Clinical Case Report

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Management of placental site trophoblastic tumor
Two case reports

Rosalba De Nola[a,*], Luca Maria Schönauer[a], Maria Grazia Fiore[b], Matteo Loverro[a], Carmine Carriero[a], Edoardo Di Naro[a]

Abstract

Rationale: Placental site trophoblastic tumor (PSTT) is a very rare malignant tumor, belonging to a family of pregnancy-related illnesses, called gestational trophoblastic diseases (GTD). Less than 300 cases of PSTT have been reported in literature, with an incidence of ≈1/50,000–100,000 pregnancies representing only 0.23% to 3.00% of all GTDs.

Patient concerns: Our report describes 2 additional cases of PSTT outlining their main diagnostic features and the subsequent management. The first case presented contemporary to a persistent hydatidiform mole in a 37-year-old woman, para 2042; whereas the second one originated 5 years after a miscarriage in 43-year-old woman, para 1031 with a previous diagnosis of breast cancer, and shared some features with placental site nodule (PSN), a benign condition.

Diagnosis: The first case had a difficult diagnosis because there was an amenorrhea of 11th week with high serum beta-human chorionic gonadotropin (beta-HCG) and an initial ultrasound image of vesicular mole. After the Dilatation and Curettage, histology confirmed the previous hypothesis. However, the final histology of PSTT was obtained after major surgery. On the contrary, the diagnosis of the second case was less challenging but surprising, thanks to a routine trans-vaginal ultrasound showing a suspicious endometrial thickness positive for PSTT at a subsequent hysteroscopic guided biopsy.

Interventions: The treatment consisted of hysterectomy and subsequent follow up. Lymphadenectomy or lymph node sampling were not performed due to the initial stage of the disease.

Outcomes: In the first case, there were high values of serum beta-HCG that plummeted after the surgery, whereas in the second one they had been always negative. Hereafter, both went through a follow up with periodic serum oncological markers, imaging studies and clinical evaluation, which have showed negative result for 3 years and 15 months, respectively.

Lessons: A detailed gynecological ultrasound examination could be extremely helpful to understand the next diagnostic step of echo-guided D&C or hysteroscopic biopsy and for a pre-operative staging assessment. On the contrary, determining the serum beta-HCG's curve is crucial just in case of an initial positive value to pursue clinical evaluation and follow-up. In case of good prognostic factors, the main therapy remains hysterectomy.

Abbreviations: beta-HCG = beta-human chorionic gonadotropin, CC = choriocarcinoma, CK pool = cytokeratin pool, CT-scan = computed tomography scan, D&C = dilatation and curettage, EMA/CO = Etoposide, methotrexate with leucovorin rescue and actinomycin D, given on day 1 and 2 and cyclophosphamide and vincristine given on day 8, EP/EMA = Etoposide and platinum alternating with etoposide, methotrexate/folinic acid rescue, actinomycin-D, ETT = Epithelioid trophoblastic tumor, FIGO = International Federation of Gynecology and Obstetrics, GTD = gestational trophoblastic Disease, GTNs = gestational trophoblastic neoplasms, GTT = gestational trophoblastic tumor, HM = hydatidiform mole, HPL = human placental lactogen, PSN = placental site nodule, PSTT = placental site trophoblastic tumor, TE/TP = Paclitaxel, cisplatin/ paclitaxel, etoposide, WHO = World Health Organization.

Keywords: beta-HCG, gestational trophoblastic disease (GTD), placental site nodule (PSN), placental site trophoblastic tumor (PSTT), pregnancy

1. Introduction

Placental site trophoblastic tumor (PSTT) is a very rare neoplasia belonging to gestational trophoblastic diseases (GTDs), identified as abnormal trophoblastic proliferations. Malignant forms of GTD include Invasive mole, PSTT, Epithelioid trophoblastic tumor (ETT) and Choriocarcinoma (CC).[1,2] Notably, no more than 300 cases of PSTT have been reported until now,[3,4] with an incidence of about 1/50,000–100,000 pregnancies covering a percentage from 0.23% to 3.00% of all GTDs.[1,2,5]

Until the discovery of chemotherapy 50 years ago, morbidity and mortality of Gestational Trophoblastic Neoplasms (GTNs) were significantly high. Nowadays, GTNs have one of the highest overall survival (98%) among solid tumors.[6]

Risk factors for GNTs are menarche after the age of 12 years old, poor bleeding during the menstrual period or even a prior use of oral contraceptive.[7] Moreover, PSSTs occur often in patients with a previous miscarriage, a termination of pregnancy or an

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ongoing pregnancy, either normal or pathological.[4] However, PSTTs differ deeply from other GTDs due to the biological characteristics, clinical behavior, slow growth and a relative resistance to chemotherapy,[7] requiring peculiar diagnostic strategies and therapeutic options.

From a pathogenic point of view, PSST could be considered an intriguing abnormal reproductive event originating mostly from the intermediate trophoblast. Until now, most clinical reports have focused attention on pathological features, clinical outcome and treatments modalities of PSTT, leaving the diagnostic efforts to each clinician case by case.

The present study focuses the attention on imaging procedures to overcome obstacles related to obtain a biopsy and an adequate quantity of biological tissue that could lead to delayed or mistaken therapeutic choices because of uncertain histological findings. Therefore, it will outline the main diagnostic features of 2 additional PSTT's cases and their management. The first one was synchronous with a persistent hydatidiform mole, whereas the second one originated 5 years after a miscarriage even though it shared borderline characteristics with the PSN, a benign condition.

Written informed consent for the publication of their clinical details and clinical images was obtained from both the patients.

2. Case report 1

A 37-year-old woman, para 2/0/4/2 (2 caesarean sections, 4 induced abortions), came to our attention for a suspected diagnosis of molar pregnancy during the 11th week of amenorrhea. In addition, she was affected by Sjögren's disease, under oral corticosteroids' treatment, psoriasis, and atopic dermatitis. Moreover, she had a smoking habit and a blood type positive for Rhesus factor. Transvaginal ultrasound imaging highlighted a sort of gestational sac sized 8 mm without a synchronous correspondence to the amenorrhea. However, embryonal echoes were absent, and the fake gestational sac was associated with a large echogenic trophoblastic mass occupying the entire uterine cavity. The ultrasound picture resembled a molar tissue because of the so-called "cluster of grapes" multicystic appearance. The color and power Doppler imaging revealed also an increased vascular density within the trophoblastic-like mass, mainly on the anterior wall of the uterus (Fig. 1A and B). The levels of beta-HCG during the observation period are reported in Figure 2.

Due to the disproportion between the high values of beta-HCG (97,140 mUI/mL) and the ultrasound picture, we decided to perform an echo-guided uterine dilatation and curettage (D&C) with vacuum aspiration. The sampled tissue was characterized by a crumbly texture, with a pink and multi-vesicular appearance like a molar pregnancy, without any identifiable gestational sac. Histology revealed hydropic and avascular chorionic villi characterized by irregular profile and circumferential proliferation of the trophoblast, suitable for a 1st grade[8] of vesicular mole. At discharge, trans-vaginal ultrasound check was completely regular.

More than a month after D&C, the patient had a very heavy and prolonged vaginal bleeding with a feeble responsiveness to emergency treatment based on methylergometrine and tranexamic acid. In this occasion, a new determination of serum beta-HCG result was very high (38,336 mUI/mL), while ultrasound examination showed again irregular hyper-echogenic images referable to persistent 22 mm thick deciduous-ovular remnants.

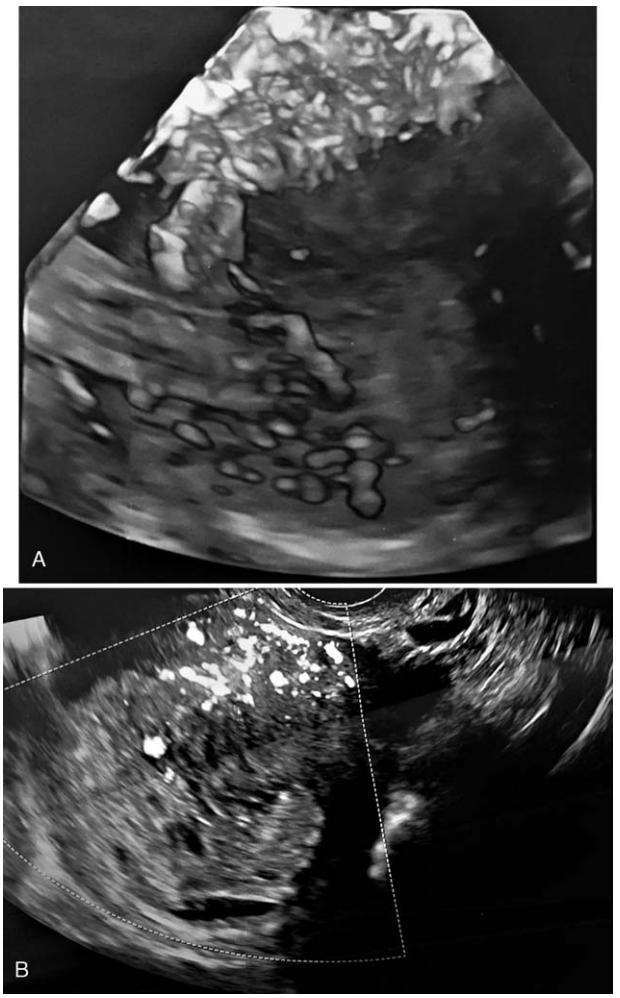

Figure 1. Transvaginal ultrasound examination of the Case 1, before D&C (Dilatation and Curettage). The present sonographic finding refers to the first case of PSTT before D&C. Notwithstanding an 11-week amenorrhea and a high beta-human chorionic gonadotropin (beta HCG), precisely 97,140 mUI/mL, the fake gestational sac measured only 8 mm and it appeared as an intrauterine fluid collection without any yolk sac nor embryos. Moreover, it was associated with a large echogenic trophoblastic mass, which occupied the entire uterine cavity, creating a multicystic appearance named "cluster of grapes" that usually depicts a molar tissue (A). At the color and power Doppler examination (B), the trophoblastic-like mass revealed a high vascular score, mainly on the anterior wall of the uterus. beta-HCG = beta-human chorionic gonadotropin; PSTT = placental site trophoblastic tumor.

Moreover, this trophoblastic-like structure infiltrated the myometrium deeply with an apparently free margin of 11 mm on the fundus (Fig. 3). After negative chest X-Rays, the patient underwent a total body computed tomography (CT) scan with a contrast agent (Fig. 4) that revealed only an enlarged uterus, especially at the fundus, with an inhomogeneous aspect during the venous phase and a thickening of the endometrial walls. In addition, there were some reactive enlarged (1 cm) lymph nodes among the pelvis and they were associated with a slight quantity of peritoneal fluid in the Douglas' pouch.

Since the patient strongly desired a surgical resolution which was designed as a total extra-fascial hysterectomy with bilateral salpingectomy and left ovarian preservation. During a right pelvic adhesiolysis, a varicocele began to bleed so easily and widely that ovariectomy was necessary.

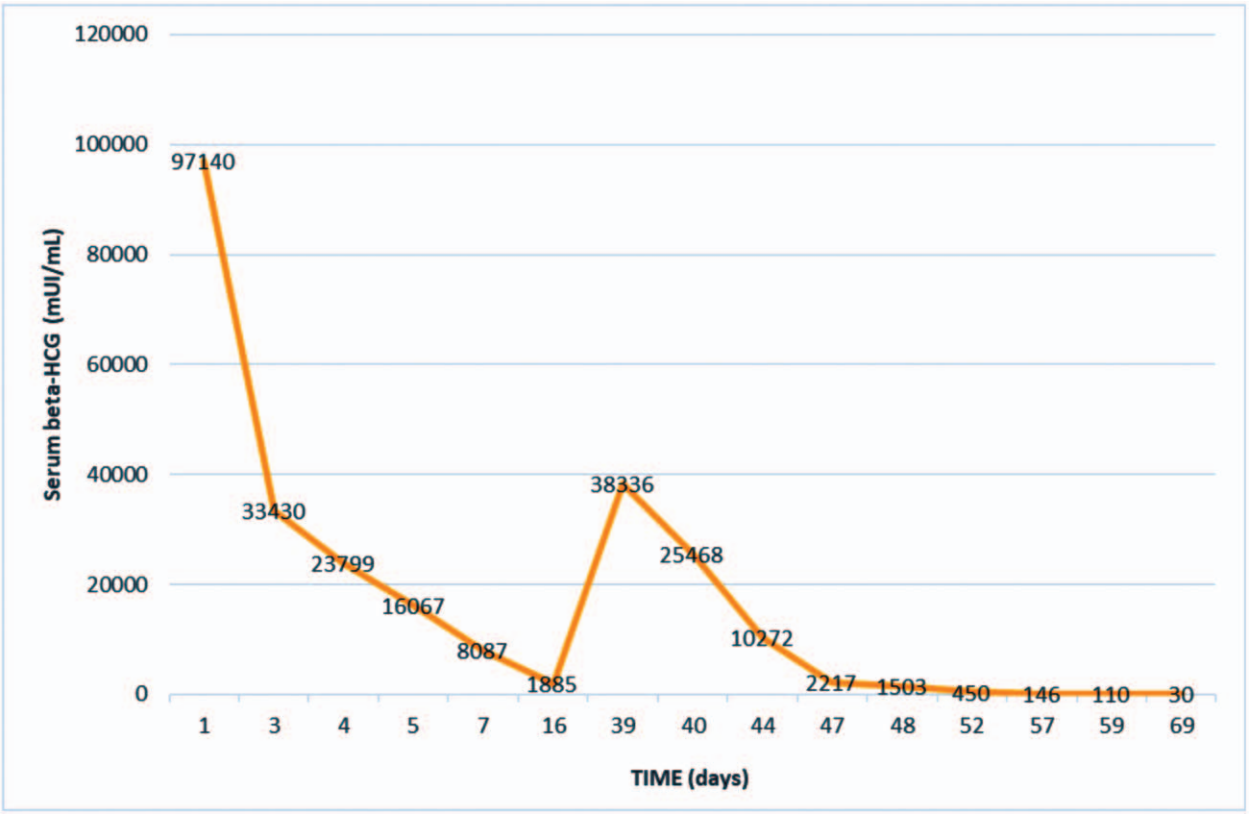

Figure 2. Serum beta-HCG follow-up of the Case 1. This graphic shows the value of beta-HCG levels during the observation period of the case report 1. Firstly, the value plummeted sharply from 97,140 mUI/mL to about a third, precisely 33,430 mUI/mL in just 3 days after the dilatation and curettage. About 2 weeks later, it decreased significantly up to 1885 mUI/mL, but then it started rocketing in 23 days to a value of 38,336 mUI/mL. Subsequently, the patient underwent hysterectomy and the beta-HCG levels began to lessen notably until a final level off that remained negative and stable. beta-HCG = beta-human chorionic gonadotropin.

Macroscopical examination of the uterus showed a brown and crumbly nodule sized about 3.5 cm, which was entrenched in the right side of the uterine fundus, corresponding to the echo-dense nodule previously evidenced by transvaginal ultrasound.

The final histology (Figs. 5 and 6) revealed the presence of a PSTT infiltrating the myometrium and deepening a 1 cm from the serosa of the posterior wall. The proliferation index (Ki67 index) corresponded to a mild value (≈8%). Immunohistochemistry

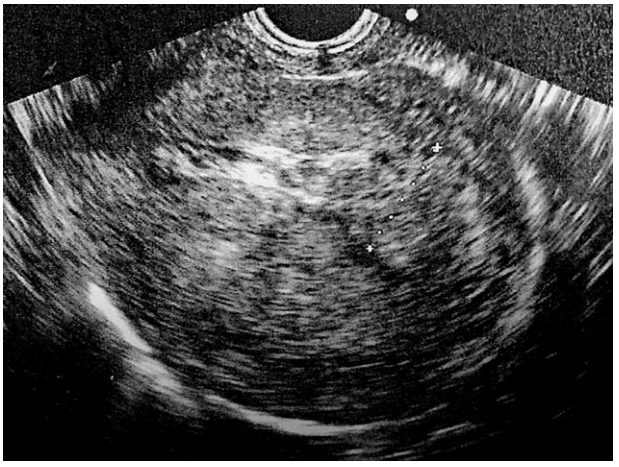

Figure 3. Transvaginal ultrasound examination of the Case 1, after D&C. A persistent deciduous-ovular debris was joined to some irregular hyperechogenic images resembling a 22 mm thick trophoblastic-like tissue that infiltrated deeply the myometrium leaving an apparently free margin of 11 mm on the fundus.

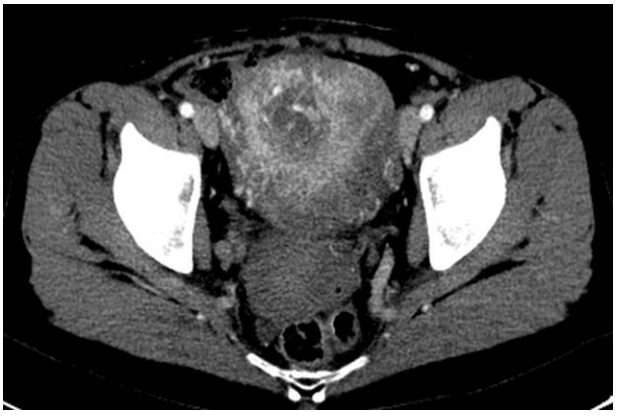

Figure 4. Pre-operative total body contrast medium CT-scan of the Case 1. This figure illustrates a transversal section of the total body contrast medium CT-scan that revealed an enlarged uterus, especially at the fundus, with an inhomogeneous aspect in the venous phase and a thickening of the endometrial walls. In context of the pelvis, few enlarged lymph nodes were identified measuring about 1 cm, but they resembled reactive ones. Moreover, there was a slight quantity of peritoneal fluid in the Douglas pouch. CT-scan = computed tomography scan.

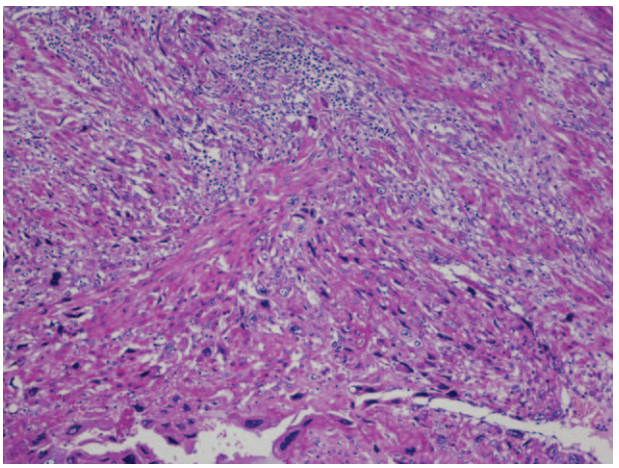

Figure 5. Microscopic examination H-E: 100x of the Case 1. The microscopic examination of uterus showed neoplastic intermediate trophoblastic cells at the implantation site arranged as sheets of polyhedral, round or occasionally spindle-shaped cells that infiltrate the myometrium extensively invading the vessel wall. Sheets of polygonal intermediate trophoblasts were observed in a background of fibrinous material. The trophoblastic cells are mono and multinucleated with abundant eosinophilic cytoplasm and large, convoluted nuclei (H-E: 100x).

showed a diffuse positivity for beta-HCG, but negative results for protein 63 and protein 53.

Postoperatively, the patient had a prolonged febrile complication with an abscess in the right pelvic fossa treated with antibiotics and then by a trans-abdominal CT guided drainage placing.

Soon after hysterectomy, beta-HCG values started to decrease rapidly from 10,272 mUI/mL, on the day before the surgery, to a negative value of 30 mUI/mL after 4 weeks. Furthermore, 3 weeks after surgery the fever went down to normal. The patient is now after a 3 years clinical and laboratory follow-up, with constant negative serum beta-HCG levels.

3. Case report 2

A 43-year-old woman, para 1/0/3/1 (1 caesarean, 2 previously induced abortions, 1 miscarriage), with a previous smoking habit. Four years ago, she underwent a mammographic screening that revealed a suspected nodule for breast cancer. The following echo-guided biopsy showed a low-intermediate grade ductal breast cancer with a 100% positivity for both estrogen and progesterone receptors that required a therapy based on tamoxifen and luteinizing hormone-releasing hormone analogues.

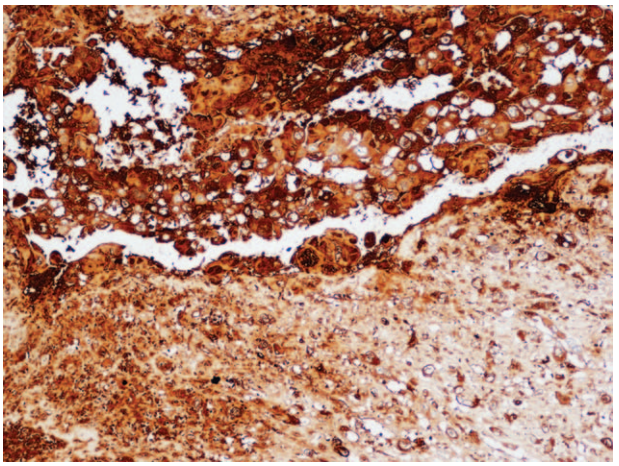

Figure 6. Immunohistochemistry for beta-HCG of the Case 1. These neoplastic intermediate trophoblastic cells were strongly positive for beta-HCG. beta-HCG = beta-human chorionic gonadotropin.

Five years after the last pregnancy, a miscarriage, a routine trans-vaginal ultrasound revealed a suspicious endometrial thickness in the medium third of the uterine cavity, measuring 4.5 mm, negative at the Color-Doppler evaluation, without myometrial invasion. Although, the remnant endometrium appeared regularly thin (Fig. 7A–C).

A subsequent hysteroscopic guided biopsy unveiled the presence of PSTT, positive for Cytokeratin pool (CK pool), but negative for beta-HCG and protein 63. Serum oncological markers (Carbohydrate Antigen 15.3; Carbohydrate Antigen 125; Carbohydrate Antigen 19.9; Carcinoembryonic antigen and beta-HCG) were all negative. Furthermore, the total body contrast medium CT-scan showed a negative result ruling out distance metastasis, pelvic organs enlargements or ascites (Fig. 8).

In order to pursue the patient's request for surgery, after a comprehensive counseling, we performed a total extra-fascial hysterectomy with bilateral salpingo-oophorectomy and an extensive adhesiolysis, because of the presence of many fibrous adhesions. No bulky lymph nodes were detected at the digital examination of the pelvic and lombo-aortic retroperitoneum.

The final histological examination (Fig. 9) confirmed the diagnosis of a minimally invasive PSTT of the uterus, sharing some features with the PSN, whereas the cervix, the fallopian tubes and the ovaries were all negative. Moreover, immunohistochemistry revealed the following results: CK pool positive, Ki67 index $< 5\%$, beta-HCG negative and protein 63 negative.

In the end, there were no post-operative complications and the clinical-laboratoristic follow up (conducted for respectively for 4 years and 15 months) has been negative for both breast cancer and PSTT-PSN until now.

4. Discussion

PSTT is a very rare malignant tumor that belongs to a family of pregnancy-related diseases. Less than 300 cases of PSTT have been reported in literature,[3,4] with an incidence of $\approx$1/50,000–100,000 pregnancies representing only the 0.23% to 3.00% of all GTDs.[1,2,5] It derives from an improper fertilization based on the duplication of paternal chromosomes and the loss of the maternal ones. Therefore, an imbalanced karyotype-control mechanism determines aneuploidies or rearranged diploidies leading to an impaired differentiation of the trophoblast.

Our report describes 2 additional cases of PSTT: the first derived from a persistent grade I hydatidiform mole, whereas the second one originated 5 years after a miscarriage. A Medline Literature Analysis of PSTT revealed that, in order of prominence, PSTT often follows a normal term pregnancy (61% of cases). Therefore, cytogenetic studies demonstrated that PSTTs are mostly diploid instead of aneuploid. However, a molar pregnancy is present in 12% of PSTTs, a miscarriage in 9%, induced abortion in 8%, whereas a percentage of 3% is represented by ectopic pregnancies, stillbirths or preterm deliveries. The remnant percentage (7%) waits to be unveiled.[9] Since the complete variant of HMs (hydatidiform moles) becomes a GTN in 15% to 20% of the cases, it can be considered a pre-malignant lesion. On the contrary, only 0.5% to 2% of the partial

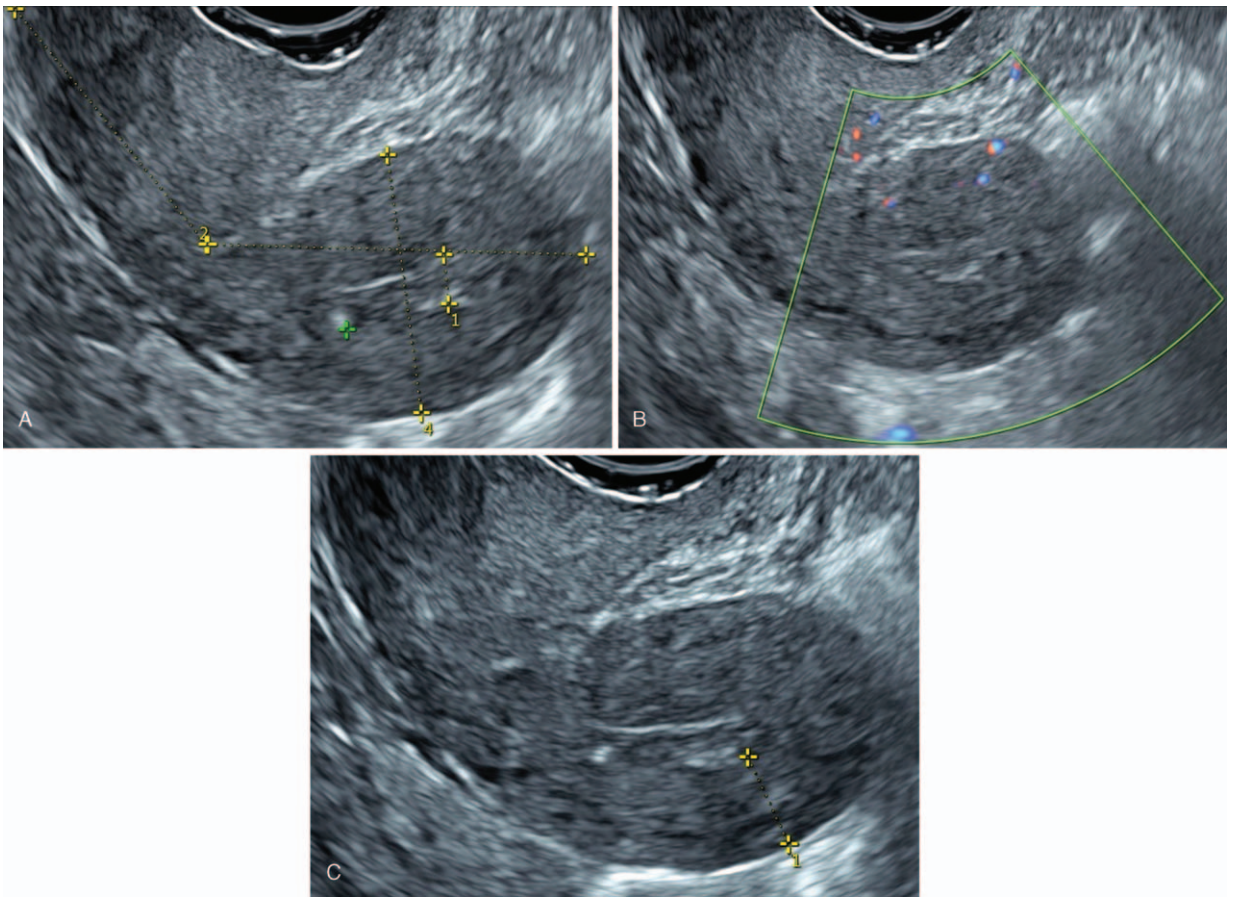

Figure 7. Pre-operative trans-vaginal ultrasound of the Case 2. A trans-vaginal ultrasound revealed a suspicious endometrial thickness, in the medium third of the uterine cavity, measuring 4.5 mm (A), negative at the Color-Doppler evaluation (B), without myometrial invasion with a maximum free myometrium of 8.80 mm. The remnant endometrium appeared regularly thin (C).

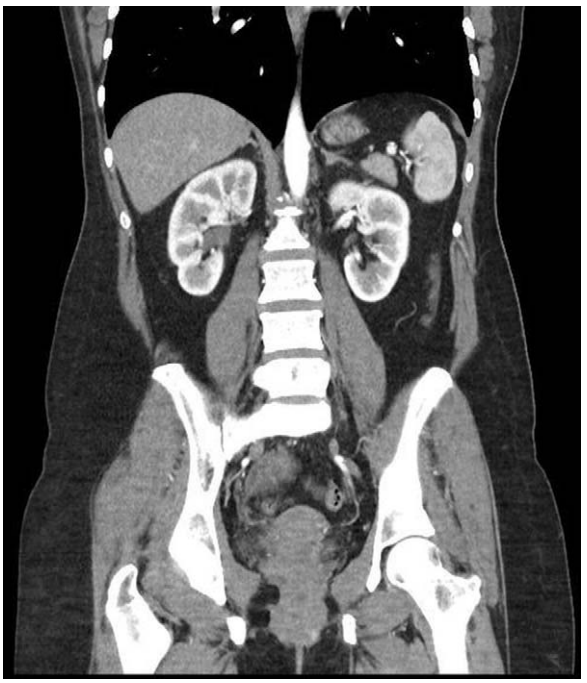

Figure 8. Pre-operative total body contrast medium CT-scan of the Case 2. This picture shows a coronal scan of the total body contrast medium CT-scan with a negative result for the presence of distance metastasis, pelvic organs enlargements or ascites. CT-scan = computed tomography scan.

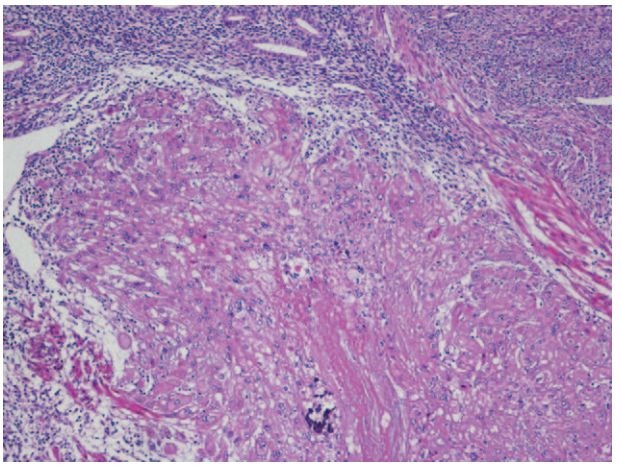

Figure 9. Microscopic examination H-E: 100x of the Case 1. On histological examination, the endometrium was consistent with proliferative phase and showed implantation of nodules composed of intermediate trophoblastic cells embedded in an eosinophilic fibrillary extracellular matrix. No mitosis was identified (H-E: 100x).

moles could evolve into malignant tumors.[9] More than two-thirds of complete HMs have a diploid genome (46, XX) arising from the duplication of the haploid genome of a single sperm fertilizing an ovum, without maternal chromosomes already lost during meiosis. By contrast, partial hydatidiform moles are usually triploid, because of the fertilization of an apparently normal ovum by 2 sperms or occasionally a diploid sperm.[10] The ultrasound examination of our first case (see Fig. 1) showed pathological trophoblastic structures and an intrauterine fluid collection without any yolk sac nor embryo that led to the initial hypothesis of a complete HM. Whereas the second one emerged 5 years after a miscarriage without any imaging or histological signs of vesicular mole.

Recently, some risk factors for GTNs have been recognized as hormonal dysfunctions, such as a late menarche, the usage of oral contraceptives and light menstrual flow.[7] Notably, both the patients under our observation had a smoking habit and the second one was under hormonal therapy for a previously diagnosed breast cancer (tamoxifen and luteinizing hormone-releasing hormone analogues). Furthermore, the first case of PSTT came from a persistent HM with high values of serum beta-HCG, whereas the second one took origin 5 years after a miscarriage with negative serum beta-HCG essay but sharing borderline features between PSTT, malignant, and PSN, benign.

Moreover, the primary tumor site is nearly always located in the fundus or the corpus of the uterus, as respectively seen in our cases. Notwithstanding, 4 cases of cervical location have been described in literature[4,11–15] probably after an ectopic cervical pregnancy or by the transport of cancer cells from a PSTT of the corpus that later underwent a silent regression.

PSTT origins exclusively from the proliferation of the intermediate interstitial trophoblast[16] lacking the syncytiotrophoblast's population.[17] Therefore, it is characterized by peculiar histological elements because of the absence of villi,[16] creating locally infiltrating nests and monomorphic sheets with a modest pleomorphism and a mild mitotic activity. Due to the absence of the syncytiotrophoblast cells, PSTT expresses a lower level of serum beta-HCG than CC so resulting possibly negative during laboratory tests, as in our second case.

From a pathological point of view, the proliferation of the intermediate trophoblastic cells evolves from the implantation site-like trophoblast nodule, which infiltrates the smooth muscle cells of the decidual spiral arterioles,[18] to a lesion characterized by necrosis and hemorrhage.[7] Vaginal bleeding and/or amenorrhea represent the usual presentation, as in our first case. The PSTT's growth covers a time period of weeks or even years, as respectively in our cases. A recent case series reported a median time from antecedent pregnancy to diagnosis of 12 months (range 0–240).[19] Sometimes, PSTT manifests with preeclampsia, beta-HCG triggered hyperthyroidism, unspecific symptoms, such as nausea or hemoptysis, enlargement of the uterus, lutein-cysts of the ovaries.[9] Surprisingly, none of these characteristics emerged from the second case that was diagnosed only after a routine ultrasound exam followed by a hysteroscopic biopsy.

Usually, the value of serum beta-HCG does not reflect properly the tumor load in PSTTs leading to false-negative results.[7,20] This marker could be negative, as in our second case, since the cancer-related beta-subunit of HCG can exist in many different forms and fragments such as nicked free beta, c-terminal peptide, beta-core and hyperglycosylated form. By contrast, immunohistochemistry usually shows Human Placental Lactogen (HPL), an extravillous trophoblast marker on surgical specimens, even though it is rarely detectable in serum.[7,10] Thence, the endometrial tissue evaluation of HPL may become a useful diagnostic instrument in case of initial stage of PSTT after a hysteroscopic biopsy or D&C. In the first case, this could have been useful to distinguish the persistent mole from the area of PSTT transformation, but it was not available. In summary, the immunohistochemical analysis of PSTT usually shows the features described in Table 1.[4,21,22]

Nowadays, the instrumental diagnosis relies mainly on transvaginal ultrasound that tends to highlight some features shared by GTNs, such as echogenic and vascular masses detectable also with echo-color Doppler, involving the endometrium and eventually deepening into the myometrium. Furthermore, GDTs are characterized by a wide range of ultrasound findings, such as a thickened endometrium (ie, our second case), a discrete mass with or without the classical echogenic and vascular enlargement containing clusters of little cysts, as in our first case, characterized by a coexistence between PSTT and a persistent hydatidiform mole. Molar diseases usually differ from PSTT because of the depth of trophoblastic invasion within the myometrium, as we detected in our first case. Recently, a Chinese study has classified the sonographic presentation of PSTT into 3 types, using a transvaginal probe: type I, heterogeneous solid mass in the uterine cavity with a degree of vascularization on color Doppler imaging from minimal to moderate; type II, heterogeneous solid mass deepening in the myometrium and coexisting with a degree of vascularization from minimal to high; type III, cystic lesions within the myometrium with a high degree of vascularization (lacunar-type lesions).[23] According to Zhou Y et al, our first case could be classified as a type II (see Fig. 1), whereas our second case is partly classifiable as type I, because the heterogeneous solid mass in the uterine cavity was completely negative at color Doppler examination (Fig. 7B).

The presence of myometrial invasion can be confirmed using dedicated pelvic T1 and T2 weighted magnetic resonance imaging and it appears, respectively, hypointense and hyperintense with disruption of the junctional zone. Whenever PSTT origins from a molar pregnancy, it could be evidenced as an enhancing multicystic tissue characterized by vascular structures within the enlarged uterus.[24–26]

For staging assessment, total body CT and contrast dye may be substituted by 18-fluorodeoxyglucose positron emission tomography CT-scan, especially for lung metastasis.[27,28] Furthermore, PSTT could be partly scored according to the anatomical staging as in International Federation of Gynecology and Obstetrics (FIGO) 2000 (see Table 2),[7,9] because there is no mention of the

Table 1

Most common immunohistochemical results of placental site trophoblastic tumor[4,21,22].

Immunohistochemical marker	Results
Human placental lactogen	Strongly positive staining
Human chorionic gonadotropin	Generally weak and focal positive staining
Cytokeratin pool	Diffuse positive staining
Epidermal growth factor receptor	Strong positive staining
Vascular endothelial growth factor	Strong positive staining
Human epidermal receptor 2/neu	Negative staining
Cluster of differentiation 117	Negative staining
Pregnancy associated major basic protein; marker of the intermediate trophoblast, useful to distinguish PSTT from epithelioid trophoblastic tumor.	Positive staining.

PSTT = placental site trophoblastic tumor.

Table 2

FIGO anatomical staging of trophoblastic tumors[7] used for placental site trophoblastic tumour and epithelioid trophoblastic tumor[9].

FIGO stage	Description
I	Gestational trophoblastic tumors strictly confined to the uterine corpus.
II	Gestational trophoblastic tumors extending to the adnexa or to the vagina, but limited to the genital structures.
III	Gestational trophoblastic tumors extending to the lungs, with or without genital tract involvement.
IV	All other metastatic sites (liver, kidney, spleen, brain).

FIGO = International Federation of Gynecology and Obstetrics

Table 3

FIGO/WHO 2000 scoring system for gestational trophoblastic neoplasms[7,10].

	Score			
Prognostic factor	***0***	***1***	***2***	***4***
Age (years)	<40	≥ 40	–	–
AP	Mole	Abortion	Term	–
Interval from the end of AP to chemotherapy (months)	<4	4–6	7 –12	>12
HCG (IU/l)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Number of metastases	0	1–4	5 –8	>8
Site of metastases	Lung	Spleen and kidney	Gastro-Intestinal tract	Brain and liver
Largest tumor mass	–	3–5 cm	>5 cm	–
Prior chemotherapy	–	–	Single drug	>2 drugs

The total score results from the addition of the individual scores for each prognostic factor: $0 <$ low risk ≤ 6; high risk ≥ 7.

AP = antecedent pregnancy; FIGO = International Federation of Gynecology and Obstetrics; HCG = human chorionic gonadotropin; WHO = World Health Organisation.

tumor's lymphatic spread. According to us, the FIGO 2000 score should consider other unclassified stages with/without a pelvic and/or abdominal lymph nodes involvement. Moreover, PSTT should not be classified using the scoring system for GTN as in FIGO 2000 based on prognostic factors, (see Table 3), but it still requires its own staging. Some authors declare that a common prognostic scoring system, as well as the other GTNs (see Table 3), could be useful to manage and compare data between different hospitals,[16,29] even though it has been mostly realized for malignant gestational tumors deriving from villi, namely invasive molar disease and CC.

In our decision-making process, we set a based on literature flowchart (see Fig. 10) to rule out the presence of poor prognosis factors that can be outlined by the following conditions[4,21,22,30–34]: a long-time interval since the last pregnancy, in particular $\geq$ 48 months[21,30] or even $\geq$24 months[31] ($P=.014$); age over 35 years ($P=.025$); a high mitotic index, described as more than 6 mitosis in median mitotic count per 10 high-power fields, ($P=.005$); the presence of cells with clear cytoplasm ($P<.0005$); a vascular invasion; a deep myometrium invasion ($P=.006$); an invasion of the serous membrane; extensive coagulative necrosis ($P=.024$); persistence of high post-operative beta-HCG levels and, more generally, a maximum HCG level >1000 mIU/mL ($P=.034$); FIGO stage III or IV ($P<.0005$).[4,21,22,30–34]

However, we tried also to use the prognostic FIGO/World Health Organization (FIGO/WHO) score (Table 3) with a final score of 1 for the first case and 3 for the second one, determining a low-risk value (<6) in both. In details, the first case had just 1 poor prognosis factor, because the patient was 37 years old (so, more than 35). Despite this, there were many other good

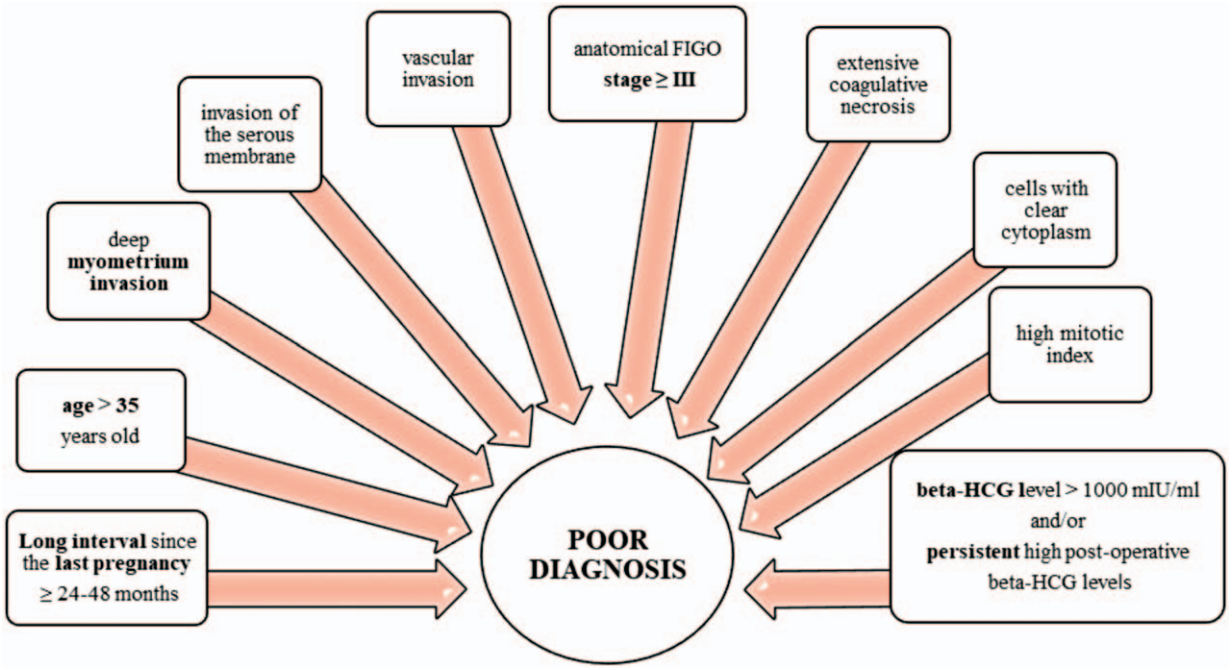

Figure 10. Poor prognostic factors for placental site trophoblastic tumors. The present flowchart shows a list of poor prognosis factors as described in literature[4,21,22,30–34]: a long-time interval since the last pregnancy, in particular ≥48 months or even ≥24 months; age over 35 years; a high mitotic index, described as more than 6 mitosis in median mitotic count per 10 high-power fields; the presence of cells with clear cytoplasm; a vascular invasion; a deep myometrium invasion; an invasion of the serous membrane; extensive coagulative necrosis; persistence of high post-operative beta-HCG levels and, more generally, a maximum HCG level > 1000 mIU/mL; FIGO stage III or IV. FIGO = International Federation of Gynecology and Obstetrics; beta-HCG = beta-human chorionic gonadotropin.

prognosis factors, such as myometrium deepening for less than 50%, the presence of a mild proliferation index, previous and concomitant molar ongoing pregnancy. Moreover, the value of beta-HCG dropped significantly after the surgery until reaching negative essays in about a month and remaining stable during the further follow-up. Our second case was managed considering the prevalence of good prognosis factors, the previous diagnosis of breast cancer and the older age (43 years old), by performing a hysterectomy with bilateral adnexectomy. Moreover, its proliferation index was very low, and the myometrial invasion was unclear, quite undetectable, with a diagnosis of minimally invasive PSTT as it shared many features with PSN at the final histology. Therefore, we decided not to consider the long interval since the last pregnancy, even though it is a pillar criterion for the prognosis of a pure PSTT. PSN may be detected several months or years after the pregnancy itself representing a sort of intermediate trophoblast remnants with a benign behavior. The PSN does not require any treatment once removed because it cannot develop a recurrence.[35]

Concerning the treatment of PSTT, the mainstay is a primary hysterectomy with the sampling of suspicious pelvic-abdominal lymph nodes or lymphadenectomy[16] and ovarian conservation, unless there is a family history of ovarian cancer or the patient is post-menopausal.[7,17,22,30] Most of the authors recommend a lymph node sampling because PSTT has a significant tendency to metastasize through lymphatic vessels.[4,7] Precisely, in the 5.9% of PSTTs there are lymphatic metastases at the time of the diagnosis or the recurrence.[4] In our cases, we did not perform lymphadenectomy or lymph node sampling because the pre-operative ultrasound assessment of the myometrium invasion was less than 50% in the first case and barely undetectable in the second one. According to some authors, these additional surgical procedures could prominently fit for stage I PSTT in presence of risk factors such as a myometrium invasion $>50\%$, as well as in all cases of stage II.[3] It is still unknown whether a complete abdominal and pelvic lymphadenectomy could influence the overall survival.

Patients with risk factors, such as a high mitotic rate or metastatic disease, will need a multi-agent adjuvant chemotherapy, either EP/EMA (etoposide and platinum alternating with etoposide, methotrexate/folinic acid rescue, actinomycin-D) or TE/TP (paclitaxel, cisplatin/ paclitaxel, etoposide).[7,20,21]

In both our cases, we avoided lymph node surgery and the adjuvant chemotherapy because the good prognostic factors outweighed the poor ones as recommended by the newest (2013) guidelines of the European Society for Medical Oncology.[3,7] Therefore, they started a follow up with periodic serum oncological markers, comprising beta-HCG test, imaging studies and clinical evaluation.

In clinical stage I without poor prognostic factors, in case of strong hope for future childbearing, the patient might undergo a fertility-sparing surgery, even with a minimally invasive approach, such as: uterine evacuation using US-guided procedures to avoid uterine perforation,[7] hysteroscopy resection and combined hysteroscopic/laparoscopic resection.[36] Another way to perform a local uterine resection is a laparotomy with the modified Strassman approach, characterized by a success percentage of 20%, although this choice of treatment requires further evaluations.[36,37] However, this fertility-sparing and minimally invasive treatment should be considered only experimental, carrying the possibility to miss microscopic multifocal uterine disease or disseminating disease, compromising the overall survival in the end.[21] Undoubtedly, the patient must be aware of the possible risk of recurrence, missed micrometastasis, tumor seeding, partial resection and of the eventual salvage hysterectomy for inadequate or involved resection margins. This could be possibly avoided with the assessment of intra-operative frozen sections or for beta-HCG post-operative increase associated with a myometrium infiltration.[4,37]

Generally, the PSTT has a good prognosis when diagnosed at the first stage (Table 3; Fig. 10), which is mainly treated with surgery. However, extra-uterine disease leads to a poor outcome[21] also because the PSTT is less responsive than other GTNs to the conventional chemotherapy based on methotrexate or actinomycin-D, for instance, EMA/CO.[7] Unfortunately, PSTT is characterized by a 61% resistance or incomplete response to chemotherapy agents.[21] Nevertheless, Swisher and Drescher[38] reported a complete response to EMA/CO in a patient with lung and vagina metastasis and in 2 of their 7 cases of PSTT. High-risk patients will need adjuvant chemotherapy, a multi-agent platinum-based regimen lasting for 8 weeks of normal HCG levels,[7] such as the most common EMA/EP[10,21,22] or the combination TE/TP.[7,10,22] Notwithstanding the high rate of cure, a substantial number of patients have recurrent disease and the main discriminator for survival and recurrence is a time-period of 48 months since the antecedent pregnancy.[21] In case of recurrence, the following outcome for patients with PSTT is worse than other forms of GTD because the former can gain a long-term remission in only a third of cases (precisely 33%), whereas the latter points up to 75% to 90% with second-line treatment.[21]

5. Conclusion

PSTT is a rare and peculiar type of tumor that can result demanding for its identification because it could be misdiagnosed as other forms of GTDs. Although the uniqueness of our work resides in the extreme rarity of the PSTT itself, this might represent at the same time a limitation because our evaluations may not easily be generalized. Our first case had a difficult diagnosis because the tumor was synchronous to a hydatidiform mole and the first D&C missed the presence of PSTT. The subsequent clinical evolution led the medical team and the patient to decide for major surgery. Notably, PSTT can also be thought of during a routine examination in case of suspicious endometrial area evaluated firstly with ultrasound and then with a hysteroscopically-guided biopsy in patient with a history of deliveries or miscarriages.

Form a clinical point of view, we should always perform a complete physical examination and collect the clinical history (age, reproductive history, amenorrhea, enlarged uterus more than gestational age, vaginal bleeding, metastasis signs). These data are extremely helpful to guide the diagnosis process and to define the prognosis. Even with some limitations, testing the value of serum beta-HCG could be helpful as a follow-up marker, as in our first case.

Among the imaging techniques, intravaginal Doppler ultrasound examination plays a key role to localize and hypothesize the malignant nature of the lesion with the help of Zhou Y et al[23] classification. If performed by an expert, it can predict also the stage of the disease evaluating the local invasion. To complete the assessment of the staging and the prognostic risk, we suggest also a CT-scan.

Whether the good prognostic factors overweight the poor ones and the childbearing desire has already been accomplished, as in our cases, the main treatment remains extra facial total

hysterectomy. In analogue cases as ours, but with a strong desire for pregnancy, a conservative surgical approach may be used. Once the reproductive purpose is achieved, the patient needs to undergo a strict clinical follow-up and a further surgical re-evaluation.

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