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CASE REPORT

# Gestational choriocarcinoma in a postmenopausal woman: a case report – lessons for the junior clinician

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Choriocarcinoma is a rare form of malignancy originating from epithelial trophoblastic tissue. Unusual and varied presentations of choriocarcinoma present clinicians with a diagnostic challenge. Education is pertinent to ensure a high index of suspicion of the condition to promote a timely diagnosis and better prognosis for patients. This case report discusses an atypical presentation of a 48-year-old postmenopausal woman with gestational choriocarcinoma, with a possible preceding molar pregnancy. It highlights learning points for clinicians regarding gestational trophoblastic diseases, the relevance of persistently high quantitative serum Beta human chorionic gonadotrophin (Beta HCG) values, differential diagnoses for postmenopausal bleeding, co-existent pathologies and choriocarcinoma.

**Keywords:** choriocarcinoma, postmenopausal bleeding, gestational trophoblastic diseases, Beta HCG, neoplasia

## Introduction

Choriocarcinoma is a rare, aggressive malignancy originating from epithelial trophoblastic tissue. It is a subtype of gestational trophoblastic disease which Hippocrates first recognised in 400 BC.[1]

Categorised into gestational and non-gestational types, the former is the most common. Gestational choriocarcinoma occurs in approximately 1 in 50 000 normal pregnancies.[2] The majority have an intrauterine origin and occur following a preceding molar pregnancy; however, there are cases following term pregnancies and spontaneous miscarriage.[3]

Women primarily present during their fertile years, though several postmenopausal cases have been described. The oldest known woman was diagnosed at age 73.[4] The duration between an index pregnancy and the development of choriocarcinoma is usually less than one year, but this can range from four weeks up to 38 years.[4,5]

Most patients present with abnormal uterine bleeding, uterine enlargement, consistently high or rising serum Beta human chorionic gonadotrophin (HCG) values post uterine evacuation of a molar pregnancy or persistent ovarian theca lutein cysts.[5] Manifestations of metastasis to the lungs (80%), vagina (30%) and liver (10%) are also fairly frequent, with approximately 30% of patients having metastatic disease at the time of diagnosis.[5]

Here we describe a 48-year-old woman with an atypical presentation of choriocarcinoma. She presented with post-menopausal bleeding with a known diagnosis of a multi-fibroid uterus, an inconclusive history of a possible preceding molar pregnancy with persistently high quantitative serum Beta HCG values, and a three-year interval from index pregnancy to diagnosis of choriocarcinoma.

## Case report

A 48-year-old $G_6P_3M_2TOP_1$ woman with well-controlled asthma presented to Mitchell's Plain District Hospital. She had a two-week history of profuse postmenopausal vaginal bleeding with associated mild lower abdominal pain, dizziness and weight loss. Her menarche was at age 19, and she had presumably been menopausal since the age of 46.

On general examination, she exhibited notable conjunctival pallor with a pulse rate of 126 beats per minute and a blood pressure of 106/72 mmHg. On systemic examination, she had suprapubic tenderness with no palpable abdominal mass. A speculum examination showed active vaginal bleeding. A bulky mobile uterus was felt on bimanual palpation. All other systemic examinations were normal.

An initial transvaginal ultrasound was attempted revealing a multi-fibroid uterus. While the examination was underway, the patient started haemorrhaging vaginally. She required stabilisation with intravenous fluids, blood products and tranexamic acid.

After stabilisation overnight, a cervical smear and an endometrial sample were attained. This precipitated another vaginal haemorrhage and blood products were again required to stabilise her. The following day a repeat transvaginal scan was performed. It demonstrated an axial, large, bulky uterus 76 x 136 mm with a distorted endometrial cavity and intramural fibroids with some areas of mixed echogenicity with notable vascular flow. Retained products of conception were queried.

A urinary pregnancy test was performed, revealing a positive result, although importantly, recent sexual activity was not reported.

Blood investigations showed a microcytic anaemia of 5.9 g/dl with a mild thrombocytopaenia of 124, with a quantitative serum Beta HCG value of 277 511 mIU/ml. Her renal, liver and thyroid function tests were within normal limits.

She was then transferred to Groote Schuur Hospital for further investigations and management. Concern regarding the possibility of choriocarcinoma was noted on transfer.

### *Background history*

The patient's obstetric history consisted of three term vaginal deliveries, two uncomplicated first-trimester miscarriages and her last pregnancy was terminated. At age 45, she opted for an elective first-trimester termination for socio-economic reasons. The pregnancy had been complicated by hyperemesis gravidarum, warranting hospitalisation for fluid resuscitation. She underwent an uncomplicated evacuation of the uterus in theatre after an incomplete medical termination. No tissue was sent for histology.

Two months later she was referred back to Mitchell's Plain District Hospital by a general practitioner for a 'chronic miscarriage'. The patient had a two-month history of persistent vaginal bleeding with associated fatigue and a positive pregnancy test. She was subsequently referred to Groote Schuur Hospital with a suspected molar pregnancy based on a persistently positive pregnancy test following the termination, a 'bulky uterus with multiple berry-shaped structures' on ultrasound examination and a symptomatic anaemia of 7.5 g/dl. Of relevance, she reported no sexual contact for the prior three months and was receiving medroxyprogesterone acetate.

On admission to Groote Schuur Hospital, her first documented quantitative serum Beta HCG value was 108 160 mIU/ml. Her full blood counts, renal, liver and thyroid function tests were within normal limits. She underwent a dilatation and curettage of the uterus with histology revealing contents 'consistent with products of conception'. Her Beta HCG values thereafter were on a downward trend. The day 3 value was 25 290 mIU/ml and 11 days after the surgery, her Beta HCG value was 1 853 mIU/ml. It appears she was then lost to follow-up.

In the same year, she continued to have abnormal uterine bleeding, now attributed as secondary to a multi-fibroid uterus, for which she had been scheduled for a hysterectomy. It was however postponed due to non-gynaecological sepsis and the patient was lost to follow up again. Her bleeding subsided with the administration of medroxyprogesterone acetate at her local clinic.

She stopped all contraception later that year and remained amenorrhoeic, presumed secondary to early menopause.

### *Results of further investigations*

In the index presentation, the patient's endometrial biopsy consisted of very scanty haemorrhagic curetting displaying small fragments of tissue showing groups of bizarre tumour cells (Figure 1). On immunohistochemistry (Figure 2), the tumour cells appeared positive for Beta HCG and cytokeratins and negative for P63 and Napsin A. The histological examination was suggestive of choriocarcinoma.

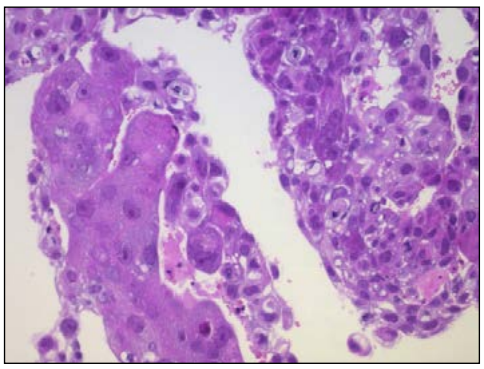

**Figure 1:** Microscopic image of endometrial biopsy: Histology of the curettage showing choriocarcinoma comprising multinucleated syncytiotrophoblasts (left) and mitotically actively cytotrophoblasts (right) (Haematoxylin and eosin stain, 200x magnification)

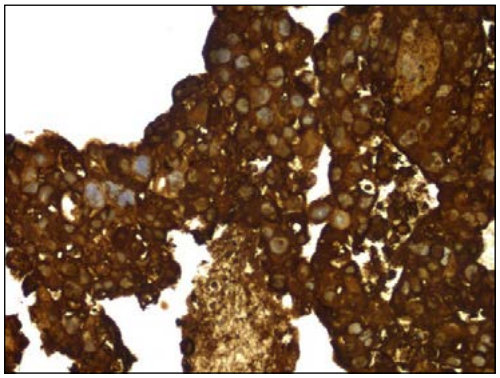

**Figure 2:** Immunohistochemistry analysis of endometrial biopsy specimen: Immunohistochemical stain for Beta HCG is strongly diffusely positive in tumour cells (200x magnification)

Her cervical smear revealed a high-grade squamous intra-epithelial lesion and her chest x-ray and computed tomography were normal.

The patient was assessed to be ultra-high risk, classified as FIGO Stage 1 choriocarcinoma, with a WHO prognostic score of 13.

Her quantitative serum Beta HCG value on presentation was 277 511 mIU/ml**.**

Intravenous chemotherapy with etoposide, actinomycin D, methotrexate (EMA) on days 1 and 2 and cyclophosphamide and vincristine (CO) on day 8 was initiated. Her Beta HCG at follow-up, after her first cycle of chemotherapy, was 42 451 mIU/ml. After six cycles of chemotherapy, her Beta HCG level was 28 mIU/ml, but started to plateau. Due to multiple neutropaenic episodes on EMA-CO requiring granulocyte colony-stimulating factor (GC-SF), she was changed to taxane and etoposide (TE) alternating with taxane and cisplatin (TP) chemotherapy every two weeks. She responded well and after two cycles, her Beta HCG level was five. Two insurance cycles of chemotherapy were added.

The patient is now clinically asymptomatic and on regular follow-up at the tertiary referral unit. Her Beta HCG level remains below five at six months post-treatment.

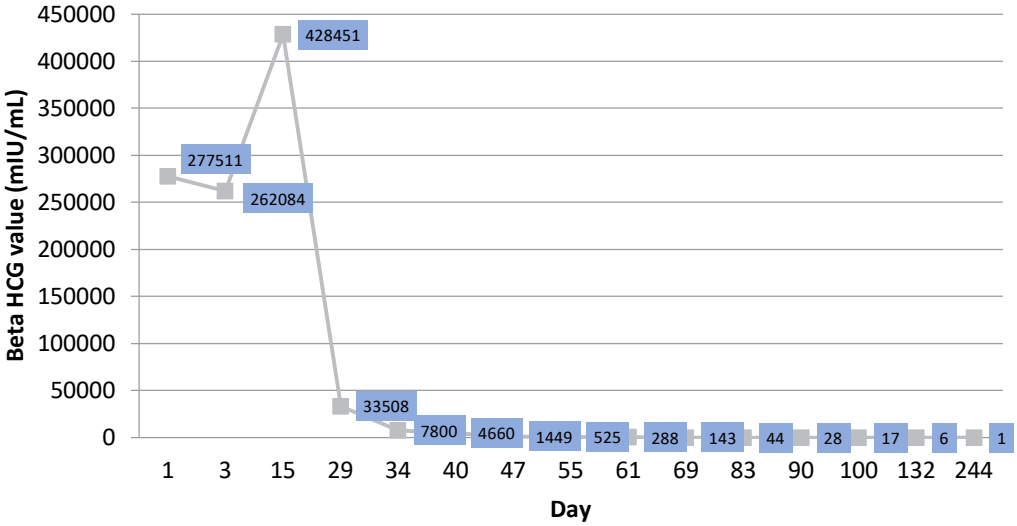


**Figure 3:** Line graph depicting the patient's Beta HCG values over time in response to chemotherapy, with logarithmic drop and then plateau

## Discussion

Gestational trophoblastic diseases (GTD) comprise of partial and complete molar pregnancies and gestational trophoblastic neoplasia (GTN). The latter includes invasive moles, choriocarcinoma, placental site trophoblastic tumours (PSTT) and epithelioid trophoblastic tumours (ETT).[6]

Molar pregnancies, otherwise known as hydatidiform moles, occur in approximately 1 in 1 500 pregnancies.[7] Abnormal uterine bleeding, a positive pregnancy test and suggestive ultra-sonographic findings are the most common features on presentation. Hyperemesis gravidarum, vaginal passage of grape-like vesicles, hyperthyroidism, uterine enlargement, early-onset preeclampsia and theca lutein cysts causing abdominal distention are also seen in molar pregnancies.[8]

In high-income countries, a pregnancy test is recommended three weeks after a miscarriage if no products were sent for histology.[9] If it remains positive, further investigations should be performed to exclude an ectopic pregnancy and GTD. Importantly, a diagnosis of choriocarcinoma can be made on clinical and biochemical grounds – histology is not a prerequisite.[10]

If vaginal bleeding persists for more than eight weeks after a pregnancy event, a pregnancy test should also be performed to evaluate for GTD.[9] This may not be possible in a low- and middle-income setting, especially when only a minority develop into choriocarcinoma (2–3% of molar pregnancies develop into choriocarcinoma).[7] Incidence is higher following a complete compared to a partial mole, with rates of appropriately 8% and 0.5% respectively.[8] Serial serum Beta HCG monitoring post-treatment of a molar pregnancy helps to establish this evolution to choriocarcinoma.

With the eventual diagnosis of choriocarcinoma, the retrospective review of our patient's prior gynaecological history provides us with a few points of interest. The index pregnancy, for which she underwent an elective termination, was complicated by hyperemesis gravidarum. Her ongoing bleeding for two months after the termination and a persistently positive pregnancy test resulted in the general practitioner's referral of the patient with a 'chronic miscarriage'. She was then found to have high quantitative serum Beta HCG levels and ultrasound findings strongly suggestive of a GTD. However, her histology results from her uterine evacuation were not suggestive of a molar pregnancy. It is pertinent to question the validity of the sample or evaluation thereof. Limited data suggests that histopathologists reliably diagnose complete molar pregnancies; however, the differentiation of non-molar and partial molar pregnancies can present challenges.[10] It appears our patient was undergoing serial Beta HCG tests when she was lost to follow-up.

Postmenopausal bleeding has a myriad of plausible aetiologies. Our patient had a known diagnosis of a multi-fibroid uterus with a prior planned hysterectomy. Without the pregnancy test result, this could have been the deemed underlying aetiology. Additionally, leiomyosarcoma and endometrial carcinoma could have been considered. According to Desai et al., it is difficult to rule out the possibility of trophoblastic differentiation within an endometrial carcinoma when choriocarcinoma occurs in postmenopausal women.[4] It is clear that an unusual combination of conditions can lead to diagnostic confusion. Without consideration for potential dual pathologies, an inherent knowledge of choriocarcinoma and its potential postmenopausal onset, choriocarcinoma could have been missed. Mangla et al. state that the 'absence of localisation of intrauterine pregnancy in the presence of elevated levels of Beta HCG should arouse suspicion.'[5]

Postmenopausal choriocarcinoma is very rare, with limited cases described worldwide.[4] The true incidence is poorly established. The diagnosis, however, is important as choriocarcinoma is highly curable even if advanced metastatic disease is present.[5]

Chemotherapy is the mainstay of the treatment for choriocarcinoma; however, hysterectomy can play a valuable role in those with intractable vaginal bleeding and as adjuvant treatment in chemo-resistant patients.[11,12]

## Conclusion

This case illustrates that patients may present with dual pathology. Although choriocarcinoma is a rare condition, it needs to be considered in the differential of both abnormal uterine and postmenopausal bleeding, especially when the presentation is unusual. It highlights the importance of skilled pathology services and availability of pathology review where the clinical picture is highly suspicious. Choriocarcinoma has a high chemo-responsive nature with a remission rate of 87.5% if the duration between index pregnancies to initiation of chemotherapy is less than four months.[5] A high index of suspicion and excellent clinical acumen can lead to a prompt diagnosis and a good prognosis.

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