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.
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.

**References**


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