Int J Clin Exp Pathol 2019;12(5):1788-1794
www.ijcep.com /ISSN:1936-2625/IJCEP0091482

Case Report

Adolescent non-gestational ovarian choriocarcinoma: report of a case and review of literature

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Received January 18, 2019; Accepted February 21, 2019; Epub May 1, 2019; Published May 15, 2019

Abstract: Non-gestational ovarian choriocarcinoma (NGOC) is a very rare and highly malignant tumor originating from primordial germ cells that is not associated with pregnancy. NGOC often invades the adjacent organs and metastasizes extensively to distant organs, especially brain and lungs, with poor prognosis. The early diagnosis of NGOC is quite difficult. We present a case of NGOC in a 14-year-old girl who presented with abdominal distension. The initial imaging and diagnostic workup suggested ovarian cyst. The patient underwent right adnexectomy. One month later, the patient had recurrence of the pelvic solid mass accompanied by pulmonary metastasis and retroperitoneal and mesenteric lymph node metastasis. The pathologic examination revealed NGOC. She received adjuvant chemotherapy and optimal cytoreductive surgery. No recurrence was found during the 1-year follow-up. Given the small number of reported cases with NGOC, there is no consensus on the treatment regimen including surgery and chemotherapy. Based on this case and the available literature, we have identified histopathological and clinical characteristics that may help to predict aggressive NGOC behavior. A high index of suspicion especially in a young teenager with abdomino-pelvic mass requires an urgent and well-thought out panel of investigations to exclude possible causes for the ovarian mass. Early diagnosis and timely initial standardized treatment of NGOC are very important. The treatment of surgery combined with multi-drug chemotherapy is significant.

Keywords: Adolescent, female, choriocarcinoma, ovarian germ cell cancer, chemotherapy, adjuvant, cytoreduction surgery

Introduction

Non-gestational ovarian choriocarcinoma (NGOC) is a group of malignant germ cell tumors of the ovary derived from embryonic gonad primordial germ cells. Less than 1% of ovarian tumors are found in children and young women. It may be due to the metastasis of choriocarcinoma of the uterus, or from a primary ovarian tumor, which is related to the transformation of a single germ cell (trophoblast or yolk sac). NGOC is an extremely rare and highly aggressive tumor that is very rarely reported in the literature. Under the microscope, the gross morphology of NGOC is unclear, with bleeding and necrosis. They often metastasize to adjacent organs and through blood to distant organs, including lung, liver, brain and bone. NGOC is mainly diagnosed by histopathology, and differential diagnosis is somewhat difficult. For acute abdomen and persistent lower abdominal pain in women, a pelvic mass should be considered as NGOC or ectopic pregnancy, and the misdiagnosis rate should be reduced. Therefore, early diagnosis and timely initial standardized treatment are very important. The present case was a 14-year-old girl who underwent ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) to evaluate pelvic masses causing persistent lower abdominal pain. The diagnosis and treatment of primary choriocarcinoma is based on serum tumor markers, such as alpha fetoprotein (AFP), human chorionic gonadotropin (hCG), and postoperative tissue.

Case presentation

A 14-year-old Chinese girl complained of persistent lower abdominal pain for 15 days and visited our hospital on January 12, 2017. She had a history of menarche at the age of 13 years,

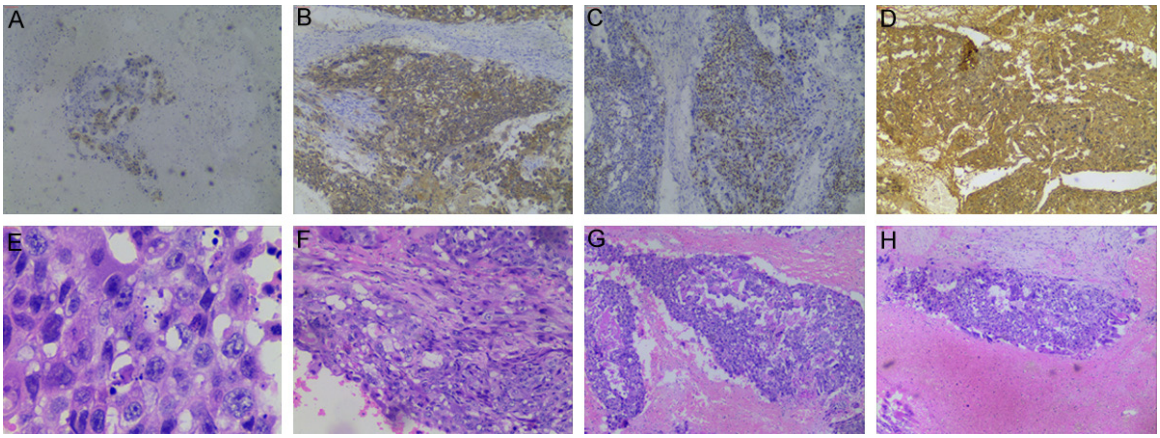

Figure 1. Immunostaining was weakly positive for HPL (A, × 100), strongly positive for CK (B, × 100), positive for Sall4 (C, × 100), and strongly positive for HCG (D, × 100). Hematoxylin/Eosin staining: The trophoblasts showed dense clear cytoplasm, distinct cell boundaries, and central nuclei with variable sizes. Mitoses were obvious. The syncytiotrophoblasts had dense eosinophilic cytoplasm, indistinct cell boundaries, and multiple pleomorphic nuclei (E, × 400; F, × 200; G, × 100; H, × 100).

with normal menstrual cycles. The last menstrual period was January 3, 2017. She was not sexually active. She had a history of asthma for 3 years, and rhinitis for 2 years. In December 2015, she had a history of head injury. The family history was normal. At the first admission, the biochemical examination showed that CA125 was 192 U/ml (normal value 0-35 U/ml); color Doppler ultrasonography showed a 119 × 112 × 71 mm cystic solid mass in the rear of the uterus that may be derived from the ovary. On January 24, 2017, she underwent open exploratory laparotomy with right oophorectomy because of the increased pain. During the operation, cystic masses were found in the right ovary with complete capsule and no rupture or bleeding, and no other lesions were found in the abdominal cavity. Postoperative pathology showed right ovarian poorly differentiated malignant tumor, and the tumor type was further clarified by paraffin extraction. No treatment was given after the operation. At a follow-up examination one month later, the patient's serum β-HCG continued to significantly increase: 1407 mIU/ml on February 6, 2017, and 281400 mIU/ml on February 28, 2017. Color Doppler ultrasonography showed a solid pelvic mass, 83 × 58 × 54 mm with a 20 mm effusion in the left iliac fossa. CT studies of the brain and chest did not show any obvious abnormality at that time. On March 7, 2017, the patient visited our hospital with chief complaints of abdominal distension for 1.5 months, aggravated with nausea and vomiting for one week. Her serum β-HCG (764826.00 IU/L) level was elevated, TSH (0.010 uIU/mL) level was decreased, and FT3 (14.49 pmol/L) and FT4 (42.17 pmol/L) levels were increased. The CA125, AFP and CA199 levels were normal (AFP: 0.93 ng/ml; CA125: 23.90 U/ml; CA199: 9.44 U/mL). H&E staining showed a poorly differentiated mixed germ cell tumor in the right ovary with hemorrhagic necrosis. Multiple paraffin sections showed that the tumor was dominated by a choriocarcinoma component mixed with <10% dysgerminoma. Immunohistochemistry showed strong β-HCG positivity and weak HPL positivity in syncytiotrophoblasts. Histopathology (**Figure 1**) confirmed the diagnosis of NGOC. Grossly, the tumor was characterized by obvious hemorrhagic and necrotic nodules and hematoma-like or cavernous angiomas. The nodules had clear boundaries and no capsules. Microscopically, the tumor consisted of a mixture of syncytiotrophoblasts, cytotrophoblasts, and intermediate trophoblasts with prominent areas of hemorrhagic necrosis and vascular infiltration. The tumor cells were aggregated into clumps or cords, consistent with previous reports indicating that tumor emboli are common in NGOC. The cells were mixed or arranged in a polar direction, i.e., the outer layer was covered by syncytial cells, but there were no villous structures. The stroma was indistinct and was infiltrated by tumor cells. Almost all of the cancerous tissues were hemorrhagic and necrotic, and confined to the edge. On gynecological examination (unmarried, rectoabdominal examination), there was a fixed, fist-sized solid mass with poor mobility in

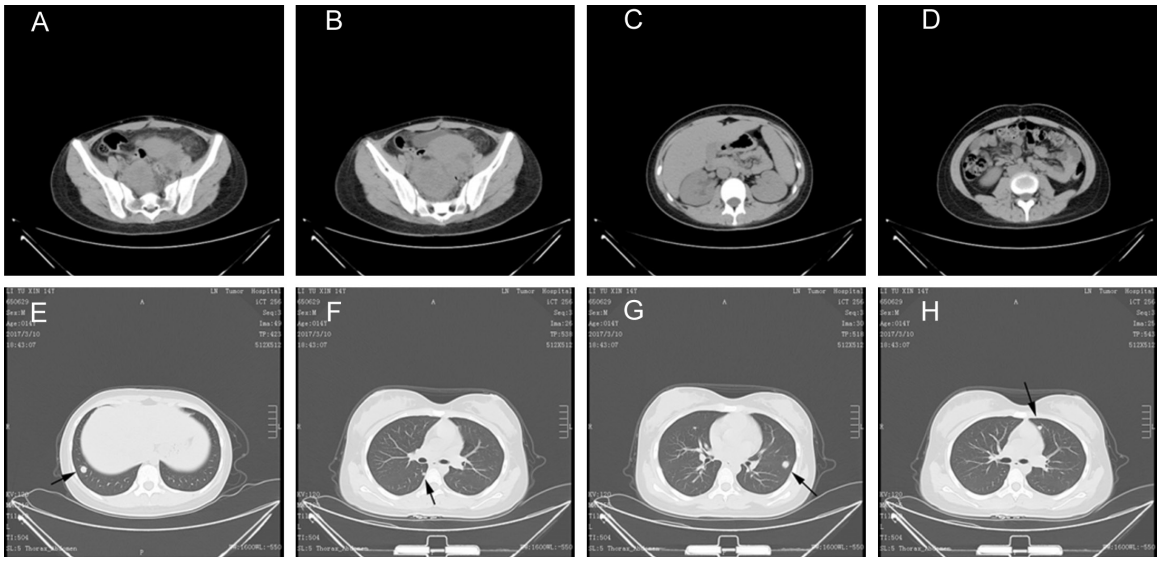

Figure 2. Abdomen and chest CT imaging at admission: Pelvic cystic solid mass and lymph nodes metastases in lung, pelvis and retroperitoneum.

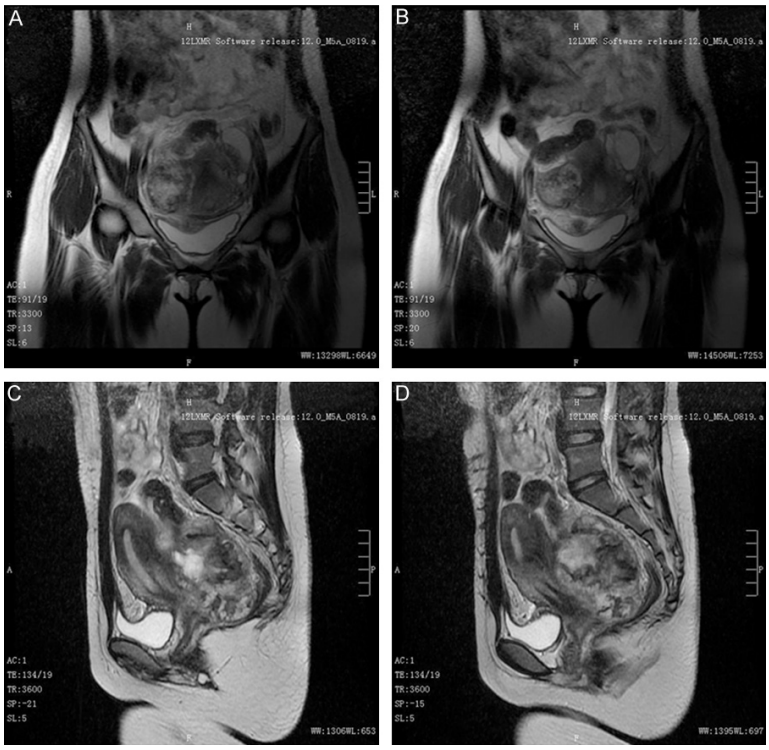

Figure 3. Pelvic magnetic resonance imaging at admission: Recurrence of bilateral pelvic mass.

the posterior uterus; the rectal mucosa was smooth. On whole abdomen CT, the tumor appeared as an irregular, poorly demarcated 107 × 91 mm cystic-solid pelvic mass with non-uniform density and an unclear boundary with the uterus. The mass was attached to distal ureter on the right, and the middle and upper segments of right ureter were dilated with effusion. The right kidney was enlarged and hydronephrosis could not be excluded. The left kidney appeared normal in shape and size. There were lymph node shadows (maximum diameter 11 mm) in the retroperitoneum and mesentery, and the chest CT indicated multiple nodes in both lungs, suggesting probable metastasis (**Figure 2**). There were no obvious abnormalities on the head CT and the electrocardiogram (ECG). The pelvic MRI (**Figure 3**) showed a space occupying lesion in the bilateral pelvis. The right posterior uterus showed mass shadow, T1W and other signals, T2W high and low mixed signals. The size of the mass was 108 × 85 × 63 mm. The right ureter to the lump area showed narrowing, proximal dilatation, a smaller lump in the left pelvic cavity, similar signal, and no pelvic lymph node in the pelvic cavity. We diagnosed the patient with autoimmune thyroid disease (hyperthyroidism), and administered Thiamazole tablets with

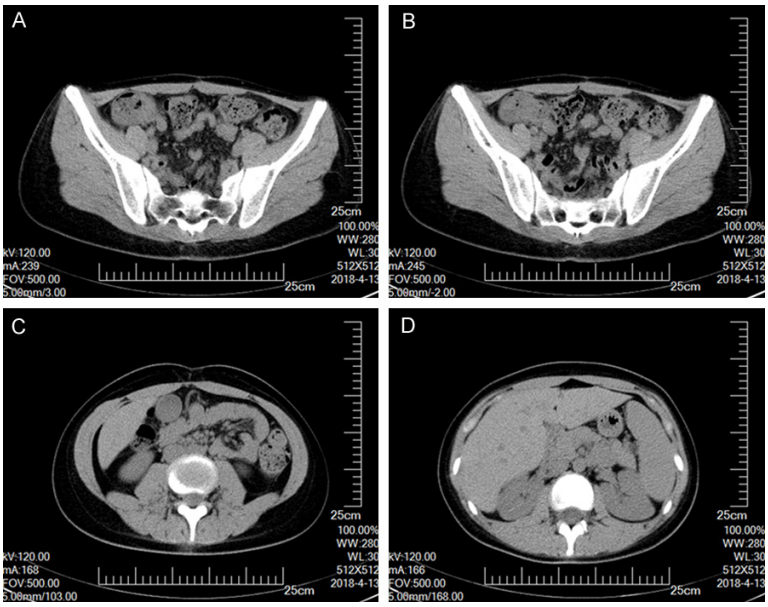

Figure 4. Abdominal CT imaging in the last two months of follow-up: Both kidneys were normal, pelvic masses had disappeared, and pelvic and retroperitoneal small lymph nodes were present.

iodine. The patient was eventually diagnosed as stage III NGOC.

After chemotherapeutic contraindications were excluded, the patient was started on a chemotherapy regimen of etoposide + actinomycin D + methotrexate + vincristine + cyclophosphamide (EMA/CO). The main adverse reaction during chemotherapy was II degree bone marrow suppression (Minimum value of leucocyte: 2.68*10^9/L), which was relieved by leukocyte therapy and tolerable. After the second cycle of chemotherapy, the β-HCG level declined to 884.90 IU/L and imaging indicated that the lung metastases were significantly reduced, the local density of the lumps in the pelvis decreased, and the right pelvis and ureter were slightly dilated. After the third cycle, the serum β-HCG level was 303.30 IU/L. After the fourth cycle, the serum β-HCG level was 108.00 IU/L and imaging examination showed that the lung fields were almost clear. The pelvic mass had decreased and the degree of hydronephrosis had also decreased. After the fifth cycle, the β-HCG level was 50.95 IU/L. After the sixth cycle, the β-HCG level was 27.32 IU/L, and the imaging examination showed that the metastatic lesion of the lung was disappearing, and a mass of cystic density in the posterior chamber of the pelvic cavity was seen on both sides of the uterus. The shape was irregular, the right side was larger, the size was about 63 mm × 39 mm, the density was not uniform, the demarcation of the uterus was not clear, and the pelvic masses were obviously narrowed during hospitalization; both kidneys were normal and the bladder filling was normal. The patient's symptoms were improved and the abdominal distension was relieved. On July 20, 2017, the patient underwent hysterectomy, right salpingectomy, and omentectomy. During the operation, the right lower ureter was found to be encased, and the anterior rectal wall was infiltrated by the tumor, but no other organs were involved. Postoperative tumor histopathology clearly indicated NGOC. The dramatic postoperative decline in the patient's serum β-HCG level, to 5.48 IU/L, demonstrated that the cytoreductive surgery was indispensable in this case. A final chemotherapy regimen of vincristine + actinomycin D + etoposide + 5-fluorouracil (FAEV) was administered. After the first cycle, the serum β-HCG had recovered to a normal level, and after two more cycles, the chest, abdomen, and pelvic CT scans indicated complete regression of the tumor and associated pelvic effusion. The patient remains in good condition, with normal serum β-HCG level. The recent whole abdominal CT showed that both kidneys were normal, pelvic masses had disappeared, and pelvic and retroperitoneal small lymph nodes were normal (**Figure 4**).

Discussion and conclusions

Non-gestational ovarian choriocarcinoma (NGOC) is a very rare, highly malignant tumor originating from primordial germ cells that is not associated with pregnancy. Malignant germ cell tumors account for less than 5% of all ovarian tumors, with an incidence of 1-6% in the West and 8-19% in Asia [1]. NGOC with teratoma was first reported in a 9-year-old girl in 1904 by Pick et al. NGOC typically has a young age of onset. It is most frequently seen in teenagers and young women. The incidence of the disease was highest in 15-19 years olds, and most of them were unilateral [2]. NGOC is thought to arise from the malignant transfor-

mation of autologous primordial germ cells, so it is a type of germ cell tumor. NGOC often invades the adjacent organs and extensively metastasizes to distant organs, especially brain and lungs. The prognosis is generally poor, with frequent relapse [3]. The incidence of NGOC is very low, and the clinical symptoms are mostly nonspecific. The most common clinical manifestation is abdominal pain, which can be differentiated from other ovarian tumors [4]. Saito et al. first described the diagnostic criteria for NGOC in 1963 [5]. The present case was a 14-year-old girl. After 15 days of persistent lower abdominal pain, a right adnexal solid mass with the maximum diameter of 8.3 cm was detected by ultrasonography. In the initial treatment, only pelvic ultrasonography combined with a tumor marker of CA125 was used, and a single appendage resection and a comprehensive exploration were simultaneously performed. No treatment was given after the initial operation. One month later, recurrence and metastasis of the lesion, abnormal increase in serum β-HCG, pelvic mass by imaging, metastasis of the lung and enlargement of multiple lymph nodes in the retroperitoneum were observed, and the diagnosis of stage III NGOC was established by histopathology. It is confirmed that there was a lack of standardized and comprehensive investigation before the first operation. The possibility of NGOC was ignored. In this patient, after the first operation, no chemotherapy was performed, and extensive metastasis occurred.

The pathogenesis of NGOC remains unknown. Some studies have indicated that it may involve arrested migration of germ cells along the urogenital ridge from the yolk sac, which subsequently differentiate to choriocarcinoma [6]. NGOC might also arise during primordial germ cell differentiation to extraembryonic adnexa, and it is often concurrent with germ cell tumors [7]. NGOC usually occurs in the unilateral appendage, accompanied by ovarian mass or bleeding. The tumor is characterized by numerous cytotrophoblasts (CTs) and syncytiotrophoblasts (STs) that secrete high levels of HCG, peptide hormones, estrogen, and other steroid hormones, which may lead to symptoms similar to morning sickness, i.e., nausea and vomiting. Germ cell tumors may be associated with premature puberty or breast development in girls [7]. Some patients also develop manifestations of hyperthyroidism [8], as observed in the present case. As seen in the present case, symptoms may also include lower abdominal pain at the early stage. Findings of a cystic mass in the adnexa with elevated serum β-HCG, FT3, and FT4 should prompt suspicion of NGOC.

The histopathologic characteristics of NGOC are as follows [9]. Gross findings: NGOC is unilateral and solid in the majority of cases. On sectioning, it is soft and friable, mostly reddish brown or blackish brown, with viable tumor tissues often found at the edge of tumor. Microscopic findings: as with gestational choriocarcinoma, NGOC is formed by a mixture of CTs and STs and possibly transitional intermediate trophoblasts (ITs). The cells are markedly atypical, mitotic, and easily identified. They are arranged in an ethmoid, papillary, or tufted form, and tumor emboli, hemorrhage, and necrosis are frequently observed. Immunohistochemistry shows strongly positive HCG expression in STs, with positive human placenta lactogen (HPL) expression. HCG and HPL levels are weakly positive in ITs and CTs, with positive expression of placental alkaline phosphatase (PLAP) and P63. Tumor markers of alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and inhibin should be combined for diagnosis. NGOC is often concurrent with other tumors, including dysgerminoma, teratoma, yolk sac tumor, and other germ cell tumors. For teenage girls who have never been sexually active, the diagnosis can be made according to the pathological characteristics and immunohistochemistry results [10], while in women of childbearing age, DNA polymorphism analysis is helpful to differentiate NGOC from gestational choriocarcinoma, as there will be no paternal genetic material in an NGOC [11]. The patient in this report was a teenager who was not sexually active, and her diagnosis was confirmed by postoperative histopathology and immunohistochemistry.

NGOC is susceptible to early metastasis and dissemination. Pulmonary metastasis is most common, and skin and supraclavicular lymph node metastases are reported as the first symptom [12]. Imaging studies show poorly circumscribed solid or cystic-solid pelvic masses, often adhering to the peripheral organs, accompanied by pelvic effusion. NGOC is susceptible to rupture and hemorrhage, and has poor prognosis [13]. NGOC is a malignant tumor that requires surgical treatment. In 1984, Bakri et al. emphasized that conservative surgery is only suitable for stage Ia when the lesion is lim-

ited to one side of the ovary. In early NGOC, the reproductive function should be retained and the lymph nodes should be actively cleaned; while advanced NGOC should be treated with cytoreductive surgery, and the suggestion for the preservation of the reproductive function in metastatic NGOC patients remains controversial. The clinical research results showed that the treatment of NGOC is based on surgery combined with multi-drug chemotherapy. The MD Anderson Hospital of University of Texas and the Houston Institute for Cancer Research [14] reviewed 42 cases of mixed ovarian germ cell tumors treated between 1944 and 1983 to discuss the management of mixed germ cell tumors, including second caesarean operations and monitoring of tumor markers, and recommended combined chemotherapy after surgery. Goswami et al. [15] reported that among 30 patients with NGOC, the 2-year survival rate in those treated by surgery and chemotherapy was 81%, while it was only 28% in those treated with surgery alone. In the present case, the tumor was confined to the right ovary with intact capsule, and was early NGOC. No chemotherapy was given after the first operation. One month later, the lesion recurred, with lung and multiple lymph node metastases in retroperitoneum and mesentery. The diagnosis was stage III NGOC. Then cytoreductive surgery and neoadjuvant chemotherapy were used to achieve the curative effect. The patients survived and no progress of disease was found. From this patient, we found that early differential diagnosis is critical for NGOC patients to avoid misdiagnosis. NGOC can be treated mainly by surgery combined with multi-drug combination chemotherapy. Appropriate chemotherapy should be given soon after the first operation to prevent metastasis and recurrence. For patients with advanced NGOC, cytoreductive surgery should be performed and the optimal chemotherapy regimen should be given after operation. After six courses of neoadjuvant chemotherapy, the serum β-HCG level decreased, lung metastasis disappeared and pelvic mass significantly decreased in our patient. When the tumor load was significantly reduced, the tumor cell reduction was performed, and the serum β-HCG level was reduced to normal level after operation, and the two courses of chemotherapy were consolidated. Standardized combination chemotherapy along with surgical treatment achieved better results. NGOC is highly sensitive to chemotherapy, and hence effective chemotherapy is extremely valuable for NGOC. At our hospital, pure NGOC is treated with EMA/CO and 5-FU, and mixed NGOC is treated with BEP or PVB. A 1992 GOG study by researchers at Indiana University confirmed that BEP was as effective as PVB, but the toxicity was significantly reduced [16]. BEP chemotherapy is the first treatment choice for ovarian germ cell tumors. Since primary ovarian choriocarcinoma is considered to be a germ cell tumor that differentiates to the trophoblastic structure, the EMA-CO scheme can also achieve good prognosis [17], so a combined chemotherapy regimen of EMA/CO or 5 fluorouracil is typically given.

NGOC is a rare tumor, with no prospective studies to define optimal management. There are over 100 cases of NGOC reported at home and abroad, with limited clinical data. It is difficult to preoperatively diagnose NGOC, and it can only be identified by postoperative histopathology. Young women with ovarian cancer or precocious puberty should be evaluated for NGOC. Recent studies have shown that elevated levels of alpha fetoprotein (AFP) and human chorionic gonadotropin (HCG) are strong predictors of low survival, which is listed as a routine test [18]. Serum β-HCG should be tested in patients with pelvic masses. Early diagnosis and proper initial treatment are important factors affecting the prognosis of NGOC. Ultrasound scans of pelvic masses in young women require the use of tumor markers including cancer CA125, β-HCG, alpha-fetoprotein (AFP), low-density lipoprotein (LDH) and inhibitors in order to exclude possible causes of ovarian masses. When NGCO is suspected, the use of MRI, CT and (if any) FDG-PET, combined with tumor markers, would have been the minimum required investigation. Clinicians should strengthen their knowledge of NGOC to avoid misdiagnosis and mistreatment, and to improve the likelihood of preserving reproductive function by early treatment of affected patients.

Surgery is the first treatment choice for ovarian malignant tumors. Postoperative adjuvant chemotherapy is also important, which may reduce the recurrence and metastasis of NGOC. The traditional view is that choriocarcinoma is a highly malignant tumor, and the scope of surgery includes the uterus and double adnexa, or cytoreductive surgery to prevent permanent loss of reproductive function in young patients with fertility requirements. The progress of chemotherapy and the improvement of gynecolog-

ic oncologists' surgical skills have greatly improved the prognosis of NGOC and made it possible to retain fertility. NGOC is highly sensitive to chemotherapy. The mortality rate is significantly reduced with an effective chemotherapy regimen. The number of courses of chemotherapy depends on the clinical stage of the tumor, the size of residual tumor, the pathologic type and differentiation of the tumor. Generally 4-6 courses are given. Patients with elevated tumor markers should continue chemotherapy until the tumor marker levels return to normal. In summary, surgery combined with postoperative chemotherapy or neoadjuvant chemotherapy is the best treatment for NGOC.

Disclosure of conflict of interest

None.

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References

[1] Lim FK, Chanrachakul B, Chong SM and Ratnam SS. Malignant ovarian germ cell tumours: experience in the National University Hospital of Singapore. Ann Acad Med Singapore 1998; 27: 657-661.

[2] Smith HO, Berwick M, Verschraegen CF, Wiggins C, Lansing L, Muller CY and Qualls CR. Incidence and survival rates for female malignant germ cell tumors. Obstet Gynecol 2006; 107: 1075-1085.

[3] Khuu HM, Crisco CP, Kilgore L, Rodgers WH and Conner MG. Carcinosarcoma of the uterus associated with a nongestational choriocarcinoma. South Med J 2000; 93: 226-228.

[4] Berek J, Hacker N, Berek J and Hacker N. Practical Gynecologic Oncology. Philadelphia: Williams and Wilkins; 2007.

[5] Saito M, Azuma T and Nakamura K. On ectopic choriocarcinoma. World Obstet Gynecol 1963; 17: 459-484.

[6] Metwalley KA, Elsers DA, Farghaly HS, Abdel-Lateif H and Abdel-Kader M. Precocious puberty secondary to a mixed germ cell-sex cord-stromal tumor associated with an ovarian yolk sac tumor: a case report. J Med Case Rep 2012; 6: 162.

[7] Gershenson DM. Update on malignant ovarian germ cell tumors. Cancer 1993; 71: 1581-1590.

[8] Chihara I, Nitta S, Kimura T, Kandori S, Kawahara T, Waku N, Kojima T, Joraku A, Miyazaki J, Iwasaki H, Suzuki H, Kawai K and Nishiyama H. Two cases of germ cell tumors with hyperthyroidism due to high serum hCGLevels. Hinyokika Kiyo 2016; 62: 489-493.

[9] Wang Q, Guo C, Zou L, Wang Y, Song X, Ma Y and Liu A. Clinicopathological analysis of non-gestational ovarian choriocarcinoma: report of two cases and review of the literature. Oncol Lett 2016; 11: 2599-2604.

[10] Hayashi S, Abe Y, Tomita S, Nakanishi Y, Miwa S, Nakajima T, Nomoto K, Tsuneyama K, Fujimori T and Imura J. Primary non-gestational pure choriocarcinoma arising in the ovary: a case report and literature review. Oncol Lett 2015; 9: 2109-2111.

[11] Fisher RA, Newlands ES, Jeffreys AJ, Boxer GM, Begent RH, Rustin GJ and Bagshawe KD. Gestational and nongestational trophoblastic tumors distinguished by DNA analysis. Cancer 1992; 69: 839-845.

[12] Masuda F, Nakada J, Kondo N, Takahashi T, Mochizuki A and Iizuka N. Treatment of non-seminomatous testicular tumor with liver metastases. Hinyokika Kiyo 1988; 34: 351-355.

[13] Gerson RF, Lee EY and Gorman E. Primary extrauterine ovarian choriocarcinoma mistaken for ectopic pregnancy: sonographic imaging findings. AJR Am J Roentgenol 2007; 189: W280-283.

[14] Gershenson DM, Del Junco G, Copeland LJ and Rutledge FN. Mixed germ cell tumors of the ovary. Obstet Gynecol 1984; 64: 200-206.

[15] Goswami D, Sharma K, Zutshi V, Tempe A and Nigam S. Nongestational pure ovarian choriocarcinoma with contralateral teratoma. Gynecol Oncol 2001; 80: 262-266.

[16] Dimopoulos MA, Papadimitriou C, Hamilos G, Efstathiou E, Vlahos G, Rodolakis A, Aravantinos G, Kalofonos H, Kouroussis C, Gika D, Skarlos D and Bamias A. Treatment of ovarian germ cell tumors with a 3-day bleomycin, etoposide, and cisplatin regimen: a prospective multicenter study. Gynecol Oncol 2004; 95: 695-700.

[17] Ozturk E, Ugur MG, Cebesoy FB, Aydin A, Sever T and Balat O. Good prognosis for primary ovarian pure nongestational choriocarcinoma using the EMA/CO regime. Eur J Gynaecol Oncol 2010; 31: 123-125.

[18] Murugaesu N, Schmid P, Dancey G, Agarwal R, Holden L, McNeish I, Savage PM, Newlands ES, Rustin GJ and Seckl MJ. Malignant ovarian germ cell tumors: identification of novel prognostic markers and long-term outcome after multimodality treatment. J Clin Oncol 2006; 24: 4862-4866.