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PLACENTAL SITE TROPHOBLASTIC TUMOR: CONSERVATIVE THERAPEUTIC APPROACH AND LITERATURE REVIEW

TUMOR LEŽIŠTA POSTELJICE: KONZERVATIVNI TERAPIJSKI PRISTUP I PREGLED LITERATURE

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Case report

Key words: placental site trophoblastic tumor, nephrotic syndrome, Doppler ultrasonography, NMR

SUMMARY. Placental site trophoblastic tumor is the least common of gestational trophoblastic diseases. Its biologic behavior is different from that of typical choriocarcinoma. Surgery is the cornerstone of therapy and the roles of chemotherapy and radiation remain uncertain. We present a case of 24-year-old woman with placental site trophoblastic tumor and nephrotic syndrome. There was no extrauterine spread which was determined by ultrasonography and computed tomography. In attempt to preserve fertility, hysterotomy and tumor excision was performed.

Prikaz bolesnice

Ključne riječi: tumor ležišta posteljice, nefrotički sindrom, dopler, NMR

SAŽETAK. Tumor ležišta posteljice (TLP) je najrjeđi oblik trofoblastične bolesti. Njegovo biološko ponašanje je drugačije od onog u koriokarcinoma, varirajući od dobroćudnog oblika do agresivne bolesti s fatalnim ishodom. Kirurgija – histerektomija je liječenje izbora, dok su rezultati kemoterapije i zračenja dvojbeni. Prikazana je 24-godišnja bolesnica s tumorom ležišta posteljice i nefrotičkim sindromom. Ultrazvučnim pregledom i kompjutoriziranom tomografijom nije nađeno izvanmaternično širenje tumora te je, u cilju očuvanja plodnosti, odstranjen samo tumor. Poslijeoperacijsko praćenje bolesnice u trajanju od godine dana nije pokazalo znakove recidiva bolesti.

Introduction

Placental site trophoblastic tumor (PSTT) is the least common of gestational trophoblastic diseases (GTD). Among 4988 patients with GTD Gillespie et al.¹ found only seven with PSTT. It was likely first described by Marchand in 1895.² In 1976 Kurman et al.³ described 12 patients with a variant of trophoblastic disease thought to represent a distinct and exaggerated placental site reaction. The lesion was designated trophoblastic pseudotumor of the uterus to reflect the apparently benign nature of the lesion. In 1981, Twiggs et al.⁴ reported the death of a woman with a trophoblastic pseudotumor secondary to metastasis. Also in 1981, Scully and Young⁵ used the term »PSTT«, which they thought to be more appropriate because of the malignant potential of the tumor.

Its biologic behavior is different from that of typical choriocarcinoma, ranging from a benign condition to an aggressive disease with fatal outcome. Surgery is the cornerstone of therapy and the roles of chemotherapy and radiation remain uncertain. In the same time, maintenance of fertility is often an important concern for many women with this tumor.

Case Report

A 24-year-old woman, gravida 1, para 1, presented in October 1999 with vaginal spotting while continuing to

breast-feed her first child, who was born vaginally 9 months earlier. Prior to that, she had one episode of vaginal bleeding in July 1999. The result of pregnancy test performed before she came to our institution was positive. On examination she was noted to be generally well but hypertensive (160/100). At this visit, the pelvic examination revealed slightly enlarged, anterior, mobile uterus with clear adnexa. The serum level of β -hCG was 204 IU/L. Transvaginal ultrasonography revealed thickened endometrium and a 5.0×4.0 cm isoechogenic solid mass just anterior to the uterine cavity (*Fig. 1*). The tumor invaded myometrium till 5 mm from the serous layer. The lesion was similar in appearance to an intramural uterine leiomyoma. Suspicion of incomplete spontaneous abortion was established and on October 25, 1999 the patient underwent D&C. The curettage produced a small amount of tissue without fetal parts, and pathologic examination revealed only decidually transformed endometrium.

The patient was discharged, but the repeated value of serum β -hCG November 2, 1999 was 209 IU/L and on November 10, 1999 was 275 IU/L. Suspicion of extrauterine pregnancy was established. The patient was admitted at our hospital again on November 17, 1999. Blood pressure was 180/110 and the patient commenced an intensive antihypertensive therapy. Repeated transvaginal ultrasonography revealed previously described tumor and a small amount of ascites in Douglas pouch. Color flow

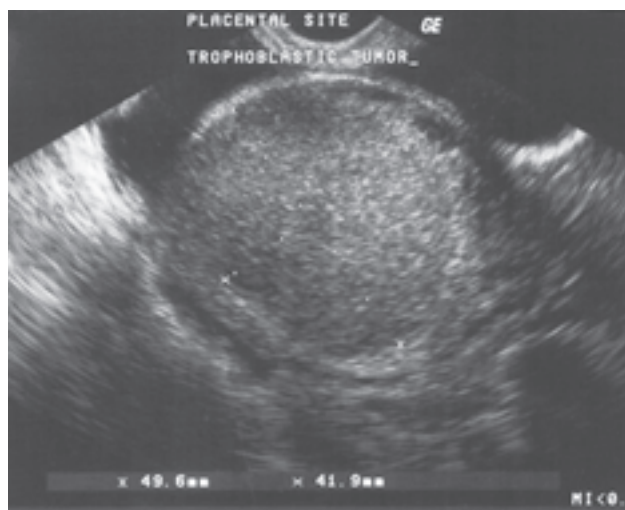


Figure 1. Transvaginal ultrasound scan of placental site trophoblastic tumor. Note: tumor invades myometrium till 5 mm from the serous layer
 Slika 1. Transvaginalni ultrazvučni prikaz tumora ležišta posteljice. Pozor: tumor prodire u miometriju 5 mm od seroze

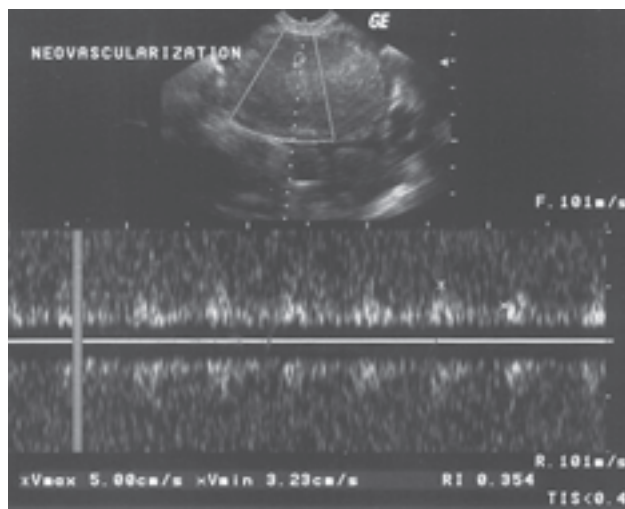


Figure 2. Transvaginal color Doppler scan of intratumoral vessels. Blood flow shows increased diastolic flow and low vascular resistance (RI=0.35)
 Slika 2. Prikaz protoka krvi kroz tumorske krvne žile transvaginalnim doplerom u boji ukazuje na povećani dijastolički protok i nizak krvnožilni otpor (RI=0,35)

Doppler showed increased intratumoral vascularity, characterised by abundant diastolic flow suggestive of low vascular impedance (RI was 0.35) (Fig. 2). On November 18, 1999, the patient underwent diagnostic laparoscopy. The intraoperative findings included enlarged uterus with tumor in the anterior wall, about 100 ccm of ascites in Douglas pouch (cytologic finding was negative) and clear adnexa. Intraoperatively, D&C was repeated and pathologic examination revealed PSTT. The average mitotic count was one mitotic figure per ten high-power fields, but in one active area four mitotic figures were seen per ten high-power fields. Revision of the previous preparation also revealed PSTT!

Chest X ray and routine hematological indices were normal. Special investigations showed normal renal and

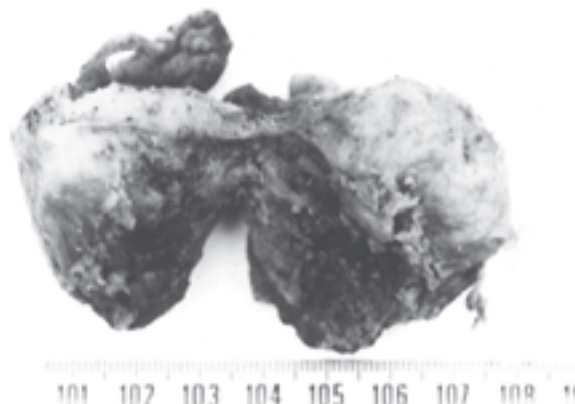


Figure 3. Excised placental site trophoblastic tumor
 Slika 3. Odstranjeni tumor ležišta posteljice

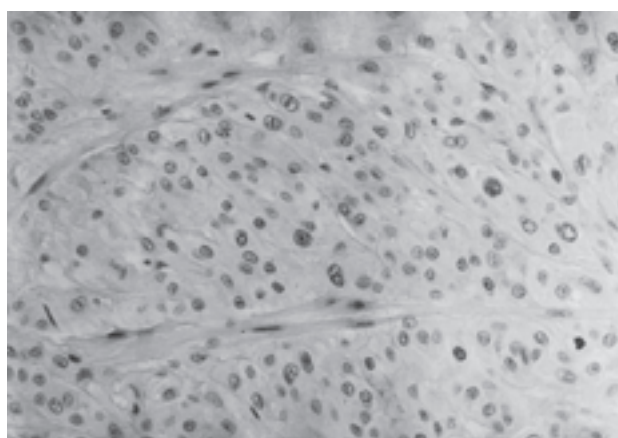


Figure 4. PSTT with uniform mononuclear intermediate trophoblast cells infiltrating among fascicles of myometrial smooth muscle (hematoxylin-eosin stain, 200× magnification)

Slika 4. TLP s jednoličnim stanicama intermedijalnog trofoblasta koje uraštaju između snopova glatkog mišićja miometrija (bojenje hematoksilin-eozinom, povećanje 200×)

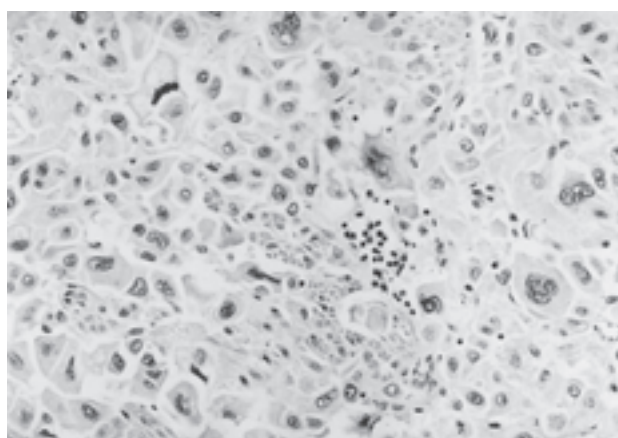


Figure 5. PSTT with polymorphic intermediate trophoblast cells. Besides well-differentiated mononuclear cells some giant mononuclear and multinuclear cells are observed (hematoxylin-eosin stain, 200× magnification)
 Slika 5. TLP s raznolikim stanicama intermedijalnog trofoblasta. Pored dobro diferenciranih mononuklearnih stanica vide se pojedinačne divovske mononuklearne i multinuklearne stanice (bojanje hematoksilin-eozinom, povećanje 200×)

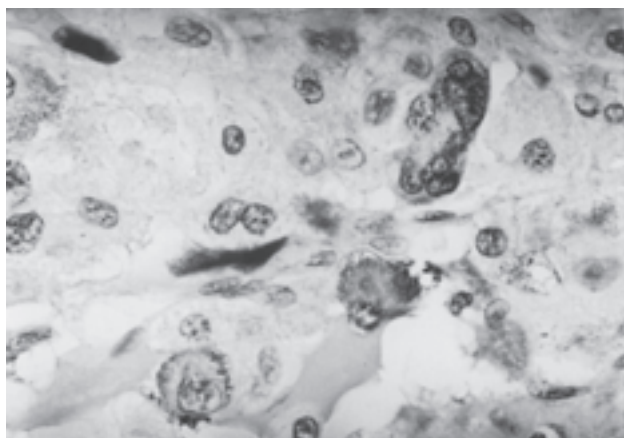


Figure 6. PSTT stained by the indirect immunoperoxidase method for hPL showing scattered positive cells (500× magnification)

Slika 6. TLP obojen indirektnom metodom imunoperoksidaze pokazuje raspršene hPL pozitivne stanice (povećanje 500×)

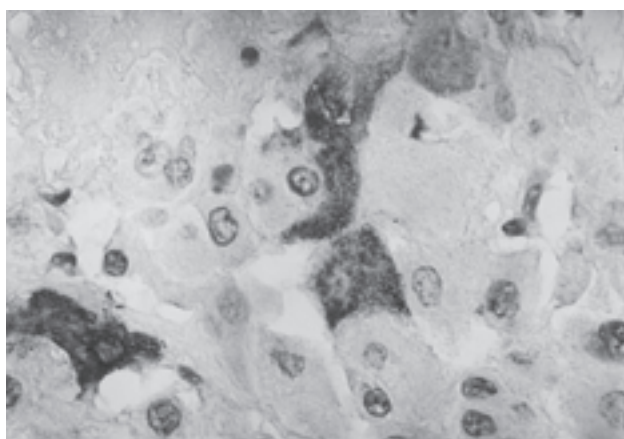


Figure 7. PSTT with hCG positive intermediate trophoblast cells (immunoperoxidase staining, 500× magnification)

Slika 7. TLP s hCG pozitivnim stanicama intermedijalnog trofoblasta (bojenje imunoperoksidazom, povećanje 500×)

liver function. The serum albumin was low (24.5 g/L) and total protein was 51 g/L. Urinary protein excretion was elevated – 10.36 g per 24 hr. Serum cholesterol was elevated (8.91 mmol/L) as well as triglycerides (2.20 mmol/L). The diagnosis of nephrotic syndrome was established. β -hCG value on November 22, 1999 was 292 IU/L, three days later 241 IU/L, and four days thereafter was 248 IU/L. A determination of serum human placental lactogen (hPL) was not technically possible. Computerized tomography (CT) scan revealed enlarged uterus with central areas of necrosis and hemorrhage. CT of the brain, abdomen, and pelvis revealed no evidence of distant metastases.

The patient was counseled about the findings and the disease process. She strongly desired preservation of fertility. On December 1, 1999, the patient underwent exploratory laparotomy, hysterotomy, and local excision of the PSTT. General exploration of the abdomen was negative for extrauterine disease. On the anterior fundus the tumor was clearly visible. A vertical anterior hysterotomy

was made, and a tumor greater than 5,0 cm in diameter was excised (Fig. 3). Then myometrium was reconstructed in layers.

Patho-histologic examination revealed a 5.5×4.5×4.5 cm PSTT that was somewhat circumscribed and infiltrated the adjacent myometrium, with the areas of hemorrhage and necrosis on section. Histologic examination revealed intermediate trophoblast infiltrating myometrial fascicles and invading vessel walls, consistent with that was seen at curettage. Most cells were mononuclear with medium-sized nuclei (Fig. 4), but numerous giant mononuclear and multinuclear cells were observed (Fig. 5). In active areas eight mitotic figures were seen per ten high-power fields. The surgical margins were not free of tumor. Immunoperoxidase staining showed strong reactivity with hPL (Fig. 6) and occasional staining with hCG (Fig. 7).

Subsequently, the serum level of β -hCG on December 6, 1999 was 18.3, and on December 10, 1999 was 2.99. Repeated value of the serum albumin was 27.2 g/L and total protein was 55 g/L. Urinary protein excretion was significantly lower, 2.75 g per 24 hr. Repeated value of serum cholesterol was 6.57 mmol/L. Hypertension was mild, 150/100. From December 29, 1999 to January 4, 2000, she received single-agent chemotherapy (methotrexate 50 mg per day for four days and folinic acid 6 mg for two days).

On January 20, 2000 she was admitted to the department because of following-up. Laboratory tests showed normal values of the serum cholesterol – 4.06 mmol/L and triglycerides – 0.87 mmol/L. The serum albumin was slightly lower than normal – 39 g/L as well as a total protein – 62 g/L. Urinary protein excretion was borderline elevated – 0.43 g/24 h. The serum level of β -hCG was not elevated. Blood pressure was normal. CT scan of abdomen was negative for recurrent tumor. Magnetic resonance imaging (MRI) study in February 2000 was also negative for recurrent disease. To date, there has been no evidence of tumor recurrence.

Discussion

Once believed to be a benign form of gestational trophoblastic disease, PSTT is now known to be a malignant and sometimes fatal tumor. The rarity of PSTT has prevented agreement on staging, therapy, and imaging appearance. Most authors have recommended hysterectomy for treatment of PSTT. We have reported an approach to treatment of localized PSTT by hysterotomy, excision, and uterine reconstruction in an attempt to preserve fertility. There was no evidence of extrauterine spread, which would be a contraindication for conservative management. The determination that the tumor was localized was based on imaging studies (ultrasonography, CT and chest X-ray). The assessment of localized PSTT on the results of these imaging studies was confirmed intraoperatively.

The etiology, epidemiology, and risk factors for the development of PSTT are not well understood. PSTT

typically occurs in women of childbearing age, with an average age of occurring of 28 years. Only one case has been described in a 53-year-old postmenopausal woman who developed PSTT 18 years after her last documented pregnancy.⁶ PSTT may develop after a normal pregnancy, an abortion, or a molar pregnancy. Presentation may be from 1 week to 14 years after pregnancy.⁷ Abnormal vaginal bleeding is the most common presentation. Rare modes of presentation have included spontaneous uterine perforation and nephrotic syndrome.⁸

The PSTT is composed of intermediate trophoblast (otherwise known as extravillous trophoblast or X cells), a morphologically and functionally distinct trophoblastic cell that predominates in the normal placental implantation site.^{7,9–11} An intermediate trophoblast is a distinctive trophoblastic cell population from which four trophoblastic lesions are thought to arise: exaggerated placental site (EPS), placental site nodule (PSN), placental site trophoblastic tumor, and epitheloid trophoblastic tumor (ETT).¹¹ EPS and PSTT are related to the differentiation of the intermediate trophoblast in the implantation site (implantation site intermediate trophoblast), whereas PSNs and ETTs are related to the intermediate trophoblast of the chorion laeve (chorionic-type intermediate trophoblast). EPS and PSN are non-neoplastic lesions, whereas PSTT and ETT are neoplasms with a potential for local invasion and metastasis. PSTT lack the bilaminar structure of the trophoblast usually seen in choriocarcinoma and consist of mononuclear cells with occasional giant cells. Chorionic villi are only rarely detected. Necrosis is common, but hemorrhage is much less common than in typical choriocarcinoma. In PSTT, the intermediate trophoblastic cells form a polypoid mass that may be within the endometrial canal or the myometrium. Characteristically the tumor invades the myometrium, dissecting between individual muscle fibers. There is less vascular invasion with PSTT and a greater propensity to metastasize via lymphatics. However, there is a peculiar behavior towards the uterine vasculature as spiral arteries are dilated and transformed the same way as occurs at the site of physiological implantation of pregnancy.¹² The tumor is usually confined to the uterine corpus but may metastasize to lung, liver, lymph nodes, brain, or other organs and about 10% of patients die of uncontrolled metastases. Metastasis can occur years after diagnosis.

The variable and often low level of hCG detected in these tumors reflects the lack of syncytiotrophoblast. The levels of hCG are not an accurate indication of tumor burden and cannot be used as a reliable tumor marker. Most of the cells of PSTT contain HPL and a minority contain hCG.⁹ In approximately 15% of PSTTs, hCG is predominantly secreted or there is an equal distribution of hCG and HPL.⁹ It has been suggested that tumors that secrete predominantly hCG have a greater resemblance to choriocarcinoma and it is possible that this group represents the more aggressive PSTTs.⁹ This has not been tested prospectively.

The clinical behavior may be extremely aggressive, with nephrotic syndrome being a rare form of presenta-

tion. Nephrotic syndrome is characterized by albuminuria, hypoalbuminemia, hyperlipidemia, and edema.¹³ The syndrome is the result of excessive glomerular permeability to plasma proteins and heavy proteinuria is a prime characteristic. The pathogenesis is unknown, but may be due to damage caused by the deposition of immune complexes stimulated by the tumor. A distinctive glomerular lesion has been described.¹⁴ In our case the excision of tumor appears to have »cured« the nephrotic syndrome.

Only about 10% of PSTT are malignant, as defined by the presence of metastatic disease.¹⁵ A well-defined indicator for malignant behavior has not been determined. A subset of patients with PSTT at high risk for metastases has been defined on the basis of a mitotic count greater than two mitoses per ten high-power fields.^{5,16} Because of the rarity of the tumor, this definition of malignant behavior is based on limited clinical experience. The predictive value of this indicator is questionable because of reports of metastatic PSTT with mitotic counts less than two per ten high-power fields,^{15,17} and of localized tumor with a mitotic count greater than ten per ten high-power fields.¹⁶ In addition, mitotic counts in the curettage specimen may differ from those in the hysterectomy specimen and from those in the resected metastasis.¹⁸

According to different authors,^{17,19,20} the long interval from the antecedent pregnancy to clinical presentation is a major adverse prognostic variable, and the outcome in patients whose last known pregnancy was >2 years prior to presentation with PSTT is poor. In the study of Chang et al,²¹ patients with metastatic diseases were 3 years older than patients with diseases confined to the uterus and had a higher incidence of term delivery as their antecedent pregnancy.

Ultrasonography has become the preferred noninvasive diagnostic imaging modality that enables early confirmation of gestational trophoblastic disease. Findings associated with PSTT comprise a variety of imaging presentations.^{22–24} It can be a solid mass with cystic lesions that correspond to dilated blood vessels²² or central hemorrhagic areas²³ or a solid tumor similar in appearance to an intramural leiomyoma²⁴ as it was in our patient. Doppler studies of PSTT showed different types of tumoral vascularity – from low blood flow with high vascular indices²⁴ to abundant blood flow suggestive of low vascular impedance^{25,26} as it was present in our case. Such hypervascularity is a consequence of trophoblastic invasion into the wall of arteries, a process which is physiological in early pregnancy and results in transformation of spiral arteries into dilated tortuous vascular channels.²⁷ The reason that prominent vascular structures are seen in some cases and not in others is unknown. As yet, there have not been any data which clearly link death and recurrence to size or vascularity of the primary tumor.

CT and MRI findings are also not specific. MR imaging can reveal the site, size, prominent vascularity and extent of PSTT and may reveal the presence of such tumors that are not seen on sonography.²⁸ Currently, no imaging study is able to demonstrate microscopic me-

Table 1. Criteria for treatment of placental site trophoblastic tumor (modified from Newlands et al)¹⁸Tablica 1. Kriteriji pri liječenju tumora ležišta posteljice (sačinjeno prema Newlands et al)¹⁸

Criteria – Kriteriji	Treatment – Liječenje
Localized disease Lokalizirana bolest	Hysterectomy + adjuvant chemotherapy (EMA/CO or EP/EMA) if disease is not completely resected Histerektomija + adjuvantna kemoterapija (EMA/CO ili EP/EMA) ukoliko tumor nije u potpunosti odstranjen
Localized disease, but patient desires preservation of fertility Lokalizirana bolest, ali bolesnica želi sačuvati plodnost	Tumor excision + adjuvant chemotherapy if disease is not completely resected Odstranjenje tumora + adjuvantna kemoterapija ukoliko tumor nije u potpunosti odstranjen
Locally bulky disease or minimally metastatic disease Lokalna opsežna bolest ili minimalna metastatska bolest	Chemotherapy (EMA/CO or EP/EMA) + hysterectomy Kemoterapija (EMA/CO ili EP/EMA) + histerektomija
Metastatic disease Metastatska bolest	Chemotherapy (EMA/CO or EP/EMA) + surgery Kemoterapija (EMA/CO ili EP/EMA) + kirurgija

tastases, but in a case in which microscopic nodal metastasis was confirmed pathologically, preoperative imaging tests showed extensive uterine tumor.²⁹

In the past, PSTT was cured in many patients by uterine curettage, consistent with benign behavior of the tumor.^{3,16} However, because of concern about potential malignant behavior, for patients with the disease localized to the uterus the treatment of choice is hysterectomy^{16,19} followed by adjuvant chemotherapy in selected cases, depending on how certain the surgeon and pathologist are that the disease has been completely resected.¹⁹ This may represent overtreatment for most patients who have benign tumors, and it does not preserve fertility in women who may not be ready to forgo childbearing. We, and some other authors^{28–30} suggest that preoperative imaging may be used to define those patients with localized PSTT who are candidates for conservative resection when preservation of fertility is a concern. In patients presenting with locally bulky disease or minimally metastatic disease, some authors¹⁹ recommend cytoreduction with the EP (etoposide, paclitaxel), EMA (etoposide, methotrexate, actinomycin D) schedule prior to debulking the disease by hysterectomy if the disease has responded satisfactorily to the chemotherapy. The treatment of PSTT considering expansion of the disease is shown in Table 1. Because of the rarity of these tumors, involvement of a gynecologic oncologist in the clinical management of these patients is encouraged. While surgery remains the most important therapeutic option for the primary and metastatic lesions, chemotherapy and radiation should be considered in metastatic disease. Unlike choriocarcinoma, PSTT is relatively insensitive to chemotherapy. Chemotherapy has developed over the 20 years since 1975. A few cases received chemotherapy

with simple schedules, such as methotrexate and folinic acid, or actinomycin D or vincristine and cyclophosphamide. However, the greatest experience has been with the EMA (etoposide, methotrexate, actinomycin D), CO (cyclophosphamide/vincristine), and patients with metastatic disease should be started on that schedule. From the limited data,¹⁹ cisplatin should be introduced into the chemotherapy schedule from the outset in a schedule such as EP (etoposide, paclitaxel), EMA (etoposide, methotrexate, actinomycin D). However, the activity of new anticancer agents, such as the taxanes (paclitaxel and docetaxel) and camptothecins (topotecan and irinotecan), needs to be assessed in this disease, which can become very resistant to previously available chemotherapy.

Radiation is most useful in the setting of localized and isolated recurrences.

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