Case Report

rare tumors

Rare Tumors
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Pure primary non-gestational choriocarcinoma originating in the ovary: A case report and literature review

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Abstract

Non-gestational choriocarcinoma (NGCO) of the ovary is rare, with a prevalence of less than 0.6% of all ovarian germ-cell tumors; and when found with other germ cell tumors, pure NGCO is exceedingly rare. We herein report the case of a 22-year-old woman who complained of menstrual disorders for over 2 months. MRI examination revealed an 11.4 cm right adnexal mass of the uterus, and the patients manifested an elevated serum level of β-hCG of 77,928 mIU/ml. Fertility-preserving surgery was performed, and the pathologic diagnosis was pure NGCO; immunohistochemical staining showed cancer cells that were positive for β-hCG, CK, hPL, SALL4, and Ki-67 (>80% of cells stained). We performed polymorphic DNA analysis and non-gestational origin was confirmed. The patient was then treated with six courses of chemotherapy with a BEP regimen, after which her serum β-hCG levels declined to normal levels, and she was free of disease at the 30-month follow-up.

Keywords

Gestational choriocarcinoma, non-gestational choriocarcinoma, ovary

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Introduction

Ovarian choriocarcinoma is very rare and accounts for less than 1% of malignant germ-cell tumors. It can arise from gestational tissue (gestational choriocarcinoma, GCO) or pure germ cells (non-gestational choriocarcinoma, NGCO) of the ovary. The estimated incidence of GCO of the ovary is 1 in 369,000,000 pregnancies—while NGCO corresponds to less than 0.6% of ovarian germ cell tumors, making this neoplasm extremely rare.[1–3] NGCO of the ovary usually occurs as a component of a mixed-germ-cell tumor, and pure non-gestational choriocarcinoma is a primary germ-cell neoplasm that has been defined as a tumor without other germ-cell elements.[4] NGCO should be distinguished from GCO because the chemotherapeutic regimens are different, but both exhibit identical clinical manifestations and histology. Although clinical and histologic findings are helpful, they are not reliable except in patients who are unable to conceive or who have never had sexual intercourse.[5,6] Thus, it is very helpful in the diagnosis of ovarian choriocarcinoma to detect paternal alleles of the tumor using STR (short tandem repeat) analysis. Fisher et al.[7] first reported the diagnosis of choriocarcinoma by analyzing DNA polymorphisms in 1992. Herein we report a case of pure NGCO, as diagnosed by morphology and

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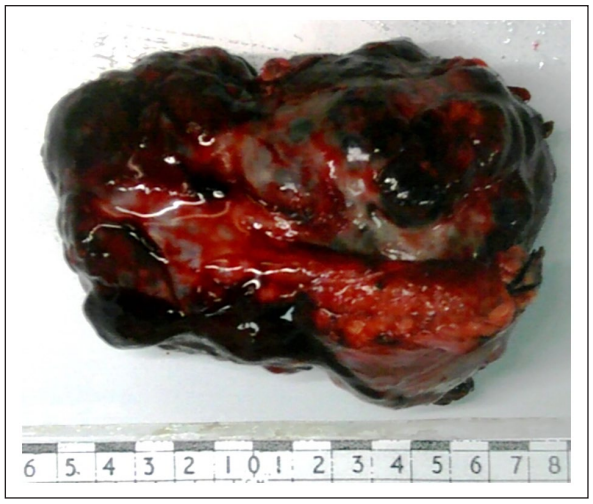

Figure 1. Upon gross examination, we found that the right ovary was replaced by a dark-red solid tumor measuring 11 × 8 × 8 cm, which showed bleeding, adhesions, and a multiple-nodular surface.

STR analysis. In order to better understand this tumor, we also reviewed the relevant literature.

Case report

A 22-year-old unmarried woman presented to a local hospital with complaints of menstrual disorders over 2 months (10+ days on/10 days off). MRI examination revealed a mixed-signal mass in the right adnexal area (11.4 × 9.0 × 7.4 cm). When the woman then visited our hospital clinic, she stated that her previous menstrual cycles were regular and she never had sexual intercourse; her past medical history was also unremarkable, and she had no previous surgeries. Ultrasonographic examination revealed a mass in the right side of the uterus (12.4 × 9.4 × 8.8 cm). Her preoperative serum tumor markers showed the following: a β-hCG of 77,928 mIU/ml (normal, 0–5 mIU/ml) and CA125 of 56.20 U/ml (normal, <35 U/ml); both were elevated, especially the β-hCG level. The other markers (CA199, CEA, and HE4) were in the normal range. These results strongly favored a diagnosis of a malignant ovarian germ-cell tumor. Chest X-ray before surgery showed no cardiopulmonary abnormalities.

Laparotomy was undertaken, and intraoperatively a dark-red, solid 11 cm mass was found to replace the right ovary, with extensive adhesions to the posterior wall of the uterus, the lateral peritoneum, the surface of the left fallopian tube, and the pelvic floor. However, the left ovary and fallopian tube were normal in appearance. A right salpingo-oophorectomy was performed for intraoperative pathologic examination, and gross examination revealed that the right ovary was replaced by a dark-red, solid tumor (Figure 1) measuring 11 × 8 × 8 cm that showed bleeding, adhesions, and a multiple-nodular surface. The tumor's cut surface showed dark brown, massive hemorrhaging and necrosis, and only a few areas were gray-pink, with the surface of the fallopian tube exhibiting bleeding and adhesions. Histologic examination uncovered cancer cells that were an admixture of two cell types: mononuclear and multi-nuclear giant cells, which were likely cytotrophoblast and syncytiotrophoblast cells, with massive hemorrhaging and necrosis. Intraoperative diagnosis of frozen histologic sections was NGCO, and in order to preserve the patient's fertility, partial omentectomy and peritoneal biopsies were performed, leaving the uterus and left salpingo-oophoron intact.

Postoperative pathologic examination uncovered cancer cells that were still an admixture of two cell types. The mononuclear cells were medium-sized, polygonal or round, with clear or amphophilic cytoplasm; they exhibited a well-defined cellular border; and the nuclei of these cells were round and hyperchromatic with conspicuous nucleoli and numerous mitotic cells, indicating cytotrophoblast cells (Figure 2(a)). Conversely, the multinuclear giant cells varied in size and were irregularly shaped, with abundant and dense amphophilic or vacuolated cytoplasm, and multiple hyperchromatic nuclei without mitosis, regarded as syncytiotrophoblast cells (Figure 2(c)). The tumor cells were surrounded by massive hemorrhage (Figure 2(b)) and necrosis, and intravascular carcinoma thrombus was observed focally (Figure 2(d)). We noted no evidence of other germ-cell elements or chorionic stroma. Immunohistochemical staining showed the cancer cells to be positive for β-hCG (syncytiotrophoblast cells) (Figure 2(f)), CK (Figure 2(e)), hPL (Figure 2(g)), SALL4 (Figure 2(h)), and Ki-67 (with more than 80% of cells stained) (Figure 2(j)), and negative for EMA (Figure 2(i)), OCT4, AFP, and P63. The final pathologic diagnosis was pure NGCO of the right ovary with intravascular carcinoma thrombus that involved the greater omentum, and that required peritoneal biopsies.

After surgery, the patient was treated with BEP (45 mg of bleomycin, 500 mg of etoposide, and 100 mg of cisplatin) chemotherapy, with each cycle lasting 5 days at one cycle per month. Serum β-hCG levels declined to 1581 mIU/ml 8 days after surgery and were within the normal range 62 days after surgery. The patient did well after surgery and tolerated six cycles of chemotherapy without problems. Her serum levels of β-hCG were not elevated, pelvic ultrasonography showed no recurrence, and she was free of disease at the 30-month follow-up.

Polymorphic DNA analysis was performed between the normal fallopian tube and the ovarian tumor to confirm the genetic origins of the choriocarcinoma. We extracted DNA from the formalin-fixed and paraffin wax-embedded material using a NuClean FFPE DNA Kit, (Jiangsu Cowin Biotech Co., Ltd., Beijing, China). All samples were quantified with a NanoDrop spectrophotometer (Thermo Scientific, Waltham MA, USA). PCR was amplified with aSTR Multi-amplification Kit (MicroreaderTM21 ID

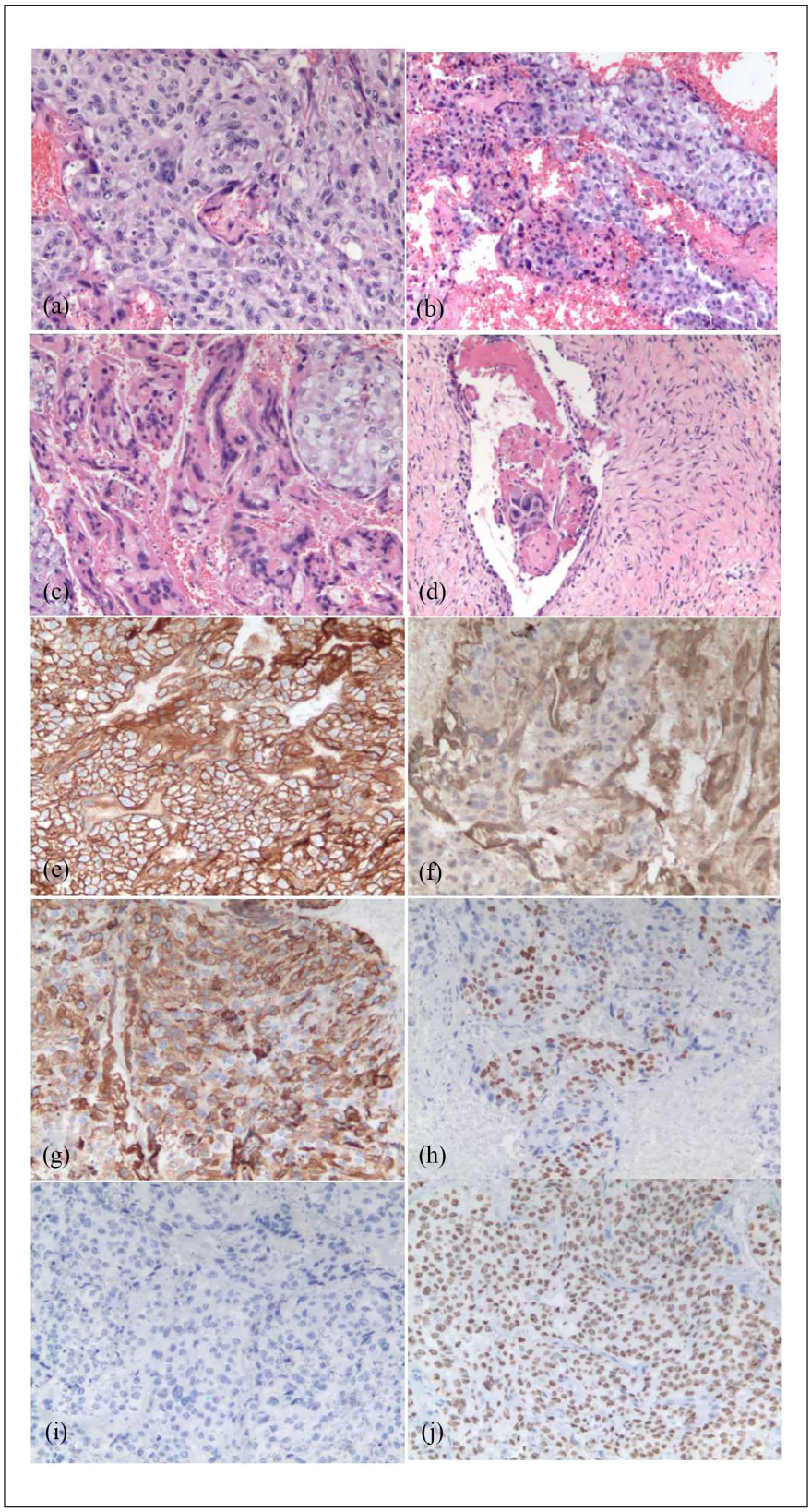

Figure 2. We observed microscopically that the tumor consisted of two types of trophoblastic cells (H&E × 100): cytotrophoblast cells (a) and syncytiotrophoblast cells (c); with hemorrhaging (b) and intravascular carcinoma thrombus (d). Immunohistochemical staining (×100) showed cancer cells to be positive for CK (e), β-hCG (f), human placental lactogen (hPL) (g), SALL4 (h), and Ki-67 (with more than 80% of cells staining; (j)), negative for EMA (i).

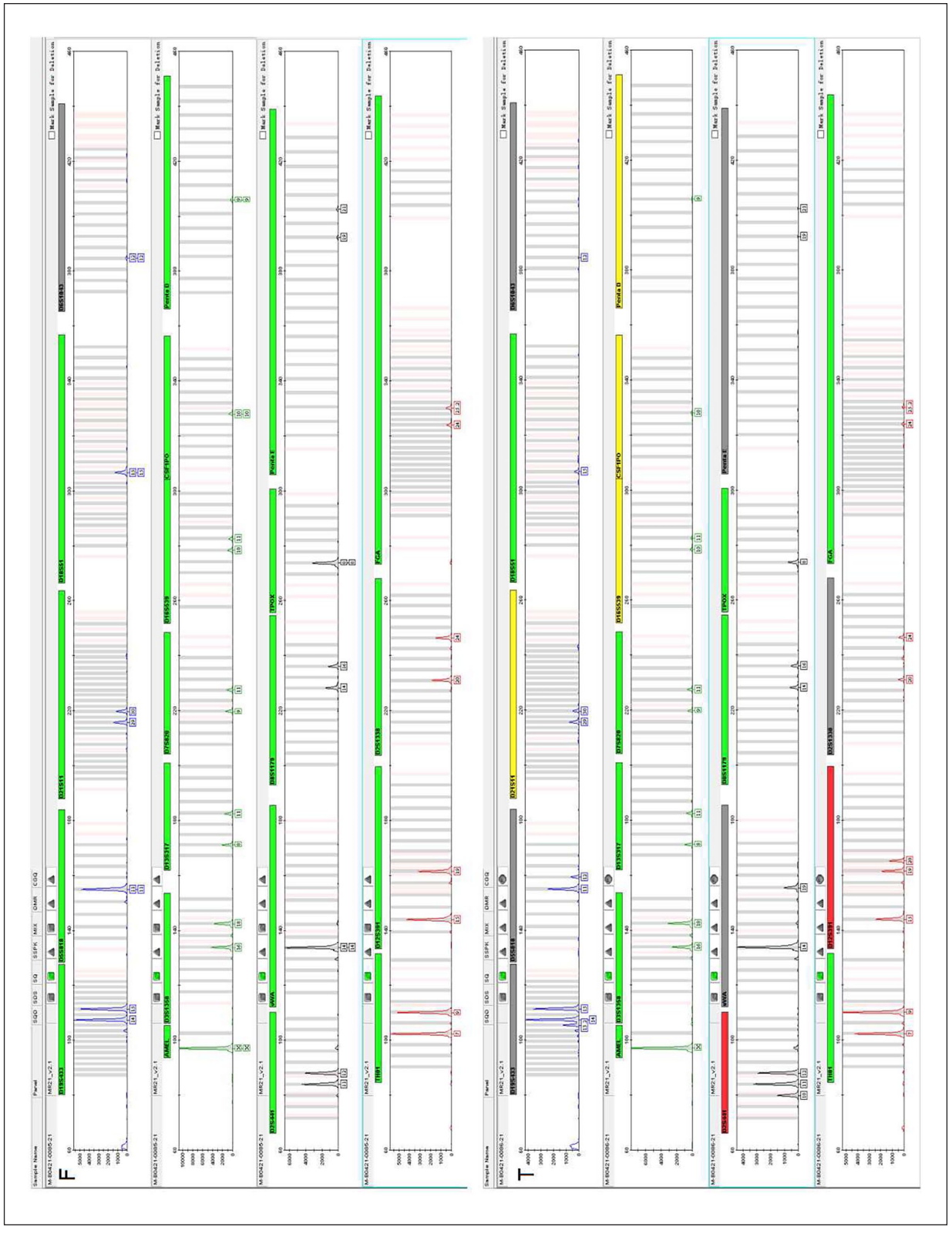

Figure 3. STR analysis of the case. DNAs from the normal fallopian tube and ovarian tumor were amplified for 21 loci.
F: fallopian tube; T: tumor.

System, Beijing Microread Genetics Co., Ltd., Beijing, China), and PCR products were assayed with an ABI 3730xl DNA Analyzer (Applied Biosystems, CA, USA). We analyzed the resulting data using GeneMapper3.2 software (Applied Biosystems). We studied the genetic profiles of 21 highly polymorphic STRs (Figure 3). At 17/21 loci examined, the tumor specimen was shown to contain the normal fallopian tube allele (D19S433, D21S11, D18S51, AMEL, D3S1358, D13S317, D7S820, D16S539, CSF1PO, Penta D, D2S441, D8S1179, TPOX, TH01, D12S391, D2S1338, and FGA). At 2/21 loci examined, the tumor specimen and normal fallopian tube shared one allele (D5S818 and vWA). Two loci (D6S1043 and Penta E) were not detected in the tumor. As a result, a non-gestational origin for the tumor was confirmed.

Discussion

Non-gestational ovarian choriocarcinoma is a very rare and high-grade malignancy, and fewer than 100 cases have been reported thus far. Most of primary NGCO occurs in admixtures with teratomas, endodermal sinus tumors, embryonal carcinomas, or dysgerminoma.[8–10] Pure non-gestational choriocarcinoma is extremely rare,[4] originates from pure germ cells of the ovary, has no association with pregnancy,[11] most frequently occurs in adolescents and young females, and is occasionally found in postmenopausal women.[12]

Clinical manifestations of NGCO include abdominal pain, pelvic masses,[12] bleeding per vaginum, amenorrhea, nausea, vomiting, weight loss, micturition disturbances, elevated serum β-hCG levels, precocious puberty, and endocrine abnormalities.[13] NGCO often occurs unilaterally and exhibits extensive hemorrhage and necrosis. Histologically, NGCO is characterized by the presence of two cell lines: the cytotrophoblast cells, which lie in sheets to form a villus-like structure, and the syncytiotrophoblast cells, which secrete β-hCG and hPL and are observed at the advancing edge of the tumor.[8] Such tumor cells are also positive for β-hCG, hPL, and CK. The most important differential diagnosis of NGCO is GCO, and both gestational and non-gestational choriocarcinoma exhibit identical clinical manifestations and histology.[1] Additionally, although these authors observed no immunohistochemical differences between them, the chemotherapeutic regimens used are different. It is generally accepted that GCO can be treated with methotrexate, actinomycin D, or etoposide as a single agent; or in combinations such as EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine) when strong risk factors are present. However, NGCO is generally treated with a BEP (bleomycin, etoposide, cisplatin) regimen.[1] Although both tumors tend to develop early hematogenous metastasis to several different sites that include the lung, liver, brain, bone, vagina, and other viscera,[14] NCGO more often invades the adjacent organs, more commonly metastasizes to distant organs such as the brain and lung,[12] and has been found to be resistant to single-agent chemotherapy—with a worse prognosis relative to GCO.[8] Therefore, it is necessary to distinguish NGCO from GCO.

Saito et al.[15] first described the diagnostic criteria for NGCO in 1963, which included the absence of disease in the uterine cavity, pathologic confirmation of disease, and exclusion of molar pregnancy and intrauterine pregnancy. Unfortunately, the clinical diagnostic criteria are not reliable except for patients who are unable to conceive or who have never had sexual intercourse,[5,6] and thus DNA polymorphism analysis may aid the diagnosis.[12] Fisher et al.[7] first diagnosed choriocarcinoma by analyzing DNA polymorphisms in 1992 using site-specific microsatellite probes to analyze DNA restriction fragment length polymorphisms (RFLP) of tumor tissue by comparing blood samples obtained from patients and their spouses. The results were as follows: if the tumor components only originated from the patient, non-gestational choriocarcinoma was diagnosed, whereas if a patrilineal component existed, gestational choriocarcinoma was diagnosed.[12] With the increases in polymorphic loci involved in this analysis, a higher accuracy of diagnosis has been achieved. However, since the method is expensive, it has not been widely used in clinical practice. In the literature, we found only eight cases that were confirmed as NGCO by DNA analysis (our case included).

The management of NGCO is a combination of surgical ablation and postoperative chemotherapy. In all cases noted in the literature, clinicians performed surgical procedures that included unilateral oophorectomy/salpingo-oophorectomy, abdominal hysterectomy with bilateral salpingo-oophorectomy, and bilateral salpingo-oophorectomy/unilateral salpingo-oophorectomy + contralateral ovariectomy. Postoperative chemotherapy was administered in most cases, and the majority of patients received platinum-based regimens, with a few receiving methotrexate-based regimens. Although NCGO is considered to result in a poor prognosis, data showed that of patients who were followed up with 2–84 months later, approximately 76% manifested no evidence of disease.

Conclusion

NGCO is a rare malignant germ-cell tumor, and DNA polymorphism analysis is helpful in distinguishing NGCO from GCO. The management of NGCO can be a combination of surgical ablation and postoperative chemotherapy, and our patient responded quite well. For young patients who have not had children, fertility-preserving surgery may thus be a viable option.

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Author contributions

Yu Xiujie wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Declaration of conflicting interests

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Ethical approval

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by The Ethic Committee of Tianjin Central Hospital of Obstetrics and Gynecology (2021KY005).

Informed consent

Written informed consent was obtained from the patient for DNA analysis, publication of this report and accompanying images.

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