Case Report

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Website: www.pogsjournal.org

DOI: 10.4103/pjog.pjog_25_21

Metastatic choriocarcinoma presenting as intracranial hemorrhage and intussusception

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Abstract:

Extrauterine choriocarcinoma is a rare entity. The criteria used for its diagnosis are as follows: (1) Absence of disease in the uterine cavity, (2) pathologic confirmation of diagnosis, (3) exclusion of molar pregnancy, and (4) absence of a coexistent intrauterine pregnancy. Delay in the diagnosis can be attributed to its nongynecologic manifestations such as bleeding from any organ system, unexplained systemic symptoms, and metastatic foci from an unknown primary malignancy. This is an unusual case of 27-year-old G3P3 (3-0-0-3) who underwent emergency left parietal craniotomy excision due to increased intracranial pressure symptoms secondary to left parietal tumor. Histopathology revealed metastatic adenocarcinoma. About a month later, she underwent exploratory laparotomy for acute abdominal symptoms secondary to a jejunal mass. Jejuno-jejunal resection anastomosis was done and histopathology revealed choriocarcinoma.

Keywords:

Brain metastasis, choriocarcinoma, gastrointestinal metastasis, gestational trophoblastic neoplasia

Introduction

Choriocarcinoma is a severe form of gestational trophoblastic neoplasia (GTN). It originates from the chorionic villi and extravillous trophoblast.[1,2] It is considered a highly aggressive cancer, and early diagnosis is paramount to initiate appropriate treatment. With immediate diagnosis and proper treatment, the prognosis is good since the tumor is extremely sensitive to chemotherapy and response to treatment can be adequately monitored using a tumor marker, human chorionic gonadotropin (hCG), that can be utilized also for the diagnosis. The most frequent presentation is vaginal bleeding from an intrauterine lesion. There are also patients presenting with problems referrable to the metastatic sites with no apparent intrauterine pathology and thus can be a diagnostic challenge.

Case Report

A 27-year-old G3P3 (3-0-0-3) presented with intermittent vaginal bleeding 4 months prior to admission after an uncomplicated normal spontaneous vaginal delivery. With a normal transvaginal ultrasound, the patient was managed symptomatically as a case of abnormal uterine bleeding. Pregnancy test was not done. Subsequently, the patient also began to experience frontal headache, throbbing, 7–8/10 in severity, associated with nonprojectile vomiting. There was no associated loss of consciousness, no blurring of vision, no nape pains. She was referred to a private neurologist and was given unrecalled medications which offered temporary relief.

Two and a half months before admission, the headache progressed followed by the four

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Submitted: 12-Aug-2021
Accepted: 24-Aug-2021
Published: 26-Oct-2021

How to cite this article: Gonzales-Acantilado GV, Jacinto EK. Metastatic choriocarcinoma presenting as intracranial hemorrhage and intussusception. Philipp J Obstet Gynecol 2021;45:171-7.

episodes of tonic – clonic seizures with upward rolling of eyeballs. On consult, a cranial computerized tomography scan was done which revealed a peripherally enhancing, lobulated heterogeneous mass, in the left parietal lobe measuring 3.2 cm × 3.4 cm × 3.7 cm [Figure 1a]. She was transferred to a tertiary hospital where she underwent emergency craniotomy with excision of left parietal space-occupying lesion. Histopathology was consistent with metastatic adenocarcinoma based on the following immunohistochemistry findings: Positive for BD anti-cytokeratin (CAM 5.2) and cytokeratin 7 (CK 7); negative for glial fibrillary acidic protein, paired-box gene 8, CDX2 protein (CDX2), thyroid transcription factor 1. Considerations were a possible breast carcinoma, cholangiocarcinoma, upper gastrointestinal carcinoma, and pancreatic carcinoma. Further diagnostic workups were requested and referrals to the pulmonology, gastroenterology, and medical oncology services were advised. In the interim; however, the patient was asymptomatic and did not comply with the additional consultations.

One month PTA, the patient had progressive generalized abdominal pain with no associated signs and symptoms. She sought consult and was medically managed with antispasmodics and pain medication but offered no relief. A chest computed tomography (CT) scan done revealed pleural effusion and a ground glass nodule in the right upper lobe of the lung. An abdominal CT scan showed multiple rim-enhancing hepatic nodules and findings in the intestines with a consideration of jejuno-jejunal intussusception. A few hours PTA, the patient began to experience severe generalized abdominal pain with associated hematochezia. The patient was subsequently admitted and underwent jejuno-jejunal resection anastomosis for jejunal mass. Intraoperatively, there was a fungating jejunal mass 120 cm from the ligament of Treitz. The mass was dark gray to green in color, pedunculated, rubbery measuring 4.0 cm × 3.5 cm × 2.0 cm, completely obstructing the lumen [Figure 2]. There was also minimal ascites and palpable hepatic nodules (Segment V, VI, and VII). Histopathology results revealed choriocarcinoma [Figure 3], hence referral to the Division of Trophoblastic Diseases.

With a consideration of choriocarcinoma, a diluted serum beta hCG (βhCG) was initially requested with a value of 869,123.66 mIU/ml. Transvaginal ultrasound showed no significant findings except for endometrial polyps [Figure 4a-c]. Chest X-ray revealed a well-defined round mass measuring 8.2 cm × 9.3 cm × 10.5 cm in the right upper to middle lung lobes highly suggestive of metastasis [Figure 5]. Whole abdominal ultrasound revealed few ill to fairly defined hyperechoic foci are seen scattered in the liver parenchyma, with the largest

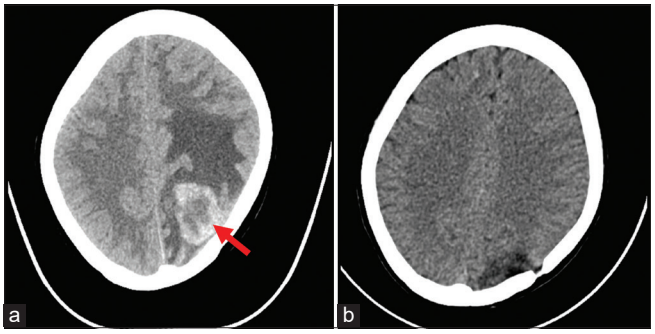

Figure 1: (a) Cranial computed tomography scan prior to craniotomy with a peripherally enhancing lobulated mass in the left parietal lobe, 3.2 cm × 3.4 cm × 3.7 cm (red arrow); (b) S/P excision of left parietal mass

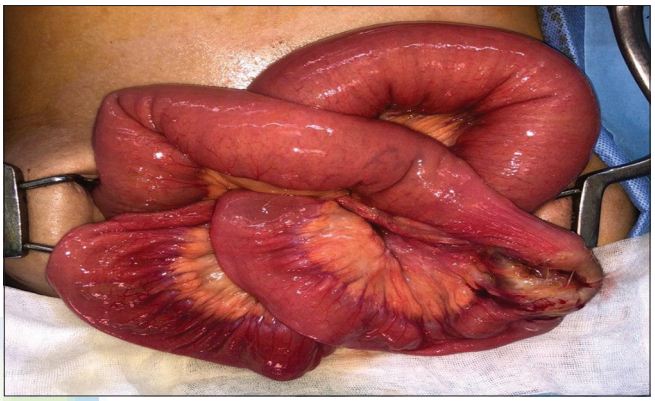

Figure 2: Jejunal mass

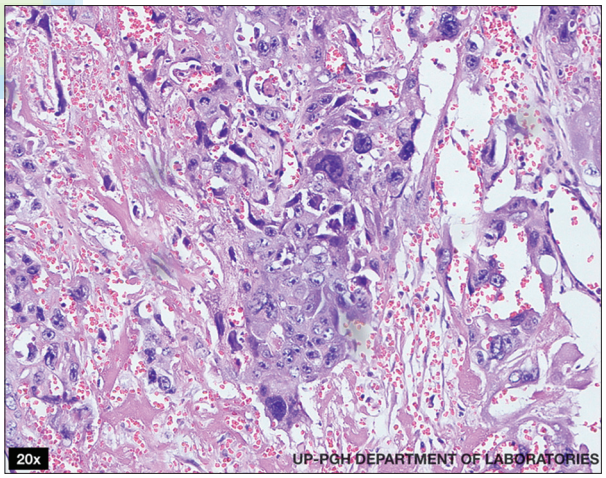

Figure 3: Histology of the Jejunal mass showing atypical dimorphic population of multinucleated syncytiotrophoblast and mononucleated cytotrophoblast

seen in segment VIII measuring 2.3 cm × 2.2 cm × 2.6 cm likely metastatic in light of a known primary malignancy. Slide review of the left parietal tumor previously excised revealed metastatic tumor compatible with choriocarcinoma.

The patient was staged and scored based on the FIGO 2000 Staging and WHO prognostic scoring system for

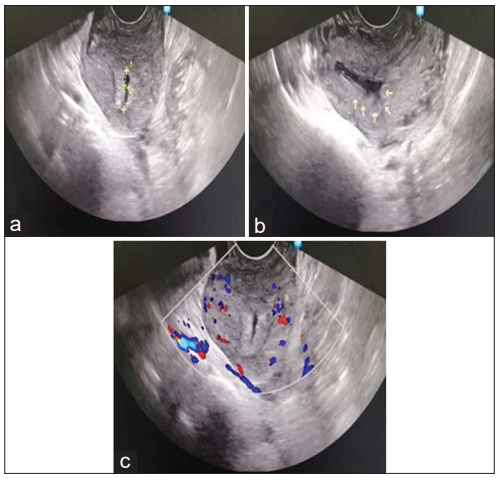

Figure 4: Transvaginal sonogram: (a) Normal sized uterus with an irregularly thickened hyperechoic endometrium; (b) anterior hyperechoic masses suggestive of polyps (arrows); (c) color mapping of the uterus and endometrium did not reveal any abnormal flow

GTN as Stage IV: 15 [Table 1]. Based on the diagnosis, multiple agent chemotherapy in the form of etoposide, methotrexate, actinomycin, cyclophosphamide, and oncovin (EMACO) were started and given cyclically every 10–14 days. The patient responded well to the treatment completing three consolidation courses [Table 2].

Discussion

GTN comprises the malignant group of the spectrum of gestational trophoblastic disease. It includes invasive mole, choriocarcinoma and the rare types of placental site trophoblastic tumor and epithelioid trophoblastic tumor. The true incidence of GTN, particularly choriocarcinoma, varies depending on the geographic location. In Europe and North America, about 1 in 40,000 pregnant patients and 1 in 40 patients with hydatidiform moles will develop choriocarcinoma.[3] The reported statistics in South-east Asia and Japan show a higher trend with 9.2/40,000 pregnant women and 3.3/40 patients with hydatidiform moles subsequently develop choriocarcinoma.[3] In the Philippines, the national prevalence rate of GTN including choriocarcinoma was reported to be 0.56/1,000 pregnancies. The University of the Philippines-Philippine General Hospital, being a national referral center, showed a high prevalence at 4.3/1,000 pregnancies.[4] The most common antecedent pregnancy is a molar pregnancy (50%), but it may originate from a term/preterm pregnancy (25%), or ectopic pregnancy/abortion (25%).[5] The most common site of metastasis is the lungs (80%) followed by the vagina (30%), pelvis (20%), the liver (10%), and central nervous system (CNS) (10%).[6] Small bowel metastasis is rare at an incidence of <5%.[7]

The most common presentation of choriocarcinoma is vaginal bleeding from an intrauterine tumor or

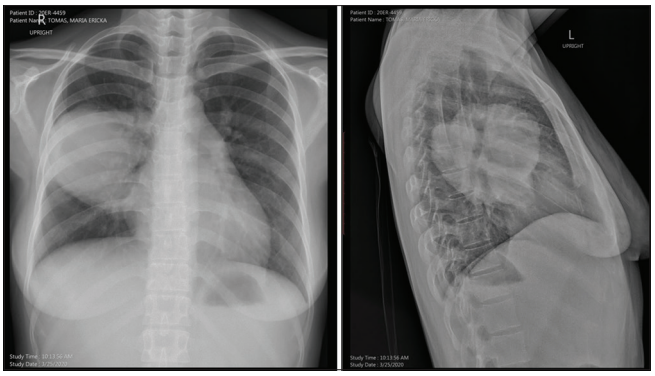

Figure 5: Well defined round mass measuring 8.2 cm × 9.3 cm × 10.5 cm in the right upper to middle lung lobes

metastatic lesions in the vagina that can often be profuse necessitating surgery, the extent of which would depend on the age and the desire of the patient for future fertility.[8] Other associated signs and symptoms include uterine enlargement, infection from necrosis of a large tumor, and acute abdomen secondary to tumor perforation. The index patient initially noted irregular vaginal bleeding, but this was dismissed because of a normal transvaginal ultrasound. There was no attempt to rule out pregnancy-related problems with a point of care pregnancy test that could have helped in establishing the diagnosis.

GTN may present with symptoms referrable to the metastatic sites with normal reproductive tract findings similar to the index patient fulfilling one of the criteria in the diagnosis of extrauterine choriocarcinoma. Furthermore, the transvaginal ultrasound of the index patient did not show any molar pregnancy or intrauterine pregnancy. There have been case reports in literature on patients with GTN with metastatic lesions in the lungs initially presenting with hemoptysis, dyspnea, pleuritic chest pain, and cough. With no evident uterine pathology, the initial diagnosis in such patients would be a primary lung carcinoma or in the local setting, a Kochs infection. Zhang *et al*. reported three cases of GTN who initially presented with hemoptysis. In all cases, radiographic pulmonary lesions were present, and an elevated serum βhCG established the diagnosis.[9] Gvinianidze reported a 42-year-old patient who recently delivered and presented with cough, shortness of breath and hemoptysis. Chest X-ray and CT scan demonstrated an isolated left upper lobe lung lesion. With a consideration of primary lung carcinoma, a left thoracotomy with upper lobectomy and systematic lymph node dissection was done. Histology was strongly suggestive of metastatic choriocarcinoma confirmed by an elevated serum βhCG (3200 UI/L). Transvaginal ultrasound was normal.[10] The index patient delivered normally 4 months from the first time she complained of headache and convulsions. There was no chest imaging

Table 1: WHO prognostic scoring system

	Prognostic score				Patient	Score
	0	1	2	4		
Age (years)	<40	>40			27	0
Antecedent pregnancy	Mole	Abortion	Term		Term	2
Interval months from pregnancy	<4	4-<7	7-<13	≥13	7	2
Pretreatment hCG (mIU/ml)	<1000	1000–<10,000	10,000-<100,000	≥100,000	869,123.66	4
Largest tumor size (including uterus), cm	<3	3-≤5	≥5		8×8 lungs mass	2
Site of metastasis	Lung	Spleen, kidney	Gastrointestinal	Liver, brain	Liver, brain	4
Number of metastasis		1-4	5-8	>8	4	1
Previous failed chemotherapy			Single drug	2 or more drugs	None	0
					Total	15

done before the craniotomy. She underwent a chest CT scan only before the abdominal surgery revealing a nodule on the upper lobe with pleural effusion but with no other associated pulmonary symptoms.

CNS involvement that led to the first surgery of the index patient can present with symptoms ranging from intra- or extraaxial hemorrhage due to oncotic aneurysm formation and its subsequent rupture, infarction or even in the form of subdural hematoma requiring decompressive craniotomy.[11,12] A case was reported by Wang *et al*. where in an 18-year-old G4P3 (2-0-1-1) who experienced irregular vaginal bleeding for 6 months and was admitted for confusion. Head CT showed multiple hemorrhages in the right temporal-parietal lobe and occipital lobe, right temporal parietal hematomas, ventricle compression, and midline shift evacuation of the hematoma in the temporal-parietal lobe. Gynecologic ultrasound was normal. Craniotomy was done and histological examination of the lesion resected was compatible with a diagnosis of choriocarcinoma.[13] Based on the immunohistochemistry results, the initial histopathology of the intracranial tumor in the index patient was metastatic adenocarcinoma. hCG was not part of the immunohistochemistry panel requested as there was no suspicion of choriocarcinoma. If it was initially requested, the diagnosis could have been made at this time and appropriate management instituted.

Involvement of the gastrointestinal tract that led to the second surgery of the patient is not very common with an incidence of <5%.[7] Choriocarcinoma has presented itself with profuse upper gastrointestinal bleeding in the form of hematemesis or melena, massive lower gastrointestinal bleeding, and unexplained severe anemia which may or may not be associated with polypoidal masses in small bowel and colon.[14-16] There are also case reports of Choriocarcinoma rarely presenting with spontaneous perforation of small bowel even at multiple points, presenting with acute abdomen and vomiting.[11] The index patient underwent resection anastomosis of a fungating jejunal mass with a histopathologic report of choriocarcinoma. Subsequently, a slide review of the initial histology of the intracranial tumor (metastatic adenocarcinoma) was reported as metastatic tumor compatible with choriocarcinoma. This finally completed the criteria for the diagnosis of extrauterine choriocarcinoma. A serum βhCG done showed markedly elevated levels compatible with a diagnosis of choriocarcinoma.

After completion of the needed blood chemistries and metastatic workup, all GTN patients should be properly staged and scored using the Combined FIGO 2000 Staging and WHO prognostic scoring system. This is how the complete diagnosis should be reported and it would be the basis for the type of chemotherapy that should be given to the patient. For the index patient, complete diagnosis is GTN (choriocarcinoma), Stage IV (lungs, brain, and gastrointestinal tract): 15 [Table 1].

Choriocarcinoma is one of those rare neoplasms that is responsive to chemotherapy even in the presence of widespread metastasis. EMACO is the first line chemotherapy for high risk GTN patients with an overall survival rate of 97.9%.[17] A local study done at the Philippine General Hospital documented a 72% primary remission rate of high risk GTN treated with EMACO, sustained remission rate of 80% and a survival rate of 86%.[18] In the index patient, had there been an initial diagnosis of GTN with brain metastasis, resection of the intracranial mass was not indicated. High dose multiple agent chemotherapy in the form of EMACO could have been started concomitant with whole brain irradiation. Surgery in the form of craniotomy is done only to patients with intracranial bleeding secondary to brain metastasis indicated for CNS decompression and stabilization. There had been case reports of isolated nodules resistant to drug treatment that are excised and this therapeutic regimen results to primary remission of 65%–80% of and up to 90% cure.[19] Surgery for the purpose of obtaining a biopsy to confirm the diagnosis of GTN is not done.

The index patient responded well to multiagent EMACO completing 12 cycles, the last three being consolidation courses. With initial resection of the intracranial mass,

Table 2: Treatment course of the index patient

	β hCG (mIU/ml)	Lung metastasis	Liver metastasis	Brain metastasis
Prior to chemotherapy	869,123.66	Well defined round mass lobulated homogenous mass is seen in the right middle lung field measuring 8.2×9.3×10.5 cm in the right middle lung filed	Few ill to fairly-defined hyperechoic foci are seen scattered in the liver parenchyma, with the largest seen in segment VIII measuring 2.3×2.×2.6 cm	Cranial CT scan not done
S/P EMACO I (28 March, 2020-4 April, 2020)	748.26	-	-	S/P craniotomy, excision of left parietal mass: Previously noted well - defined, lobulated, mixed-attenuating, peripherally hyperdense focus in the left parietal lobe is no longer visualized. All ill - to fairly defined hypodense focus measuring 2.4×3.2×1.6 cm is now seen in its place, likely representing the surgical bed
S/P EMACO II (6 May, 2020-13 May, 2020)	770.28	Previously noted lobulated homogenous mass is seen in the right middle lung field now measures 7.2×7.5×8.1 cm	Interval resolution of the previously noted hepatic foci	-
S/P EMACO III (10 June, 2020-11 June, 2020, 18 June, 2020)	48.31	-	-	-
S/P EMACO IV (16 July, 2020-23 July, 2020)	20.99	-	-	-
S/P EMACO V (4 August, 2020-11 August, 2020)	13.19	Previously noted lobulated homogenous mass in the right middle lung now measures 7.24×5.74 cm from a previous measurement of 7.2×7.5×8.1 cm	-	-
S/P EMACO VI (25 August, 2020-1 September, 2020)	8.3	-	-	-
S/P EMACO VII (12 September, 2020-13 September, 2020, 24 September, 2020)	5.77	Previously noted lobulated homogeneous mass in the right middle lung now measures 5.0×6.8×6.1 cm		
S/P EMACO VIII (1 October, 2020-8 October, 2020)	4.75	-	-	-
S/P EMACO IX CUC I (15 October, 2020-22 October, 2020)	4.28	-	-	-
S/P EMACO X CUC II (29 October, 2020-5 November, 2020)	4.84	-	-	-
S/P EMACO XI CUC III (12 November, 2020-19 November, 2020)	2.23	-	-	-

Note of delay in the chemotherapy schedule was due to enhanced community quarantine. EMACO=Etoposide, methotrexate, actinomycin, cyclophosphamide, oncovin, CT=Computed tomography, β hCG=Beta human chorionic gonadotropin, CUC=clean up course, S/P=status post

repeat imaging showed no other focus [Figure 1b]. There was also no recurrence of lesions in the gastrointestinal tract. Similarly, ill-defined hyperechoic foci in the liver parenchyma resolved with completion of chemotherapy. What remained was the pulmonary mass initially measuring 8.2 cm × 9.3 cm × 10.5 cm decreasing in size to 5.0 cm × 6.8 cm × 6.1 cm [Figure 6]. There has been report in the literature of the persistence of lung lesions in the form of scarring or fibrosis after chemotherapy with normal hCG levels. In a study done by Powles *et al.*, it was documented that patients with residual disease at the end of treatment have larger lung metastasis at diagnosis. The larger pulmonary metastasis may result in more nonviable tissue after the

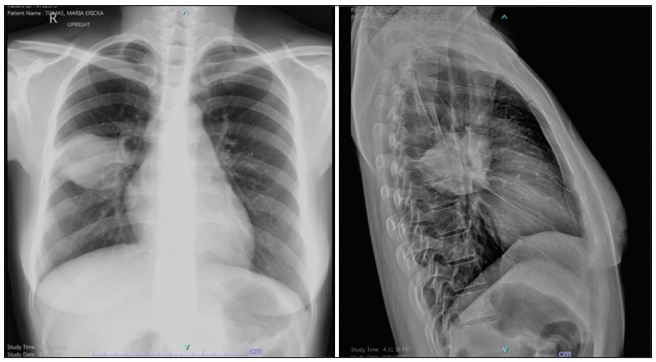

Figure 6: Lung mass after completion of chemotherapy (5.0 cm × 6.8 cm × 6.1 cm)

completion of treatment. Radiological abnormalities at the end of treatment are of no prognostic significance if the patient's βHCG levels remain normal, and excision of these lesions does not therefore seem reasonable.[20] Since hCG is the final arbiter in GTN, these residual lesions can be observed with annual chest X-ray as long as the hCG levels continue to be normal. The remaining lung lesion in the index patient was still significantly large enough to warrant a possible biopsy to rule out the possibility of another lung pathology other than GTN. Proper referral to the division of thoracovascular surgery has been done. After her last chemotherapy cycle, she was advised serum βhCG monitoring monthly for the 1st 6 months, every 2 months for the next 6 months, every 3 months for the 2nd year of follow-up, and every 6 months thereafter. On her 4th month postchemotherapy, the patient remains to be asymptomatic with normal monthly βhCG levels. Currently, the patient is on oral contraceptive pills for family planning while taking advantage of its suppressive effect to endogenous luteinizing hormone which may interfere with the measurement of βhCG at low levels.[3] The patient expressed her desire for a future pregnancy but it was emphasized to her to delay it for 1 year to be able to properly monitor her βhCG level.

Conclusion

GTN should be considered in a reproductive aged woman presenting with metastatic lesions from an unknown primary site. In extrauterine choriocarcinoma, as in the index patient, there may be mild or no referrable symptoms in the reproductive tract. A high index of suspicion of GTN will lead to prompt diagnosis and management with avoidance of unnecessary surgery and a relative decrease in adverse outcomes related to this aggressive but curable malignancy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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