Aggressive Angiomyxoma

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Aggressive angiomyxoma is a rare mesenchymal tumor that most commonly arises in the vulvovaginal region, perineum, and pelvis of women. The term aggressive emphasizes the often infiltrative nature of the tumor and its frequent association with local recurrence. Patients often present with nonspecific symptoms which are frequently misdiagnosed with more common entities, such as a Bartholin cyst, lipoma, or hernia. Histologic examination reveals a paucicellular tumor consisting of bland spindle cells in a myxoid background studdred with blood vessels of varying calibers. Resection margins frequently have positive findings because the AAM tumor is poorly circumscribed and infiltrates adjacent soft tissue. Tumor recurrence is a significant cause of patient morbidity, and recurrence rates from the largest case series range from 25% to 47%. Although 2 cases of metastasis have been reported,8 AAM is considered an indolent neoplasm with locally aggressive behavior.

CLINICAL PRESENTATION

Patients are often asymptomatic, with a visible perineal or vulvar mass that is discovered during routine pelvic examination or with radiographic imaging. The true extent of AAM is often underestimated on initial physical examination because the visible portion of the tumor usually represents only a fraction of the more-extensive involvement of the deep soft tissues of the pelvis and retroperitoneum. In patients who do experience symptoms, pelvic fullness and pressure, perineal swelling, vulvar pain, dysmenorrhea, dyspareunia, and changes in bowel and bladder function have been reported.4,10,11 Aggressive angiomyxoma is often clinically mistaken for more common entities, such as a Bartholin cyst, vaginal cyst, abscess, leiomyoma, lipoma, fibroepithelial polyp, and inguinal or perineal hernia.5 Early recognition requires a high index of clinical suspicion because the tumor is rare and the symptoms are nonspecific; thus, the diagnosis is usually made histologically.13 This tumor should also be considered in the differential diagnosis of tumors in the analogous regions of men. Aggressive angiomyxoma has been reported in the scrotum, spermatic cord, and perineum and has even been discovered incidentally during inguinal hernia surgery.6

RADIOLOGIC FEATURES

The appearance of AAM on computed tomography is variable; it may be a well-defined, homogeneous mass that is hypodense relative to muscle, or it may be predominantly cystic with solid components.14 Characteristic appearances on magnetic resonance imaging include hypointensity on T1-weighted images and hyperintensity on T2-weighted images. Aggressive angiomyxoma exhibits avid and heterogenous enhancement after administration of intravenous contrast and may show a distinct, low-intensity, swirling pattern (Figure 1).14 These findings are thought to be attributed to the abundant myxoid matrix and high water content of the tumor.15 Given these characteristic features, magnetic resonance imaging can be helpful in delineating the extent of disease, in determining patient suitability for

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Figure 1. A T2-weighted sagittal view of a magnetic resonance imaging scan from a 42-year-old woman shows a 14-cm soft tissue mass extending from the presacral space down to the subcutaneous soft tissue of the right buttock.

Figure 2. A, Aggressive angiomyxoma is characterized by myxoid stroma with numerous variably sized blood vessels. B, Some blood vessels may exhibit peripherally condensed collagen. C, The tumor is infiltrative and may entrap surrounding soft tissue. D, The tumor cells are cytologically bland with ovoid or stellate nuclei and indistinct cytoplasmic borders (hematoxylin-eosin, original magnifications ×100 [A and C], ×200 [B], and ×600 [D]).

Figure 3. Progesterone receptor staining shows strong nuclear reactivity in the tumor cells (immunoperoxidase, original magnification ×400).
surgery, and in continuing clinical follow-up of patients for recurrent tumor.  

**PATHOLOGIC FEATURES**

**Gross Features**

On gross examination, AAM is unencapsulated, is poorly or vaguely circumscribed, and may blend imperceptibly with surrounding soft tissue. Tumor size is highly variable and ranges from 1 cm to 60 cm. The tumor is often tan-pink to tan-gray, bulky, and has a rubbery consistency with a glistening, gelatinous cut surface. Areas of congested blood vessels, hemorrhage, or fibrosis may be present.

**Microscopic Features**

Histologic examination shows a sparsely cellular tumor composed of pale to eosinophilic stroma studded with numerous haphazardly arranged blood vessels that stand out against the myxoid background and range in size from thin-walled capillaries and venules to larger muscular arteries (Figure 2, A). The stroma is distinctly myxoid with intermixed, wispy collagen fibrils; scattered, smooth-muscle bundles; and extravasated erythrocytes. Perivascular rings of condensed collagen may be a prominent feature (Figure 2, B). Soft-tissue infiltration is a frequent finding characterized by entrapment of muscle, nerve, and adipose tissue (Figure 2, C). The tumor cells are cytologically bland and have a spindled, ovoid, or stellate appearance with ill-defined cytoplasmic borders (Figure 2, D). Nuclear chromatin is evenly dispersed with minimal to no cellular atypia. Mitotic figures are rare but are not atypical if present. Rare case reports describe AAM infiltrating the bladder, bowel, and even bone.

**Immunohistochemical Features**

There is no specific immunohistochemical marker for AAM, but the tumor does exhibit a characteristic pattern of reactivity. The tumor generally shows diffuse immunopositivity for vimentin and desmin. Smooth muscle actin highlights myoid bundles and may be positive in individual tumor cells. S100 reactivity is not a feature of AAM but may be observed in entrapped nerves. Perhaps the most characteristic feature is estrogen receptor and progesterone receptor positivity. One or both of these hormone receptors displays strong nuclear positivity in most of the tumor cells (Figure 3). Labeling for Ki-67 consistently demonstrates a low proliferative index (<1% of tumor cells).

**Genetic Features**

Chromosomal translocations involving 12q13-15 have been reported in a variety of mesenchymal neoplasms, including lipomas, liposarcomas, leiomyomas, and pulmonary hamartomas. These translocations involve the high mobility group A (HMGA2) gene. HMGA2 belongs to a family of transcription factors that function during embryogenesis and are not usually detected in adult tissues. Cyogenetic analysis and fluorescent in situ hybridization have confirmed the presence of HMGA2 gene rearrangement in AAM and have shown that AAMs, or at least a subset of them, have the same molecular genetic background as other common mesenchymal tumors. These molecular data have led to the investigation of the role of HMGA2 immunohistochemistry in mesenchymal tumors. One recent study characterized HMGA2 immunohistochemical expression in a variety of neoplasms and evaluated its utility as a discriminatory marker. There was strong nuclear positivity in 90% of AAMs compared with weaker reactivity in 27% of fibroepithelial stromal polyps and no staining in angiofibromatosis or cellular angiofibroma.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of AAM includes angiofibromatosis, superficial angiomyxoma, fibroepithelial stromal polyps, myxoid lipomatous tumors, and myxoid leiomyoma. Angiofibromatosis is a more recently described, benign, myxoid, and vascular soft tissue neoplasm of the vulva. In the original description of the tumor, angiofibromatosis was localized to the superficial soft tissue, was well-circumscribed without entrapment of adjacent glands or nerves, and was usually smaller than 5 cm, all of which contrasts with the larger size (often ≥10 cm) and infiltrative nature of AAM. Histologically, angiofibromatosis contains hypocellular and hypercellular zones composed of cytologically bland cells that appear more plump or epithelioid than those of AAM and often aggregate around blood vessels. Multinucleated giant cells with linearly arranged nuclei are another key histologic feature. Like AAM, mitotic activity is minimal. The recurrence rate for angiofibromatosis is thought to be much lower than that of AAM, and recurrences are generally nondestructive.

Superficial angiomyxoma, also known as cutaneous myxoma, is more commonly located in extragenital sites, such as the head and neck, but may involve the vulvovaginal region. This mesenchymal neoplasm arises in the dermis or subcutis and has a distinct lobular or multinodular architecture. Histologically, the tumor is myxoid and vascular but lacks large-caliber vessels like those seen in AAM. Superficial angiomyxoma has a nonspecific immunophenotype but is generally negative for estrogen receptor and progesterone receptor and may be immunoreactive for S100.

Fibroepithelial stromal polyps are relatively common benign lesions of the vulvovaginal region that may be present in multiples and are associated with pregnancy or exogenous hormone use. As the name implies, the tumor is polyoid with unremarkable or hyperplastic squamous epithelium and an underlying edematous or myxoid stroma. The stroma contains centrally located, variably-sized vessels and multinucleated stromal cells that may have a wreathlike appearance. Occasionally, fibroepithelial stromal polyps exhibit sarcomatous features including increased cellularity, cytologic atypia, increased mitotic rate (>10 mitoses per 10 high-power fields), and atypical mitoses and are termed pseudosarcomatous fibroepithelial stromal polyps. Though worrisome in appearance, these benign lesions exhibit indolent behavior and must be differentiated from true sarcomas. Local excision is usually curative, even if pseudosarcomatous features are present.

The entrapment of adipose tissue by an AAM may give the appearance of a benign or malignant lipomatous tumor, and therefore, they must be considered in the differential diagnosis. The most relevant lesions to consider are myxolipoma and myxoid liposarcoma. Myxolipoma is a benign tumor composed of mature adipose tissue with a myxoid stroma that may contain rare
bland stellate or spindled cells similar to those of AAM. A similar appearing myxoid lipoma with prominent blood vessels has been termed angiomyxolipoma.23 Both myxolipoma and angiomyxolipoma can be differentiated from AAM by first recognizing adipose tissue, which is often more abundant, as a primary component of the tumor. Additionally, these lipomas show a lower degree of cellularity.4 Myxoid liposarcoma, on the other hand, can be much more cellular and contain numerous stellate to spindled cells as well as characteristic lipoblasts. An arborizing capillary network is a characteristic finding in myxoid liposarcoma, as opposed to the disorganized thin- and thick-walled blood vessels of AAM.4

Myoid leiomyoma is another pelvic tumor that can grow quite large and should be considered in the differential diagnosis. Like AAM, myoid leiomyomas of the vulvovaginal region are often mistaken for Bartholin cysts. However, there are several histologic features that help differentiate them. Myoid change may be focal or involve the entire tumor, and a helpful diagnostic clue is to identify an area of transition between the myxoid features and more-classic smooth muscle differentiation.46 The cells are spindled to stellate and may contain more abundant eosinophilic cytoplasm than that seen in AAM. Juxtanuclear vacuoles and a loose fascicular growth pattern may be seen. The diagnosis is primarily based on morphology, as an immunophenotype of desmin, smooth muscle actin, estrogen receptor, and progesterone receptor positivity is similar to AAM.46

TREATMENT AND PROGNOSIS

The first line of therapy for AAM is surgery, although achieving negative resection margins is difficult because of the infiltrative nature of the tumor and the absence of a defined capsule.12 Smaller, more-superficial tumors of the vulva or vagina may be removed with wide, local excision, but larger, deep-seated tumors of the pelvis may require more extensive surgery with partial or complete resection of some pelvic organs, conferring a higher risk of morbidity. A review of 111 cases of AAM called into question the necessity of such radical resections by comparing patients’ risk of recurrence based on margin status. The data showed that there was no statistical difference in remaining disease-free between groups of patients with positive and negative resection margin results (40% and 50% in 10 years, respectively).2 Even though complete surgical resection is the desired goal, incomplete removal is acceptable when significant operative morbidity is anticipated or when preservation of fertility is a concern.2

Chemotherapy and radiation therapy do not have well-defined roles in the treatment of AAM. Preoperative and intraoperative radiation have been used, together with tumor embolization, to decrease the risk of recurrence in a patient with a large pelvic AAM, but no follow-up data were provided.12 Radiation therapy has also been used to treat several cases of tumor recurrence with reported tumor-free intervals of 2 to 3 years.24,25

A newer approach to the treatment of AAM involves hormonal therapy. Given that the tumor occurs primarily in premenopausal women and is positive for estrogen receptor and progesterone receptor, estrogen and proges-terone may play a role in its development. In one patient, a vulvar AAM was discovered during the first trimester of pregnancy and progressively increased in size throughout the pregnancy.26 Several case reports using a gonadotropin-releasing hormone agonist as medical management for AAM showed complete radiographic resolution of the tumor.27,28 Although surgery remains the standard of care, the medical treatment of AAM with a gonadotropin-releasing hormone agonist in the primary or adjuvant setting may offer an alternative to radical surgery.27

Despite the morbidity associated with tumor recurrence and repeat surgeries, the prognosis for patients with AAM is generally considered good. Recurrence rates from the largest case series22,27 range from 25% to 47%, with 85% of those occurring within 5 years of initial surgery.2 Close clinical follow-up with imaging studies has been advocated.4 To our knowledge, only 2 cases of AAM metastasis have been reported in the literature. The first case occurred in a 63-year-old woman who initially presented with nonspecific abdominal symptoms and was found to have a pelvic AAM with abdominal and lung metastases.2 The second case occurred in a 27-year-old woman who developed several local recurrences after primary resection of an AAM and subsequently died from multiple lung metastases.9 In light of these reports, some authors have proposed classifying AAM as a tumor of intermediate malignancy with unpredictable behavior, but at this point, metastasis remains an exceedingly rare event and necessitates the collection and evaluation of more data.

References


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**CAP ‘12 Abstract Program Accepting Submissions**

Abstracts and case studies are now being accepted for the College of American Pathologists (CAP) 2012 meeting, which will be held September 9th through the 12th in San Diego, California. Submissions for the CAP ‘12 Abstract Program will be accepted through Monday, April 2, 2012.

Accepted submissions will appear in the September 2012 issue of the *Archives of Pathology & Laboratory Medicine*. Visit the CAP ‘12 website at [www.cap.org/cap12](http://www.cap.org/cap12) for a link to the submission site and additional abstract program information as it becomes available.