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Solid Tumour Section

Review

Soft tissue tumors: Aggressive angiomyxoma

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Identity

Other names: Deep 'aggressive' angiomyxoma
Note: The term aggressive was introduced to emphasize the locally aggressive behaviour and the high potential for local recurrence, it does not reflect a high probability for metastasis, as only 2 cases with metastatic disease have been reported. The name angiomyxoma was chosen because of the similarity to myxoma and the notable vascular component.

Classification

Aggressive angiomyxoma (AA) is a soft tissue neoplasm. The term AA was not coined until 1983 but similar tumours were described as early as in the 1860ies. In the latest WHO-classification AA is now classified under 'Tumours of uncertain differentiation'.

Clinics and pathology

Disease

AA is a neoplasm. It is defined as benign but has infiltrative potential into skeletal muscle and fat. The disease is therefore considered locally aggressive although it does not infiltrate surrounding viscus. Only 2 cases with metastatic disease have been published.

Etiology

No etiologic factors are known.

Epidemiology

AA is a rare neoplasm with about 150 reported cases. It is most often found in women in reproductive age with a peak incidence in the fourth decade of life. The female:male ratio is 6:1.

Clinics

AA is most often found in or in proximity to the lower pelvis, more specifically perineum, vulva, vagina or inguinal regions. The majority of patients present with a slow-growing mass which is otherwise asymptomatic and this is frequently the only symptom/sign. Observed accompanying symptoms and signs are regional pain, a feeling of local pressure, or dyspareunia. Tumour size is often underestimated by physical examination. It is worth noticing that the frequency of symptoms and signs attributable to local growth is lower than what would be expected from the relatively large size of most of these tumours. AA is often clinically misdiagnosed, most often mistaken for a Bartholin cyst. Radiographically, AA is isointense or has low signal intensity on T1-weighted MRI, and have a whorled pattern of high signal intensity on T2-weighted MRI. These tumours show contrast enhancement, reflecting their inherent vasculature, and tend to displace and grow around structures rather than infiltrate them.

Pathology

Most AA are big, often more than 10 cm in largest diameter. These tumours are macroscopically lobulated and may adhere to surrounding soft tissue. Microscopically, cells with a spindled or stellate morphology are seen, embedded in a loose matrix consisting of wavy collagen and oedema. Cellularity is generally low to moderate. Infiltration into fat, muscle, and nerves is seen. The hallmark of AA is vessels of varying calibre haphazardly scattered throughout the tumour parenchyma, whereas mitotic figures are scarce. Immunohistochemically, most AA are positive for desmin, smooth muscle actin, muscle-specific actin, vimentin, oestrogen receptor, and progesterone receptor.

Some tumours are positive for CD34, whereas S100 is invariably negative. Based on these observations, a myofibroblastic differentiation of the neoplastic cells is suggested.

Treatment

Radical surgery with wide margins is the treatment of choice. Because most tumours are large, grow infiltrative and blends with adjacent soft tissue, and are located in close proximity to vital organs such as bladder and rectum, wide excision is not always possible and/or may cause significant morbidity. In such situations watchful waiting may be advisable because these tumours may be stable with no or very limited growth over long periods of time. Several reported attempts using chemotherapy and radiotherapy as part of the treatment for AA have been disappointing, probably due to the low mitotic activity/growth fraction of cells. Most AA express oestrogen and progesterone receptors and are likely to have a hormone-dependent growth. Because of this, treatment with GnRH agonists has been administered to AA patients, and some case reports with dramatic responses to such GnRH agonists have been reported.

Prognosis

The prognosis is very good. Only 2 cases with metastatic disease followed by death have been reported. Recurrences are common, though, reported to be between 9 and 72 %. These numbers are uncertain because late recurrences may develop several years after the primary tumour was found, and long-term follow-up of the patients is therefore very important. The major problem posed by this tumour is the often mutilating surgery necessary to cure the patient.

Cytogenetics

Cytogenetics morphological

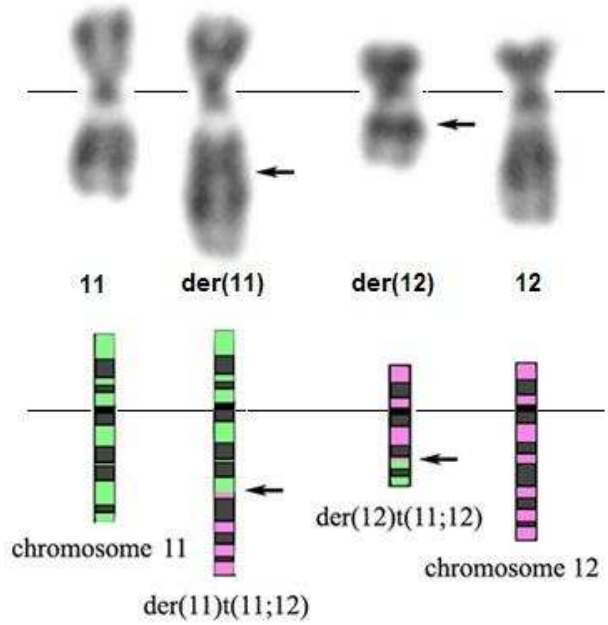
Although only 6 cases of AA showing chromosomal aberrations have been described so far, a non-random involvement of chromosomal band 12q15 has been identified. The cytogenetic rearrangements hitherto described, involving this band, are: t(11;12)(q23;q15), t(7;12)(q22;q13-14), t(8;12)(p12;q15), and der(12)t(5;12)(q31;p11)inv(12)(p11q14). An additional case with 12q15 rearrangement has been described using fluorescence in situ hybridization.

Cytogenetics molecular

The 12q15 rearrangements lead to alterations of the high mobility group (HMG) gene HMGA2 (previously known as HMGIC).

Additional anomalies

Monosomy of the X chromosome has been reported in one AA, whereas another AA showed monosomy 12 among other abnormalities.



Ideograms and G-banded images of chromosomes 11 and 12 from an AA are depicted. Normal chromosome homologs and rearranged chromosomes are shown. Arrows indicate breakpoint positions.

Genes involved and Proteins

HMGA2

Location: 12q15

DNA/RNA

The HMGA2 gene consists of 5 exons spanning 141 kb of genomic DNA. It is highly expressed in embryonic tissue. In normal adult tissues, only low gene expression levels have been detected, and only in kidney, lung, and synovia. In all other terminally differentiated cells, no expression of this gene has been detected.

Protein

The HMGA2 gene encodes a member of the high-mobility group A (HMGA) of small, non-histonic, chromatin-associated proteins. These proteins are believed to affect transcription in several ways. They act as architectural elements by bending the DNA, they interact with a large number of other proteins, mainly transcription factors, and they also influence upon chromatin changes during cell cycle. As all proteins in this family, HMGA2 contains three copies of a conserved DNA-binding peptide motif called AT-hook. This AT-hook preferentially binds to the minor groove of stretches of AT-rich sequences.

Somatic mutations:

Increased protein levels of HMGA2 have been reported in a variety of benign mesenchymal tumours, including lipoma, leiomyoma, chondroid tumours, pulmonary hamartoma, endometrial polyps, and fibroadenoma of

the breast. In all these neoplasms rearrangements of chromosomal band 12q15 have been found at the cytogenetic resolution level.

Result of the chromosomal anomaly

Hybride Gene

Description

In general, two types of HMGA2 rearrangement are known. In some cases, HMGA2 is interrupted after the end of the third exon, whereby the AT hook domains are separated from the 3' portion of the gene. This 3' portion of the gene, coding for the protein-binding domains of HMGA2, is thereby lost. In other cases, breakpoints outside the coding region of the gene are found. These extragenic breaks suggest a disruption of regulatory sequences, which lead to abnormal expression of HMGA2. Expression of the entire HMGA2 gene is achieved through alterations affecting 5' regulatory elements or the 3' untranslated region, leading to a stabilized mRNA. It is important to note that even if the fusion products mentioned above are in-frame, some of HMGA2's partner genes contribute with very few amino acids to the chimeric product. It has therefore been suggested that the minimal requirement for tumourigenesis would be activating HMGA2 rearrangements leaving at least exons 1-3 of HMGA2 intact. For the specific translocation t(11;12)(q23;q15), the result is the abnormal expression of an intact, full-length product of HMGA2.

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