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# Placental-site Trophoblastic Tumor 11 Years After Complete Molar Pregnancy

## ( A Case Report )

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**Abstract**:

Here is a reporting case of a placental site trophoblastic tumor (PSTT) in a 35-year-old Saudi woman 11 years after molar pregnancy. She had three normal pregnancies after this molar pregnancy. Four years after the last normal vaginal delivery, the patient presented with nausea, and the pregnancy test was positive. Initially, she received a single course of methotrexate (in another hospital) for the unexplained low level of beta hCG without evidence of clinical pregnancy by her local hospital. The woman did not receive further treatment until finding a 1 cm mass in the pelvic MRI seven months later. The final diagnosis was confirmed by histological examinations in conjunction with immunohistochemical studies. Since the patient had potential risk factors, she was successfully treated with a hysterectomy. The latest follow-up (10 years after diagnosis) was uneventful, and the patient exhibited no signs of recurrence nor metastasis.

**Keywords:**

Gestational trophoblastic disease (GTD), Placental site trophoblastic tumor (PSTT), Gestational trophoblastic neoplasia (GTN), Beta-human Chorionic Gonadotropin (β-hCG).

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# ورم الأرومة الغاذية المشيمية بعد 11 عامًا من الحمل العنقودي الكامل

## تقرير حالة

**الملخص:**

فيما يلي يتم عرض حالة لورم الأرومة الغاذية المشيمية (PSTT) في امرأة سعودية تبلغ من العمر 35 عامًا، بعد 11 عامًا من الحمل العنقودي. كان لديها ثلاث حالات حمل طبيعية بعد هذا الحمل العنقودي. وبعد أربع سنوات من آخر ولادة طبيعية، عانت المريضة من الغثيان وأعراض الحمل، وكان اختبار الحمل إيجابيًا. في البداية تلقت جرعة واحدة من دواء الميثوتريكسيت (في مستشفى آخر) على افتراض انه حمل عنقودي آخر ولكن مستوى هرمون (beta hCG) لم يتغير ودون دليل على الحمل السريري. لم تتلق المرأة مزيدًا من العلاج حتى تم تحويلها الي مركزنا المتخصص في الاورام النسائية وبعد عمل الفحوصات والتحاليل تم العثور على كتلة 1 سم في التصوير بالرنين المغناطيسي للحوض داخل الرحم. تم تأكيد التشخيص النهائي من خلال الفحوصات النسيجية وعمل منظار الرحم وأخذ خزعة من الكتلة وتأكيد التشخيص. وتم علاجها بنجاح من خلال استئصال الرحم وإبقاء المبيضين. لم تحتاج المريضة أي علاج كيماوي وكانت المتابعة الدورية مطمئنة. كانت المتابعة الأخيرة (بعد 10 سنوات من التشخيص) سليمة، ولم تظهر على المريضة أي علامات رجوع للورم أو الانتشار.

**الكلمات المفتاحية:** مرض ورم الأرومة الغاذية الحملي (GTD) ، ورم ورم الأرومة الغاذية المشيمي (PSTT) ، ورم ورم الأرومة الغاذية الحملي (GTN) ، و Beta-human chorionic Gonadotropin (G-hCG).

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## Introduction:

The placental site trophoblastic tumor (PSTT) is a rare form of gestational trophoblastic disease(Baergen *et al.*, 2006). In 1976, PSTT was firstly defined by Kurman as syncytial endometritis and designated a trophoblastic pseudotumor(Kurman, Scully and Norris, 1976). In 1981, when Twiggs reported a patient that died from PSTT, the malignant characteristics of the condition gathered attention(Twiggs *et al.*, 1981). At the same time, Scully reappraised the morphological aspects and malignant potential of the condition, designating it PSTT(Zeng *et al.*, 2015). The World Health Organization (WHO), in 1983, formally acknowledged this lesion's neoplastic nature and adopted the terminology PSTT. PSTT has since become the third most common gestational trophoblastic neoplasm (GTN), second to Choriocarcinoma (CC) and invasive moles (IMs). The incidence of PSTT is approximately 1 in 100,000 of all pregnancies and around 1–2% of all GTNs, while it has a 25% mortality rate(Piura and Shaco-Levy, 2007). To date, almost 300 cases of PSTT have been reported around the world(Luiza *et al.*, 2013). PSTTs can develop long after previous gestational events. It is a slowly growing tumor and, in some cases, recurrent or metastatic PSTT can occur in patients long after the initial treatment(Feng *et al.*, 2019). Its uncharacteristic clinical presentation, low mitotic activity, and non-specific auxiliary examinations pose substantial challenges to clinicians. These challenges lead to a low preoperative diagnosis rate. The term gestational trophoblastic disease encompasses interrelated but distinct tumors that include Choriocarcinoma, complete/incomplete mole, and placental-site trophoblastic tumor (PSTT)(Baergen *et al.*, 2006).

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**The Case:**

A 35-years-old female, G4 P3+1, who is otherwise healthy, presented to the General Gynecology clinic in a local hospital in July 2008 with a complaint of nausea and a recent urine pregnancy test positive. She had a history of molar pregnancy 11 years before this presentation. It was a complete mole treated by suction curettage followed by normal post-operative recovery and follow up; the Beta-human Chorionic Gonadotropin (β-hCG) followed for one year after normalization. Subsequently, there were three pregnancies; ended by normal full-term vaginal delivery. The last delivery was four years before the current presentation.

On the first visit (at the referring hospital), a serum β-hCG and Transvaginal ultrasound were requested, quantitative β-hCG was 147 IU/L, and the ultrasound was unremarkable with no evidence of intrauterine gestation sac. Ectopic pregnancy was excluded. Repeated β-hCG was 250 IU/L (2 weeks after presentation). Pelvic Magnetic Resonance Imaging (MRI) and full body CT (chest, abdomen, pelvic, and Brain) were done as a metastatic workup. All the imaging was normal. Empirical single-agent chemotherapy with intramuscular methotrexate treatment started (1 mg/kg IM on days 1, 3, 5, and 7) alternating with Folinic acid (0.1 mg/kg, given once, 24 hours after each dose) for one week. Initially, the Serum hCG level declined to 80IU/L, then the level plateau at around 155 IU/L again.

In December 2008, the patient was referred to the Gynecologic Oncology service - King Faisal Specialist Hospital and Research Center – Jeddah, where she was asymptomatic. Her serum β-hCG level was 114 IU/L (normal level ≤2 IU/L). The differential diagnosis of Phantom Human Chorionic gonadotrophin vs. Quiescent GTD vs. Gestational Trophoblastic Disease was considered. The exclusion of Phantom hCG after the repeat of hCG in an outside laboratory with a different assay and persistence of positive urine pregnancy test was assured. In February 2009 repeat (metastatic workup) of the pelvic, abdomen, and chest was done. Pelvic MRI showed a uterine filling defect estimated as 1 cm intrauterine mass; other imaging was normal.

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Hysteroscopic resection of the lesion was planned with preoperative differential diagnosis of a benign endometrial lesion vs. PSTT. Hysteroscopy showed about 1 cm fundal polypoid hyperemic brownish mass with ulceration; partial resection of the lesion was done uneventfully.

Histopathological examination showed Trophoblastic proliferation composed of nests of cells with cytological atypia in the form of enlarged nuclei, pleomorphism, and mitotic figures. Focal areas of necrosis were seen. Scattered multinucleated cells were identified. There were infiltrations of the proliferating atypical cells between smooth muscle fibers. On immune-staining, the atypical cells showed positive staining for pan keratin and focally for hCG. More than 15% of the cells were positive for Ki-67. The features were strongly suggestive of a Placental-Site Trophoblastic Tumor (PSTT).

Ten days later, a total abdominal hysterectomy (TAH) with preservation of the ovaries was performed. Intra-operative exploration and peritoneal wash were negative for any abnormal findings.

The final pathology showed; uterus weighing 118 gms. A lesion (polypoidal fleshy) was located mainly on the fundus toward the anterior wall measuring 1.8 X 1.4 cm. The tumor depth is 1 cm. Microscopic findings were tumor necrosis with a slight increase in mitotic activity and areas with epithelioid morphology and multifocality with a similar histologic and immuno-staining feature consistent with the placental-site trophoblastic tumor. The tumor is circumscribed to the inner half of the myometrium with a small focus on the endocervical mucosa.

The patient had an uneventful recovery. Her follow-up β-hCG was normal by day 11 postoperatively (was ≤2 IU/L). The tumor board discussed the case in the tumor board, and the plan was for conservative management, and no adjuvant treatment is indicated. She remained disease-free with normal β-hCG up to date (more than ten years).

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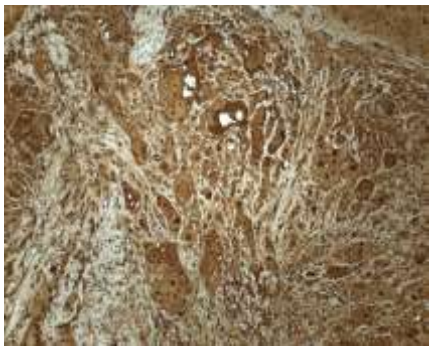
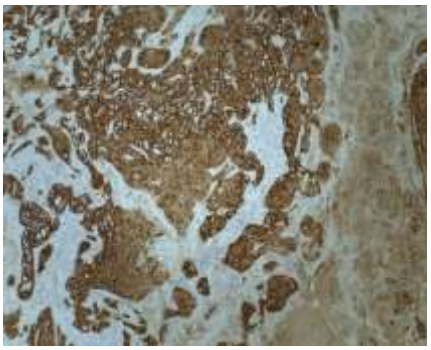
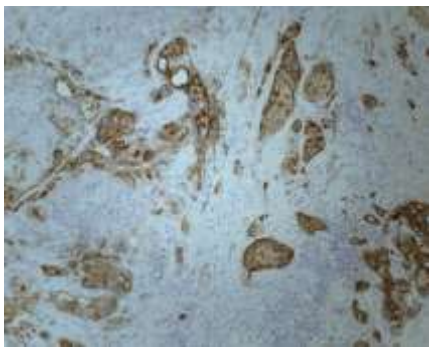
The following pictures presenting the histopathology for the patient:



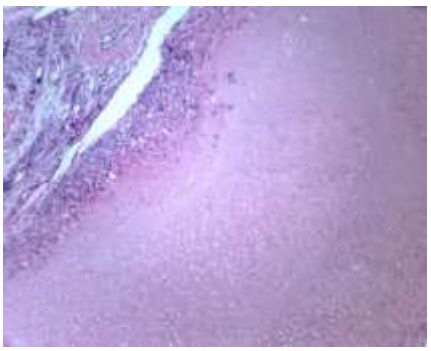
B-hCG



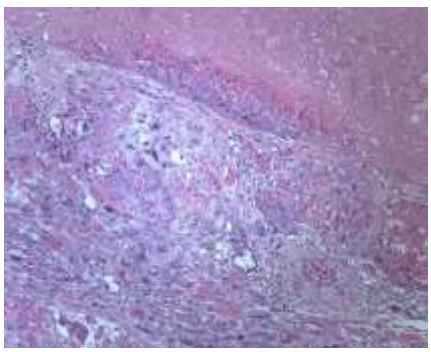
Keratin Stain



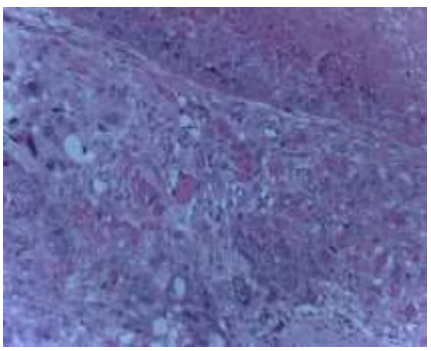
PLAB Immunohistochemical Stain



Extensive Necrosis



Tumor Nests with Necrosis



Higher Magnification

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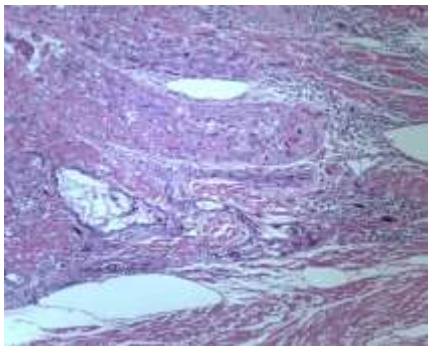
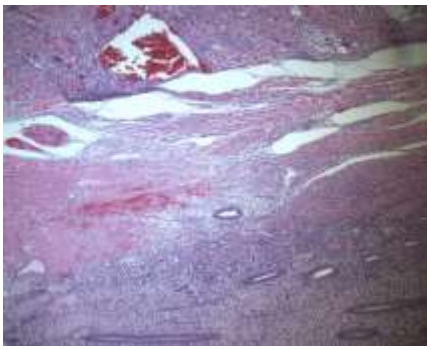


Tumor Nests



Tumor with Endometrium

**Discussion:**

The detection of persistent low-level human chorionic gonadotropin (β-hCG) with or without a preceding pregnancy gives a rare but clinically important challenge. Special care is needed to understand the persistent low levels of hCG in patients with no history of the recent trophoblastic disease(Kohorn, 2002). In this case, the patient arrived with persistent low-level β-hCG with a history of molar pregnancy 11 years before presentation, followed by three full-term normal pregnancies (the latest was four years before the presentation). Recent studies have established that, in some cases, the pregnancy-associated with the development of the gestational trophoblastic disease is not always time-related(Feng *et al.*, 2019).

There were at least 3-5 months of persistent low-level human chorionic gonadotropin (hCG) titers in the absence of gestational trophoblastic disease or clinical evidence of pregnancy. Initially, CT and magnetic resonance imaging (MRI) did not identify the tumor. The patient Received single-agent empirical chemotherapy (in another facility), which is not the standard of care. Despite the treatment, low hCG titers persisted, and the presumptive diagnosis of gestational trophoblastic disease was made at that time with no clear radiological or histological diagnosis. However, histological diagnosis is a must to determine which sub-type of GTD.

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Because no discernable tumor was identified, there was a suggestion; that the persistent low levels of hCG were arising within slow-growing noninvasive trophoblast cells, such as fully differentiated syncytiotrophoblastic cells. That was based on the hypothesis that fully differentiated syncytiotrophoblastic cells are the source of the persistent hCG, based on their limited response to chemotherapy, the production of regular intact hCG, and the absence of clinically recognizable tumor (unavailability of the ITA test).

After four months of follow up/investigations; the repeat of metastatic workup followed by hysteroscopic resection confirmed the diagnosis of placental site trophoblastic tumor. It was a localized tumor and confined to the uterus with no detectable local spread (extra-uterine) in the pelvis or any other sites. According to the International Federation of Gynecology and Obstetrics (FIGO) stage at diagnosis was stage I as the anatomic distribution of disease. The Modified WHO prognostic scoring system in GTN (as adapted by FIGO) total score < 6 = low risk as to the Prognostic Scoring Index. Surgery is recommended as a first-line option. All patients with PSTT should undergo initial hysterectomy with or without oophorectomy (as indicated). Chemotherapy, usually EMA/EP (etoposide methotrexate and actinomycin-D/ etoposide and cisplatin), should be used in patients with advanced PSTT and may be considered in patients with FIGO stage I disease with length of time from antecedent pregnancy>2 years or high mitotic(Hoekstra, Keh and Lurain, 2004). Post-hysterectomy, her hCG concentration normalized to undetectable levels (<2 IU/L) without any further intervention and has remained normal for the past months up to preparing this report (more than ten years).

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The gestational trophoblastic disease comprises a spectrum of disorders from premalignant hydatidiform moles through to malignant invasive moles, choriocarcinoma, and placental-site trophoblastic tumor. Placental site trophoblastic tumors (PSTT) are rare sub-type, slowly-growing malignant tumors derived from intermediate cytotrophoblast cells present in the placenta (unlike choriocarcinoma, which arises from villous trophoblast). These diseases affect women of child-bearing age(Kurman and Shih, 2014). They estimate <0.2 percent of all cases of GTD(Froeling *et al.*, 2019). PSTT generally present months to years after a term gestation. In this patient, the diagnosis was about four years after term gestation. The placental-site trophoblastic tumor usually metastasizes more slowly and frequently is a curative disease if diagnosed and treated in an early stage. It tends to be more chemo-resistant. Thus, hysterectomy is recommended, especially when the condition is confined to the uterus, therefore, to be curative(Bouquet de la Jolinière *et al.*, 2014).

## Conclusion:

The finding of an unexplainable low-level hCG in a patient without evidence of a uterine lesion or trophoblastic metastases provides a diagnostic and therapeutic challenge. The administration of chemotherapy has no or minimal impact on the level of hCG as well as the disease control. The presence of persistent low-level hCG titers defines a subset of women with the pre-invasive or quiescent gestational trophoblastic disease. PSTT is a rare subtype of gestational trophoblastic disease. Tissue diagnosis is a must, and hysterectomy carries the best chance of cure in a well-selected patient.

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