Epithelioid trophoblastic tumor in a postmenopausal woman: A case report and review of the literature in the postmenopausal group

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ABSTRACT

Epithelioid trophoblastic tumor is a rare gestational trophoblastic neoplasm arising from the intermediate trophoblasts. Although usually seen in the reproductive period, it may be encountered during the postmenopausal period. A 56-year-old woman who had given her last birth 21 years ago presented to the hospital with a complaint of postmenopausal bleeding. She had a history of eight live pregnancies and had been in menopause for 4 years. With the help of typical histopathologic and immunohistochemical findings, a diagnosis of “epithelioid trophoblastic tumor” was made. The diagnosis was made at an advanced age and the case had extraordinary features such as high mitotic activity and Ki-67 proliferation index (70%). Gestational trophoblastic neoplasms are rare causes of postmenopausal bleeding which may cause differential diagnosis problem. They should be kept in mind even if the patient age does not comply with because of the differences in treatment.

KEY WORDS: Epithelioid trophoblastic tumor, postmenopause, uterus

INTRODUCTION

Epithelioid trophoblastic tumor (ETT) is a rare gestational trophoblastic neoplasm arising from the intermediate trophoblasts (ITs). ETT was first described in 1998 as a distinct entity from placental site trophoblastic tumor (PSTT) and choriocarcinoma. It is usually seen in the reproductive period and is rare in the postmenopausal period. In this article, a case of ETT in a postmenopausal patient who had her last birth 21 years ago is presented with clinical and pathological features.

CASE PRESENTATION

A 56-year-old woman presented to the hospital in January 2017 with a complaint of postmenopausal bleeding. The patient was gravida 8, para 8, and had her last birth 21 years ago. She had been in menopause for 4 years. She also had a history of lentigo maligna of the facial skin from October 2016. Abdominal ultrasonography revealed a lesion of 4 cm in diameter posterior to the uterus. Serum β-hCG level was detected as 80.9 mU/mL. The result of the probe curettage was evaluated as proliferative endometrium. The patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO). The macroscopic examination revealed a white-yellow, soft, rubbery, and smooth lesion of 4.5 × 4.5 × 3 cm on the right side of the corpus [Figure 1]. Microscopically, middle-sized, uniform, granular tumor cells with clear cytoplasm were observed in a nodular, solid, and occasional nested growth pattern. Eosinophilic hyaline-like material reminiscent of keratinization in the center of tumor nests and in between tumor cells and geographic necrosis in some areas were noticed [Figure 1]. Mitotic activity was 27/10 high power fields (HPFs). Tumor thrombi were observed in vascular structures. Immunohistochemically, tumor cells stained positive with cytokeratin AE1/AE3, cytokeratins 8/18, 19, 7, CD10, p63 and hCG, focally positive with epithelial membrane antigen (EMA) and inhibin, and negative with PAX-2, PAX-8, vimentin, cytokeratin 5/6, hPL.
and malignant melanoma markers [Figures 2 and 3]. Ki-67 proliferation index was 70%.

Histologically, even though the tumor resembled squamous cell carcinoma (SCC), it was ruled out because of cytokeratin 5/6 negativity and cytokeratin 8/18 positivity. The patient’s high level of serum β-hCG made to think whether it could be a tumor from the gestational trophoblastic disease group. Macroscopic and histological features were more suggestive of ETT and PSTT, which are derived from ITs. The expression of immunohistochemical markers p63 and CD10, in particular, made us diagnose this case as “epithelioid trophoblastic tumor” which originates from chorionic-type ITs.

The cervix, endometrium, and bilateral adnexa appeared normal. Serum β-hCG level decreased after surgery. The patient received four cycles of paclitaxel cisplatin and paclitaxel etoposide, and the treatment was stopped after bilateral forearm thrombophlebitis developed. No recurrence or metastasis was found in the thoracoabdominal computed tomography performed 8 months after the surgery. The patient is still alive and has been disease-free for 19 months.

DISCUSSION

Gestational trophoblastic diseases include mole hydatidiform, choriocarcinoma, PSTT, and ETT. ETT and PSTT originate from ITs. ETT arises from chorionic-type ITs and PSTT arises from implantation-site ITs.[4,5] ETT is the disease of reproductive period, and the average age is reported as 36.1.[6] However, seven cases have been reported in the postmenopausal period and one of them is localized in the ovary.[4,5,7-9] In the postmenopausal group, the age ranges from 47 to 75 and the average age is reported to be 59.2 in the literature and our case is 56 years old. The most common symptom is vaginal bleeding.[3,10] ETT may be seen right after the pregnancy, whereas it may also be seen after spontaneous abortus and mole hydatidiform.[3,5] The serum β-hCG level is generally high before the operation as our case but never reaches the levels in choriocarcinoma. The preoperative clinical diagnosis is usually leiomyoma and sometimes may be carcinoma, especially in cases that are localized to cervix. For this reason, the patients usually undergo TAH+BSO±lymph node dissection. The clinical and pathological features of ETTs seen in the postmenopausal period are shown in Table 1.

Macroscopically, ETT is localized to lower uterine segment (LUS), endocervix, and uterine wall. It is usually well-circumscribed but sometimes focal infiltrative areas may be seen. The tumor size varies between 2 and 6.5 cm.[3,7] In our case, the tumor was intramurally located with the biggest diameter of 4.5 cm. Microscopical features of ETT include nodular growth pattern as in our case. The cells forming these nodules are monomorphic within hyaline-like matrix and they have eosinophilic or clear cytoplasm. Necrosis and apoptotic cells are frequently seen. Mitotic activity is usually between 0 and 9/10 HPFs; however, it was strikingly high in our case.[2,3] Immunohistochemically, cytokeratin AE1/AE3, cytokeratin 18, EMA, CD10, and inhibin are diffuse positive; β-hCG, hPL, PLAP, and Mel-CAM are focally
positive. Ki-67 proliferation index is reported to be around 10–25% and there are also some cases reported with a high Ki-67 proliferation index as in our case. [6-8,10] The immunohistochemical features of the ETT cases seen in the postmenopausal period are listed in Table 2.

Keratinized SCC has an important role in the differential diagnosis, especially in LUS localized tumors. As in our case, among immunohistochemical indicators, cytokeratin 5/6 negativity and cytokeratin 18 positivity are critical in ruling out SCC. Other entities that should be considered in the differential diagnosis include PSTT, placental site nodule (PSN), and choriocarcinoma. In PSTT, p63 expression is absent whereas hPL and Mel-CAM expression is seen. PSN is well-circumscribed, very small in size, and has low cellularity, whereas ETT usually shows necrosis and is more cellular. Presence of 63 expression and hPL negativity led us to ETT diagnosis. In choriocarcinoma, hemorrhage and necrosis are conspicuous features besides dimorphic cell pattern. [3,5,6]

Differential diagnosis in gestational trophoblastic diseases is of great importance due to differences in treatment. The first treatment option for choriocarcinoma is chemotherapy, whereas in ETT and PSTT it is hysterectomy. Chemotherapy is preferred in metastatic or advanced disease. In ETT, metastasis is reported as 25% and the death rate as 10%. [10] High mitotic index and proliferation index are the parameters that affect prognosis. Our patient has been alive and disease-free for 19 months.

Here, a case of ETT localized in the uterine corpus seen in the postmenopausal period is presented. In conclusion, it should be kept in mind that gestational trophoblastic diseases such as ETT may rarely be seen in the postmenopausal period even though the patient age does not comply with, and they should be considered as one of the reasons for postmenopausal bleeding. Immunohistochemistry and distinct microscopical features are helpful in the differential diagnosis.

**Declaration of patient consent**
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**
There are no conflicts of interest.

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