Int J Clin Exp Med 2016;9(11):22041-22047
www.ijcem.com /ISSN:1940-5901/IJCEM0033193

Original Article

Extrauterine epithelioid trophoblastic tumor of the vagina: a case report and literature review

Ru Luo[1], Haiyan Shi[2], Xiaoduan Chen[2], Bingjian Lü[2], Huawei Shao[3]

[1]Department of Pathology, The Second Affiliated Hospital of Zhejiang University College of Medicine, Hangzhou 310009, Zhejiang Province, PR China; [2]Department of Pathology, The Affiliated Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, PR China; [3]Department of Burns and Wound Care Center, The Second Affiliated Hospital of Zhejiang University College of Medicine, Hangzhou 310009, Zhejiang Province, PR China

Received June 2, 2016; Accepted August 8, 2016; Epub November 15, 2016; Published November 30, 2016

Abstract: Epithelioid trophoblastic tumors (ETTs) are a rare form of gestational trophoblastic disease and extrauterine ETTs are extremely rare. Gross examination of the vaginal tumor and immunohistochemical analysis for human CK18, CK, CD10, p63, HCG-β, CD146, and inhibin-α were performed. A 32-year-old female presented with a vaginal mass and elevated serum β-HCG. Histological and immunohistochemical features of the vaginal mass were characteristic of an ETT. Three years later, a metastasis to the right lung was found. An ETT was identified in right lung by histopathological diagnosis after patient underwent video-assisted thoracoscopic pulmonary wedge resection. After patient received 2 cycles of chemotherapy (cyclophosphamide, etoposide, methotrexate, actinomycin D, vincristine/oncovine), her serum β-HCG levels returned to normal, and there was no clinical evidence of disease at 16 months after surgery. In conclusions, an ETT in the vagina with no intrauterine lesion and subsequent metastasis to the lung was observed and reported.

Keywords: Epithelioid trophoblastic tumor, lung, gestational tumor, vagina

Introduction

Gestational trophoblastic disease (GTD) is a group of uncommon conditions associated with an abnormal pregnancy. Histologically, it includes the benign partial and complete hydatidiform mole, invasive and metastatic mole, as well as the malignant choriocarcinoma (CC), placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) [1]. ETT was first proposed in 1994 and was initially described as resistant disease in the lungs of patients after chemotherapy for choriocarcinoma [2]. In 1998, Shin and Kurman [3] reported 14 ETT cases without any history of antecedent GTD. They suggested that ETT was an unusual type of trophoblastic tumor that was distinct from PSTTs and CC, with features mimicking a carcinoma [3]. The most common primary disease sites are the uterus and cervix [4, 5]. Only 13 cases of isolated extrauterine disease without uterine lesions originating in the broad ligaments, small bowel, lungs, fallopian tube, and ovaries have been reported [3, 6-9].

Herein, we here present a unique extrauterine ETT that occurred in the vagina and metastasized to the lung.

Case report

A 32-year-old female, gravida 3, para 1 presented with a vaginal tumor. A polypoid mass 2 cm in diameter was detected on the right vaginal wall at the 4th gestational week of pregnancy, and at 4 months she had a surgical abortion. She had a normal vaginal delivery 7 years prior, and an elective abortion 6 months prior.

The vaginal mass subsequently increased in size to 3×4×2 cm at which time it was excised. The postoperative diagnosis was ETT. Following 1 cycle of chemotherapy (5-fluorouracil plus dactinomycin) the patient's serum β-human chorionic gonadotropin (HCG) declined from 70 mIU/mL to 20 mIU/mL, and no further chemotherapy was administered as the β-HCG level was normal. Twenty-nine months after the vaginal tumor excision, her β-HCG level increased to 162 mIU/mL. Forty months after the vaginal

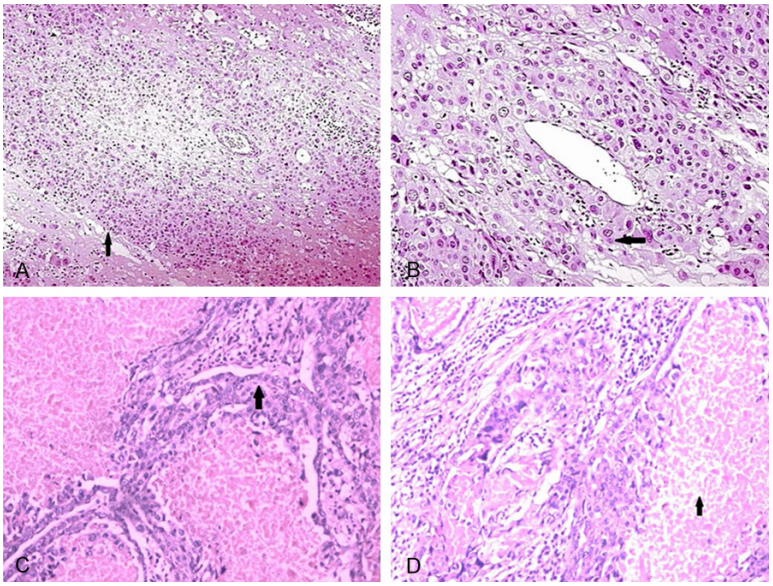

Figure 1. A: The vaginal tumor was composed of a predominantly monotonous growth of atypical mononucleated cells, arranged in sheets and nests, with a pushing margin. (hematoxylin and eosin [HE], ×100). B: Some tumor cells were noted to be growing around blood vessels, and the neoplastic cells were small and epithelioid with eosinophilic cytoplasm in a hyaline matrix (HE, ×200). C: The lung tumor exhibited a proliferation of atypical mononucleated cells involving the alveolar spaces (HE, ×200). D: Central eosinophilic necrotic debris was present in the lung tumor (HE, ×200).

tumor excision, computed tomography (CT) of the chest revealed a metastasis to the right lung. Video assisted thoracoscopy pulmonary wedge resection was performed, and histological examination confirmed ETT metastasis. She received 2 cycles of EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine/oncovine), and her serum β-HCG level returned to normal (< 1.2 mIU/mL). Enhanced magnetic resonance imaging (MRI) and CT scan of pelvis was unremarkable. There was no clinical evidence of disease at her last follow-up visit, 19 months after the pulmonary surgery.

Gross examination of the vaginal tumor showed a mass measuring 4.5×3×1 cm with a dusty color and a grayish white, friable cut surface. The lung tumor was well-circumscribed nodules of firm consistency with a white-yellow cut surface measuring 1×0.6×0.6 cm.

On light microscopy, the vaginal tumor was composed of predominantly monotonous growth of atypical mononucleated cells, arranged in sheets and nests, with a pushing margin (**Figure 1A**). The neoplastic cells were small and epithelioid with eosinophilic cytoplasm, and were embedded in a hyaline matrix (**Figure 1B**). Central eosinophilic necrosis and a few scattered multinucleate syncytiotrophoblasts were present. Some tumor cells were growing around blood vessels. The lung tumor was composed of atypical mononucleated cells, with predominant involvement of the alveolar spaces resulting in nests of tumor cells encircled by septal connective tissue (**Figure 1C**). Central eosinophilic necrotic debris was present (**Figure 1D**). A few degenerating tumor cells were mixed with the necrotic material. The tumor cells had a moderate amount of amphophilic cytoplasm, distinct cell borders, and large vesicular oval nuclei with prominent nucleoli.

Immunohistochemical analysis was performed on a portion of the vascular tissue. Briefly, 5-μm paraffin sections were obtained, dewaxed, and dehydrated. Sections were incubated with antibodies specific for human CK18, CK, CD10, p63, HCG-β, CD146, and inhibin-α (Supplementary Table 1). After incubation with the primary antibody, samples were incubated with proteinase K (Sigma Aldrich, St. Louis, MO, USA), autoclaved, and stained using the ABC kit (Vector Laboratories, Inc., Burlingame, CA. USA). Other sections were only stained with hematoxylin and eosin (HE), dehydrated, and mounted with neutral gum. Vascular morphology and immunostaining were observed by light microscopy using an Olympus BX41 image analysis system (Olympus China, Shanghai, China).

Samples were viewed at high magnification (×400), and 10 fields of each sample were visualized for semi-quantitative analysis. The total staining score was based on a system previously described by Fromowitz et al. [10] Each field was scored as “0” (no staining), “1” (light yellow staining), “2” (light brown staining), or “3” (dark brown staining). The overall percentage of positive staining per field was scored as “0” (≤ 5% staining), “1” (6~25% staining), “2” (26~50% staining), “3” (51~75% staining), or “4” (> 75% staining). The final score was sim-

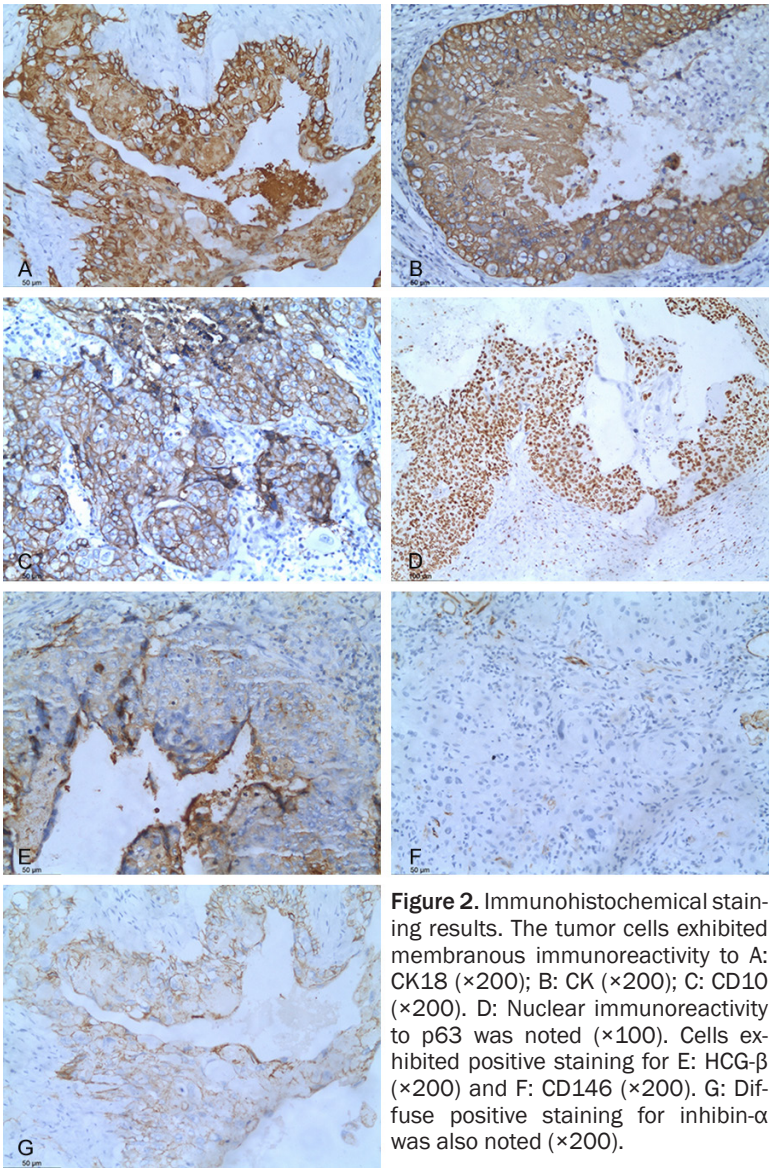

Figure 2. Immunohistochemical staining results. The tumor cells exhibited membranous immunoreactivity to A: CK18 (×200); B: CK (×200); C: CD10 (×200). D: Nuclear immunoreactivity to p63 was noted (×100). Cells exhibited positive staining for E: HCG-β (×200) and F: CD146 (×200). G: Diffuse positive staining for inhibin-α was also noted (×200).

ply the sum of these 2 individual scores, and was "-" (0-1 points), "+" (2-3 points), "++" (4-5 points), or "+++" (6-7 points). Immunohistochemical results included diffusely positive staining for cytokeratin, CK18, epithelial membrane antigen EMA, p63, inhibin-α, vimentin, and CD10 (**Figure 2**). A few cells were positive for HCG and CD146. The Ki-67 proliferative index was approximately 60%. Cells were negative for human placental lactogen, E-cadherin, and actin (data not shown).

Discussion

The current patient was diagnosed with an extrauterine ETT based on age, pregnancy history, clinical symptoms, light microscopic features, and immunohistochemical phenotype. The features of metastatic lesions in the lung and immunophenotype also met the diagnostic criteria for epithelioid trophoblastic tumor.

ETT is a rare trophoblastic neoplasm derived from chorionic-type intermediate trophoblastic cells, and primarily presents in reproductive-age women at a median of 76 months (range, 2-300 months) after a preceding gestation [11]. Three rare cases have been reported in perimenopausal women, and two cases in a postmenopausal woman [12, 22]. The antecedent gestations have included full-term deliveries (48%), miscarriages (25.3%), hydatidiform moles or GTD (24%), and tubal pregnancies (1.3%), and abnormal vaginal bleeding is the most common presenting symptom (67%). At the time of diagnosis, serum β-HCG levels are usually slightly elevated, and generally do not exceed 2500 mIU/mL [13], which is in contrast to that seen in CC.

In our review of the literature, we found only 20 cases of ETTs occurring at extrauterine sites without uterine lesions [3, 8, 14-21], and these cases are summarized in **Table 1**. Shen et al. [25] performed a retrospective analysis of 9 patients with ETTs, and in 2 of the patients uterine tumors metastasized to the vagina or vaginal fornix. Zhao et al. [21] reported the only other case of an isolated vaginal ETT, and there are some similarities and differences between that case and ours. Both patients had 2 abortions, both had an isolated vaginal lesion and no uterine lesions, and both developed recurrence or metastasis. In Zhao's patient *in situ* recurrence was seen at 5 months after surgery, while in our patient lung metastasis was found at 40 months after surgery. In both cases, chemo-

Table 1. Summary of 20 cases of extrauterine epithelioid trophoblastic tumors reported in the literature

Case	Reference	Site	Metastases	Age	Prior pregnancy	Pregnancy interval (mo)	Presenting symptoms	Maximum HCG (mIU/ml)	Treatment	Documented survival (mo)
1	Shin et al. 1998	Small bowel	Lung	39	Full-term delivery	Unknown	Bowel obstruction	60	Bowel resection + VMC	Died of disease (36)
2	Shin et al. 1998	Lung	No	42	Full-term delivery	Unknown	Lung mass	300	Lung resection + DVML	Lost to follow-up
3	Hamazaki et al. 1999	Lung	No	47	Invasive mole	36	Abnormal chest radiograph	Not recorded	Thoracoscopic resection of tumor	Alive (24)
4	Hamazaki et al. 1999	Lung	No	32	Mole	60	Abnormal chest radiograph	Not recorded	Right upper lobectomy	Alive (36)
5	Hamazaki et al. 1999	Lung, liver	No	42	Full-term delivery	Unknown	Hemoptysis and cough	1300 ng/ml	Left upper lobectomy + chemotherapy	Alive (24)
6	Parker et al. 2003	Fallopian tube	No	39	Abortion	24	Pelvic pain	52,065	TAH + BSO, EMACO	Alive (12)
7	Kuo et al. 2004	Right broad ligament	No	41	GTD	108	Vaginal bleeding	12,6763	TAH + BSO, EMD	Alive (24)
8	Macdonald et al. 2008	Gallbladder	Liver	41	Full-term delivery	72	Heavy vaginal bleeding and nausea	14,425	CEC, EMA/CO	Died of disease (7)
9	Noh et al. 2008	Paracervix, parametrium, paraadnexal soft tissue	No	44	Full-term delivery	180	Distension and pain of lower abdomen	Unknown	TLH + BSO, EMD	Alive (12)
10	Lewin et al. 2009	Lung	No	38	Full-term delivery	42	Adnexal mass	400	Completion lobectomy	Alive (90)
11	Lewin et al. 2009	Lung	No	49	Miscarriage	12	Vaginal bleeding	2204	Right lower lobectomy, TAH + BSO	Alive (45)
12	Lewin et al. 2009	Lung	No	34	Full-term delivery	24	Irregular menses and fainting	426	Methotrexate + lobeseg-mentectmy + EMD + TAH	Alive (22)
13	Chohan et al. 2010	Spine	Liver, lung	36	Full-term delivery	Unknown	Low back pain and T10 radiculopathy	16	Corpectomy + laminectomy + EMACV	Died of disease
14	Khunamornpong et al. 2011	Ovary	Recurrence	32	Hydatidiform mole	60	Palpable pelvic mass	60,000	Left salpingo-oophorecto-my + EMA CI	Alive (19)
15	Ahn et al. 2013	Lung	No	26	Suspected subclinical miscarriage	Unknown	Pulmonary mass	11.37 (postoperatively)	Lobectomy + EM DCV	Alive (9)
16	Kim et al. 2013	Lung	No	35	Unknown	Unknown	Abdominal pain, nausea and vomiting	Normal	Lobectomy	Alive (15)
17	Zhao et al. 2013	Vagina	Recurrence	43	Induced abortion	42	Vaginal mass	Unknown	Mass resection + VFDE	Alive (13)
18	Park et al. 2014	Ovary	Lung	75	Normal pregnancy	47	Multiple pulmonary masses	57971	Total abdominal hysterecto-my and bilateral salpingo-oophorectomy + EMA-CO	Alive (5)
19	Fénichel et al. 2014	Lung	No	29	Normal pregnancy	48	Nausea, abnormal bleeding	250	Leftsuperior lobectomy + EP-EMA	Alive (12)
20	Arafah et al. 2015	Ovary	Peritoneum, liver, lung	50	Normal pregnancy	120	Abdominal pain and distension	806.7	Multiple biopsies + EMA-EP	Unknown
21	Present case	Vagina	Lung	33	Abortion	6	Vaginal mass	162	Resection of tumor + chemotherapy	Alive (57)

TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy; VMC = vincristine, methotrexate, and cytoxan; EMACO = etoposide, actinomycin-D, methotrexate, vincristine, cyclophosphamide; EMD = etoposide, methotrexate, actinomycin; CEC = cyclophosphamide, etoposide, cisplatin; EMA = etoposide, methotrexate, dactinomycin; EMACV = etoposide, methotrexate, actinomycin D, EMA CI = etoposide, methotrexate, actinomycin D, cisplatin, ifosfamide, EMA DCV = etoposide, methotrexate, dactinomycin, cyclophosphamide, and vincristine; VFDE = vincristine, floxuridine, dactinomycin, etoposide; EP-EMA = etoposide, methotrexate, actinomycin, and cisplatinum.

therapy was performed after surgery and both were disease free at the final follow-up. In Zhao's patient, β-HCG returned to a normal level after vaginal surgery, and chemotherapy was not administered, while our patient received one course of chemotherapy after vaginal surgery. In Zhao's patient recurrence occurred 5 months after surgery, while in our patient lung metastasis was noted 40 months after surgery, and *in situ* recurrence was not observed. These findings suggest that postoperative chemotherapy is necessary to prevent or delay recurrence and metastasis.

ETTs should be distinguished from primary and metastatic cancer, especially keratinizing squamous cell carcinoma (SCC). Differentiation of an ETT from SCC requires recognition of keratin pearls and intracellular bridges in the latter. In addition, immunohistochemical features can also be helpful. ETTs are typically positive for HLA-G, α-inhibin, and CK18, which are generally not present in SCC. Also, SCCs always have a high Ki-67 labeling index (> 50%), which is relatively low in ETTs (10-25%). Next, differentiating an extrauterine ETT from other metastatic GTTs, particularly CC and PSTTs, is important. CC consists of dimorphic of cytotrophoblasts and syncytiotrophoblasts growing in a plexiform-like pattern with marked central hemorrhagic necrosis. However, ETTs exhibit the predominant growth of monomorphic intermediate trophoblastic cells in the chorion, with a few multinucleated syncytiotrophoblasts intermingled. Furthermore, ETTs are devoid of extensive hemorrhage or necrosis. PSTT cells, derived from implantation site intermediate trophoblasts, infiltrate the myometrium in a distinctive pattern weaving between muscle bundles and fibers, and often invading blood vessels [3]. On the other hand, in ETTs a nodular growth pattern and a pushing margin are common, and vascular permeation is typically absent. ETT cells grow in nests and cords, and are associated with an eosinophilic, fibrillar, hyaline-like material, and surrounding necrosis [3]. Recently, p63 has been recognized as a useful aid for differentiating between ETT and PSTT [26]: it is only positive in chorionic-type intermediate trophoblastic cells and negative in implantation-type intermediate trophoblastic cells. Fadare et al. [26] reported 5 cases of ETTs of the uterine cervix all positive for p63. Doppler ultrasound may also be useful to distinguish ETTs from other gestational trophoblastic neoplasms as ETTs have been reported to have a well-circumscribed border with hypoechogenic halo which is not present on other gestational tumors [27]. It is also important to distinguish extrauterine ETTs from other epithelioid tumors, such as epithelioid leiomyosarcoma. This can be done based on the lack of expression of muscle markers, including desmon and smooth muscle actin, in ETTs.

There are 3 possible etiologies of extrauterine ETTs. First, extrauterine ETTs may arise in an unidentified ectopic pregnancy that resolved without diagnosis or treatment [28]. Second, an extrauterine ETT could be a solitary metastasis from an unidentified (regressed) primary uterine ETT. Finally, an extrauterine ETT could originate from trophoblastic cells that were passed to the extrauterine site during the prior pregnancy. A case of a primary uterine ETT metastasizing to the vagina has been reported [29], so we are inclined to accept the second etiology in our case.

The biological behavior of ETTs has not been firmly established. Generally, the behavior of ETTs is similar to that of PSTTs, which behave in a relatively benign fashion. In the literature, the overall metastasis and mortality rates of ETTs are reported to be 25% and 10%, respectively. The metastasis and mortality rates of the 14 extrauterine ETTs, including our case, are 29% and 21%, respectively. ETTs may not be responsive to the chemotherapeutic agents used in the treatment of other types of gestational trophoblastic disease. A review by Zavadil et al. [30], revealed that curettage in combination with chemotherapy is an effective treatment for ETTs, but a consensus treatment has not been reached. Because of the rarity of the neoplasm, it has not been determined if total hysterectomy with bilateral salpingo-oophorectomy is required, or if resection of the extrauterine tumor plus the chemotherapy is sufficient. Zhang et al. [5] reviewed 78 cases of ETTs, and Kaplan-Meier analysis indicated that chemotherapy (surgery with postoperative chemotherapy vs surgery alone) was associated with increased ETT relapse, even after stratification by International Federation of Gynecology and Obstetrics (FIGO) stage; but FIGO stage remained the only significant prognostic indicator for ETTs.

In summary, we report an ETT in the vagina with no intrauterine lesion and subsequent metastasis to the lung. ETTs are rare, and frequently found in the uterus. When extrauterine lesions suspicious for an ETT is present, light microscopic features and immunohistochemical examination are useful for the diagnosis. Standard chemotherapy for GTD should be performed, and β-HCG closely monitored.

Disclosure of conflict of interest

None.

Address correspondence to: Haiyan Shi, Department of Pathology, The Affiliated Women's Hospital, School of Medicine, Zhejiang University, 2 Xueshi Road, Hangzhou 310006, Zhejiang Province, PR China. Tel: 86-571-89991702; Fax: 86-571-87061878; E-mail: haiyan_shi123@sina.com

References

[1] Ngan HY, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK and Lurain JR. Update on the diagnosis and management of gestational trophoblastic disease. Int J Gynaecol Obstet 2015; 131 Suppl 2: S123-S126.

[2] Mazur MT and Kurman RJ. Gestational trophoblastic disease. In: Kurman RJ, editor. Blaustein's Pathology of the Female Genital Tract. 6th edition. New York: Springer; 2010. pp. 1075-1135.

[3] Shin IM and Kurman RJ. Epithelioid trophoblastic tumor: a neoplasm distinct from choriocarcinoma and placental site trophoblastic tumor simulating carcinoma. Am J Surg Pathol 1998; 22: 1393-1403.

[4] Scott EM, Smith AL, Desouki MM and Olawaiye AB. Epithelioid trophoblastic tumor: a case report and review of the literature. Case Rep Obstet Gynecol 2012; 2012: 862472.

[5] Zhang X, Lü W and Lü B. Epithelioid trophoblastic tumor: an outcome-based literature review of 78 reported cases. Int J Gynecol Cancer 2013; 23: 1334-1338.

[6] Kuo KT, Chen MJ and Lin MC. Epithelioid trophoblastic tumor of the broad ligament: a case report and review of the literature. Am J Surg Pathol 2004; 28: 405-409.

[7] Urabe S, Fujiwara H, Miyoshi H, Arihiro K, Soma H, Yoshihama I, Mineo S and Kudo Y. Epithelioid trophoblastic tumor of the lung. J Obstet Gynaecol Res 2007; 33: 397-401.

[8] Parker A, Lee V, Dalrymple C, Valmadre S and Russell P. Epithelioid trophoblastic tumour: report of a case in the fallopian tube. Pathology 2003; 35: 136-140.

[9] Khunamornpong S, Settakorn J, Sukpan K, Suprasert P and Siriaunkgul S. Ovarian involvement of epithelioid trophoblastic tumor: a case report. Int J Gynecol Pathol 2011; 30: 167-172.

[10] Fromowitz FB, Viola MV, Chao S, Oravez S, Mishriki Y, Finkel G, Grimson R and Lundy J. ras p21 expression in the progression of breast cancer. Hum Pathol 1987; 18: 1268-1275.

[11] Allison KH, Love JE and Garcia RL. Epithelioid trophoblastic tumor: review of a rare neoplasm of the chorionic-type intermediate trophoblast. Arch Pathol Lab Med 2006; 130: 1875-1877.

[12] Coulson LE, Kong CS and Zaloudek C. Epithelioid trophoblastic tumor of the uterus in a postmenopausal woman: a case report and review of the literature. Am J Surg Pathol 2000; 24: 1558-1562.

[13] Palmer JE, Macdonald M, Wells M, Hancock BW and Tidy JA. Epithelioid trophoblastic tumor: a review of the literature. J Reprod Med 2008; 53: 465-475.

[14] Hamazaki S, Nakamoto S, Okino T, Tsukayama C, Mori M, Taguchi K and Okada S. Epithelioid trophoblastic tumor: morphological and immunohistochemical study of three lung lesions. Hum Pathol 1999; 30: 1321-1327.

[15] Macdonald MC, Palmer JE, Hancock BW and Tidy JA. Diagnostic challenges in extrauterine epithelioid trophoblastic tumours: a report of two cases. Gynecol Oncol 2008; 108: 452-454.

[16] Noh HT, Lee KH, Lee MA, Ko YB, Hwang SH and Son SK. Epithelioid trophoblastic tumor of paracervix and parametrium. Int J Gynecol Cancer 2008; 18: 843-846.

[17] Lewin SN, Aghajanian C, Moreira AL and Soslow RA. Extrauterine epithelioid trophoblastic tumors presenting as primary lung carcinomas: morphologic and immunohistochemical features to resolve a diagnostic dilemma. Am J Surg Pathol 2009; 33: 1809-1814.

[18] Chohan MO, Rehman T, Cerilli LA, Devers K, Medina-Flores R and Turner P. Metastatic epithelioid trophoblastic tumor involving the spine. Spine (Phila Pa 1976) 2010; 35: E1072-E1075.

[19] Ahn HY, Hoseok I, Lee CH, Jung YJ, Shin NR, Kim KH, Lee MK, Kim YD and Cho JS. Pulmonary mass diagnosed as extrauterine epithelioid trophoblastic tumor. Thorac Cardiovasc Surg 2013; 61: 97-100.

[20] Kim JY, An S, Jang SJ and Kim HR. Extrauterine epithelioid trophoblastic tumor of lung in a 35-year-old woman. Korean J Thorac Cardiovasc Surg 2013; 46: 471-474.

[21] Zhao J, Xiang Y, Zhao D, Ren T, Feng F and Wan X. Isolated epithelioid trophoblastic tumor of the vagina: a case report and review of the lit-

erature. Onco Targets Ther 2013; 6: 1523-1526.
[22] Park SY, Park MH, Ko HS, Cha EJ, Sohn JS and Kim CJ. Epithelioid trophoblastic tumor presenting as an ovarian mass in a postmenopausal woman. Int J Gynecol Pathol 2014; 33: 35-39.
[23] Fénichel P, Rouzier C, Butori C, Chevallier P, Poullot AG, Thyss A and Mouroux J. Extragestational βHCG secretion due to an isolated lung epithelioid trophoblastic tumor: microsatellite genotyping of tumoral cells confirmed their placental origin and oriented specific chemotherapy. J Clin Endocrinol Metab 2014; 99: 3515-3520.
[24] Arafah MA, Tulbah AM, Al-Husaini H, Al-Sabban M, Al-Shankiti H and Al-Badawi IA. Extrauterine epithelioid trophoblastic tumor arising in the ovary with multiple metastases: a case report. Int J Surg Pathol 2015; 23: 339-344.
[25] Shen X, Xiang Y, Guo L, Ren T, Feng F, Wan X and Xiao Y. Analysis of clinicopathologic prognostic factors in 9 patients with epithelioid trophoblastic tumor. Int J Gynecol Cancer 2011; 21: 1124-1130.
[26] Fadare O, Parkash V, Carcangiu ML and Hui P. Epithelioid trophoblastic tumor: clinicopathological features with an emphasis on uterine cervical involvement. Mod Pathol 2006; 19: 75-82.
[27] Qin J, Ying W, Cheng X, Wu X, Lu B, Liang Y, Wang X, Wan X, Xie X and Lu W. A well-circumscribed border with peripheral Doppler signal in sonographic image distinguishes epithelioid trophoblastic tumor from other gestational trophoblastic neoplasms. PLoS One 2014; 9: e112618.
[28] Parker A, Lee V, Dalrymple C, Valmadre S and Russell P. Epithelioid trophoblastic tumour: report of a case in the fallopian tube. Pathology 2003; 35: 136-140.
[29] Ohira S, Yamazaki T, Hatano H, Harada O, Toki T and Konishi I. Epithelioid trophoblastic tumor metastatic to the vagina: an immunohistochemical and ultrastructural study. Int J Gynecol Pathol 2000; 19: 381-386.
[30] Zavadil M, Feyereisl J, Safár P and Pán M. [Malignant trophoblastic tumors (MTT) treated in the years 1955-2004 in trophoblastic disease center in the Czech Republic (TDC-CZ): clinical-pathological features, curability, typing, pathogenesis]. Ceska Gynekol 2004; 69 Suppl 1: 9-15.

Supplementary Table 1. Immunohistochemical antibody data

Name of antibody	Lot number	Reactivity to human and dilution	Manufacturer	Manufacturer location
p63	4892	1:150	Cell signaling technology	Danvers, MA, USA
Cytokeratin-pan	[AE1/AE3] (ab27988)	1:20	Abcam	Cambridge, MA, USA
CK18	ab82254	1-2 μg/ml	Abcam	Cambridge, MA, USA
Inhibin-α	[4A2F2] (ab47720)	1:200	Abcam	Cambridge, MA, USA
CD10	EPR 5904	1:200	Abcam	Cambridge, MA, USA
HCG-β	[5H4-E2] (ab9582)	1:100	Abcam	Cambridge, MA, USA
CD146	[P1H12] (ab110142)	20 μg/ml	Abcam	Cambridge, MA, USA