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Smooth Muscle Tumours of the Uterine Corpus: a Clinicopathologic Study with Immunohistochemical Aspects

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Abstract. *Background: Based on a clinicopathologic study conducted at the University of Rostock, Germany, between 1/1997 and 6/2003, the histological records of 1761 patients who had been hysterectomized were evaluated. 1422 of these patients were suffering from smooth muscle tumours: 1389 were diagnosed as multiple leiomyomas, 26 as leiomyomas of uncertain malignant potential and 7 as leiomyosarcomas. Patients and Methods: The data about the microscopic findings were obtained by use of both conventional histology (HE and Giemsa) and immunohistochemistry with markers for leiomyosarcomas (desmin, actin, sm-actin, myoglobin, vimentin, MIB1) and evaluated by statistical methods. Three case reports are also presented: 2 patients with leiomyosarcoma and 1 patient with an UMP tumour. Results: The statistical evaluation included the frequencies of the different tumours subdivided into age groups, their localizations (with 23 distinctions), the associated microscopic findings (with 12 distinctions and most important combinations) and, finally, the number of tumours per patient and their (grouped) sizes. The case reports showed the presence of nuclear atypia, a heightened mitotic index and tumour cell necrosis. Immunohistochemical methods confirmed the histological diagnosis of a leiomyosarcoma. Conclusion: In accordance with earlier studies, more than 95% of the smooth muscle tumours were leiomyomas. Leiomyosarcomas were rare (<1% in our study). In 3 out of 7 cases, a leiomyosarcoma had its origin in a leiomyoma.*

Uterine leiomyomas are the most frequent smooth muscle tumours of the uterus, whereas uterine leiomyosarcomas are rare. The different types of smooth muscle tumours, their frequencies and correlations, as well as their localization and the associated microscopic findings, were the subject of the present study. Further, two case reports of patients suffering from leiomyosarcoma and an additional one of a patient suffering from a leiomyoma of uncertain malignant potential are presented.

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Key Words: Leiomyoma, leiomyoblastoma, leiomyoma of uncertain malignant potential, leiomyosarcoma, immunohistochemistry.

Patients and Methods

The following results are based on a clinicopathologic study conducted at the University of Rostock, Germany, from January 1, 1997, to June 30, 2003. In this study, the histological records of 1761 patients who had been hysterectomized were evaluated. One thousand four hundred and twenty-two of these patients were suffering from smooth muscle tumours: 1389 (97.7%) were diagnosed as multiple leiomyomas, 26 (1.8%) as leiomyomas of uncertain malignant potential (UMP tumour) and 7 (0.5%) as leiomyosarcomas. The data about the microscopic findings were obtained by use of both conventional histology (hematoxylin-eosin (HE) stain and Giemsa stain) and immunohistochemistry with markers for leiomyosarcomas (desmin, actin, sm-actin, myoglobin, vimentin and MIB1).

Results

Figure 1 illustrates both the absolute and relative values of the frequency of smooth muscle tumours. Additionally, each bar in the chart is divided into 7 segments. The length of each segment represents the frequency (resp. relative frequency) of the tumours within the age group under consideration, *i.e.* up to an age of 30, between 31 and 40, 41 and 50, 51 and 60, 61 and 70, 71 and 80 and older than 80 years.

A total of 1333 (93.7%) smooth muscle tumours were located in the corpus of the uterus, 14 (1.0%) in the cervix and 42 (3.0%) in the corpus as well as the cervix. Further, we observed a strong dominance in the age group 41-50 independent of the localization. Some more details are given

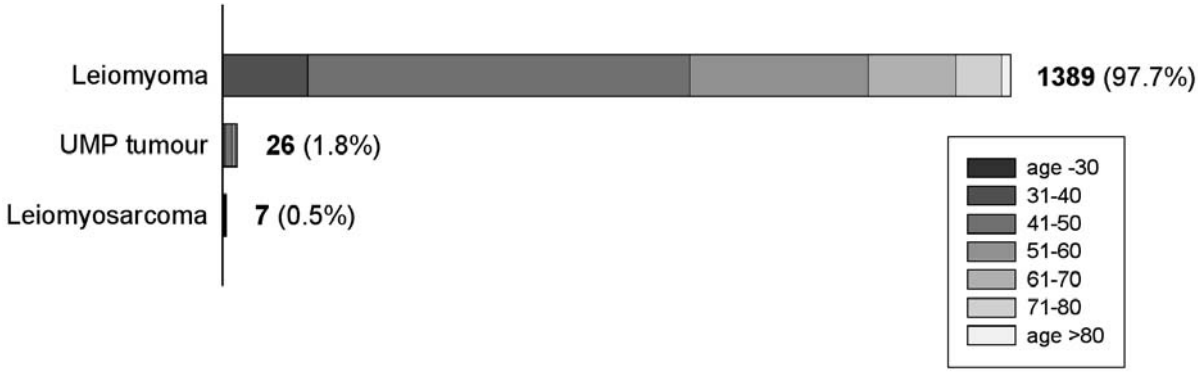

Figure 1. *Frequencies of the smooth muscle tumours.*

Table I. *Localization of the tumours.*

	Localization		
Age	Corpus	Cervix	Both
≤30	0	0	0
31-40	151	2	3
41-50	649	7	16
51-60	308	2	4
61-70	137	2	13
71-80	73	1	6
>80	15	0	0
Total	1333	14	42
Total (in %)	93.7	1.0	3.0

in Table I. The data of localization of the remaining 33 (2.3%) tumours are not reported. Finally, in Figure 2, we report on the localization of the tumours in full detail, *i.e.* subdivided in 23 localizations (L_1-L_{23}).

Figure 3 presents the microscopic findings (MF_1 - MF_{11}) and their combinations. Further details of the microscopic findings can be found in Table II. The relative frequencies given in the columns 2-8 of the Table represent the conditional distribution of the combinations given the occurrence of a microscopic finding in the localization under consideration. The localizations L_1–L_7 (Figure 2) were observed with the following relative frequencies: L_1 = 8.3%, L_2 = 33.1%, L_3 = 11.5%, L_4 = 9.0%, L_5 = 2.7%, L_6 = 14.8%, L_7 = 14.1%. Thus, 93.5% (and, together with L_{18}–L_{21}, 93.7%) of the microscopic findings were located in the corpus. Therefore, we could restrict our attention to the corpus only. Additionally, including all patients without any of these microscopic findings, the relative frequencies changed in an obvious way. This fact, however, had no influence on the interpretation of our results.

Figure 3 and Table II show that more than one microscopic finding can occur simultaneously. Indeed, we observed up to eight microscopic findings at a localization. However, there was only one (in 689 cases or 48.5%) and the number h(x) of cases decreased with an increase of the number (x) of microscopic findings (*i.e.* h(2) = 237 (16.7%), h(3) = 69 (4.9%), h(4) = 32 (2.3%), h(5) = 14 (1.0%), h(6) = 6 (0.4%), h(7) = 1 (0.0%), h(8) = 1 (0.0%). In 373 (26.2%) cases we found none (of these microscopic findings).

The data on tumour size (in cm) are grouped in 5 intervals of equal length and an additional one containing the remaining sizes (Figure 4). In case of more than one tumour, the size of the largest one was used. In analogy to Figures 1 and 2, the bars are subdivided into the segments associated with the age groups under consideration.

In Figure 1 it can be seen that 7 smooth muscle tumours were diagnosed as leiomyosarcomas. Three out of these 7 leiomyosarcomas had an origin in a leiomyoma.

Case Report 1

Anamnesis. The patient (44 years old) received medical treatment because of a prolapse of the uterus as well as uterine leiomyomas. She reported one spontaneous delivery, one stillbirth, one abortion, one EUP with laparoscopic salpingectomy, chronic adnexitis, pain and nausea during menstruation, otherwise normal menstruation. No hormone replacement therapy was used.

Clinical diagnosis. Anteflexion of the uterus was diagnosed, size of fist, mobile and coarse. A vaginal hysterectomy was performed without adnexectomy.

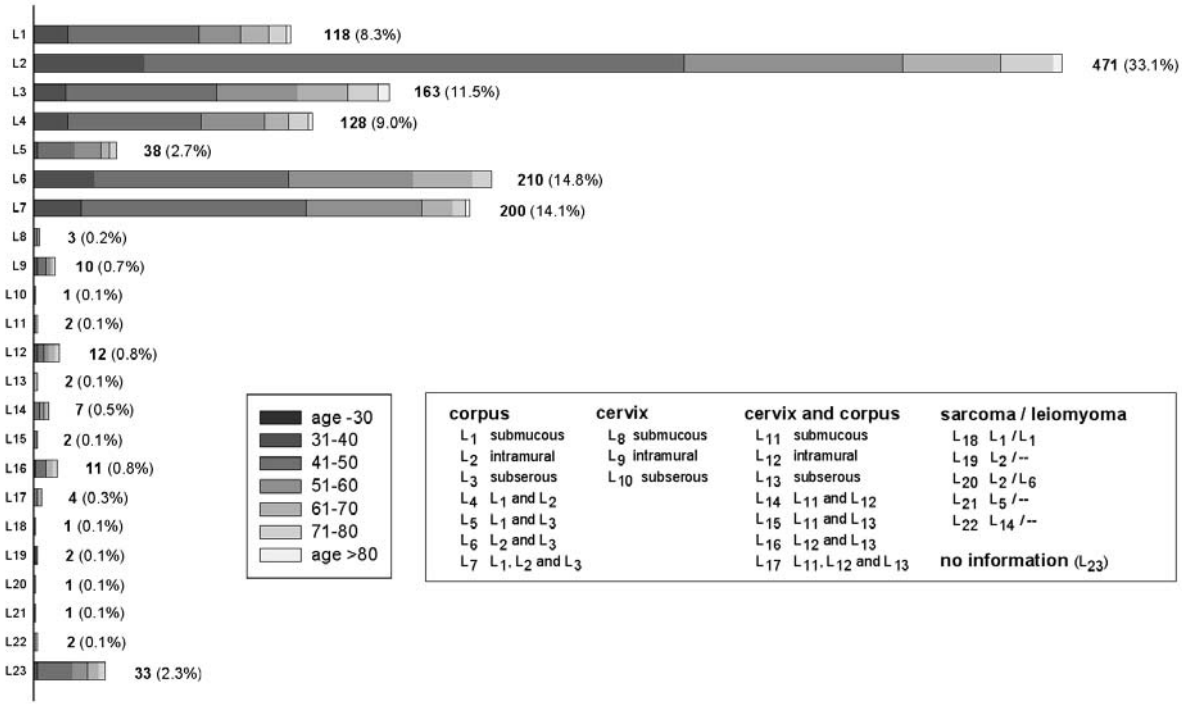

Figure 2. *More detailed localization of the tumours.*

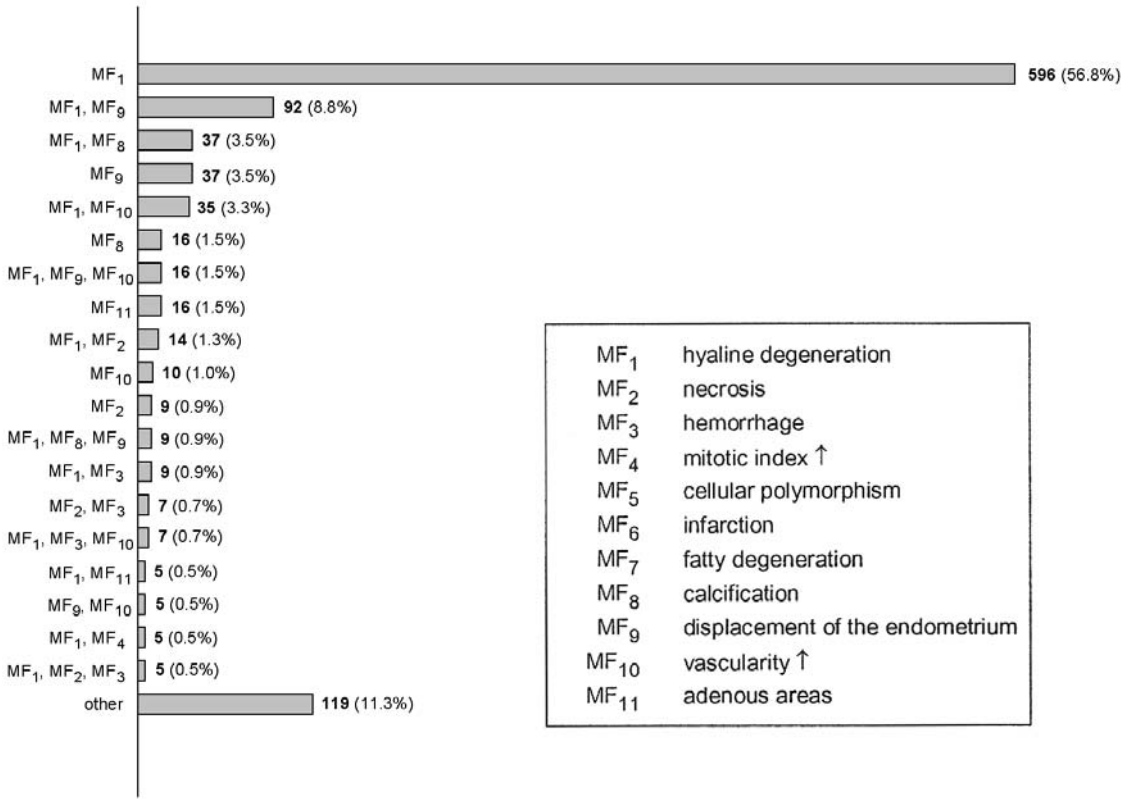

Figure 3. *Most frequent combinations of the microscopic findings MF_1–MF_{11}.*

Table II. *Relative frequencies (in %) of the microscopic findings given L_1–L_7.*

	Localization						
Microscopic findings	L_1	L_2	L_3	L_4	L_5	L_6	L_7
MF_1	44.3	49.7	87.8	53.1	58.1	61.7	61.3
MF_1, MF_9	11.4	11.8	1.0	9.4	6.5	3.9	12.7
MF_1, MF_8	1.4	3.7	3.1	2.1	0.0	7.1	3.5
MF_9	15.7	3.7	0.0	3.1	0.0	1.3	4.0
MF_1, MF_{10}	1.4	3.4	3.1	2.1	3.2	5.2	3.5
MF_8	4.3	0.9	1.0	1.0	3.2	1.3	2.3
MF_1, MF_9, MF_{10}	1.4	3.2	0.0	2.1	0.0	0.0	1.2
MF_{11}	2.9	1.7	2.0	5.2	0.0	0.0	0.0
MF_1, MF_2	0.0	1.1	1.0	0.0	3.2	0.6	3.5
MF_{10}	0.0	1.1	1.0	2.1	3.2	0.0	0.0
MF_2	2.9	0.6	0.0	0.0	3.2	1.3	0.6
MF_1, MF_8, MF_9	0.0	1.1	0.0	3.1	3.2	0.0	0.6
MF_1, MF_3	0.0	1.1	0.0	1.0	0.0	1.9	0.0
MF_2, MF_3	1.4	0.9	0.0	0.0	0.0	0.6	0.6
MF_1, MF_3, MF_{10}	0.0	0.9	0.0	1.0	0.0	0.6	0.6
MF_1, MF_{11}	0.0	0.6	0.0	1.0	0.0	1.3	0.0
MF_9, MF_{10}	0.0	0.6	0.0	0.0	0.0	1.3	0.0
MF_1, MF_4	0.0	1.1	0.0	0.0	0.0	0.0	0.0
MF_1, MF_2, MF_3	0.0	0.6	0.0	1.0	0.0	0.0	1.2
Other	12.9	12.1	0.0	12.5	16.1	11.7	4.6
Total	100	100	100	100	100	100	100

Preparation of the uterus. The size (in cm) of the uterus was 12.5 x 7.0 x 5.5cm. A yellow-coloured leiomyoma was visible which was 2.5 cm in diameter and had penetrated the uterine cavity.

Histology. The tumour was fibrogenic and of moderate cellularity, with partly elongated, moderately polymorphic nuclei and perinuclear vacuoles. The mitotic index was 3 per 10 high-power fields (HPF). In some parts, stronger atypism of nuclei with formation of giant tumour cells was observed. (Figure 5)

Immunohistochemistry. The tumour tissue showed a modest reaction to the marker sm-actin and a very positive one to desmin. Using the proliferative marker MIB1, the rate of proliferation was less than 1% in cancer cells and especially the giant cells were negative.

Diagnosis. A diagnosis of pleomorphic leiomyoma of the uterus with symblastic giant cells, was made.

Case Report 2

Anamnesis. A 42-year-old patient was admitted to the hospital because of spasmodic pain of the lower abdomen, which had occurred for a week, and night sweats. A computed tomography of the abdomen and a coloscopy had already been carried out. The level of CA 125 was high. Her history included two spontaneous deliveries, hypermenorrhoea, but no hormone replacement therapy.

Clinical diagnosis. An uneven, nodular and immobile tumour was detected during palpation, which was mostly indolent and filled the whole of the lower abdomen up to two fingers above the navel. Sonography showed the tumour to have several lumps and it gave a mainly solid echo. Ascitis was found in the lower abdomen as well as subhepatically. A laparotomy as well as a hysterectomy were performed together with adnexectomy on both sides, removal of the pelvic and para-aortal lymph nodes and biopsy of the omentum.

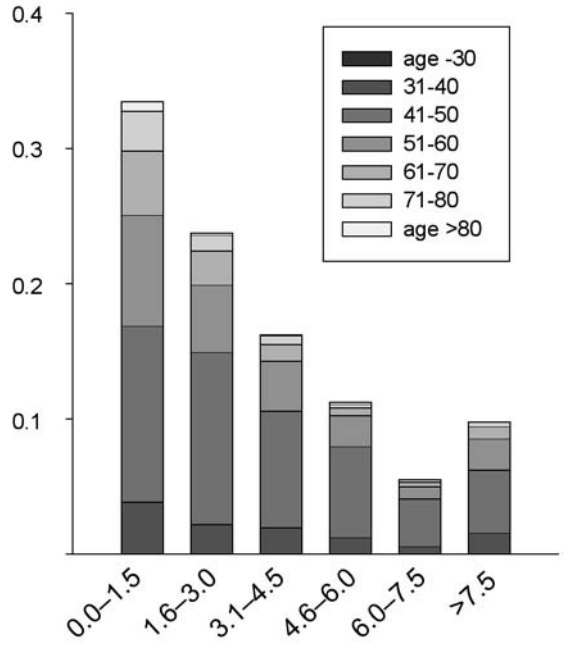

Figure 4. *Histogram of grouped tumour sizes.*

Preparation of the uterus. The size of the uterus was 16 x 15 x 7.5 cm. Several tumours were seen in the uterine cavity, the right fallopian tube and the serosa, reaching up to 11.5 cm in diameter. The sectional areas of the tumours were greyish-yellow, necrotic as well as bloody.

Histology. Fully grown leiomyoblasts, several short spindle cells with scarce myofibriles and a distinctive nuclear and cellular polymorphism with polyploidy were found in the tumours. The index of mitosis per 10 HPF was significantly increased. Corresponding to the macroscopic findings, necrosis and haemorrhages were visible.

Immunohistochemistry. The tumour tissue reacted positively to sm-actin, desmin and vimentin. The rate of proliferation was significantly increased (MIB1 over 70%).

Diagnosis. A diagnosis of leiomyosarcoma of the uterus having its origin in leiomyomatosis was made. Widespread metastases were present in both of the adnexes, in the peritoneum, in the greater and lesser omentum, as well as in the para-aortic lymph nodes.

Case Report 3

Anamnesis. The 52-year-old patient received medical treatment because of pain in the lower abdomen of four weeks' duration, along with an increase of girth and pain radiating to both the right leg and spine. The general gynaecological anamnesis was negative. Her further history was 1 spontaneous delivery, menopause since the previous year, but no hormone replacement therapy.

Clinical findings. Palpation showed a tumour, which was tender to pressure, clearly defined and reaching up to the navel. Sonography showed a heterogeneous tumour 15 cm in diameter. It was mostly liquid, but contained areas of clear echoes parietally as well. The uterine cavity could not be defined. An explorative laparotomy was subsequently conducted, which revealed a soft, magnified uterus with multiple leiomyomas, reaching up above the navel. Consequently, a hysterectomy was performed along with adnexectomy on both sides.

Preparation of the uterus. The uterus was 21x16x15 cm. A cyst, 12.5 cm in diameter and filled with a liquid rich in cholesterol, was located in the sectional area. It was necrotic at the paries, focally covered by fibrin and blood. Several leiomyomas, reaching up to 2.5 cm in diameter, were additionally found beneath the serous membrane in some areas of the paries.

Histology. The outside of the tumour was composed of highly cellular but still mostly isomorphic smooth muscle tissue. Nuclei of different sizes and mitoses appeared in some isolated cases. Pleomorphic tumour tissue with bizarre nuclei was located close to the tumour's edge. Plurinuclear giant cells were frequently found. The cystically degenerated area appeared towards the centre. Necroses with granulocytotic reaction appeared there as well, but also with foamy cellular mesenchymal reaction with occurrence of multinucleated giant cells. The mitotic index was increased (9-14 per 10 HPF) (Figure 6).

Immunohistochemistry. The tumour tissue, in areas of high cellularity reacted positive to desmin, myoglobin (Figure 7), sm-actin and actin (Figure 8). The pleomorphic, giant cellular part reacted positively for actin, while other markers were scarce or absent. Both the reactive foam cells, as well as the reactive multinucleated giant cells, reacted in a positive way to vimentin, CD 68 and lysozyme. Positive nuclei could be found in the pleomorphic parts of the tumour with MIB1.

Diagnosis. A diagnosis of undifferentiated leiomyosarcoma of the uterus (partly still differentiated into spindle cells, partly undifferentiated into pleomorphic giant cells) with central cystic degeneration, having its origin in one of several leiomyomas, was made.

Discussion

In accordance with earlier studies (1, 2), more than 95%

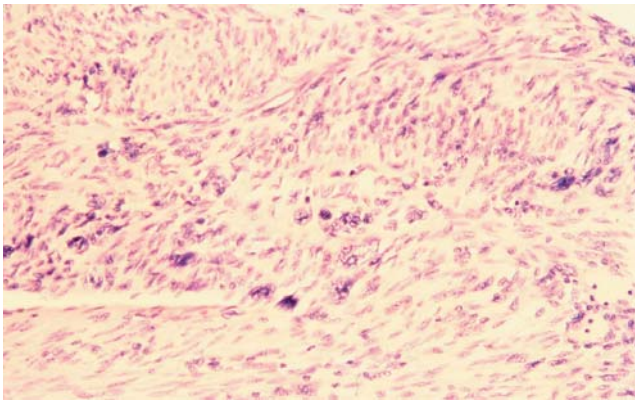

Figure 5. *Leiomyoblastoma: HE stain (80x).*

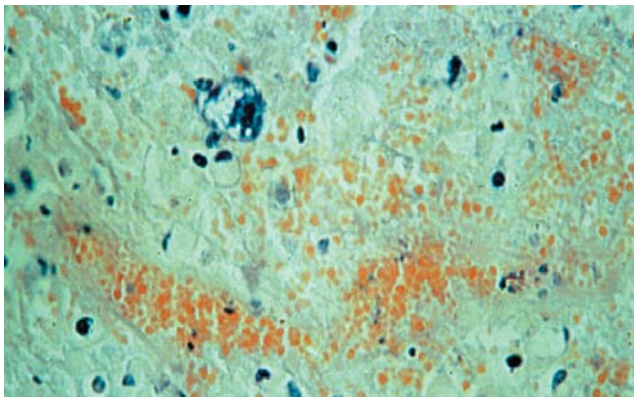

Figure 6. *Leiomyosarcoma: HE stain (80x).*

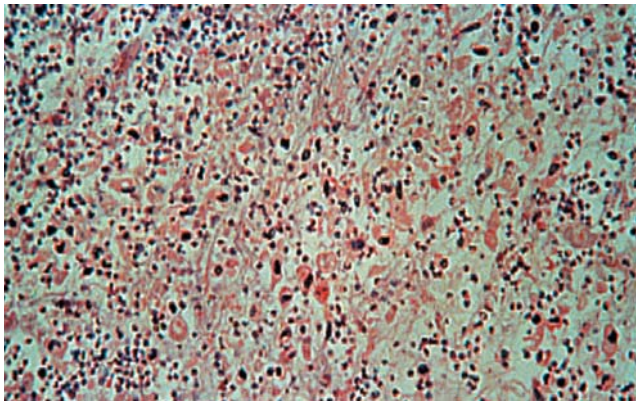

Figure 7. *Leiomyosarcoma: immunohistochemistry, anti-myoglobin (80x).*

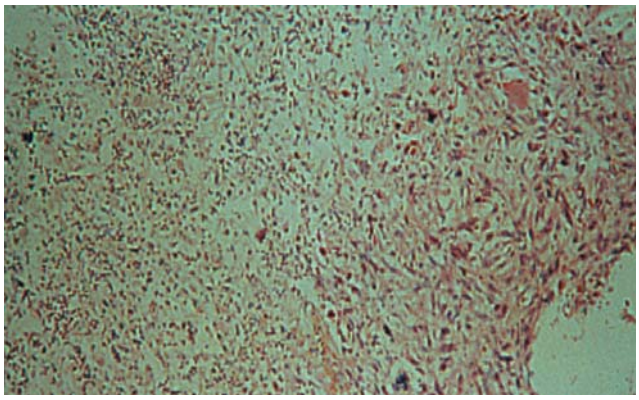

Figure 8. *Leiomyosarcoma: immunohistochemistry, anti-actin (80x).*

of smooth muscle tumours are leiomyomas. Mainly they are located in the corpus and are, in particular, intramural. They are usually observed in the 41-50 age group. The microscopic finding MF_1 (hyaline degeneration) is dominant, but there are many possible combinations with and without MF_1. Also, the number of different microscopic findings observed simultaneously in a single patient varies from 0 to 8. A similar large variance is also observed for the number of tumours of a patient as well as the size of the tumours. Furthermore, among the localizations L_1–L_7, the most likely microscopic finding is MF_1, followed by combinations differing from localization to localization.

The formation of a leiomyosarcoma out of a leiomyoma is usually thought of as an exceptional process (3-9); only a minority of authors have expressed a different opinion (10, 11). In this study, this aspect was verified in three out of seven cases by macroscopical, histological and immunohistochemical methods. Due to the small number of cases, however, the result is only of a limited statistical significance.

The generation of a sarcoma from the centre of a leiomyoma, as described in the literature, was confirmed in all cases (12). In diagnosing leiomyosarcomas of the uterus, the presence of nuclear atypia, a high mitotic index (of over 5 mitoses per 10 HPF) and coagulative tumour cell necrosis are the prominent criteria (12-17). Immunohistochemical tests are also of importance, as they lead to the confirmation of the histological diagnosis of a leiomyosarcoma. The most important markers are desmin, actin, sm-actin and myoglobin (15, 18, 19). Further investigations using vimentin and, particularly, MIB1 are recommended.

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