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Benign metastasizing leiomyoma of the uterus: documentation of clinical, immunohistochemical and lectin-histochemical data of ten cases

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Abstract The clinical histories of 10 women suffering from benign metastasizing leiomyoma (BML) after hysterectomy and information on lung lesions detected in these women are presented, together with corresponding data for 2 women with metastasizing leiomyosarcoma of the uterus for comparison: gross appearance, survival, and light microscopical, immunohistochemical and lectin-histochemical findings are reported. All patients with BML had undergone hysterectomy for uterus leiomyomatosus without any detection of sarcomatous lesions in the uterus wall. After a median period of 14.9 years intrapulmonary masses were detected by imaging techniques. On average, six nodules with a mean diameter of 1.8 cm were seen. Resection of the lesions was performed in all cases. The immunohistochemical and lectin-histochemical examination of the tumors included analysis of the proliferation-associated protein Ki-67, the p53 protein, estrogen and progesterone receptor, sarcolectin as an indicator of the presence of lymphokine macrophage migration inhibitory factor, antibodies and the labeled protein to assess galectin (galactoside-binding animal lectin)-dependent parameters, analysis of tumor vascularization (CD-34), and expression of bcl-2, vimentin, smooth muscle actin, desmin, and keratin. The lesions were characterized by low proliferation activity of 2.9% (measured with Ki-67), frequent hormone receptor expression (8 of the 10 cases presented hormone-specific receptors), low to moderate vascularization compared with metastases from the two uterine sarcomas, remarkable p53 overexpression and frequent expression of the lymphokine, the galectins and accessible binding sites. The median survival of the BML patients was 94 months after excision of the intrapulmonary lesions, and the maximum survival of the two sarcoma patients was 22 months. The results recorded in this patient sample with the methodology applied suggest that benign metastasizing leiomyomas are a slow-growing variant of leiomyosarcoma of the uterus, which becomes clinically apparent at a young age and progresses with low velocity.

Keywords Benign metastasizing leiomyoma of the uterus · Lectins · Sarcoma · Steroid hormones · Vascularization

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Introduction

With only a few dozen cases reported in the literature, benign metastasizing leiomyoma (BML) is obviously a rare disease, but nonetheless clinically interesting. The term was introduced by Steiner in 1939. It refers to a type of lesion characterized by well-circumscribed, singular or, often, multiple nodules of proliferating smooth muscle cells in the lungs of women with a history of hysterectomy [36]. Such lesions have commonly been reported in young premenopausal women, whose resected uteri have displayed leiomyomatous alterations without any indication of malignancy [1, 4, 9, 11–13, 26]. The nodules in the lungs are usually detected years after hysterectomy and are made up of benign-looking aggregates of smooth muscle cells with rather homogeneous nuclear size and volume rarely including mitotic figures [21–26, 36]. Any inflammatory response of the host tissue is scant. The size of the nodules can range from several millimeters to some centimeters. In addition to pulmonary lesions, lesions of the skin, mediastinum and bones have been described, with similar growth characteristics [1, 7, 11–13, 22, 24, 36–38, 40].

The pulmonary lesions have a benign morphology, which has led to the contradictory term 'benign metastasizing leiomyoma.' Several hypotheses on the histogenesis of these lesions have been suggested, which include

a) Metastases of low grade and undetected sarcomas of the uterus [12, 13, 25, 26]
b) Lung emboli of cells from a benign leiomyoma of the uterus [7, 14, 23]
c) Smooth muscle proliferation in various organs, such as the lungs and uterus, resulting from an abnormal sexual hormone status [5, 15, 16].

In order to extend the information available on the biological status of these lesions, expression of various markers has been monitored by immunohistochemistry and lectin-histochemistry. These include antibodies against desmin, keratin, smooth muscle actin, vimentin, and S-100 for diagnostic purposes, antibodies against estrogen and progesterone receptors for therapeutic strategies, antibodies against the Ki-67, p53, and blc-2 proteins for measurements of proliferation, potential suppressor oncogene modification and apoptosis, an affinity label against the macrophage migration inhibitory factor (MIF) for analysis of the lesion–host interaction, and the analysis of expression and binding capacities of galectins. These endogenous lectins have been proven to be involved in intercellular and cell–matrix interactions and in the regulation of cell migration and proliferation [2, 17, 18].

In this paper, we report clinical and morphological details of pulmonary lesions found in ten women who had been subjected to hysterectomy several years before the development of circumscribed pulmonary nodules. In addition, two cases of sarcoma of the uterus with lung metastases are included for comparison. A panel of immunohistochemical and lectin-histochemical probes was used for further characterization of the tumor cells.

Materials and methods

The patients were treated in the Department of Thoracic Surgery of the Thoraxklinik during the period 1988–1999. The ten women with BML had a history of hysterectomy performed for leiomyomatous uterus. Owing to the long period between hysterectomy and the detection of lung lesions in each case no tissue specimens from the resected uteri were available; however, detailed reports of the histological findings were accessible. Additionally, specimens from two women with sarcoma of the uterus (cases 11 and 12) were processed. All pulmonary lesions were resected by minithoracothomy or video-assisted thoracotomy. The histological diagnosis was based upon HE stains and additional immunohistochemical analyses, which routinely included antibodies against keratin, vimentin, desmin, smooth muscle actin, and S100. In addition, a panel of the following probes was applied to provide further insights into cellular characteristics: monoclonal antibodies against Ki-67 (MIB1), p53, bcl-2, estrogen and progesterone receptors (DAKO, Glostrup, Denmark) and three non-cross-reactive polyclonal antibody preparations against galectins 1, 3, and 8, prepared as described elsewhere [3, 31]. In addition, biotinylated galectins 1 and 3 and a binding protein for the macrophage migration inhibitory factor (MIF; sarcolectin) were prepared and covalently modified by label incorporation under activity-preserving conditions, as described elsewhere [20, 28, 31, 42].

The lectin histochemical procedures were based upon the avidin–biotin technique (ABC), as described previously [20, 27,28]. Immunohistochemical detection of hormone receptors, p53,bcl-2 and MIB1 (Ki-67) included pretreatment of the sections by microwaving (3×5 min at 600 W) and was performed as recommended by the protocol of the distributor. In both protocols, the conventional peroxidase–antiperoxidase method was used with horseradish peroxidase and diaminobenzidine/H_2O_2 as chromogens for visualization of the specifically bound probes. All cases were classified as positive if a dark-brown color was seen in all or in clusters of the tumor cells. Positive and negative controls were routinely performed, including processing of tumor sections known to be positive, and as quality control for any reagent to delineate any staining-dependent on binding of kit reagents the incubation step with the primary markers was omitted. Preadsorption of galectin-specific antibodies with an excess of the cognate antigen was undertaken to detect any antigen-independent (e.g. Fc part-mediated) binding, and competitive inhibition was routinely carried out in lectin histochemistry.

Three different self-written programs based upon the basic image-analyzing software DIAS (Institute of Visual Data Processing, University of Jena, Germany) were instrumented for quantification of the stained slides: one program for the measurement of the vascularization, a second for that of nuclear staining (hormone receptors, p53, Ki-67), and a third program for processing of the distribution of cytoplasmic staining (lectins and their antibodies). The areas of interest were selected interactively, and the images were grabbed by use of a color CCD camera (JVC TK1070) mounted on a Leica microscope MB2000 equipped with an objective ×40 (Fluorar, 0.75). The feature segmentation and intensity measurements were performed interactively on HSI-transformed images. A constant upper and lower intensity threshold guaranteed stable segmentation conditions. The details of the program structures are described in detail elsewhere [27, 29, 30]. At minimum, 300 cells or 50 vessels per case were measured. The mean staining intensity was graded (none = 0, intensive = 3), and the grade multiplied by the percentage of stained nuclei. The result was divided by 4 to calculate the immunoreactive score (range 0–12). The statistical analysis was performed with commercially available programs (NCSS, Number Cruncher Statistical System, Kaysville, Utah). The patients were followed up by repeatedly sending questionnaires to the house physicians and evaluating the responses carefully.

Results

The basic clinical data on the ten women who developed BML and the two women with metastasizing sarcomas of the uterus (SARC) are listed in Table 1. All women underwent potentially curative surgical resection of the pulmonary lesions; in case 9 both the right and the left lungs were operated on within a period of 10 months. Patient 1 developed a breast carcinoma at the age of 45 years. The resected breast carcinoma was staged T1cN0M0GIII and classified as an invasive ductal carcinoma. Patient 2 developed a solitary mass in the minor pelvis which was classified as leiomyoma, and patient 3, an ovarian lesion, which was radiologically consistent with a leiomyomatous mass. Only three patients had a history of smoking, with totals of 24 pack-years (case 3), 42 pack-years (case 5), and 15 pack-years (case 10). The intrapulmonary lesions were all located in the periphery of the lungs. A characteristic CT (case 2) is shown in Fig. 1.

Histologically, all lesions were circumscribed tumor-like masses consisting of proliferating smooth muscle fibers with a completely benign appearance. In particular,

Table 1 Clinical details of the ten cases with benign metastasizing leiomyoma (cases 1–10) and of two cases with intrapulmonary metastases of uterine sarcomas

Case no.	Age (years) at excision of uterus	Period to occurrence of lung lesions (years)	Survival (months)[a]	Therapy	No. of pulmonary nodules	Maximum size of pulmonary nodules (mm)	Additional tumor presentation
1	43	23	12[b]	Cytostatic	9	45	Mamma Ca
2	32	12	78	Cytostatic	24	16	Myoma of minor pelvis
3	30	11	101	Hormonal	7	10	Ovarian lesion
4	37	18	96 (+)	None	1	20	None
5	31	15	7	None	7	20	None
6	40	7	10	None	5	15	None
7	30	21	49	None	1	9	None
8	45	3	26	Hormonal	1	25	None
9	23	17	42	None	2	21	5 BML, both lung sides
10	40	22	6	Cytostatic	3	4	None
Median	35	16	94	–	4	16	–
11	53	5	6	Cytostatic	2	4	None
12	59	4	22 (+)	Cytostatic	1	2	None

[a]After excision of pulmonary lesions
[b]Patient has died

Table 2 Lectin- and immunohistochemical results in the ten BML cases investigated and the two cases of metastasizing uterine sarcoma (+ detectable expression of binding capacities, receptors, or presence of applied antigen)

Case no.	Gal-1	Gal-3	Anti-Gal-1	Anti-Gal-3	Anti-Gal-8	Sarcolectin	p53	Progesterone	Estrogen	bcl-2
1	+	+	+	+	+	+	+	–	–	–
2	+	+	+	+	–	+	+	+	+	+
3	+	+	+	+	–	+	+	+	+	–
4	+	+	+	+	–	+	–	+	+	+
5	+	–	+	+	+	+	+	+	+	+
6	–	+	+	+	–	+	–	–	–	+
7	+	+	+	+	+	+	+	+	+	–
8	+	+	+	+	–	+	+	–	+	–
9	+	+	+	+	–	+	+	+	+	+
10	+	+	+	+	–	+	–	+	+	–
11	–	–	+	–	–	–	+	+	+	–
12	+	+	+	+	+	+	–	–	–	–

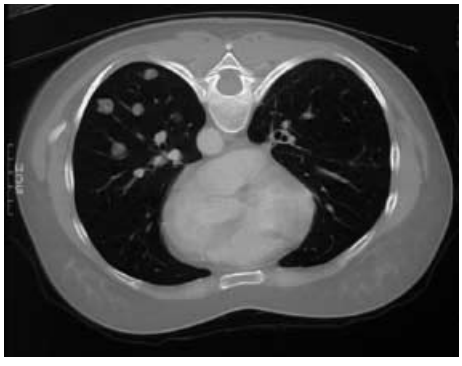

Fig. 1 High-resolution CT of case 2, showing four circumscribed intrapulmonary lesions

no mitoses, necrosis or inflammatory response of the host tissue were detected. A typical microphotograph of an HE-stained lesion is given in Fig. 2. No additional features, such as mature cartilage, fatty tissue, or myxoma-like formation, which are commonly present in pulmonary hamartomas, were noted.

The quantitative immunohistochemical and ligand histochemical findings are shown in Table 2. The majority of the lesions displayed an expression of hormone (estrogen and progesterone) receptors with strong intensity. Abnormal p53 expression was detected in seven of ten lesions. Expression of binding capacities for endogenous lectins and the presence of galectins 1 and 3 could be observed in at least nine of the ten cases of BML. Only minor differences were seen in the expression patterns of accessible binding sites for these two endogenous lectins, whereas galectin-8 (a tandem-repeat-type galectin) was only detected in three of the ten cases. Based on sarcolectin binding, the lymphokine macrophage MIF was present in the tumor tissue of all cases. Interestingly, this parameter has been correlated with favorable prognosis in lung carcinomas [22].

The results of the stereological analysis of tumor vascularization are presented in Table 3. The smallest ves-

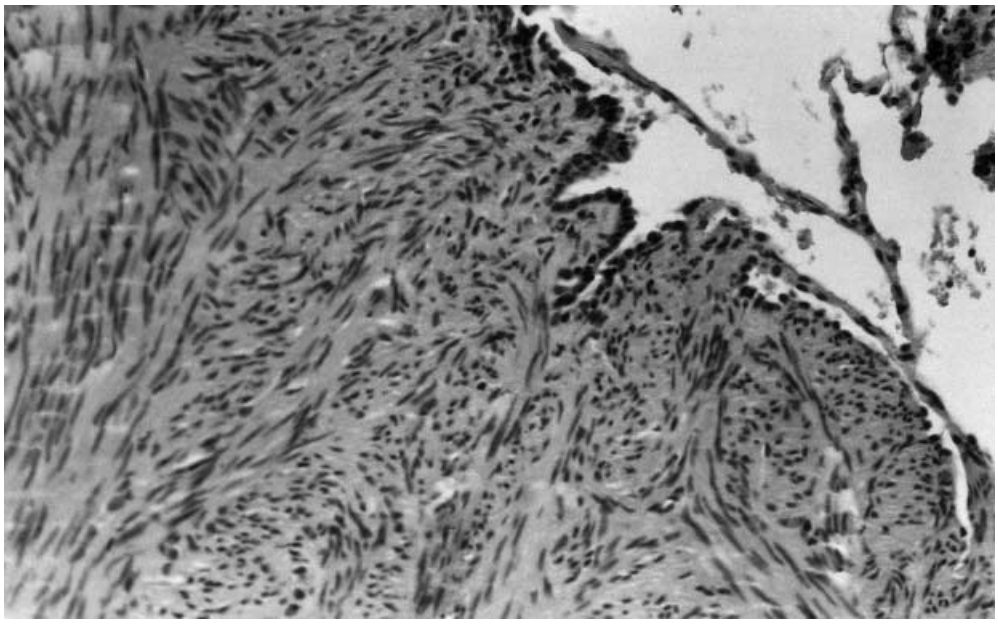

Fig. 2 Microphotograph of BML (case 2), showing characteristic spindle-shaped cells with low nuclear and cellular variance in size and shape. HE, ×300

Table 3 Tumor vascularization in the ten cases with BML and the two cases with metastasizing uterine sarcoma

Feature BML vessels	BML (n=10)		Sarcomas (n=2)	
	Mean	SD	Mean	SD
Area (μm^2)	154.3	78.4	176.1	110.3
Circumference (μm)	37.0	10.1	40.5	12.0
Minimum diameter (μm)	8.9	3.6	10.0	1.4
Circumference fraction La (%)	9.5	5.6	10.0	4.2
Area fraction Aa (%)	5.5	3.3	6.5	4.9
Perivascular connective tissue (‰)	4.3	2.0	5.5	2.1

Table 4 Quantification of proliferation data (Ki-67 staining) and of p53 positivity in the ten cases with BML and the two cases with metastasizing uterine sarcoma

Feature	BML		Sarcomas	
	Mean	SD	Mean	SD
Ki-67	(n=10)		(n=2)	
Total nuclear area fraction Aa (%)*	20.4	4.9	37.5	7.2
Area fraction of stained nuclei Aa (%)*	2.1	0.6	8.5	4.1
Percent of stained nuclei*	2.9	1.9	11	6.7
No of nuclei per cluster of stained nuclei	5.4	5.2	12	11.3
Minimum diameter (μm) of clusters formed by stained nuclei	103.7	40.6	123.5	68.5
No of nuclei per cluster of unstained nuclei	44.5	22.1	24.5	7.7
Minimum diameter (μm) of clusters formed by unstained nuclei	61	54.8	94	29.6
Distance between nuclei (μm)	8.9	0.8	9.5	0.7
p53	(n=7)		(n=1)	
Area fraction of stained nuclei Aa (%)	36.7	4.0	30.2	
Percent of stained nuclei	52	23.5	28.0	
No of nuclei per cluster of stained nuclei	34.7	15.9	24	
Minimum diameter (μm) of clusters formed by stained nuclei	102	28.8	86	
No of nuclei per cluster of unstained nuclei	8	5.9	7	
Minimum diameter (μm) of clusters formed by unstained nuclei	65.2	48.2	98	

*P<0.05

Table 5 Quantification of hormone receptor status (estrogen and progesterone)

Feature	BML		Sarcomas
	Mean	SD	
Estrogen	(n=8)		(*n*=1)
Area fraction of stained nuclei Aa (%)	17.3	9.9	26
Percent of stained nuclei	33.6	19.7	42
No of nuclei per cluster of stained nuclei	26.3	10.5	44
Minimum diameter (µm) of clusters formed by stained nuclei	104.1	14.2	109
No of nuclei per cluster of unstained nuclei	10	5.7	10
Minimum diameter (µm) of clusters formed by unstained nuclei	89	26.4	114
Immunoreactive score	5.8	2.1	6.3
Progesterone	(*n*=7)		
Area fraction of stained nuclei Aa (%)	24.4	10.8	27
Percent of stained nuclei	50	14.6	75
No of nuclei per cluster of stained nuclei	39	11.6	27
Minimum diameter (µm) of clusters formed by stained nuclei	95.5	8.6	67
No of nuclei per cluster of unstained nuclei	8.8	4.0	10
Minimum diameter (µm) of clusters formed by unstained nuclei	67.2	9.5	87
Immunoreactive score	7.9	2.3	9.2

Table 6 Quantification of expression of galectin-1, -3 and –8

Feature	BML		Sarcomas	
	Mean	SD	Mean	SD
Antigalectin-1	(*n*=10)		(*n*=2)	
Area fraction of moderately stained cells Aa (%)	14.6	4.9	14	1.4
Area fraction of intensely stained cells Aa (%)	2.9	1.3	2.4	0.1
Percent of moderately stained cells	46.6	14.0	57.3	17.4
Percent of intensely stained cells	4.4	7.2	2	0
No of cells per cluster of moderately stained cells	2.3	1.4	5.8	0.2
No of cells per cluster of intensely stained cells	0.7	1.3	0	0
Minimum diameter (µm) of clusters formed by moderately stained cells	50.6	30.1	26	0
Minimum diameter (µm) of clusters formed by intensely stained cells	17.1	26.2	0	0
No of cells per cluster of unstained cells	3.8	1.4	2.7	2.4
Minimum diameter (µm) of clusters formed by unstained cells	37.3	14.7	36	5.6
Antigalectin-3	(*n*=10)		(*n*=1)	
Area fraction of moderately stained cells Aa (%)	17.4	3.2	14	
Area fraction of intensely stained cells Aa (%)	2.7	1.2	1.5	
Percent of moderately stained cells	68.2	11.2	76	
Percent of intensely stained cells	4.5	5.7	6.5	
No of cells per cluster of moderately stained cells	5.4	1.3	3	
No of cells per cluster of intensely stained cells	0.4	0.5	1	
Minimum diameter (µm) of clusters formed by moderately stained cells	31.3	9.6	83	
Minimum diameter (µm) of clusters formed by intensely stained cells	8.9	16.9	14	
No of cells per cluster of unstained cells	3.0	1.4	3	
Minimum diameter (µm) of clusters formed by unstained cells	40.1	19.6	50	
Antigalectin-8	(*n*=3)		(*n*=1)	
Area fraction of moderately stained cells Aa (%)	13.3	2.7	13.5	
Area fraction of intensely stained cells Aa (%)	1.9	1.0	4	
Percent of moderately stained cells	34.6	5.3	72.5	
Percent of intensely stained cells	0.25	0.4	12.5	
No of cells per cluster of moderately stained cells	1.7	1.3	3.5	
No of cells per cluster of intensely stained cells	0	0	0	
Minimum diameter (µm) of clusters formed by moderately stained cells	72.3	33.8	51	
Minimum diameter (µm) of clusters formed by intensely stained cells	0	0	0	
No of cells per cluster of unstained cells	3.0	0.9	3	
Minimum diameter (µm) of clusters formed by unstained cells	52.6	30.8	37	

Table 7 Quantification of binding sites for galectin-1 and -3, and sarcolectin

Feature	BML		Sarcomas
	Mean	SD	
Galectin-1	(*n*=10)		(*n*=1)
Area fraction of moderately stained cells Aa (%)	20.1	2.61	16.5
Area fraction of intensely stained cells Aa (%)	3.1	1.2	7
Percent of moderately stained cells	69.03	6.3	71.5
Percent of intensely stained cells	4.1	2.9	24
No of nuclei per cluster of moderately stained cells	4.4	2.1	4.5
No of cells per cluster of intensely stained cells	0.72	0.7	2.5
Minimum diameter (µm) of clusters formed by moderately stained cells	46.2	21.2	32
Minimum diameter (µm) of clusters formed by intensely stained cells	22.6	35.6	73
No of cells per cluster of unstained cells	2.7	1.2	0
Minimum diameter (µm) of clusters formed by unstained cells	50.5	23.9	0
Galectin-3	(*n*=10)		(*n*=1)
Area fraction of moderately stained cells Aa (%)	19.3	4.5	13.5
Area fraction of intensely stained cells Aa (%)	1.5	0.6	1.5
Percent of moderately stained cells	76.6	11.6	78.5
Percent of intensely stained cells	3.1	3.9	0.5
No of cells per cluster of moderately stained cells	6.6	3.5	6
No of cells per cluster of intensely stained cells	0.7	1.2	1
Minimum diameter (µm) of clusters formed by moderately stained cells	33.4	15.6	32
Minimum diameter (µm) of clusters formed by intensely stained cells	15	30.5	0
No of nuclei per cluster of unstained cells	1.5	0.6	2
Minimum diameter (µm) of clusters formed by unstained cells	46.2	29.0	98
Sarcolectin	(*n*=3)		(*n*=1)
Area fraction of moderately stained cells Aa (%)	20.7	4.6	22.5
Area fraction of intensely stained cells Aa (%)	1.9	1.1	1
Percent of moderately stained cells	78.9	9.0	71
Percent of intensely stained cells	2.3	2.5	0
No of cells per cluster of moderately stained cells	6	1.9	7.5
No of cells per cluster of intensely stained cells	0.5	0.5	0
Minimum diameter (µm) of clusters formed by moderately stained cells	26.6	7.6	25
Minimum diameter (µm) of clusters formed by intensely stained cells	14.1	22.8	0
No of cells per cluster of unstained cells	1.6	0.9	3.5
Minimum diameter (µm) of clusters formed by unstained cells	62.8	29.0	37

sels had a minimum diameter of 8.9 µm, and about 5.5% of the tumor area (volume) was occupied by the intratumorous vascular system. The percentage of nuclear staining of tumor cells was defined on both the relative number of positively stained tumor cell nuclei and the nuclear area fraction. The results for nuclei displaying the Ki-67 antigen and for tumor cells with expression of the p53 protein are compiled in Table 4. The Ki-67 antigen could be detected in about 3% of the tumor cell nuclei, while p53 was present in 52% of the tumor cell nuclei in seven of the ten BML cases. Cellular aggregations or clusters of tumor cells with marked staining features (positive vs negative) were present in BML and sarcomas. The average diameter of the formed clusters and the mean number of tumor cells forming a cluster are also listed in Table 4. Clusters formed by proliferating tumor cells were larger in diameter and possess less cells compared to nonproliferating tumor cells.

The data on the immunohistochemical hormone receptor status are given in Table 5. Tumor cells expressing estrogen receptors were detected in eight of the ten cases of BML, and in one case with metastasizing sarcoma. The percentage of tumor cell nuclei with expression of estrogen-specific receptors amounted to 34%. In total, only 17% of the tumor area (volume) were occupied by estrogen-receptor-expressing tumor cell nuclei. Clusters of estrogen-receptor-expressing tumor cells contained about 20–30 tumor cells and exhibited an average cluster diameter of 100 µm. The data on progesterone-specific receptors are in the same range, the number of positive tumor cells being relatively elevated. Tables 6 and 7 compile results on binding capacities for the endogenous lectins and the presence of the three galectins selected as representatives of the three subfamilies of prototype (galectin-1), chimeric (galectin-3) and tandem-repeat-type (galectin-8) proteins. Again, the staining intensities were not uniformly distributed, and several tumor cell clusters with different staining intensities were detected.

The morphological and biological features of the apparently benign lesion are also reflected in the survival data of the patients. Although we are aware of the limited implications based on survival data of only ten cases, the low frequency of this disease justifies interpreting this presentation with a grain of salt (Fig. 3) Only two patients died after a minimum follow-up of 6 months and a maximum follow-up period of 101 months. The cause of

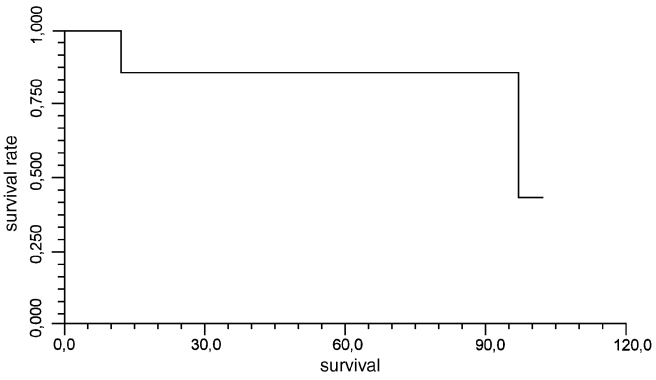

Fig. 3 Survival curve for ten cases with BML; survival time after (first) resection of pulmonary lesions

death was directly associated with the disease in case 1, who died from respiratory failure after extensive surgery and postsurgical treatment. It was not associated with BML in patient 4, who died from acute lung embolism.

Discussion

BML is a rare lesion of the lung, appearing years after hysterectomy in young women [1, 4–13, 26, 33, 37]. Morphologically, it is characterized by multiple or single, solid, spatially well-delimited tumor masses, which are composed of spindle-shaped, rather densely packed cells. These cells usually have a benign appearance [11, 26, 38]. Mitoses are rare, necrosis is absent, and the inflammatory response of the host tissue is minimal [12, 13, 26, 38]. The origin of the lesion continues to be controversial. It may be a generalized leiomyomatosis mainly involving the uterus and the lungs [5, 15, 16], late metastases of an unrecognized well-differentiated leiomyosarcoma of the uterus [12, 13, 25, 26], or benign uterine leiomyoma that embolizes to the lungs [7, 14, 23]. Indeed, some cases that have been reported tend to support the theory of a generalized leiomyomatous disease [9]. The theory of intrapulmonary embolisms of uterine leiomyomas is based upon the reported spontaneous regression of a pulmonary leiomyoma during pregnancy [24], lack of evidence for necrosis, and the absence of increased mitotic activity or nuclear heterogeneity in the clinical reports of the excised uteri. However, the majority of authors have considered these lesions to be late metastases from an extrapulmonary highly differentiated leiomyosarcoma of the uterus [13, 22, 26, 37, 38]. Tietze et al. [38] reported a case with normal karyotype without any evidence for an unbalanced loss or gain of DNA measured by comparative genomic hybridization (CGH), an uncommon result in leiomyosarcoma or leiomyoma. Nonetheless, the authors basically accepted the theory of a metastasizing neoplasm. Jautzke et al. [25] reported five cases of BML. Like our cases, their patients were premenopausal women who had undergone hysterectomy because of a uterus leiomyomatosus. Four of their five intrapulmonary lesions expressed hormone-specific receptors (estrogen and progesterone), which were graded semiquantitatively by the authors.

In terms of the differential diagnosis, both primary leiomyoma (leiomyomatosis) of the lungs [15, 24, 26, 39] and metastases of highly differentiated leiomyosarcomas [34, 41] have to be excluded. Their morphology within the lungs is similar to that of BML, and the clinical history has to be thoroughly evaluated to obtain a correct diagnosis. Concomitant bilateral lung involvement might suggest a sarcomatous disease; however, it does not exclude a BML. Levebre et al. [32] reported a rare case with bilateral lung involvement, similar to that in our case 9. In our cases of BML and in all reported cases the morphological findings differed completely from those of the more common pulmonary hamartomas, which comprise a cytogenetically, histologically, and clinically distinct entity.

We included two cases of proven metastasizing leiomyosarcoma of the uterus for comparison and are aware that only limited conclusions can be drawn from these few cases. The patients with BML were premenopausal women who underwent hysterectomy prior to the age of 45. The two cases of sarcoma were older women (53 and 59 years of age). The period between hysterectomy and the detection of the intrapulmonary lesions was 14.9 years on average in patients with BML and only 4.5 years in the two leiomyosarcoma cases. There were additional differences in the gross appearance between the two types of lesions. BML developed several nodes with an average of six nodules, with an average maximum diameter of 18.4 mm. In the case of the sarcoma patients there were only one to two nodules with an average diameter of only 3 mm. The small size of the lung metastases can be attributed to the thorough follow-up of the patients after the diagnosis and resection of the sarcomas of the uterus, i.e. to early clinical detection of the intrapulmonary metastases.

With respect to the hormone receptor status, eight of the ten BML lesions expressed estrogen- and progesterone-specific receptors, while only one sarcoma case did. Abnormal p53 expression was observed in six of the ten cases of BML and in one of the two sarcoma cases. The majority of BML cases expressed galectin-1 and galectin-3 and accessible binding sites for these tissue lectins. Only galectin-8 expression exhibited interindividual variability. These similarities among the tumors argue in favor of a common origin. Concerning proliferation the monitoring of the marker Ki67 (MIB-1) revealed an index of 3% for BML and 11% for leiomyosarcoma (Table 4). The proliferating cell fractions tended to form clusters in both the BML and sarcoma cases. The cellular density in both lesions was nearly identical, with a mean cellular distance of 8.9 µm in BMLs and 9.5 µm in sarcomas (Table 4). The quantification of p53 protein revealed that only about 30% of sarcoma cells expressed immunoreactive p53 protein, compared with about 50% in BML lesions. A similar result was obtained for bcl-2 (Table 2).

The vascularization was similar in both types of lesion. However, the size, diameter, circumference, and area fraction of the vessels in BMLs were smaller than in the two sarcoma cases, though the difference was not statistically significant. Both lesions revealed a low vascularization density compared with that reported for lung carcinomas [29]. The quantification of the hormone receptor status revealed differences in the expression of estrogen/progesterone receptors. Estrogen receptors were present in fewer cells than progesterone receptors, and the corresponding immunoreactive score (IRS) was lower. For comparison, Jautzke et al. [25] reported an estrogen IRS of 6 and a progesterone IRS of 9. In view of cell communication via glycans [17, 27], we also monitored expression of endogenous lectins. Galectins are involved in regulation of cell proliferation and cell–cell/cell–matrix interaction [17, 18, 28]. They can furnish diagnostic information such as is obtained by immunohistochemical means for breast cancer [18, 19]. In addition, the presence of galectin-reactive binding sites monitored by labeled galectins is of promising relevance [2], as also recently underscored by the reliable capacity for distinguishing leiomyomas from leiomyosarcomas [35]. The measured intensity of the presence of galectins 1 and 3 in tumor cells was similar in BML, and about 70% of the cells exhibited moderate staining intensity of binding capacities and galectins (Tables 6, 7). The expression of galectin-8 was less intense and less frequent (Tables 2, 6). In aggregate, the rather similar properties of the BML and sarcoma cases support the notion of a close relationship between the BML and leiomyosarcomas of the uterus. Thus, based upon our material and the methodology applied, it is rather unlikely that the lesions in the lung represent either multiple pulmonary leiomyomas or a pulmonary leiomyomatosis.

With regard to the clinical data, the gross findings, and the microscopical analysis, our patients present similar features to previously described in published case reports [11, 13, 26, 36]. All the women with BML had undergone hysterectomy at a premenopausal age (mean age 35 years). The mean interval between hysterectomy and the development of lung lesions was 14.9 years. The patients had a favorable outcome, in general, as illustrated by the calculated median survival of 94 months. Only one patient died of the disease during the follow-up period.

In conclusion, the analysis of our group of BML cases reveals the following clinical, morphological, functional and potentially therapeutic characteristics. A uterus leiomyomatosus had been detected and treated at a rather young age. The numerous intrapulmonary lesions 1–3 cm in size developed after a long interval, and had a low proliferation index (2.9% MIB-positive cells), frequent expression of steroid hormone receptors (about 80% of the lesions), and a moderate degree of vascularization. Such patients can expect a good prognosis if potentially curative resection of the lesions can be performed.

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