Current Problems in Cancer 45 (2021) 100667

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Extraovarian dysgerminoma in a pregnant woman: an extremely rare finding

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ABSTRACT

Extraovarian germ cell tumors are very rare and their occurrence during pregnancy is exceptional. In this case report an abdominal mass was shown by ultrasonography, during a routine monitoring of a 26-year-old pregnant woman. The patient was left under radiological control in the following months in order to bring the pregnancy to term. A few months after the delivery, the patient underwent surgery and a diagnosis of extraovarian (abdominal) dysgerminoma was made. To the best of our knowledge, there are only 3 other case reports describing an extra-gonadal dysgerminoma occurring during pregnancy. The aim of this study was to report an extremely rare tumor, whose management can be challenging first because this neoplasm has some differences from its ovarian and testicular counterparts. Furthermore, the occurrence during pregnancy makes the multidisciplinary approach mandatory since 3 distinct but not independent entities are involved (tumor, mother and fetus).

ARTICLE INFO

Key words: Dysgerminoma; Extraovarian; Pregnancy

☆ Conflict of Interest: None to declare.

☆☆ Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.1016/j.currproblcancer.2020.100667
0147-0272/

Background

Dysgerminoma is the most common form of ovarian germ cell tumor, it is the female seminoma counterpart and represents 1%-2% of all malignant ovarian neoplasms.[1] It usually presents in young age (10-30 years) with abdominal pain, swelling or vaginal bleeding. Torsion may cause severe pain but it can also be an incidental finding, with no gynecological symptoms. On ultrasound examination, it typically[2] appears as a highly vascularized, purely solid tumor with heterogeneous internal echogenicity divided into several lobules, smooth and sometimes lobulated contour and with a good definition relative to the surrounding organs.

Among malignant germ cell tumors, there are also nondysgerminatous forms that are represented by embryonal carcinoma, choriocarcinoma, yolk sac tumor and immature teratoma, being the latter 2 the most frequent. Mixed forms are rarely observed.

Ovarian dysgerminoma often has high serum levels of lactic dehydrogenase and in 3%-5% of cases it produces human chorionic gonadotropin (hCG) simulating a pregnancy.[3,4] In mixed forms alpha-fetoprotein is secreted, depending on the type and quantity of yolk sac elements in the tumor. In 10% of cases the tumor is grossly bilateral and it was observed[1] that, after bioptizing the grossly normal contralateral ovary, in 10% of cases the tumor was discovered to be bilateral. This tumor can also occur in phenotypic female patients with the 46, XY karyotype and gonadal dysgenesis. In this setting, patients often have a gonadoblastoma from which a dysgerminoma may arise.

The tumor is composed of cells with the same morphologic, ultrastructural and histochemical profile of primordial germ cells.[5,6] They are believed to be in an indifferent stage of development at which they have not yet gained the ability for further differentiation. The most widely accepted theory for the histogenesis of dysgerminoma is that it originates form primordial cells that migrate from their site of origin in the wall of the yolk sac to the ovary.[7] Favoring this hypothesis is the evidence of occurrence of homologous neoplasms along this migration route (mediastinum, retroperitoneum, posterior abdominal wall, parapineal and sacrococcygeal regions).

Herein is presented a case of neoplasm occurring during pregnancy in a young woman and that was definitely diagnosed as extragonadal dysgerminoma some months after the delivery.

Case report

A 26-year-old pregnant woman (2 para) referred to the gynecological ward of the military hospital, at the facility where the husband worked, to monitor the third trimester of pregnancy. Fetal parameters were normal but, at the ultrasound check of the abdomen, a hypoecoic mass measuring about $6.2 \times 4.3 \times 5.3$ cm and with an inner vascular flow on color Doppler was found. It was located in the upper middle quadrant, it bordered the left hepatic lobe, without definitely originating from the liver, and was also separated from the gallbladder, the right kidney and the right adrenal gland. No ascites was evident. One month later a new echography and a magnetic resonance imaging were performed in our hospital and the mass appeared increased in size (it measured 10.1×6.4 cm) and occupied the left upper quadrant. At 39 weeks, the patient delivered a male baby by cesarean section and the abdominal mass was left there. The baby was born with an APGAR score 9. The patient was addressed to a surgical team which removed the lesion after carefully evaluating the relationships of the mass with the adjacent organs on computed tomography (CT) with contrast. It showed a coarse mass with inhomogeneous density because of the presence of some internal colliquated areas. The lesion had grown (cm $13 \times 9.4 \times 8.7$) further, it was extended mainly in the peritoneal cavity and was dissociable from the lower margin of the spleen and the left kidney (Fig 1). The patient never reported fever, weight loss or symptoms related to alvo and diuresis alterations. Blood tests were normal.

Exploratory laparotomy surgery was performed after 2 months from the delivery. Nothing was found in the peritoneal cavity and abdominal and pelvic viscera, except for a large polylobed

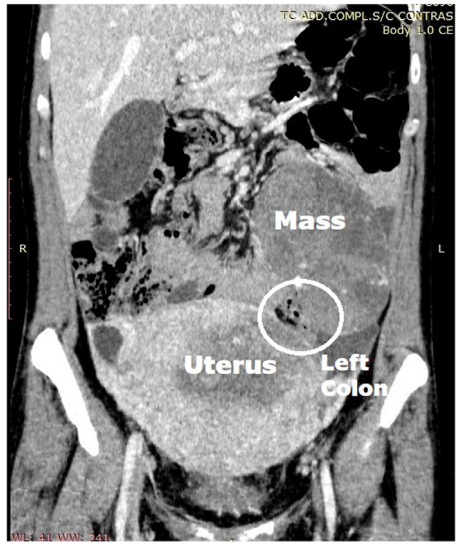

Fig. 1. CT scan with contrast. At the level of the upper left quadrant and extended by 13 cm in length, the presence of a mass with a regular profile and anteroposterior and lateral-lateral diameter, of 8.7 and 9.4 cm respectively, was appreciated. It showed inhomogeneous density and inner colliquate areas and was dissociable from the lower splenic margin and the left kidney.

mass measuring $19 \times 17 \times 8$ cm, located in the left side to the left iliac fossa, without connections to annexes, nor to the left colon. The lesion was removed en-block and the abdominal wall was reconstructed. The postoperative course was normal. The mass was sent to the pathology department for histological examination. Macroscopically it showed a smooth and shiny capsule (Fig 2). On cut section, the tumor was partly solid and yellowish-white, partly multicystic. Extensive sampling was carried out and all samples were formalin-fixed and/or paraffin-embedded. Histopathological sections showed a very cellular tumor, with a solid growth pattern. Neoplastic cells were rather monomorphic, medium-large sized, with rounded nuclei and prominent nucleoli, and abundant, often clear, cytoplasms. The cellular sheets were disrupted by fibrous septa infiltrated by lymphocytes (Fig 3A). Mitotic activity was high (about 36/50 HPF) (Fig 3B). Hemorrhagic changes and necrosis (Fig 3C) were observed. Immunohistochemically, these cells were strongly positive to Oct4 (Fig 3D), PLAP (Fig 3E), CD117 (c-Kit) (Fig 3E) and podoplanin; negative were pan-cytokeratin, S100 protein, Human mElanoma Black (HMB-45), Sry-like HMG bOX (SOX10), epithelial membrane antigen (EMA), actin, desmin, WT1, CD10 and caldesmon. Morphology and immunophenotype were consistent with extragonadal intraperitoneal dysgerminoma. The main concern was to understand if the ovaries were affected by a primitive lesion and a postoperative ultrasound dispelled this doubt. The 2 ovaries and the 2 tubes appeared in place and of regular size for age. Due to the rarity and peculiarity of this case, a multidisciplinary approach was mandatory. The pathologist, the gynecologist, the surgeon and 3 oncologists were involved in this assessment where opinions were contrasting. After carefully evaluating different therapeutic options, they decided to monitor the patient without performing no other additional therapies.

Discussion

Cancer occurrence during pregnancy is an uncommon but not so rare finding. In a relevant study,[8] it was observed that breast cancer, preinvasive and invasive cervical cancer and hemato-

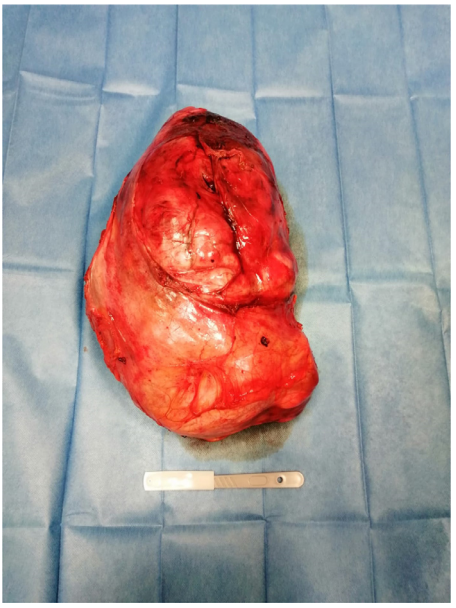

Fig. 2. Gross features of the mass. The mass was polylobed and showed a smooth external surface. It measured $19 \times 17 \times 8$ cm.

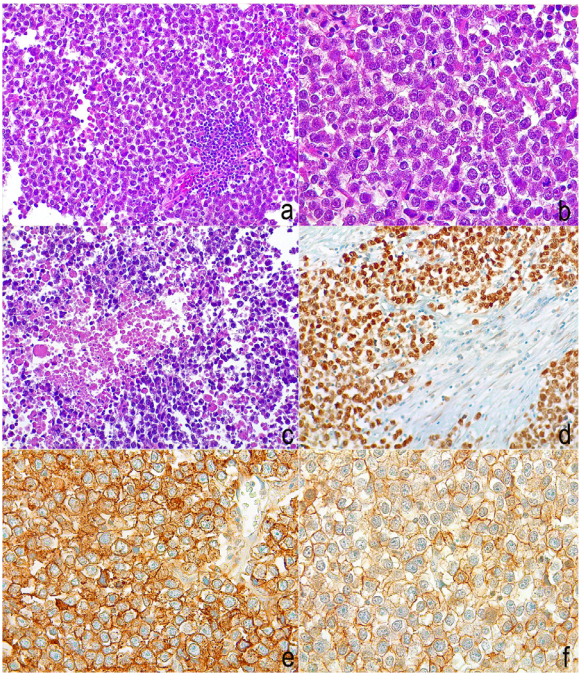

Fig. 3. Histopathologic features. Neoplastic cells were arranged into sheets disrupted by fibrous septae infiltrated by lymphocytes (A, Haematoxylin and eosin, 200×). They were medium-sized cells with round-oval nuclei, with central nucleoli and clear cytoplasm. Mitotic figures could be easily recognized (B, Haematoxylin and eosin, 400×). Foci of necrosis were present (C, Haematoxylin and eosin, 200×). Immunohistochemical evaluation showed positive reaction to Oct4 (D, 400×), PLAP (400×) and c-Kit (400×).

logical malignancies represented the most common forms of neoplasms complicating pregnancy. Much less frequent were melanoma, brain tumors, thyroid cancer, ovarian cancer and colon cancer. Ovarian cancer represented the second most common gynecological tumor occurring in this setting (incidence of 4-8 cases/100,000 patients). Around 90% of such lesions diagnosed during the first trimester usually disappear spontaneously[9,10] but 6% of all the operated adnexal masses are malignant. Among these 6%-40% are germ cell tumors. To the best of our knowledge, only 22 cases[11] of ovarian dysgerminomas diagnosed in pregnancy were described so far. Patients were aged between 17 and 32 years, were mostly nulliparous and in most cases were asymptomatic; when symptomatic, they only had abdominal pain or abdominal distension. The diagnosis was made in all 3 trimesters of pregnancy and in 3 cases it was made after the delivery. The tumor was mainly unilateral and the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage was mostly IA (in 13 cases), rarely IB (3 cases), IC (1 case), IIB (1 case), IIIB (1 case) or IIC (1 case) but in 2 cases the tumor was in advanced FIGO stage (IV).

The management of cancer occurring in pregnancy is complicated because it involves 3 distinct but not independent entities, the mother, the fetus and the tumor.[12] No specific recommendations do exist because each case should be discussed with multidisciplinary approach. In general, a balance between fetal and maternal benefit should be achieved by prolonging, respectively, the pregnancy and the delivery. Factors influencing the decision are patient's age, parity, desire for fertility preservation, tumor stage and gestational age. The experience accumulated with the cases described,[8,13,14] showed that the best time to perform adnexal surgery is the second trimester. Although it is strongly dependent by the surgeon's skill, laparoscopic procedure can be performed in safety.[15] When the disease is at an advanced stage, there is rapidly increasing ascites, large tumor size and a high surgical risk, and adjuvant chemotherapy can be advised. However, in the first trimester, the exposure to chemotherapy can increase the risk of spontaneous abortion, fetal death and major malformations, while in the second and third trimester intrauterine growth restriction (IUGR), low birth weight, preterm delivery, fetal toxicities, fetal and neonatal death are possible complications. In most cases, a delayed treatment is preferred. Current guidelines for the treatment of gynecologic cancer in pregnancy[16] established that the best chemotherapy regimen is based on paclitaxel-carboplatin or cisplatin-vinblastin-bleomycin, instead of bleomycin-etoposide- cisplatin that is usually used in nonpregnant women for the treatment of nonepithelial ovarian cancer.

Whatever strategy is implemented, a correct preoperative diagnostic is mandatory and it is based, first of all, on diagnostic imaging. When the imaging is unclear, histologic or cytologic evidence is necessary, requiring exploratory laparoscopy. With few exceptions, dysgerminomas are typically purely solid. A lobular pattern can be highlighted both at ultrasonography (US) and computed tomography (CT).[17] Highly vascularized and enhancing septa can be easily observed, respectively at color-Doppler US and CT scan. It may sometimes display cystic spaces, representing hemorrhage or necrosis. Magnetic resonance imaging is also quite peculiar.[17]

However, in some cases, ovarian dysgerminoma was mistaken for extrauterine pregnancy,[3,4] being the serum β-hCG elevated.

The case that is presented here is exceptional not only for the rarity of the histotype associated with pregnancy but also because of its extraovarian origin complicating pregnancy. A systematic search was performed in the Pubmed database identifying articles published from 1951 to 2020 by using the following combination of words: gestation OR gestational OR pregnant OR pregnancy AND extraovarian dysgerminoma OR extraovarian dysgerminomas OR mediastinal dysgerminoma OR retroperitoneal dysgerminoma OR abdominal dysgerminoma OR pituitary dysgerminoma. Only 3 cases were found[18-20]: 1 was mediastinal, 1 abdominal and another was located in the uterine wall (Table).

Extragonadal germ cell tumors represent 2%-5% of adult germ cell malignancies[21] and the most common primary site is the anterior mediastinum, followed by the retroperitoneum and, much less commonly, the pineal gland and the presacral area. In all these cases, the presence of a gonadal primary malignancy should be excluded by US and physical examination. Although they share the same histomorphological features with the ovarian and testicular counterparts, specially the primary mediastinal form is considered as a separate unique entity with different

Table
Clinical features in 4 cases of extraovarian dysgerminomas occurring during pregnancy.

Study	Age (years)	Parity	Onset (weeks)	Site	Onset symptoms	Delivery	Surgical intervention	Nonsurgical therapy	Fetal outcome	Maternal prognosis
Manikandan K et al[18]	26	0	23	Mediastinum	Bulging substernal mass	Induced at 31 weeks	None	BEP regimen during pregnancy and radiotherapy after the labor	The neonate expired after 24 hours due to prematurity and hypoxia	The disease worsened 2 weeks after the completion of radiotherapy
Akbarzadeh-Jahromi M et al[19]	21	1	33	Intrauterine	Labor pain	Cesarean section at 33 weeks of gestation	Total histerectomy	BEP regimen after labor	The fetus was delivered with appearance, pulse, grimace response, activity, respiration (APGAR) score = 7	Alive and well 30 months after the delivery
Litzka C et al[20]	35	1	20	Intrabdominal	Abdominal mass	34 weeks	Tumor debulking in conjunction with cesarean section and hysterectomy after BEP therapy	BEP regimen after the delivery	Alive and well	After 16 months the patient was still in complete remission
Present case	26	2	33	Intraperitoneal	Abdominal mass	Cesarean section at 39 weeks of gestation	Tumor debulking	None	Alive and well. APGAR score = 9	Alive and well. Now on follow up

BEP, bleomycin, etoposide, and platinum.

multimodality approach in the management of patients. Mediastinal seminomas/dysgerminomas comprise 25%-50% of malignant mediastinal germ cell tumors and they occur almost exclusively in males during the period from the second to fourth decades of life.[22] In the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology[23] it is stated that patients with an extragonadal primary site, whether retroperitoneal or mediastinal, are managed similarly to patients with testicular germ cell tumors (GCTs) regarding systemic therapies and management of residual masses. Testicular seminomas are generally treated with orchiectomy followed by additional treatment according to the histology. In 3 rare cases chemotherapy may be started immediately without waiting for a bioptic or surgical diagnosis: when β-hCG or alpha-fetoprotein levels are markedly elevated, when there is a testicular mass and or mediastinal and/or retroperitoneal localizations and when there are evident bulk, sign and symptoms of the disease. In general, due to their rarity, the National Comprehensive Cancer Network Panel recommends that patients with extragonadal GCTs be referred to high-volume centers with experience in managing these tumors. Mediastinal forms have an excellent prognosis, with almost 90% rate of long-term cure[24,25]; they are usually treated with chemotherapy, with no need of surgery. Furthermore, in the last 20 years, the VIP (etoposide, ifosfamide-cisplatin) regimen was preferred over the classic bleomycin-etoposide- cisplatin, since bleomycin use has been associated with decreased pulmonary function and increased perioperative pulmonary complications. Retroperitoneal germ cell tumors represent 10% of all malignancies in this site. No specific distinctions were identified from the gonadal primary and the management is that used for metastatic testicular forms. Some authors believe that retroperitoneal germ cell tumors do not exist[26] but could represent metastatic disease deriving from viable occult testicular tumor or from burned-out testicular tumor with spontaneous regression.[27-29] Most intracranial germ cell tumors are seminomas and/or dysgerminomas and they occur in males during the second and third decades of life. In this site, the use of chemotherapy and radiotherapy or single modality therapy remains controversial and unresolved. The role of surgery in these patients has evolved over the time. Postchemotherapy malignancy rate is very low if the tumor size is $<$3 cm; in that case, observation is advised. When tumor residual after chemotherapy is $\geq$3 cm the patient should be submitted to Positron Emission Tomography scan and if it is positive, a biopsy or surgery should be performed.[23]

Overall, the lack of consensus on the treatment of germinal neoplasms in the extragonadal site, the tendency to assimilate these tumors to testicular forms, since these neoplasms are more frequent in males, and the low number of cases of ovarian dysgerminoma diagnosed in pregnancy so far described make our case quite exceptional. Moreover, the intraperitoneal site of onset is not even among the rare extragonadal sites commonly reported. To the best of our knowledge, this is the fourth case of extragonadal dysgerminoma occurring in pregnancy ever described in literature and it could represent a valuable example of case where the multidisciplinary and multicentric approach is mandatory.

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