INVESTIGATIONS ON UTERINE FATTY LESIONS

HENRYK SOŚNIK, KATARZYNA SOŚNIK

Department of Pathomorphology, Regional Specialist Hospital, Wroclaw, Poland

Uterine fatty lesions (UFLs) continue to arouse great interest because of their rare occurrence and unknown histogenesis. The aim of the study was to determine the occurrence of UFLs and the dynamics of their development, as well as to evaluate the histopathology and relationship with regressive stromal changes. 3750 uterine specimens were reviewed during the period between 1984 and 2003. In the examined series of 3750 uteruses removed due to tumors or prolapse, 50 cases with four types of changes were chosen: adipocytic metaplasia of primary uterine leiomyomas (70% of cases), adipocytic metaplasia of interlobular stroma of primary uterine tumors (16%), adipocytic aggregates in the uterine muscle (8%), and pure lipomas (6%). Additionally, the cases were divided into three groups depending on the extent of fatty changes. Group 1 (48% of cases) consisted of cases in which less than 25% of the changes were present in the examined material. In group 2 (28% of cases) the fatty changes were between 25 and 50%. In group 3 (16% of cases) fatty changes constituted more than 50% of the examined specimen. The extent of adipocytic changes was connected with patient age, being significant between groups 1 and 3 (p < 0.01). Regressive stromal changes in leiomyomas occurred more often in middle-aged patients, with stage 2 lipomatosis than in other subgroups. Among 46 cases of UFLs two patients were diagnosed with a coexisting malignant uterine neoplasm (4.35%). In four patients with muscular lipomatosis, two were diagnosed with a coexisting malignant uterine tumor too (50%).

Conclusions: 1. Uterine fatty lesions are rarely diagnosed, although they occur more often than previously thought. 2. Mixed tumors predominate over pure lipomas. 3. The histogenesis of these lesions seems to be multi-factorial, considering the different types of UFLs. 4. The extent of uterine fatty metaplasia positively correlated with the age of operated women. 5. The coexistence of UFLs with other malignant uterine neoplasms is accidental.

Key words: uterine fatty lesions, uterine carcinomas, women age.

Introduction

The presence of fatty tissue in the myometrium is abnormal. The above-mentioned alteration has been interpreted either as a lipomatous degeneration, or as metaplasia of smooth muscle cells, or as a real neoplasm [1-9], frequently called lipoleiomyoma [10-15] or fibrolipoleiomyoma [16-18], lipomatous tumors of the uterus [19, 20], lipomatous lesions [21], lipomatous neometaplasia [22], and according to Salm [23] as fatty fibroids. Resta et al. [20] and Sieinski [22] also distinguished angiolipoleiomyoma, underlining that the vascular component was always detectable but never abundant.

Lipomatous uterine tumors primarily occur in postmenopausal women [1, 22]. They are uncommon [2, 15, 20, 24]. Their frequency of occurrence ranges between 0.001% and 2.1% [1, 2, 11, 13, 15, 19, 21-23]. Extensive sampling of all 620 uterine tumors by Dellachá et al. [12] enabled them to diagnose 7 cases of lipomas, accounting for 0.8%.
Considering the location of the lesion, no portion of the uterus is favored [24]. Descriptions of endocervix lipomas are also known [3, 9]. The above-mentioned constitute 3.6% according to Brandfass and Everts-Suarez [24] and 14.3% according to Salm [3].

Histochemically, all tumors contain neutral lipids, but also may contain phospholipids, glycolipids, and all hydropic unsaturated lipids [21]. The difference between lipoma and lipoleiomyoma is not as prominent as it may seem [10, 19]. A leiomyosarcoma arising from the uterine lipoleiomyoma, which had metastasized to the vaginal wall, was described by Scurry and Hack [25]. Wojnar [17], Tolkta-Pluszczyk and Bogajewski [16], and Di Gesu et al. [8] reported cases of uterine lipomas coexisting with other malignant neoplasms of the uterus. In the material of Brandfass and Everts-Suarez [24] the coexistence was observed in 4.16%, according to Sieinski [22] in 27.3%, while Lin et al. [11] observed the coexistence in 37.5% of cases.

Due to the significant diversity of literature data the authors of the study analyzed their own material obtained from one department of a regional specialist hospital.

Material and methods

The studied material obtained between 1984 and 2003 was subjected to histopathological analysis. Considering the 3750 uterine specimens removed during surgery (because of a tumor or prolapse), samples were collected from the most suspicious lesions, uterine muscle, mucous membrane of the cervical canal and uterine cavity. All sections were stained with hematoxylin and eosin. Additionally, 8 UFLs, 5 adenoids, 3 leiomyomas, and 3 uterine muscular wall specimens were subjected to toluidine staining. In selected cases Sudan III staining was performed, as well as van Gieson, Mallory and Gomori stainings. Three stages of lipomatosis were distinguished: 1 (+) – below 25%; 2 (+++) – between 25 and 50%; 3 (++++) – more than 50% of adipocytic cells in the analyzed specimen. Additionally, four topographic groups of lipomatosis were diagnosed: 1 – lesions located in the parenchyma of the primary tumor, 2 – lesions located in the interlobular connective tissue of the primary tumor, 3 – in the uterine muscle, and 4 – the so-called “pure lipomas”. Student’s t-test and χ² test were used during analysis. P < 0.05 was considered as statistically significant.

Results

Uterine fatty lesions were observed in 50 patients, which comprised 1.33% of all investigated specimens. Adipocytic lesions were observed only in the body of the uterus. The uterine cervix and some enucleated leiomyomas were free of UFLs. The age of operated patients ranged between 14 and 84 years (mean: 48.61 ± 10.7 years), and in the case of UFLs between 30 and 83 years (mean: 50.4 ± 10.8 years). The difference was statistically insignificant (Table I).

Table II presents the dynamics of uterine lipomatous changes. Mild lipomatous changes of the primary tumor were observed more frequently (48%). Moderate lipomatous changes were diagnosed in 28% and “pure lipomas” in 16% of cases. The remaining 8% were observed in the parietal wall of the uterus.

The stage of the lipomatous lesion was dependent on patient age. The increase was gradual; however, the mean age difference between patients with mild and severe lipomatosis was significant (p < 0.01).

Considering the 4 histotopographic subtypes of UFLs, in 35 cases the lipomatous changes were noticed in the parenchyma of the leiomyoma (70%), including 18.22% of cases with advanced hyaline lesions (Figs. 1-3).

There were 16% of cases in the second histotopographic group (Fig. 4).

The third group comprised 4 cases of lipomatosis of the uterine parietal muscle (8%) (Fig. 5).

| Table I. Patient age and the type of specimen studied | N | % | AGE OF OPERATED WOMEN |
|---|---|---|---|---|---|---|
| | | MIN. | MAX. | x ± SD |
| NO. | TYPE OF MATERIAL | | | |
| 1. | uterus: tumor-free | 3111 | 82.96 | 14 | 74 | 50.71 ± 12.56 |
| 2. | uterine cancer without myomas | 339 | 9.04 | 26 | 84 | 57.20 ± 12.56 |
| 3. | isolated myomas | 124 | 3.30 | 23 | 72 | 41.33 ± 9.48 |
| 4. | myomatous uterus and coexisting uterine malignant neoplasm | 107 | 2.85 | 33 | 79 | 56.57 ± 9.21 |
| 5. | uterine lipomatosis | 50 | 1.33 | 30 | 83 | 50.40 ± 10.80 |
| 6. | uterine adenomatoid tumor | 13 | 0.34 | 40 | 52 | 46.76 ± 3.00 |
| 7. | uterine angiomyomatosis | 6 | 0.16 | 47 | 67 | 54.83 ± 8.03 |
| Summary | 3750 | 99.96 | 14 | 84 | 48.61 ± 10.70 |

N – number of cases, % – percent, Min. – minimal, Max. – maximal, x ± SD – average plus minus standard deviation
Figure 6 presents a fully mature adipose tissue penetrating from the subserous space of the body of the uterus, which together with the nerve and vessels could lead towards the development of “pure lipomas”. In our own material they constituted 6% of all UFLs cases (Fig. 7).

Table III presents the coexistence of hyalinized myomas subject to lipomatous transformation. There was no relationship between the above-mentioned parameters, although hyalinization occurred more often (57.14%) in middle-aged patients (46.88 ± 5.9 years) with moderate lipomatous changes.

### Table II. Stage of lipomatosis, depending on the age of operated female patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Stage of lipomatosis</th>
<th>N</th>
<th>%</th>
<th>Age of operated women</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MIN.</td>
<td>MAX.</td>
</tr>
<tr>
<td>1.</td>
<td>(+) less than 25% of lipomatous component</td>
<td>24</td>
<td>48</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>component in the primary tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>(++) between 25 and 50% of lipomatous component</td>
<td>14</td>
<td>28</td>
<td>33</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>component in the primary tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>(+++) more than 50% of lipomatous component</td>
<td>8</td>
<td>16</td>
<td>43</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>component in the primary tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>uterine muscle lipomatosis</td>
<td>4</td>
<td>8</td>
<td>43</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N – number of cases, % – percent, Min. – minimal, Max. – maximal, x ± SD – average plus minus standard deviation

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![Fig. 1. Adipocytic cells tend to form clusters in a highly hyalinized environment of the primary tumor. HE, medium magnification](image1)

![Fig. 2. Adipocytic cells scattered throughout hyaline lesions. SIII staining, low magnification](image2)

![Fig. 3. Presence of free lipids in the lipocytes and lumen of small vessels, SIII, medium magnification](image3)

![Fig. 4. Adipose metaphasia in the interlobular connective tissue of the tumor, S-100, low magnification](image4)
Adipose cells often were located near blood vessels (Figs. 8, 9). Their cytoplasm was abundant in lipids, which were also visible in the lumen of some vessels (Fig. 3).

Surprisingly, the differentiation of adipocytic cells is observed mainly in the part of the tumor with edematous-hyaline changes. These cells, initially small with a strongly stained nucleus and clear cytoplasm, became swollen and created clusters of normal-sized adipocytic cells (Figs. 10, 11). Such adipose cells were rarely accompanied by inflammatory mononuclear cell infiltration. Intense inflammatory infiltration was observed only once; noteworthy, it was separated from the adipocytic cell clusters (Fig. 12). Mononuclear cell infiltrations were observed in 11 cases of lipomatosis, which constituted 22% of all UFLs. They were observed most often in cases of moderate intensity lesions (28.6%), then mild intensity lesions (25%), and pure lipomas 12.5%. In 7 of 8 UFLs cases an insignificant number of mastocytes was noticed. Conversely, mastocytes were not found in adenomatoid tumors (5 cases), leiomyomas (3 cases) and 3 specimens of normal uterine muscle.

Table IV presents results considering the stage of the lipomatous changes and number of thick-walled blood vessels. No correlation between them was seen.

**Fig. 5.** Lipocytes dissecting uterine myometrium, HE, low magnification

**Fig. 6.** Adipose tissue with nerves (top) and vessels (center) penetrating into the uterine subserous space, HE, high magnification

**Fig. 7.** Uterine “pure lipoma”. Uterine muscle (left side) surrounded by adipose tissue, HE, low magnification

**Fig. 8.** A complex of lipocytes around a thin-walled large vessel in hyalinized environment, HE, medium magnification

**Fig. 9.** Lipocyte system running along the small vessel, surrounded by small lymphocyte inflammatory infiltration, HE, medium magnification
Thick-walled blood vessels were in no direct connection with the adipose cells (Fig. 13).

In 4 (8%) of 50 cases of UFL, a coexistent malignant uterine neoplasm was diagnosed. Table I also...
demonstrates that there were 339 malignant neoplasms in all (3700) diagnosed uterine specimens (9.16%).

Conclusions:
1. Uterine fatty lesions are rarely diagnosed, although they occur more often than previously thought.
2. Mixed tumors predominate over pure lipomas.
   1. The histogenesis of these lesions remains unknown, although it seems to be multi-factorial, considering the different types of UFLs.
   2. The extent of fatty metaplasia was positively correlated with the age of operated patients.
   3. The coexistence of UFLs with other malignant uterine neoplasms is accidental.

Discussion

Our study results provided many insights into the already existing histogenetic hypotheses of UFLs, presented by Brandfass and Everts-Suarez [24].

The evidence of the presence of neutral lipids, not only in adipose cells, but also in the vascular lumen of the hyalinized leiomyoma, can support the suggestion of the role of lipid and other metabolism disturbances which are observed during the postmenopausal period [4, 11, 27]. Therefore, it is necessary to perform prospective, anthropologic, biochemical, and pathological investigations in female patients with uterine myomas.

Another interesting observation was the formation of adipose cells in the edematous-hyaline environment of the primary tumor. Such cells developed characteristic features, which made them unsusceptible to atrophy, even in the hyalinized tumor, which also was presented by Honoré [18]. It is hard to say whether primary embryonal cells with the possibility of multi-directional differentiation really exist. Meinhof and Bersch [28] considered them as a necessary element in the development of “pure lipomas”. However, Cliff [29] investigated the ultrastructure of the granulation tissue derived from

Fig. 13. Average amount of thick-walled vessels with small hyalinization foci, at a distance from adipose cells, HE, high magnification

<table>
<thead>
<tr>
<th>AMOUNT OF VESSELS</th>
<th>LIPOMATOSIS (+)</th>
<th>LIPOMATOSIS (+++)</th>
<th>UTERINE MUSCLE LIPOMATOSIS SUMMARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>small amount</td>
<td>7</td>
<td>35.00</td>
<td>5</td>
</tr>
<tr>
<td>medium amount</td>
<td>2</td>
<td>10.00</td>
<td>3</td>
</tr>
<tr>
<td>large amount</td>
<td>11</td>
<td>55.00</td>
<td>6</td>
</tr>
<tr>
<td>summary</td>
<td>20</td>
<td>100.00</td>
<td>12</td>
</tr>
</tbody>
</table>

N – number of cases, % – percent, Min. – minimal, Max. – maximal, x ± SD – average plus minus standard deviation

Table IV. Coexistence of thick-walled blood vessels and stage of lipomatosis

13
healing wounds, and observed no presence of cells resembling mesenchymal embryonal cells.

Novel immunocytochemical investigations demonstrated the presence of desmin antigens in adipose cells, which might suggest the hypothesis of their muscular origin [14, 20]. Thus, the degenerative fatty uterine leiomyocytes would gain the ability to proliferate and form UFLs. Cytogenetic investigations speak in favor of the proliferative ability of the above-mentioned cells [15, 30, 31]. This phenomenon was also observed in our statistical analysis. Similar suggestions were presented by Ikonomou [32]. However, after analysis of his study material the mean age of female patients with “pure lipoma” forms was insignificantly lower than that of mixed forms.

In general, one is forced to wonder if the origin of the true lipomas is the same as that of mixed tumors. It is more likely that the pure lipomas arise from misplaced lipoblasts, which were observed by Kuttassow [33], or by other cell remnants, and that the mixed types are the result of fatty degeneration or metaplasia from leiomyomatous tumors [24].

Uterine fatty lesions probably have a complex histogenesis [9]. Ultrastructurally, evidence was obtained that in the course of differentiation or recently formed vessels fibroblast-like cells are incorporated into vascular walls to become adventitial cells. These cells may undergo conversion to vascular smooth muscle cells [29]. Indirect evidence was added for the “vascular” origin of leiomyoma and it was suggested – on the basis of experimental studies – that the mother cell was the multipotential adventitial fibroblast. Thus, the fibrolipoma can be considered as a tumor expressing three basic potencies of a single cell, namely, the adventitial fibroblast [18]. The observed tendency of adipose cell alignment along the vessels might be evidence of the hypothesis considering the development of lipocytes within the uterine leiomyomas. Finally, the perivascular detection of arcades of perivascular immature mesenchymal cells with differentiation into lipocytes supports the hypothesis of neometaplasia presented by Sieinski [22] and Resta [20].

It was evident, also in our material, that the mixed type of growth occurs more often than the “pure” type of UFLs, an indication that the process of fatty metamorphosis is gradual. Salm came to the same conclusions [23].

Considering the analysis of data obtained by Jacobs et al. [10], all of the seven tumors were composed of an admixture of mast cells and eosinophils. The lipoleiomyoma generally contained considerably more mast cells than the leiomyoma and adjacent myometrium in the same specimen, or in leiomyomas of 30 randomly selected uterines examined for mast cell content. Mast cells are said to enlarge with increased protein quantities, such as conditions of hyperemia with vascular dilation and stasis. Mast cells are thought to accompany degenerative lesions, possibly by liberating histamine, which induces hyperemia. A similar phenomenon was observed in some cases of our UFLs. According to Pounder et al. [19], scattered mast cells and eosinophils may be found, but were not observed in any of the three presented cases.

One of the presented hypotheses described by Brandfass and Everts-Suarez [24] was the “implantation” hypothesis of UFL development. Dhakar et al. [7] described 3 pure lipomas – all in postmenopausal women. There was a history of 3 caesarian sections in patient number 3. An endocervical lipoma was also found in a 73-year-old female patient, three years after cervical amputation [9]. We also described a case of liposarcoma in the uterine body, which was observed many years later after leiomyoma enucleation in a 71-year-old woman [26].

Regardless of the amount of the adipose component that was included in the otherwise conventional leiomyoma, the diagnosis of lipoleiomyoma was confirmed by Aung et al. [15]. In the fully developed uterine lipoma it is difficult to state whether the lesion originally arose in a leiomyoma and eventually replaced it completely, or developed de novo in the myometrium.

Thus, the nature of the lesions and their pathogenesis remain obscure and there is no overall agreement as to their pathogenesis and nomenclature [11, 19, 21].

As previously mentioned, uterine fatty lesions are uncommon [2, 20, 24]. According to Akbulut et al. [27], their prevalence ranged between 0.03% and 0.8%. Considering our own material, UFLs were diagnosed in 1.33% of cases. Together with the increased number of collected samples the above-mentioned percentage would also increase.

Brandfass and Everts-Suarez [24] collected 96 cases of UFLs, including 33 cases of pure lipomas, and 63 of mixed lipomatous tumors. Therefore, mixed lipomatous tumors occur twice as often as pure lipomas. Our study results were completely different. Mixed tumors exceeded 15-fold the occurrence of pure lipomas.

In conclusion, the exact frequency of these tumors remains unknown, because most cases are not referred, due to their benign behavior, and also because in most circumstances the fat component represents a more or less cellular population in the context of common leiomyomas of the uterus [1, 9, 10, 15, 20]. On the other hand, most tumors remain undetected because the lipomatous component may be focal and irrelevant, or might be considered as remnants of entrapped lipocytes [20]. The lipomatous component may also be misinterpreted as a vessel space or artifact [11].

Finally, we would like to respond to the issue of the coexistence of UFLs with other malignant uterine neoplasms. According to Dilek et al. [34] uterine lipomas coexisting with cervical cancer were not previously reported, but Poniatowska described a similar case in Polish literature just in 1965 [5].
Di Gesu et al. [8] observed adenocarcinoma focis on the endometrium surrounding the uterine lipoma, which might suggest that adipose tissue could have probably favored and increased the local conversion of androgens to estrogen, possibly contributing to the development of endometrial cancer. This hypothesis is interesting. Considering our material, 4 patients (8%) were diagnosed with a coexisting malignant uterine neoplasm. Of the 3700 uterine samples, 539 were diagnosed as malignant neoplasms (9.16%). Similar data were obtained by other authors [11, 21, 24]. These observations do not allow the occurrence of UFLs to be associated with other uterine malignant neoplasms, due to the small number of cases.

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The authors declare no conflict of interest.

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33. Kuttassow J. Akusch Dzensk Boln 1911; 26: 12 (quoted according to 34).

Address for correspondence

Henryk Sośnik MD, PhD
ul. Jaracza 82 B/4
50-305 Wrocław, Poland
tel. +48 71 791 41 29
fax +48 71 328 01 23
e-mail: abr@kn.pl