

# Disseminated gestational choriocarcinoma presenting with hepatic and uveal metastases, hook effect, and choriocarcinoma syndrome

Yashant Aswani, Hemangini Thakkar, Priya Hira

Department of Radiology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India

**Correspondence:** Dr. Yashant Aswani, Ground Floor, Department of Radiology, Seth GS Medical College and KEM Hospital, Acharya Donde Marg, Parel, Mumbai - 400 012, Maharashtra, India. E-mail: yashant\_aswani@rediffmail.com

## Abstract

Choriocarcinoma is a human chorionic gonadotrophin (HCG)-secreting tumor that comprises vascular channels. It has a tendency for widespread metastasis, common sites for which include the lung, vagina, brain, liver, bone, intestine, and kidney. We describe a 30-year-old female who presented with hepatitis-like features and bilateral diminution of vision, and subsequently developed hemothorax and hemoperitoneum—all rare and seemingly unrelated manifestations which were finally attributable to metastases from gestational choriocarcinoma. To further complicate the clinical scenario, the serum HCG of the patient was mildly raised (due to a phenomenon called hook effect). Subsequently, the patient developed disseminated intravascular coagulation and succumbed to her illness. In this report, we discuss the imaging findings of choriocarcinoma, its potential sites of metastases, and the hook effect.

**Key words:** Choriocarcinoma; chorionic gonadotrophin; color; Doppler; hemoperitoneum; hemothorax; ultrasonography

## Introduction

A pathology text describes choriocarcinoma (CC) as an epithelial malignancy of trophoblastic cells that lacks villous organization,<sup>[1]</sup> with sites of origin being gestational as well as nongestational tissues. The former includes placental tissue (whether intra or extrauterine) whereas the latter comprises sites such as the ovary, testis, pineal gland, and ectopic rests in the mediastinum, retroperitoneum, stomach,<sup>[2]</sup> esophagus, spleen, prostate, urinary bladder,<sup>[3]</sup> and pancreas.

CC is a rapidly invasive and widely metastasizing neoplasm. Tendency to metastasis is seen quite early with blood stream being the preferential route of spread.<sup>[1,4]</sup> Literature unfolds lungs to be the most common site of metastasis followed by the vagina, brain, liver, bone, intestine, and kidney.<sup>[1]</sup> Metastasis to uveal tissue is a rarity with the number of cases reported for gestational and nongestational CC, respectively, to be one and eighteen. Additional sites of distant spread for nongestational CC include the spleen and small bowel. The metastases are typically hemorrhagic and hypervascular.

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In the present case, we describe various rare manifestations of gestational CC in a 30-year-old female patient.

## Case Report

A 30-year-old female presented with generalized weakness, easy fatigability, high colored urine, icterus, and diminution of vision in both eyes since 2 months. There was no history of blood transfusion, drug intake, or recent travel.

The vision loss was painless and had gradually progressed to finger counting in the right eye and perception of light in the left. She was nondiabetic and nonhypertensive. There was no history suggestive of autoimmune affliction. Fundoscopy revealed bilateral retinal detachment.

On enquiry she was gravida 4, para 2, live 2, and abortion 2. She also gave a history of amenorrhea since 2.5 months; however, the urine pregnancy test was negative. Prior to the amenorrhea, she had episodes of heavy intermenstrual bleed for a few months for which she had undergone dilatation and curettage which led to partial relief of her complaints.

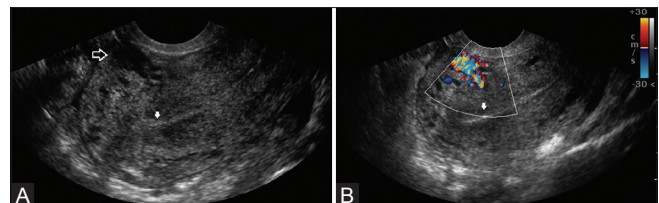
The patient was pale with a hemoglobin of 8.9 gm/dL (normal 12–15.8 g/dL) and a peripheral blood smear negative for hemolysis. Laboratory investigations revealed a total bilirubin of 3.57 mg/dL (normal up to 1.2 mg/dL) with direct fraction being 0.62 mg/dL (normal up to 0.4 mg/dL), albumin 3.1 g/L (normal 4–5 g/L), globulin 2.3 g/L (2.3–3.5 g/L), serum glutamic-oxaloacetic transaminase (aspartate aminotransferase) 59 U/L (normal 12–38 U/L), serum glutamic-pyruvic transaminase (alanine aminotransferase) 70.1 (normal 7–44 U/L), and alkaline phosphatase 144 IU/L (20–140 IU/L). Viral markers were negative.

Sonography demonstrated coarse echotexture of the liver suggestive of liver parenchymal disease [Figure 1]. In addition, there were a few anechoic intraparenchymal spaces which on Doppler interrogation had color signals with a velocity ranging between 55 to 79 cm/s and low impedance. Pelvic sonography revealed bulky uterus with coarse echotexture [Figure 2] with numerous myometrial serpiginous vascular channels showing high blood flow of peak systolic velocity (PSV) 113 cm/s. There was color aliasing with chaotic arrangement of vessels [Figure 3]. Based on the available history of dilatation and curettage, a tentative diagnosis of iatrogenic uterine vascular malformation was made.

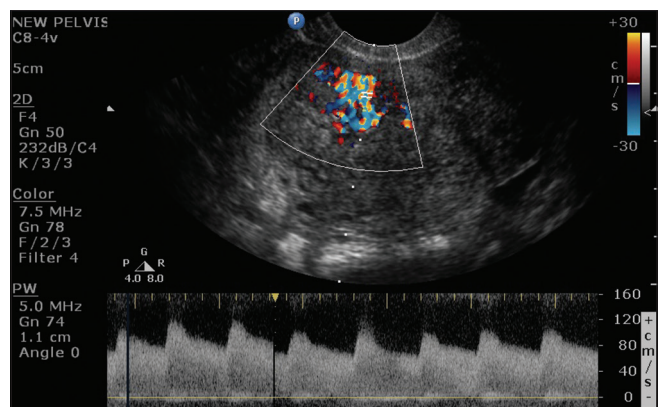
In the next 2 days, she developed breathlessness and a computed tomography (CT) was performed. CT revealed hyperdense loculated collection in the anterior part of the right pleural cavity suggestive of hemothorax [Figure 4]. In



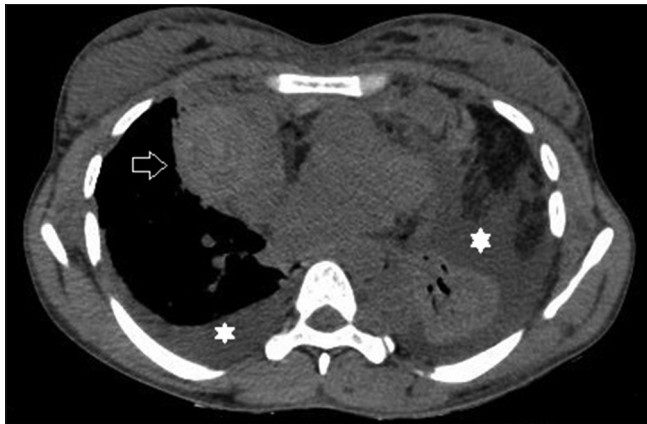
**Figure 1:** Sonogram using a linear transducer shows coarse echotexture of the liver parenchyma. (A = anterior; P = posterior)



**Figure 2 (A and B):** Endovaginal scan depicts a bulky uterus with anechoic spaces located in its anterior wall (open arrow in A), which on Doppler interrogation shows chaotic flow (B). The block arrow points towards thinned endometrium, which at one place shows blurred interface with the myometrium



**Figure 3:** On pelvic sonogram, the uterus reveals color aliasing in the region of the anechoic spaces [Figure 2]. The flow has high velocity (113 cm/s) and low impedance

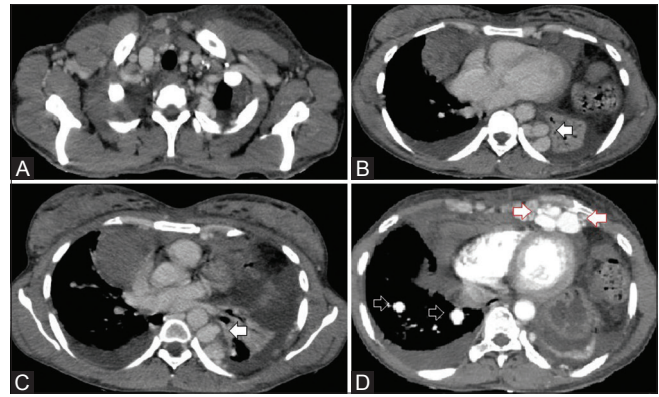


**Figure 4:** Non-contrast computed tomography of chest demonstrates a hyperdense lesion suggestive of an acute hemorrhage (arrow). The asterisk denotes bilateral pleural effusion (left > right). There is a collapse of the underlying left lung

addition, there was bilateral pleural effusion (left > right) with collapse of the left lung [Figure 4]. Further, numerous haphazardly placed vascular spaces were present in anterior, superior, and posterior mediastinum, along left internal mammary and intercostal vessels, intraparenchymal in the right lung [Figure 5], spleen [Figure 6], liver [Figure 7], and uterus [Figure 8]. A normal thrombophilia profile and multiplicity of sites of vascular channels made thrombosis a less likely etiology. Further, there was a relative absence of stroma without local hypertrophy, as is seen typically in congenital vascular malformations. Moreover, the patient did not have signs of cardiac failure despite numerous vascular channels suggesting short history of development of them. Hence, based on clinical and imaging findings, uterine CC was suspected, and a B scan was done to rule out ocular metastasis from the same. B-scan revealed bilateral exudative retinal detachment with anechoic channels present in the subretinal space with high flow on B-mode and a peak systolic velocity of 61.6 cm/s and a low impedance [Figure 9, Videos 1 and 2]. Serum HCG titres were sent which, however, was mildly raised to 183.15 mIU/mL (in nonpregnant females: <5 mIU/mL). The very same day she bled inside the peritoneal cavity and developed hemorrhagic shock. Her hemoglobin dropped to 3.4 gm/dL. Other laboratory parameters included total bilirubin 4 mg/dL, direct bilirubin 1.2 mg/dL, prothrombin time (PT) 22 s (normal 11.9–17 s), INR 1.9 (normal <1.41), activated partial thromboplastin time (aPTT) 46.9 s (normal 25.3–37.9 s), D-dimer 6.8 mg/L (normal 0.3 mg/L), creatinine 3.8 mg/dL (normal 0.5–1.4 mg/dL). Patient went into disseminated intravascular coagulation (DIC) with acute hepatic failure and acute renal shut down and finally succumbed. Finally, the histopathologic analysis established the diagnosis of disseminated CC.

## Discussion

Gestational CC is a rare malignancy with occurrence of 1 in 30000 pregnancies.<sup>[4]</sup> Molar gestation holds the biggest



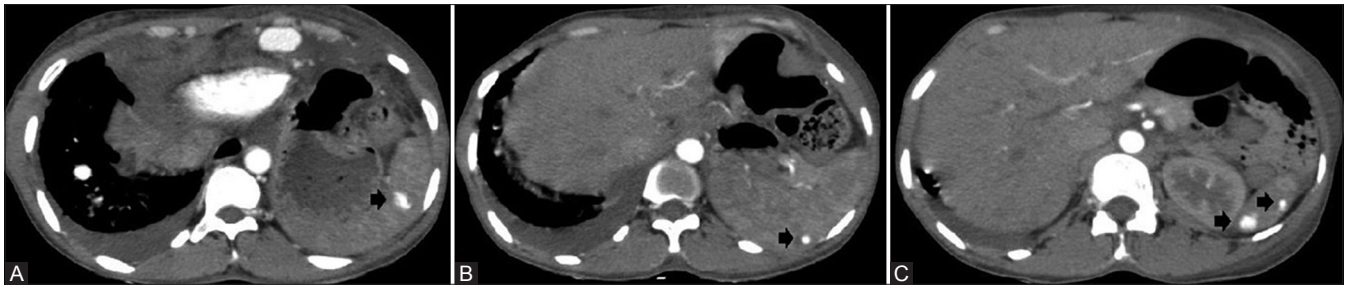
**Figure 5 (A-D):** (A-D) Contrast enhanced computed tomography of the chest in axial plane reveals multiple serpentine, dilated, and tortuous vessels along the left paraspinal space (white arrow) and internal mammary vessels (red-bordered arrow). Also noted are multiple intraparenchymal abnormal vessels within the right lung (open arrows)

risk,<sup>[4]</sup> although a normal pregnancy also can culminate into tumorigenesis. Sixty percent of women present with uterine enlargement. Spotting and foul smelling discharge may be seen.<sup>[1]</sup> One of the remarkable features of CC is extensive necrosis so much so that the primary site may sometimes be barely discernible.<sup>[1]</sup> Necrosis sometimes can give rise to clinically manifest hemorrhage at high tumor-volume metastatic sites, described by Logothetis as choriocarcinoma syndrome,<sup>[5]</sup> with diffuse alveolar hemorrhage as the most common manifestation.<sup>[5]</sup> The syndrome portends a poor prognosis<sup>[5]</sup> and needs early recognition and urgent treatment.<sup>[5]</sup> Our patient underwent hemorrhage within the pleural space followed by the peritoneal cavity.

Recognition of gestational CC is usually straightforward in the correct clinical setting of a recent molar pregnancy, rising titre of serum HCG, and a previously documented normal sonogram;<sup>[4]</sup> although a host of confounding factors may exist. These factors include CC following a normal or ectopic gestation or a spontaneous abortion. In addition, presentation with non-gynecologic problems such as respiratory compromise, hyperthyroidism, cerebral, gastrointestinal, or urologic hemorrhage add to the confusing clinical scenario.<sup>[6]</sup> Finally, negative or low HCG levels further complicate the diagnosis.<sup>[6]</sup>

Sonography plays an important role in detecting and staging CC and monitoring response to therapy.<sup>[4]</sup> Gray scale findings include a myometrial nodule that can either be hyperechogenic<sup>[6,7]</sup> or echopoor.<sup>[4]</sup> Alternatively, the tumoral mass is composed of anechoic cystic spaces which either represent extensive necrosis or vascular channels (arterio-venous shunts).<sup>[7]</sup> This cystic appearance can mimic a mole, retained products of conception (RPOC), or arteriovenous malformation. Characteristic of CC is the presence of trophoblastic signals on spectral Doppler ultrasound, which include a high PSV with low impedance flow (due to arteriovenous shunts), a low RI, and color





**Figure 6 (A-C):** (A-C) Arterial phase computed tomography axial view depicts multiple vascular spaces in spleen (arrows)



**Figure 7 (A-C):** (A) Postcontrast axial computed tomography at the level of upper abdomen shows abnormal vascular spaces within the liver parenchyma (arrows). Besides, there are multiple ill-defined hypoechoic hepatic nodules (more prominent in B, C)



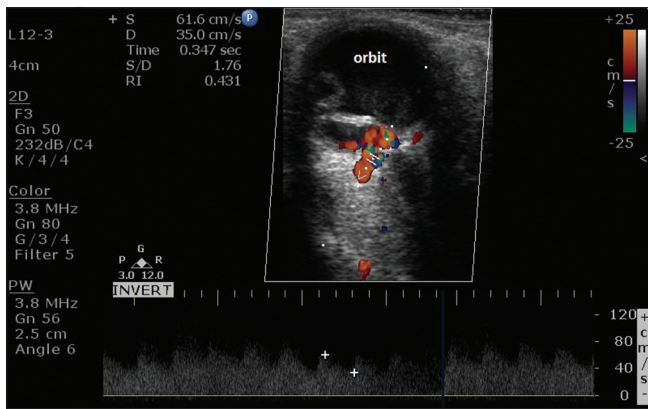
**Figure 8:** Sagittal reformation of venous phase computed tomography demonstrates multiple dilated vessels within the myometrium; largest of which is located in the anterior wall (open arrow) (also see Figures 2, 3). Also noted are vessels within the anterior (white block arrow) and posterior mediastinum (black arrow)

aliasing.<sup>[8]</sup> The PSV is usually greater than 50 cm/s and is often more than 100 cm/s and an RI less than 0.5.<sup>[4]</sup> The hypervascularity causes admixture of color signals and

a loss of discreteness of vessels. Unfortunately, this flow pattern is not pathognomonic for CC; various differentials include ectopic gestation, RPOC, and AVM.<sup>[4]</sup> Pattern of vascularity may help differentiate the entities. An RPOC exhibits endometrial vascularity extending from myometrium but vascularity in uterine AVM is isolated to myometrium.

Contrast enhanced CT helps in the detection of distant spread. It reveals a bulky uterus with an ill-defined, inhomogenously enhancing mass with areas of hypervascularity.<sup>[9,10]</sup> There is associated necrosis and hemorrhage.<sup>[9,10]</sup> The metastases are also hypervascular like primary and often undergo hemorrhage and necrosis resulting in a variety of non-gynecologic problems.<sup>[6]</sup>

Biochemical marker for detecting presence of CC or its response to therapy is human chorionic gonadotropin (HCG). It is a heterodimer secreted by trophoblastic cells to facilitate corpus luteum to secrete the pregnancy hormone (progesterone).<sup>[11,12]</sup> Once secreted, HCG undergoes multiple modifications to form different subtypes of HCG which may be secreted in urine and/or serum. Further, the timing of secretion following conception is different for different forms. For example, while beta core form of HCG is secreted only in urine, rising in concentration from 5 to 8 weeks of gestation and peaking in midtrimester, the hyperglycosylated form (the only bioactive form other than the intact HCG), on the contrary, is secreted in excess soon after implantation and reaches undetectable levels toward the end of the first trimester. Detection of HCG in urine or serum depends on the formation of a sandwich with



**Figure 9:** Doppler examination of the high flow in the subretinal space on right reveals chaotic flow with a peak systolic velocity of 61.6 cm/s and low impedance. Similar features were noted on the contralateral side (not shown)

HCG being the meat and two different antibodies (binding to two different epitopes on the same HCG molecule) being the bread. Knowledge of this biochemistry is of prime importance since when to detect HCG (timing after conception), which form to detect, and which commercially available kit to use (since all kits do not measure all forms) can avoid misinterpretation.<sup>[11,12]</sup>

A negative or low HCG titre does not exclude the possibility of CC. The test can be negative due to extremely high titre of HCG! It is a phenomenon wherein excess HCG saturates both the antibodies separately resulting in half-formed sandwiches (so to speak) and consequently falsely low titres (the Hook effect).<sup>[11,12]</sup> Similarly, variant hook effect too results in low detectable HCG levels. In variant hook effect, excess beta core variant in urine sample saturates one of the binding antibodies causing an incomplete reaction. Both these phenomena of falsely negative tests can be surmounted by sample dilution especially in clinically suspected cases. Our patient had low serum HCG probably because of the hook effect. Yet another cause for low titre can be extensive necrosis of the tumor so much so that it becomes functionally inactive.<sup>[11,12]</sup>

The gestational variety differs from the nongestational one in terms of response to chemotherapy.<sup>[1]</sup> Spectacular results have been obtained with single drug (methotrexate) regimen for the former while the latter is usually fatal. For those of gestational type who fail to respond to single drug therapy, multi-agent regimen (EMA-CO: etoposide, methotrexate and actinomycin D alternating with cyclophosphamide and vincristine) comes to rescue.<sup>[13]</sup> Those with high HCG more than 40000 mIU/mL, hepatic, or brain metastasis and presentation 4 or more months after pregnancy also benefit from this multiagent chemotherapy.<sup>[13]</sup>

## Conclusion

CC has typical sonographic and CT findings. However, myriad clinical features may add to the confusion. Presentation such as hepatitis-like features, uveal metastases, CC syndrome, and the hook effect are rarely encountered; simultaneous presence of these is unheard of. Thus, if the clinical picture is confusing with a low HCG titre, radiological diagnosis should still be considered.

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## Conflicts of interest

There are no conflicts of interest.

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