Leiomyosarcoma

148

Definition

Leiomyosarcoma (LMS) is a malignant tumor originating from smooth muscle cells. In this section the so-called deep soft tissue LMS is considered; for superficial LMS (i.e., LMS of the skin), → see Chap. 62; for uterine leiomyosarcoma → see dedicated section.

Epidemiology and Presentation

LMS accounts for about 10–15% of all adult soft tissue sarcomas. LMS generally occurs in middle-aged or older adults, although cases in young adults and even in children have been reported.

LMS is one of the most frequent types of retroperitoneal/pelvic sarcomas and is the most frequent type of sarcoma of the large blood vessels (e.g., vena cava). It represents about 10–15% of extremity sarcomas. Females are overrepresented in patients with retroperitoneal or large vessel LMS, but this is not the case for LMS arising elsewhere. Gastrointestinal cases of LMS should be carefully reviewed in order to rule out the much more likely diagnosis of gastrointestinal stromal tumor (GIST).

Clinically, the tumor presents as a mass that can reach large diameters before diagnosis, especially when it is located in the retroperitoneum. The lesion may be painful and/or cause symptoms related to the compression/infiltration of adjacent structures.

S. Mocellin, *Soft Tissue Tumors*, https://doi.org/10.1007/978-3-030-58710-9_148

Etiology and Predisposition

The cancer predisposition condition known as **Li-Fraumeni syndrome** is associated with a significant risk of developing LMS. This syndrome has an estimated prevalence of 1/20,000 people. The lifetime risk of cancer is about 70% for men and close to 100% for women. Typical cancers observed in this condition include breast carcinoma, soft tissue and bone sarcomas (including rhabdomyosarcoma, osteosarcoma, and LMS), and brain tumors (choroid plexus carcinoma, astrocytoma, medulloblastoma, and glioblastoma). However, other malignancies have been associated with the syndrome, which is caused by germline mutations in the tumor suppressor gene TP53 (located on chromosome 17p13.1) in about 80% of families. The syndrome is inherited in an autosomal dominant pattern. Most patients with Li-Fraumeni syndrome inherit an altered copy of the gene from an affected parent; however, in up to 20% of cases, the altered gene is the result of a new gene mutation in germ cells. The development of a malignancy in Li-Fraumeni syndrome requires a somatic mutation involving the other copy of the TP53 gene (during the patient lifetime), according to the classic two-hit hypothesis formulated by Knudson.

Finally, infection by **Epstein-Barr virus** (EBV) in immunocompromised patients has been associated with a higher than expected risk of developing LMS.

Pathology

Macroscopically, the lesion may show hemorrhage, necrosis, or cystic change. The tumor may be well circumscribed but can also frankly infiltrate surrounding structures. Microscopically, the common appearance is that of intersecting fascicles of spindle cells. The tumor is typically compactly cellular, but fibrosis or myxoid change as well as hypocellular zones and coagulative tumor necrosis may be present. Cell nuclei are characteristically elongated and blunt-ended.

Nuclear hyperchromasia and pleomorphism are generally evident although they may be mild or even absent. Mitotic figures are usually found readily, although they may be few; atypical mitoses are often found.

Rarely, areas with poorly differentiated, pleomorphic appearance (in addition to conventional areas) can be observed, which leads to the definition of so-called dedifferentiated leiomyosarcoma.

The tumor may show hemangiopericytoma-like vasculature, nuclear palisading, myxoid change, and osteoclast-like giant cells; some lesions have extensive pleomorphism mimicking undifferentiated pleomorphic sarcoma.

The following malignant criteria by site have been proposed:

- Deep soft tissues: 1–2 mitoses/10 high-power field (HPF).
- Cutis/subcutis: 1–2 mitoses/10 HPF.
- Retroperitoneum: 5 mitoses/10 HPF or 1–4 mitoses/10 HPF plus necrosis and size >7.5 cm.
- Vascular: 1–4 mitoses/10 HPF, plus large size and necrosis.

Cases with fewer mitoses should be probably better diagnosed as smooth muscle tumors of unknown malignant potential (STUMP → see dedicated section).

Differential diagnosis may be needed with dedifferentiated liposarcoma (better prognosis, well-differentiated component present, MDM2 and CDK4 amplification), leiomyoma (mitotic activity rare or absent, atypia minimal or absent, smaller size, neither hemorrhage nor necrosis, never infiltrating), and STUMP.

Biomarkers

LMS usually stains positive for smooth muscle actin (SMA), desmin, and h-caldesmon, although none of these biomarkers is completely specific for smooth muscle (positivity for at least two of these biomarkers confers more specificity). Of note, "dedifferentiated" areas are negative for SMA and desmin. CD117 (c-Kit) is typically negative (as opposed to GIST).

From the cytogenetics viewpoint, LMS is characterized by highly complex karyotypes. Tumor suppressor genes frequently altered in LMS are TP53, RB1, and PTEN. **Gene amplification** of myocardin (MYOCD, located on chromosome 17p and encoding a smooth muscle-specific transcriptional coactivator) is found in approximately 70% of cases.

Prognosis

LMS is a malignant neoplasm associated with both local recurrence and distant metastasis (mainly lungs; lymph node metastasis is rare). Of note, LMS is the sarcoma that most frequently metastasizes to the skin; soft tissue and bone metastases can also be observed.

The most significant prognostic factors are tumor location (superficial versus deep) and size (which are correlated). Retroperitoneal LMS is typically large (>10 cm), is often difficult or impossible to remove with clear margins, tends to recur locally recurrence and metastasize, and ultimately results fatal in most cases. LMS of large vessels is also associated with a poor prognosis, although generally better than that of retroperitoneal LMS. LMS arising from other sites are usually smaller and associated with a better prognosis. Superficial LMS (i.e., LMS developing above the muscular fascia) have a better prognosis as compared to deep tissue LMS.

Histological grading is another reliable prognostic factor; of note, the World Health Organization recognizes the classic three differentiation grades for LMS (G1, well differentiated; G2, moderately differentiated; and G3, poorly differentiated).

LMS arising in immunocompromised patients tends to involve parenchymal organs rather than soft tissues, occurs predominantly in children and young adults

who are HIV positive or have been transplanted, and is associated with EBV infection; on average, these tumors have a better prognosis as compared to conventional LMS.

Therapy

Surgery is the mainstay of treatment for localized (resectable) LMS. For cases located in the somatic soft tissues (i.e., extremities and trunk wall), neoadjuvant or adjuvant **chemotherapy** and **radiotherapy** are generally considered for large and high-grade lesions. For retroperitoneal LMS, the only available randomized controlled trial (RCT) called STRASS failed to demonstrate any advantage for patients undergoing neoadjuvant radiotherapy.

For locally advanced (i.e., non resectable) and metastatic disease, anthracyclines remain the first choice agents. Although LMS is deemed to be somewhat more sensitive to gemcitabine plus dacarbazine, this drug combination resulted inferior to epirubicin plus ifosfamide in terms of disease-free survival in a RCT of neoadjuvant chemotherapy for soft tissue sarcomas including LMS (ISG-STS 1001). Doxorubicin plus dacarbazine appears to provide some tumor response and survival advantage (as compared to doxorubicin alone or combined with ifosfamide), but no RCT-based evidence is available. Based on the results of a RCT, trabectedin has been approved for the treatment of patients with unresectable or metastatic LMS (as well as liposarcoma) who received a prior anthracycline-containing regimen.

As regards **target therapy**, anti-angiogenic agent pazopanib (a tyrosine kinase inhibitor targeting VEGFR, PDGFR, and KIT) has been approved (based on the findings of the RCT PALETTE) for the treatment of advanced/metastatic soft tissue sarcomas (including LMS but excluding both adipocytic sarcomas and GIST) in patients who have received prior chemotherapy.

Suggested Readings

Bonvalot (2019) STRASS (EORTC 62092): a phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma. J Clin Oncol 37(15_suppl):11001

D'Ambrosio (2020) Doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, or doxorubicin alone as a first-line treatment for advanced leiomyosarcoma: a propensity score matching analysis from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Cancer 126(11):2637–2647

Demetri (2016) Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. J Clin Oncol 34(8):786–793

Fletcher (2020) WHO classification of tumours of soft tissue and bone (5th edition)

Gronchi (2017) Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. Lancet Oncol 18(6):812–822

Pantoja (2020) Caval reconstruction with undersized ringed graft after resection of inferior vena cava leiomyosarcoma. Ann Vasc Surg 65:25–32

Patel (2019) Overall survival and histology-specific subgroup analyses from a phase 3, randomized controlled study of trabectedin or dacarbazine in patients with advanced liposarcoma or leiomyosarcoma. Cancer 125(15):2610–2620

Shannon-Lowe (2019) The global landscape of EBV-associated tumors. Front Oncol 9:713

van der Graaf Winette (2012) Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 379:1879–1886

Vella (2020) Case of primary hepatic leiomyosarcoma successfully treated with laparoscopic right hepatectomy. BMJ Case Rep 13(2):e233567