Ochsner Journal 17:284–287, 2017

Recurrent Pneumothoraces in a Patient With Pulmonary Benign Metastasizing Leiomyoma

Miranda Hann, BA,[1] Rinu Manacheril, MD,[2] Jerry St. Pierre, MD,[3] Rajiv Gala, MD[1,3]

[1]The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, LA [2]Department of Neurology, Ochsner Clinic Foundation, New Orleans, LA [3]Department of Obstetrics and Gynecology, Ochsner Clinic Foundation, New Orleans, LA

Background: Pulmonary benign metastasizing leiomyoma (BML) is a rare disease with a malignant characteristic of spread from the uterus. Most cases are asymptomatic, and only 1% are associated with pneumothorax.

Case Report: We present the case of a 42-year-old female with recurrent pneumothoraces leading to an incidental finding of diffuse bilateral pulmonary nodules. The diagnosis of BML was based on the patient's history of uterine leiomyomata and confirmed by a biopsy showing benign smooth muscle staining for desmin and vimentin.

Conclusion: BML should be considered in women with a history of leiomyomata who develop pneumothoraces resulting from peripheral pulmonary nodules. A standardized treatment regimen has yet to be established, and therapy plans require a multidisciplinary approach, involving gynecology, cardiothoracic surgery, and pulmonology.

Keywords: *Leiomyoma, lung neoplasm, neoplasm metastasis, pneumothorax*

Address correspondence to Jerry St. Pierre, MD, Department of Obstetrics and Gynecology, Ochsner Baptist Hospital, 4429 Clara St., Suite 400, New Orleans, LA 70115. Tel: (504) 842-9885. Email: jstpierre@ochsner.org

INTRODUCTION

Uterine leiomyomata are the most frequently occurring benign uterine tumor, affecting 20%-30% of women >35 years.[1] Leiomyomata have low mitotic activity, no anaplasia or necrosis, and limited vascularization. In rare cases, these tumors can exhibit malignant behavior and metastasize. This phenomenon, known as benign metastasizing leiomyoma (BML), is characterized by smooth muscle nodules located at sites distant from the uterus. BML often presents in the lung as diffuse bilateral pulmonary nodules; it is usually asymptomatic and identified incidentally on pulmonary imaging.[2] Because of the limited number of cases of BML, the incidence, pathogenesis, and treatment are not well established.

We present a case of pulmonary BML in a patient with recurrent pneumothoraces and review the literature about pathogenesis, diagnosis, and treatment.

CASE REPORT

A 42-year-old female presented in December 2015 with extreme shortness of breath and a worsening dry cough occurring 2 months after a thoracocentesis for her fourth pneumothorax. No chest pain, wheezing, or hemoptysis was present on admission. Chest computed tomography (CT) identified nodular opacities scattered throughout both lungs, high-density material in the pleural space of the right lung, pleural fluid, and atelectasis (Figure 1). Most of the pulmonary nodules were <4 mm, with the largest (10 mm) found in the superior segment of the lingula. The findings were identical to those seen in a CT scan of the patient following her first pneumothorax in October 2013 when she presented with extreme shortness of breath and chest tightness (Figure 2).

The patient's medical history was significant for asthma, interstitial lung disease, chronic obstructive pulmonary disease, stage 4 endometriosis with spread documented to the intestines, and uterine fibroids (the largest being 3.5 × 3.1 cm) diagnosed in November 2011. She had had a right salpingo-oophorectomy 9 years prior to treat her endometriosis and had been medically managed since then with continuous combined oral contraceptive pills. While catamenial pneumothoraces were initially postulated as the cause of her recurrent disease, lung biopsies never revealed histologic endometriosis.

A left apical lobe segmentectomy was performed after her initial pneumothorax in October 2013. Biopsy analysis of the tissue found emphysematous change, consistent with chronic obstructive pulmonary disease, and benign smooth muscle proliferation. At that time, immunohistochemical stains were positive for desmin and vimentin with blush staining with CD99, BCL-2, and actin. The nodule biopsy was negative for CD34, S100, and HMB-45. The biopsy profile suggested leiomyomata, and when these findings were combined with the clinical data, BML was diagnosed. The patient was referred to gynecology; hysterectomy and left oophorectomy were recommended to definitively prevent the growth of new leiomyomata. As the patient awaited this procedure, she had a complete decortication

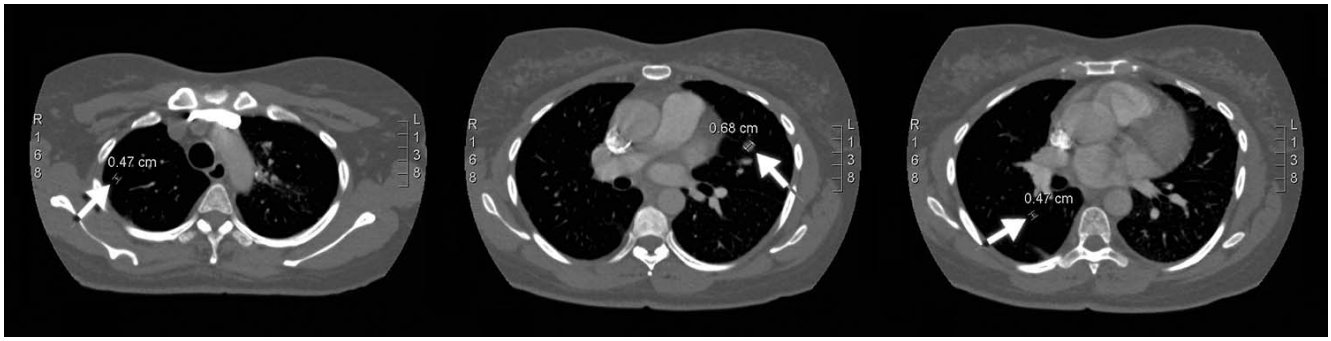

Figure 1. Current presentation (December 2015): Computed tomography scans show nodular opacities scattered throughout both lungs during the patient's presentation of respiratory difficulty 1 month status post thoracocentesis for her fourth pneumothorax. Most of the pulmonary nodules were <4 mm (left and right image with arrows pointing to nodule) with the largest (10 mm) found in the superior segment of the lingula (center image with arrow pointing to nodule).

with mechanical and chemical pleurodesis along with right chest tube placement for the treatment of her third and fourth pneumothoraces in May and October 2015, respectively.

During the December 2015 hospitalization, breathing regimens of albuterol sulfate-ipratropium bromide (DuoNeb) 3.0/0.5 mg inhaler were given every 4 hours in addition to the patient's home breathing treatments: budesonide-formoterol (Symbicort) 160/4.5 mcg actuation inhaler every 12 hours and albuterol 90 mcg actuation inhaler every 6 hours that had been started in May 2014 and October 2013, respectively. Additionally, the patient was continued on her

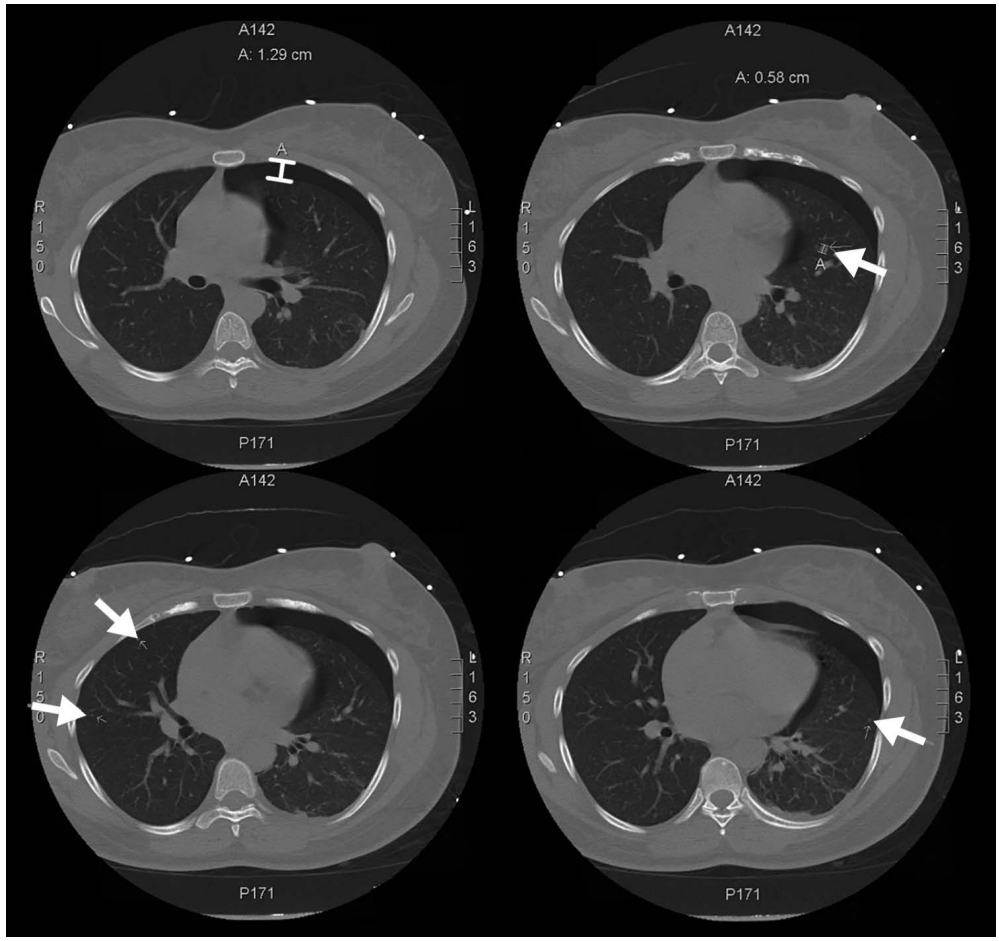

Figure 2. First presentation (October 2013): Computed tomography scans show nodular opacities scattered throughout both lungs (arrows pointing to nodules in images) and a left pneumothorax (identified space on first image) at the patient's first presentation. The nodules are roughly the same size, with the largest (6 mm) in the superior segment of the lingula (second image with arrow and letter A identifying the nodule).

home medications that included norethindrone/ethinyl estradiol-iron (Femcon Fe) 0.4 mg/35 mcg and 75 mg and norgestrel/ethinyl estradiol (Lo/Ovral) 0.3 mg/30 mcg, both given daily and prescribed in January 2013 to control excessive bleeding from the patient's leiomyomata and endometriosis. These estrogen-containing contraceptive pills were not discontinued until the patient's hysterectomy in March 2016.

Four months after the resolution of the patient's acute breathing difficulty, she underwent a robotic-assisted laparoscopic hysterectomy with left salpingo-oophorectomy in March 2016. One year after this procedure, the patient had completed her pulmonary rehabilitation and had resolution of her hypoxia and cough. She continues to have postoperative pain from her thoracotomies.

DISCUSSION

BML is a rare manifestation of leiomyomata with a malignant-like character that spreads to sites distant from the uterus. To our knowledge, only 120 cases have been reported between Steiner's first description of BML in 1939[3] and 2013. BML is usually diagnosed incidentally in premenopausal women (average age 46.7 years) with a history of uterine leiomyomata.[2,4] Most cases are asymptomatic, but patients can occasionally experience coughing, hemoptysis, dyspnea, and decreased pulmonary function. Only 1% of cases are associated with pneumothorax.[5] The proposed mechanism for the pneumothorax in one study was uterine myoma cells in the distal airway becoming check valves, causing the formation of cystic lesions that upon rupture induced a pneumothorax.[5] Malignant and metastatic disease can mimic the destructive process of those myoma cells in the distal airways. Secondary spontaneous pneumothorax is most commonly attributable to chronic obstructive pulmonary disease and emphysematous changes as a result of bullae rupture. This pathologic process could have contributed to the recurrent spontaneous pneumothoraces in our patient. Given the complex lung pathology in our patient, multiple factors likely contributed to her recurrent spontaneous pneumothoraces.

The pathogenesis of BML is uncertain. A number of proposed mechanisms for the origin of BML juxtapose those reported for endometriosis. These include retrograde menstruation causing peritoneal seeding, pelvic surgery causing transcoelomic spread, lymphatic or vascular spread,[6] or metaplastic transformation of mesenchymal epithelium in the coelom or lungs.[7] The first 2 mechanisms do not explain pulmonary BML. Vascular spread occurs when the leiomyomata invade the uterine vein and then spread to the ovarian vein, common iliac vein, inferior vena cava, right atrium and ventricle, and then to the pulmonary circulation.[8] Several cases have been reported with metastases at various points along the vascular pathway. Metaplastic transformation occurs because the tumor arises from mesenchymal cells that can metaplastically differentiate under hormonal influences into myofibroblasts, causing tumorigenesis.[9] This mechanism could explain tumors posthysterectomy. Despite these theories, the natural history of BML is still uncertain.

Metastatic lesions can occur not only in the lungs but also in the lymph nodes, bone, spine, skull base, retroperitoneum, deep soft tissues, omentum and mesentery, and heart. Jautzke et al reviewed 74 cases of BML and reported that the lungs were the most common site.[10] In radiologic studies, pulmonary BML shows multiple lesions within the interstitium that are not enhanced by contrast and spare the endobronchial and pleural regions. Lesions often have a low proliferative state, no cytologic atypia, mitosis <5 per 10 high power field (hpf), and a low Ki-67 index.[11] Histologically, most BML lesions show interlacing fascicles of smooth muscle cells without anaplasia or vascular invasion and are positive for desmin, muscle-specific actin, and estrogen and progesterone receptors.[4]

BML should be distinguished from lymphangioleiomyomatosis, a proliferation of abnormal smooth muscle-like cells in lymphatics that exhibit neoplastic features, and primary pulmonary leiomyomata that are not estrogen or progesterone receptor positive and bind monoclonal HMB-45 antibody.[2] Additionally, leiomyosarcoma must be ruled out. Leiomyosarcoma is poorly differentiated with a high mitotic index (>9 mitoses per 10 hpf), multiple atypical nuclei, coagulative necrosis, and pseudocyst formation.[2] As Wei and Chen state, definitive diagnosis of BML must combine the pathologic reports of the tissue with the clinical data.[12]

Because BML is rare, treatment is not standardized and should be tailored to each patient. Hysterectomy and bilateral oophorectomy are currently the recommended first-line treatment for all patients to control the source of leiomyomata and female gonadal hormone production.[13] BML is thought to be responsive to estrogen and progesterone given its hormone receptor expression and occurrence in premenopausal women.[13] As a result, progestins, aromatase inhibitors, and medical castration with luteinizing hormone-releasing hormone analogues have been used to treat BML.[12] Some patients experienced disease control or regression with hormonal manipulation; however, hormone therapy does not generate a response in all patients, and adverse effects such as flushing, fatigue, and malaise must be considered.[12] In our patient, combined estrogen and progesterone contraceptive pills were continued for 3 years after discovery of her BML and may have contributed to the exacerbation of the disease process in her lungs.

CONCLUSION

Although rare, BML should be ruled out in women presenting with unusual pulmonary complications and a history of uterine leiomyomata. Pulmonary specialists and oncologists should be aware of BML when determining differentials for multiple pulmonary nodules. Presentation with spontaneous pneumothorax is exceptionally rare. Combining this unique presentation with the overall clinical picture will allow physicians to assess and prevent this unusual complication. A standardized treatment regime has yet to be established, and therapy plans require a multidisciplinary approach, involving gynecology, cardiothoracic surgery, and pulmonology.

ACKNOWLEDGMENTS

The authors have no financial or proprietary interest in the subject matter of this article. A poster based on these data was presented at the Ochsner Health System Research Day 2016, New Orleans, LA, May 17, 2016.

REFERENCES

1. Khan AT, Shehmar M, Gupta JK. Uterine fibroids: current perspectives. *Int J Womens Health*. 2014 Jan 29;6:95-114. doi: 10.2147/IJWH.S51083.
2. Awonuga AO, Shavell VI, Imudia AN, Rotas M, Diamond MP, Puscheck EE. Pathogenesis of benign metastasizing leiomyoma: a review. *Obstet Gynecol Surv*. 2010 Mar;65(3): 189-195. doi: 10.1097/OGX.0b013e3181d60f93.
3. Steiner PE. Metastasizing fibroleiomyoma of the uterus: report of a case and review of the literature. *Am J Pathol*. 1939 Jan; 15(1):89-110.7.
4. Miller J, Shoni M, Siegert C, Lebenthal A, Godleski J, McNamee C. Benign metastasizing leiomyomas to the lungs: an institutional case series and a review of the recent literature. *Ann Thorac Surg*. 2016 Jan;101(1):253-258. doi: 10.1016/j.athoracsur.2015.05.107.
5. Okabe R, Shoji T, Huang CL. Benign metastasizing leiomyoma of the lung with spontaneous pneumothorax. *Thorac Cardiovasc Surg Rep*. 2013 Dec;2(1):26-28. doi: 10.1055/s-0033-1345266.
6. Javert CT. Pathogenesis of endometriosis based on endometrial homeoplasia, direct extension, exfoliation and implantation, lymphatic and hematogenous metastasis, including five case reports of endometrial tissue in pelvic lymph nodes. *Cancer*. 1949 May;2(3):399-410.
7. Suginami H. A reappraisal of the coelomic metaplasia theory by reviewing endometriosis occurring in unusual sites and instances. *Am J Obstet Gynecol*. 1991 Jul;165(1):214-218.
8. Chung YH, Lee SW, Shin SY, et al. Single-port laparoscopic debulking surgery of variant benign metastatic leiomyomatosis with simultaneous lymphatic spreading and intraperitoneal seeding. *Obstet Gynecol Sci*. 2015 Jul;58(4):314-318. doi: 10.5468/ogs.2015.58.4.314.
9. Awonuga AO, Rotas M, Imudia AN, Choi C, Khulpateea N. Recurrent benign metastasizing leiomyoma after hysterectomy and bilateral salpingo-oophorectomy. *Arch Gynecol Obstet*. 2008 Oct;278(4):373-376. doi: 10.1007/s00404-008-0581-z.
10. Jautzke G, Müller-Ruchholtz E, Thalmann U. Immunohistological detection of estrogen and progesterone receptors in multiple and well differentiated leiomyomatous lung tumors in women with uterine leiomyomas (so-called benign metastasizing leiomyomas). A report on 5 cases. *Pathol Res Pract*. 1996 Mar;192(3):215-223.
11. Rege AS, Snyder JA, Scott WJ. Benign metastasizing leiomyoma: A rare cause of multiple pulmonary nodules. *Ann Thorac Surg*. 2012 Jun;93(6):e149-e151. doi: 10.1016/j.athoracsur.2011.12.047.
12. Wei WT, Chen PC. Benign metastasizing leiomyoma of the lung: a case report and literature review. *Oncol Lett*. 2015 Jul;10(1): 307-312.
13. Egberts JH, Schafmayer C, Bauerschlag DO, Jänig U, Tepel J. Benign abdominal and pulmonary metastasizing leiomyoma of the uterus. *Arch Gynecol Obstet*. 2006 Aug;274(5):319-322.

This article meets the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties Maintenance of Certification competencies for Patient Care and Medical Knowledge.