Uterine leiomyosarcoma: A 10-year review in a referral hospital in Peru, 2005 - 2014

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Background. Uterine leiomyosarcoma (LMS) accounts for more than 50% of uterine sarcomas, representing 1.3% of all uterine malignancies. The presenting symptoms of uterine LMS are the same as those of leiomyoma. This characteristic hinders a prompt diagnosis, or suspicion, before a surgical intervention. Patients diagnosed with uterine LMS are often in an early stage of the disease. Nonetheless, the overall prognosis is poor.

Objective. To describe the general characteristics, clinical features, diagnosis and treatment of patients with LMS.

Methods. From 2005 to 2014, clinical files of patients diagnosed with a uterine LMS at Hospital Nacional Edgardo Rebagliati Martins in Peru were reviewed.

Results. Eleven cases with complete information were identified. The mean age at diagnosis was 45.36 years (range 27 - 61 years); the most frequent symptom reported was pelvic pain in 54% (*n*=6/11) patients; 72% (*n*=8/11) patients were diagnosed after surgical intervention. The most frequent clinical stage was IB in 90% (*n*=10/11) cases. Initial treatment was total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) in 62% (*n*=7/11) cases. The prevalence of undiagnosed uterine LMS in hysterectomies and myomectomies performed for presumed leiomyomas was 0.24% and 0.22%, respectively.

Conclusion. The clinical presentation of uterine LMS does not differ from usual leiomyomas. Most of the cases were diagnosed incidentally after surgical specimen analysis. The most accepted initial management to date is still *en bloc* TAH and BSO. Follow-up strategies should be implemented and be the goal of any long-term programme.

S Afr J Obs Gynae 2018;24(3):95-99. DOI:10.7196/SAJOG.2018.v24i3.1355

Uterine leiomyosarcoma (LMS) accounts for more than 50% of uterine sarcomas, constituting 1.3% of all uterine malignancies. The estimated annual incidence is 0.55 per 100 000 women, and the frequency of LMS diagnosed incidentally on hysterectomy specimen analysis is reported to be between 0.2 and 0.49%, with notable rises in the fourth and seventh decades of life.[1-4]

The presenting symptoms of uterine LMS are the same as those of leiomyoma. This characteristic hinders a prompt suspicion and diagnosis before any surgical intervention. Signs and symptoms frequently associated with uterine LMS are abnormal uterine bleeding, pelvic pain and a rapidly enlarging fibroid.[3-7]

To date, even though morphological features (margins, necrosis, haemorrhage, vascularity, calcifications and heterogeneity) and especially diffusion-weighted magnetic resonance imaging can help to characterize large uterine lesions, we are unable to accurately predict the presence of malignancy based solely on individual imaging features in any available imaging studies.[3-9,11]

Patients diagnosed with uterine LMS are often in an early stage of the disease. Nonetheless, the overall prognosis is poor. The standard of care in this disease is *en bloc* total hysterectomy, with bilateral salpingo-oophorectomy not well established in premenopausal women. Adjuvant pelvic radiotherapy may help to reduce the local recurrence rates, but have little or no impact on overall survival. Similarly, the clinical benefit of combination chemotherapy v. single-agent chemotherapy is still under investigation.[3-10]

In Peru, there are no reports detailing uterine LMS alone; this study provides a description of demographic, clinic and pathological features of patients diagnosed with uterine LMS in Hospital Nacional Edgardo Rebagliati Martins (HNERM), the largest reference hospital in the state healthcare system in Peru. Additionally, the frequency of incidental uterine LMS in a series of hysterectomies and myomectomies performed for presumed leiomyoma is reported.

Methods

This was a retrospective single-centre cohort study. It included all cases of uterine LMS in the Pathology Department Database of HNERM that were identified at histopathological examination between 1 January 2005 and 31 December 2014. HNERM is a tertiary care hospital of the Peruvian state healthcare system located in Lima, which serves a population of 1 816 605 habitants. For prevalence data, only cases of incidental uterine LMS that were identified at a histopathological examination in women undergoing hysterectomy or myomectomy for suspected leiomyomas were taken into account. Hysterectomy and myomectomy data were obtained from the Statistics Unit of HNERM. All information was obtained by reviewing the clinical files.

Patient variables

The following variables were assessed: age at the moment of diagnosis; age of menarche; parity; smoking habits; related signs and

symptoms; clinical stage; treatment received; disease-free period; and time and site of recurrence.

Tumour morphology

Pathology reports were obtained from the archive, and evaluation of the following variables was performed: uterine size; tumour size; histological grade; myometrial invasion; and spread to other organs. Tumour size was assessed in all patients by measuring the surgical specimen. Whenever a patient was surgically operated on outside HNERM, the specimen was also reviewed at our institution.

Treatment

Reports of the surgical procedures were reviewed. Additional data such as adjuvant treatment with radiotherapy or chemotherapy were reported on the data collection sheet in detail.

Follow-up

Follow-up data were obtained by reviewing the patients' clinical files. In patients lost to follow-up or those who were followed up at other institutions, this information was obtained by telephone contact. Standard parameters were applied for the definition of the disease-free period and overall survival.

Ethics

None of the principles of ethics was violated. The information gathered as part of the study was maintained completely confidentially, with access only available to the author. The Office for Training, Teaching and Research of HNERM approved the protocol of the study (ref. no. 586-GRAR-ESSALUD-2016).

Results

Patients

Eleven patients were identified with a diagnosis of uterine LMS in the 10-year period. From 2005 to 2014, 2 501 hysterectomies and 922 myomectomies were performed for presumed leiomyomas in our institution. The distribution of surgical route in hysterectomies was: abdominal, *n*=2 395; vaginal, *n*=6; and laparoscopic, *n*=100. All myomectomies were performed via the abdominal route. Pathological analysis of samples of patients operated on at our institution for presumed leiomyomas revealed uterine LMS in six patients (0.24%) in the hysterectomy group and two patients (0.22%) who had undergone myomectomy.

The mean age at diagnosis was 45.36 years, with a range of 27 - 61 years. The mean age of menarche was 11.73 years. All patients referred had not used a contraceptive method during the previous 3 years. In 36% (*n*=4/11) of patients the disease was diagnosed after the menopause, and none of these had received hormonal replacement therapy. 'Smoking habit' was reported as negative in 90% (*n*=10/11) of patients, and only one patient reported non-daily smoking. The disease was diagnosed in patients with previous pregnancies, a history of miscarriages and one or more children (Table 1).

Table 1. General patient characteristics (*N*=11)

Characteristic	Value
Age (years), mean (range)	45.36 (27 - 61)
Menarche (years), mean (range)	12.91 (10 - 15)
No contraception (last 3 years), *n* (%)	11 (100)
Age of menopause (years; 4 patients (36%)), mean (range)	48.75 (46 - 54)
No HRT	4 (100)
Smoking habit, *n* (%)	
Daily	0
Occasional	1 (10)
No	10 (90)
Number of pregnancies, *n* (%)	
0	3 (27)
1	3 (27)
2	1 (10)
≥3	4 (36)
Number of children, *n* (%)	
1	2 (22)
2	2 (22)
3 or more	3 (27)

HRT = hormone replacement therapy.

Table 2. Clinical characteristics of patients (*N*=11)

1st sign/symptom (*N*=11)	
Pelvic pain, *n* (%)	6 (54)
Transvaginal bleeding, *n* (%)	5 (46)
2nd S/S (*n*=4; 36%)	
Pelvic pain, *n*	2
Transvaginal bleeding, *n*	2
Duration of clinical picture (months), mean (range)	9.8 (3 - 24)

Signs and symptoms

The most frequent symptom was pelvic pain, in 54% (*n*=6/11) patients, followed by abnormal vaginal bleeding (46%); 36% (*n*=4/11) of patients identified both symptoms at the time of diagnosis. The mean duration of symptoms pre-diagnosis was 9.8 months, with a range between 3 and 24 months (Table 2).

Diagnosis

In 18% (*n*=2/11) of patients, uterine LMS was diagnosed before surgical intervention, in one case through an endometrial biopsy performed as an outpatient. In the second case the patient was diagnosed by removal of a pedunculated supposed fibroid prolapsing through the cervix, also performed as an outpatient. In only 10% (*n*=1/11) of patients was the diagnosis made during surgery, owing to a frozen section performed during the operation. In the remainder of cases, 72% (*n*=8/11) of patients, the diagnosis was made postoperatively on histological assessment.

Pathology

The mean size of the uterine masses was 90.27 mm, with a range 48 - 140 mm, and 90% of the tumours were more than 50 mm in diameter. The histological grade was reported as 1 in 5/11 samples (46%), 2 in 1/11 samples (9%) and 3 in 4/11 samples (36%); in one sample histologic grade was not reported (Table 3).

Treatment and adjuvant therapy

Initial treatment in all 11 patients (100%) was surgery (Table 4). Only one patient (*n*=1/11) had both chemotherapy (with doxorubicin plus cisplatin) and radiotherapy treatment (adjuvant pelvic radiation with 50 Gy). The main reason for this decision was the diagnosis of the malignancy during surgery, and the identification of a patient with a high-risk disease. Unfortunately, the patient died 2 months after diagnosis. The second patient who

Table 3. Anatomopathological characteristics of samples (*N*=11)

Characteristic	Value
Size	
Mean (mm), range	90.27 (48 - 140)
Number ≤5 cm, *n* (%)	1 (10)
Number >5 cm, *n* (%)	10 (90)
Histology grade, *n* (%)	
1	5 (46)
2	1 (9)
3	4 (36)
Not reported	1 (9)
Clinical stage, *n* (%)	
IA	1 (10)
IB	10 (90)

Table 4. Treatment of patients with uterine leiomyosarcoma (*N*=11)

Treatment	*n* (%)
Surgery	
Myomectomy only	2 (18)
TAH and BSO	7 (62)
TAH, BSO and (L)	1 (10)
TAH, BSO, L and omentectomy	1 (10)
Radiotherapy	
Yes	1 (9)
No	6 (55)
NR	4 (36)
Chemotherapy	
Yes	2 (18)
No	5 (46)
NR	4 (36)

TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy; L = lymphadenectomy; NR = not reported.

underwent adjuvant therapy was provided with adjuvant pelvic radiation, 50 Gy over 4 weeks, with no unexpected toxicity seen during follow-up. Five patients (*n*=5/11) were not offered adjuvant therapy. From the files, a further four patients were likely not offered adjuvant therapy, but completion of the data and follow-up of these four patients was not possible as described below.

Follow-up

The mean follow-up time was 53 months (range 7 - 96 months) and the mean disease-free period 52 months (range 2 - 96 months). However, four patients were lost to follow-up. Recurrence of the disease occurred in 1 case (9%), or one of seven cases with follow-up (14%), though we have no means of knowing the outcome in four cases. The site of recurrence was the pelvic cavity, and it occurred 2 months after surgery. This case was also the only reported death from progression of the disease.

Table 5 summarises the general characteristics, presenting symptoms, moment of diagnosis, uterine size, tumour size, clinical stage, type of surgery, adjuvant therapy and follow-up for all study subjects.

Discussion

Uterine LMS is the most common histological variant of uterine sarcoma. Recognition of the heterogeneous clinical and biological behavior of LMS, compared with endometrial cancer, and the fact that LMS tends to be more aggressive and to have a worse prognosis led the Federation of Gynaecology and Obstetrics (FIGO) to develop a new staging system for uterine sarcoma in 2009, which may have started a new era in the research of this uncommon pathology.[1,4,6,7,12,13] The present study represents the first time that data has been gathered from our own institution, rather than relying on information gathered elsewhere.

The study confirms that the epidemiological profile of the patients does not identify any unique characteristic that defines the group diagnosed with the disease, making screening in a selected group of patients almost impossible, as reported previously.[5] Of the symptoms, Cantú de León *et al.*,[15] in a study in Mexico, described vaginal bleeding as the most frequent symptom reported in a group of patients with uterine sarcomas. Giuntoli *et al.*,[16] in a group of patients diagnosed with uterine LMS, also described vaginal bleeding as the most frequent symptom, followed closely by the presence of a pelvic mass in a study in the USA. We noted that in our patients, the most frequent symptom was pelvic pain (54% of cases), followed by abnormal transvaginal bleeding (46%), and that in four (36%) patients, both symptoms were present.

Harry *et al.*[8] reported that the most common presentation of uterine LMS was an incidental finding at the time of surgery. In France, Leung *et al.*[17] studied a 1 297-patient cohort who were hysterectomised for probable uterine leiomyomas, and found three patients with the final diagnosis of LMS (0.23%). In our study, nine (72%) patients were diagnosed incidentally after a surgical intervention, and only two (18%) were diagnosed before major surgery. Similarly, the prevalence of uterine LMS in our cohort was 0.24% in the group of patients with hysterectomies performed for presumed leiomyoma, and 0.22% in the myomectomy group. Even though total hysterectomy has been established as the safest surgical procedure for cases where the diagnosis is reached during the histological exam of a myomectomy, Gadducci *et al.*[10] have reported successful cases of survival free of disease in Italy, including some with future pregnancies, when conservative surgery was requested. This also occurred in our own study. Two patients were treated by myomectomy, and pathological analysis after surgery revealed the diagnosis. These patients, after counselling, elected not to have hysterectomies, and were kept under clinical and radiological follow-up, and showed no recurrence of the disease. One of these patients had two subsequent pregnancies. Giuntoli *et al.*[16] reported that in their study, more than 60% of cases were in stage I among 208 patients diagnosed with uterine LMS. No correlation between histology grade and FIGO stage was observed. When multivariate analysis was performed, histological grade >1 had the largest influence on mortality, with a relative risk of 6.05, and FIGO stage above I had a relative risk of 2.78. In our study, the average size of the uterine LMS was 90.27 mm, with 90% of tumours >5 cm. All cases were limited to the uterus, making stage IB the most common in 90% of cases. Different histological grades were encountered in all 11 patients, and in the only death reported, the histological grade was the highest.

As noted before there is a lack of consistency among various studies regarding the correlation between survival and patient age, clinical stage, tumour size, type of border (pushing v. infiltrative), presence or absence of necrosis, mitotic rate, degree of nuclear pleomorphism and vascular invasion.[7,11,14] Therefore total abdominal hysterectomy and debulking of tumour if present outside the uterus is the main component of surgical treatment.[4,7,8,18] However,

Table 5. Summary of general characteristics, clinical presentation, anatomopathological features and management of patients with uterine LMS

Patient number	Diagnosis, age (years)	Pregnancies, *n* (parity, *n*)	Menarche, age (years)	Menopause, age (years)	HRT	Sign/symptom	Moment of diagnosis, surgical	Uterine size (mm)	LMS size (mm)	Histology grade	Stage	Surgery	R	C	Follow-up (months)	Death
1	51	6 (4)	12	47	No	Transvaginal bleeding, pelvic pain	Post	127	100	3	IB	TAH, BSO	NR	NR	NR	ND
2	61	6 (5)	13	48	No	Transvaginal bleeding	Pre	100	70	1	IB	TAH, BSO	No	No	60	No
3	31	0 (0)	12	-	-	Abnormal uterine bleeding, pelvic pain	Post	90	48	1	IA	Miomectomy	No	No	12	No
4	27	1 (0)*	15	-	-	Dysmenorrhoea, hypermenorrhea	Post	90	100	1	IB	Miomectomy	No	No	96	No
5	49	3 (2)	15	-	-	Hypermenorrhea	Pre	105	80	3	IB	TAH, BSO, L	NR	NR	NR	ND
6	48	4 (2)	13	-	-	Pelvic pain, abnormal uterine bleeding	Post	160	100	1	IB	TAH, BSO	No	No	12	No
7	60	0 (0)	10	54	No	Abdominal and pelvic pain	Intra	200	120	3	IB	TAH, BSO	Yes	Yes	2	Yes
8	51	3 (3)	14	-	-	Hypermenorrhea	Post	130	140	1	IB	TAH, BSO	NR	NR	60	ND
9	33	1 (1)	14	-	-	Pelvic pain, hypermenorrhea	Post	140	95	NR	IB	TAH, BSO, L, omentectomy	NR	NR	NR	ND
10	34	0 (0)	14	-	-	Abdominal and pelvic pain	Post	180	60	2	IB	TAH, BSO	No	Yes	84	No
11	54	1 (1)	10	46	No	Pelvic pain	Post	60	80	3	IB	TAH, BSO	No	No	NR	No

LMS = leiomyosarcoma; HRT = hormone replacement therapy; R = radiotherapy; C = chemotherapy; TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy; L = lymphadenectomy; NR = not reported; ND = no data. Blank cells = not applicable.
*Patient completed two consecutive pregnancies after diagnosis.

as reviewed by D'Angelo and Prat,[7] removal of the ovaries and lymph node dissection remain controversial, as metastases to these organs occur in only a small percentage of cases. In our study, the adnexa and lymph nodes removed from our patients (in only two cases) were free of disease. In addition, in premenopausal patients with an incidental finding of uterine LMS, conservative management can be successful with close follow-up, as reported in our study.

Our main study limitation was patient follow-up; data were not available in four cases. This resulted from loss of social health insurance, change of home address, with the reassignment of social security health facility, or change to another health facility (public or private) by patient choice. Lack of complete follow-up data does not allow us to generate survival curves with the Kaplan-Meier method. In addition, the absence of local protocols with respect to radiotherapy and chemotherapy in patients with uterine LMS make the therapy decision-making process even more difficult in specific cases.

In conclusion, uterine LMS is an extremely rare diagnosis with no clinical and imaging findings distinguishing it from the more usual leiomyoma. Diagnosis before any surgical intervention is only feasible in patients with tumour presentation located in the endometrial cavity or protruding from the cervix. In patients with completed families, *en bloc* total abdominal hysterectomy, with or without bilateral salpingo-oophorectomy, is the standard of care. Myomectomy alone can be offered to patients desiring fertility, with full counselling, including on the uncertainty of outcome, and with closely maintained follow-up. Follow-up strategies should be implemented to record local recurrences and survival curves and to consider the best therapeutic option for each patient. Prospective studies should be done worldwide to see any benefits of adjuvant radiotherapy, chemotherapy or both in terms of overall survival.

Acknowledgements. None.

Author contributions. Sole author.

Conflicts of interest. None.

Funding. None.

1. Seddon B, Davda R. Uterine sarcomas – recent progress and future challenges. Eur J Radiol 2011;78(1):30-40. https://doi.org/10.1016/j.ejrad.2010.12.057
2. Ueda S, Kapp D, Cheung M, et al. Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths. Am J Obstet Gynecol 2008;198(2):218.e1-218.e6. https://doi.org/10.1016/j.ajog.2007.08.075
3. Gadducci A, Guerrieri M. Pharmacological treatment for uterine leiomyosarcomas. Expert Opin Pharmacother 2015;16(3):335-346. https://doi.org/10.1517/14656566.2015.985205
4. Tropé C, Abeler V, Kristensen G. Diagnosis and treatment of sarcoma of the uterus. A review. Acta Oncologica. 51(6):694-705. http://doi.org/10.3109/0284186X.2012.689111
5. Harter P, El-Khalfaoui K, Heitz F, du Bois A. Operative and conservative treatment of uterine sarcomas. Geburtshilfe und Frauenheilkunde 2014;74(3):267-270. https://doi.org/10.1055/s-0034-1368204
6. Sutton G. Uterine sarcomas. Gynecol Oncol 2013;130(1):3-5. https://doi.org/10.1016/j.ygyno.2013.05.015

7. D'Angelo E, Prat J. Uterine sarcomas: A review. Gynecol Oncol 2010;116(1):131-139. https://doi.org/10.1016/j.ygyno.2009.09.023
8. Harry V, Narayansingh G, Parkin D. Uterine leiomyosarcomas: A review of the diagnostic and therapeutic pitfalls. Obstet Gynaecol 2007;9(2):88-94. https://doi.org/10.1576/toag.9.2.088.27309
9. Gaetke-Udager K, McLean K, Sciallis A, et al. Diagnostic accuracy of ultrasound, contrast-enhanced CT, and conventional MRI for differentiating leiomyoma from leiomyosarcoma. Acad Radiol 2016;23(10):1290-1297. https://doi.org/10.1016/j.acra.2016.06.004
10. Gadducci A, Landoni F, Sartori E, et al. Uterine leiomyosarcoma: Analysis of treatment failures and survival. Gynecol Oncol 1996;62(1):25-32. https://doi.org/10.1006/gyno.1996.0185
11. Kobayashi H. The biology of uterine sarcomas: A review and update. Mol Clinic Oncol 2013;1(4):599-609. https://doi.org/10.3892/mco.2013.124
12. World Health Organization. Pathology and genetics of tumours of the breast and female genital organs. In: World Health Organization. WHO Classification of Tumours. Geneva: WHO, 2003.
13. Tse K, Crawford R, Ngan H. Staging of uterine sarcomas. Best Prac Res Clin Obstet Gynaecol 2011;25(6):733-749. https://doi.org/10.1016/j.bpobgyn.2011.05.011
14. Matsuda M, Ichimura T, Kasai M, et al. Preoperative diagnosis of ssual leiomyoma, atypical leiomyoma and leiomyosarcoma. Sarcoma 2014:498682. https://doi.org/10.1155/2014/498682
15. Cantú de León D, González H, Pérez Montiel D, et al. Uterine sarcomas: Review of 26 years at the Instituto Nacional de Cancerologia of Mexico. Int J Surg 2013;11(7):518-523. https://doi.org/10.1016/j.ijsu.2013.04.013
16. Giuntoli R, Metzinger D, DiMarco C, et al. Retrospective review of 208 patients with leiomyosarcoma of the uterus: Prognostic indicators, surgical management, and adjuvant therapy. Gynecol Oncol 2003;89(3):460-469. https://doi.org/10.1016/S0090-8258(03)00137-9
17. Leung F, Terzibachian J, Gay C, et al. Hystérectomies pour léiomyomes présumés: La crainte du léiomyosarcome doit-elle faire appréhender la voie d'abord chirurgicale autre que laparotomique? Gynécologie Obstétrique Fertilité 2009;37(2):109-114. https://doi.org/10.1016/j.gyobfe.2008.09.022
18. Sagae S, Yamashita K, Ishioka S, et al. Preoperative diagnosis and treatment results in 106 patients with uterine sarcoma in Hokkaido, Japan. Oncology 2004;67(1):33-39. https://doi.org/10.1159/000080283

Accepted 11 February 2019.