Pulmonary benign metastasizing leiomyoma: a report of two cases

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Benign metastasizing leiomyoma (BML) is a rare pathological process associated with pelvic leiomyoma. We present two cases of BML that are associated with giant pulmonary metastasis. BML is a rare benign metastatic phenomenon that could easily be mistaken for malignant neoplasms. Both cases occurred in middle-aged women who presented with cough and dyspnea. They previously underwent hysterectomy for uterine leiomyoma. After history taking, computed tomography, integrated PET/computed tomography and pathological assessment, a multidisciplinary treatment was offered for the diagnosis of BML. Physicians should consider BML among the differential diagnoses in women of reproductive age with a history of uterine leiomyoma presenting with pulmonary nodules, and accurate histopathological analysis should be made.

Plain language summary: This article reports two cases of a rare pathological process called benign metastasizing leiomyoma. Since it can be mistaken with malignant neoplasm, the report provides evidence and guidance for clinicians and histopathologists to be considered when dealing with similar cases.

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Case 1
A 51-year-old woman presented with cough for 1 year and shortness of breath for 4 months. The patient is para 3; all were normal vaginal deliveries at full term. She had a history of uterine fibroids and myomectomy 17 years ago. CT showed multiple enlarged bilateral pulmonary nodules, the largest measuring 11.7 × 11.2 × 11 cm (Figures 1A–C). Abdominopelvic CT showed heterogeneous soft tissue mass at the uterine cervix junction measuring 3.8 × 3.1 cm with a well-defined cystic lesion in the left adnexa measuring 3 cm.

Brain CT was free. PET showed numerous large hypermetabolic masses, and the largest one was located in the left upper lobe, measuring 10.2 × 6.8 cm, with no evidence of abnormal focal uptake in the neck, chest or abdomen. CT-guided biopsy showed benign spindle-cell proliferation forming fascicles that intersect at right angles, which
confirmed pulmonary BML. The tumor cells showed cigar-shaped nuclei with no evidence of tumor necrosis, mitosis or nuclear pleomorphism. The tumor cells were positive for smooth muscle actin, desmin, ER, PR and BCL2 immunohistochemical markers and negative for CD99, CD34, CD31, S-100 protein and beta-catenin immunohistochemical markers (Figures 2A–D).

The pulmonary function test showed severe restrictive lung disease with a forced vital capacity (L) of 48% and forced expiratory volume in the first second (L) of 46%. The patient was started on hormonal therapy, including letrozole, an aromatase inhibitor, goserlin and gonadotropin releasing hormone agonist and planned for total abdominal hysterectomy with bilateral salpingo-oophorectomy.

Case 2

In 2013, a 47-year-old women presented to the emergency department at King Abdullah University Hospital with a cough and shortness of breath. She had a history of diffuse uterine leiomyomatosis, for which she underwent a hysterectomy in 2008. Chest CT showed bilateral multiple variably sized pulmonary masses and nodules. The results of a CT-guided biopsy appeared inadequate. Therefore, video-assisted thoracoscopic lung-wedge resection was performed, which confirmed pulmonary BML by showing a well-demarcated grayish nodule measuring $1.5 \times 1.5 \times 1$ cm, composed of epithelioid cells arranged as nests and separated by steaks of hyalinized stroma. The cells showed no atypia, and the nuclei were vesicular with small nucleoli. Mitotic figures were up to $4/10$ high power field with no apparent necrosis. The tumor cells were strongly positive for SMA, desmin and ER. The specimen appeared hostile for HMB-45, CD10, CK, S-100 protein, synaptophysin, chromogranin, CD34 and thyroid transcription factor 1, with Ki-67 showing 3% proliferative activity.
In 2014, she underwent bilateral salpingo-oophorectomy and pelvic lymph node biopsy. The pelvic lymph node biopsy showed similar histopathological features to the previously mentioned pulmonary nodule leading to the diagnosis of BML. Later, in 2015, the patient presented with sudden shortness of breath and chest pain. CT showed pulmonary embolism in the posterior right pulmonary vein with multiple bilateral pulmonary nodules that increased in size. Unfortunately, in the same year, the patient died of massive pulmonary embolism.

Discussion

Pulmonary BML is thought to affect women at a mean age of 47.3 ± 10.02 years with a previous history of uterine leiomyoma and primary surgery at a mean age of 38.5 ± 8.99 years. The mean age at primary surgery correlated with the mean age of diagnosis [5]. Despite that, only a few cases were reported for cases with an intact uterus and no previous history of leiomyoma [5,8].

The exact pathogenesis of BML has not been completely identified yet. Various theories have been proposed to understand its pathogenesis better; peritoneal seeding after myomectomy or hysterectomy, benign smooth muscle cells metastasizing from uterine leiomyoma and low-grade uterine leiomyosarcoma. The peritoneal seeding hypothesis was reported based on that most of the patients previously underwent hysterectomy or myomectomy, suggesting a surgically related hematogenous spread and that BML and intravascular leiomyomatosis are related entities [4,9,10]. Despite that, in some cases, the uterine tumor was discovered simultaneously or after the associated metastasis [11].

A multifocal origin has also been linked to BML in multiple reports. However, extrauterine leiomyomas are usually ER negative, whereas most BML is ER positive and heavily relies on ER and PR, with the disease occurring in premenopausal women and the tumor demonstrating growth reduction post menopause or during pregnancy [11]. Therefore, hormonal therapy controlling estrogen levels is deemed effective in preventing tumor progression with a good prognosis [7]. The third hypothesis relates BML to low-grade uterine leiomyosarcoma. Despite that, pulmonary BML is considered much less aggressive than leiomyosarcoma, with several asymptomatic cases found incidentally in routine radiological investigations [11].

In 2020, Kayser et al. reported that the mean interval between hysterectomy and the development of BML was 14.9 years, whereas in 2017, Barnaś et al. reported it as 8.8 years regardless of the surgery type. Of the two patients, one was diagnosed 5 years after hysterectomy, whereas the second was diagnosed 17 years after myomectomy.

The treatment for pulmonary BML has not been standardized yet. Among those is surgery by excising the foci and observing the development of new foci [7]. Other options work on its hormonal relation, whether through oophorectomy or medical castration, altering the hormone release and stabilizing the pulmonary lesion. Oophorectomy was previously linked to progressive and complete regression of some low-grade BML cases [12]. This modality of hormonal control was challenged by hormonal treatment as an effective, reversible and less aggressive alternative. Moreover, hormonal replacement is superior to oophorectomy in inoperable cases and women who desire to retain their fertility and can be used in progressing diseases despite oophorectomy or menopause [11,13].

Conclusion

BML is a rare borderline tumor combining benign histological features with a metastasizing biological behavior indicating malignancy. It should be in the differential diagnoses of women of reproductive age with a history of uterine disease presenting with pulmonary nodules; thus, an accurate histopathological analysis should be performed. To the best of our knowledge, fewer than ten cases were reported in the Middle East, with no previous cases reported in Jordan.

Executive summary

- Benign metastasizing leiomyoma (BML) is a rarely reported phenomenon that primarily affects women with a previous history of uterine leiomyoma.
- Various theories are proposed to understand the pathogenesis of BML including peritoneal seeding after myomectomy, benign smooth muscle that metastasize from uterine leiomyoma and low-grade uterine leiomyosarcoma.
- Hormonal therapy can be an effective modality in preventing tumor progression.
- BML should be among the differential diagnoses in women of reproductive age with a history of uterine disease when presenting with pulmonary nodules.
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Ethical conduct of research
Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal. Ethical approval was granted by the Institutional Review Board (IRB) Committee of King Abdullah University Hospital.

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