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Case Report

Placental Site Trophoblastic Tumor Reveled by Uterine Arterio-Venous Malformation in Post-Menopausal Women: An Uncommon Case Report Usually Misdiagnosed

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Abstract

Placental Site Trophoblastic Tumor (PSTT) is a distinctive and rare form of Gestational Trophoblastic Neoplasm (GTN) [1]. The epidemiologic and risk factors are not well known. Usually, the relationship to previous gestations is uncertain. In addition, clinical and morphological features are very variable, which complicates the diagnosis [2]. In this paper, we report an uncommon presentation of PSTT in presumed post-menopausal woman reveled by uterine arterio-venous malformation. It's about a 44-year-old gravid 0 para 0 presumed post-menopausal Moroccan woman. She suffered from intolerable post-menopausal bleeding. Pelvic ultrasound showed a large sinusoid channels within the myometrium with colors showing multidirection on Doppler that suggested the diagnosis of pelvic Arterio-Venous Malformation (AVM). Computed Tomography and pelvic Angiography confirmed the diagnosis of an AVM. Thus, a preoperative embolization and total hysterectomy were performed. In the gross examination we noted variable seized thin-well cavities with blood clots within the myometrial tissues that are devoid of clearly obvious lesion. Microscopically, these ecstatic and congested vascular cavities were invaded by intermediate tophoblastic cells proliferation that infiltrates 60% of the myometrium. In immunohistochemical stain, the tumor cells expressed the Cytokeratin AE1/AE3 with Ki67 at 5%. Human chorionic gonadotropin (β-hCG), P63, smooth muscle markers and P53 were negative in the tumor cells. Through this case, we present a rare disease that often difficulty diagnosed and may be inappropriately treated.

Keywords: Arteriovenous Malformation; Placental Site Trophoblastic Tumor; Uterus

Abbreviations:

GTD	:	Gestational Trophoblastic Disease
PSTT	:	Placental Site Trophoblastic Tumor
hCG	:	Human Chorionic Gonadostropin
AVM	:	Arterio-Venous Malformation
WHO	:	World Health Organisation
FIGO	:	Federation of International of Gynecologists and Obstetricians
hPL	:	Human Placental Lactogen
PLAP	:	Placental Alkaline Phosphatase
ETT	:	Epithelioid Trophoblastic Tumor
hpf	:	high power field

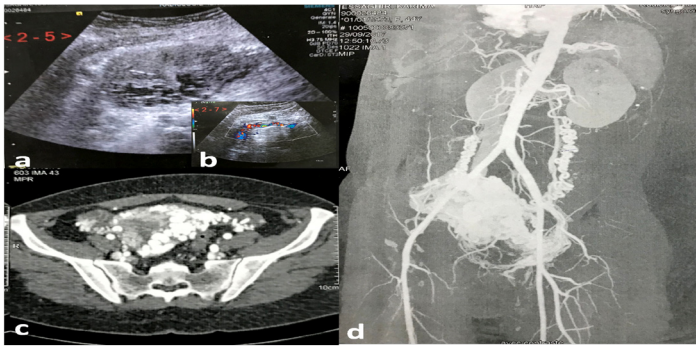
Introduction

Gestational Trophoblastic Disease (GTD) is a heterogeneous group of gestational and neoplasic conditions arising from trophoblast, including molar gestations and Gestational trophoblastic

neoplasms [1]. Placental Site Trophoblastic Tumor (PSTT) is a distinctive and rare form of Gestational Trophoblastic Neoplasm (GTN). The epidemiologic and risk factors are not well known. Usually, the relationship to previous gestations is uncertain [2]. It can cause uterine arteriovenous malformation, because of its ability to invade and destroy myometrial vasculature engendering uterine hemodynamic changes [3]. In such cases, correct diagnosis and management can be challenging.

Case Report

It's about a 44-year-old gravida 0 para 0 presumed post-menopausal Moroccan women. She suffered from intolerable postmenopausal bleeding with Hemoglobin at 7,3g/dl. Pelvic ultrasound showed an intra uterine large sinusoid channels within the myometrium. The uterine cavity contained large amount of blood. On Color flow and Doppler, the anechoic channels were filled with colors showing multidirection and suggesting the diagnosis of pelvic arterio-venous malformation (Figure 1a). Computed Tomography (Figure 1b) and pelvic Angiography (Figure 1c) confirmed the diagnosis of an AVM supplied by dilated and tortuous arteries from the hypogastric arteries and communicating with enlarged hypogastric veins.



Figures 1(a-d): (a) Pelvic ultrasound showed an intra uterine large sinusoid channels. **(b)** On Color flow and Doppler the anechoic channels were filled with colors showing multidirection suggesting the diagnosis of pelvic arterio-venous malformation. **(c) Computed Tomography** and **(d) Pelvic Angiography** revealed an AVM supplied by dilated and tortuous arteries from the hypogastric arteries and communicating with enlarged hypogastric veins.

Thus, a preoperative embolization with "Curaspon", completed by a total hysterectomy, was performed. In our laboratory, we received a total hysterectomy with salpingo-ovarectomy. In the gross examination we noted a variable seized thin-well cavities with blood clots witch appear as region (8cm of diameter) of irregular blood spaces within the myometrial tissues that is devoid of clearly obvious lesion (Figure 2).

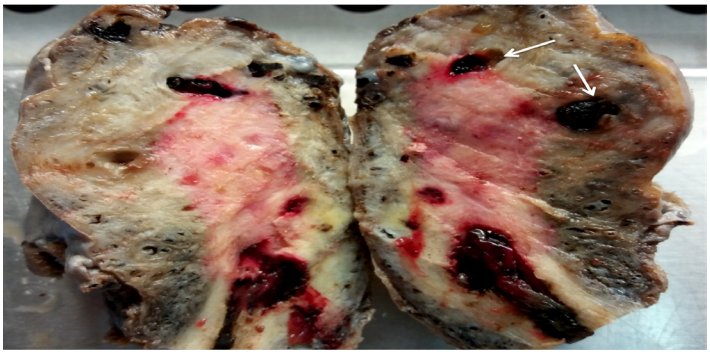
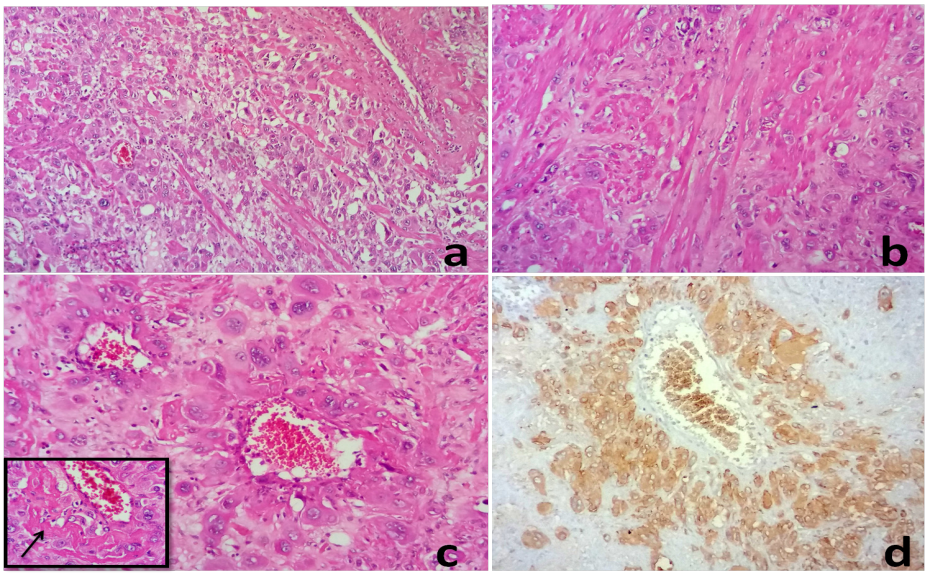


Figure 2: Grossly, the uterus was occupied by a variable seized thin-well cavities with blood clots witch appear as region (8cm of diameter) of irregular blood spaces (arrow) within the myometrial tissues that is devoid of clearly obvious lesion.

Microscopically, these ecstatic and congested vascular cavities were invaded by intermediate tophoblastic cells proliferation that infiltrates 60% of the myometrium. It consisted of sheets of large and polygonal eosinophilic cells with few nuclear atypia and unremarkable mitotic activity (Figure 3a). These cells insinuate themselves between the smooth muscle fibers (Figure 3b). They invade the well of blood vessels and focally replacing the entire well (Figure 3c). Elsewhere, medial and elastic layers of vessels were abnormally thickened and dilated. Endometrium, uterine serosa, cervix, ovaries and fallopian tubes were free from tumor. In immunohistochemical stain, the tumor cells expressed the Cytokeratin AE1/AE3 (Figure 3d) and the CD10. Ki 67 index was estimated at 5%. Human chorionic gonadotropin (β-hCG), P63, smooth muscle markers and P53 were negative in the tumor cells. Finally, the pathological diagnosis was an intra-uterine Placental Site Trophoblastic Tumor associated with uterine AVM, classified at pT 1b N0 M0 of World Health Organization classification (WHO) stage Ib of FIGO. The patient was referred to the oncologist for additional care.



Figures 3(a-d): (a) Microscopically, we noted an intermediate tophoblastic cells proliferation in the form of sheets of large and polygonal eosinophilic cells with few nuclear atypia and unremarkable mitotic activity (Hematoxylin-eosin, original magnification x 10). **(b)** These cells insinuate themselves between the smooth muscle fibers and **(c)** invade the well of blood vessels and focally replacing the entire well with a deposition of a fibrinoid materiel (arrow) (Hematoxylin-eosin, original magnification x 10). **(d) In immunohistochemical stain**, the tumor cells expressed the Cytokeratin AE1/AE3 with a remarkable vascular invasion.

Discussion and Conclusion

PSTT is the rarest subtype of gestational trophoblastic disease, with an incidence of approximately 1-5 per 100,000 pregnancies, accounting for approximately 0.2% of all cases, as suggested by population-based studies [4]. Because of the rarity of this type of tumor, the current medical knowledge is mainly based on the results of a few published trophoblastic disease center series and sparse reports of small series or singular cases [4]. PSTT has been thought to develop as a result of neoplastic transformation of cytotrophoblastic cells, and transformed cells assume the differentiation toward implantation site intermediate trophoblast [2]. Molecular genetic data, together with immunohistochemical finding, support the trophoblastic nature of PSTT [5].

It most frequently occurs during the reproductive years, although several patients have been older than 50 years of age when their tumors were diagnosed. Most patients have been parous; term pregnancies, spontaneous abortions, and hydatiform moles have preceded the diagnosis of PSTT. Usually, the relationship to previous gestations is uncertain, because the PSTT are diagnosed long after the last known pregnancy [2,6]. The most common presenting symptom is irregular vaginal bleeding, followed by abdominal pain and amenorrhea. Less frequent presentations include galactorrhea, virilization, nephrotic syndrome, polycythemia and symptoms related to the metastatic involvement of distant organs including the brain and lungs [2,6]. In most patients with PSTT, serum levels of Human chorionic gonadotropin (β-hCG) are not highly elevated, which differs from other forms of gestational trophoblastic disease, as this tumor originates from intermediate trophoblastic cells. On the other hand, the expression of Human Placental Lactogen (hPL) is usually high on histological sections and in the serum, and up regulation of b1-glycoprotein and CA-125 is also common [4,6]. Ultrasound findings often lack specificity, and little is known about the characteristic ultrasound findings in cases of PSTT. The preferred access is transvaginal since it provides better details of the lesion morphology and myometrial invasion due to its superior spatial resolution and proximity to the anatomy of interest [7]. The differential diagnosis of PSTT includes other forms of GTN, Retained Products of Conception (RCP) and uterine Arteriovenous Malformation (AVM) [5]. Indeed, in Color flow and spectral Doppler, PSTT may be hypovascular or hypervascular mimicking AVM [8].

Computed Tomography and Magnetic Resonance Imaging Computed Tomography (CT) is principally used for the metastatic workup. Locally, the uterine lesion is seen as an enlarged uterus with focal irregular low-attenuation lesions [7]. Grossly, PSTT has a highly varied gross appearance. The tumors range from diffuse to microscopic findings to tumors that enlarge and distort the uterus. It may project into the uterine cavity or grow predominantly into the myometrium. The neoplasm is soft and tan and may have areas of hemorrhage or necrosis. Many PSTTs have invaded through the entire thickness of the myometrium, extending to the serosa. Perforation or extension into the extrauterine site including ligament or adnexa also occurs [1,2]. Microscopically, PSTT composed

of implantation site intermediate trophoblastic cells. The typical growth pattern is characterized by infiltration of the myometrium by large, polygonal cells that insinuate themselves between the smooth muscle fibers. The cells may be present singly but most often occur in large nests or masses. Although most of the implantation site intermediate trophoblastic cells are polyhedral, they can also be spindle cell shaped [2]. They are mononuclear or multinucleated with mild to marked nuclear atypia, prominent nucleoli, eosinophylic to clear cytoplasm, scattered mitoses and occasional intranuclear inclusions [1].

The implantation site intermediate trophoblastic cells of PSTT also characteristically invade blood vessels in a manner that results in replacement of the muscle wall by tumor cells with a typical deposition of a fibrinoid materiel. These "transformed" blood vessels can be detected even at a low magnification and are diagnostic of PSTT because this feature is generally not seen in other trophoblastic and non-trophoblastic tumors [2]. In addition, PSTT is not associated with the presence of chorionic villi or fetal parts [2]. PSTT has a unique immunohistochemical phenotype. Mel-CAM (CD146) and Human Placental Lactogen (hPL) are strongly positive while Placental Alkaline Phosphatase (PLAP) is only focally positive.

The specificity of this staining pattern for PSTT is approximately 60%. Additionally, marked positive staining with Ki-67 (generally < 14%), alpha-inhibin, and cytokeratin 8/18 and negative staining for smooth muscle markers help confirm the diagnosis of PSTT. It is positive for hCG, p63 and CD10 in a relatively small proportion of cells [2]. PSTT must be differentiated from Choriocarcinoma rather than other types of neoplastic diseases because the clinical behavior and management are very different. Choriocarcinoma is highly sensitive to chemotherapy, wherears PSTT is relativelt indolent neoplasm for wich the treatment of choice is surgical resection or total hysterectomy. Usually, the distinction is not difficult. PSTT is composed of monophasic implantation site intermediate cells with occasional multinucleated intermediate trophoblastic cells. In contrast, choriocarcimnoma is characterized by the biphasic growth pattern with mononucleate trophoblastic cell sheets or masses alternating with syncytiotrophoblastic cells. PSTT has a different immunohistochemical staining pattern from choriocarcinoma; hCG staining is usually focal because of the lack of syncytiotrophoblastic cells, and only scattered multinucleated intermediate trophoblastic cells are positive [1,2].

A wide variety of other malignancies, especially epithelioid leiomyosarcoma, can mimic PSTT. The differential diagnosis from leiomyosarcoma can be difficult based solely on morphologic grounds because PSTT often has a highly infiltrative pattern within the myometrium, dissecting among the smooth muscle fibers and simulating origin from these cells, but in immunohistochemical staining, PSTT is negative staining for smooth muscle markers [2]. PSTT may be confused with Epithelioid Trophoblastic Tumor (ETT). This tumor is characterized by mononucleate chorionic-type intermediate trophoblastic cells forming discrete nests and cords infiltrating the myometrium. Geographic necrosis, calcification and fibrillar eosinophilic material resembling keratin are unique to ETT and are usually not present in PSTT. ETT is focally immunoreactive for hPL but strongly and diffusely immunoreactive for P63 [2].

Also, PSTT may be difficult to distinguish from Exaggerated placental site. The presence of chorionic villi, abundant multinucleated intermediate trophoblastic cells and the absence of vascular invasion with the deposition of fibrinoid materiel or so-colled "transformed arteries" suggest the diagnosis of Exaggerated placental site rather than a PSTT [2]. As for the acquired uterine Arteriovenous Malformation (AVM), this is a rare cause of vaginal bleeding and, although hysterectomy is the definitive therapy, transcatheter embolization provides an alternative treatment option [9]. PSTT may cause uterine AVM because of the trophoblast's ability to invade the myometrium; Bettencourt et al. reported that PSTT caused the formation of blood lacunae and arteriovenous shunts following invasion and destruction of myometrial vasculature, that were responsible for uterine hemodynamic changes amenable to diagnosis by Doppler ultrasound [9,3]. Histologically, AVM appears as admixture of malformed vessels such as capillaries, arteries and venules with abrupt changes in thickness of medial and elastic layers of vessels and abnormal vascular dilatation.

The optimal management, long-term outcome, and prognostic factors for PSTT is limited by the rarity of these malignancies and the difficulties of performing appropriate statistical analyses of risk factors identified in small series [10]. There is conflicting data concerning most of the reported potential prognostic factors in PSTT. Reviewing the available literature however, a few risk factors generally appear to be associated with favorable or unfavorable outcomes. Advanced age (>34 years old), deep myometrial invasion (>50%), and tumor size (>1 cm3) have been associated with worse outcome for women with PSTT; A high mitotic rate (> 5 mitotic figures/10 hpf) has also correlated with a higher risk of recurrence [2]. Although the exact duration from antecedent pregnancy to diagnosis of PSTT that is most predictive of outcome is not known, there are multiple studies that indicate that this is may be the most important risk factor. In two series duration of approximately ≥2 years seemed to be important [11]. The rarity of PSTT along with its unpredictable biological behavior and reduced chemosensitivity means that optimum management is difficult to plan.

When the tumor is localized in the uterus, total hysterectomy without salpingo-ovarectomy (unless the patient has a family history of ovarian cancer or is postmenopausal) is recommended. Nevertheless, it may be possible to carry out fertility preserving

management using hysteroscopic resection of the tumor in young patients with limited myometrial involvement [11]. However, it should be underlined that no standard therapy has been reported for young PSTT patients desiring to preserve their fertility [12]. It is important to highlight the issue of lymphadenectomy. Indeed, it is hard to indicate the precise surgical choice between lymph node sampling versus lymphadenectomy. The use of preoperative imaging and operative inspection of lymph nodes may identify the need for selected lymph node sampling. Radical pelvic lymphadenectomy is associated with long term morbidity.

Thus, based on literature findings, routine pelvic lymphadenectomy should be omitted to reduce treatment complications without compromising cure [12]. For patients with stage I disease, surgery alone is the preferred treatment because PSTTs tend to be more resistant to chemotherapy than other forms of GTD. The role of adjuvant chemotherapy in patients with stage I and II disease is controversial. There is a lack of randomized trials to support the use of chemotherapy and such data are unlikely to be generated due to the rarity of the disease. However, based on the poor outcome for patients with recurrent disease, adjuvant chemotherapy is recommended in women with risk factors for recurrence and/or persistently raised postoperative serum b-hCG. For advanced-stage diseases, (stage III and IV) a combination of surgery and polychemotherapy is required [5]. Our case, presumed postmenopausal women, had benefited from hysterectomy with salpingo-ovarectomy to stop the bleeding caused by the MAV and the PSTT. 4 months after surgery, the patient was in good health with no evidence of recurrence or metastasis. Finally, as a pathologist, the difficulty that we have encountered is to convince the patient and the oncologist by the diagnosis of PSTT outside a pregnancy and uterine mass in radiology. Indeed, in the absence, of accurate predictive risk factors, the appropriate management of PSTT is a challenge.

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Authors' Contribution

HE retrieved clinical information, wrote the manuscript and performed the literature review. FZ first identified this case, proposed the study and revised the manuscript for important intellectual content. YC acquired photomicrographs. AJ, KZ, AM and ZB provided valuable insight during manuscript preparation. All authors read and approved the final manuscript.

Consent for Publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Competing Interests

The authors declare that they have no competing interests.

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