A rare case of epithelioid trophoblastic tumor: An ultrasound dilemma*

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ABSTRACT

Gestational trophoblastic neoplasia (GTN) represents the malignant end of the gestational trophoblastic disease spectrum and includes the more common types, invasive mole (IM) and choriocarcinoma (CC) and the rare types, placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT).

This is a case of a 42-year-old, G2P2 (2002) patient who complained of left lower quadrant pain and a 1 year history of amenorrhea. Urine pregnancy test done just prior to the surgery revealed positive result. Pre-operative diagnosis was abdominopelvic mass mass probably Sarcoma, ovarian new growth probably benign, right. Patient underwent exploratory laparotomy, adhesiolysis, bilateral internal iliac artery ligation, total hysterectomy with bilateral salpingo-oophorectomy, targeted biopsy, appendectomy, JP drain insertion under epidural anesthesia. Final histopathologic and immunohistochemical diagnosis is Epithelioid Trophoblastic Tumor.

Differential diagnoses, diagnostics, and therapeutic options are presented, with focus on the description of sonographic features.

Keywords: ultrasound, uterine sarcoma, epithelioid trophoblastic tumor

INTRODUCTION

Gestational trophoblastic neoplasia represents the malignant end of the gestational trophoblastic disease spectrum and includes the more common types, invasive mole and choriocarcinoma and the rare types, placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT).

The term "epithelioid trophoblastic tumor" was first introduced by Mazur and Kurman to describe an unusual type of trophoblastic tumor that is distinct from placental site trophoblastic tumor and choriocarcinoma and has a feature mimicking a carcinoma[1]. Histologically speaking, epithelioid trophoblastic tumor is a rare trophoblastic neoplasm which is the malignant counterpart of the intermediate trophoblasts of the chorion laeve.[2] There are 94 reported cases of ETT in literature.[3] The first case of ETT reported locally was diagnosed in the Philippine General Hospital last 2008 [4]. To our knowledge, this case will be the second documented case of ETT.

Clinically, ETT occur from age 15 to 66 (average 38 years).[5] The tumor follows full-term deliveries in 67% of cases, 16% had a previous history of spontaneous abortions as well as hydatidiform moles. The reported interval between the previous gestation and the diagnosis ranged from 1 to 18 years, with a mean of 6.2 years.[6] The most common presenting symptom is vaginal bleeding. The serum level of beta HCG are usually slightly elevated (<2,500 mIU/mL) compared to those with choriocarcinoma.[7]

The role of transvaginal sonogram in gestational trophoblastic diseases cannot be over emphasized. It has become the standard imaging protocol in the evaluation and diagnosis of the more common GTDs like molar pregnancies, invasive mole, and choriocarcinoma. However, for the rare conditions like the PSTT and ETT, there has been very limited data in the literature regarding ultrasound characteristics.

Histopathologic examination is mandatory in the diagnosis of ETT. Grossly, the tumor presents as a solitary, discrete uterine mass, that usually invade the cervix and myometrium, either solid or cystic in nature, with varying amounts of hemorrhage and necrosis.[8] Microscopically, the tumor is composed of relatively uniform population of mononucleate intermediate trophoblastic cells forming nests and solid masses [1]. In most ETTs, p63 is positive and can be particularly useful when the differential diagnosis is with PSTT [5], as in this index case.

The primary treatment of ETT is surgery. They do not respond to the chemotherapeutic agents currently being used in the treatment of other types of GTDs[7]. Hence, identification of ETT among cases of GTN is warranted for correct therapeutic intervention, and ultrasound ideally should be very helpful.

ETT is a rare form of GTD with unpredictable biological behavior. Together with PSTT, it must be considered

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potentially curable though prognosis is worse than other forms of GTD [7].

THE CASE

This is a case of GS, 42 years old, married, from Laguna, admitted for the first time at Philippine General Hospital last August 26, 2016 due to left lower quadrant pain.

Patient has no history of hypertension, diabetes mellitus, bronchial asthma and other medical problems. She has no previous hospitalizations and surgeries, and she has no allergies to food and drugs.

Her family medical history revealed that she has a sister with liver and colon cancer. There is also hypertension in the maternal side.

Patient is married, a high school graduate and is a vendor. She has no known vices. First coitus was at age 20 with one non-promiscuous sexual partner. She had a 2 year history of oral contraceptive pills use and stopped 10 years ago. She had no history of sexually transmitted diseases.

The patient had her menarche at 13 years old with subsequent menses coming at regular monthly intervals, 5 days duration, consuming 1 pad per day. There was no note of dysmenorrhea during menses.

Patient had 2 pregnancies, all alive and carried to term, delivered via cesarean section due to cephalopelvic disproportion, at Sta. Cruz, Laguna with no note of fetomaternal complications. Her last delivery was last 2000.

History started 2 years prior to admission when she had onset of amenorrhea. There were no other complaints noted thus no consult was done.

One year prior to admission, she had persistent amenorrhea and there was note of a palpable abdominal mass, with no other signs and symptoms noted. Still no consult was done.

Three months prior to admission, she noted intermittent gnawing abdominal pain with increasing severity from pain score of 5/10 to 9/10. This was associated with anorexia and weight loss. In the interim, the patient noted gradually enlarging abdomen, but still no consult was done.

On the day of admission, the patient was complaining of persistent left lower quadrant pain prompting consult at PGH OBAS. She was subsequently admitted with impression of abdominoplevic mass probably uterine sarcoma, bilateral ovarian new growth, in complication.

On admission, vital signs were stable with a blood pressure of 130/90 mmHg, heart rate of 85 beats per minute, respiratory rate of 18 cycles per minute. Patient was afebrile. Physical examination centered on the abdomen which revealed a soft abdomen with normoactive bowel sounds. The abdominal girth was 121 cm. There was a palpable 20 x 18 cm solid mass at the abdominopelvic cavity with direct and rebound tenderness on the left lower quadrant area. On speculum examination and internal and bimanual examination, there was normal external genitalia, smooth and parous vagina, cervix measured 3 x 3 cm, smooth with no masses noted, and with no vaginal discharge or bleeding. There is a palpable 20 x 18 cm predominantly solid mass with limited mobility at the abdominopelvic area, and with direct and rebound tenderness at the left lower quadrant area.

Laboratories and other diagnostic procedures were taken. A transvaginal and transabdominal ultrasound revealed the following: "the cervix measures 2.4 x 2.6 x 2.3 cm, with homogeneous stroma and distinct endocervical canal (Figure 1); the corpus is converted into an irregular lobulated abdominopelvic mass measuring 21.3 x 19.3 x 12.3 cm, with calcifications and irregular cystic areas; the endometrium is indistinct (Figures 4 and 5); At the right adnexal area is a unilocular cystic mass with irregular contour measuring 3.9 x 4.4 x 4.9 cm with anechoic fluid within; the capsule measures 0.3 cm (Figure 2); a similar cystic mass is seen at the left adnexal area measuring 4.1 x 5.3 x 5.4 cm with anechoic fluid within; the capsule measures 0.1 cm (Figure 3); there is no free fluid in the cul de sac; bilateral renal calyces are not dilated; color flow mapping of the abdominopelvic mass revealed abundant intratumoral scattered branching vascularity (Figure 6) which on Doppler interrogation revealed low resistance indices (PI- 0.82, RI- 0.59)" . The sonologic impression was abdominopelvic mass consider uterine pathology probably sarcoma, bilateral adnexal masses consider bilateral ovarian new growth with benign sonologic features.

Urine pregnancy test was done just prior to start of surgery which turned out to be positive. Clinical impression

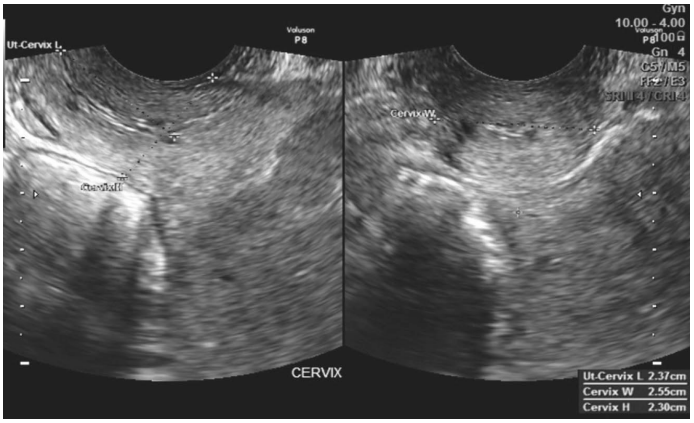

Figure 1. Transvaginal ultrasound of the cervix on anteroposterior (left) and transverse (right) views showed the following: the cervix measures 2.4 x 2.6 x 2.3 cm, with homogeneous stroma and distinct endocervical canal.

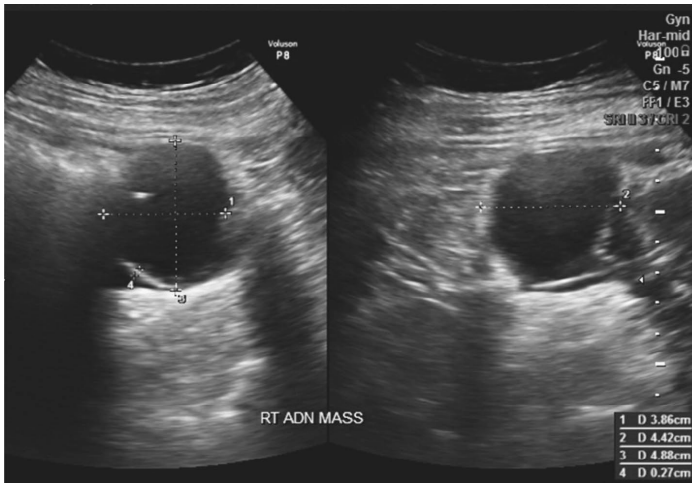

Figure 2. Transabdominal ultrasound of the right adnexal mass on anteroposterior (left) and transverse (right) views.

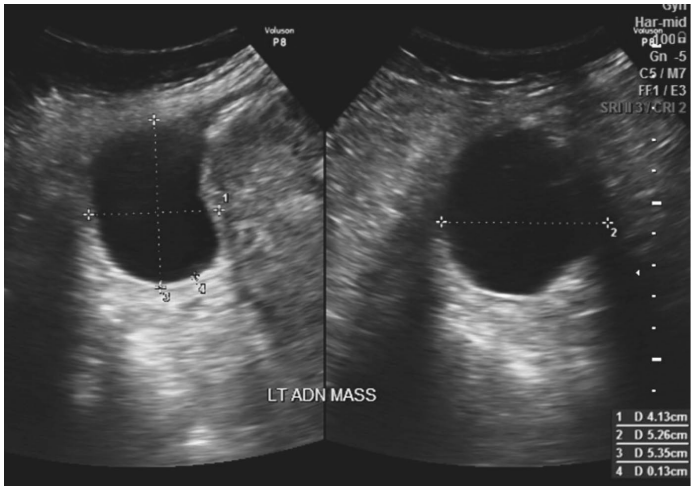

Figure 3. Transabdominal ultrasound of the left adnexal mass on anteroposterior (left) and transverse (right) views.

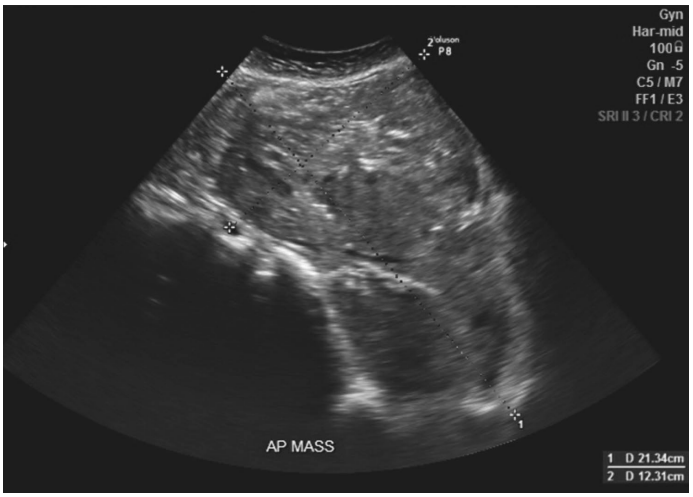

Figure 4. Transabdominal anteroposterior view of the uterus showing the following: the corpus is converted into an irregular lobulated abdominopelvic mass measuring 21.3 x 19.3 x 12.3 cm, with calcifications and irregular cystic areas.

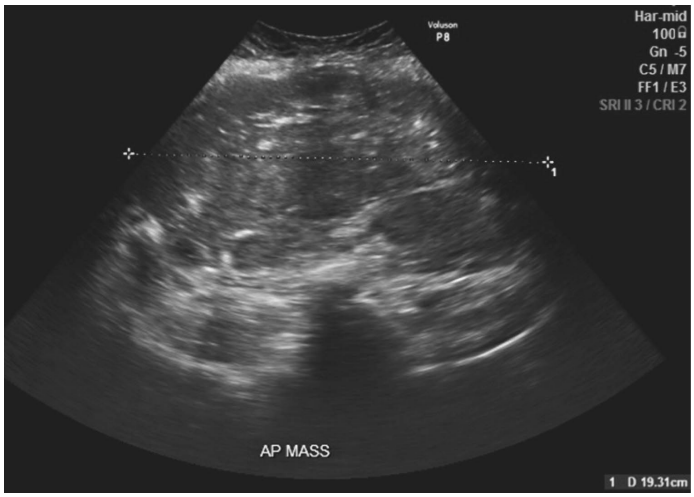

Figure 5. Transabdominal transverse view of the uterus.

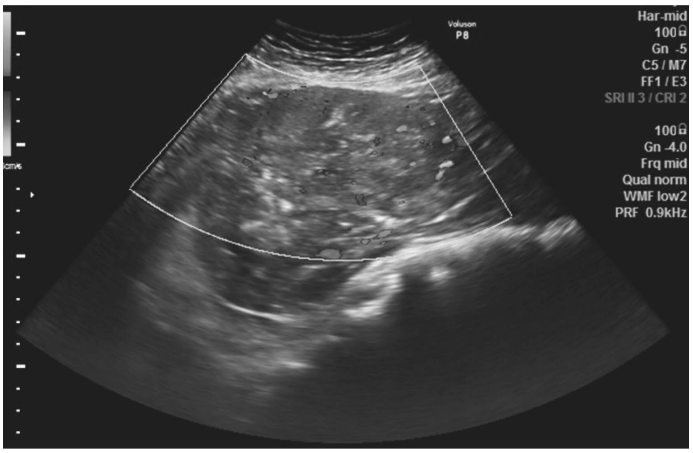

Figure 6. Color flow mapping of the abdominopelvic mass on transabdominal ultrasound revealed abundant intratumoral scattered branching vascularity.

at this time was abdominopelvic mass probably Sarcoma, ovarian new growth probably benign, right. Patient was still in pain thus underwent exploratory laparotomy, adhesiolysis, bilateral internal iliac artery ligation, total hysterectomy with bilateral salpingo-oophorectomy, targeted biopsy, appendectomy, JP drain insertion under epidural anesthesia. Operative findings revealed minimal hemoperitoneum, and there was a 3.0 x 3.0 cm cystic mass at the left fundal area with serosanguinous fluid inside. The spleen, stomach, kidneys and omentum were grossly normal on inspection and palpation. At the mesenteric surface was a 2.0 x 3.0 cm tumorous implant. The uterus was converted to a 32.0 x 20.0 x 10.0 cm (cervix measures 6.0 x 4.0 x 3.0 cm) necrotic friable mass, which was densely attached to the bladder, cul de sac and pelvic sidewalls (Figure 5). There was a 3.0 x 4.0 cm point of rupture at the fundal area extruding necrotic material. On cut section, the uterine cavity measured 15 cm in length

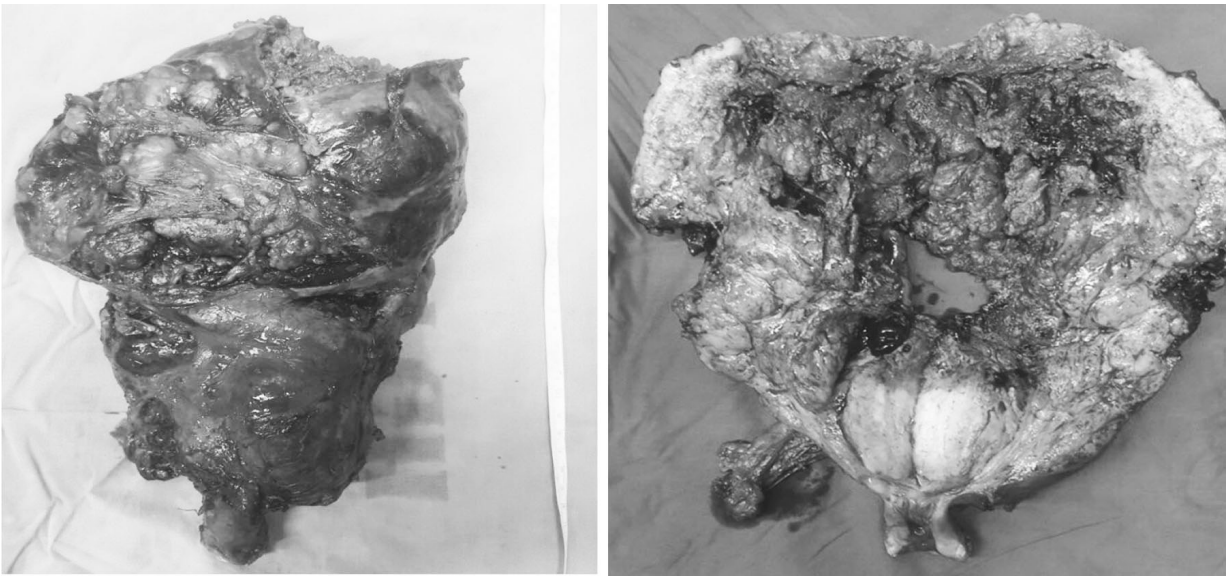

Figure 7. Gross picture of the uterus (left) showing the uterus to be converted into a 32.0 x 20.0 x 10.0 cm necrotic friable mass, which was densely attached to the bladder, cul de sac and pelvic sidewalls. Cut section (right) shows necrotic areas with almost full thickness myometrial involvement. The cervix appears normal.

and the endocervical cavity measured 5 cm long. The left ovary was densely adherent to the posterior surface of the uterus and measured 2.5 x 2.0 x 2.0 cm and was also converted to a solid mass. The left fallopian tube was not identified. The right ovary measured 7.0 x 5.0 x 2.0 cm, and was converted to a unilocular cyst with serous fluid within. There were no solid areas nor papillary excrescences seen. The right fallopian tube measured 3.5 x 2.5 x 2.0 cm and appeared grossly normal. The appendix was inflamed and measured 7.0 x 3.0 x 3.0 cm and was also adherent to the mass. Cut section of the appendix appeared normal. Post operative diagnosis was abdominoplevic mass consider uterine leiomyosarcoma, rule out gestational trophoblastic neoplasia.

Patient's post operative course was unremarkable. Serum beta HCG was taken prior to discharge, which was elevated at 6,980 mIU/mL. She was then discharge improved on her day 5 post op.

Histopathology revealed the following: "poorly differentiated neoplasm involving the uterus, tumor invades more than 50% of the myometrial thickness, tumor is very near the uterine serosa (<1 mm), tumor size 23 cm in widest dimension, positive for lymphovascular space invasion, positive for tumor, left ovary and left paratubal soft tissues, appendix and periappendiceal tissues, "pseudocyst" right ovary, abdominal, bowel and omental implants, mucinous cystadenoma, right ovary, atrophic endometrium, chronic cervicitis with nabothian cyst and squamous metaplasia, paratubal cyst, right". The primary consideration was placental site trophoblastic tumor. Due to the dilemma of the diagnosis, immunohistochemical tests were done which revealed strongly and diffusely positive for cytokeratin, focally and strongly positive for p63, focally and moderately positive for inhibin, negative for smooth muscle actin (SMA) and 30-40% positive for Ki67. These results were compatible with a gestational trophoblastic neoplasm, considerations include: 1. ETT and 2. PSTT. The pathologist further recommended immunohistochemical staining with Sal-like 4 (SALL4) and placental alkaline phosphatase (PLAP) for differentiation. However, since the immunohistochemical test was positive with p63, the final diagnosis was epithelioid trophoblastic tumor.

DISCUSSION

We are presented with a case of a 42 years old who was admitted for the first time due to left lower quadrant pain. Pertinent to the history of the patient was a history of amenorrhea for 2 years, and a history of a previous unremarkable term delivery 16 years ago (year 2000). For patients who are in the reproductive age group, a pregnancy test should have been done to rule out pregnancy as the cause of the amenorrhea. However, this was not done in this patient. Urine pregnancy test was done when the patient was at the operating room which turned out to be positive. A serum beta HCG test was done prior to discharge which was elevated at 6,980 mIU/mL. If the pregnancy test was done, the diagnosis would have been focused to conditions that presents with amenorrhea and an abdominopelvic mass.

As with any gynecologic conditions, the role of ultrasound in the diagnosis of abdominopelvic masses cannot be overemphasized. For our index patient,

she had an ultrasound with the description of an abdominopelvic mass described as irregular and lobulated, with calcifications and cystic areas. Color flow and Doppler mapping of the said mass was done which revealed abundant intratumoral scattered branching vascularity which on Doppler interrogation revealed low resistance indices (PI- 0.82, RI- 0.59). For any patient with an abdominopelvic mass and ***without*** the benefit of a pregnancy test, sonologic diagnosis would focus on uterine pathologies such as myoma with degenerative changes or the more rare types such as uterine sarcoma. In our index case, uterine sarcoma was considered over just a simple uterine leiomyoma due to the sonologic appearance of an irregularly vascularized mass, with an irregular outline, and often with irregular anechoic areas due to necrosis.[9] A study was done which described the gray-scale and Color Doppler sonographic features of uterine sarcomas.[10] The conclusion of the study is that uterine sarcomas are a heterogeneous group of tumors showing a range of preoperative sonographic aspects depending on the histological subtype, and opposite to the most common benign uterine mesenchymal tumors (leiomyomas), uterine sarcomas never show cones of shadow and invariably present as single vascular uterine masses, similar to the sonologic findings of some reported cases of ETT *(vide infra)*. It is thus a challenge for sonologists to diagnose such uterine tumors.

If there is a benefit of a positive pregnancy test prior to the ultrasound scan, then the differential diagnosis will be on conditions that present with a uterine enlargement and a positive pregnancy test, such as gestational trophoblastic tumors. In gestational trophoblastic neoplasia (GTN), transvaginal sonography and preferably with Color flow Doppler is used not only to help confirm the diagnosis but also in determining the degree of myometrial invasion, detecting recurrence and evaluating good response to chemotherapy.

For our index patient, the initial histopathologic diagnosis was that of a poorly differentiated neoplasm of the uterus, primary consideration of placental site trophoblastic tumor and thus recommended immunohistochemical studies. The immunohistochemical findings turned out to be diagnostic for ETT.

Due to the rarity of ETT, there is little information available in the literature reagrding its appearance on ultrasound imaging. ETT has been described by some authors as a subtype of PSTT and that there are no specific sonologic features to reliably distinguish and diagnose PSTT.[11] It should be in conjunction with the history and a finding of an irregular, usually localized, uterine mass lesion. One study also cited that most reported cases of ETT have solitary nodules with a sharp tumor border growing in an expansive fashion, invading the cervix or myometrium deeply.[12] In our index case, the cervix was normal but the corpus was converted into an irregular and lobulated mass.

Another study was done last 2014 by Quin et al that aimed to identify the sonographic features of ETT that are distinct from other GTNs, including PSTT, and invasive mole/choriocarcinoma.[13] They retrospectively analyzed ultrasound images of 12 patients with ETT in comparison with those of 21 patients with PSTT and 24 patients with invasive mole/choriocarcinoma. The results of their study showed that maximal diameter and hemodynamic parameters were not significantly different among ETT, PSTT and IM/CC ($P > 0.05$). However, a well circumscribed border with hypoechogenic halo was identified in the gray-scale sonogram in all 12 cases of ETT, while only in 1 out of 21 cases of PSTT and 1 out of 16 cases of IM/CC ($P < 0.001$ for ETT vs. PSTT or IM/CC). Moreover, a peripheral pattern of Doppler signals was observed in 11 out of 12 ETT lesions, showing relatively more Doppler signal spots around the tumor border than within the boundary, while a non-peripheral pattern of Doppler signals in all 21 PSTT cases and 14 out of 16 IM/CC cases: with minimal, moderate or remarkable signal spots within the tumor, but not along the tumor ($P < 0.001$ for ETT vs. PSTT or IM/CC). They concluded that the well-circumscribed border with peripheral Doppler signal may serve as a reliable sonographic feature to discriminate ETT from other types of GTNs. However due to the small population, the authors recommend further validation in a larger patient setting.

For our index patient, the Color and Doppler studies revealed an irregular uterine mass with intratumoral flow. With these findings, plus the absence of a positive pregnancy test, the sonologist decided to give the impression of a uterine pathology probably a sarcoma.

CONCLUSION

Sonographically, it is difficult to diagnose and differentiate uterine sarcomas with gestational trophoblastic neoplasia. It is thus important to have a complete history and physical examination with the conjunction of diagnostic test such as ultrasound to be able to clinch the diagnosis.

Epithelioid trophoblastic tumor has a cell of origin that is different from other forms of GTN (intermediate trophoblastic cells of chorion laeve). With this, it is not surprising that the clinical presentation, tumor marker profile, and treatment paradigm for this condition is quite different as well. The distinction between ETT and other GTNs is only made possible by the use of immunohistochemical tests. ■

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