Uterine smooth muscle tumours of uncertain malignant potential: a case report and literature review

T Seloka, MC Van Aardt
Department of Obstetrics and Gynaecology, University of Pretoria, Pretoria, South Africa

Case report
A 41 year-old, gravida 2, para 2, was referred with abnormal uterine bleeding that got progressively worse over the past 6 months. Examination and ultrasound reveiled a large fundal myoma of 8 x 8cm. Pap smear and endometrial biopsy was normal. Patient opted for a histerectomy after appropriate counselling. Histopathology reported a smooth muscle tumours of uncertain malignant potential (STUMP).

Introduction
Uterine smooth muscle tumours are common, and they range from benign leiomyomas to high-grade leiomyosarcomas. Uterine leiomyomas are the most frequently seen benign tumours of the female genital tract, affecting up to 25% of females in general.[1]

Smooth muscle tumours of uncertain malignant potential (STUMP) are a heterogenous group of tumours that cannot be diagnosed as either benign or malignant and have an unpredictable clinical behaviour.[1] They can be gynaecologic or somatic, with the uterus being the most common site for the gynaecological group.[2] They have a risk of recurrence and metastasis outside the pelvis. There is currently no consensus regarding the risk of malignancy, recurrence, management and follow-up as there is very little data on these tumours.

Classification
Smooth muscle tumours of the uterus are classified into benign and malignant based on three main histopathologic features: 1) mitotic activity, 2) presence or absence of coagulative tumour cell necrosis and 3) degree of nuclear atypia.[3]

Benign leiomyomas have the following diagnostic features: 1) low mitotic index of <5 mitotic fields/10 high power fields, 2) no cytologic atypia, 3) no cell necrosis, although they may have ischaemic necrosis, 4) spindle-shaped cells that are uniform in size and shape, 5) no intravascular component, and 6) they are well circumscribed.[4] However, there are benign variants of leiomyomas that have the same clinical picture as ordinary leiomyomas.[4,5]

Malignant leiomyosarcomas are diagnosed if any two of the following three criteria are present: 1) a mitotic index of ≥10 mitotic fields/10 high power fields, 2) presence of coagulative tumour cell necrosis, and 3) moderate to severe atypia.[5]

There is a group of tumours that have an unusual combination of the criteria and are classified as variants of leiomyomas.[4] See Table 1.

Correspondence
MC Van Aardt
email: mcvanaardt@gmail.com

Table 1. Variants of leiomyomas[4]

Benign variants of leiomyomas:
Mitotically active leiomyomas
Myxoid leiomyomas
Epitheloid leiomyomas
Plexiform leiomyomas
Dissecting leiomyomas
Neoplasms with uncertain clinical behaviour
STUMP
Leiomyoma with bizarre nuclei
Cellular leiomyoma
Neoplasms with extrauterine disease
Leiomyomatosis peritonealis disseminate
Intravenous leiomyomatosis
Benign metastasing leiomyomas
Multiorgan or primary extrauterine neoplasms
Hereditary leiomyomatosis & renal cell carcinoma syndrome
Lymphangioleiomyomatosis
Cowden syndrome
Vulvar and oesophageal leiomyomatosis

The term STUMP was first used by Kempson in 1973.[5] According to the 2003 World Health Organisation classification, STUMPs are a subgroup of uterine smooth muscle tumours. These tumours are heterogenous as they cannot be diagnosed as either benign or malignant.[1,3,6] They have an unusual combination of the three diagnostic criteria for leiomyosarcomas. They have also been described as benign-appearing tumours with tumour cell necrosis.

STUMPs are diagnosed based on presence of at least two of the following:[1,3]
- no tumour cell necrosis
- mitotic index <20 mitoses/10 high power fields (HPF)
- moderate to severe atypia

These tumours have an unusual and unpredictable clinical behaviour with local recurrences and less often, metastases.[2]

Clinical presentation
Most patients present in their reproductive years, with a median age at diagnosis being 43yrs.[3] Although age does not predict

prognosis and recurrence in STUMP, it has been shown that women diagnosed with leiomyosarcomas are on average 10 years older than those diagnosed with benign leiomyomas.[3] Because STUMPs are so rare, we do not have epidemiological information for them. Leiomyomas are observed more in black females than caucasians. The risk of leiomyomas is higher in nulliparous women and decreases with the number of births. A higher body mass index (BMI) also increases the risk of developing leiomyomas.[7] The latter two risk factors are thought to be because of increased chronic oestrogen exposure and are thus also risk factors for malignant leiomyosarcoma. Cigarette smoking and the use of combined oral contraceptive pill decreases the risk of developing uterine leiomyomas and malignant leiomyosarcomas.[7]

Patients with STUMP present with similar symptoms such as those with benign leiomyomas and those with leiomyosarcomas.[6] Most patients are asymptomatic at diagnosis, and the leiomyomas are found on routine clinical examination.[3] Some patients will present with abnormal uterine bleeding, infertility, chronic pelvic pain and pelvic pressure symptoms.[3,8] Anaemia may be present secondary to abnormal uterine bleeding with symptoms of fatigue and palpitations and clinical signs of pallor and tachycardia.[2]

Investigations

The diagnosis of STUMP is made on pathological assessment of a specimen following excision, therefore workup would be for a uterine smooth muscle tumour most often thought to be leiomyoma.

Uterine smooth muscle tumours are often found on pelvic ultrasound. Transvaginal ultrasound is the best method to evaluate the uterus, although if the uterus is significantly enlarged a transabdominal approach may be used. These tumours cannot be catagorised into benign, malignant, leiomyoma variants or STUMPs on ultrasound as they have a similar appearance.[8] They can be subserosal, intramural or submucous. They appear as well circumscribed heterogenous tumours, may be hypo- or hyperechoic depending on the mixture of muscle and connective tissue, may have calcifications which appear as hyperechoic areas which may be a rim around or scattered in the tumour. Anechoic or hypoechoic areas may be present if there is cystic degeneration. There is usually no free fluid in the pouch of Douglas.[9] Other imaging studies, such as CT scan or MRI can be done but they cannot distinguish between benign, malignant and borderline tumours, though it is advised that once patients are diagnosed with STUMP they should have a baseline CT scan of the chest, thorax and pelvis.[3,6,8] There are MRI features that can raise suspicion of leiomyoma variants or STUMP, but they are inconclusive.[8]

There are several tumour markers that are used for screening and monitoring in a gynaecological malignancy, and these are CA125, CEA, CA19-9, CA15-3 and AFP. CA125 is usually elevated in a group of patients with ovarian cancer. In a study by Babacan et al, high CA125 levels were associated with large tumours of 5 cm or more and the coexistence of adenomyosis.10 There were no associations with the levels of CA19-9, CEA, CA15-3 and AFP. CA125 can be used to workup for the differential of malignant leiomyosarcoma, although studies are conflicting.[10]

Diagnosis

Diagnosis is made on pathologic assessment of the tissue specimen following myomectomy or hysterectomy. It is estimated that patients diagnosed with STUMP is 1/1000 of those undergoing myomectomy or hysterectomy for a benign tumour.[11] As mentioned before, the diagnosis of uterine STUMP is made with the presence of at least two out of these three criteria: 1) diffuse moderate to severe atypical tumour cells, 2) absence of tumour cell necrosis, and 3) a low mitotic index (<20/10 HPF). Other supporting features are mitotic index >4/10 HPF, irregular margins and vascular invasion at the periphery of the tumour.[1,2] These are also useful features in predicting the behaviour of the tumour, but still need to be studies further.[12]

Uterine STUMP can be divided into four subgroups: 1) atypical leiomyomas with low risk of recurrence, 2) atypical leiomyomas with limited experience, 3) leiomyomas with increased mitotic index but with limited experience, and 4) smooth muscle tumours with low malignant potential.[3,12] The World Health Organisation classification makes the diagnosis broader, as it includes all uterine smooth muscle tumours that don't meet criteria for benign or for malignant.

Coagulative tumour cell necrosis is the feature mostly associated with or diagnostic of malignancy. This type of necrosis should be differentiated from ischaemic type necrosis, which may be present in both tumours, although this can be difficult especially in the early stages of necrosis.[13] A study by Lim et al showed that the presence of coagulative cell necrosis is observer dependant, therefore evaluation of nuclear atypia and mitotic activity is also important in differentiating between benign leiomyomas and malignant leiomyosarcomas.[13] Atypia is however more often associated with adverse outcome.[12]

Immunohistochemistry has a place to distinguish between the malignant type and the borderline type. High expression of estrogen and progesterone receptors is associated with a more benign profile.1 In a study by Maltese et al, estrogen and progesterone receptor expression decreased from benign leiomyoma to malignant leiomyosarcoma1.

P16 is a tumour-suppressor gene and loss of its function results in cell proliferation associated with many carcinomas. P16 overexpression has been reported in cervical cancer, endometrial cancer and uterine leiomyosarcomas.[6] In a study by Kanayama et al, p16 expression was 10.3% in leiomyoma, 38.4% in STUMP, and 76.4% in leiomyosarcoma.[14] In patients with leiomyosarcoma the p16 score was linked with clinical stage, mitotic activity and relapse rate. Therefore, p16 expression may be used as a diagnostic marker for the diagnosis of malignant leiomyosarcoma. It's clinical importance in STUMP is not yet clear, but it is suggested that it might be useful in predicting prognosis of STUMP tumours.[14]

P53 mutation is a common event in carcinogenesis and is associated with aggressive disease. P53 overexpression has been found in leiomyosarcomas but not in leiomyomas.[15]

Management

Management of uterine STUMPs should be multidisciplinary, with the team comprising a gynaecologist, pathologist with experience in gynaecological pathology and an oncologist.[16]

The surgical management may be myomectomy or hysterectomy based on the patient's desire to retain fertility, although the treatment of choice is hysterectomy for those who have completed their families.[3]

Fertility sparring surgery for those still desiring to conceive can be offered. Patients need to be counselled thoroughly about the risk of recurrence versus the possibility of falling pregnant, as most would be advanced maternal age at the time of diagnosis.[6] Following fertility-sparring myomectomy, patients need to be followed up closely with thorough clinical examination plus imaging such as pelvic ultrasound every six months, and annual MRI of the abdomen and chest x-ray for the first five years.[6,8] A number of successful pregnancies have been reported following fertility sparring myomectomy.[5,6]

Laparoscopic myomectomy or hysterectomy is also possible, although this might have to involve morcellation of the specimen. There is currently not enough evidence to suggest that this will increase the risk of recurrence due to peritoneal implants, but patients will then need to be followed up closely.[17]

Adjuvant therapy following surgical excision after initial diagnosis has not been shown to improve outcome or decrease recurrence rate.[8,16] Patients should be followed up at least every six months for the first five years, and then annually for another five years.[5] At each visit a thorough clinical examination and pelvic ultrasound should be done. A CT and/or MRI scan and chest x-ray may be done annually.

Prognosis

There is very little data to predict the prognosis for STUMPs, mainly because of varying diagnostic criteria and different terminology used. Overall survival rates of 92% at five years have been reported.[18] Age at diagnosis is not a poor prognostic factor, although one study did show that women diagnosed with recurrence after STUMP are younger than those with uneventful follow-up.[3] Most of these tumours have a benign clinical course.[18]

Recurrence

Recurrence can be local or metastatic and the tumour can recur as a STUMP or as leiomyosarcoma (10 – 25%).[1,2,3] Recurrence can be either early or late, with late recurrence occurring more than five years after initial diagnosis.[6] Uterine STUMPs usually have delayed recurrence, occurring years after initial diagnosis.[16] In some studies recurrence was reported to be between 8.7 and 11%, whereas in another retrospective study 40.7% (11 of 27 patients) had disease recurrence after a median follow up of 33.5 months.[1,2] Another study showed a recurrence rate of 11%, with more than half of them recurring as leiomyosarcoma and the average time to recurrence was 51 months.[6] The varying numbers in risk of recurrence are influenced by the diagnostic criteria for STUMPs.[6] The risk of recurrence does not appear to be influenced by the type of surgery and preservation of ovaries.1 However, laparoscopy and morcellation of leiyomyosarcoma is associated with peritoneal implants and thus may theoretically increase the risk of recurrence.[8]

STUMPs have the highest median survival following recurrence, compared to other malignant uterine cancers.[16] P16 and p53 positive tumours are associated with a higher risk of recurrence, with p16 positive tumours experiencing earlier recurrence1. Other factors that increase the risk of recurrence are extensive tumour cell necrosis and incomplete excision of the tumour at myomectomy.[1,6]

The suggested treatment for recurrence is surgical excision, which can be followed by adjuvant therapy. This can be pelvic radiotherapy, chemotherapy with doxorubicin and cisplatin, hormonal therapy such as medroxyprogesterone and gonadotropin-releasing hormone analogue.[2,8,16]

Conclusion

The definition of STUMPs is evolving, with their classification still controversial. Their clinical behaviour is unpredictable, with the risk of malignant behaviour unknown. They are characterised by delayed recurrence which makes long term follow up very important. Patients need to be counselled about risk of malignancy and recurrence following diagnosis. Surgical management of choice is hysterectomy, although fertility-sparring myomectomy should be offered to those still desiring fertility. There is still many aspects to study with regards to these tumours, and standardisation of the diagnostic criteria may provide important data to understand them better.

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