Original Research Article

Clinico-Pathological observational study of the spectrum of tumours of mesenchymal origin in the female genital tract - a prospective study in a tertiary care hospital

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Abstract

Aim: The current study aims to evaluate uterine tumours of mesenchymal origin, their incidence, and to analysethe various gamut of clinical and histopathological findings which lead to diagnosis and optimal management. **Material & Methods:** A two year prospective study was conducted in the department of pathology in a tertiary care teaching hospital on mesenchymal tumors of the female genital tract, which were grossed, processed and reported. A case sheet for study was studied and analysed for statistical data. **Result:** 172 cases were reported in period of 2 years, common in multiparous women in their 4th decade of life, presented with menorrhagia, pain and dysmenorrhea, amongst which 95.93% were benign, 4.07% were diagnosed malignant on histopathology. Leiomyosarcoma, endometrial stromal sarcoma, smooth muscle tumour of uncertain malignant potential, carcinosarcoma were noted. **Conclusion:** Hysterectomy is routine procedure surgical procedure for gynaecological cause, and histopathological diagnosis is mandatory for multidisciplinary management of patient. Though the immunohistochemistry are supportive for diagnosis, but the morphological features trumphs all the ancillary testing required for diagnosis of mesenchymal origin of tumours.

Keyword: Mesenchymal Tumour, Uterus, female genital tract

Introduction

Smooth muscle tumour is mesenchymal origin, being most frequent neoplasm of female genital tract leading to hysterectomy as a curative measure [1]. Uterine smooth muscle tumours benign or malignant, occur throughout the female genital tract from vulva to broad ligament to ovary [2]. This heterogeneous group of neoplasms can frequently pose a diagnostic challenge. Majority of tumors in this group show homogenous mesodermal tissue differentiation. Differentiation between benign and malignant mesenchymal tumours are required due to differences in clinical outcome, and the role of pathologist is significant to understand and make these distinctions especially in difficult cases.

Uterine leiomyoma and leiomyosarcomas are two different ends of the pathological spectrum among the uterine smooth muscle tumours. Various different entities like cellular leiomyoma, atypical leiomyomas and smooth muscle tumour of uncertain malignant potential (STUMP) lie within this spectrum.

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Uterine leiomyomas are the most common gynecologic neoplasms. The clinical presentation of leiomyomas depends on their size and location. Leiomyomas need hormonal milieu for their growth and maintenance. This is supported by molecular studies exhibiting more estrogen receptors as compared to the normal myometrium [3,4,]. In contrast uterine sarcoma, the malignant entity of mesenchymal origin in uterus occurs in 1.7 in 100,000 women, with the majority being leiomyosarcomas [5].

Patients frequently present with abnormal vaginal bleeding, pain or both. Rarely hemoperitoneum and tumour rupture may be the presenting manifestation. As the symptoms and signs greatly overlap with those seen in leiomyomas, malignancy should be suspected when abdominal mass is detected in menopousal women who are not on hormonal replacement therapy.

The purpose of this study is to determine the incidence of post operative histological diagnosis of tumours of mesenchymal origin of female genital tract, including the problematic smooth muscle tumours, variants of

leiomyoma, smooth muscle tumor of uncertain malignant potential, endometrial stromal sarcoma and carcinosarcoma.

Materials and Methods

Study Place: The study is conducted in Department of Pathology Chirayu Medical College and Hospital. Bhopal.

Study Type: This is a prospective observational study.
Study Duration: The study duration was of two years from January 2017 to December 2018.

Inclusion Criteria: The study included 172 cases of specimens ofmasses of female genital tract received from gynecology department.

Exclusion Criteria: Specimensof infective etiology and small endometrial, cervical biopsies and POC specimens were excluded from the study.

Study Conduct: The prospective observational study was conducted on 172 gynecological specimens to evaluate the incidence and to analyse the various gamut of clinical and histopathological findings which lead to diagnosis. The material consists of specimens from female genital tract which were received in department of pathology and analysed in the study period of 2 years from January 2017 to December 2018. The clinical information and relevant history of patients were obtained from the histopathological requisition forms and clinical record files. All the hysterectomy cases due to uterine, cervical and ovarian pathology were included in this study. The receivedspecimens were labelled properly, numbered and fixed in 10% buffered formalin.

After detailed gross examination of the specimens, multiple sections were taken from different parts of cervix, endometrium, myometrium, tubes, ovaries were processed and paraffin locks were prepared. Sections of 3-4 micrometer thickness were cut from these blocks and stained routinely with hematoxylin and eosin. After staining sections were examined under microscope. The histopathological diagnosis was given and results obtained were analysed. The cases were further divided into benign and malignant. In each case, tumours were further sub classified and analyzed.

The clinical data and histopathological finding were recorded including frequency of various lesions, and their clinical correlation, age of patient, parity, presentation, clinical indication for hysterectomy.

Sample size: 172 cases of the female genital tract specimens received in the department of pathology of Chirayu medical college and hospital.

Statistical analysis: Data was collected and analyzed.

Results

A total of 172 hysterectomy specimens with mesenchymal tumours were studied in the study period. Patients with tumours were aged between 3rd and 9th decade of life the youngest was 30 years and oldest was 95 years. The majority were multiparous women (165 cases 94.19%) in their 3rd and 4th decade of life and 1.19% were nulliparous women. Out of 172 patients there were 26(15.11%) in age group 30-39 years, 112(65.16%) in age group 40-49 years, 25 (14.5%) in age group 50-59 years, 06(3.48%) in age group 60-69 years, 03(1.74%) in age group >70 years. On the basis of parity there were 162(94.19%) multipara, 08(4.65%) primipara and 02(1.16%) were nulliparous.

Menorrhagia was the commonest clinical manifestation accounting for 63.9% (110) followed by pain abdomen 23.83% (41), dysmenorrhea 10.5% (18), and retention of urine 1.74% (03) cases.

The most common site of tumour was uterine corpus 131 (76.16%), while cervix was involved in 19 (11.04%), uterine corpus and cervix 16(9.30%) and 03(1.75%) of tubo-ovarian and 03 cases (1.75%) of broad ligament shows mesenchymal tumour (Table 1)

Table-1: Site of Tumours.

Site	Number	Percentage
Uterine corpus	131	76.162%
Cervix	19	11.04%
Uterine corpus and cervix	16	09.30%
Tubo-ovarian	03	1.75%
Broad ligament	03	1.75%
Total	**172**	**100%**

Out of 172 cases, 165(95.93%) are benign and 07 case (04.07%) were malignant. Among which secondary changes associated with leiomyoma were present in 70 cases (42.43%) hyaline degeneration (84.4%), cystic changes (5.4%) myxoid changes (4.4%) and one case each of (1.45%) red degeneration and calcification.

Table-2: Secondary changes with benign tumours.

Secondary changes	Number	Percentage
Absent	95	57.57%
Present	70	42.43%
Total	**165**	**100%**

Table-3: Secondary changes associated with benigntumours.

Secondary changes	Number	Percentage
Hyalinisation	59	84.4%
Cystic change	04	05.4%
Myxoid change	03	04.4%
Haemorrhage	02	02.9%
Red degeneration	01	01.45%
Calcification	01	01.45%
Total	**70**	**100%**

Among the malignant mesenchymal cases 04 cases were leiomyosarcoma and one each of STUMP, endometrial stromal sarcoma and carcinosarcoma were diagnosed.

Table-4: Malignant Mesenchymal tumours

Malignant lesion	Number	Percentage
Leiomyosarcoma	04	57.4%
STUMP	01	14.2%
Endometrial stromal sarcoma	01	14.2%
Carcinosarcoma	01	14.2%
Total	**07**	**100%**

Discussion

Female genital tract tumors nearly always present with symptoms of dysmenorrhea and vague abdominal pain and are eventually operated on, either with or without adequate radiological investigations and in absence of biopsies. These procedures aim for immediate relief of symptoms and patient satisfaction, and are done in all cases comprising leiomyomas, uterine polyps, prolapse, adenomyosis, endometriosis and malignancy [6,7]. Charles Clay was the first to perform subtotal and total hysterectomy in Manchester, England in 1843 and 1929 respectively[8].

In this present study, patients were most common in the age group 40-49 years, which was comparable with Verma et al. and Siwatchet al[9,10]. Mesenchymal uterine tumours were more common in multiparous women in 94.19% cases and clinically manifested with menorrhagia in 63.9% cases. This was similar to Begum S et al and Gowri et al, but their cases presenting with menorrhagia was 49.03%, which is less than present study [11,12].

76.16% of leiomyomas were uterine in origin, majority being intramural. Cases which presented as cervical fibroids accounted for 11.04% of cases. 16 patients had both uterine and cervical involvement. There were three cases (01.75%) each of ovarian and broad ligament masses. One of the broad ligament masses was signed out as a myxoid leiomyosarcoma (Fig 1)[13,14].

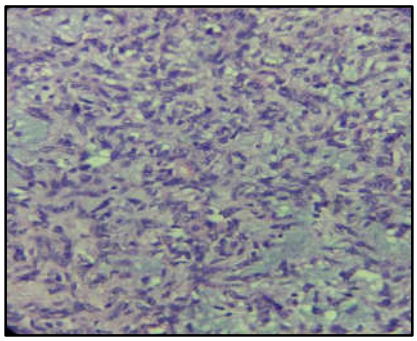

Fig-1

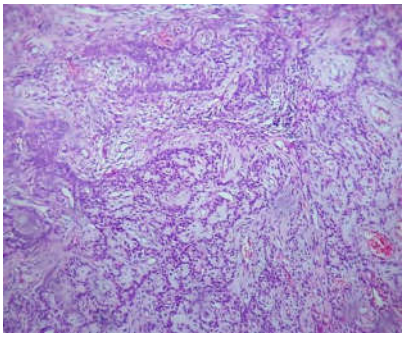

Fig-2

Figure-1: Myxoid leiomyosarcoma: Highly pleomorphic sarcomatoid cells with high mitotic activity in myxoid background (40X, H&E)

Figure-2: Pictomicrograph of cellular leiomyoma with abundant cellularity, nuclear palisadingwithout atypia or areas of necrosis. (10X, H & E)

In present study 95.93% (165/172) cases are diagnosed as benign lesions represented by leiomyomas (Fig 2). Secondary changes of hyalinisation in leiomyoma was seen in 42.43% (70/165) cases and the second most common was degeneration seen in 5.4% cases. Similar changes were studied by Begum et al [11] and Gowrietal [12]. The degenerative changes in leiomyoma occur due to improper blood supply, leading to cystic change, hydropic change, calcification, hemorrhage and rarely red degeneration. Red degeneration of leiomyomas is a painful condition commonly seen in pregnancy. In the present study 01 case of red degeneration was seen in a 42 year pregnant woman in her 2nd trimester, as also reported by Gowri M et al[12].

In the present study only 4.06% (7 /172) cases are diagnosed as malignant. These include 04 cases (57.4%) of leiomyosarcoma, 01 case each of STUMP, endometrial stromal sarcoma and carcinosarcoma with squamoid differentiation.

In present study of uterine mesenchymal tumours, 95.93% (165/172) cases were leiomyomas which are benign. On gross pathological analysis, leiomyomas are well circumscribed, solid, rubbery, firm and bulging on cut surface. These may show various degenerative processes including cystic, hylinised, myxoid, red degeneration and some time calcified. Focal areas of coagulative necrosis may simulatea malignant lesion.

The diagnosis of malignant uterine smooth muscle tumours has important prognostic and therapeutic implications. The diagnosis is based on a systematic practical approach with extensive sampling from unusual areas suspected on gross finding of poorly circumscribed large masses, displaying fleshy variegated cut surface, with area of necrosis and hemorrhage. Final diagnosis is based on the assessment of histological parameters as well as systematic approach to its differential diagnosis on histological features.

The World Health Organisation (2014)[15] has updated its criteria for mesenchymal tumors of the female reproductive tract and various variants of benign smooth muscle tumors which were diagnosed on their histologic features. Leiomyomas variants are in between mitotically active, cellular, atypical leiomyomas where defined criteria for mitotically active leiomyoma is presences of 10-15 mitoses/ 10 high power fields (hpf) without cellular atypia. Increased cellularity, higher than adjacent myometrium is seen in cellular leiomyoma as seen in Fig 2. Sometimes cellular leiomyoma may have spindle cells resembling endometrial stromal tumor. Leiomyoma with bizarre nuclei showing atypical features will be considered as symplasticor pleomorphic leiomyomas. Such atypical smooth muscle cell tumours always create controversy. These atypical smooth muscle cells have abundant eosinophilic cytoplasm, irregular nuclear shapes, and multinucleation. The nuclei are hyperchromatic and may show intranuclear inclusions, chromatin condensation and fragmentation resembling mitotic figures.

Atypical leiomyomas are always controversial for both clinician and pathologist, because of their unclear nature whether completely benign or to classify them as STUMP (smooth muscle tumour of uncertain malignant potential). The WHO defines STUMP as tumours that do not fulfill the histopathology criteria for typical leiomyoma or leiomyosarcomas

being neither benign nor malignant. The histopathology criteria required for atypical leiomyoma are: (1) absence of coagulative necrosis (2) mitotic index < 10 / 10 HPF. (3) diffuse, focal, multifocal moderate to severe atypia.

The study of Bell et al [16] included 213 cases, in which they segregated problematic uterine smooth muscle tumours into 4 groups:

1. Cases with diffuse moderate to severe cellular atypia, without coagulative cell necrosis and MI <10/10HPF, termed as atypical leiomyoma with low risk of recurrence.
2. Cases with focal / multifocal moderate to severe atypia without necrosis and MI <20/10 HPF. termed atypical leiomyoma with limited experience of recurrence
3. Cases without atypia or with mild atypia with coagulative cell necrosis and MI >20/10 HPF.Termed leiomyomas with increase mitotic index but with limited experience of recurrence.
4. Cases without atypia or with mild atypia with coagulative cell necrosis and MI <10/10HPF, termed smooth muscle tumour with low malignant potential [16,17].

In present study 01 case of STUMP (Fig 3) was diagnosed, while 4 cases of leiomyosarcoma were diagnosed.

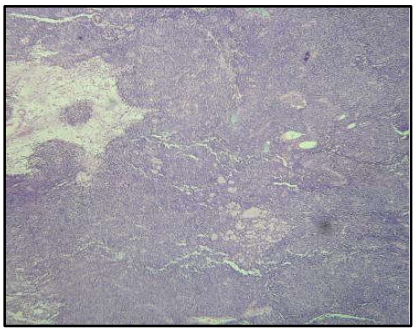

Fig-3

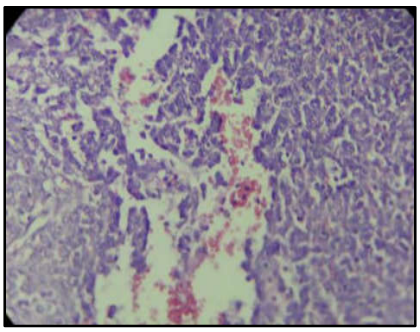

Fig-4

Figure-3: Pictomicrograph showing Smooth muscle tumor of uncertain malignant potential: area of coagulative necrosis with no atypia and <10 mitotic activity (10X, H&E)

Figure-4: Pictomicrograph of Endometrial stromal sarcoma showing atypical stromal cells (40X, H&E)

STUMPs show slow tumour growth and lower recurrence rate, as compared to leiomyosarcomas which are aggressive in clinical course and have a high rate of recurrence and metastasis. Thus histopathology plays important role to correctly differentiate between STUMP and leiomyosarcoma [18,19,20].

The criteria to establish the diagnosis of malignant smooth muscle tumours differs for each subtype and for each of the different variants. This may lead to difficulties in diagnosis and reproducibility among pathologist. Criteria for leiomyosarcoma microscopically includes spindle cells with fibrillary eosinophilic cytoplasm and elongated blunted nucleus with diffusely variable atypia. These tumors are frequently hypercellular, with mitotic count of 10/10hpf and areas of coagulative tumor cell necrosis. Additional finding of atypical mitoses, vascular invasion or infiltrative border might be seen in leiomyosarcoma but these finding are not considered as diagnostic of malignancy. Close differential diagnosis for conventional leiomyosarcoma is mitotically active leiomyoma where lack of tumour cell necrosis and nuclear atypia are the features to rule outmalignancy [15]. On diagnosis of leiomyosarcoma on myomectomy specimens, hysterectomy should be treatment of choice to avoid risk of recurrence and required long close follow up.

Endometrial stromal sarcoma (ESS) are a rare variant of malignant mesenchymal tumours, with a prevalence of 1/million cases [21], usually developing in the uterine corpus and may occasionally arise at various extrauterine sites. WHO classified ESS into three categories: low- grade endometrial stromal sarcoma (LG-ESS), high grade endometrial stromal sarcoma (HG-ESS), and undifferentiated uterine sarcoma (UUS)[22]. In the present study we report one case of HG-ESS of the ovary in a 50 year old female(Fig 4). ESS may arise as a primary extrauterine endometrial sarcoma, on the background of endometriosis. In the present case HG-ESS was considered as metastatic to ovaries as previous hysterectomy specimen and slides were not available for review.

Uterine carcinosarcomas are also known as malignant mixed mullerian tumors of uterus, and have a very poor overall outcome. These are rare metaplastic tumours that include both carcinomatous and sarcomatous elementsand have high risk of metastasis. However they account for less than 5% of uterine malignancies [23]. Extensive sampling is needed, as the pattern of metastasis depends on whether mesenchymal or carcinomatous elements dominate [24].

Conclusion

Therefore clinico-pathological correlation is required for optimal management of patients whether the lesion is benign or malignant. A thorough histopathological examinationis required for diagnosis, proper management and counseling regarding potential risk of recurrence to establish treatment of choice. In diagnosis of atypical leiomyosarcoma on myomectomy specimen, hysterectomy should be treatment of choice to avoid risk of recurrence and long close follow up are needed. Carcinosarcomas are highly aggressive malignant tumours of uterus associated with poor prognosis. Surgery remains the cornerstone of management for these tumours with pelvic and paraaortic lymphadenectomy, peritoneal and omental biopsies required for staging of disease.

Recommendations- Extensive and thorough sampling is highly recommended while dealing with smooth muscle tumour of female genital tract with unusual gross finding (at least one section per two centimeter of lesion). The diagnostic criteria for malignant lesion should be strictly applied while diagnosing malignancy that include cellular atypia, high mitotic count and tumour cell necrosis. Clinical information is of utmost importance to aid pathological diagnosis, this includes history of exogenous hormone intake, menstrual history & pregnancy for final interpretation.

What this study adds to existing knowledge?

This study sheds light on the spectrum of mesenchymal tumors of the female genital tract presenting in a tertiary care hospital. This study revealed the predominance of benign tumors over malignant cases even in a speciality hospital. High index of suspicion and up to date awareness of current literature and diagnostic criteria will aid in diagnosis and prognostication of patients for better health care.

Limitation- Major limitation of present study is small number of malignant cases and regular follow up.

Findings: Nil; **Conflict of Interest**: None initiated
Permission from IRB: Yes

Contribution of Authors- MAA contributed in diagnosis collection of data and editing. SSS contributed in manuscript writing, editing and final review. All authors read and approve final version of the manuscript.

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