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Original Article

Uterine adenomatoid tumor: a clinicopathologic study of 102 cases

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Abstract: Objective: Uterine adenomatoid tumors (UATs) are tubercle without significant clinical features. The study aims to summarize the clinicopathological characteristics of UATs to improve diagnostic accuracy. Methods: Between January 2014 and December 2015, 4326 uterine specimens were collected from patients who received hysterectomy or myomectomy, of which 102 cases were pathologically confirmed as UATs. The clinical features, pathological parameters and immunohistochemical staining were analyzed. Results: One hundred and two UATs were identified by gross and microscopic examination, which accounts for 2.4% of all the uterine tumors. UATs were usually located in the uterus myometrium, near the serosa or cornua. Most of them were solitary, without an enveloping membrane or clear demarcation. Microscopically, typical features were glandular structures and cavities with various sizes and shapes found within the hyperplastic smooth muscle tissues. Immunohistochemical staining showed that all tumors were positive for HBME-1 and CK (pan). Most of them were positive for CR (89.6%) and D2-40 (92.4%), negative for CD31 and CEA, while cast-off cells in glandular cavities and lymphocytes were positive for LCA. Conclusion: Adenomatoid tumors are not very rare in the uterus. The diagnosis of UATs can be improved by carefully gross and microscopic examination. Immnohistachemical staining is helpful for diagnosis and differential diagnosis of UATs.

Keywords: Adenomatoid tumor, HBME-1, immunophenotype, LCA, uterus

Introduction

Adenomatoid tumors (ATs) are benign neoplasms of mesothelial origin that occur in the genitalia. ATs were first reported and named by Golden and Ash [1] in 1945 and usually found in uterine, fallopian tubes and ovaries in females [2]. Uterine adenomatoid tumors (UATs) are often accompanied with smooth muscle tumors and endometriosis. UATs are tubercular without clear boundaries, without specific clinical presentations or radiographic features and thus are easily confused with uterine lymphangioma and leiomyoma. Thus differential diagnosis of UATs has significant clinical benefits. Here, we summarize and analyze the clinicopathological parameters from 102 UATs cases to improve diagnostic accuracy.

Materials and methods

Between January 2014 and December 2015, 4326 specimens were collected from patients who received hysterectomy or myomectomy procedures performed at Qilu Hospital of Shandong University and Yidu Central Hospital of Weifang. For all of the patients who participated in this study, written informed consent was obtained, which was approved by the Ethical Committee of Shandong University (Jinan, China). The clinical and pathological data were reviewed for this study. The preoperative clinical diagnoses of the patients were hysteromyoma or endometriosis. Representative sections of each case were cut at 4 μm and stained with hematoxylin and eosin (H&E) for histopathologic review. Finally, 106 adeno-

Table 1. Clinicopathologic features of uterine adenomatoid tumors (n=102)

Variable	Number of cases
Age (years)	
≤30	5
31-40	30
41-50	51
51-60	15
>60	1
Size range (cm)	
≤1	31
1.1-2	29
2.1-3	21
>3	21
Missing	4
Site	
Near the serosal	13
Subserous	8
Cornua	10
Myometrium	68
Sub-endometrial	1
Diffused	2
Number	
Single	98
Multiple	4
Concomitant disease	
Uterine leiomyoma	56
Uterine adenomyosis	21
Full-time pregnancy	20
Early pregnancy and leiomyoma	1
Fallopian tube pregnancy	4
Cervical cancer	3
Isolated	13

matoid tumors from 102 patients were diagnosed as UAT by gross and microscopic examination.

Formalin-fixed, paraffin-embedded tissue sections were consecutively cut and immunohistochemical staining was performed by automatic immunohistochemistry machine (Benchmark XT, Roche, Switzerland) according to manufacturer's instructions. Mesothelial Cell (MC) (clone HBME-1, Fuzhou, China), Calretinin (CR) (clone SP13, Fuzhou, China), D2-40 (clone D2-40, Fuzhou, China), CK (pan) (polyclone, Fuzhou, China), CEA (clone ZC23, Fuzhou, China), CD31 (clone JC/70A, Fuzhou, China), LCA (clone PD7/26+2B11, Fuzhou, China) were used. Five

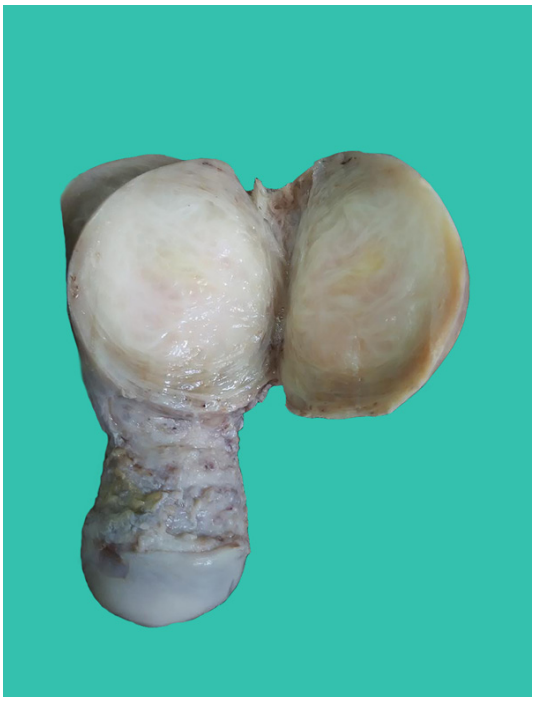

Figure 1. Gross specimen show adenomatoid tumor was located in the myometrium, near the serous surface, without a clear capsule. The tumor sections were moist and slimy, which were in grayish-white and grayish-yellow. Bundles of smooth muscle were interlacing in the tumor mass.

hundred tumor cells were counted in randomly chosen fields. Cases were evaluated according to the proportion of positive cells and subclassified as: negative (less than 5% of positive cells), focally positive (5%-50% of positive cells) and diffused positive (more than 50% of positive cells).

Results

Clinical data

ATs of the uterus tend to occur in women of reproductive age, ranging from 25 to 63 years (mean 39.3 years; median 37 years) (**Table 1**). Reasons for visiting hospitals were menstrual disorder, vaginal bleeding or dysmenorrhea. Some were pelvic mass found in physical exam (**Table 1**). UATs were identified in 102 (2.4%) out of the 4326 cases investigated in the present study. For patients with UATs, most of them had uterine leiomyoma (56/102), or uterine adenomyosis (21/102). And the others (13/102) had adenomatoid tumor alone. No UAT was recognized during the preliminary histologic examina-

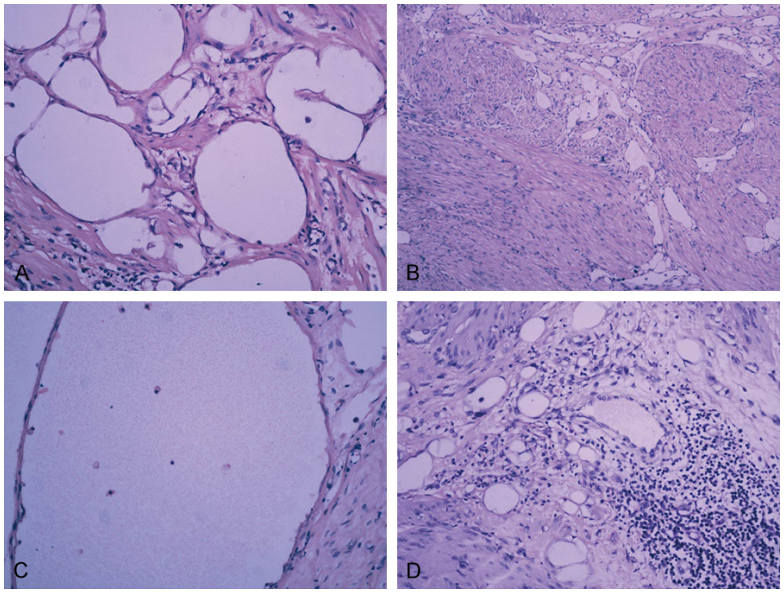

Figure 2. Tissue morphology of uterus adenomatoid tumors: UATs were composed of smooth muscle and tiny glands or lacuna with various sizes and shapes (A). Smooth muscle cells around the tumor were hyperplastic (B). Glandular cavities were filled with mucus-like stained pink discharge and cast-off cells (C). Interstitial lymphocytic infiltrates were consistently found between tumor cells (D). (Original magnification, ×200).

tion. Post-operation follow-up for this group of patients lasted 6-30 months, with no incidence of recurrence or metastasis.

Clinicopathologic features

On gross examination, all masses originated from the uterus. The tumor size ranged from 0.3 to 7 cm with an average of 2.3 cm, most being less than 3 cm (81/106, **Table 1**), although huge adenomatoid tumors up to 13-15 cm have been reported [3, 4]. UATs were solitary, seldom multiple, occasionally occupying most of the uterine muscle wall in the form of diffusibility (**Table 1**). Most adenomatoid tumors were located in the myometrium, near the serous surface, subserous or cornua (**Table 1**) [5].

Of the 106 samples from 102 patients, 104 cases appeared to be spherical or tuberculate, with no enveloping membrane or clear demarcations. The gross pathological sections were solid with medium of callous texture, which were in grayish-white or grayish-yellow (**Figure 1**). Some of them had spongy appearances or cavities [6]. Cavities contained translucent mucus. In addition, all samples contained stripes of various thickness arranged in a grid-like manner or small pore-like structures, and filled with braid or swirl patterns like smooth muscle tumors. The tumor sections were slimy and sticky, and a few samples had glair thread like silk. No clear demarcation existed between tumor tissue and the muscular wall, and there were no pseudo-membranes.

Tissue morphology

Histologically, uterus adenomatoid tumors were composed of smooth muscle and tiny glands or lacunar. In the regions of smooth muscle cells, glands and lacunar structures with various sizes and shapes could be observed (**Figure 2A**). Smooth muscle cells around the tumor were hyperplastic (**Figure 2B**). The lumens were either singular, string like, or plate-like. Among the lacunar structures there were loose fibrous connective tissues, which were often accompanied by edema. UAT sections were small solid tumors or large cystic tumors [7]. Glandular cavities were lined with squamous, cuboidal or columnar cells, while occasionally this lining was not obvious. The cavities were either vacant, or found to be filled with a mucus-like pink or pale blue discharge (**Figure 2C**). Cast-off cells were found in glandular cavities (**Figure 2C**), and a few were in signet-ring shape. Within the tumor tissue, various numbers of epithelial cells were also present, and the tumor borders were not clear. The cells were round or oval in shape, rich in cytoplasm, acidophilic or lightly stained, with medium or large nuclei. In some cells, empty vacuoles could be found; the nucleus was present in signet-ring shape, and mitosis was not present. While most tumor cells did not have atypical shapes, a few cells show mild atypical changes. Interstitial lymphocytic infiltrates were consistently found between tumor cells, either diffused or focally distributed (**Figure 2D**).

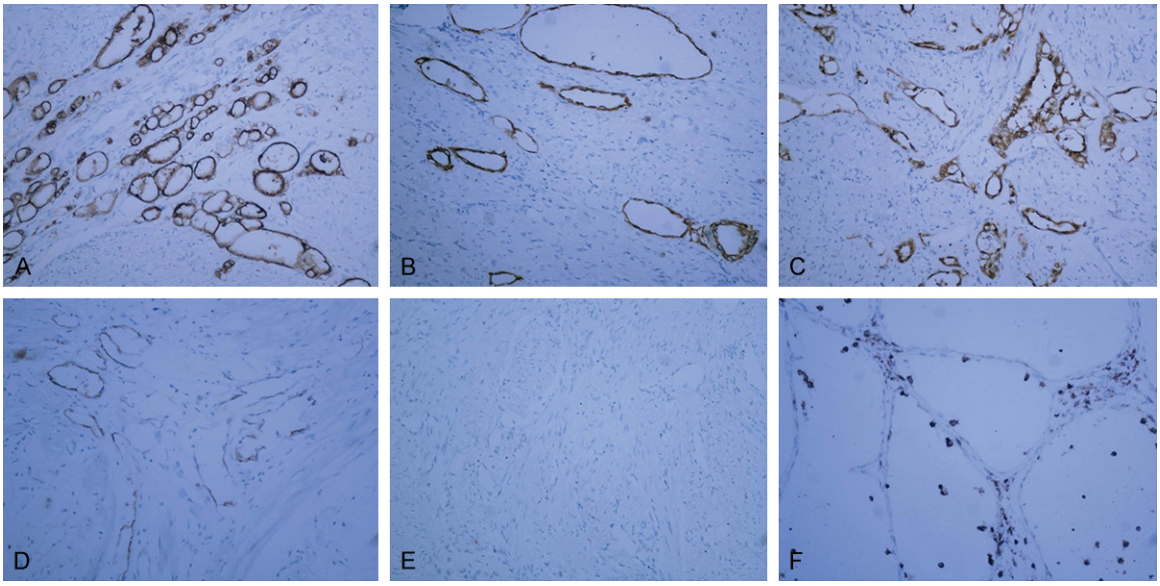

Figure 3. Immunohistochemical staining of uterus adenomatoid tumors: HBME-1 and CK (pan) immunostaining were positive in all the UATs (A, B). CR and D2-40 immunoreactivity were local positive in the majority of UATs (C, D). UATs were negative for CEA (E). Lymphocytes infiltrated into tumors were positive for LCA (F). (Original magnification, ×200).

Immunohistochemical staining

Immunohistochemical staining revealed that HBME-1 and CK (pan) (**Figure 3A**, **3B**) immunostaining were positive in 100% (106/106) of UATs. CR and D2-40 immunoreactivity were seen in the vast majority of UATs (95/106, 89.6% and 98/106, 92.4%, **Figure 3C**, **3D**). All were negative for CEA or CD31 (**Figure 3E**). LCA-positive lymphocytes were found in all samples, while cast-off cells in glandular cavities were also positive (**Figure 3F**).

Discussion

ATs of the uterus tend to occur in the women of reproductive age and are difficult to diagnose. Other studies have reported that UATs are discovered in 1.3%-5% [8, 9] of hysterectomy specimens. The detection rate of UATs reported in the present study is 2.4%. However, the true incidence is probably greater because these tumors are frequently mis-diagnosised as uterine lymphangioma or leiomyoma. Pathologists underestimate the adenomatoid tumors clinicopathological features and ignore the gross examination. Adenomatoid tumors are not diagnosed pre-operatively. When the tumor without clear boundary or difficult to separate from myometriumor neoplasms, pathologists should check up carefully and be aware of the UAT.

Generally speaking, UATs have the following characteristics: (1) Tumors mostly occur as a tubercular mass with unclear boundary. No clear demarcation exists between the tumor and muscular tissues. They rarely spread and have no pseudo-membranes. (2) The tubercles are generally smaller than 3 cm, located in the myometrium, often occurring near the serous or cornua. (3) Tumor sections are sticky and slimy, and some are even mucous-drawing. (4) The gross pathological sections are solid with medium of callous texture, which are filled with braid or swirl patterns. One can see large fibers forming small yet visible grids or pore-like structures. (5) Among the lacunar structures there are loose fibrous connective tissues, which are often accompanied by edema. Microscopically, typical features include glandular structures and cavities of various sizes and shapes found within the hyperplastic smooth muscle tissues, along with the typical squamous, cuboidal, or columnar cells that line the cavities. Cavities may be empty or filled with mucous secretions that are stained pink or pale blue. Cast off cells are found in glandular cavities.

Positive expression of HBME-1 and Calretinin support the evidence of mesothelial origin. Diagnosis can be carried out for adenomatoid tumor in combination with CK and positive

immunohistochemical staining for mesothelial origin labels. Investigation has shown that the lymphocyte collections, chronic lymphoid follicles, or lymphoid aggregates within adenomatoid tumor were useful diagnostic features [10]. Sangoi et al [11] reported that 100% of the male patients with AT exhibit lymphocytic infiltrates, while only 13% in the female. Our study found lymphocytic infiltrates could be observed in all of the female samples, mostly focally distributed and occasionally dispersed. Immunohistochemical staining showed that cast-off cells in glandular cavities were positive for LCA and lymphatic vessel antigen D2-40 were also found to be focally distributed. Terada T [12] suggested adenomatoid tumors and lymphatic vessels expressed a common antigen, as well as the existence of similar lymphatic cells in both tissues. The date from this study was consistent with the research.

Interestingly, we noticed that in the patients with UAT tend to merge pregnancy, the incidence of UATs accompanied by pregnancy was 24.5% in the present study. The existence of the UAT and the occurrence of pregnancy may not just a coincidence of time and space, there may be a causal relationship. We are looking forward to more research to confirm this conclusion, and can further reveal the relationship between AT and pregnancy.

Uterine AT has diverse microscopic morphology and thus should be differentiated from the following diseases. (1) Leimyomas with steatosis: Unlike UATs, leiomyomas have clearly defined boundaries, and occur as singular or multiple or tubercular nodules. Leimyomas occur with fat degeneration, and the steatosis regions are easy to be misdiagnosed as lacuna. UATs have glands and lacunar structures of various sizes and shapes with cavities liner cells, while the fat cells are uniform and have no liner cells. Immunohistochemical staining can be used to differentiate these two tumors. (2) Lymphangioma: The cross sections of lymphangioma generally show obvious lumen filled with fluid, while cystic adenomatoid tumors also have a multilocular appearance. Some UAT lumens are lined with squamous cells akin to lymphatic vessels, but the lumens may be vacant or may contain a small amount of pink or pale blue secretions as well as glandular structures, epithelioid cells or nests of cells. There are still difficult to identify, in conjunction with H&E and IHC to improve the diagnosis. Immunohistochemical staining can be used to differentiate these two tumors: epithelial cells of lymphangioma are positive for CD31 and CD34, but negative for HBME-1 and Calretinin. On the contrary, UAT lumens are positive for CK (pan) HBME-1 and Calretinin, while negative for CD31 and CD34. (3) Adenocarcinoma: Some well differentiated adenocarcinoma have benign morphologies. They may form diffuse infiltration in uterine muscles and can easily to be mistaken for UATs. However, UATs grow slowly and rarely invade neighboring tissues. Moreover, UATs are often asymptomatic, with no obvious mitosis or other changes in tumor cells. In contrast, all adenocarcinoma involve atypical changes of various extent, as well as pathological mitosis. These findings and immunohistochemical studies can help clinicians make accurate diagnoses. (4) Uterine adenomyoma: Both uterine adenomyoma and adenomatoid tumors have no clear demarcation. Uterine adenomyoma have endometrium glands and interstitial cells in smooth muscle, fresh and stale bleeding could be seen. ATs also have glands and lacunar structures but no interstitial cells, pink or pale blue mucous secretions could be seen in cavities.

In summary, we analyzed the clinicopathological parameters of 102 cases of UATs, emphasized the gross, histological examination and immunohistochemical staining features. Most UATs are located in the myometrium, without enveloping membranes or any clear demarcations. Microscopically, typical features include glandular structures and cavities with various sizes and shapes found within the hyperplastic smooth muscle tissues. UATs are positive for HBME-1, CK (pan), complete lack of CD31 and CEA. The finding in this study is conducive to differential diagnosis of UATs.

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Disclosure of conflict of interest

None.

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