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ORIGINAL ARTICLE

Clinicopathological Features and Treatment Analysis of Rare Aggressive Angiomyxoma of the Female Pelvis and Perineum – a Retrospective Study

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Abstract The study was to evaluate the clinicopathological features of aggressive angiomyxoma (AAM) of the female pelvis and perineum and its treatments. This was a retrospective study of female patients with AAM admitted to our hospital. Clinical and pathological data were analyzed, as well as the postsurgical follow-up. Median age at initial presentation was 41 years. Thirteen patients had lesions involving adjacent organs. Eighteen patients underwent complete tumor resection, while one patient underwent partial tumor resection. The tumors were soft in texture, pink in color, and had mucus on the surface. A microscopic examination revealed that the tumors were non-encapsulated, with spindle cells and stellate cells of almost identical size loosely distributed in the myxoid stroma, and vessels of different sizes and wall thicknesses. Immunohistochemistry indicated that AAMs were strongly positive for CD34 and smooth muscle actin, moderately positive for desmin, estrogen receptors and progesterone receptor, and mostly negative for S-100. After a median follow-up of 24 months, the recurrence rate was 33.3 %. Four recurrences were in patients with positive initial margins. AAM is a slow growing, locally invasive, benign tumor. Complete resection could lead to lower recurrence rate compared with incomplete resection. Follow-up is necessary for recurrent cases with repeated surgeries. The overall prognosis could be favorable.

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Introduction

Aggressive angiomyxoma (AAM) is a rare angiogenic soft tissue neoplasm that is usually locally invasive, non-metastasizing and predominantly affects the pelvic and perineal areas of premenopausal women. Steeper and Rosai first reported nine cases of AAM in 1983 [1]. Since 1983, about 250 cases of AAM have been reported in the literature [2]. The estimated male-to-female ratio is 1:6.6 but could be even lower [2]. The age distribution is wide, with most cases occurring in 20 to 40-year old women of childbearing age (range:6 to 77 years) [1–6]. The disease course is highly variable, ranging from several months to years; the longest course reported was 78 years [5].

Clinically, AAM manifests as slow growing, painless solid mass with unclear borders, with the cephalad border often extending into the deep tissues. The tumor often grows expansively, and can extend from the perineum to the vagina and pararectal spaces, or even occupy the whole pelvic cavity [7]. The clinical manifestations are not obvious. The mass is usually painless with presenting symptoms of oppression, polyuria and a 'sagging sensation' due to the enlarging mass. However, approximately 70 % of patients are symptom free even when the tumor invades the bladder, rectum, or levator ani muscle.

Due to its rare occurrence, misdiagnosis is common. Imaging studies, particularly magnetic resonance imaging (MRI), are helpful for the clinical management of AAM and

follow-up [8]. Precise preoperative assessment is a crucial step in planning the best surgical approach for tumor removal [9].

This retrospective analysis explores the clinical features, pathological characteristics, treatment and prognosis of AAM in 20 patients admitted to the Peking Union Medical College Hospital, Beijing, China between 2000 and 2014.

Materials and Methods

Ethics

The study was approved by the Ethics Committee of the Peking Union Medical College Hospital. The committee waived the need for individual consent because of the retrospective nature of the study.

Management

All diagnoses of AAM were confirmed after surgery by at least two pathologists, based on the review of the pathological slides and immunohistochemistry.

Surgery was the first choice of treatment for patients with primary and recurrent AAM. The surgery aimed to remove the tumors completely without seriously impacting the genital anatomy or pelvic organ function. Radiotherapy was used for patients with recurrent AAM and in those with persistent symptoms.

Data Collection

Medical charts were reviewed to record clinical characteristics including physical examination, ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI). The characteristics of the treatments were extracted from the charts. Pathological data were reviewed and included in the analysis.

Follow-up

Patient follow-up, including physical examinations and imaging, was undertaken every month for the first year, every 2 months for the second year, every three months during Years 3 and 4, and every 6 months thereafter.

The date of the first definitive signs of recurrence, identified by physical examination or imaging was recorded. Follow-up was censored on 31 December 2014.

Data Analysis

No formal analysis or hypothesis testing was undertaken on the data from this small series of patients.

Results

Clinical Manifestations

The clinical data are shown in Table 1. All patients were female: the median age was 41 (14 to 58) years. The interval between the detection of a mass and the first treatment ranged from 3 months to 13 years. Seven lesions involved the vulva alone Thirteen patients had lesions involving adjacent organs: vagina (n = 2); pelvis and peritoneum (n = 3); peritoneum (n = 2); cervix (n = 1); vagina and rectum (n = 1); uterus (n = 1); pelvis (n = 1), bladder and ureter (n = 1); rectum (n = 1).

Management

Eighteen patients underwent complete tumor excision, and in four patients this included a positive surgical margin. One patient with a tumor invading the rectal serosal layer underwent partial excision. One patient who was pregnant at the time of presentation received six injections of GnRHa and did not undergo surgery. No radical resections were performed.

Tumor location in 13 of the 20 originally presenting cases was relatively limited, and excision was uncomplicated with a surgical duration of less than 45 min and blood loss of less than 50 mL. In the other seven relapsing/progressing cases, the surgical duration was 110 to 240 mins and blood loss was 100 to 3000 mL.

One patient developed a postoperative wound infection, and another patient required follow up surgery due to intraperitoneal hemorrhage.

Pathological Characteristics and Immunohistochemistry

Tumor size ranged from 4 to 24 cm. In the 13 non relapsing/progressing cases tumor diameter was <5 cm compared with a diameter > 10 cm in the other three patients.

Gross examination revealed that the tumors were soft in texture, pink in color, and had mucus on the surface (Fig. 1). Microscopic examination revealed non-encapsulated lesions, with spindle cells and stellate cells of almost identical size loosely distributed in the myxoid stroma. The tumors contained blood vessels of different sizes and the tumors had differing wall thicknesses (Fig. 2).

The immunohistochemistry results are summarized in Table 2. The AAM tumors tended to be strongly positive for CD34 and smooth muscle actin (SMA), moderately positive for desmin, estrogen and progesterone receptors, and mostly negative for S-100.

Follow-up

Median follow-up was 24 (7 to 288) months. Six patients (33.3 %) presented with tumor relapse/progression after

Table 1 Clinical data of patients with aggressive angiomyxoma

Case	Age	Location of tumor	Time from onset to treatment	Initial treatment	Postoperative follow-up	Retreatment	Outcome
1	34	Right labium majus	13 years	Labium majus mass resection without cephalad border incision	Tumor progression in 4 months	1. Transvaginal mass resection in 4 months 2. Resection of the vaginal mass and repair of the rectal wall, combined with radiotherapy in 5 years	No recurrence for another 3 years follow-up
2	34	Left vaginal wall and vaginal-rectal diaphragm	More than 5 years	Tumor resection without cephalad border incision	Tumor progression in 4 years	Transvaginal vaginal-rectal diaphragm mass resection	No recurrence for another 4 years follow-up
3	32	Right labium majus and cervix	7 years	Labium majus mass resection, with unclear incisal margin	Tumor progression in 6 months	Labium majus mass resection and bladder repair	No recurrence for another 2 years follow-up
4	35	Left labium majus and pelvic cavity.	3 years	Labium majus mass resection	Relapse in 2.5 years	1. GnRHa therapy; 2. Labium majus and vaginal mass resection with clear incisal margin	No recurrence for another 6 months follow-up
5	18	Right labium majus.	7 years	Labium majus mass resection with possibly positive incisal margin	Relapsed in 1 year	Labium majus mass resection and labium majus plastic	No recurrence for 1 year follow-up
6	45	Presacral posterior pelvic peritoneum, with labium majus involved	3 months	Transvaginal mass resection with clear incisal margin	——	——	No recurrence for 2 years follow-up
7	48	Right labium majus pudenda.	3 years	Labium majus mass resection with clear incisal margin	——	——	No recurrence for 1 year follow-up
8	14	Bladder and ureter involvement.	5 months	Transabdominal bladder resection and left ureterovesical implantation with clear incisal margin	——	——	No recurrence for 6 years follow-up
9	51	Left vaginal wall and rectum involved.	——	Partial resection of the vaginal wall mass, and residual mass was found on the surface of rectum.	——	——	Followed up for 3 years, the tumor size did not change significantly.
10	61	Left labium majus pudenda.	7 months	Labium majus mass resection with clear incisal margin	——	——	No follow up.
11	23	Left labium majus.	More than 3 years	Labium majus mass resection with clear incisal margin	——	——	No recurrence for 1 year follow-up
12	43	Left labium majus pudenda.	1 year	Labium majus mass resection, the resection margin was clear.	——	——	
13	32	Left uterus and left labium majus	——	6 injections of GnRHa (no effect)	Natural pregnancy. The tumor size increased from 18 cm to 22 cm during pregnancy	——	Full-term cesarean delivery, the primary tumor is still under observation.

Table 1 (continued)

Case	Age	Location of tumor	Time from onset to treatment	Initial treatment	Postoperative follow-up	Retreatment	Outcome
14	52	Right pelvic cavity with right perineum involved.	1.5 years	Complete mass resection	——	——	No recurrence for 1 year follow-up
15	40	Left labium majus pudendi, with pelvic cavity involved.	2 years	Labium majus mass resection	——	——	No recurrence for 6 months follow-up
16	50	Right labium majus pudendi	3 years	The mass at the right labium majus pudendi was resected completely.	——	——	No recurrence for 18 months follow-up
17	41	Right peritoneum	7 years	Right peritoneal mass resection.	Relapse in 2 years (mass extended to the right pelvic cavity)	Transperineal and pelvic resection of peritoneal and pelvic mass	No recurrence for another 15 months follow-up
18	24	Left labium majus pudendi, with pelvic cavity involved	4 years	Laparoscopic and transperineal resection of the mass posterior to the pelvic peritoneum and labium majus mass	——	——	No recurrence for 14 months follow-up
19	58	Right labium majus pudendi	4 months	Labium majus mass resection	——	——	No recurrence for 15 months follow-up
20	41	Left labium majus pudendi with vaginal vault involed	2 years	Resection of the labium majus mass with positive incisal margin	——	——	No recurrence for 7 months follow-up

surgery (including two patients with negative margins at first surgery, and four patients with positive margins) at a median of 18 (4–48) months after initial surgical treatment. All six patients underwent a second surgical resection of the tumor. One patient (Patient 1) had a third surgical resection (Table 1). No patient developed distant metastases. No tumor- or surgery-related death occurred.

Discussion

AAM is an uncommon angiogenic soft tissue neoplasm that preferentially occurs in the pelvic and perineal areas of women of reproductive age [5, 9]. A few cases have been reported in the genital area of men [5]. These tumors are characterized by an abundant arterial blood supply [10].

The lesions in all 20 patients were located in the pelvis and perineum. After a median follow-up of 24 months (range 7 to 288 months), the recurrence rate was 33.3 % (6/18). Half of the presenting lesions and all relapsing lesions involved adjacent organs. Most relapses were related to incomplete resection.

The disease characteristics were consistent with previous studies [1–6]. The AAMs range from 1 cm [3] to 60 cm [7], with an average of >10 cm [11]. The tumor is usually non-encapsulated with unclear borders, which can invade surrounding tissues. The mass is usually soft and stretchy like rubber, but sometimes can be hard like fibroma. The tumor surface is pink or brown in color, while the cross section is greyish pink in color and has been described as looking like translucent gelatum.

Ultrasonic revealed solid masses with homogeneous echo patterns and unclear borders with no inflammation, but was unable to provide a definite diagnosis or fully evaluate the resection margin. For this CT or MRI were of use. CT reveals a low-density mass, equivalent or slightly lower than that of muscles, with clear borders and 'swirling' appearance, inter-observer agreement was high (83 %) [11, 12]. T1-weighted MRI shows iso-intense tumors compared with muscle tissue. Contrast medium results in moderate enhancement of tumor signal density. High signal intensity within the tumor is usually observed with T2-weighted MRI [12, 13].

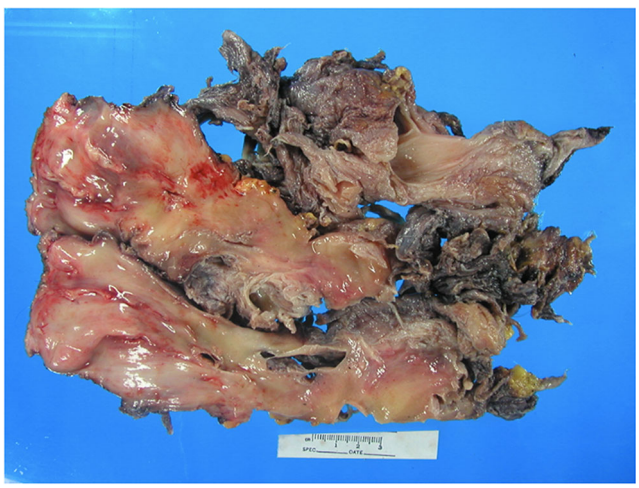

Fig. 1 Gross examination of a resected tumor. The tumor was solid and soft in texture with mucus on the surface. The cross section was grey and pink in color

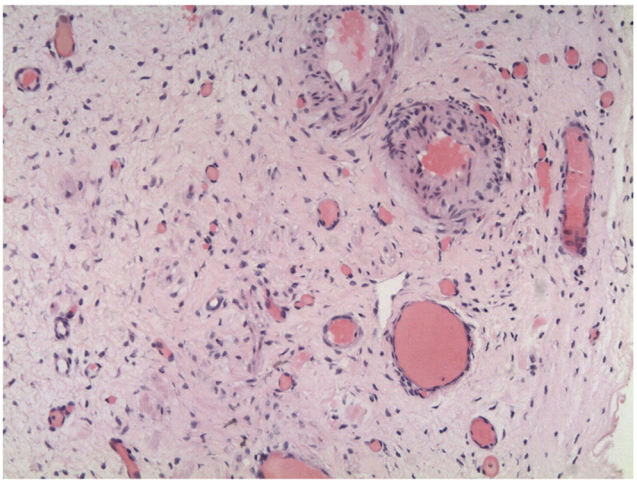

Fig. 2 Microscopic examination revealing diffuse stellate cells and collagenous fibers, which were distributed in a myxoid stroma, with vessels of different sizes and wall thicknesses (low-power, HE staining)

Diffuse stellate cells and collagenous fibers were distributed in the myxoid stroma, with vessels of different sizes and wall thicknesses. AAMs usually have an invasive border, often with entrapment of adipose tissues and skeletal muscles at the periphery [14]. Mitotic activity is rare; and mastocytes and erythrocytes are often seen in the intercellular substance [14]. Blood vessels of different sizes are usually seen, and this is a significant histological feature [11, 14, 15].

Benign tumors of the perineum, especially angiomyofibroblastoma (AMFB), should be histologically differentiated from AAMs [16]. The borders of AMFBs are usually well-defined, and the tumor size is relatively small. AMFB are soft or slightly stretchy, and the cross section of the tumor is brown, pink, or yellow in color. Characteristically, there are alternating hypocellular and hypercellular areas. The risk of

Table 2 Immunohistochemistry profile of AAM

Antigen	Cases (Number/Number tested)	Positive rate (%)
SMA	14/15	93.3
CD34	10/10	100
Desmin	9/14	64.3
ER	7/11	63.6
PR	8/11	72.7
S-100	1/7	14.3

AAM Aggressive angiomyxoma, *ER* Estrogen receptor, *PR* Progesterone receptor, *SMA* Smooth muscle actin

local recurrence of AFMB is very low but is occasionally reported [3, 4, 14, 16–19].

AAM does not have any specific immunohistochemistry marker [3, 19]. Desmin and SMA were mostly positive. The Ki-67 index is usually <1 %, which indicates low proliferation [15, 20]. About 90 % of tumor cells are positive or weakly positive to estrogen and progesterone receptors [3].

Complete resection with wide margins, especially on the cephalad border, is recommended to avoid recurrence [21]. However, these tumors often invade surrounding tissues and the visceral peritoneum, making complete resection difficult. Blood loss is quite high, and in cases of extensive tumor growth it has been reported to be as high as 10,000 mL [22, 23].

Since AAM is benign and not life-threatening, repeated surgery can be performed. Conservative surgery with partial resection or positive margin is also acceptable. Here, second resection resulted in satisfactory prognosis in all four patients with relapse/progression due to incomplete resection at the first attempt. One patient had tumor involvement of the rectal serosal layer, requiring a partial resection. Long-term follow-up in this patient showed no evidence of tumor progression and quality of life was maintained.

Lymph node dissection is not required as AAMs do not metastasize to lymph nodes. Angiogenesis embolization is not used as routine therapy, as the blood supply in AAM is quite abundant [2, 24].

With low mitotic activity, it is unlikely that chemotherapy and radiotherapy are useful adjuvant therapies [25]. However, radiotherapy is reportedly effective for relapsing AAM [26]. One patient received radiotherapy following a third resection for AAM relapse, and this resulted in a good prognosis.

AAMs may be associated with gonadal hormones and gravidity quickly increases the growth of the neoplasm [20]. Indeed, tumor size rapidly increased from 18 to 22 cm in a single pregnant patient in the present series.

GnRHa administration can achieve long-term remission of the tumor [27], and may be effective [23, 27–29], but this is not definitive. Drug resistance may be a problem, resulting in quick relapse after GnRHa withdrawal [18]. Overall, GnRHa may be useful in cases with incomplete resection or in inoperable case and preoperatively may reduce the size of the tumor [14]. Here, GnRHa was administered to two patients: one woman who was pregnant at the time of presentation and another woman who suffered a relapse at 2.5 years, but the outcomes were unsatisfactory.

Antiestrogenic therapies such as ovariectomy, tamoxifen, or aromatase inhibitor are not effective in the treatment of AAM [25]. Consequently, these approaches were not adopted here.

The AAM relapse rates are between 36 % and 72 % [1–5, 12]. Here this was 31.6 % (6/19). All patients with a positive margin relapsed, and 13.3 % of those with negative margins. 70 % of patients might be expected to have relapsed within 3 years of primary surgery [2]. The initial relapse is usually located in the primary surgery area.

Careful follow-up instead of surgery, radiotherapy, embolization or hormone therapy might be the correct approach, especially for patients with recurrent tumors and in those with large tumors in which resection may increase morbidity [30]. Five of the six patients with relapsing/progressing AAM in this study underwent a second surgery 2 to 3 years after relapse/progression. One patient who presented with a second recurrence (6 months after the second surgical treatment) underwent a third surgical therapy 5 years later, illustrating the importance of long-term follow-up.

To date, fewer than 250 cases of AAM have been reported in total, and cytogenetic abnormalities have been identified only in seven cases [31]. In China, AAM is regarded as having a low malignant potential, while in other countries it is considered as a benign tumor associated with repeated recurrence and a satisfactory prognosis. The ‘aggressive’ nature of AAM refers to the proliferation of tumor blood vessels and local invasion, as well as its propensity for recurrence [30]. Only two patients in the literature have been reported to develop lung metastases leading to death [17, 32].

The present series is one of the largest to date, but it remains a retrospective study with a small sample size. The rarity of the disease precludes any firm conclusion on its treatment. Multicenter studies at the national level should be designed provide larger sample sizes and confirm treatment recommendations.

Conclusions

AAM is a slow growing, locally invasive, benign tumor. Preoperative diagnosis is difficult, and CT and/or MRI can help to increase the preoperative diagnosis rate. Complete resection should reduce recurrence rates compared with incomplete resection. Close follow-up is necessary for recurrent cases requiring repeated surgery.

Compliance with Ethical Standards All procedures performed in studies involving human participants were in accordance with the ethical standards of Peking Union Medical College Hospital Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The committee waived the need for individual consent because of the retrospective nature of the study.

Authors' Contribution Ying Sun and Lan Zhu contributed to conception and design; Ying Sun, Lan Zhu, Xiaoyan Chang, Jie Chen and Jinghe Lang contributed to acquisition of data, or analysis and interpretation of data; Ying Sun and Lan Zhu have been involved in drafting the manuscript or revising it critically for important intellectual content; all authors have given final approval of the version to be published. Guarantor: Lan Zhu.

Conflict of Interest The authors declare that they have no conflict of interest.

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