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Original Article

Smooth muscle tumor of uncertain malignant potential (STUMP): a clinicopathologic analysis of 26 cases

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Abstract: Background: To investigate the clinicopathologic features, differential diagnosis, and factors associated with recurrence in patients with smooth muscle tumors of uncertain malignant potential (STUMP). Methods: The clinical and pathologic data of STUMP patients diagnosed in Mindong Hospital of Ningde City from 2017 to 2018 were collected and slides reviewed, the high-frequency color Doppler ultrasound and pathological characteristics were observed, and the literature was reviewed. Results: All the STUMP diagnoses were confirmed by slide review. The age of onset was 23-61 years (mean 42.96 years). The main clinical symptoms were leiomyoma of uterus, prolonged menstruation, and increased menstruation. Color Doppler ultrasonography showed hypoechoic uterine wall nodules. The mean follow-up time was 62.9 months (range: 13-96 months). Conclusions: Smooth muscle tumors of undetermined malignant potential (STUMP) in the uterus are one of the rare gynecologic neoplasms. Although not malignant, they should be considered as low malignant potential tumors because they occasionally recur. Six of 13 recurrent tumors recurred in the years following hysterectomy with preservation. These six recurrent tumors are the only ones that had a strong immune response to p16 and p53. In support of early observation, these markers may help predict STUMP behavior. Patients diagnosed with STUMP should be monitored over time.

Keywords: Uterine neoplasm, smooth muscle tumor of uncertain malignant potential (STUMP), immunohistochemistry, clinicopathologic characteristic

Introduction

Uterine smooth muscle tumor (uSMT) is the most common mesenchymal tumor in the gynecologic tract. At present, smooth muscle tumors are found by high-frequency color Doppler ultrasound, surgical resection of the tumor to send to pathology, and postoperative pathological examination to judge the biologic behavior of the tumor and evaluate the prognosis. Uterine leiomyoma (LM), smooth muscle tumor of uncertain malignant potential (STUMP) and leiomyosarcoma (LMS) were classified by WHO. LM and LMS each contain multiple histologic subtypes. There is no difficulty in diagnosing LM and LMS, but STUMP often causes diagnostic confusion to pathologists. We reviewed the clinicopathologic features of 26 cases of STUMP in an attempt to find any additional clinicopathologic features that could help identify cases with recurrence. Our results were compared with those in the literature.

Materials and methods

Case selection

From 2010 to 2018, 26 cases of STUMP were diagnosed in the Mindong Hospital of Fujian Medical University. All cases with an initial diagnosis of STUMP and adequate follow-up received the slide review.

Clinical and pathologic data

The patient's age at diagnosis of the primary tumor, presenting complaints, intraoperative findings, operative procedure performed, and follow-up information were obtained from pathology reports, inter-hospital computerized clinical information system, or by contacting the original pathologists or the patients' physicians. The pathology reports and representative slides of these cases were reviewed. The number of sections taken from each tumor was noted to assess the thoroughness of sampling.

In all cases at least 1 block was taken for each 1 cm of the tumor. All slides were cut to 4 μm in thickness and stained with hematoxylin and eosin. The size of the lesion, its location (submucosal, intramural, or subserosal), and other gross features were recorded.

Cellularity was assessed using a modified method similar to that described by Sreenan et al. In grade 1 cellularity, most nuclei were widely separated without touching or overlapping of nuclear membranes; in grade 2 cellularity, most nuclei were more crowded with touching and slight overlapping of nuclear membranes; in grade 3 cellularity, most nuclei extensively overlapped. The extent of hypercellularity was classified as diffuse, focal, or multifocal. A tumor was considered diffusely hypercellular if this feature was present in most sections; focal, if present in an occasional section; and multifocal, if foci were separated by at least one 4 × field.

Cytologic atypia was graded as 0, 1, 2, and 3 for tumors showing absent, mild, moderate, or severe atypia, respectively. Significant cytologic atypia was considered present if tumor cells demonstrated grades 2 or 3 nuclear atypia, which was appreciable on low magnification, as described by Bell et al. The extent of the atypia was classified as diffuse, focal, or multifocal. Atypia was considered diffuse if this feature was present in most sections; focal, if present in an occasional section; and multifocal, if foci were separated by at least one 4 × field.

Mitotic activity was assessed using the highest count method, and only definite mitotic figures (MFs) were counted. The definition of a true MF included absence of nuclear membrane and presence of hairy extensions of chromatin extending from a central clot-like dense mass of chromosomes, either singularly (as in metaphase) or separated (as in telophase). The number of MFs was counted in 40 high-power fields (HPFs) (HPF=0.57 mm^2, Olympus BX41 microscope, 10 × eyepiece, 40 × objective) and expressed as MFs/10 HPFs.

The type of necrosis, that is, infarct-type, tumor cell, or ulcerative (commonly seen in submucosal tumors), was determined using criteria previously described. Although Bell et al. introduced the term “coagulative tumor cell necrosis”, we, like Hart, prefer simply “tumor cell necrosis” as the use of coagulative tumor cell necrosis leads to confusion with the common infarct-type necrosis that is frequently encountered in benign leiomyomas. Any individual tumor cell apoptosis was recorded.

Ancillary studies

Immunohistochemical staining was performed by the department of Pathology, Mindong Hospital of Fujian Medical University, in Fujian, using standardized procedures accredited by China Committee of Pathology Industry.

EnVision method was used for immunohistochemistry. All the antibodies were purchased from Fuzhou Maixin Biotechnology Co. Ltd. All the antibodies were of ready-to-use type. Immunohistochemistry was performed according to the instructions and DAB colored. The antibodies used were CD10, H-Caldesmon, P53, P16 and Ki-67, and non-tumor tissues were used as an internal control.

Interpretation of immunohistochemical staining

Microscopic examination was performed by two senior pathologists. Criteria of positive results were as follows. CD10 was positive for the presence of brownish yellow granules in the membrane; H-Caldesmon was positive for the presence of brownish yellow granules in the cytoplasm; P53, P16 and Ki-67 were all positive if there was nuclear staining. The number of positive cells in 100 tumor cells was counted in the most important area of high power field as a statistical result, and 10 high power fields were counted repeatedly, and the average value was taken. The number of positively stained cells was expressed as a percentage.

Results

Clinical findings

The age of onset of STUMP in 26 cases ranged from 23 to 61 years old, with an average of 42.96 years old. Clinically, leiomyoma of uterus, prolonged menstruation, and increased menstruation were the main symptoms. In addition, high-frequency color Doppler ultrasound found hypoechoic nodules in the uterine wall (**Figure 1A**). The tumor was surgically

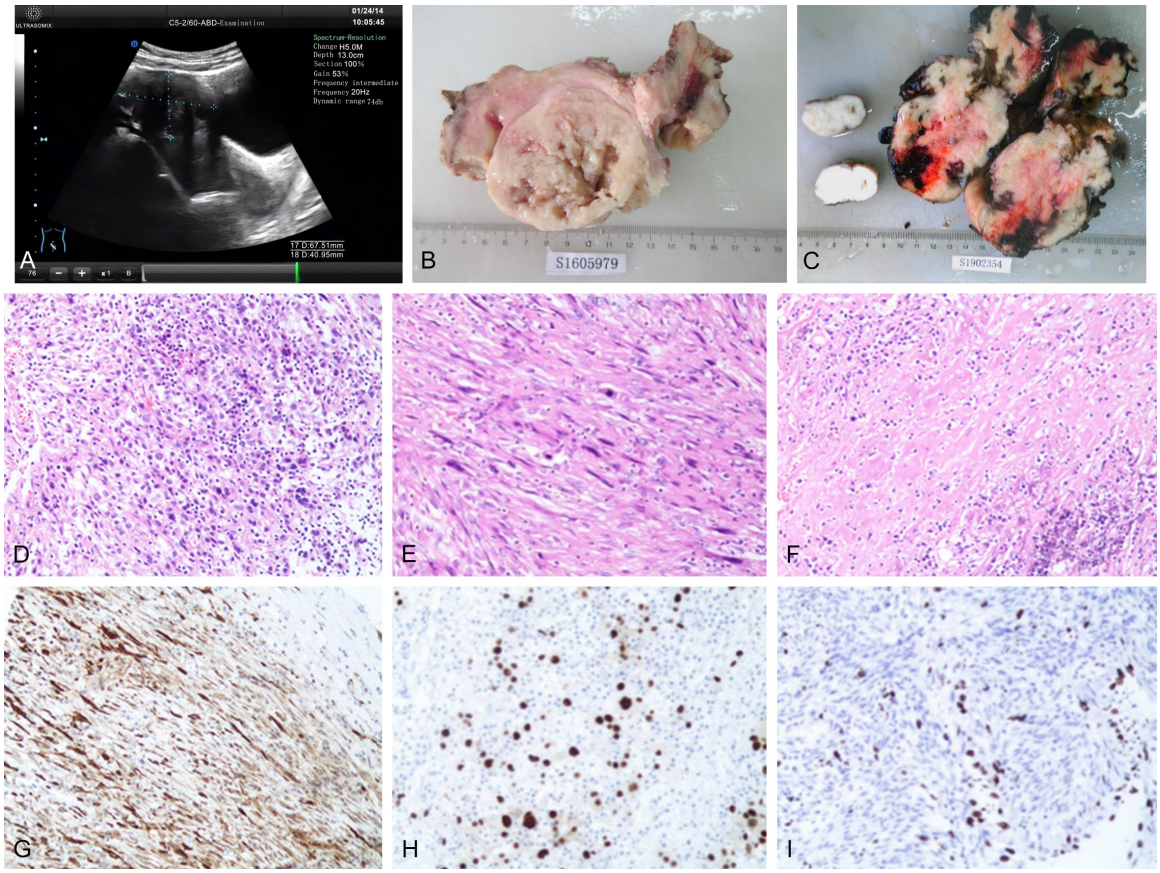

Figure 1. A. Sonography demonstrates hypoechoic nodules on the uterine wall; B. Gray and white nodules are seen between the muscle walls of a total hysterectomy specimen; C. A grayish white nodule with hemorrhage and cystic degeneration is seen in a myomectomy specimen; D. The tumor cells showed moderate to severe heteromorphism (100 ×); E. Mitotic figure is shown (100 ×); F. Tumor necrosis is shown (100 ×); G. Tumor was positive for P16 (100 ×) EnVision. H. Tumor was positive for P53 (100 ×) EnVision. I. Tumor was positive for Ki-67 (100 ×) EnVision.

removed without metastasis. During follow-up, none of the 13 patients who underwent hysterectomy recurred. 6 patients with hysteromyomectomy had recurrence, but without distant metastasis (**Table 1**).

Treatment

Six patients had myomectomy alone without additional surgical procedures, The remaining patients underwent hysterectomy and bilateral salpingo-oophorectomy as initial surgery. Intraoperatively, all tumors seemed to be confined to the uterus with noevidence of extrauterine disease. None of the patients received adjuvant therapy after the diagnosis of STUMP was made.

Pathologic findings

In gross pathological examination, the largest diameter of the tumor was 19 cm, and the smallest was 2.5 cm (mean, 8.2). Tumor localization data were available for 26 cases. 17 STUMPs were intramural, 5 were submucosal, and 4 were subserosal. Of those cases with an available macroscopic description, there was one or more gray-white nodules in the uterus, or only one or more gray-white nodules. The maximum diameter is 2.5 cm to 19 cm, the texture is tough, and it may be accompanied by rupture and bleeding. There was no concurrent pathology other than leiomyomas in any of the uteri removed (**Figure 1B**, **1C**).

On microscopic examination, when evaluable, the lesions had circumscribed borders and showed limited or no infiltration of the adjacent myometrium. None of the tumors showed evidence of lymphatic or vascular invasion. 21 tumors (81%) were hypercellular. 7 of the hypercellular tumors also showed diffuse overlapping of nuclei. Cytologic atypia was evident in

Table 1. 26 Clinical Manifestations and Operative Methods of Uterine STUMP

Number	Age	Clinical features	Maximum diameter (cm)	High frequency color Doppler ultrasound	Treatment	Metastasis	Recurrence Histology, Time, and Localization	Outcome (mo)
1	31	Increased menstrual volume, prolonged menstrual period and cycle for 5 years, abdominal pain once.	6.5	Uterine enlargement, right wall hypoechoic mass (myoma?)	Laparotomic myomectomy	No	None	ANED (96)
2	48	"Hysteromyoma" 2 years, classics amount increases half an year.	10	Multiple intrauterine hypoechoic nodules (myoma?)	Laparotomic myomectomy	No	STUMP, 50 mo within uterus	AAR (95)
3	42	Prolonged menstrual period for 3 years.	5.5	Multiple hypoechoic masses of uterus (leiomyoma?)	Subtotal hysterectomy	No	None	ANED (91)
4	42	Half a year's increase in the volume of classics.	3.5	Hypoechoic tubercle of uterine wall	Laparotomic myomectomy	No	None	ANED (36)
5	50	Prolonged menstruation and increased menstruation for 1 year.	8	Intrauterine moderate echogenic mass (submucous myoma not excluded)	Total hysterectomy with bilateral adnexectomy	No	None	ANED (76)
6	44	Irregular vaginal bleeding for more than 2 months.	11	Uterine enlargement, multiple myomas, sonogram	Extensive total hysterectomy	No	None	ANED (75)
7	50	Tumors were found in the lower abdomen for 5 months and vaginal bleeding for 11 days.	11	Hypoechoic nodule of left anterior tubercle of uterine wall	Laparotomic myomectomy	No	STUMP, 30 mo within uterus	AAR (68)
8	34	"Uterine leiomyoma" was found by B-ultrasound for 10 years, with frequent urination and acute urination for 23 days.	7	Low echo mass on the left wall of uterus (myoma?)	hysteromyomectomy	No	None	ANED (88)
9	47	"Uterine fibroids" found by B-mode ultrasound for 3 years.	8	Hypoechoic tubercle of uterine wall	Total hysterectomy	No	None	ANED (85)
10	39	8 days after induced labor, repeated abdominal pain for 5 days.	19	A hypoechoic mass (myoma?) In the right posterior wall of the uterus	accepted total abdominal hysterectomy	No	None	ANED (77)
11	23	It was found that "hysteromyoma" was accompanied by enlargement for 4 years and increase of menstruation for 1 year.	9	Enlargement of uterus, multiple hypoechoic nodules in uterine wall (myoma possible)	Laparotomic hysteromyomectomy	No	STUMP, 35 mo within uterus	AAR (74)
12	44	Multiple uterine fibroids were found for 1 month.	5.3	Multiple myoma of uterus	Total hysterectomy	No	None	ANED (73)
13	38	Increased menstruation with prolonged menstrual period for more than 5 months.	8	Hypoechoic mass of uterine wall	Laparoscopic myomectomy	No	None	ANED (72)
14	54	Increased menstruation with dysmenorrhea for 17 years.	6.7	Adenomyosis may be associated with multiple uterine fibroids	accepted total abdominal hysterectomy + bilateral adnexectomy	No	None	ANED (70)
15	35	Discovery of "hysteromyoma" for 3 years.	3.7	Hypoechous tumor of right uterine wall	Laparotomic hysteromyomectomy	No	None	ANED (69)
16	48	"Hysteromyomectomy" after 9 years, and then more than 1 year.	2.5	Posterior uterine wall hypoechoic nodule, size 37 × 36 × 29 mm (myoma?)	Laparotomic hysteromyomectomy	No	STUMP, 40 mo within uterus	AAR (68)
17	43	The volume of classics has increased for more than six years.	10	Multiple hypoechoic nodules in uterine wall (myoma?)	Subtotal hysterectomy	No	None	ANED (66)
18	35	"Hysteromyoma" was found with enlargement for 7 years.	7.5	Pelvic right hypoechoic mass 6.0 × 4.1 mm	Laparotomic hysteromyomectomy	No	None	ANED (67)
19	45	Increased menstruation for 3 months.	6.4	Hypoechous tumor of uterus	Laparoscopic total hysterectomy	No	None	ANED (59)
20	47	It was found that "hysteromyoma" lasted for 4 years and the menstrual cycle was shortened for 1 year.	14	Uterine wall hypoechoic nodule, large 62 mm × 54 mm × 41 mm (myoma?)	Laparoscopic myomectomy	No	STUMP, 43 mo within uterus	AAR (58)

21	43	Discovery of lower abdominal mass for half a year.	8.5	Posterior uterine wall hypoechoic mass (subserous myoma?)	accepted total abdominal hysterectomy + bilateral salpingectomy	No	None	ANED (54)
22	61	Menopause 9 years, repeated vaginal bleeding 9 months.	2.5	Uterine wall hypoechoic nodules (42 mm × 32 mm, irregular, lobulated).	accepted total abdominal hysterectomy + bilateral adnexectomy	No	None	ANED (53)
23	49	The menstrual period was prolonged for more than 2 years.	5.3	Hypoechoic tubercle of uterine wall	Laparoscopic total hysterectomy	No	None	ANED (49)
24	44	17 days of pelvic tumor discovery.	11	Hypoechous tumor in uterine wall	Laparoscopic myomectomy	No	STUMP, 25 mo within uterus	AAR (36)
25	39	Increased menstruation with prolonged menstrual period for 3 months.	6.7	Uterine wall hypoechoic nodule (myoma with cyst?) (68 mm × 63 mm × 61 mm)	Laparoscopic total hysterectomy	No	None	ANED (35)
26	42	Color Doppler ultrasound found “uterine fibroids” for more than 6 years, lower abdominal pain for 2 days.	15	The right side of the uterine fundus process outward heterogeneous echogenic mass (myoma rupture bleeding to be discharged).	Hysteromyomectomy	No	None	ANED (13)

Outcome: AAR indicates alive after recurrence; ANED,alive with no evidence of disease.

Table 2. 26 pathological features and immunohistochemistry of Uterine STUMP

Number	Site	Cellularity	Atypia	MF/10 HPF	Necrosis	p16	p53	Ki-67 (%)
1	IM	Diffuse 2	Multifocal, 2	4-6	ITN	0	0	<5
2	IM	Diffuse 3	Multifocal, 2	3	ITN(UN)	Diffuse	Diffuse	5
3	IM	Diffuse 2	Diffuse, 1	0	TCN	Diffuse	Diffuse	3-5
4	IM	Diffuse 3	Diffuse, 1	3-4	TCN	0	0	4-6
5	IM	Diffuse 1	Diffuse, 1	2	TCN	Diffuse	Diffuse	6-8
6	IM	Diffuse 1	None	3-4	TCN	0	0	3-4
7	IM	Diffuse 2	Multifocal, 2-3	3-5	ITN(UN)	Diffuse	Diffuse	<5
8	IM	Diffuse 2	Diffuse, 1	16-20	TCN	Focal	0	20
9	SS	Diffuse 2	None	18-20	ITN(UN)	Focal	Focal	20-25
10	SS	Diffuse 1	None	5-6	TCN	0	0	3-5
11	IM	Diffuse3	Multifocal, 2-3	6-8	ITN(UN)	Diffuse	Diffuse	4
12	IM	Diffuse 3	Multifocal, 2-3	3-4	None	0	0	4-5
13	IM	Diffuse 2	Diffuse, 1	4-5	TCN	0	Focal	6-8
14	SM	Diffuse 2	Diffuse, 1	5-6	TCN	0	0	6-7
15	SS	Diffuse 2	Focal, 2	4-6	ITN(UN)	0	0	4-5
16	IM	Diffuse 3	Multifocal, 2-3	5-6	ITN(UN)	Diffuse	Diffuse	4-5
17	IM	Diffuse 3	Multifocal, 2-3	3-4	ITN(UN)	0	0	3-5
18	SM	Diffuse 1	Diffuse, 2	6	TCN	Focal	0	2-3
19	SM	Diffuse 3	Multifocal, 2-3	2-3	ITN(UN)	0	0	3-4
20	IM	Diffuse 1	None	5-6	TCN	Diffuse	Diffuse	1-2
21	SS	Diffuse 2	Diffuse, 2	7-8	ITN(UN)	Diffuse	Diffuse	5-6
22	IM	Diffuse 2	Focal, 2	3-4	ITN(UN)	Focal	0	3-5
23	IM	Diffuse 2	Diffuse, 1	3-4	TCN	0	0	6-7
24	IM	Diffuse 2	Multifocal, 2-3	1-2	ITN(UN)	Diffuse	Diffuse	3-4
25	IM	Diffuse 2	Multifocal, 2-3	3-4	None	Focal	0	6-8
26	SS	Diffuse 3	Multifocal, 2-3	6-7	ITN(UN)	0	0	4-6

Site: IM, intramural; SM, submucosal; SS, subserosal. Cellularity: 1 = nuclei widely separated; 2 = nuclear crowding with slight overlapping; 3 = nuclear crowding and extensively overlapping. Atypia: 0 = none; 1 = mild; 2 = moderate; 3 = severe. MF, mitotic figures; HPF, high-power-field. Necrosis: ITN, infarct-type necrosis; TCN, tumor cell necrosis; UN = initially considered as necrosis of uncertain type; A= individual tumor cell apoptosis. p16 and p53 staining: 0 = negative; focal = <33%; moderate = 33%-66%; diffuse = >66%. Ki-67 receptor: expressed as percentage of positively stained cells.

fifteen cases (57.7%), 11 tumors (42.3%) had multifocal atypia, and 2 (7.7%) had diffuse atypia. Of those with cytological atypia, the atypia was mild in 7 (26.9%), moderate in 5 (19.2%), and severe in 9 (34.6%). Mitotic activity was found in 25 tumors (96.2%); 1 lesion had no identifiable MFs. The mitotic count ranged from 0 to 20 MFs/10 HPFs (mean, 5.5) and no atypical mitoses were found. 2 individuals (7.7%) had more than 15 mitoses/10 HPFs. Necrosis was found in 24 of the 26 cases (92.3%): 13 tumors had necrosis of infarct type and 11 had tumor cell necrosis. In 5 of these tumors (cases 9, 11, 17, 22 and 26), the necrosis was initially considered of an uncertain type (**Figure 1D-F**; **Table 2**).

Immunohistochemistry: H-Caldesmon expression was positive, and CD10 expression was negative, suggesting that the tumor was a smooth muscle tumor, not an endometrial stromal tumor. P16 and P53 were diffusely positive, indicating a poor prognosis. Patients who did not undergo hysterectomy had recurrence within 5 years after operation, while 3 patients who underwent hysterectomy had no recurrence at 91 months, 76 months, and 54 months after operation. Ki-67 staining showed that the cell proliferation index did not increase significantly in patients with tumor recurrence (**Figure 1G-I**; **Table 2**).

Follow-up information was obtained for all twenty-six patients (100%). The mean follow-up

time was 65.9 months (range, 13-96 months). Six patients (23.1%) developed recurrent disease. None of the patients had metastases. At the time of last known contact all women were alive and without evidence of disease. Six of the 16 patients (cases 2, 7, 11, 16, 20 and 24, 23.1%) developed recurrences at 50, 30, 35, 40, 43 and 25 months, respectively, after the initial operation. The recurrence in both patients was confined by the operation approach. The recurrent tumor exhibited diffuse immunoreactivity for p16 and p53, identical to the findings in the initial tumor. Histologic examination of recurrent tumors was consistent with that of the primary tumors. The patient did not receive other therapy after surgical operation and was alive without evidence of disease at 3 years after the second operation (**Table 1**).

Discussion

Smooth muscle tumor of uncertain malignant potential (STUMP) is a smooth muscle tumor that cannot be diagnosed as leiomyosarcoma, and cannot meet the diagnostic criteria of leiomyoma or its subtypes, but it may have malignant biologic behavior. STUMP usually excludes LM and LMS before diagnosis. However, the diagnostic criteria and clinicopathologic features of STUMP are not completely clear. Ip et al. [2] described four types of STUMP: (1) Atypical leiomyoma with limited experience (AL-LE); (2) Smooth muscle tumor of low malignant potential (SMT-LMP); (3) Mitotically active leiomyoma, limited experience (MAL-LE); (4) Atypical leiomyoma, low risk of recurrence (AL-LRR). Guntupalli et al. [3] added two types of STUMP: (1) Cellular leiomyoma (CLM) with mitotic figures > 4/10 HPF. (2) Irregular infiltration around the tumor or vascular invasion around the tumor. In the actual pathologic diagnosis work, the STUMP diagnosis relies on an elimination method. LMS and LM and their subtypes are excluded. In recent years, there have been three important diagnostic indicators to determine benign and malignant smooth muscle tumors: Mitosis number, cell atypia, and tumor cell necrosis (TCN) [4, 5]. Leiomyosarcoma requires at least two of the three diagnostic indicators. STUMP usually has only one. According to the literature, there were four diagnostic criteria for STUMP: (1) Focal or multifocal moderate to severe cell atypia, mitosis numbering < 10/10 HPF, undefined necrosis; (2) Diffuse moderate to severe cell atypia, mitosis numbering < 10/10 HPF, no tumor necrosis; (3) Tumor necrosis was found, and the mitosis number was less than 10/10 HPF; (4) Mitosis number was more than 15/10 HPF, and there were no tumor necrosis or cell pleomorphism [6].

However, correctly grasping the above standards is the focus and difficulty in pathologic diagnosis. Cell pleomorphism was classified by two levels [7]. Mild pleomorphism was characterized by cellular uniformity, only mild nuclear pleomorphism, fine granular chromatin, and consistent enlargement of the inner nucleus of the whole tumor. Moderate to severe pleomorphism is characterized by low-power field, marked nuclear hyperchromatism (coarse particles and clotted chromatin) and nuclear pleomorphism, and sometimes abnormal mitotic figures. The range of heterotypic cells was localized, diffuse or multifocal under a 4-fold objective. When counting mitosis numbers, we should pay attention not to mistake nuclear pyknosis, nuclear fragmentation, and nuclear apoptosis for pathologic mitosis. Necrosis must be neoplastic, not infarct type or ulcerative.

By immunohistochemistry, CD10 (-) and H-Caldesmon (+) can be used to differentiate endometrial stromal nodules; P16, P53 and Ki-67 are considered to be useful in the diagnosis of STUMP [8, 9]. P16 gene, located on chromosome 9p21, is a tumor suppressor gene directly involved in the regulation of the cell cycle. It competes with Cyclin D1 to bind to CDK4 or CDK6, and prevents cells from entering the S phase from the G1 phase, thus inhibiting cell proliferation. P16 is often overexpressed in leiomyosarcoma, and has a certain expression in STUMP, but rarely expressed in leiomyoma [10]. P53 gene is on chromosome 17p13.1. It plays an important role in cell cycle regulation and apoptosis, and inhibits cell growth. A disorder of P53 gene leads to the uncontrolled growth and transformation of cells, which is an important molecular event in the occurrence and development of many malignant tumors. P53 is often overexpressed in leiomyosarcoma, and is also expressed in STUMP. In this study, P16 and P53 were positive in 6 patients with recurrence. Interestingly, although P16 and P53 were expressed in the other 3 patients after hysterectomy, no recurrence

was found after 91 months, 76 months, and 54 months of follow-up. These results suggest that the positive staining of P16 and P53 may indicate a higher risk of STUMP malignant behavior in the uterus, but only in the uterus. Ki-67 is the most commonly used antibody in routine diagnostic work, which has a certain auxiliary role in the diagnosis of uterine smooth muscle tumor, but also has a high assessment of mitotic index of non-malignant tumors [12-14]. In this study, we found that Ki-67 was not a useful marker to differentiate STUMPs that recurred from other that did not.

In conclusion, surgical treatment was used for STUMP. The surgical methods were hysteromyomectomy and total hysterectomy [15-17]. None of the 13 patients who underwent hysterectomy recurred. Six of the 13 patients who underwent total hysterectomy recurred (46.2%). The recurrence rate of hysteromyomectomy patients was significantly higher than that of total hysterectomy patients. Therefore, although patients want to retain their uterus, in the absence of reproductive needs, it is still recommended that they undergo total hysterectomy to prevent recurrence.

Disclosure of conflict of interest

None.

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