Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Solid Tumour Section

Review

Uterus: leiomyoma

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Identity

Alias

Uterine fibromyoma; Fibroma; Fibroleiomyoma; Fibroid myoma

Note

Uterine leiomyomas are the most common neoplasms of the female genital tract. They are benign tumors composed of smooth muscle and fibrous connective tissue. On the basis of the symptomatology, they are estimated to occur in 20 to 30% of women in the reproductive age, but a study of serial sections of uteri raises the estime up to 77%. They are frequent in women older than 30 years of age, very rare in woman below the age of 18, and tend to regress after menopause. Rarely, if ever, progress to malignant leiomyosarcoma. Multiple nodules have been found in approximately 25% of women, with an average of 6.5 tumors per uterus. They are one of the most frequent indication for major surgery during the reproductive period. Distribution of estrogen receptors is similar to that of adjoining miometrium, whereas the concentration of progesteron receptors seems to be lower.

Classification

Note

Classification of leiomyomas can be based on: location and uterine layer affected.

Location

Cervical (2.6%): generally grows toward vagina, causing sinusiorragia and infection.
Isthmic (7.2%): more frequently causes pain and urinary problems.
Corporal (91.2%): this is the most common location, and frequently causes no symptoms.
Uterine Layer
Subserous: located just beneath the serosal surface. They grow out toward the peritoneal cavity, and can be sessile or pedunculated. The pedunculated ones may attach themselves to adjacent structures like the bowel, omentum or mesentery, and develop a secondary blood supply, loosing its primary uterine blood supply (parasitic leiomyoma). Subserous leiomyomas may also extend into the broad ligament (intraligamentary leiomyomas).
Submucous: located beneath the endometrium. They may be sessile or pedunculated. The pedunculated nodules may protrude through the cervical os, and may undergo torsion, infarction, and separation from the uterus. Submucous leiomyoma are often associated with an abnormality of the endometrium, resulting in a disturbed bleeding pattern;
Intramural: occurring within the walls or the uterus, they are the most common.

Clinics and pathology

Epidemiology

Leiomyomas are more frequent (from three to nine fold) in women of African origin than women of other ethnic groups.

Clinics

The clinical presentation depends on the size, location and number of the lesions. They may occur singly but often are multiple, with variations in size. The most common signs and symptoms are pain, a sensation of pressure, abnormal uterine bleeding, fetal wastage, infertility. Leiomyomas may be cause of pregnancy complications, such as abortion, hemorragic degeneration, disseminated intravascular coagulation, hemoperitoneum, premature rupture of membranes, dystocia, inversion of the uterus, postpartum hemorragia. They are steroid hormone dependent. Based on the observation that nodules with abnormal karyotype fail in lowering DNA content after GnRH

agonist therapy, it has been proposed that karyotypically abnormal nodules are less steroid hormone-dependent than nodules with a normal karyotype. No specific association between cytogenetic subgroups and histologic subtypes has been found.

Pathology

Leiomyomas are spherical, firm, and bulge above the surraounding myometrium. The cut surfaces are white to tan in color, with worled trabecular pattern. The appearence is often altered by degenerative changes. Microscopically, they consist of whorled, anastomosing fascicles of uniform, spindle-shaped, smooth muscle cells. Cells have indistinct borders and abundant fibrillar, eosinophilic cytoplasm. The nuclei are elongated and have finely dispersed chromatin. They may show areas of hemorragia, as well as cystic degeneration and microcalcification in a minority of lesions. Despite the variety in the histologic subtypes of leiomyomas, all are grossly similar. Beside ordinary leiomyoma (composed of whorled anastomosing fascicles of uniform, fusiform smooth muscle cells showing eosinophilic cytoplasm and elongated nuclei) several specific subtypes are distinguished, some of which are very rare:
Cellular leiomyoma (composed of densely cellular fascicles of smooth muscle with little intervening collagene).
Atypical leiomyoma (containing atypical cells, clustered or distributed through the lesion).
Epithelioid leiomyoma (composed of round or poligonal cells rather than spindle-shaped. This subtype includes leiomyoblastoma, clear cell leiomyoma, plexyform leiomyoma).
Myxoid leiomyoma (containing abundant amorphous myxoid substance between the smooth muscle cells).
Vascular leiomyoma (containing dense proliferations of large, caliber, thick-walled vessels).
Lipoleiomyoma (consisting of a mixture of mature adipocytes and smooth muscle cells).
Leiomyoma with tubules (containing tubular structures).
Benign metastasizing leiomyoma (occurrence of multiple smooth-muscle nodules, most often located in the lung after previous hysterectomy). see:http://www-medlib.med.utah.edu/WebPath/
FEMHTML/FEM030.html
Microscopic Pathology: see Cytogenetics.

Treatment

Only the nodules that are symptomatic, enlarge rapidly, or pose diagnostic problems, are removed. Myomectomy, when possible, is performed in female desiring to preserve fertility, hysterectomy in case of large or multiple lesions.

Genetics

Note

Possible predisposition to uterine leiomyoma in first-degree relatives of families with leiomyoma accumulation has been proposed. Glucose-6-phosphate dehydrogenase isoenzyme and X-inactivation studies have demonstrated that uterine nodules develop as clonal lesions. The random pattern of inactivation among multiple nodules in the same uterus revealed that they arise independently.

Cytogenetics

Note

Approximatively 40% of cytogenetically investigated cases show abnormal karyotypes, usually with single or few changes. Rarely, they may show complex karyotypes. The clonal chromosome changes are clustered to specific chromosome regions, leading to the identification of four main cytogenetically abnormal subgroups characterized by: t(12;14)(q14-15;q22-24), del(7)(q22q32), 6p21 rearrangements and trisomy 12. In addition, rearrangements of the 3q,10q,13q as well as ring of the chromosome 1 are observed in a minority of cases. Correlation between cytogenetics and clinical phenotype:
Myoma location / incidence of abnormal karyotype: intramural - 35%; subserosal - 29%; submucosal - 12%.
Type of chromosome abnormality / tumor mean size: tumors with normal karyotype -5.4 cm; tumors with del(7q) -5cm; tumors with chromosome 12 abnormalities - 8.5 cm.
No correlation between lesions with abnormal karyotyes and age or parity of patients.

Cytogenetics Morphological

t(12;14)(q14-15;q22-24) subgroup

It is found in approximately 20% of the abnormal cases.
The t(12;14)(q14-15;q22-24) translocation is the first chromosome alteration reported in uterine leiomyoma.
It may be observed as the sole cytogenetic abnormality, or together with other clonal changes, such as del(7q).
The chromosome segment 12q14-15 may joint other translocation partners (such as chromosome X, 2, 8, 9, 10, 22) or may undergo paracentric inversion.
Myoma cells with these abnormalities are responsive to the immortalization by the "early region" of the SV40 genome.

del(7)(q22-32) subgroup

It is found in approximately 17% of the abnormal cases.
It may be observed as the sole cytogenetic abnormality, or together with other changes. It is often associated with t(12;14) or alterations of the chromosome segment 12q14-15.
The del(7q) clone is almost invariably found together with a normal clone.
A few cases with translocations involving 7q22 have been described.

Myoma cells with del(7q) are not responsive to the immortalization by the "early region" SV40 virus, unless they also contain 12q14-15 abnormalities.
Myoma with del(7q) tend to be smaller than those showing 12q14-15 abnormalities.

6p21 rearrangement subgroup

Rearrangements of the 6p21, including deletions, translocations, and inversions are found in about 5% of the abnormal cases.
6p21 rearrangements may be observed as the sole cytogenetic abnormality, or together with other clonal changes. Simple and complex rearrangements of 6p21 have been observed.
The most frequent translocation partners are chromosome regions 1q32, 10q22, 14q24, although other partner chromosome regions may be involved.
Complex rearrangements are sometimes identifiable only by FISH analysis.

Cytogenetics Molecular

t(12;14)(q14-15;q22-24) subgroup

In this subgroup the dysregulation of HMGA2 (formely HMGIC) gene located at 12q15 has been observed.
Chromosome 12 breakpoint is often located 10 kb up to 100 kb 5' to HMGA2 gene, and in a majority of cases there is no fusion gene. However, in a number of cases the gene is altered:
Case with paracentric inversion: HMGA2 exon 3 is fused to ALDH2 exon 13 (12q24.2).
Case with apparently normal karyotype: HMGA2 exon 3 is fused to retrotransposon-like sequences RTVLH 3' LTRs.
Case with complex karyotype including chromosome 12 and 14 rearrangements: cumulative dosage effect of a RAD51L1/HMGA2 fusion and RAD51L1 loss.
Case without cytogenetic analysis: HMGA2 exon 3 is fused to COX6C exon 2 (8q22-23).
Cases without cytogenetic analysis: HMGA2 exon 2 or 3 is fused to RAD51L1 exon 7 (14q23.3-24).
Cases without cytogenetic analysis: HMGA2 isoforms due to aberrant alternative splicing.
Case without cytogenetic analysis: HMGA2 exon 2 is fused to the 3' portion of the HEI10 gene, located at 14q11.

del(7)(q22-32) subgroup

LOH or decreased expression of CUTL1, ORL5L, PAI1, are reported.
Molecular cytogenetic characterization of the del(7q) has been reported in myoma-derived cell lines as well as in primary cultures and non cultured samples. Fine-deletion mapping with 25 microsatellite markers from the 7q22 region reveales a minimal common deletion unit of approximately 4 cM, bounded by the markers D7S2453 proximally and D7S496 distally. A subset of lesions shows two discrete regions of deletion at 7q22.

6p21 rearrangement subgroup

HMGA1 (formely HMGIY) (6p21.3) is a candidate gene. No hybrid gene has been described yet.
A genomic PAC clone containing the gene spans the 6p21.3 breakpoint. The breakpoint seems to be extragenic, located within a 80 b region 3' of HMGA1.
One case of aberrant transcript with truncation of 1295 bp from the 3' UTR has been described.

Genes involved and proteins

Note

Dysregulation of HMGA2 (12q15) and HMGA1 (6p21.3) genes have been observed in uterine leiomyomas.
Mechanisms leading to these dysfunctions are not yet clarified. However:
It has been suggested that a fusion event, resulting in the separation of the DNA-binding domains of HMGA2 from the spacer and the acidic carboxy-terminal regulatory domain, is a common tumorigenic mechanism in the development of uterine myomas.
It has been suggested that the expression of HMGA1 and HMGA2 is controlled by negatively acting regulatory elements within their 3'UTR: luciferase assays with HMGA1 3'UTRs of different length show increase in luciferase activity by the truncation of the 3'UTRs. Chromosomal aberrations affecting the HMGA genes may influence their expression by an altered stability of the truncated transcripts as a result of the cytogenetic aberrations.

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