

## Case report

## Choriocarcinoma coexisting with epithelioid trophoblastic tumor of the uterine horn



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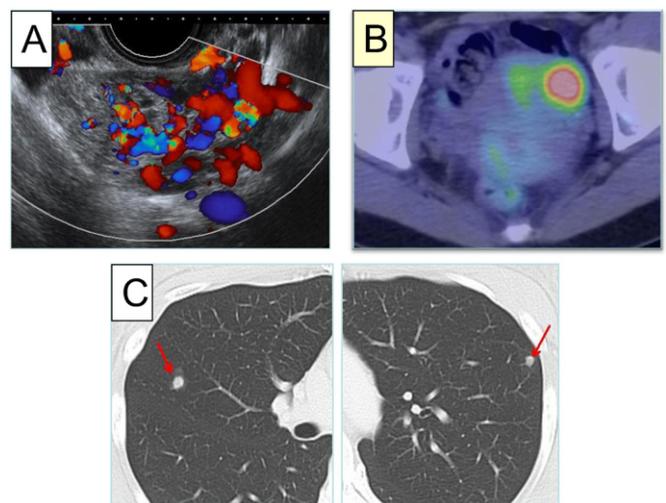
## 1. Introduction

Clinicopathological studies have provided some evidence regarding the pathogenesis of at least three distinct types of gestational trophoblastic neoplasia (GTN), including the most common type, choriocarcinoma, and two less common ones, placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT). Choriocarcinoma is composed of variable proportions of neoplastic cytotrophoblast, syncytiotrophoblast, and intermediate trophoblast, the latter of which is composed of a similar mixture of trophoblastic subpopulations. While the neoplastic cytotrophoblast in PSTT differentiates mainly into intermediate trophoblastic cells at the implantation site, the neoplastic cytotrophoblast in ETT differentiates into chorionic-type intermediate trophoblastic cells in the chorion laeve. However, the pathogenesis of the differentiation of GTN, especially ETT, is still unknown because these tumors are extremely rare. Furthermore, there is little evidence regarding therapeutic strategies for GTN, including ETT. Here we present a case of mixed choriocarcinoma coexisting with an ETT, which might elucidate the pathogenesis of ETT and identify an appropriate treatment approach for mixed-type GTN.

## 2. Case report

A 32-year-old Japanese woman, gravida 2, para 1, visited a previous hospital complaining of secondary amenorrhea. Her medical history was notable for treatment with systemic chemotherapy with methotrexate (MTX) at age 26 for an invasive hydatidiform mole that had developed from a complete mole; she had an uncomplicated full-term delivery 2 years later. Pelvic examination revealed no abnormal findings. Her serum human chorionic gonadotropin (hCG) level was 93,820 mIU/ml. Transvaginal ultrasonography showed a mass in the left uterine horn without a gestational sac. She was first diagnosed with an ectopic pregnancy in the interstitial part of the fallopian tube. Laparoscopic surgery was performed, resulting in the resection of a

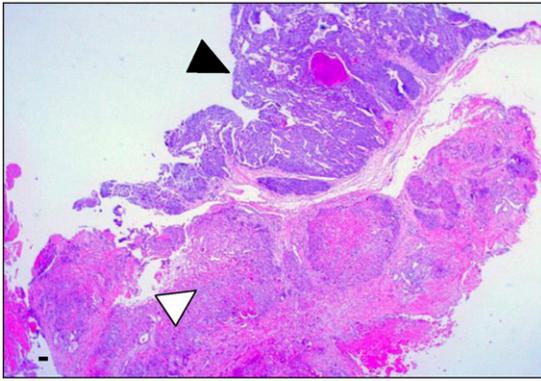
2.0-cm mass in the uterine horn. She was monitored closely via serum hCG levels; while these levels decreased postoperatively, they increased again 4 weeks later. The presence of residual chorionic villi was suspected, and she was treated with single-agent chemotherapy with intramuscular MTX 1 mg/kg per day on days 1, 3, 5 and 7 with intramuscular folinic acid 0.1 mg/kg per day on days 2, 4, 6 and 8 every 2 weeks. After a transient decrease, her serum hCG levels again increased at the 5th cycle of chemotherapy. The patient was referred to Kumamoto University Hospital due to the possible diagnosis of gestational trophoblastic disease. Transvaginal Doppler ultrasound examination showed extensive vascularization within the myometrium (Fig. 1, A). Pelvic magnetic resonance imaging demonstrated a high-signal-intensity focus in the myometrium on T2-weighted images. Evaluation by positron emission tomography/computed tomography (PET/CT) revealed increased fluorodeoxyglucose uptake in the uterine mass (Fig. 1, B). Multiple nodules in both lungs were detected on a CT scan (Fig. 1, C).



**Fig. 1.** Imaging findings. (A) Transvaginal Doppler ultrasound results show extensive vascularization within the myometrium. (B) A PET/CT image reveals increased FDG uptake in the mass. (C) A CT image shows multiple nodules in both lungs.

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**Fig. 2.** Histopathological findings of the uterine mass. Choriocarcinoma (►) is composed of basophilic cells and the ETT (▷) contains eosinophilic cells. Tissue was stained with hematoxylin–eosin (HE). Image was taken at 2× magnification. Scale bar = 50 μm.

The tumor presented as a discrete nodule in the myometrium. On microscopic examination, the tumor displayed biphasic proliferation (Fig. 2). Histopathological review of the first excised specimen from the previous hospital confirmed a trophoblastic tumor consisting of the trimorphic proliferation of intermediate trophoblast, syncytiotrophoblast, and cytotrophoblast, with no chorionic villi, and the tumor cells showed abnormal mitotic figures (Fig. 3, A). Tumor cells were diffusely positive for hCG (Fig. 3, B). Although the histological and immunohistochemical findings were characteristics of choriocarcinoma, the tumor was partially composed of cells that were intimately associated with surrounding eosinophilic, hyaline-like material and necrotic debris capable of simulating keratin. The cells contained round, uniform nuclei and eosinophilic or clear cytoplasm surrounded by a well-defined cell membrane (Fig. 4). Immunohistochemical analysis revealed that the tumor cells were diffusely positive for hCG. Those histological features of the component indicated characteristics of ETT notwithstanding the immunopositivity for hCG. Therefore, the patient was diagnosed with choriocarcinoma coexisting with an ETT.

Combination chemotherapy with etoposide, methotrexate and actinomycin-D alternating with cyclophosphamide, and vincristine (EMA-CO) is a standard, effective and well-tolerated regimen for high-risk GTN. MEA also has the same effectiveness as EMA-CO and less toxicity (Matsui et al., 2000), and MEA is one of the standard chemotherapeutic regimens for choriocarcinoma in Japan. She was treated with 6 cycles of combination chemotherapy consisting of MEA. Her serum hCG levels normalized and a follow-up CT scan confirmed that the lung nodules had disappeared. Consequently, she has not undergone

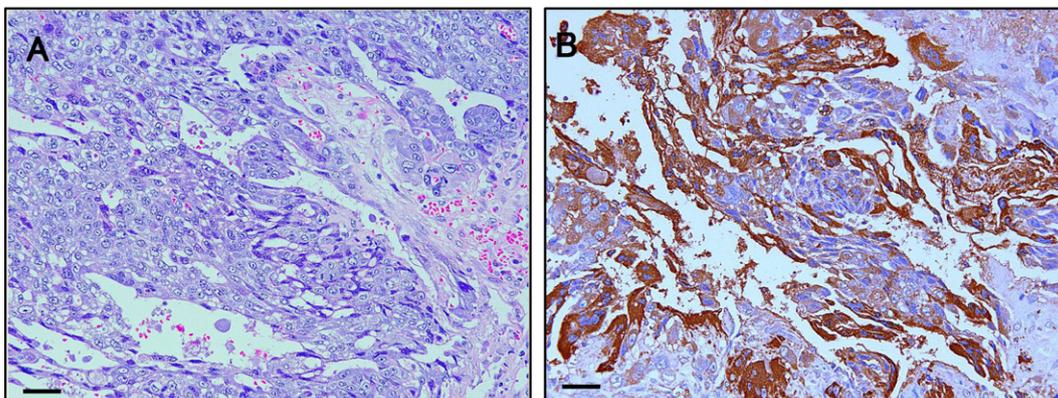
additional hysterectomy or chemotherapy, and has had regular menstrual cycles without recurrence in 26 months since the chemotherapy with MEA.

### 3. Discussion

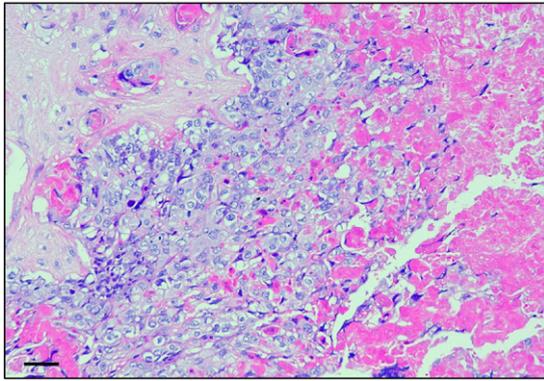
Our pathological review of the present case showed a mixed choriocarcinoma coexisting with an ETT, which is a rare gestational trophoblastic tumor. In 1998, Shih and Kurman reported 14 cases of mixed choriocarcinoma and ETTs, and in more than half the cases there was a history of either a hydatidiform mole or choriocarcinoma that preceded the diagnosis (Luk and Friedlander, 2013; Shih and Kurman, 1998). Recently, they proposed that choriocarcinoma, PSTT, or ETT may develop as a result of neoplastic transformation of the same cytotrophoblast, which is presumably the trophoblastic stem cell (Shih and Kurman, 2001). This theory explains the existence of gestational trophoblastic neoplasia with mixed histological features, choriocarcinoma, and ETT, as found in the present case.

Although there is extremely limited experience with choriocarcinoma coexisting with an ETT, previous reports suggest that pure-type ETT may not be responsive to the chemotherapeutic agents used in the treatment of other types of GTN (Shih, 2007). A high-dose chemotherapy regimen consisting of cyclophosphamide, etoposide, and carboplatin, however, resulted in a successful outcome in metastatic ETT (Stacey et al., 2002). Once treatment has been completed, most relapses occur within the first year of follow-up, and careful hCG monitoring should be recommended in pure-type ETT (Fieke and Michael, 2014). In this case, serum hCG ultimately rose within 1 month despite an initial response to laparoscopic surgery and MTX under the clinical diagnosis of an ectopic pregnancy, and residual villi without an adequate pathological examination in the previous hospital. Given the potential for the progression of choriocarcinoma coexisting with an ETT after our pathological review, we successfully treated the case with MEA, the chemotherapy regimen for the usual form of choriocarcinoma. Repeated transvaginal ultrasound examinations showed no mass in the uterus, and serum hCG levels have remained negative for over 2 years, conserving fertility.

Here we reported a rare case of choriocarcinoma coexisting with an ETT. The clinical behavior of a mixed choriocarcinoma and ETT seems similar to that of the usual form of choriocarcinoma despite the chemoresistance of pure-type ETT. This case suggests that choriocarcinoma coexisting with an ETT has a high probability of cure with appropriate chemotherapy. Study of additional cases is necessary to reliably determine the behavior of mixed choriocarcinoma coexisting with an ETT, as well as the optimal multimodal treatment approach.



**Fig. 3.** Histopathological and immunohistochemical findings of a choriocarcinoma component. Cytological atypia and mitotic figures are numerous. The tumor consists of a trimorphic population of syncytiotrophoblast, intermediate trophoblast and cytotrophoblast (A). The tumor exhibits diffuse immunoreactivity with hCG (B). Tissues were stained with HE (A) and hCG (B). Images were taken at 200× magnification. Scale bar = 50 μm.



**Fig. 4.** Histopathological findings of ETT. A nest of tumor cells with a relatively uniform population of mononucleate intermediate trophoblastic cells surrounded by necrotic debris and hyaline degeneration. Tissue was stained with HE. Image was taken at 200× magnification. Scale bar = 50  $\mu$ m.

#### Conflict of interest statement

No authors have any conflicts of interest to declare.

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