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Recurrent smooth muscle tumor of uncertain malignant potential - The dilemma on its diagnosis and treatment: A Case Report

Alexis Madarang Martinez[1], Jean Anne Balajadia Toral[1]

Abstract:

Uterine smooth muscle tumor of uncertain malignant potential (STUMP) is a mesenchymal tumor which lies along the spectrum of smooth muscle neoplasm of the uterus. This type of neoplasm has morphologic features intermediate between the benign leiomyoma and the malignant leiomyosarcoma but is characterized by distinct pathologic findings. STUMPs are rare and standardized treatment for these neoplasms remains to be controversial as its behavior and clinical course is unpredictable and response to various treatments remains to be challenging up to this time. Due to the rarity of these cases, consensus on the standardized treatment on the best surgical approach and adjuvant therapy has not been reached. This study presents a 40-year-old nulligravida who had initial surgical resection of uterine mass but had recurrence of a suprapubic mass with complete treatment of eight cycles of doxorubicin and now presenting with stable disease.

Keywords:

Doxorubicin, management, prognosis, recurrence, smooth muscle tumor of uncertain malignant potential

Introduction

Smooth muscle tumor of uncertain malignant potential (STUMP) is categorized as a subtype of uterine smooth muscle neoplasm. According to the World Health Organization (WHO), this neoplasm has histomorphology in between the typical benign leiomyoma and malignant leiomyosarcoma. It has a potential for malignancy for either one of these features: the presence of tumor necrosis, cytologic atypia, and mitotic activity; however, it does not fully fulfill the criteria for leiomyosarcoma.[1] Integrating gross and morphologic features is vital in classifying smooth muscle neoplasm as either a leiomyoma or a leiomyosarcoma. Every attempt should be made to categorize into one of these two before classifying it as STUMP. STUMPs are rare tumors with 0.01% of leiomyoma diagnosed as STUMP, and it also represents one-third of uterine sarcomas and 1.3% of uterine cancer.[2] Due to its rarity, heterogeneity, and inconsistencies in diagnosis, the true prevalence of STUMP is difficult to establish, and there are still no standardized guidelines to its treatment and follow-up.

Case Report

This is a case of a 40-year-old nulligravida who had a chief complaint of prolonged vaginal bleeding. She was initially diagnosed with myoma uteri described as a well-circumscribed 7.7 cm × 7.3 cm × 6.0 cm mass at the fundus. She was advised to undergo myomectomy. She was lost to follow-up for 2 years but came back due to

[1]*Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Philippine General Hospital, University of the Philippine, Manila, Philippines*

Address for correspondence:
Dr. Alexis Madarang Martinez, 10-O Future Point Plaza 2, Mother Ignacia Ave., Quezon City, Philippines.
E-mail: ammartinez3@up.edu.ph

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a sudden increase in abdominal girth with associated constitutional symptoms of weight loss, early satiety, and loss of appetite. Leiomyosarcoma was then considered. She underwent total abdominal hysterectomy, right salpingo-oophorectomy, adhesiolysis with bilateral pelvic lymph node dissection, and tumor debulking. Intraoperatively, the abdominopelvic mass arising from the anterior surface (isthmic area) of the uterus was adherent to the peritoneum. The abdominopelvic mass measured 32 cm × 23 cm × 26 cm which was cystic in consistency with irregular borders.

Histomorphology showed spindle cell neoplasm with extensive necrosis, mild atypia, and mitotic count of 0–1 per 10 high-power fields [Figures 1 and 2]. Immunohistochemistry stains done include smooth muscle actin (SMA) (diffuse, weak-to-moderate cytoplasmic staining) [Figure 3], caldesmon (diffuse, moderate-to-strong cytoplasmic staining) [Figure 4], and cluster of differentiation 10 (CD-10) (patchy, moderate cytoplasmic staining) [Figure 5]. The Ki-67 value was unfavorable at 45%–60%. Given all these data, the case was signed out as consistent with smooth muscle of uncertain malignant potential.

The following immunohistochemistry stains were requested on the specimen of the patient: (1) SMA is a ubiquitous protein found in muscle tissue which is vital for contraction. (2) Caldesmon is also vital in muscle contraction relaxation and binds to calcium, calmodulin, and tropomyosin to regulate smooth muscle contraction. Both markers are useful to differentiate smooth muscle tumors from myofibroblastic tumors. These were used in this case to differentiate leiomyosarcoma from endometrial stromal sarcoma (ESS). SMA and caldesmon will stain positive for leiomyosarcoma and negative for ESS. On the other hand, CD-10 is a membranous marker which aids in the diagnosis of solid tumors. This will stain diffusely positive for ESS while leiomyosarcoma will stain negative or patchy.[3] The Ki-67 is a cell proliferation marker which is high in leiomyosarcoma and weakly positive (<10%) in STUMP and leiomyoma. Hence, based on Stanford criteria for histologic diagnosis of leiomyosarcoma, two morphologic features of smooth muscles should be present. The patient only fulfilled the criteria for coagulative tumor cell necrosis (CTCN). She was negative for moderate-to-severe atypia and a mitotic count of at least 10 mitotic figures/10 high-power

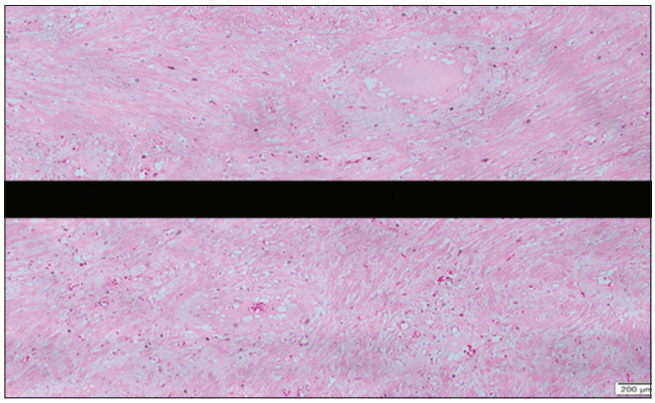

Figure 1: Slide review in hematoxylin and eosin stain in low-power objective field showing extensive necrosis

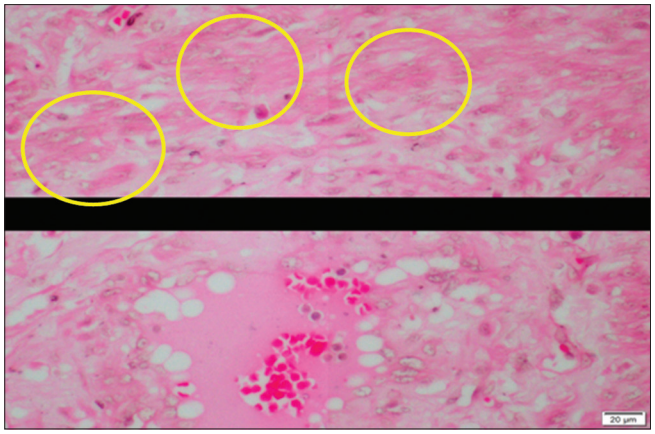

Figure 2: Slide review in hematoxylin and eosin stain in high-power objective field showing loss of nuclear details of the cells and atypia highlighted (yellow circles)

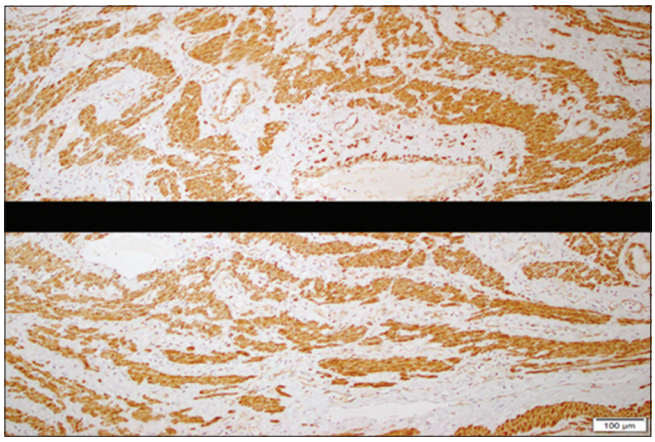

Figure 3: Smooth muscle actin immunohistochemistry stain showing diffuse, weak-to-moderate cytoplasmic staining in low-power objective field

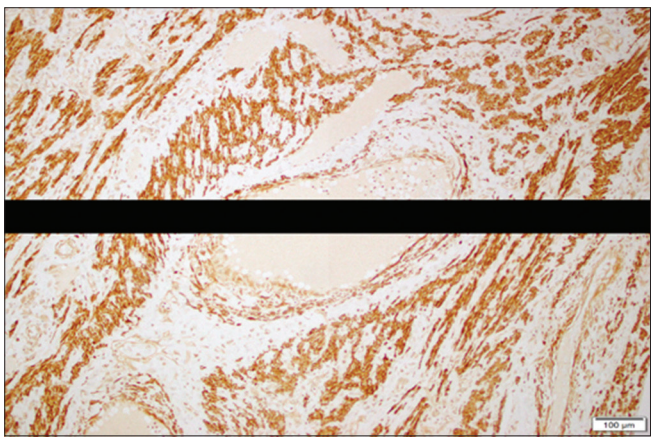

Figure 4: Caldesmon immunohistochemistry stain showing diffuse, moderate-to-strong cytoplasm staining in low-power objective field

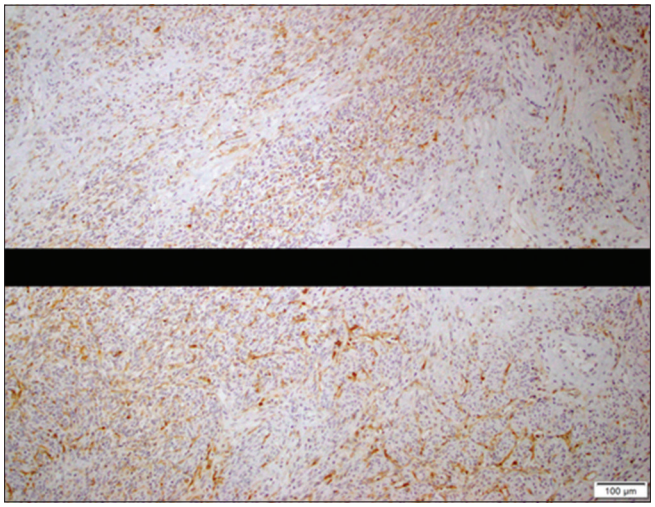

Figure 5: Cluster of differentiation 10 immunohistochemistry stain showing patchy, moderate staining in low-power objective field

fields (10 HPFs). ESS was the differential considered for the immunohistochemistry staining work-up where it showed diffuse staining for SMA and caldesmon and patchy staining for CD-10. In conclusion, results were signed out as consistent with smooth muscle of uncertain malignant potential.

Due to financial constraints, she was lost to follow-up for 17 months after she was advised to undergo chemotherapy. Baseline abdominal examination upon return to the clinic showed a palpable 4 cm × 5 cm suprapubic cystic mass. On computed tomography (CT) scan, pertinent findings were an apicoposterior pulmonary nodule on the left measuring 1.3 cm × 1.5 cm × 1.2 cm and a 2.0 cm × 5.7 cm × 4.0 cm fairly defined irregular complex mass with heterogeneously enhancing solid component at the suprapubic region. This mass was intimately related and cannot be differentiated from the superior aspect of the bladder and intimately related as well to the vaginal stump and peritoneal lining. She was managed as STUMP stage IB with tumor recurrence (suprapubic mass) and was started on doxorubicin 60 mg/m^2 planned for eight cycles (maximum dose of 480 mg/m^2). After four cycles of doxorubicin, repeat chest and abdominal CT scan showed that the solid pulmonary nodule on the left upper lobe remained to be stable measuring 2.0 cm × 1.5 cm × 1.2 cm (previously 2.0 cm × 1.6 cm × 1.3 cm) and the right paravesical cystic mass with extensions and mass effect to the urinary bladder, vaginal stump, and peritoneal lining had increased in size measuring 4.2 cm × 4.1 cm × 7.6 cm (previously 2.0 cm × 5.7 cm × 4.0 cm). Considerations for the pelvic mass were pelvic lymphocele or tumor residual.

She continued her chemotherapy completing a total of seven cycles. Positron emission tomography-CT scan showed that the spiculated pulmonary nodule at the apicoposterior segment now measured 1.3 cm × 0.8 cm × 0.7 cm (previously 2.0 cm × 1.5 cm × 1.2 cm) and the nodule is fluorodeoxyglucose (FDG)-avid while the right paravesical cystic mass was seen as a multiseptated fluid-attenuating focus measuring 4.5 cm × 3.2 cm × 2.8 cm (previously measuring 4.2 cm × 4.1 cm × 7.6 cm) with no significant FDG uptake with considerations including postsurgical lymphocele or cystic metastatic focus showing treatment response. She already had the maximum dose of doxorubicin at 480 mg/m^2. She still had a stable pulmonary and pelvic mass. Hence, the plan was to shift systemic chemotherapy to second-line agents gemcitabine (900 mg/m^2) on D1 and docetaxel (100 mg/m^2) on D1 and D8 every 21 days until disease progression or toxicity. As of this writing, she has yet to start her second line of systemic chemotherapy.

Discussion

Based on the local 5-year census of a tertiary hospital, only 1 case of STUMP was recorded out of 54 uterine sarcomas seen in the past 5 years, and their management remains to be individualized depending on its behavior and aggressiveness. The true global prevalence of STUMP is difficult to determine, and there were no literature on this due to the rarity of the disease and the inconsistencies with the diagnostic criteria. The incidence is not well known as well, but according to Picerno *et al*., 0.01% of leiomyomas are diagnosed as STUMP.[4]

In a systematic review by Di Giuseppe *et al*., they reviewed 189 cases of STUMP. The median age was 43 years. Symptomatology was typical of fibroid, and the most common initial presentation was abnormal uterine bleeding and menorrhagia which comprised 45.6% of cases. More than 82.5% presented with a large uterine mass, defined as ≥5.0 cm diameter.[5]

The study of Di Giuseppe *et al*. aimed to identify the risk factors for recurrent STUMP. The studies were searched through PubMed and Scopus, and 34 relevant studies included 189 cases in accordance with the Stanford criteria for diagnosing STUMP. One of the characteristics considered was the diameter with a median diameter of 8.0 cm and a range of 0.7–39.0 cm.[5] In our case, the maximum diameter was 32.0 cm and tumor recurrence was documented 17 months postoperative. To date, the largest documented size of STUMP was 38.9 cm in diameter with no tumor recurrence documented at 18 months postoperative.[6]

In diagnosing STUMP, there are three histologic features being considered: mitotic index (counted per 10 high-power fields), degree of cytologic atypia (graded as mild, moderate, or severe), and presence of CTCN.

Stanford criteria reported by Bell *et al*. for leiomyosarcoma requires at least two of the histologic features stated above, and for STUMP diagnosis, only one out of the three criteria is fulfilled. In our case, she had extensive tumor cell necrosis but with mild atypia and 0–1 mitotic figure <10 HPFs.[7]

Bell *et al*. further subdivided STUMP into three histologically distinct groups with different clinical behaviors, where our case fell into the (1) smooth muscle tumors of low malignant potential given that there was CTCN, <10 mitotic figures/10 HPFs, and mild-to-absent cytologic atypia. Other histological distinct groups were (2) atypical leiomyoma with low risk of recurrence characterized by diffuse, moderate-to-severe cytologic atypia, <10 mitotic figures/10 HPFs, and no CTCN and (3) atypical leiomyoma but experience limited which is characterized by focal, severe cytologic atypia, <20 mitotic figures/10 HPFs, and no CTCN.[7]

In 2020, Liu *et al*. did a review of 25 articles with 579 cases included in the analysis. STUMP recurrence was observed in 81 patients, with a recurrence rate of 14%. There was histologic type recorded for the recurrence in 59 out of the 81 cases. The following were the rates: 64.4% recorded as STUMP recurrence, 28.8% recorded as leiomyosarcoma recurrence. It was also recorded that STUMP recurred as liposarcoma in two patients (3.4%). In 53 cases, the interval from diagnosis to recurrence was recorded which ranged from 1 month to 144 months with a median interval of 34 months.[1] In our report, tumor recurrence was documented at 17 months after her operation. Given the presence of a paravesical cystic mass in our case, biopsy should be considered to determine the histopathology of the mass, either by doing a noninvasive approach with Trucut biopsy or resection by exploratory laparotomy. The patient already received her maximum dose of doxorubicin, and determining the histopathology of the tumor recurrence will guide us with further management and prognostication before proceeding with the second line for chemotherapy.

Diagnosis of STUMP is typically done postoperatively when patients undergo hysterectomy or myomectomy. There was recorded relapse from myomectomy in 6.6% of the cases, and recurrence ranges from 0.1 to 18 years.[1] Due to the indolent nature of STUMP, fertility preservation may be offered, but the consequence must be fully explained because of the unpredictable course of the disease.[1] Adjuvant therapy after excision of the mass using hormone or chemotherapy still has no proven value to prevent tumor recurrence.

Surgical resection remains to be the first line to eliminate the tumor. However, in this case where stump recurrence was described to be adherent to the bladder and will incur further morbidity, salvage therapy may be considered. The common chemotherapeutic agents that were reported to be used for STUMP were doxorubicin, ifosfamide, cisplatin, gemcitabine, and docetaxel which were either used as single agents or in combination.[1] One of the few case reports that mentioned the use of doxorubicin was in a 50-year-old patient with postmenopausal bleeding who underwent hysterectomy for a 5 cm × 8 cm STUMP mass. Pulmonary masses were initially seen preoperatively and were monitored to increase after 3 years where wedge resection was done to the three pulmonary nodules showing STUMP on two nodules and sarcoma on the third nodule. There was also a recurrence of a pelvic parietal mass measuring 8 cm × 9 cm with histology as well of leiomyosarcoma. Adjuvant radiotherapy was given and delivered to the paravertebral tumor bed, and chemotherapy with doxorubicin was also given. However, few of the pulmonary nodules were still noted to be stable. Hence, second-line gemcitabine-based chemotherapy was initiated with note of stabilization of the nodules, and follow-up will be done after 5 years.[8]

STUMP lies in the spectrum of smooth muscle tumor in between the benign leiomyoma and the malignant end of the spectrum would be the leiomyosarcoma. It has the potential to behave as a benign disease with no documented recurrence, but it also has a reported risk of recurrence. There were various clinical and histopathological characteristics identified to increase the recurrence of STUMP and had showed shorter recurrence free survival.. These features were summarized by a study done by Borella *et al*., including (1) doing morcellation as a procedure for the myomectomy, (2) pathologic features such as epithelioid feature with high mitotic count, and (3) immunohistochemistry result with Ki-67 value >20%, expression of progesterone receptor <83%, and diffuse p16 expression.[9] Other studies showed that p53 expression and the presence of coagulative necrosis showed an increased risk of recurrence as well.[1] In our case, the patient had extensive coagulative necrosis and high Ki-67 value of 45%–60%, which were features noted to have a high risk for recurrence.

STUMP has better prognosis than leiomyosarcoma where relapse for STUMP was reported at a rate of 27% while leiomyosarcoma relapse is at 69%. It also had a better 5-year overall survival of 92% for STUMP versus 40% for leiomyosarcoma, respectively.[8] However, given the incidence of relapse, regular surveillance after surgery of every 6 months for 5 years and yearly thereafter has been suggested. Gynecologic examination with annual imaging should be done for surveillance of STUMP patients.[1]

There were also molecular investigations conducted to investigate the alteration of driver genes in uterine smooth

muscle tumors. It was noted that atypical leiomyoma and leiomyosarcoma had similar miRNA signatures. STUMP and leiomyosarcoma had higher frequencies of p53 mutations and PTEN deletions compared to the benign leiomyoma and leiomyoma variants.[1] In this study, Zhang *et al*. concluded that although atypical leiomyoma, STUMP, and leiomyosarcoma shared similar molecular characteristics, most of the atypical leiomyomas and STUMP had comparable pathological and clinical features that were significantly different from the leiomyosarcoma.[10] Further investigations are still needed to explain the molecular pathways for the development of the STUMP. Other molecular markers that were being investigated for STUMP were *ATRX* and *DAXX* genes, and mutations of these genes showed poorer prognosis. An array-comparative genomic hybridization (CGH) genomic profiling was developed by Croce *et al*., where the genomic index of ≥10 had a high risk for recurrence and no recurrence was found for those <10. It was proposed in this study that CGH genomic profiling can be used to categorize STUMP as the benign group versus the potentially malignant group with a risk of recurrence.[11] These molecular studies still require further investigation together with examining the role of the following cancer-related genes *PRKDC, MLL3, ROCK2, CTSB, STAT 2,* and *PUM2* in the pathogenesis of STUMP.[1]

In our case, she is yet to receive her second line of treatment. A biopsy can be considered to determine the histopathologic diagnosis of the recurrent pelvic mass. Molecular markers may be requested for targeted therapies and prognostication. In the future, it will be vital to document the result of her subsequent treatment with gemcitabine and docetaxel to augment further the knowledge on the treatment of STUMP and its further sequelae to possibly behave as leiomyosarcoma.

Conclusion

STUMPs remain to have diagnostic and therapeutic dilemmas, and reporting cases are vital to aid in possible options to treat the recurrence of this tumor.

This study presented the difficulty in diagnosing STUMP as well as the challenge in managing recurrence given that there had been no guidelines to manage them up to the present time.

Declaration of patient consent

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

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Authorship contributions

Alexis M. Martinez - Involved in conceptualization, methodology, validation, resources, data curation, writing of the original draft, review of the draft, editing, and visualization.

Jean Anne B. Toral - Involved in conceptualization, validation, resources, writing review and editing, and supervision.

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Conflicts of interest

There are no conflicts of interest.

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