Benign pulmonary metastasizing leiomyomatosis: case report

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Summary

The authors report a rare case of leiomyomatosis of the lung diagnosed in a 43-year-old woman, with uterine intravenous leiomyomatosis. Benign metastasizing leiomyoma (BML) is an extremely rare lesion characterized by usually multiple, benign-appearing smooth muscle tumors of the lung in females with coexisting uterine leiomyoma. On the basis of their histological and immunohistological features, a unified histogenetic view of leiomyomas with vascular invasion (LWVI) and BML of the uterus is proposed. LWVI and BML may be the same pathological entity and microscopic vascular invasion may represent the metastatic mechanism of BML. LWVI seems to be the precursor of BML.

Key words: Benign metastasizing leiomyoma (BML); Uterine intravenous leiomyomatosis (LWVI); Pulmonary nodules.

Introduction

Benign metastasizing leiomyoma (BML) is a lesion extremely rare characterized by usually multiple, benign-appearing smooth muscle tumors of the lung [1,2] in females with coexisting uterine leiomyoma [3]. The entity is not described in the Word Health Organization (WHO) blue book. Less than 100 cases of leiomyoma of the lung have been reported in the literature [4-8].

The nature of BML has been debated since it was first reported in the English literature in 1939 [9]. In contrast to the original hypothesis that this was a benign leiomyoma colonizing the lung, some investigators believed it was a low-grade leiomyosarcoma [10] while others argued that it may represent primary pulmonary leiomyomatosis coexisting with a uterine leiomyoma. New evidence supports the notion that BML is clonally derived from benign-appearing uterine leiomyomas [3].

Total resection of the multiple nodules can only be performed in a very limited number of cases [11, 12]. These patients are usually asymptomatic and the clinical suspicion begins with the incidental discovery of pulmonary lesions [13]. The authors report here an interesting case of BML in a 43-year-old woman.

Case Report

A 43-year-old woman was referred to the authors' attention, at the Second University of Naples, for the appearance of cough lasting about one month, with expectoration of thick and dark mucus, but any other respiratory symptoms like hemoptysis, purulent sputum or exertional dyspnea were absent. She denied any fever, chills, weight loss, headache, myalgia or any other major symptoms. Her past medical history was remarkable in that she was previously diagnosed with uterine leiomyoma and underwent myomectomy with right-sided oophorectomy approximately 12 years ago. She also underwent surgery for two cesarean sections.

Laboratory studies including a complete blood count, a serum metabolic assay with liver function tests, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and anti-nuclear antibodies; all the tests showed normal results. Routine urine analysis for the cell count and casts, and the thyroid function test were also normal. Tumor markers: CEA, CA 19.9, CA 15.3, CA 125, and AFP were all negative.

Therefore, a chest radiograph was taken, which showed the presence of bilateral parenchymal nodules. Further evaluation led to a computed tomography (CT) scan of the chest (Figure 1: A, B) which showed: multiple parenchymal nodules, recurring type, in both lung fields, of which the most left upper lobe of 2.5 cm, and the basal of 1.86 cm. Bilateral axillary lymph node with package of 2.03 cm on the right. A CT scan of the abdomen and skull, mammography, and breast ultrasound were also performed to search for the primary origin of suspicious metastatic lung nodules. CT abdomen-pelvis (Figure 1: D) showed inhomogeneous uterus with heterogeneous impregnation area of about four cm.

After, the patient underwent a gynecological consultation, with a pelvic ultrasound which showed the presence of a solid formation of 35 x 24 mm at the bottom of the uterus and at the right side wall, with medium vascularization (R.I. 0.51), likely to be due to submucosal-intramural leiomyoma. Irregular endometrial echoes with thickness of five mm at the bottom were also seen. and hysterometry confirmed dimensions of 55 x 28 x 30 mm. Diagnostic hysteroscopy was also attempted, although during which the uterine cavity was not explored due to difficulty in passing the internal uterine orifice, probably due to a myomatous formation. Pap-test was negative.

Positron emission tomography-CT (PET-CT): high glucose metabolism in the following anatomical was performed in the following areas: basal anterior, basal-lateral, and lingular inferior segments of the left lung (Figure 1: C); basal anterior segment of the right lung, and cervix-body of the uterus (Figure 1: E). All these areas are related to eteroproliferative injuries.

In November 2012 the patient was hospitalized at the Operative Unit of Thoracic Surgery where she was subjected to atypical resection of the lingula and the culmen of the upper lobe of the left lung through video-assisted thoracic surgery (VATS). The patient was discharged in good general condition, afebrile, and with regular breathing at rest.

Subsequently, anatomical and histological analysis of the specimens resected was performed, and histological specimens were further analyzed at the National Cancer Institute of Milan.

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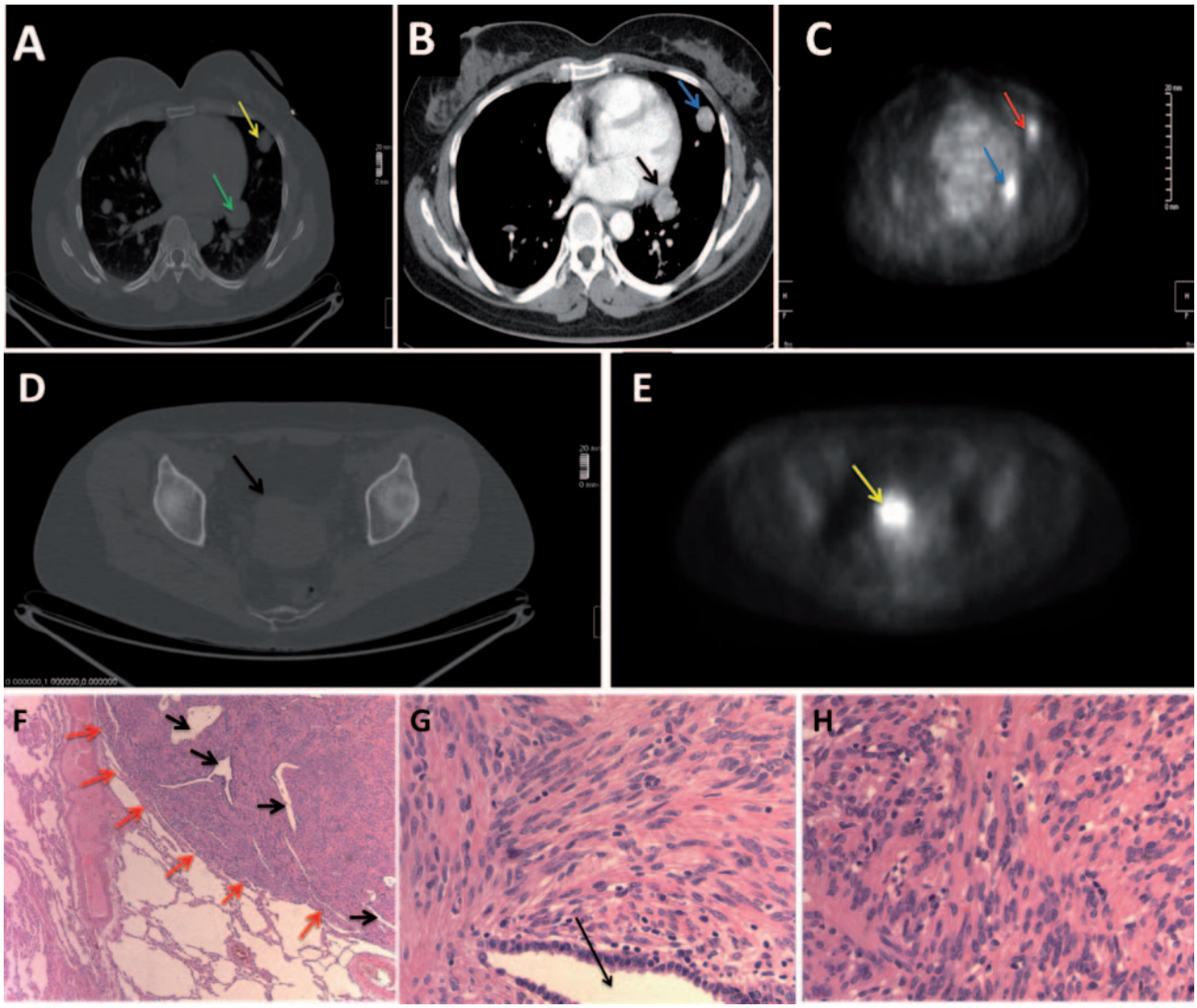

Figure 1. — A) CT scan of the chest showing multiple parenchymal nodules in both lung fields. The two major nodules are on the upper lobe of left lung: one in the lingular segment (green arrow), measuring 2.5 cm; the other in the anterior basal segment (yellow arrow), measuring 1.86 cm. B) CT scan with contrast showing marked enhancement of the pulmonary nodules; in particular the two major ones at the lingual (black arrow) and anterior basal segments (blue arrow) of upper lobe of left lung. C) PET scan: high glucose metabolism in the lingula (blue arrow) (SUV max 3.5) and anterior basal segment (red arrow) (SUV max 1.4) of upper lobe of left lung. D) CT scan of the abdomen and pelvis: inhomogeneous uterus with an heterogeneous impregnated area of about four cm (black arrow). E) PET-scan: high fluorodeoxyglucose uptake at/of cervix-body of the uterus (yellow arrow) (SUV max 5.6). F) Pathological examination of the pulmonary nodule of the lingula (red arrows) demonstrating smooth muscle cells arranged in broad, intersecting fascicles with entrapped bronchial epithelium (black arrow) G) Pathological examination of the pulmonary nodule of the left lung upper lobe: proliferation of spindle-shaped elements without marked nuclear atypia, compared with bronchiolar structures (black arrow). No significant mitotic index (<1x10 HPF) or necrosis were observed. H) Pathological examination of the uterus demonstrated the presence of smooth muscle tumor, with no necrosis, high mitotic index (<1/10 HPF), and nuclear atypia. Thus, uterine histology resulted similar to pulmonary one.

Macroscopically two nodular lesions of about 0.4 cm in diameter in the lingula, and a whitish nodule of 0.8 cm in the culmen of the upper lobe were described. Both lesions appeared to consist of proliferative spindle-shaped elements without marked nuclear atypia, a nodular growth, with net margins, compared with bronchiolar structures. A significant mitotic index was not observed (< 1 x 10 HPF), or necrosis (Figure 1: F, G). The immunohistochemical examination showed: caldesmin +, smooth muscle actin +, S100 -, Ki67 < 7%, hormone receptors estrogen-progestin +, WT1 (180 and C19) +, TFE3, and FLI1 -. The overall finding is attributable to well-differentiated smooth muscle tumors, gynecological type, with multiple locations in the lungs, consistent with the entity described as BML [3].

The patient was then admitted to the Second University of Naples, where she underwent in January 2013 total hysterectomy, left salpingectomy and oophorectomy, partial omentectomy, and omental biopsy. Macroscopically a 3 x 3 x 3.5 cm intramural nodule was seen, surrounded by other nodules of

about one cm, all sorted-homogeneous appearance, whitish and smooth margins. Microscopically: endometrium poorly represented with diffuse atrophy from compression. The nodules (Figure 1: H), described macroscopically, appeared to be composed of a proliferation of smooth muscle (desmin and smooth muscle actin +) and showed no necrosis, a high mitotic index (<1/10 HPF), and nuclear atypia, negative for S100, CD10, and CD34; focal positivity for p16 and p53, Ki67 5%. The morphological and immunohistochemical appearance seem consistent with leiomyomatosis of the uterine wall with a focal growth pattern paravenous (intravenous leiomyomatosis).

The patient was discharged from the hospital without any early postoperative complications. She will undergo close follow-up.

Discussion

The authors observed a patient with BML, which is an extremely rare lesion characterized by usually multiple, benign-appearing smooth muscle tumors of the lung [1, 2] in females with coexisting uterine leiomyoma [3]. The entity is not described in the WHO blue book. Approximately 100 cases have been reported in the literature, and the lungs were the most common site of metastases [5-8, 14, 15].

The nature of BML has been debated since it was first reported in the English literature in 1939 [9]. In contrast to the original hypothesis that this was a benign leiomyoma colonizing the lung, some investigators believed it was a low-grade leiomyosarcoma [15] while others argued that it may represent primary pulmonary leiomyomatosis coexisting with a uterine leiomyoma. New evidence supports the notion that BML is clonally derived from benign-appearing uterine leiomyomas [2].

The pathogenesis of this disease is unclear. Of the several possible mechanisms, hormone-dependent tumor growth might be most popularly accepted as spontaneous regression of the disease in pregnancy [16] and during the menopause [11] has been reported. Generally, uterine leiomyomas are known to be estrogen sensitive. In fact, both estrogen and progesterone receptors were identified in the lung tissues of the presented case, which is similar to other cases, suggesting that the pulmonary lesions represented metastatic nodules from benign tumors [13].

Uterine leiomyoma is the most common gynaecological neoplasm, with a prevalence of more than 50% of women above the age of 30 years. The majority of uterine leiomyomas are benign, and malignant behaviour was presented only in 0.13 to 6% of them [17].

Recently it has been suggested that BML is a result of monoclonal, hematogenous spread of benign-appearing uterine leiomyoma. The morphology, molecular, and immunohistochemical futures are characteristic of benign neoplasms in spite of the metastatic potential. As was shown in the presented case, as in others presented in the literature [14], BMLs have a low mitotic rate and MIB-1 index supporting the low proliferate activity of these tumours [12, 18–30].

Most of the BML patients have undergone a hysterectomy 0 to 24 years earlier [22] (in the presented case, the patient had already performed a myomectomy ten years before).

Patients are generally asymptomatic; therefore, the initial detection of the disease derives from other examinations for other purposes, like an annual health check examination. Yet there are a few cases presenting with symptoms such as dyspnea, dry cough, or chest pain [22, 23].

BML usually express estrogen and progesterone receptors, and the specimens from the presented patient were positive for sex hormone receptors [12, 15, 19-20]. This observation led to treatment based on antihormonal therapy and/or surgical resection [3, 12, 24-29].

Another new therapeutic option is tyrosine kinase inhibition. An overexpression of c-kit was shown in low-grade leiomyosarcoma and gastrointestinal stromal tumours, and suppression by imatinib was beneficial. It was suggested that this type of treatment might also be useful in BML patients [30].

It has also been postulated that BML may be the results of vascular invasion of a uterine leiomyoma or it may be related to intravenous leiomyomatosis [13, 30].

In conclusion, the authors report here a rare case of leiomyomatosis of the lung diagnosed in a 43-year-old women with uterine intravenous leiomyomatosis. Despite their histological benignity, these lesions have a strong tendency to metastasize and are closely related to the so-called BML. From a clinical point of view, the pulmonary nodules of LWVI are stable or slow-growing. On the basis of their histological and immunohistological features, a unified histogenetic view of LWVI and BML of the uterus is proposed. LWVI and BML may be the same pathological entity and microscopic vascular invasion may represent the metastatic mechanism of BML. LWVI seems to be the precursor of BML [30].

References

[1] Alessi G., Lemmerling M., Vereecken L., De Waele L.: "Benign metastasizing leiomyoma to skull base and spine: a report of two cases". *Clin. Neurol. Neurosurg.,* 2003, *105*, 170.

[2] Joseph V., Chacko G., Raghuram L., Rajshekhar V.: "Benign metastasizing leiomyoma causing spinal cord compression". *Surg. Neurol.*, 2003, *60*, 575.

[3] Patton K.T., Cheng L., Papavero V., Blum M.G, Yeldandi A.V., Adley B.P., et al. Benign metastasizing leiomyoma: clonality,telomere length and clinicopathologic analysis; Mod Pathol, 2006; 19, 130–140.

[4] Agnos J.W., Starkey G.W.: "Primary leiomyosarcoma and leiomyoma of the lung". *N. Engl. J. Med.*, 1958, *258*, 12.

[5] Orlowski T.M., Stasiak K., Kolodziej J.: "Leiomyoma of the lung". *J. Tjrac Cadiovas. Surg.*, 1978, *76*, 257.

[6] White S.H., Ibrahim N.B., Forrester-Wood C.P., Jeyasingham K.: "Leiomyoma of the lower respiratory tract". *Thorax*, 1985, *40*, 306.

[7] Gal A.A., Brooks J.S., Pietra G.G.: "Leiomyomatous neoplasms of the lung: a clinical, histologic and immunohistochemical study". *Mod. Pathol.*, 1990, *2*, 209.

[8] Tadashi T.: "Case Report: Vascular leiomyoma of the lung arising from pulmonary artery". *Int. J. Clin. Exp. Pathol.*, 2013, *6*, 97.

[9] Steiner P.: "Metastasizing fibroleiomyoma of the uterus: a report of a case and review of the literature". *Am. J. Pathol.*, 1939, *15*, 89.
[10] Cho K.R., Woodruff J.D., Epstein J.I.: "Leiomyoma of the uterus with multiple extrauterine smooth muscle tumors: a case report suggesting multifocal origin". *Hum. Pathol.*, 1989, *20*, 80.
[11] Arai T., Yasuda Y., Takay T., Shibayama M.: "Natural decrease of benign metastasizing leiomyoma". *Chest*, 2000, *117*, 921.
[12] Uchida T., Tokumaru T., Kojima H., Nakagawaji K., Imaizumi M., Abe T.: "A case of multiple leiomyomatous lesions of the lung: an analysis of flow cytometry and hormone receptors". *Surg. Today*, 1992, *22*, 265.
[13] Kwon Y.I., Kim T.H., Sohn J.W., Yoon H.J., Shin D.H., Park S.S.: "Benign pulmonary metastasizing leiomvomatosis: case report and a review of the literature". *Korean J. Intern. Med.*, 2006, *21*, 173.
[14] Radzikowska E., Szczepulska-Wójcik E., Langfort R., Oniszh K., Wiatr E.: "Benign pulmonary metastasizing leiomyoma uteri. Case report and review of literature". *Pneumonol. Alergol. Pol.*, 2012, *80*, 560.
[15] Abramson S., Gilkeson R.C., Goldstein J.D., Woodard P.K., Eisenberg R., Abramson N.l.: "Benign metastasizing leiomyoma: clinical, imaging, and pathologic correlation". *AJR Am. J. Roentgenol.*, 2001, *176*, 1409.
[16] Horstmann J.P., Pietra G.G., Harman J.A., Cole N.G., Grinspan S.: "Spontaneous regression of pulmonary leiomyomas during pregnancy". *Cancer*, 1977, *39*, 314.
[17] Robboy S.J., Bentley R.C., Butnor K., Anderson M.C.: "Pathology and pathophysiology of uterine smooth muscle tumors". *Environ. Health Perspect.*, 2000, *5 Suppl.*, 779.
[18] Kim Y.S., Kim E.J., Park C.H., Park J.S., Jee Y.K., Lee K.Y.: "A case of benign metastasizing pulmonary leiomyomatosis". *Tuberc. Respir. Dis.,* 2002, *53*, 190.
[19] Esteban J.M., Allen W.M., Schaerf R.H.: "Benign metastasizing leiomyoma of the uterus: histological and immunohistochemical characterization of primary and metastatic lesions". *Arch. Pathol. Lab. Med.,* 1999, *123*, 960.
[20] Kayser K., Zink S., Schneider T. Dienemann H, André S., Kaltner H., et al.: "Benign metastasizing leiomyoma of the uterus: documentation of clinical, immunohistochemical and lectin-histochemical data of ten cases". *Virchows Arch.*, 2000, *437*, 284.
[21] Shneider T., Kugler C., Kayser K., Dienemann H.: "Benign, pulmonary metastatic leiomyoma of the uterus". *Chirurg*., 2001, *72*, 308.
[22] Salminen U.S., Halttunen P., Miettinen M., Mattila S.: "Benign mesenchymal tumours of the lung including sclerosing hemangiomas". *Ann. Chir. Gynaecol.*, 1990, *79*, 85.
[23] Rivera J.A., Christopoulos S., Small D., Trifiro M.: "Hormonal manipulation of benign metastasizing leiomyomas ; Report of two cases and review of the literature". *J. Clin. Endocrinol. Metab.,* 2004, *89*, 3183.
[24] Tietze L., Günther K., Hörbe A., Pawlik C., Klosterhalfen B., Handt S., Merkelbach-Bruse S.: "Benign metastasizing leiomyoma: a cytogenetically balanced but clonal disease". *Hum. Pathol.*, 2000, *31*, 126.
[25] Abu-Rustum N.R., Curtin J.P., Burt M., Jones W.B.: "Regression of uterine low–grade smooth–muscle tumors metastatic to the lung after oophorecetomy". *Obstet. Gynecol.*, 1997, *89*, 850.
[26] Jacobson T.Z, Rainey E.J, Turton C.W.: "Pulmonary benign metastasizing leiomyoma: response to treatment with goserelin". *Thorax*, 1995, *50*, 1225.
[27] Saynajakangas O., Maiche A.G., Liakka K.A.: "Multiple progressive pulmonary leiomyomatous metastases treated with tamoxifen: a case report with a review of the literature". *Acta. Oncol.*, 2004, *43*, 113.
[28] Ishikawa H., Fenkci V., Marsh E.E., Yin P., Chen D., Cheng Y.H., *et al.*: "CCAAT/Enhancer Binding Protein b regulates aromatase expression via multiple and novel cis-regulatory sequences in uterine leiomyoma". *J. Clin. Endocrinol. Metab.*, 2008, *93*, 981. doi: 10.1210/jc.2007-2507. Epub 2008 Jan 8.
[29] Jo J.H., Lee J.H., Kim D.C., Kim S.H., Kwon H.C., Kim J.S., Kim H.J.: "A case of benign metastasizing leiomyoma with multiple metastasis to the soft tissue, skeletal muscle lung and breast". K*orean J. Intern. Med.*, 2006, *21*, 199.
[30] Canzonieri V., D'Amore E.S., Bartoloni G., Piazza M., Blandamura S., Carbone A.: "Leiomyomatosis with vascular invasion. A unified pathogenesis regarding leiomyoma with vascular microinvasion, benign metastasizing leiomyoma and intravenous leiomyomatosis". *Virchows Arch.*, 1994, *425*, 541.

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