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Case Report

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TB or Not TB; that should not be the Question! Learning Points from Misdiagnosed Metastatic Placental Site Trophoblastic Tumour

Jones BP[1,2*], Odonde RI[3] and Abughazza O[3]

[1]West London Gynaecological Cancer Centre, Hammersmith Hospital, Imperial College NHS Trust, United Kingdom
[2]Department of Surgery and Cancer, Imperial College London, United Kingdom
[3]Department of Obstetrics & Gynaecology, Royal Surrey County Hospital, United Kingdom

[*]**Corresponding Author:** Jones BP, Department of Surgery and Cancer, Hammersmith Hospital, Imperial College London, United Kingdom, E-mail: benjamin.jones@nhs.net

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Abstract

Gestational trophoblastic disease encompasses a group of conditions, including both benign and malignant subtypes, which are characterised by the abnormal proliferation of placental trophoblast tissue. Placental site trophoblastic tumour is a rare, malignant subtype, which can occur following any pregnancy event. We present a rare case of stage IV PSTT in a 47-year-old woman, who was originally misdiagnosed as tuberculosis. A urinary pregnancy test was not initially undertaken owing to the woman's age and history of sterilisation, despite pathognomonic radiological signs evident on the chest x-ray. This case highlights the importance of undertaking a urinary pregnancy test in women presenting with abnormal vaginal bleeding whilst emphasising the need for such cases to be managed as part of a multi-disciplinary team, including discussion and referral to a tertiary referral centre for further treatment.

Keywords: *Gynaecology; Gestational trophoblastic disease; Placental Site Trophoblastic Tumour; Multi-disciplinary team; Oncology*

Abbreviations: *Chest x-ray: CXR; General Practitioner: GP; Gestational trophoblastic disease: GTD; Gestational trophoblastic neoplasia: GTN; Haemoglobin: Hb; Human chorionic gonadotrophin: hCG; Human Immunodeficiency Virus: HIV; Royal College of Obstetricians and Gynaecologists: RCOG; Termination of pregnancy: TOP; Tuberculosis: TB; Urinary pregnancy test: uPT*

Introduction

GTD is a rare condition, characterised by abnormal proliferation of placental trophoblast tissue, with a reported incidence of 1 in 714 live-births [1]. GTD incorporates both benign and malignant subtypes. The benign subtypes include partial and complete hydatidiform moles whereas malignant lesions, collectively referred to as GTN, include invasive moles, choriocarcinoma, PSTT and epithelioid trophoblastic tumour. GTN can occur after any type of pregnancy, with an estimated incidence of 1 in 50,000 after a live birth [2]. PSTT is very rare, attributing to just 0.2% of cases of GTN in the UK [3]. PSTT originates within the uterus, commonly causing irregular vaginal bleeding, lower abdominal pain and bloating. Common sites of distant metastasis include the lungs, which may cause shortness of breath, chest pain and haemoptysis whilst metastases to the brain, which are associated with worse prognosis, can cause headaches, dizziness and seizures. GTD causes an elevation in serum hCG, in a similar fashion to pregnancy, which may subjectively cause symptoms of pregnancy and objectively results in a positive uPT. Optimal management of such patients includes prompt diagnosis and referral to a tertiary referral centre for treatment.

Case Presentation

A 47-year-old woman presented to the emergency department following a two-month history of continuous, heavy vaginal bleeding with blood clots. Over the preceding three weeks she felt increasingly short of breath, fatigued and noticed a metallic taste in her mouth. She reported increased urinary frequency, reduced appetite, and weight loss of 8kg over a period of three months and feeling feverish for the previous two days. She was otherwise fit and well with no significant medical problems. She had two previous uncomplicated vaginal deliveries in 2000 and 2002, before

undergoing a laparoscopic sterilisation following a surgical TOP in 2005.

She has never smoked, consumes minimal alcohol and had no recent travel history. She is married and lives with her husband and two children.

She visited her GP four weeks previously where a full blood count was undertaken revealing iron deficiency anaemia (Hb; 8.7 g/dL). Oral iron supplementation was commenced and she received a routine referral to gynaecology outpatient's clinic. A pelvic ultrasound revealed an enlarged uterus, which was attributed to uterine fibroids.

Clinical examination was largely unremarkable other than a persistent tachycardia in combination with general pallor. She was otherwise haemodynamically stable and apyrexial. Respiratory, cardiovascular and abdominal examinations were unremarkable. Blood tests revealed persisting anaemia (Hb 8.2g/dL) with an elevated C-reactive protein (93mg/l), whilst her white blood cells were normal (10.2 x109/l). Her lactate, glucose, renal function, liver function and clotting were all within normal ranges. A CXR was performed which is displayed in figure 1.

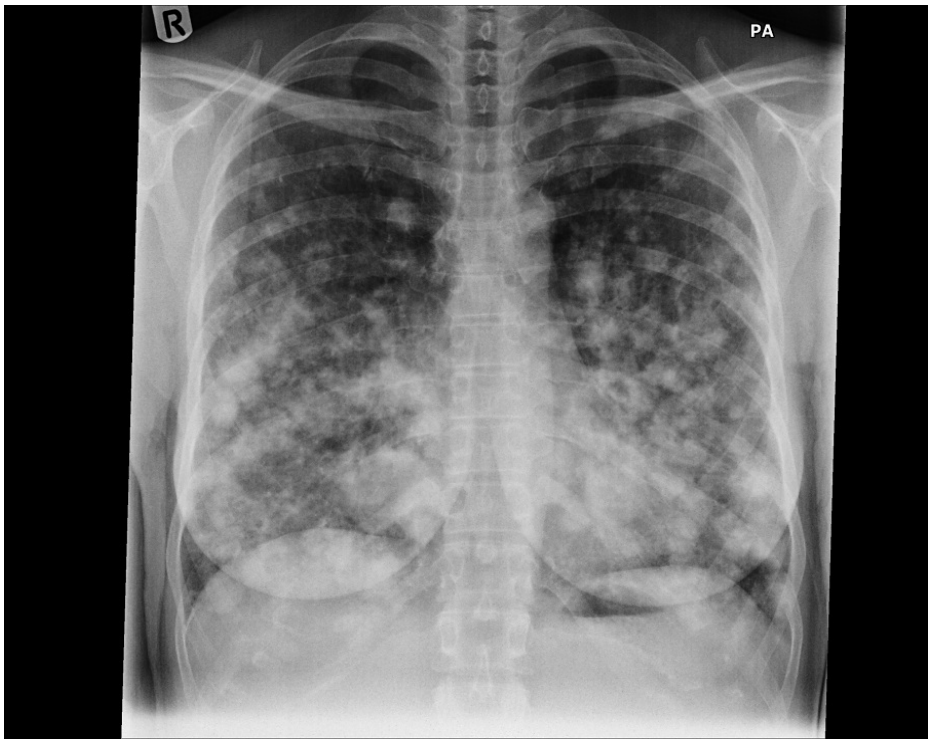

Figure 1: Chest X ray revealing multiple bilateral confluent non-cavitating airspace opacifications affecting the mid and lower zones bilaterally

In light of the CXR findings she was referred to the medical physicians who felt the most likely diagnosis was TB with sarcoidosis and HIV being possible differential diagnoses. The patient was subsequently isolated, counselled and consented for further testing and referred to the respiratory team. She was transfused two units of packed red blood cells, as she was symptomatic of anaemia, with pallor and tachycardia.

During handover, the history and imaging were reviewed and the initial question asked by the succeeding night team was the result of the uPT. Amidst sniggers of scepticism, the day team proclaimed that the woman was 47 years old and had been sterilised over a decade previously, so it was highly unlikely she was pregnant and as such, it had not been performed. Having explained that the CXR appeared pathognomonic of pulmonary metastases secondary to GTN, and that the uPT would be essentially diagnostic, the day team departed.

The uPT was positive. The serum hCG was 579,000IU/L. Computed tomography imaging revealed a large mass within the uterus with central necrosis and multiple collateral vessels throughout the periuterine tissues. There were also numerous pulmonary metastases, the largest of which measured 5.1cm, enlarged hilar and mediastinal lymph nodes, brain metastases and a solitary hepatic metastasis. The remaining abdominal and pelvic organs appeared normal.

Outcome and Follow-up

The case was discussed with the local tertiary referral centre for GTD who advised against performing hysteroscopy and endometrial biopsy in the first instance, owing to the potential risk of profuse bleeding intraoperatively. She was transferred to the tertiary referral centre for further management, where she was treated as Stage IV choriocarcinoma,

in the absence of histology. She underwent eight cycles of multi-agent chemotherapy with etoposide, methotrexate, actinomycin-D, etoposide and cisplatin. Following an initial biochemical improvement, her hCG plateaued and her cerebrospinal fluid hCG began to rise, prompting a switch to paclitaxel, etoposide and cisplatin. After six cycles she developed worsening peripheral neuropathy and demonstrated radiological progression of the brain lesions. Due to the relative chemotherapy insensitivity PSTT was suspected and confirmed following hysteroscopy and biopsy of the lesion seen on the anterior aspect of the uterus. She was subsequently commenced on immunotherapy, in the form of pembrolizumab. She responded well, with radiological regression of the uterine, pulmonary and intracranial lesions along with a reduction of her serum hCG to within the normal range (4 IU/L). Once the uterus had returned to its normal size she underwent hysterectomy where the diagnosis of PSTT was reaffirmed. She remains disease free twelve months post-operatively.

Discussion

The woman in this case received multi-disciplinary care including her GP on multiple occasions, an emergency physician, the gynaecology team and the medical team. Despite utilising such expertise, the patient was initially misdiagnosed, in part at least, because a uPT was not undertaken. UPTs are cheap, easily accessible and highly sensitive. The RCOG guidelines recommend that a pregnancy test should be performed in all cases of persistent or irregular vaginal bleeding after a pregnancy event [2]. In women where pregnancy is exceedingly unlikely, as it was in this case, a positive uPT provides a high level of diagnostic certainty in cases of GTD.

In this case TB was provisionally diagnosed, subjecting the woman to the distress of being isolated, despite the woman not exhibiting any risk factors for TB. Adverse effects of isolation include anxiety, depression, increased anger and hostility, and reports of fear and loneliness [4-7]. Moreover, infection control measures, encompassing the use of protective clothing such as gowns, gloves and protective facemasks, may also have a negative impact on effective communication. This is of particular relevance in this case, where excellent communication skills were necessary when discussing the sensitive subject of potential widespread metastatic cancer. She was further put through the anguish of HIV being considered as a diagnosis, raising further questions of uncertainty and potential concern regarding partner infidelity and the stigma associated with HIV. Ultimately, the misdiagnosis of patients has been estimated to cause 80,000 deaths each year [8]. Although the consequences in this case were not fatal, it delayed treatment and potentially caused mistrust between the woman and the medical team, potentially jeopardising the on-going doctor-patient relationship.

The antecedent pregnancy in this case was following surgical TOP over a decade previously. Whilst GTN can occur after any pregnancy event, the need for chemotherapy after a complete mole and partial mole is 15% and 0.5% respectively [2]. The Royal College of Pathologists recommends that histology specimens do not routinely need to be sent following TOP if fetal parts are visible. However, given that fetal parts may be present in partial molar pregnancies, and that 1 in 200 may require chemotherapy, this may result in occasional missed cases [9]. Guidance from the RCOG recommends the use of ultrasound prior to TOP, to exclude molar and non-viable pregnancies, but in viable pregnancies, histopathology examination should not routinely be undertaken. Given that ultrasound has only a 56% detection rate of molar pregnancies, this again may result in further missed cases [10]. Confusingly, the more recently published RCOG evidence based clinical guideline on 'The Care of Women Requesting Induced Abortion' advises that routine pre-abortion ultrasound is unnecessary and that fetal products do not routinely need to be sent for histological examination [11]. This potentially leaves women undergoing TOP at risk of having an undiagnosed molar pregnancy, which in the absence of appropriate follow up, would inherently increase their future risk of developing GTN.

Conclusion

This case exemplifies how UPTs can provide high diagnostic probability of GTD/GTN in women who are not of reproductive age. Current guidance from professional associations in the UK does not completely safeguard against the diagnosis of molar pregnancies. As such GTD should be considered in any abnormal bleeding following a pregnancy event, particularly after TOP. Moreover GTN produces pathognomonic findings on CXR, which all O&G trainees should be aware of. It is vital that such cases are managed as part of a multi-disciplinary team at senior level.

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