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CervixEpithelioidTrophoblasticTumor:ARareCaseReportandReviewoftheLiterature

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1. Abstract

Rationale: Theepithelioidtrophoblastictumour(ETT)is a very rare type of gestational trophoblast neoplasm (GTN), accountingfor0.5%-2.0%ofallGTNs.Withtheirunusualabilityto 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 inter- mediate trophoblasts, so they are not sensitive to chemotherapy. Surgery is the primary treatment.

Patientconcerns: Wehereinreportthecaseofa42-year-old femalewithpersistentvaginalbleedingfor30days.Pelvicexaminationshowedthatthecervixwasslightlyerosive,hypertrophied, and barrel-shaped; was 4 cm in diameter and 3cm in length; and had no abnormal hyperplasia on the surface.The serum human chorionicgonadotropin(HCG)levelwas0.30mIU/ml.Ultrasound revealed 2.3×2.2×2.4-cm mixed echogenic masses in the cervical myometrium. Pelvic MRI showed cervical malignant tumours.

Diagnoses: ThefinalpathologicaldiagnosiswasCETT.

Interventions: The patient was treated with radical hysterectomy.TheEMA-EPregimenconsistingofthreetreatmentswas given after the surgery.

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

Lessons: TheincidenceofETTsislow,andclinicalmanifestationsarenotspecific.Itiseasytomisdiagnose.Itisnecessaryto

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 literatureare few, and the few such reports comprise mostly case reports and small-samplereportsonETT.Approximately140ETTcaseswere retrievedinPubMeduptoSeptember2020.Acervicalepithelioid trophoblastictumour(CEET)isanepithelialtrophoblastictumour occurringinthecervixandisevenrarer.Thereareoccasionalcase 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,4cmindiameterand3cminlength. 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 revealeda 2.3×2.2×2.4-cm solid mass in the cervical myometrium, which hadunclearboundarieswiththecervicalcanal.TheHPVdetection result was negative, and cervical smear cytological examination wasnormal.PelvicMRIshowedacervicalmalignanttumour(Fig- ure 1 and 2). The result of colposcopy was chronic inflammation of the cervical mucosa. Hysteroscopy (Figure 3) showed a large whiteandgreycauliflower-likemassinthelowеruterinesegment anduppersegmentofthecervicalcanal,whichwaswidened,and tortuous arteries were on the surface of the mass, with white coagulatednecrosisinthelocalarea.Theuterinecavitywasnormal.

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).Thepathologicaldiagnosiswasanepithelioidtrophoblastictumouroftheuteruswithcalcification.Immunocytochemicalresults wereasfollows: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-EPregimen, 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 firstday;VP-16100mg/m2,Act-D0.5mg,andCF15mgq12hon theseconday;andVP-16150mg/m2andDDP75mg/m2onthe eighthday.After24monthsoffollow-up,therewasnoevidenceof residual tumour regrowth or metastasis.

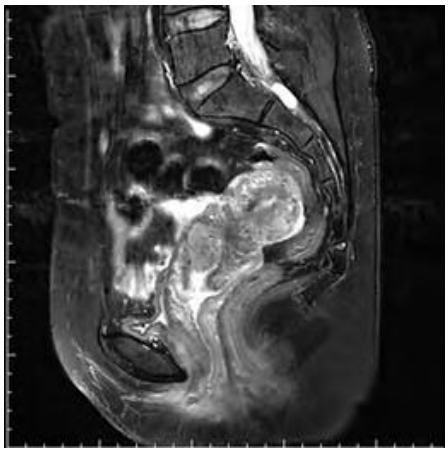

Figure1:MRI(sagittalT2WI):Mixedsignalshadowoftheanteriorwall of the cervical canal

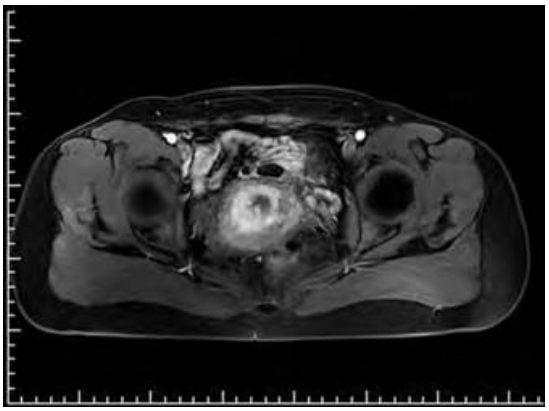

Figure 2: MRI (cross-sectional DWI): The DWI signal of the cervicalcanal was increased

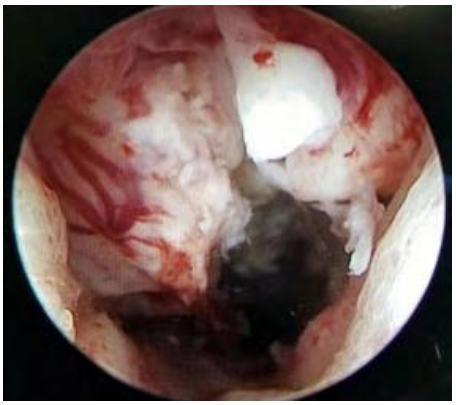

Figure3: Hysteroscopicimage

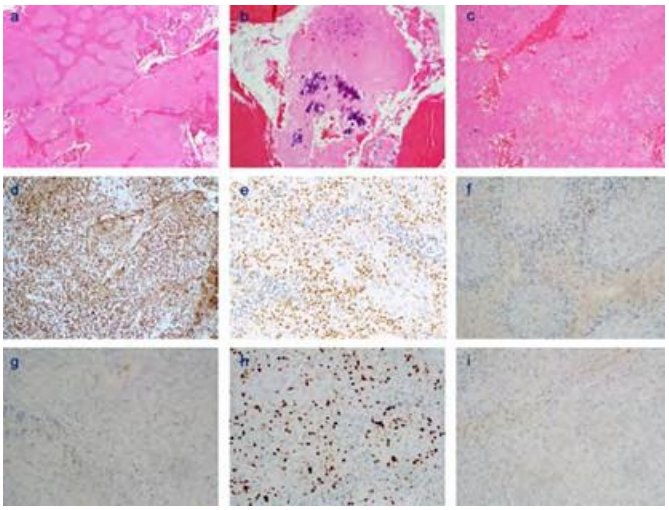

Figure4: Immunohistochemicalresults(immunohistochemistry,40×amplification)

a. Thetumourtissueshowednodulargrowthandwasarrangedintonests of cords, and the cell size was relatively consistent (HE, 40× amplification)

b. Eosinophilichyalinedegenerationdepositionwasseenbetweentumour cells,accompaniedbygroundpatternnecrosis(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 (+++)

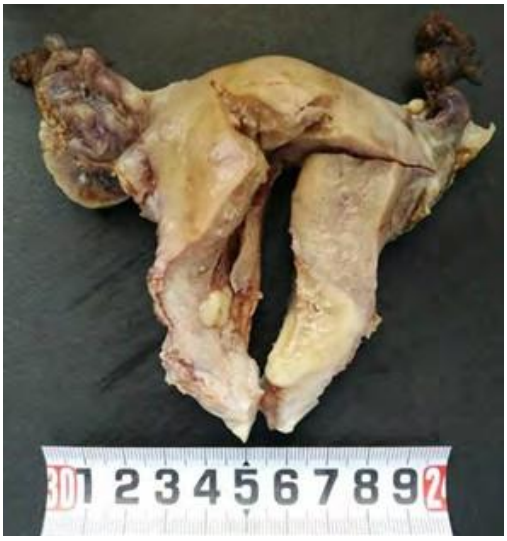

Figure5: Extensiveuterusanddoubleappendages

4. Discussion

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 ETTis 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. ShinandKurmanwerethefirsttoreportthat66.7%ofETTsoccur after a term pregnancy . Subsequently, many studies found that approximately 60%-80% of ETTs occurred after a term pregnancy;however,itwasalsoreportedthatonly8.9%ofETTsoccurred afterfull-termdelivery,with51.1%occuringafteranabortion[9].

Therefore, the relationship between ETT and previous pregnancy needs to be further clarified in future research. The interval betweenthepreviouspregnancyandthediagnosisofanETTfluctu- ates 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 mostcommonsiteofmetastasis[10],butmetastasiscanalsooccur inthevagina[11],ovary[12],uterinescar[13],andrectocele[14].

ETTs originate from intermediate trophoblasts, lacking syncytial cells for the synthesis of β-HCG. Generally, the levels of serumβ-HCGareslightlytomoderatelyelevatedbutcanbenormal[1,3, 4]. The levels of serum β-HCG are below 1000 IU/Lin 77.4% of cases and below 5 IU/Lin 23.8% of cases [3]. The clinical manifestationsofanETTlackspecificity,andpreoperativediagnosisis difficult.Duetoirregularvaginalbleedingandhighserumβ-HCG, itiseasilymisdiagnosedasanectopicpregnancy,anabortion,and anothertrophoblastictumour.ETTsoccurmostlyinthelowerseg- ment of the uterus and cervix, and serum β-HCG may be normal; therefore,anETTcanbemisdiagnosedascervicalcancer.Preoperative diagnosis is difficult, as it is based mainly on the surgical pathological diagnosis.

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 wassurroundedbyanextensivenecroticareaandhyaline-likematerial, showing a "map-like" appearance [15], which was rare in squamous,adenocarcinoma,orundifferentiatedcancer.Themean 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 fromothertypesofGTNandepithelioidtumours.Intermsofimmunohistochemistry, 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 negativeinplacentaltrophoblastsandstronglypositiveinanETT. Human placental lactogen(HPL) is strongly positive in placental trophoblastsbutnegativeinanETT.Ki67isamarkerofcellproliferationactivity,whichismorethan15%inanETTandlessthan 8%inplacentalnodules.ThecellmorphologyofanETTissimilar tothatofsquamouscellcarcinoma,andthefocusoccursmostlyin the lower segment of the uterus and cervical canal; thus, an ETT needstobedifferentiatedfromcervicalsquamouscellcarcinoma. 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 cellsintypicalmap-likenecrosiscouldbeseenandweresuspect- ed to indicate an epithelioid trophoblastic tumour. CAM5.2 and P63werestronglypositive,CK5/6andβ-HCGwerenegative,and Ki67positivitywas20%-25%;therefore,thepathologicaldiagno- sis was an epithelioid trophoblastic tumour.

TreatmentandPrognosis

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]. HysterectomyisthefirstchoiceoftreatmentandcanbeappliedtO patientswithoutfertilityrequirementsandwiththefocusconfined totheuterus(FIGOstageI).Thediseaseishormone-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,itisstillcontroversialwhetherpelvicandabdominalaor- tic lymphadenectomy should be performed. Some studies includ- ing those by Frijstein et al. [19] suggested that lymphadenectomy could not improve the survival rate; however, in the 2020 NCCN Guideline,itwassuggestedthatlymphadenectomyshouldbeper- formed.Morestudiesareneededonthistopic.Whentherareex- trauterinelesions(FIGOII-IV),allthelesionsshouldberemoved as much as possible, which may require multidisciplinary collab- orative 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 treatedbysurgery,andcombinedchemotherapywasperformedin 14patients,amongwhom4patientsdied.Theintervalbetweenthe previouspregnancyandthediseasewas56monthsto202months. Therewere18caseswithFIGOstage≥IIdisease,amongwhom6 casesdiedofthediseaseand1diedofotherfactors[19].Therefore, anintervalbetweenonsetandpreviouspregnancy≥48monthsand FIGO stage ≥II are the two most important independent adverse prognostic factors. Other adverse prognostic factors include old- er age, deep myometrial invasion, tumour necrosis, and mitotic index>5/10 HPF. These results are consistent with the researchof 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,actinomycinD,cyclophosphamideandvincristine), EP/EMA(etoposide,cisplatin,methotrexate,andactinomycinD), and TP (paclitaxel and cisplatin) are the most frequently select-ed 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 ETTonsetandthemostrecenttermpregnancyanddeliveryof12 years. In view of these factors, extensive hysterectomy was per- formed,andaftertheoperation,threecyclesofEP/EMAweregiv- en.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 mis- diagnosed in the clinic. It is necessary to combine serology and imaging,especiallypathologyandimmunohistochemistry,fordi- agnosis. The CETT is composed of villous intermediate tropho- blastswithhighdifferentiationandinsensitivitytochemotherapy. It is usually treated by hysterectomy and focal resection and con- solidatedbychemotherapyaftersurgery.Inthefuture,multicen- tre research should be carried out to further explore its diagnosis, treatment, causes of disease, and prognostic factors, among other features.

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