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Case Report

Central primary primitive neuroectodermal tumor (cPNET) arising from an ovarian mature cystic teratoma in pregnancy: A case report and review of medical literature

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Introduction

Primary primitive neuroectodermal tumor (PNET) of the ovary is a rare entity. PNETs may be classified under 2 broad categories with differing clinical characteristics, immunohistochemical profiles and genetics: (i) central PNET (cPNET) and (ii) peripheral PNET (pPNET). PNETs in general are aggressive cancers associated with a high mortality (Kovar, 1998). We present a case of a patient diagnosed with cPNET arising from a mature cystic teratoma during pregnancy, managed with fertility-preserving surgery.

Case report

A 27 year old nulliparous Chinese woman presented to her obstetrician at 12 weeks of gestation. Ultrasound showed a left triloculated cyst measuring 8.9×7 cm and serum tumor markers (CA-125, CEA and AFP) were normal. She underwent an open ovarian cystectomy at 14 weeks of gestation in June 2009. There was an iatrogenic capsular rupture during the cystectomy.

Gross examination of the resected ovarian cyst revealed locules containing sebaceous material and hairs (Fig. 1). The largest locule showed a mural nodule measuring 8×5×3 cm, with adipose, cartilaginous and bony areas. Histological examination of the ovarian cyst revealed a mature cystic teratoma comprising skin, adipose, gastrointestinal tract, respiratory tract, cartilage, lamellar bone, hematopoietic and neural tissue (Fig. 2). However, the mural nodule from the largest locule showed an area of malignant transformation, comprising a nodular focus of PNET measuring 7 mm in greatest dimension (Fig. 3A). The PNET was composed of sheets of primitive round cells with high nuclear-cytoplasmic ratio, frequent mitoses and focal necrosis, set in a finely fibrillary background (Fig. 3B and C). At its edges, the PNET showed infiltration into surrounding mature teratomatous neural tissue (Fig. 3D). Several adjacent foci of lymphovascular invasion were also seen (Fig. 3E). Immunohistochemical studies demonstrated within the PNET expression of neural markers chromogranin A and synaptophysin, and a Ki67 labeling index of 90% (Fig. 3B). There was absence of immunoreactivity for CD99, indicating that the tumor was a central-type PNET.

Chest X-ray (abdominal shielding) and MRI of the abdomen and pelvis did not reveal any distant metastases. She had at least a FIGO Stage IC cPNET of the ovary (T1c NX M0). Subsequently, she was managed by a multidisciplinary team comprising of a gynecologic oncologist, a medical oncologist, as well as a maternal fetal medicine specialist.

In view of the lymphovascular space invasion and high risk of metastases, coupled with the highly aggressive nature of cPNET, the patient was counseled for staging surgery and the pros and cons of chemotherapy were also discussed. However, she declined further surgery and chemotherapy during pregnancy. She was followed up closely throughout pregnancy, which remained largely uneventful. She delivered a healthy baby boy at 37 weeks of gestation via an elective lower segment cesarean section (LSCS), with a birth weight of 2925 g. At the same time, she underwent a left salpingo-oophorectomy, left pelvic lymph node sampling, omentectomy and peritoneal washing for staging. She had opted for a fertility sparing surgery instead of a full staging surgery. Intra-operatively, the left ovary was slightly nodular, but the right ovary appeared normal. There was no enlarged retroperitoneal lymphadenopathy or peritoneal disease. Histological examination of the remnant left ovary did not show any residual disease, and the left pelvic lymph nodes, omentum and peritoneal washing were all negative for malignancy. The patient was then counseled for adjuvant chemotherapy after her delivery in view of the aggressive nature of cPNET and evidence of lymphovascular invasion on histology. However, she declined any further treatment, and was given regular follow-up in the gynecologic oncology clinic.

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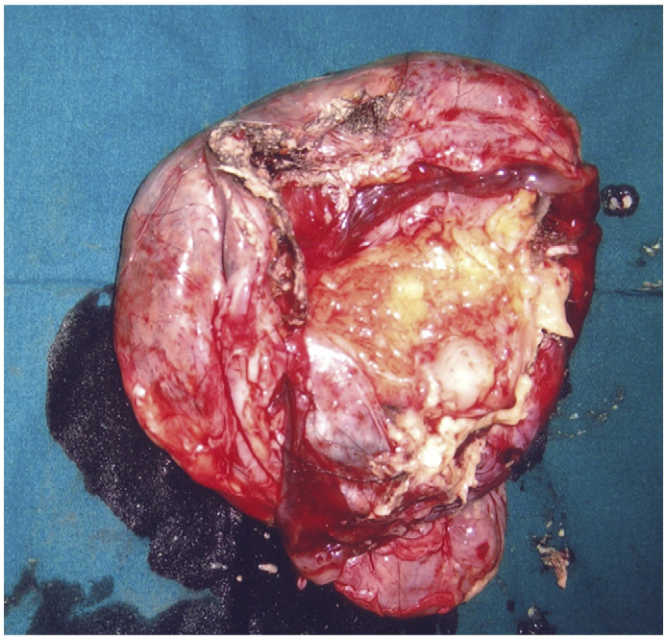

Fig. 1. Gross specimen of resected ovarian cyst.

Half a year later, the patient became pregnant with her second child in July 2010. She was well antenatally. She delivered her second child by elective LSCS, with a birth weight of 3438 g. She continued to be on regular follow up in our hospital, with no cancer relapse 2.5 years after her diagnosis.

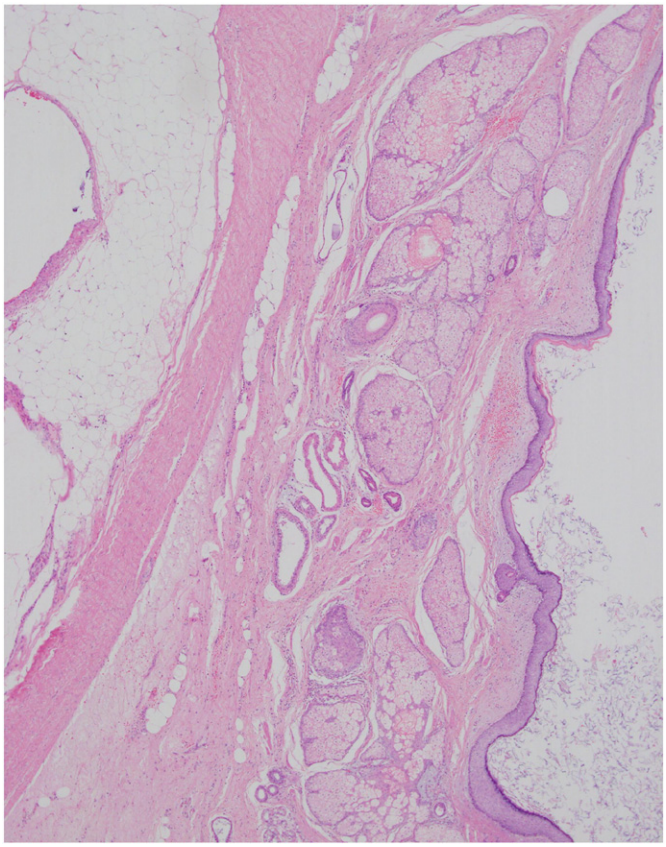

Fig. 2. Histological diagnosis of mature cystic teratoma. The main tumor was a mature cystic teratoma, with skin and adipose tissue elements shown here (H&E, low power).

Discussion

The incidence of ovarian cysts during pregnancy varies from 1 in 100 to 1 in 2000 pregnancies and malignant ovarian tumors are relatively uncommon.

The primary diagnostic challenge in this case involved distinguishing between an immature teratoma with only a minor focus of immature neuroepithelial elements, versus a mature teratoma with focal secondary malignant (PNET) transformation. The risk of malignant transformation develops in about 0.17 to 2% of mature cystic teratomas, and occurs most often in postmenopausal women (Hinshaw et al., 2012). Malignant neural tumors arising in mature cystic teratomas are rare, and those reported in young women usually but not always represent immature teratomas that characteristically contain immature neuroepithelial elements. Nonetheless, in this case, the following features indicated the diagnosis of mature cystic teratoma with secondary malignant (PNET) transformation, i.e. the nodular focus of primitive round cells arising from the cystic teratoma did not resemble normal embryonal neural tissue, but instead displayed anaplastic features consistent with PNET, such as nuclear atypia, a high mitotic rate and Ki67 labeling index, necrosis, infiltrative edges and lymphovascular invasion. Having established the diagnosis of PNET arising in a mature teratoma, we further performed immunohistochemistry for CD99 to distinguish between cPNET and pPNET. Though histologically similar, cPNET and pPNET are different clinical entities, with different localizations, immunohistochemical profiles and genetics (Morovic and Damjanov, 2008b), and are often confused or not differentiated by authors. cPNET is an embryonal tumor deriving from the central nervous system (CNS), whereas pPNET arises outside the CNS and is grouped under the Ewing sarcoma family of tumors. pPNET expresses MIC2 glycoprotein (CD99) and shows the specific chimeric gene EWS-FLI1, which can be detected by immunohistochemical staining for CD99 (Ishii et al., 2001). Often, distinguishing between cPNET and pPNET is uncomplicated due to the location of the tumor. However, in this case, the origin of the PNET within the ovarian teratoma necessitated the performance of CD99 immunohistochemistry, and the negative staining result confirmed a cPNET. This is consistent with findings from previous studies that demonstrate that the majority of PNET transformed from testicular or ovarian germ cell tumors exhibit morphological features of central rather than peripheral PNETs (Ulbright et al., 2010).

The rarity of cPNET of the ovary precludes randomized clinical study to guide the management of this disease hence the optimal treatment strategies have not been established. In general, ovarian PNET malignancies are highly aggressive and the prognosis is poor especially in the presence of extra-ovarian spread. One of the largest studies by Morovic and Damjanov (2008a) identified that disease stage appears to be the most important prognostic factor in PNET of the ovary. The majority of patients with Stage I disease (nine out of eleven cases) were alive and free of disease at a follow-up period of between three to five years. Many of the patients with Stage IA disease were treated with staging laparotomy, total hysterectomy bilateral salpingo-ophorectomy, omentectomy and pelvic/para-aortic lymphadenectomy only, whereas the Stage IC patients received chemotherapy in addition to surgery. On the other hand, women with Stage III or IV disease were often treated with surgery in combination with chemotherapy and or radiotherapy. Despite treatments, the prognoses of these women with advanced disease remained poor, the diseases were highly aggressive and rapidly gave rise to metastases and death.

Fertility-preserving surgery followed by chemotherapy for early stage PNET of the ovary with successful pregnancies has been reported recently by Demirtas et al. (2004). He reported a young patient with Stage IC PNET of the ovary who was treated with unilateral salpingo-oophorectomy, wedge resection of the right ovary and complete pelvic and para-aortic lymphadenectomy. She received adjuvant chemotherapy consisting of bleomycin, etoposide and cisplatin (BEP protocol). Her