What is your diagnosis?

A 39 year-old woman, P2L2, presented to the emergency department with vaginal bleeding. She was diagnosed as having a molar pregnancy one and half months previously, for which surgical evacuation was performed at a private clinic. Beta-human chorionic gonadotropin (β-hCG) level before evacuation was 40,738 mIU/mL and follow-up values followed a declining trend from 3,820 mIU/mL 48 hours after evacuation, to 1,342 mIU/mL after one week. Histopathological examination (HPE) ruled out any possibility of malignancy. During follow-up, she had an episode of severe vaginal bleeding on the fifteenth day after evacuation. Magnetic resonance imaging of the pelvis suggested uterine arteriovenous (A-V) malformation with the possibility of residual gestational trophoblastic disease (GTD), in view of medical history and raised β-hCG (1,083 mIU/mL) (Figure1a-c). She received a blood transfusion and single-agent chemotherapy (methotrexate) at her primary centre, however, her β-hCG values continued to fall. After one month, she had another episode of severe vaginal bleeding and was referred to our centre. Here, her vitals were stable and systemic examination showed no abnormality. Gynecological examination revealed normal vulva, vagina, cervix, and soft and enlarged uterus of 14 weeks size. β-hCG was 23.55 mIU/mL. Transvaginal sonography showed thin endometrium and a cystic lesion in the uterine fundus invading the anterior myometrium, which was hyper-vascular on colour Doppler, suggestive of A-V malformation (Figure 2a,b). Therefore, bilateral uterine artery embolization (UAE) was performed. The patient was then discharged in a stable condition. After one week of UAE, she again presented with severe vaginal bleeding. She had pallor, pulse rate of 110/minute, and blood pressure of 90/60 mmHg. After thorough discussion, a plan for emergency hysterectomy was made, and written informed consent was taken.

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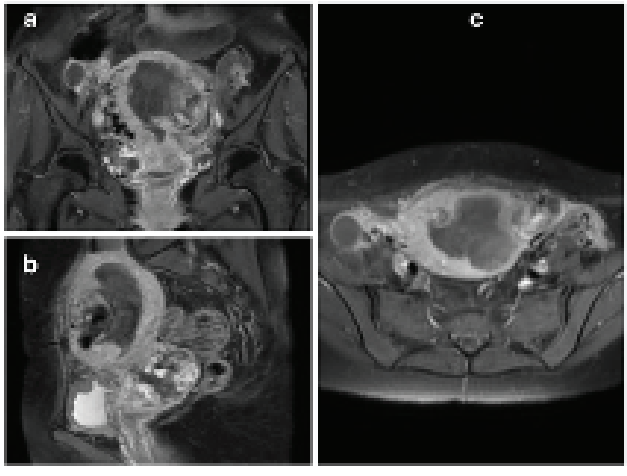

Figure 1. MRI of pelvis showing an enhanced bunch of vascular flow, void size ~53.8x88.8x79.3 mm, involving the anterior aspect of the fundus of the uterus, compressing and displacing the irregular endometrium posteriorly: a) sagittal; b) coronal; and c) axial view
MRI: Magnetic resonance imaging

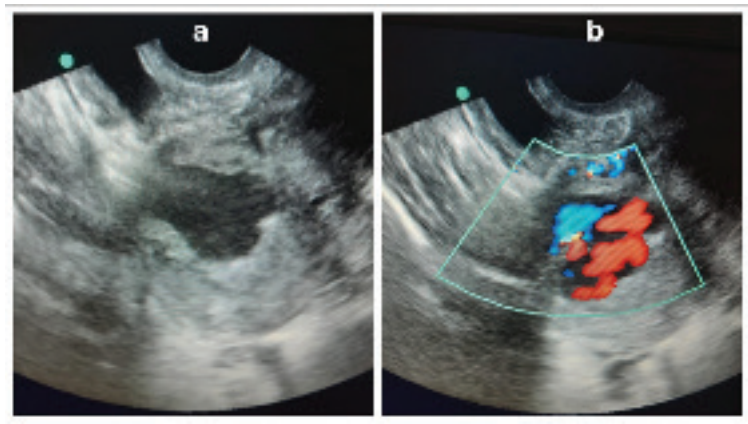

Figure 2. Transvaginal sonography. (a) This showed thin endometrium and cystic lesion in the uterine fundus invading the anterior myometrium. Color Doppler (b) showed hyper-vascularity, suggestive of A-V malformation

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Answer

Total abdominal hysterectomy was performed under general anaesthesia. Intra-operatively, the uterus was 14 weeks size, regularly enlarged, and bilateral fallopian tubes and ovaries were healthy. Cut section of the uterus showed an irregular endometrial cavity with thick-walled cysts involving endomyometrium filled with blood clots, but the uterine serosa was intact (Figure 3). The postoperative course was uneventful. Her β-hCG was undetectable (<5 mIU/mL) on day 1 after surgery. The final HPE was suggestive of placental site trophoblastic tumor (PSTT) (Figure 4a-d). After this HPE diagnosis, no distant metastasis was found on CECT abdomen, pelvis and thorax. She had FIGO stage 1 disease and The International Federation of Gynecology and Obstetrics/World Health Organization prognostic score was 0. Postoperative management was discussed with medical oncology and the decision to follow-up by monitoring β-hCG was taken. Currently, she is on monthly β-hCG follow-up and has had no relapse for the last six months.

Discussion

PSTT is a rare malignant tumor with an incidence of between 1/50,000-1/100,000 pregnancies and 0.23-3% of all GTDs (1). PSTT often occurs after a normal term pregnancy (61%), or less commonly after molar pregnancy (12%), and occasionally after miscarriages, ectopic pregnancies, stillbirths, and preterm deliveries (2). In this case, PSTT was diagnosed a few weeks after molar pregnancy. Sometimes, PSTT is diagnosed even after years of antecedent pregnancy. A median delay of 13 months (range 0-240) was reported by Alexander et al. (3).

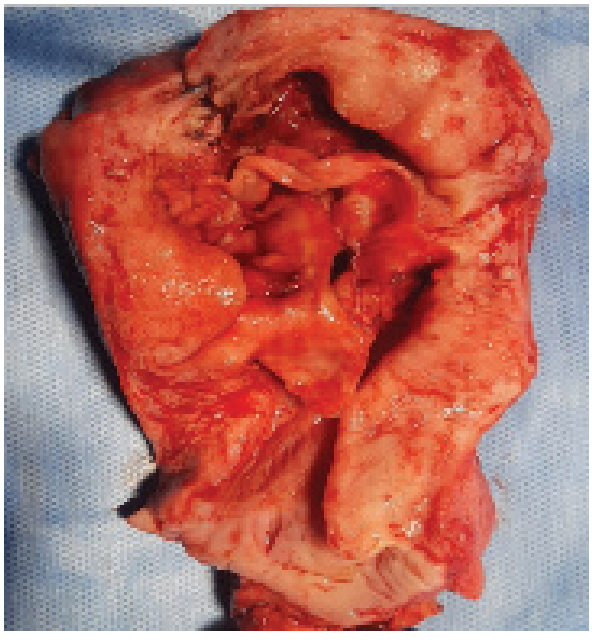

Figure 3. Irregular endometrial cavity with thick walled cyst involving endomyometrium in the cut specimen of uterus

The diagnosis of PSTT is usually difficult as it lacks specific and sensitive tumor markers, and radiological diagnostic criteria, and can be confirmed on HPE only. PSTT originates exclusively from the proliferation of the intermediate interstitial trophoblast and is characterised by the absence of villi and a mild mitotic activity (4). β-hCG level remains low in PSTT due to the absence of syncytiotrophoblast (5). Apart from HPE, immunohistochemical markers play an important role in differentiating it from other intermediate trophoblast tumor-like epitheloid trophoblastic tumor. Human placental lactogen, epidermal growth factor, and vascular endothelial growth factor stains strongly positive, β-hCG generally stains weakly and is focally positive, cytokeratin stains diffuse positive, and human epidermal receptor 2/neu and cluster of differentiation 117 stain negative in PSTT (6,7).

Surgery remains the cornerstone of management, with primary hysterectomy being the optimal therapy (8,9). Ovaries should be conserved unless there is a family history of ovarian cancer or the patient is post-menopausal. PSTT tends to metastasise through lymphatic vessels with a reported incidence is 5.9% (6). Therefore, lymphadenectomy is recommended in stage I PSTT with >50% myometrium invasion and in advanced stages (II or more) (6). The impact of complete abdominal and pelvic lymphadenectomy on overall survival is yet to be elucidated. Some patients with metastatic disease or a high mitotic index might require adjuvant platinum based multi-agent chemotherapy.

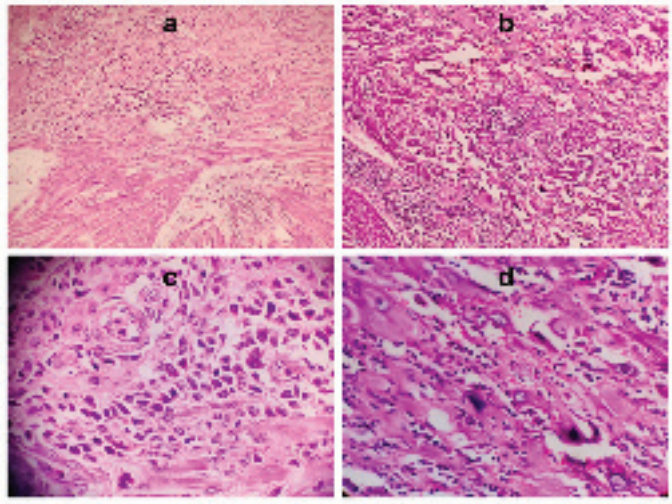

Figure 4. a) Endomyometrium showing areas of necrosis and hemorrhage (H&E, x200); b) Sheets and cords of mononucleated tumor cells infiltrating through the myometrium (H&E, x200); c) Higher magnification shows round to polyhedral intermediate trophoblastic cells with high nucleocytoplasmic ratio and eosinophilic cytoplasm *(H&E, x400); d) Scattered multinucleated bizarre cells (H&E, x400)*

PSTT is mostly confined to the uterus (stage I) and has a good prognosis. However, extra-uterine disease leads to a poor prognosis (10). Additionally, it has a poor prognosis in contrast to other GTDs, which are exquisitely chemosensitive. PSTT is relatively unresponsive to chemotherapy (11).

In our case, the disease was confined to the uterus and there was no evidence of metastasis. A total hysterectomy was performed, lymph node sampling could not be done as we did not suspect a malignancy, and the disease was limited to the uterus. The patient is being closely followed up with β-hCG and routine clinical checkups on regular basis.

Unlike other GTDs, follow-up in PSTT cannot be done with β-hCG alone, particularly in cases with very low β-hCG at presentation. Clinical examination and imaging to be considered to detect recurrence. Lok et al. (12) suggested β-hCG level weekly monitoring for six weeks (after normalisation), followed by monthly for 12 months and then less frequently for 10 years.

In this case there was a diagnostic challenge; PSTT or uterine A-V malformation. History, examination, and imaging findings showed that distinguishing between PSTT and A-V malformation is clinically challenging. Therefore, in these cases we suggest a strong suspicion should be kept for PSTT.

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