Epithelioid trophoblastic tumor: a case report and literature review

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Abstract
Epithelioid trophoblastic tumor (ETT) is a very rare case of malignant trophoblastic tumor, which can occur particularly during the fertile age of women with a long history of abortion and delivery. ETT originates from the intermediate trophoblastic cells of chorion laeve. The main features of this tumor include lack of vessels within the tumor, nuclear hyperchromasia and pleomorphism and a large zone of necrosis and hyalinization. The clinical features of ETT are specific to each case and often consist of vaginal bleeding or amenorrhea in the absence of other complains. The beta-human chorionic gonadotropin (β-hCG) serum level cannot be an absolute criterion useful in defining diagnosis. The right diagnosis can only be established by a histopathological examination of the tissue picked-up via intrauterine curettage. This paper describes the case of a 35-year-old woman who required gynecological investigation for amenorrhea. The diagnosis established by biopic curettage and the clinical evolution have influenced the physician’s decision to perform hysterectomy. The only method to differentiate between the microscopic diagnosis of ETT and choriocarcinoma was the immunohistochemical staining of trophoblastic cells for cytokeratin AE1/AE3, p63, Ki67. Despite the diagnosis of malignity, this tumor does not usually require a recommendation for chemotherapy and does not seem to have a bad prognostic. However, these data do not rule out that clinical behavior is sometimes difficult to predict. We analyzed the clinical and histology criteria in line with the data published in literature.

Keywords: epithelioid trophoblastic tumor, choriocarcinoma, gestational trophoblastic disease.

Introduction

The foremost characteristic of gestational trophoblastic disease (GTD) consists in abnormal proliferation of the placental trophoblast. There are two different changes in the abnormal proliferation of placental trophoblast, which lead to the classification of GTD in two groups of lesions known as benign and malignant gestational diseases. The benign placental changes include three types of abnormal placental trophoblast, such as placental site nodule, exaggerated placental site and hydatidiform moles. There are different types of malignant trophoblastic diseases, known in the scientific literature review as gestational trophoblastic neoplasia, including: choriocarcinoma (CC), placental site trophoblastic tumor (PSTT), epithelioid trophoblastic tumor (ETT) and invasive mole (IM) that could not resolve spontaneously [1–3]. The GTD management is specific to each type of proliferative trophoblast disease and is endorsed by different types of follow-up programs.

Epithelioid trophoblastic tumor was first described by Shih, Mazur & Kurman, in 1998. These authors remarked that it is a rare gestational trophoblastic tumor, which grows from intermediate trophoblastic cells of chorion laeve [1]. The ETT has many clinical symptoms and usually the diagnosis is only established following the histopathological examination of the tumor tissue. Despite the diagnosis of malignity, this tumor does not usually require a recommendation for chemotherapy and does not seem to have a bad prognostic. However, these data do not rule out that clinical behavior is sometimes difficult to foresee. Tackling this topic has statistical and clinical significance, since there were only 94 cases displaying this pathology worldwide four years ago [4]. Establishing an accurate diagnosis based on morphological and immunohistological features allows to differentiate between non-neoplastic lesions and neoplastic lesions such as PSTTs and ETTs, which might become locally invasive or trigger metastases [5].

Case presentation
A 35-year-old woman – with two pregnancies that occurred 17 and 12 years ago, respectively, and two abortions, the last one having been performed 10 years ago – required a gynecological exam for menstrual period changes. This woman reported that she was worried because over the last six months menstrual bleeding progressively slowed down until it stopped three months ago. The woman told that she experienced neither the...
specific symptoms of pregnancy, nor pelvic discomfort. She did not describe any complain and confirmed that the pregnancy test was constantly negative during this interval.

The physical exam showed moderate cystocele and rectocele, cicatricial lesions of the cervix without exocervical changes, distinct bleeding or vaginal leukorrhea. The uterus was small in terms of width, had a steady shape, and no pain was experienced following the deep pressure applied to the pelvic region. Both uterine appendages were inspected with difficulty. The gynecological exam did not confirm the suspected presence of Douglas fluid.

The endovaginal ultrasound revealed endometrial changes. The endometrium features consisted of changes in the architectural shape, with a large region of mixed echogenicity oriented very close to the top of the uterus, so that the ultrasound scan revealed that the endometrium tumor reached a 2–3 mm proximity to the surface of the myometrium. The changes did not progress up to the endocervix. The ovaries were described as normal in size, showing a regular surface structure.

The laboratory analysis revealed normal serum levels of beta-human chorionic gonadotropin (β-hCG), α-fetoprotein, CA125 and carcinoembryonic antigen (CEA). All such biomarkers constantly had negative values.

The next step was to perform a biopsy curettage of the endometrium aiming to explore the uterine cavity and particularly to collect tissue for hispathological examination.

The procedure allowed getting a tissue of unspecific structure whose morphology mimics a solid tissue material. The biopsy tissue sample was collected into formalin liquid medium and was sent to the Department of Pathology. Although the biopsy tissue was gathered with great difficulty, we noticed that it caused no bleeding. One week after the date of the curettage, the woman developed a pelvic inflammatory disease, very similar to sepsis, with the following signs: high fever, pelvic pain and some changes on the vaginal smear.

A complex antibiotherapy was quickly initiated (Cefort 4 g, Metronidazole 1000 mg daily), combined with anti-inflammatory drugs. The first result of the histopathological examination we obtained from the pathologist inclined us to establish the diagnosis of previous early pregnancy, which was not even known or acknowledged by the patient herself. Therefore, it was a pregnancy, which stopped in evolution some time ago (in the past). It is worth noting that the last known abortion was undergone by the patient 10 years ago. The clinical evolution after curettage and the result of the histopathological examination significantly favored a surgical procedure meant to remove the contents of the uterus following the stopped pregnancy. The surgery was performed under endotracheal intubation anesthesia. A longitudinal arch section on the fundus of the uterus, highlighted changes in the structure of the wall of the uterus, and was accompanied by a strong and bad odor. These characteristics contributed to the decision of removing the entire body and cervix of the uterus except for the ovaries that did not show any pathological changes in keeping with the patient’s age. The post-surgery evolution was favorable under antibiotherapy taken for five days and the patient left the hospital with a good health status.

The woman made two visits to the doctor 10 days and three weeks after the last surgical procedure. The gynecological check-up showed that the woman had a good health status. The gold standard for the diagnosis was triggered by the histopathological examination that helped in identifying an epithelioid trophoblastic tumor inside the uterus. The clinical examination and the laboratory test results did not reveal any discomfort and the patient confirmed that she was in perfect health, but had psycho-emotional problems and many worries regarding her health in the future following this diagnosis.

The patient was included in a scheduled follow-up system consisting in regular visits to the doctor in order to manage the level of β-hCG, α-fetoprotein, CEA, CA125, the clinical and echographic status of the ovaries and any potential metastases that might have developed in the lungs, brain or bones. Disease management consisted in periodical imaging investigations such as chest X-ray, computed tomography (CT) scans of the chest, abdomen and pelvis.

Based on the data published by acknowledged specialists in this field, chemotherapy was not recommended in this case due to the absence of symptoms, abnormal serum β-hCG levels or metastases.

The pathologist encountered difficulties in establishing whether the diagnosis was coriocarcinoma or epithelioid trophoblastic tumor, and immunohistological tests were used to enhance the diagnosis accuracy.

The patient was asked to come to the hospital six months after undergoing the surgical procedure for a new qualitative β-hCG blood test, chest X-ray and CT of the pelvis. All results were negative. We can thereby conclude that at this moment the patient has no disease. She will undergo regular yearly check-ups that will include, as a minimum, a qualitative β-hCG blood test, the ultrasound assessment of the ovarian size and structure and a chest X-ray when no symptoms are present. It is relevant to stress that for this particular case, the results of the tests required were negative for β-hCG, α-fetoprotein, CEA, CA125 upon the dynamic assessment conducted before and after surgical procedure.

The macroscopic description of the body of the uterus and the cervix showed that the size of uterus was 7/5 cm and the length of the cervix was 4/2.5 cm. The specimen was sectioned to reveal the tumor tissue, which seemed to have a solid structure of 5<4×2.5 cm. The tumor that exists inside the uterus exhibits a white yellowish appearance, strongly penetrates into the wall of the uterus, but has free margins. The tumor does not have any vessels or cystic areas (Figure 1).

The microscopic evaluation reveals a tumor within the uterus that has infiltrative characteristics composed of trophoblast cells with many nuclear atypia and a large area of necrosis and hyalinization. Granulocyte tissue infiltration is also present. There are no vessels within the tumoral mass. The endocervical epithelium shows zones with decidualized stromal cells and rich granulocyte inflammatory infiltrate inside the chorion. Based on the
microscopic examination, the pathologist also reported the presence of round and large polyhedral cells with nuclear hyperchromasia and pleomorphism.

The tumor cells were described as nests of different size, which are aggregated in a hyaline-like matrix associated with variable areas of necrotic debris (Figures 2–8).

The aforementioned pathological features lead to the diagnosis of malignant endometrial epithelioid trophoblastic tumor. At this point, however, the pathologist acknowledged that there were doubts about the accuracy of the tumor diagnosis. Therefore, the pathologist required immunohistochemistry (IHC) tests aiming to achieve differential diagnosis between this malignant trophoblastic disease and other trophoblastic malignant tumors.

Figure 1 – Epithelioid trophoblastic tumor. Macroscopy of the tumor – longitudinal section of the uterus.

Figure 2 – Epithelioid trophoblastic tumor. Geographic necrosis zones [Hematoxylin–Eosin (HE) staining, ×100].

Figure 3 – Epithelioid trophoblastic tumor. Tumoral necrosis zones (HE staining, ×100).

Figure 4 – Epithelioid trophoblastic tumor. Groups of polygonal tumoral trophoblastic cells (HE staining, ×200).

Figure 5 – Epithelioid trophoblastic tumor. Inflammatory infiltrate and tumoral cells with atypia (HE staining, ×200).

Figure 6 – Epithelioid trophoblastic tumor. Nodules with trophoblastic atypical cells (HE staining, ×100).
The IHC test was performed for the following nine immunomarkers: placental alkaline phosphatase (PLAP) – Leica, 1:14 dilution, clone 8A9; cytokeratin AE1/AE3 – Leica, 1:100 dilution, clone cocktail AE1 & AE3; Ki67 – Dako, 1:50 dilution, clone MIB-1; P63 – Dako, 1:50 dilution, clone DAK-p63; β-hCG – Leica, 1:500 dilution, polyclonal; E-cadherin – Dako; 1:100 dilution, clone NCH-38; human placental lactogen (hPL) – Thermo, 1:250 dilution, polyclonal; epidermal growth factor receptor (EGFR) – Sigma, 1:1000 dilution, clone 29.1.1; inhibin alpha antibody, clone R1. Immunohistochemical staining of trophoblastic cells revealed strong and diffuse reactivity for cytokeratin AE1/AE3, p63 positivity and 25% Ki67 positivity. Focal reactivity was observed for hPL and PLAP (Figures 9–12).
The IHC staining for β-hCG was negative. The IHC staining for inhibin alpha showed that this was positive in many tumor cells, but the E-cadherin immunoeexpression displayed weak focal positivity in the tumor cells.

**Discussion**

The primary differentiation between ETT and other malignant trophoblastic tumors – such as choriocarcinoma or placental site trophoblastic tumor – was attributed to Shih, Mazur & Kurman (1998). Before this discovery, these individual malignant entities have only been described for patients with a history of chemotherapy for gestational trophoblastic disease and seen as an inadequate response to chemotherapy initiated in cases with hydatiform mole or choriocarcinoma [6]. The ETT has been described over time as a mass that either grows as an isolated uterus or cervical disease, or is just isolated in an extra-uterine site. ETT develops in the cavity of the uterus (40% of cases), inside the cervix (31% of cases) or the lungs (19% of cases). In rare instances, it may also occur in other sites such as vagina, broad ligament, Fallopian tubes and other pelvic organs [6–11]. ETT usually occurs in women of reproductive age following a prior gestation. The interval between a pregnancy and the diagnosis ranges from one year to as long as 18 years. Sometimes ETT occurs in postmenopausal women [12]. Clinical symptoms are very different and vary from one case to another. Patients with ETT often complain about vaginal bleeding [13], but in certain cases (including ours) the only complaint is amenorrhea [14]. It is possible that only the metastases of the ETT are discovered, most often in the lung. Many cases are associated with a high level of β-hCG, but in a small number of cases, β-hCG level might be very low, as Vemula et al. (2015) mentions. β-hCG might also be absent, as in our case, which conflicts with the findings published by Palmer et al., in 2008.

Our case has many peculiarities that must be underlined because they contribute to the complexity of the diagnosis. Such particular features include absence of vaginal bleeding and the negative results of the β-hCG test. In line with what is published in the literature, the ETT morphological features in our case are not entirely in keeping with the previously published data. The specialized literature indicates both morphological criteria and cell markers that favor the TTE diagnosis and also differentiate this anatomopathological entity from other pathologies such as PSTT, placental site nodule (PSN) and squamous cervical carcinoma (SCC). The microscopic features that tip the balance in favor of ETT diagnosis are the growth pattern that displays many features such as epithelioid nests and solid tumor masses, circumscribed margins, cell necrosis, absence of vascular invasion, fibrinoid changes, variable mitosis and absence of chorionic villi. The ETT is a trophoblastic disease characterized by intermediate trophoblastic cells. Trophoblasts are a primary cell type found in exaggerated placental site, PSTT, PSN and the ETT. Placental chorionic-type intermediate trophoblast has a nodular growth pattern that is similar both for placental site nodule and ETT, while placental implantation site intermediate trophoblast has an infiltrative growth pattern. The features that allow for the discrimination between PSN and ETT consist in the size of site nodules, necrosis and the Ki67 index value. Patients with PSN displayed smaller site nodules, absence of necrosis and lower Ki67 index compared to the ETT [15]. There are microscopic features capable to distinguish ETT from PSTT and choriocarcinoma [5, 6].

The features which allow to distinguish between PSTT and ETT are presence of large cells with pleomorphic shape, infiltrating borders, absence of cell necrosis and calcification, presence of vascularity from periphery to lumen, reduced mitosis for the former of the two tumor types [6].

The characteristics that the two tumors, i.e., PSTT and ETT, share are cellular population that grows from the intermediate trophoblast, presence of fibrinoid change and absence of chorionic villi.

As regards the microscopic features that could help in differentiating between the choriocarcinoma and ETT, the following features were mentioned in the published data: dimorphic cell population, which grows from the primitive previllous-type trophoblast, irregular size and shape of the cells, massive and central hemorrhage, vascular invasion from lumen to periphery, absence of fibrinoid change, very high mitosis. All these are specific microscopic features for choriocarcinoma. The investigation that allows for the quantitative versus qualitative differentiation in the analysis of cervical squamous cell carcinoma can be extrapolated to differentiate between PSTT and SCC, particularly in the tumors exteriorized through the cervix. Therefore, the histopathological examination result, used in conjunction with the morphometric investigation findings, forms the basis of improved diagnosis accuracy and allows a correct therapeutic approach [16].

The immunohistochemical markers capable of differentiating between the malignant trophoblast tumor types also allow a highly accurate diagnosis. In this respect, it is important to analyze the expression of immunohistochemical markers such as p63, inhibin alpha antibody, β-hCG, hPL, cytokeratins AE1/AE3, prolyl-4-hydroxylase epidermal growth factor receptor, PLAP, E-cadherin, Ki67 index. The research literature showed that PSTT versus ETT is typified by the absence of p63 following IHC tests and a lower value of the Ki67 index, i.e., approximately 7–21%. The p63 expression level varies between 45 and 65% in ETT and is absent in PSTT [17].

The level of Ki67 proliferation marker is in the range of 1025% in ETT, 15–25% in PSTT and exceeds 50% in SCC [18].

As regards PSN versus ETT, the differential criteria only consist of reduced cell necrosis and a Ki67 index less than 10% versus 10–25%. The immunoeexpression markers that favor the ETT diagnosis rather than squamous cell carcinoma (SCC) are cytokeratin-18 and inhibin alpha antibody present in patients with ETT, but missing in patients with SCC [19–22].

In our case, the strong diffuse reactivity for cytokeratin AE1/AE3, the positive tests for p63, the inhibin alpha antibody and the Ki67 index, which was around 25%, as well as the focal reactivity immunoeexpression for hPL, PLAP and E-cadherin are arguments in favor of the ETT diagnosis.

Choriocarcinoma tumor versus ETT is characterized by a higher Ki67 index, i.e., 50% versus 10–25%. According to the data published by Shen et al. (2003), there is the
possibility that these two tumors coexist together [23]. Human leukocyte antigen-G (HLA-G) is one of the other potential markers capable to differentiate between intermediate trophoblast (IT) in gestational trophoblastic disease and non-trophoblastic uterine neoplasms. HLA-G marker has high levels in patients with PSTT and ETT, ranging between 70 and 100%, and is missing in patients with SCC, which makes it a reliable tool in establishing a differential diagnosis as concerns these pathological entities [24]. The above-mentioned immunomarkers are instrumental in supporting the histopathological diagnosis of the complex gestational trophoblastic disease and in finding the right treatment approach.

Conclusions

Epithelial trophoblastic tumor is a rare type of gestational trophoblastic neoplasia. Clinical features vary, and only a small number of patients experiences amenorrhea and have negative β-hCG. The distinction between the ETT and choriocarcinoma is only made possible by the use of immunohistological tests. Increased diagnosis accuracy helps clinicians in opting for the most appropriate disease management approach.

Conflict of interests

The authors declare that they have no conflict of interests.

References


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