Distinctive Cytogenetic Profile in Benign Metastasizing Leiomyoma: Pathogenetic Implications

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Abstract: "Benign metastasizing leiomyoma" is the terminology used to describe a controversial entity characterized by a proliferation of bland-appearing smooth muscle in lung or abdominopelvic lymph nodes. In this report, we describe 5 cases of pulmonary-based smooth muscle tumors that are clinically and histologically consistent with this entity, and in which we identified consistent chromosomal aberrations (19q and 22q terminal deletion in all cases). This cytogenetic profile is found in approximately 3% of uterine leiomyoma, but has not been described in other types of benign or malignant neoplasia. These findings suggest that the nodular pulmonary smooth muscle proliferations termed "benign metastasizing leiomyoma," are a genetically distinct entity, which likely originate from a biologically distinctive subset of uterine leiomyoma.

Key Words: leiomyoma, pulmonary, uterus, cytogenetics, metastasis

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The origin of smooth muscle proliferations involving the lung is diverse but can be separated broadly into 2 categories: those that arise in the lung and those that are secondary (ie, metastatic to that site). Smooth muscle proliferations primary to the lung include pulmonary hamartomas (which can either entirely be composed of smooth muscle or, more commonly, in which smooth muscle is one component of the neoplasm), lymphangioleiomyomatosis (an entity characterized by the proliferation of bland-appearing smooth muscle cells around bronchial lymphatics), leiomyoma, and leiomyosarcoma. Smooth muscle proliferations in the lung can also be the result of metastatic disease (metastatic leiomyosarcoma), with common primary sites including somatic soft tissue, retroperitoneum, and female genital tract (most commonly originating in the uterus). Benign metastasizing leiomyoma (BML) is a controversial entity in which benign-appearing uterine smooth muscle tumors are associated with similar-appearing tumors at distant sites, most commonly involving lung and abdominal lymph nodes.[1,6,10,26] Although many other smooth muscle neoplasms have been analyzed cytogenetically, there have been no reports of chromosomal aberrations in BML. By prospectively karyotyping a series of cases that were clinically and histologically consistent with BML, the goal of this study was to answer the question as to whether BML is a biologically and diagnostically homogenous entity, with genetic relationships to uterine smooth muscle tumors.

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MATERIALS AND METHODS

The 5 cases reported herein were consecutive examples of BML submitted to the Cytogenetics Laboratory at Brigham and Women's Hospital, Boston, MA.

Cytogenetic Analyses

Sterile specimens of the pulmonary tumors were obtained immediately after resection, during intraoperative consultation. Tumor tissue was disaggregated, cultured, and karyotyped according to methods previously described.[7] Conventional terminology as proposed in the International System for Human Cytogenetic Nomenclature[17] was used to describe chromosomal abnormalities.

Immunohistochemical Analysis

Immunohistochemical stains for smooth muscle actin and desmin were performed on all pulmonary tumors. Immunohistochemical analysis for desmin (monoclonal antibody D33, dilution 1:700, DAKO, Carpinteria, CA) and smooth muscle actin (monoclonal antibody 1A4, dilution 1:25000, Sigma, St Louis, MO) were performed using the streptavidin-biotin-peroxidase complex (SAB) method. Appropriate positive and negative control slides were stained in parallel.

CASE REPORTS

Case 1

At the time of initial presentation, the patient was a 53-year-old previously healthy woman, who during evaluation for gallbladder disease was noted to have a 2-cm lung nodule in the medial segment of the right middle lobe by chest radiograph. At

surgery, 2 separate well-circumscribed, white, lobulated masses without gross evidence of hemorrhage or necrosis (2.5 and 3.9 cm) were present and wedge resected from the right middle and lower lobes of the lung, respectively (Fig. 1A). Histologically, the tumor masses were composed of intersecting fascicles of bland eosinophilic spindle cells with elongate nuclei with blunt or tapered ends (Fig. 1B); there was no nuclear pleomorphism, necrosis, or mitotic activity identified. Immunohistochemistry revealed that the tumor cells were diffusely positive for desmin and smooth muscle actin consistent with a smooth muscle tumor. There was no evidence of recurrent disease 7 years postsurgery. Past medical history was remarkable for a hysterectomy and right salpingo-oophorectomy for removal of a benign right ovarian cyst 32 years before her current presentation, which was not available for review. No information regarding a history of uterine fibroids was found upon review of this patient's medical record.

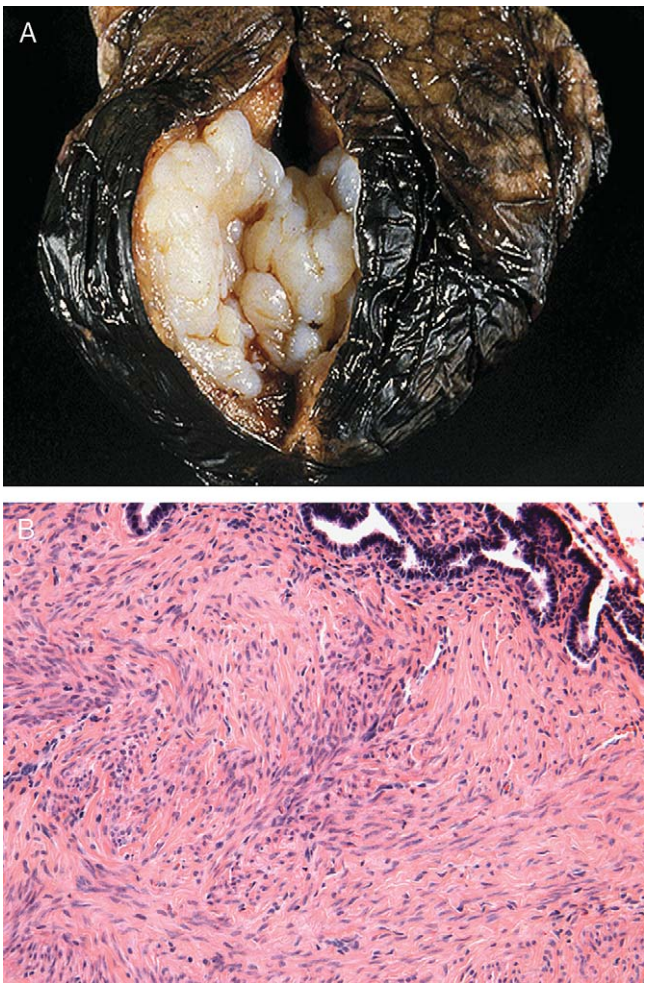

FIGURE 1. Benign metastasizing leiomyoma (case 1). A, Pulmonary wedge resection showing a well-circumscribed, white lobulated tumor mass (2.5 cm) that has a similar gross appearance to uterine leiomyomata. B, Bland-appearing smooth muscle cells without nuclear pleomorphism. Note entrapped benign lung epithelium at periphery suggestive of indolent growth.

Case 2

A 45-year-old G2P0 presented with cough and flulike symptoms and a chest radiograph showed bilateral pulmonary nodules measuring up to 2.0 cm. A pelvic computed tomography (CT) scan revealed a uterine mass with a possible necrotic center. The patient underwent pulmonary wedge resection of one of the nodules from the right middle lobe of the lung followed 1 month later by myomectomy. The tumor involving the lung measured 0.9 cm and was well circumscribed, white, firm, and whorled with bulging cut surfaces. Histologically, the tumor was composed of spindle cells with elongate nuclei arranged in intersecting fascicles, typical of smooth muscle differentiation that were separated by hyalinized stroma. Entrapped alveolar epithelium was present. There were no areas of necrosis, hemorrhage, or nuclear pleomorphism. Mitoses numbered only up to 1 per 50 high power fields. Immunohistochemistry showed that the tumor cells were diffusely positive for desmin and smooth muscle actin consistent with a smooth muscle tumor. The myomectomy specimen, which was available for review, revealed 2 histologically benign-appearing smooth muscle tumors measuring 4.4 and 2.4 cm, the smaller exhibiting focal stromal hyalinization. There was no evidence of necrosis, hemorrhage, or nuclear pleomorphism. Cytogenetic analysis was not performed. Three months after excision of one of the lung nodules, a chest radiograph documented persistence of bilateral pulmonary nodules. No further follow-up information is available.

Significant past medical history included uterine fibroids. The patient was twice status postmyomectomy 16 and 8 years before presentation with lung tumors. By clinical report, the smooth muscle neoplasm resected 16 years prior was histologically cellular and had up to 2 mitoses per 10 high power fields. Pathologic materials (slides, blocks, and report) were requested from the hospital where the surgery was performed but were no longer available. No information was available regarding the myomectomy specimen from 8 years prior.

Case 3

A 45-year-old G0 woman was found to have a pulmonary nodule on chest radiograph performed after treatment for pneumonia. A CT scan revealed an 8-mm left upper lobe and a 3-mm left lower lobe nodule. A left upper lobe pulmonary wedge resection was performed and it contained a 1.0 cm well-circumscribed, white nodule. Histologically, the tumor nodule was composed of fascicles of eosinophilic spindle cells with morphologic features consistent with smooth muscle differentiation. There was minimal cytologic atypia, no necrosis and mitoses numbered only up to 1 per 50 high power fields. Immunohistochemistry revealed that the tumor cells were diffusely positive for desmin and smooth muscle actin consistent with a smooth muscle tumor. Due to the possibility that the lesion in the lung could represent a tumor that had spread from the uterus, a pelvic ultrasound was performed 2 months postsurgery. Uterine nodules consistent with leiomyomata were present and the patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, from which the slides were available for review. The uterus weighed 224 g and contained 2 intramural and 2 submucosal well circumscribed, white whorled nodules grossly consistent with benign leiomyomata, measuring up to 4 cm in greatest dimension; cytogenetic analysis was not performed. One of the submucosal nodules was extensively calcified. Histologically, the tumors were consistent with benign leiomyomata, being well circumscribed, without cytologic atypia, mitotic activity or evidence of hemorrhage or

necrosis. There was no evidence of extension into vascular spaces. Twenty-three months after initial excision of the tumor nodule in the lung, a chest CT scan showed an additional small nodule involving the right lower lobe of the lung. Seven months later, a follow-up CT scan showed that the nodules in the right lower and left lower lobes were stable in size without change from the prior study.

Case 4

A 55-year-old woman was found to have a right lower lung mass on chest radiograph as part of a routine physical examination. Pulmonary wedge resection revealed a 2.5-cm polypoid mass projecting from the pleural surface to which it was attached by a thin pedicle. The tumor was pink, well circumscribed and surrounded by a thin pseudomembrane. Histologically, the tumor was well circumscribed, with morphologic features of smooth muscle differentiation. No necrosis or cytologic atypia was present. Mitoses numbered up to 1 per 30 high power fields. Immunohistochemistry showed that the tumor cells were diffusely positive for desmin and smooth muscle actin consistent with a smooth muscle tumor. Three years after excision, a follow-up CT scan showed multiple bilateral subcentimeter pulmonary nodules. These nodules have been stable in size over the next 7 years by yearly follow-up CT scanning. Past medical history is significant for a hysterectomy 36 years prior for fibroids. Pathologic material (report, slides, paraffin blocks) corresponding to this surgery was requested from the hospital of origin but these were no longer available.

Case 5

A 49-year-old woman with a history of stage T3 colon cancer and stage T1 renal cell carcinoma presented with bilateral pulmonary nodules clinically thought to be metastatic disease, 2 years after surgical removal of both primaries. The patient underwent 2 thorascopic resections, 2 months apart, of right and left pulmonary nodules, respectively. Four right pulmonary wedge resections (1 from the right middle and 3 from the right lower lobe) were performed and each contained a well-circumscribed white-gray nodule. The tumor nodules measured $0.9 \times 0.5 \times 0.5$ cm, $0.5 \times 0.4 \times 0.4$ cm, $0.2 \times 0.2 \times 0.2$ cm, and $0.1 \times 0.1 \times 0.1$ cm, and the third largest was partially calcified. Histologically, each was composed of a spindle cell proliferation with morphologic features of smooth muscle differentiation. Mitoses numbered up to 1 per 10 high power fields in the largest nodule and up to 3 per 10 high power fields in the second largest tumor mass; no necrosis was present. Immunophenotypically, tumor cells were diffusely positive for smooth muscle actin and desmin. Two months later, given continued concern that some of the pulmonary nodules could represent metastasis from one of the patient's known epithelial malignancies, the patient underwent a thoracoscopic resection of the left pulmonary nodules. Two left pulmonary wedge resections (1 from the left lower and 1 from the left upper lobe) were performed. One pulmonary wedge contained a nodule 0.3-cm in greatest dimension and the other pulmonary wedge resection was grossly unremarkable. Histologically and immunophenotypically, the nodule in the left lower wedge resection was similar in appearance to those resected from the right lung. Microscopic examination of the left upper wedge resection revealed 2 small smooth muscle lesions measuring less than 0.1 cm in greatest dimension. No necrosis or mitoses were identified. Given the histologic appearance of the lesions involving the lung and the possibility that they originated from a uterine primary, an magnetic resonance imaging of the pelvis was performed which revealed uterine adenomyosis and a single uterine well circumscribed nodule measuring 9 mm, radiologically consistent with a fibroid. The patient declined hysterectomy. No further therapy for the lung lesions was instituted, although the patient did receive adjuvant radiation and chemotherapy for her rectal carcinoma. One year after resection of her pulmonary nodules, a CT scan of the lungs showed stable subcentimeter pulmonary nodules.

Case 6

A 63-year-old woman presented with dyspnea on exertion and an enlarging mass of the left lower lobe of the lung. The patient was known to have this lung mass for 12 years before her current presentation but initially elected to receive periodic follow-up instead of surgery; a prior needle core biopsy 11 years earlier was nondiagnostic. Past medical history was significant for cigarette smoking and a hysterectomy for fibroids; further information concerning the patient's hysterectomy was not available. Due to increased dyspnea on exertion and an increase in the size of the mass, a left lower lobectomy was performed

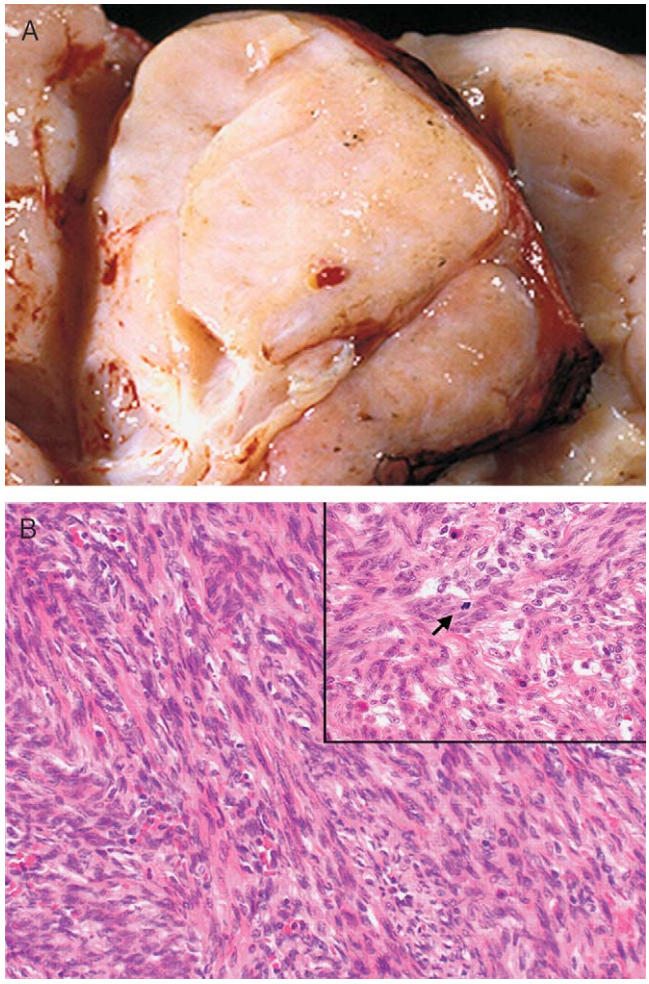

FIGURE 2. Primary pulmonary leiomyosarcoma (case 6). A, Lobectomy specimen almost entirely replaced by a large, fleshy, homogeneous tumor mass (14.0 cm). B, Cellular smooth muscle proliferation with mild nuclear atypia and mitotic activity (inset, arrow).

TABLE 1. Cytogenetic Findings of Benign Metastasizing Leiomyoma and Primary Pulmonary Leiomyosarcoma

Case No.	Diagnosis	Karyotype
1	BML	46,XX,add(13)(p10),dic(19;22)(q13;q13), + 22
2	BML	45,XX,add(1)(p11),–13, + 16,add(19)(q13),–22
3	BML	46,XX,add(1)(p35),t(1;11)(q32;q12),del(3)(q22),add(6)(p21-22),–13,der(19)t(13;19)(q12;q13),add(22)(q12), + mar
4	BML	44,XX,add(1)(p21),add(1)(p36),–2,add(2)(p25),del(4)(p12),add(7)(q36),–10,del(11)(q21q23),–12,–14,add(19)(q13.3), add(22)(q13), + mar1, + mar2
5	BML	44,XX,del(6)(p21.1?p25),–8,add(12)(q22-24),–14,dic(19;22)(q13;q13), + mar1
6	PPL	45,XX,der(1;11)(q10;q10),add(3)(p13),?add(8)(p12),–11

which revealed a well-circumscribed 14.0 × 6.0. × 5.0 cm tan-white mass that almost completely replaced lung parenchyma (Fig. 2A). The tumor had a homogeneous fleshy surface without necrosis or hemorrhage. Histologically, the tumor was cellular and consisted of fascicles of spindle cells with mild nuclear pleomorphism (Fig. 2B). Mitoses numbered up to 1 per 10 high power fields and no necrosis was present. Immunohistochemically, tumor cells were positive for smooth muscle actin and desmin. Because of the tumor size, mild but undoubted atypia and mitotic activity, this lesion was classified as low-grade leiomyosarcoma. There was no evidence of a primary elsewhere. A chest radiograph 4 months after surgery revealed no evidence of a recurrence. The patient was subsequently lost to follow-up.

CYTOGENETIC RESULTS

The results of conventional cytogenetic analysis are outlined in Table 1. In summary, lung tumor tissue analyzed from the 5 patients (cases 1 to 5) with the clinicopathologic diagnosis of ''BML'' showed 19q and 22q terminal deletions in all cases. The critical 19q13 deletion region, based on the cytogenetic data from case 4, was within subband 19q13.3. In addition, 2 of the BML had deletion of 1p, 2 had deletions of 13q (Fig. 3A; case 4), and 2 had rearrangements of chromosome band 6p21. In contrast, the primary pulmonary leiomyosarcoma (case 6) had aberrations of chromosomes 3, 8, and 11, in addition to 1p deletion (Fig. 3B).

DISCUSSION

''Benign metastasizing leiomyoma'' is a term used to describe the presence of cytologically bland, mitotically inactive smooth muscle proliferations occurring in the lung or lymph nodes of patients with similar-appearing uterine smooth muscle tumors.[1,6,10,26] This terminology is based upon the generally assumed premise that the origin of these tumors is from the spread of histologically benign-appearing uterine smooth muscle tumors (leiomyoma) that cannot, based upon morphologic criteria alone, be recognized as a tumor with metastatic potential (leiomyosarcoma). However, it has been unclear whether BML represents a biologically distinct clinicopathologic entity, or whether this is loosely defined category of entities, which are histologically similar, but biologically unrelated. Although strict diagnostic criteria are proposed for BML,[11] including examination of all smooth muscle tumors of the uterine corpus and their classification as benign based upon morphologic criteria, many times this is not possible. In some cases, the prior hysterectomy or myomectomy specimens are not thoroughly sampled and in many cases, including some in our series, the specimens are not available for critical retrospective review.

BML usually presents as lung nodules in women who have had a history of prior hysterectomy/myomectomy for uterine leiomyomata or who have concurrent leiomyomata at the time of presentation (as seen in 4 of our cases). The finding that these tumors may express estrogen and progesterone receptors[13,14] coupled with the observation that they may undergo complete clinical regression after presentation during pregnancy[12] suggests that they may be hormonally responsive. If a patient's pulmonary disease persists, they typically have an indolent clinical course although the pulmonary lesions may continue to enlarge ultimately resulting in pulmonary insufficiency and death.[14] Histologically, the tumors are composed of a proliferation of bland-appearing smooth muscle cells, which show no evidence of nuclear pleomorphism, necrosis, or significant mitotic activity. In addition, the tumor nodules usually contain entrapped benign lung epithelial elements suggestive of slow growth and consistent with the indolent course of disease.

A variety of hypotheses have been proposed to explain the pathogenesis of BML, including: (1) lymphatic/vascular dissemination of a benign uterine leiomyoma,[12] possibly secondary to mechanical instrumentation[1,26]; (2) metastasis from a low grade uterine leiomyosarcoma, which is not recognized as malignant due to undersampling of the primary, ''maturation'' of the metastasis, or the rare occasion when the currently established criteria for diagnosing uterine leiomyosarcoma are inadequate[4,6,16,21,26]; (3) a metastatic deposit of intravenous leiomyomatosis,[22] (4) a smooth muscle-rich pulmonary hamartoma, (5) hormonally induced non-neoplastic hyperplasia,[10] and (6) multifocality of primary smooth muscle neoplasia that is a primary pulmonary smooth muscle neoplasm (leiomyoma, leiomyosarcoma).[2,4,15,21,23,25] The finding of a shared cytogenetic profile in our cases characterized by 19q deletion (5 cases), 22q deletion (5 cases), 1p deletion (2 cases), 6p rearrangement (2 cases), and 13q deletion (2 cases) is the first evidence that tumors classified as BML are a genetically definable and homogenous entity.

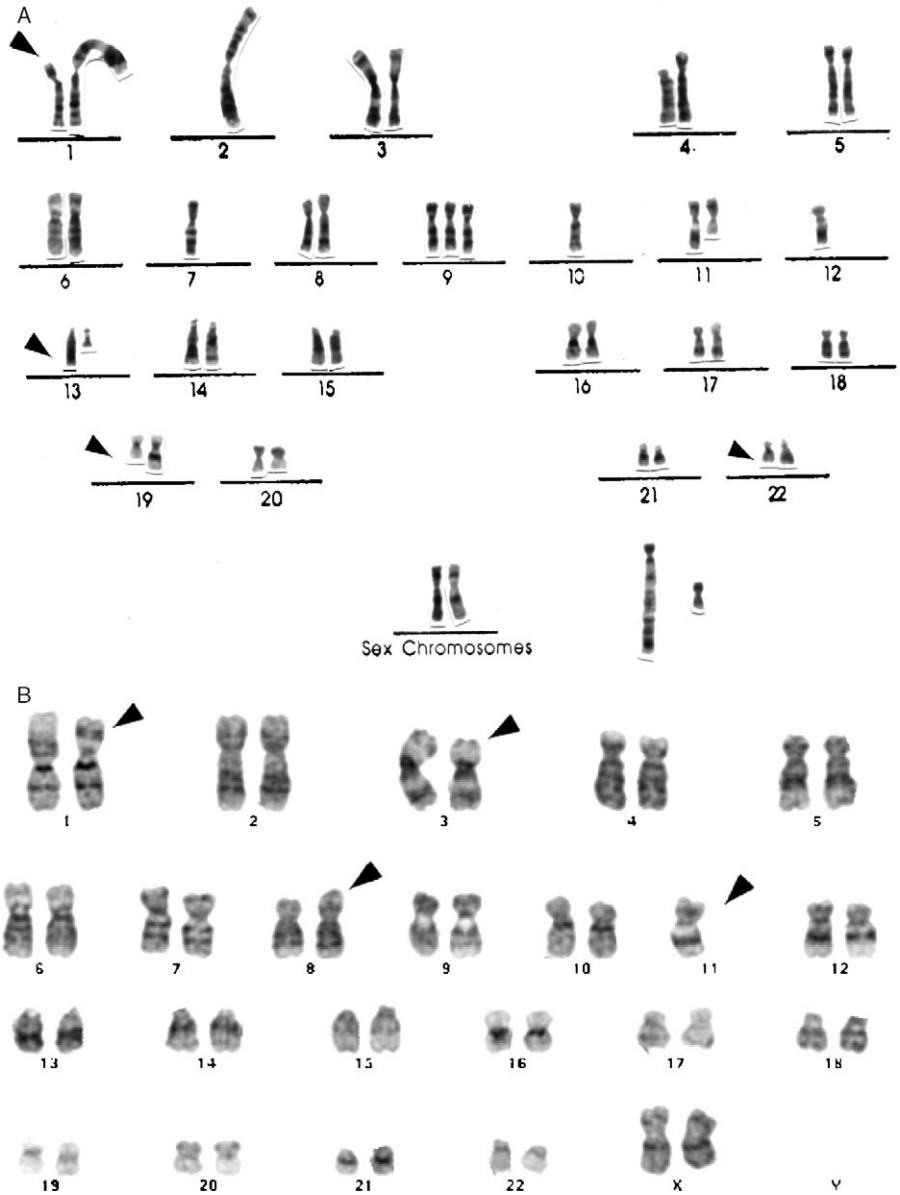

FIGURE 3. A, Cytogenetic profile of benign metastasizing leiomyoma (case 4) revealing loss of 1p, 13q, 19q, and 22q (arrows). B, In contrast, the primary pulmonary leiomyosarcoma (case 6) had aberrations of chromosomes 1, 3, 8, and 11 (arrows).

This finding also helps exclude some of the hypotheses proposed to explain this entity. Pulmonary chondroid hamartomas, irrespective of histologic components, typically exhibit a different cytogenetic profile, having rearrangements of 12q15 and 6p21, and lacking 19q and 22q deletions. This profile is distinct from that described for the BML reported herein, which—despite having 6p21 aberrations in 2 of 5 cases—consistently showed 19q and 22q deletions.[8] Non-neoplastic hyperplasias typically do not exhibit karyotypic abnormalities; whereas our finding of consistent clonal genetic aberrations proves that BML are in fact neoplasms. Although it is still possible that BML may represent a primary pulmonary smooth muscle neoplasm, cytogenetic analysis of a case of a primary pulmonary leiomyosarcoma (PPL) in our series revealed a different profile. Although the case of PPL had loss of 1p, it did not contain the 19q and 22q deletions that were found in all BML.

As the terminology for BML suggests, historically these bland smooth muscle tumors are thought to originate from uterine smooth muscle tumors. One hypothesis is that BML could represent distant deposits of intravascular leiomyomatosis. Cytogenetic analysis of 2 cases of intravascular leiomyomatosis have been performed at our institution and both tumors exhibited abnormalities of chromosome 12q15, similar to the

aberrations found in 25% of benign uterine leiomyomata,[5,19] and different from the cytogenetic profile in BML. Although it is possible that some cases classified as BML represent undersampled uterine leiomyosarcoma, the latter typically exhibit a more complex karyotype often with extra chromosomes, complex rearrangements and marker chromosomes.[9] With regard to the proposal that BML represents vascular dissemination of a conventional leiomyoma, possibly secondary to mechanical trauma, it is well known that approximately 60% of all uterine leiomyomata are diploid and do not show karyotypic abnormalities.[9] In those tumors that do have cytogenetic aberrations, the most common abnormalities are rearrangements involving chromosomes 12q14-15 and 7q22,[20] which is a profile distinct from our cases. Therefore, it is unlikely that BML arise from cytogenetically conventional uterine leiomyomas. Nonetheless, there are several lines of evidence suggesting that BML do arise from uterine primaries. For one thing, BML may express estrogen and progesterone receptors, in keeping with derivation from a hormonally driven uterine smooth muscle tumor.[13,14] In addition, in 2 cases studied by Patton et al,[18] the BML pulmonary tumors had similar patterns of androgen receptor allelic inactivation in comparison to the patient's uterine leiomyoma. Also, in a case analyzed by Tietze et al,[24] an identical X-chromosome inactivation pattern was found in all of the pulmonary tumorlets and uterine myomas of one patient with BML suggesting that the pulmonary lesions were metastatic deposits. Moreover, 3% of uterine leiomyomata that have been cytogenetically analyzed do share a similar cytogenetic profile with BML, having 19q, 22q, and 1p deletions.[3] Some of these uterine tumors, but not all, were associated with increased cellularity by histologic examination, that is the uterine tumor was classified as a cellular leiomyoma.[11] It is interesting to note that in one of our cases (case 2) and in some of the reports in the literature, prior uterine smooth muscle tumors in patients with BML have been described as "cellular."[10,12,13,26] Interestingly, the transcriptional profiles of these uterine smooth muscle tumors with 1p deletion were more similar to those of uterine leiomyosarcoma than to leiomyoma suggesting these tumors may share a common pathogenetic mechanism.[3]

Our cytogenetic profiles of BML, which are less complex than those in uterine leiomyosarcoma but more complex than those in most uterine leiomyoma, show consistent chromosomal deletions, suggesting a key pathogenetic role for sequential tumor suppressor inactivation events. As these genetic alterations are associated with histologically benign smooth muscle involving both the uterine corpus and pulmonary parenchyma, some of these mutations would likely predate alterations in cell morphology but would be associated with invasive/metastatic potential. These observations suggest that BML arise from a biologically distinctive minority of uterine "leiomyomas," which have metastatic potential, despite their bland histologic appearance. A shared cytogenetic profile suggests a shared biologic pathway and perhaps a link between uterine smooth muscle tumors and BML.

In summary, BML is a clinically, histologically, and now genetically definable entity. Similar genetic aberrations are present in 3% of typical leiomyomata and this shared karyotypic profile supports a shared biology and derivation from a genetically distinctive subset of uterine leiomyomata.

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