Case Report

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Metastatic placental site trophoblastic tumor with pelvic arteriovenous malformation: A case report

Victoria May Hembrador Velasco-Redondo, Ma. Bernadette R. Octavio

Abstract:

Placental site trophoblastic tumor (PSTT) with uterine arteriovenous malformation (AVM) is a rare and potentially catastrophic occurrence. A high index of suspicion and immunohistochemistry secured the diagnosis. The use of appropriate imaging modalities led to the identification of the extent of the disease. Sequential planned management from neoadjuvant intensive chemotherapy, bilateral uterine artery embolization, and laparotomy, and coordinated among different medical disciplines resulted to a successful definitive treatment. Due to its relatively chemoresistant nature, hysterectomy is the mainstay of treatment. Adjuvant platinum-based intensive chemotherapy has been shown to improve overall survival in patients with metastatic disease and those with poor prognostic factors. This case of PSTT with a typical clinical profile was noteworthy due to the development of a significant AVM, a rare complication of PSTT. This case report included a review of treatment experiences as well as peculiarities that set PSTT apart from the more common gestational trophoblastic diseases.

Keywords:

Gestational trophoblastic neoplasia, placental site trophoblastic tumor, uterine arteriovenous malformation

Introduction

Placental site trophoblastic tumor (PSTT) is not only a rare histologic subtype of gestational trophoblastic neoplasia (GTN) but it behaves differently from the more common invasive mole and choriocarcinoma. Unlike the latter entities, PSTT has a relatively slow growth rate and is not as responsive to chemotherapy. It is derived from intermediate trophoblasts at the implantation site making it a very vascular tumor invading blood vessels intraluminally.[1] The definitive management is primary surgery. The presence of uterine arteriovenous malformation (AVM) developing in PSTT has been reported in only four instances.[2] The objective of this report is to describe a case of metastatic PSTT and the treatment challenges complicated by a significant AVM.

Case Report

A 37-year-old Gravida 2 Para 2 (2002) was referred to this institution due to histopathologic findings of atypical trophoblastic cells after endometrial curettage. Her last pregnancy was a female live birth delivered spontaneously 6 years ago.

Two months prior, the patient underwent endometrial biopsy for persistent vaginal bleeding following 14 months of amenorrhea. Her pregnancy test was negative. Baseline ultrasound showed thickened endometrium with adenomyosis. Her histopathologic result showed few clusters of atypical trophoblastic cells with hemorrhagic necrosis, consider gestational trophoblastic tumor. She was then referred to a trophoblastic disease specialist for further evaluation and management.

On the day of the consult, she had vaginal spotting and mild hypogastric pain. She had stable vital signs and essentially normal

Department of Obstetrics and Gynecology, Division of Trophoblastic Diseases, Philippine General Hospital, University of the Philippines, Manila, Philippines

Address for correspondence:
Dr. Victoria May Hembrador Velasco-Redondo, Philippine General Hospital, University of the Philippines, Taft Avenue, Ermita, Manila 1000, Philippines.
E-mail: kookyvelasco@gmail.com

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systemic findings. On speculum examination, there were no vaginal/cervical masses and there was minimal bleeding per cervical OS. On internal examination, she had smooth vaginal walls, the cervix was smooth, the uterus was symmetrically enlarged to 10–12 weeks gestation size, and there were no adnexal masses. Serum beta human chorionic gonadotrophin (βhCG) was 30.64 mIU/mL. Transvaginal ultrasound showed an irregular, solid endomyometrial mass measuring 6.7 cm × 7.8 cm × 5.9 cm at the anterofundal area, and a spongy vascular mass at the anterior midcorpus with turbulent flow up to the bilateral parametria and urinary bladder base; consider AVM [Figure 1]. Pelvic computed tomography (CT) angiogram showed diffuse tortuous vessels exhibiting aneurysmal dilatation in the myometrium with extension to the parametrial vessels and draining into bilateral dilated and tortuous ovarian vessels [Figure 2]. Chest radiography and whole abdominal ultrasound were unremarkable. Contrast-enhanced chest CT scan revealed a 0.4 cm noncalcified pulmonary nodule in the right lower lobe, probably metastatic.

Slide review and immunohistochemistry of the endometrial tissue showed that the tumor was strongly positive for mucin-4 (MUC4), negative for both p63 and Sal-like protein 4 (SALL4), KI67 proliferation index of 10%–15%, and was most compatible with PSTT [Figure 3].

The working impression was metastatic PSTT (Stage III). The definitive management was total hysterectomy with bilateral salpingectomy (TAHBS) with prelaparotomy uterine artery embolization due to the AVM. However, financial constraints delayed the embolization. Having observed the rapid progression of the tumor, she was given neoadjuvant chemotherapy with etoposide, cisplatin/etoposide, methotrexate, and actinomycin (EP/EMA) while waiting for embolization. After the first EP/EMA, βhCG rose to 44.97 mIU/mL with the appearance of an anterior vaginal wall mass measuring 1 cm × 1 cm, hence the diagnosis of tumor progression.

A week after EP/EMA I, the patient underwent bilateral uterine artery embolization under local anesthesia and intravenous sedation. Initial angiograms showed a hypervascular mass-like tangle of vessels in the pelvic cavity, supplied predominantly by the uterine arteries. Using a French 5 Cobra catheter, selective embolization of the bilateral uterine and inferior vesicular/vaginal arteries was performed using polyvinyl alcohol particles (355–500 μ) and Gelfoam® particles while ensuring that blood supply of both ovaries remained uncompromised. Postprocedural angiograms showed complete devascularization of the mass-like tangle of vessels in the pelvis [Figure 4].

To prevent the development of collateral vascular supply, TAHBS was done within 24 h of embolization. Intraoperatively, an ileal segment with a firm serosal mass measuring 1 cm × 1 cm was densely adherent to the anterior surface of the uterus. Enterolysis, ileal resection, and side-to-side reanastomosis were done by general surgery. The uterus was symmetrically enlarged to 12 weeks gestation, with a 1 cm × 1 cm dark red, smooth mass protruding from the serosa at the anterior midcorpus. This mass was contiguous with an irregular, heterogenous, firm, tan to dark red endomyometrial mass measuring 6 cm × 6 cm × 4 cm, indicating invasion up to the serosa. It occupied the endometrial cavity from the midcorpus to the fundus and contained dilated vessels within [Figure 5]. Both adnexae were grossly normal and there were no palpable pelvic

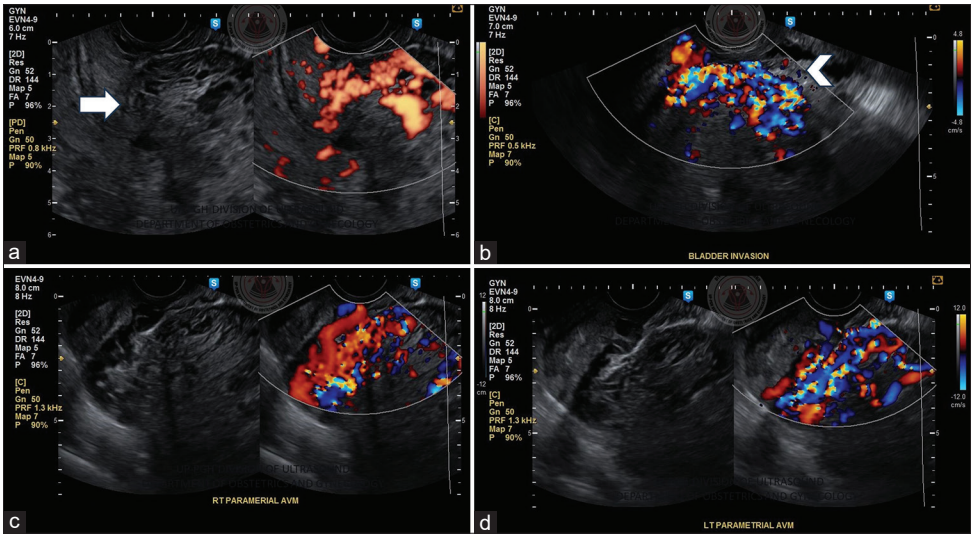

Figure 1: Transvaginal ultrasound with Doppler study: (a) The spongy vascular mass at the anterior midcorpus (arrow), (b) Extension of the turbulent flow to the urinary bladder base (arrowhead), (c and d) demonstrates extension of the turbulent flow up to the bilateral parametria

lymph nodes. Finally, resection of bilateral AVMs in the parametrial areas and which were mainly supplied by the ovarian arteries was performed by the department of vascular surgery. Estimated blood loss was 1600 cc. The patient was transfused with 2 units packed RBC. Histopathologic examination showed a PSTT with more than 50% invasion of the myometrium. Both fallopian tubes, bilateral AVMs, and ileum were negative for malignancy.

Her serum βhCG became normal a week after surgery. Adjuvant chemotherapy resumed 4 weeks postsurgery to allow healing of ileal reanastomosis. As of this writing, the patient has completed six cycles of adjuvant EP/EMA, with the resolution of the vaginal mass and pulmonary nodule. Her serum (βhCG) remained undetectable (<1.2 mIU/mL) throughout the six cycles of chemotherapy [Figure 6].

Discussion

PSTT is a rare type of gestational trophoblastic disease (GTD) originating from the placental implantation site. Tumors from intermediate trophoblasts account for only 1%–2% of GTN cases.[3] Only about 725 PSTT cases and 110 cases of epithelioid trophoblastic tumors (ETTs) have been reported.[4] In the national referral center for GTDs, this case is the 8th since 1998 and the only case for the past 6 years. This accounts for 2.4% of the total GTN admissions for the past 10 years.

The index case fits the typical clinical profile of PSTT, seen in reproductive-aged women, following term pregnancy, and may develop long after the antecedent pregnancy.[1,3] Interestingly, PSTTs are more common after pregnancy with a female baby. In an XX diploid conceptus, it is believed that inactivation of the paternally-derived X chromosome is crucial to the development of normal extraembryonic tissue. In PSTT, it has been found that the majority of

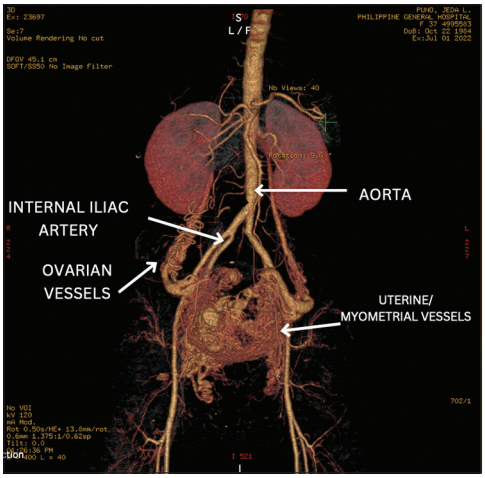

Figure 2: Computed tomography pelvic angiography showing dilated and tortuous vessels in the myometrium, surrounding the uterus and extending into the parametrial vessel (white arrow)

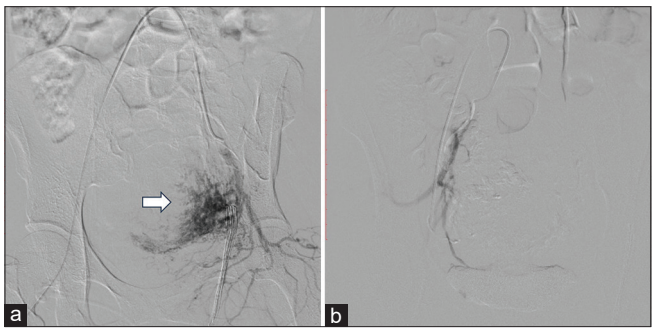

Figure 4: Selective arterial embolization: (a) The initial angiogram with the mass-like tangle of vessels in the pelvis (arrow) and (b) complete devascularization of the tangle of vessels after selective embolization of the uterine arteries

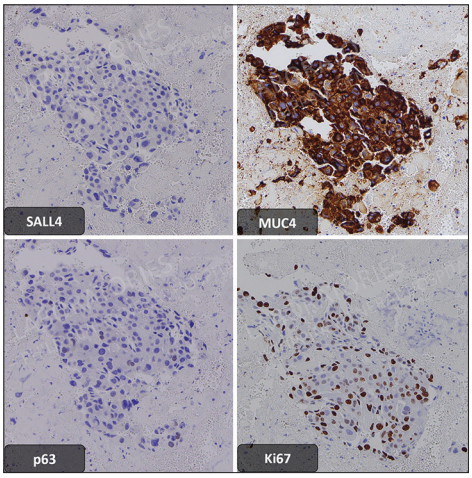

Figure 3: Immunohistochemistry profile of the patient showing negative staining for SALL 4, diffuse staining for MUC 4, negative staining for p63, and Ki-67 proliferation index of 10%–15%. SALL 4: Sal-like protein 4, MUC 4: Mucin-4

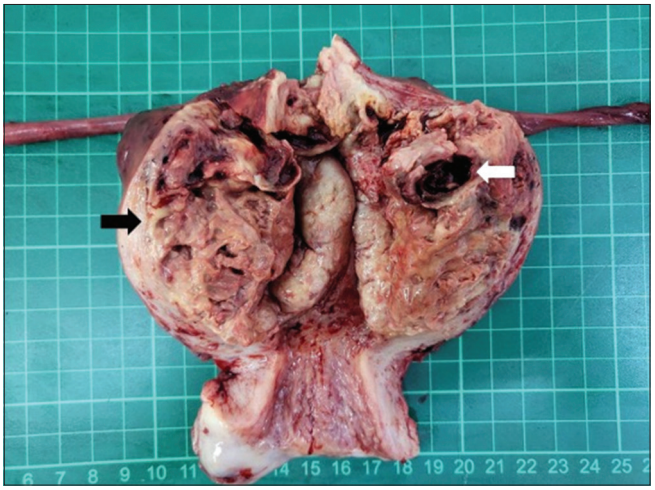

Figure 5: Cut section of the uterus showing a heterogenous, irregular, tan to dark red mass measuring 6 cm × 6 cm × 4 cm (black arrow), occupying the endometrial cavity from the midcorpus to the fundus. It contained markedly dilated vessels within (white arrows) and there was >50% myometrial invasion

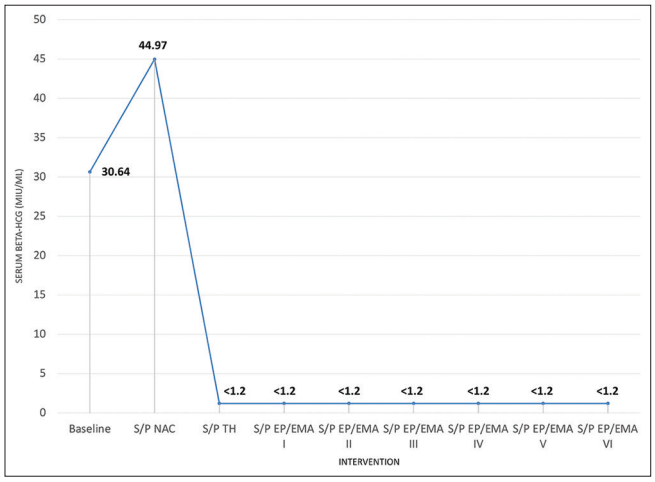

Figure 6: Serum βhCG trend of the index case showing a rise after neoadjuvant chemotherapy and normalization after total hysterectomy and throughout adjuvant chemotherapy. S/P: Status post, NAC: Neoadjuvant chemotherapy, TH: Total hysterectomy, EP/EMA: Etoposide, cisplatin, methotrexate, actinomycin, βhCG: Beta human chorionic gonadotrophin

cases were derived from the extraembryonic tissue of a female conceptus with a functional paternal X chromosome. It is theorized that activation of the paternal X chromosome results in the expression of an unidentified dominant oncogene or that the abnormal dosage of functional X chromosomes results in tumorigenesis.[5] This would explain the correlation between female antecedent pregnancies and PSTT since male babies do not receive a paternal X chromosome. The most common symptom of PSTT is irregular vaginal bleeding, at times preceded by amenorrhea.[6] In the majority of cases, serum βhCG is elevated but at levels that are markedly lower than in invasive mole and choriocarcinoma. In a series of 88 cases, serum βhCG ranged from 1.1–8300 mIU/mL. Oftentimes, βhCG level does not correlate with the burden of disease.[4] This is because PSTT consists mainly of intermediate trophoblasts, rather than the βhCG-producing syncytiotrophoblasts found in choriocarcinoma or invasive mole.[1,4]

PSTT originates from intermediate trophoblasts at the implantation site, whose function is to facilitate successful placental implantation. Proposed mechanisms for the pathogenesis of PSTT include hyperplasia of intermediate trophoblasts and the formation of small nodules of placental tissue in the myometrium during placental detachment at childbirth. Alterations in the signaling pathways and in the expression of adhesion molecules are also thought to contribute to the development of PSTT. Finally, the upregulation of human leukocyte antigen-G (HLA-G), a class I histocompatibility complex responsible for maintaining maternal–fetal immunological tolerance, is thought to cause abnormal proliferation and invasion of trophoblasts.[5]

A third of PSTT cases are misdiagnosed.[6] The availability of endometrial biopsy specimens and access to immunohistochemistry confirmed the clinical diagnosis in this case. Immunostaining with SALL4 yielded negative effectively ruling out choriocarcinoma. In a series of 31 GTN cases, all choriocarcinomas stained positive for SALL4, while all PSTTs and ETTs were negative.[1] Strong positivity for p63 is found in ETTs and negative for this case, as is with PSTT.[1] Markers of implantation site trophoblasts in PSTT include human placental lactogen, MUC-4, Mel-CAM, CD10, and HLA-G.[4] This case exhibited strong diffuse staining for MUC-4. Finally, Ki-67 which is a marker of cellular proliferation differentiated PSTT from the benign exaggerated placental site reaction with the patient's Ki-67 labeling index of 10%–15% compatible with PSTT (8%–20%).[4]

There are no PSTT-specific sonologic features. Instead, it can present with three sonologic patterns: Type 1 - solid, heterogeneous endometrial mass with minimal to moderate vascularity; Type 2 - solid, heterogenous myometrial mass with minimal to high vascularity; and Type 3 - cystic lesions in the myometrium with a high degree of vascularization (lacunar-type lesions).[4] It seems the index case presented with a Type 2 lesion - an irregular, solid, endomyometrial mass with minimal vascularity.

The preoperative sonologic suspicion of AVM, later confirmed by angiogram, facilitated appropriate surgical planning of this case. AVMs are abnormal direct communications between arteries and veins, bypassing the capillaries. Acquired uterine AVMs occur in 10%–15% of GTDs. Mechanisms for this phenomenon include (1) disorganized trophoblastic proliferation, (2) hCG-driven angiogenesis and vascular proliferation, and (3) formation of a myometrial scar following endometrial curettage.[2] PSTT is characterized by an infiltrative pattern of invasion and prominent vascular invasion which could predispose to vascular re-organization and uterine AVM formation.[1] To date, there are only four PSTTs complicated with AVMs in the literature [Table 1].[7-10] Three women were reproductive-aged with a recent full-term pregnancy, while one was postmenopausal with no identifiable antecedent pregnancy. Almost all had irregular vaginal bleeding, and one presented with acute abdomen from uterine rupture. Almost all had slightly elevated serum βhCG levels (27.6–250 mIU/mL). All four cases underwent pelvic angiography to confirm the uterine AVM. Half of the patients underwent preoperative embolization and all patients underwent total hysterectomy. One patient initially had embolization alone to conserve the uterus but due to persistent AVM, she eventually underwent hysterectomy. The primary treatment for the PSTT and

Table 1: Placental site trophoblastic tumors with co-existing uterine arteriovenous malformations

Author	Age/obstetric history	Antecedent pregnancy/interval	Symptoms	Serum beta-HCG (mIU/mL)	Diagnostics done	Intervention
Ichikawa[7]	33/G2P2	Full term, 9 months	Vaginal bleeding	27.6	MRI angiography	Total hysterectomy
Gupta[8]	28/G1P1	Full term, 2 years	Amenorrhea for 1 year, followed by acute abdominal pain and distension	250	MRI angiography	Preoperative embolization, followed by total hysterectomy
Elouazzani[9]	44/G0	-	Postmenopausal bleeding	-	CT angiography	Preoperative embolization, followed by total hysterectomy with bilateral salpingo-oophorectomy
Nakamura[10]	33/G1P1	Full term, 13 months	Vaginal bleeding	45.2	CT angiography	Transcatheter arterial embolization initially total laparoscopic hysterectomy

HCG: Human chorionic gonadotropin, CT: Computed tomography, MRI: Magnetic resonance imaging

AVM in our index case was still total hysterectomy. Preoperative embolization was an adjunct procedure done to minimize intraoperative blood loss.

The FIGO anatomic staging *without* the WHO prognostic scoring system is applied to both PSTT and ETT cases. In the presence of malignancy, any pulmonary nodule found is more likely metastatic such as in this case thus assigned stage III. Since serum βhCG is not a reliable tumor marker to monitor the subcentimeter metastatic lung lesion, serial chest X-ray and/or contrast-enhanced chest CT should be done.

TAHBS, with or without oophorectomy, is the definitive treatment for PSTT. Focal uterine resection has been reported.[6] Pelvic lymphadenectomy may be performed if there is deep myometrial invasion, grossly enlarged lymph nodes intraoperatively, or preoperative suspicion of nodal involvement.[4,6] In the index case, ileal resection was done under the suspicion that it was a metastatic spread from the uterus where it was adherent. Furthermore, the appearance of a vaginal mass and βhCG elevation (from 30.64 to 44.97 mIU/mL) after the first neoadjuvant EP-EMA demonstrates the chemoresistance and fast progression of this tumor [Figure 6].[10]

The evidence regarding the optimal management of PSTTs is limited due to the paucity of cases. In 2019, the International Society for the Study of Trophoblastic Diseases (ISSTDs) issued guidelines for stage-adapted treatment: Stage 1 with <48-month interval from antecedent pregnancy, surgery alone; Stage 1 with ≥48-month interval from antecedent pregnancy, surgery with adjuvant chemotherapy; and Stages II–IV with total hysterectomy, adjuvant chemotherapy, and resection of residual disease postchemotherapy are recommended. For all stages with antecedent pregnancy intervals of ≥48 months, high-dose chemotherapy or experimental therapies are also recommended.[3] Immune checkpoint inhibitors, such as pembrolizumab, have also been used for recurrent and chemotherapy-resistant GTN. However, its role in the treatment of PSTT is experimental and still requires further evaluation.[5]

Poor prognostic variables in PSTT include older age, advanced stage, long interval from antecedent pregnancy, distant metastases, high βhCG levels, deep myometrial invasion, high mitotic index, the presence of necrosis, and the presence of cells with clear cytoplasm.[4] Multivariable analyses of 326 patients from the ISSTD PSTT/ETT database showed that Stage IV disease and interval from antecedent pregnancy of ≥48 months were significant poor prognostic variables. This finding is consistent with the retrospective analysis of 125 PSTT/ETT patients in the United Kingdom. Those whose antecedent pregnancy was ≥48 months prior (n = 30) had a median survival of 3.05 years, whereas for those with shorter intervals, median survival time could not be computed because the survival curve did not drop below 50% (n = 95). Patients with nonmetastatic disease had a 10-year overall survival (OS) probability of 89% compared to 65% for Stage III disease and 42% for Stage IV disease.[3]

To improve prognosis in the presence of two adverse factors (pulmonary nodule and 6-year interval from antecedent pregnancy), this case was given platinum-based chemotherapy, which has been shown to significantly improve outcomes in patients whose pregnancy interval was ≥48 months. The UK PSTT/ETT study consisted of two cohorts: the first cohort (1976–2006) consisted of 62 patients whose outcomes have previously been reported in 2009, while the second cohort (2007–2014) consisted of 63 patients.[3] In the first cohort, in which the pregnancy interval was ≥48 months, all patients died. Such observation affected a change in treatment such that all patients in the second cohort with pregnancy intervals of ≥48 months were given platinum-based high-dose chemotherapy for 12 weeks, regardless of stage. A markedly improved median OS of 8.3 years is seen in the second cohort compared to 2.6 years in the first.[3]

There are no established guidelines for posttreatment surveillance of PSTTs. Regular βhCG monitoring for life with regular imaging surveillance is rational.[6] In the UK, chest X-ray and contrast-enhanced abdominopelvic magnetic resonance imaging are done every 6 months for the first 2 years, then annually for 5 years.[3] In the Philippines, serum βhCG is measured monthly for 6 months, then every 2 months for the next 6 months, every 3 months during the 2nd year, and then every 6 months thereafter. Chest radiography is also done annually for those with residual lung lesions postchemotherapy. Given that serum βhCG is not a good marker for tumor recurrence, regular imaging of the chest and abdomen seems reasonable.

In summary, PSTT, a case that is difficult to diagnose and treat, can become even more complicated in the presence of an AVM. Successful treatment is possible if carried out through a multidisciplinary approach involving several specialties in a center with experience.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authorship contributions

Victoria May H. Velasco-Redondo - Conceptualization, writing (original draft), visualization.

Ma. Bernadette Octavio - Writing - review and editing, supervision.

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Conflicts of interest

There are no conflicts of interest.

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