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Uterine Sarcoma: Experience and Outcome from a Tertiary Care Rural Cancer Center

ABSTRACT

Aim: This is a retrospective study of clinical profile and outcomes of uterine sarcomas presenting to a tertiary cancer center in rural Punjab. **Background:** All uterine sarcomas (USs) excluding carcinosarcoma registered at our center from 2015 to 2019 were included in the analysis. **Case Description:** A total of 16 cases of US were diagnosed and treated. Among them, seven patients were endometrial stromal sarcoma, six were leiomyosarcoma, and three were undifferentiated uterine sarcoma. Most patients presented with per vaginal bleeding and pelvic pain. Total nine patients died out of 16. **Conclusion:** Uterine sarcomas are rare tumors, which presents with advance disease and recurrence in follow-up period.

Key words: Rural center, Uterine sarcoma, Prognosis

INTRODUCTION/DISCUSSION

Uterine sarcomas (USs) are aggressive malignant tumors comprising less than 1% of all gynecologic malignancies associated with high rates of local recurrences and distant metastasis despite aggressive treatment. Most common subtypes include endometrial stromal sarcoma (ESS) (21%); high and low grade, leiomyosarcoma (LMS) (63%), and undifferentiated uterine sarcoma (UUS).[1] Rare subtypes include, rhabdomyosarcoma, and PEComa. Risk factors proposed for uterine sarcoma include long-term tamoxifen use,[2] pelvic radiation, hereditary leiomyomatosis, and renal cell carcinoma (HLRCC) and long-term survivors of retinoblastoma.

LMS and ESS are the two most important categories of uterine sarcoma. The other types of sarcoma being reported at this site are only rare instances. The malignant mixed Mullerian tumor (MMMT) or carcinosarcoma although included under uterine sarcoma by several previous studies is essentially treated as carcinoma and is hence not technically classified as uterine sarcoma.[3] Further, given the prognostic differences, it is also essential to correctly subtype the ESS. The recently described molecular signatures turn out to be really useful for this purpose.

LMS for most of the instances is a relatively easy diagnosis. On gross examination, these tumors are intramural, with the fleshy appearance and irregular margins. This is in contrast with its benign counterpart (leiomyoma), which is well defined and has a whorled appearance. Microscopically, this tumor is composed of spindle cells arranged in long fascicles. The nuclei of the individual spindle cells are elongated with blunt ends and tend to display moderate to severe anaplasia. Unlike its benign counterpart, LMS is usually associated with tumor necrosis. Increased mitotic activity although not diagnostic, a mitotic count above 15/HPF is highly indicative of LMS.[4] The increased mitosis (>5/HPF) is although more crucial in the diagnosis of an epithelioid and myxoid variant of LMS.[4] Immunohistochemistry for p16 and p53 is frequently used to diagnose LMS when the differential diagnosis considered is leiomyoma.[5]

ESS, as the name suggests, arises from the stromal cells of the endometrium. On a limited pathology material (biopsy/curettage), differential diagnosis of the endometrial stromal nodule (ESN) should always be considered as it is very often difficult to establish a presence of definite invasion or vascular emboli on such material.[6] The diagnosis of ESS, for the same reasons, is frequently established on a resection specimen. On gross examination, the tumor is infiltrative in nature and appears. Since the tumor is frequently associated with vascular invasion, worm-like structures can be identified in the larger myometrial vessels on gross examination.[7] Microscopically, the tumor has three subtypes, namely, low-grade ESS (LG-ESS), high-grade ESS (HG-ESS), and USS.[5] Low-grade ESS is composed of stout monotonous oval cells (identical to endometrial stromal cells) infiltrating the myometrium typically in a "tongue-like" growth pattern.[8] The tumor cells

Sachin Khandelwal[1], Priyanka Goel[2], Rakesh Sharma[1], Vikram Singh[1], Debashish Chaudhary[1], Akash Pramod Sali[3]

[1]Department of Surgical Oncology, Homi Bhabha Cancer Hospital, Punjab, India, [2]Department of Radiation Oncology, Homi Bhabha Cancer Hospital, Punjab, India, [3]Department of Pathology, Homi Bhabha Cancer Hospital, Punjab, India

Corresponding Author:
Dr. Akash Pramod Sali, Homi Bhabha Cancer Hospital, Civil Hospital Campus, Sangrur - 148 001, Punjab, India. E-mail: aakki1910@gmail.com

have minimal nuclear atypia and are frequently associated with fine vasculature and spiral arterioles.[8] The high-grade ESS is usually associated with destructive growth pattern and is typically composed of area reminiscent of typical LG-ESS juxtaposed with high grade round component.[5] This is in contrast with undifferentiated ESS, wherein it is impossible to make a diagnosis based on the histomorphology which is typical of undifferentiated tumors composed of sheets pleomorphic cells. Immunohistochemically, ESS is positive for CD10, ER, and PR. The expression of these markers is, however, decreased in the HG-ESS or USS.[5,9] Diffuse expression of cyclin-D1 is postulated to be associated with high-grade ESS.

Pre-operative biopsy is less sensitive; hence, most patients are diagnosed on imaging or after hysterectomy. Most common surgery is total abdominal hysterectomy with or without salpingo-ophorectomy (THBSO). Role of nodal dissection is unclear.[10-12] Adjuvant therapy for low-grade ESS mostly includes hormonal therapy (aromatase inhibitors, megestrol acetate, and gonadotropin-releasing harmone (GnRH) analogs. Adjuvant radiation therapy (RT) may be added for higher stages (II-IVA).

Adjuvant therapy for UUS, LMS, and high-grade ESS is not clear due to lack of survival benefit due to tendency of extrapelvic recurrence.[13,14] Routine post-operative RT is not recommended for stage 1 disease[15] but can be individualized for higher stages. Role of adjuvant chemotherapy is also poorly defined but should be considered for high risk of distant relapse.

MATERIALS AND METHODS

Our center is a tertiary cancer hospital situated in rural Punjab, India, under aegis of Tata Memorial Center, Mumbai. Since ours is a referral center, we do get lot of patients referred to us after surgery. Cases of uterine sarcomas after excluding MMMT, diagnosed between 2015 and 2019 at our institute, were retrieved from the archives and electronic medical records (E.M.R). MMMT was excluded from the study. Age, clinical presentation, stage, histology, and treatment received were analyzed. Patients who had defaulted were contacted telephonically. The histopathological slides (hematoxylin and eosin [HE] and immunohistochemistry [IHC]) were retrieved and reviewed by a single histopathologist with adequate experience in reporting oncopathological specimens. The histopathological features noted were as follows: tumor cell type (spindle and oval), pleomorphism (mild, moderate, and marked), tumor vasculature (thin, thick, and spiral arterioles), mitosis, and necrosis. The IHC findings were noted and tabulated.

RESULTS

A total of 16 cases were diagnosed for 4 years. The patient and tumor characteristics are shown in Table 1.

Table 1: Demography

N=16	
Age	Mean: 50 years Range: 28–73 years
Symptoms	Per vaginal bleeding: 8 Pelvic pain: 6 Discharge per vaginum: 2 History missing: 3
Histology	ESS: 7 LMS: 6 UUS: 3
Tumor size	Mean : 10.6 cm (*N*=8)
Stage	IA: 1 IB: 5 IIIC: 1 IVB: 6 Unknown: 3

Surgery done was mainly THBSO barring 1 young patient with ESS, in which ovaries were preserved. Pelvic node dissection was done in four patients (three were operated outside) and only one patient was found to be node positive.

Four ESS patients received adjuvant hormonal therapy, while one received adjuvant radiotherapy [Table 2]. Among LMS patients, two received palliative chemotherapy.

Among LMS, there were five deaths. Two Stage IVb patients on palliative chemotherapy, 1 Stage IVb on palliative care, and one default patient had died. One patient on observation after surgery with Stage Ib disease developed vault and distant metastasis and eventually died. Among ESS patients, there were two deaths (one Stage IVb and one default patient). Among UUS, both metastatic patients died.

CASE DISCUSSION

This is a study from a tertiary care referral center in rural Punjab with all patients from Punjab except one. Unlike other Indian studies,[16-18] we have excluded MMMT. The largest series for US is by Sampath *et al*.[14] of 3650 patients from United States discussing the role of adjuvant radiation. This study had 51.4%, 25.2%, and 14.9% as MMMT, LMS, and ESS, respectively.

Mean age in our series is 50 years and most of uterine sarcoma occurs above 40 years of age. Unlike literature, we had more of ESS than LMS, but the bias can be due to fewer patients. Six out of seven ESS patients were LGESS (five limited to uterus and one with nodal metastasis). One was HGESS with with liver metastasis. Three out of six LMS patients were Stage IVb with lung and abdominal disease. Two out of three UUS patients had lung and abdominal metastasis.

All the cases in this series were reviewed and confirmed by an experienced oncopathologist. It is extremely difficult to preoperatively diagnose ESS due to resemblance with proliferative endometrial stroma and LMS due to resemblance

Table 2: Treatment offered in different types of uterine sarcomas

Type of Uterine Sarcoma	Adjuvant RT	Adjuvant Harmonal therapy	Palliative chemotherapy	Observe	Default	Palliative care
ESS	1	4	0		2	1
LMS			2	2	1	1
USS	1					2

with leiomyoma. Among our patients, pre-operative biopsy was conclusive in four patients only and all had LGESS. Histologically, while it was relatively easy to differentiate LMS and ESS toward the lower grade of the spectrum, it was diagnostically challenging to differentiate higher grades of these two entities, even after immunohistochemical evaluation. Immunohistochemically, LMS is positive for smooth muscle markers such as SMA, desmin, and h-caldesmon. However, these smooth muscle markers can even be focally expressed in ESS, especially in tumors with smooth muscle differentiation, which is often seen in ESS.[19] CD10, often used in the diagnosis of ESS, can also be positive in a significant number of LMS.[4] Estrogen receptor (ER), progesterone receptor (PR), and androgen receptor (AR) as often expressed in LMS (30–40% cases) can aid in expanding the therapeutic options.[20] ER and PR are also expressed in ESS. Discretely, ER and PR are expressed in 53% and 67% of LGESS, 45% and 65% of LMS, 23% and 31% of HGESS, and 47% and 63, respectively, of all uterine sarcomas.[21] In our series, five out of six LGESS were ER and PR positive. Hormone receptor status was not routinely checked in our LMS patients. Since each of the uterine sarcomas are associated with specific molecular signatures. Performing these molecular tests can be worthy in difficult situations. Approximately half of the LG-ESS is associated with *JAZF1-SUZ12*.[8] The high-grade ESS, in contrast, typically displays YWHAE-FAM22 gene rearrangement. These molecular signatures thus become essential in differentiating HG-ESS from LG-ESS since the former is associated with advanced-stage disease and progression.[19] The USS is associated with complex karyotype and distinctly lacks YWHAE translocations, while molecularly, the LMS display complex karyotype and the molecular tests are rarely used for diagnosis or prognosis.[22]

CONCLUSION

US is an uncommon uterine malignancy with a high potential for metastasis. The limitation of this study is it's retrospective nature. The strength of this study lies in the fact that it is exclusive to rural Punjab patients from a peripheral cancer center.

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