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Successful treatment of gestational choriocarcinoma in a low resource setting and literature review.

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Abstract

Aim: Gestational choriocarcinoma is a rare pregnancy related malignancy that we see about once in two years in our centre. It is an interesting malignancy because, although, it is rapidly fatal, it remains one of the few malignancies that can be cured even in advanced stages. Few cases we managed in the past did not show good outcome mainly because of noncompliance on the part of the patients. This case complied adequately with treatment and was cured with modified MAC III chemotherapy regimen with resultant successful reproductive outcome thereafter.

Presentation: - Our patient was a 32-year-old para3^{+1} A3 at presentation. She presented with two months history of intermittent vaginal bleeding which started about seven weeks after the cessation of normal vaginal lochia following normal vaginal delivery. There was associated vulva lesion and hemoptysis. She was investigated and a diagnosis of gestational choriocarcinoma was made, and she was successfully cured of the malignancy with modified MAC III Chemotherapy regimen resulting in her having another successful reproductive outcome thereafter.

Conclusion: Gestational choriocarcinoma may be fatal but it can be cured if there is adequate compliance from the patient and appropriate multiple chemotherapy is used for treatment.

Keywords: *Gestational Choriocarcinoma; case report; modified MAC III regimen; successful treatment; normal future reproductive outcome after successful treatment.*

Introduction/Literature Review

Choriocarcinoma belongs to a spectrum of diseases called Gestational Trophoblastic diseases which ranges from premalignant benign diseases such as complete hydatidiform mole and partial hydatidiform mole; and potentially malignant entities such as invasive mole, choriocarcinoma and placental site trophoblastic tumor (PSTT). The latter potentially malignant diseases are collectively called gestational trophoblastic neoplasia (GTN).[1] Gestational choriocarcinoma is the most malignant of the GTN. It is composed of malignant trophoblastic cells which may arise from trophoblastic tissue of term pregnancies, as well as from ectopic gestation, spontaneous or induced abortions. However, 50% of cases arise from hydatidiform mole.[2] Choriocarcinoma is a highly invasive tumor and at the time of diagnosis, it is often widespread. Lungs are the most common sites for metastasis. Other sites of metastasis include the liver, vagina, kidney, intestines and the brain. Women over the age of 40 are at increased risk for choriocarcinoma. [3] The prevalence is greatest in Asia, Africa & Latin America and substantially lower in North America, Europe and Australia.[4] It occurs with a frequency of only one in 40,000 pregnancies in the USA, whereas the incidence in Asia, Africa & Latin America is one in 500 to 1000 pregnancies. Women of blood group A have been shown to have a greater risk than group O women, and there is evidence of particular risk for women of group A married to men with blood group O and women of group O married to group A men, in comparison with combinations of O x O and A x A. [5] The reasons for these specific associations have remained obscure. Women with Blood group B or AB are even said to have a worse prognosis.[6]

The clinical presentation of choriocarcinoma can be in the form of vaginal bleeding resulting from the local disease in the uterus or resulting from effect from

distant mestastasis which can manifest in a wide variety of symptoms such as haemoptysis, severe abdominal pains or even stroke-like symptoms. This can apparently make diagnosis difficult in such distant metastasis cases. However, the combination of obstetric history and elevated serum β HCG usually makes diagnosis clear. Rarely though, the use of CT scan, or histology may be necessary for clear diagnosis.

The treatment of choriocarcinoma depends on the classification group the disease falls into according to WHO and FIGO classification. [7,8] The classification system is shown in table 1.

Table 1 The classification system by the WHO and FIGO for classifying gestational trophoblastic tumors and treatment protocols

Risk factor	Risk Score			
	0	1	2	4
Age (years)	<40	≥40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval (end of antecedent Pregnancy to Chemotherapy) in months	<4	4-6	7-13	>13
Human chorionic Gonadotropin (IU/L)	$<10^3$	10^3-10^4	10^4-10^5	$>10^5$
Number of metastasis	0	1-4	5-8	>8
Site of metastasis	Lungs	Spleen, Kidney	Gastrointestinal tract	Brain, Liver
Largest tumor mass	-	3-5cm	>5cm	-
Previous chemotherapy	-	-	single drug	≥2 drugs

The classification places GTN, including choriocarcinoma into low-risk group, moderate-risk group and high-risk group. This scoring system was originally devised by Bagshawe in 1976.[6] This group classification does not only determine the treatment protocol, but it also suggests the prognosis of the disease. The low-risk group has a score of 0-4, the moderate-risk group has a score between 5 and 7 and the high-risk group will have a score of 8 or higher. Low-risk metastatic disease is usually treated with single or multiple drug chemotherapy while moderate-risk metastatic disease is treated with multiagent chemotherapy. High-risk metastatic disease requires aggressive multidrug chemotherapy. Generally, once a diagnosis of choriocarcinoma is made, it is regarded as a moderate-risk or high-risk metastatic disease and multiagent chemotherapy is usually recommended. While low-risk disease has cure rates of nearly 100%; high risk disease has cure rates of about 95%. This makes choriocarcinoma a very interesting cancer as it is one of the few advanced malignancies in medicine that can literally be cured and hence the need for appropriate treatment.

Treatment Protocols for Gestational Trophoblastic Tumors

Ideally, consultation with a gynecologic oncologist is required for treatment of metastatic diseases.

Low-risk Metastatic Disease

(WHO score: less than 6)

Women belonging to this low-risk group must receive intramuscular methotrexate. Methotrexate is determination of HCG levels until they have become administered intramuscularly, alternating daily with folinic acid for 1week followed by 6 rest days

Chemotherapy is changed from methotrexate to intravenous dactinomycin if the HCG level plateaus (implying resistance to methotrexate) or if toxicity to methotrexate precludes adequate chemotherapy. With the development of metastases or and elevation of β-HCG titres, combination chemotherapy should be started. Treatment is continued for one to two courses past the first normal HCG levels.

Moderate-risk patients

(WHO score: 5 to 7)

Traditionally, moderate-risk patients are treated with multiagent chemotherapy. The most commonly used combination chemotherapy are MAC (methotrexate dactinomycin, cyclophosphamide or chlorambucil) or EMA (Etoposide, methotrexate and dactinomycin).[9]

High-risk patients

(WHO score: 8 or Greater)

This set of patients usually require combination chemotherapy with selective use of surgery and radiotherapy. The standard chemotherapy regimen in this high-risk group patients is EMA/CO (Table 2) In which the drugs like etoposide dactinomycin and methotrexate are alternated at weekly interval with Vincristine and cyclophosphamide.[9]

Follow-up After Chemotherapy

After chemotherapy treatment, HCG is measured weekly until HCG levels have become normal for 3 consecutive weeks, followed by monthly

normal for 24 consecutive months (2 years).

In the UK, follow-up continues indefinitely because it is unclear when it is safe to stop. However, in other countries, time varies from one centre to the other.[10] Women are therefore advised not to become pregnant for 12 months following chemotherapy treatment because this may interfere with early detection of relapsed disease and also to reduce the risk of delayed tetratogenicity.[11]

The commonly used regimen for resistant disease is EP/EMA (Table 3),

Table 2 EMA/CO regimen for high-risk patients with gestational trophoblastic disease
Regimen 1 (EMA)
Week 1 – Day 1
• Actinomycin D 0.5mg IV bolus • Etoposide 100mg/m^2 IV in 500ml N saline over 30 minutes • Methotrexate 300 mg/m^2 IV in 1 liter N saline over 12 hours
Day 2
• Actinomycin D 0.5mg IV bolus • Etoposide 100mg/m^2 IV in 500ml N saline over 30 minutes • Folinic acid 15mg IM 12-hourly x 4 doses starting 24 hours after commencing methotrexate
Regimen 2 (CO)
Week 2 - Day 1
• Vincristine (oncovin) 1.4 mg/m^2 IV bolus (maximum 2mg) • Cyclophosphamide 600 mg/m^2 IV in 500 ml N saline over 30 minutes

which include etoposide, cisplatin, methotrexate and dactinomycin.

Table 3 EP/EMA regimen for patients with disease resistant to EMA/CO
Regimen 1 (EP)
Week 1 – Day 1
• Etoposide 150mg/m^2 IV in 500ml N saline over 30 minutes • Cisplatin 25mg/m^2 IV over 4 hours
Regimen 2 (EMA)
Week 2 – Day 1
• Etoposide 100mg/m^2 IV over 30 minutes • Methotrexate 300 mg/m^2 IV over 24 hours • Actinomycin D 0.5mg IV bolus
Day 2
• Folinic acid 15mg PO 12-hourly for four doses • (to start 24 hours after starting methotrexate

Choriocarcinoma Case Report

The patient was a 32year old para 3^{+1} A3 at presentation. She presented in October 2018 with 2-month history of intermittent vaginal bleeding and 10-day history of haemoptysis. She had her last delivery (uneventful vaginal delivery) in June 2018 associated with normal lochia flow for 4weeks. This intermittent vaginal bleeding then started about 7weeks after cessation of normal lochia. There was no associated cough or dyspnoea but there was associated abdominal discomfort with excessive bowel movement.

Essential findings on examination were moderate palor, vital signs were within normal range, chest was clinically clear. Vaginal examination revealed a darkish red suburethral vaginal nodule measuring about 3cm in diameter. An urgent serum and urinary pregnancy test (neat & dilution) was ordered as our laboratory did not have the facility for serum β HCG assay then and the result came out to be positive both in neat and dilutions. A diagnosis of Choriocarcinoma was made and further investigations were ordered. Chest x-ray revealed right basal consolidated changes. Her packed cell volume (pcv) was 34%. Serum electrolytes, urea & creatinine levels were within normal limits, Liver Function Test (LFT) were also within normal limit. Platelet count was normal. A prognostic scoring classification was carried out and she was scored at 5 (moderate-risk patient). She was then counseled and commenced on chemotherapy as follows: -

(a) Intramuscular methotrexate 15mg daily x 5 days

(b) Intravenous Actinomycin D 600mg daily x 5 days

(c) Intravenous cyclophosphamide 150mg daily x 5 days

She was made to stop breast feeding before the commencement of chemotherapy. The above chemotherapy regimen is called the MAC regimen (although a modification of the original MAC III regimen). For this patient, it was repeated every 2 weeks for a total of 5 courses. At each follow up visit for a course of chemotherapy, she was investigated and the pcv, platelet count, serum electrolytes, urea & creatinine & LFT were found to be normal before commencement of each course of chemotherapy. She was also monitored at each follow up visit with serum and urinary pregnancy test results, neat and in dilution. After the 5th course of chemotherapy, the pregnancy test was found to be negative both in neat & in dilutions. The chemotherapy was then stopped & she was given 3-month appointment to come back with serum β hcG assay to be done in a private laboratory in Owerri, capital city of Imo State. She was also counseled against getting pregnant again & was advised to have bilateral tubal ligation (BTL) which she objected to and she was the placed on temporary contraceptive (COC Pills) to prevent pregnancy so as to allow reliable monitoring of serum β hcG due to persistent or recurrent trophoblastic disease. When she reported at 3-month appointment, her β hcG assay done in a private lab in Owerri was 2.5miu/ml (Negative: ≤5.0 miu/ml). No history of abnormal vaginal bleeding and her chest was clinically clear and a repeat chest x-ray revealed no abnormalities. She was discharged from the clinic & told to continue the COC Pills for another nine months (making a total of 12months) & told to come back in 6 months for review. Surprisingly, this woman presented in October 2020 pregnant, at 25weeks gestation! This was about 1 year, 3 months after she was certified cured from the choriocarcinoma. She had an uneventful pregnancy and was eventually delivered of a live female baby per vaginum on 21/1/2021. She was counseled again for bilateral tubal ligation (BTL) soon after delivery which she consented to this time around and on the third day post-partum she had BTL. She has been followed up now for close to 1 year including one serum β hcG level of 2.0miu/ml

Discussion

Not surprising, this woman presented with abnormal vaginal bleeding many weeks following the cessation of lochia. This is probably one of the commonest presentations of choriocarcinoma [11]. Choriocarcinoma should always be suspected if a woman starts bleeding abnormally per vaginum some weeks following the cessation of lochia. Although the time interval between the antecedent pregnancy and the diagnosis of choriocarcinoma is usually short; however, there are occasional patients with documented asymptomatic periods of 5 -17 year between the last known pregnancy and the diagnosis of choriocarcinoma[12]. Another common symptom this woman presented with was haemoptysis which is a symptom of lung metastasis although the chest x-ray carried out on her did not reveal the classical cannon ball metastases but rather revealed right basal consolidation which is probably a sign of early lung metastasis. The suburethral vaginal reddish nodule seen in this woman is another common presentation in choriocarcinoma which further raised the suspicion for choriocarcinoma in her. Grossly elevated serum β hcG level is essential for the diagnosis of choriocarcinoma as a normal serum β hcG level in this woman would have excluded choriocarcinoma. Unfortunately when this woman presented there was no facility for detection of serum β hcG level in our centre which led to the alternative use of pregnancy test positivity or negativity both in neat and diluted urine samples. Persistent pregnancy test positivity in the more diluted urine samples is indicative of a higher serum β hcG levels. Though this later method of assessing β hcG levels may be considered crude, it is quite reliable in making diagnosis of choriocarcinoma in high urine dilutions combined with the clinical features of choriocarcinoma as seen in this patient. With this, we made a presumptive diagnosis of choriocarcinoma and treatment was started as further delay may be inimical to the patient's life. However, for follow-up of treatment, she was referred to a private laboratory in the state capital for serum β hcG assay whose result is essential for making a diagnosis of cure. The combination chemotherapy adopted by us in the treatment of this patient is the MAC based combination chemotherapy (Methotrexate, dactinomycin, cyclophosphamide or chlorambucil) which is one of the most commonly used chemotherapy for choriocarcinoma [10]. The original MAC therapy, "Li's triple therapy" was introduced by Li Mc in 1971 in which methotrexate, dactinomycin and chlorambucil were the three cytotoxic drugs [13]. Li's triple therapy was later modified by Berkowitz and Gold stein in 1987 who substituted chlorambucil for cyclophosphamide and called it MAC III [14]. In MAC 111 regimen, however, the methotrexate dose was higher (1mg/kg body weight IM) and because of this, it is given along with folinic acid (citrovorum rescue factor) to reduce the toxic effects of methotrexate. In this our patient, however, we used IM methotrexate of 15mg daily as

folinic acid was not readily available to reduce the possible toxic effects of methotrexate. Gladly, this patient did very well with our regimen.

Although, it is recommended that treatment is continued for one or two courses past the first normal hcG level[10], we did not see any further need to do this in this case as her response to treatment was very good and we made sure we saw her 3 months after the last course that revealed normal β hcG levels and gracefully, at that visit her serum β hcG level was normal. This case further confirmed that patients successfully treated with chemotherapy for choriocarcinoma can expect normal reproduction in the future[15], although we preferred an end to her reproductive career being para3 at the end of her successful chemotherapy but she declined bilateral tubal ligation.

Conclusion

Gestational choriocarcinoma is a potentially very fatal malignancy but luckily, it can be diagnosed early enough with β serum hcG assay or with simple urine pregnancy test measurement in neat and dilutions especially when it is combined with well-known clinical features of it. Multiple chemotherapy remains the mainstay for its cure and even a modified form of MAC III as we used in this case, in which a lower dose of methotrexate is used, is feasible.

References

1. Soper, J. T., Mutch, D. G., Schink, J. C., & American College of Obstetricians and Gynecologists. (2004). Diagnosis and treatment of gestational trophoblastic disease: ACOG Practice Bulletin No. 53. *Gynecologic oncology*, *93*(3), 575-585.
2. Philip savage and Michael Seckl. Trophoblastic disease . In: D. Keith Edmonds (ed) Dewhurst's Textbook of obstetrics and Gynaecology, 7th edition. Oxford: Black well publishing, 2007: 117-124.
3. Bracken, M. B., Brinton, L. A., & Hayashi, K. E. N. J. I. (1984). Epidemiology of hydatidiform mole and choriocarcinoma. *Epidemiologic reviews*, *6*, 52-75.
4. Grimes, D. A. (1984). Epidemiology of gestational trophoblastic disease. *American journal of obstetrics and gynecology*, *150*(3), 309-318.
5. Schottenfeld, D., & Fraumeni Jr, J. F. (Eds.). (2006). *Cancer epidemiology and prevention*. Oxford University Press.
6. Bagshawe, K. D. (1976). Risk and prognostic factors in trophoblastic neoplasia. *Cancer*, *38*(3), 1373-1385.
7. World Health Organization. (1983). *Gestational trophoblastic diseases: report of a WHO scientific group [meeting held in Geneva from 6 to 10 December 1982]*. World Health Organization.
8. Oncology, F. I. G. O. (2002). Committee: FIGO staging for gestational trophoblastic neoplasia 2000. FIGO Oncology Committee. *Int J Gynaecol Obstet*, *77*(3), 285-7.
9. Deng, L., Yan, X., Zhang, J., & Wu, T. (2006). Combination chemotherapy for high-risk gestational trophoblastic tumour. *Cochrane Database of Systematic Reviews*, (3).
10. Richa Saxena. Hydatidiform Mole In: Richa Saxena. Bedside obstetrics and Gynecology, second edition. Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India, 2014: 300-322.
11. G.J.S. Rustin. Trophoblastic Diseases. In: Robert W. Shaw, W. Patrick Soutter and Stuart L. Stanton (eds) Gynaecology. London: Churchill Livingstone, 1992: 557-567.
12. PJ, D. (1975). Morrow CP. Townsend DE. Gestational Trophoblastic Disease: In Synopsis of Gynecologic Oncology.
13. Li, M. C. (1971). Trophoblastic disease: natural history, diagnosis, and treatment. *Annals of Internal Medicine*, *74*(1), 102-112.
14. Berkowitz, R. S., & Goldstein, D. P. (1987). Modified triple chemotherapy. *Gestational trophoblastic disease*, 146-154.
15. FEDERSCHNEIDER, J. M., GOLDSTEIN, D. P., BERKOWITZ, R. S., MAREAN, A. R., & BERNSTEIN, M. R. (1980). Natural history of recurrent molar pregnancy. *Obstetrics & Gynecology*, *55*(4), 457-459.