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Case Report

Misdiagnosis of epithelioid trophoblastic tumors: a case report and literature review

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Abstract

Background: The most common clinical types of gestational trophoblastic neoplasia are invasive hydatidiform mole and choriocarcinoma, which can be diagnosed without pathology, and be cured by chemotherapy. Epithelial trophoblastic tumor, a rare type of gestational trophoblastic neoplasia, does not exhibit precise clinical manifestations upon auxiliary examinations. Therefore, since epithelial trophoblastic tumors are prone to misdiagnoses and missed diagnoses, their diagnosis have to be confirmed through pathology and immunohistochemistry. **Case**: We describe a case of a 37-year-old woman that had been misdiagnosed at a local hospital after she had presented with irregular vaginal bleeding and elevated human chorionic gonadotropin. The initial diagnosis was ectopic pregnancy and she was subjected to left salpingectomy, however, after treatment, there was no significant drop in human chorionic gonadotropin. Later, she was diagnosed with gestational trophoblastic neoplasia and was treated with multiple chemotherapy and hysterectomy. However, after treatment, her human chorionic gonadotropin was found to repeatedly fluctuate. Eventually, pathological examination of a resected lung lesion confirmed the presence of epithelial trophoblastic tumors. **Conclusions**: Epithelial trophoblastic tumor is an intermediate trophoblastic tumor that is not sensitive to conventional chemotherapy. Surgical resection is the recommended therapeutic option. Gestational trophoblastic neoplasia patients presenting with persistently low levels of human chorionic gonadotropin and resistance to conventional chemotherapy should, therefore, be considered for early surgical resection, or tissue biopsy to pathologically confirm the diagnosis and inform treatment options.

Keywords: Epithelial trophoblastic tumor; Misdiagnosis; Pathology; Surgery; Chemotherapy

1. Introduction

Gestational trophoblastic neoplasia (GTN) is a type of gestational trophoblastic disease that consists of diseases such as invasive hydatidiform mole (IHM), choriocarcinoma (CC), placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT). Clinically, it is manifested through human chorionic gonadotropin (hCG) elevation. The most common are IHM and CC, which do not require pathology for diagnosis, and are sensitive to chemotherapy, which is the preferred therapeutic option. Rare diseases, such as PSTT and ETT are pathologically diagnosed and respond poorly to chemotherapy, therefore, surgical resection is the preferred therapeutic option. ETT, the most rare form of GTN, was first described in 1998 as originating from chorionic intermediate trophoblasts [1]. It is distinct from PSTT, which originates from placental intermediate trophoblasts. Due to this distinction, ETT became an independently classified pathological type that was subsequently accepted by the World Health Organization in 2003, and entered into the classification system of gynecological tumors. Approximately 1.39–2.00% of all gestational trophoblastic diseases are ETT [2]. Due to its low incidence rates, the clinical features of ETT have not been clearly elucidated, making its diagnosis to be pathology dependent. This enhances the probability of either missing or misdiagnosing ETT as ectopic pregnancy, cervical cancer, etc. In this study, we describe a case of a 37-year-old woman who was initially misdiagnosed with ectopic pregnancy, and later diagnosed with multi-drug resistant GTN. After pathological lung lesion resection, she was eventually diagnosed with ETT.

2. Case presentation

We describe a case of a 37-year-old woman (gravida 5, para 3) whose last delivery was a normal vaginal delivery, that occurred in October 2013. On 10 July 2018, she sought medical intervention from a local hospital, presenting with irregular vaginal bleeding for half a month as the main complaint. Her β-human chorionic gonadotropin (β-hCG) level was 228 mIU/mL, while transvaginal ultrasound revealed a thickened left fallopian tube. Her condition was, therefore, diagnosed as ectopic pregnancy and she was subjected

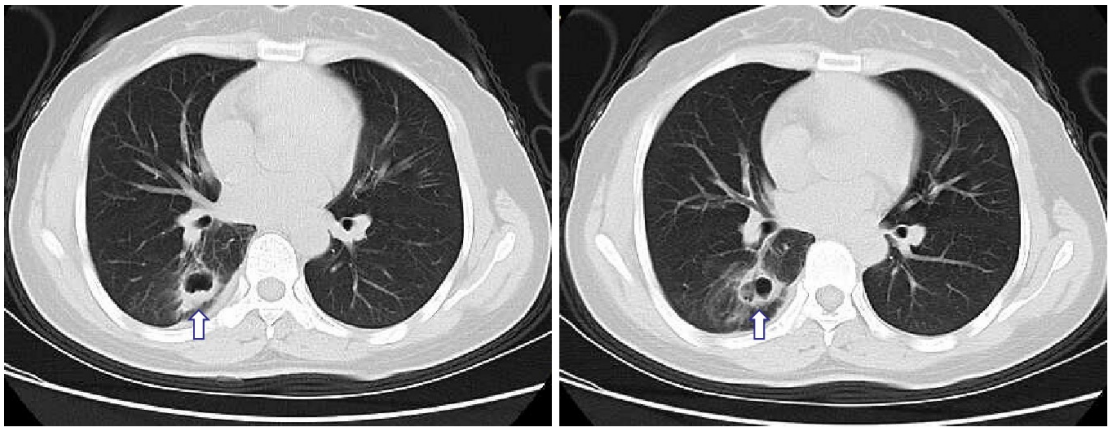

Fig. 1. Chest CT scan was performed on 27 November 2012. The area indicated by the arrow was the thick-walled cavity-like lesion of the right lower lobe.

to laparoscopic left salpingectomy + curettage at the local hospital on 11 July 2018. However, the operation did not reveal any significant embryos or villous tissue. Since her β-hCG level was 213 mIU/mL, she was administered with intramuscular methotrexate (50 mg) on the third day post-operation. At 1 week post-operation, pathology revealed chronic inflammation of the left fallopian tube with bleeding and irregular endometrial hyperplasia.

Even though her β-hCG levels rapidly decreased after chemotherapy to 26.56 mIU/mL, by 2 August 2018, they began to rise again and on 5 September 2018, they were 222.78 mIU/mL. She was subjected to another curettage, and her postoperative pathology revealed simple endometrial hyperplasia. After curettage, fluctuations in β-hCG levels were again observed, with levels dropping to 75.6 mIU/mL after the procedure before rising to 263.6 mIU/mL by 25 September 2018. Further, the patient developed cough symptoms without hemoptysis, chest tightness or difficulties in breathing. A computed tomography (CT) scan of the chest revealed low-density changes in the right lower lobe. Moreover, postoperative bronchial biopsy did not reveal any cancer cells on the brush smear.

Between 29 September and 23 October, 2018, two courses of chemotherapy (methotrexate/tetrahydrofolate (MTX/CF)) were administered to the patient, yielding a significant reduction in β-hCG levels to 3.0 mIU/mL. However, on 16 November 2018, β-hCG levels had risen, again, to 119 mIU/mL. When admitted to The First Affiliated Hospital, ZheJiang University School of Medicine on 27 November 2018, her β-hCG level was 138.5 mIU/mL. Chest CT revealed a blade-like high-density shadow in the right lower lobe, with unclear boundaries, and a cavity shadow inside. The inner wall was smooth and was in communication with the bronchus. We considered this to be an infected lesion in the right lower lobe with cavity formation (Fig. 1), and diagnosed her condition as GTN.

Hysteroscopic biopsy was performed on 30 November 2018, and it did not reveal any abnormal lesions in the uterine cavity. Even though postoperative pathology revealed a small piece of decidual tissue, no clear villi and trophoblast components were found. The β-hCG levels continued to rise and reached 566.4 mIU/mL on 6 December 2018. Two FA courses (5-fluorouracil, actinomycin D) were immediately administered to the patient, resulting in a drop in β-hCG levels to 15.8 mIU/mL and 9.8 mIU/mL after the first and second courses, respectively. Due to the slow decline in β-hCG levels, treatment dose was changed to four courses of FAEV (5-fluorouracil, actinomycin D, etoposide, vincristine) therapy, which yielded a normal β-hCG level (0.8–1.6 mIU/mL).

On 9 April 2019 chest CT revealed a nodular and patchy density increase in the right lower lobe, with unclear borders; and localized thickening of the surrounding pleura, suggesting that the cavity in the right lower lobe was not visible, and less lesion than before. On 7 May 2019, the β-hCG level was 6.0 mIU/mL rising to 11.7 mIU/mL after a week. The patient was subjected to laparoscopic hysterectomy + right salpingectomy on 15 May 2019, and postoperative pathology revealed right salpingal tissue and changes in endometrial hyperplasia. One day post-operation, β-hCG levels rose to 13.4 mIU/mL, and two courses of EMA/CO (etoposide, methotrexate, actinomycin D/cyclophosphamide, vincristine) therapy were administered. β-hCG levels dropped to 8.9 mIU/mL after the first course and rose to 13.8 mIU/mL after the second course. Chest CT revealed similar findings to those of 9 April 2019 (Fig. 2).

On 1 July 2019 she was subjected to thoracic surgery, and right lower lobe dorsal segment resection was performed under video-assisted thoracoscopic surgery (VATS). Postoperative pathology revealed a metastatic trophoblastic tumor, which was considered ETT based on the patient's history and immunohistochemistry. Immunohistochemical findings were CK(pan) (+), CK5/6 (individual +), CK7 (+), P63 (+), hCG (partial +), human placental lactogen (hPL) (small amount +), Ki-67 (60%), TTF-1 (-), and Napsin A

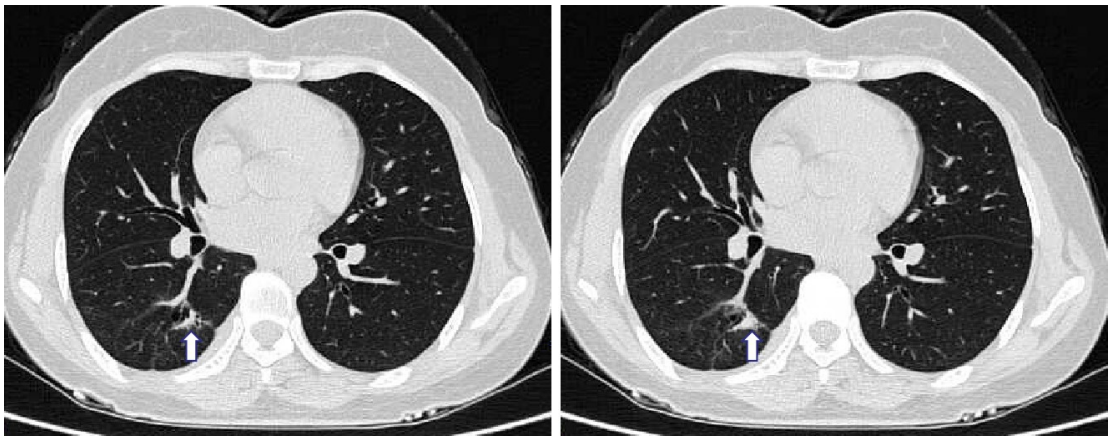

Fig. 2. After multiple chemotherapy, chest CT was re-examined on 24 June 2019. The area indicated by the arrow shows that the lesion of the right lower lobe was significantly reduced and the thick wall disappeared.

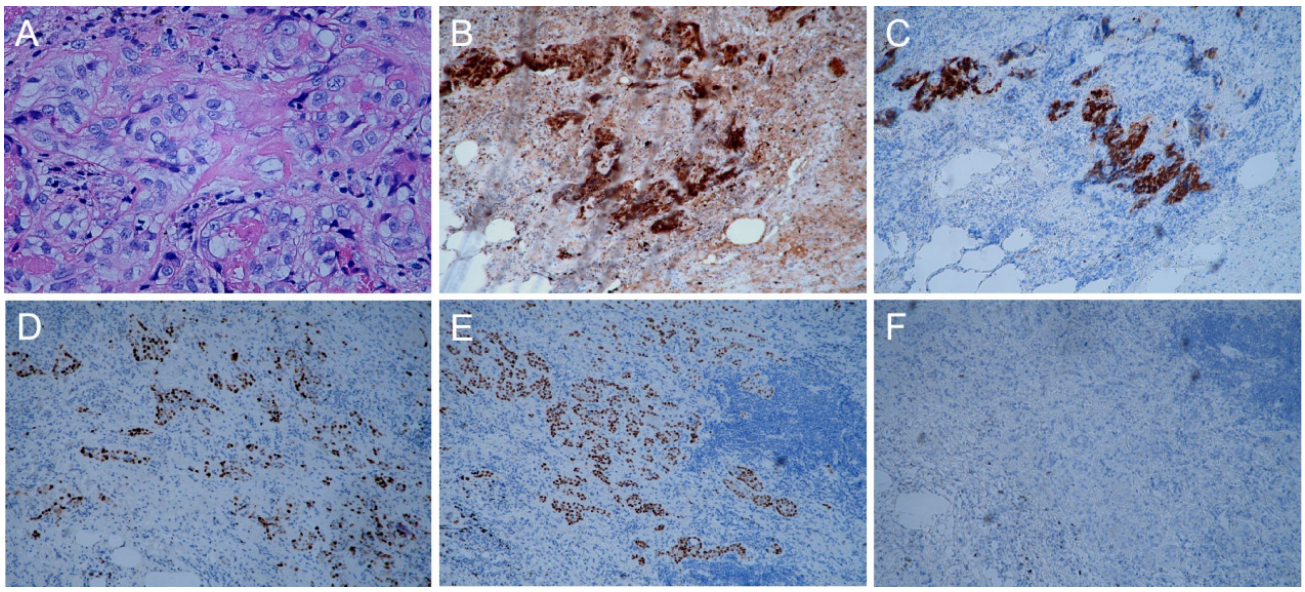

Fig. 3. Hematoxylin and eosin (HE) staining and immunohistochemistry of the tumor cells. (A) Hematoxylin and eosin (HE) staining showed that the tumor cells were relatively single in shape and arranged in a nested arrangement (40× magnification). (B) Immunostaining for hCG (10× magnification). (C) Immunostaining for hPL (10× magnification). (D) Immunostaining for Ki-67 (10× magnification). (E) Immunostaining for P63 (10× magnification). (F) Immunostaining for TTF-1 (10× magnification).

(-) (Fig. 3). β-hCG decreased after the operation and was recorded to be 1.1 mIU/mL on 16 July 2019. She was further administered with three courses of TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide) therapy, with the last course being administered on 27 September 2019. During both treatment and follow-up periods, the β-hCG level was normal (0.6–1.0 mIU/mL). In addition, chest CT did not reveal any evidence of tumor recurrence. Besides treatment, the patient's β-hCG level was monitored and is shown in Fig. 4.

3. Discussion

We used the available information in literature and the characteristics of this patient to describe. Clinical manifestations, auxiliary examinations, pathological diagnosis, and treatment were used to understand the course of the disease.

There is no obvious specificity in the clinical manifestations of ETT. Even though vaginal bleeding and lower abdominal pain are the most common ETT symptoms, cough, hemoptysis, chest pain and other discomforts can also be experienced when lung metastases occur. ETT is prevalent among women of child-bearing age (15–48 years), with a pregnancy history. Its development occurs between 1 and 18 years, from the last pregnancy [3]. Approximately 40% of these lesions occur in the uterine corpus while 31% occur in the uterine cervix [4]. The most common lesions outside of the uterus occur in the lungs, accounting for about 19% [4,5]. This patient was 37 years old and had had her last pregnancy when she was 33 years old. Her initial symptoms

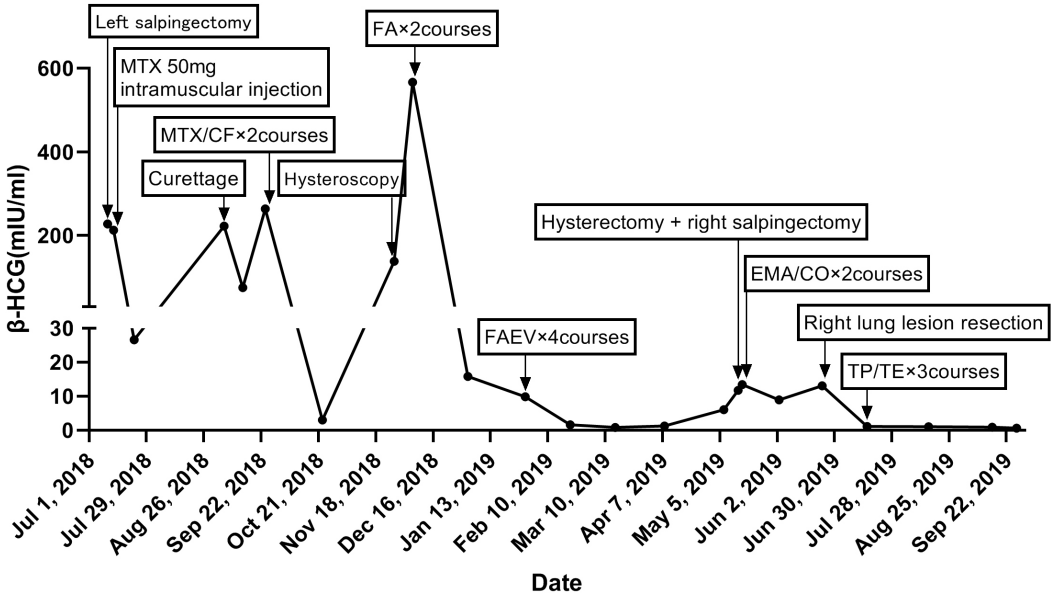

Fig. 4. Main treatment and β-hCG monitoring in this patient.

were vaginal bleeding and she later developed symptoms of metastatic sites such as cough, consistent with previous reports in literature.

In urine and serum of both pregnant women and tumors patients a fifteen various forms of hCG were identified. Upon auxiliary examination, hCG levels in ETT patients is usually slightly elevated (<2500 mIU/mL) [5,6]. In this case, serum β-hCG was detected during the course of the disease. We did not do urine hCG test. In our hospital, peripheral venous blood sample for biomarkers were obtained, and were separated by centrifugation (at 1700$\times$ g for 5 min), and aliquots were stored at –20 °C until further assayed. β-hCG were detected with E-170 automatic analyzer (Roche) according to the SOP operation manual of the laboratory and instrument instructions. The detection reagent (Elecsys HCG+β) and diluent were provided by Roche company. Meanwhile the internal quality control of the laboratory was provided by Bio-Rad. In this case, the highest β-hCG level was 566.4 mIU/mL. Studies have shown that hyperglycosylated human chorionic gonadotropin (H-hCG) is invasive. Gestational trophoblastic disease (GTD) and some non-pregnant malignant tumors (such as testicular tumors, ovarian germ cell tumors, etc.) have ectopic expression of H-hCG molecules in their invasion and growth, which may be used as a specific marker of disease [7]. And it adviced that the development of a new test identifying all hCG-related molecules in one assay is needed to monitor pregnancy, pregnancy disorders and cancer cases.

Through ultrasound imaging, a retrospective study reported that ETT lesions exhibited clearly bordered hypoechogenic halo, and that there were more doppler blood flow signals around the tumor than within the tumor [8]. Space-occupying lesions, and some calcified lesions that had been previously observed in CT images, are ETT symptoms [9]. Calcifications are usually small, and they are often not typical in CT images. In this case, a thick-walled cavity-like mass was seen on chest CT, without any visible calcifications. The radiology department considered them as infections, since calcifications are usually small in size and are not typical in CT images. Through Magnetic Resonance Imaging (MRI), ETT lesions exhibit a high signal on the T2 weighted image (T2WI) [10], while tumors show a low vascular mass on enhanced MRI [9]. These imaging characteristics have not been systematically evaluated, and therefore, they cannot be used as a reference in clinical practice.

Due to the low prevalence of ETT cases, clinical manifestations and auxiliary examinations of the disease are not clear, therefore, ETT is prone to missed diagnoses and misdiagnoses. For instance, elevated hCG levels, abnormal vaginal bleeding and lung metastatic tumors are also common clinical CC manifestations, and usually before surgery, tubal thickening can be misdiagnosed as ectopic pregnancy [6,11]. Besides, this patient's condition had been initially misdiagnosed as an ectopic pregnancy in a local hospital. In addition, since ETT often occurs in the cervix and lower uterus, it is often misdiagnosed as cervical cancer [12]. Therefore, due to the importance of pathology and immunohistochemistry in the diagnosis of ETT, it is necessary to conduct a pathological examination for an accurate diagnosis [13].

Pathologically, ETT lesions are cystic solid or solid nodular masses with a soft texture, clear boundaries, and swollen growth; but less invasive in growth. Moreover, they are dark brown or gray brown and are occasionally accompanied by hemorrhagic and necrotic lesions. Micro-

scopically, the tumors comprise relatively single mononuclear trophoblasts, with eosinophilic or transparent cytoplasms and a mitotic image of about 0–9/10 HPF. Microscopic examinations revealed that tumor cell islands are surrounded by necrotic areas, which appear as map-like or island-like features [5,14,15]. Immunohistochemical analyses of epithelial-derived markers such as cytokeratin (CK), epidermal growth factor receptor (EGFR), epithelial membrane antigen (EMA), and epithelial cadherin (E-cadherin), are also helpful in the diagnosis and differential diagnosis of ETT. Furthermore, placental alkaline phosphatase (PLAP) and P63 become positive in the presence of ETT, while hCG and hPL are usually focally positive. The expression of Ki-67, a marker of cell proliferation activity, in ETT is usually higher than 10% [14,16]. Levels above 50% are correlated with a higher risk of recurrence [17]. Despite PSTT and ETT being intermediate trophoblastic tumors, they can be differentiated on the basis of P63 and hPL expression levels. P63 is negative in PSTT and positive in ETT [16], while hPL is diffusely positive in PSTT and focally positive in ETT [16,18]. In addition, hCG expression in CC is usually positive, while hPL and P63 are usually negative [16], which are distinguishing features for CC from ETT. Currently, for tumors located in the cervix or lower uterus, P16 is used to differentiate between ETT and cervical cancer. Unlike cervical cancer, P16 is negative in ETT [19] while hCG is negative in cervical cancer. In our case, immunohistochemistry showed that P63 was positive; hCG as well as hPL were both focal positive; while Ki-67 was 60% positive, consistent with ETT characteristics. In addition, a lesion in the lung had to be confirmed to being different from a primary lung tumor. We used thyroid transcription factor (TTF)-1 and Napsin A, which are highly sensitive and specific in the positive expression of primary lung adenocarcinoma, to differentiate the two [20]. However, expressions of TTF-1 and Napsin A in this case were both negative.

Typically, ETT follow normal term pregnancies but can occur after any pregnancy event including molar pregnancy and typically present from months to many years after the antecedent pregnancy. In this case, there was no histological confirmation of either gestation or trophoblastic disease at the fallopian tube or uterus, so we speculate that ETT lesions in the lungs presumably originated from the normal term pregnancy in 2013.

ETT was previously called “multiple nodules of intermediate trophoblasts” and “atypical CC” because they occurred after intensive chemotherapy for pulmonary CC metastasis [21]. So it was previously suggested to be associated with chemotherapy-resistant CC [21]. And Lu *et al.* [22] reported on 4 patients with CC who underwent surgery after chemotherapy and found that these tumor cells showed immunohistochemical results similar to ETT. In this case, the patient also received multiple courses of chemotherapy before lung surgery, so it should be differentiated from CC. The serum hCG is significantly elevated in CC patients, usually $>$5000 mIU/mL. However, this patient’s serum β-hCG was only slightly elevated (228 mIU/mL) in the early stage of the disease, even during the entire course of the disease, the highest value of HCG was only 556.4 mIU/mL. In the report [22], their immunostaining patterns for trophoblastic markers showed high hCG staining. But in this case, immunohistochemistry showed that hCG was only focally positive. In addition, there was no typical dimorphic pattern of CC found on pathological examination in this patient. Taken together, we didn’t consider this patient to be CC.

Based on the GTN clinical staging issued by the International Federation of Gynecology and Obstetrics (FIGO) in 2002 [15], the ETT tumor in this case was at FIGO stage III and is recommended for surgery [23,24]. However, for patients with FIGO stage I, hysterectomy is recommended. Since ovarian metastases from ETT are rare, premenopausal women can retain bilateral ovaries, while for patients with FIGO II-IV stage, hysterectomy, coupled with extensive removal of metastatic lesions, is recommended [25]. For postoperative treatment, the National Comprehensive Cancer Network (NCCN) guideline 2019 [25] recommends classification based on tumor stage and potential high-risk factors including; tumor cell mitosis $>$5/10 HPF, extensive coagulative necrosis, duration since last pregnancy $\geq$2 years, deep myometrial infiltration, and lymphatic vasculature infiltration. For low-risk FIGO I patients, chemotherapy is not necessary after hysterectomy, but regular follow-up should be performed. However, for FIGO I stage patients with any high-risk factors or FIGO II stage and above, chemotherapy is recommended after surgical resection of the lesion. Due to the poor sensitivity of ETT to conventional GTN chemotherapies [3] this guideline recommends a combination chemotherapy containing platinum/etoposide [25], such as TP/TE, EMA/EP (etoposide, methotrexate, actinomycin D/etoposide, cisplatin), BEP (bleomycin, etoposide, cisplatin), VIP (etoposide, ifosfamide, cisplatin), etc. Besides, chemotherapeutic options such as EMA/EP or TP/TE have also been proposed by previous studies [15,26,27]. In this case, after the confirmation of pathological diagnosis, three courses of TP/TE therapies were administered. No tumor recurrence has since been observed.

Since ETT is an intermediate trophoblast tumor, hCG is a less reliable marker for its detection. Therefore, hCG is used as a marker for follow-up monitoring, while imaging is more important for ETT diagnosis [28]. This case is still being followed up, her hCG levels have always been normal, and no recurrent lesions have since been detected on chest CT.

4. Conclusions

Low incidence rates, lack of clear and specific clinical manifestations as well as very low routine auxiliary examinations of ETT, enhances its clinical misdiagnosis and

missed diagnosis. For a more accurate diagnosis, the diagnosis of ETT should be based on a combination of clinical data, pathology, and immunohistochemistry. Therefore, for patients with persistently low hCG levels and who are resistant to conventional chemotherapy, early surgery or tissue biopsy should be considered to confirm the diagnosis by pathological examination and to guide treatment.

Abbreviations

GTN, gestational trophoblastic neoplasia; IHM, invasive hydatidiform mole; CC, choriocarcinoma; PSTT, placental site trophoblastic tumor; ETT, epithelioid trophoblastic tumor; hCG, human chorionic gonadotropin; β-hCG, β-human chorionic gonadotropin; CT, computed tomography; MTX/CF, methotrexate/tetrahydrofolate; FA, 5-fluorouracil, actinomycin D; FAEV, 5-fluorouracil, actinomycin D, etoposide, vincristine; EMA/CO, etoposide, methotrexate, actinomycin D/cyclophosphamide, vincristine; VATS, video-assisted thoracoscopic surgery; H-hCG, hyperglycosylated human chorionic gonadotropin; GTD, Gestational trophoblastic disease; T2WI, T2 weighted image; MRI, Magnetic Resonance Imaging; EGFR, epidermal growth factor receptor; CK, cytokeratin; EMA, epithelial membrane antigen; E-cadherin, epithelial cadherin; PLAP, placental alkaline phosphatase; hPL, human placental lactogen; TTF, thyroid transcription factor; FIGO, International Federation of Gynecology and Obstetrics; NCCN, National Comprehensive Cancer Network; EMA/EP, etoposide, methotrexate, actinomycin D/etoposide, cisplatin; BEP, bleomycin, etoposide, cisplatin; VIP, etoposide, ifosfamide, cisplatin.

Author contributions

TZ collected the clinical data and drafted the manuscript. JHQ, JY and PY participated in the surgical treatment. WQW completed the pathological examination. JWF and JS reviewed the manuscript. TZ and QHW consulted the relevant literature. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study participant gave a written informed consent, and this study was ethically approved by the Ethics Committee of the First Affiliated Hospital, ZheJiang University School of Medicine (approval number: 201800536).

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Conflict of interest

The authors declare no conflict of interest.

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