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Review Article

Leiomyosarcoma: A rare soft tissue cancer arising from multiple organs

Zorawar Singh*

Department of Zoology, Khalsa College, Amritsar, Punjab, India

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ABSTRACT

Leiomyosarcoma (LMS), a smooth muscle connective tissue tumor, is a rare form of cancer which accounts for 5–10% of soft tissue sarcomas. This type of cancer is highly unpredictable. LMS is a resistant type of cancer and can remain in the dormant state for long time. It can recur in the later stages of life. LMS has been reported in different animals including humans. A wide literature search was done. The PubMed database was used to search for journal articles on the occurrence of LMS in different organs from 1950 to 2016. LMS has been reported to be associated with different organs, including esophagus, stomach, intestine, anus and uterus. In this article, an attempt has been made to review the studies based on occurrence of LMS with respect to the organs affected and frequency of publications. Finding the organ-associated occurrence of LMS may be useful in assessing the overall risk and formulating future cancer preventive strategies.

1. Background

Sarcoma refers to a cancer that arises from transformed cells of mesenchymal origin. These tumors are most common in the bones, muscles, tendons, cartilage, nerves, fat, and blood vessels. Leiomyosarcoma (LMS) is a type of soft tissue sarcoma (STS) and is referred to as malignant smooth muscle tumor. STS occurs throughout life[1] and can develop in muscle, fat, blood vessels or any of the other tissues that support or protect the organs of the body. STS spans a wide range of differentiation including adipocytes (liposarcoma), peripheral nerve tissues (malignant peripheral nerve sheath tumor), smooth (leiomyosarcoma) or striated muscle (rhabdomyosarcoma), vascular tissues (angiosarcoma), and other origins (such as undifferentiated pleomorphic sarcoma). Due to the rarity and complexity of STS, large population-based studies are required to elucidate its incidence and the potential contributing factors.[2] It has been proposed that tumor size, tumor necrosis, and vascular invasion are strong and reliable factors that can be used to improve prognostic accuracy in STS.[3]

LMS is one of the more common types of soft tissue sarcoma to develop in adults. It should not be confused with leiomyoma, which is a benign tumor originating from the same tissue. LMS is an extremely rare type of cancer and can be very unpredictable. It can remain dormant for long periods of time and recur after years.[4] LMS is not very responsive to chemotherapy or radiation, thus is considered a resistant cancer type. Furthermore, the best way to get rid of it is to remove it surgically in the early stages. LMS can arise in any type of organ. Cutaneous LMS originates from the pilo-erector muscles in the skin, gastrointestinal LMS arises from smooth muscle in the GI tract or from a blood vessel and uterine LMS comes from the smooth muscle in the uterine muscular layer. At most other primary sites—retroperitoneal extremity (in the abdomen, behind the intestines), truncal, abdominal organs, etc.—leiomyosarcomas appear to grow from the muscle layer of a blood vessel (the tunica media). Thus a leiomyosarcoma can have a primary site of origin anywhere in the body where there is a blood vessel. Due to its rare occurrence and unpredictability, this short review focuses on the reports available on the occurrence of LMS, its association with different organs, capability of metastasis and potential genetic biomarkers.

* Corresponding author. Department of Zoology, Khalsa College, Amritsar, Punjab, 143001, India.
E-mail address: zorawarsinghs@rediffmail.com.
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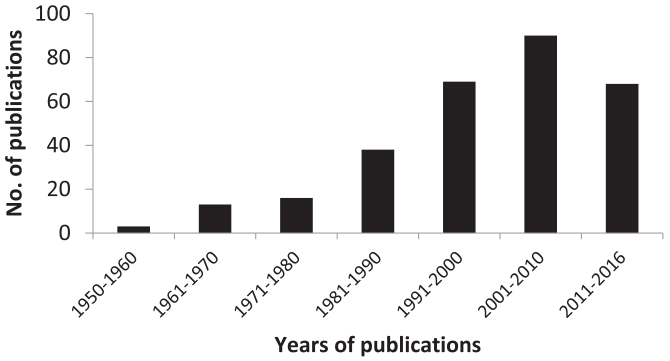

Fig. 1. Number of publications on occurrence of LMS of different organs from 1950 to 2016 (Studies taken from PubMed database search; N = 297).

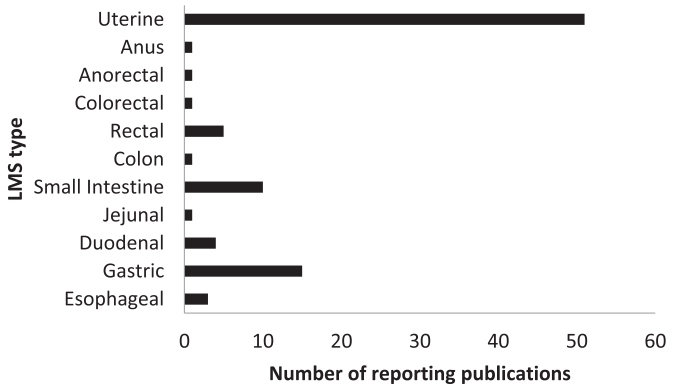

Fig. 3. Comparative number of reports on different LMS types (N = 93).

2. Literature search

A computerized literature search was done for identifying relevant studies. Articles on the occurrence of LMS in different organs were searched from 1950 to 2016 using the PubMed database. Abstracts of all the selected papers from the search were thoroughly studied and manuscripts were identified for full-text review. Different keywords and various combinations of terms related to the topic of research were used. Finally, the references at the end of the papers were also reviewed to identify any papers that were missed. Fig. 1 shows the number of publications by year (N = 297; Search from 1950 to 2016).

3. Occurrence of different types of LMS

3.1. Epidemiological studies

LMS has a low incidence rate. Hung et al.[2] reported an age-standardized incidence rate (ASR) of 1.63 per 100,000 persons. Many epidemiological studies on STS have reported the occurrence of LMS.[2,3,5–8] Most of the epidemiological studies on STS have been conducted in western countries and limited data is available for Asian countries.[2] In Taiwan, 292 LMS cases (0.075%) out of a total of 3843 primary STS cases were reported, yielding a crude rate of 0.14. ASRs for males and females were found to be 0.12 (150 cases) and 0.11 (142 cases), respectively.[2] Another study from Karachi, Pakistan reported a total of 7 LMS cases (0.072%) out of a total of 96 STS cases with ASR of 3.3 and 2.1 for males and females, respectively. The most common histological tumor was rhabdomyosarcoma.[5] Similarly, a U.S.-based study reported 104 LMS cases (29%), in addition to liposarcoma (n = 40; 11%), synovial sarcoma (n = 12; 3%) and 27 histologic subtypes (n = 207; 57%).[9] Toro et al.,[8] while showing the incidence patterns of STS, found 23.9% LMS cases out of a total of 26,758. The study also found 40% of the total LMS cases among women to be uterine in nature. Ferrari et al.[1] presented LMS as the most common type along with Kaposi sarcoma and fibrohistiocytic tumors out of a total of 48,012 STS cases. In the same line, Rydholm et al.[10] also reported LMS as the most common histologic group among the 278 STS cases.

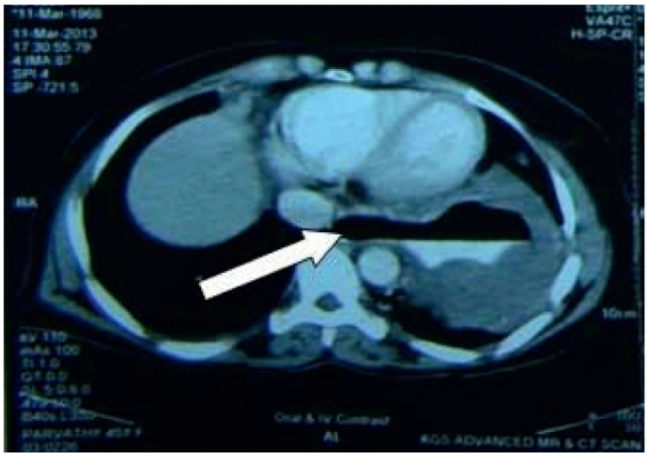

Fig. 2. CECT abdomen showing large mass in left lower thorax arising from distal esophagus. Centre of the mass was ulcerated and it was communicating with the esophageal lumen (Reprinted from Reddy et al.[12] DOI: https://doi.org/10.17659/01.2013.0100).

3.2. LMS of esophagus and stomach

Leiomyosarcoma is a rare tumor that accounts for 0.5% of esophageal sarcomas. Lise et al.[11] reported leiomyomas and LMS of the esophagus in 1972. A paper presented two cases of LMS of esophagus in a 45-year-old lady and a 52-year-old gentleman who presented with dysphagia, and whose LMS was confirmed by immunohistochemistry.[12] The lady presented normal routine biochemical and hematological parameters. Fig. 2 represents the CECT abdomen showing a large mass in the left lower thorax arising from the distal esophagus.

Miettinen et al.[13] reclassified a total of 68 stromal/smooth muscle tumors by current histologic and immunohistochemical criteria and found 3 LMSs, 17 gastrointestinal stromal tumors (GISTs) and 48 leiomyomas (LMs). All tumors were from the lower third of the esophagus, and the most common complaint was dysphagia. Similar to esophageal LMS, LMS of the stomach has also been reported[14–19] (Fig. 3). In 1948, Marvin and Walters[14] presented a case of multiple LMSs of the stomach and reviewed 16 cases. Later in 1953, Crile and Groves[15] reported 5 cases of massive LMSs of the stomach. In 1987, nuclear DNA patterns were studied by flow cytometry in LMS and benign smooth muscle tumors of the stomach.[17] In this study, paraffin-embedded tissue samples were used for determination of DNA ploidy by flow cytometry on surgically resected gastric smooth muscle tumors, including 44 LMSs. The DNA histograms of the 44 LMSs showed 20 cases (45%) of DNA diploid pattern, 14 cases (32%) of DNA tetraploid/polyploid pattern, and 10 cases (23%) of DNA aneuploid peaks. In the patients with LMS, the DNA ploidy pattern was significantly correlated with survival ($p < 0.001$), as were tumor grade ($P < 0.001$) and tumor size ($p < 0.05$). Both benign and malignant gastric smooth muscle tumors with DNA tetraploid/polyploid patterns were significantly

Table 1
Occurrence of different LMS types with respect to the organs affected.

Sr. No.	Authors	Year of publication	Type of LMS studied	Reference No.
1.	Lise et al.	1972	Esophagus	11
2.	Reddy et al.	2013	Esophagus	12
3.	Miettinen et al.	2000	Esophagus	13
4.	Chatterjee and Powell	1982	Gastric	16
5.	Crile, Jr. and Groves	1953	Gastric	15
6.	Forlini et al.	1992	Gastric	18
7.	Geshelin and Grachev	1995	Gastric	19
8.	Marvin and Walters	1948	Gastric	14
9.	Tsushima et al.	1987	Gastric	17
10.	Andreu et al.	1988	Gastric	28
11.	Choen and Rauff	1990	Gastric	29
12.	Davis and Adams	1956	Gastric	30
13.	Eriguchi et al.	1998	Gastric	31
14.	Matsuyama and Suzuki	1969	Gastric	32
15.	Matsuyama et al.	1970	Gastric	33
16.	Persson et al.	1992	Gastric	34
17.	Ramos and Mitsudo	1984	Gastric	35
18.	Sobrino Cossio et al.	1995	Gastric	36
19.	Miettinen et al.	2003	Duodenum	37
20.	Sachdev et al.	1998	Duodenum	38
21.	Cho and Reuter	1980	Duodenum	39
22.	Rosenberg	1964	Duodenum	40
23.	Das Gupta et al.	1961	Jejunum	41
24.	Chiotasso and Fazio	1982	Small intestine	20
25.	Koyama et al.	1976	Small intestine	23
26.	Fornaro et al.	1991	Small intestine	21
27.	Deck and Silverman	1979	Small intestine	42
28.	Lampertico et al.	1969	Small intestine	24
29.	Vincenzoni et al.	1998	Small intestine	22
30.	Tiberio et al.	1984	Small intestine	43
31.	Starr and Dockerty	1955	Small intestine	27
32.	Mizon et al.	1976	Small intestine	26
33.	Matsuda et al.	1990	Small intestine	25
34.	Miettinen et al.	2000	Colon	44
35.	Bakran et al.	1971	Rectum	45
36.	Leoutsakos	1961	Rectum	46
37.	Robert et al.	1963	Rectum	47
38.	Miettinen et al.	2001	Rectum	48
39.	Letessier et al.	1992	Rectum	4
40.	Friesen et al.	1992	Colorectal	49
41.	Wang and Chung	1998	Anorectal	50
42.	Miettinen et al.	2001	Anus	48
43.	Akhan et al.	2005	Uterine	51
44.	Barker et al.	2002	Uterine	52
45.	Bae et al.	2004	Uterine	53
46.	Azizi et al.	1979	Uterine	54
47.	Ayhan et al.	2009	Uterine	55
48.	Anderson and Aghajanian	2005	Uterine	56
49.	Amant and Vergote	2002	Uterine	57
50.	Allen et al.	2015	Uterine	58
51.	Bartosch et al.	2016	Uterine	59
52.	George et al.	2014	Uterine	60
53.	Gadducci and Guerrieri	2015	Uterine	61
54.	Fujii	1988	Uterine	62
55.	Durand-Reville et al.	1996	Uterine	63
56.	de et al.	1994	Uterine	64
57.	D'Angelo et al.	2011	Uterine	65
58.	Bernstein-Molho et al.	2010	Uterine	66
59.	Caraffi et al.	2015	Uterine	67
60.	Colombatti et al.	2002	Uterine	68
61.	Hall et al.	1997	Uterine	69
62.	Hayashi et al.	2008	Uterine	70
63.	Hart and Billman, Jr.	1978	Uterine	71
64.	Hayashi et al.	2006	Uterine	72
65.	Kato et al.	2004	Uterine	73
66.	Kapp et al.	2008	Uterine	74
67.	Kao et al.	2011	Uterine	75
68.	Jones and Norris	1995	Uterine	76
69.	Kainsbak et al.	2015	Uterine	77
70.	Ip et al.	2010	Uterine	78
71.	Ip and Cheung	2011	Uterine	79
72.	Huang et al.	2011	Uterine	80
73.	Horiuchi et al.	2000	Uterine	81

(*continued on next page*)

Table 1 (*continued*)

Sr. No.	Authors	Year of publication	Type of LMS studied	Reference No.
74.	Hu et al.	2001	Uterine	82
75.	Hensley et al.	2014	Uterine	83
76.	Mayerhofer et al.	2004	Uterine	84
77.	Miller et al.	2000	Uterine	85
78.	Mittal and Joutovsky	2007	Uterine	86
79.	Makinen et al.	2016	Uterine	87
80.	Mittal et al.	2009	Uterine	88
81.	Moore et al.	2000	Uterine	89
82.	Nugent et al.	2015	Uterine	90
83.	Kelley et al.	2004	Uterine	91
84.	O'Reilly et al.	1997	Uterine	92
85.	Lieng et al.	2015	Uterine	93
86.	O'Neill et al.	2007	Uterine	94
87.	Lee et al.	1994	Uterine	95
88.	Lee et al.	2011	Uterine	96
89.	Lee et al.	2011	Uterine	97
90.	Laberge	1962	Uterine	98
91.	Kulak et al.	2014	Uterine	99
92.	Kubo et al.	1995	Uterine	100
93.	Pavlakis et al.	1982	Bone	101
94.	Mori et al.	2016	Bone	102
95.	Cristina et al.	2015	Bone	103
96.	Kim et al.	2013	Bone	104
97.	Brewer et al.	2012	Bone	105

larger than those with a DNA diploid histogram ($p < 0.05$).

3.3. Intestinal LMS

Leiomyosarcoma of the small intestine is a rare tumor, comprising 0.2% of all malignant tumors of the gastrointestinal tract.[20] These are rarely observed malignant tumours, which sometimes are difficult to diagnose and have a poor prognosis.[21] These have nonspecific symptoms thus their diagnosis is often made at a late stage.[22] Many of the studies focused on the occurrence of LMS in the intestine.[20–27] Chiotasso and Fazio[20] reviewed the charts of 28 patients and found that the outstanding characteristics were a slow growing, but sometimes, fast growing locally malignant lesion, more than half being in the ileum. Adjuvant therapy was found to be of no benefit and for diagnostic purposes, arteriograms were found to be better than roentgenographic series of the small intestine. Similarly, Fornaro et al.[21] stressed the main clinical and anatomico-pathological aspects of small bowel leiomyosarcomas. A substantial difficulty in histologically defining the malignancy grade was encountered.

LMS of the small intestine were found in dogs during experimental induction of gastric carcinoma by oral administration of N-methyl-N′-nitro-N-nitrosoguanidine (MNNG) in drinking water (50 μg/ml).[23] These sarcomas developed in 3 months–5 years after MNNG administration. LMS were found most frequently in the duodenum and jejunum. These were sometimes observed in the stomach but never in the lower part of the small intestine namely ileum, colon or rectum. This study also revealed a frequent metastasis of MNNG-induced LMS to the liver. Matsuda et al.[25] analyzed case reports of LMS in the Japanese literature from 1980 through 1989. In two patients (22.2%), a perforation was seen, and the frequency of perforation was found to be 8.6%. The distribution of the perforated LMS was the same as in the non-perforated cases. The 5-year postoperative survival rate was found to be 41.2%. The study emphasized that 3 out of 10 patients (that had survived for 5 years) subsequently died of sarcomatosis, a condition in which a sarcoma has disseminated throughout the body. Vincenzoni et al.[22] presented three cases of large, abdominal masses, originally evaluated as ovarian tumors. Histologically, all three cases were diagnosed as LMS of the small intestine. On the same line, Table 1 shows the occurrence of LMS in different organs.

3.4. LMS of rectum and anus

A few studies have also reported the occurrence of rectal and anal LMS.[45,46,48] The first paper reporting LMS of the rectum was published in 1961 by Leoutsakos.[46] In 1992, Letessier et al.[4] reported two cases of high grade leiomyosarcoma of the rectum treated by local excision. Both patients presented recurrence and died after treatment. The first patient presented a local recurrence associated with liver and pulmonary metastases whereas the second patient presented with tumor recurrence 3 months after excision. Local surgical excision in comparison to a more radical surgical approach, such as abdominoperineal resection, was found to be more effective in improving survival.[4] Another study analyzed the clinicopathologic features of 133 anorectal GISTs, 3 intramural leiomyomas (LMs) and 8 LMSs. Six of the 8 LMS cases formed a polypoid intraluminal mass and were found to be actin-positive and KIT-negative.[48]

3.5. Uterine LMS

Uterine leiomyosarcoma is the most frequent malignant gynecologic mesenchymal tumor.[59] Uterine LMS has also been shown to affect other body organs, and Bartosch et al.[59] characterized the body sites and time to metastasis in women by evaluating 130

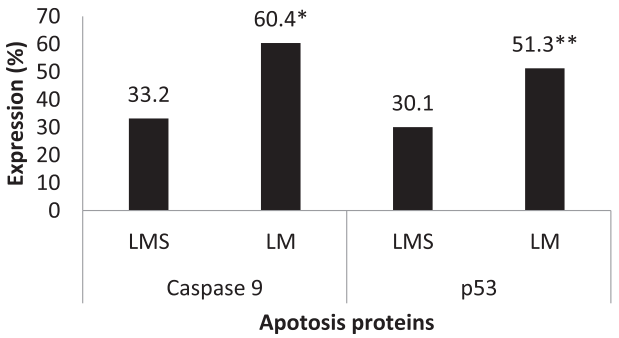

Fig. 4. Comparative expressions of Caspase 9 and p53 in leiomyosarcomas (LMS) as compared to leiomyomas (LM) [Drawn as per results from Kulak et al.[99]].

Table 2
Studies involving the expression of different genes/proteins in uterine LMS.

Sr. No.	Author	Year	LMS type	Genes studied	Reference
1	De Vos	1994	Uterine	p53	64
2	Hall et al.	1997	Uterine	p53, Ki-ras, MDM2	69
3	O'Reilly et al.	1997	Uterine	p53, Ki-67	92
4	Zhai et al.	1999	Uterine	p53, Ki-67	110
5	Kato et al.	2004	Uterine	mig-2	73
6	Akhan et al.	2005	Uterine	p53, Ki-67	51
7	O'Neill et al.	2007	Uterine	p53, p16, MIB1	94
8	Kulak et al.	2014	Uterine	p53, caspase 9	99
9	Makinen et al.	2016	Uterine	TP53, ATRX, MED12	87
10	Kubo et al.	1995	Uterine	Tsc-2 gene locus	100
11	D'Angelo et al.	2011	Uterine	Ki-67, Bcl-2	65
12	Mayerhofer et al.	2004	Uterine	Ki-67	84
13	Brewer Savannah et al.	2012	Uterine	Aurk-A	112
14	Shan et al.	2012	Uterine	Aurk-A	113

Tsc, Tuberous sclerosis; Aurk-A, Aurora Kinase A.

uterine LMS cases. The most frequent metastatic sites were found to be the lung (67.7%), cranial/intracranial (16.2%), skin/soft tissues (15.3%) and bone (13.8%). Other sites included thyroid, salivary gland, heart, liver, pancreas, adrenal gland, bowel, and breast.[59] Laparoscopic morcellators were used during laparoscopic surgeries involving removal of large masses. Morcellation is also a subject of importance.[93,106] Morcellation has been found to increase the risk of death in patients affected by undiagnosed LMS.[107] Caraffi et al.[67] characterized the microvessel distribution and morphology in a retrospective series of LMSs of the soft tissues and the uterus. The study found that microvessel density correlated with tumor grade in LMS of soft tissues but this did not apply to uterine LMS, possibly due to the abundant myometrial vascularization.[67]

Uterine sarcomas are clinically and histologically heterogeneous malignancies. The process of oncogenesis depends on gene mutations and uncontrolled mitotic cell division that is promoted by blocking pathways of apoptosis.[99,108] Caspase 9 and p53 protein play an important role in the process of cell apoptosis.[99] Kulak et al.[99] assessed the expression of these apoptosis proteins (Fig. 4) in 28 tissue samples using immunohistochemistry. A significantly lower expression of caspase 9 ($p < 0.05$) was observed in LMS tissues (33.2%) as compared to leiomyomas (60.4%). Expression of p53 protein was also found to be significantly lower in LMS tissues than in leiomyomas (30.1% vs. 51.3%, $p < 0.001$).

3.6. Genetic biomarkers in uterine LMS

Genetic abnormalities may lead to neoplasia resulting in abnormal growth of tissues, eventually leading to LMS. However, little is known of the genetic abnormalities including the loss of p53 function in the pathogenesis of many human tumors. The cell cycle regulators p16 and p53 are frequently over-expressed and appear to be involved in key modifications of sarcomagenesis.[109] p53, Ki-67, p16 and p21 were reported to be strongly expressed in LMS and PTEN, FSCN1, ER, PR and MIB1 to be moderately expressed.[109] De Vos et al.[64] evaluated eight LMSs for alterations in exons 5–8 of p53, which are the mutational hotspots for this gene in human malignancies. Genomic DNA of the samples was studied by single-strand conformation polymorphism (SSCP) analysis and positive samples were analyzed by direct sequencing of PCR-amplified products. Three alterations in a total of eight LMS samples were found. The changes were found to be point mutations (exon 5, codon 165; exon 8, codon 275; exon 8, codon 266) and revealed that p53 mutations were frequent in uterine leiomyosarcomas.[64] This study was conducted in 1994 and was the first to report the role of p53 in LMS. Many studies subsequently reported the effect of p53 mutation in uterine LMS.[51,69,92,94,99,110] One study used comparative genomic hybridization (CGH) to analyze eight cases of uterine LMSs, and all eight cases showed gains or losses of DNA.[111] Table 2 shows the studies reporting the association of different genes and proteins in uterine LMS.

DOG1 is a recently described marker of GIST which is considered to be extremely sensitive. Sah and McCluggage stained 26 uterine LMSs and found that DOG1 immunoreactivity was present in 7 of 26 (27%) LMS cases.[114] Table 3 (Reprinted from Kobayashi et al.[109]) shows the genetic aberrations involved in uterine sarcoma biology. The LMP2 gene is transcribed from a promoter containing an

Table 3
Review of the clinical features, imaging characteristics and genetic aberrations in uterine sarcoma biology (Reprinted from Kobayashi et al.[109]; https://doi.org/10.3892/mco.2013.124).

Gene/protein expression	Better prognosis	Poor prognosis
Overexpression	Bcl-2	Ki-67, p53, p16, p21
Moderate expression		PTEN, FSCN1, ER, PR, MIB1
Low expression or absence	Ki-67, p53, p16, TWIST1	BRCA1, MED12
Specific genetic aberrations	LOH on chromosome 10, LMP2 deficiency	
Age	Relatively young women in the age group of 40–55 years	
Clinical manifestations	Most patients had uterus-confined disease	
Gross examination	Higher incidence of hemorrhage or necrosis compared to carcinosarcoma	
Magnetic resonance imaging	Lobulated mass of moderately high- signal intensity on T1-weighted images and high-signal intensity on T2-weighted images	

ER, estrogen receptor; PR, progesterone receptor; LOH, loss of heterogeneity.

interferon (IFN)-gamma-response factor element and IFN-gamma - signal strongly induces LMP2 expression. LMP2-deficient mice have been shown to exhibit spontaneous development of uterine LMS with a disease prevalence of approximately 37% by 12 months of age.[70] The role of TAP1 gene has also been discussed along with LMP2 in uterine LMS cases.[72] Germline mutations in fumarate hydratase (FH) may also be associated with development of LMSs.[115]

Aurora Kinase A (Aurk-A) is a member of a family of mitotic serine/threonine kinases which affects chromosomal separation and mitotic spindle stability through interaction with the centrosome during mitosis. Aurk-A has been reported to be involved in the occurrence of several types of soft tissue sarcomas. Aurora kinases are mitotic enzymes that are highly expressed in uterine malignancies.[116] It has also been explored widely in other cancer types.[117-120] Aurk-A deregulations have also been reported to occur in uterine LMS.[112] Han et al. analyzed clinical and pathological data of 24 patients and expression patterns of aurora kinases. Aurora kinases A and B were found to be dominantly expressed in the cytoplasm whereas phospho-aurora kinases A and B were expressed in the nuclei.[116] The pathogenesis of uterine sarcoma remains largely unknown, although recent basic science and preclinical animal models have provided a better understanding of tumor biology. Recent genome-wide studies have also identified complex chromosomal rearrangements as oncogenic mechanisms.[109] Further research is needed to reveal new areas of study targeting molecular and genetic pathways.

4. Conclusion

STS spans a wide range of differentiation including adipocytes, nervous tissues and muscles. LMS is a smooth muscle connective tissue tumor which is a rare form of cancer and accounts for 5–10% of STSs. Studies have reported the occurrence of LMS of esophagus, stomach, intestine, colon, rectum, bone, skin and uterus. Different genes/proteins including Ki-67, Bcl-2, p53, p16, p21 and Aurk-A have been found to be associated with LMS. Revealing the associations of LMS with different organs may be useful in assessing the overall risk. Review of the clinical features, imaging characteristics and genetic aberrations related to a particular LMS type may be helpful in formulating future cancer prevention strategies.

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Conflict of interest

The authors declare no competing interests.

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