CASE REPORT

Placental-site trophoblastic tumor with deep myometrial invasion - a rare entity: The Malaysian experience

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SUMMARY

A placental-site trophoblastic tumor (PSTT) is a sporadic form of gestational trophoblastic neoplasm characterized by minimal secretion of beta-hCG and notable resistance to chemotherapy. This report presents the case of a 43-year-old multiparous woman with a previous initial diagnosis of an arteriovenous malformation (AVM). The patient exhibited recurrent episodes of abnormal uterine bleeding (AUB) accompanied by rising beta-hCG levels following successful embolization. The subsequent assessment revealed a vascular intrauterine mass measuring at least 5 cm, accompanied by an elevated serum beta-hCG level. Option of definitive treatment - total abdominal hysterectomy was offered for optimal management and precision in diagnosis via histopathological assessment. The histopathological analysis confirmed the diagnosis of PSTT. As the initial beta-hCG was declining following surgical intervention, initiation of methotrexate (MTX) treatment was done. However, the lack of clinical response necessitates escalation to EMA/CO chemotherapy; hence, complete remission is achieved. To date, our patient remains disease-free with no evidence of early recurrence or metastasis. Thus, we highlight the critical importance of histopathological evaluation in women presenting with persistent bleeding, even in the presence of low beta-hCG levels. The characteristics of AVM can hinder early diagnosis; thus, the critical value of beta-hCG should be emphasized in assisting this rare diagnosis of PSTT. Additionally, we emphasize the potential for ovarian preservation following definitive treatment and the efficacy of multi-agent EMA/CO chemotherapy over single-agent methotrexate in managing high-risk PSTT patients aiming for early remission.

INTRODUCTION

A placental-site trophoblastic tumor (PSTT) is the rarest type of malignant gestational trophoblastic tumor. Since its first formal description by Scully in 1976, fewer than 350 well-documented cases have been published worldwide; its incidence is estimated at roughly 1 in 50,000–100,000 pregnancies, though the true rate may be higher due to misclassification of indolent lesions.[1] Clinically, PSTT arises from intermediate trophoblasts at the implantation site, which generally serve to anchor the placenta and remodel the maternal spiral arterioles. These cells produce human placental lactogen (hPL) and inhibin α more readily than beta human chorionic gonadotropin (β hCG), resulting in low β hCG levels and potential diagnostic confusion. Biologically, PSTT occupies an intermediate niche between benign placental site nodules and aggressive choriocarcinoma; it grows relatively slowly with a "pushing" myometrial invasion pattern and later metastasis (commonly to lung, pelvis, brain, liver), yet is relatively resistant to single agent chemotherapy once metastatic.[2] To date, the pathologists identify PSTT by sheets of monomorphic intermediate trophoblasts with abundant eosinophilic cytoplasm, distinct cell membranes, and absence of chorionic villi; immunohistochemistry is pivotal, with diffuse hPL and cytokeratin, patchy β hCG, and a Ki 67 index typically 5–30%, helping distinguish PSTT from epithelioid leiomyosarcoma, epithelioid trophoblastic tumour (ETT), and placental site nodule.[3] Consequently, management principles differ markedly from those for choriocarcinoma or invasive moles. Surgery is the primary modality because complete excision offers the highest likelihood of cure while avoiding multi agent chemotherapy toxicities based on international guidelines recommendation.[4] Nevertheless, controversy persists over surgical extent either simple hysterectomy versus hysterectomy with bilateral salpingo oophorectomy and/or lymphadenectomy and indications for adjuvant treatment. Current FIGO and NCCN guidance supports considering adjuvant EMA/CO (etoposide, methotrexate, dactinomycin, cyclophosphamide, vincristine) or other multi agent regimens when histopathologic risk factors are present, including deep myometrial/serosal invasion, lymphovascular space involvement, high mitotic index, and an interval >4 years since prior pregnancy.[4] Thus, managing PSTT is challenging, particularly ensuring precise diagnosis to guide appropriate therapy. Our case consolidates current evidence and underscores the importance of revisiting the initial diagnosis to offer accurate management. Thorough counselling and judicious refinement of diagnostic modalities are paramount.

CASE PRESENTATION

Background Clinical Presentation

A 43-year-old woman with no known medical illnesses and a history of three childbirths (the last one occurring eight

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months ago via spontaneous vaginal delivery) presented for evaluation. She had a healthy baby boy without any complications during her antenatal, intrapartum, or postpartum periods. She was doing well until she started taking a hormonal contraceptive pill 40 days after giving birth. Following this, she began to experience irregular bleeding despite adhering to her contraceptive schedule. Consequently, she was assessed at an outpatient gynecology clinic for possible abnormal uterine bleeding (AUB) and expressed interest in exploring other contraceptive methods. Her bleeding pattern had been erratic for the past six months, but she reported no constitutional symptoms or changes in bowel habits. She denied experiencing any symptoms of anemia, such as lethargy or palpitations. A basic assessment confirmed that she was not anemic, with a clinical hemoglobin level between 11-12 g/dL. Her abdomen was soft and non-tender. A speculum examination revealed blood but showed a normal cervical contour with no polyps or abnormal growths. A pelvic examination yielded normal findings: the uterus was non-tender and non-palpable, and both adnexa appeared unremarkable.

A bedside transvaginal ultrasound (USG) was performed, revealing a 5.0 x 4.8 cm heterogeneously echogenic, highly vascular mass occupying the uterine cavity. The uterus was noted to be bulky, and a right hemorrhagic cyst measuring less than 4 cm was observed. The left ovary was of normal size, and no free fluid or adnexal mass was documented during the initial scan. Suspecting retained products of conception (POC), serum β-hCG concentrations were checked and found to be elevated at approximately 140 mIU/mL. Further imaging with pelvic Magnetic Resonance Imaging (MRI) was conducted, which when compared with the previous pelvic ultrasound, suggested a uterine arteriovenous malformation (AVM) with intrauterine bleeding/ hematoma of variable ages despite the elevated baseline levels of beta-hCG (Figure 1). She subsequently underwent uterine embolization for the AVM without any complications. A follow-up schedule was established, including ongoing monitoring of beta-hCG levels, which initially showed a declining trend, along with normal gynecological findings on bedside USG scanning. After six months, she was deemed well and discharged for community clinic follow-up as per local protocol.

Unfortunately, three months later, she experienced five weeks of amenorrhea despite consistent use of hormonal contraceptives. Suspecting a possible pregnancy, she sought medical attention and presented with findings similar to those of her previous AVM. Imaging revealed a uterine mass located within the endometrium, measuring 3.7 x 3.6 cm, with evidence of vascularity found in both the anterior and posterior myometrium (Figure 2). Her beta-hCG level was measured at 6464 mIU/mL during her initial diagnosis. A comprehensive imaging workup, including a computed tomography scan of the thorax, abdomen, and pelvis, was offered, which revealed findings similar to those in the recent USG result with no evidences of possible metastasis. A comparison of CT scan findings was reviewed. Otherwise, her beta-hCG levels remained elevated, fluctuating between 6204 and 6464 mIU/L. The trend of beta hCG level were summarized (Table I). She was counselled regarding definitive management, and a potential recurrence of the AVM was discussed. The risks of bleeding from a possibly aggressive AVM within one year of embolization, along with the necessity for histopathological evaluation due to her high beta-hCG levels, were communicated before surgical intervention, which she agreed to. As planned, she underwent an elective total abdominal hysterectomy with bilateral salpingectomy and right ovarian cystectomy. Intraoperatively, we examined both ovaries and found them to be clinically normal. Thus, we opted for the decision to preserve them, given her age, to prevent the risk of surgical menopause. Otherwise, the operation was uneventful, with minimal blood loss and no intraoperative or postoperative complications occurring.

Diagnostic Evaluation Following Operative Intervention

The anatomical assessment revealed a cross-section of the uterine wall from the cervical to the fundus, which exhibited a variegated mass; the area near the fundus was reported to be painful. Microscopic evaluation revealed infiltrative sheets of predominantly mononuclear intermediate trophoblast, along with scattered multinucleated cells that invaded the myometrium. This invasion separated the smooth muscle cells and extended from the upper to the lower uterine wall, accompanied by extensive necrosis and hemorrhage. The atypical trophoblasts displayed significant nuclear atypia, characterized by coarse chromatin and some cells possessing prominent nucleoli, along with amphophilic to eosinophilic cytoplasm. Additionally, the mitotic activity was brisk and aberrant, with 16 instances observed per 10 high-power fields (hpf). Vascular invasion was prominent, with tumor cells replacing the walls of the myometrial vessels. However, no malignant trophoblast was observed breaching the serosal layer. The malignant trophoblasts exhibited focal expression of human chorionic gonadotropin (hCG) but did not express SALL4. A focal area with normal endometrial tissue, mainly composed of tubular glands lined by stratified columnar epithelium, was noted (Figure 3). In contrast, other structures, including the cervix, both fallopian tubes, and parametrium, appeared unremarkable. The right ovarian cyst was identified as a corpus luteum. Based on the operative and histopathological examination, the final diagnosis was concluded as Placental Site Trophoblastic Tumor (PSTT), classified at least as stage I.

Clinical Management

Postoperatively, the patient was stable, and her beta-hCG levels were monitored in an outpatient setting. Initially, no adjuvant chemotherapy was administered. However, after two months, her beta-hCG levels began to rise, prompting the initiation of single-agent methotrexate (MTX). Following the second cycle of MTX, her beta-hCG levels became undetectable. Unfortunately, subsequent monitoring indicated an increase in beta-hCG, raising concerns about potential tumor recurrence or resistance, although she remained asymptomatic. To further investigate, a Positron Emission Tomography (PET) scan was conducted, revealing a hypodense, ametabolic lesion in the left adnexa, indicative of a left ovarian cyst measuring 7.8 x 6.6 x 7.1 cm. The PET results could not definitively confirm the presence of metastatic disease; however, they did show a localized area of increased absorption of the radioactive tracer,

Table I: The beta-hCG level trend

Initial Diagnosis						
Date	4.8.23	14.8.23	28.8.23	13.9.23	26.9.23	10.10.23
Level	140	150.7	36.7	22	13.6	7.6
Prior Op						
Date	1.10.24	8.10.24	15.10.24	6.11.24	12.11.24	19.11.24
Level	3837.1	550.8	154.9	43.1	55.4	71.6
During MTX						
Date	29.11.24	18.12.24	5.1.25	22.1.25		
Level	124.5	15.2	4.5	4		
Prior EMA/CO						
Date	24.2.25	10.3.25	27.3.25	6.4.25		
Level	42.6	406.4	4177.7	6425.6		
During EMA/CO						
Date	10.4.25	2.5.25	21.5.25	29.5.25	13.6.25	25.6.25
Level	8080.37	3748.74	1265.31	1074.12	368.83	81.01
During EMA/CO						
Date	30.6.25	15.7.25	4.8.25	12.8.25	20.8.25	8.9.25
Level	48.46	10.32	5.25	3.42	1.32	<1.2

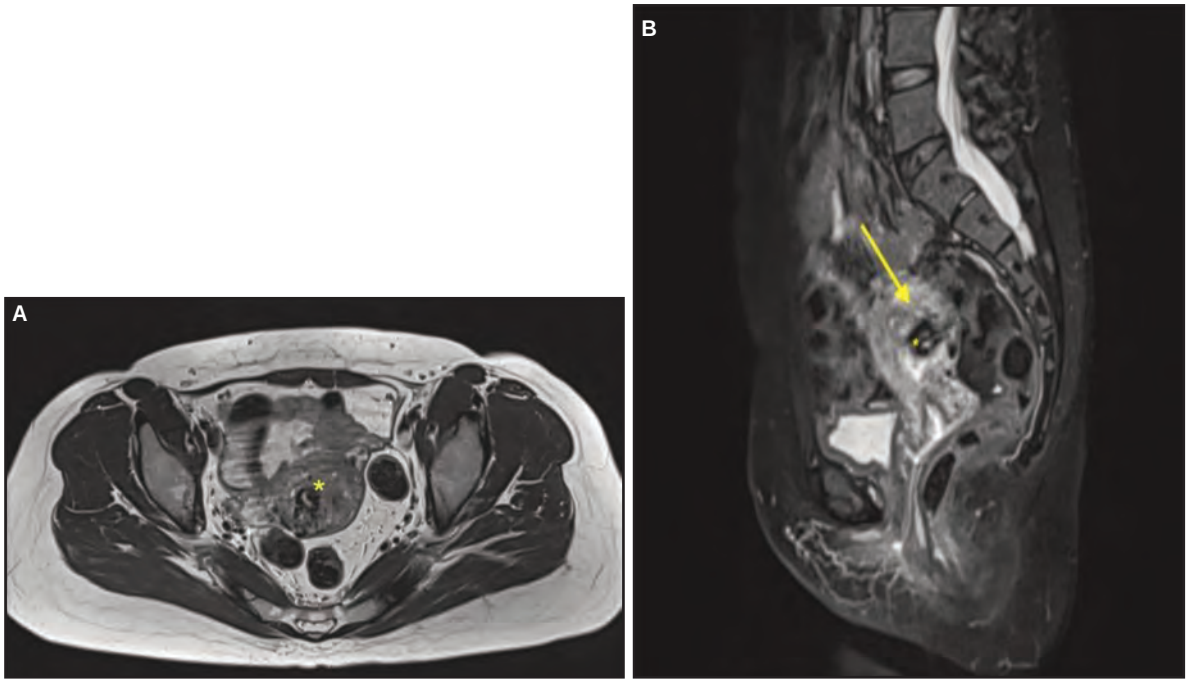

Fig. 1: A - T2W image show myometrium invasion by the AVM (*)
B - Sagittal T2 STIR image (MRI 1.8.2023) shows signal void lesion (*) within the myometrium of uterus(arrow) suggestive of AVM invading the posterior uterine wall myometrium.

fluorodeoxyglucose (FDG), at the left vertebral body without any evident lytic or sclerotic changes, suggesting the possibility of bone metastasis. No other locations showed abnormal FDG uptake or definitive evidence of FDG-avid metastases. Based on the PET findings, she was scheduled for an oophorectomy. However, this procedure was canceled upon preoperative assessment, which indicated no evidence of a left ovarian cyst, suggesting that it may have resolved prior to the surgical intervention. Despite this, her beta-hCG levels continued to rise from 4000 to 6000. A subsequent CT TAP confirmed the absence of an ovarian cyst or adnexal mass. However, it did identify an enhancing intraspinal lesion at L2, which could not rule out the possibility of dural metastasis. To facilitate a more informed treatment approach, a multidisciplinary team (MDT) discussion was held, including input from an oncologist and a pathologist. The EMA/CO adjuvant chemotherapy regimen was recommended to enhance disease control. Unfortunately, the patient developed severe neutropenia sepsis with myelosuspression after completing the second cycle of chemotherapy. In the subsequent cycle, the dosage was adjusted with deduction to 15% and viscritine was omitted.Targeting this regimen proved effective, as serum beta-hCG levels became normalized after the seventh cycle and a total of nine cycles of chemotherapy were given. She has remained well during the past six months of ongoing follow-up. Throughout this period, she has remained well, tolerating the side effects of the chemotherapy regimen effectively.

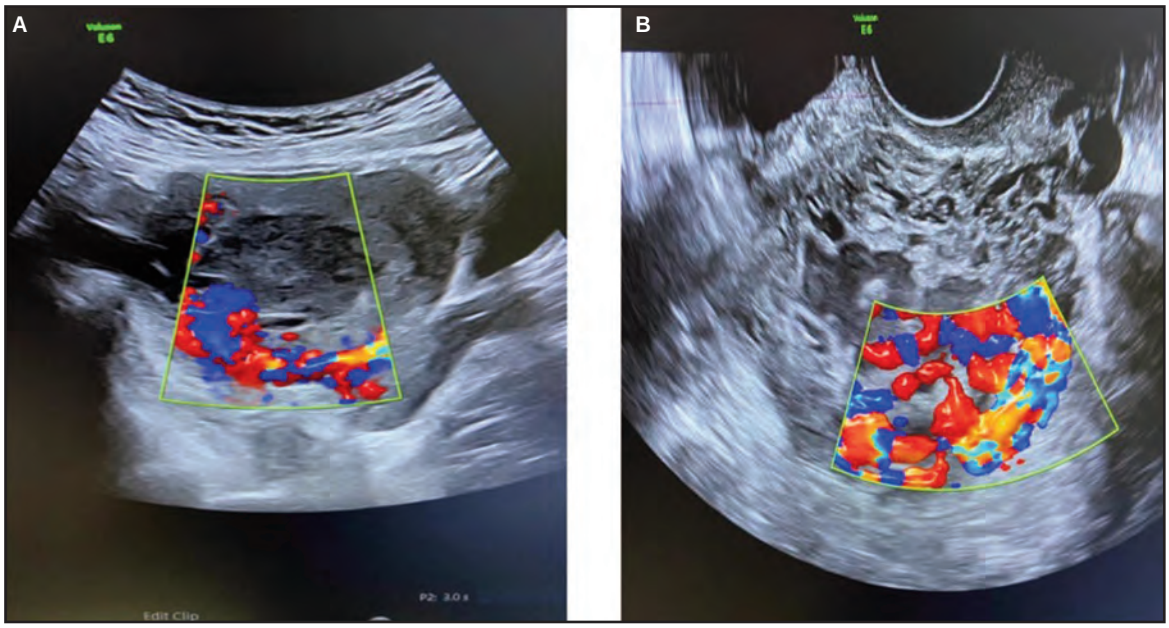

Fig. 2: A,B - The heterogeneously echogenic, highly vascular mass occupying the uterine cavity

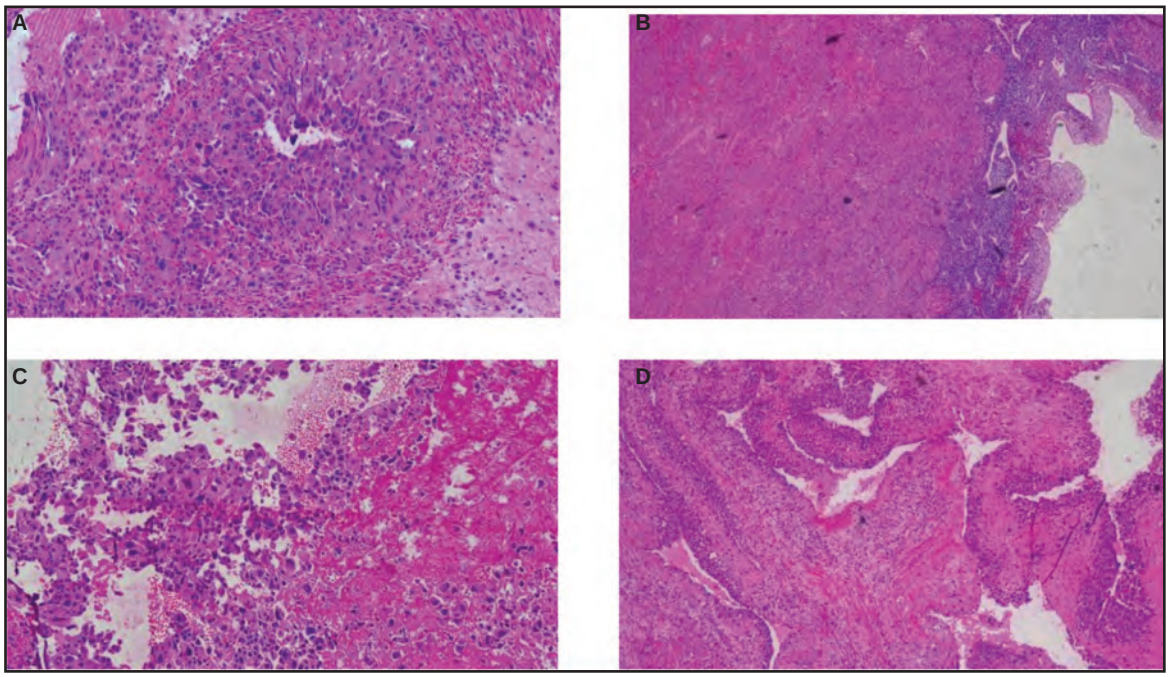

Fig. 3: A, B - Infiltrative sheets of predominantly mononuclear intermediate trophoblast, along with scattered multinucleated cells that invaded the myometrium, separated the smooth muscle cells and extended from the upper to the lower uterine wall, accompanied by extensive necrosis and haemorrhage.
C,D - The malignant trophoblasts exhibited focal expression of hCG but did not express SALL4. A focal area with normal endometrial tissue, mainly composed of tubular glands lined by stratified columnar epithelium

DISCUSSION

Our case highlights the potential diagnosis dilemma following the revision of AVM diagnosis to PSTT, which suggests that the low index of suspicion should be emphasized, especially in cases where beta-hCG is detected. However, it is not markedly high, ensuring that a possible PSTT diagnosis can be made in the initial stages.[5] Our case also underscores several diagnostic and therapeutic nuances that distinguish PSTT from other gestational trophoblastic neoplasms. First, although the patient's six-month history of intermittent bleeding might be dismissed as abnormal uterine bleeding (AUB), the persistence of symptoms after delivery with raised β-hCG is considered pathological and should be explored.[1,4] As established, at least 70% of PSTT cases arise after an expected term delivery, and at least 15% follow abortion or miscarriage, making our patient's

antecedent event somewhat atypical.[3] In addition to that, her consistently low beta-hCG—a plateau around 250 mIU/mL—mirrors the tumor's modest secretory profile and highlights why biochemical surveillance alone can mislead diagnosis and management; incorporating hPL or inhibin α into post pregnancy surveillance panels, where available, may improve early detection.

Thus, not surprisingly, our diagnosis is hindered, as it is based on imaging, mainly the MRI, which led to the initial diagnosis of AVM. From a radiological standpoint, Doppler ultrasonography (USG) is the primary investigative tool; however, its specificity is limited, as PSTT can resemble submucosal fibroids or arteriovenous malformations.[6] In contrast, MRI provides a superior assessment of myometrial depth and junctional zone disruption and is recommended whenever uterine preserving surgery is being considered or when decisions regarding adjuvant therapy depend on the depth of invasion. In our case, the MRI revealed disease adjacent to the serosa, prompting the surgical team to proceed with en bloc removal to avoid any potential tumor spill.[7]

A total or simple hysterectomy is the primary treatment for PSTT because they often don't respond well to chemotherapy. For localized disease, a total abdominal hysterectomy is often effective. Additionally, the choice to preserve both ovaries merits further discussion. Removing the ovaries through oophorectomy eliminates the rare possibility of hidden microscopic metastasis and any theoretical hormonal stimulus; however, estrogen and progesterone receptors are not consistently expressed in PSTT.[8] Furthermore, the sudden loss of ovarian function in a 43 year old can lead to a 2–3 fold increase in long term cardiovascular and osteoporotic complications.[9] In population based and multi institutional studies, no survival difference has been observed between ovarian preservation and oophorectomy in stage I PSTT, provided that adjuvant chemotherapy is administered when necessary.[10] Therefore, in our case, choosing to preserve the ovaries aligns with contemporary survivorship principles without compromising prognosis.

There is ongoing controversy regarding surgical procedures, particularly concerning lymph node assessment related to pelvic and para aortic nodal metastases, which are reported in up to ~10% of clinically localized PSTT/ETT cases. However, routine lymphadenectomy can increase operative time and morbidity without a clear survival benefit; sentinel node mapping with indocyanine green fluorescence is being evaluated and could rationalise staging while reducing routine lymphadenectomy. In our case, we opted not to perform routine lymphadenectomy based on current literature, and PET/CT showed no suspicious nodal involvement. Additionally, the patient has responded well to the EMA/CO regimen, as reported.[1,7]

In choosing the optimal chemotherapy, balancing outcomes and side effects is crucial. We escalated from MTX to EMA/CO based on overall diagnosis and risk factors following FIGO scoring which in her case consider high risk. She was starting with MTX to reduce toxicity but prepared to transition as β hCG rose. The EMA/CO's inclusion of etoposide and cyclophosphamide targets DNA topoisomerase and alkylation pathways and achieves higher cytotoxic synergy, which may overcome resistance suggested by copy number gains in cell cycle regulators and drug efflux pumps. Nevertheless, EMA/CO entails significant short and long term toxicity—including myelosuppression, alopecia, premature ovarian insufficiency, and secondary leukaemia—necessitating informed consent and robust supportive care.[2,7] In our case, the patient experienced grade 4 neutropenia during cycle 2 (ANC $<0.5 \times 10^9$/L), underscoring the value of vigilant monitoring, prompt G CSF, and dose adjustments such as withholding vincristine to mitigate further neutropenia.

Once a diagnosis of PSTT is confirmed, careful long term follow up is essential after completing chemotherapy. At least 25% of recurrences occur more than two years after remission, often at extra uterine sites.[8] In accordance with our local protocol, we implemented the FIGO endorsed surveillance plan: monthly β hCG for 12 months, then quarterly for four years, with annual chest radiographs and symptom triggered imaging.[4] Given evidence that PD L1 is expressed in roughly one third of PSTT specimens, we discussed enrolment in an immunotherapy registry should relapse occur, resources permitting.

Our case highlights a possible misdiagnosis of PSTT during the initial stages, primarily due to diagnostic challenges and limited resources. Lack of access to MRI and immunohistochemistry can delay diagnosis, and non availability of multi agent chemotherapy can defer treatment, leading to suboptimal outcomes. Establishing a local GTN network and a multidisciplinary trophoblastic disease board can improve pathways and outcomes, as demonstrated in our institution.

CONCLUSION

As a conclusion, our case underscores the importance of vigilant clinical suspicion, image-guided staging, and histology-driven therapy in achieving a cure for PSTT. Tailored surgical conservatism—specifically, ovarian preservation—and judicious use of EMA/CO can maximize both oncologic and quality-of-life outcomes. Furthermore, ongoing research into molecularly targeted agents and immunotherapy is crucial for improving survival rates in advanced or recurrent cases.

REFERENCES

1. Lucas R, Cunha TM, Santos FB. Placental site trophoblastic tumor: a case report and review of the literature. J Radiol Case Rep. 2015; 9(4): 14-22.
2. Zampacorta C, Pasciuto MP, Ferro B, Lucidi A, Maestro AS, Espinosa I, et al. Placental site trophoblastic tumor (PSTT): a case report and review of the literature. Pathologica. 2023; 115(2): 111-6.
3. Chaves MM, Maia T, Cunha TM, Veiga VF. Placental site trophoblastic tumour: the rarest subtype of gestational trophoblastic disease. BMJ Case Rep. 2020; 13(10).
4. Ngan HYS, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, et al. Diagnosis and management of gestational trophoblastic disease: 2021 update. Int J Gynaecol Obstet. 2021; 155 Suppl 1(Suppl 1): 86-93.

5. Horowitz NS, Goldstein DP, Berkowitz RS. Placental site trophoblastic tumors and epithelioid trophoblastic tumors: Biology, natural history, and treatment modalities. Gynecol Oncol. 2017; 144(1): 208-14.
6. Lin LH, Polizio R, Fushida K, Francisco RPV. Imaging in Gestational Trophoblastic Disease. Semin Ultrasound CT MR. 2019; 40(4): 332-49.
7. Seckl MJ, Sebire NJ, Fisher RA, Golfier F, Massuger L, Sessa C, et al. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013; 24 Suppl 6: vi39-50.
8. Lurain JR. Gestational trophoblastic disease II: classification and management of gestational trophoblastic neoplasia. Am J Obstet Gynecol. 2011; 204(1): 11-8.
9. Parker WH, Broder MS, Chang E, Feskanich D, Farquhar C, Liu Z, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. Obstet Gynecol. 2009; 113(5): 1027-37.
10. Matsuo K, Machida H, Shoupe D, Melamed A, Muderspach LI, Roman LD, et al. Ovarian Conservation and Overall Survival in Young Women With Early-Stage Low-Grade Endometrial Cancer. Obstet Gynecol. 2016; 128(4): 761-70.