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Clinical characteristics and outcomes of extrauterine epithelioid trophoblastic tumors

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Abstract

Background Epithelioid trophoblastic tumor (ETT) derived from intermediate trophoblasts is one type of gestational trophoblastic neoplasia (GTN), and it accounts for less than 2% of all gestational trophoblastic diseases (GTD). Extrauterine ETT is extremely rare, and there is currently no consistent strategy for its treatment and management. Therefore, the aim of the study is to analyze and summarize the clinicopathologic features of extrauterine ETT with or without metastasis.

Method The Web of Knowledge, Google Scholar, EMbase, congress of library, and PubMed were searched for extrauterine ETT without primary uterine lesions. All available data were extracted from published case reports or serial case reports, and then, the clinical and pathological characteristics were analyzed.

Results Twenty-two clinical studies consisting of 27 patients diagnosed with extrauterine ETT, according to the given inclusion and exclusion criteria, were included in the study. A total of 27 cases of extrauterine ETT were identified. Of these cases, four (14.81%) were located in the lungs, three (11.11%) in the ovaries, two (7.41%) in the vagina, and eight (29.63%) patients had other primary lesions. The patients originated from different continents, with 59% located in Asia and 26% in North America. Among 23 patients, the antecedent pregnancy prior to the diagnosis was full-term in 12 cases, abortion in 6 cases, hydatidiform mole in 3 cases, and invasive mole in 1 case. From the available antecedent information on pregnancy, the median interval from pregnancy to diagnosis of extrauterine ETT was 4 years. Additionally, the median gravidity and para of the patients was three times and two times, respectively. The median hCG titer was 14,374 mIU/mL in 5 patients, and the mean β-HCG titer was 3,724,805 mIU/mL in 14 patients. For all patients, the disease was confined to extrauterine ETT at diagnosis. From the available information, 20 cases were successfully treated by extraction of local lesions, and 12 cases received chemotherapy. Diagnosis was confirmed by histological tests. The Ki-67 staining ranged from 8.7 to 80%, and tumors were positive for hCG, PLAP, EMA, and p63.

Conclusion In this study, we observed that abnormal levels of serum hCG titers and the local presentation of lesions with varying intervals after antecedent term pregnancy were the most common presenting features of extrauterine ETT. In addition, we found that the extraction of extrauterine lesions was needed for the treatment of extrauterine ETT. Of course, the follow-up was also important.

Keywords Gestational trophoblastic disease · Epithelioid trophoblastic tumor · Extrauterine lesion · Immunohistochemistry · Surgery · Chemotherapy

Introduction

The epithelioid trophoblastic tumor (ETT) is an extremely rare type of gestational trophoblastic neoplasia (GTN) derived from intermediate trophoblast cells, and it was first described in 1998 [1, 2]. ETT represents less than 2% of all gestational trophoblastic diseases [3, 4]. In 80% of the cases of ETT that originated from the lower segment, the cervix, or the corpus of the uterus, extrauterine lesions or metastases from primary uterine lesions were present in the lungs,

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the small bowel, the vagina, the ovaries, and others sites [3, 5–8]. ETT usually occurs in reproductive-aged women following a previously normal or ectopic gestation [3, 9]. According to the previous reports, there have been approximately 130 cases of ETT reported thus far. Metastases were reported in 25% of these cases, and cases of extrauterine lesions were very rare [10–12]. Therefore, the biological behavior, the clinical and imaging characteristics, and the therapeutic strategy for extrauterine ETT have not been fully established.

Thus, the aim of this study is to investigate the clinical features and outcomes of extrauterine ETT by searching for published literature using PubMed, Web of Knowledge, Google Scholar, and other websites.

Research methods

This study was performed as shown in the workflow presented in Fig. 1. First, we screened for research articles that reported on screening for ETTs. Most importantly, the language was confined to English. The following databases were searched: Web of Knowledge, Google Scholar, EMbase, Congress of Library, and PubMed. The search strategy was developed by two librarians (co-authors Taohong Zhang and Xianling Zeng), and the useful information from the papers was extracted. Inclusion criteria were as follows: (a) patients were female; (b) patients were diagnosed with ETT by pathology and immunohistochemistry; (c) there were no primary lesions of ETT in the uterus; and (d) the background information included illness history, treatment, immunohistochemistry, and outcomes at follow-up. Exclusion criteria mainly included: (a) patients with the pathological diagnosis of invasive mole (IM), choriocarcinoma (CC), and placental site trophoblastic tumor (PSTT); and (b) the article was a not case report or case serial report.

Results

Twenty-seven patients had histologically confirmed ETT with primary lesions located outside of the uterus, including the lungs (14.81%, 4/27), the ovaries (11.11%, 3/27), the vaginal wall (7.41%, 2/27), and other locations (29.63%, 8/27) (Fig. 1). Furthermore, the patients originated from different continents; 59% were from Asia and 26% from North America. This reflects the rarity of the extrauterine ETT of GTN (Fig. 2).

Table 1 summarizes the clinical features, primary lesions, treatment strategy, and follow-up outcomes for all extrauterine ETT patients. The median age of the patients was 39 years, and the ages ranged from 26 to 75 years. Among the 23 patients that claimed antecedent pregnancy prior to the diagnosis, a full-term vaginal delivery was identified in 11 cases. There were six cases of abortion identified, which included spontaneous, missed, or artificial abortion. Hydatidiform mole was identified in three cases, and a full-term cesarean delivery was found in one case. An invasive mole was found in one case. In five cases, there was no documented information about pregnancies prior to the diagnosis of extrauterine ETT. The median gravidity of the patients was three times (ranging from one to six times), but

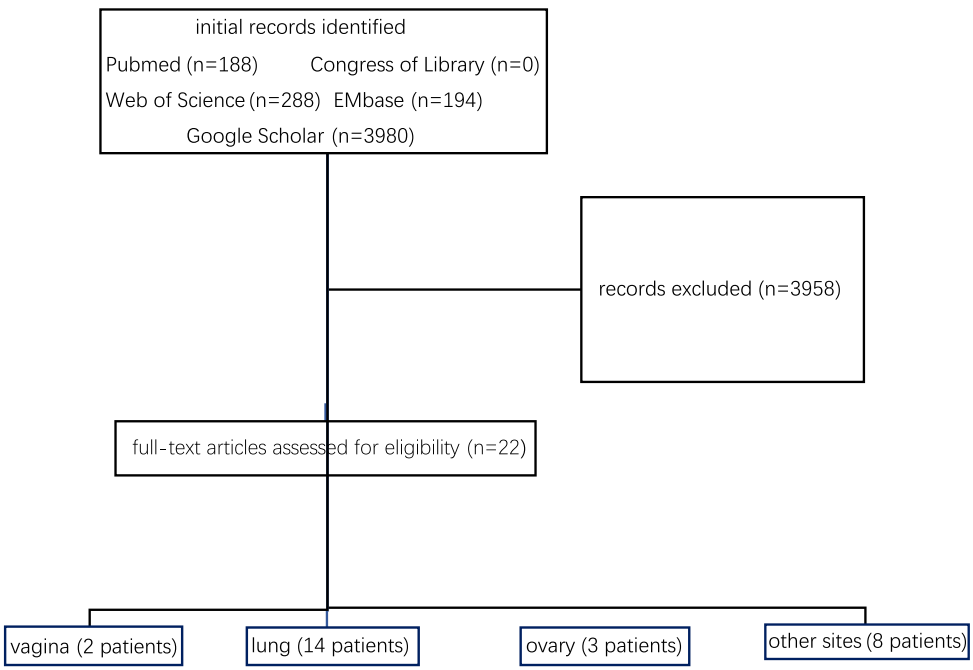

Fig. 1 Flow diagram and the site of lesions at all 27 patients

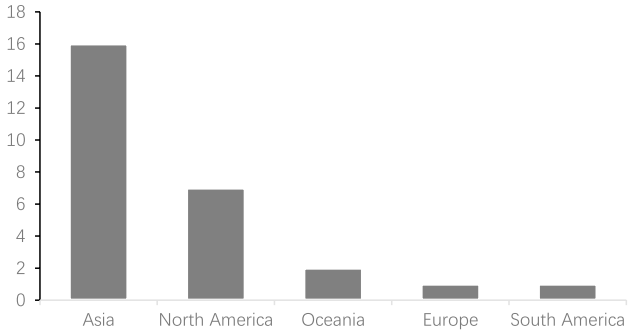

Fig. 2 The distribution of extrauterine ETT patients on different continents

the mean para was two times (ranging from 0 to 4 times) (Table 1).

In the 22 patients who had documented an interval between termination of previous pregnancy and diagnosis, the median interval from pregnancy to diagnosis of extrauterine ETT ranged from 2 weeks to 47 years. However, information about the period between antecedent pregnancy and diagnosis was not available for eight patients. Furthermore, 22.2% (6/27) of patients presented with abnormal vaginal bleeding, 22.2% (6/27) had tumors on different sites, 22.2% (6/27) had abdominal discomfort or back pain, 11.11% (3/27) had irregular menstruation, 14.8% (4/27) occasionally found by physical or preoperative examination, 3.7% (1/27) had elevated serum HCG, and 3.7% (1/27) had local symptom.

The serum human chorionic gonadotropin (HCG) concentration was measured by different assays. The median HCG titer was 14,374 mIU/mL (ranging from 16 to 60,000 mIU/mL) in five patients (cases 13, 14, 19, 26, and 27). The mean β-HCG titer was 3,724,805 mIU/ml (ranging from 16 to 52,065,000 mIU/mL) in 14 patients (cases 2, 4, 5, 6, 8, 9, 10, 12, 15, 16, 17, 20, 21, and 22). A concentration over 2500 mIU/mL was found in four patients, as indicated by either HCG or β-HCG. In four patients, HCG concentration was not reported (cases 11, 18, 24, and 25). Thus, half of the patients (19/27) had elevated serum HCG levels or β-HCG.

Surgical management was a part of the treatment for all patients. Fourteen patients with lung lesions underwent video-assisted thoracoscopic surgery (VAST). Two of these patients received a hysterectomy with or without a bilateral salpingo-oophorectomy (BSO) at the same time, but one of these patients underwent dilation and curettage (D&C) for diagnosis. Six of the 27 patients with lesions at different sites underwent surgical resection of the tumor. Of these, one was resected by pulmonary surgery due to lung metastasis, and one was resected by Hartmann's procedure. Three patients only received biopsy for diagnosis, and then they received chemotherapy using etoposide, methotrexate, and actinomycin D/etoposide, and cisplatin (EMA/EP), etoposide, methotrexate, and dactinomycin (EMD) or etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMACO).

Multiagent chemotherapy with EMA/CO was given to eight patients with extrauterine ETT. The regiment of one of these patients was modified to cyclophosphamide, etoposide, and cisplatin (CEC) after six cycles due to raised HCG levels. The rest of the patients received two to six cycles of chemotherapy. There was no evidence of disease in 50% (4/8) of patients who underwent EMA/CO treatment during the follow-up, regardless of the length of time analyzed. However, two patients were dead of disease at follow-up, but the rest one cannot get more information about chemotherapy effect. Four patients received EMA/EP. Of these four patients, one delivered a baby after six cycles, one had no evidence of disease, and some underwent EMA, cisplatin and etoposide (CE), EMD, VMC (regiments including vincristine, methotrexate, and cytoxan), or dactinomycin, VP16, methotrexate, and leucovorin (DVLM) chemotherapy.

The follow-up time of the survivors ranged from 2 weeks to 24 years in 24 patients. In these follow-ups, there were two patients that were not available and one patient was lost. There was no evidence of disease recurrence in the follow-up period in 17 cases, and 3 cases had recurrence. Additionally, three cases were dead of disease, and one patient unexpectedly delivered a baby within 12 months of follow-up.

The mean tumor size in all patients was greater than 1.5 cm, but the ovarian tumor size was much greater. Five patients had metastatic diseases of the lung, the liver, or both the lung and liver, and one patient also had VAST [13–15].

Extrauterine ETT was confirmed in 27 patients by pathological tests. However, in all patients, some results needed to be reviewed and diagnosed by immunohistochemistry tests. The immunohistochemical staining revealed that the tumor cells were positive for Ki-67, and the staining index ranged from 8.7 to 80%. The tumor cells were also positive for hCG in 15 cases. The staining was focally positive in three cases (patients 4, 9, and 14), but it was negative in four cases (patients 12, 18, 26, and 27). hPL was observed in ten cases (10/18) tested by immunohistochemistry, but it was negative in eight cases (8/18). Additionally, 54.5% (6/11) of cases stained positive for PLAP, and it was negative in 36.1% (4/11) of cases. Furthermore, the staining was focally positive for only 1 patient (patient 14), and it was not available in 16 cases (16/27). Positive immunoreactivity for EMA accounted for 77.8% (7/9) of cases, and 22.2% (2/9) of cases tested negative for EMA. EMA immunoreactivity was not available for 18 cases. There were 13 cases (13/27) that had positive p63 staining, but 14 cases were not available. The tumor cells stained positive for inhibin-α in eight cases, and it was negative in five cases (patients 5, 8, 10, 21, and 26). It was focally positive in one case (patient 22) (Table 2).

Table 1 Primary lesions, clinical features, treatment, and outcomes of extrauterine ETT in patients

Case number	Author	Year published	Site of primary lesions	Age (years)	G/P	AP	Interval from AP	Presenting features	HCG/β-hCG at diagnosis (mIU/mL)	Surgery	Chemotherapy	Response to chemotherapy	Follow-up (m)	Outcome
1	Lei et al. [13]	2018	Lung	48	1/1	HM	N/A	Physical examination	N/A	VATS	N/A	N/A	3	NED
2	Jiang et al. [14]	2018	Recto-uterine pouch	30	2/1	Abortion	2 years	Vaginal bleeding	427.7	D&C Mass excision	EMA/CO	3 cycle	N/A	N/A
3	Kim et al. [15]	2017	Midline lower abdominal wall	42	3/2	N/A	N/A	Abdominal pain	Not performed because of previous hysterectomy	Mass excision by Hartmann's procedure	N/A	N/A	9	NED
4	Luo et al. [16]	2016	Vaginal wall	32	3/1	Abortion	6 m	Vaginal tumor	70	Mass excision Pulmonary surgery	EMA/CO	2 cycle	19	NED
5	Arafah et al. [6]	2015	Ovary	50	4/1	FTCS	10 years	Abdominal distension, pain	806.7	Biopsy	EMA-EP	N/A	N/A	N/A
6	Ikenna et al. [17]	2014	Lung	40	N/A	N/A	N/A	Vaginal bleeding	1100	VATS	CE	4 cycle	12	NED
7	Patrick et al. [18]	2014	Lung	29	1/1	FTVD	4 years	Vaginal bleeding	Low levels	Unilateral ovariectomy VATS	EP-EMA	6 cycle	12	Delivered a baby
8	Shin et al. [19]	2014	Ovary	75	5/1	FTVD	47 years	Multiple pulmonary masses	57,971	Biopsy Total abdominal hysterectomy and BSO	EMA/CO	5 cycle	5	NED
9	Ahn et al. [20]	2013	Lung	26	1/0	Abortion	2 years	Delayed and heavy menstruation	11.37	VATS	EMA/CO	6 cycle	9	NED
10	Zhao et al. [7]	2013	Vaginal wall	43	2/0	Abortion	4 years	Vaginal tumor	15.5	Mass excision	N/A	N/A	5	Recurrence

Table 1 (continued)

Case number	Author	Year published	Site of primary lesions	Age (years)	G/P	AP	Interval from AP	Presenting features	HCG/β-hCG at diagnosis (mIU/mL)	Surgery	Chemotherapy	Response to chemotherapy	Follow-up (m)	Outcome
11	Joo et al. [8]	2013	Lung	35	N/A	N/A	N/A	Abdominal pain	Not performed	VATS	N/A	N/A	15	NED
12	Fernando et al. [21]	2011	Lung	31	2/2	FTVD	8 years	Vaginal bleeding	320	VAST	N/A	N/A	12	NED
13	Surapan et al. [22]	2011	Ovary	32	2/1	HM	5 years	Pelvic mass	60,000*	Mass excision	EMA	6 cycles	6	Recurrence
14	Chohan et al. [23]	2010	Spine	36	4/4	FTVD	2 w	Severe low back pain	16*	Laminectomy	EMA/CO	N/A	9	DOD
15	Lewin et al. [24]	2009	Lung	38	N/A	FTVD	3 years	Elevated serum hCG	400	D&C VAST	N/A	N/A	90	NED
16	Lewin et al. [24]	2009	Lung	49	N/A	Abortion	1 year	Vaginal bleeding	400	VAST LAVH BSO	EMA/EP	2 cycles	45	NED
17	Lewin et al. [24]	2009	Lung	34	N/A	FTVD	2 years	Irregular menses	426	VAST Hysterectomy	EMA/EP	3 cycles	22	NED
18	Noh et al. [25]	2008	Paracervix and parametrium	44	6/4	FTVD	25 years	Abdominal pain	Not performed	LAVH BSO Ascites cytology peritoneal biopsies	EMD	4 cycles	12	NED
19	Macdonald et al. [26]	2008	Gallbladder	41	2/2	FTVD	6 years	Vaginal bleeding	10,494*	Biopsy	Altering to EMA/CO after CEC (6 cycles)	N/A	7	DOD
20	Satoshi et al. [27]	2007	Lung	38	5/4	FTVD	N/A	Poor physical condition	80.1	VAST	EMA/CO	6 cycles	6	Recurrence
21	Kuo et al. [28]	2004	Broad ligament	41	3/1	N/A	N/A	Irregular menses	20,244	LAVH BSO	EMA	9 cycles	24	NED
22	Parker et al. [29]	2003	Fallopian tube	39	2/1	Abortion	2 years	Intermittent pelvic pain	52,065,000	LAVH LSO Infracolic omentectomy	EMA/CO	2 cycles	12	NED

Table 1 (continued)

Case number	Author	Year published	Site of primary lesions	Age (years)	G/P	AP	Interval from AP	Presenting features	HCG/β-hCG at diagnosis (mIU/mL)	Surgery	Chemotherapy	Response to chemotherapy	Follow-up (m)	Outcome
23	Hamazak et al. [30]	1999	Lung	47	N/A	IM	3 years	Preoperative evaluation for breast cancer	Slight elevation	VAST	N/A	N/A	24	NED
24	Hamazak et al. [30]	1999	Lung	32	3/1	HM	5 years	Physical examination	Not performed	VAST	N/A	N/A	36	NED
25	Hamazak et al. [30]	1999	Lung	42	2/2	N/A	N/A	Hemoptysis and cough	Not performed	VAST	Chemotherapy	Several courses	24	NED
26	Shih et al. [31]	1998	Bowel	39	N/A	FTDV	N/A	Bowel obstruction	60*	Bowel resection	VMC	N/A	36	DOD
27	Shih et al. [31]	1998	Lung	42	N/A	FTDV	N/A	Lung mass	1300*	VAST	DVLM	N/A	Lost	N/A

G/P gravida/para, *AP* antecedent pregnancy, *N/A* not available, *DOD* dead of disease, *NED* no evidence of disease, *HM* hydatidiform mole, *IM* invasive mole, *FTDV* full-term vaginal delivery, *FTCS* full-term cesarian section, *VATS* video-assisted thoracoscopic surgery, *NR* not require, *CE* cisplatin/etoposide, *D&C* dilation and curettage, *BSO* bilateral salpingo-oophorectomy, *LAVH* laparoscopic-assisted vaginal hysterectomy, *VMC* vincristine, methotrexate, and Cytoxan, *DVLM* dactinomycin, VP16, methotrexate, and leucovorin, *W* week or weeks, *m* month or months

*The value represents serum HCG

Table 2 The immunohistochemistry features of extrauterine ETT

Case number	Author	Year published	Site of primary lesions	Diameter of tumor (cm)	Ki-67 index	HCG	hPL	PLAP	EMA	P63	Inhibin-α	CK
1	Lei et al. [13]	2018	Lung	3.0	N/A	P	N/A	N/A	N/A	N/A	N/A	N/A
2	Jiang et al. [14]	2018	Recto-uterine pouch	2.7	45%	P	P	N/A	P	P	N/A	N/A
3	Kim et al. [15]	2017	Midline lower abdominal wall	N/A	50%	P	P	N/A	N/A	P	P	FP
4	Luo et al. [16]	2016	Vaginal wall	3.0	60%	FP	N	N/A	P	P	P	N/A
5	Arafah et al. [6]	2015	Ovary	13.6	80%	P	P	N/A	N/A	P	N	N/A
6	Ikenna et al. [17]	2014	Lung	7.2	NA	P	N	N/A	N/A	P	P	P
7	Patrick et al. [18]	2014	Lung	0.8	50%	P	N/A	P	N/A	N/A	N/A	N/A
8	Shin et al. [19]	2014	Ovary	12.7	80%	P	N/A	N/A	N/A	P	N	N/A
9	Ahn et al. [20]	2013	Lung	6.0	NA	FP	N/A	N/A	N/A	P	N/A	P
10	Zhao et al. [7]	2013	Vaginal wall	N/A	15%	P	P	P	N/A	P	N	P
11	Joo et al. [8]	2013	Lung	2.6	NA	P	N	P	N/A	P	P	N/A
12	Fernando et al. [21]	2011	Lung	5.0	NA	N	N	N	N/A	P	N/A	P
13	Surapan et al. [22]	2011	Ovary	9.0	62.4%	P	P	N	P	P	N/A	N/A
14	Chohan et al. [23]	2010	Spine	N/A	15–20%	FP	NA	FP	P	P	N/A	N/A
15	Lewin et al. [24]	2009	Lung	2.0	50%	P	P	N	P	N/A	P	P
16	Lewin et al. [24]	2009	Lung	5.3	NA	P	N	N/A	N/A	N/A	N/A	N/A
17	Lewin et al. [24]	2009	Lung	1.8	10–60%	P	P	N/A	N/A	P	P	N/A
18	Noh et al. [25]	2008	Paracervix and parametrium	N/A	10%	N	N	N/A	P	N/A	P	P
19	Macdonald et al. [26]	2008	Gall bladder	N/A	N/A	P	N/A	P	N/A	N/A	N/A	N/A
20	Satoshi et al. [27]	2007	Lung	N/A	35.6 ± 8.7%	N/A	P	N/A	N/A	N/A	P	N/A
21	Kuo et al. [28]	2004	Broad ligament	6.5	47.2%	P	P	N/A	N/A	N/A	N	P
22	Parker et al. [29]	2003	Fallopian tube	7.2	N/A	N/A	P	P	N	N/A	FP	N/A
23	Hamazak et al. [30]	1999	Lung	1.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
24	Hamazak et al. [30]	1999	Lung	2.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
25	Hamazak et al. [30]	1999	Lung	4.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
26	Shih et al. [31]	1998	Bowel	N/A	16%	N	N	N	N	N/A	N	P
27	Shih et al. [31]	1998	Lung	N/A	18%	N	N	P	P	N/A	N/A	P

P positive, *FP* focally positive, *N* negative, *N/A* not available, *HCG* human chorionic gonadotropin, *hPL* human placental lactogen, *PLAP* placental alkaline phosphatase, *EMA* epithelial membrane antigen, *CK* cytokeratin

Discussion

Extrauterine ETT with regional differences is a very rare type of ETT [16], and there is no consistent guideline to manage and treat patients worldwide [7, 17–31]. Previous studies have shown that an interval of > 48 years since antecedent pregnancy, the age of patients over 40 years old, the nuclear division such as > 5/10 HPFs, FIGO stage and extrauterine lesions are high-risk factors of ETT [3, 32, 33]. Therefore, it is important and necessary to analyze the treatment and management of patients with extrauterine ETT.

Several databases about extrauterine ETT were searched, and 27 patients were ultimately analyzed for symptoms, treatments, follow-up outcomes, and other characteristics. In this study, the results indicated that Asia had the highest incidence of extrauterine ETT (59%), and no cases were found in Africa and Antarctica. This result may be because extrauterine ETT is rarely seen, and the study was limited to the screening of five databases for reports only in the English language. Importantly, the incidence of GTD is correlated with ethnicity. Maestá has shown that Asian women with low-risk GTN required second-line chemotherapy, and they required chemotherapy regimens with more components to achieve complete remission than Caucasian and Afro-American women [34–36]. In addition, the reported incidence of choriocarcinoma is 1 in 40,000 pregnancies in North America and Europe, and it is 9.2 and 3.3 per 40,000 pregnancies in Southeast Asia and Japan [37], respectively. Thus, we speculate that differences in race, diet, and lifestyle may be potential factors that affect extrauterine ETT.

Currently, there is no defined mechanism of extrauterine ETT, and there have only been clinical cases reported [6, 7, 13–29]. Therefore, extrauterine ETT may be confused with other primary tumors when it occurs outside of the uterus. In the pathology of 27 cases, over 50% were located in the lungs, and GTN were commonly involved in hematogenous metastasis. Thus, we speculate that the main mode of metastasis for this disease is through hematogenous metastasis, local implantation, proliferation, and reproduction to become a tumor. This needs to be verified by basic experiments. Of course, intraperitoneal implantation metastasis and lymph node metastasis could not be excluded. There were some cases that occurred in the broad uterine ligaments, ovaries, and intestines. However, this is only a hypothesis, and it needs to be confirmed by clinical and experimental studies.

This study was the first to systematically analyze extrauterine ETT by evaluating the characteristics of presentation of symptoms, serum HCG, surgery, chemotherapy, and follow-ups. It is well known that ETT is most common in reproductive-aged women. It usually occurs 2 weeks to 30 years after antecedent pregnancy, and it usually presents with irregular vaginal bleeding [10, 33]. Nevertheless, this study identified patients had a history of pregnancy. Some patients presented with irregular vaginal bleeding, and some patients presented with local mass of extrauterine ETT (22.2% and 22.2%, respectively). It is thought that extrauterine ETT may be closely related to pregnancy history, either normal or abnormal pregnancies. Also, the patients usually exhibited evident local signs, such as local masses with mildly abnormal gynecological symptoms.

In classic choriocarcinomas, hCG levels are often found to be above 10,000 mIU/mL, but the HCG concentrations of ETT patients are usually only slightly elevated (< 2500 mIU/mL) [14, 38]. The serum hCG concentrations in most patients with ETT or PSTT are normal or slightly elevated. However, in the current study, over half of the patients (19/27) had elevated hCG levels. Therefore, hCG titers maybe a reliable marker for the diagnosis and follow-up examination of extrauterine ETT. In addition, extrauterine ETT should be suspected in the pre-diagnosis process when hCG concentrations are normal or elevated and there are no lesions found in the uterus of reproductive-aged females, as detected by ultrasound or pelvic MRI/CT.

Clinically, distinguishing ETT from other types of GTN or other epithelial malignancy is important for treatment plans [39]. Immunohistochemistry and pathological examination have invaluable in diagnosing ETT, and it is currently considered the golden standard for the diagnosis of ETT and extrauterine ETT. ETTs are typically positive for HLA-G, α-inhibin, CK18, p63, cyclin E, CD10, inhibin-α, EMA, and CK (CK18, CAM5.2, AE1/AE3), which are generally not present in SCC [16, 39]. Additionally, SCCs always have a high Ki-67 labeling index (> 50%), but it is relatively low in ETTs (10–25%) [16]. The Ki-67 expression index is a marker of cell proliferation activity, and it is usually greater than 10% in ETT tumor cells [39]. In the current study, we found that patients with over 50% Ki-67 expression in extrauterine ETT tumor cells have a high risk of recurrence. However, low expression of Ki-67 did not indicate safety, and those with low expression may still die from the disease. We observed diffuse expression of hCG, EMA, and CK. However, a previous study showed that ETT is negative for or only focally positive for hPL and Mel-CAM (CD146), but p63 is strongly positive in ETT and PSTT [39]. Thus, this may distinguish ETT from PSTT. In the meantime, there is a new marker to distinguish gestational choriocarcinoma from ETT and PSTT because it is expressed in 100% of choriocarcinomas [40].

Both the International Federation of Gynecology and Obstetrics (FIGO) and the European Society of Oncology have stated that hysteroscopic surgery, curettage, or

laparoscopic surgery should be considered for obtaining histological tissues, since a clinical diagnosis of GTN is difficult to obtain [41, 42]. However, both PSTT and ETT are less chemo-sensitive than choriocarcinomas. Thus, hysterectomy is the primary mode of treatment in most cases, and further surgery is important for metastatic diseases [43]. Additionally, oophorectomy is not routinely considered because ovarian metastases are uncommon, and an oophorectomy cannot improve prognosis [10]. In the current study, 20 patients with lesions at different sites underwent surgical resection of tumors. Therefore, tumor extraction may absolutely be the right choice. Of course, chemotherapy is also needed in extrauterine ETT. In the current study, chemotherapy regimens, such as EMA-EP, EMD or EMACO, that are usually applied in high-risk gestational choriocarcinoma, drug-resistant choriocarcinoma, PSTT or ETT were used to treat patients with extrauterine ETT. Due to the rarity of the disease and the length of clinic trials, there are no uniform and absolute chemotherapy regimens to treat extrauterine ETT with or without metastatic disease. However, Sobecki showed that regimens containing latinum/etoposide can be good for ETT, and Worley et al. reported that a woman with metastatic and refractory choriocarcinoma experienced a stable remission after receiving therapy with TRC105 and bevacizumab [44, 45]. Therefore, the options for treatment may increase, which would improve patient prognosis.

According to a retrospective study, the long-term survival for stage I patients with ETT that had a low risk of disease after hysterectomy was nearly 90% at 10 years [38]. However, the follow-up time of the survivors ranged from 2 weeks to 24 years for 24 patients, and 3 patients had died from disease. Thus, a follow-up of centralized care is needed for optimal management of a rare disease. Centralized management can vary from only hCG monitoring with treatment advice to patient referral.

Many limitations exist in the present study. First, this study was limited to the screening of five databases and included only reports in the English language. Second, the number of patients was small, and the data about the patients were incomplete or lost. For these reasons, the results of our study are limited and should be interpreted with caution. Additionally, the value of specific pathological features could be subjected to biases due to the use of different laboratories, test methods, immune antibodies, operators, and other uncertainties. Despite these limitations, we have acquired more characteristics, treatments, and outcomes of extrauterine ETT, and we have obtained knowledge on how to manage, treat, and follow-up on this rare disease in patients.

Conclusion

In conclusion, extrauterine ETT is an extremely rare type of GTN with unpredictable biological behavior. Its diagnosis should be suspected when a local mass is observed in extrauterine sites and the serum levels of the hCG or β-HCG titer is elevated in patients presenting with local masses accompanied with or without irregular vaginal bleeding at varying intervals after antecedent term pregnancies. Pathologic and immunohistochemistry findings are most important for an accurate diagnosis. Extraction of the tumor mass remains the main primary treatment of patients with extrauterine ETT. In this study, we also demonstrated that the extraction of the local mass in addition to adjuvant chemotherapy was successful for the treatment of extrauterine ETT. Although extrauterine ETT has been known to be relatively resistant to chemotherapy, further studies are necessary to determine the role of chemotherapy in this disease, and further studies are needed to indicate the appropriate chemotherapy.

Author contributions TZ conceived the scientific idea, TZ, XZ andHX performed the analyses and prepared the manuscript, TZcontributed to the preparation of the manuscript, LX and LG provided clinicaldata and contributed to the discussion of the data, while RA and YXsupervised the project. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Horowitz NS, Goldstein DP, Berkowitz RS (2017) Placental site trophoblastic tumors and epithelioid trophoblastic tumors: biology, natural history, and treatment modalities. Gynecol Oncol 144(1):208–214
2. Shih IM, Kurman RJ (1998) Epithelioid trophoblastic tumor: a neoplasm distinct from choriocarcinoma and placental site trophoblastic tumor simulating carcinoma. Am J Surg Pathol 22(11):1393–1403
3. Davis MR, Howitt BE, Quade BJ, Crum CP, Horowitz NS, Goldstein DP, Berkowitz RS (2015) Epithelioid trophoblastic tumor: a single institution case series at the New England Trophoblastic Disease Center. Gynecol Oncol 137(3):456–461
4. Brown J, Naumann RW, Seckl MJ, Schink J (2017) 15 years of progress in gestational trophoblastic disease: scoring, standardization, and salvage. Gynecol Oncol 144(1):200–207
5. Prabha Devi K, Bindhu Priya N, Himabindu P, Padmavathi C (2014) Metastatic epithelioid trophoblastic tumor: a rare case report. J Obstet Gynaecol India 64(3):212–214
6. Arafah MA, Tulbah AM, Al-Husaini H, Al-Sabban M, Al-Shankiti H, Al-Badawi IA (2015) Extrauterine epithelioid trophoblastic tumor arising in the ovary with multiple metastases: a case report. Int J Surg Pathol 23(4):339–344

7. Zhao J, Xiang Y, Zhao D, Ren T, Feng F, Wan X (2013) Isolated epithelioid trophoblastic tumor of the vagina: a case report and review of the literature. Onco Targets Ther 6:1523–1526
8. Kim JY, An S, Jang SJ, Kim HR (2013) Extrauterine epithelioid trophoblastic tumor of lung in a 35-year-old woman. Korean J Thorac Cardiovasc Surg 46(6):471–474
9. Chohan MO, Rehman T, Cerilli LA, Devers K, Medina-Flores R, Turner P (2010) Metastatic epithelioid trophoblastic tumor involving the spine. Spine (Phila Pa 1976) 35(20):E1072–1075
10. Frijstein MM, Lok CAR, Trommel NE, Kate-Booij MJT, Massuger L, Werkhoven E, Kaur B, Tidy JA, Sarwar N, Golfier F et al (2018) Management and prognostic factors of epithelioid trophoblastic tumors: results from the international society for the study of trophoblastic diseases database. Gynecol Oncol 152:361–367
11. Baergen RN, Rutgers J, Young RH (2003) Extrauterine lesions of intermediate trophoblast. Int J Gynecol Pathol 22(4):362–367
12. Yang J, Zong L, Wang J, Wan X, Feng F, Xiang Y (2019) Epithelioid trophoblastic tumors: treatments, outcomes, and potential therapeutic targets. J Cancer 10(1):11–19
13. Lei W, Zhang F, Zheng C, Zhao C, Tu S, Bao Y (2018) Metastatic epithelioid trophoblastic tumor of the lung: a case report. Medicine (Baltimore) 97(16):e0306
14. Jiang F, Xiang Y, Guo LN (2018) Laparoscopic diagnosis and treatment of an isolated epithelioid trophoblastic tumor in rectouterine pouch. J Obstet Gynaecol Res 44(5):960–965
15. Kim JH, Lee SK, Hwang SH, Kim JS, Yoon G, Lee YY, Kim TJ, Choi CH, Kim BG, Bae DS et al (2017) Extrauterine epithelioid trophoblastic tumor in hysterectomized woman. Obstet Gynecol Sci 60(1):124–128
16. Ru Luo HS, Chen X, Lü B, Shao H (2016) Extrauterine epithelioid trophoblastic tumor of the vagina: a case report and literature review. Int J Clin Exp Med 9(11):22041–22047
17. Okereke IC, Chen SX (2014) Primary epithelioid trophoblastic tumor of the lung. Ann Thorac Surg 97(4):1420–1421
18. Fenichel P, Rouzier C, Butori C, Chevallier P, Poullot AG, Thyss A, Mouroux J (2014) Extragestational beta HCG secretion due to an isolated lung epithelioid trophoblastic tumor: microsatellite genotyping of tumoral cells confirmed their placental origin and oriented specific chemotherapy. J Clin Endocr Metab 99(10):3515–3520
19. Park SY, Park MH, Ko HS, Cha EJ, Sohn JS, Kim CJ (2014) Epithelioid trophoblastic tumor presenting as an ovarian mass in a postmenopausal woman. Int J Gynecol Pathol 33(1):35–39
20. Ahn HY, Hoseok I, Lee CH, Jung YJ, Shin NR, Kim KH, Lee MK, Kim YD, Cho JS (2013) Pulmonary mass diagnosed as extrauterine epithelioid trophoblastic tumor. Thorac Cardiovasc Surg 61(1):97–100
21. Abra FC, Canzian M, Fernandez A, Fushida K, Fernandes PM, Jatene FB (2011) Isolated epithelioid trophoblastic tumor mimicking non-small cell lung cancer. J Thorac Oncol 6(5):966–967
22. Khunamornpong S, Settakorn J, Sukpan K, Suprasert P, Siriaunkgul S (2011) Ovarian involvement of epithelioid trophoblastic tumor: a case report. Int J Gynecol Pathol 30(2):167–172
23. Chohan MO, Cerilli LA, Devers K, Medina-Flores R, Turner P (2010) Metastatic epithelioid trophoblastic tumor involving the spine. Spine 35(20):1072–1075
24. Lewin SN, Moreira AL, Soslow RA (2009) Extrauterine epithelioid trophoblastic tumors presenting as primary lung carcinomas. Am J Surg Pathol 33(12):1809–1814
25. Noh HT, Lee KH, Lee MA, Ko YB, Hwang SH, Son SK (2008) Epithelioid trophoblastic tumor of paracervix and parametrium. Int J Gynecol Cancer 18(4):843–846
26. Macdonald MC, Palmer JE, Hancock BW, Tidy JA (2008) Diagnostic challenges in extrauterine epithelioid trophoblastic tumours: a report of two cases. Gynecol Oncol 108(2):452–454
27. Urabe S, Fujiwara H, Miyoshi H, Arihiro K, Soma H, Yoshihama I, Mineo S, Kudo Y (2007) Epithelioid trophoblastic tumor of the lung. J Obstet Gynaecol Re 33(3):397–401
28. Kuo KT, Lin MC (2004) Epithelioid trophoblastic tumor of the broad ligament a case report and review of the literature. Am J Surg Pathol 28(3):405–409
29. Parker A, Lee V, Dalrymple C, Valmadre S, Russell P (2003) Epithelioid trophoblastic tumour: report of a case in the fallopian tube. Pathology 35(2):136–140
30. Hamazaki S, Okino T, Tsukayama C, Mori M, Taguchi K, Okada S (1999) Epithelioid trophoblastic tumor: morphological and immunohistochemical study of three lung lesions. Hum Pathol 30(11):1321–1327
31. Shih IM, Kurman RJ (1998) Epithelioid trophoblastic tumor: a neoplasm distinct from choriocarcinoma and placental site trophoblastic tumor simulating carcinoma. Am J Surg Pathol 22(11):1393–1403
32. Zhang X, Shi H, Chen X (2014) Epithelioid trophoblastic tumor after induced abortion with previous broad choriocarcinoma: a case report and review of literature. Int J Clin Exp Pathol 7(11):8245–8250
33. Zhang X, Lu W, Lu B (2013) Epithelioid trophoblastic tumor: an outcome-based literature review of 78 reported cases. Int J Gynecol Cancer 23(7):1334–1338
34. Braga A, Uberti EM, Fajardo Mdo C, Viggiano M, Sun SY, Grillo BM, Padilha SL, de Andrade JM, de Souza CB, Madi JM et al (2014) Epidemiological report on the treatment of patients with gestational trophoblastic disease in 10 Brazilian referral centers: results after 12 years since International FIGO 2000 Consensus. J Reprod Med 59(5–6):241–247
35. Maesta I, Berkowitz RS, Goldstein DP, Bernstein MR, Ramirez LA, Horowitz NS (2015) Relationship between race and clinical characteristics, extent of disease, and response to chemotherapy in patients with low-risk gestational trophoblastic neoplasia. Gynecol Oncol 138(1):50–54
36. Tempfer C, Horn LC, Ackermann S, Beckmann MW, Dittrich R, Einenkel J, Günthert A, Haase H, Kratzsch J, Kreissl MC et al (2016) Gestational and non-gestational trophoblastic disease. Guideline of the DGGG, OEGGG and SGGG (S2k level, AWMF registry no. 032/049, December 2015). Geburtshilfe Frauenheilkd 76(2):134–144
37. Lurain JR (2010) Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. Am J Obstet Gynecol 203(6):531–539
38. Bolze PA, Attia J, Massardier J, Seckl MJ, Massuger L, van Trommel N, Niemann I, Hajri T, Schott AM, Golfier F (2015) Formalised consensus of the European organisation for treatment of trophoblastic diseases on management of gestational trophoblastic diseases. Eur J Cancer 51(13):1725–1731
39. Hui P (2018) Gestational trophoblastic tumors: a timely review of diagnostic pathology. Arch Pathol Lab Med 143:65–74
40. Stichelbout M, Devisme L, Franquet-Ansart H, Massardier J, Vinatier D, Renaud F, Kerdraon O (2016) SALL4 expression in gestational trophoblastic tumors: a useful tool to distinguish choriocarcinoma from placental site trophoblastic tumor and epithelioid trophoblastic tumor. Hum Pathol 54:121–126
41. Li X, Feng F, Xiang Y, Wan X, Ren T, Yang J (2015) Value of laparoscopic surgery in the diagnosis of suspected gestational trophoblastic neoplasia cases with uterine mass. Zhonghua Fu Chan Ke Za Zhi 50(12):910–914
42. Seckl MJ, Sebire NJ, Fisher RA, Golfier F, Massuger L, Sessa C (2013) Gestational trophoblastic disease: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 24(Suppl 6):vi39–50

43. Ngan HYS, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, Lurain JR, Massuger L (2018) Update on the diagnosis and management of gestational trophoblastic disease. Int J Gynaecol Obstet 143(Suppl 2):79–85
44. Worley MJ Jr, Elias KM, Horowitz NS, Quade BJ, Berkowitz RS (2018) Durable remission for a woman with refractory choriocarcinoma treated with anti-endoglin monoclonal antibody and bevacizumab: a case from the New England Trophoblastic Disease Center, Brigham and Women's Hospital and Dana-Farber Cancer Institute. Gynecol Oncol 148(1):5–11
45. Sobecki-Rausch J, Winder A, Maniar KP, Hoekstra AV, Berry E, Novak K, Lurain JR (2018) Surgery and platinum/etoposide-based chemotherapy for the treatment of epithelioid trophoblastic tumor. Int J Gynecol Cancer 28(6):1117–1122