



# Omnipresent, Omnipotent-Extra-Uterine Leiomyosarcoma with Varied Presentation: Case Series of A Dozen!!

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## ABSTRACT

**Background:** Leiomyosarcoma (LMS), accounting for 7-10% of all soft tissue tumors, is derived from smooth muscles and arises most commonly from uterus, retroperitoneum, extremities, but can potentially involve any site of the body. Through this case series of 12 extra-uterine LMSs, we highlight the wide variety of clinical presentations of this tumor.

**Methods:** Retrospective analysis of clinical details, histopathological examination (HPE) and immunohistochemistry (IHC) of LMSs diagnosed in the extra uterine sites from 2012-2016 in our tertiary care institute.

**Result:** The mean age of presentation was 55.8 years, with male: female ratio 2:1. The site distribution was: stomach (3), non visceral soft tissue-thigh (2), breast (2), cutaneous (2), ileum(1), esophagus(1), and larynx (1).

**Conclusion:** The variable presentations of LMS at extra-uterine sites, makes it a challenging diagnosis for the unsuspecting clinicians and histopathologists. Thus, any soft tissue tumor in similar clinical scenarios may turn out to be LMS.

**Keywords:** Extra Uterine, Leiomyosarcoma, Immunohistochemistry, Sarcoma

## Introduction

Soft tissue sarcomas are cancers with mesenchymal differentiation. They are relatively infrequent and account for 1% of all the malignancies. Amongst these, leiomyosarcoma (LMS) is the second most common subtype and constitutes about 7-10% of all soft tissue sarcomas.<sup>1,2</sup> LMS are a heterogenous group of neoplasms composed of cells with smooth-muscle differentiation.<sup>3</sup> In general, they are positive for smooth muscle actin (SMA) and desmin on immunohistochemistry (IHC). This is how they can be differentiated from other soft tissue sarcomas. Over the years, a decreasing incidence of LMS has been reported. Rather than an actual decrease in the frequency of the disease, this appears to be because of fewer cases being misclassified as LMSs. The application of more stringent diagnostic criteria has resulted in some gastric malignant mesenchymal tumors, which were earlier categorised as LMSs, to be reclassified as gastrointestinal stromal tumors (GIST), aided by positive IHC expression of CD34 and c-kit.<sup>4-7</sup>

Among women, about 40% of LMSs originate from the uterus.<sup>4</sup> Extra-uterine LMS can arise from any site which harbours smooth muscle. The most common site of origin is the retroperitoneum (20-75%), followed by peripheral soft tissues (12-41%), especially the lower extremities. The other sites are skin, vessels, head and neck region, trunk, bone, gastrointestinal and genitourinary tract.<sup>8,9</sup> Rare

primary locations described in isolated case reports and case series include thyroid, gallbladder, base of tongue, larynx, skin, liver, bronchus, kidney and pancreas.<sup>10-13</sup>

## Materials and Methods

This was a retrospective analysis of 12 cases, diagnosed in our tertiary care hospital between 2012 and 2016 as LMS, the study model approved by the Institute's ethical committee.

*Exclusion criteria:* All uterine LMS

The admission files of the patients were retrieved from the medical records department, and studied carefully for relevant clinical details. The gross descriptions of resected specimens submitted for histopathology were noted from histopathological requisition forms. The routine H&E slides were reviewed, along with IHC, wherever performed in our institute. Reports of the cases where IHC was performed in the outside laboratories, were procured.

## Result

Clinicopathologic features of the patients, histopathological examination (HPE) and IHC findings are shown in Table 1. Among the 12 cases, the mean age of presentation was 55.8 years with male to female ratio of 2:1. The tumors were large masses with average maximum dimension of 8.8 cms. Gastrointestinal tract (GIT) was the commonest site, with 3 cases from stomach, 1 from ileum and 1 from



oesophagus. Other sites were thigh, breast, and skin, with 2 cases each and one case in larynx.

On microscopic examination, these tumors were predominantly composed of sheets and fascicles of spindle shaped cells with variable nuclear atypia and cigar shaped blunt ended nuclei. Some cases showed few large, bizarre cells with vesicular chromatin, prominent nucleoli, moderate to abundant cytoplasm. Mitotic count was high, >10/10 HPF in most of the cases with presence of few atypical mitotic figures.

**Stomach:** The patients of LMS from stomach were a 77 years old lady, and 2 gentlemen aged 30 and 60 years. All three were clinically suspected to have GISTs. On gross examination, the tumors were large masses, ranging in the maximum dimension from 15-18cm. These were largely nodular growths with solid, cystic and necrotic areas.

**Heum:** This patient was a 56 year old man with a large (8cm maximum dimension) nodular growth, suspected clinically to be abdominal Koch's.

**Esophagus:** The fifth case from GIT was from a 60 year old male patient with a polypoidal growth of oesophagus, measuring 6.5 cm in maximum dimension. On HPE, possibilities of a spindle cell (squamous) carcinoma and a mesenchymal stromal tumor were suggested.

On IHC, all of them were found to be positive for SMA and negative for c-kit, S100 and CD 34. Two cases were positive for Vimentin.

**Thigh(2):** The patients were a 55 years old lady and a 50 year old gentleman. Grossly, these masses were firm and grey-tan in color, measuring 5cm and 16cm in maximum dimensions respectively. The clinical suspicion in one of the cases was rhabdomyosarcoma or malignant fibrous histiocytoma. Histopathological report of Malignant Mesenchymal Tumor was confirmed to be LMS after IHC positivity with SMA and Vimentin. S-100 and CK were negative.

**Cutaneous (2):** Among the cutaneous lesions, one was a chronic ulcer on nose in a 60 year old male patient, who was also a kidney transplant recipient. The tumor was positive for Vimentin and SMA with 40% MIB-I labelling index in the highest proliferating areas. S-100, CD34 and CD31 were negative. Another was a scalp nodule alongwith a subcutaneous swelling in left posterior axillary fold in a 72 year old man. On FNAC, it was diagnosed to be a sarcoma. On cell block preparation, the tumor was positive for SMA and negative for S-100. On investigating further, the patient was found to be a post - operative case of surgical

resection of a retroperitoneal mass in 2010, which had been diagnosed on HPE and IHC (positive for Vimentin, Desmin and SMA; negative for S-100, Chromogranin, NSE, HMB-45, CD-117, CD-34, CK and EMA) as LMS. A final diagnosis of metastatic deposits from leiomyosarcoma was made. The patient was eventually lost to follow up, and the resected surgical specimen was not received in the department. Cutaneous and subcutaneous metastasis from a retroperitoneal LMS, 5 years after its diagnosis is very rare. This entity has already been published as a case report in literature.<sup>14</sup>

**Breast (2):** Amongst the cases from breast, one was a 55 years old lady who had undergone hysterectomy 10 years ago. On FNAC of the breast lump, she was diagnosed with a spindle cell tumor, for which she underwent tumor excision. The other case, a 47 years old female patient had been diagnosed invasive ductal carcinoma on FNAC of breast lump, reported outside. She underwent Modified Radical Mastectomy with axillary lymph node dissection. The tumors measured 8cm and 3.5 cm in maximum dimension respectively. Morphologically, metaplastic carcinoma of breast and phyllodes tumor were considered as differential diagnosis in the latter. On IHC, the tumor cells in both the cases were diffusely positive for Vimentin and SMA and negative for ER, PR, Her 2 neu, Myogenin, CD 117, CK and S100. One case showed focal positivity for CD 34 while the other case demonstrated focal positivity for Desmin. The diagnosis was confirmed as LMS after evaluating HPE and IHC.

**Larynx:** A 48 years old male had a mass on anterior commissure in larynx which was confirmed as LMS with IHC positivity for SMA and negativity for CD 34.

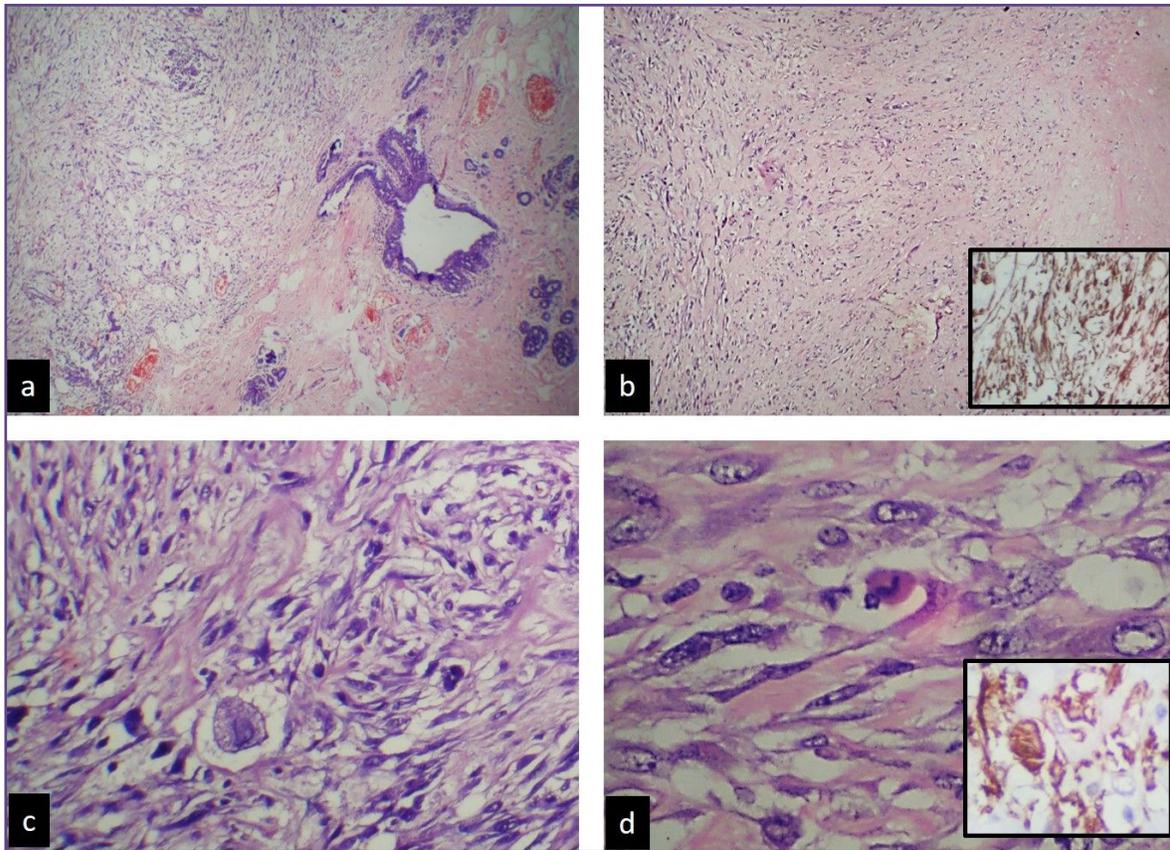
## Discussion

LMS accounts for 7-10% of all soft tissue tumors. It occur mainly in middle-aged to older adults (5th and 6th decades of life).<sup>15</sup> This correlates with our results where mean age was 55.8 years. The extra-uterine LMSs are more commonly found in males as compared to females, which again supports our results. The mean tumor size in our series was 8.8 cms, which is in concordance with the finding that these tumors are large masses. The most commonly involved sites are retroperitoneum, followed by peripheral soft tissues, especially lower extremities. Other sites include skin, vessels, head and neck region, trunk, bone, gastrointestinal (non GIST) and genitourinary tract.<sup>16</sup> Larynx is one of the very rarely involved sites by LMS.<sup>17</sup>

With the advent of IHC, the morphology-based classification scheme has improved. Well-differentiated LMSs are usually positive for smooth muscle markers

**Table 1: Clinical and pathology findings of cases.**

S.NO	AGE	SEX	SITE	CLINICAL POSSIBILITY	DIMENSIONS (cms)	GROSS EXAMINATION	POSITIVE IHC	NEGATIVE IHC
1	55	F	Left thigh mass	-	5x5x3.5	Hard, grey-white	Vimentin, SMA	CK, S100, CD31, CD34
2	50	M	Swelling thigh	Rhabdomyosarcoma, malignant fibrous histiocytoma	16x14x4	Solid with grey-white and necrotic areas	Vimentin, SMA, desmin	CK, S100
3	77	F	Stomach mass	GIST	20x15x10	Nodular mass, Cystic and solid with necrotic areas	SMA	S100, CD117
4	56	M	ileum	Abdominal Koch's	8x3x3	nodular	SMA	S100, CD117
5	60	M	Stomach mass	GIST	15x8x8	Nodular growth with grey-white areas	SMA	S100, CD117, CD34
6	30	M	Stomach mass	GIST	18x15x3	Nodular growth with cystic and solid areas	Vimentin, SMA	S100, CD117
7	48	M	Anterior commissure, larynx	-	1.5x1x0.5	Multiple tan soft tissue pieces	SMA	S100, CD34
8	60	M	Chronic ulcer on nose	Chronic ulcer in kidney transplant recipient	1.5x1x0.5		Vimentin, SMA MIB-I 40% in highest proliferating areas	S100, CD34, CD31
9	47	F	Right breast lump	Carcinoma breast	3.5x3x2.5	Grey white, firm	Vimentin, SMA, desmin	S100 ER, PR, Her 2 neu, Myogenin, CD 117, CK and S100
10	55	F	Breast lump	Carcinoma breast	8x6x5	Grey white, firm, solid growth with mucoid, haemorrhagic and calcified areas	Vimentin, SMA, CD34	ER, PR, Her 2 neu, Myogenin, CD 117, CK and S100
11	60	M	Growth esophagus	Carcinoma esophagus	6.5x3x2	Polypoidal growth	Vimentin, SMA	CK, S100, CD117, CD34
12	72	M	Scalp swelling	Metastasis from previous resected retroperitoneal LMS	3x2x1.5	FNAC	SMA	S100



**Fig. 1:** H&E section showing a) Sharply circumscribed LMS in breast with surrounding normal parenchyma (x100); b) sheets of spindle cells with focal hyalinised areas (x100). Inset showing SMA positivity of cells.; c) bizarre cells with marked nuclear atypia (x400); d) markedly pleomorphic spindle cells with atypical mitotic figure (x400). Inset shows Vimentin positivity in tumor cells.

such as actin and desmin, diffusely positive with calponin, h-caldesmon, and negative for S100, c-kit and CD34. Now, many tumors which were formerly called high-grade spindle-cell sarcomas are classified as LMS.<sup>18</sup> However, none of these markers is absolutely specific for smooth muscle differentiation.

Different authors opine differently on the origin of LMSs. Increasing clinical and genetic data suggests that LMSs arising from extrauterine primary sites are different from uterine tumors.<sup>19-21</sup> On the other hand, a recent study investigating differences between uterine and non-uterine LMS found that these two entities are not distinct diseases on a clinical level.<sup>22</sup> Similarly, no significant differences have been demonstrated between the two in molecular studies.<sup>23</sup> The extra-uterine LMSs, according to the French Sarcoma Group's study, have been divided into two main categories, retroperitoneal and peripheral LMS on the basis of variable clinical outcomes and different molecular clusters. The retroperitoneal LMSs overexpress

genes involved in smooth muscle differentiation, are more common in women and are associated with a poorer prognosis than non-retroperitoneal LMSs. The latter show overexpression of genes involved in extracellular matrix, wounding, and adhesion pathways. These are more common in men and have a better clinical outcome.<sup>24</sup>

Patients with LMS should be treated with multidisciplinary therapeutic approach which combines surgery, chemotherapy and radiotherapy. Based on the location of the tumor, prognosis and possible treatments can differ. For example, the retroperitoneal LMSs are reported as large masses because they develop insidiously, and are diagnosed only when they assume big sizes and start causing pressure symptoms.<sup>25</sup> Although retroperitoneal LMS are larger and of higher grade compared to their extremity and trunk counterparts, they still have largely similar survival outcomes and recurrence patterns. Again, it is yet to be established whether LMS of various sites of origin exhibit differential chemosensitivity, molecular signatures, and staging features.

Complete surgical resection is the treatment of choice. The overall prognosis of LMS is poor with an overall survival rate of 35%. Various prognostic markers are age, tumor depth, tumor size, tumor grade and metastatic spread. Only the presence of synchronous metastatic disease is an independent predictor of survival.<sup>3,22,25</sup> Hematogenous spread is common and they usually metastasize to lung, liver, kidney and brain. Retroperitoneal tumors have the highest rate of metastasis, followed by subcutaneous tumors. Cutaneous metastasis of leiomyosarcoma occurs very unusually.

## Conclusion

In this article, we have highlighted the myriad of presentations that extra uterine LMS can exhibit. This sarcoma can involve any site of the body where smooth muscles are present. More and more cases of metastasis or recurrence from extra uterine LMS are being reported. The clinicians and histopathologists should keep a high index of suspicion when dealing with such soft tissue masses. The features and behaviour of LMS is an upcoming topic for research and more multi-institutional studies are needed to identify clinicopathologic prognostic factors and biological behaviour of these tumors to offer better treatment options, and predict survival outcome more accurately.

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