Imaging Shapes of Gestational Trophoblastic Disease

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Learning objectives

To review the pathophysiology of gestational trophoblastic disease (GTD).

To illustrate and describe the imaging spectrum of GTD presentations on ultrasound (US), magnetic resonance imaging (MRI) and computed tomography (CT).

To recall the utility of the different imaging techniques in GTD management.

Background

GTD is an uncommon outcome of very early gestation, accounting for less than 1% of gynaecologic neoplasms. This entity is usually benign and easily treatable, but occasionally progresses to an aggressive, potentially fatal process.

It encompasses a broad spectrum of conditions which include commonly complete hydatidiform mole, invasive mole, choriocarcinoma, and less frequently partial hydatidiform mole and placental site trophoblastic tumour. All these forms have in common an initial fertilization event which evolutes to a proliferative process similar to normal trophoblast. The chromosomal makeup of these different lesions varies, being always different from that of the maternal host. They present morphologic and histologic similarities among themselves, and the exact radiologic diagnosis is not always possible, with the final diagnosis often based on the patient’s outcome after months or even years of follow-up.

Actually, GTD is staged by the latest International Federation of Gynecology and Obstetrics (FIGO) staging system (and modified World Health Organization [WHO] prognostic scoring system) (Figure 1).
Fig. 1: International Federation of Gynecology and Obstetrics (FIGO) staging and classification of Gestational trophoblastic disease and modified World Health Organization (WHO) prognostic scoring system.


**Findings and procedure details**

The radiologic forms of presentation of this diverse group of gynaecologic malignancies, depends on their aggressiveness.

**US** is the key imaging tool for **GTD initial diagnosis** and for exclusion of normal intrauterine pregnancy.
MRI and CT are usually reserved for the evaluation of loco-regional spread, by determining the extension of molar tissue into the myometrium or outside the uterus, into pelvic organs and lymph node involvement, or distant metastatic disease evaluation, and associated complications.

HYDATIDIFORM MOLE (COMPLETE or PARTIAL)

Hydatidiform mole constitutes 80% of cases of GTD and includes both complete hydatidiform mole (also known as classic hydatidiform mole) and partial hydatidiform mole. These are noninvasive processes that demonstrate both proliferation and hydropic swelling of the villi. On histology, the villi have a prominent, central acellular space, which accounts for the macroscopic appearance of fluid-filled vesicles. Occasionally, necrosis is seen. In addition, microscopic evaluation shows trophoblastic hyperplasia, which accounts for the characteristic marked elevation of #-hCG levels, which may lead to hyperemesis or development of theca lutein cysts.

Complete Hydatidiform Mole

Complete hydatidiform mole typically presents with hyperemesis gravidarum or uterine size larger than expected for the estimated gestational age. The serum #-hCG level is usually considerably higher than expected for the estimated gestational age. This finding is variable, and #-hCG level may be within the expected range for a first trimester pregnancy.

US is used primarily to rule out a normal intrauterine pregnancy. However, the imaging appearance may also allow one to suggest the diagnosis of complete hydatidiform mole. US confirms uterine enlargement in more than 60% of cases. A moderately echogenic, central uterine mass is seen on sonograms (Figure 2 A and B).
Fig. 2: Complete hydatidiform mole in a 26-year-old woman. Transversal (A) and longitudinal (B) sonogram images of the uterus shows distention of the uterine cavity by echogenic material. Axial (C), sagittal (D) T2-weighted images and sagittal fat-suppressed T1-weighted image (E) demonstrate in the uterine fundus a large and heterogeneous mass with cystic spaces distending the uterine cavity, with flow void images (pink arrows) from high flow blood vessels. On sagittal dynamic study (F) this lesion presents intense enhancement of the solid component, due to hypervascularity. There is no obvious myometrial invasion.

References: Department of Radiology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon/PT

The previously described as "snowstorm" or "granular" appearance of multiple echogenic foci, with the modern equipment, is now identified as numerous, discrete, anechoic (cystic) spaces within a central area of heterogeneous echotexture (Figure 3 A and B).

The small cystic areas correspond to the hydropic villi tipically seen at gross pathologic examination, rather than to areas of haemorrhage. Haemorrhage is not a typical pathologic feature of complete hydatidiform mole, although it is occasionally associated with choriocarcinoma.
**Complete hydatidiform mole** has an extremely variable presentation in the first trimester. It can correspond to large, central fluid collection mimicking an anembryonic gestation or abortion (missed or incomplete). Occasionally, there is merely a central mass of variable echogenicity, presumably because the villi are too small to be seen with sonography at this time.

The coexistence of a fetus with a complete hydatidiform mole is uncommon, in opposition to the partial hydatidiform mole, the former occurring in 1%-2% of cases, usually results from dizygotic twinning, and in contrast to the mole, the fetus is chromosomally normal. However, fetal survival until term is unlikely because of the maternal complications of the mole itself.

Ovarian enlargement with cyst formation, in up to 40% of cases, is another clue to the diagnosis of GTD. These theca lutein cysts are a form of ovarian hyperstimulation and result from high circulating levels of #-hCG typically associated with GTD. Theca lutein cysts are multiloculated and often bilateral (Figure 3 D). Occasionally, they can complicate with haemorrhage or rupture, and usually resolve within a few months after removal of the causative factor. They can be associated with more aggressive forms of GTD, like invasive mole or choriocarcinoma; and nonneoplastic complications as hyperthyroidism, bleeding or anaemia.

MRI may demonstrate a heterogenous mass with cystic spaces distending the uterine cavity (Figure 3 E, F and G). Fetal parts are notably absent. Uterine zonal anatomy is often distorted although a hypoechoic irregular myometrial boundary may be seen (Figure 2 C, D and E). T1-weighted images may show areas of high signal corresponding due to foci of haemorrhage. Usually, on T2-weighted images there is heterogenous high signal from the cystic spaces (Figure 2 C and D), (Figure 3 E and F). Dynamic studies often demonstrates intense enhancement due to hypervascularity (Figure 2 F and Figure 3 H). MRI may also demonstrate bilateral theca lutein cysts.
Fig. 3: Complete hydatidiform mole. Transversal sonogram image (A) of the uterus shows distention of the uterine cavity by numerous, discrete, anechoic (cystic) spaces within a central area of heterogeneous echotexture, previously known as "snowstorm" or "granular". Doppler ultrasound (B) shows a hypervascularized lesion. Axial enhanced-CT scans show a low-attenuation uterine central mass with intact myometrium (C) and bilateral theca lutein cysts (pink arrows)(D). Sagittal (E) and axial (F) T2-weighted images and axial T1-weighted image (G) demonstrate an heterogeneous intrauterine mass with cystic spaces. On sagittal dynamic study (H) this lesion presents early enhancement of the solid component, due to hypervascularity, without obvious myometrial invasion.

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Treatment is curative in approximately 85% of patients, typically consisting in dilatation and suction curettage, confirming the diagnosis.

15% of women with complete hydatidiform mole will develop recurrent disease in the form of invasive mole or choriocarcinoma. These cases cannot be identified at the time of initial diagnosis. Because of this unpredictable outcome in a patient with a presumptive diagnosis of complete hydatidiform mole based on laboratory,
radiologic, and microscopic features, all patients are followed-up with successive serum #-hCG measurements during the 1st year after treatment of complete hydatidiform mole, to allow early detection of persistent gestational trophoblastic neoplasia, like invasive mole and choriocarcinoma.

This way, clinical diagnosis of complete hydatidiform mole is reached only when serial testing levels during the 1st year after treatment of complete hydatidiform mole shows progressive decrease in the serum #-hCG level, confirming the absence of persistent gestational trophoblastic neoplasia.

Partial Hydatidiform Mole

Partial hydatidiform mole has different pathologic characteristics from those of complete hydatidiform mole, since the former has normal villi interspersed with hydropic villi. In comparison with complete hydatidiform mole, partial hydatidiform moles have much less trophoblastic proliferation, which typically appears as focal projections of syncytiotrophoblast. The abnormal gametogenesis that precedes the partial hydatidiform mole results in a triploid karyotype with both maternal and paternal DNA, usually due to fertilization of a single ovum with two sperm. The fetus is also triploid and does not survive.

Clinically, patients with partial hydatidiform mole may present in a manner indistinguishable from those with complete hydatidiform mole, or from patients with a first- or second-trimester pregnancy. Frequently, these patients present with spontaneous abortion.

Sonographic clues for this diagnosis are the presence of a fetus in combination with a formed placenta containing numerous cystic spaces (Figure 4 A and B).

CT and MRI evaluation are not usually performed initially but may be used to determine if there is extension of molar tissue outside the uterus (Figure 4 C, D and E). CT may show an enlarged uterus with areas of low attenuation, or hypoattenuating foci surrounded by highly enhanced areas in the myometrium.
Fig. 4: Partial hydatidiform mole. Transversal sonogram image (A) of the uterus shows a fetus in combination with a formed placenta containing numerous cystic spaces. Doppler ultrasound (B) shows an hypervascularized lesion. Sagittal T2-weighted image (C) and fat-suppressed T1-weighted image (D) show an heterogeneous lesion in the posterior myometrial wall. On sagittal dynamic study (E) this lesion presents early enhancement of the solid component, due to hypervascularity, with areas of decreased myometrial thickness, without obvious uterine serosal invasion.

References: Department of Radiology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon/PT

These patients are normally followed-up with serial measurements of $\Delta$-hCG level, even though the risk for persistent gestational trophoblastic neoplasia is lower (3%) than for patients with a complete hydatidiform mole.

INVASIVE MOLE
Invasive mole is the less aggressive of the two forms of persistent GTD and is seen in about 10% of patients after treatment of complete hydatidiform mole, and less frequently in patients with partial hydatidiform mole.

Clinical presentation consists in bleeding and persistent elevations in the serum #-hCG level.

Like complete hydatidiform mole, an invasive mole has hydropic villi, along with trophoblast proliferation. However, as the term invasive mole implies, there is macroscopic and microscopic invasion into the myometrium and blood vessels by the trophoblastic neoplasm itself. This presentation is similar to the normal vascular invasion that must occur as the early trophoblast establishes communication with the maternal circulation. Villous elements are occasionally seen in the maternal pulmonary circulation in normal third trimester pregnancies and in the peripartum period. Although venous invasion, and occasionally spread to the lungs (Figure 5), may occur in the presence of an invasive mole, these metastases do not necessarily mean that the lesion is a true malignancy.
Fig. 5: Chest CT images of a 26-year-old woman with an invasive mole. Multiple bilateral pulmonary small nodules (pink arrows) secondary to an invasive mole. References: Department of Radiology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon/PT

Imaging may show a central uterine process similar to that described for complete hydatidiform mole, myometrial invasion may be seen (Figure 6).

The most important utility of US in the patient with suspected persistent GTD is to exclude pregnancy as a cause for the elevated hCG level. Occasionally, extension of the mass into the myometrium can be evaluated, as well as involvement of the parametrium. On US, invasive mole may be seen as a heterogeneous echogenic vascular mass invading the myometrium (Figure 6 A). Doppler US may be useful in the characterization of GTD, because these vascular tumours tend to show high blood flow, typically with high diastolic flow (Figure 6 B), probably in relation with decreased vessel tone in the proliferating neoplasm, which have been identified in patients with persistent GTD.

On MRI these lesions appear as a poorly defined, heterogeneous, hypervascular masses that deeply invades the myometrium and distort the normal zonal anatomy (Figure 6 D, E, F and G). Abnormal signal intensity may be seen in the myometrium or parametrium indicating tumour invasion. On T1-weighted images appear isointense to the myometrium with scattered foci of high signal intensity (from the presence of haemorrhage). On T2-weighted-images has mixed signal intensity (Figure 6 D and E). Molar-like structures appear as tiny cystic lesions within the well-enhanced zone of trophoblastic proliferation in a mass of the invasive mole. With the penetration of the tumour into the myometrium, the invasive mole can appear as a more aggressive entity compared with a choriocarcinoma.
**Fig. 6:** Invasive mole in a 22-year-old woman. Transversal (A) and sagittal (B) sonogram images of the uterus shows an heterogeneous echogenic mass invading the myometrium. Sagittal Doppler US (C) tipically demonstrate a hypervascularized lesion. Coronal (D) and sagittal (E) T2-weighted images and fat-suppressed T1-weighted image (F) show two heterogeneous lesions in the anterior myometrial wall. On sagittal dynamic study (G) these lesions present solid component early enhancement, due to hypervascularity, with areas of decreased myometrial thickness, without obvious uterine serosal invasion.

**References:** Department of Radiology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon/PT

The **treatment** for either **invasive mole** is generally **chemotherapy**, therefore exact histologic diagnosis is not usually needed. This way, a patient with **persistent GTD**, typically characterized by **failure of the #-hCG to return to undetectable levels after treatment of a complete hydatidiform mole**, is **presumed** to have an **invasive mole unless** there is **clinical** or **radiologic evidence for metastases. Hysterectomy** for invasive mole may be required in a **minority of case**, when the patient is thought to be at **risk for uterine perforation.**
CHORIOCARCINOMA

Approximately 5% of cases of complete hydatidiform mole are followed by choriocarcinoma, although in the United States this number may be decreasing and may be less than 2%. Only about half the cases of choriocarcinoma arise from complete hydatidiform mole. An additional 25% of cases arise after normal pregnancies, and 25% follow spontaneous abortion or ectopic pregnancy.

Histologically, choriocarcinomas have extensive necrosis and hemorrhage. A biphasic population of cytotrophoblasts and syncytiotrophoblasts predominates; some intermediate trophoblasts may also be seen, but there are no villi. Early and extensive vascular invasion is common, which may result in metastatic disease even when the primary tumour is quite small. The majority of metastases go to the lungs (75%) (Figure 7 A and B) and vagina (50%). Vulva, kidneys, liver (Figure 7 D, E and F), ovaries, brain (Figure 7 C), and bowel are also frequent sites of secondary involvement. Commonly, the gross morphologic characteristics reflect the aggressive and invasive nature of the lesion, with prominent haemorrhage and necrosis.
Fig. 7: Choriocarcinoma metastases. Chest x-ray (A) and chest CT (B) images show multiple bilateral pulmonary nodules. Head CT (C) demonstrates three brain secondary lesions. Axial T2-weighted image (D) demonstrates a choriocarcinoma metastasis on the right liver, with high signal intensity on diffusion b1000 (E) and restriction on ADC map (F), in concordance with hypercellular nature.

References: Department of Radiology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon/PT

The presence of an elevated # hCG level in the absence of an intrauterine pregnancy gives rises the suspicion of a GTD, including choriocarcinoma.

On the different imaging techniques, choriocarcinoma often appears as a mass enlarging the uterus (Figure 8), sometimes it manifests as a discrete, central, infiltrative mass. Its heterogeneous appearance results from necrosis and haemorrhage, characteristic in these lesions (Figure 8). MRI evaluation of disease extension through the uterine wall and into the parametrium, is important and may determine therapeutic approach (Figure 8 D, E, F and G).
Fig. 8: Choriocarcinoma. Sagittal (A), axial (B) and coronal (C) enhanced pelvic CT scan images and sagittal (D) and coronal (E) T2-weighted images, and sagittal (F) and coronal (G) fat-suppressed T1-weighted images show a central, heterogeneous, infiltrative mass enlarging the uterus. Its heterogeneous appearance results from necrosis and haemorrhage. Areas of decreased myometrial thickness are present.

**References:** Department of Radiology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon/PT

*Metastatic foci* tend to show evidence for *haemorrhage* and may be *quite large* at the time of diagnosis. Although the search for *metastatic disease* varies with the experience of the practitioner and the clinical situation, *chest CT* and *head CT* are frequent components of the *work-up*. *Metastases to bone* and *lymph nodes* are relatively *uncommon*.

While this is an *aggressive malignancy*, *effective chemotherapy is available*. *Clinical response* is *predicted* on the basis of a *complex staging system*, which includes *clinical factors* (patient age, prior pregnancy, prior chemotherapy, #-hCG level) and *radiologic findings* (tumour size and the number and site of metastases) (Figure 1). Even in patients with *metastatic disease*, *response rates exceed 85%* and *cure is common*. *Timely diagnosis* is *crucial* to *effective treatment*.

As in invasive mole, *choriocarcinoma treatment* is also in general *chemotherapy*. Patients with *large uterine tumours*, especially those who *do not desire future pregnancies*, are occasionally treated with *hysterectomy* if there is substantial *risk for uterine rupture*.

**PLACENTAL SITE TROPHOBLASTIC TUMOUR**

*Placental site trophoblastic disease* is a *very rare neoplasm* that some believe represents a type of choriocarcinoma. At *pathologic analysis*, though, these tumours are composed *predominantly* of *intermediate trophoblasts* and *lack the biphasic features of choriocarcinoma* (which typically contains cytotrophoblast and syncytiotrophoblast).

Patients *present* with either *abnormal bleeding* or *amenorrhea*. *#-hCG level* is usually "*positive*" for *pregnancy, simulating that situation*. Thus, relative to other forms of GTD, in this entity the *levels of #-hCG are quite low*, because of the *lack of syncytiotrophoblast proliferation*. 
These tumours vary widely in clinical course; many behave in a benign fashion, whereas others are highly malignant.

The tumour may be microscopic or may cause diffuse nodular enlargement of the myometrium. It may project into the uterine lumen or predominantly invades the myometrium.

Radiologic manifestations vary, including both cystic and solid lesions, with or without a central component, which usually invade the myometrial wall (Figure 9). The junctional zone is disrupted (Figure 9 E and F). In the majority of the cases there are cystic spaces and vascular structures. On T1-weighted images typically present as isointense compared with healthy myometrium (Figure 9 D), and on T2-weighted images are isointense to slightly hyperintense compared with myometrium (Figure 9 B and C). Thus, the uterus with placental site trophoblastic disease may have a similar appearance to a uterus involved by invasive mole or choriocarcinoma.

Fig. 9: Placental site trophoblastic tumour in a 33-year-old woman. Transversal US (A) shows a submucosal fundal tumour isoechogenic to myometrium. We can detect
a small amount of fluid in the uterine cavity. On sagittal (B) and axial (C) T2-weighted images the mass has peripheral low signal with a central high signal intensity area relative to normal myometrium. On axial T1-weighted image (D) this neoplasm typically presents as isointense compared with healthy myometrium. Sagittal (E) and axial (F) dynamic demonstrate sparse central enhancement of the mass relative to the surrounding myometrium. The tumour superficially invades the myometrium.  


In general, **hysterectomy** is the **accepted treatment**.

**Conclusion**

GTD is a rare group of gynecologic neoplasms. The final diagnosis of this potentially curable group of tumours is often based on patient’s clinical and laboratorial outcome after months or even years of follow-up after treatment.

Imaging studies play an essential role in excluding myometrial involvement in the invasive forms, and distant metastases.

This way, radiologic features should always be integrated with the clinical history and laboratorial data, which are essential for the correct diagnosis and appropriate treatment approach to these tumors.

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