

## A metastatic unclassified trophoblastic tumour with spontaneous bilateral pneumothoraces

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### Abstract

Gestational trophoblastic disease (GTD) is a spectrum of diseases associated with pregnancy. Epithelioid trophoblastic tumour (ETT) is a rare neoplastic proliferation of the intermediate trophoblast that can be distinguished from choriocarcinoma. A 35-year-old female presented with persistent vaginal bleeding, raised beta human chorionic gonadotrophin ( $\beta$ -HCG) (13 175 IU/l) and, on ultrasound, what appeared to be a molar pregnancy. Microscopy and immunohistochemistry confirmed the diagnosis of ETT. Computed tomography (CT) scan confirmed bilateral small lung and liver metastases, and vaginal sonar, a single metastasis next to the urethra. Combination etoposide and cisplatin chemotherapy was completed. Restaging lung CT detected numerous cystic lesions and bilateral spontaneous pneumothoraces, caused by the rupture of subpleural cystic lesions. After second-line methotrexate-based chemotherapy, the patient was admitted to hospital with shortness of breath. Bilateral underwater drains were inserted to address the complication of persistent spontaneous bilateral pneumothoraces, but she passed away. ETT is a rare malignant disorder associated with pregnancy. No standard treatment guidelines exist, and these patients need the efforts of a multidisciplinary team with experience in oncology

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### Introduction

Gestational trophoblastic disease (GTD) is a rare spectrum of benign and malignant diseases that affect women of child-bearing potential. Malignant forms are referred to as gestational neoplastic disease or gestational trophoblastic tumour. Chemotherapy regimens for GTD are well established, so that the majority of patients are cured. Placental-site trophoblastic tumours (PSTT) are a slow growing form of GTD, arise from the intermediate trophoblasts at the site of implantation, and produce little beta human chorionic gonadotrophin ( $\beta$ -HCG). Distant metastases can occur in the vagina, extrauterine pelvis, retroperitoneum, lymph nodes, lungs and brain.

Both epithelioid trophoblastic tumour (ETT) and PSTT are neoplastic proliferations of intermediate trophoblasts that investigators can clearly distinguish from choriocarcinoma.<sup>1</sup> ETT appears in patients who have had chemotherapy treatment for an invasive mole or choriocarcinoma in women of childbearing potential, but cases have been described in postmenopausal women and even males. Shih and Kurman reported a metastasis rate of 25% and

a mortality rate of 10%.<sup>2</sup> No standard treatment guidelines exist and literature suggests a poor response to conventional chemotherapy. Current management includes hysterectomy for localised disease. It has been suggested that patients with liver metastases should be treated with platinum-based therapy.<sup>1</sup> We describe a case of recently diagnosed ETT, and the clinical management and outcome of our patient.

### Case report

A 35-year-old female presented with persistent vaginal bleeding, raised  $\beta$ -HCG (13 175 IU/l) and, on ultrasound, what appeared to be a molar pregnancy. On vaginal examination, a metastatic lesion next to the urethra (3 x 3 cm) was confirmed. Post-curettage blood investigations showed a raised  $\beta$ -HCG value of 3 066 IU/l. Her staging examinations included a chest X-ray, which showed multiple small bilateral lung lesions, and an abdominal computed tomography (CT) scan, which confirmed a single hepatic metastatic lesion. A brain CT was normal, with no signs of metastasis.

The curettage specimen consisted of bloody and fibrous tissue. Microscopic sections showed haemorrhage,

necrosis and multiple fragments of malignant trophoblastic tissue of intermediate origin. No villi were seen and the cells infiltrated in solid sheets. The cells appeared epithelioid, with hyperchromatic nuclei. In some areas, the cells had become more spindle-shaped. Syncytotrophoblastic giant cells were scanty. The mitotic rate was 10 per 10 high-power fields (HPF), and atypical mitoses were noted.

The morphology and focal positivity of human placental lactogen (HPL), HCG, inhibin and placental alkaline phosphatase (PLAP), with more intense p63 and high K167 immunohistochemistry, were in keeping with a diagnosis of ETT. There was no evidence of a choriocarcinoma. According to the revised international Federation of Gynecology and Obstetrics (FIGO) classification system, the patient had Stage IV disease, because of lung, liver and vagina metastases.

Combination systemic chemotherapy was offered, consisting of etoposide 100 mg/m<sup>2</sup> intravenous (iv) and cisplatin 20 mg/m<sup>2</sup> iv on days one to five, every 21 days. After the first cycle of multi-agent therapy, she developed symptomatic anaemia and was admitted and transfused with three units of blood. Her haemoglobin had decreased from 11.7 g/dl to 8 g/dl. After consultation with the gynaecology oncology team, a hysterectomy was performed to address the excessive and persistent vaginal bleeding that had caused the anaemia.

Microscopy of the uterine neoplasm revealed morphological features of PSTT, as well as ETT, and large cells with the appearance of syncytotrophoblasts, which also raised the possibility of a choriocarcinoma. The growth pattern was infiltrating rather than circumscribed or expansile, which was more suggestive of PSTT. Since p63 is always negative in PSTT and E-cadherin is positive, the histological and immunohistochemical profile was suggestive of ETT. However, the fact that HPL was diffusely positive was more in favour of PSTT. Because the morphological and immunohistochemical features were a combination of both ETT and PSTT, the diagnosis made was one of unclassified trophoblastic tumour.

The patient completed six cycles of chemotherapy, accompanied by a slow decline in  $\beta$ -HCG (98 IU/l), but no normalisation of this hormonal marker (Figure 1). Restaging examinations included vaginal sonar and lung and abdominal CT. Numerous cystic metastatic lesions were detected bilaterally throughout both lungs, and seemed to be secondary to systemic treatment. Bilateral pneumothoraces were present (Figure 2). A single low-density area was detected in the periphery of the right lobe of the liver. This lesion was too small to characterise and could be due to a

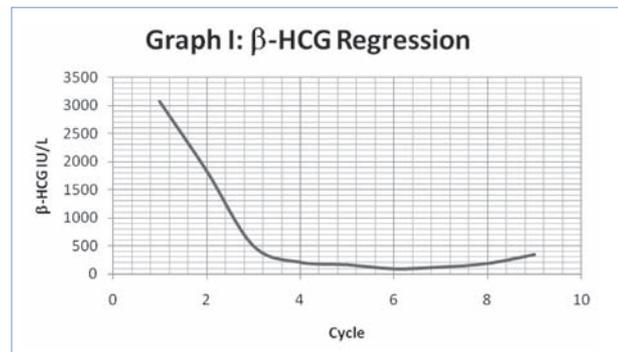


Figure 1:  $\beta$ -HCG regression observed during six cycles of chemotherapy with etoposide and cisplatin

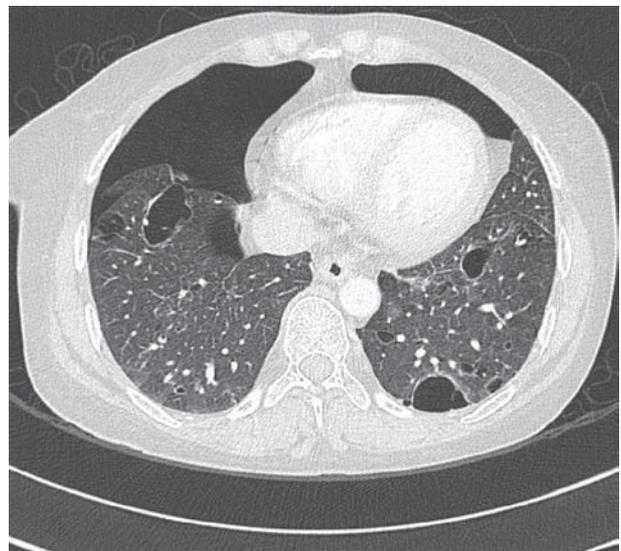


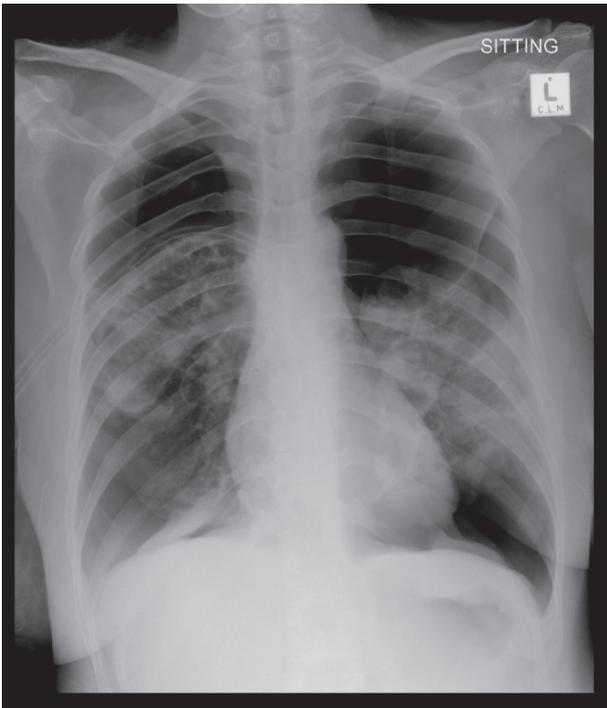
Figure 2: Lung CT scan, showing post-chemotherapy thin-walled metastatic cystic lesions and bilateral spontaneous pneumothoraces

benign cyst or a cystic metastasis. A vaginal ultrasound revealed no metastases.

She continued with second-line methotrexate-based chemotherapy, and there was a steady increase in  $\beta$ -HCG. After two cycles, she was admitted to ICU with shortness of breath secondary to the bilateral pneumothoraces (Figure 3). Bilateral underwater drains were inserted, but both lungs collapsed. Severe desaturation resulted, and the patient demised.

## Discussion

Persistent trophoblastic diseases are tumours of the non-villous trophoblast and include PSTT and ETT. ETT represents a recent addition to the gestational trophoblastic tumour category,<sup>3</sup> and, because it is such a rare neoplasm, its biological behaviour has not been well established. It seems, however, as if the metastatic potential is similar to PSTT. In a literature review of 52 cases of ETT, the mean age



**Figure 3:** Chest X-ray, showing bilateral spontaneous pneumothoraces and lung collapse

at diagnosis was 38 years, and 67% presented with abnormal vaginal bleeding, 36% had a prior molar pregnancy and 35% presented with metastases. A total of 13% died from the disease, one to 39 months after diagnosis.

Prognostic factors are still unknown but, although the histological features that predict outcome have not been well established, investigators suggest an association between mitotic index and more aggressive behaviour.<sup>4</sup> In a recent series, the only patient who died of the disease had a mitotic rate of 48 mitoses per 10 HPF.<sup>5</sup>

Characteristic morphology and immunohistochemistry distinguish ETT from other trophoblastic tumours and squamous carcinoma. ETT can occur in postmenopausal women, even years after a gestational event. One case of metastatic ETT was described in a male patient, with an initial diagnosis of a mixed germ cell testis tumour. Two years post-orchidectomy and -chemotherapy, a metastatic lesion of the para-aortic nodes had to be excised, which was confirmed as ETT. ETT should be considered histologically in patients who have had treatment for mixed germ cell tumours.<sup>6</sup>

No standard treatment guidelines for ETT exist. Patients have been treated with various regimens for GTD, for example EMA/CO (etoposide, methotrexate and actinomycin D alternating weekly with cyclophosphamide and oncovin), and, if there is liver involvement, a platinum-based regimen has been suggested.

Our patient initially presented with the histological features of ETT and completed six cycles of chemotherapy. Post-hysterectomy, the diagnosis was revised to an unclassified trophoblastic tumour, because of the morphological and immunohistochemical features, of both PSTT and ETT (and even choriocarcinoma), that were present. Serial  $\beta$ -HCG values showed a dramatic initial response, as can be expected with choriocarcinoma responding to chemotherapy, and this response correlated with the radiological picture. The  $\beta$ -HCG reached a plateau, with low  $\beta$ -HCG values (as is the case with PSTT), but also suggested platinum resistance, as her  $\beta$ -HCG started to rise again. Second-line treatment with EMA/CO was then initiated.

The post-treatment CT appearance of her lung metastases was marked with clearly visible thin-walled cystic lesions, indicating a rapid tumour response to chemotherapy. Bilateral spontaneous pneumothoraces arose as a complication from ruptured cavitations, and this led to collapse of her left lung and eventual demise.

## Conclusion

This case, the first at our unit, highlights the difficulties and complications associated with the management of patients with metastatic ETT and PSTT. No standard treatment guidelines exist, and these patients need the efforts of a multidisciplinary team with experience in oncology.

## Declarations

Written informed consent and ethics approval was obtained. Some of these data were used for a poster presentation at the University of Stellenbosch Annual Academic Year Day. No conflict of interest is declared.

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