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Case report

Disseminated disease including intra-cardiac metastasis from intermediate trophoblastic tumor of unspecified subtype, presenting in pregnancy

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1. Introduction

Gestational trophoblastic disease (GTD) describes a spectrum of disorders from benign to malignant arising from an aberrant fertilization event, whereby trophoblastic tissue proliferates abnormally. While the biology and management of GTD entities such as hydatidiform moles and choriocarcinoma are relatively well described, lesions of the intermediate trophoblast, which includes placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT) are rarer, and thus poorly understood. Over a 25-year period at Charing Cross Hospital, a tertiary GTD center, only 2% of total GTD were classified as PSTT (Papadopoulos et al., 2002).

Intermediate trophoblastic lesions usually present as locally advanced disease confined to the uterus. However approximately 10–15% of cases present with symptomatic distant metastatic disease (Shih & Kurman, 2001). Over 50% of cases have a normal antecedent term-pregnancy (Papadopoulos et al., 2002). Unlike choriocarcinoma, b-HCG is often only marginally elevated in intermediate trophoblastic tumors and is a poor reflection of disease burden. Intermediate trophoblastic tumors are much less chemo-responsive than their choriocarcinoma counterparts and thus metastatic disease often portends a poor prognosis (Shih & Kurman, 2001).

Choriocarcinoma is the most malignant end of the spectrum among GTDs and commonly presents with metastatic disease, most frequently in the lungs (80%), followed by vagina (30%), pelvis (20%), liver (10%) and brain (10%) (McDonald & Ruffolo, 1983). Intra-cardiac metastasis from GTD however is exceptionally rare. In one autopsy series, cardiac metastases were found present in 4% of choriocarcinomas (Ober et al., 1971). Almost invariably, the diagnosis of cardiac metastasis is made post-mortem rather than ante-mortem (Bozaci et al., 2005). We present a unique case of a 3rd trimester patient presenting with disseminated disease including an intra-cavitary cardiac metastasis, from an intermediate trophoblastic tumor of unspecified subtype.

2. Case report

A 33-year-old lady (G3P1) of Filipino origin presented 33 weeks gestation with a 1-week history of haemoptysis and 5 weeks history of progressive dyspnoea. Her previous obstetric history included a termination with a previous partner 11 years ago; and an uneventful term pregnancy 20 months previously with her current partner. She was a lifelong non-smoker with no previous history of malignancy. Her initial chest x-ray revealed a large right lower-lobe pulmonary mass with mediastinal extension (Fig. 1A). A subsequent CT chest showed a 7 cm right lower-lobe mass, with extension into the left atrium via the pulmonary veins and extensive mediastinal lymphadenopathy (Fig. 1B). A transthoracic echocardiogram (Fig. 1C) showed a 2.7 × 4.5 cm mass in the left atrium obstructing pulmonary venous inflow from the left lower and middle pulmonary veins. The patient underwent a Caesarian-section at 34/40 weeks and delivered a healthy baby boy, who went on to achieve normal developmental milestones. She was also noted to have a rapidly growing scalp lesion, which was biopsied day 1 post Caesarian-section.

The scalp biopsy showed a poorly differentiated tumor composed of large pleomorphic epitheliod cells. The tumor was negative for TTF1, CK8/18, P40, Melan A, PAX8 and OCT4.

Macroscopically the placenta showed multiple cream to pale nodular lesions measuring 2 mm to 15 mm in diameter (Fig. 2A). The placenta histology revealed a high-grade tumor with epithelioid and spindle-shaped morphologies with no tumor necrosis or hemorrhage. Mitoses were readily seen. Prominent tumor-infiltrating neutrophils were present.

An extensive panel of immunohistochemistry was performed on the placental tumor nodules to clarify the primary site. The tumor labeled for vimentin but not for epithelial markers (CK8/18, CK19,

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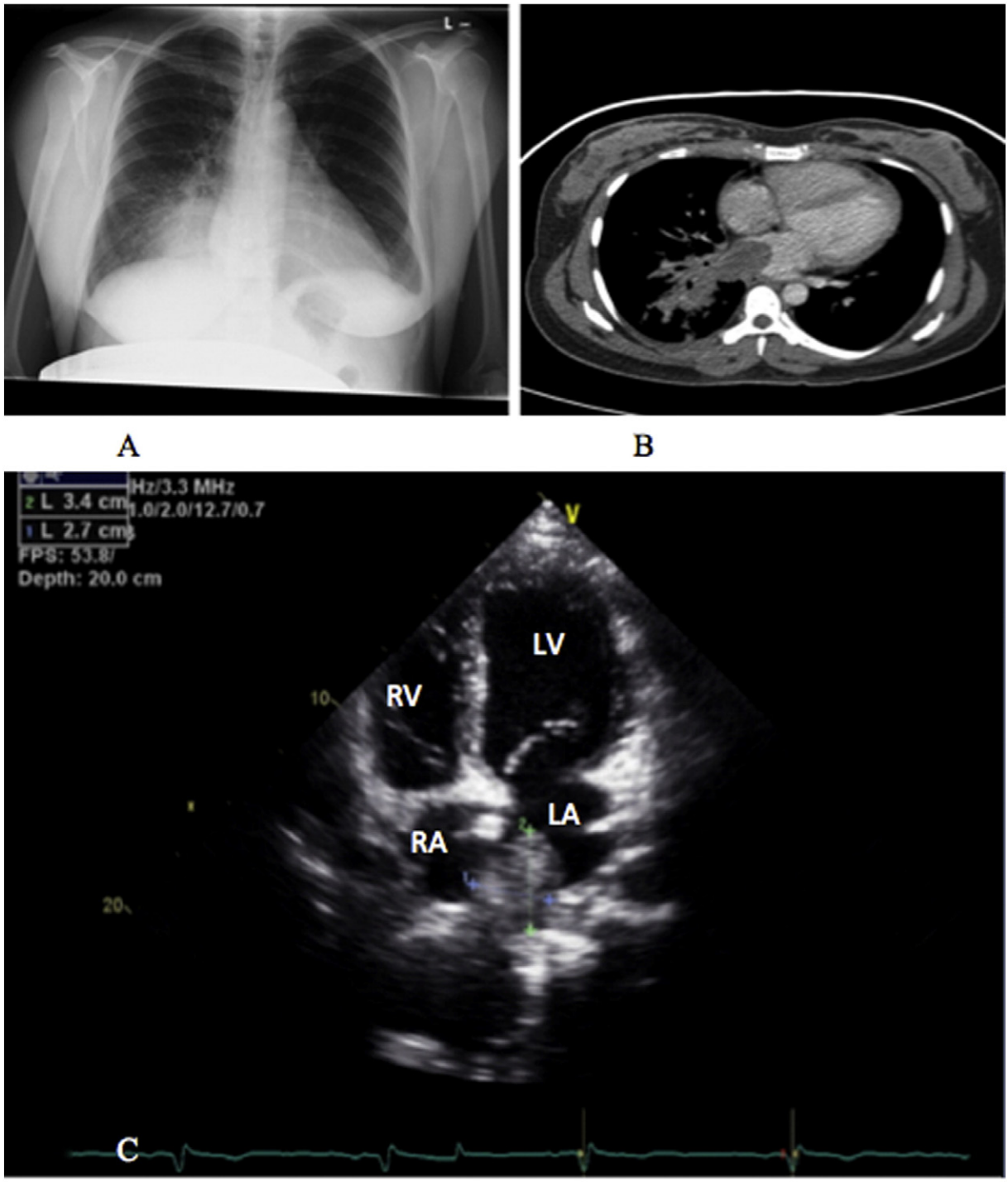

Fig. 1. A: Initial CXR: large right lower lobe pulmonary mass with mediastinal extension B: CT chest: 7 cm right lower lobe mass with extension to the left atrium via the pulmonary veins C: Transthoracic echocardiogram: 2.7 cm × 4.5 cm mass in left atrium obstructing pulmonary venous inflow from left middle and lower pulmonary veins.

AE1/AE3, MNF116) or germ cell/trophoblastic markers (beta HCG, GATA3, PLAP, GPL, inhibin, OCT4, SALL4, CD117). It was also negative for melanocyte-lineage markers (S100, Melan A, MITF, HMB45). Specific markers to lung (TTF1, Napsin), renal (CD10, PAX8), gynecological and breast tumors (ER, PR, HER2) were also negative.

Choriocarcinoma was excluded on the basis of the comparatively low Ki67 index (25% versus >50%) and the morphology of tumor nodules. The scalp lesion biopsied matched the placental tumor in morphology.

On H&E morphology alone, areas of epithelioid morphology with pleomorphic tumor giant cells resembled epithelioid type intermediate trophoblastic (Fig. 2B); whilst areas of spindle-shaped morphology resembled placental type trophoblastic tumor (Fig. 2C). Metastatic pleomorphic sarcoma was considered and excluded.

Based on clinical presentation, patient demographics, pattern of tumor spread, intra-departmental morphological review of the tumor and consensus of the oncology team, this tumor, was considered for pragmatic reasons, to be a trophoblastic tumor of unspecified subtype with a null phenotype.

The patient's post-partum serum b-HCG 3-days post delivery remained elevated at 860 iu/L. An MRI brain immediately post-partum revealed asymptomatic brain metastasis, with 2 enhancing lesions in

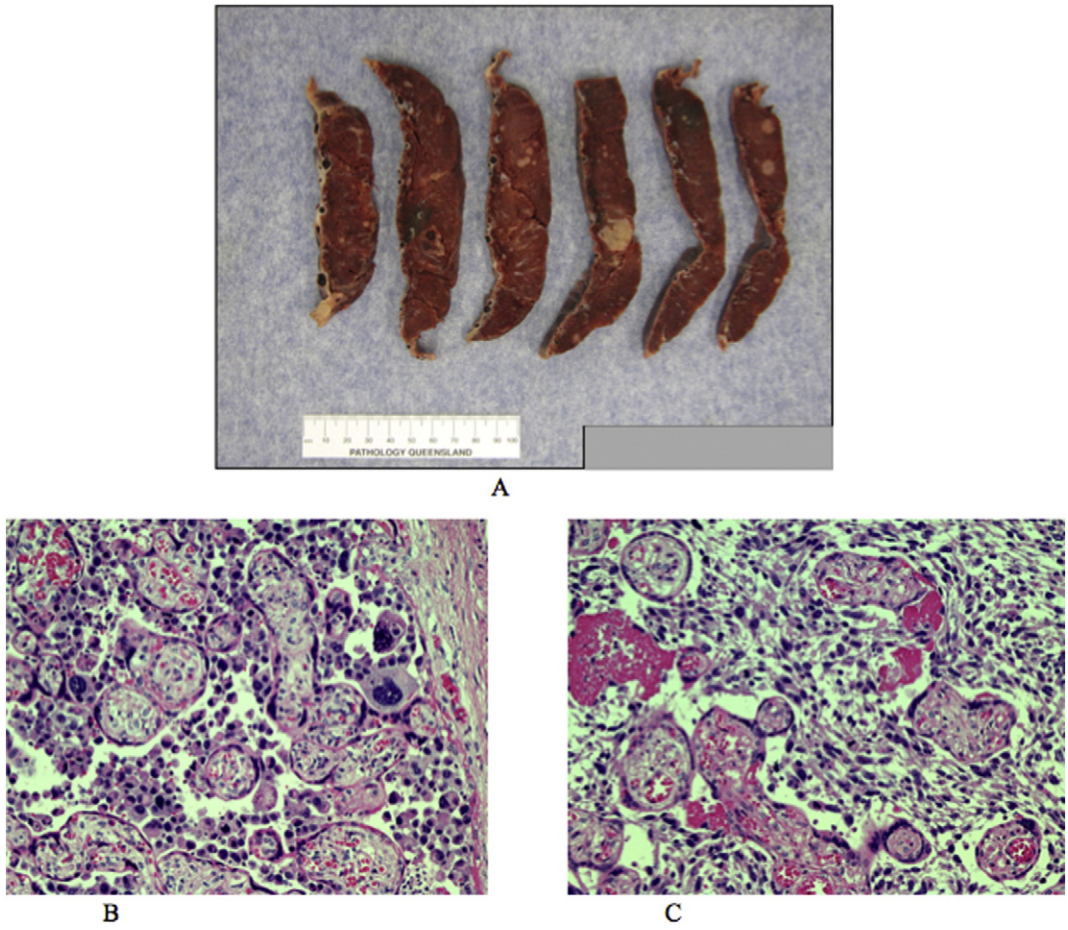

Fig. 2. A: Macroscopic appearance of placenta, showing multiple cream to pale nodular lesions measuring 2 mm to 15 mm in diameter B: Areas of epithelioid morphology with pleomorphic multinucleate tumor giant cells, resembling a chorionic-type intermediate trophoblastic lesion such as ETT C: Spindle-shaped morphology, resembling an implantation site intermediate trophoblastic lesion such as PSTT.

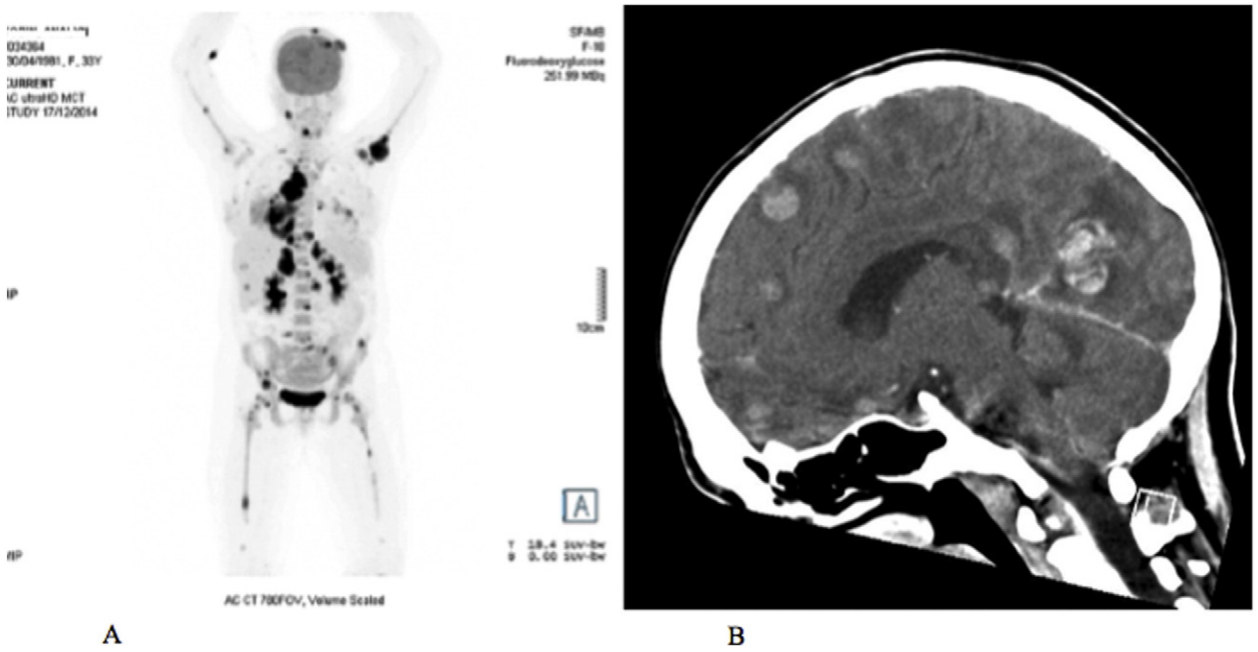

Fig. 3. A: PET Scan: widespread FDG avidity consistent with pulmonary, pericardial, mediastinal nodal, cerebral, hepatic, adrenal, bony, breast and subcutaneous metastasis B: CT Brain: multiple haemorrhagic supra and infra-tentorial brain metastasis.

Table 1
Cases in the literature of cardiac metastasis from gestational trophoblastic tumors.

Author	Year of publication	Pt Age	Preceeding gestation	GTD History	Histology	Site and nature of cardiac metastasis	Other sites of metastasis	Management	Outcome
MacLowry et al.(MacLowry & Roberts, 1966)	1966	28	Term pregnancy	Yes Previous molar pregnancy terminated 5 years ago	Choriocarcinoma	Left atrium. Extension from right lung into pulmonary vein to left atrium, thru mitral orifice	Lung, spleen, liver, kidney, small intestine, brain, perineum	Craniotomy for brain metastasis Metrotrexate + Prednisolone	Died 3 weeks after diagnosis from brain metastasis
Akaike et al.(Akaike et al., 1977)	1977	29	Molar pregnancy 2 years prior	Yes	Choriocarcinoma	Left ventricle. 8 cm lesion from base to apex of left ventricle. Left anterior descending artery embedded in tumor. Presented with ST elevation myocardial infarction. Cardiac rupture causing cardiac tampondade	Lung, kidney, brain	Metrotrexate Actinomycin D Vinblastin	Died 11 months after diagnosis from cardiac tamponade 2ndary to cardiac rupture
Seigle et al.(Seigle et al., 1987)	1987	28	Term Pregnancy	No	Choriocarcinoma	Left ventricle apex	Lungs, Spleen, GI tract, kidneys, brain (oncotic aneurysms)	Nil	Died 23 days after presentation from haemorrhagic brain metastasis
Kishore et al.(Kishore et al., 1992)	1992	27	Unknown	Unknown	choriocarcinoma	Left atrium extending to pulmonary veins	Brain	Atrial mass excision Methotrexate + Doxorubicin	Died 12 days post cardiac surgery from brain metastasis
Perroni et al.(Perroni et al., 1993)	1993	22	Term	No	choriocarcinoma	Right ventricle thru pulmonary valve		Ventricular mass excision EMA-CO ×12, intrathecal methrotrexate	Disease free at 4 years
Bohlmann et al.(Bohlmann et al., 2002)	2002	41	Term	No	choriocarcinoma	Left atrium with obstruction of left pulmonary vein Pulmonary hypertension	Lung, kidneys, liver, spleen, brain	Left atrial mass excision 9× EMA-CO	Disease free at 1 year
Bocazi et al.(Bohlmann et al., 2002)	2005	53	Miscarriage at 8/40 Not pathological examined	Unknown	choriocarcinoma	Right ventricle	Lungs, Tumor pulmonary emboli	4× EMA-CO, 4× EMA-EP	Disease free at 6 months
Present case	2015	33	Term	Unknown Previous miscarriage	Intermediate trophoblastic tumor, unclassified	Left atrium obstruction of pulmonary vein	Lungs, liver, adrenal, bone, breast, subcutaneous mediastinal nodes, brain	6× EMA-CO 2× EMA-EP	Died 4½ months post diagnosis from haemorrhagic brain metastasis

the left frontal and occipital lobes. Staging PET scan 1-week postpartum further demonstrated widespread FDG-avid disease consistent with pulmonary, pericardial, mediastinal nodal, hepatic, adrenal, bony, breast and subcutaneous metastasis (Fig. 3A).

Multi-agent chemotherapy with EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine) was commenced 6-days post Caesarian-section. The patient was given high dose IV methotrexate 1000 mg/m2 for central nervous system (CNS) penetration. Due to the known left atrial tumor deposit, she was therapeutically anticoagulated with enoxaparin to mitigate risk of systemic emboli/stroke.

Our patient completed 6 cycles of EMA-CO with initially an excellent clinical and biochemical response to treatment. Her b-HCG dropped to a nadir of 1.7 iu/L. A restaging PET scan showed a partial response, with significant interval improvement in volume of metastatic disease. However residual FDG-avid disease in the lungs and mediastinal nodes were noted. A follow-up echocardiogram showed near complete resolution of her cardiac lesion.

Unfortunately, 3 months after commencing EMA-CO, the patient's b-HCG had started to rise again from 1.7 iu/L to 18 iu/L. A repeat MRI brain showed near resolution of the large left frontal-lobe metastasis, but ominously the presence of innumerable new scattered enhancing lesions throughout both hemispheres ranging from 1 to 4 mm in size, suggestive of diffuse CNS disease.

The patient's chemotherapy was switched to second line EMA-EP (etoposide, methotrexate, actinomycin D, cisplatin). After two cycles of EMA-EP, the patient had a biochemical response with her bHCG decrementing from 18 iu/L to 1.5 iu/L. However her treatment was complicated by neutropenic line-sepsis with sternotrophomonas bacteraemia, which compromised her dose intensity.

Haemotology was consulted regarding consideration of stem-cell collection with view to autologous transplantation rescue. However in the interim, she presented with a 3-day history of headache, vomiting, homonymous hemianopia and altered level of consciousness. A CT brain demonstrated multiple haemorrhagic brain metastasis both supra and infra-tentorially, with significant mass effect (Fig. 3B). Therapeutic enoxaparin was immediately ceased. Despite high dose dexamethasone and whole brain radiotherapy, she rapidly deteriorated from overwhelming intracranial disease and was subsequently palliated. She succumbed to her disease four and a half months after diagnosis. An autopsy was not performed.

3. Discussion

Our patient presented during 3rd trimester of a normal pregnancy, with disseminated disease, including intra-cardiac metastasis, from an intermediate trophoblastic malignancy. After an initial response to EMA-CO, her disease became rapidly chemo-refractory and she died due to CNS failure.

Cardiac metastasis as a manifestation of GTD has only been reported in the literature on seven occasions to our knowledge (Table 1), with all cases documented as aggressive choriocarcinoma histology. Our case is unique, being an intermediate trophoblastic malignancy of unspecified subtype.

From previously described cases, cardiac metastasis seems never to be an isolated finding in GTD, but is almost always associated with disseminated multi-organ disease, including pulmonary and CNS metastasis (Bozaci et al., 2005; Seigle et al., 1987; MacLowry & Roberts, 1966; Akaike et al., 1977; Bohlmann et al., 2002). Mirroring our own case, five out of the seven cases of choriocarcinoma described in the literature also manifested in left sided cardiac involvement, often with extension to or obstruction of the pulmonary veins (MacLowry & Roberts, 1966; Akaike et al., 1977; Bohlmann et al., 2002; Kishore et al., 1992). In the majority of cases, haemorrhagic CNS disease was the cause of death (Seigle et al., 1987; MacLowry & Roberts, 1966; Kishore et al., 1992); including a case of multiple cardio-embolic oncotic aneurysms, without parenchymal brain invasion (Seigle et al., 1987). Only one case described in Japan, died directly as result of cardiac involvement with a trans-mural infarction causing left ventricular rupture and cardiac tamponade (Akaike et al., 1977).

Cases in the literature prior to the 1990s invariably had poor outcomes (MacLowry & Roberts, 1966; Akaike et al., 1977; Kishore et al., 1992), with cardiac surgery usually futile (Kishore et al., 1992) and the diagnosis of GTD often made post-mortem. With the advent of effective chemotherapeutic regimens such as EMA-CO (Bower et al., 1997), prolonged survival has been achievable in isolated cases of cardiac metastasis in choriocarcinoma from either chemotherapy alone (Bozaci et al., 2005) or combination with cardiac surgery (Bohlmann et al., 2002; Perroni et al., 1993).

Unlike choriocarcinoma, the FIGO prognostic score(Kohorn, 2001) is of little value in intermediate trophoblastic tumors, where prognosis is largely governed by anatomical stage. Our case highlights the chemoinsensitivity of intermediate trophoblastic tumors. The b-HCG was only modestly elevated in our patient, which is typical for PSTT or ETT. Although the b-HCG trend still appeared to correlate as a useful marker for treatment response with regards to systemic disease for our patient, it ultimately turned out to be a poor indicator for CNS relapse.

The pathological features of the tumor in our case were difficult to classify precisely, exhibiting features of both PSTT and ETT. We came to the diagnosis of an intermediate trophoblastic tumor of unclassified subtype on pragmatic grounds. Previously, similar unclassified intermediate trophoblastic tumors to our case have also been described to cause metastatic disease, including pneumothoraces in two case reports (Multani et al., 2015; Barnardt & Fourie, 2011).

In conclusion, although rarely encountered, cardiac metastasis can be a feature of disseminated trophoblastic malignancy. Intermediate trophoblastic tumors are a rare chemo-resistant variant of gestational trophoblastic disease, for which more experience and better therapies are needed. The management of haemorrhagic brain metastasis in drug resistant disease is particularly challenging.

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