Published in final edited form as:

Int J Gynecol Cancer. 2011 July ; 21(5): 918–922. doi:10.1097/IGC.0b013e31821a278d.

Differentiating Squamous Cell Carcinoma of the Cervix and Epithelioid Trophoblastic Tumor

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Abstract

Background—Epithelioid trophoblastic tumor (ETT) is a recently described subtype of gestational trophoblastic neoplasia (GTN). Its diagnosis requires a high level of suspicion because it is often mistaken for more common cervical or uterine corpus epithelial neoplasms.

Case—This is a 39-year-old woman who presented with a cervical mass and positive human chorionic gonadotropin and was diagnosed with both locally advanced squamous cell cervical carcinoma and nonmetastatic GTN. She was treated unsuccessfully with concurrent intravenous cisplatin plus pelvic radiation and single-agent intravenous methotrexate. A retrospective review of the cervical biopsy using immunohistochemistry as well as genotyping of the tumor changed the original diagnosis to ETT. It is known that ETT is relatively unresponsive to chemotherapy compared with most other types of GTN; therefore, surgery would have been the optimal treatment. She died despite multiple salvage chemotherapies.

Conclusions—Malignant GTN is one of the most curable gynecologic malignancies; however, its correct diagnosis is critical for the appropriate treatment. It can be easily misdiagnosed as a carcinoma because of their morphologic similarity. Genetic finger-printing and immunohistochemistry are potentially valuable tools to confirm the diagnosis of ETT.

Keywords

Epithelioid trophoblastic tumor; Gestational trophoblastic neoplasm; Immunohistochemistry

Malignant gestational trophoblastic neoplasia (GTN) is one of the most curable gynecologic malignancies; however, its correct diagnosis is critical for the appropriate treatment. Gestational trophoblastic neoplasia is a type of gestational trophoblastic disease that consists of persistent or invasive disease. Gestational trophoblastic neoplasia is divided into 4 tumor

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subtypes including invasive mole, choriocarcinoma, placental-site trophoblastic tumor, and epithelioid trophoblastic tumor (ETT).

Epithelioid trophoblastic tumor was first described recently by Shih et al[1] in 1998 as a separate entity, and since then, only 70 cases have been reported. Most cases occur in reproductive-age women after a term pregnancy; however, cases have also been reported in postmenopausal women and one third occur after molar pregnancies or spontaneous abortions. Two thirds of patients present with local, nonmetastatic disease and is curable in approximately 90% if treated appropriately.[2] The correct diagnosis of ETT, however, requires a high level of suspicion and potentially the use of DNA genotyping and immunohistochemistry (IHC).

The diagnosis of ETT is challenging because of its morphologic similarity to carcinoma. Macroscopically, ETT appears as a solid-to-cystic well-defined mass that is usually confined to the lower uterine segment or cervix. Microscopically, ETT consists of a neoplastic proliferation of intermediate trophoblasts with eosinophilic cytoplasm resembling keratin and often replacing the endocervical epithelium. The differentiation between ETT and squamous cell carcinoma (SCC) of the cervix is therefore challenging.[3]

The correct diagnosis is critical because the treatment of ETT is quite different from the treatment of most other types of GTN or cervical cancer. Epithelioid trophoblastic tumor is relatively resistant to both chemotherapy and radiotherapy compared with the more common subtypes of GTN such as the highly chemosensitive invasive mole or choriocarcinoma. Similar to placental-site trophoblastic tumor, the treatment of ETT is primarily surgery.[4,5]

CASE

This is a case report of a 39-year-old gravida 6 para 5 Hispanic woman who initially presented in October 2006 to a community emergency department with a 2-month history of urinary retention and suprapubic pain that immediately became worse. She was then referred to our institution. Although she reported having a bilateral tubal ligation 7 years previously, she had a spontaneous abortion 18 months before her current presentation. This abnormal pregnancy was managed expectantly. She had 5 prior normal vaginal deliveries. She denied any history of abnormal Papanicolaou tests, and her last Papanicolaou test was 1 year before presentation. On further questioning, she reported postcoital bleeding since the time of her spontaneous abortion.

On examination, she was found to have a 10-cm exophytic and necrotic cervical mass compressing the bladder and the urethra. There was no pelvic sidewall involvement. She had a human chorionic gonadotropin (hCG) level of 965 mIU/mL and a hemoglobin level of 8.8 g/dL. A computed tomographic (CT) scan of her pelvis revealed a 10-cm pelvic mass and bilateral hydronephrosis without evidence of local tissue infiltration or retroperitoneal lymphadenopathy. A CT scan of her head, chest, and abdomen did not reveal a metastatic disease. Her pelvic ultrasound showed a 10-cm cervical mass but did not reveal an intrauterine pregnancy. A biopsy of her cervical mass was consistent with a moderately to poorly differentiated SCC.

She was therefore diagnosed with 2 primary malignancies: SCC of the cervix FIGO stage IIIB due to hydronephrosis and nonmetastatic GTN based purely on persistent elevated hCG because there was no tissue diagnosis of GTN at that time.

She was treated concurrently for both primary malignancies. She was treated with whole pelvic radiation of 45 Gy and 6 doses of radiosensitizing intravenous (IV) cis-platin 40 mg/m^2 weekly that was completed in December 2006 followed by a high-dose rate brachytherapy (85 Gy total to point A) that was completed in February 2007. Her GTN was treated with IV methotrexate 30 mg/m^2 weekly. At the completion of this treatment, she was believed to have a partial response of her cervical carcinoma with a decrease in size of the cervical mass from 10 to 4 cm on the second CT scan. There was a complete response of her GTN with a decrease in hCG level from 965 to 5 mIU/mL. Soon after treatment, however, her hCG level began to rise again, and actinomycin D 1.2 mg/m^2 IV was started every 2 weeks.

When her hCG level continued to rise despite single-agent actinomycin D, the original diagnosis of 2 primary malignancies was questioned, and her case was presented to the multidisciplinary tumor board. As recommended, a second biopsy of the cervical mass was performed and was consistent with ETT. A positron emission tomographic/CT scan revealed pelvic lymphadenopathy. A percutaneous biopsy of the enlarged iliac node was also consistent with ETT.

She was started on etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine, but because of the continued elevation of her hCG level, her chemotherapy was changed to etoposide, methotrexate, actinomycin D, and cisplatinum in March 2007. She received 2 cycles of etoposide, methotrexate, actinomycin D, and cisplatinum. A second positron emission tomography/CT scan in November indicated disease progression with a new left periaortic lymph node metastasis and enlarged bilateral iliac lymph nodes in addition to the cervical mass. She was started on paclitaxel, ifosfamide, and cisplatin of which she received 4 cycles. Further progression of the left periaortic and bilateral internal iliac lymph nodes was noted. The decision to initiate chemotherapy with paclitaxel, ifosfamide, and bevacizumab was made. After cycle 3, bevacizumab was discontinued because of hemorrhagic cystitis. She had 1 more cycle of dose-reduced ifosfamide with mesna and paclitaxel. Her hCG level was never less than 400 mIU/mL. Because of a strong desire to continue aggressive therapy, palliative oral capecitabine was given. Her disease progressed (Fig. 1), and she died of disease 2 years after her initial presentation.

As part of this case report, a retrospective molecular analysis was performed using IHC and genetic fingerprinting. Figure 2 depicts an hematoxylin and eosin stain of the malignant tissue. Figure 3 illustrates the IHC findings, and Table 1 shows the results of genetic fingerprinting. The hypothesis was that these techniques could have been applied to her initial cervical biopsy slides to confirm a diagnosis of GTN and exclude the diagnosis of SCC. In Figure 3, dark brown pigmentation (A–C) signifies expression of the proteins in question, whereas light blue (D–F) indicates no expression of the protein. As anticipated, hCG, inhibin, and cytokeratin 18 were all positive. The antibody to cytokeratin 5/6, usually positive in SCC, was absent. Human placental lactogen, usually positive in placental-site

trophoblastic tumor, was also absent. The *P57* gene is a paternally imprinted and maternally expressed protein. It was negative, suggesting that her spontaneous abortion after her bilateral tubal ligation was, in fact, a complete hydatidiform mole that led to the development of ETT. Figure 3G illustrates p57 staining of intermediate trophoblasts, a positive control.

To further confirm that this patient's initial cervical biopsy was GTN rather than SCC, genetic fingerprinting was performed. The tumor and adjacent nontumor tissues were genetically compared. It is expected that tumor derived from host tissue has the same genetic fingerprint as the host tissue.[6] Our results (Table 1) show mismatched alleles in the tumor compared with host tissue in 3 of 6 markers, suggesting the tumor to contain both maternal and paternal DNA due to a complete molar pregnancy. The maternal allele is identified in 5 of 6 markers but is absent from D21S11, suggesting the presence of a mutation in the tumor.[7] This is a known pitfall when tumor samples are used for identity testing.[8]

COMMENT

Epithelioid trophoblastic tumor presents a very rare form of trophoblastic disease that is commonly misdiagnosed. Seventy cases have been reported in the literature.[1] Clinically, ETT primarily occurs in reproductive-age women up to 18 years after a prior gestation. Most ETTs occur after a full-term pregnancy, but approximately one third arise after a spontaneous abortion or hydatidiform mole.[2] Vaginal bleeding is the presenting symptom in two thirds of patients; approximately one third of patients present with metastatic disease.[2] Serum hCG levels are elevated, but usually do not exceed 2500 mIU/mL. Prognosis is similar to placental site trophoblastic tumor (PSTT), another rare form of gestational trophoblastic neoplasia, but a minority of ETTs act more malignant and present a challenge in terms of treatment. When ETT results in mortality, the cause is most commonly widespread metastatic disease.

Histologically, the growth of ETT is nodular, with monomorphic cell nests that display an eosinophilic to clear cytoplasm within a hyaline matrix. Epithelioid trophoblastic tumors are composed of chorionic-type intermediate trophoblasts based on histologic characteristics and molecular markers.[9] Necrosis, apoptotic cells, and numerous mitoses are characteristic features of ETT, reflecting its rapid growth and clinical aggressiveness. Epithelioid trophoblastic tumor can easily be mistaken for other tumors. It is most often confused with SCC because of its frequent involvement of the lower uterine segment or endocervix and because of its epithelioid histologic appearance. It can also be erroneously diagnosed as adenocarcinoma because of the presence of rosettes and glandlike structures on microscopic evaluation.

This case illustrates 2 important diagnostic concepts in terms of gynecologic malignancies. First, any prior abortion that was managed expectantly without ultrasonic or pathologic diagnosis should heighten concern for possible abnormal pregnancy such as a molar pregnancy as in this case. Second, an elevated β-hCG level in a nonpregnant woman should always prompt further workup for GTN. Two primary rare cancers would be unusual, and

again this diagnosis should likely be challenged. Nonetheless, ETT is rare and easily misdiagnosed, and treatment is often challenging.

Immunohistochemistry and genetic fingerprinting are 2 potential modalities to differentiate between ETT and other tumor subtypes. Epithelioid trophoblastic tumor normally shows expression of hCG, inhibin, and cytokeratin 18. Antibodies to cytokeratin 5/6 and human placental lactogen are usually not expressed in ETT but are expressed in SCC and placental-site trophoblastic tumor, respectively. Genetic fingerprinting is used to compare tumor tissue with host tissue. Tumor tissue with a different DNA can be explained by tumor caused by foreign DNA as is the case in ETT caused by a complete molar pregnancy. Of note, IHC and genetic fingerprinting would likely only be performed and useful in cases where ETT was already suspected, in which case the diagnosis could possibly be made by an astute pathologist without further staining or genetic studies.

In this case, a correct diagnosis of epithelial trophoblastic tumor would have significantly affected the therapeutic decisions and, possibly, outcome. For example, radiation may not have been the treatment of choice had this patient been correctly diagnosed. Although the tumor mass did decrease in size after radiation treatment, it is believed that her radiation limited the ability for cytotoxic drugs to be delivered to the tumor bed. Even so, it is known that epithelial trophoblastic tumors are not as sensitive to chemotherapy as other types of gestational trophoblastic tumors; therefore, surgery would have been the optimal choice of treatment had the correct diagnosis been made. Diagnosis of ETT requires a high index of suspicion and sophisticated pathologic testing. Immunohistochemistry and DNA genotyping can be used in rare cases such as this one to differentiate between SCC of the cervix and malignant GTN.

Acknowledgments

Genetic analyses were funded by the Pathology Research Services Core, Department of Pathology and Laboratory Medicine, University of California, Irvine, CA.

The authors thank Daniele Sumner for her assistance with this brief report.

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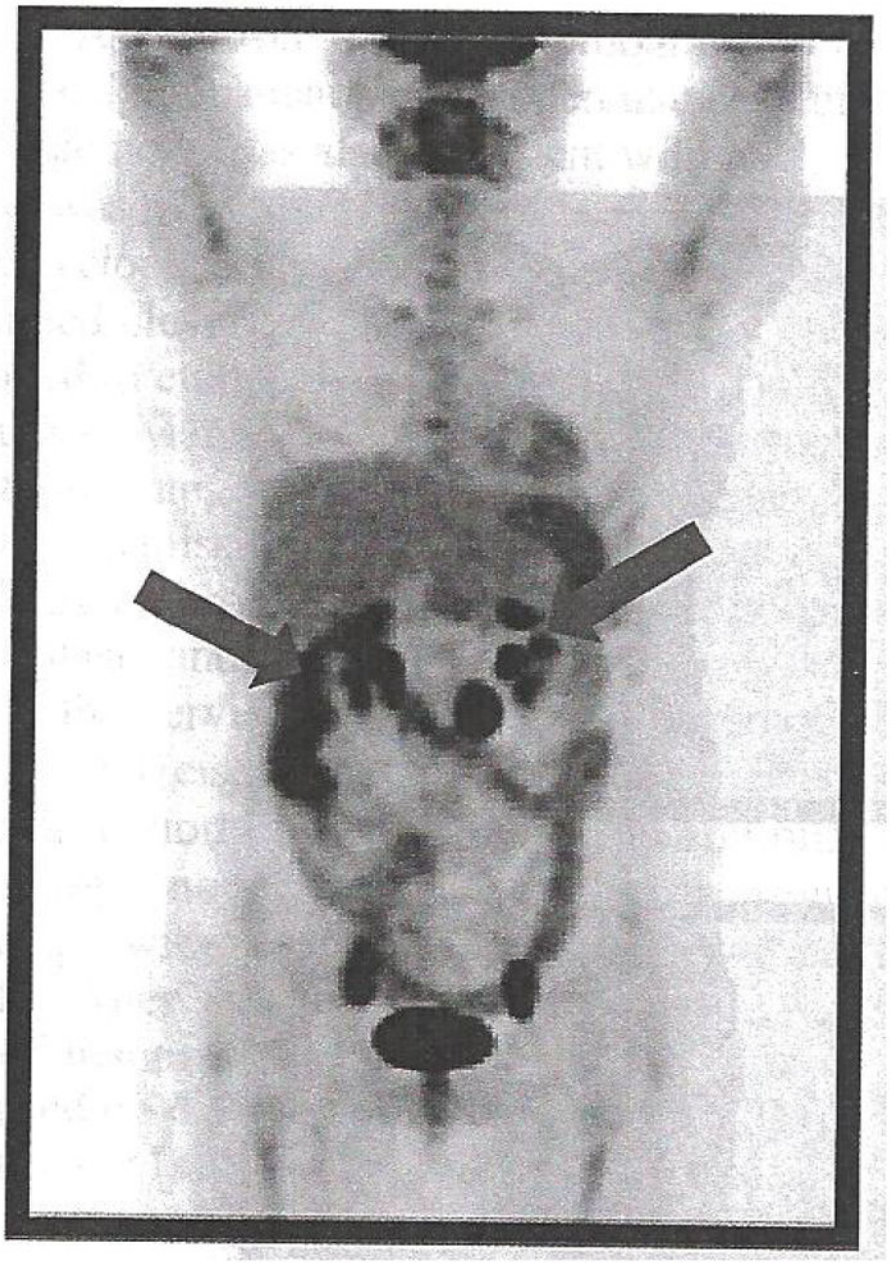

FIGURE 1.

Positron emission tomographic/CT scan revealing widely metastatic disease (red arrows). Note physiologic isotope uptake in brain, renal collecting systems, and bladder.

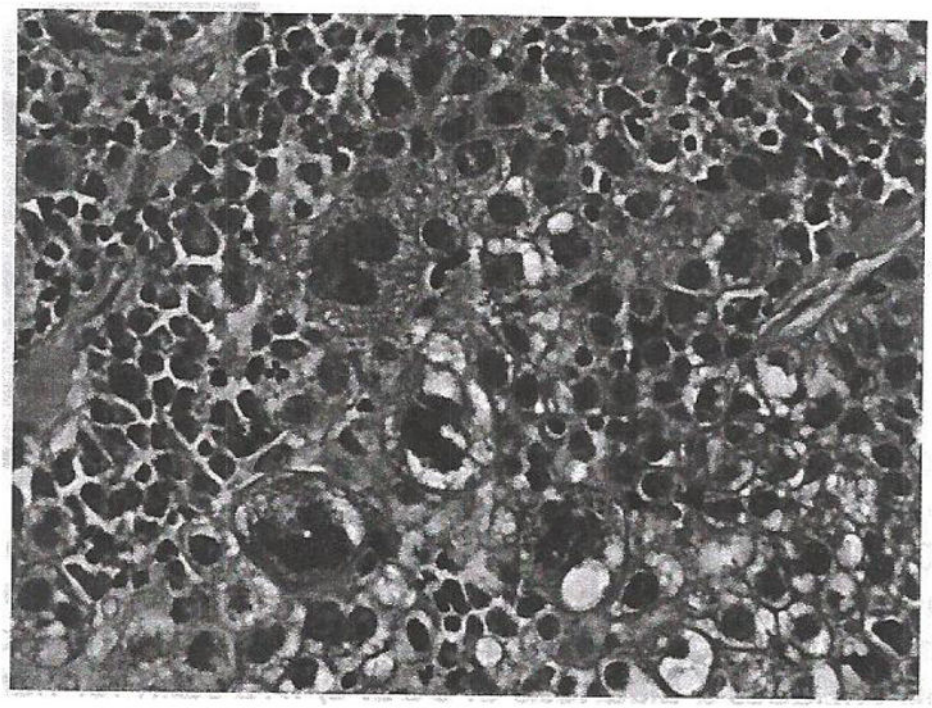

FIGURE 2.
Hematoxylin and eosin stain of the malignant tissue.

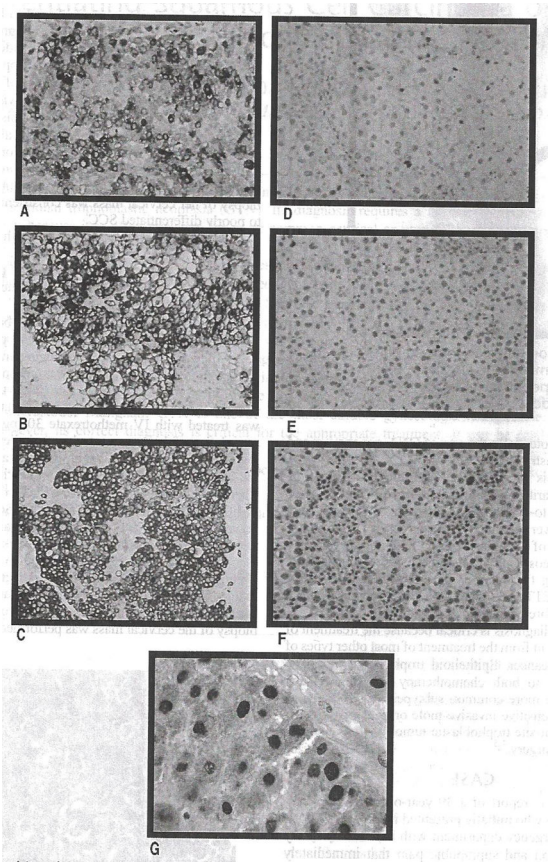

FIGURE 3.

Immunohistochemistry stains. A to C, Dark brown indicating a positive expression of the protein in question. D to F, Light blue indicates a negative result with no expression of the protein of interest. β-hCG (A), inhibin (B), and cytokeratin 18 (C). These stains support a diagnosis of ETT. D, IHC stain for cytokeratin 5/6. This excludes a diagnosis of SCC. E, IHC stain for human placental lactogen. This argues against a diagnosis of placental-site trophoblastic tumor. F, IHC p57 stain of ETT. This is negative and confirms a prior complete molar gestation. G, IHC p57 stain of intermediate trophoblasts—positive control.

TABLE 1

Genetic fingerprinting allelic results

	Alleles		
Short Tandem Repeat	**Nonneoplastic Tissue**	**ETT**	**Interpretation**
D3S1358	15, 17	15, 17	Match
vWA	16, 19	16, 18	Mismatch
D5S818	11, 13	11, 13 *	Mismatch
D13S317	12, 14	10, 12	Mismatch
D8S1179	10, 15	10, 15	Match
D21S11	29.2, 32	28, 30	Mismatch

The polymerase chain reaction amplification system used for DNA genotyping was the AmpFISTR Profiler Plus ID PCR amplification kit (Applied Biosystems).

* Gestational trophoblastic neoplasia (11, 13) alleles displayed instability.