Gestational Trophoblastic Disease: Clinical and Imaging Features

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Abbreviations: AVF = arteriovenous fistula, β-hCG = β-human chorionic gonadotropin, CHM = complete hydatidiform mole, ETT = epithelioid trophoblastic tumor, FIGO = International Federation of Gynecology and Obstetrics, GTD = gestational trophoblastic disease, GTN = gestational trophoblastic neoplasia, PMM = partial hydatidiform mole, PSTT = placental site trophoblastic tumor, PMD = placental mesenchymal dysplasia, ETT = epithelioid trophoblastic tumor, FIGO = International Federation of Gynecology and Obstetrics, CT = computed tomography, MRI = magnetic resonance imaging, US = ultrasound

Introduction
The term gestational trophoblastic disease (GTD) encompasses a spectrum of tumors with a wide range of biologic behavior and potential for distant metastases. GTD refers to both the benign and malignant entities in the spectrum and includes hydatidiform mole (complete and partial), invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) (1). The last four are referred to as gestational trophoblastic neoplasia (GTN). All may metastasize and are potentially fatal if untreated.

Epidemiology
A wide global variation in the prevalence of molar pregnancy has been reported, ranging from 12 per 1000 pregnancies in Indonesia, India, and Turkey to one to two per 1000 pregnancies in Japan and China and 0.5 to one per 1000 pregnancies in North America and Europe (2). Likewise, the reported prevalence of choriocarcinoma varies widely worldwide, from a low of two per 100 000 pregnancies in the United States to a high of 202 per 100 000 pregnancies in China (3). The prevalence rates of both hydatidiform mole and...
Figure 1. Genetics of hydatidiform moles. A, Most CHMs are androgenetic, resulting from fertilization of an empty ovum by a single sperm followed by duplication of the paternal haploid genome, resulting in a 46,XX karyotype. B, About 10% of CHMs result from fertilization of an empty ovum by two sperms, resulting in a 46,XX or 46,XY karyotype. C, Most PHMs are androgenetic triploid with two paternal and one maternal haploid set of chromosomes, resulting in triploid karyotype 69,XXX, 69,XXY, or 69,XYY. Rarely, PHMs can be tetraploid with a 92,XXXY genotype.

Pathophysiology and Genetics

Trophoblast cells are the first to differentiate from the fertilized ovum: they form the outer layer of the blastocyst, providing nutrients to the embryo and ultimately forming the fetal portion of the placenta. Normal placental trophoblasts are composed of the cytotrophoblasts, syncytiotrophoblasts, and intermediate trophoblasts. Molar pregnancies and GTNs all take their origin from the placental trophoblasts. Hydatidiform moles and choriocarcinoma arise from the cytotrophoblasts and syncytiotrophoblasts, whereas PSTTs and ETTs arise from intermediate trophoblasts (5).

In 90% of cases, complete hydatidiform mole (CHM) arises when an empty ovum that lost its maternal chromosomes is fertilized by one sperm, which then duplicates its own DNA, resulting in a “complete” 46-chromosome set. A diploid 46,XX androgenetic karyotype then develops, in which all chromosomes are of paternal origin (6,7). About 10% of CHMs are 46,XY, which results when there is fertilization of an ovum void of any chromosomes by two different sperms (6). Partial hydatidiform moles (PHMs) are almost always triploid as a result of fertilization of a healthy ovum by two sperms (6) or by one sperm that reduplicates itself, resulting in the genotypes 69,XXX, 69,XXY, or 69,XYY. Rarely, PHMs can be tetraploid with a 92,XXXY genotype. The genetics of CHMs and PHMs are illustrated in Figure 1.

GTN (invasive mole or choriocarcinoma) follows CHM in 15%–20% of cases and PHM in less than 5% of cases (6). Invasive mole is the most common form of persistent GTD. It almost always occurs after CHM and thus usually has a diploid karyotype that is completely paternal in origin.

Choriocarcinoma is a rare type of GTN and may manifest after a hydatidiform mole, a normal pregnancy, or an abortion (3). Of these, hydatidiform moles are the most common precursor, representing 50% of cases (6). Choriocarcinoma is a malignant β-human chorionic gonadotropin (β-hCG)–producing epithelial tumor with abnormal syncytiotrophoblasts and cytotrophoblasts that lack chorionic villi. It has the potential to invade pelvic structures and metastasize to distant sites.
PSTT and ETT arise from the placental implantation site and are the rarest forms of GTN. They represent neoplastic proliferation of intermediate trophoblasts. PSTT and ETT are two different types of tumors that share many similarities. Both tumors manifest after pregnancy (term pregnancy, abortion, or molar pregnancy) and affect women of reproductive age. These tumors typically occur after nonmolar gestations and may manifest many years after a full-term delivery. They usually grow slowly, tend to spread locally through the uterus, and have a propensity for lymphatic metastasis before hematogenous metastases ensue.

Molar Pregnancy

Clinical Presentation

Because of routine use of ultrasonography (US) and β-hCG testing, patients with CHM are often diagnosed early in gestation and are often asymptomatic at the time of diagnosis (8–10). Common presenting symptoms include vaginal bleeding, usually at 6–16 weeks gestation (46%), large-for-date uterine size (24%), and hyperemesis (14%) (10). The traditionally reported late complications of molar pregnancy such as anemia, pre-eclampsia, hyperthyroidism, and respiratory distress are now rare (8,11,12).

Patients with PHM are less likely to be diagnosed before uterine evacuation, and the diagnosis is usually made with histologic analysis of curettage specimens after incomplete or missed abortion (6,13). As with CHM, the majority of patients with PHM (75%) present with vaginal bleeding; they typically present later than those with CHM (5,13).

CHMs are commonly associated with a markedly elevated β-hCG level. Approximately 50% of patients with CHM have pre-evacuation β-hCG levels greater than 100,000 mIU/mL. On the other hand, such elevated β-hCG levels occur in less than 10% of patients with PHMs (6,13). The clinical differences between various types of GTD are presented in Table 1.

Imaging Findings

Ultrasonography.—US remains the imaging modality of choice for initial evaluation of molar pregnancy. These tumors may be incidentally discovered in asymptomatic patients undergoing routine first-trimester US or patients with clinically suspected molar pregnancy who present with vaginal bleeding or β-hCG titers higher than expected for gestational age.

The salient US feature of CHM during the first trimester is an enlarged uterus filled with a heterogeneous predominantly echogenic mass with several hypoechoic foci, resulting in the so-called snowstorm appearance. The uterine mass contains multiple small anechoic cystic spaces varying in size from 1 to 30 mm. This is described as the “cluster of grapes” appearance and is due to hydropic chorionic villi. In addition to the small cystic spaces, larger irregular fluid collections may be seen in the endometrial mass (14). With advancing pregnancy (particularly during the second trimester), the small cystic spaces become larger and more numerous at imaging. The fetus or fetal parts are absent, except in the rare event of a CHM with a coexisting diploid twin. Multiple large, bilateral, functional ovarian cysts called theca lutein cysts are seen in less than 20% of cases of CHM (8) and result from ovarian stimulation by the high level of β-hCG (Fig 2) (15).

US findings suggestive of PHM include (a) empty gestational sac or one containing amorphous echoes representing fetal parts; (b) elongated or ovoid gestational sac (ratio of transverse to anteroposterior dimension of gestational sac > 1.5) (Fig 3); (c) fetal demise, anomalies, or growth restriction; (d) oligohydramnios; and (e) enlarged placenta relative to the size of the uterus with internal cystic change producing a “Swiss cheese pattern” (Fig 4) (16,17). Differentiating between PHM and CHM carries prognostic significance because of the higher rate of postmolar GTN in CHM (15%–20%) compared with PHM (<5%).

The US appearance of CHM is classic and often florid, yet the performance of US in diagnosing all molar pregnancies is surprisingly poor, predominantly due to the difficulty of differentiating PHM from nonmolar abortion and retained products of conception. Fowler et al (18) reported sensitivity, specificity, positive predictive value, and negative predictive value of 44%, 74%, 88%, and 23%, respectively, for routine pre-evacuation US in detection of all types of hydatidiform moles. Less than 50% of all molar pregnancies are detected at routine US. The detection rate is better for CHM (58%–95%) than for PHM (17%–29%) (18–20).

False-negative results are particularly common, as the presence of a large central fluid collection often mimics an anembryonic gestation or miscarriage (20). In such cases, correlation with clinical features and β-hCG level is imperative, since an anembryonic gestation or miscarriage manifests as normal or declining β-hCG levels, while molar pregnancies have significantly elevated β-hCG levels. False-positive US diagnosis of molar pregnancy also occurs; 10% of cases initially thought to be molar pregnancy at US are diagnosed as nonmolar hydropic abortions at histologic analysis (Fig 5) (18). Because of the poor performance of US in diagnosing molar pregnancies, particularly...
### Table 1: Clinical Features of Various Types of GTD

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Molar Pregnancy</th>
<th>GTN</th>
<th>PSTT and ETT</th>
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<tr>
<td></td>
<td>CHM</td>
<td>PHM</td>
<td></td>
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<tr>
<td>Clinical presentation</td>
<td>Vaginal bleeding, large-for-date uterine size, and hyperemesis</td>
<td>Vaginal bleeding</td>
<td></td>
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<td>Progression to GTN</td>
<td>15%-20%</td>
<td>&lt;5%</td>
<td>NA</td>
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<tr>
<td>Baseline β-hCG level</td>
<td>Very high, &gt;100000 mIU/mL in about 50% of patients</td>
<td>High, &gt;100000 mIU/mL in &lt;10% of patients</td>
<td>High</td>
</tr>
<tr>
<td>Relation to antecedent pregnancy</td>
<td>NA</td>
<td>NA</td>
<td>50% follow molar pregnancy, 25% follow abortion or tubal pregnancy, and 25% follow term or preterm gestation</td>
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<tr>
<td>Time since antecedent pregnancy</td>
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<td>NA</td>
<td>Immediate</td>
</tr>
<tr>
<td>Primary route of metastases</td>
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<td>NA</td>
<td>NA</td>
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<td>Suction dilation and curettage</td>
<td>Suction dilation and curettage</td>
<td>Chemotherapy</td>
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<td>Chemotherapy</td>
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Note.—NA = not applicable.

**Figure 2.** CHM in a 23-year-old woman at 7 weeks and 5 days gestation based on last menstrual period (LMP). (a) Transabdominal gray-scale US image shows an enlarged uterus containing a complex echogenic intrauterine mass (arrows) containing several small cystic areas. (b) Transabdominal gray-scale US image shows an enlarged ovary (arrows) measuring 9 cm that contains multiple large simple-appearing cysts separated by thin septa.
PHM, some authors recommend that all products of conception from nonviable pregnancies undergo histologic analysis (7), irrespective of US findings, and that β-hCG levels be obtained 3–4 weeks after evacuation to ensure normalization of levels.

Computed Tomography.—The role of CT is limited in evaluation of molar pregnancy: it is typically used to stage a suspected malignancy and evaluate for metastatic disease in cases of GTN. Moles are seen at contrast-enhanced CT as an intrauterine mass of low attenuation relative to the enhancing myometrium, with thin enhancing septa (Fig 6). Bilateral ovarian theca lutein cysts may be seen as enlarged ovaries containing multiple fluid-attenuation cysts separated by thin septa in a classic “spoke-wheel” pattern.

MR Imaging.—Pelvic magnetic resonance (MR) imaging has a limited role in assessment of molar pregnancies and is usually used as a problem-solving tool when US is inadequate because of body habitus or when evaluation of the endometrium is limited due to the presence of multiple uterine leiomyomas. In CHM and PHM early in the first trimester, little or no abnormality may be present, although the tumor may be visualized as an expansile heterogeneous mass distending the uterine cavity. When present, the mass demonstrates high signal intensity on T2-weighted images and low signal intensity on T1-weighted images relative to the normal myometrium.

With advancing pregnancy, numerous small internal cysts can be seen within the endometrial mass on T2-weighted images. A thin rim of hypointense myometrium is seen surrounding the mass. The interface between the myometrium and the molar mass is typically sharp and smooth. Numerous signal voids can be seen in the myometrium and adnexa, representing dilated vessels due to intratumoral arteriovenous
Figure 6. CHM in a 21-year-old woman with uterine enlargement and markedly elevated β-hCG levels. Axial contrast-enhanced CT image shows a heterogeneously enhancing expansile mass distending the endometrial cavity (long arrow). Both ovaries are enlarged (short arrows) and contain multiple theca lutein cysts.

Figure 7. CHM in a 38-year-old woman with a large uterus and passage of tissue. (a) Coronal T2-weighted image shows a mass (arrow) filling and distending the endometrial cavity. The mass has high signal intensity relative to the myometrium. (b) Axial T1-weighted image shows a low-signal-intensity mass (long arrows) filling the endometrial cavity. A small focus of high signal intensity (short arrow) is likely due to hemorrhage. (c) Axial gadolinium-enhanced fat-suppressed T1-weighted image shows heterogeneous enhancement of the intrauterine mass (arrow).

shunting and tumor neovascularity (21–25). After administration of gadolinium contrast material, moles typically demonstrate enhancing heterogeneous tissue containing multiple small cystic spaces within the distended endometrial cavity (Fig 7) (21–25).

Unusual Presentations of Molar Pregnancy
Molar pregnancies most commonly occur within the uterine cavity. Two unusual situations may occur that may complicate the clinical picture: (a) twin pregnancy with a CHM and a coexisting normal fetus and (b) ectopic molar pregnancy.

Twin Pregnancy with Molar Pregnancy and Coexisting Normal Fetus.—A healthy co-twin can develop alongside a CHM or PHM in one per 20 000–100 000 pregnancies (26). CHM and healthy co-twin pregnancies have a high risk of spontaneous abortion, but 40% result in live births, without a significant increase in the risk of malignant transformation of the CHM (26).

Twin pregnancy with a CHM and a coexisting normal fetus should be differentiated from other conditions where a fetus is present together with a cystic placenta: (a) PHM and (b) placental mesenchymal dysplasia (PMD). In PHM, cystic spaces within the placenta are seen in conjunction with an anomalous or dead fetus. Thus, if a normal alive fetus with an appropriate size for its gestational age is present together with an abnormal cystic placenta, one should suspect a twin pregnancy consisting of a normal fetus and a CHM (27). Another helpful US sign that may be seen in this situation is the “twin peak” sign, in which chorionic tissue extends into the intertwin membrane, forming a triangular echogenic structure that separates the normal twin sac from that of the molar preg-
nancy, confirming the presence of a dichorionic twin gestation (Fig 8) (28).

Differentiating twin pregnancy with a CHM and a coexisting normal fetus from PMD can be challenging, as both conditions are characterized by an enlarged cystic-appearing placenta at US. The cystic appearance of the placenta in cases of PMD is due to dilated placental vessels, which result in a varying degree of increased vascularity at color Doppler US. This increased vascularity has been described as the “stained-glass” sign by Kuwata et al (29). Conversely, the cysts in molar pregnancy are caused by hydropic swollen villi and do not show blood flow on color Doppler images (29). MR imaging can help distinguish between the two conditions and may obviate amniocentesis and karyotyping. The abnormal placenta in PMD, being a singleton pregnancy, is located within the gestational sac. In contrast, a twin pregnancy with a live fetus and a CHM, being a dizygotic pregnancy, is composed of two separate sacs: one containing the fetus and its normal placenta and the other containing the molar gestation (30,31).

Ectopic Molar Pregnancy.—Ectopic molar pregnancy is an extremely rare condition with an estimated prevalence of approximately 1.5 per 1 million births in the United Kingdom (32). Both CHM and PHM can develop in ectopic sites, with reported cases in the fallopian tube (including the interstitial portion), cervix, and ovaries (33–35). Patients with ectopic molar pregnancies are clinically indistinguishable from patients with ectopic nonmolar pregnancies, although there is a higher tendency to rupture at the time of presentation, resulting in hemoperitoneum (33). US findings include an empty uterus and a complex adnexal mass with or without a live embryo in the setting of tubal and ovarian ectopic pregnancies (33). To our knowledge, the MR imaging features of ectopic molar pregnancy have not been reported in the literature.

We encountered a single case (Fig 9) where MR imaging showed an empty uterus and an adnexal mass, separate from the ovary, with well-defined cysts on T2-weighted images. Areas of high signal intensity on T1-weighted images, presumably attributed to hemorrhage, were seen within the mass. The mass was surrounded by numerous signal voids corresponding to prominent vascular structures and showed heterogeneous enhancement after intravenous administration of gadolinium contrast material. GTN can complicate ectopic GTD, as with an intrauterine molar pregnancy (36). Management of an ectopic molar pregnancy is surgical; the prognosis is similar to that of intrauterine GTD.

Treatment of Hydatidiform Moles
The treatment of choice in women with a hydatidiform mole who wish to preserve fertility is suction dilation and curettage, performed under US guidance to avoid uterine perforation (1). Although
rarely required, hysterectomy may be a viable option for women who have completed childbearing or present with life-threatening hemorrhage.

**Gestational Trophoblastic Neoplasia**

GTN refers to malignant entities in the spectrum of GTD and includes invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT).

**Diagnosis and Clinical Presentation**

Postmolar GTN is usually diagnosed with β-hCG surveillance in asymptomatic patients (37), although some patients present with irregular bleeding after evacuation of a molar pregnancy. After suction evacuation of a molar pregnancy, β-hCG levels should decline, and levels must be thoroughly followed to confirm successful treatment. Patients with β-hCG levels that fail to normalize should be evaluated for GTN, particularly since such patients are generally asymptomatic. A variety of β-hCG criteria have been used to diagnose postmolar GTN; the most accepted are those developed by the International Federation of Gynecology and Obstetrics (FIGO) (Table 2).

Patients with nonmolar GTN may present with abnormal uterine bleeding months to years after delivery. β-hCG levels are usually elevated in choriocarcinoma and only modestly elevated or normal in PSTT and ETT (1). Patients may also initially present with symptoms related to distant metastases: patients with brain metastasis may present with headaches, seizures, or hemiplegia, and patients with lung metastasis may present with dyspnea, cough, and chest pain (6).

**Imaging of Primary Tumor**

**Ultrasonography.**—Pelvic US should be performed in patients with persistently elevated β-hCG levels after initial dilation and suction evacuation for molar pregnancy to exclude a new pregnancy, measure uterine volume, and assess for spread of disease within the pelvis (38). Invasive mole, choriocarcinoma, PSTT, and ETT are seen at gray-scale US as nonspecific focal masses centered within the myometrium with a variable endometrial component (Fig 10a). Patients with more extensive disease may demonstrate invasion through the myometrium and beyond the uterus into the parametrium, vagina, and other pelvic organs. The mass may be hyperechoic or hypoechoic and homogeneous.
Figure 10. Choriocarcinoma in a 24-year-old patient who was referred for vaginal bleeding that developed 2 months after evacuation of a molar pregnancy. (a) Transabdominal gray-scale US image shows a large hyperechoic uterine mass (long arrows) that fills the uterine cavity and invades the posterior myometrium (short arrow), reaching to the serosal surface. Myometrial invasion was confirmed at examination of the biopsy specimen. (b) Transabdominal color Doppler image shows a large, heterogeneous, predominantly hyperechoic vascular mass (long arrows) filling the endometrial cavity and surrounded by highly vascular myometrium (short arrows).

or heterogeneous and may show small anechoic cystic spaces, which represent hemorrhage, necrosis, cysts, or vascular spaces (37,39).

At color Doppler US, the mass is usually highly vascular due to intrallesional arteriovenous shunts, resulting in increased vascularity within the myometrium (Fig 10b). However, varying degrees of vascularity have been described with different types of GTN, ranging from minimally to highly vascular lesions (37,39,40). At spectral Doppler US, trophoblastic vessels demonstrate a high-velocity low-resistance waveform (37). The size of the uterine mass has prognostic value, and the maximal diameter of the mass, in centimeters, should be measured in every case.

The gray-scale and Doppler US appearance of GTN is not specific for any particular variant and may be difficult to differentiate from those of benign uterine processes, including fibroids, adenomyomas, and retained products of conception, or primary and secondary pelvic malignancies. Accurate diagnosis depends on correlation with clinical findings and β-hCG levels.

A specific US appearance that may aid in differentiating ETT from other types of GTN has been described as a well-circumscribed mass with sharp borders and a peripheral halo of low echogenicity at gray-scale US and peripheral increased vascularity at color Doppler US (41,42). However, this pattern is not characteristic of all cases of ETT, and lesions may demonstrate decreased vascularity (Fig 11) (42).

Certain Doppler parameters such as the resistive indexes (RIs) and uterine artery pulsatility index (UAPI) can help in evaluation of GTN. Zhou et al (37) showed significantly lower RIs in invasive moles (0.28) and choriocarcinoma (0.25) compared with CHM (0.55) and PHM (0.56).

UAPI is inversely proportional to tumor vascularity, and a low UAPI is indicative of increased uterine blood flow and arteriovenous shunting, a feature of neo-angiogenesis, classically seen in tumors. Multiple studies demonstrated that a median UAPI of 1 or less can serve as an independent marker to predict methotrexate resistance (43,44), and this is now being evaluated in a prospective trial (45).

Computed Tomography.—While CT is useful in evaluation and staging of metastatic disease, it has a limited role in evaluation of the primary tumor. Nevertheless, the primary tumor may be seen as a focal low-attenuation mass within an enlarged uterus that typically involves the myometrium (Fig 12).

MR Imaging.—The MR imaging appearance of GTN is nonspecific, and differentiation between the various types of GTN is limited. Accurate differentiation between GTN and benign processes such as retained products of conception is likewise difficult. MR imaging features include a sharply margined or ill-defined mass centered within the myometrium that distorts or displaces
the junctional zone. Such a mass is usually isointense on T1-weighted images and hyperintense on T2-weighted images, relative to the normal myometrium, with avid enhancement after intravenous administration of gadolinium contrast material (Fig 13). Areas of increased signal intensity on T1-weighted images may be seen due to hemorrhage. Numerous prominent vessels are typically seen within the myometrium surrounding the tumor due to increased vascularity (Figs 13–15) (24,46). MR imaging is superior to US in evaluation of extrauterine pelvic tumor extension and pelvic lymph nodes and may be useful in tumors that are poorly visualized at US.

Two different MR imaging patterns have been described with PSTTs. A hypervascular pattern may be seen that is indistinguishable from that of other types of GTN. A hypovascular pattern may occur as a mass without signal voids that is isointense to normal myometrium on T1-weighted images and isointense to slightly hyperintense on T2-weighted images. The degree of enhancement after intravenous administration of gadolinium contrast material is similar to that of normal myometrium, but there may be a central area of nonenhancement (22).

Few reports are available on the MR imaging appearance of ETT in the literature (47,48). The tumor has been described as a well-circumscribed mass that is hyperintense to normal myometrium on T2-weighted images and isointense on T1-weighted images, with heterogeneous enhancement after gadolinium contrast material administration. We encountered a case of ETT that demonstrated low signal intensity relative to normal myometrium on T2-weighted images, intermediate signal intensity on T1-weighted images, and poor enhancement with gadolinium contrast material (Fig 15). The mass was initially thought to represent a leiomyoma or adenomyoma at imaging; the diagnosis of ETT was eventually established with histopathologic analysis.

Imaging of Distant Metastases

Approximately 30% of patients with GTN have metastases at the time of diagnosis, most commonly to the lungs (80% of cases), vagina (30%), liver (10%), and brain (10%). Other sites include the skin, gastrointestinal tract, kidney, breast, and bones (49). Therefore, imaging of the lungs is recommended for all patients with GTN. However, there is an ongoing debate regarding whether chest radiography is sufficient for staging or whether there is a need for chest CT. While chest CT is much more sensitive and allows detection of lung metastases with greater accuracy than plain radiography, some researchers argue that there is no potential advantage in terms of overall patient outcome to justify the increased radiation exposure of chest CT, particularly in women of reproductive age (38,50,51).

Patients with lung metastases, detected with chest radiography or chest CT, are at increased risk for central nervous system and abdominal solid organ metastases. Therefore, MR imaging
Figure 13. Choriocarcinoma in a 26-year-old woman with metastatic pulmonary nodules. (a) Axial T2-weighted image shows a hyperintense myometrial mass (arrows). (b) Axial T1-weighted image shows a myometrial mass (long arrow) with areas of high signal intensity due to hemorrhage (short arrow). (c) Sagittal gadolinium-enhanced fat-suppressed T1-weighted image shows intense enhancement of the mass (arrows).

Figure 14. PSTT in a 17-year-old girl with vaginal bleeding 9 months after full-term vaginal delivery. (a) Sagittal T2-weighted image shows a mass centered in the inner myometrium (arrow) that distorts the junctional zone and projects into the endometrial canal. The interface between the mass and surrounding myometrium is ill defined. The mass has high signal intensity relative to the myometrium. (b) Sagittal gadolinium-enhanced fat-suppressed T1-weighted image shows moderate enhancement of the mass (arrow).

of the brain and CT of the abdomen are recommended to evaluate for extrapulmonary metastatic disease, as such findings may substantially alter staging and subsequent management.

The reported prevalence of brain metastases in GTN ranges from 3.4% to 8.8% (52,53). The majority of cases (85%) occur in women with nonmolar choriocarcinoma, who have an approximate 20% risk of developing brain metastasis, emphasizing the importance of routine brain imaging in this group (54). On the other hand, the estimated prevalence of brain metastases in post–molar pregnancy GTN is extremely low, approximately one in 22,000. Brain metastases often develop in the setting of disseminated disease, and the majority of patients have lung metastases at the time of diagnosis (55).

Patients with postmolar GTN who have no evidence of lung metastasis are not required to have brain MR imaging or abdominal CT. For those with a histologic diagnosis of choriocarcinoma or suspected GTN after a nonmolar pregnancy, initial evaluation should include US of the pelvis, CT of the chest and abdomen, and MR imaging of the brain and pelvis (38).

Although positron emission tomography (PET)/CT can demonstrate sites of metastatic disease as areas of increased metabolic activity, the technique offers no clear advantage in tumor staging compared with conventional imaging (56).
Figure 15. ETT in a 31-year-old woman. (a) Axial T2-weighted image shows a well-circumscribed mass centered in the myometrium and projecting into the endometrial canal (arrows) with a sharp interface between the mass and surrounding myometrium. The mass has low signal intensity relative to the myometrium. (b) Axial gadolinium-enhanced fat-suppressed T1-weighted image shows a well-circumscribed mass centered in the myometrium and projecting into the endometrial canal (long arrows), with poor enhancement relative to the myometrium. Note the right ovarian physiologic follicle (short arrow).

Table 3: Indications for Imaging Tools Used in Staging of GTN, Characteristic Findings, and Important Findings to Include in the Radiology Report

<table>
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<th>Imaging Study</th>
<th>Indications</th>
<th>Characteristic Findings</th>
<th>Important Findings to Report</th>
</tr>
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<tbody>
<tr>
<td>Pelvic US with Doppler imaging</td>
<td>Both postmolar and nonmolar GTN</td>
<td>Nonspecific focal mass centered in myometrium with variable endometrial component</td>
<td>Location of mass (myometrial or endometrial)</td>
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<td>Size of lesion in centimeters</td>
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<td>Resistive index</td>
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<td>Uterine artery pulsatility index</td>
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<td>Pelvic MR imaging</td>
<td>Both postmolar and nonmolar GTN</td>
<td>Nonspecific focal mass centered in myometrium with variable endometrial component</td>
<td>Location of mass (myometrial or endometrial)</td>
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<td>Pelvic lymphadenopathy</td>
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<td>Chest radiography or CT</td>
<td>Both postmolar and nonmolar GTN</td>
<td>Multiple pulmonary nodules with or without halo of ground-glass attenuation</td>
<td>Number of lesions and size in centimeters</td>
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<td>Abdominal CT</td>
<td>Postmolar GTN with confirmed lung metastases</td>
<td>Arterially enhancing focal masses in solid abdominal organs</td>
<td>Organs involved</td>
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<td></td>
<td>Nonmolar GTN</td>
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<td>Number of lesions and size in centimeters</td>
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<tr>
<td>Brain CT or MR imaging</td>
<td>Postmolar GTN with confirmed lung metastases</td>
<td>Hemorrhagic and enhancing brain masses</td>
<td>Number of lesions and size in centimeters</td>
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<td></td>
<td>Neurologic manifestations</td>
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However, PET/CT may be helpful in discriminating ambiguous lesions at routine imaging workup and in evaluating disease recurrence that may not be detected at conventional imaging in the setting of elevated β-hCG level (57). Figure 16 represents an algorithm for imaging staging of GTN.

**Lung Metastases.**—The most frequent thoracic manifestation of metastatic disease is multiple well-defined, rounded, soft-tissue-attenuation pulmonary nodules (23,58), although some patients may present with a single nodule. Other patterns of pulmonary metastatic disease have been reported and can be detected with chest CT. A common pattern is a small nodule surrounded by a halo of ground-glass attenuation, the so-called halo sign, which results from peritumoral hemorrhage (Fig 17) (59). Cavitory and bulla-forming pulmonary metastases may occur, which can result in pneumothorax (60,61).

Tumor embolism can be seen, in which tumor growth is limited to the pulmonary arteries without extension into the lung parenchyma. Imaging findings of tumor embolism include multifocal dilatation and beading of the peripheral subsegmental arteries. Peripheral wedge-shaped areas of increased parenchymal attenuation may likewise develop due to adjacent pulmonary infarction (59). Endobronchial tumors have been reported, resulting in obstructive atelectasis, and may
manifest as an intrabronchial mass at CT (62). Pulmonary arteriovenous fistulas (AVFs) can develop after chemotherapeutic treatment of metastatic choriocarcinoma (63), while calcifications can be seen in treated lesions (64).

**Brain Metastases.**—Brain metastases from GTN may be single or multiple (52,53,55), are usually located at the gray-white matter junction of the cerebral hemispheres, and have a propensity to spontaneously hemorrhage (Fig 18). Such lesions show high attenuation at nonenhanced CT and variable signal intensity at MR imaging, depending on the chronicity of the intralesional hemorrhage. Brain metastases are highly vascular and usually avidly enhance after contrast material administration.

**Other Sites of Metastatic Disease.**—The prevalence of liver metastases from GTN approximates 1.8%–3.4% (65). As with brain metastases, liver metastases are rare and more likely to manifest with nonmolar GTN (75% of cases) and in the presence of other distant metastases (66). Lesions are typically multiple and rounded and may be heterogeneous due to the presence of hemorrhage. Similar to other hypervascular metastases, liver metastases avidly enhance during the arterial phase and may not be visible during the portal venous phase after intravenous contrast material administration. Arterial phase imaging should be part of the screening protocol in such patients (Fig 19) (21). At MR imaging, their appearance is essentially identical to that of other hypervascular liver metastases.

A variety of other hematogenous metastatic sites have been reported, including the spleen (Fig 20), kidneys, ovaries, gastrointestinal tract, spine, and skin (67). Lymphatic spread (to pelvic lymph nodes) is usually seen with PSTTs (67).

The indications for different imaging tools used in staging of GTN, characteristic imaging findings, and important findings to include in the radiology report are summarized in Table 3.

**Treatment of GTN**

Treatment of GTN generally involves chemotherapy, although surgical intervention may be required for management of complications. The optimal regimen depends on the anatomic stage and a scoring system based on prognostic factors. Tables 4 and 5 summarize the 2000 FIGO staging and classification system. A risk score of 6 or below is considered low risk, while a score above 6 is considered high risk.

Patients with low-risk GTN should be treated with a single chemotherapeutic agent, either methotrexate or actinomycin D. Patients in whom first-line therapy fails (generally due to drug resistance) can be easily treated with second-line or occasionally third-line salvage chemotherapy, with an overall survival rate approaching 100% (68). Multiagent chemotherapy regimens are used to treat high-risk GTN. The most commonly used is EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine), with a complete remission rate of approximately 85%.

Simple hysterectomy is the most appropriate treatment option in most cases of PSTT and ETT, since both tumors are less chemosensitive than choriocarcinoma (69). Radical resection
including bilateral salpingo-oophorectomy and abdominal/pelvic lymph node dissection is indicated in patients with advanced disease, and imaging can guide the management decision. CT of the thorax and abdomen, transvaginal US, MR imaging of the brain, and fluorodeoxyglucose (FDG) PET/CT may be performed if there is suspicion of metastatic disease. Conservative management such as uterine curettage, hysteroscopic resection, and chemotherapy may be considered in young patients with localized disease who wish to preserve fertility (1,7).

**Prognosis and Follow-up after Treatment**

Patients with nonmetastatic GTN (stage I) and low-risk metastatic GTN treated with single-agent chemotherapy have cure rates approaching 100%. Patients classified as having high-risk metastatic disease treated with multiagent chemotherapy with or without adjuvant radiation therapy or surgery have cure rates of 80%-90% (70).

Frequent β-hCG surveillance is recommended for at least 12 months after GTN treatment to ensure remission. Imaging is not routinely

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**Figure 18.** Brain metastasis in a 28-year-old woman with choriocarcinoma who presented with seizures. (a) Axial nonenhanced CT image shows a left occipital hyperattenuating mass (arrow) due to the presence of hemorrhage. (b) Axial T2-weighted image shows a heterogeneous left occipital mass (long arrow) with a dark hemosiderin ring, surrounded by extensive vasogenic edema (short arrows). (c) Axial T1-weighted image shows a heterogeneous left occipital mass (arrow) with areas of high signal intensity due to the presence of blood products. (d) Axial gadolinium-enhanced fat-suppressed T1-weighted image shows heterogeneous enhancement of the mass (arrow).
performed unless complications are suspected. Uterine abnormalities and ovarian theca lutein cysts usually resolve at imaging after effective chemotherapy. However, abnormal imaging findings may temporarily persist after clinical improvement and β-hCG normalization (46). US usually shows a progressive decrease in the size and echogenicity of the uterine mass (71).

At pelvic MR imaging, uterine lesions tend to decrease in size with concomitant restoration of uterine zonal anatomy. The degree of tumoral enhancement appears to correlate with β-hCG level, which decreases after repeated courses of chemotherapy (Fig 21) (46).

**Other Complications of GTD**

**Acquired Uterine AVM**

An arteriovenous malformation (AVM) can be defined as a vascular structural anomaly involving abnormal communication between arteries and veins that bypass the capillary system (72). The presence of arteriovenous shunting is part of the pathogenesis of GTD and results from uncontrolled proliferation of trophoblasts and invasion of the myometrium. Uterine vascular malformations may persist in up to 10%–15% of patients even after complete resolution of GTD (73). A small minority of patients (2%) with uterine AVMs may require treatment for...
Table 4: FIGO Staging and Classification for GTN

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Gestational trophoblastic tumors strictly confined to uterine corpus</td>
</tr>
<tr>
<td>II</td>
<td>Gestational trophoblastic tumors extending to adnexa or vagina but limited to genital structures</td>
</tr>
<tr>
<td>III</td>
<td>Gestational trophoblastic tumors extending to lungs, with or without genital tract involvement</td>
</tr>
<tr>
<td>IV</td>
<td>All other metastatic sites</td>
</tr>
</tbody>
</table>

Table 5: FIGO/WHO Scoring System for GTN Based on Prognostic Factors

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Risk Factor Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factor Scores</td>
<td>0</td>
</tr>
<tr>
<td>Age (y)</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>Mole</td>
</tr>
<tr>
<td>Interval from index pregnancy (mo)</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Pretreatment β-hCG level (mIU/mL)</td>
<td>&lt;10^3</td>
</tr>
<tr>
<td>Largest tumor size including uterus (cm)*</td>
<td>...</td>
</tr>
<tr>
<td>Site of metastases including uterus*</td>
<td>Lung</td>
</tr>
<tr>
<td>Number of metastases identified*</td>
<td>...</td>
</tr>
<tr>
<td>Previous failed chemotherapy</td>
<td>...</td>
</tr>
</tbody>
</table>

Note.—To stage a tumor and assign a risk factor score, the stage is represented by Roman numeral I, II, III, or IV. This is then separated by a colon from the sum of all the risk factor scores expressed in Arabic numerals (eg, stage II:4, stage IV:9). WHO = World Health Organization.

*Information obtained with imaging.

Figure 21. Invasive mole in a 33-year-old woman with vaginal bleeding. (a) Sagittal T2-weighted image at initial diagnosis shows a predominantly hyperintense heterogeneous mass (arrow) centered in the myometrium in the region of the fundus. (b) Sagittal gadolinium-enhanced fat-suppressed T1-weighted image at initial diagnosis shows that the mass has heterogeneous enhancement (arrow). Pathologic evaluation revealed hydropic villi, consistent with an invasive mole. (c) Sagittal T2-weighted image after methotrexate treatment shows interval decrease in the size of the mass (arrow) and in its signal intensity. (d) Sagittal gadolinium-enhanced fat-suppressed T1-weighted image after methotrexate treatment shows interval decrease in the degree of enhancement of the mass (arrow).
refractory vaginal bleeding. AVMs may complicate any type of GTD and may be evident at initial presentation or develop many months after treatment. The median time interval for an AVM presentation is 5 months after completion of chemotherapy with a range of 0–13 years (74).

The gray-scale US findings of uterine AVMs are usually subtle and nonspecific, and a definitive diagnosis of a uterine AVM cannot be made on the basis of gray-scale findings alone. A heterogeneous mass or subtle area of uterine heterogeneity may be seen, occasionally with anechoic tortuous tubular structures within the myometrium. Color and spectral Doppler features of a uterine AVM are generally straightforward, consisting of a tangle of vessels with multidirectional high-velocity flow that produces a chaotic color mosaic pattern (Fig 22). Spectral Doppler analysis shows the characteristic features of arteriovenous shunting with high-velocity and low-resistance blood flow (75,76).

Typical MR imaging findings of an AVM include a focal uterine mass consisting of a group of distinct serpentine flow voids on T2-weighted images, with an ill-defined border that disrupts the junctional zone. Prominent parametrial vessels are likewise commonly seen (Fig 22) (77). Intrauterine and parametrial vascular enhancement with an early draining vein is commonly seen after intravenous administration of gadolinium contrast material.

Imaging findings at conventional angiography include an enlarged feeding uterine artery, an associated vascular nidus in the endometrium or myometrium, and early venous drainage, occasionally with a pseudoaneurysm (Fig 22) (77). Transcatheter vascular embolization has become the treatment of choice for patients wishing to preserve fertility or who present with massive bleeding (77,78).

Pulmonary AVF

As with uterine AVMs, persistent arteriovenous shunts may develop within pulmonary metastases from choriocarcinoma after successful completion of chemotherapy (63,79,80). While patients with small lesions are generally asymptomatic, patients with larger lesions may present with hemoptysis, exertional dyspnea, cyanosis, and clubbing. Cerebral complications such as stroke and cerebral abscess may develop as a result of paradoxical cerebral emboli.

After treatment of GTN with pulmonary metastatic lesions, follow-up chest CT usually shows a progressive decrease in size of the pulmonary nodules with eventual complete resolution or focal scar. Persistence of lung nodule(s), when all other nodules have resolved, should raise the possibility of an AVF (63,79). CT may reveal the supplying pulmonary artery and draining pulmonary vein (63). Perilesional ground-glass opacities (halos) may be seen in the setting of recent hemorrhage (80). Transcatheter embolization is the procedure of choice for treatment of amenable pulmonary AVFs (81).

Conclusion

GTD is a complex spectrum of related disorders originating from the placenta. The morbidity and mortality from GTD were substantial before the advent of sensitive assays for β-hCG. However, the vast majority of women currently afflicted with GTD have favorable outcomes, largely due to improved surveillance techniques and state-of-the-art chemotherapeutic regimens.

Imaging plays an important role in diagnosis and management of GTD. US remains the modality of choice for initial evaluation of suspected GTD and likewise allows reliable assessment for residual or recurrent disease. CT plays an important role in staging of suspected systemic metastatic disease in the chest and abdomen. MR imaging allows reliable assessment for spread of extrauterine disease and local complications. Brain MR imaging likewise provides a superior means of assessing for central nervous system metastases.

Transcatheter embolization is an essential tool for managing complications of GTD, including refractory uterine hemorrhage or chemomobilization of liver metastases. Clinical radiologists involved in assessment of GTD must be familiar with the salient imaging features of these complex disorders, as well as appropriate application of various imaging modalities to provide an early diagnosis and guide effective clinical management.

References

Figure 22. AVM in a 33-year-old woman with massive vaginal bleeding 2 weeks after initiation of treatment for an invasive mole. (a) Transvaginal color Doppler image shows a focal area of markedly increased vascularity and multidirectional flow (arrows), producing a chaotic color mosaic pattern. (b) Sagittal T2-weighted image shows a hyperintense mass (arrow) centered on the endometrium and invading the anterior myometrium. Multiple signal voids (enlarged vascular structures) are seen in the mass and adjacent myometrium. (c) Right internal iliac artery angiogram during the arterial phase shows opacification of an enlarged right uterine artery (arrow). (d) Right internal iliac artery angiogram during the late arterial phase shows a nidus of contrast material blush (long arrow) with early venous drainage (short arrows).


38. Chou SH, Goo JM, Kim HC, Im JG. Pulmonary arteriovenous fistulas developed after chemotherapy of metastatic choriocarcinoma. AJR Am J Roentgenol 2015;204(3):630–634.
