

## Case Report

# Epithelioid trophoblastic tumor after induced abortion with previous broad choriocarcinoma: a case report and review of literature

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**Abstract:** Epithelioid trophoblastic tumor (ETT) is a rare trophoblastic tumor originating from chorionic-type intermediate trophoblasts (ITs). It is usually associated with a prior gestational event. We present a 44-year-old woman who had unusual pregnancy related history. The patient received her second spontaneous abortion at the age of 25 years and had suffered from choriocarcinoma in left broad ligament at the age of 29 years. She admitted no more treatment after 3 courses of multiagent chemotherapy when serum  $\beta$ -hCG returned to normal. Then she had Full-term delivery, induced abortion at the ages of 32, 33 years. The patient had high serum levels of beta-human chorionic gonadotropin (6587 IU/L). Microscopically, the tumor was composed of mainly mononuclear tumor cells, grew in cords, nests, and sheets within which were aggregates of hyaline material. Most were with distinct cell borders, eosinophilic cytoplasm. Immunohistochemical staining revealed strong diffuse reactivity for cytokeratins (AE1/AE3, CK18), P63, focal reactivity for beta-human chorionic gonadotropin, human placental lactogen, and inhibin-alpha. The Ki-67 index was 77%. The histological and immunohistochemical features were characteristic of epithelioid trophoblastic tumor. This is the first reported case of these two gestational trophoblastic tumor happened on one person with the intervening normal pregnancy.

**Keywords:** Gestational trophoblastic tumor, epithelioid trophoblastic tumor, choriocarcinoma, immunohistochemistry

## Introduction

Gestational trophoblastic neoplasms are a group of fetal trophoblastic tumors including choriocarcinomas, epithelioid trophoblastic tumors (ETTs), and placental site trophoblastic tumors (PSTTs) [1]. ETT is considered a neoplasm composed of chorionic-type intermediate trophoblasts based on histological characteristics, immunohistochemical expression, and polymerase chain reaction analysis [2, 3]. Although cellular differentiation of ETT has clearly been elucidated, the pathogenesis remains poorly understood. ETT is usually associated with a prior gestational event. The antecedent gestational events include normal pregnancy, spontaneous abortion, and gestational trophoblastic tumor. With the increased reported cases in the literature, a history of prior gestational trophoblastic tumor seems to be present in around

20% of cases and a history of a prior normal pregnancy is reported in around 55% of cases [4-6]. The reported Gestational trophoblastic tumors mostly were hydatidiform mole. In the present report a case of uterine ETT that was diagnosed in a woman who had an unusual pregnancy related history, following 4 pregnancies and a choriocarcinoma is presented. ETT with such complex pregnancy related history has not been previously reported.

## Case report

A 44-year-old Chinese woman, gravida 4, para 1, presented with vaginal spotting after Menopause four months in 1999. At the 12<sup>th</sup> gestational weeks, transvaginal ultrasound showed no gestational sac in uterine cavity, but a left adnexal mass. Serum  $\beta$ -hCG was 86520 IU/L. A provisional diagnosis of ectopic pregnancy was

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**Figure 1.** A grossly well-circumscribed, spongy-looking, tanned to dark-brown mass, is located in the lower uterine segment, extending to endocervix, invading whole wall of the uterus.

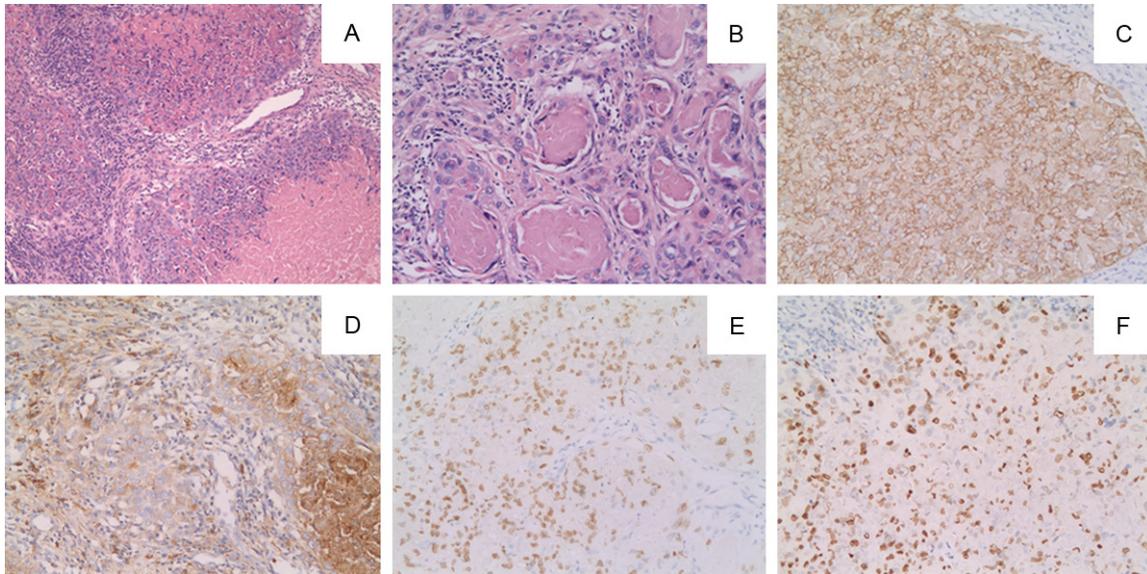
made, exploratory laparotomy was performed. Intraoperative findings included a dark-brown mass (6×5×5 cm) at the left broad ligament. Pathologic examination showed choriocarcinoma. She was commenced on actinomycin D, methotrexate, cyclophosphamide for chemotherapy. After 3 cycles of chemotherapy, the serum  $\beta$ -hCG level returned to normal. And she received no additional chemotherapy. Three years later, she had normal pregnancy and delivered. One years after full-term delivery, she had isthmus pregnancy and heavy vaginal bleeding happened when dilatation and curettage. Eleven years later, she visited our hospital complaining of vaginal spotting. Transvaginal ultrasound showed a uterus isthmus mass (3.0×2.1×1.4 cm) with elevated serum  $\beta$ -hCG (6587 IU/L). A computed tomographic (CT) scan of the abdomen and pelvis, revealed a mass (3.6×3×3.3 cm) located at the lower uterine segment, brain and lung CT scan showed no evidence of metastatic disease. She was diagnosed with GTD and began multiagent chemotherapy with EMA-EP (etoposide, methotrexate, actinomycin D/etoposide and cisplatin).

After administration EMA for one course, She underwent total hysterectomy, bilateral salpingectomy and left oophorectomy. Intraoperative findings included a yellowish to dark-brown mass located at the lower uterine segment, invaded rectum serosa, and normal fallopian tubes, left ovary. Grossly, a well-circumscribed, spongy-looking, tanned to dark-brown mass, was located in the lower uterine segment, extending to endocervix, invading whole wall of the uterus. Severe hemorrhagic foci was also noted. The tumor measured 4×3×3 cm (**Figure 1**). There were three leiomyomas in uterus. The bilateral fallopian tubes and left ovary were unremarkable.

Microscopically, the tumor was nodular and well circumscribed. It had an expansile pushing border mixed with lymphoplasmacytic infiltrate. Tumor composed of a monomorphic population of intermediate trophoblasts arranged in nests and sheets, a geographic pattern of necrosis surrounding the nests of neoplastic cells (**Figure 2A**). Dense eosinophilic hyaline-like material and necrotic debris, which in some areas vaguely resembled keratin, resembling squamous cell carcinoma (**Figure 2B**). The tumor cells contained moderate amounts of lightly eosinophilic or amphophilic cytoplasm, distinct cell borders. The nuclei were vesicular and oval to round in shape. Mitotic figures of the mononuclear tumor cells averaged 10 to 13 mitotic figures per 10 high power fields. Immunohistochemistry showed a diffuse positive staining for Cytokeratins 18 (CK18) (**Figure 2C**), AE1/AE3, E-cadherin, and epidermal growth factor receptor. There was focal reactivity for  $\beta$ -hCG (**Figure 2D**), human placental lactogen (hPL), inhibin- $\alpha$ , Mel-CAM (CD146). Nuclear p63 (**Figure 2E**) expressed in 58% of tumor cells. Ki-67 proliferation index was 77% (**Figure 2F**). The tumor cells were negative for CK5/6.

The patient serum  $\beta$ -hCG level decreased to 522.9 IU/L after operation. She then received 4 courses of chemotherapy with a regimen of EMA-EP over a 2-month period. The serum  $\beta$ -hCG level decreased to 3 IU/L after completion of 3 cycles of chemotherapy. The scheduled fifth course chemotherapy was cancelled because of myelosuppression.  $\beta$ -hCG gradually increased to 39 IU/L four months after operation, brain and chest computed tomography (CT) showed no evidence of lesions. She then received

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**Figure 2.** Epithelioid trophoblastic tumor (ETT). (A) The tumor displays mononucleated intermediate trophoblastic cells, a geographic pattern of necrosis surrounding the nests of neoplastic cells, (B) Dense eosinophilic hyaline-like material and necrotic debris vaguely resembled keratin. The neoplastic cells are diffuse and strong positive for CK18 (C), focal reactivity for  $\beta$ -hCG (D), Nuclear p63 (E) expressed in 58% of tumor cells. Ki-67 proliferation index was 77% (F).

2 courses of chemotherapy with a regimen of TP (Anzatax, carboplatin),  $\beta$ -hCG decreased to 10 IU/L. Follow-up is ongoing.

### Discussion

ETT is a rare neoplasm of intermediate trophoblasts, there are less than 100 cases reported in the English literature till now. It primarily affects women of reproductive age and is extremely rare in postmenopausal women. The reported age range is from 15 to 66 years [4]. The most common presenting symptom is vaginal bleeding [4], which is associated with elevated serum  $\beta$ -hCG, with levels only mildly elevated ( $< 2,500$  IU/l) in contrast to high levels in cases of choriocarcinoma [4, 7]. A high level of serum  $\beta$ -hCG is seldom found in ETT, hinted the presence of a large tumor volume and unusually high mitotic activity [8]. However, there were six ETTs of more than seventy reported cases, had higher levels  $> 10,000$  IU/L [2, 7, 9]. Four were extrauterine ETT, the other two were located in uterus, while one uterine ETT with metastatic disease in lung, liver, cervical LNs, Kidney 10 years later. Two ETT died of disease at 7 months and 12 years respectively. It seemed that higher levels serum  $\beta$ -hCG maybe related to more advanced clinical stage and poorer prognosis. The high level of serum  $\beta$ -hCG (6587 IU/L) in

this patient was thought to be a result of the huge uterine mass with high mitotic rate and rectal serosa lesions.

Uterine ETT can present in the fundus of the uterus, lower uterine segment or endocervix. Extrauterine ETT in the absence of a uterine tumor has been documented in the lung, parametrial tissue, broad ligament, liver, spine, orbit and lymph nodes [2, 5].

ETT is usually associated with a previous gestational event, With the increased reported cases in the literature, a history of prior gestational trophoblastic tumor seems to be present in around 20% of cases, a prior normal pregnancy around 63% of cases and a prior spontaneous abortion around 17% of cases [10]. The interval between the preceding gestation and the diagnosis of ETT has ranged from 2 weeks to 30 years. With an average interval of  $> 6$  year (average, 6.2 years). That is longer for ETT than for choriocarcinoma or PSTT [2].

We reviewed reported English literatures till now, found that prior gestational is almost hydatidiform mole, choriocarcinoma is rare. Our patient had unusual previous trophoblastic tumor history, she had left broad ligament choriocarcinoma, her serum  $\beta$ -hCG decreased to

normal after 3 courses of chemotherapy. After that, she had full-term delivery. Prior gestational event was induced abortion because of isthmus pregnancy. Clinically, the immediately antecedent pregnancy is perceived as the causative pregnancy. However, using genetic analysis, two choriocarcinoma patients have been identified previous HM were causative pregnancy, not the immediately antecedent pregnancy full term normal delivery [11, 12]. We began to interested in previous choriocarcinoma or immediately antecedent induced abortion, which caused the ETT. Based on morphologic and histochemical features, ETT appears to develop from neoplastic transformation of chorionic-type intermediate trophoblasts, pathogenesis of ETT remains unknown. Originally, it was described as a secondary phenomenon seen in patients who receive chemotherapy of choriocarcinoma [13, 14]. Choriocarcinoma is composed of variable amounts of neoplastic cytotrophoblast, syncytiotrophoblast, and intermediate trophoblast. In PSTTs, neoplastic cytotrophoblast differentiates mainly into implantation site intermediate trophoblastic cells, whereas in ETTs neoplastic cytotrophoblast differentiates into chorionictype intermediate trophoblastic cells. Choriocarcinoma is the most primitive trophoblastic tumor whereas PSTT and ETT are more differentiated. Whether differentiation occurs toward villous trophoblast or implantation site intermediate trophoblast depend on a range of other factors. This model of pathogenesis also explains the finding of ETTs after intense chemotherapy of metastatic choriocarcinoma in the lung [13]. In these cases, it is plausible that chemotherapeutic agents eradicated the more primitive cytotrophoblastic component permitting differentiation of chorionic-type intermediate trophoblastic cells which are more refractory to chemotherapy than the original choriocarcinoma component [15]. Our patient received nonstandard chemotherapy, After serum  $\beta$ -hCG values returned to normal, she had not administered additional course. From above, we could not rule out the possibility that ETT may be associated with that previous choriocarcinoma in our patient despite the presence of the intervening normal pregnancy, this requires more clues to verify.

ETT composed of a relatively monomorphic population of intermediate trophoblasts arranged in nests and sheets. Cells are character-

ized by eosinophilic to clear cytoplasm, well-defined cell membranes and oval nuclei with prominent nucleoli. Tumor cells are surrounded by extensive necrosis and are associated with a hyaline like matrix creating a geographic pattern that is quite characteristic of this lesion [3]. ETT has immunohistochemical expression of markers seen in normal chorionic-type intermediate trophoblasts, including diffuse expression of pancytokeratin, CK 18, epithelial membrane antigen, focally express of  $\beta$ -hCG, hPL, CK7, Mel-CAM and inhibin- $\alpha$ . p63 is a nuclear stain expressed in chorion-type intermediate trophoblasts, it is expressed in ETT in a strong diffuse pattern (45-80%). p63 had important role in differentiation ETT from choriocarcinoma or PSTT, since it is only focally present in choriocarcinoma and absent in PSTT [16].

ETT possibly representing a malignant counterpart of PSN, and both typical and atypical PSN (APSN) has been reported adjacent to ETT [3]. PSNs are usually small nodules (0.11-0.4 cm in diameter) in the endometrium or the superficial myometrium. ETTs are solitary, discrete nodules (> 0.5 cm in diameter) that invade the uterine cervix and myometrium although the cut surface might be solid-cystic occasionally [3]. PSN presents well circumscribed nodule with low cellularity, while ETT is more cellular and necrotic. APSN has been identified recently [17, 18]. This uncommon lesion is recognized as a possible intermediate between PSN and ETT. APSN is intermediate between PSN and ETT in size, and rarely exceeds 0.4 cm. APSN did not invade the myometrium. The trophoblastic cells were arranged in cohesive sheets and nests. Some trophoblastic cells showed enlarged degenerated nuclei. The Ki67 index was moderate (10%), much higher than that in PSN (3%) and lower than that in ETT (18%) [2].

When ETTs located in the cervix and the lower uterine segment, they can be misdiagnosed as squamous cell carcinoma of the cervix because of their epithelioid appearance and the resemblance of the hyaline and necrotic debris to keratin. Helpful clinical clues are presentation in a woman of reproductive age with elevated serum  $\beta$ -hCG in comparison to older patients with a history of human papillomavirus infection. Histologically, the lack of intercellular bridges, definite keratin pearls and a unique immunohistochemical pattern would help in arriv-

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ing at the correct diagnosis. Lack of Cervical squamous intraepithelial neoplasia and dysplasia would support ETT. SCC is positive for p16, CK5/6 and negative for CK18 and inhibin- $\alpha$ , whereas ETT is positive for CK18 and inhibin- $\alpha$ , with an absence of CK5/6 and p16 staining [17]. However, the percentage and intensity of positive cells for inhibin- $\alpha$  in ITTs are limited. Only about 40% of ITT display focal immunoreactivity for inhibin- $\alpha$  and in some cases completely absent [19]. Our patient showed focally positive areas for inhibin- $\alpha$ . In addition, the Ki-67 labeling index may be helpful, is more than 50% in SCC compared to a low mitotic index in most cases of ETT [3].

The limited information available suggests that the clinical behavior, malignant potential, and management of ETTs do not differ significantly from other forms of PSTT. The prognosis in ETT cases is difficult to assess due to the rarity of this neoplasm and the lack of long-term follow-up. Shih and Kurman reported metastasis in 25% of their cases and death in 10% [2]. Pathologic features such as tumor size, percentage of tumor necrosis, and cytological atypia may not be related to the prognosis. However, mitotic activity is suspected to be associated with malignant behavior of ETT [14, 20]. Mitoses in ETT are reported to range from 0 to 9 per 10 high power fields (mean of 2/10) and the Ki-67/MIB1 proliferative index ranges from 10% to 25% [2, 3]. However, there is an occasional report of higher Ki-67/MIB1 proliferative index > 85% [21]. Our patient showed active mitotic activity (13/10 high power field) and MIB-1 labeling index (77%). After operation and one course of chemotherapy, her serum  $\beta$ -hCG level decreased to 3 IU/L. The prognosis requires more time to follow-up.

Surgery is the primary treatment modality for stage I ETT. Hysterectomy with lymph node dissection is the recommended treatment for ETT, because of the relative resistance of ETT to chemotherapy and propensity for lymphatic spread. Chemotherapy (EMA-CO) should be used in patients with metastatic disease and in patients with nonmetastatic disease who have adverse prognostic factors. Because of the rarity of ETT, data regarding the best chemotherapeutic regimen to treat advanced stage is limited.

In summary, we present a unusual case of gestational trophoblastic tumor of ETT, with previ-

ous broad choriocarcinoma history, relative higher serum  $\beta$ -hCG and index of Ki-67. This is the first reported case of these two gestational trophoblastic tumor happened on one person with the intervening normal pregnancy. We could not rule out the possibility that ETT may be associated with previous broad choriocarcinoma. Due to the rarity of this neoplasm, Long-term studies are needed to better understand of long-term prognosis and best treatment modalities.

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### Disclosure of conflict of interest

None.

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