Non-gestational choriocarcinoma of the ovary complicated by dysgerminoma: a case report

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Background: Non-gestational ovarian choriocarcinoma (NGOC) is a highly malignant tumor derived from germ cells, accounting for <0.1% of ovarian germ cell tumors. Mixed germ cell tumor (MGCT) containing a choriocarcinoma component is extremely rare. Dysgerminoma is one of the most common malignant primordial germ cell tumors, accounting for 3–5% of all malignant tumors of the ovary. The co-existence of these two tumors is even rarer.

Case Description: The patient was an 11-year-old female student of Han ethnicity who still had not started her menstrual period. She experienced intermittent and repeated vaginal bleeding without obvious cause 6 months prior to presenting to our hospital, which was regarded as her period and was not managed clinically. Twenty days prior to presenting, she was suffering from severe pain in her right lower abdomen and began to seek medical treatment. Computed tomography (CT) in another hospital showed that there were large, cystic or solid masses in the pelvic and abdominal cavities, which were considered to be malignant tumors originating from adnexa. The main pathological diagnosis was MGCTs containing dysgerminoma and NGOC. We diagnosed our patient as stage IC2 germ cell cancer. After the fourth cycle of bleomycin + etoposide + cisplatin (BEP), all the markers returned to normal. After 10 months of follow-up, carbohydrate antigen 125 (CA125), alpha fetoprotein (AFP), carcinoembryonic antigen (CEA) and other indicators were normal, and the follow-up was lost.

Conclusions: Few studies in China and abroad have reported on MGCTs. Mixed germ cell tumor is extremely rare and no consensus has been reached on the treatment options. Chemotherapy can achieve good outcome in stage I mixed germ cell tumor patients and therefore early detection, early diagnosis, and early treatment are required.

Keywords: Ovary; germ cell tumor; dysgerminoma; non-gestational ovarian choriocarcinoma (NGOC); case report

Introduction

Non-gestational ovarian choriocarcinoma (NGOC) is a highly malignant tumor derived from germ cells, accounting for <0.1% of ovarian germ cell tumors. Mixed germ cell tumor (MGCT) containing a choriocarcinoma component is extremely rare. NGOC occurs most frequently in adolescents and young females: 50% of the NGOC cases occur before childhood and adolescence and can be associated with precocious puberty. It is rare in adult women and can manifest as irregular vaginal bleeding or menstrual disorders (1). Dysgerminoma is one of the most common malignant primordial germ cell tumors, accounting for 3–5% of all malignant tumors of the ovary (2). Most dysgerminoma

patients are aged 10–30 years, and half of them are younger than 20 years old. The clinical manifestations of dysgerminoma are mostly related to the compression induced by the mass. The co-existence of these two tumors is even rarer. Here, we report one case of NGCO complicated by dysgerminoma, along with a literature review. We present the following article in accordance with the CARE reporting checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-20-59/rc).

Case presentation

The patient was an 11-year-old female student of Han ethnicity who still had not started her menstrual period. She experienced intermittent and repeated vaginal bleeding without obvious cause 6 months prior to presenting to our hospital, which was regarded as her period and was not managed clinically. Twenty days prior to presenting, she was suffering from severe pain in her right lower abdomen and began to seek medical treatment in October 2019. Computed tomography (CT) in another hospital showed that there were large, cystic or solid masses in the pelvic and abdominal cavities, which were considered to be malignant tumors originating from adnexa. Vaginal color Doppler ultrasound in the outpatient department of our hospital revealed heterogeneous weak echoes at the right adnexal area that was close to the right wall of the uterus, and these echoes reached two fingers above the umbilicus and could also be found on the right abdominal wall. Slightly rich blood flow signals were detected around and inside the masses. Notable tumor markers were the following: alpha fetoprotein (AFP), 39.3 ng/mL; carbohydrate antigen (CA)125, 54.6 U/mL; and human chorionic gonadotropin (HCG), >200,000 mIU/mL. An exploratory laparotomy was then performed. During the operation, a small amount of light-yellow ascites was seen, and the omentum and the right ovarian mass were densely adhered. After the adhesion was separated, the anteversion of the uterus was found, and there was no obvious abnormality. There was also no obvious abnormality found in her left fallopian tube or left ovary. The right fallopian tube became swollen. A huge mass sized about 16 cm in diameter was seen in the right ovary, and had a smooth surface and occupied the entire pelvic cavity. A large number of lymph nodes were enlarged in the mesentery, with the largest one having a diameter of about 1 cm; the remaining tissues had no obvious abnormalities. Part of the mass in the right ovary was removed during the operation and sent for rapid frozen section biopsy, which suggested the possibility of malignant tumors, especially germ cell tumors. Right adnexectomy was then performed, during which appendix, peritoneum on the left pelvic wall, and mesenteric lymph nodes were sent for pathology. A bleomycin + etoposide + cisplatin (BEP) regimen was applied after surgery.

The 10% formalin-fixed, paraffin-embedded (FFPE) postoperative specimens were stained with hematoxylin and eosin (HE) and observed under a light microscope. Immunohistochemistry used the EnVision™ system (Agilent, USA), and the required antibodies, including Sal-like protein 4 (Sall-4), placental alkaline phosphatase (PLAP), CD117, D2-40, OCT3/4, vimentin, anti-endomysial antibody (EMA), HCG, AFP, glypican3, CD30, and Ki-67. The expression and location of each protein in cells were detected.

The mass in the right adnexa was 13 cm × 13 cm × 7.5 cm in size. Its surface envelope was mostly smooth and intact, and no definite ovarian tissue was seen. The cut surface was colorful: it appeared grayish-white, grayish-yellow, and grayish-red, being solid and soft in nature, with visible bleeding. Edema occurred in the 9.5 cm fallopian tube; the tube lumen was 0.3–1.2 cm in diameter, the serous membrane was smooth, and the umbrella end was open.

Extensive hemorrhage and necrosis were seen in tumor tissues, which were composed of two tumor components: one tumor component contained cytotrophoblasts and syncytiotrophoblasts, and had no placental villous tissue; the other tumor component consisted of medium-sized, round or polygonal cells. Their nuclei were medium-sized, and the cytoplasm was lightly stained or had an empty appearance similar to primordial germ cells. Tumor cells were clustered into cell nests of different sizes or arranged in strips and sheets, surrounded by different amounts of lymphocytes. These two tumor components were staggered and mixed (*Figure 1*).

Germ cell tumors were considered based on the histological morphological features of the HE-stained slices. Immunolabel staining of the large cells and syncytial cells revealed the following: Sall-4 (–), PLAP (+), CD117 (–), D2-40 (–), OCT3/4 (–), vimentin (–), EMA (+), HCG (+++), AFP (–), glypican3 (–), and CD30 (–); immunohistochemistry of another tumor component revealed the following: Sall-4 (+++), PLAP (+++), CD117 (+), D2-40 (++), OCT3/4 (+++), vimentin (–), EMA (–), HCG (++), AFP (–), glypican3 (–), CD30 (–), and an 80% proportion of Ki-67-positive tumor cells (*Figure 2*).

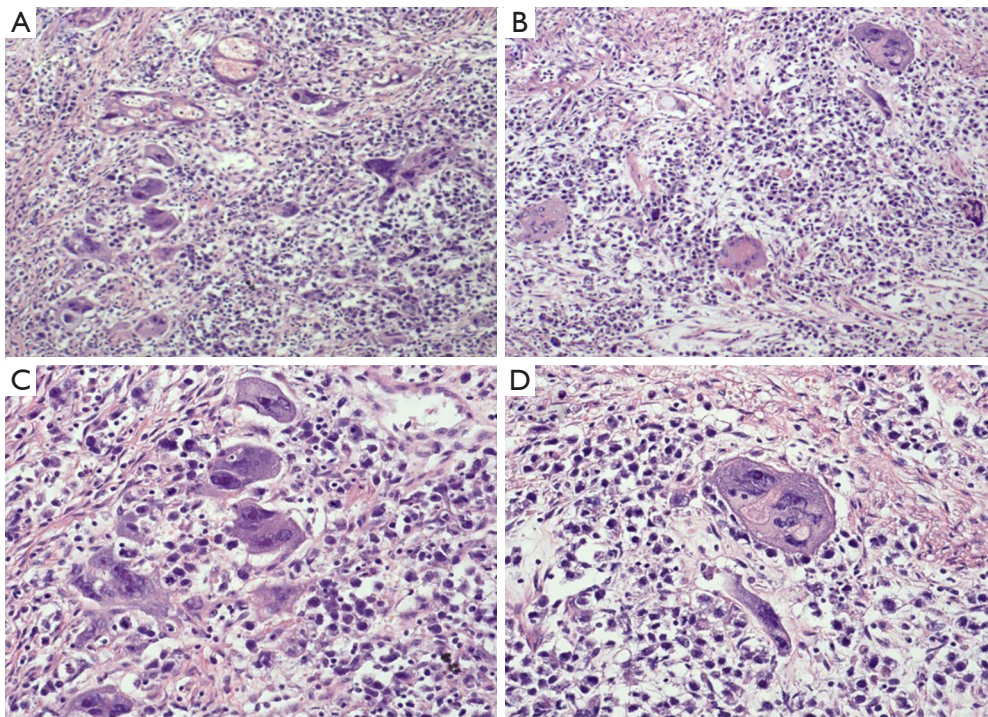According to the microscopic morphological characteristics

Figure 1 The tumor is composed of two components: one is cytotrophoblast- and syncytiotrophoblast-like cells, and the other is medium-sized, round tumor cells appearing with large nuclei and lightly stained cytoplasm. The cells are distributed in nests, surrounded by lymphocytes. Both A and B were shown magnification ×100 in HE staining; Both C and D were shown magnification ×100 in HE staining.

and the immunohistochemical staining results, the main pathological diagnosis was MGCTs containing dysgerminoma and NGCO.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Discussion

Germ cell tumors mainly occur in young women under the age of 20, with 90% being simple and 10% being mixed. MGCTs containing both dysgerminoma and NGCO are particularly rare. These can occur in prepubertal girls, with huge abdominal masses and abdominal pain as the main clinical symptoms. In our current case, the child still had her first menstrual period and presented with abdominal symptoms. Ultrasound and CT revealed huge masses in her abdomen and pelvis, which were considered to be tumors originating from adnexa. The CA125 level may increase in patients with dysgerminoma; in contrast, the blood HCG

level is markedly elevated in NGCO patients, which can be associated with endocrine disorders such as precocious puberty and early pregnancy reaction-like symptoms (3).

Ovarian dysgerminoma, a rare malignancy, is a single-proliferating primitive germ cell tumor containing varying numbers of lymphocytes and phagocytes (4). Microscopically, the tumor cells are mostly strip-shaped and showed nest-like arrangement. In our case, these round or polygonal cells had clear intercell boundaries, with rich slightly stained or acidophilic cytoplasm and a large and centered nucleus. Sometimes megakaryocytes could be seen, and mitotic figures were easily visible. Immunohistochemistry of other cases has shown most dysgerminomas express OCT3/4 and PLAP, and CD117 and D2-40 can also be expressed. In our case, the microscopic morphology and immunohistochemical staining results supported the diagnosis of dysgerminoma. NGCO usually occurs unilaterally and is large in size. The cut surface of an NGCO often appears dark red in color and fragile in nature, and is often accompanied by bleeding and necrosis. Its microscopic appearance is the same as that of gestational choriocarcinoma: the tumor cells are often arranged in a sieve shape, with cytotrophoblasts and
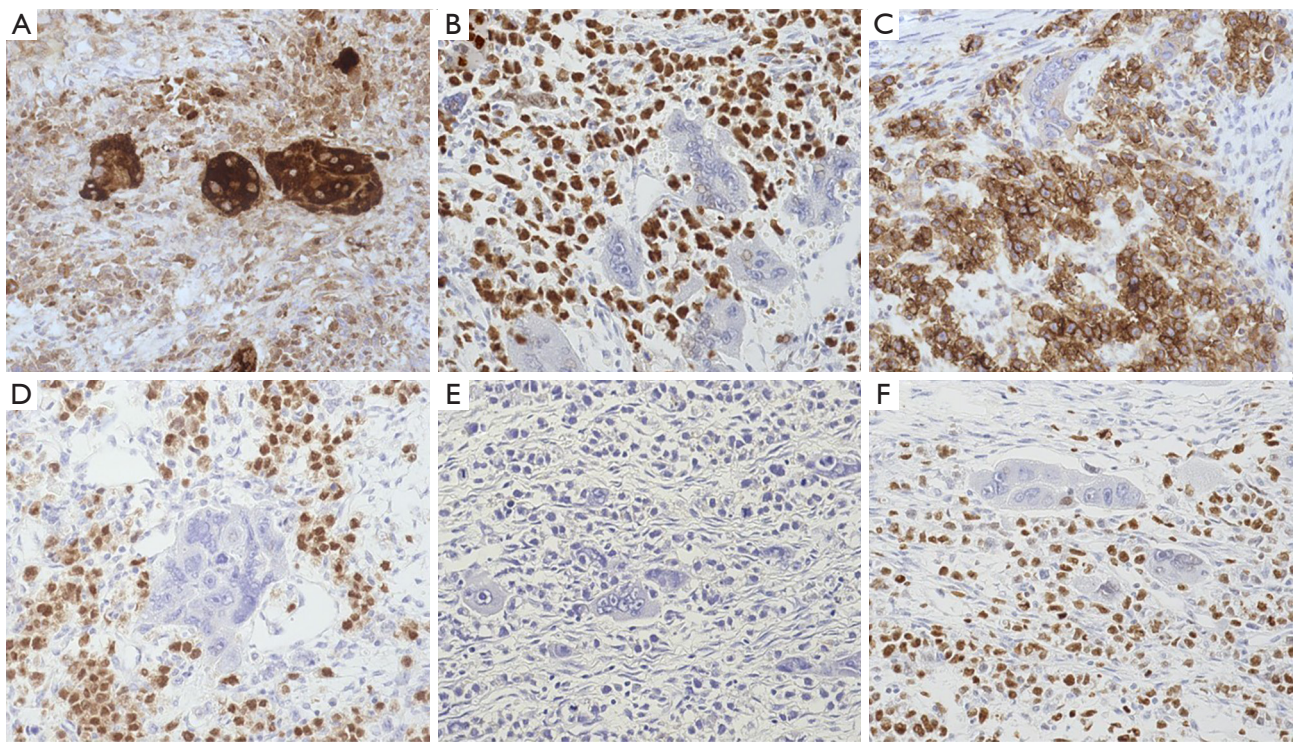
Figure 2 Immunolabeling staining. (A) HCG, trophoblast, and dysgerminoma components are positive; (B) Sall-4; (C) PLAP; (D) OCT3/4, in which trophoblasts are negatively expressed and dysgerminoma components are strongly positive; (E) CD117, neither of the two tumor components are expressed; (F) the positive rate of Ki67 for dysgerminoma is significantly higher than that for syncytiotrophoblasts (×200 EnVision). HCG, human chorionic gonadotropin; Sall-4, Sal-like protein 4; PLAP, placental alkaline phosphatase.

syncytiotrophoblasts being the main tumor components. The syncytiotrophoblasts are large and round; the cytoplasm is lightly stained, with or without cytoplasmic vacuoles; and the nuclei are darkly stained and may be associated with increased syncytiotrophoblastic knotting. HCG was positive. Immunohistochemically, NGCO expresses HCG, human placental lactogen (HPL), inhibin, and low-molecular-weight keratin to varying degrees, and PLAP may also be detected in a few patients. Similar microscopic morphologies and immunolabeling findings were found in our current case. Therefore, the final diagnosis was a MGCT, which contained both NGCO and dysgerminoma.

NGCO and dysgerminoma can be differentiated from other germ cell tumors as described below (1). Gestational choriocarcinoma has a characteristic biphasic trophoblastic differentiation structure, and the differentiation of simple isolated syncytiotrophoblasts can appear in multiple germ cell tumors. A key difference between gestational choriocarcinoma and NGCO is whether there is a prior history of pregnancy and whether the patient is a prepubertal

girl or an adolescent. The co-existence of other tumorous germ cell components is particularly helpful for differential diagnosis in girls after menarche. DNA sequence analysis also helps to identify the common antigen of paternal human leukocytes (2). Compared to yolk sac tumor, dysgerminoma is more immature, with almost no specific differentiation, and has the characteristics of tumor cells, including homogeneity, nesting, presence of fibrous septum, and obvious lymphocyte infiltration. In contrast, the structures of yolk sac tumor cells are more diverse. The tumor cells have a moderate amount of lightly stained or hyaline cytoplasm, with prominent nucleoli and active mitosis; there are varying degrees of cell atypia including the characteristic S-D corpuscles, hyaline bodies, and papilla-shaped giant sac structure. Elevated blood AFP level and positive AFP expression also help to distinguish these two diseases (3). Embryonal carcinoma is derived from pluripotent stem cells. The tumor is composed of epithelioid cells of the blastoderm, with adenoid, tubular, papillary, or solid morphologies. The tumor cells are medium- or large-sized, with overlapping nuclei and unclear

Table 1 The 2014 FIGO ovarian, fallopian tube, and peritoneal cancer staging system and corresponding TNM

FIGO stage	Tumor distribution	TNM stage
I	Tumor confined to ovaries or fallopian tube(s)	T1
IA	Tumor limited to one ovary (capsule intact) or fallopian tube. No tumor on ovarian or fallopian tube surface. No malignant cells in the ascites or peritoneal washings	T1a
IB	Tumor limited to both ovaries (capsules intact) or fallopian tubes. No tumor on ovarian or fallopian tube surface. No malignant cells in the ascites or peritoneal washings	T1b
IC	Tumor limited to one or both ovaries or fallopian tubes, with any of the following:	T1c
IC1	Surgical spill intraoperatively	
IC2	Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface	
IC3	Malignant cells present in the ascites or peritoneal washings	
II	Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer (Tp)	T2
IIA	Extension and/or implants on the uterus and/or fallopian tubes/and/or ovaries	T2a
IIB	Extension to other pelvic intraperitoneal tissues	T2b
III	Tumor involves one or both ovaries, or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	T3
IIIA	Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis	T1, T2, T3aN1
IIIA1	Positive retroperitoneal lymph nodes only (cytologically or histologically proven)	T3a/T3aN1
IIIA1(i)	Metastasis ≤10 mm in greatest dimension (note this is tumor dimension and not lymph node dimension)	T3a/T3aN1
IIIA1(ii)	Metastasis N >10 mm in greatest dimension	T3b/T3bN1
IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes	T3c/T3cN1
IIIB	Macroscopic peritoneal metastases beyond the pelvic brim N 2 cm in greatest dimension, with or without metastases to the retroperitoneal nodes	Any T, any N
IIIC	Macroscopic peritoneal metastases beyond the pelvic brim N 2 cm in greatest dimension, with or without metastases to the retroperitoneal nodes (Note 1)	M1
	Distant metastasis excluding peritoneal metastases	
IVA	Pleural effusion with positive cytology	
IVB	Metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of abdominal cavity) (Note 2)	T3c/T3cN1

Note 1: this includes extension of the tumor to the capsule of the liver and spleen without parenchymal involvement of either organ; Note 2: parenchymal metastases are stage IV B. *Table 1* from (FIGO) *Gynecol Oncol* 2014;133(3):401-4.

boundaries. Syncytiotrophoblast-like giant cells, located near the tumor epithelial nest or in the stroma, are easily visible. Immunohistochemistry typically reveals PLAP, OCT3/4, cytokeratin (CK), and CD30 to be positive and EMA to be negative. Mononuclear tumor cells often express AFP, and the syncytiotrophoblast-like giant cells are HCG-positive.

Dysgerminoma grows rapidly and can easily spread locally. Compared with other germ cell tumors, dysgerminoma rarely spreads to distant organs in its early stage. Therefore, early-stage dysgerminoma can be treated conservatively, and a recurrent dysgerminoma is highly sensitive to radiotherapy and chemotherapy. NGCO can easily invade adjacent organs and metastasizes through the lymphatic and blood systems. It requires postoperative adjuvant radiotherapy and chemotherapy, and the prognosis is poor. According to the recent International Federation of Gynecology and Obstetrics (FIGO) staging system, we diagnosed our patient as stage IC2 germ cell cancer (*Table 1*).

A bleomycin + etoposide + cisplatin (BEP) regimen was applied after surgery. After five cycles of BEP during the 6-month follow-up, etoposide was changed to vincristine on the sixth cycle, and thus the BVP regimen (bleomycin + vincristine + cisplatin) was used. After three cycles of BEP regimen, serum CA125, AFP, and carcinoembryonic antigen (CEA) basically returned normal, HCG was slightly high, and the other markers showed no obvious abnormalities. After the fourth cycle of BEP, all the markers returned to normal. During chemotherapy, the child had common adverse reactions after chemotherapy, such as vomiting, hair loss, white blood cell and platelet symptoms, and no other adverse reactions. Currently, her condition is stable, and no metastasis or recurrence has occurred. After 10 months of follow-up, CA125, AFP, CEA and other indicators were normal, and the follow-up was lost. Young female patients with stage I malignant germ cell tumors tend to have a good prognosis. The 5-year survival rate can exceed 85% after standard treatments. Radiochemotherapy in patients with early-stage simple dysgerminoma can achieve a 5-year survival rate of >95%, and the prognosis of dysgerminoma with syncytiotrophoblast differentiation is similar to that of simple dysgerminoma in the same stage (5,6).

Few studies in China and abroad have reported on MGCTs. The clinical features of the mixed malignancies are unclear, and no consensus has been reached on the treatment options. Furthermore, the prognosis of patients cannot be systematically evaluated. Early detection and timely treatment are still the key to a good prognosis. Here, we summarize the clinicopathological features of the disease and will continue to focus on its follow-up treatment and prognosis.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gpm.amegroups.com/article/view/10.21037/gpm-20-59/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://gpm.amegroups.com/article/view/10.21037/gpm-20-59/coif). YS serves as an unpaid editorial board member of *Gynecology and Pelvic Medicine* from May 2019 to Apr 2021. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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