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Case Reports

The longest period to recurrence of granulosa cell ovarian tumor: 41 years after initial diagnosis

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Summary

Granulosa cell tumors (GCTs) are characterized by slow growth, local spread, and late recurrence. The authors report the case unique for both unusually large dimensions of the recurring tumor and the fact that it was confined only to the omentum, where it has recurred 41 years after the initial surgery including salpingo-oophorectomy. This is the longest reported period from initial diagnosis to the recurrence of GCT. This case report is important as it proves that recurrence of GCT is possible even after an extremely long period of time after the initial surgery, due to the nature of this tumor, and the inhibition of apoptosis process.

Key words: Granulosa cell tumor; Ovary; Omentum; Relapse; Apoptosis.

Introduction

Granulosa cell tumors (GCT) are the most common type of malignant ovarian sex cord–stromal tumor [1]. The adult form of GCT accounts for 1-2% of all ovarian tumors and 95% of all granulosa cell tumors. GCT is usually smaller than 10cm in diameter, with the peak age of occurrence of 50-55 years [2]. These tumors are associated with a good prognosis due to early diagnosis and high survival rates. The natural history of this disease is characterized by slow growth, local spread, and late recurrence, as late as 37 years [3]. Metastatic disease can involve any organ system, although tumor growth usually is confined to the abdomen and pelvis. Here we present a case of GCT with an extremely late occurrence, 41 years after diagnosis and initial surgery. This case presents the longest period of time of relapse after the initial diagnosis, on the very unusual site, focusing on the hypothetic causes for relapse.

Case Report

An 80-year-old woman was admitted to the Clinic of Obstetrics and Gynecology complaining of pelvic and abdominal pain. The patient stated that she had a right adnexectomy due to ovarian cancer 41 years prior. Histopathological finding showed GCT. However, she refused the subsequently proposed chemotherapy treatment. Furthermore, her medical history included an appendectomy and a cholecystectomy 25 years ago. She was treated for diabetes mellitus and arterial hypertension. The laboratory findings showed anemia (Hgb=97 g/l), increased values of erythrocyte sedimentation rate (ESR=70 mm/h), serum creatinine 106 μmol/L (normal range=45-84 μmol/L), while other biochemical parameters were in referral range. Out of all tested serum tumor markers (Ca 125, HE4, CEA, CA 19-9, and CA 15-3), only levels of CA 125 were elevated (76 U/mL).

Pelvic and abdominal multi-slice computed tomography (MSCT) showed a semi-solid, non-homogenous, multilocular tumor measuring 112×100×82 mm, in front of the uterus and above the bladder. In the left adnexal region, MSCT revealed another tumorous mass of the same characteristics 128×104×131 mm in diameter. Ascites was also observed (Figures 1a and 1b).

After thorough evaluation, the patient was operated. Intraoperatively, there was about 500 ml of free hemorrhagic fluid in the abdomen, which was sent to cytology. Furthermore, two necrotic hemorrhagic masses were found, belonging to the omentum, which was entirely callous. Tumor located in the right pelvic region partly adhered to the parietal and bladder peritoneum. The other omental tumor was found to be below the spleen, without adhesions to the surrounding organs. The uterus was normal in size and shaped, with smooth and pink serosa, corresponding to the patient's age. The right adnexa were surgically removed 41

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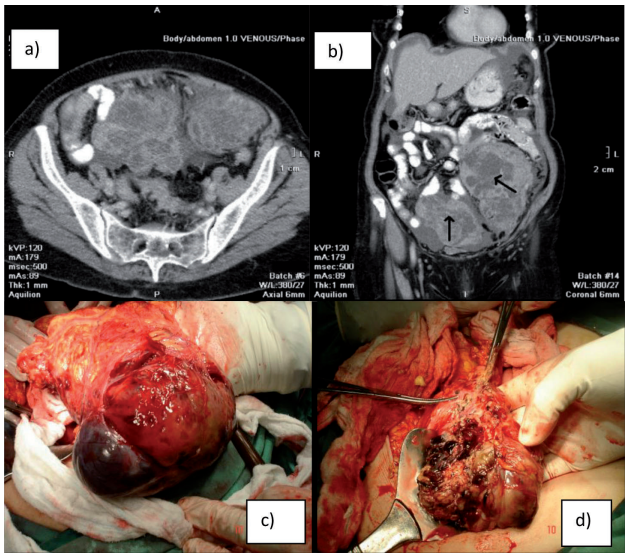

Figure 1. — a) Pelvic MSCT. b) Abdominal and pelvic MSCT: two heterogenous tumorous masses in pelvis. c) Intraoperative finding: first GCT in omentum. d) Intraoperative finding: second GCT in omentum.

years prior, while the left ovary and the left fallopian tube showed no macroscopically visible pathological changes. There was no malignant infiltration of the liver, spleen, and pelvic peritoneum. A classical hysterectomy with left salpingo-oophorectomy was performed, alongside with total omentectomy, multiple parietal peritoneum biopsies, as well as pelvic and para-aortal lymphadenectomies (Figures 1c and 1d).

On histopathological examination the omentum contained two masses measuring 110×98×85 mm and 150×125×85 mm, respectively, and weighing 980 grams. The masses had uneven, brownish, smooth outer surface, and upon sectioning showed hard consistency, pale yellow to brownish color, and numerous cystic structures up to 20 mm in diameter, filled with clear yellowish and reddish fluid. Serial sections of omental adipose tissue revealed diffuse neoplastic infiltration. Microscopically the neoplasm was characterized by small uniform, poorly demarcated cells with oval, monomorphous, on occasion grooved nuclei, which showed rare mitoses. Call-Exner bodies were detected. Histological characteristics and immunoprofile of the neoplasm were consistent with omental deposits of the ovarian GCT. Cytopathological analysis of ascites showed a number of malignant cells.

Postoperative course was uneventful. The patient was discharged from the Clinic in good general condition seven days after surgery. Throughout postoperative period, the patient was monitored in six-month intervals and was asymptomatic. MSCT findings of the abdomen and pelvis at six, 12, and 18 months after surgery showed no recurrence of malignant tumor and the results of tumor markers on check-ups were all within normal ranges. Adjuvant chemotherapy was recommended to the patient, but she refused it once again.

Discussion

Although most GCTs have very low potential for malignant behavior, with 90% tumors being Stage Ia at detection, they do have a propensity for late recurrence up to 10-20 years or more after initial diagnosis [2, 4]. Recurrences develop in 15–25 % of patients in early stage and in 50–70 % in advanced stages. Estimated five-year disease-free survival according to literature reaches 80-90%. Recurrence is mostly influenced by tumor stage and size at the time of diagnosis, mitotic index, and presence of residual tumor after surgery. So far the longest registered periods from initial diagnose to the recurrence were 37 and 25 years [5-8].

Patients with GCT have, very often, unspecific symptoms: abdominal pain and bloating or abdomen distension due to large tumor. Approximately two-thirds of patients have endocrine manifestation due to hormone secretion from tumor [9]. The main complaint of the present patient on admission was acute pain in the pelvis and abdomen, which is very common sign of this type of tumor. The clinical presentation is different in premenopausal and postmenopausal women. Before menopause, one-third of patients suffer from acute abdominal pain, while bleeding is the most common symptom in postmenopausal women [10]. The present patient had no vaginal bleeding.

Literature data show that adjuvant chemotherapy reduces the recurrence of the disease for one-third [11]. Moreover, use of adjuvant radiotherapy might give a better prognosis [12]. The present patient refused this treatment after the first surgery, despite being informed and aware of the disease process in patients that do not receive adjuvant therapy after surgery for malignant tumors of the ovary. Nevertheless, it took 41 years for the symptoms and tumor to recur. Surgical removal of GCT is the treatment of choice, as it was done in the case presented, although application of radiotherapy, chemotherapy, GnRH agonists, and aromatase inhibitors can also be found in the literature [13-15].

The late relapse of a malignant tumor in the present patient may be explained in two ways. The first is the substantial nature of this histological type of malignant tumor and its tendency to relapse. Another explanation is the inhibition of apoptosis that occurs during the aging process. It is possible that malignant cells were dormant in the omentum for as long as 41 years. Cessation of proliferation, inhibition, and lack of recognition of foreign cells in this patient could have led to activation of neoplastic process. It is believed that disturbances in granulosa cell apoptosis have an important role in the pathogenesis of granulosa cell tumors. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a potent cytokine that induces apoptosis in a variety of malignancies without toxic effects on benign cells [16]. It was demonstrated that the TRAIL receptors DR4 and DR5 are expressed in a majority of human GCTs, and that TRAIL can effectively induce apoptosis in isolated primary tumor cells and that GATA4 (named after its binding to a consensus W-GATA-R motif), a transcription factor implicated in ovarian apoptosis and GCT pathobiology, can protect tumor cells from TRAIL induced apoptosis in vitro [17]. Also, the role of specific ge-

netic mutations in patients suffering from non-epithelial ovarian tumors must not be underestimated. In the recently published data, it was found that mutations in processing RNA were common in those patients [18]. In the present patient, the proliferation of malignant cells was extensive, but only in the omentum. The left ovary showed neither macroscopic nor microscopic changes that would indicate that there had been 'de novo" appearance of the same histological type of malignant tumor (as it was initially 41 years ago), with secondary deposits into the omentum. The significance of this case is multiple. It supports the hypothesis of apoptosis inhibition throughout aging, as well as the nature of this malignant tumor and its tendency to relapse. The case is unique for such extreme dimensions of the recurring tumor and the fact that it was confined only to the omentum, where it recurred 41 years after the initial surgery.

Conclusion

Recurrence of GCT is possible even after a very long period of time after the initial surgery, due to the nature of this tumor, and the inhibition of apoptosis process. Its clinical manifestation is non-specific, as well as in other ovarian tumors, and depends (predominantly) on the recurrence location.

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