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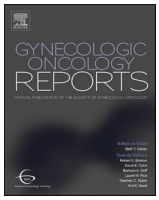

Case report

A case of placental site trophoblastic tumor managed in a low resource setting

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ABSTRACT

Placental trophoblastic site tumor (PSTT) is a rare type of gestational trophoblastic neoplasia (GTN). PSTT has a higher mortality than other types of gestational trophoblastic disease (GTD), with a rate of 16.1%, due to its relatively unpredictable behavior and reduced response to chemotherapy. Its diagnostic and management are very challenging in Low resources settings particularity in Haiti where MRI, PET Scan and IHC are not available. Further, the follow-up is very difficult because of social, political, and economic issues limiting the capacity of our patients to be present at all scheduled visits. No case of PSTT has been publicly described yet the Haitian experience in the literature in the management of such case compared to the developed world. We present a case of PSTT successfully diagnosed and managed at Mirebalais University Hospital (MUH) in Haiti with the support of telepathology and intentional partners while highlighting the difference that we observed compare to the developed world.

1. Introduction

Placental site trophoblastic tumor (PSTT) is a rare gestational trophoblastic neoplasia first described in 1976 (Kurman et al., 1976). It is believed to arise from the trophoblast located at the placental site and can occur after term, abortion or molar pregnancy. Its incidence is approximately 1/100,000 live births and it accounts for approximately 0.2 % of gestational trophoblastic disease (GTD), with differences in incidence worldwide (Kohorn, 2014; Feng et al., 2019). Though PSTT does not always behave aggressively, it has a higher mortality than other types of GTD, with a rate of 16.1 %, due to its relatively unpredictable behavior and reduced response to chemotherapy (Kohorn, 2014; Feng et al., 2019). Genetically, PSTT has a female genotypical predominance, as compared to complete mole which has a male genotypical predominance (Gadducci et al., 2019).

PSTT most often occurs in women of childbearing age with a previous pregnancy interval ranging from months to years, with most occurring within 1 year (Feng et al., 2019). Tumors are often confined to the uterus, and symptoms include abnormal vaginal bleeding or amenorrhea. The serum hCG level is frequently elevated (Lurain, 2011). Metastatic disease is rare and occurs mainly to the lung and central nervous system (Horowitz et al., 2017). Predisposing factors for malignant behavior of molar pregnancy include older age, advanced stage of disease, previous term pregnancy, long period after previous pregnancy, high blood concentration of hCG, high mitotic activity, tumor necrosis, and clear cytoplasm (Vardar and Altintas, 1995; Baergen et al., 2006). On ultrasound PSTT often appears as solid, cystic or mixed with solid capsules without an obvious boundary between the lesion and surrounding tissue (Feng et al., 2019). It can be classified on the basis of transvaginal ultrasound into Type I (protruding into the uterine cavity), Type II (in the uterine cavity and part of the myometrium) or Type III (whole lesion in the myometrium).

In low resources environments, the management of PSTT is very challenging. This is particularly true in Haiti where immunohistochemistry is often unavailable to confirm diagnostics and imaging such as PET scan and MRI are absent nationally. Further, follow-up is very difficult because of social, political, and economic issues limiting the capacity of patients to be present at all scheduled visits. No case of PSTT

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in such a setting has been described in the literature, making the management of such cases in low-resource environments particularly difficult. We present a case of PSTT managed in the very low-resource environment of Mirebalais, Haiti, and describe the issues associated with management of PSTT in our environment.

2. Case description

A 23-year-old woman, G3P0A3EV0 presented to the Mirebalais University hospital (MUH) in May of 2021 complaining of amenorrhea, increased abdominal girth, and ascites. She reported that her symptoms had begun about 6 months ago, with amenorrhea beginning about two months after her last abortion, followed by progressive distension of the abdomen. She was treated by a traditional healer for one month without resolution of symptoms. She then went to a hospital in Port-Au-Prince which referred her to MUH.

2.1. Medical history

She had no significant medical problems. Her menarche was at age 12 and menses were regular. She previously had three spontaneous abortions. She had no significant family history.

2.1.1. Physical exam

Her vital signs were: BP: 154/94; respirations 20/min, T: 36.5, O2 sat: 98 %. On physical exam, she was malnourished, with no palpable lymphadenopathy. Auscultation revealed absent breath signs on the left thorax. Hearth examination was unremarkable. Abdominal exam revealed ascites with positive wave sign without pain at palpation. Lower extremity edema was observed. On pelvic exam, the vulva, vagina and cervix appeared normal, and her cervix was closed and normal to palpation.

2.1.2. Laboratory exams

Her hemoglobin was 11.3 g, and all other labs were within normal limits. Her plasma hCG was 556.74 Mu/ml.

2.1.3. Imaging

Chest x-ray revealed (Fig.1) a left pleural effusion managed by thoracentesis prior to surgery to temporarily relieve symptoms.. Transabdominal ultrasound (Fig.2) revealed a hyperechogenic uterine mass associated with fluid inside the abdominal cavity. Transvaginal ultrasound was unavailable.

2.1.4. Diagnosis and treatment

In the absence of availability of further diagnostic testing in our low-resource environment, we proceeded, after consultation with our international academic collaborators, with a plan for total abdominal hysterectomy with preservation of the ovaries. The patient was provided counseling and psychological support by a multidisciplinary team of social workers, psychologists and physicians attentive to the issues at stake for this 23-year-old nulliparous patient who desired future fertility. Ultimately the patient opted for surgical treatment. We performed a median laparotomy and drained 8 L of ascites fluid —which may have further drained the pleural effusion, followed by an exploration of the abdominal cavity which showed tumor extending through the uterine serosa to involve the right ovary. We performed a total abdominal hysterectomy, right salpingo-oophorectomy and left salpingectomy (Fig.3). At the end of the procedure, the abdominal cavity was macroscopically without tumor. On the basis of these findings, the patient was believed to have an advanced stage (FIGO stage 3) gestational trophoblastic neoplasm. The clinical differential diagnosis included PSTT and Epithelioid Trophoblastic Tumor (ETT).

Pathologic evaluation of the tumor was performed at MUH, where the tumor was grossly sectioned, and slides were scanned and sent in partnership with Brigham Women's Hospital (BWH) via a telepathology

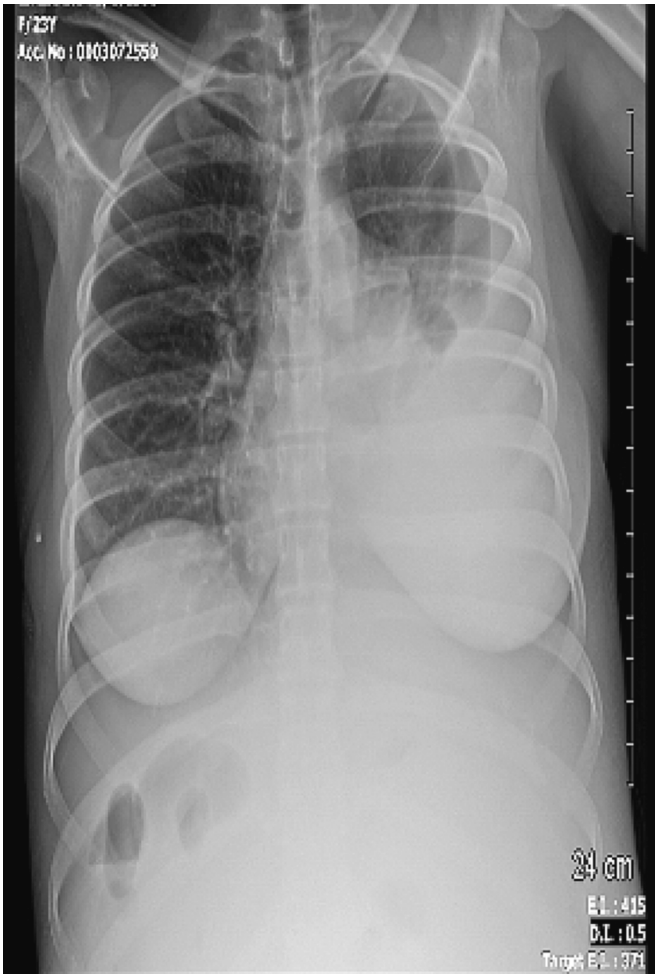

Fig. 1. Chest x ray: Left pleural effusion.

system supported by the American Society for Clinical Pathology (ASCP).The uterus measured 10 x 9 x 6 cm and contained a friable mass entirely occupying the endometrial cavity and invading up to the middle third of the myometrium. Microscopic examination revealed an expansile proliferation of highly atypical epithelioid cells associated with extensive hemorrhage and necrosis (Fig. 4). Cells were arranged in sheets y variably sized clusters.

Immunohistochemistry (IHC) performed at BWH revealed strong and diffuse positivity for AE1/AE3, GATA3 and CD146 in tumor cells. The following markers were negative: P63, PAX8, HMB 45, and desmin. The Ki-67 proliferation in AE1/AE3 and CD146-positive cells was abnormal (>10 %). With these morphologic and immunohistochemical findings, a final diagnosis of PSTT was made.

2.1.5. Follow-up

Forty-eight hours after surgery, the hCG was 1.36 mIU/ml; upon follow-up it was and 25mIU/ml.

Six months after surgery, the hcG was negative, the patient was asymptomatic, and chest x-ray was without particularity.

The patient missed her one-year follow up visit due to local insecurity and lack of transportation. At her 2-year follow up visit, she reported feeling well and her clinical exam revealed no evidence of recurrence; the serum hCG was negative. The patient was offered surveillance with CT scan, but she could not afford it.

3. Discussion

Placental trophoblastic site tumor is a rare entity that is difficult to

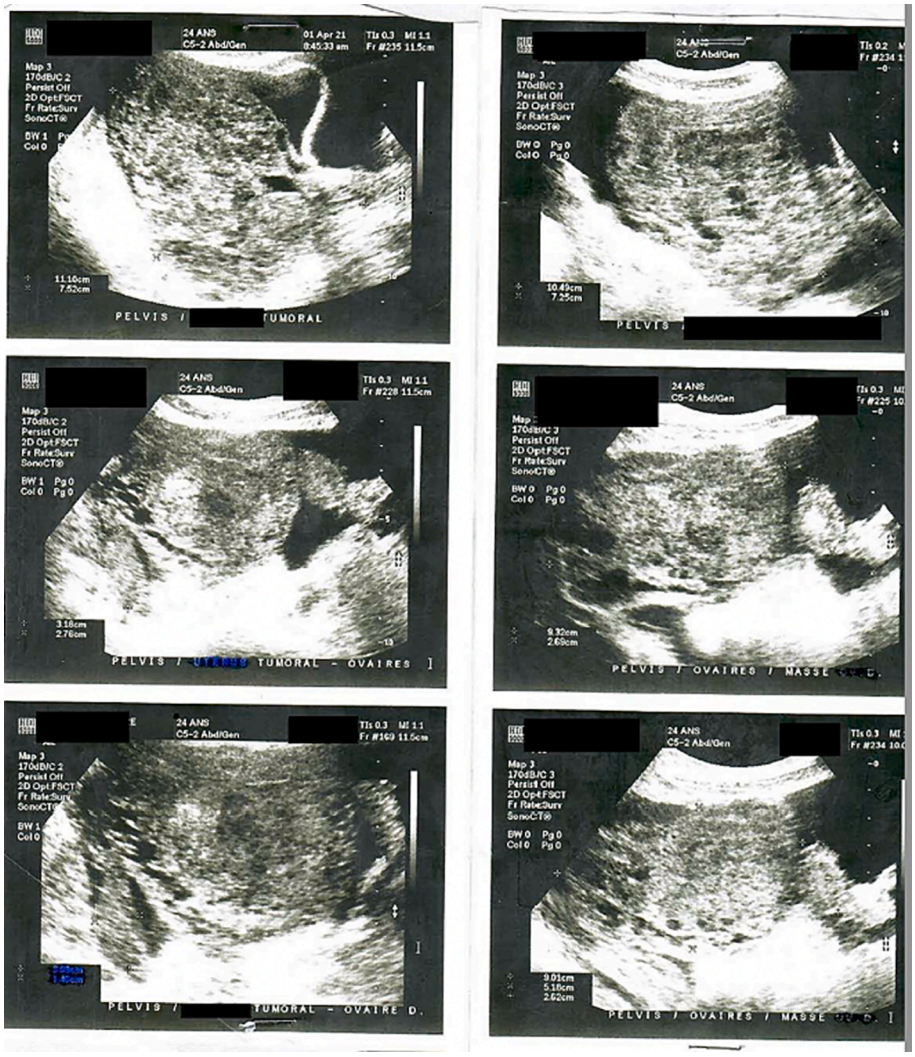

Fig. 2. Hyper echogenic mass associated with fluid inside the abdominal cavity.

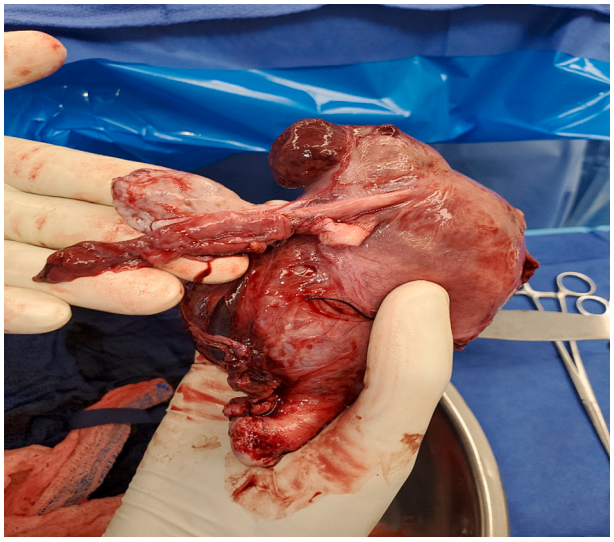

Fig. 3. Uterus, right tube and ovary. Note the protrusion of tumor through the serosa of the right lower uterine segment.

identify in low-income countries because of the lack of availably of serum tumor markers, CT/MRI, and IHC. We present a case of PSTT successfully managed through partnership with a supportive international team, and leveraging telepathology, and suggest that such partnerships may be considered as a short-term strategy to establish an accurate diagnosis. The diagnosis of PSTT often requires immunohistochemistry, which can establish the lineage of the tumor cells (in this case, extra-villous implantation-site trophoblast) and exclude mimickers (such as endometrial carcinoma, choriocarcinoma and epithelioid trophoblastic tumor). The immunohistochemical results, performed in consultation with international pathology experts, enabled us to distinguish PSTT from similar entities. This is important as cross-sectional imaging with CT or MRI were not available, and we relied solely on the pathologic examination of the hysterectomy specimen for diagnostic and management decision purposes. When faced with a difficult to define clinical entity like PSTT, providers in low-resource environments must develop a differential diagnosis on the basis of clinical data and available imaging, and develop a plan that allows management in the face of uncertainty.

Surgery represents an important option for the treatment of PSTT in low-income countries; this is especially true because treatment for metastatic disease, such as multi-agent chemotherapy with etoposide, cisplatin, metrotrexate, and actinomycin D, or immunotherapy such as with pembrolizumab, is frequently unavailable. Through our International Gynceologic Cancer Society supported ECHO tumor board, we

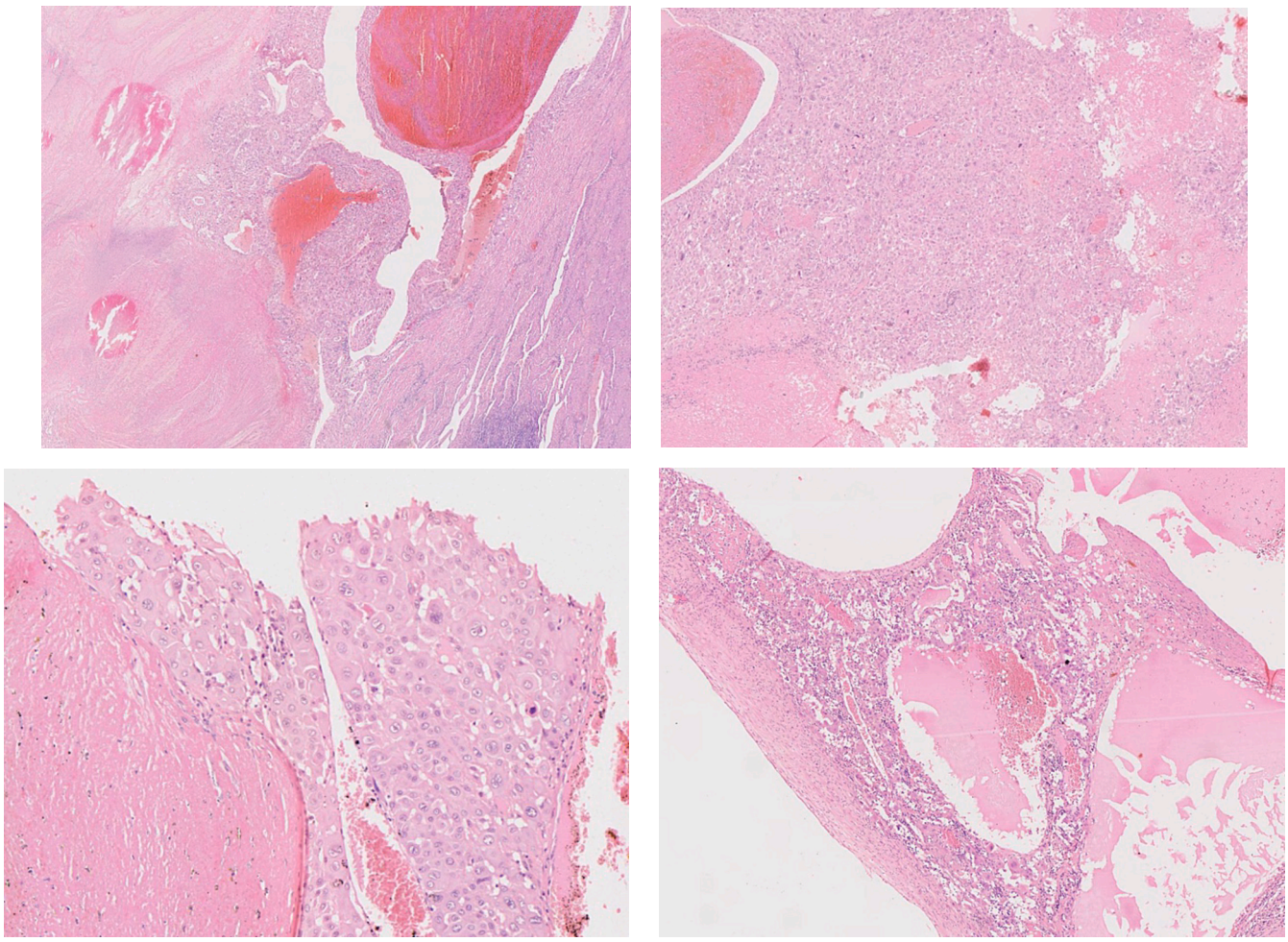

Fig. 4. Microscopic examination of tumor. A. Large expansile and infiltrative mass with necrosis and hemorrhage (both recent and organizing). B. The tumor is composed of sheets of epithelioid cells. C. Tumor cells have abundant pink cytoplasm and pleomorphic nuclei. D. Tumor cells were often associated with blood lakes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

consulted with international experts to determine the best course of action after the surgery due to the lack of chemotherapy and the presence of a pleural effusion upon initial evaluation. The tumor board recommended chemotherapy after the surgery. While awaiting definitive pathological diagnosis, we continued to monitor the patient, and upon reevaluation 6 months post-op, our patient had a negative hCG, remained without any respiratory symptoms and had a normal chest x-ray. The delay in follow-up, continued negativity of HCG, the clinical presentation of the patient, and the socioeconomic hardships repeated visits for chemotherapy would present to this patient guided our decision to not pursue adjuvant chemotherapy. She will, therefore, need follow-up for a longer period than if she had chemotherapy after the surgery, although difficulties in travel due to economic, social, and political considerations make such follow-up difficult, costly, and hazardous.

While there is no consensus on how to stratify PSTT in benign and malignant groups, several clinical and pathologic factors have been associated with aggressive (malignant) behavior. Among those, the most ominous present in our case was the advanced stage of disease imparted by the macroscopic extension of the uterine tumor to one ovary.

In additional to the limitations inherent to our healthcare system, which include high costs of care and limitations in access to high quality imaging and diagnostic tests, several additional barriers impacted our patient's journey. She was symptomatic for six months before seeking care in part due to economic limitations and a national security situation that made travel unsafe. She also spent more than a month seeking care from a traditional healer before coming to the hospital. In Haiti, patients will often turn to spiritual or herbal healers as a first resort, due not only to beliefs but local availability and relatively lower cost. Furthermore, in Haiti medical pluralism is extremely common, and patients are often willing to make use of both biomedical and spiritual practitioners. Clinicians should be aware of these realities and find a way to understand and integrate the cultural aspect in the treatment of their patient to potentially avoid such delay. The nature of PSTT and other GTD, following and sometimes mimicking pregnancy, makes it a condition that is particularly likely to be interpreted through a cultural lens. For example, in Haiti, beliefs related to prolonged pregnancy or false pregnancy, especially related to vodou practitioners are very common. In Haiti this state is referred to as being "an pedition," a state of delayed or prolonged pregnancy, and is regarded as something which may require supernatural solutions. It is therefore important to clarify the role of traditional healers in the Haitian health system to eliminate delays in care.

We have now followed this patient for 2 years and she is in good health. However, in general we have observed that social economic conditions limit the capacity for an adequate follow-up for patients with GTD in limited resource settings.

4. Conclusions

Management of PSTT poses particular challenges in a low-resource setting. It is often difficult to diagnose without immunohistochemistry

and serum tumor markers, and may present at a late stage due to diagnostic delay. Although as in this case it can be managed efficiently with surgery, malignant metastatic PSTT requires treatments often unavailable in this context. Cultural beliefs, economic and social barriers, and lack of infrastructure make follow-up a challenge. Partnerships between low- and high-income collaborators can be a good strategy to better diagnose and manage rare diseases such as PSTT. Other strategies include better integration of traditional healers to decrease delay in the management of patients with malignant or potentially malignant neoplasia, for which traditional medical treatments are indicated and should take priority. Health system reinforcement, improved availability of health care providers, good international partnerships, and better availability and accessibility of radiological, biological and immunohistochemical diagnostics are necessary in low-income countries to manage cases of PSTT.

CRediT authorship contribution statement

Christophe Millien: Conceptualization, Writing – original draft. **Rebecca Henderson:** Writing – review & editing. **Jean Joel Saint Hubert:** Writing – review & editing. **Carlos Parra-Herran:** Writing – review & editing. **Thomas Randall:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Baergen, R.N., Rutgers, J.L., Young, R.H., Osann, K., Scully, R.E., 2006 Mar. Placental site trophoblastic tumor: A study of 55 cases and review of the literature emphasizing factors of prognostic significance. Gynecol. Oncol. 100 (3), 511–520.

Feng, X., Wei, Z., Zhang, S., Du, Y., Zhao, H., 2019. A review on the pathogenesis and clinical management of placental site trophoblastic tumors. Front. Oncol. 9, 937.

Gadducci, A., Carinelli, S., Guerrieri, M.E., Aletti, G.D., 2019 Jun 1. Placental site trophoblastic tumor and epithelioid trophoblastic tumor: Clinical and pathological features, prognostic variables and treatment strategy. Gynecol. Oncol. 153 (3), 684–693.

Horowitz NS, Goldstein DP, Berkowitz RS. Placental site trophoblastic tumors and epithelioid trophoblastic tumors: Biology, natural history, and treatment modalities. Gynecologic oncology. 2017 Jan 1;144(1):208-14.

Kohorn, E.L., 2014. Worldwide survey of the results of treating gestational trophoblastic disease. J. Reprod. Med. 59, 145–153.

Kurman, R.J., Scully, R.E., Norris, H.J., 1976. Trophoblastic pseudotumor of the uterus: an exaggerated form of "syncytial endometritis" simulating a malignant tumor. Cancer 38, 1214–1226. https://doi.org/10.1002/1097-0142(197609)38:3<1214::AID-CNCR2820380323>3.0.CO;2-J.

Lurain JR. Gestational trophoblastic disease II: classification and management of gestational trophoblastic neoplasia. American journal of obstetrics and gynecology. 2011 Jan 1;204(1):11-8.

Vardar, M.A., Altintas, A., 1995. Placental-site trophoblastic tumor. Principles of diagnosis, clinical behaviourand treatment. Eur. J. Gynaecol. Oncol. 16 (4), 290–295.