have some effect in minimal residual disease [6].

It is well established that GCTs of the ovary have a tendency to recur late. The median time to relapse is four to six years after initial diagnosis [2], although disease has recurred as late as 37 years [3]. Due to the long interval to relapse, assessing the impact of any adjuvant treatment on overall survival is difficult. The total reccurence risk for these tumors is diffcult to assess, since it may be obscured by deaths from other diseases. Given this, any abdominal, retroperitoneal or pelvic mass in these patients should be considered recurrent GCT until proven othewise, regardless of the time of initial diagnosis. There is no standard approach to the management of relapsed disease. Repeat surgical resection for optimal cytoreduction is a reasonable option given the tumor's indolent growth and late recurrence. Radiation treatment in the metastatic or recurrent setting may lead to prolonged disease-free survival [8]. Chemotherapy may be an option for patients with large residual disease, metastases and

inoperable tumors. Cisplatin is the most active agent in GCT of the ovary [9]. Hormonal therapies, such as progestins (medroxyprogeserone acetate), antiestrogens (tamoxifen) and GnRH agonists (leuprolide) have been used for recurrent GCTs and have the advantage of low side-effect profiles [10].

The long natural history of this disease highlights the importance of extended follow-up for patients with GCT. The use of tumor markers for surveillance is controversial. Serum estradiol levels are too insensitive to be a reliable marker of disease activity, particularly in premenopausal women. Serum inhibin, which is a hormone produced by granulosa cells, may be a useful tumor marker. In one prospective study, serum inhibin levels were found to be elevated preoperatively in patients with GCTs and became elevated up to two years before secondary surgery was performed for recurrent disease [11]. Serial inhibin levels may be useful in monitoring patients post-therapy, but should be interpreted with caution since they may be elevated in other conditions as well (during the menstrual cycle, pregnancy) [12].

Our case represents a recurrence of a GCT 25 years after initial diagnosis, which is one of the latest recurrences reported in the literature [3,4]. These recurrences emphasize the necessity for lifetime follow-up. The recurrent tumor was treated only with surgical resection, which remains an acceptable approach given the natural history of the disease.

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