Case Report

Choriocarcinoma following term pregnancy with successful subsequent pregnancy

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ABSTRACT

Gestational trophoblastic neoplasia (GTN) denotes subtypes of gestational trophoblastic disease that have invasion potential, for example, invasive mole. Gestational choriocarcinoma (CC). Gestational CC is an extremely malignant tumor and considered the most common histologic type of GTN encountered following normal pregnancy; however, CC is a potentially curable disease, and the outlook is excellent in most cases. This case report involves clinical management and long-term follow-up of a 32-year-old female who presented 28 days after cesarean delivery with recurrent episodes of massive delayed postpartum hemorrhage. Her evaluation revealed an elevated beta-human chorionic gonadotropin level (36053.9 mIU/mL) and uterine vascular mass on pelvic ultrasound. Diagnosis of CC was confirmed histologically on the specimen retrieved during suction and curettage. The patient received 6 cycles of chemotherapy (vincristine-cisplatin) with a good response. She got pregnant 1 month after the last dose of chemotherapy. Her subsequent pregnancy was uneventful, and she gave birth to a healthy baby at 38 weeks. Such cases display a diagnostic challenge in low-resource settings and concerns regarding fertility preservation in survivors of CC.

Key words: Postpartum choriocarcinoma, Delayed postpartum hemorrhage, Beta-human chorionic gonadotropin, chemotherapy

Gestational trophoblastic neoplasia (GTN) denotes subtypes of gestational trophoblastic disease (GTD) that have invasion potential, for example, invasive mole, choriocarcinoma (CC) [1], also, it entails evidence of persistent GTD. Most GTN cases are diagnosed on the basis of persistent elevation of beta-human chorionic gonadotropin (β-HCG). GTN may develop after a molar pregnancy, a non-molar pregnancy, or a live birth. Prognosis is usually excellent for most varieties of GTN, but for women with GTN after a non-molar pregnancy, it may be worse (21% mortality after a live birth, 6% after a non-molar miscarriage), which is partially due to delay in diagnosis [2].

Gestational CC is an extremely malignant tumor that initially invades the endometrium and myometrium and tends to develop early blood-borne systemic metastases. Most of the cases follow a molar pregnancy, but may also follow a non-molar pregnancy. Gestational CC develops in approximately 1 in 30,000 non-molar pregnancies: Two-thirds of such cases follow term pregnancies, and one-third develop after spontaneous abortion or pregnancy termination [3]. CC is considered the most common histologic type of GTN after normal pregnancy, characterized by rapid growth and a tendency for distant metastasis. Following term delivery, a single high level of β-HCG will suffice for the diagnosis in the absence of other conditions explaining such a high measurement. On some cases, CC is diagnosed by tissue histology retrieved from endometrial curettage or at hysterectomy. Once diagnosis is made, the risk of disease progression should be assessed (Table 1) along with staging; (Stage I: Disease confined to the uterus. Stage II: Spread limited to genital structures. Stage III: Lung involvement. Stage IV: Other metastatic sites), through clinical history, physical examination including pelvic assessment, imaging modalities such as pelvic ultrasound with Doppler studies and chest X-ray [4,5]. Weekly follow-up of β-HCG level during treatment and then monthly after normalization for 1 year is a commonly accepted practice. A reliable contraceptive method is strongly advised till completion of follow-up [6]. Major concerns among survivors of CC who are treated with chemotherapy are the ability to retain fertility and the impact on subsequent pregnancies. Although long-term follow-up regarding these issues

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Table 1: Modified World Health Organization prognostic scoring system as adapted by the International Federation of Gynaecology and Obstetrics

Risk factor	Score			
	0	1	2	4
Age (years)	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval (months)	4	4–6	7–12	>12
Pre-treatment serum hCG (mIU/mL)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Largest tumor (including uterus)	<3 cm	3–4 cm	≥5 cm	–
Site of metastases	Lung	Spleen, Kidney	GI tract	Brain, Liver

hCG: Human chorionic gonadotropin, GI: Gastrointestinal

is scarce, available data indicate that preservation of fertility is visible in most women with subsequent successful pregnancy outcomes [7]. This case report involves presentation, diagnosis, management, and long-term follow-up of a 32-year-old female who presented 28 days post-cesarean delivery with recurrent episodes of delayed postpartum hemorrhage.

CASE PRESENTATION

A 32-year-old woman, Para 2 (caesarean deliveries), presented to the emergency department of obstetrics and gynaecology, Dongola Maternity Hospital, Northern State, Sudan, 28 days post-cesarean delivery with complaint of massive vaginal bleeding associated with passage of clots and tissues. Fever or symptoms suggestive of respiratory or neurological pathology were denied. Her antecedent pregnancy was uneventful apart from gestational diabetes in the third trimester, controlled by diet modifications, and terminated at 39 weeks by elective cesarean section. The outcome was a healthy baby with an unremarkable post-operative course.

On clinical evaluation, the patient was conscious, pale, and hemodynamically unstable (pulse 120 bpm, respiratory rate 29 pm, blood pressure 55/30 mmHg). Mild tenderness was elicited at the suprapubic area, and the uterus was just palpable at the level of the symphysis pubis. The cesarean scar site was well-healed with no signs of infection. Speculum examination revealed ongoing bleeding with passage of clots and placenta - like tissues through the dilated cervical os.

Macroscopically, the cervix looked healthy, as well as the vaginal walls. Besides, the side ultrasound revealed a heterogeneous intra-cavitary mass with thickened endometrial echoes (>5 cm), features that were described as consistent with retained placental tissues.

Her hemoglobin level was 6.9 g/dL, while cell count was 12000 cell/μL, and platelet count was 240000/μL. Other blood tests were within normal limits (renal function test and electrolytes, liver function tests and enzymes, coagulation profile).

The patient resuscitated with 2 L of normal saline (0.9% sodium chloride) and 4 units of cross-matched packed red blood cells (RBCs), received 1 g of tranexamic acid infusion, and underwent evacuation and curettage under anesthesia. Tissues retrieved at evacuation were not sent for histological studies. 12 h post-evacuation, the patient was comfortable with stable vital signs and insignificant vaginal bleeding.

Patient discharged from hospital after 2 days on hematinic and scheduled for outpatient follow-up. Three days later, the patient presented again with her second episode of heavy vaginal bleeding and passage of clots. She was hemodynamically unstable and resuscitated with normal saline and 5 units of cross-matched packed RBCs. Her clinical scenario raised the suspicion of retained placental tissues, uterine artery pseudo-aneurysm, and GTN. Measurement of quantitative serum β-HCG revealed high levels (36053.9 mIU/mL), transvaginal and abdominal ultrasound scan examination showed a bulky uterus (size 11.3 × 7 × 6.2 cm), an echo complex intra-cavitary collection, and a posterior uterine mass measuring 5.4 × 3.9 cm with strong Doppler flow, no Doppler flow suggesting pseudoaneurysm (bidirectional flow), both ovaries were normal in size, and echo pattern and free of cysts or masses. Abdominal organs (liver, spleen, pancreas, kidneys) showed normal size, echo pattern with no visible masses or lesions. Para-aortic space was free, with no evidence of pelvic or abdominal lymph node enlargement or fluid collections. The patient's chest X-ray study was normal, lacking any white spots or fluid build-up. The patient had been subjected to suction and curettage again, and tissues yielded at evacuation sent for histologic studies, which reported a malignant tumor composed of syncytiotrophoblast, cytotrophoblast, and intermediate trophoblast in a background of hemorrhage and necrosis, malignant cells showing increased mitosis, and an absence of villous structures, a feature consistent with CC. In light of her clinical history and imaging studies, the patient was considered to have Stage 1 disease and low risk (Stage 1:6) according to the staging and prognostic scoring system adapted by the International Federation of Gynaecology and Obstetrics (FIGO) (Table 2).

After being counselled about the implications of the diagnosis and treatment options, the woman was referred to the regional oncology center (no dedicated centre for GTD), where she received six cycles of chemotherapy (Vincristine+Cisplatin). Apart from recurrent mild vaginal bleeding in the first few weeks on initiation of treatment, chemotherapy was well tolerated by the patient with a mild toxicity profile (nausea, fatigue,

Table 2: Our patient prognostic scoring system

Risk factor	Score			
	0	1	2	4
Age (years)	0		–	–
Antecedent pregnancy			Term	–
Interval (months)	0			
Pre-treatment serum hCG (mIU/mL)			10^4–10^5	
Largest tumor (including uterus)			≥5 cm	–
Site of metastases	0			
Number of metastases	0			
Prior failed chemotherapy	0	–		

The total score of the patient according to her risks was 6 points. hCG: Human chorionic gonadotropin

mild neutropenia, anemia, and alopecia). Response to treatment was followed by serial quantitative serum β-HCG every 2 weeks (Fig. 1). Normalization of β-HCG level was documented after the third dose of chemotherapy (9 weeks after start of treatment) by 3 consecutive negative results (<5 mIU/mL), along with clearance of ultrasonic features related to the disease and resumption of regular menses.

The couple were on barrier method (male condom) as a contraceptive; the woman had been advised to use a reliable method (combined oral contraceptive, implanon) after normalization of serum β-HCG, but this was not preferred by the patient or her husband over barriers and withdrawal techniques. However, the patient got pregnant 1 month after the last dose of chemotherapy. At booking visit, she was doing well with normal blood indices (hemoglobin 11g/dL, white blood cells 4.4 × 10^3, Platelets 240 × 10^3), liver and renal functions within normal limits, and normal blood glucose levels at 75 g-oral glucose tolerance panel. Quantitative serum β-HCG level at booking was 50000 μIU/mL, subsequent readings through her antenatal period (every 4 weeks) were as follows: 21000, 17000, 14000, 15000, 15000, 13000 μIU/mL. The Booking scan showed a single viable fetus corresponding to 11 weeks 4 days gestational age. An anomaly scan at 20 weeks revealed no apparent fetal structural anomaly with a normally situated placenta. Serial growth scan with Doppler studies done at 28, 32, and 36 weeks of gestation reported fetal size appropriate for the index gestational age with normal umbilical artery Doppler indices. The patient developed gestational diabetes at 32 weeks, evident by high random blood sugar (240 mg) and glycosuria, controlled by metformin 500 mg twice/day. The patient underwent an elective cesarean at 38 weeks, gave birth to a healthy baby boy weighing 3.5 kg and was admitted to the nursery for follow-up of blood glucose level, and discharged after 24 h. The post-operative course was uneventful. Intra-operative findings were unremarkable; macroscopic examinations of the uterus, tubes, ovaries, and other pelvic organs were in the usual anatomical arrangement. Placenta was sent for histologic studies, and reported as normal placental tissues, no histological evidence of malignancy, metastatic disease, or chemotherapy-related

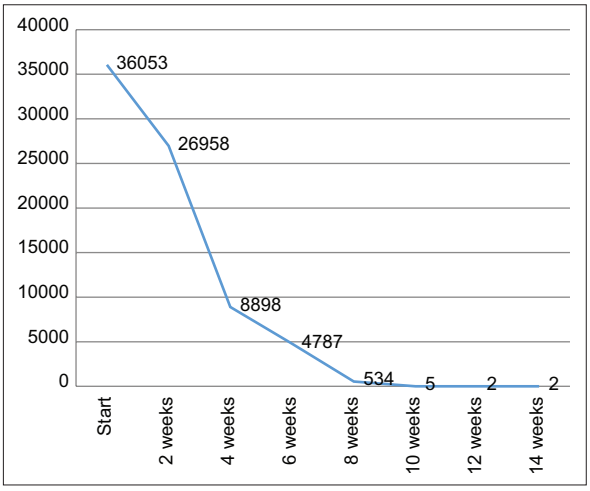

Figure 1: Beta-human chorionic gonadotropin regression curve of our patient during chemotherapy. Follow up every 2 weeks after initiation of chemotherapy

placental injury, with recommendation for clinical follow-up. Quantitative β-HCG on discharge (72 h post-delivery) was 872 μIU/mL and 10 μIU/mL, then undetectable (<2 μIU/mL) at 6 and 8 weeks postpartum, respectively. Up to this point, the female and her baby are in good health, and scheduled for follow-up of her serum β-HCG level monthly ×12 months.

DISCUSSION

Most of the cases of GTDs are hydatidiform moles (80%), while 15% and 5% are invasive mole and CC, respectively. GTN develops in approximately 15–20% of patients after a complete mole and in 5% after a partial molar pregnancy. Patients with molar pregnancy undergo close follow-up with serial β-HCG measurements to uncover cases manifesting persistent or invasive disease necessitating chemotherapy (Table 3).

On the contrary, GTN existing after a term uneventful pregnancy could pose a diagnostic challenge, as there are no well-known associated risks that may enable the clinician to stratify women developing GTN after an apparently normal term pregnancy; furthermore no established routine clinical or laboratory guidelines for screening. Delayed diagnosis, along with the tendency to metastasize, makes sufferers from this malignant tumor tend to develop metastatic disease and a poorer outlook than those patients harboring the disease following hydatidiform molar pregnancy [4,5].

The usual presentation of postpartum CC is abnormal postpartum vaginal bleeding; such a presentation is in line with other common etiologies, for instance, retained placental tissues and postpartum genital infection that could make the diagnosis of GTN remote, emphasising a high index of suspicion in every case and case presenting with abnormal genital bleeding. Some patients will present with metastatic manifestation, while others may be asymptomatic, and the diagnosis is made upon histologic examination of the placenta for antenatal adversities (e.g., fetal growth restriction, unexplained

Table 3: International Federation of Gynaecology and Obstetrics/World Health Organization criteria for diagnosis of post-molar gestational trophoblastic neoplasia

Criteria	Description
1	Plateauing of hCG±10% for 4 consecutive values over 3 weeks (i.e., days 1, 7, 14, 21).
2	A rise in hCG levels of ≥10% for 3 values over 2-week period (i.e., days 1, 7, 14).
3	Histologic diagnosis of choriocarcinoma or clinical and/or radiologic evidence of metastases.

hCG: Human chorionic gonadotropin

fetal anemia), aiding in the perplexity in anticipating and diagnosing these rare tumors, especially when a long time has elapsed since the antecedent pregnancy event (>12 months). Usually, the diagnosis of CC will reveal when high levels of HCG are detected in association with such clinical scenarios. HCG is a glycoprotein that is considered to be an ideal tumor marker, attributed to its sensitivity toward GTN. β-HCG has a crucial role in the diagnosis, follow-up, response to treatment, and recurrence of GTN, besides its prognostic value when stratifying patient's risk scores. Although the clinical usefulness of HCG is proven in cases of GTN, it is not the case for placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT), where these extremely rare GTNs are associated with low levels of HCG; in addition, false-negative and false-positive results may occasionally occur at extremes of HCG values.

Following the diagnosis of CC, radiological surveillance to assess the extent of the disease is crucial for optimum outcome, along with evaluating the patient's prognostic score. Pelvic and abdominal ultrasound supported by Doppler studies could be the primary and readily available tools to detect the primary tumor and associated abdominal metastatic features. Chest X-ray is another primary radiological study that could detect lung metastatic deposits. Other imaging modalities may be requested in accordance with disease characteristics and clinical manifestations [4,8,9].

Chemotherapy is the mainstay of treatment in cases of gestational CC, allowing eradication of the disease in most cases with an affirmative prognosis and fertility preservation. Surgery may play a role in certain clinical situations, for instance, hysterectomy for low-risk patients who have no desire for future fertility, chemotherapy-resistant disease with genital hemorrhage, and other rare types of GTN less sensitive to chemotherapy (e.g. PSTT and ETT). Radiation in conjunction with chemotherapy has been reported to have some benefit in cases of CC with metastatic brain disease [6,10]. Patients who categorized as low risk group (0–6) according to FIGO prognostic score with no metastatic lesions other than pelvic organs and the lungs will usually treated with single agent chemotherapy commonly methotrexate (MTX), some reports suggest Dactinomycin is superior to MTX but at the expense of increased toxicity profile, however CC is considered treatable cancer especially in low risk patients with remission rate approaching 75–90%, on the other hand high risk patients with prognostic score ≥7, or with wide spread metastatic disease (Stage IV) will be opted for multi-agent chemotherapy commonly EMA-CO regimen (Etoposide, MTX, Actinomycin D, Cyclophosphamide, Vincristine), with reported cumulative 5-years survival rate of 86%, noteworthy diagnosis of CC *per se* is a high risk, on top of that clinical characteristics of these patients such as long interval between pregnancy event and diagnosis, wide metastatic disease, and very high HCG level elucidating large bulk of malignant tissues secreting this hormone will make their outlook less favorable, and the condition may be more challenging in resistant or recurrent tumor, where salvage chemotherapy regimens, for example, EMA-EP (substituting etoposide and cisplatin for cyclophosphamide and vincristine) can be used. Radiation and surgical intervention may be included in the management of this group of patients. For all patients of GTN who opted for chemotherapy, a reliable and strong contraceptive method should be implemented till completion of follow-up, as the occurrence of a new pregnancy will cause a diagnostic dilemma and will weaken the reliability of serial HCG measurements as a follow-up tool [4].

Our patient had been categorized as low risk, with Stage 1 disease; despite that, she received 6 cycles of combined chemotherapy (cisplatin and vincristine) with an excellent response. Justification for using such a regimen is that, following the war crisis, inflicting medical supply and services all over the country, oncology centers were obliged to formulate their institutional protocols according to available resources.

Concerns regarding fertility preservation in terms of impact on ovarian function and reserve and ability to bear a normal subsequent pregnancy in patients surviving CC after chemotherapy are interesting, and available data showing these issues is scarce, especially in patients who got pregnant before completion of follow-up, as in our patient. Factors that influence chemotherapy-related morbidity might include patient age, type and number of chemotherapeutic agents used, duration of treatment, and interval between the treatment and subsequent pregnancy event. However, available reports are promising, and most of the patients can retain their fertility and are capable of accomplishing a successful subsequent pregnancy [7].

CONCLUSION

Implementing institutional protocols for evaluation of cases with postpartum hemorrhage encompassing rare etiologies could aid in early diagnosis of this potentially curable malignancy. Although available data are reassuring, wide-scale and long-term follow-up studies are needed to address fertility issues among patients with CC exposed to chemotherapy.

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