



## Case report

## Pulmonary benign metastasizing leiomyoma: A case report

Malik Khan<sup>a,1</sup>, Annum Faisal<sup>b,\*</sup>, Hussain Ibrahim<sup>a,2</sup>, Terrance Barnes<sup>c,3</sup>, Glenn M. VanOtteren<sup>c</sup><sup>a</sup> Grand Rapids Medical Education Partners/ Michigan State University, Grand Rapids, MI 49503, USA<sup>b</sup> Spectrum Health/Michigan State University Internal Medicine Residency, Grand Rapids, MI 49503, USA<sup>c</sup> Department of Pulmonary and Critical Care, Spectrum Health Medical Group, 100 Michigan St NE, Grand Rapids, MI 49503, USA

## ARTICLE INFO

## Keywords:

Benign metastasizing leiomyoma  
Pulmonary metastasis  
Aromatase inhibitors

## ABSTRACT

Uterine leiomyoma is the most common benign gynecological tumor. Rarely, it has benign extra-uterine growth patterns, including benign metastasizing leiomyoma (BML), with lungs being the most common metastatic site.

We present a case of a 47-year-old female who, 3 years prior to presentation, underwent abdominal supra-cervical hysterectomy for benign leiomyoma. Approximately 6 months prior to presentation, she was seen for shortness of breath and chest pain. A CT of the chest revealed multiple new non-calcified pulmonary nodules bilaterally. PET/CT demonstrated mild FDG uptake in multiple lung nodules, with no significant extra-thoracic sites of abnormal FDG uptake. A CT guided lung biopsy showed a low grade, smooth muscle tumor. Immunohistochemical staining was positive for smooth-muscle actin and desmin, estrogen and progesterone receptor and was negative for CD117, HMB-45, CD34, pan cytokeratin and EMA. She underwent wedge resection of one of the nodules which confirmed the above findings. A cytogenetic analysis was also performed, which was consistent with pulmonary BML. She ultimately underwent left lower lobe resection and was started on a daily aromatase inhibitor.

BML is a rare disease usually seen in women of reproductive age. The pathogenesis and treatment remain controversial. BML mostly tends to have an indolent course and a favorable outcome.

## 1. Introduction

Uterine leiomyoma is one of the most common benign gynecological tumors [1–3]. Rarely, it has been shown to have benign extra-uterine growth patterns, including benign metastasizing leiomyoma (BML) [1,2,4]. Lungs are the most common metastatic site amongst others such as lymph nodes, deep soft tissues, central nervous system, mesentery, bones and heart [2,5–9]. Most pulmonary BMLs (PBML) are discovered incidentally in asymptomatic patients with scattered, well-circumscribed, multiple, non-calcified bilateral nodules on imaging studies [2,3,10].

## 2. Case description

We present a case of a 47-year-old, morbidly obese African American female, G6 P4-0-2-4, with a 22 pack per year smoking history who had quit 5 years prior to presenting. She had an abdominal supra-cervical hysterectomy 3 years prior to presentation for uterine fibroids.

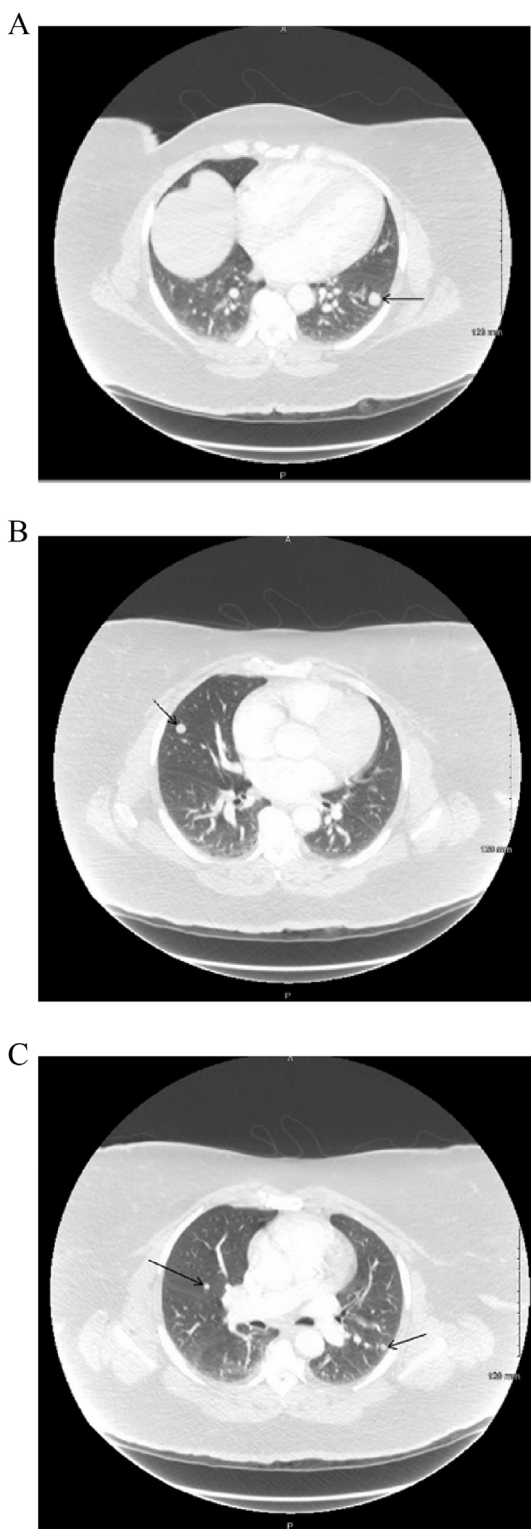
Surgical pathology had confirmed benign leiomyomata with no malignant findings. A CT of the abdomen/pelvis was performed a year later for abdominal pain which showed a 42 × 47 mm right ovarian cyst and multiple ventral hernias. She did not follow up for the ovarian cyst.

Six months prior to presentation the patient was seen in the hospital for shortness of breath and chest pain. She underwent a CT of the chest with pulmonary embolus (PE) protocol, which showed multiple, non-calcified pulmonary nodules bilaterally, with the largest being 14 mm in the left lower lobe (LLL), accompanied by a 10 mm nodule in the right middle lobe amongst others, concerning for metastatic disease. No pulmonary embolism was seen (Fig. 1A–C). As part of the initial workup, given her history of ovarian cyst, she underwent a CT of the abdomen and pelvis again which showed bilateral cystic masses in the adnexa, likely ovarian in nature. She subsequently had a pelvic ultrasound confirming right and left ovarian cysts which were 13 × 24 × 20 and 33 × 23 × 27 mm, respectively. No other masses were seen.

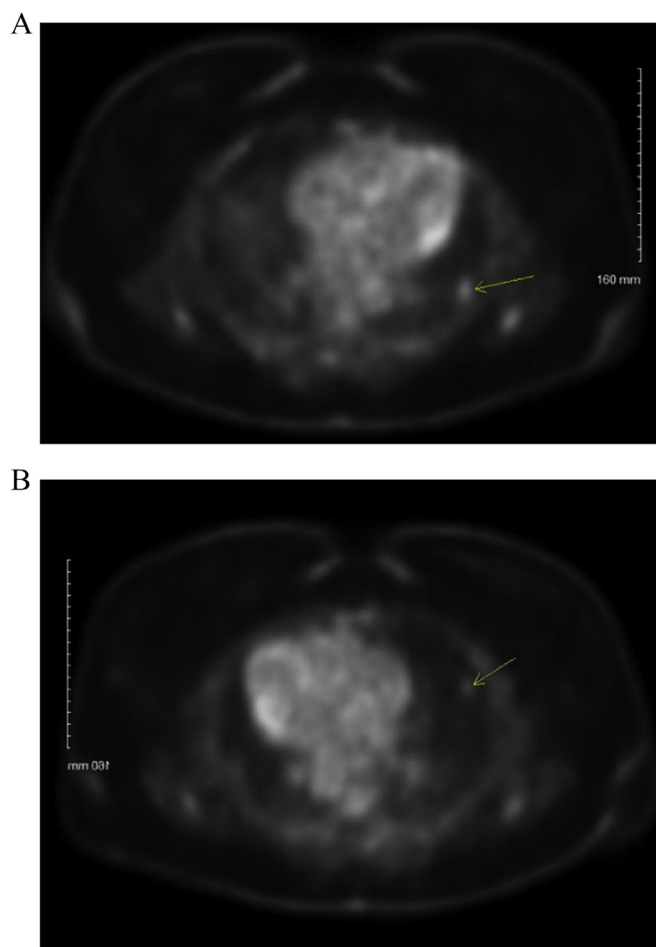
This prompted a repeat visit to her gynecologic oncologist. Her

\* Corresponding author. 407 Briar lane NE, Grand Rapids, MI, 49503, USA.

E-mail addresses: [khurramsher86@gmail.com](mailto:khurramsher86@gmail.com) (M. Khan), [annumfaisal@gmail.com](mailto:annumfaisal@gmail.com) (A. Faisal), [hussain.ibrahim12@gmail.com](mailto:hussain.ibrahim12@gmail.com) (H. Ibrahim),[Terrance.barnes@metrogr.org](mailto:Terrance.barnes@metrogr.org) (T. Barnes), [glenn.vanotteren@spectrumhealth.org](mailto:glenn.vanotteren@spectrumhealth.org) (G.M. VanOtteren).<sup>1</sup> Present affiliation and address: University of Cincinnati Medical Center, Division of Pulmonary, Critical Care & Sleep Medicine; Cincinnati, OH, 45267, USA.<sup>2</sup> Present affiliation and address: University of Texas Medical Branch, Division of cardiology; Galveston, Texas, 77555, USA.<sup>3</sup> Present affiliation and address: Department of Pulmonary Medicine, Metro Health, University of Michigan Health, 2212 Health dr SW, Suite 220, Wyoming, MI 49519, USA.



**Fig. 1.** A: CT chest with PE protocol showing a non-calcified 14 mm pulmonary nodule in left lower lobe. B: CT chest with PE protocol showing a non-calcified 10mm pulmonary nodule in Right Middle Lobe. C: CT chest with PE protocol showing small non-calcified pulmonary nodules in Right and Left Upper Lobes.



**Fig. 2.** A: PET/CT scan showing mild FDG uptake in the Left Lower Lobe Nodule. B: PET/CT scan showing mild FDG uptake in the Right Middle Lobe Nodule.

tumor markers, including CA-125 and CEA, were normal. FSH was normal as well. Based on the nature of the cysts and negative tumor markers, metastatic ovarian cancer to the lungs was deemed highly unlikely and a referral was made to the lung cancer center.

PET/CT was ordered to further assess the nodules and assess for any extra-pulmonary areas of abnormal uptake. It again showed the largest nodule measuring 13 × 14 mm in the LLL, and a middle lobe nodule measuring 10 × 10 mm, both demonstrating mild FDG uptake (Fig. 2A and B).

When compared with a CT performed four years prior, the LLL nodule was new and the middle lobe nodule had increased in size since that time (Fig. 3). Also, at least 7 other smaller nodules, which were beneath the threshold of reliable characterization with PET FDG imaging, were seen with no significant extra-thoracic sites of abnormal FDG uptake.

Based on these findings she underwent a CT guided biopsy of the LLL nodule. Pathology identified a low grade (2/8 HPF mitosis), benign appearing, smooth muscle tumor. Immunohistochemical staining showed smooth-muscle actin and desmin, but was negative for CD117, HMB-45, CD34, pan cytokeratin and EMA. An estrogen receptor was

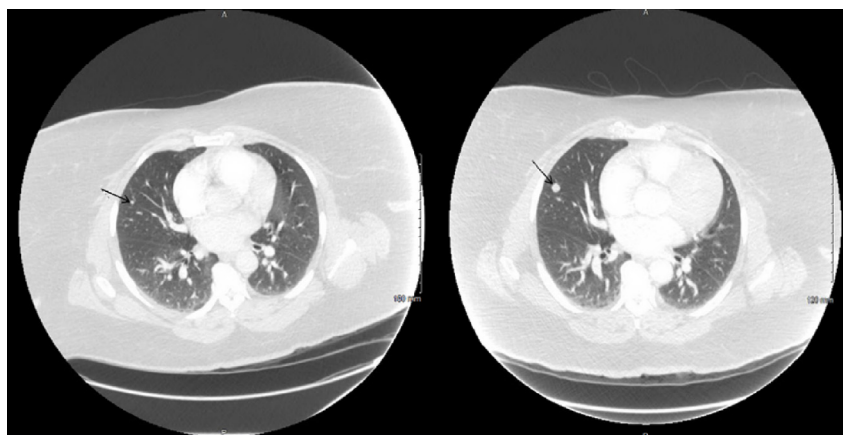


Fig. 3. CT chests with PE protocol comparing Right Middle Lobe nodule over 4 years.

present with patchy positivity and a progesterone receptor was strongly and diffusely positive. Given her history, these findings were suggestive of benign metastasizing uterine leiomyoma.

Due to concerns about a possible sampling error missing features of a more aggressive leiomyosarcoma, as well as to get fresh tissue for cytogenetic analysis, she underwent a video-assisted thoracoscopic surgery (VATS) wedge resection of the LLL nodule. Pathology again confirmed cytologically bland-appearing spindle cell neoplasm, with entrapment of bronchiolar epithelium and no significant nuclear atypia or necrosis. Mitotic activity was low (up to 2 mitoses per 10 high power fields), with no margin involvement identified. Properly controlled immunostaining showed the neoplastic cells to lack expression of HMB-45 and CD117 (c-kit) (no support for lymphangioliomyomatosis or gastrointestinal stromal tumor, respectively) as before. A properly controlled DOG-1 (discovered on GIST) immunostain was positive, a result typically associated with gastrointestinal stromal tumor. However, this result has also been reported for uterine type retroperitoneal leiomyomas and peritoneal leiomyomatosis [19] (Fig. 4A–F). Cytogenetic analysis was also performed. Karyotyping showed an abnormal result, including loss of chromosomes 19 and 22 and deletion of 1p, in addition to other abnormalities (Fig. 5). This was consistent with the diagnosis of pulmonary benign metastasizing leiomyoma.

The patient was started on the daily aromatase inhibitor, Anastrozole. She tolerated the medication without any side effects. Three-month follow up CT scans showed a decrease in the size of pulmonary nodules. Six and 12-month CT scans have shown stable disease.

### 3. Discussion

BML is a rare disease, first described in 1939 by Steiner [11], with about 100 cases described in the literature to date [2]. The pathogenesis and etiology have remained controversial with hematogenous spread of benign uterine tumor, local smooth muscle tissue proliferation or metastatic low grade leiomyosarcoma as proposed etiologies [2]. It is usually seen in women of reproductive age with a history of uterine leiomyoma who underwent hysterectomy, favoring the hematogenous/iatrogenic spread of the tumor, yet in some cases lung nodules existed even before hysterectomy, as in our case [3,8]. However, the cytogenetic studies demonstrating a monoclonal origin of both uterine and lung tumors, along with positive hormone receptors and response to hormonal therapy, support the hypothesis [2,12,13]. Cytogenetic

studies have also shown that BML is a genetically distinct and definable entity with a 19q and 22q deletions, amongst others. Such changes are also found in a small genetically distinctive subset of uterine leiomyomata, supporting a common origin [18].

The average age of patients diagnosed with BML is 48 years with about a 3 month to 20 year span between hysterectomy and lung findings [14,16]. Open/thoracoscopic lung biopsy is the standard diagnostic modality [3].

Pulmonary smooth muscle proliferations can either be primary, including hamartomas, lymphangioliomyomatosis, leiomyoma and leiomyosarcoma, or metastatic, including metastatic leiomyosarcoma and BML. The low mitotic index (< 5 mitoses per 10 high power fields), lack of nuclear pleomorphism, lack of local invasion and distinctive karyotypic profile helps differentiate BML from other possible diagnoses [4,15,18].

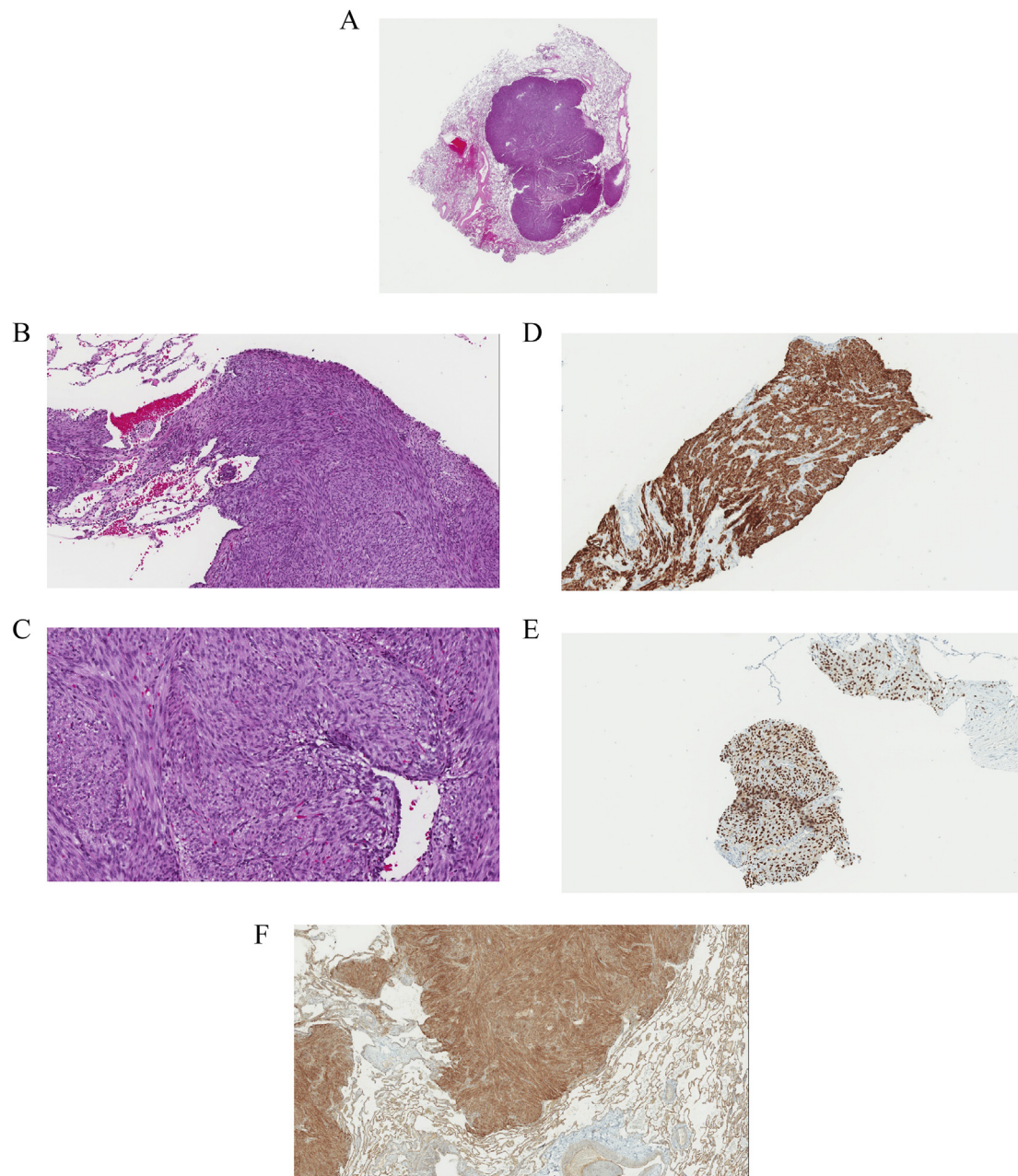
Due to the rarity of the disease, currently there are no treatment guidelines for BML. Multiple options have been reported in the literature, including close observation, surgical resection or antiestrogen therapy (e.g., selective estrogen receptor modulator, progesterone, aromatase inhibitors, oophorectomy and gonadotropin-releasing hormone analogues) [5,17]. The preferred treatment is surgical resection if possible with hormonal therapy as an alternate. BML tends to typically have an indolent course and a favorable outcome, although pulmonary lesions may continue to progress, resulting in pulmonary insufficiency and even death [18].

### 4. Conclusion

Despite BML being a rare condition, it should be considered in the differential diagnosis in women of reproductive age with a history of uterine leiomyoma presenting with pulmonary nodules, solitary or multiple. Accurate histopathological analysis along with immunohistochemical staining and cytogenetic analysis are necessary to exclude other spindle cell neoplasms.

### Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.



**Fig. 4.** A: Low power view of the lung wedge resection specimen showing a well-circumscribed nodule composed of cytologically bland appearing spindle cells arranged in a fascicular pattern. B: Medium power view of the lung wedge resection specimen showing the fascicular pattern of the nodule with entrapped benign bronchiolar epithelium (epithelial entrapment rather than obliteration being a reflection of indolent rather than aggressive growth of the neoplasm). C: High power view of the lung wedge resection specimen showing the cytologically bland appearance of the spindle cells (lack of any significant nuclear atypia); also, inconspicuous mitoses (no significant mitotic activity), and no necrosis. D: Core biopsy, desmin immunostain (marker of smooth muscle and skeletal muscle differentiation), showing strong and diffuse expression in the neoplastic cells. The appearance of the smooth muscle actin (SMA) immunostain, which was also done on the core, is identical. E: Core biopsy, progesterone receptor immunostain, showing strong and diffuse nuclear expression in the neoplastic cells. The estrogen receptor immunostain showed similar results. F: Wedge resection specimen, DOG-1 immunostain, showing unexpected diffuse expression in the neoplastic cells. The CD117 (c-kit) immunostain was negative. The DOG-1 is typically positive for GIST, but has also been reported to show expression in some uterine type retroperitoneal leiomyomas and peritoneal leiomyomatosis.

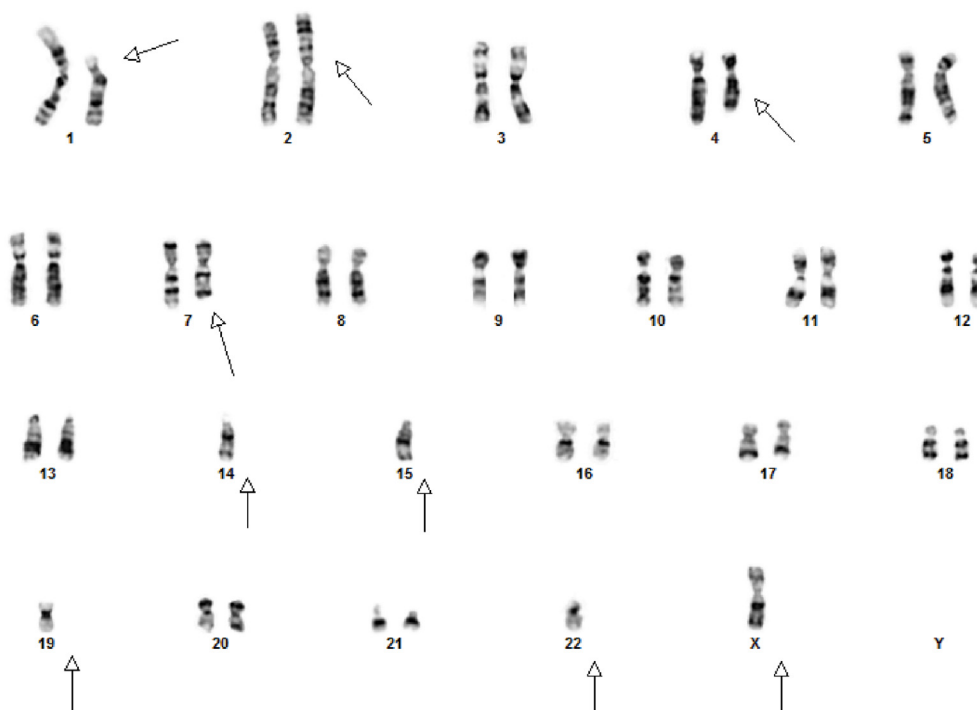


Fig. 5. Karyotype showing 41,X,-X,add(1)(p13),add(2)(p17),del(4)(q12q21),add(7)(q22),-14,-15,-19,-22[14]/46,XX[6].

## Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

## Acknowledgement

The authors would like to express their gratitude to Alan T. Davis, PhD and Tracy J. Koehler, PhD from Spectrum Health GME – Research and Scholarly Support Department for reviewing this article.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmcr.2018.04.017>.

## References

- [1] S.J. Robboy, R.C. Bentley, K. Butnor, M.C. Anderson, Pathology and pathophysiology of uterine smooth-muscle tumors, *Environ. Health Perspect.* 108 (Suppl 5) (2000 Oct) 779–784 Review. PubMed PMID: 11035982.
- [2] D. Fan, X. Yi, Pulmonary benign metastasizing leiomyoma: a case report, *Int. J. Clin. Exp. Pathol.* 7 (10) (2014 Sep 15) 7072–7075 eCollection 2014. PubMed PMID: 25400799; PubMed Central PMCID: PMC4230157.
- [3] S. Chen, R.M. Liu, T. Li, Pulmonary benign metastasizing leiomyoma: a case report and literature review, *J. Thorac. Dis.* 6 (6) (2014 Jun) E92–E98, <http://dx.doi.org/10.3978/j.issn.2072-1439.2014.04.37> PubMed PMID: 24977035; PubMed Central PMCID:PMC4073417.
- [4] M.E. Vaquero, J.F. Magrina, K.O. Leslie, Uterine smooth-muscle tumors with unusual growth patterns, *J. Minim. Invasive Gynecol.* 16 (3) (2009 May-Jun) 263–268, <http://dx.doi.org/10.1016/j.jmig.2009.01.013> Review. PubMed PMID: 19423058.
- [5] R. Taftaf, S. Starnes, J. Wang, R. Shipley, T. Namad, R. Khaled, N. Abdel Karim, Benign metastasizing leiomyoma: a rare type of lung metastases-two case reports and review of the literature, *Case Rep. Oncol. Med.* 2014 (2014) 842801, <http://dx.doi.org/10.1155/2014/842801> Epub 2014 Feb 12. PubMed PMID: 24716049; PubMed Central PMCID: PMC3970365.
- [6] H.W. Jeon, S.H. Choi, S.W. Sung, J.K. Park, Pulmonary benign metastasizing leiomyoma: report of three cases, *World J. Surg. Oncol.* 11 (2013 Oct 20) 281, <http://dx.doi.org/10.1186/1477-7819-11-281> PubMed PMID: 24139514; PubMed Central PMCID:PMC3828480.
- [7] L. Cobellis, M.A. Castaldi, L. Mosca, V. Frega, D. Ambrosio, F. Corvino, N. Colacurci, Benign pulmonary metastasizing leiomyomatosis: case report, *Eur. J. Gynaecol. Oncol.* 35 (2) (2014) 195–198 PubMed PMID: 24772929.
- [8] J.A. Rivera, S. Christopoulos, D. Small, M. Trifiro, Hormonal manipulation of benign metastasizing leiomyomas: report of two cases and review of the literature, *J. Clin. Endocrinol. Metab.* 89 (7) (2004 Jul) 3183–3188 Review. PubMed PMID: 15240591.
- [9] A.S. Rege, J.A. Snyder, W.J. Scott, Benign metastasizing leiomyoma: a rare cause of multiple pulmonary nodules, *Ann. Thorac. Surg.* 93 (6) (2012 Jun) e149–e151, <http://dx.doi.org/10.1016/j.athoracsur.2011.12.047> PubMed PMID: 22632533.
- [10] H. Ma, J. Cao, Benign pulmonary metastasizing leiomyoma of the uterus: a case report, *Oncol. Lett.* 9 (3) (2015 Mar) 1347–1350 Epub 2015 Jan 15. PubMed PMID:25663911.
- [11] P.E. Steiner, Metastasizing fibroleiomyoma of the uterus: report of a case and review of the literature, *Am. J. Pathol.* 15 (1) (1939 Jan) 89–110.7. PubMed PMID:19970436; PubMed Central PMCID: PMC1965022.
- [12] L. Tietze, K. Günther, A. Hörbe, C. Pawlik, B. Klosterhalfen, S. Handt, S. Merkelbach-Bruse, Benign metastasizing leiomyoma: a cytogenetically balanced but clonal disease, *Hum. Pathol.* 31 (1) (2000 Jan) 126–128 PubMed PMID: 10665925.
- [13] H.J. Lee, J. Choi, K.R. Kim, Pulmonary benign metastasizing leiomyoma associated with intravenous leiomyomatosis of the uterus: clinical behavior and genomic changes supporting a transportation theory, *Int. J. Gynecol. Pathol.* 27 (3) (2008 Jul) 340–345, <http://dx.doi.org/10.1097/PGP.0b013e3181656dab> PubMed PMID: 18580311.
- [14] S. Abramson, R.C. Gilkeson, J.D. Goldstein, P.K. Woodard, R. Eisenberg, N. Abramson, Benign metastasizing leiomyoma: clinical, imaging, and pathologic correlation, *AJR Am. J. Roentgenol.* 176 (6) (2001 Jun) 1409–1413 PubMed PMID: 11373202.
- [15] A.O. Awonuga, V.I. Shavell, A.N. Imudia, M. Rotas, M.P. Diamond, E.E. Puscheck, Pathogenesis of benign metastasizing leiomyoma: a review, *Obstet. Gynecol. Surv.* 65 (3) (2010 Mar) 189–195, <http://dx.doi.org/10.1097/OGX.0b013e3181d60f93> Review. PubMed PMID:20214834.
- [16] G. Jautzke, E. Müller-Ruchholtz, U. Thalmann, 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.* 192 (3) (1996 Mar) 215–223 Review. PubMed PMID: 8739468.
- [17] Y. Fu, H. Li, B. Tian, B. Hu, Pulmonary benign metastasizing leiomyoma: a case report and review of the literature, *World J. Surg. Oncol.* 10 (2012 Dec 12) 268, <http://dx.doi.org/10.1186/1477-7819-10-268> Review. PubMed PMID: 23234399; PubMed Central PMCID:PMC3545911.
- [18] M.R. Nucci, R. Drapkin, P. Dal Cin, C.D. Fletcher, J.A. Fletcher, Distinctive cytogenetic profile in benign metastasizing leiomyoma: pathogenetic implications, *Am. J. Surg. Pathol.* 31 (5) (2007 May) 737–743 PubMed PMID: 17460458.
- [19] M. Miettinen, Z.F. Wang, J. Lasota, DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases, *Am. J. Surg. Pathol.* 33 (9) (2009 Sep) 1401–1408, <http://dx.doi.org/10.1097/PAS.0b013e3181a90e1a> PubMed PMID: 19606013.