Complete remission of a recurrent epithelioid trophoblastic tumor at the vaginal cuff with liver metastases following surgical resection and EP/EMA chemotherapy

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Abstract. Epithelioid trophoblastic tumor (ETT) is a rare type of gestational trophoblastic neoplasia derived from intermediate trophoblasts. The present study reports a case of recurrent ETT with liver metastases in which complete remission was achieved after surgical resection and chemotherapy with the etoposide, cisplatin/etoposide, methotrexate and actinomycin D (EP/EMA) regimen. The patient had undergone transvaginal hysterectomy due to suspected placental site nodule 3 years prior to the present study, and the postoperative pathological diagnosis was ETT. The patient was regularly followed up, during which a slight elevation in the serum human chorionic gonadotropin (hCG) level had been noted, leading to the referral to Wakayama Medical University Hospital. Pelvic MRI revealed a 5-cm mass at the vaginal cuff. The serum hCG level was elevated at 95.6 mIU/ml. Resection of the tumor was performed. The histopathological findings demonstrated a diagnosis of recurrent ETT. Postoperatively, the serum hCG level decreased to 2.7 mIU/ml; however, it increased again, and CT revealed a solitary hepatic metastatic lesion. Surgical resection of the metastatic liver lesion was performed. At 1 month post-operation, multiple hepatic metastatic lesions recurred and chemotherapy with the EP/EMA regimen was initiated. The patient responded well to treatment and the serum hCG level became undetectable after the third cycle. After three additional cycles were administered, all metastatic lesions disappeared. The patient has remained free of recurrence for 6 years.

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Introduction

Epithelioid trophoblastic tumor (ETT) is an extremely rare subtype of gestational trophoblastic neoplasia (GTN) (1). It is considered to originate from chorionic-type intermediate trophoblasts (IT) of the chorion laeve and is distinguished from placental site trophoblastic tumor (PSTT), which arises from implantation site IT (2,3). To date, only slightly more than 100 cases have been reported worldwide, highlighting the extreme rarity of this malignant tumor (4-7). Unlike gestational choriocarcinoma, ETT is generally resistant to chemotherapy, and the prognosis of patients with metastatic disease is poor (6). Notably, patients with stage I disease have a favorable prognosis after hysterectomy, whereas those with extrauterine or recurrent/metastatic disease have a poor prognosis, with an overall survival rate of approximately 50-60% (6). Therefore, surgical resection is recommended for recurrent or metastatic lesions of ETT when complete resection is feasible (5-7). We herein report a case of ETT that recurred at the vaginal cuff after hysterectomy and subsequently metastasized to the liver. The patient underwent surgical resection of the metastatic tumors and responded well to chemotherapy with alternating etoposide/cisplatin and etoposide/methotrexate/actinomycin D (EP/EMA) cycles targeting residual liver metastases, achieving complete remission. The patient has remained free of recurrence for 6 years, indicating an excellent response to EP/EMA therapy. The present case suggests that a multimodal approach combining the complete resection of resectable disease and systemic chemotherapy may be effective for recurrent or metastatic ETT.

Case report

The patient was a 50-year-old gravida 6, para 1 woman. Her previous medical history included ectopic pregnancy, with no history of hydatidiform mole. Her last pregnancy had resulted

in a full-term delivery 10 years earlier. In July 2016, she first presented to Kinan Hospital with irregular menstrual cycles and subsequently underwent total vaginal hysterectomy in September 2016 because a placental site nodule was suspected. The preoperative serum human chorionic gonadotropin (hCG) level was 57.9 mIU/ml. A gross examination of the resected uterus revealed that the tumor had arisen near the junction between the lower segment of the uterine body and the cervix and had exhibited invasive growth (Fig. 1A). A histopathological examination showed the monomorphic proliferation of mononuclear chorionic-type intermediate trophoblastic tumor cells in nested, trabecular, and geographic growth patterns while maintaining an epithelioid morphology, a pattern distinct from that of PSTT, which is characterized by implantation-site intermediate trophoblastic cells infiltrating between bundles of myometrial smooth muscle (Fig. 1B-D). Neither biphasic trophoblastic proliferation characteristic of choriocarcinoma nor a distinct PSTT component was identified, arguing against mixed gestational trophoblastic neoplasia. On immunohistochemical staining, tumor cells were positive for cytokeratin (CK) and inhibin-α, showed diffuse positivity for p63, and were focally positive for human placental lactogen (hPL) and placental alkaline phosphatase (PLAP), and very focally positive for hCG (Fig. 1E-J). The MIB-1 labeling index was 30% (Fig. 1K). Pathological and immunohistochemical findings in the present case are summarized in Table I. Based on these findings, the tumor was diagnosed as ETT. Histopathological examination confirmed negative surgical margins. Postoperative CT revealed no radiologically evident metastatic disease. Accordingly, the tumor was considered confined to the uterus and was classified as FIGO stage I according to the FIGO 2000 staging system (8). Postoperatively, the serum hCG level decreased to within the normal range, and the patient subsequently underwent regular follow-ups at the previous hospital.

During a routine follow-up visit at Kinan Hospital in September 2019, approximately three years after hysterectomy, an elevation in the serum hCG level was detected. The patient developed abnormal genital bleeding in October 2019 and was subsequently referred to Wakayama Medical University Hospital, where she first presented in November 2019. Pelvic MRI revealed a 5-cm mass at the vaginal cuff with suspected invasion into the right ureter and part of the bladder (Fig. 2A). PET/CT showed fluorodeoxyglucose uptake in the tumor at the vaginal cuff with a maximum standardized uptake value of 4.84 (Fig. 2B); however, no obvious lymph node or distant metastases were identified. Since the serum hCG level was elevated at 95.6 mIU/ml and the recurrence of ETT was suspected, surgical treatment was selected. Intraoperatively, the tumor at the vaginal cuff was found to be extensively adherent to the bladder and right ureter. The recurrent tumor was resected en bloc with the involved segment of the right ureter and adjacent bladder wall. Right ureteroneocystostomy and bilateral salpingo-oophorectomy were also performed. A histopathological examination revealed the proliferation and infiltration of IT-like tumor cells in nested and trabecular patterns while maintaining an epithelioid morphology (Fig. 2C, D). These pathological findings were consistent with those observed in the hysterectomy specimen obtained 3 years earlier (Fig. 1), leading to the diagnosis of recurrent ETT. The surgical margins were negative. Postoperatively, the serum hCG level initially decreased to 2.7 mIU/ml, but subsequently increased again to 3,313 mIU/ml (Fig. 3). Contrast-enhanced CT revealed a solitary hepatic metastatic lesion (Fig. 2E), and, thus, hepatic caudate lobectomy was performed. The hepatic metastatic lesion was completely resected with pathologically negative surgical margins (R0 resection). No additional hepatic lesions were identified intraoperatively. The postoperative course after hepatic caudate lobectomy was uneventful, with no major surgery-related complications. The results of a histopathological examination on the resected liver lesion confirmed metastatic ETT, with features consistent with those of the primary uterine tumor and vaginal cuff recurrence (Fig. 2F, G). No additional metastatic foci were detected pathologically in the resected specimen. After the resection of hepatic metastasis, the serum hCG level decreased to 150 mIU/ml; however, it subsequently increased again to 39,617 mIU/ml, and contrast-enhanced CT revealed multiple small hepatic metastatic lesions (Fig. 2H). EP/EMA chemotherapy was initiated according to the dose and schedule shown in Table II, resulting in a marked decline in the serum hCG level (Fig. 3). After three cycles of EP/EMA therapy, the serum hCG level became negative (Fig. 3). Three additional consolidation cycles were administered to reduce the risk of relapse, and CT confirmed the complete disappearance of the metastatic lesions. The patient was considered to have achieved complete remission. During the six cycles of EP/EMA chemotherapy, grade 2 neutropenia (Common Terminology Criteria for Adverse Events [CTCAE], version 4.0) occurred after the second cycle. As secondary prophylaxis, a single dose of pegfilgrastim (a pegylated granulocyte colony-stimulating factor; 3.6 mg/body) was administered on Day 10 of each of cycles 3 through 6, and no further neutropenia was observed. Grade 1 renal toxicity occurred after the fifth and sixth cycles and resolved with observation alone. No chemotherapy dose reductions or treatment delays were required.

The patient has continued to undergo regular follow-ups and has remained free of recurrence for 6 years.

Discussion

Shih and colleagues were the first to summarize the clinicopathological characteristics of ETT in 1998 (1); therefore, ETT is regarded as a relatively newly recognized category of GTN. Histologically, ETT is characterized by the proliferation of mononuclear chorionic-type IT-like tumor cells in nested, trabecular, and geographic patterns with infiltrative growth while maintaining an epithelioid morphology (1-3). Immunohistochemically, tumor cells are diffusely positive for CK and inhibin-α, focally positive for hPL and PLAP, and only very focally positive for hCG. In addition, reflecting the biological characteristics of chorionic-type IT, diffuse nuclear positivity for p63 is a characteristic feature of ETT and serves as an important distinction from PSTT (2). In the present case, the pathological and immunohistochemical findings of all three lesions, namely, the primary uterine tumor resected during initial hysterectomy at the previous hospital, the recurrent tumor at the vaginal cuff, and the hepatic metastatic lesion resected during hepatic caudate lobectomy were entirely consistent with the typical features of ETT. No mixed

Table I. Summary of pathological and immunohistochemical findings in the present case.

Findings	Result
Morphological	
Proliferation of mononuclear chorionic-type IT-like tumor cells	Yes
Nested, trabecular and geographic growth/infiltration patterns	Yes
Maintaining an epithelioid morphology distinct from PSTT	Yes
Biphasic trophoblastic proliferation shown in choriocarcinoma	No
Mixed GTN component, such as choriocarcinoma or PSTT	No
Immunohistochemical	
Cytokeratin	Diffusely +
Inhibin-α	Diffusely +
hCG	Very focally +
hPL	Focally +
PLAP	Focally +
p63	Diffusely +
MIB-1 labeling index	30%

IT, intermediate trophoblast; PSTT, placental site trophoblastic tumor; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; hPL, human placental lactogen; PLAP, placental alkaline phosphatase; MIB-1, MIB E3 ubiquitin protein ligase 1.

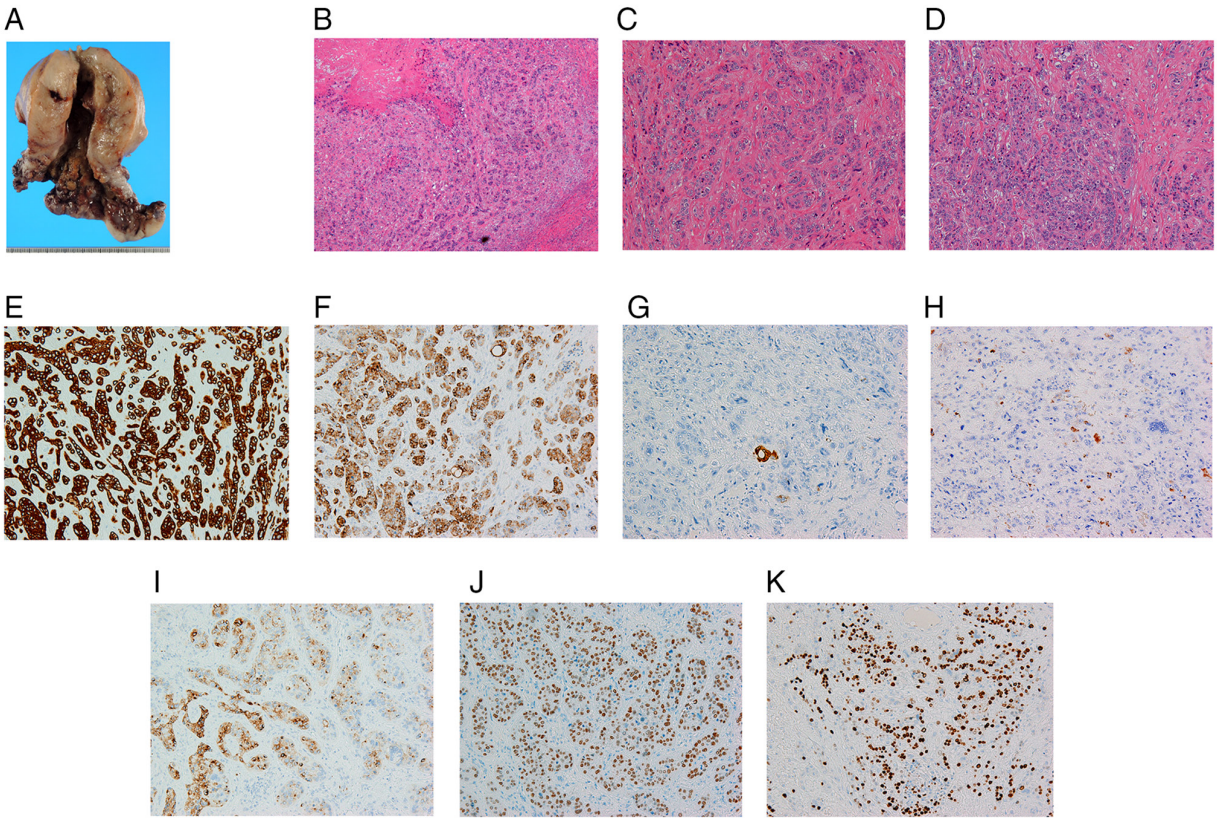


Figure 1. (A) Gross appearance of the resected uterus at the initial hysterectomy. (B-D) Histopathological findings with hematoxylin and eosin staining [(B) magnification, x40; (C) and (D) magnification, x100]. The tumor showed monomorphic chorionic-type intermediate trophoblastic proliferation with nested, trabecular or geographic growth, maintaining an epithelioid morphology. Immunohistochemical staining for (E) cytokeratin, (F) inhibin-α, (G) hCG, (H) hPL, (I) PLAP, (J) p63 and (K) MIB-1 (magnification, x100). Tumor cells showed diffuse nuclear p63 positivity, cytoplasmic cytokeratin and inhibin-α positivity, focal hCG expression, focal hPL and PLAP expression and a MIB-1 labeling index of 30%. hCG, human chorionic gonadotropin; hPL, human placental lactogen; PLAP, placental alkaline phosphatase; MIB-1, MIB E3 ubiquitin protein ligase 1.

components of other GTN were identified. Therefore, these lesions were considered to represent a continuous clinical course of recurrence and metastasis originating from the initial ETT. Furthermore, the location of the primary lesion

Table II. EP/EMA chemotherapy administered in the present case.

Regimen	Dose and schedule
Day 1 EP	
Etoposide	150 mg/m^2 IV over 60 min
Cisplatin	75 mg/m^2 IV over 2 h
Day 8 EMA	
Etoposide	100 mg/m^2 IV over 60 min
Methotrexate	300 mg/m^2 IV infusion over 12 h
Actinomycin D	0.5 mg/body IV bolus
Days 9-10	
Folinic acid	15 mg/body PO or IM every 12 h for 4 doses, starting 24 h after initiation of methotrexate

Repeat every 2 weeks alternating EP and EMA weekly. IV, intravenous; PO, *per os*; IM, intramuscular; EP, etoposide/cisplatin; EMA, etoposide/methotrexate/actinomycin D.

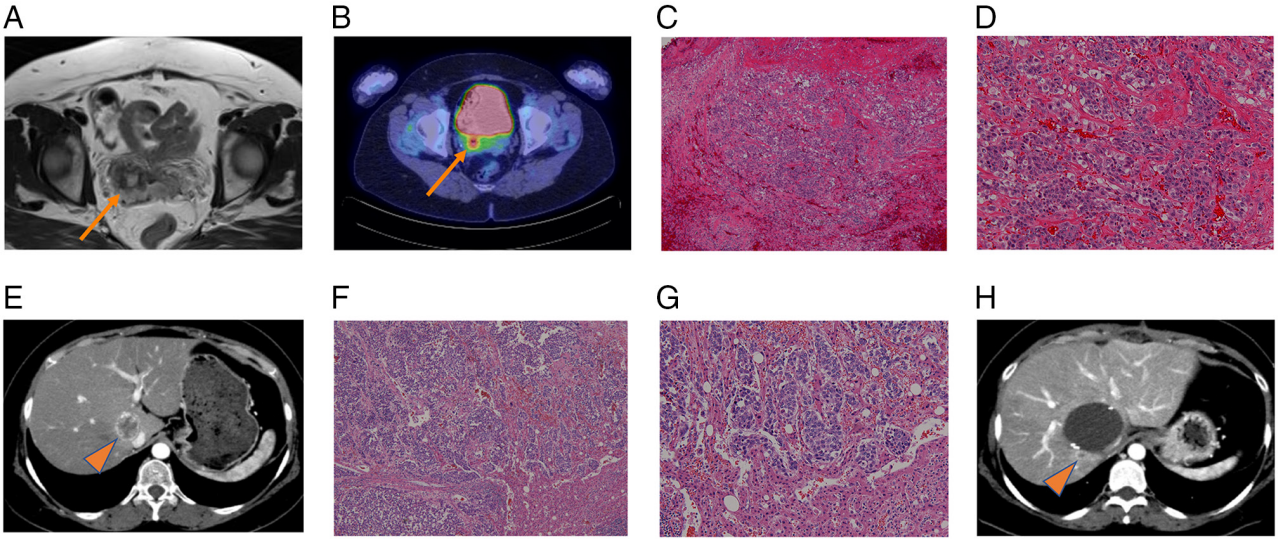


Figure 2. (A) Pelvic MRI (T2-weighted image). The arrow indicates the recurrent tumor at the vaginal cuff detected 3 years after initial hysterectomy. The tumor was suspected to have invaded the right ureter and part of the bladder. (B) Preoperative PET/CT. The arrow indicates fluorodeoxyglucose uptake in the tumor at the vaginal cuff. (C and D) Histopathological findings of the recurrent tumor at the vaginal cuff with H&E staining. The tumor showed the typical histopathological features of ETT, consistent with those observed in the initial hysterectomy specimen. Magnifications: (C) x40; (D) x100. (E) A contrast-enhanced CT image 3 months after resection of the vaginal cuff tumor. The arrowhead indicates the solitary metastatic lesion at the caudate lobe of the liver. (F and G) Histopathological findings of hepatic metastasis with H&E staining. The tumor showed the typical histopathological features of ETT, consistent with those observed in the primary uterine tumor and recurrent tumor at the vaginal cuff. Magnifications: (F) x40; (G) x100. (H) A contrast-enhanced CT image 1 month after the resection of hepatic metastasis. The arrowhead indicates the newly detected small metastatic lesion adjacent to the postoperative cystic cavity-like change. Similar small lesions were detected in other sites of the liver. H&E, hematoxylin and eosin; ETT, epithelioid trophoblastic tumor.

in this patient, arising from the lower uterine segment to the cervix, was consistent with previous findings indicating that 30-50% of primary ETTs originate in the cervix or lower uterine segment (3-5).

At the initial diagnosis following vaginal hysterectomy in 2016, the disease was considered confined to the uterus on the basis of the pathological findings and postoperative imaging, and was classified as FIGO stage I according to the FIGO 2000 staging system for GTN (8). Although the subsequently identified hepatic metastases represented disease at an anatomical site corresponding to FIGO stage IV, they do not alter the stage assigned at initial presentation, and restaging at recurrence should not be adapted.

Clinically, serum hCG levels in ETT are generally lower than those observed in choriocarcinoma and are often below 1,000 mIU/ml, similar to PSTT (5-7). The interval between the antecedent pregnancy and diagnosis widely varies, ranging from several months to more than 10 years, and 40-70% of cases reportedly occur after full-term delivery (6,7). In the present case, the antecedent pregnancy had been a full-term delivery 10 years earlier, representing a long interval before disease onset. Therefore, it may have been difficult to suspect the development of ETT based solely on the clinical course after the previous pregnancy. However, since placental site nodule had been suspected at the previous hospital and the serum hCG level was mildly elevated at approximately

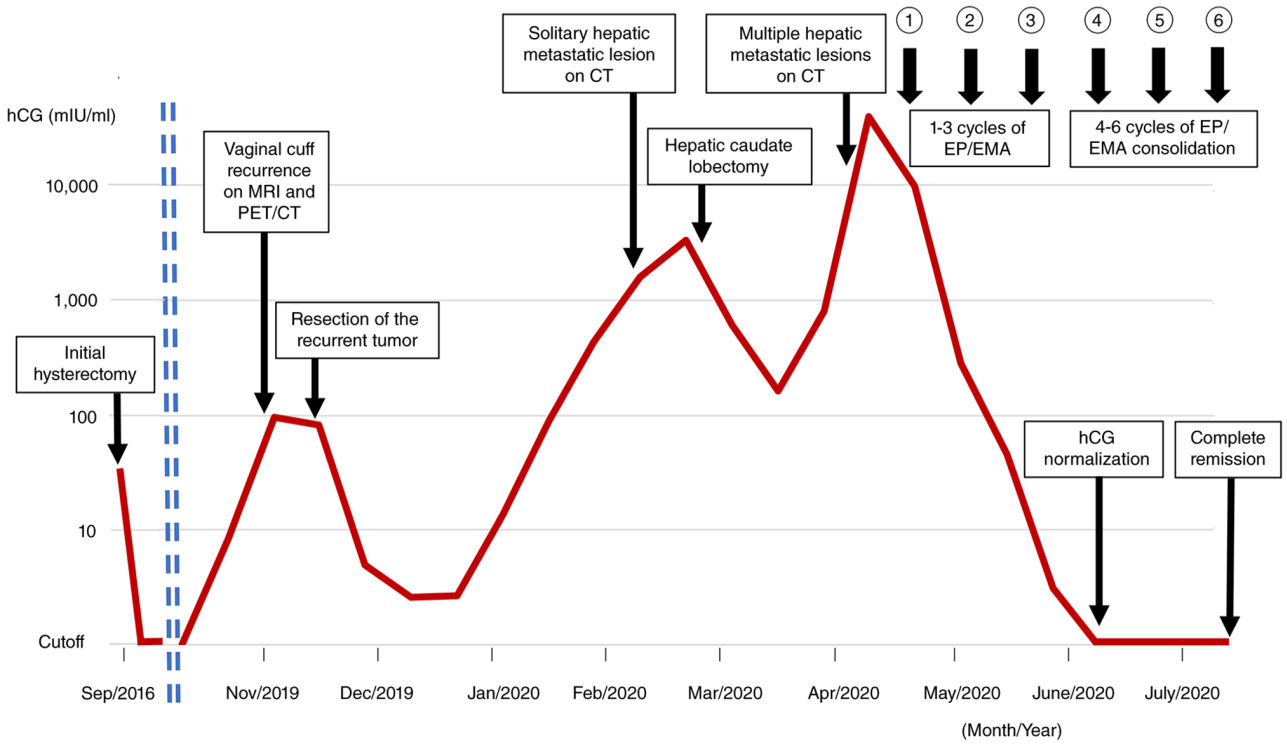


Figure 3. Clinical course of the patient, including the timing of surgery, imaging findings and EP/EMA chemotherapy, with changes in serum hCG levels. EP/EMA, etoposide/cisplatin and etoposide/methotrexate/actinomycin D; hCG, human chorionic gonadotropin.

50 mIU/ml, hysterectomy was performed, and a postoperative pathological examination incidentally led to the diagnosis of ETT. Three years later, during a regular follow-up, a slightly elevated serum hCG level was again detected, and the patient was promptly referred to our hospital, enabling the early diagnosis and treatment of recurrent ETT. Therefore, the regular monitoring of serum hCG levels may also be useful in ETT, as in other GTN.

Regarding treatment, ETT is generally considered to be relatively resistant to chemotherapy, similar to PSTT. Therefore, patients with stage I disease typically have a favorable prognosis after hysterectomy, whereas those with extrauterine or recurrent/metastatic disease have a poor prognosis, with an overall survival rate of approximately 50-60% (6,9). Surgical resection is recommended for recurrent or metastatic lesions whenever complete resection is feasible (9,10). Surgery remains an important component of the multimodal treatment for localized or resectable metastatic GTN, particularly for ETT, which is relatively resistant to chemotherapy (11-13). In the present case, hepatic caudate lobectomy for the initially solitary hepatic lesion was completed without major postoperative complications. However, multiple small hepatic metastatic lesions became apparent shortly thereafter, suggesting the presence of occult micrometastatic disease and emphasizing the importance of systemic therapy in addition to local surgical control in metastatic ETT.

As for chemotherapy to treat ETT, platinum-containing regimens, such as EP/EMA therapy and paclitaxel/cisplatin-paclitaxel/etoposide (TP/TE) therapy, are the first-line options; however, their response rates are not necessarily high (9,10). From this perspective, the surgical resection of recurrent ETT at the vaginal cuff was considered to be the most appropriate approach in the present case. Nevertheless, a solitary hepatic metastatic lesion appeared soon thereafter, and although hepatic resection was performed, multiple small hepatic metastatic lesions subsequently recurred. At the time of the recurrence of multiple liver metastases, the serum hCG level had markedly increased to more than 30,000 mIU/ml, which is unusually high for ETT. The patient responded well to EP/EMA chemotherapy, with the normalization of the serum hCG level after only three cycles. This clinical course slightly differed from the conventional clinical characteristics of ETT. Although the diagnosis of ETT was histopathologically/immunohistochemically confirmed for both the primary uterine lesion and metastatic lesions at the vaginal cuff and liver, this patient may have represented a rare case of ETT with unusually high chemosensitivity. After the serum hCG level had normalized, three additional cycles of chemotherapy were administered to reduce the risk of relapse (14), resulting in complete remission. The patient has remained free of recurrence for 6 years, indicating an excellent response to EP/EMA therapy. Similarly, Nakamura *et al* (15) described a case of stage IV ETT with liver and brain metastases that was successfully managed with multimodal treatment including surgery, EP/EMA chemotherapy, and stereotactic brain radiotherapy. Helbig *et al* (16) also reported an ETT patient with liver metastases who achieved a complete remission with multimodal therapy including EP/EMA chemotherapy, surgical resection, and immune checkpoint inhibitors, although the response to EP/EMA therapy was partial, but not complete. Taken together, the present case supports the potential clinical activity of EP/EMA chemotherapy as part of multimodal management for recurrent or metastatic ETT. However, because durable remission was achieved following

both surgical resection and systemic chemotherapy, the relative contribution of each treatment modality cannot be established from a single case.

Recent international treatment guidelines for PSTT/ETT recommend adjuvant chemotherapy after hysterectomy, even for stage I disease when more than 48 months have elapsed since the antecedent pregnancy (10). In the present case, 10 years had passed since the antecedent pregnancy at the time of hysterectomy at the previous hospital. Therefore, in retrospect, postoperative chemotherapy might have been considered in light of current recommendations and the long interval from the antecedent pregnancy. However, it remains unknown whether adjuvant chemotherapy at that time may have prevented the subsequent recurrence of ETT. Although the initial postoperative CT showed no radiologically evident metastases and the hysterectomy specimen had negative surgical margins, occult metastatic disease at the time of the initial diagnosis cannot be excluded. The initial operation had been undertaken for a presumed benign placental site nodule rather than a known malignant ETT. Although histologically negative margins were achieved, total vaginal hysterectomy had not been planned specifically to ensure the extent of oncologic resection advocated for ETT in current guidance (10). The subsequent recurrence at the vaginal cuff raises the possibility that the original surgical approach or staging evaluation may have affected recurrence risk; however, this cannot be established retrospectively. Whether a different initial surgical strategy, more extensive staging assessment, or postoperative chemotherapy would have prevented recurrence remains unknown.

This case illustrates that durable remission may be achievable in selected patients with recurrent or metastatic ETT through a multimodal approach combining the complete resection of resectable disease and systemic chemotherapy. The good response to EP/EMA observed in this patient supports the further evaluation of this regimen as part of the multimodal treatment for metastatic ETT.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KI and NI conceptualized and wrote the manuscript. KNi, NO, MF, KNa, TN, TY, YH and YM collected clinical and pathological data. FK and TO contributed to the histopathological and immunohistochemical analyses. KI supervised the preparation of the manuscript. All authors approved the final version of this manuscript. KI and NI confirmed the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report.

Competing interests

The authors declare that they have no competing interests.

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