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Case Report

Epithelioid trophoblastic tumor

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ABSTRACT

Objective: To describe a case of epithelioid trophoblastic tumor (ETT) in a postmenopausal woman, which had several peculiar features that differentiate it from previously reported ETTs.
Case report: ETT of the uterus is a rare form of trophoblastic tumor with only 100 cases distinguished until now. Our case differs from the previously reported ones due to its several exceptional features. Our patient had no history of trophoblastic or gynecological disease; is postmenopausal; had endocervical extension from the beginning; recurrences and metastasis at follow up; and had a high Ki-67 index and a normal beta-human chorionic gonadotropin value.
Conclusion: Because precise differential diagnosis will alter the therapeutic approach and prognosis, it is necessary for treating physicians to be aware of these unusual presentations.

Introduction

Gestational trophoblastic disease (GTD) is a term used for a group of tumors including complete and partial hydatidiform mole, invasive mole, choriocarcinoma (CC), placental site trophoblastic tumor (PSTT), exaggerated placental site (EPS), placental site nodule (PSN), and epithelioid trophoblastic tumor (ETT) [1]. ETT, the most recent addition to GTD, is an uncommon but unique proliferative lesion whose features mimic those of squamous-cell carcinoma (SCC) [2,3]. To date, less than 100 cases of ETT have been reported in the literature [4,5].

The histological characteristics of ETT were first described by Mazur in 1989, although he used the term “atypical CC.” Later, the term “ETT” was coined by Shih and Kurman in 1998 [2,6] for neoplasms composed of chorionic-type intermediate-trophoblast cells (ITCs) [2,6–8]. This term then became widely accepted and was eventually added to the latest 2003 World Health Organization classification of uterine corpus tumors [3]. In this paper, we present a case of ETT, which had several peculiar features that differentiate it from previously reported ETTs.

Case report

A 47-year-old woman (gravida 5, para 5, live 4) whose last child was born 16 years ago and who is postmenopausal for 11 years presented with distension and abdominal pain. She had no history of dilatation and curettage (D&C), trophoblastic disease (TD), or gynecological complaints. An intrauterine collection was discovered and a D&C was performed. Histological examination revealed epithelioid-type atypical cell proliferation. Subsequently, total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. Her uterus measured 8 cm × 6 cm × 5 cm and had an irregular endometrial surface due to whitish tumoral lesions with locally irregular borders, the largest of which measured 3.5 cm × 2 cm × 2 cm. The lesions were expansive, locally infiltrating the myometrium, and extending to the endometrial cavity and endocervical canal. In hematoxylin/eosin sections, a tumor was recognized, and was found to be composed of pleomorphic epithelioid-like cells with a large single vesicular nucleus and moderately or large eosinophilic or clear cytoplasm. The cells formed nests or solid islands, and in the center of tumor nests there was an area of hyalinization or eosinophilic debris of tumor cell

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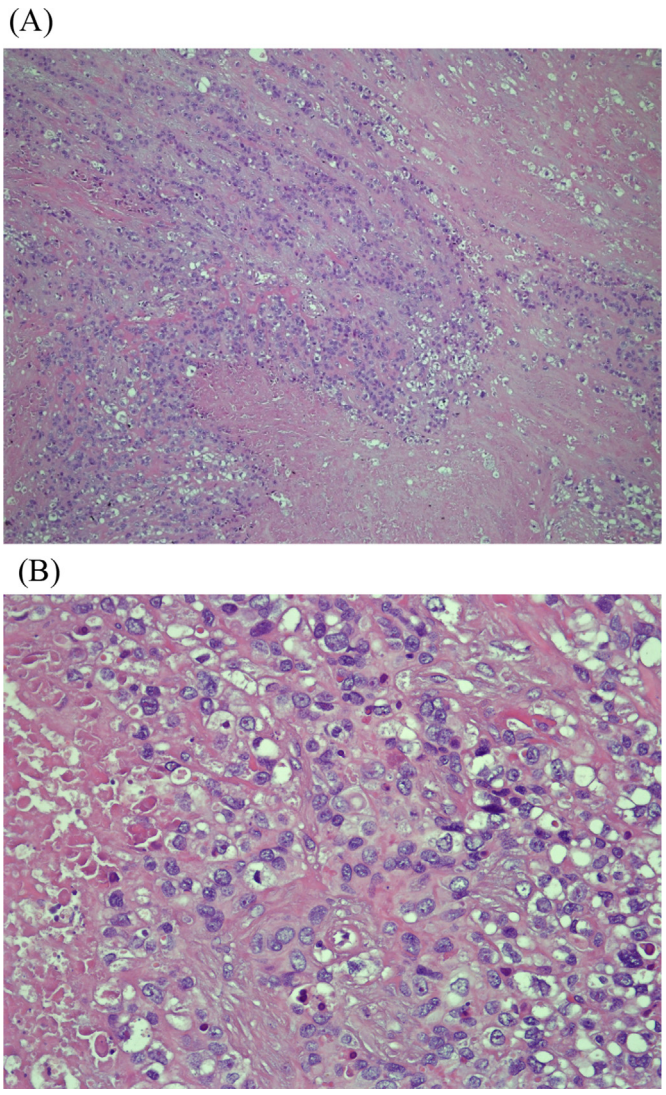

Figure 1. Expansive tumor infiltrating the myometrium. (A) The tumor is composed of pleomorphic epithelioid-like cells with areas of hyalinization and necrosis [hematoxylin/eosin (HE) 100×]. (B) The tumor is composed of pleomorphic epithelioid-like cells with a large single vesicular nucleus and moderately or large eosinophilic or clear cytoplasm (HE 400×).

necrosis (Figure 1A and B). Although ETT or intermediate-trophoblast-derived tumor was the most likely diagnosis, epithelial malignancies and epithelioid malignant smooth muscle tumor (ESMT) were not ignored. The findings of immunohistochemical (IHC) analysis are presented in Table 1 and Figure 2. Based on all the findings, the patient was diagnosed as a case of ETT. In laboratory examinations, beta-human chorionic gonadotropin level (5.09 mIU/mL) and tumor markers [carcinoembryonic antigen, 1.34 ng/mL; carbohydrate antigen (CA) 125, 16.01 U/mL; CA 15-3, 25.68 U/mL; alpha-fetoprotein, 1.41 ng/mL; and CA 19-9, 0.915 U/mL] showed no abnormality. The patient preferred to receive only surgical therapy. During subsequent hospital visits, recurrences and metastasis occurred (4 years and 5 years later, respectively; Figure 3). The new lesions showed the same histopathological and IHC characteristics of the initial tumor. The detailed clinicopathologic features of the tumor are presented in Table 2.

Discussion

ETT is an unusual type of trophoblastic tumor with antecedent gestational events such as full-term deliveries, spontaneous abortions, and hydatidiform moles. The interval between the preceding gestation and the diagnosis of ETT ranges from 1 year to 18 years (average 6.2 years) [7]. Although mostly seen in patients between 15 years and 48 years of age (average 36.1 years) [2], it has occasionally been described in patients in the postmenopausal age as well [9,10]. Abnormal vaginal bleeding is the most common symptom observed in ETTs [2]. Like PSTs, serum beta-human chorionic levels are nearly always elevated at the time diagnosis, although the levels are generally low (<2,500 mIU/ml) compared with those in patients with choriocarcinoma [2].

In literature, tumor sizes varied from 0.5 cm to 4.0 cm, the cut surface is either solid or cystic, and focal infiltrative features may be seen at the periphery [1]. The tumor cells are typically arranged in nests, cords, and masses of cells that are intimately associated with an eosinophilic, fibrillar, hyaline-like material [1]. Neoplastic cells are small and epithelioid with eosinophilic cytoplasm [9].

ETT has IHC expression of markers seen in normal chorionic-type ITCs. There is diffuse expression of cytokeratin (CK) (AE1/AE3), CK18, epithelial membrane antigen, and p63 [11]. p63 has recently been demonstrated as a useful aid for differentiating between chorionic-type ITCs and implantation-type ITCs [11]. ETTs are positive for inhibin-alpha, with positive cells ranging from 20% to 80%. Human placental lactogen (hPL), human chorionic gonadotropin (hCG), and Mel-CAM (CD146) are only focally expressed [1].

The mitotic index varies from 0 mitoses/high-power field to 9 mitoses/high-power field [2]. The mean Ki-67 labeling index in ETTs is 17.7 ± 4.5% [1]. Histologic features to predict outcome are not well established, however, some have suggested an association between high mitotic index and more aggressive behavior [5].

ETT can occur in the uterine tissues as well as in the surrounding or distant organs [2]. There are reports of ETT arising in the broad ligament and fallopian tube, paracervix, parametrium, periadnexal soft tissue, and ovary [12–14]. The morphologic and IHC features of extrauterine ETTs are similar to those placed in the uterus [1].

For ETT, metastasis and death occur in approximately 25% and 10% of patients, respectively [2]. It is reported that ETT can metastase to the lung as well as to the tissues such as brain, tonsil, and pelvic lymph node [15].

For differential diagnosis, SCC and PSTT are the most important cases to be kept in mind. The hyaline matrix and necrosis can resemble keratin, and ETT can grow along the surface of the cervix, similar to cervical SCC [5]. In differential diagnosis, almost all ETTs are positive for inhibin-alpha and CK18, whereas SCC of the cervix is negative for these two markers [2]. Furthermore, unlike ETT, cervical SCC almost invariably has a very high Ki-67 labeling index (>50%) [1]. PSTT is differentiated from ETT by its very infiltrative growth pattern, prominent vascular invasion, and slightly larger implantation site-type ITCs. PSTT are more diffusely positive for hPL and Mel-CAM, and lack p63 expression [1]. Although seldom

Table 1
Immunohistochemical features of the case.

CK	CK 18	Beta-human chorionic gonadotropin	Inhibin	Placental alkaline phosphatase	E-cadherin	p63	Human placental lactogen	Desmin and actin
+	+	Focal +	Focal +	–	+	+	–	–

CK = cytokeratin.

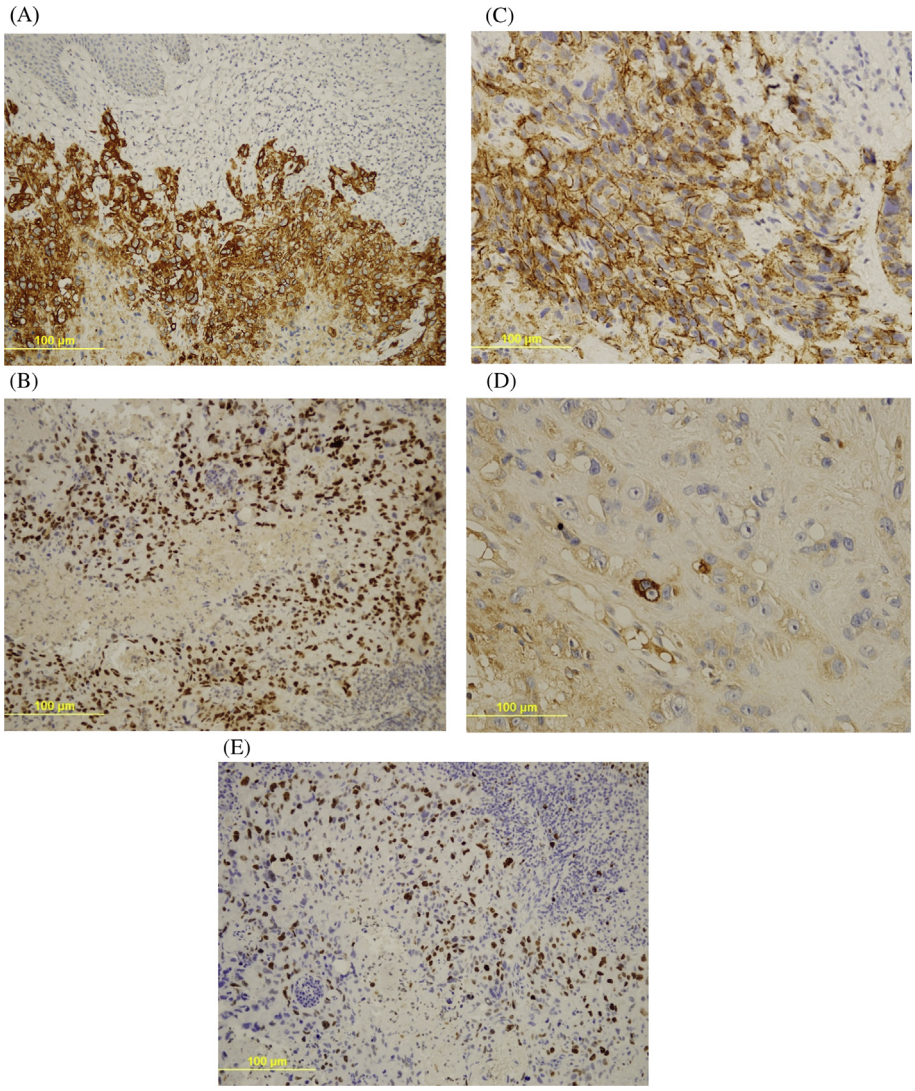

Figure 2. Immunohistochemical features of the epithelioid trophoblastic tumor (ETT). (A) Diffuse CK18 positivity (200×). (B) Nuclear p63 expression (200×). (C) Diffuse E-cadherin positivity (400×). (D) Beta-human chorionic gonadotropin was focally positive in ETT (400×). (E) High Ki-67 index (200×). CK = cytokeratin.

confused, PSN, EPS, and ESMT also should be taken into account. The low serum β-hCG levels, benign behavior in most instances, and the failure to respond to conventional chemotherapy are the characteristic features of ETT [2].

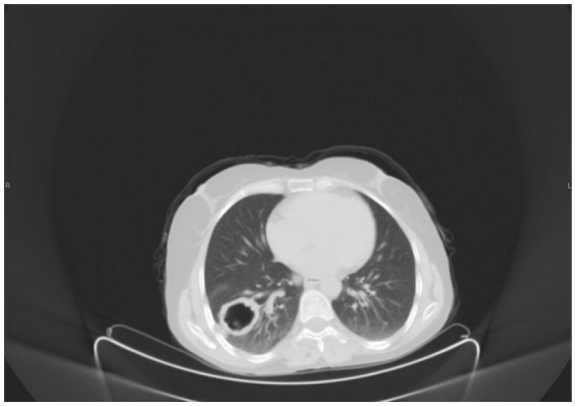

Figure 3. At spiral computerized tomography of the thorax, a large cavitary lesion measuring 5.5 cm × 4.4 cm × 4.3 cm on the costal pleura with thin borders and septations was found at the right lung laterobasal segment.

A literature review for ETT revealed that our case has certain inconsistent features worth mentioning. First, in contrast to most of the previous reports, our patient was a 47-year-old postmenopausal woman. In addition, she had no history of TD or D&C. Admission to hospital with abdominal pain and distension instead of presenting with a gynecological complaint was another diversity. Furthermore, the serum β-hCG level was very close to the normal level and it continues to be normal. In addition, mitotic counts and Ki-67 rates were relatively high. Not surprisingly, and in accordance with some reports that suggested an association between high mitotic index and more aggressive behavior [5], recurrence had occurred after the first operation. Unfortunately, a lung metastasis appeared at the 4^{th} year. Although the level of β-hCG was low, a benign behavior was not observed.

ETT is an extremely infrequent tumor, seen mostly in the reproductive age and is associated with GTD. The diagnosis of ETT can usually be made on morphological grounds. However, one should be aware that it can also be present in postmenopausal women and without a history of GTD. Thus, accurate differential diagnosis would properly guide therapy and change prognosis.

Table 2
Clinicopathologic features of the case.

Period	Symptoms and signs	Procedure	Level of β-hCG (mIU/mL)[a]	MC 10/high-power field	Ki-67 index (%)	Histopathologic diagnosis
May 2007	Epithelioid-type atypical cell proliferation in D&C	TAH and BSO	5.09	6–7	38	ETT
July 2011	Lesion in the vagina and below the abdominal incision line	Excisional biopsy	5.25	1–2 and 7–8, respectively	50 and 50, respectively	ETT (recurrence)
December 2011	Dyspnea; in PET/CT, a lesion in the right lung inferior lobe laterobasal segment with a central cavern	Transthoracic fine-needle biopsy	48.98	—	—	Epithelioid-type atypical cells
March 2012	Lesion in the vaginal cuff	Excisional biopsy	14.26	9–10	45	ETT (recurrence)
March 2012	Lesion in the right lung	Lobectomy	16.20	7–8	20	ETT (metastasis)

BSO = bilateral salpingo-oophorectomy; D&C = dilatation and curettage; ETT = epithelioid trophoblastic tumor; MC = mitotic count; PET/CT = positron emission tomography/computed tomography; TAH = total abdominal hysterectomy; β-hCG = beta-human chorionic gonadotropin.
[a] Normal range for β-hCG: 5–50 mIU/mL.

Therefore, it is critical for physicians to be aware of the distinct presentations.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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