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CASE REPORT

High-risk gestational trophoblastic neoplasia: a case report – an atypical presentation with salient features to the suspicious clinician

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Gestational trophoblastic neoplasia (GTN) is a cancer originating from placental tissue with the potential for widespread metastases. Varied presentations present clinicians with a diagnostic challenge. A high index of suspicion will promote timely diagnosis and improved prognosis. This case report discusses an atypical presentation of a young woman with high-risk GTN, with salient features on a routine investigation. It highlights learning points for both gynaecologists and non-gynaecologists regarding GTN, the importance of gynaecological ultrasonography, the relevance of human chorionic gonadotropin (hCG), and how essential gestational trophoblastic disease (GTD) is in the differential diagnoses for reproductive women presenting with amenorrhoea.

Keywords: gestational trophoblastic neoplasia, hCG, theca lutein cysts, chemotherapy, hook effect

Introduction

Gestational trophoblastic neoplasia (GTN) is a term used to describe malignant lesions arising from placental trophoblastic cells with the secretion of persistent amounts of human chorionic gonadotropin (hCG).[1] GTN includes malignant forms, such as persistent mole, invasive mole, choriocarcinoma, placental site trophoblastic tumour, and epithelioid trophoblastic tumour.[2]

GTN classification uses the staging of the International Federation of Gynaecology and Obstetrics (FIGO, 2002) with the modified World Health Organization (WHO) risk scoring system.[3] FIGO staging is anatomically based (stages I–IV), and the modified WHO risk scoring system uses prognostic factors for resistance to chemotherapy.[3] Patients with a risk score ≥ 7 are diagnosed with high-risk GTN and are primarily treated with combination chemotherapy.[3]

GTN has a varying presentation depending on the antecedent pregnancy event, as well as disease type and extent.[4] GTN can be associated with an enlarged uterus and bilateral ovarian enlargement.[4] Patients often present with symptoms of metastatic disease.[4] The most common metastatic sites are the lungs, but metastases can also be found in the vagina, liver, brain, spleen, kidneys, and bowel.[4] Embolisation of trophoblastic tissue is also possible and causes dyspnoea, coughing, chest pain, tachypnoea, and haemoptysis.[4] Liver metastases are rare and often have a poor prognosis.[4]

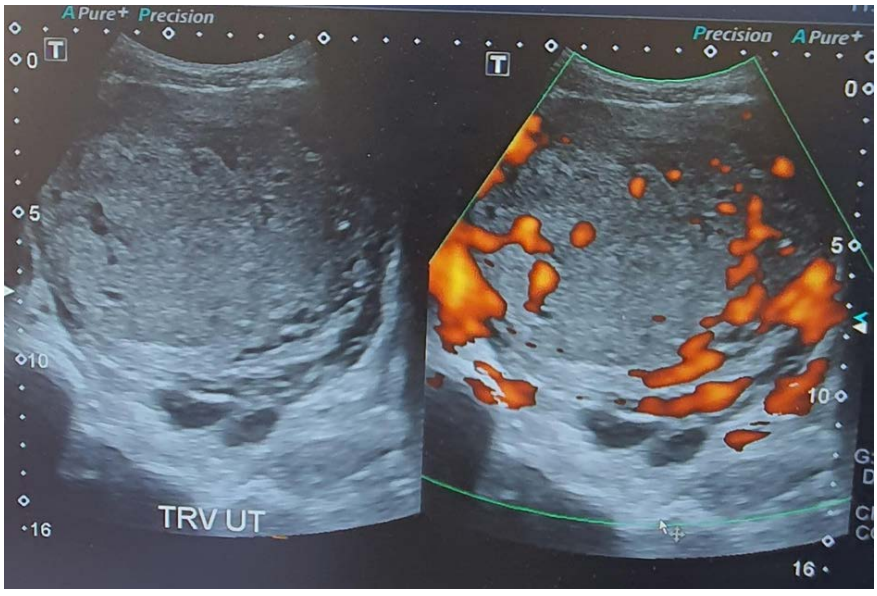

Figure 1: Transvaginal ultrasound showing an enlarged uterus with a honeycomb appearance and hypervascular flow seen within the mass

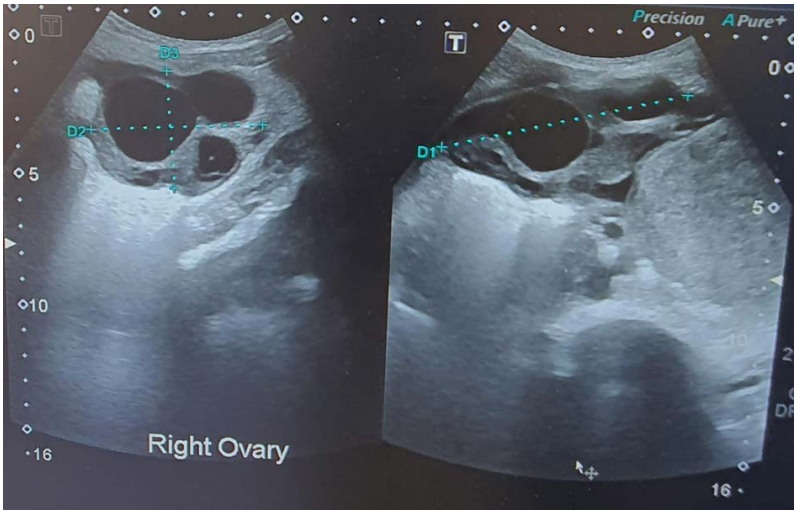

Figure 2: Sonographic evidence of an enlarged ovary with many large follicles in keeping with hyperstimulated ovaries

Here, we describe a 21-year-old woman with an atypical presentation of high-risk GTN. The patient presented with constitutional symptoms of pulmonary tuberculosis (TB), amenorrhoea, a negative pregnancy test, an elevated hCG, and bilateral adnexal masses on transvaginal ultrasound.

Case report

A 21-year-old nulliparous woman presented to Mitchells Plain Hospital. She complained of a four-month history of lower abdominal pain associated with nausea, vomiting, significant weight loss, shortness of breath, night sweats, non-productive cough, chest pain, and amenorrhoea. She was admitted via internal medicine and treated for community-acquired pneumonia with minimal improvement. After ten days, a gynaecological ultrasound revealed bilateral adnexal masses.

Her pregnancy test was negative. Notably, the patient revealed being sexually active and never having used any form of contraception. Abdominal ultrasound showed hepatomegaly, an enlarged uterus with a honeycomb appearance, and hypervascular flow. Blood investigations showed an iron deficiency anaemia of 6.6 g/dl. She had a lactate dehydrogenase of 1 232, a hCG of 6 854, a cancer antigen (Ca) 125 of 437, and normal alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA). She was also hyperthyroid with a thyroid stimulating hormone (TSH) of < 0.01 and a T4 of 38.3. Her GeneXpert was negative for pulmonary TB.

She was transfused before being transferred to Groote Schuur Hospital (GSH) for further management. The differential diagnosis upon transfer included germ cell ovarian tumour, pelvic inflammatory disease, and genital TB.

Background history

Originally from the Eastern Cape, the patient migrated to Cape Town in January 2023. She had been previously well. Menarche was at 17 years, and she had always had a normal, regular menstrual cycle until January 2023.

On general examination, the patient was notably pale with no obvious lymphadenopathy. She had a tachycardia of 145 beats per minute, apyrexial, but obviously short of breath with a raised respiratory rate. On systemic exam, she was found to have a 20-week smooth, solid, mobile central abdominal mass with no ascites but obvious hepatomegaly. The rest of the systemic examination was unremarkable.

Results of further investigations

Her formal gynaecology scan at GSH showed an endometrial cavity filled with a solid homogenous mass with extensive blood vessels, atypical of a fibroid (Figure 1). Both ovaries were enlarged in keeping with hyperstimulated ovaries (Figure 2).

Her chest X-ray showed multiple lung metastases (Figure 3), which were confirmed by a computed tomography (CT) scan. Furthermore, her CT showed a large hypervascular uterine mass (120 × 115 × 130 mm) with suspected myometrial invasion, enlarged multiloculated ovaries with theca lutein cysts, and a massive hepatomegaly with diffuse infiltration. There were no nodal or bone metastases, and her CT brain scan was normal.

The patient was assessed to have high-risk GTN, FIGO stage IV, with a WHO prognostic score of 11. Her serum hCG before commencing chemotherapy was 8 093 IU/L. Endocrine physicians were consulted to manage the hyperthyroidism. The patient was started on induction chemotherapy consisting of etoposide and cisplatin (EP) due to the large burden of the disease, placing her at high risk for tumour lysis syndrome. During her third cycle, she developed an acute anaphylactic reaction to etoposide, which was subsequently omitted. Before starting her third induction cycle, her hCG was 484 897 IU/L, 70 times higher than her initial hCG. This finding epitomises the high-dose hook effect.

An attempt was made to use ETOPOPHOS (etoposide phosphate), a water-soluble prodrug of etoposide that is rapidly and completely converted to the parent compound after intravenous dosing.[5] Even though the pharmacokinetic profile, toxicity, and clinical activity of etoposide and ETOPOPHOS are the same, ETOPOPHOS can be given as a five-minute bolus, in high doses in small volumes, and as a continuous infusion due to its water solubility.[5] Furthermore, it is not formulated with polyethylene glycol, polysorbate 80 and ethanol, and does not cause acidosis when given at high doses.[5] Unfortunately, the drug could not be sourced despite being approved by the clinical pharmacology department.

The patient was then started on paclitaxel and cisplatin (TP) twice weekly as second-line chemotherapy. Upon starting her first cycle of TP, her hCG was 415 361 IU/L, which dropped to 88 833 IU/L. She subsequently received seven cycles of TP, during which time she became significantly anaemic and dehydrated after the fifth cycle, requiring correction of her calcium, magnesium, and a blood transfusion.

Upon administration of cycle seven of TP, the patient complained of severe constipation complicated by haemorrhoids, productive cough, a significant weight loss of 6 kg in two weeks, and herpes

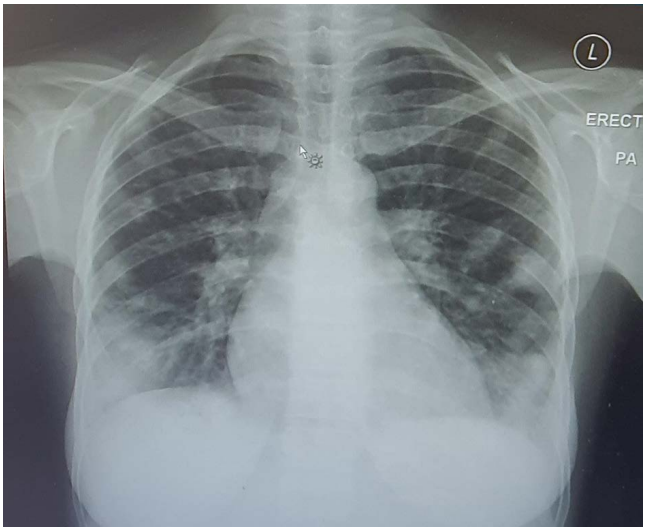

Figure 3: Chest X-ray depicting multiple variable-sized pulmonary metastatic nodules bilaterally

zoster over her scalp. She was managed with stool softeners, acyclovir, and the decision to switch her to actinomycin D. After the first cycle, she developed pancytopenia, significant loss of appetite, and looked emaciated.

A follow-up CT scan showed overall interval improvement and treatment response, with an impressive interval reduction of all metastases. Her hCG continued to decline, and her latest hCG was 16 IU/L (Figure 4). Unfortunately, the patient never returned for her subsequent follow-up, and all attempts to contact her have been unsuccessful.

Discussion

GTN is now one of the most curable tumours, with a cure rate exceeding 90%.[6] Improvements in survival are attributed to advances in chemotherapy, better assays for hCG, specialised treatment centres, prognostic scoring systems to predict treatment response, enhanced therapy individualisation, and the use of combined modality treatment to treat the highest-risk patients.[6]

A false-negative hCG test can occur due to the high-dose hook effect, a phenomenon to which immunoassays are prone.[7] If the hCG exceeds the binding capacity of both the capture and the labelled antibodies in the assay reagents, an incomplete formation of the immune complexes required for signal creation occurs.[7] This gives falsely low results and can impair patient care.[7] If a high-dose hook effect is suspected, dilution of the analyte can be applied to restore the imbalance between the analyte and antibodies.[7]

Ultrasound is the radiological investigation of choice for the initial diagnosis of GTN.[8] Invasive trophoblast can be identified by the presence of heterogeneous myometrial masses, which can be echogenic or hypoechoic, often showing internal cystic cavities.[8] These masses are usually hypervascular and can distort the uterine profile.[8] The differential diagnosis of myometrial masses includes adenomyosis and uterine fibroids, which can be ruled out by the lack of exaggerated vascularity on colour Doppler.[8] Enlarged, hyperstimulated ovaries with theca lutein cysts due to the excess of hCG are highly suggestive of the diagnosis, but only occurs in less than 20% of cases.[8]

A high FIGO score is associated with poor survival, where death is linked to chemoresistance but also to early and severe complications, such as haemorrhagic metastases, infection, multisystem organ failure, or tumour lysis syndrome.[9] A ten-fold reduction in early deaths can be achieved by using induction low-dose EP in patients with high-risk GTN after the exclusion of non-gestational diseases by genetic analysis.[9]

Multi-agent chemotherapy regimens are used to treat high-risk GTN.[10] The most commonly used is EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine); however, the Cochrane Database review failed to conclude the best combination.[10] About 20% of patients do not attain complete response with EMA-CO; the overall survival rates for patients with high-risk GTN are now as high as 95%.[10] For patients with liver metastases, with or without brain metastases, or a very high-risk score, EP/EMA (etoposide, cisplatin and etoposide, methotrexate, actinomycin D) or another more intensive chemotherapy regimen, rather than EMA-CO, may yield a better response and outcome.[10]

Alternatives including TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide), BEP (bleomycin, etoposide, cisplatin), and FAEV

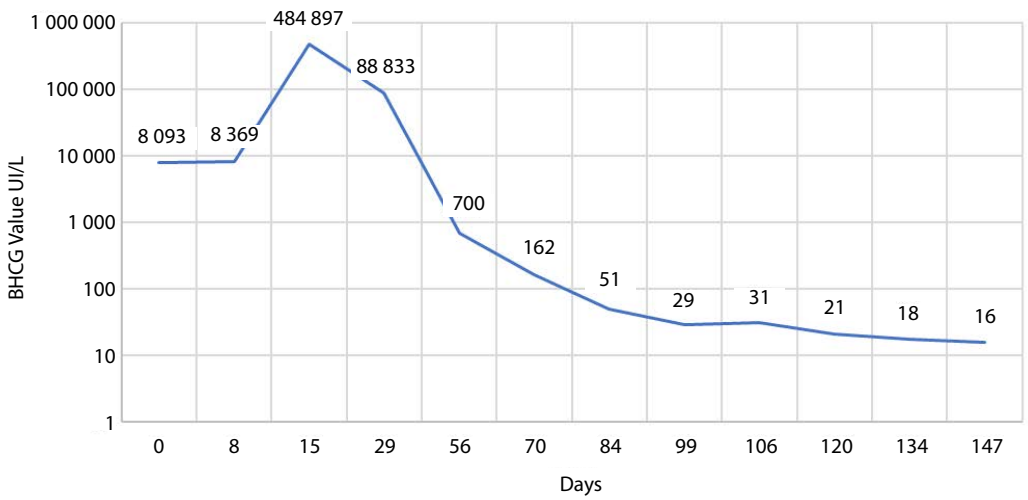

Figure 4: Line graph depicting the patient's hCG values over time in response to chemotherapy, with logarithmic drop and then plateau

(floxuridine, actinomycin D, etoposide, vincristine) may be as effective as EP/EMA and associated with fewer side effects; however, this is not clear from the available evidence.[11] We are favouring the use of the much less toxic TP alternating two weekly with TE regimen in our institution for all high-risk GTN due to cost-effectiveness, outpatient-based administration, and improved toxicity profile. This regimen was contraindicated in this patient as it contained etoposide, to which she developed a hypersensitivity reaction.

Etoposide, a semisynthetic derivative of podophyllotoxin, is one of the most important chemotherapy drugs in the treatment of GTN, but an acute hypersensitivity reaction occurs in around 1% of patients.[12] Retreatment with etoposide in these patients is difficult and generally alternative drugs/regimens have to be used.[12] A small number of case reports have suggested that etoposide phosphate can be safely used in these patients.[12] Treatment with etoposide phosphate proceeds typically without any symptoms, or repeated steroid cover can be utilised.[12] Etoposide hypersensitivity is a rare clinical problem and responds promptly to drug discontinuation, steroids, and chlorpheniramine.[12] TIP (paclitaxel, ifosfamide, cisplatin) has also proven to be effective in patients with GTN who experience hypersensitivity reactions to etoposide.[13]

The retrospective review of this case provides us with a few points of interest. Despite the patient's negative pregnancy test, she presented with features warranting a suspicion of gestational trophoblastic disease (GTD). She presented with classic features, namely hyperemesis gravidarum, enlarged uterine size, respiratory insufficiency, a raised hCG, hyperthyroidism, and bilateral theca lutein cysts. Furthermore, an ultrasound reported findings of an enlarged vascular uterus with a honeycomb appearance and bilateral enlarged ovaries together with an associated hepatomegaly. Ultrasound presentations of GTN may overlap with findings of fibroids and adenomyosis.[14] However, correlation with hCG levels, clinical history, and lack of extreme vascularity aid in their differentiation.[14]

Between advances and challenges, the truth is that GTN is still an unknown disease for many physicians worldwide.[15] Our women with GTN will suffer, sometimes losing their uteri or even their lives.[15]

Conclusion

Patients in middle-income countries still present with classic features of GTN. Although rare, GTN must be considered in the differential diagnosis of any woman who presents with amenorrhoea. This case highlights the importance of skilled ultrasonography and the availability of specialised gynaecology-oncology units. The early diagnosis of this disease and the appropriate treatment should avoid maternal death, allowing healing and maintenance of the reproductive potential of these women.[15]

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Conflict of interest

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Ethical approval

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