The pregnancy that wasn't: challenges of gestational trophoblastic neoplasia management in low- and middle-income countries

Anisa Mburu
Gynecologic Oncology, Aga Khan Hospital, Mombasa, Kenya

Phillip Tonui
Reproductive Health and Pathology, Moi University, Eldoret, Uasin Gishu County, Kenya

Kibet Keitany
Reproductive Health and Pathology, Moi University, Eldoret, Uasin Gishu County, Kenya

Raymond J Osborne
Gynecologic Oncology, University of Toronto, Toronto, Ontario, Canada

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ijgc-2022-003569).

Correspondence to
Dr Anisa Mburu, Gynecologic Oncology, Aga Khan Hospital, Mombasa, 80100, Kenya; nissiemburu@gmail.com

Accepted 7 April 2022

To cite: Mburu A, Tonui P, Keitany K, *et al*. *Int J Gynecol Cancer* 2022;**32**:944–948.

CASE PRESENTATION

A 26-year-old G2 P0 A2 (gravida 2, parity 0, abortions 2) was referred to the gynecologic oncology clinic in Eldoret, Kenya with persistent vaginal bleeding 2 months after uterine evacuation for an 8 week incomplete abortion at a peripheral facility. She had a good performance status on admission with a β human chorionic gonadotropin level of 50 000 mIU/mL, negative chest x-ray, and an ultrasound that showed a 3 cm intrauterine echogenic mass with increased vascularity on Doppler imaging. She did not have a repeat curettage at presentation to confirm the histologic diagnosis of hydatidiform mole, choriocarcinoma or placental site trophoblastic tumor.

Dr Tonui: At this point what was the differential diagnosis and what were the treatment options?

Due to the patient's age, a consideration of a normal pregnancy can still be entertained. The differential diagnosis could include an element in the spectrum of pre-malignant and malignant gestational trophoblastic diseases, such as complete or partial hydatidiform mole, invasive mole, choriocarcinoma, epithelioid trophoblastic tumor, placental-site trophoblastic tumor, or an atypical placental site nodule. Human chorionic gonadotropin, hCG, can be variably elevated in epithelioid trophoblastic tumor, placental site trophoblastic tumor, and atypical placental site nodule. Treatment for the premalignant lesions involves suction evacuation and curettage, preferably under ultrasound guidance, while for the malignant lesions chemotherapy is the treatment of choice. Chemotherapy may be administered as a single agent for low-risk disease or as a multi-drug protocol in high-risk and ultra-high-risk cases based on the WHO prognostic scoring system. Hysterectomy or resection of an isolated drug-resistant tumor can be curative.[1]

This patient was staged as low-risk disease (I:4) and therefore she was started on intravenous single-agent bi-weekly actinomycin D 1.25 mg/m^2. She received four cycles of actinomycin D but the weekly human chorionic gonadotropin titers subsequently rose to 158 900 mIU/mL (Figure 1A) necessitating a re-assessment.

Dr Osborne: What was the regression slope like on first-line dactinomycin?

Single agent chemotherapy is often employed for low-risk gestational trophoblastic neoplasia (WHO score 0–4).[1] *Bi-weekly intravenous dactinomycin is preferred to weekly intramuscular methotrexate because it is easy to administer, has a low toxicity profile, and a higher complete response rate based on data from several randomized trials.*[2] *However, it is considerably more costly than methotrexate-containing regimens (weekly intramuscular, 5-day and 8-day) and is sometimes also in short supply. Serial human chorionic gonadotropin testing for gestational trophoblastic neoplasia patients should be obtained at least weekly to identify flattening of the regression curve as early as possible. Some tertiary trophoblastic centers like Charing Cross, London, UK, test twice a week.*[3] *A rising human chorionic gonadotropin titer indicates treatment failure/resistant disease and warrants re-evaluation/restaging and regimen change (Figure 1A). Patients with newly diagnosed, non-metastatic, low risk gestational trophoblastic neoplasia, regardless of the amount of intrauterine disease or the human chorionic gonadotropin level, may benefit from a second curettage as a first*

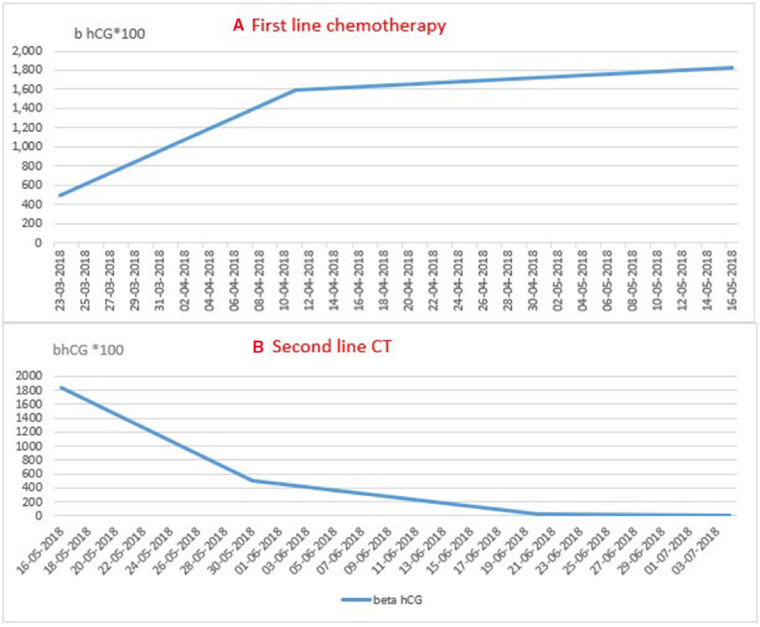

Figure 1 (A) Graph showing serial βhCG measurements from the time the patient was on single agent chemotherapy (actinomycin D) with constant rise in weekly βhCG. (B) Graph showing serial βhCG measurements from the time the patient was on polychemotherapy, EMA/CO with constant drop in βhCG indicating good clinical response. βhCG, β human chorionic gonadotropin; A, actinomycin D; C, cyclophosphamide; E, etoposide; M, methotrexate; O, vincristine.

line alternative to chemotherapy with a cure rate of 40% with no additional morbidity.[4]

Following a negative chest X-ray and ultrasound diagnosis of a 7 cm uterine mass, she was reclassified as high-risk gestational trophoblastic neoplasia (GTN) (I:10) (Table 1).

Due to treatment failure on a single-agent, she was started on a **second line** of EMA/CO (day 1: etoposide 100 mg/m^2; methotrexate 100 mg/m^2; followed by 200 mg/m^2 over a period of 12 hours and actinomycin D 0.5 mg; day 2: actinomycin D 0.5 mg; etoposide 100 mg/m^2 and leucovorin 15 mg every 6 hours (four doses, 24 hours after the first methotrexate dose); and day 8: vincristine 1 mg and cyclophosphamide 600 mg/m^2) (Figure 1B). She received eight cycles with one delay after the second cycle due to bone marrow suppression necessitating blood transfusion. Due to rising β human chorionic gonadotropin levels after the eighth cycle, she was changed to a **third line** regimen of paclitaxel-etoposide/cisplatin-paclitaxel (day 1: paclitaxel 135 mg/m^2 and cisplatin 60 mg/m^2; day 15: paclitaxel 135 mg/m^2 and etoposide 150 mg/m^2), but encountered multiple interruptions due to neutropenia that required filgrastim administration.

Dr Osborne: Was the patient re-staged before she was switched to EMA/CO and what did the chest film show?

Chest imaging is a staging requirement for persistent/metastatic trophoblastic disease. There are three basic forms of radiological presentation of metastatic pulmonary gestational trophoblastic neoplasia on chest x-ray: typical, alveolar, and embolic. The typical image is one of dense nodules (cannon balls) with well-defined contours and tend to be multiple and bilateral. Rarer radiographic changes associated with gestational trophoblastic neoplasia

Table 1 WHO scoring system based on prognostic factors

WHO prognostic factor	First assessment	Second assessment
Age	0	0
Antecedent pregnancy	1	1
Interval from index pregnancy, months	0	1
Pretreatment hCG mIU/mL	1	4
Largest tumor size including uterus, cm	2	2
Site of metastases including uterus	–	–
Number of metastases identified	–	–
Previous failed chemotherapy	–	2
Total score	4	10

hCG, human chorionic gonadotropin.

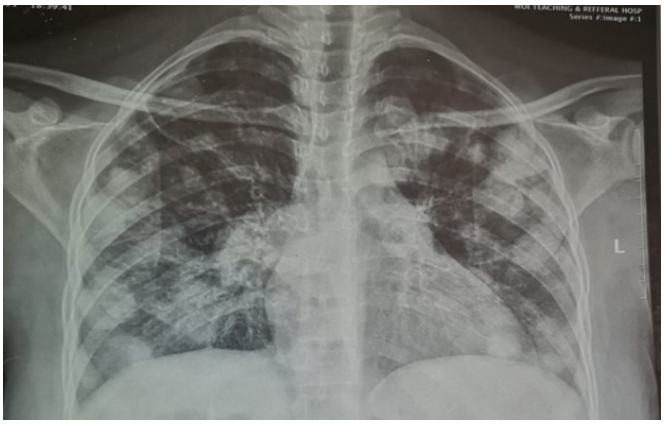

Figure 2 Chest X-ray findings showing multiple diffuse dense bilateral pulmonary nodules highly suggestive of metastatic gestational trophoblastic neoplasia.

include pleural effusion, interlobular septal thickening, cavitations, and air bronchogram[5] (Figure 2).

Approximately 40% of patients with a negative chest x-ray will have micro-metastases detected by a chest CT scan.[6] *A chest CT scan improves prediction of single-agent chemotherapy resistance but does not influence overall treatment outcome or the time to human chorionic gonadotropin normalization.*[7]

With a positive chest film, an MRI of the brain is required to determine if there are brain metastases present at this point. In case of brain lesions, the options include a multi-agent regimen of etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine, EMA/CO, with high-dose methotrexate (1 g/m^2 to improve drug perfusion of the blood–brain barrier), cranial radiotherapy (2 Gray daily for a total of 15 fractions) with or without concomitant intra-thecal methotrexate 12.5 mg. Some centers treat existing or residual brain lesions with stereotactic or gamma knife radiation following chemotherapy[1]*. Since this patient had not achieved a normal titer despite eight cycles of EMA/CO, the curve was fairly flat suggesting that re-imaging and/or a change in regimen or hysterectomy might have been indicated earlier. The etoposide, cisplatin, methotrexate, actinomycin D (EP/EMA) protocol is quite (marrow) toxic and patients will need filgrastim (Neupogen) by at least the fourth cycle.*

Dr Tonui: Please provide details as to the reasons for failure of EMA/CO and potential subsequent options

The probability of developing chemoresistance has been associated with large tumor size, high human chorionic gonadotropin titers of more than 100 000 IU/L, less than 4 months interval since antecedent pregnancy, and metastatic disease.[8] *It is, however, noteworthy that there has been inconsistency regarding risk factors for chemoresistance among different studies. Inability to fully characterize the histological type of gestational trophoblastic neoplasia and interruptions in treatment schedules, both common issues in low- and middle-income countries, may also play some role in development of multi-agent chemoresistance.*

Once chemoresistance to an EMA/CO regimen is documented the other options widely used for treating these patients include etoposide/platinum alternating with etoposide, methotrexate and actinomycin D (EP-EMA) and taxane/platinum alternating with taxane/etoposide (TP/TE; common drug choices include paclitaxel and cisplatin). Other drug combinations that are used infrequently include FAEV (floxuridine, actinomycin-D, etoposide, vincristine), VIP or ICE (etoposide, ifosfamide, and cisplatin or carboplatin), and BEP (bleomycin, etoposide, cisplatin). These patients will often need autologous peripheral stem cell support due to the toxicity of these agents.[9] *The positive response seen with checkpoint immunotherapies, particularly pembrolizumab, may circumvent these toxicities associated with the high-dose chemotherapeutic regimens by reducing the need to use them.*[10]

After the patient had received six cycles of paclitaxel, cisplatin/paclitaxel, etoposide (TP/TE), she defaulted on treatment for 3 months due to financial constraints, but returned due to profuse vaginal bleeding and a 7 cm uterine mass was reported on ultrasound. Her hemoglobin level was critically low at 3 g/dL. An abdomino-pelvic CT scan showed a 10×6.2×8 cm endometrial mass with evidence of retroperitoneal lymphadenopathy, basal lung metastases, and the pelvic bone of her left iliac wing appeared hypoplastic. Her human chorionic gonadotropin titer was elevated at 310 881 mIU/mL, rising to 485 969 7 days later. Given the positive chest x-ray, a brain MRI was ordered but not performed due to insufficient patient finances.

She received multiple transfusions and underwent urgent abdominal hysterectomy and bilateral salpingectomy due to massive bleeding. Intra-operatively, the tumor involved the left adnexa with invasion through the posterior wall of the uterus and a highly vascularized omentum adherent to the uterus. Histology confirmed choriocarcinoma (Figures 3 and 4).

Dr Keitany: What are the expected findings on histopathological review?

Grossly, the uterine cavity has a bulky, destructive, soft and fleshy tumor with extensive central hemorrhage and large areas of necrosis (Figure 3). *Uncommonly, choriocarcinoma can also present in extra-uterine sites of ectopic pregnancy.*

*On microscopy, choriocarcinoma exhibits a purely trophoblastic proliferation without chorionic villi. The hallmark is a mixture of small mononuclear cyto-trophoblastic cells and larger, often multinucleate syncytio-trophoblasts. Marked nuclear pleomorphism, brisk mitotic activity, prominent lympho-vascular invasion, extensive hemorrhage, and necrosis are usually evident (*Figure 4*).*[11]

The patient was started on fourth line etoposide/cisplatin alternating with etoposide, methotrexate and actinomycin D (EP/EMA) protocol (100 mg/m^2 of etoposide on days 1 and 2, 0.5 mg of actinomycin D on days 1 and 2, and 1 g/m^2 of methotrexate on day 1, followed by folinic acid rescue; on day 8, she received 100 mg/m^2 of etoposide and 60 mg/m^2 of cisplatin, alternating every 2 weeks) to which she responded over a period of 4 months with reducing β human chorionic gonadotropin levels (online supplemental material). However, she had grade 3 adverse events related to cisplatin (intractable nausea and vomiting) necessitating a change in the regimen to fifth-line carboplatin/paclitaxel[12] (carboplatin AUC 5 and paclitaxel 175 mg/m^2).

While on carboplatin and paclitaxel, she had acute onset confusion, grand-mal seizures, and loss of consciousness. She was seen at a different facility where a brain MRI revealed brain metastases with active intra-cranial bleeding. She received whole brain radiation at 5 Gy per fraction for a total of 20 Gy intent (palliative/curative) remains unclear. The confusion and seizures resolved but she had residual slow mentation. Following the cranial radiotherapy, she was to resume chemotherapy but her family decided against further

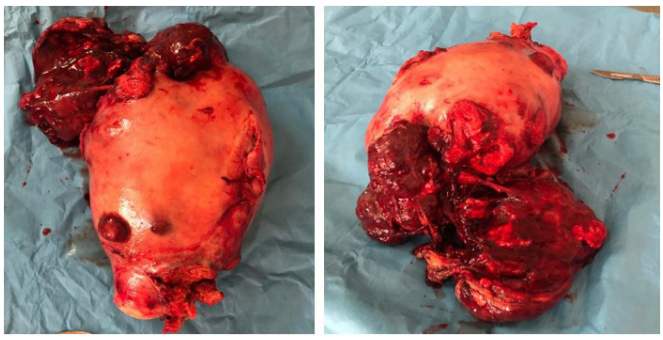

Figure 3 Simple hysterectomy specimen following massive bleeding due to choriocarcinoma.

systemic treatment. Consequently, she passed away 2 months after brain radiation.

Dr Tonui: What are some challenges faced by low- and middle-income countries when managing gestational trophoblastic neoplasia?

Gestational trophoblastic neoplasia, GTN, is a common medical problem in low- and middle- income countries largely affecting young women of reproductive age. It is highly curable when managed in a timely and appropriate manner. It still causes significant morbidity and mortality in low- and middle-income countries where its management is fraught with various challenges

Lack of regionalization of GTN care: Regionalizing management of GTNs has been clearly demonstrated to result in improved outcomes. Establishment of centers of excellence for the management of GTNs has not largely happened in low-income countries mostly due to limited resources. There is no single gestational trophoblastic diseases (GTD) center *in the whole of the African continent and the management of these cases are generally unstandardized, and a multi-disciplinary approach to care is severely lacking.*

Limited personnel with specialized knowledge on GTN: Healthcare workers (gynecologic oncologists, medical oncologists, nurses and laboratory technologists) with interest and specialist training on the management of GTN are very limited in low- and middle- income countries; subsequently GTN cases are managed by generalists or lower cadre professionals and such management is usually suboptimal and results in poorer outcomes.

Late diagnosis and suboptimal supportive and definite treatments: The majority of GTN patients present at tertiary centers late and in advanced stages of the disease. Additionally, due to the high cost of laboratory and imaging evaluations, limited choice and frequent stock outs of chemotherapeutic agents coupled with inadequate supportive management of therapeutic side effects, they ultimately receive suboptimal care.

High burden of loss to follow-up: While comprehensive data are largely lacking in this region, a study in Nigeria showed a loss to follow-up of 64.7%.[13] *This was linked to several factors such as the long duration of treatment and adverse drug events, particularly bone marrow suppression, resulting in treatment interruptions due to unavailability of blood and blood products and expensive agents. This leads to drug resistance/treatment failure with last resort to salvage therapies. Newer agents, such as pembrolizumab, are cost prohibitive and therefore not available. The majority of those lost to follow-up end up relapsing and subsequently registering poor oncological outcomes.*

Overall, the lack of a dedicated GTN center presents unique challenges that culminate in an inability to provide the essential services in a timely manner.

Dr Osborne: What are the proposed solutions?

Based on a phase II Gynecologic Oncology Group study, second curettage is not recommended for patients with very high human chorionic gonadotropin titers or for older patients[4]*. If the community medical officers and nurses are performing repeat curettages for postpartum bleeding in the absence of a diagnosis, they need to be made aware that per vaginal bleeding >4 weeks is GTN until proven otherwise, and that a simple pregnancy test will usually suffice to make the diagnosis, but a tissue diagnosis is preferred. Unusually, hydatidiform mole may de-differentiate into choriocarcinoma, placental-site trophoblastic tumor, and epithelioid trophoblast tumor necessitating potentially different treatment. The serum human chorionic gonadotropin levels should normalize by day 28 in 97.5% of women (3 SD)*[14].

Given the geographical issues and distances involved, the lost-to-follow-up issue might be addressed by increasing patient/midwife/physician awareness of the importance of quickly recognizing the possible significance of unexplained postpartum bleeding occurring

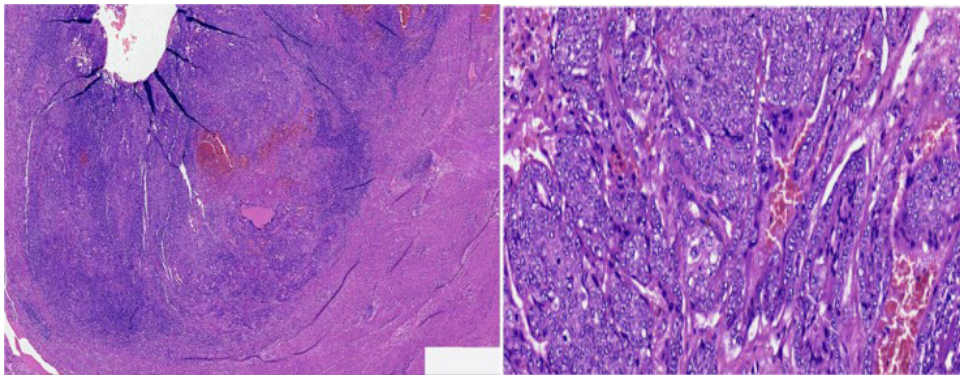

Figure 4 Histology of choriocarcinoma of the uterus; online supplemental material: graph showing serial βhCG trends from the time patient was on EP/ EMA. βhCG, β human chorionic gonadotropin; A, actinomycin D, E, etoposide; M, methotrexate; P, cisplatin.

more than 4 weeks after delivery. Perhaps a patient education booklet that describes GTD/GTN and the high likelihood of cure with appropriate, active management might be useful. Treatment interruptions might be anticipated and prophylactic marrow support given early, particularly with the protocol including etoposide, cisplatin, methotrexate and actinomycin D (EP/EMA) which frequently causes early onset neutropenia. There is ample evidence that specialized trophoblastic units dramatically improve clinical outcomes, particularly with respect to high-risk (WHO Risk Score >5) and ultra-high-risk (Risk Score >13) disease or brain/liver metastases. An East African unit may be the most feasible approach depending on national politics, patient numbers, and available resources. Utilizing existing cervical cancer screening clinics in the community to educate patients about miscarriages/GTD and undiagnosed postpartum bleeding might be a good opportunity to disseminate a GTD/GTN information pamphlet to patients, district nurses, and physicians.

Closing summary

Despite gestational trophoblastic neoplasia being a highly treatable cancer, it is a very lethal diagnosis in low- and middle-income countries due to challenges in testing and treating. With increased education in low level facilities to enhance quick referral and centralizing GTN care, there is a possibility of improving overall survival.

Acknowledgements I would like to acknowledge Professor Allan Covens of Sunnybrook Health Sciences, Toronto, Canada for his mentorship and guidance in this case study.

Contributors AM identified the patient, RB and PT contributed to management of the patient, and KK contributed with diagnostic investigations.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

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