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Case report

An incidentally diagnosed epithelioid trophoblastic tumor in hysterectomy

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Key words

Gestational trophoblastic disease • Epithelioid trophoblastic tumor • Immunohistochemistry • Placental site nodule • Differential diagnosis

Summary

Epithelioid trophoblastic tumor is a rare non-molar gestational trophoblastic disease. A 40-year-old multiparous woman was incidentally diagnosed with epithelioid trophoblastic tumor after hysterectomy. Hysterectomy specimen revealed multiple small, tan to yellow nodules measuring 0.3-0.8 cm just below the endometrium. In the microscopic examination uniform neoplastic cells with varying cellularity were accompanied by necrotic zones and eosinophilic hyaline material. Immunohistochemically neoplastic cells were diffusely stained with CK 7, inhibin-alpha, p63, hPL, and CD146. There was no staining with beta-HCG, SMA, PLAP, or h-caldesmon. Ki-67 proliferative index was approximately 10 % and cyclin E was stained in approximately 10 % of the neoplastic cells. Although immunohistochemical studies are helpful in classifying gestational trophoblastic lesions, borderline values can cause diagnostic confusion between neoplastic and reactive lesions, particularly in inadequate endometrial biopsies.

Introduction

Gestational trophoblastic diseases can be categorized into molar and non-molar lesions. Molar lesions are complete hydatidiform, partial hydatidiform mole and invasive mole. In contrast, exaggerated placental site (EPS), placental site nodule (PSN), choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) are non-molar lesions [1]. The PSN and EPS are benign non-neoplastic trophoblastic lesions of intermediate trophoblasts, whereas the ETT and PSN are malignant lesions arising from intermediate trophoblasts.

Since the initial description by Shih and Kurman in 1998, only less than 100 cases of epithelioid trophoblastic tumor (ETT) were reported in the literature [2 3]. Pathogenesis of these trophoblastic lesions is not clear; however, previous studies suggested that the PSN and ETT arise from chorionic intermediate trophoblasts, and the PSTT and EPS arise from implantation site trophoblasts. Since the PSN and ETT share a common origin, it has been proposed that the PSN can be the precursor lesion of the ETT [4].

In the present study, a case of ETT incidentally diagnosed after hysterectomy is reported. The case had common morphologic features with PSN and common immunohistochemical features with PSTT. We discussed the value of immunohistochemistry in differential diagnosis and pathogenesis of ETT.

Case report

A 40-year-old multiparous (G5P5) woman was admitted to our outpatient clinic with symptoms of chronic pelvic pain and intermittent vaginal spotting. She had been suffering from spotting for 5 months. Her last delivery was uncomplicated after full term pregnancy 2 years ago. Gynecologic examination revealed an enlarged uterus in three month-gestational size and the ultrasonography

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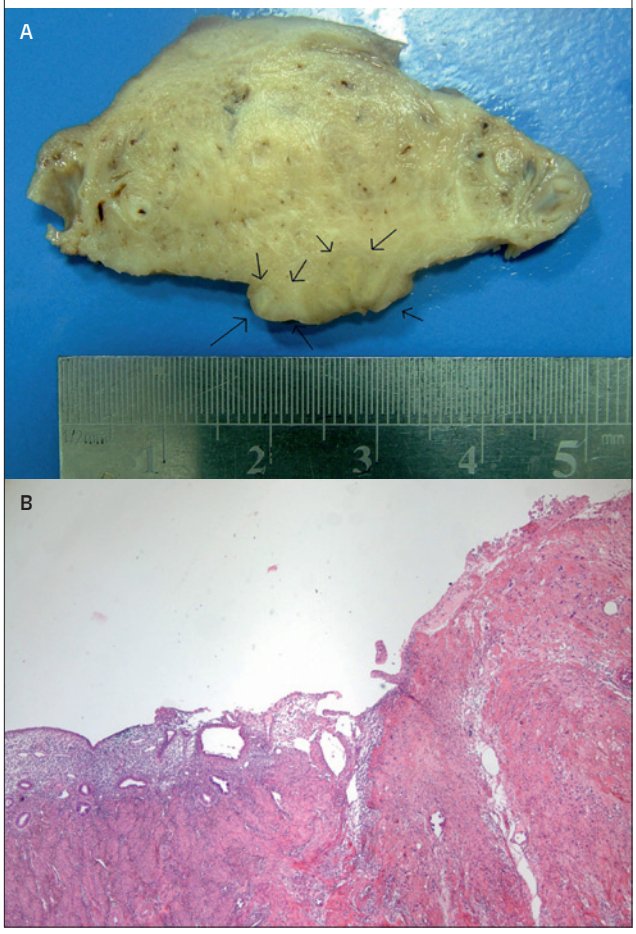


Fig. 1. A) Small, tan to yellow nodules can be seen just below the endometrium in the uterine corpus. **B)** Microscopic appearance of the tumor; myometrial invasion and the relation of the tumor with the endometrium can be seen.

showed multiple intramural leiomyomas ranging from 2 to 3 cm in diameter. The serum β-hCG level was not determined preoperatively. Since the patient reported failure of medical therapy to alleviate her symptoms, surgical intervention was planned. The patient underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Hysterectomy specimen was measured 160 grams with dimensions of 15x10x5 cm. The macroscopic evaluation revealed multiple small, tan to yellow nodules measuring 0.3-0.8 cm, localized to a certain area in the uterine corpus without any relation to endocervix. These tumor nodules were in the endometrium and the tumor superficially invaded the myometrium (Fig. 1A). Microscopic appearance of the tumor and the relation of the neoplasm with the endometrium and myometrial invasion can be seen in Figure 1B. Endometrial thickness was 0.1 cm and multiple intramural leiomyomas were also recorded. No other pathology was observed in the uterus or the ovaries.

In the microscopic evaluation, there were varying sizes of nodules consisting of large uniform polygonal cells with mononucleated eosinophilic cytoplasms (Fig. 2A-C). Uniform neoplastic cells with a clear cytoplasm and a few multinucleated neoplastic cells were also present. Most of the nodules were found to be highly cellular; however, some were less cellular (Fig. 2C). Nodules generally had a well-delineated pushing border (Fig. 2A), but focal infiltrating zones between smooth muscles were also present. Large necrotic zones and eosinophilic hyaline material were accompanying the lesion (Fig. 2B). Mitotic activity was less than 1 in 10 HPF and there was no lympho-vascular invasion. Although lesions were localized in the endometrium, superficial myometrial invasion was also present (Fig. 2A).

Morphologic features resembled intermediate trophoblastic lesions as well as an epithelioid leiomyoma. In the immunohistochemical studies, neoplastic cells were diffusely stained with CK 7 (invitrogen 1/75), inhibin-alpha (Novocastra 1/100), p63 (Biocare 1/100), hPL (Therma 1/250), and CD146 (Mel- CAM) (Novo 1/20). There was no staining with beta-HCG (Therma

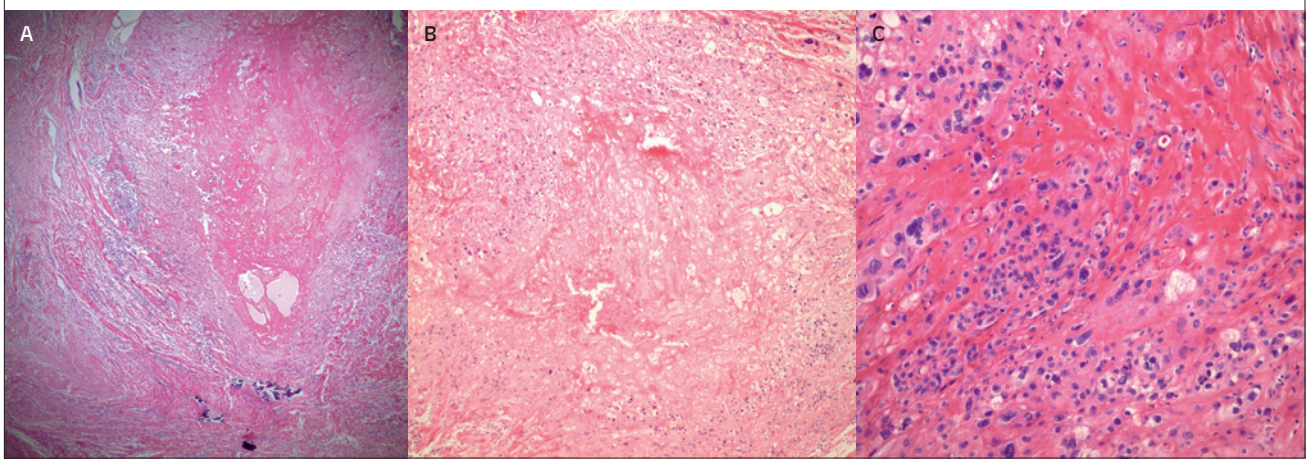
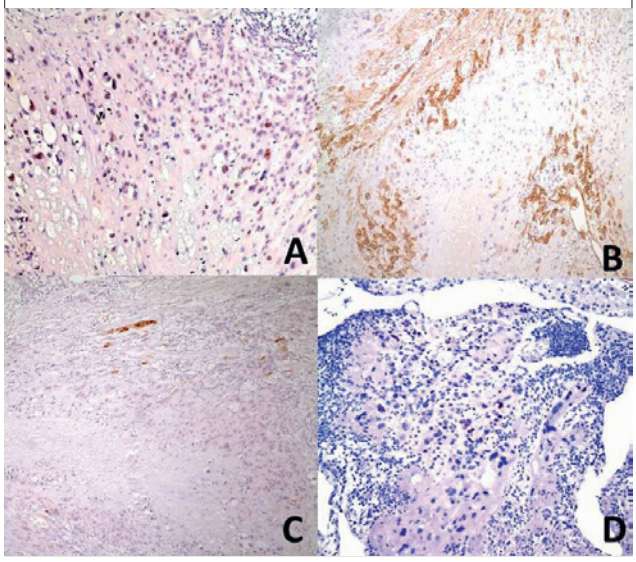


Fig. 2. A) Nodular myometrial infiltration had a central hyalinized and necrotic foci. Nodule had a well circumscribed pushing border and calcification accompanied the lesion. **B)** Necrosis accompanying the neoplastic cells also supported the diagnosis. **C)** Most of the nodules were highly cellular.

Fig. 3A-D. Neoplastic cells showed diffuse positivity with p63 (Fig. 3A), patchy positive staining with CD146 (Mel-CAM) (Figure 3B), focal staining with HPL (Fig. 3C) and cyclin E (Fig. 3D) with immunohistochemistry.



1/50), SMA (Therma 1/800), PLAP (Therma 1/40), or h-caldesmon (Therma 1/100). Ki-67 (Therma 1/1000) proliferative index was approximately 10% and cyclin E (Neomarkers 1/40) was stained in approximately 10% of the neoplastic cells (Fig. 3 A-D). The histopathological diagnosis was reported to be epithelioid trophoblastic tumor of the uterus.

The patient showed an uneventful recovery after the surgery and was discharged from the hospital on the 3rd postoperative day. Following the availability of final pathological diagnosis, the patient underwent a clinical re-staging procedure including computed tomography of the chest and the abdomen. No evidence of metastasis was observed. The postoperative level of serum β-hCG was also negative. The patient was advised to have a close follow-up. The patient is still alive after 2 years of surgical therapy without any evidence of the disease.

Discussion

Epithelioid trophoblastic tumor is a very rare pathological entity with limited number of reported cases in the literature [3]. Most of the reported cases are in reproductive period and commonly present with vaginal bleeding [3]. The age of the patients is between 15 and 48 years with a mean of 36.1 years. Tumor mostly ensues after a full term pregnancy. It can also follow spontaneous abortion and hydatidiform mole [3]. The presented patient was in late reproductive years and multiparous. She had the symptoms of pelvic pain and vaginal spotting similar with the cases reported in the literature. The gestational event that may be related to the development epithelioid trophoblastic tumor was a full term pregnancy 2 years ago. The interval between the gestational event and the development of the tumor was reported 1-18 years with a mean 6.2 years in previous studies [3 5].

Serum human chorionic gonadotropin levels are usually elevated in the epithelioid trophoblastic tumor, but in contrast to choriocarcinoma, levels generally do not exceed 2,500 mIU/mL [1]. An increased preoperative β-hCG level can be a predictor of a large tumoral mass [5]. However, preoperative value of β-hCG was not available in the presented case. Since the tumoral lesion was in microscopic size at pathological examination, an increased level of β-hCG was not expected. Although macroscopic examination of the hysterectomy specimen is very important for small focal ETTs, the case we presented here had macroscopic small, unremarkable tumor nodules located in the uterine corpus. Incidental tumor nodules can easily be overlooked without careful inspection.

The ETT is composed of mononuclear intermediate trophoblasts and has a nodular proliferation pattern. Although the intermediate cells of the tumor containing eosinophilic, hyaline-like material and necrotic debris that form nests and cords is characteristic [3], microscopic features can resemble a squamous cell carcinoma or an epithelioid leiomyoma. Immunohistochemistry can be very helpful for the differential diagnosis in most cases [6]. Epithelioid trophoblastic tumors are positive for immunohistochemical markers such as cytokeratins, epithelial membrane antigen, hPL, p63, and also inhibin-alfa [7]. In our case, the immunohistochemical staining resulted in diffuse positivity with inhibin, CK7, and p63; and focal staining with hPL and CD146. This result proves the trophoblastic nature of the lesion, and points the chorionic intermediate trophoblasts as the origin.

The PSN is supposed to be the precursor lesion of the ETT and has similar morphologic and immunohistochemical features with ETT. Sometimes it can be hard to differentiate these two lesions [4]. Placental site nodule do not contain necrosis, it is less cellular with sharp borders and has a low proliferative index which is generally < 10% [8]. Epitheloid trophoblastic tumors usually have a Ki-67 index between 10% and 25% [5]. The presented case had both morphologic and immunohistochemical features indicating both an ETT and a PSN. Having cellular large nodules with tumor cells infiltrating the myometrium with focal calcifications supported the ETT diagnosis. Sometimes cyclin E can be helpful for the differential diagnosis of PSN and ETT [4]. Although, our case had characteristic morphologic fetaures for ETT showing cellular large nodules with tumor cells infiltrating the myometrium with focal calcifications and necrosis, immunohistochemical studies showed borderline values for Ki-67 and cyclin E. The pathologist must be aware of the variability of these markers, particularly when working on inadequately small endometrial biopsies. The other related issue is a new entity called 'atypical epithelioid trophoblastic lesion' which was described for lesions that have borderline microscopic Ki-67 and cyclin E features between PSN and ETT [4 9]. Although some suggestions exist that the ETT can develop from a placental site nodule [4 9], all nodules observed in the pre-

sented case were larger than the nodules seen in the PSN and showed the characteristic features of ETT.

Epitheloid trophoblastic tumors are generally benign in nature, and hysterectomy or local excision of the tumor can be the sufficient treatment. Chemotherapeutic agents used for the treatment of other GTDs may not be useful for the treatment of ETTs, but the rates of metastasis and death are 25% and 10%, respectively [10]. Lung, liver and vagina are the three most common metastatic organs [2]. Multifocal disease in uterus, serosal involvement, necrosis, high mitotic index, cytologic atypia, and vascular invasion are all signs of a poor prognostic, metastatic ETT [11]. In our patient the mitotic index and Ki-67 index were low, and the β-hCG level was negative after hysterectomy; and the evaluation of the patient postoperatively revealed no metastasis on computed tomography.

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