Uterine Leiomyoma

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Definition

Uterine leiomyoma (ULM) is a benign tumor originating from the smooth muscle cells of the myometrium.

It is also known as uterine fibroma, uterine fibroid, uterine myofibroma, uterine fibromyoma, uterine leiomyofibroma, uterine leiomyomata, and uterine myoma.

It belongs to the family of leiomyomas (→ see Chap. 146).

Epidemiology and Presentation

ULM is an extremely common neoplasm, as it is found in up to 70% of adult women. Often asymptomatic (ULM can be found as an incidentaloma in about 70% of cases), ULM can cause abnormal uterine bleeding (metrorrhagia, menorrhagia, or a combination of the two) and/or pelvic pain at least 30% of affected women. Large ULM can interfere with pregnancy (infertility) or block ureters. Rarely, it is associated with polycythemia (which regresses upon tumor removal). Pedunculated subserosal ULM may undergo torsion and thus cause acute abdominal pain. As an estrogen responsive neoplasm, ULM may regress after menopause or upon castration and enlarge during pregnancy. Transvaginal ultrasound is the gold-standard imaging method. Magnetic resonance imaging provides a better overall picture of the number, size, vascular supply, and boundaries of the ULMs, but it is unnecessary for a routine diagnosis and cannot differentiate ULM from leiomyosarcoma.

Many other diseases share the chief ULM complication (i.e., bleeding); they can be remembered using the mnemonic PALM-COEIN, which groups structural and nonstructural causes of abnormal uterine bleeding: polyps, adenomyosis, leiomyoma, malignancy, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and those not yet classified.

It is important to realize that leiomyosarcoma can present similar to ULM and that there is no reliable way to clinically or radiologically differentiate the two

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entities: therefore, a biopsy is necessary but is not always sufficient (due to limitations in representativeness of the specimen), and exeresis of the entire lesion is often required for a definitive diagnosis.

Etiology and Predisposition

Both naturally occurring (e.g., genistein) and synthetic (e.g., diethylstilbestrol) xenoestrogens have been linked to a higher risk of developing ULM. In contrast, oral contraceptives and progestin-only compounds are associated with a reduced risk. No clear association between overall dairy consumption and uterine leiomyoma risk has been observed.

ULM is most often sporadic; however, women with an autosomal dominant genetic syndrome called **multiple cutaneous and uterine leiomyomatosis** (MCUL) are at higher risk of developing both skin and uterine leiomyomas. This condition, also known as Reed syndrome and hereditary leiomyomatosis with renal cell carcinoma (HLRCC), typically occurs as a result of a heterozygous germline mutation of the fumarate hydratase (FH) gene, which is involved in the Krebs's cycle and could act as a tumor suppressor gene. Approximately 90% of patients with multiple cutaneous leiomyomas harbor a heterozygous germline mutation in the FH gene. Female patients with FH mutations commonly display both piloleiomyomas (85%) and symptomatic uterine leiomyomas (>90%). Uterine leiomyomas associated with FH mutation tend to be larger (up to 10 cm), more numerous, develop at a younger age, and more frequently require hysterectomy in comparison to non-hereditary uterine leiomyomas. However, the most concerning feature of an FH mutation is the association with an aggressive variant of renal cell carcinoma (type II papillary renal cell carcinoma) which develops in approximately 15% of patients: of note, in this subgroup of patients developing renal cell carcinoma the malignancy is metastatic at presentation in about 50% of cases.

Pathology

Macroscopically, ULM is sharply circumscribed, round, firm, and grayish white in color; it usually develops within the myometrium (intramural), but it may be submucosal or subserosal; of note, only 8% of ULMs occur in the uterine cervix. It can grow up to several centimeters in diameter and often is multicentric.

Microscopically, ULM is characterized by a fascicular pattern of smooth muscle bundles separated by well-vascularized connective tissue. Larger lesions may develop areas of degeneration including hyaline or mucoid change, calcification, and cystic change. Typically, it grows in a non-infiltrative manner. Mitotic figures are usually fewer than 5 per 10 HPF in the most mitotically active area, without significant atypia.

The following ULM variants have been described:

- Lipoleiomyoma: a rare variant of ULM that combines leiomyoma with mature adipocytes; it accounts for 2% of all ULMs; it might transform into a primary liposarcoma of the uterus, an (extremely rare) malignant uterine neoplasm.
- Mitotically active leiomyoma: it typically occurs in young women as a submucous lesion; it is characterized by 5–15 mitoses per 10 HPF; it lacks nuclear atypia, abnormal mitotic figures, and tumor cell necrosis; although the behavior is usually benign, recurrence as leiomyosarcoma has been reported, which calls for adequate follow-up.
- Cellular leiomyoma: it is characterized by increased cellularity, but it lacks atypia and mitotic figures; generally it has large, thick-walled blood vessels; its behavior is benign.
- Leiomyoma with bizarre nuclei: it is characterized by bizarre multinucleated tumor cells (moderate to severe atypia), but mitotic figures are fewer than 10 per 10 HPF, and there is no tumor cell necrosis; it has been associated with progestin use; its behavior is generally benign although leiomyosarcoma may rarely arise from this lesion; it was formerly called symplastic leiomyoma or atypical leiomyoma.
- Myxoid leiomyoma: it is composed of islands of smooth muscle cells in myxoid connective tissue containing large vessels, without infiltrative growth; it lacks both atypia and mitotic activity; its behavior is generally benign, although myxoid leiomyosarcoma may rarely arise from this lesion.
- Epithelioid leiomyoma: it is composed of round epithelioid, rhabdoid, and large vacuolated cells intermingled with spindled cells; nuclear atypia is not prominent; tumor cell necrosis and mitotic figures are lacking; it stains positive for desmin and SMA but also for cytokeratins, while it is negative for CD1a and HMB45; it should be differentiated from PEComa (positive for HMB45 and CD1a) and endometrial carcinoma (atypia, mitotic figures, and tumor cell necrosis are present); it is also known as clear cell leiomyoma and leiomyoblastoma.
- Intravenous leiomyomatosis: this very rare condition occurring when mature smooth muscle grows inside the lumen of uterine and pelvic veins and can reach the heart chambers (usually right heart); it has an excellent prognosis as distant metastases are exceptional; however, it may recur or embolize.

Differential diagnosis is needed with leiomyosarcoma and (less often) endometrial stroma sarcoma (h-caldesmon negative). In typical cases, ULM can be easily distinguished because of the low/absent mitotic activity, lack of cytologic atypia, lack of necrosis, lack of pleomorphism, and non-infiltrative growth. However, low-grade leiomyosarcoma may resemble ULM, with special regard to some of its variants (e.g., mitotically active leiomyoma).

As regards the differential diagnosis with smooth muscle tumor of uncertain malignant potential (STUMP) and benign metastasizing leiomyoma → see dedicated sections.

Biomarkers

ULM stains positive for SMA,[1] MSA,[2] desmin, h-caldesmon, and vimentin. It is generally (but not always) negative for cytokeratins and EMA.[3]

About 40% of ULMs have nonrandom tumor-specific chromosomal rearrangements, the most common being chromosomal translocation t(12;14)(q15;q23-q24), which leads to dysregulated expression of HMGA2.[4]

Prognosis

ULM is a benign tumor.

Therapy

Surveillance is the method of choice to manage women with asymptomatic ULM; current guidelines do not recommend serial imaging for these patients.

Medical therapy is utilized to decrease the severity of bleeding and pain symptoms. Hormonal contraceptives (i.e., oral contraceptive pills and the levonorgestrel intrauterine device) are common options, although there is only limited data showing their effectiveness; the levonorgestrel intrauterine device (IUD) is currently the recommended hormonal therapy for symptomatic ULMs due to the low side effect profile. GnRH agonist leuprolide acts on the pituitary gland to decrease gonadal hormone production, thus decreasing the hormone-stimulated growth of the neoplasm; however, as GnRH agonist has a short-term effect and is associated with significant bone loss (in the long run), its use should be limited to 6 months and is considered mainly as pre-surgical therapy for symptomatic ULM. Nonsteroidal anti-inflammatory drugs (NSAIDs) are utilized to palliate pain and bleeding, but they have no impact on ULM size. Other potential medical treatments include aromatase inhibitors and selective estrogen receptor modulators (SERM), such as raloxifene or tamoxifen: however, there is little evidence supporting the use of these medications. Tranexamic acid has been approved for the treatment of abnormal and heavy uterine bleeding, but it does not decrease the disease burden.

[1] SMA: smooth muscle actin

[2] MSA: muscle specific actin

[3] EMA: epithelial membrane antigen

[4] HMGA2: High-mobility group AT-hook 2 encodes a protein that belongs to the non-histone chromosomal high-mobility group (HMG) protein family. HMG proteins function as architectural factors and are essential components of the enhanceosome; HMGA2 contains structural DNA-binding domains and may act as a transcriptional regulating factor; rearrangements of this gene that have been associated with myxoid liposarcoma suggest a role in adipogenesis and mesenchymal differentiation.

As regards operative treatments, **endometrial ablation** offers an alternative to more radical surgery in patients whose primary complaint is heavy bleeding. **Uterine artery embolization** is a minimally invasive approach for women who wish to preserve fertility: this technique decreases the total blood supply to the uterus, thereby minimizing bleeding symptoms. Surgery includes myomectomy and hysterectomy. **Myomectomy** is an invasive surgical option for women who desire fertility preservation (although there is no definitive evidence showing that myomectomy can improve fertility, which is highly dependent on the location and size of the lesion). **Hysterectomy** remains the definitive treatment for ULM and continues to be the leading indication for hysterectomy. The laparoscopic approach is largely diffuse for this type of surgery: nevertheless, the use of intraoperative morcellation is highly debated due to the risk of tumor cell dissemination in the (rare) case where the pathological examination reveals the unexpected presence of a leiomyosarcoma.

Suggested Readings

Cohen (2016) Updates in uterine fibroid tissue extraction. Curr Opin Obstet Gynecol 28(4):277–282

Dubuisson (2019) The current place of mini-invasive surgery in uterine leiomyoma management. J Gynecol Obstet Hum Reprod 48(2):77–81

Emoto (2018) Power morcellation-induced dissemination of sarcomatous component arising in leiomyoma. J Obstet Gynaecol Res 44(9):1843–1849

Lewis (2018) A comprehensive review of the pharmacologic management of uterine leiomyoma. Biomed Res Int 2018:2414609

McDonald (2011) Liposarcoma arising in uterine lipoleiomyoma: a report of 3 cases and review of the literature. Am J Surg Pathol 35(2):221–227

Orta (2020) Dairy and related nutrient intake and risk of uterine leiomyoma: a prospective cohort study. Hum Reprod 35(2):453–463

Seidman (2012) Peritoneal dissemination complicating morcellation of uterine mesenchymal neoplasms. PLoS One 7(11):e50058

Wang (2020) MED12 exon 2 mutation is uncommon in intravenous leiomyomatosis: clinicopathologic features and molecular study. Hum Pathol 99:36–42