Adenomatoid Tumors of the Uterus

Quigley, James C., and Hart, William R.: Adenomatoid tumors of the uterus. Am J Clin Pathol 76: 627–635, 1981. Adenomatoid tumors arising in the uterus are not well-recognized and are sometimes mistaken for other benign or malignant neoplasms. This study is a clinicopathologic analysis of 12 uterine adenomatoid tumors. Characteristically, they were small nodular lesions (mean diameter 2.1 cm) in the subserosa or outer wall of the myometrium. Four distinctive histologic types (adenoid, angiomatoid, solid, and cystic) were identified; each tumor consisted of a combination of one major and at least one minor type. The nodular proliferation of smooth muscle which accompanied some tumors was regarded as a non-neoplastic hyperplasia of myometrium. In two cases, small foci of serosal endosalpingiosis were adjacent to the tumor. Theories of histogenesis are discussed, and classification of the adenomatoid tumor as a type of benign mesothelioma is endorsed. (Key words: Adenomatoid tumor; Mesothelioma; Neoplasm; Uterus.)

ADENOMATOID TUMORS are relatively rare benign neoplasms which usually arise in or near organs of the genital tract. Rarely, they originate in extragenital sites such as the adrenal,21 omentum,10 and intestinal mesentery.3 In women, the adenomatoid tumor is widely known as the most common benign neoplasm of the fallopian tubes. Less well-recognized are identical tumors of the uterus, although over 75 cases have been reported.2,4,6,11–15,19,22,25–30 During the past several years, several uterine adenomatoid tumors were seen in consultation. The difficulties they have caused in diagnosis have been impressive. Consequently, we decided to analyze our experience with these unusual lesions in order to focus attention on their existence and to characterize their most distinctive features.

Materials and Methods

The diagnostic files of the Department of Pathology of the University of Michigan were searched for possible examples of adenomatoid tumors of the uterus. After reviewing available microscopic slides and, when necessary, preparing new histologic sections from paraffin blocks of cases diagnosed between January 1942 and June 1980, 12 acceptable cases were found. Six of these had been sent to our department for consultation from outside hospitals while the other six were from patients hospitalized at the University of Michigan Medical Center.

In addition to routine hematoxylin and eosin stains, the following histochemical stains were performed on new sections from paraffin blocks in six cases: colloidal iron with and without predigestion with testicular hyaluronidase, periodic acid-Schiff (PAS) reaction with and without predigestion with diastase, phosphotungstic acid hematoxylin and Mallory’s trichrome. The number of available sections or paraffin blocks from different areas of each tumor ranged from one to seven with a mean of 3.6 per case.

Results

Clinical Findings

A summary of the clinicopathologic findings is presented in Table 1. Of the 12 tumors 11 were detected in hysterectomy specimens and one lesion was found at autopsy. The patient’s age at the time of diagnosis was known in 11 cases and ranged from 30 to 51 years with a mean of 42 years. In each surgical case, the adenomatoid tumor seemed to have been an incidental finding in a uterus removed for other reasons. Four patients had a history of abnormal uterine bleeding. Three patients had leiomyomas of the uterus and the fourth had adenomyosis and slight adenomatous hyperplasia of the endometrium; these lesions and not the adenomatoid tumor were the probable causes of the patient’s bleeding. Two other patients had undergone radical hysterectomy for invasive squamous cell carcinoma of the cervix. Preoperative diagnosis for the other five surgical patients included adenomyosis, “fibroids”, atypical endometrial hyperplasia, endometrial carcinoma, and chronic endometritis with cystic ovaries.

Pathologic Findings

All 12 tumors were in the uterine corpus. A more precise location was recorded in seven cases. Three tumors were in a uterine cornu (one on the right, one on the left and no side given for the third case). Three tumors were located in the anterior, lateral, and pos-
Table 1. Summary of Clinical and Pathologic Findings of 12 Cases of Uterine Adenomatoid Tumors

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age (Yr)</th>
<th>Tumor Size (cm)</th>
<th>Tumor Location</th>
<th>Histologic Type</th>
<th>Histology of Endometrium</th>
<th>Other Uterine Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>?</td>
<td>2.0</td>
<td>Cornu</td>
<td>Adenoid</td>
<td>Proliferative</td>
<td>Leiomyomas</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>3.0</td>
<td>Corpus</td>
<td>Adenoid</td>
<td>Proliferative</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>2.5</td>
<td>Right cornu</td>
<td>Cystic</td>
<td>Slight adenomatous hyperplasia</td>
<td>Adenomyosis</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>4.0</td>
<td>Posterior wall</td>
<td>Solid</td>
<td>Secretary</td>
<td>Fibrous serosal adhesions</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>1.8</td>
<td>Fundus</td>
<td>Angiomatoid</td>
<td>Secretary</td>
<td>Fibrous serosal adhesions &amp; endosalpingiosis</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>2.3</td>
<td>Near isthmus</td>
<td>Angiomatoid</td>
<td>Proliferative</td>
<td>Leiomyoma</td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td>1.5</td>
<td>Corpus</td>
<td>Adenoid</td>
<td>Indeterminate</td>
<td>Leiomyoma, fibrous serosal adhesions, &amp; endosalpingiosis</td>
</tr>
<tr>
<td>8</td>
<td>43</td>
<td>2.0</td>
<td>Corpus</td>
<td>Adenoid</td>
<td>Inactive</td>
<td>Leiomyoma</td>
</tr>
<tr>
<td>9</td>
<td>51</td>
<td>1.5</td>
<td>Lateral corpus</td>
<td>Adenoid</td>
<td>Proliferative</td>
<td>Adenomyosis</td>
</tr>
<tr>
<td>10</td>
<td>44</td>
<td>1.0</td>
<td>Left cornu</td>
<td>Angiomatoid</td>
<td>Proliferative</td>
<td>Carcinoma of cervix</td>
</tr>
<tr>
<td>11</td>
<td>45</td>
<td>2.0</td>
<td>Anterior wall</td>
<td>Angiomatoid</td>
<td>Proliferative</td>
<td>Carcinoma of cervix &amp; leiomyomas</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>1.5</td>
<td>Corpus</td>
<td>Adenoid</td>
<td>Inactive</td>
<td>Leiomyoma</td>
</tr>
</tbody>
</table>

Gross descriptions were available for ten tumors. Their sizes ranged from 1.0 to 4.0 cm (mean 2.1 cm). Two tumors were associated with tiny (1-3 mm) vesicles over their serosal surface and small vesicular spaces were also seen on the cut surface of another lesion. The color of the tumors varied from white to grey to grey-tan. Two of the tumors were thought to be leiomyomas. Five other tumors were described as uterine wall "nodules;" two had irregular fibrous trabecula, two had a whorled appearance, and the other was noted to be less well-circumscribed than other leiomyomas in the same uterus. Two tumors were believed to have been due to adenomyosis, one having indistinct boundaries and the other showing coarse trabeculations. The remaining tumor presented as a cystic mass with a mucoid cut surface.

The microscopic features of the adenomatoid tumors were diverse. Four relatively distinctive histologic types were identified and classified as (1) adenoid, (2) angiomatoid, (3) solid, and (4) cystic. Others have used similar designations. Combinations of two or more patterns occurred in all tumors, but one major type prevailed in each case (Tables 1, 2). Transitional forms of the four types were frequently observed, indicating they represented morphologic variants of the same neoplasm and not different tumors. The major histlogic pattern did not correlate with the phase or activity of the endometrium, the age of the patient or size of the neoplasm (Table 1).

Table 2. Frequency of Major and Minor Histologic Types in 12 Uterine Adenomatoid Tumors

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>Major Component</th>
<th>Minor Component</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoid</td>
<td>6</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Angiomatoid</td>
<td>4</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Solid</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cystic</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

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The adenoid and angiomatoid types were most frequent, each occurring in 11 of the tumors. The adenoid pattern comprised the major pattern in six of the cases and was a minor element in five other tumors. It was characterized by small anastomosing gland-like spaces lined by cuboidal or irregularly shaped cells (Figs. 1, 2). Their cytoplasm usually contained vacuoles of varying size. Some cells with large vacuoles had a signet ring shape. In the past, the adenoid type has also been referred to as the tubular, glandular, or microfollicular pattern.

The angiomatoid type was the major pattern in four tumors and a minor component in seven others. In this variant the spaces were somewhat larger (Figs. 3, 4). They were lined by flattened neoplastic cells with inconspicuous attenuated cytoplasm which resembled endothelial cells. Frequently, these pseudovascular channels were widely separated by bundles of myometrial
smooth muscle cells. Admixtures and gradations with the adenoid pattern were frequent. When accompanied by nodular aggregates of lymphocytes, this variant could easily be mistaken for a lymphangioma. Similar patterns have been reported as "canalicular" or "macrofollicular" types of adenomatoid tumor.

The solid type was identified in three tumors. It was the major pattern in only one case and was a minor element in two others. In this variant, the neoplastic cells were arranged into small sheets, columns, or solid cords. The cells had more abundant, eosinophilic cytoplasm and fewer vacuoles than those of the adenoid type and they simulated plump epithelial cells (Fig. 5). With coalescence of the vacuoles, small gland-like spaces were formed (Fig. 6). In areas where the cords of the cells were interwoven, a so-called plexiform pattern was produced.

The least common variant was the cystic pattern, occurring in two lesions. One tumor was almost entirely cystic with numerous large cavities subdivided by thin cords. The cells had more abundant, eosinophilic cytoplasm and fewer vacuoles than those of the adenoid type and they simulated plump epithelial cells (Fig. 5). With coalescence of the vacuoles, small gland-like spaces were formed (Fig. 6). In areas where the cords of the cells were interwoven, a so-called plexiform pattern was produced.

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Columns of plump epithelial-like cells with abundant cytoplasm constitute the solid type of adenomatoid tumor. A few cells are vacuolated (hematoxylin and eosin stain, X330).

A transitional area between solid and adenoid patterns. Cytoplasmic vacuoles in epithelial-like cells have coalesced to form gland-like spaces (hematoxylin and eosin stain X330).

This lesion was well-circumscribed and more discrete than the other 11 adenomatoid tumors.

Stains for mucosubstances were performed on six tumors. The colloidal iron stain for acid mucopolysaccharides demonstrated positively stained material within cytoplasmic vacuoles of the neoplastic cells, along their luminal borders and within the lumens. Predigestion with hyaluronidase diminished the positivity but did not completely eliminate it. PAS stains demonstrated a delicate basement membrane around many of the adenoid and angiomatoid structures and a small amount of secretory material along the luminal edges of the cells.

It was possible to microscopically evaluate the proximity of the adenomatoid tumors to the uterine serosa in 11 cases. In every instance neoplastic elements were within 5 mm of the serosa, and in five of the 11 cases
they were within 1 mm or less of the serosal surface. In two tumors direct continuity was documented between neoplastic cells and the serosal mesothelium which had a micropapillary configuration (Fig. 8). In both instances the surface involvement had been seen grossly as small vesicles. A third tumor had a small tongue-like extension over the uterine surface while a fourth example extended up to the serosal edge but did not have a definite surface component or demonstrable continuity with mesothelial cells. All four of these tumors were associated with fibrous serosal adhesions, and in two instances small inclusion cysts lined by metaplastic epithelium of tubal type (endosalpingiosis) were also present (Fig. 9).

The adenomatoid tumors were intimately associated with smooth muscle of the myometrium. In all but the single example of a predominantly cystic adenomatoid tumor, the neoplasms had an infiltrative growth pattern with neoplastic cells interspersed between muscle cells. The smooth muscle in the immediate vicinity of the
FIG. 9 (upper). Small inclusion cysts of endosalpingiosis lined by metaplastic tubal-type epithelial cells are within a serosal fibrous adhesion. Small foci of serosal endosalpingiosis were found adjacent to two adenomatoid tumors in this study (hematoxylin and eosin stain, ×132).

FIG. 10 (lower). Low magnification photomicrograph of an adenomatoid tumor of angiomatoid type which is obscured by a nodular proliferation of myometrial smooth muscle. Grossly, such lesions may be mistaken for a small subserosal leiomyoma or nodule of adenomyosis and not be sampled for microscopic examination (Masson trichrome stain, ×5).

lesion appeared hyperplastic in ten of the cases and in some instances had a nodular or leiomyomatous configuration (Fig. 10). In contrast, smooth muscle bundles were absent from those portions of three tumors that extended over the serosal surface of the uterus.

Fibrous connective tissue was also associated with the tumors. It was especially conspicuous in the solid and adenoid types but was less plentiful in the angiomatoid or cystic areas. Collections of lymphocytes in the vicinity of the tumor were seen in 11 cases; in seven instances, discrete lymphoid nodules were found. Typical leiomyomas separate from the adenomatoid tumors were known to be present in six cases and may have been present in another. Adenomyosis was observed in two cases.

Discussion

Adenomatoid tumors seem to be rare in the uterus. Only six examples were found in our retrospective search of surgical and autopsy cases at our hospital over
a 38-year interval. The other six cases were referred to us from other hospitals. Yet, it is doubtful that they are so uncommon. Because of their small size, they may be easily overlooked during gross examination of the uterus. Even when seen, they may be mistaken for a small leiomyoma or nodule of adenomyosis and not be selected for microscopic examination. During a seven year period at the Mayo Clinic when tumors of the uterus with the gross appearance of fibromyomas were carefully scrutinized, ten adenomatoid tumors were detected in over 8,000 hysterectomy specimens. In the same interval, two additional examples were found in a group of more than 300 myomectomy specimens. Honoré personally studied 624 excised uteri and four individually submitted myometrial tumors and found five adenomatoid tumors in four different operative specimens. Tiltman assessed the incidence of uterine adenomatoid tumors in 1,000 unselected hysterectomy specimens received during a two year period by cutting them into 1 mm slices and microscopically examining all myometrial lesions. Twelve of the uteri (1.2%) contained 14 adenomatoid tumors.

There are several clues to the gross recognition of uterine adenomatoid tumors. Generally they are small tumors, 0.5 to 4 cm in greatest diameter, although lesions up to 7.5 cm have been recorded. The posterior aspect of the uterus, especially in the region of a cornu, is a site of predilection. Most are subserosal or situated in the outermost zone of the myometrium. Although nodular, they tend to be less well-demarcated than leiomyomas and are more likely to be tan-grey or slightly yellow than white. Small vesicles or cysts are sometimes seen on the cut surface or over the serosa. Careful sampling of all uterine lesions with these gross features is likely to disclose otherwise unsuspected adenomatoid tumors. Occasionally more than one adenomatoid tumor is discovered in the same uterus, and bilateral cornual tumors have been documented.

Uterine adenomatoid tumors usually are accompanied by bundles of smooth muscle. Often the muscle is merely entrapped myometrium which has been permeated by the adenomatoid tumor. In some instances an abundance of muscle in a nodular arrangement obscures the adenomatoid tumor and simulates a leiomyoma. It is doubted whether the muscle in such cases is actually a neoplastic component of the adenomatoid tumor. Instead, it is believed to be a reactive hyperplasia of indigenous myometrial smooth muscle which encompasses the adenomatoid tumor in a fashion analogous to the muscular encirclement of ectopic islands of endometrium in adenomyosis of the uterus. This contention is supported by the absence of smooth muscle bundles in adenomatoid tumors occurring in sites where muscle is not normally present. Smooth muscle is not found in adenomatoid tumors of the ovary, mesentery, omentum, or adrenal gland, and smooth muscle in intratesticular extensions of adenomatoid tumors arising in the epididymis has not been observed. Furthermore, muscle bundles were also absent from those portions of the three uterine tumors in our series that had extended beyond the myometrium onto the serosal surface. Of course, it is impossible to completely dismiss the possibility of a collision tumor composed of a leiomyoma and an adenomatoid tumor as an explanation for some rare lesions of the uterus or spermatic cord. Intermingled fibrous tissue and elastic tissue, however, may well be produced by the neoplastic cells, and some consider adenomatoid tumors to be biphasic neoplasms.

The preponderance of evidence indicates that adenomatoid tumors are a type of benign mesothelioma. Ultrastructural and histochemical studies have supported this notion. One epididymal adenomatoid tumor with Weibel-Palade bodies and multilayered basal lamina, ultrastructural features usually associated with endothelium and vascular neoplasms, has been briefly described. We are skeptical of these findings until they are corroborated by others since we are keenly aware of the difficulty in always being able to confidently distinguish normal dilated capillaries from some of the neoplastic channels in angiomatoid types of adenomatoid tumors.

The characteristic subserosal location of adenomatoid tumors is in keeping with the mesothelial theory of origin. Direct continuity and transition between the neoplastic cells and overlying serosal mesothelial cells was observed in our series and in several other reported cases of uterine and extrauterine adenomatoid tumors. Such continuity, however, is not always obvious and we were unable to demonstrate it with multiple sections in most of our cases. There are plausible explanations for this phenomenon. Adenomatoid tumors may arise from inclusions of mesothelium incorporated into subserosal connective tissue or myometrium. The presence of fibrous adhesions overlying the tumor in three of our cases was impressive. In two of these cases mesothelial inclusion cysts had undergone metaplasia into tubal-type epithelium producing the lesion known as endosalpingiosis. Patients who develop adenomatoid tumors may have a labile peritoneum with a propensity to form a variety of proliferative lesions of mesothelial cells. Some adenomatoid tumors conceivably could arise directly from uterine mesenchymal cells which have retained a potential to differentiate into mesothelial cells. This theory, however, would not account for their universal location beneath the serosa or in the outermost portion of the uterine wall. All 11 of the tumors in our series which could be appropriately...
evaluated were within 5 mm of the uterine serosal surface as were seven of the 14 cases reported by Tiltman.\(^{28}\) The 14 uterine lesions reported by Youngs and Taylor\(^{30}\) were "invariably found beneath the serosa" and all 12 in the series of Lee and associates\(^{15}\) were subperitoneal. Whether arising directly from mature mesothelial cells of the uterine serosa, from mesothelial inclusions or from less differentiated mesenchymal cells of the uterine wall, the evidence is overwhelming in support of the classification of adenomatoid tumors as benign mesotheliomas.

Because adenomatoid tumors have been more widely publicized as lesions of the fallopian tube than of the uterus, problems in diagnosis are especially likely to occur when they are incidentally discovered in a hysterectomy specimen. The solid and adenoid types may be mistaken for a metastatic carcinoma, as occurred in one of our consultation cases, and the angiomatoid and cystic types may be misinterpreted as angiomas or angiomyomas. An awareness of the characteristic four histologic patterns of adenomatoid tumors and their transitional forms coupled with an appreciation of their usual gross appearance and topographic location in the uterus will greatly aid in proper diagnosis.

References