Concurrent term pregnancy and choriocarcinoma: A case report*

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ABSTRACT

Term pregnancy with choriocarcinoma is a rare entity and cases where both the mother and fetus survive are even more rare. This paper discusses the case of a term pregnancy with a concomitant choriocarcinoma in a 21 year-old, gravida 2 para 0, who presented with hematochezia on the third trimester. She delivered via cesarean section for non-reassuring fetal status with good neonatal outcome. She underwent exploratory laparotomy postdelivery due to profuse gastrointestinal bleeding associated with deteriorating hemodynamic status. Histopathologic report revealed Ileal Choriocarcinoma. Metastatic work up showed liver and lung metastasis. The patient achieved remission after 8 cycles of EMACO chemotherapy. There was no evidence of recurrence in the subsequent 10 months of regular follow up.

Keywords: chemotherapy, choriocarcinoma, gastrointestinal hemorrhage, hematochezia, pregnancy

INTRODUCTION

Choriocarcinoma is a rare malignant type of gestational trophoblastic neoplasm (GTN). Globally, the highest rate is observed in Asia where Indonesia has 10 per 1000 gestations followed by Japan with 2 per 1000.[1] In our country, the prevalence rate is 0.56 per 1,000 pregnancies.[1]

Choriocarcinoma is anteceded by molar pregnancy in approximately 50% of patients, extrauterine pregnancy and intrauterine miscarriage in 25% and after a normal pregnancy in about 25% of cases.[2] Occurrence of concurrent term pregnancy and choriocarcinoma is 1 per 160,000 gestations and is commonly associated with adverse outcomes such as hydrops fetalis, intrauterine fetal death, fetomaternal hemorrhage and postpartum hemorrhage.[3] GTN presenting during a term pregnancy is very rare. To date, there are fewer than 10 cases reported in English literature. There is no published report of this rare condition here in the Philippines. This paper presents the successful treatment of a patient with GTN who presented with hematochezia at 40 weeks and 2 days age of gestation.

THE CASE

This is the case of a 21-year-old, Gravida 2 Para 0, Filipina who sought consult at the emergency room of a tertiary government hospital for hematochezia.

She had her menarche at 13 years old with subsequent menses coming at regular monthly intervals. Her first pregnancy was a miscarriage for which she underwent a completion curettage. However, histopathology result was not secured.

For the current pregnancy, patient had an unremarkable prenatal course until 35 weeks age of gestation (AOG) when she was diagnosed with gestational hypertension for which she was maintained on Methyldopa 250mg/tab taken at a dose of one tablet three times a day.

History of present illness started a day prior to admission, on her 40 2/7 weeks AOG, when she noticed bleeding per rectum amounting to approximately 2-3 cc. There were no other associated signs and symptoms. No consult was done until a few hours prior to admission, when she had another bout of bleeding per rectum associated with a blood pressure of 150/100 mmHg. This prompted consult at the emergency department with subsequent admission. Patient denied any fever or weight loss. Review of systems revealed occasional easy fatigability and shortness of breath relieved by rest on the third trimester. She did not have abdominal pain, diarrhea, constipation and difficulty in urination.

On admission, patient was conscious and coherent. Her blood pressure was elevated at 150/110 mmHg, heart rate was at 110 beats per minute, respiratory rate was 19 cycles per minute and temperature at 36.9°C. Physical examination findings centered on the abdomen. Fundic height was 31cm with a fetal heart rate of 138 beats per minute, best heard at the right lower quadrant. On Leopolds maneuver, baby was in cephalic presentation. Magnesium sulfate loading dose was given. On internal

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examination, cervix was soft, closed, anteriorly located, with no bleeding nor foul smelling discharge. Bishop score was 4. On anal inspection, there were thrombosed external hemorrhoids measuring about 0.5 x 1.0 centimeter. Digital rectal examination revealed good sphincter tone, smooth, intact rectal vault with minimal bleeding per examining finger.

Admitting impression was Gravida 2 Para 0 (0010) Pregnancy Uterine 40 2/7 weeks AOG by LMP, Preeclampsia with Severe Features, External Hemorrhoids. The plan was to induce labor, monitor the progress of labor and deliver vaginally. Laboratory examinations were done with normal results except for a +1 proteinuria on urine dipstick. Hydralazine 5mg IV was given on admission. She was referred to General Surgery service for evaluation of hemorrhoids.

Baseline cardiotocography (CTG) was reassuring. Induction of labor was done. Four hours into induction, there was spontaneous rupture of membrane which revealed thickly meconium stained amniotic fluid. There were episodes of fetal bradycardia at 90-100 bpm prompting an emergency cesarean section for non-reassuring fetal status. Upon opening, no hemoperitoneum was noted. A gravid uterus with a well-formed lower uterine segment was seen. A transverse curvilinear incision was made on the lower uterine segment. She delivered a live, term, baby girl in cephalic presentation with Apgar score of 7 and 9 at 1 minute and 5 minutes, respectively. Birth weight was 3.0 kilograms. The amniotic fluid, placenta and umbilical cord up to the level of the baby's umbilicus were thickly meconium stained. The placenta appeared grossly normal with a 3-vessel cord. Both ovaries and fallopian tubes were grossly normal. Estimated blood loss was 600-700cc. Intravenous antibiotics and analgesics were started. Upon transfer to the post-anesthesia care unit, the patient had stable vital signs: BP- 130/90mmHg; PR-90 bpm; RR- 20cpm; oxygen saturation - 97% via nasal cannula.

Twelve hours post-cesarean section, the patient bled per rectum amounting to around 300 cc, soaking 1 adult diaper. Tranexamic Acid 1 gram was given intravenously. She underwent emergency gastroscopy and colonoscopy. Gastroscope was inserted down to the level of the second portion of the duodenum. The esophagus was normal and the stomach was empty and distensible on air insufflations. The mucosa was smooth with no ulcer or bleeding lesions noted. The duodenum was likewise normal down to the second portion. Final gastroscopy finding was hiatal hernia. Upon insertion of the colonoscope, internal and external hemorrhoidal vessels were engorged. Fresh and clotted blood were noted up to the terminal ileum. During the procedure patient bled profusely with an estimated blood loss was 2.5-3 liters. Her blood pressure went down to 80/50mmHg with a cardiac rate of 139 bpm. Bleeding parameters were done, which showed normal results. Hemoglobin at this time was 62 g/L, for which 4 units of packed RBC were transfused Calcium gluconate was also given to prevent citrate toxicity and hypocalcemia. Despite adequate fluid and blood replacement, vital signs deteriorated. Blood pressure dropped to 70/50 mmHg and HR increased to 125 bpm. Immediate exploratory laparotomy under general endotracheal anesthesia was done, which revealed a 0.5 x 0.5 cm perforation at the level of the ileum. The area was actively bleeding. Both the stomach and duodenum were normal. The surgical team proceeded with resection and anastomosis of the diseased portion (Figure 1). Another 3 units of packed RBC were transfused followed by calcium gluconate. Postoperative diagnosis was arteriovenous malformation (AV) to consider malignancy. She was immediately transferred to the intensive care unit with the following vital signs: BP-110/80mmHg; PR-150 bpm; RR- 20cpm; oxygen saturation - 98% via nasal cannula.

On the second day post-exploratory laparotomy, patient was closely monitored and antibiotics were continued. Anemia was corrected with a total of seven units of packed RBC. On the third day post-exploratory laparotomy, chest x-ray revealed pneumonia on the right, possible Koch's etiology, rule out pulmonary mass. Computed tomography (CT) scan was done which showed multiple lung nodules, to consider metastases and an incidental finding of concurrent hepatic hypo-dense masses. CT scan guided fine needle aspiration biopsy of the pulmonary and liver mass showed few atypical cells probably malignant. Patient was discharged asymptomatic on the 7th hospital day while awaiting final histopathologic report.

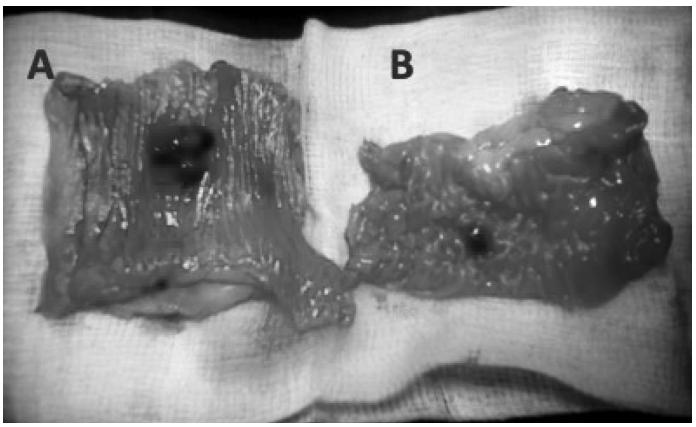

Figure 1. Ileal segment. **A**. Previously opened mid proximal segment of ileum measuring 6.5 x 5.0 x 0.4 cm with noted 1.5 cm dark brown discoloration surrounded by normal-looking mucosa. **B**. Previously opened segment of ileum measuring 6.0 x 4.5 x 1.4 cm with noted 0.5 cm dark brown discoloration surrounded by normal looking mucosa

One week after her discharge, histopathologic reading of the resected ileum showed choriocarcinoma versus endometriosis. Immunostaining with human chorionic gonadotropin (hCG) revealed positive result consistent with a diagnosis of choriocarcinoma. Serum beta hCG (BhCG) was at 10,000 mIU/ml. The final diagnosis was Choriocarcinoma Stage IV prognostic score of 12. Chemotherapy in the form of Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide and Vincristine (EMACO regimen) was given. Patient achieved remission after eight cycles of EMACO, inclusive of three consolidation therapies. The patient remained in remission for 10 months after treatment. She was lost to follow-up thereafter.

CASE DISCUSSION

Choriocarcinoma is classified as either gestational or non-gestational.[4] Gestational choriocarcinoma is more common than the non-gestational type and can occur following any form of pregnancy.[4] Conversely, non-gestational choriocarcinoma is believed to arise from germ cells and is characterized by its presentation in males and children.[4] The patient is considered to have gestational choriocarcinoma given her history of an abortion even in the absence of a uterine lesion. There have been recent reports of GTN presenting with a normal uterus but with metastasis in other parts of the body.[5] Increased risk of having gestational choriocarcinoma are observed with the following: 1) women older than 45 years old; 2) non-white; 3) prior spontaneous abortion; 4) unmarried

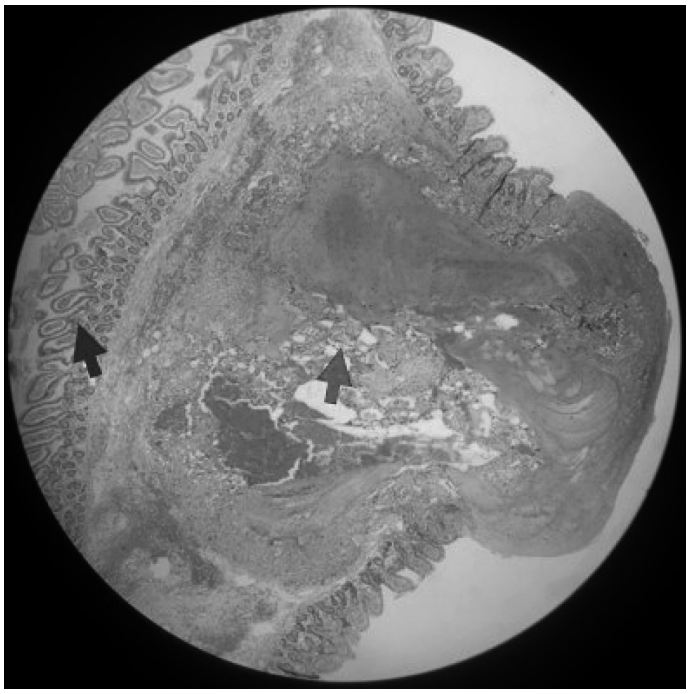

Figure 2. Scanning view of resected ileum: Normal Intestinal mucosa (dark gray arrowhead) underneath is the focus of choriocarcinoma (light gray arrowhead)

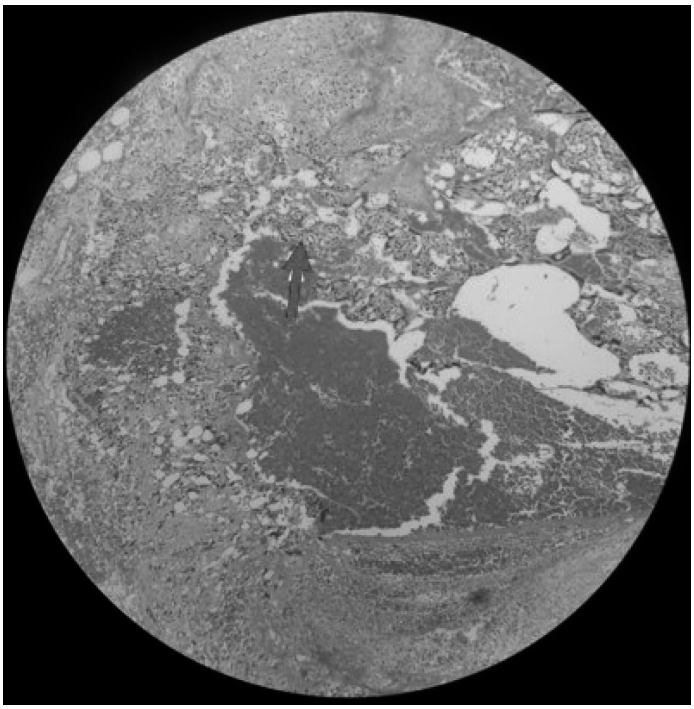

Figure 3. Low power view. Fragments of intestinal mucosa with submucosal mass composed of nests and lobules of a biphasic tumor composed of cytotrophoblasts having clear to granular cytoplasm and distinct cell border, and occasional syncytiotrophoblasts (light gray arrowhead) with large, hyperchromatic and pleomorphic nuclei (hematoxillin and eosin staining)

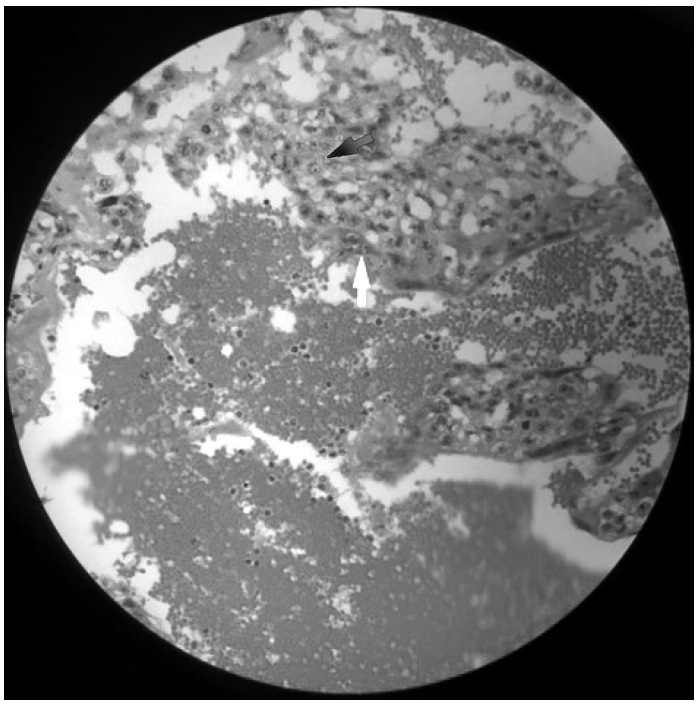

Figure 4. High power view: Choriocarcinoma consist of two cell population. The syncytiotrophoblast (white arrowhead) which are multinucleated and has hyperchromatic neoplasm and cytotrophoblast (gray arrowhead) which has pale/clear cytoplasm

women or those who held professional jobs; 5) extremes of reproductive age group; 6) menarche at age older than 12 years; 7) family history of twins; 8) multiple marriages; and 9) infrequent intercourse.[6] Hypothesis was made that decreased levels of estrogen below normal were associated with disintegration of ovulation which might be associated with development of choriocarcinoma in subsequent gestation.[6] Those with history of dieting or regular exercise have a decreased risk for choriocarcinoma.[6] This patient is a 21 years old with a history of abortion who had her menarche at the age of 13.

Patients with gestational choriocarcinoma may present with any of the following: a) vaginal bleeding; b) anemia; c) uterine enlargement; d) acute abdomen secondary to tumor perforation; e) infection; f) signs and symptoms referable to the site of metastasis.[1] The most common clinical presentation is irregular bleeding, which may present as uterine subinvolution or puerperal bleeding early in the disease process.[1] The index patient presented with rectal bleeding, which was referable to the colonic metastasis. However, due to the rarity of gastrointestinal involvement in cases of choriocarcinoma, diagnosis was not immediately made. The placenta was not sent for biopsy because it appeared grossly normal therefore the exact histopathology of the placenta remains unknown.

Theories on the coexistence of choriocarcinoma and normal intrauterine gestation include the following: (1) it may be caused by the immediate transformation of normal trophoblasts into choriocarcinoma during an intrauterine gestation, (2) it may be an aftermath of a multiple gestation with 1 conceptus undergoing malignant change to choriocarcinoma and (3) the malignant change may befall in the trophoblastic remnants of previous gestation and developed into choriocarcinoma in the present gestation.[7]

The index patient presented with hematochezia before, during and after delivery. There are several causes of hematochezia, which include: anatomic (hemorrhoids), inflammatory (ulcerative colitis), vascular (AV malformation), and neoplastic.

Hemorrhoids are clusters of vascular structures, smooth muscle, and connective tissue lined by the normal epithelium of the anal canal that act as cushions to help with fecal control. As the gravid uterus expands, it compresses the inferior vena cava, causing decreased venous return and distal engorgement. Colonoscopy of the patient revealed mixed hemorrhoids. However, this will not cause profuse bleeding. The second differential is the inflammatory cause of gastrointestinal bleeding such as ulcerative colitis, which primarily affects males, nonsmokers and certain ethnic groups such as Caucasians. Intestinal arteriovenous malformation (AVM) is an uncommon cause of bleeding from the small intestines. AVM is most often located in the cecum and right side of the colon. It is more common in people over the age of 50 and is associated with other medical problems such as chronic kidney disease and valvular heart disease. Ulcerative colitis and AVM cannot be highly considered for this patient. The last consideration that may present with hematochezia is malignancy. Although the common signs and symptoms associated with the presence of a neoplasm such as unexplained weight loss, fever, fatigue and pain were not experienced by the patient, presence of unusual rectal bleeding can happen in early or advanced stages of cancer. Resection of the diseased ileum which was sent for histopathology and immunostaining with BhCG confirmed the diagnosis of ileal choriocarcinoma.

The patient's choriocarcinoma presented as rectal bleeding before, during and after delivery. Thus, understanding the behavior of this tumor is clinically important. Gestational choriocarcinoma, readily invades into blood vessels, producing metastasis through the hematogenous route of dissemination.[6] The embolic metastatic sites tend to rapidly outgrow their blood supply, producing central necrosis which can result in massive local hemorrhage.[6] Choriocarcinoma usually progresses rapidly and is fatal without treatment.[6]

Secretion of hCG is the hallmark of gestational choriocarcinomas, because the tumor is derived from elements of both cytotrophoblast and syncytiotrophoblast.[6] The tumor marker correlates well with the volume of the disease except in a few cases of drug-resistant disease. It is, likewise, a sensitive marker for response to treatment.[6]

Metastasis occurs early in the course of the disease.[8] The most common site of metastasis is the lungs (>75%) followed by the vagina (50%).[8] Other sites of metastasis are the liver, brain, ovaries, intestines and kidneys.[8] Involvement of the gastrointestinal tract is rare even in the presence of disseminated disease.[8] In her case, metastases were present in the lung, liver and small intestine.

Patients with choriocarcinoma are primarily diagnosed based on clinical presentation, serum BhCG level and typical ultrasonographic findings.[1] Histopathology is not required in the diagnosis of GTN. Baseline evaluation should include work-up for anemia, kidney and liver dysfunction as well as infection.[1] Imaging studies such as chest x-ray or CT scan, cranial CT scan, pelvic and abdominal ultrasound or CT scan are done to rule out metastases.[1] Following a comprehensive metastatic work-up, patients must be staged based on the FIGO 2000 Anatomic Staging and categorized according to the WHO Prognostic Scoring System.[1] The FIGO anatomic staging system (Table 1) defines the extent of the disease while the WHO prognostic scoring system (Table 2) is needed for classifying the disease into low-risk or high-risk.[8] A FIGO score of <7 indicates low-risk disease whereas a score of

>7 classifies a patient as having high-risk disease.[8] In terms of prognosis, patients with low-risk disease have a 100% chance of cure while for those with high-risk disease, cure is achieved as much as 95% of the time.

Chemotherapy remains to be the foundation in the treatment of choriocarcinoma.[1] Single-agent chemotherapy is the first-line treatment for non-metastatic and low-risk choriocarcinoma while multi-agent chemotherapy is recommended for patients with metastatic high-risk diseases.[1]

The EMACO regimen composed of Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide and

Table 1. FIGO 2000 Staging for Gestational Trophoblastic Neoplasia*

STAGE I	Disease confined to the uterus
STAGE II	Disease extends outside the uterus but confined to the genital organs
STAGE III	Pulmonary metastases
STAGE IV	Metastases in other sites

Table 2. Modified WHO Prognostic Scoring*

	SCORE			
	0	1	2	4
Age (years)	< 40	≥ 40		
Antecedent Pregnancy	Mole	Abortion	Term	
Pregnancy Interval (months)	< 4	4 – 7	7 - < 13	13
HCG (IU/liter)	< 1000	10^3 - < 10^4	10^4 - < 10^5	10^5
Largest tumor, including the uterine tumor (cm)	< 3	3 - < 5	> 5	
Site of metastases	Lungs	Spleen Kidney	GI Tract	Liver Brain
Number of metastases		1 – 4	5 – 8	> 8
Prior Failed Chemotherapy			Single agent	2 or more agents

* *Format for reporting to FIGO Annual Report: in order to stage and allot a risk factor score, a patient's diagnosis is allocated to a stage as represented by a roman numeral I, II, III, and IV. This is then separated by a colon from the sum of all the actual risk factor scores, which is expressed in Arabic numerals (e.g., stage II:4, stage IV:9). This stage and score will be allotted for each patient.*

Vincristine or the Bagshawe regimen is the first-line therapy used to treat high risk GTN.[1] The index case was classified as Stage IV with a prognostic score of 12 and was thus given EMACO for treatment. Chemotherapy is continued until BhCG reaches normal levels (<5 mIU/mL) followed by consolidation therapy, which consists of 3 additional cycles after the first normal BhCG value.[1] A patient is diagnosed to be in remission once she has three consecutive normal BhCG titers.

Adjuvant therapy such as radiation treatment and surgical intervention may also be used in select cases to achieve a high cure rate.[1] The patient underwent ileal resection and anastomosis which played a vital role in controlling the tumor hemorrhage and decreasing the tumor load. Hysterectomy was not considered in this patient since she is young and wishes to preserve her fertility.

Choriocarcinoma has a direct effect on a concurrent pregnancy. It may lead to hydrops fetalis, intrauterine fetal death, fetomaternal hemorrhage, and postpartum hemorrhage.[9] Term pregnancy with choriocarcinoma is a rare entity and survival of both the mother and fetus is even rarer. The case presented is one of the few cases to reach a term gestation and was able to give birth to a live fetus. Patients with choriocarcinoma who are treated successfully with chemotherapy can expect normal future reproductive function with no increased risk of congenital anomalies.[10] The secondary infertility rate in women who were previously treated with chemotherapy is approximately 7%.[6] However, patients, like the index case, are advised to avoid pregnancy until two years post-treatment due to an increased risk of miscarriage and recurrence.[1] A barrier method of contraception, low dose combined contraceptive pill, injectable progestins or implants may be used.[10]

Follow up plan is for serial serum BhCG testing, which is imperative in confirming remission and monitoring for recurrence of the disease.[4] The BhCG levels are measured monthly for the first 6 months then every 2 months for the next 6 months, every 3 months for the second year and every 6 months thereafter.[1] The index patient was able to achieve remission after eight cycles of chemotherapy. There was no evidence of recurrence in the subsequent 10 months of regular follow up. However, she was lost to follow up thereafter.

SUMMARY

This paper reported the case of a 21-year-old, G2P1 (0010) who presented with hematochezia at term and delivered successfully via cesarean section. She underwent exploratory laparotomy with ileal resection and anastomosis a few hours after delivery due to profuse rectal bleeding. Histopathology and immunostaining with hCG of the ileal segment confirmed the diagnosis of choriocarcinoma. Metastatic work up showed liver and lung metastases. Patient achieved remission after eight cycles of EMACO. There was no evidence of recurrence in the subsequent 10 months of regular follow up. This case report is an apt reminder to clinicians to include choriocarcinoma in the list of differential diagnoses for pregnant women with atypical bleeding to achieve early diagnosis, institute timely management and avoid life threatening consequences. ■

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