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CASE BASED REVIEWS

Lung metastases from benign uterine leiomyoma: does 18-FDG-PET/CT have a role to play?

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Abstract

Uterine leiomyomas are the most common benign gynaecological tumours. However, 0.13 to 6% of them have malignant potential (Robboy et al. Environ Health Perspect 108(Suppl 5):779–784, 2000). Uterine smooth muscle tumours with unusual growth patterns include a spectrum of lesions such as intravenous leiomyomatosis, benign metastasizing leiomyoma and disseminated peritoneal leiomyomatosis (Vaquero et al. J Minim Invasive Gynecol 16:263–268, 2009). Benign metastasizing leiomyoma (BML) is a very rare condition with around 100 cases reported to date. BML is a cytologically bland, mitotically inactive smooth muscle tumour in extra uterine sites, occurring in conjunction with similarly appearing or previously removed uterine leiomyomas (Beck et al. Hong Kong Med J = Xianggang yi xue za zhi 18:153–155, 2012). Pulmonary metastases are the most common sites of metastases, but other sites include skin, bladder, liver, lymph nodes, oesophagus, skeletal muscles, heart, bones and central nervous system (Jo et al. Korean J Int Med 21:199–201, 2006; Arai et al. Chest 117:921–922, 2000; Kwon et al. Korean J Int Med 21:173–177, 2006; Rivera et al. J Clin Endocrinol Metab 89:3183–3188, 2004; Jautzke et al. Pathol Res Pract 192:215–223, 1996; Goyle et al. Am J Clin Oncol 26:473–476, 2003; Schneider et al. Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen 72:308–311, 2001; Andrade et al. Pathol Oncol Res: POR 4:44–47, 1998; Abramson et al. AJR Am J Roentgenol 176:1409–1413, 2001; Yoon et al. Cancer Res Treat 43:131–133, 2011; Egberts et al. Arch Gynecol Obstet 274:319–322, 2006). The condition is more common in late childbearing age, mean age of diagnosis is 43 years (Kwon et al. Korean J Int Med 21:173–177, 2006), suggesting that it is hormone related. Lung metastases in BML are usually an incidental finding during the preoperative assessment; however, on rare occasions, patients are symptomatic with cough, chest pain, haemoptysis or dyspnoea. The differential diagnosis includes pulmonary metastases from leiomyosarcoma, intravenous leiomyomatosis or metastasis from other malignancies. Lung biopsy is the only way to confirm the benign nature of these lesions. Recently, positron emission tomography (PET) scan showed promise in differentiating these benign lesions from malignant lung lesion (Sawai et al. Oncol Lett 14:3641–3646, 2017). We present three cases with pulmonary metastases from BML and discuss the pathogenesis and management of this rare condition.

Keywords Leiomyoma · PET scan

Case 1

A 55-year-old post-menopausal patient presented with an incidental finding of multiple pulmonary nodules on a chest x-ray and she was investigated for a possible stage IV cancer of unknown primary. CT thorax, abdomen and pelvis revealed multiple bilateral pulmonary nodules, the largest measuring 1.5 × 1.2 cm in the right upper lobe (Fig. 1a). No mediastinal lymphadenopathy or pleural effusion was found. Several subcentimetre soft tissue nodules within the lateral and outer aspect of the left breast were deemed to be small intermammary lymph nodes. A mammogram was negative for malignancy. A 2.1 × 2.0 cm enhancing mass within the right lateral aspect of the uterine body was identified. No pelvic lymphadenopathy or ascites were found. PET (positron emission tomography) CT revealed strong FDG (fluorodeoxyglucose) avid uterine mass, but the pulmonary

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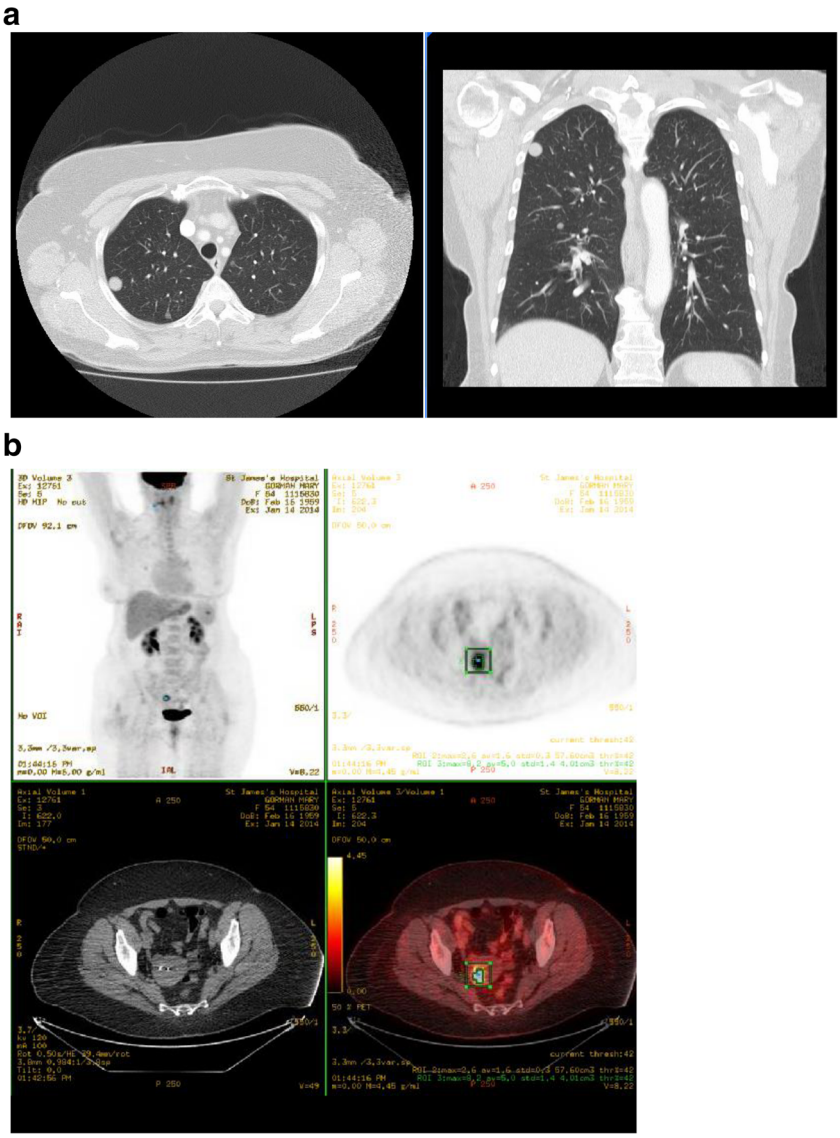

Fig. 1 Radiological findings for case 1. **a** CT scan of multiple pulmonary nodule the largest measure 1.5 × 1.2 cm. **b** The fusion image of 18-FDG-PET/CT in the coronal and transverse plane. Only one lesion in the uterus exhibited a positive accumulation of 18-FDG with negative pulmonary nodules

nodules were not FDG avid (Fig. 1b). The patient underwent a CT-guided lung biopsy of the subpleural right upper lobe lesion. The procedure was complicated by a moderate pneumothorax without symptoms which did not require a chest drain. The biopsy revealed a bland smooth muscle tumour with cells which were strongly smooth muscle actin, desmin, calsdesmon and oestrogen receptor positive, focally CD10 positive, but negative for pancytokeratin, S100, HMB45 and CD34 (Fig. 2). The findings were suggestive of metastasising leiomyoma. Pelvic surgery was postponed for 6 weeks pending resolution of pneumothorax. The patient underwent a laparoscopic hysterectomy and bilateral salpingo-oophorectomy and the final histology revealed no evidence of malignancy, a benign endometrial polyp, multiple benign leiomyomata, including one cellular leiomyoma and adenomyosis. Both adnexa were normal. The leiomyomata showed no evidence of atypia, necrosis or increased mitoses and immunohistochemistry supported smooth muscle differentiation. The patient had an uneventful recovery. Patient had a follow-up CT thorax at 12 and 24 months post surgery. There were no changes on the size of pulmonary lesion. Patient remains asymptomatic 42 months post treatment.

Case 2

A 52-year-old post-menopausal patient with history of idiopathic thrombocytopenic purpura presented with chest pain. X-ray showed increased density in left hilum and a calcified upper lobe granuloma. A follow-up CT thorax showed multiple pulmonary nodules concerning for metastasis; the largest measured 2.2 cm (Fig. 3a). Patient had a history of uterine fibroid embolization 2 years before this presentation. PET scan showed strong FDG avid uterine mass; however, the

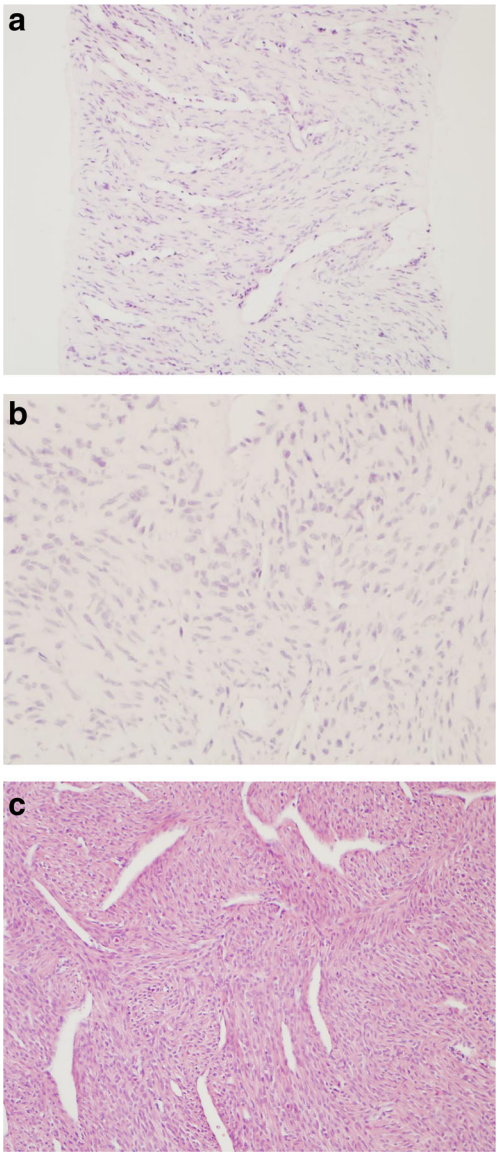

Fig. 2 Case 1 Biopsy of lung lesion showed a bland proliferation of smooth muscle without atypia, necrosis or increased mitotic activity (H&E stain, × 100 magnification) (**a**). There was strong oestrogen receptor staining (**b**). Case 1 Hysterectomy showed a bland uterine leiomyoma (H&E stain × 100 magnification) (**c**)

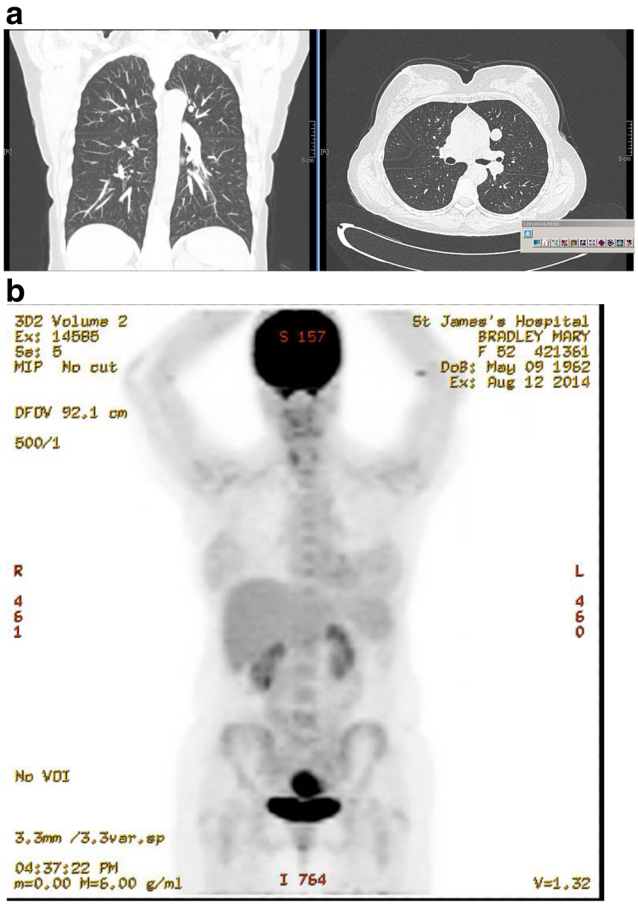

Fig. 3 Radiological findings for case 2. **a** CT scan of multiple pulmonary nodule the largest measure 1.5*1.2 cm. **b** The fusion image of 18-FDG-PET/CT in the coronal plane. Only one lesion in the uterus exhibited a positive accumulation of 18-FDG with negative pulmonary nodules

pulmonary nodules were not FDG avid (Fig. 3b). Patient had CT-guided pulmonary biopsy; this was complicated with pneumothorax which required a chest drain. The biopsy revealed a bland smooth muscle tumour without necrosis, mitosis or pleomorphism, with cells staining strongly for smooth muscle actin, desmin and oestrogen receptor positive, focally CD10 positive, but negative for pancytokeratin, S100, HMB45 and CD34 (Fig. 4). The findings were suggestive of metastasising leiomyoma. Patient had laparoscopic hysterectomy with bilateral salpingo-oophorectomy after resolution of pneumothorax. Final histology confirms benign uterine leiomyoma. Patient had two CT thorax scans at 12 and 24 months post-surgery. Pulmonary lesion remained stable and she remains asymptomatic 36 months after surgical treatment.

Case 3

A 56-year-old post-menopausal patient attended the emergency room with interscapular chest pain; admission chest X-ray was negative, but CT thorax showed multiple bilateral pulmonary nodules concerning for metastasis (Fig. 5). Investigation for a primary site included a pelvic MRI that revealed an 8-cm cervical tumour but without parametrial extension. The differential diagnosis was cervical cancer, cervical leiomyoma or pedunculated polyp. Clinical examination revealed apparent cervical fibroid. The patient was advised to have lung biopsy and to progress to hysterectomy to obtain a definite histology diagnosis, but she declined surgery. PET CT scan was performed and that did not show any increase in FDG avidity in either pulmonary nodules or cervical mass. Patient had a follow-up CT thorax, abdomen and pelvis at 6 and 12 months.

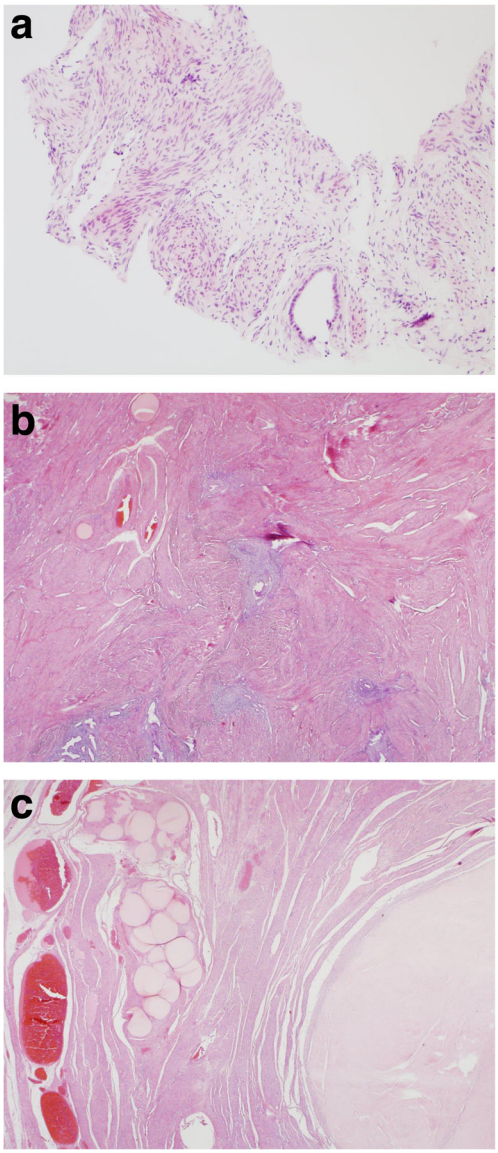

Fig. 4 Case 2 Biopsy of lung lesion showed a bland proliferation of smooth muscle without atypia, necrosis or increased mitotic activity (H&E stain, × 100 magnification) (**a**). Hysterectomy showed extensive adenomyosis (**b**) with a 9-mm hyalinised leiomyoma (**c**). Embolisation beads can be seen in the upper left aspect of Fig. 2b, c

Pelvic and pulmonary lesions remain stable. She is 18 months now since diagnosis with no symptoms.

Discussion

Steiner in 1939 reported the first case in the literature and presented it as fibroleiomyomatous hamartoma [1]. Based on the unusual pattern of metastases from a benign tumour, some authors believe that benign metastasizing leiomyoma (BML) is a misnomer for low-grade malignant tumours that have a low proliferation index [2, 3].

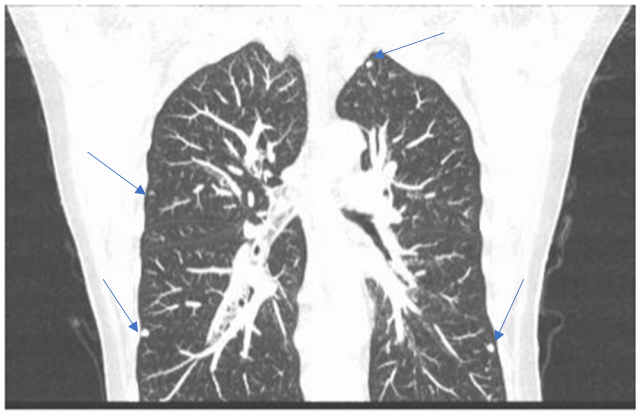

Fig. 5 CT Thorax for case 3. Imaging performed with oral and intravenous contrast multiple bilateral pulmonary nodules, some of which are calcified. No hilar lymphadenopathy

There are several theories on the pathogenesis of metastases in BML. It is likely that haematogenous spread of a monoclonal element of the tumour occurs. Chromosomal abnormalities have been demonstrated in 25% of such tumours including balanced translocation, trisomy 12 or rearrangement of 6p [4, 5]. Other suggested mechanisms include lymphovascular embolization, mesothelial mesenchymal metaplasia and seeding from ruptured leiomyomas, as well as true metastases from low-grade uterine leiomyosarcomas [6, 7]. Similar to our cases, multiple or solitary non-calcified contrast-enhancing nodules are found in the chest x-ray or CT scan, varying in size between millimetres to even few centimetres. The lesions may arise late after myomectomy or hysterectomy and intervals of up to 26 years have been described [8]. Our patients were diagnosed preoperatively and the third patient decided not to have surgery.

Definite diagnosis could be achieved either with open lung, transbronchial or transthoracic lung biopsy based on the comparison with the pathologic findings of the leiomyoma. However, this is not without risk of complication. Pneumothorax complicates 6–20% of CT-guided transthoracic biopsies [9]. Two of our patients had pneumothorax, as a result of which their surgery was postponed. Full resolution of pneumothorax is necessary before general anaesthesia.

In our patients, none of the pulmonary nodules showed metabolic uptake of 18-fluoro-deoxy-glucose (FDG) in the total body PET CT scan, although the primary tumour in the uterus was FDG avid in two patients. The PET-negative metastasis may help to differentiate BML from sarcomas. Thirty-six cases of BML and PET scan have been reported previously. In 33 cases, there was none or little FDG uptake similar to our patients. The remaining three cases did show uptake, and in one of these three cases, the tumour showed aggressive behaviour [10]. When the PET scan is negative for lung metastasis it may be reasonable to forgo the lung biopsy. More clinical series are required.

The histological and immunohistochemical findings of BML are those of a typical uterine leiomyoma: no tumour cell necrosis, no nuclear atypia and low mitotic rate (< 1 mitotic figure/10 high-power field) [11, 12] with oestrogen and progesterone receptor positive. Despite that, it is still unclear why the BML did not show FDG uptake while the uterine leiomyoma did. Some reports showed an association between FDG uptake in uterine fibroid and oestrogen receptor status. In our cases, the two BML stain strongly for oestrogen receptor, yet not FDG avid.

The management of BML varies from expectancy, withdrawal of external oestrogen, pharmacological treatment including (high-dose progestogens (e.g. megestrol acetate), GnRH analogues, oestrogen receptor blockers (e.g. tamoxifen, raloxifen), aromatase inhibitors, tyrosine kinase inhibitors (e.g.imatinib)) and surgical castration by doing oophrectomy [6, 13–20] . Some studies describe regression of the pulmonary nodules after pharmacological management [6, 21]. Surgical excision of solitary or few nodules is considered to definitively exclude malignancy [14, 19] . With regard to follow-up we did CT imaging of the chest every 6 months. Radiological exposure from repeat CT scanning is a concern for women. Since there has been no change in the first 2 years of follow-up, we are recommending further follow-up with chest X-ray only. In the knowledge, these lesions are PET negative; it may emerge that chest X-ray surveillance from the start may be sufficient.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

References

1. Steiner PE (1939) Metastasizing fibroleiomyoma of the uterus: report of a case and review of the literature. Am J Pathol 15:89–110.7
2. Bodner-Adler B, Bartl M, Wagner G (2009) Intravenous leiomyomatosis of the uterus with pulmonary metastases or a case with benign metastasizing leiomyoma? Anticancer Res 29:495–496
3. Banner AS, Carrington CB, Emory WB, Kittle F, Leonard G, Ringus J, Taylor P, Addington WW (1981) Efficacy of oophorectomy in lymphangioleiomyomatosis and benign metastasizing leiomyoma. N Engl J Med 305:204–209. https://doi.org/10.1056/nejm198107233050406
4. Esteban JM, Allen WM, Schaerf RH (1999) Benign metastasizing leiomyoma of the uterus: histologic and immunohistochemical characterization of primary and metastatic lesions. Arch Pathol Lab Med 123:960–962. https://doi.org/10.1043/0003-9985(1999)123<0960:bmlotu>2.0.co;2
5. Uchida T, Tokumaru T, Kojima H, Nakagawaji K, Imaizumi M, Abe T (1992) A case of multiple leiomyomatous lesions of the lung: an analysis of flow cytometry and hormone receptors. Surg Today 22:265–268
6. Beck MM, Biswas B, D'Souza A, Kumar R (2012) Benign metastasising leiomyoma after hysterectomy and bilateral salpingo-oophorectomy. Hong Kong Med J = Xianggang yi xue za zhi 18:153–155
7. Awonuga AO, Rotas M, Imudia AN, Choi C, Khulpateea N (2008) Recurrent benign metastasizing leiomyoma after hysterectomy and bilateral salpingo-oophorectomy. Arch Gynecol Obstet 278:373–376. https://doi.org/10.1007/s00404-008-0581-z
8. Radzikowska E, Szczepulska-Wojcik E, Langfort R, Oniszh K, Wiatr E (2012) Benign pulmonary metastasizing leiomyoma uteri. Case report and review of literature. Pneumonol Alergol Pol 80:560–564
9. Dhooria S, Mehta R, Srinivasan A, Madan K, Sehgal IS, Pattabhiraman V, Yadav P, Sivaramakrishnan M, Mohan A, Bal A, Garg M, Agarwal R (2017) A multicenter study on the safety and efficacy of different methods for obtaining transbronchial lung cryobiopsy in diffuse lung diseases. Clin Respir J. https://doi.org/10.1111/crj.12734
10. Sawai Y, Shimizu T, Yamanaka Y, Niki M, Nomura S (2017) Benign metastasizing leiomyoma and 18-FDG-PET/CT: a case report and literature review. Oncol Lett 14:3641–3646. https://doi.org/10.3892/ol.2017.6609
11. Kayser K, Zink S, Schneider T, Dienemann H, Andre S, Kaltner H, Schuring MP, Zick Y, Gabius HJ (2000) Benign metastasizing leiomyoma of the uterus: documentation of clinical, immunohistochemical and lectin-histochemical data of ten cases. Virchows Arch 437:284–292
12. Patton KT, Cheng L, Papavero V, Blum MG, Yeldandi AV, Adley BP, Luan C, Diaz LK, Hui P, Yang XJ (2006) Benign metastasizing leiomyoma: clonality, telomere length and clinicopathologic analysis. Mod Pathol 19:130–140. https://doi.org/10.1038/modpathol.3800504
13. Robboy SJ, Bentley RC, Butnor K, Anderson MC (2000) Pathology and pathophysiology of uterine smooth-muscle tumors. Environ Health Perspect 108(Suppl 5):779–784
14. Rivera JA, Christopoulos S, Small D, Trifiro M (2004) Hormonal manipulation of benign metastasizing leiomyomas: report of two cases and review of the literature. J Clin Endocrinol Metab 89:3183–3188. https://doi.org/10.1210/jc.2003-032021
15. Tietze L, Gunther K, Horbe A, Pawlik C, Klosterhalfen B, Handt S, Merkelbach-Bruse S (2000) Benign metastasizing leiomyoma: a cytogenetically balanced but clonal disease. Hum Pathol 31:126–128
16. Abu-Rustum NR, Curtin JP, Burt M, Jones WB (1997) Regression of uterine low-grade smooth-muscle tumors metastatic to the lung after oophorectomy. Obstet Gynecol 89:850–852
17. Horstmann JP, Pietra GG, Harman JA, Cole NG, Grinspan S (1977) Spontaneous regression of pulmonary leiomyomas during pregnancy. Cancer 39:314–321
18. Ruther U, Nunnensiek C, Sessler R, Stilz S, Ulshofer T, Muller H, Bader H, Bokemeyer C, Toomes H, Jipp P (1996) Efficacy of antiestrogen treatment in a benign metastasizing leiomyoma with paraneoplastic estradiol production. Oncol Rep 3:293–299
19. Saynajakangas O, Maiche AG, Liakka KA (2004) Multiple progressive pulmonary leiomyomatous metastases treated with tamoxifen–a case report with a review of the literature. Acta oncologica (Stockholm, Sweden) 43:113–114
20. Ishikawa H, Fenkci V, Marsh EE, Yin P, Chen D, Cheng YH, Reisterd S, Lin Z, Bulun SE (2008) CCAAT/enhancer binding protein beta regulates aromatase expression via multiple and novel cis-

regulatory sequences in uterine leiomyoma. J Clin Endocrinol Metab 93:981–991. https://doi.org/10.1210/jc.2007-2507
21. Wentling GK, Sevin BU, Geiger XJ, Bridges MD (2005) Benign metastasizing leiomyoma responsive to megestrol: case report and review of the literature. Int J Gynecol Cancer 15:1213–1217. https://doi.org/10.1111/j.1525-1438.2005.00190.x
22. Vaquero ME, Magrina JF, Leslie KO (2009) Uterine smooth-muscle tumors with unusual growth patterns. J Minim Invasive Gynecol 16:263–268. https://doi.org/10.1016/j.jmig.2009.01.013
23. Jo JH, Lee JH, Kim DC, Kim SH, Kwon HC, Kim JS, Kim HJ (2006) A case of benign metastasizing leiomyoma with multiple metastasis to the soft tissue, skeletal muscle, lung and breast. Korean J Int Med 21:199–201
24. Arai T, Yasuda Y, Takaya T, Shibayama M (2000) Natural decrease of benign metastasizing leiomyoma. Chest 117:921–922
25. Kwon YI, Kim TH, Sohn JW, Yoon HJ, Shin DH, Park SS (2006) Benign pulmonary metastasizing leiomvomatosis: case report and a review of the literature. Korean J Int Med 21:173–177
26. Jautzke G, Muller-Ruchholtz E, Thalmann U (1996) 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 192:215–223. https://doi.org/10.1016/s0344-0338(96)80224-x
27. Goyle KK, Moore DF Jr, Garrett C, Goyle V (2003) Benign metastasizing leiomyomatosis: case report and review. Am J Clin Oncol 26:473–476. https://doi.org/10.1097/01.coc.0000037737.78080.E3
28. Schneider T, Kugler C, Kayser K, Dienemann H (2001) Benign, pulmonary metastatic leiomyoma of the uterus. Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen 72:308–311
29. Andrade LA, Torresan RZ, Sales JF Jr, Vicentini R, De Souza GA (1998) Intravenous leiomyomatosis of the uterus. A report of three cases. Pathol Oncol Res: POR 4:44–47
30. Abramson S, Gilkeson RC, Goldstein JD, Woodard PK, Eisenberg R, Abramson N (2001) Benign metastasizing leiomyoma: clinical, imaging, and pathologic correlation. AJR Am J Roentgenol 176:1409–1413. https://doi.org/10.2214/ajr.176.6.1761409
31. Yoon G, Kim TJ, Sung CO, Choi CH, Lee JW, Lee JH, Bae DS, Kim BG (2011) Benign metastasizing leiomyoma with multiple lymph node metastasis: a case report. Cancer Res Treat 43:131–133. https://doi.org/10.4143/crt.2011.43.2.131
32. Egberts JH, Schafmayer C, Bauerschlag DO, Janig U, Tepel J (2006) Benign abdominal and pulmonary metastasizing leiomyoma of the uterus. Arch Gynecol Obstet 274:319–322. https://doi.org/10.1007/s00404-006-0165-8