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CASE REPORT

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Pulmonary Benign Metastasizing Leiomyoma from the Uterine Leiomyoma: A Case Report

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Summary

Background: Benign metastasizing leiomyoma (BML) is a rare condition described as multiple well-differentiated leiomyomas at sites distant from the uterus. Apart from lungs it has also been reported in lymph nodes, heart, brain, bone, skin, eye and spinal cord. We present a case of pulmonary benign metastasizing leiomyoma in a female patient admitted to our hospital with suspicion of left adnexal tumor.

Case Report: A 45-year-old woman was referred to our hospital with suspicion of left adnexal tumor. The control transvaginal ultrasound examination performed at admission to the Gynecological Department excluded adnexal neoplasm. However, a large amount of fluid within the Douglas pouch raised the oncological concern. The patient underwent myomectomy in 2005. In the same year she was diagnosed with multiple lung nodules and underwent pulmonary wedge resection with the diagnosis of pulmonary benign metastasizing leiomyoma being stated. The decision of reevaluation of the specimen, control CT and puncture of the Douglas pouch fluid was made. Computed tomography performed at the Department of Diagnostic Imaging and Interventional Radiology of the Pomeranian Medical University Hospital revealed multiple, bilateral nodules. The microscopic examination of the samples confirmed the initial diagnosis of benign metastasizing leiomyoma with no evidence of neoplastic cells within the fluid.

Conclusions: Pulmonary benign metastasizing leiomyoma is a rare entity. However, it should be always taken into consideration in women with a previous or coincident history of uterine leiomyoma, especially when no evidence of other malignancy is present.

MeSH Keywords: Leiomyoma • Multidetector Computed Tomography • Multiple Pulmonary Nodules

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Background

Benign metastasizing leiomyoma (BML) is a rare entity first described by Steiner in 1939 [1–5]. The clinical course is usually indolent with incidental finding of pulmonary nodules on routine chest X-rays [2,3]. It affects middle-aged women with a previous or coincident history of uterine leiomyoma. Despite its ability to metastasize, BML is considered benign due to the lack of mitotic figures or anaplasia [5]. The lung is the most common site of involvement, whereas lymph nodes, heart, brain, skin and eye are more rarely affected [1–3,5]. There is much controversy concerning pathogenesis and treatment of this condition [6]. We present a case of pulmonary BML in a 45-year-old

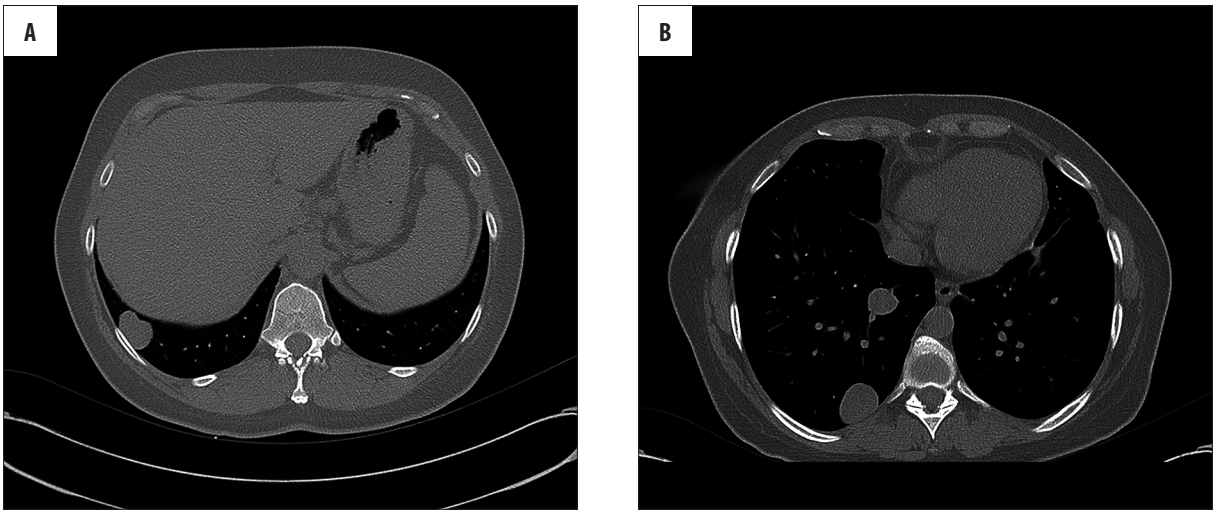

Figure 1. (**A, B**) Axial chest computed tomography scans show multiple, well-defined pulmonary nodules in the right lower lobe.

woman admitted to our hospital with suspicion of left adnexal tumor.

Case Report

A 45-year-old asymptomatic woman was referred to our hospital with suspicion of left adnexal tumor revealed after transvaginal ultrasonography (TVUS) performed in a private practice. The patient had a past medical history significant for depression and gallbladder calculosis. She did not smoke and occasionally drank alcohol. She underwent appendectomy several years ago and her family history was significant for liver cancer in her aunt. In 2005 she was diagnosed with uterine leiomyoma with subsequent myomectomy. In the same year she was found to have multiple, well-defined nodules of the lungs on a routine chest radiograph. The lesions approx. 15 mm in size were located in both lungs. The fiberoptic bronchoscopy, lavage and sputum examinations performed at a local hospital did not show any tumor, therefore the patient was sent for open pulmonary biopsy for diagnosis. After chest CT examination the wedge resection of the left lower and upper lobe was performed at the Thoracosurgery Department and the pathologic diagnosis of benign metastasizing leiomyoma was made. She was then referred to the Pulmonary Institute in Warsaw for further follow-up. In 2007 due to recurrence of leiomyomas, the patient underwent hysterectomy without oophorectomy.

In 2012 she was admitted to our hospital with suspicion of left adnexal tumor. The control TVUS performed at admission to the Gynecological Department revealed corpus luteum. However, the presence of fluid within the pouch of Douglas raised the oncological concern. The decision of reevaluation of the specimen, control CT and puncture of the Douglas pouch fluid was made, with fluid cytology being negative for malignant cells.

Chest Computed Tomography (CT) performed at our department showed multiple, sometimes round, with a perfect contour, slightly enhancing nodules of maximum 35 mm in size. The lesions increased in size as compared to the results of the initial CT examination performed before thoracotomy in 2005. No mediastinal lymphadenopathy was observed. We could not compare our results to those from the Pulmonary Institute in Warsaw, as her medical records from that time period were lost (Figure 1.)

During reevaluation of the specimen the pathologic findings from the open lung biopsy were compared to the pathologic findings of the resected uterine leiomyomas with additional staining for estrogen and progesterone receptors.

The histopathological report revealed that the resected lung tumors were of similar microscopic appearance. Irregular cystic areas lined with a single layer of lung cells were noted and between those areas, spindle cells were present. There were no mitotic figures, areas of necrosis or nuclear atypia. The immunohistochemical staining results of the epithelial cells were positive for CK AE1/AE3 and TTF-1, all of which are lung cell antigens, whereas the immunohistochemical staining of the spindle cells was positive for SMA, desmin, estrogen and progesterone receptors. The specimen was also positive for Ki-67 (1%), but negative for HMB-45.

The histopathological results ruled out the possibility of lymphangioleiomyomatosis and confirmed the presence of smooth muscle cells related to the uterine body, thus the diagnosis of BML was made.

The histopathological appearance of the resected uterine tumors was typical for benign leiomyomas. The biggest lesion was 25 mm in size. There were no mitotic figures, areas of necrosis or nuclear atypia. The immunohistochemical staining results were identical to those of the spindle cells of lung nodules and were positive for SMA, desmin, Ki-67 (1%), estrogen and progesterone receptors.

After the initial diagnosis of BML was confirmed, the patient was offered hormonal treatment with GnRH agonists and was referred to the outpatient clinic for further observation (Figure 2).

Discussion

Uterine leiomyomas are the most common tumors of the uterus in women [4]. By contrast, benign metastasizing

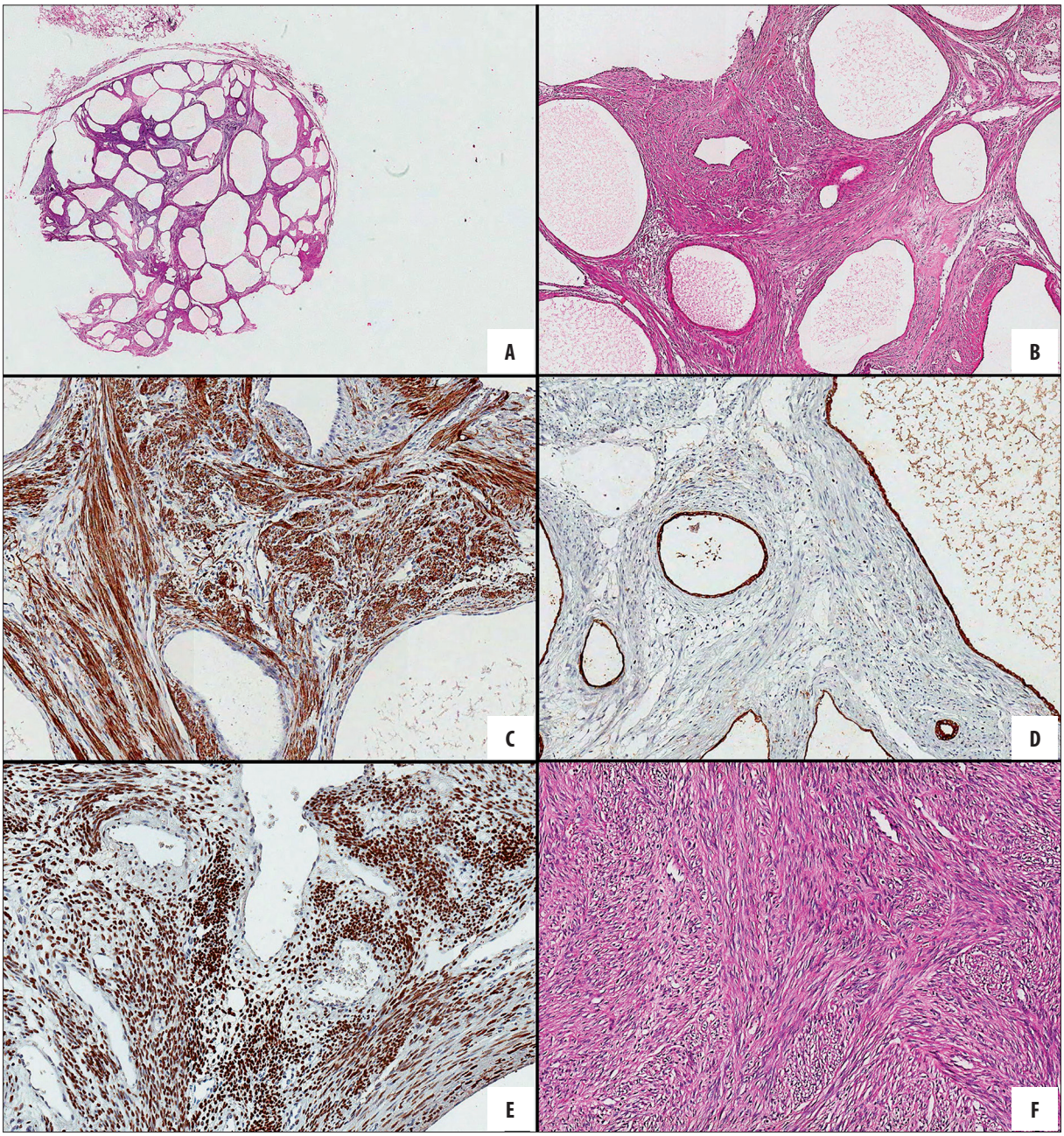

Figure 2. (**A**) Pathological appearance of benign metastasizing leiomyoma at low magnification (haematoxylin and eosin staining). (**B**) Pathological appearance of benign metastasizing leiomyoma at high magnification (haematoxylin and eosin staining). (**C**) Positive staining for desmin in smooth muscle cells of the lung nodule. (**D**) Immunohistochemical staining for keratin (CK AE1/AE3) is positive in pulmonary alveoli. (**E**) Immunohistochemical staining for ER is positive in muscle cells of the lung nodule. (**F**) Histological appearance of uterine leiomyoma at high magnification (haematoxylin and eosin staining).

leiomyoma is a rare disease described as multiple well-differentiated leiomyomas at sites distant from the uterus [1–3,7]. The lung is the most common location of involvement, whereas lymph nodes, heart, brain, bone, skin, eye and spinal cord are more rarely affected [1–3,5].

Though first described by Steiner in 1939, the pathogenesis of pulmonary BML has not been completely identified yet [2,3,8]. Steiner drew a hypothesis of benign smooth muscle cells being transported from uterine leiomyoma and colonized in the lung [3,8]. On the contrary, some authors accept these lesions as low-grade leiomyosarcoma metastases or coexisting with lymphangioleiomyomatosis of the lungs uterine leiomyomas [2]. However, the histological structure of BML, as well as currently used immunohistochemical tests and molecular analysis exclude the latter mechanisms. Patton et al. assessed clonality by analyzing the variable length of the polymorphic CAG repeat sequence within the human androgen receptor gene [9]. The pulmonary and uterine tumors showed identical patterns of androgen receptor allelic inactivation, indicating that they were clonal [9]. The authors also evaluated the length

of telomere with FISH method, which appeared long or very long in both BML and corresponding uterine tumors. Therefore the reduction of telomere did not prove to be the crucial stage in metastasis formation.

Nuovo and Schmittgen analyzed micro-RNA with FISH method in BML, leiomyomas and leiomyosarcomas [10]. In none of the 10 cases of BML as well as none of the 8 cases of leiomyomas the altered expression of strongly correlating with neoplastic phenotype micro-RNA was observed. It was however present in 13 of 15 cases of leiomyosarcomas.

Our patient was asymptomatic and had lung nodules discovered several months after myomectomy, during an annual health check examination. Most of the BML patients reported on remain asymptomatic and are diagnosed when pulmonary lesions are incidentally found on imaging. In rare cases, symptoms such as cough, chest pain, dyspnea and bloody sputum have been described [2,4,5,7]. The entity usually occurs in women with a previous or coincident history of uterine leiomyoma [1–3,7]. The mean time period from hysterectomy to the appearance of lung nodules is 15 years. However, metastatic foci of leiomyoma have been discovered up to 24 years after hysterectomy [4,5].

The typical radiological findings of BML include diffuse, bilateral nodular opacities on chest X-rays. Computed tomography usually reveals solitary or multiple soft tissue, well-defined masses scattered in both lungs, with no enhancement after intravenous contrast medium administration, ranging in size from a few millimeters to several centimeters [2–4]. Miliary patterns, interstitial lung disease, cavitary nodules and multiloculated fluid-containing cystic lesions have rarely been noted. Endobronchial and pleural sparing is also characteristic; there is no mediastinal lymphadenopathy. Pulmonary nodules may remain stable, decrease or increase in size [2–4]. In our case, the patient had multiple, perfectly outlined, slightly enhancing nodules which increased in size as compared to the CT examination performed before thoracotomy. There was no evidence of enlarged lymph nodes.

Before stating the diagnosis of BML, it is important to exclude leiomyosarcoma [4]. In BML, a typical histological pattern includes spindle-shaped cells with a low cellular variance in size and shape; without mitotic figures or disorganized growth pattern. Moreover, the Ki67 index for BML is less than that for leiomyosarcoma [4]. It is considered that leiomyosarcoma, even with low cellular atypia or no necrotic areas, has distinctly higher proliferative activity. Nuovo and Schmittgen reported that a mean Ki 67 index for BML was 3.4% (range: 0.7% to 8.1%) and for leiomyosarcoma 28.6% (range: 14.4% to 62%) ($p<0.025$) [5]. The Ki-67 index for both lung and uterine tumors in our patient was 1%.

Another entity with which BML should not be confused is lymphangioleiomyomatosis (LAM). Contrary to BML, in the course of LAM there is proliferation of atypical smooth muscle cells along with blood vessels, lymphatics and small airways. Immunohistochemical staining for HMB-45 is positive in LAM, but negative in BML [2,3]. The reevaluated specimen of tumors in our case was negative for HMB-45.

Because of the presence of estrogen and progesterone receptors in BML, its treatment modalities are based on hormonal manipulation by means of surgical or medical oophorectomy. Lung nodules tend to remain stable or occasionally regress after variable treatment options including: GnRH agonists, progesterone, estrogen receptor antagonists and aromatase inhibitors [2–4]. Some authors however prefer a 'wait-and-see strategy', especially that in some cases regression of metastatic lesions was observed in situations where estrogen levels naturally drop, such as termination of pregnancy and menopause [2,3]. Our patient was offered medical treatment with GnRH agonists due to size progression of the lung lesions.

Conclusions

Pulmonary BML is a rare entity. However, it should always be taken into consideration in women with a previous or coincident history of uterine leiomyoma, especially when no evidence of other malignancy is present. The accurate diagnosis should be based not only on the medical history but also on histopathological and immunohistochemical examinations of lung nodules. Since standard treatment of BML has not been established yet, an individual approach in particular clinical cases should be considered.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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