

Original Article

Uterine smooth muscle tumor of uncertain malignant potential (STUMP) with coagulative necrosis: a comprehensive clinicopathologic study of 10 cases with long-term follow up

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Abstract: To observe the importance of coagulative tumor cell necrosis (CTCN) in the diagnosis of uterine smooth muscle tumors and to find ancillary methods that could help identify cases with potential of recurrence. Ten cases were selected. Complete clinical dates and pathological findings were reviewed for each case. Immunohistochemical stains for p16, p53, DOG-1, CD117 and Ki-67 were performed. The follow-up data was all available. Large areas of geographical CTCN were noted in 3 cases and multiple small foci of CTCN were found in 7 cases. Cytological atypia was absent to mild. The highest mitosis was 5 MFs/10 HPFs. One case was treated with leuprolide acetate before operation. P16, P53 and DOG-1 that were negative in other cases were diffusely positive in this case which also had a higher proliferation index (Ki-67) than others. This case developed recurrence at 27 months after the initial operation. This study suggests that a minority of STUMPs with CTCN will recur latterly. The combined results of P16, p53 and Ki-67 stains are useful to identify the STUMPs with an increased risk of recurrence supporting earlier observations. DOG1 may be a useful marker for STUMPs with potential malignancy. Our study adds to the limited experience of the clinical behavior of uterine smooth muscle tumors with coagulative necrosis treated with Leuprolide acetate (GnRH agonist).

Keywords: Uterine smooth muscle tumor of uncertain malignant potential, coagulative tumor cell necrosis, p16, p53, Ki-67

Introduction

The histological distinction between benign and malignant uterine smooth muscle tumors (USMT) is usually based on an assessment of combination of features including diffuse moderate to severe atypia, mitotic rate of ≥ 10 MFs/10 HPFs, and coagulative tumor cell necrosis (CTCN). A tumor with any 2 of these 3 features is often enough to warrant a diagnosis of uterine leiomyosarcoma. This approach to diagnosis was derived by Stanford investigators after studying 213 cases of problematic USMTs [1]. The World Health Organization classification indicates that a USMT that cannot be histologically diagnosed as unequivocally benign or malignant should be termed "Uterine smooth muscle tumor of uncertain malignant potential (STUMP)" [2]. Some STUMP may have

both significant nuclear atypia and a mitotic count of ≥ 10 MFs/10 HPFs, but only with coagulative tumor cell necrosis, these tumors are labeled as "smooth muscle tumors of low malignant potential (SMT-LMP)" which was one distinct group of STUMP [1, 2]. In this study we named the SMT-LMP as "STUMP with CTCN". Few studies [1, 3-7] have focused on this issue, and some of these studies lacked clinicopathologic details and/or follow-up data. The diagnosis of these tumors may be in argument sometimes using light microscopic features alone. Some recent investigations studied a variety of ancillary laboratory techniques in an attempt to identify useful markers that could help differentiate the benign and malignant tumors including immunohistochemical stains and various molecular techniques. We reviewed the clinicopathologic features of 10 cases of STUMP with

Uterine smooth muscle tumor of uncertain malignant potential (STUMP)

CTCN in an attempt to observe the importance of CTCN in the diagnosis of USMT and to establish any additional pathologic features that could help identify cases with potential of recurrence. Our results were compared with those in the literature.

Materials and methods

Case selection

Thirteen cases of USMT initially diagnosed as STUMP with CTCN between 2008 and 2016 were selected from the surgical pathology files of Beijing Friendship hospital. The diagnosis was confirmed by 2 gynecologic pathologists using the current World Health Organization criteria [8]. The necrosis in 3 cases was regarded as infarct-type necrosis or necrosis of uncertain type by one gynecologic pathologist. These three cases were excluded. Consensus was reached in 10 cases.

Clinical and pathologic data

The pathology reports and the medical records were reviewed, and the following information was obtained: patient's age at the time of diagnosis, presenting complaints, the type of initial surgical procedure, any subsequent therapy and follow-up information. History of hormone use, in particular, progestogen and contraceptive pill usage, administration of tranexamic acid and gonadotropin-releasing hormone (GnRH) analogues or the GnRH agonist (Leuprolide Acetate) was noted.

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 μ m 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 and Ip et al [3, 9]. In grade 1, most nuclei was widely separated without touching or overlapping of nuclear membranes; in grade 2, most nuclei were more crowded with touching and slight overlapping of nuclear membranes; in grade 3, most nuclei extensively overlapped. The extent of hyper-

cellularity 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 \times field.

Cytological atypia was graded as 0, 1, 2, and 3 for tumors showing absent, mild, moderate, or severe, respectively. Significant cytological atypia was considered present if tumor cell demonstrated grades 2 or 3 nuclear atypia, which was appreciable on low magnification, as described by Bell et al [1]. The extent of 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 \times field [10].

Mitotic activity was assessed using the highest count method, and only definite mitotic figure (MF) was counted. The definition of a true MF includes 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) [11]. To determine the final mitosis score, first we screened all the slides to find the most active areas using low power magnifications (\times 10 and \times 20) and then we counted 10 consecutive high power fields. The number of MF was counted in 40 high-power (HPFs) (HPF: field diameter 0.63 mm, field area 0.312 mm², Olympus CX31, 9 \times eyepiece, 40 \times objective) and expressed as MFs/10 HPFs.

The World Health Organization criteria was used for the assessment of CTCN [2, 8]. The CTCN is defined as an area of necrosis exhibiting abrupt transition from viable cells to necrotic cells where the ghost outlines of tumor cells are usually seen, hemorrhage and inflammation are uncommon.

Ancillary studies

The representative paraffin blocks were obtained for immunohistochemistry studies for all cases. Immunohistochemistry was performed on formalin-fixed and paraffin-embedded tissue by the biotin-streptavidin-peroxidase complex method with antigen retrieval. Appropriate positive and negative controls were

Uterine smooth muscle tumor of uncertain malignant potential (STUMP)

Table 1. Clinicopathologic Features of 10 cases of Uterine STUMP with CTCN

Case	Age (y)	Size (cm)/site	Symptom	Operation	Cellularity	Atypia	MF/10 HPF	Necrosis	P16	P53	Ki-67 (%)	CD117	DOG1	Outcome (month)
1	40	5, IM	Mass	Subtotal-hysterectomy	Diffuse 2	None	1	Multiple foci of CTCN	Focal		<5	0	0	ANED (24)
2	43	9, IM	Mass	Hysterectomy	Diffuse 1	None	1	Multiple foci of CTCN	0		<5	0	0	ANED (35)
3	45	6, IM	AVB	Subtotal-hysterectomy	Diffuse 2	None	3	Multiple foci of CTCN	Focal		<5	0	0	ANED (22)
4	42	6, IM	AVB	Hysterectomy	Diffuse 2	None	1	Focal CTCN & Hyaline necrosis	0		<5	0	0	ANED (36)
5	51	1, SM	NS	Hysterectomy and bilateral adnexectomy	Diffuse 1	None	0	Minimal foci of CTCN	0		<5	0	0	ANED (48)
6	51	13, IM	AVB & Mass	Hysterectomy	Diffuse 3	None	1	Multiple extensive geographical CTCN	Focal		<5	0	0	ANED (80)
7	38	8.5, SM	AVB	Myomatectomy, Hysterectomy latterly	Diffuse 3	Diffuse mild	5	Multiple extensive geographical CTCN	Diffuse	Diffuse	20	0	Diffuse	Alive with recurrent tumor (30)
8	41	3.5, NS	NS	Myomatectomy	Diffuse 2	None	0	Multiple foci of CTCN	0		<5	0	0	ANED (55)
9	35	5.5, NS	AVB	Myomatectomy	Diffuse 3	Diffuse mild	3	Multiple extensive geographical CTCN	0		<5	0	0	ANED (80)
10	29	6, NS	NS	Myomatectomy	Diffuse 2	Focal mild	5	Small foci of CTCN	0		5	0	0	ANED (4)

IM: intramural; SM: submucosal; NOS: not specific; AVB: abnormal vaginal bleeding or menorrhagia. CTCN: coagulative tumor cell necrosis; NS: not specific; ANED: alive with no evidence of disease. 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.

Table 2. Clinicopathologic Features and Follow-up Data of STUMP with CTCN in literature

Source	Total of cases	Age (years)	Size (cm)	Atypia	MF/10 HPF	CTCN	Follow up time (mo)	Recurrence or metastasis
Atkins et al	2	NS	NS	All were mild	1 and 4	Yes	NS	2 case, all were liver metastasis
Amant et al	1	48	7 cm	Mild	3	Yes	48	1 case, 48 mo, peritoneal and pelvis
Bell et al	4	1 case >50 3 case <50	NS	None~mild	3 and 5	Yes	29~165 (median 65)	1 case, 60 mo, omentum and uterus
Ip et al	7	25~59, (median 48)	0.7~18 cm, (median, 12)	None~mild	<5	Yes	36-144 (median 55)	None
Zhang et al	10	35~51, (median 41.5)	1~13 cm, (mean, 6)	None~mild	≤5	Yes	6~56 (median 36)	1 case, 27 mo, liver
Viols et al	1	39	10.5 cm	Mild	<1	Yes	24	None
Deodhar et al	1	NS	NS	NS	NS	Yes	36	Liver metastasis
Perrone et al	1	NS	NS	Moderate atypia	5	Yes	102	None

NS: not specific; mo: months.

Uterine smooth muscle tumor of uncertain malignant potential (STUMP)

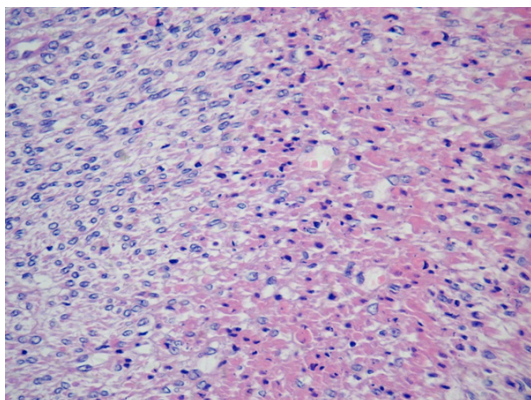


Figure 1. Small foci of coagulative tumor cell necrosis in STUMP with CTCN: the necrotic cells aggregated to be a focalized change and not scattered in the normal cell singly, there was an abrupt transition from viable cells to necrotic cells without reparative connective tissue between tumor and necrosis.

used. The following antibodies were chosen: p16 (Neomarkers, Fremont, CA, 6H12, 1:100 dilution); p53 (Neomarkers, Fremont, CA, DO-7, 1:300 dilution); Ki-67 (Neomarkers, Fremont, CA, MIB-1, 1:200 dilution); CD117 (Neomarkers, Fremont, CA, 2E4); DOG1 (Neomarkers, Fremont, CA, SP31). Masson trichrome stain was applied to 6 cases (case 1-5 and case 8) with focal or minimal foci of CTCN to highlight possible collagen deposition often seen in early infarct-type necrosis.

Interpretation of immunohistochemical staining

For p16, either strong nuclear or cytoplasmic staining or a combination was considered positive. Faint cytoplasmic or nuclear staining was regarded negative. For p53, only a strong nuclear staining was considered positive. CD117 and DOG1 were positive in cytoplasm and/or cytomembrane. The extent of positivity for these antibodies was scored as negative, focal (positively stained cells <33%), moderate (positively stained cells 33% to 66%), or diffuse (>66% of cells stained) [4, 12]. Immunohistochemical evaluation for Ki-67 was performed using a semiquantitative analysis [13-15].

Results

Clinical findings

The clinical and pathologic features of the cases are listed in **Table 1**. The age ranged

from 29 to 51 years (mean 41.5 years; median 41.5 years). The presenting symptoms were abnormal vaginal bleeding, pelvic mass, or a combinations thereof. One patient (case 7) was treated with GnRH agonist (Leuprolide Acetate) 3.75 mg/mo for 3 months before operation. The remaining patients did not receive any pre-operative medication and the preoperative diagnosis was benign uterine leiomyoma.

Treatment

Four patients had myomectomy (include case 7), two patients had subtotal hysterectomy, three patients had hysterectomy and one patient (case 8) underwent hysterectomy and bilateral salpingoophorectomy. One case (case 7) had the subsequent hysterectomy after the diagnosis of STUMP with CTCN was made. None of the patients received adjuvant therapy after the operation and the diagnosis of STUMP with CTCN.

Pathologic findings

The tumors ranged in size from 1 to 13 cm (mean 6.4 cm). Multiple typical leiomyomas, in addition to the lesion diagnosed as STUMP with CTCN, were present in 5 cases. Single lesion was present in 5 cases. Multiple nodules which all were diagnosed as STUMP with CTCN were present in 1 case (case 7). Five cases were intramural, 2 cases were submucosal and another 3 cases was not specified for the tumor location. The gross appearance in each case was white or pink, whorled sectioned surface; the fleshy appearance commonly seen in leiomyosarcoma was not evident. Grey to yellow foci consistent with necrosis was grossly evident in 3 cases (6, 7 and 9). Foci or small area of hemorrhage was observed in 4 cases (4, 6, 8 and 9).

For cellularity, 2 cases were grade 1, 5 cases were grade 2, 3 cases were grade 3. The mitotic counts ranged from 0 to 5 MFs/HPFs. The cytological atypia was absent in 7 tumors. Mild atypia was found in 3 tumors, two were diffuse (case 7 and case 9), and one was focal (case 10). All tumors had coagulative tumor cell necrosis. Multiple small foci of CTCN were found in 7 cases which is shown in **Figure 1**, Large areas of geographical CTCN were noted in 3 cases which is shown in **Figures 2 and 3**. The 3 cases with large areas of CTCN had none to light cytological atypia, all were hypercellular

Uterine smooth muscle tumor of uncertain malignant potential (STUMP)

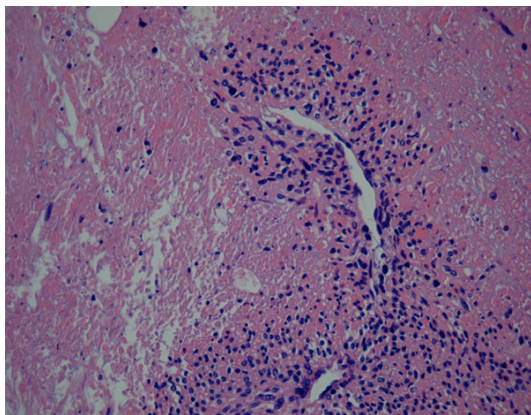


Figure 2. H&E staining of large areas of coagulative tumor cell necrosis in STUMP with CTCN: some tumour cells around the vascular are left alive in a large areas of tumor cell necrosis.

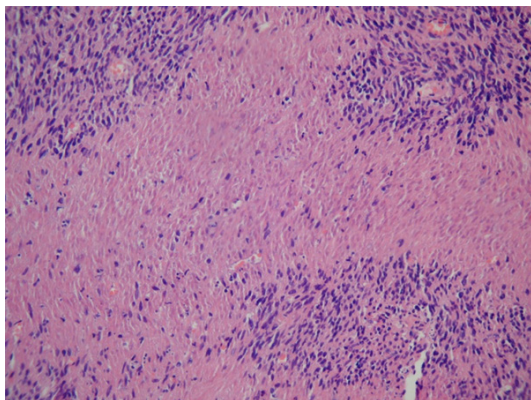


Figure 3. Large areas of geographical coagulative tumor cell necrosis in STUMP with CTCN. There is an abrupt transition from viable cells to necrotic cells without an interposed zone of fibrous tissue. Ghost outlines of tumor cells are seen within necrotic areas.

(grade 3), the mitosis was 1 MFs/10 HPFs, 3 MFs/10 HPFs and 5 MFs/10 HPFs respectively.

The p16 were diffusely positive (cytoplasm and nuclear) in 1 case (**Figure 4**) and were focally positive in 3 cases, 6 cases were negative. P53 was diffusely positive with strong nuclear staining pattern in this case (**Figure 5**) and 9 cases were negative. DOG1 was also diffusely positive with weak to moderate cytoplasmic staining pattern in this case and 9 cases were negative. CD117 was negative in all cases. Ki-67 was below 5% in 9 cases and was near to 20% in 1 case (case 7).

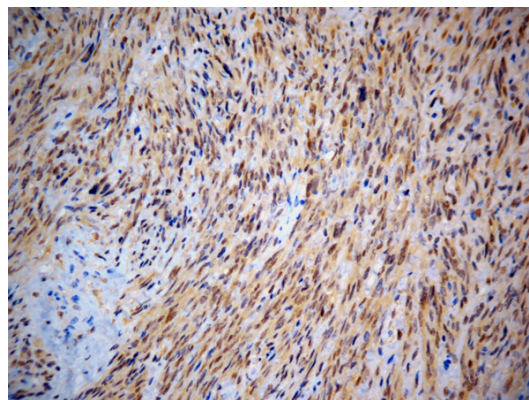


Figure 4. The tumor cells show diffuse (cytoplasmic and nuclear) immunoreactivity for p16.

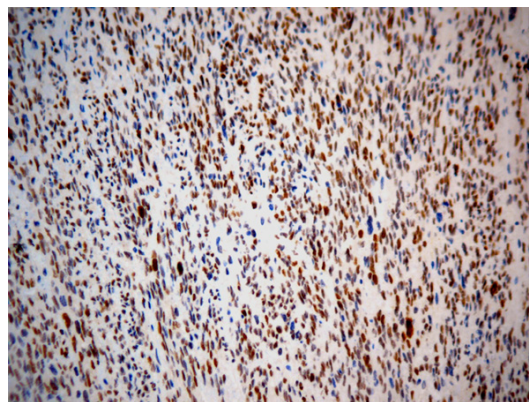


Figure 5. The majority of tumor cells show strong nuclear immunoreactivity for p53.

There was no obvious collagen deposition identified around the CTCN with Masson trichrome stain in 6 cases (case 1-5 and case 8).

Follow up information

Complete follow-up information was obtained for all 10 cases. The time of postoperative follow-up ranged from 4 to 80 months (mean 41 months and median 36 months). At the time of last known contact, all women were alive. One patient developed recurrence at 27 months after the initial operation. The recurrent sites were in the liver and were multifocal. The recurrent tumor was diffusely hypercellular with moderate atypia and a mitotic count of 12 MFs/10 HPFs fulfilling the criteria for leiomyosarcoma. The CTCN was not found possibly because the tissue for diagnosis was core biopsy. This patient underwent chemotherapy after the recurrence. She was alive with tumor at last

Uterine smooth muscle tumor of uncertain malignant potential (STUMP)

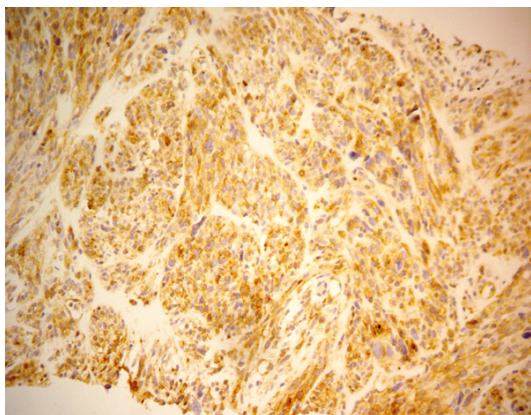


Figure 6. The tumor cells are positive for DOG-1 in the recurrent tumor which was the same as the initial STUMP in uterine.

follow-up, 30 months after the initial operation. The recurrent tumor showed diffusely strong immunostaining for p16, p53, ER, PR and diffusely moderate immunostaining for DOG1 (**Figure 6**), identical to the findings of the initial tumor in uterine. The Ki-67 was also near to 20% in the recurrent tumor.

Discussion

The definition of smooth muscle tumor of uncertain malignant potential (STUMP) is: a smooth muscle tumor that cannot be diagnosed reliably as benign or malignant on the basis of generally applied criteria [2]. STUMP had been subdivided into 4 histological subgroups [1, 10]. These subgroups were (1) atypical leiomyoma with limited experience in which the tumor cells showed focal significant cytological atypia, <10 MFs/10 HPFs, and no CTCN. (2) atypical leiomyoma with low risk of recurrence defined tumors with diffuse moderate to severe cytological atypia, <10 MFs/10 HPFs, and no CTCN. (3) mitotically active leiomyoma, limited experience in which the only worrisome feature is a mitotic count of ≥ 20 MFs/10 HPFs. (4) smooth muscle tumors of low malignant potential (SMT-LMP) which was composed of neoplasm with CTCN, <10 MFs/10 HPFs, and absent to mild cytological atypia. In this study we named the SMT-LMP as "STUMP with CTCN". There were different pathologic features and recurrence rate in these subgroups, it is necessary to study them separately with putting importance on the potential malignant feature and the most suit-

able treatment for each subgroup. The difficulty in studying STUMP with CTCN lies in their rarity. Combining our results with the previous studies, there were total 27 cases of STUMP with CTCN have been reported (**Table 2**) [1, 3, 4, 6, 16-18], six of them had recurred and the rate of recurrence was 22.2%.

CTCN must be distinguished from infarct-type necrosis, which is a common finding in benign leiomyomas. In infarct-type necrosis there is usually a zone of granulation and/or fibrous tissue that separates the viable areas of the tumor from the necrotic areas. Tumor cell necrosis is characterized by an abrupt transition from viable cells to necrotic cells without an interposed zone of granulation tissue or fibrous tissue. Ghost outlines of the tumor cells are usually seen within the necrotic areas. The assessment of necrosis is complicated by its occasional presence in otherwise morphologically benign tumors of foci of individual tumor cell necrosis unaccompanied by infarct-type necrosis or CTCN. It is probably impossible to confirm whether this form of cell death represents the earliest necrosis of any particular type, in view of the fact that rare tumors with these features have recurred, some investigators classify the tumor with this feature as STUMPs [6, 10]. In our study, 7 cases had focal or minimal foci of CTCN. For the necrotic cells aggregated to be a focalized change and not scattered in the normal cell singly which was the character of individual tumor cell necrosis, there was an abrupt transition from viable cells to necrotic cells without an interposed zone of granulation tissue or fibrous tissue mostly demonstrated by the Masson trichrome stain, they were regarded as CTCN. All these 7 patients had uneventful follow-up. Three cases with large areas of geographical CTCN have significant increased cellularity. This may suggest that in a compressed space where the blood supply of the cells can be reduced, the tumor cell necrosis may occur thereby. This may also account for the difficulty in distinction of infarct-type necrosis and CTCN sometimes [19].

Numerous immunohistochemical studies have endeavored to overcome the limitation of light microscopy in differentiating benign USMT from malignant tumors. The most consistent results have been related to the over expression of p16 and p53 [3, 4, 13, 15, 20, 21]. P16 protein

was a tumor suppressor protein which acts as a negative cell cycle regulator. The overexpression of p16 has been identified in uterine leiomyosarcomas and fewer STUMPs. In Atkins et al's report [4], 86.7% of leiomyosarcomas were positive for p16, only 13% (3 of 23) of benign leiomyomas showed focal positive staining with this marker. 38% (3 of 8) STUMP in the same study expressed p16 strongly and diffusely, two of these patients with CTCN, mild atypia and <5 MFs/10 HPFs recurred, the third patient was lost to follow-up. In Bodner-Adler et al' study [20], 57% (12 of 21) of leiomyosarcomas expressed p16 compared with only 12% (3 of 26) of leiomyomas. In this study, 21% (5 of 24) STUMPs were focally (<33% of tumor cells) immunoreactive for p16. All of these patients were alive at a median follow-up of 41 months. Mutation of the p53 gene is one of the most common molecular events in human carcinogenesis and is sometimes associated with aggressive disease. Most investigators have found an overexpression of p53 protein in uterine leiomyosarcomas but not in leiomyomas, and the frequency of positive p53 in uterine leiomyosarcomas has ranged from 13% to 56.5% [21-25]. A few studies found negative, Weak or focal expression of p53 in STUMPs, and all patients followed a benign clinical course [15, 25-27]. In Ip et al's report, 2 cases of STUMP with focal mild atypia, 4 MF/10 HPF and none CTCN that recurred had diffuse and strong immunoreactivity for p16 and p53 [3].

Some investigators advocate the use of Ki-67 immunostaining to better estimate mitotic activity in USMT. A higher proliferation index has been demonstrated in leiomyosarcomas and some STUMP, but not in leiomyomas [27, 28-30]. In the study by Chen L, more than 10% of cells which was positive for Ki-67 were observed in 83% of uterine leiomyosarcoma, 100% (2 of 2) of STUMP, but none of benign leiomyomas [28]. There was no follow-up data in the Chen L's study. DOG1 was first identified as a potential marker of GISTs in a microarray-based study investigating gene expression profiling in GISTs compared with other mesenchymal neoplasms. It has been realized that DOG1 is in fact the same protein as a calcium-activated chloride channel in the interstitial cells of Cajal. DOG1 have been described to diffusely express in some uterine leiomyosarcoma by Sah's study, and it was negative or focal positive in the uterine leiomyoma [31].

In our study, case 9 had been diagnosed as uterine leiomyosarcoma by two pathologists of other hospitals. The patient didn't receive any further therapy or operation. A longtime follow-up (80 months) demonstrated that the tumor was not malignant. Case 7 have large areas of geographical CTCN and mild cell atypia which was similar to case 9, but experienced a multiple liver metastasis. Why the latter behaved malignantly? In a further contrast, the case 7 have a striking higher proliferation index (Ki-67) than the case 9. The p53, p16 and DOG1 were also diffuse positive in case 7 but negative in case 9 and other cases. This suggest that diffusely strong positive staining of p53, p16, and a high proliferation index (>10%) seems to be helpful in the prediction of the behavior of STUMPs. Our results also suggest that DOG1 may be a potential useful marker for STUMPs which will recur and deserve further study.

It is important to be aware of the range of possible morphologic changes that may induced by hormonal treatment in USMTs, as their presence may cause diagnostic difficulty or potentially even misdiagnosis. GnRH agonists (GnRH-a) are sometimes used to create a temporary artificial menopause that leads to the shrinkage of large uterine leiomyomas facilitating their operative removal and to reduce excessive bleeding. Reports on the range of histological changes associated with GnRH-a are conflicting. Some investigators found no light microscopic differences between treated versus untreated tumors [9, 32]; some other studies showed that increased cellularity and coagulative necrosis was associated with preoperative GnRH-a treatment [33, 34]. One of three cases with large areas of geographical CTCN and hypercellularity in our study had been treated with GnRH agonists (leuprolide acetate) monthly for 3 months before operation. Considering the drug history and the absence of other worrisome features, such as myometrial infiltration, intravascular growth, diffuse severe atypia, high mitotic count (≥ 10 MFs/10 HPFs) in this case, we put it in STUMP with CTCN. The patient developed metastasis at 27 months after the initial operation. Although it is difficult to distinguish the STUMP with CTCN which will recur later from benign USMT with CTCN induced by the preoperative GnRH-a treatment, a combination of p53 and p16 over expression with high proliferation

index may help identify these clinically aggressive STUMPs with CTCN.

There is no consensus for the management of this tumor up to now. The report about it was rarely seen. In Ip et al's study [3], six of the 7 cases of STUMP with CTCN received hysterectomy and bilateral salpingo-oophorectomy; one case had initial myomectomy followed by hysterectomy. None of the STUMP with CTCN recurred in Ip et al's study. In Bell and Hendrickson et al's study [1], the case recurred had twice myomectomy, and then hysterectomy and omentectomy were performed. The case with malignant behavior reported by Amant et al had hysterectomy alone without additional surgical procedures [3]. In this study, one case recurred underwent myomectomy initially followed a hysterectomy after the diagnosis of STUMP with CTCN. For the case that not recurred in our study, three patients had myomectomy, two patients had subtotal hysterectomy, three patients had hysterectomy, and one patient underwent hysterectomy and bilateral salpingo-oophorectomy. All of these dates seem to show that the manners of operation don't influence the biological behavior of the tumor of SMT-LMP directly. Hysterectomy and bilateral salpingo-oophorectomy may be a safe choice for the patients with STUMP with CTCN.

In conclusion, the rare UMSTs with small foci or large area of coagulative tumor cell necrosis, but lack both significant nuclear atypia and a mitotic count of ≥ 10 MFs/10 HPFs are appropriately designated STUMPs, for some of these tumors could develop recurrence. More caution should be put to the STUMP with coagulative necrosis treated with GnRH-a. Diffusely strong positive staining of p53, p16, and a high proliferation index are helpful to identify the STUMPs that may behave in a malignant fashion.

Disclosure of conflict of interest

None.

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Uterine smooth muscle tumor of uncertain malignant potential (STUMP)

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