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Cervix Epithelioid Trophoblastic Tumor: A Rare Case Report and Review of the Literature

Yang B[1], Deng J[2] and Cao Y[2*]

[1]Department of Obstetrics and Gynecology, Shanghai Minhang Central Hospital, China

[2]Department of Gynecology, Shanghai Jiading Maternal and Child Health Hospital, China

[*]Corresponding author:

Yungui Cao and Juan Deng,
Department of Gynecology, Shanghai Jiading Maternal and Child Health Hospital, Shanghai 201800, China, Tel: +86-18939861393 and +86-13817985825;
E-mail: 18930861393@163.com and cygui@126.com

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1. Abstract

1.1. Rationale: The epithelioid trophoblastic tumour (ETT) is a very rare type of gestational trophoblast neoplasm (GTN), accounting for 0.5%-2.0% of all GTNs. With their unusual ability to simulate an invasive epithelioid neoplasm, ETTs frequently pose a diagnostic challenge, especially when they involve the uterine cervix. ETTsare caused by the malignant transformation of intermediate trophoblasts, so they are not sensitive to chemotherapy. Surgery is the primary treatment.

1.2. Patient concerns: We herein report the case of a 42-year-old female with persistent vaginal bleeding for 30 days. Pelvic examination showed that the cervix was slightly erosive, hypertrophied, and barrel-shaped; was 4 cm in diameter and 3cm in length; and had no abnormal hyperplasia on the surface.The serum human chorionic gonadotropin (HCG) level was 0.30 mIU/ml. Ultrasound revealed 2.3×2.2×2.4-cm mixed echogenic masses in the cervical myometrium. Pelvic MRI showed cervical malignant tumours.

1.3. Diagnoses: The final pathological diagnosis was CETT.

1.4. Interventions: The patient was treated with radical hysterectomy. The EMA-EP regimen consisting of three treatments was given after the surgery.

1.5. Outcomes: After 20 months of follow-up, there was no evidence of residual tumour regrowth or metastasis.

1.6. Lessons: The incidence of ETTs is low, and clinical manifestations are not specific. It is easy to misdiagnose. It is necessary to combine serology and imaging, especially pathology and immunohistochemistry.

2. Introduction

An epithelioid trophoblastic tumour (ETT) is a very rare type of Gestational Trophoblast Neoplasm (GTN), accounting for 0.5%-2.0% of all GTNs [1-4]. Large-sample reports in the literature are few, and the few such reports comprise mostly case reports and small-sample reports on ETT. Approximately 140 ETT cases were retrieved in PubMed up to September 2020. A cervical epithelioid trophoblastic tumour (CEET) is an epithelial trophoblastic tumour occurring in the cervix and is even rarer. There are occasional case reports to date [5]. In this paper, we report a case that was diagnosed as cervical cancer preoperatively but pathologically diagnosed as an ETT postoperatively. Here, we aim to learn more about the clinical and pathological characteristics, treatment, and prognosis of the CETT through the literature and this rare case.

3. Case Presentation

A 42-year-old Chinese woman presented with irregular vaginal bleeding for one month. She had normal menstruation except for irregular vaginal bleeding during this period. She had 3 normal pregnancies, including 2 deliveries and 1 induced abortion. Her lastpregnancy was delivered in 2006.

Pelvic examination showed that the cervix was slightly erosive, hypertrophied, barrel-shaped, 4 cm in diameter and 3 cm in length. No abnormal hyperplasia was found on the surface.

Her blood serum HCG was 0.30 mIU/ml, and her CEA/CA125/CA199 and SCC levels were normal. Pelvic ultrasound revealed a 2.3×2.2×2.4-cm solid mass in the cervical myometrium, which had unclear boundaries with the cervical canal. The HPV detection result was negative, and cervical smear cytological examination was normal. Pelvic MRI showed a cervical malignant tumour (Figure 1 and 2). The result of colposcopy was chronic inflammation of the cervical mucosa. Hysteroscopy (Figure 3) showed a large white and grey cauliflower-like mass in the lower uterine segment and upper segment of the cervical canal, which was widened, and tortuous arteries were on the surface of the mass, with white coagulated necrosis in the local area. The uterine cavity was normal.

The mass was removed and pathologically diagnosed as an ETT. Immunohistochemical results (Figure 4) showed CAM5.2(+), P63(+), CD10(+), Ki-6720%-25%(+), HCG (-), H-caldesmon (-), B-catenin (cell membrane+), and inhibin-a (-).

Laparoscopic radical hysterectomy, double appendectomy, and retroperitoneal lymphadenectomy were performed. Postoperative findings of the uterus included a grey yellow area that was approximately 3×2×2 cm in size in the lower segment of the uterus and cervix, and the deepest part was near the serosa layer (Figure 5). The pathological diagnosis was an epithelioid trophoblastic tumour of the uterus with calcification. Immunocytochemical results were as follows: CKpan(++), CAM5.2(++), β-catenin(+), VIM(-), P63(+), P53(-), EGFR(++), HCG(-), PLAP(++), E-CAD(+), inhibin-α(-), CD10(++), and Ki67(15%+).

After surgery, the patient was treated with the EMA-EP regimen, and the treatment course was as follows: an intravenous drip of VP-16 100 mg/m2, Act-D 0.5 mg, and MTX 100 mg/m2 on the first day; VP-16 100 mg/m2, Act-D 0.5 mg, and CF15 mg q12 h on the second day; and VP-16 150 mg/m2 and DDP 75 mg/m2 on the eighth day. After 24 months of follow-up, there was no evidence of residual tumour regrowth or metastasis.

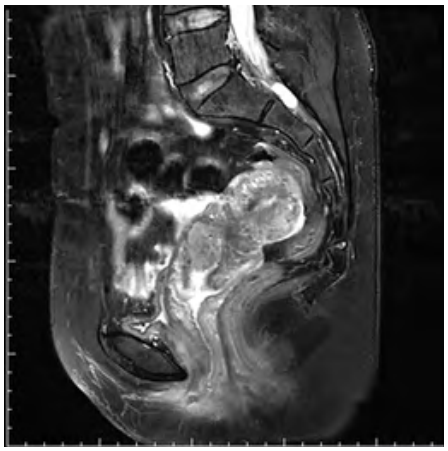

Figure 1: MRI (sagittal T2WI): Mixed signal shadow of the anterior wall of the cervical canal

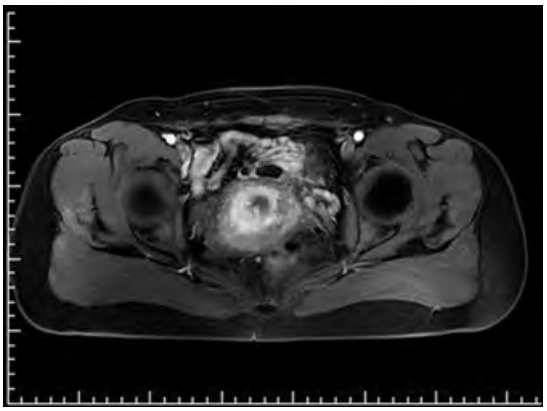

Figure 2: MRI (cross-sectional DWI): The DWI signal of the cervical canal was increased

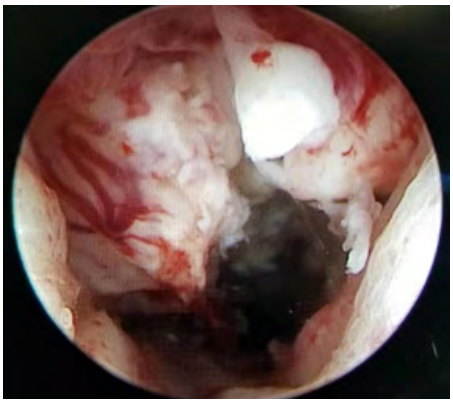

Figure 3: Hysteroscopic image

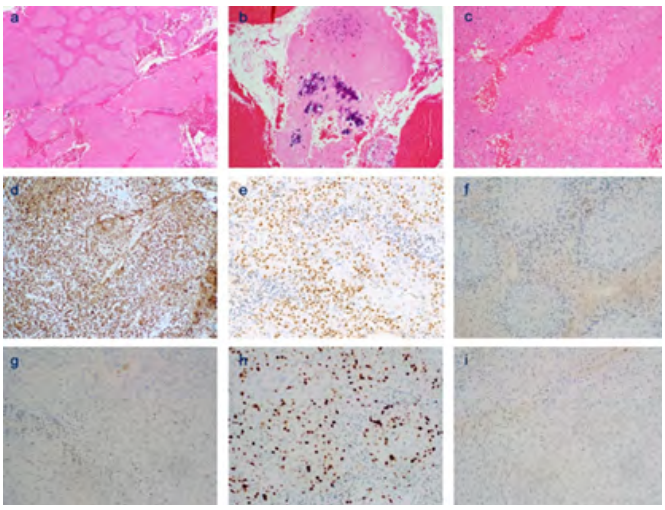

Figure 4: Immunohistochemical results (immunohistochemistry,40× amplification)

a. The tumour tissue showed nodular growth and was arranged into nests of cords, and the cell size was relatively consistent (HE, 40× amplification)

b. Eosinophilic hyaline degeneration deposition was seen between tumour cells, accompanied by ground pattern necrosis (HE, 100× amplification)

c. CD10(+), small nucleoli could be seen, the nucleus was moderately atypical, and there were two mitotic phases/10HPF (HE, 40× amplification)

d. CAM5.2 (+++)

e. P63 (+++)

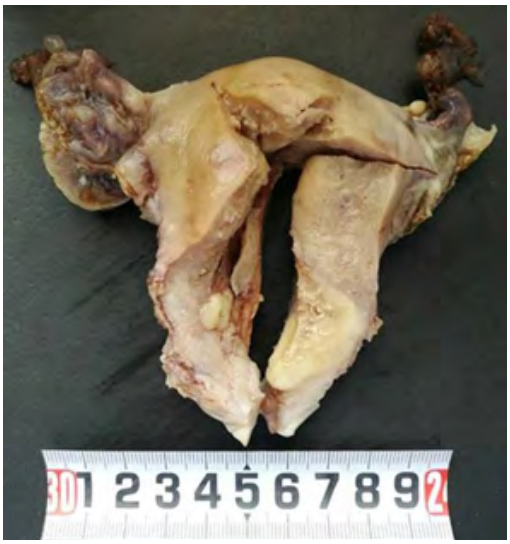

Figure 5: Extensive uterus and double appendages

4. Discussion

4.1. Clinical Characteristics

An ETT was first described and distinguished from choriocarcinoma(CC) and the placental site trophoblastic tumour (PSTT) by Shih and Kurman in 1998 [6]. The ETT was classified as a GTN by the WHO in 2003 for the first time.The onset age of an ETT is 20-60 years, with an average age of 36 years. Approximately 71% of patients are younger than 40 years [1, 3], and ETTs have been reported to occur in postmenopausal women [7, 8]. AnETT can occur in any form of pregnancy, such as a term birth, premature delivery, abortion, hydatidiform mole, or ectopic pregnancy. Shin and Kurmanwere the first to report that 66.7% of ETTs occur after a term pregnancy . Subsequently, many studies found that approximately 60%-80% of ETTs occurred after a term pregnancy; however, it was also reported that only 8.9% of ETTs occurred after full-term delivery, with 51.1% occurring after an abortion [9]. Therefore, the relationship between ETT and previous pregnancy needs to be further clarified in future research. The interval between the previous pregnancy and the diagnosis of an ETT fluctuates greatly, ranging from 2 months to 30 years. Irregular vaginal bleeding is the main clinical presentation. Zhang et al. [9] reported that 70% of cases presented with irregular vaginal bleeding; furthermore, patients with an ETT can present with amenorrhea, abdominal pain, and haemoptysis due to metastasis. Most ETTs occur in the uterus, and approximately 50% of them occur in the lower segment of the uterus and cervical canal. The lung is the most common site of metastasis [10], but metastasis can also occur in the vagina [11], ovary [12], uterine scar [13], and rectocele [14].

ETTs originate from intermediate trophoblasts, lacking syncytial cells for the synthesis of β-HCG. Generally, the levels of serum β-HCG are slightly to moderately elevated but can be normal [1, 3, 4]. The levels of serum β-HCG are below 1000 IU/L in 77.4% of cases and below 5 IU/L in 23.8% of cases [3]. The clinical manifestations of an ETT lack specificity, and preoperative diagnosis is difficult. Due to irregular vaginal bleeding and high serum β-HCG, it is easily misdiagnosed as an ectopic pregnancy, an abortion, and another trophoblastic tumour. ETTs occur mostly in the lower segment of the uterus and cervix, and serum β-HCG may be normal; therefore, an ETT can be misdiagnosed as cervical cancer. Preoperative diagnosis is difficult, as it is based mainly on the surgical pathological diagnosis.

4.2. Pathological Characteristics

Gross examination showed that the growth of the mass was scattered or isolated, forming solid or cystic solid nodular lesions. The cut surface was yellow-tan and soft. Microscopically, the tumour consisted of strips and cords of monomorphic intermediate trophoblasts, with different degrees of haemorrhage, necrosis, or calcification. The typical focus was that the trophoblastic island was surrounded by an extensive necrotic area and hyaline-like material, showing a "map-like" appearance [15], which was rare in squamous, adenocarcinoma, or undifferentiated cancer. The mean mitotic image could be 2-30/10 HPF (HPF: per high power of the field of view). In some cases, the cell morphology may not be typical, and immunohistochemistry can be used to distinguish it from other types of GTN and epithelioid tumours. In terms of immunohistochemistry, low-molecular-weight cytokeratin (such as CK18, cam5.2) and 3β-hydroxysteroid dehydrogenase (HSD3B) are detected when trophoblastic disease is suspected. When it is strongly positive, a trophoblastic tumour is basically diagnosed. In most choriocarcinomas, β-HCG is positive, while in intermediate trophoblasts, β-HCG is negative or weakly positive. P63 is negative in placental trophoblasts and strongly positive in an ETT. Human placental lactogen(HPL) is strongly positive in placental trophoblasts but negative in an ETT. Ki67 is a marker of cell proliferation activity, which is more than 15% in an ETT and less than 8% in placental nodules. The cell morphology of an ETT is similar to that of squamous cell carcinoma, and the focus occurs mostly in the lower segment of the uterus and cervical canal; thus, an ETT needs to be differentiated from cervical squamous cell carcinoma. In squamous cell carcinoma, P63 is strongly positive, CAM5.2 is usually negative, and CK5/6 [6, 16] is strongly positive.

In this case, microscopically, monocytes and relatively uniform cells in typical map-like necrosis could be seen and were suspected to indicate an epithelioid trophoblastic tumour. CAM5.2 and P63 were strongly positive, CK5/6 and β-HCG were negative, and Ki67 positivity was 20%-25%; therefore, the pathological diagnosis was an epithelioid trophoblastic tumour.

4.3. Treatment and Prognosis

Epithelioid trophoblastic tumours are caused by the malignant transformation of intermediate trophoblasts, so they are not sensitive to chemotherapy. Surgery is the primary treatment [17-20]. Hysterectomy is the first choice of treatment and can be applied to patients without fertility requirements and with the focus confined to the uterus (FIGO stage I). The disease is hormone-independent,

and it has been reported that ovarian metastasis is rare; therefore, premenopausal patients having ovaries with a normal appearance who want to retain ovarian function can retain their ovaries. At present, it is still controversial whether pelvic and abdominal aortic lymphadenectomy should be performed. Some studies including those by Frijstein et al. [19] suggested that lymphadenectomy could not improve the survival rate; however, in the 2020 NCCN Guideline, it was suggested that lymphadenectomy should be performed. More studies are needed on this topic. When there are extrauterine lesions (FIGO II-IV), all the lesions should be removed as much as possible, which may require multidisciplinary collaborative surgery or multiple operations to achieve tumour control.

Only a few cases have been reported regarding the operation of retaining fertility function, and its safety has not been confirmed. The results from the International Association for the Study of Trophoblastic Diseases database show that among 54 cases,45 were diagnosed as an ETT, and 9 were confirmed to be a PSTT and an ETT. Thirty-six patients with FIGO stage I disease were treated by surgery, and combined chemotherapy was performed in 14 patients, among whom 4 patients died. The interval between the previous pregnancy and the disease was 56 months to 202 months. There were 18 cases with FIGO stage ≥II disease, among whom 6 cases died of the disease and 1 died of other factors [19]. Therefore, an interval between onset and previous pregnancy ≥48 months and FIGO stage ≥II are the two most important independent adverse prognostic factors. Other adverse prognostic factors include older age, deep myometrial invasion, tumour necrosis, and mitotic index>5/10 HPF. These results are consistent with the research of Froeling et al. [18] FEM. According to many studies [18, 20], chemotherapy should be performed in patients with FIGO stage I with high-risk factors and FIGO stage ≥II. EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine), EP/EMA (etoposide, cisplatin, methotrexate, and actinomycin D), and TP (paclitaxel and cisplatin) are the most frequently selected treatment options. In addition, targeted treatment is also worth studying [1]. In this case, the patient had many high-risk factors: aged 42 years, a focus located in the lower segment of the uterus and cervical canal near the serous layer, and an interval between ETT onset and the most recent term pregnancy and delivery of 12 years. In view of these factors, extensive hysterectomy was performed, and after the operation, three cycles of EP/EMA were given. At the two-year follow-up, there were no signs of recurrence.

In summary, the incidence of CETTs is low, and their clinical manifestations are not specific, which means that it is easily misdiagnosed in the clinic. It is necessary to combine serology and imaging, especially pathology and immunohistochemistry, for diagnosis. The CETT is composed of villous intermediate trophoblasts with high differentiation and insensitivity to chemotherapy. It is usually treated by hysterectomy and focal resection and consolidated by chemotherapy after surgery. In the future, multicentre research should be carried out to further explore its diagnosis, treatment, causes of disease, and prognostic factors, among other features.

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