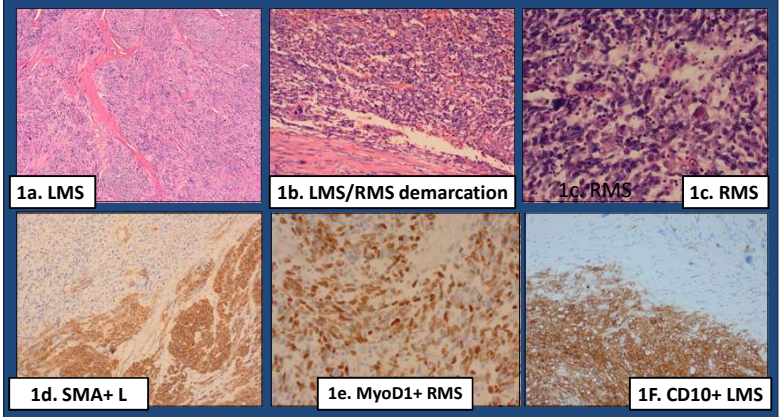
HETEROLOGOUS DIFFERENTIATION IN LEIOMYOSARCOMAS: TWO CASES OF THIS UNUSUAL ENTITY

Authors: Grant L, Williams A, Ganesan R, Boyle W. **Institution:** Birmingham **Women's Hospital, Birmingham, B15 2TG.**

NHS Birmingham Women's and Children's NHS Foundation Trust

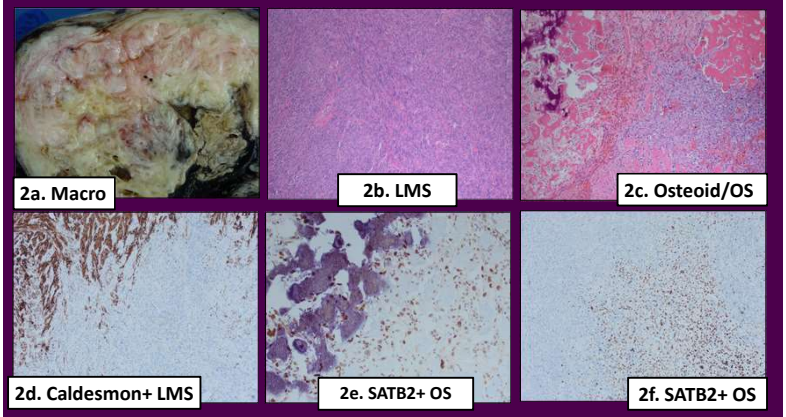
Introduction: Smooth muscle neoplasms are the most common tumours that arise in the uterus. Whilst the majority are easily classifiable as either benign or malignant, degenerative changes and the numerous histological variants that can occur (with varying criteria for malignancy) can prove diagnostically challenging [1]. In addition, smooth muscle tumours can also sometimes, exceptionally, show heterologous elements, these can range from entirely benign to frankly malignant. Whilst leiomyosarcomas (LMSs) are the most common uterine sarcomas they only account for 1–2% of uterine malignancies overall [1] and within recent literature only ~16 cases of LMSs with heterologous elements have been reported in the last 20 years (see table below). We describe here two additional cases of this unusual entity:

Case 1: 69 year old female with radiologically detected pelvic masses underwent radical hysterectomy and excision of intra-abdominal deposits on the colon, bladder and ileum. **Macroscopically:** a relatively well circumscribed large grey/tan necrotic tumour was identified at the right cornu which measured 90mm in maximum diameter. No macroscopically distinct areas were described. There were multiple serosal deposits which had a similar appearance but also showed additional areas of haemorrhage. The omental nodules were "gelatinous". **Microscopically:** the tumour was strikingly biphasic. The predominant morphology was that of conventional LMS showing tumoural necrosis and high mitotic activity (>20/10hpf). It showed diffuse SMA, desmin, caldesmon and CD10 positivity whilst MyoD1 was negative. In addition there was abrupt transition to a morphologically distinct second component with smaller, hyperchromatic spindled cells interspersed by rhabdomyoblasts. These cells showed diffuse MyoD1 and caldesmon positivity and patchy SMA positivity whilst CD10 was negative. No epithelial elements were identified within the tumour. Oestrogen receptor was negative in both components.



Final Diagnosis: LEIOMYOSARCOMA (LMS) WITH HETEROLOGOUS RHABDOMYOSARCOMA (RMS) showing direct extension into the parametrium and widespread mixed LMS/RMS deposits throughout the abdomen (FIGO stage IIIb). Patient still alive on chemoradiotherapy 6 months after primary surgery.

Case 2: 81 year old female with "enlarged uterus in keeping with uterine sarcoma" underwent radical hysterectomy and pelvic lymph node dissection. **Macroscopically:** the uterine corpus was extensively effaced by a circumscribed ovoid tumour 160mm in maximum diameter with firm, white whorled cut surface showing areas of haemorrhage and necrosis. The inferior surface was ragged with no identifiable cervix. **Microscopically:** the uterine cavity was distorted by a large, well-circumscribed, tumour that comprised predominantly intersecting fascicles of bland smooth muscle cells that showed only occasional areas of high grade atypia, atypical mitoses and coagulative necrosis. The smooth muscle cells showed SMA, desmin, caldesmon and patchy cytokeratin positivity. MyoD1, CD10, S100, CD34, CD117 and SATB2 were negative. Focally, higher grade spindled and epithelioid areas showing high mitotic rate (13/10hpf) and scattered osteoclast-type multinucleated cells were noted. Intermingled osteoid with abortive lacunae was present in these areas and the high grade and multinucleate cells showed strong nuclear SATB2 expression (other markers were negative).



Final Diagnosis: LEIOMYOSARCOMA (LMS) WITH HETEROLOGOUS OSTEOSARCOMA (OS) (<5%) Tumour confined to uterus. (FIGO 1B). Deemed to be completely resected, undergoing conservative monitoring and follow up. Still alive 8 months after initial surgery..

Discussion: LMSs with heterologous elements have tissue types that retain both morphological and immunophenotypic features of other cell lineages whilst dedifferentiated LMSs are LMSs with high grade, undifferentiated areas, that lack morphological or immunophenotypic features of differentiation. Reported cases of heterologous elements in LMSs include lipomatous, rhabdoid, osseous and cartilaginous tissues (see table). Historically, the terms "mesenchymoma"/ "malignant mesenchymoma" was used to describe tumours that comprised two mesenchymal elements (excluding fibrous tissue) or two malignant mesenchymal elements (excluding 'undifferentiated' or 'fibrosarcomatous' areas) however these terms have now been abandoned as "non-specific" [2-3].

The pathogenesis of heterologous element is unclear, proposed theories include divergent differentiation from a common low grade progenitor cell (myometrial dysplasia theory), aberrant "transdifferentiation" from a common high grade progenitor cell (i.e. clonal cell proliferation) or (least likely) collision tumours. The varied components are usually distinct and well demarcated [2-3]. Occasionally the heterologous elements can occur in metastatic deposits only (please see table).

Clinically, presentation is typically with mass effects including disordered uterine bleeding. The radiological impression is usually that of fibroid(s). Clinical and histological differentials include adenosarcoma and carcinosarcoma (excluded by thorough sampling showing lack of epithelial elements and negative cytokeratins if carcinosarcoma is suspected). Other sarcomatous lesions such as endometrial stromal sarcomas and pure non-smooth muscle sarcomas (including the growing number of translocation defined entities) require multi-modal morphological, immunohistochemical and molecular work-up to exclude [2-3]. Standardised treatment protocols are lacking and adjuvant therapy is thus often considered to counteract the presumed aggressive course of these rare tumours.

TAKE HOME MESSAGES:

Improving understanding of LMS with heterologous elements is vital to:

- Highlight the need for thorough **tumour sampling** (1 block per cm targeting heterologous areas).
- Encourage **multi-modal approach** to diagnosis (clinical, radiological, macroscopic, microscopic, molecular).
- Aid in recognition of **metastatic deposits** of these tumours.
- Gain adequate **epidemiological**, clinical and **prognostic** information and help guide suitable **treatment protocols** for these rare tumours.

Reference	Components	Clinical Data
2022 Sadiq and Khan.	Leiomyosarcoma, Chondorsarcoma.	68 year old, p/w vaginal bleeding. No additional follow up data available.
2022 Baris et al.	Leiomyosarcoma. Rhabdomyosarcoma in metastasis.	67 year old, p/w fibroids. Developed femur, adductor and nodal metastasis 9 years after primary surgery.
2021 Thiryayi et al.	Myxoid Leiomyosarcoma, Osteosarcoma, Liposarcoma.	41 year old, p/w pelvic pain and urinary frequency. Died of pulmonary metastasis 6 months after primary surgery.
2015 Parikh et al. (2 cases).	Leiomyosarcoma, Osteosarcoma.	1. 60 year old, p/w abdominal pain. Lost to follow up. 2. 38 year old, p/w infertility. Lost to follow up.
2012 Rawish et al.	Leiomyosarcoma. Post-chemo Osteoid in metastasis.	48 year old p/w fibroids. Metastatic disease post-chemotherapy. Alive 8 months after primary surgery.
2012 Tran and Holloway.	Leiomyosarcoma. Post-chemotherapy Osteosarcoma, Chondrosarcoma and Liposarcoma in metastasis.	80 year old p/w lower abdominal pain. Died of post-chemoradiotherapy metastasis 2 years after primary surgery.
2012 Lee et al. (2 cases).	Myxoid Leiomyosarcoma, Liposarcoma.	**1.** 47 year old, p/w urinary frequency and enlarging abdomen. Died of metastatic liposarcoma 4.5 years after primary surgery. **2.** 49 year old p/w menorrhagia. No recurrence at 2 years.
2009 Verma et al.	Leiomyosarcoma, Embryonal Rhabdomyosarcoma. Immature cartilage.	66 year old p/w post-menopausal bleeding and feeling of abdominal fullness. No metastatic disease at presentation. No follow up data.
2007 Sheldon et al.	"Mesenchymoma" Leiomyosarcoma, Chondrosarcoma, Osteosarcoma.	41 year old p/w dysmenorrhoea and abdominal pain. Surgery delayed by patient. Patient died with pulmonary metastasis 36 months after initial symptoms.
2006 Damjanov and Fan.	Liposarcoma. Post-radiotherapy Chondrosarcoma in metastasis.	42 year old, no additional clinical data available.
2005 Rosenblat et al.	Leiomyosarcoma, Liposarcoma	59 year old p/w post menopausal bleeding. Treated with radiotherapy. Disease free at 2 years follow up.
2004 Kew et al.	"Mesenchymoma" Leiomyosarcoma, Liposarcoma, Osteosarcoma.	64 year old p/w abdominal pain. No additional data.
2004 Shintaku et al.	Leiomyosarcoma, Rhabdomyosarcoma,	70 year old female p/w pelvic fullness and dyspnoea. Pulmonary and liver metastasis at diagnosis. Treated with chemotherapy, no additional follow up data available.
2002 Den Bekker et al.	"Mesenchymoma" Leiomyosarcoma, Liposarcoma, Osteosarcoma	54 year old 18 year old fibroid suddenly increased in size. Metastatic omental nodules 18 months post-surgery.

N.b. Heterologous elements arising in benign leiomyomas/lipoleiomyomas excluded for clarity. Leiomyosarcomas with osteoclast –like giant cells excluded as defined "variant" (i.e. not truly "heterologous").

References: 1. WHO Classification of Tumours Editorial Board. Female genital tumours. Lyon (France): International Agency for Research on Cancer; 2020. (WHO classification of tumours series, 5th ed.; vol. 4) **2.** Verma et al. 2009. Uterine Composite Tumour Composed of Leiomyosarcoma and Embryonal Rhabdomyosarcoma With Immature Cartilage. International Journal of Gynaecological Pathology. 28: pp. 338-342. **3.** Parikh et al. 2015. Two uncommon cases of uterine leiomyosarcoma displaying heterologous osteosarcoma differentiation. Journal of Cancer Research and Therapeutics. 11:3; pp. 654-654.