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Authors: Caglar Helvacioglu, Mustafa Eroğlu, Cem Yalçınkaya, Cumhur Selcuk Topal, Işıl Ada Akgul, Sumeyye Cimenli, İbrahim Kale

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Smooth muscle tumor of uncertain malignant potential (STUMP): a case-based analysis

Caglar Helvacioglu[1], Mustafa Eroğlu[2], Cem Yalçınkaya[1], Cumhur Selcuk Topal[3], Işıl Ada Akgul[1], Sumeyye Cimenli[1], İbrahim Kale[1]

[1]Department of Obstetrics and Gynecology, Maternal-Fetal Unit, University of Health Sciences Umraniye Training and Research Hospital, Istanbul, Turkey
[2]Department of Obstetrics and Gynecology, Health Sciences University Zeynep Kamil Women and Children's Diseases Training and Research Hospital, İstanbul, Turkey
[3]Department of Pathology, Umraniye Training and Research Hospital, Istanbul, Turkey

Corresponding author:
Caglar Helvacioglu
Department of Obstetrics and Gynecology, Maternal-Fetal Unit, University of Health Sciences Umraniye Training and Research Hospital, Istanbul, Turkey
e-mail: caglarhel@hotmail.com

ABSTRACT

Objectives: The present study aimed to analyze of uterine smooth muscle tumors of uncertain malignant potential (STUMP) and the outcomes of patients with STUMP.

Material and methods: In this retrospective study, the data of patients diagnosed with STUMP in a single tertiary center between January 2005–January 2020 were reviewed. We assessed the demographic variables, treatment outcomes, time until recurrence, disease-free and overall survival of the patients.

Results: Twenty-five patients diagnosed with STUMP were included in the study. The mean age of the patients was 43.2 ± 10.3 years. Thirteen of the 25 patients (52%) were treated by myomectomy, others received diagnoses following hysterectomy. The median follow-up time was 45.2 months. Recurrence was observed in three cases (12%), two of which were followed up without hysterectomy, and the third patient died by peritonitis carcinomatosa 60 months

after diagnosis although she received cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) treatment.
Conclusions: This study evaluates the data of patients with STUMP. Our results reveal a STUMP recurrence of 12%, like those previously reported in the literature. Despite the possibility of malignant recurrence, fertility-preserving treatment with close follow-up should be tried, because of the relatively early age at diagnosis.
Key words: uterus; leiomyoma; smooth muscle tumor; sarcoma

INTRODUCTION

Uterine leiomyomas are one of the most frequent tumors of the reproductive system in women. Although surgery is mostly involved in current treatment, therapeutic choice depends on the patient's symptoms, age, and reproductive status and plans [1, 2]. The differential diagnosis of leiomyoma and less common variants of uterine sarcoma is made as a result of the histopathological examination of the surgically removed specimen. Variants of leiomyoma are considered benign or malignant based on their histopathological features [3, 4]. Increased mitotic activity [> 10 High Power Fields (HPF)], nuclear atypia, and tumor cell necrosis indicate malignant myomas [5]. Myomas which show some, but not all sarcomatoid properties are defined as smooth muscle tumors of uncertain malignant potential (STUMP) [6]. STUMP, a rare heterogenous tumor, is diagnosed in patients around perimenoposal age [7]. Its diagnosis can be difficult due to bizarre findings and the accuracy can vary from one histopathologist to another [8]. Majority of STUMP patients have favorable outcomes; however, some tumors may progress aggressively [9]. Uterine STUMP rarity, the etiology, factors which affect prognosis, outcomes and recurrence risks are not well defined so we aimed to present the histopathological and clinical features of 25 patients with uterine STUMPs admitted to a tertiary hospital.

MATERIAL AND METHODS

A retrospective review was performed of 27 patients who underwent myomectomy or hysterectomy and were histopathologically diagnosed with STUMP at Health Science University Umraniye Training and Research Hospital, between January 2005–2020. Ethics committee approval was obtained from the local Ethics and Research Committee (REF: 19/11/2020 — 369). Two patients were excluded due to lack of follow up after the surgery. Uterine STUMPs were diagnosed in accordance with the criteria defined by Ip et al. and Bell et al. based on focality, atypia, and necrosis [10, 11]. A team of pathologists experienced in

gynecology and gynecologic oncology evaluated resection materials. Our multidisciplinary local tumor board investigated the clinical, operative, histopathological, and radiological data. Patients' data were collected from the hospital computerized registry. The parity, body mass index (BMI), preoperative CA 125 level, intraoperative findings, postoperative clinical course, and follow-up duration as well as the age of the patients were recorded, along with the histopathological findings. Cellularity was categorized as mild and high. Tumors showing nuclei with overlying nuclear membranes indicated mild cellularity, while tumors in which numerous nuclei were aggregated with overlying nuclear membranes and sparse stroma in between indicated high cellularity. Cytologic atypia was defined as the presence of tumor cells with grade 2 and 3 nuclear atypia. Observation of this finding in most sections showed diffuse atypia, whereas its occurrence in occasional sections indicated focal atypia. Mitotic activity was evaluated with the highest count method and using definitely mitotic figures only, which included the absence of a nuclear membrane, and extensions of chromatin from a center of aggregated chromosomes. The mitotic figures were examined in 10 HPFs. Necrosis was noted when present. Hyaline necrosis was characterized by viable and non-viable collagen deposition sites or granulation tissue between tumors, showing bleeding and less clear cellular lines. In some cases, estrogen receptor (ER), progesterone receptor (PR), p53, Ki67, cd10, caldeson and desmin immunohistochemical stainings were performed to assist in the differential diagnosis. In the annual follow-up examination, each patient underwent pelvic examination, pelvic ultrasonography, chest X-ray, every 6 months in the first 5 years, and annually thereafter, computerized abdominal tomography and thorax magnetic resonance imaging if needed. The state of recurrence, time until recurrence, histopathological evaluation of the recurring tumor, disease-free survival and overall survival times were analyzed.

Statistical analysis

Statistical analyses conducted with IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp). Categorical variables were presented with numbers and percentages, and numerical variables were given as, median, minimum and maximum. Descriptive data are given as medians and percentage distributions. Statistical significance was set at $p < 0.05$

RESULTS

Twenty-five patients with uterine STUMP were analyzed in this study. The clinical and pathological features are shown in Table 1. The median age of the patients at the time of

diagnosis was 44 years (range: 20–67 years). The median parity was 2 (0–7). Twenty percent of the patients were postmenopausal. The median BMI was 31.9 kg/m^2 (range: 24.5–40 kg/m^2). The BMIs of eighteen patients (72%) were over 30 kg/m^2. In one patient (4%), preoperative serum CA 125 was 67.6 U/mL, above the cut-off level of 35 U/mL. The patients did not have a history of pelvic radiation or hormone replacement therapy.
Among the patients, the most common symptom was abnormal uterine bleeding (68%), followed by pelvic mass (16%), chronic pelvic pain (12%) and infertility (4%). Fourteen (56%) patients had type 3 tumor according to Figo leiomyoma classification system. Myomectomy was performed in 13 (52%) patients, while the other 12 (48%) patients underwent hysterectomy at the first operation. In all myomas, surgical margins were clear from STUMP. The median age of the patients who underwent myomectomy and hysterectomy at the first operation were 37.5 (n = 12) years and 48 (n = 13) years, respectively ($p < 0.0001$).

Twenty-three percent (n = 3/13) of patients who initially received myomectomy subsequently underwent hysterectomy. In one case (Case 7), palpable lymph nodes were observed during hysterectomy, and bilateral pelvic and paraaortic lymphadenectomy were performed. No residual tumors were found in the specimens of hysterectomy. The median tumor size was 8.8 cm (Range: 2–20). Three patients (Case 1, Case 17 and Case 23) had histories of previous myomectomies, and histopathological examination revealed benign leiomyoma.

Eleven cases (44%) had mild and three cases (12%) had high atypia. Cellularity was not increased in four patients (16%). The mean mitotic index of the tumors was 3–4 (in 10 HPF) (range: 1–18/ 10 HPF). Seven patients (28%) had ≥ 10 mitoses/10 HPFs. Hyalin necrosis was observed in 20%. No cases had lymphatic or vascular involvement. The immunohistochemical results and receptors are shown in Table 2. P16 and p53 positivity were observed in six and seven cases, respectively, while progesterone and estrogen receptor positivity were observed in six and four cases, respectively. Eleven patients had ≥10% Ki-67 positivity while 14 showed ≤ 10% Ki-67 positivity. In patients with recurrence (Case 9, 20, and 23), Ki- 67 positivity rates were 30%, 2–3% and 4–5%, respectively. Case 20 and Case 23 had progesteron receptor positivity. In Case 4, CD10 and Caldesmon staining were negative, while desmin staining was positive.

The median follow-up time was 45.2 months (Range: 5–132). The patients did not receive adjuvant treatment after STUMP diagnosis. In Case 9, who had recurrence, multiple peritoneal nodules were thoroughly resected during cytoreductive surgery, after which hyperthermic intraperitoneal chemotherapy (HIPEC) was administered. She died 60 months

after STUMP diagnosis and 12 months after secondary surgery. Case 20 had undergone laparotomic myomectomy due to infertility. Limited tumor recurrence occurred 27 months after the initial surgery. There are no signs of distant metastasis in the 34th month of her follow up. Case 23 had undergone laparotomic myomectomy due to chronic pelvic pain. She had a history of myomectomy and the histopathological examination was in accordance with benign leiomyoma. We discussed the option of hysterectomy with the patient at the 27th month of her follow-up, which she refused. She is being followed-up watchfully.

The median age of patients with recurrence was 41 years at diagnosis and that of the cases with no recurrence was 44 years ($p = 0.647$). One patient with desire for fertility became pregnant 46 months after abdominal myomectomy (Case 18). No complications were observed during pregnancy and in the neonate, as caesarian section was performed at the 39th gestational week.

DISCUSSION

Smooth muscle tumor of uncertain malignant potential (STUMP) is not leiomyosarcoma (LMS), and does not meet the diagnostic criteria of leiomyoma or its subtypes, but it may display malignant behavior [12]. However, the diagnostic criteria and clinicopathologic features of STUMP are not completely clear [9, 13, 14]. STUMP may be focal/multifocal, show moderate or severe atypia with less than or equal to 10 mitosis/10 HPFs and no tumor cell necrosis (TCN); they may be diffuse, show moderate to severe atypia with less than or equal to 10 mitosis/10 HPFs and no TCN; some may show no atypia with less than or equal to 10 mitosis/10 HPFs and have tumor cell necrosis; or no atypia with more than 20 mitosis/10 HPF and no TCN may be observed, and finally, they may have no atypia, less than or equal to 10 mitosis/10 HPFs and ambivalent necrosis.

STUMP can relapse in forms of STUMP or leiomyosarcoma. Three patients (12%; 3/25) in our study had recurrences. Recurrence rates ranging between 0-36% have been reported in the literature [10, 15, 16]. However, as the definition of uterine STUMP varies widely, determining the recurrence rate among a large group of patients may be challenging. In their cohort of patients, Guntupalli et al. [16] assessed the risk factors for recurrence, and reported none. In our study, one of the patients with recurrence was diagnosed with LMS with multiple peritoneal nodules present in the upper abdomen, all of which were completely resected during cytoreductive surgery with HIPEC. The preferred treatment of recurrent disease is surgical excision, however, chemoterapy protocol is not clear [17, 18]. Guntupalli et al. [16] recommends for recurrent cases, surgical treatment followed by additional therapy

such as medroxyprogesterone acetate, Gn-RH agonists, and chemotherapy, with non-clear data about the efficacy of these agents. In their studies, Karatasli et al. [7] administered systemic chemotherapy (cisplatin and ifosfamide), while Kotsopoulos et al. [17] used chemotherapy with different combinations, including agents such as ifosfamide, epidoxorubicin, docetaxel, gemcitabine, bevacizumab, cisplatin, cyclophosphamide and vincristine. No case other than ours was treated with HIPEC in the literature, however, our patient died 12 months later.

No consensus exists for the management and follow-up of STUMP. Ip et al. [10] recommended follow-up examinations to be performed at least every 6 months within the first 5 years after hysterectomy, followed by annual follow-up for the next five years, not to miss delayed recurrence. Follow-up examinations should include general and pelvic examinations, and imaging studies including pelvic ultrasonography, CT, or MRI for assessment of new lesions and chest radiography to check for lung metastasis. If STUMP is diagnosed by myomectomy, hysterectomy is recommended in female patients who no longer want to preserve their fertility to eliminate the risk of residual tumor and recurrence [6, 19]. We recommended hysterectomy to Cases 20 and 23, both of who had recurrences, but they chose to be followed up instead. They were closely followed and are currently in their 7th months of recurrence. In case the patients want to preserve their fertility, informed consents, stating the recommended treatment and their refusal must be obtained, because preservation of the uterus may lead to recurrence. These patients must also be followed very closely and with imaging studies [9, 13]. Fertility sparing should be consider in STUMP patients, in the literature there are cases that have undergone in vitro fertilization treatments [20, 21].

The use of immunohistochemical stainings such as p16, p53, KI-67, p21, ER, PR, bcl-2 and Twist in the differential diagnosis of uterine smooth muscle tumors with potential malignant behavior has been investigated in the literature [5, 15, 22]. Of these, p16, p53, and KI-67 are thought to be the most useful in detecting clinically aggressive smooth muscle tumors, but their routine diagnostic use is not currently recommended because reports of their efficacy are scarce [5, 22, 23]. KI-67 immunohistochemical staining can help distinguish pycnotic nuclei from true mitotic figures and may be useful in evaluating mitotic activity, especially in tumors with atypia but without necrosis. The fact that Ki-67 was 30% in our patient who developed relapse as LMS may support the role of Ki-67 in predicting aggressive behavior.

Our study has some limitations. First is the small sample size, short duration of follow-up and the fact that it was conducted retrospectively. On the other hand, we think our results contribute to the literature with further information.

CONCLUSIONS

The diagnosis of STUMPs presents a challenge, and needless interventions due to misdiagnosis may end up in prolonged follow-up. As in most complex cases, consultation with experienced professionals in this regard constitute the cornerstone of management. It should be noted that these tumors may result in mortality, and albeit not high, recurrence risk exists.

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Conflict of interest

The Authors declare that they have no conflict of interests.

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Table 1. Clinico-pathological Characteristics of uterine smooth muscle tumor of uncertain malignant potential patients

Table 2. Receptors expression and immunochemical features of cases

Case	P16	P53	PR	ER	Ki-67 (%)
1			+	+	3--4
2					10--15
3	Diffuse +	Diffuse +			3--4
4	Patchy +	-	+	+	10--15
5					10--15
6		50%			1--2
7	Diffuse +				25--30
8	Focal +	50%			10--15
9					30
10	-	4%	+		20--25
11	-			+	1--2
12					10--15
13					25
14					1--2
15	Patchy +	Wild Type	+	+	1
16			-	-	1
17					1
18					1--2
19					15--20
20	-	+	+		2--3
21					1
22					10--15
23	+	15%	+		4--5
24					4--5
25					3--4

PR — progesterone receptor; ER — estrogen receptor