

Pulmonary benign metastasizing leiomyoma: case report and review of the literature

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Summary

We present a case of a middle-aged woman who was admitted to the hospital for abdominal pain and was found to have multiple nodules on her CT scan. After CT-guided biopsy, we finally diagnosed PBML case. The patient had a very effective response to bilateral oophorectomy and hysterectomy. A brief review of the literature for PBML is also included.

Key words: Lung; Pulmonary benign metastasizing leiomyoma (PBML); Hormonal manipulation.

Introduction

Pulmonary benign metastasizing leiomyoma (PBML) occurs very rarely and was first described by Steiner in 1939. It occurs more frequently in women of reproductive age, especially those who have had a hysterectomy due to leiomyoma [1]. The diagnosis of BML should be considered when a reproductive-aged woman presents with multiple pulmonary nodules and has a prior history of hysterectomy. The prognosis of BML is good if estrogen levels are well controlled.

Case Report

A 46-year-old female was referred to the emergency department in Ruijin Hospital, Shanghai Jiaotong University, with "intermittent right upper abdominal pain", which had begun two months before. The abdominal pain was relieved after anti-inflammatory and anti-spasmodic treatment. During treatment, multiple pulmonary nodules were observed on chest X-rays. The patient had no pulmonary symptoms. Her past medical history showed that she had undergone a subtotal hysterectomy four years before. The previous postoperative pathological diagnosis was "multiple intramural uterine leiomyoma, with hemorrhage, cell-rich". To confirm the diagnosis, the patient was admitted to the pulmonary department after being treated in the emergency department.

The patient did not present any infectious symptoms such as cough, fever, night-sweats, and was negative for bacteria, fungi, and tuberculosis in sputum, so we excluded infectious diseases first. Chest computed tomography (CT) results showed multiple, diffuse, bilateral, well-circumscribed pulmonary nodules ranging from 0.5-1.5 cm in diameter, with pleural thickening on both sides (Figure 1). Due to lack of an irregular spiculated edge on CT imaging, metastasizing lung tumor was considered. Considering the abdominal pain and history of uterine leiomyomas, the primary tumor was speculated to originate from the uterus. We had thought that the previous diagnosis of uterine leiomyoma could have been a misdiagnosis of uterine leiomyosarcoma. Moreover positron emission tomography (PET) CT results showed multiple pulmonary nodules, some of

which were hypermetabolic (Figure 2), and hypermetabolic lymphadenopathy in front of the abdominal aorta measuring 1.5 cm in diameter (Figure 3), which supported our speculation. Then we did CT-guided lung biopsy of the hypermetabolic nodules. The following pathological diagnosis performed for this biopsy was "leiomyoma" (Figure 4). Due to the typical morphology, no further analysis such as immunohistochemistry was performed.

During hospitalization, the patient experienced intermittent, severe right lower abdominal pain accompanied by vomiting. Anti-spasmodic treatment had no effect. Pelvic CT showed a suspicious cystic lesion in the right adnexa of the uterus. Given the definite diagnosis of pulmonary nodules and the severe abdominal pain, we advised bilateral oophorectomy and hysterectomy. After the operation, the pain disappeared. Seven months later, chest CT showed a significant reduction of the pulmonary nodules (Figure 5). Considering both the pathological diagnosis and the efficacy of the bilateral oophorectomy and hysterectomy, pulmonary benign metastasizing leiomyoma (PBML) was finally confirmed.

Discussion

Benign metastasizing leiomyoma (BML) was first reported by Steiner in 1939 [1]. About 100 cases were reported in the literature up to 2003 by searching Pubmed. BML is more common in women of reproductive age, especially in those who have undergone hysterectomy for leiomyomas. The lung is the most common organ of metastasis. Other organs include the lymph nodes, peritoneum and retroperitoneal structures. Pulmonary nodules can be detected from three months to 20 years after hysterectomy [2]. Patients are usually asymptomatic with incidental discovery of pulmonary lesions. Some patients may manifest with hemoptysis, cough, chest pain, and dyspnea.

Typical radiographic findings include well circumscribed solitary or multiple pulmonary nodules ranging from a few millimetres to several centimetres in diameter. In a few case reports, BML manifests as cavitory lung nodules and interstitial lung disease. Typically, nodules are not calcified and are not contrast-enhanced on CT. Endobronchial and pleural sparing is one of the features [2].

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Fig. 1

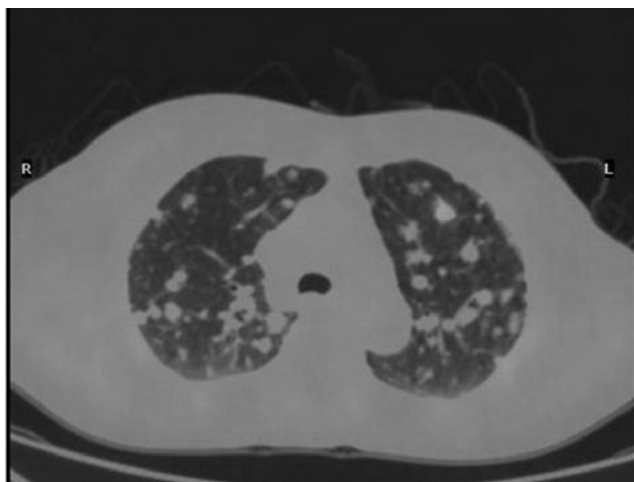


Fig. 3



Fig. 5



Fig. 2



Fig. 4

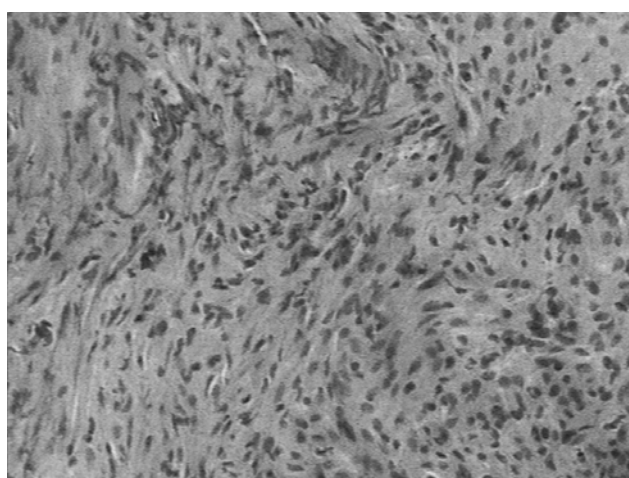


Figure 1. — Chest CT showed bilateral multiple pulmonary nodules.

Figure 2. — PET-CT showed well circumscribed, bilateral, multiple pulmonary nodules ranging from 0.3 cm to 1.5 cm in diameter. Some nodules had an increased radioactivity distribution, SUV_{max} was 3.1.

Figure 3. — PET-CT showed hypermetabolic lymphadenopathy near the abdominal aorta measuring 1.5 cm in diameter.

Figure 4. — Pathological section of tissue obtained by CT-guided lung biopsy (hematoxylin and eosin stain, $\times 100$).

Figure 5. — Chest CT seven months after surgery showed significant regression of pulmonary nodules.

Upon histological analysis, these tumors consist of well differentiated, benign-appearing smooth muscle cells lacking mitotic figures, anaplasia, or vascular invasion [3]. Because some cases have been diagnosed as metastasis of low-grade leiomyosarcomas [4], some authors pointed out that these lesions actually represent metastatic foci from low-grade leiomyosarcomas. Nuovo and Schmittgen [5] found that the expression of microRNA-221 (miR-221) was negatively associated with carcinogenesis of BML and uterine leiomyoma, but positively associated with most cases of leiomyosarcoma. The authors also proposed that increased miR-221 expression may be a molecular marker to differentiate leiomyosar-

coma from BML. Other groups demonstrated that smooth muscle tumors in the lung may represent multiple native smooth muscle hamartomas rather than actual metastatic foci in women with a predisposition to hamartomas [3].

In 1983, Martin *et al.* proposed a classification system for multiple smooth muscle lesions in the lung [6]. They suggested that the lesions can be classified into three categories: BML, metastatic leiomyoma, and multiple fibroleiomyomatous hamartoma. Although these lesions are histologically indistinguishable, distinctions can be made based on the clinical manifestation and the response to certain treatment. BML develops from a primary uterine source in childbearing-age women. These

tumors are typically hormonally responsive, demonstrating progression with estrogen and regression with progesterone. Thus, treatment may include hysterectomy, bilateral oophorectomy and long-term hormone therapy. The second category includes metastatic leiomyomas, which arise in men and children from an extra-uterine primary source. These tumors are not hormonally responsive and may actually represent slow-growing sarcomas that can be treated with surgical resection with mixed success. The third category, multiple fibroleiomyomatous hamartoma, consist of multiple leiomyomas of the lung, without a primary source. These lesions are benign.

In our case, the patient had a history of subtotal hysteromyomectomy. The pulmonary nodules significantly regressed after hysterectomy and bilateral oophorectomy. Therefore, the diagnosis was one of BML, and the hypermetabolic lymph node in front of the abdominal aorta observed on the PET-CT was also considered to be BML.

The pathogenesis of BML is still unclear so far. Although uterine leiomyoma is common, pulmonary metastasis is rare. The mechanism for metastasis may involve the dissemination of tumor cells from surgical operations including uterine curettage, hysteromyomectomy and hysterectomy. However, this mechanism cannot explain why pulmonary nodules manifest before a surgical operation. Patton and colleagues [7] analyzed the pathological and immunohistochemical features, clonality, and telomere length of multiple lung and uterine tumors in three patients with benign metastasizing leiomyoma. The results showed that pulmonary nodules had the same characteristics with those observed in uterine leiomyomas, which supports the notion that BML is clonally derived from benign-appearing uterine leiomyomas.

Due to its origin from uterine leiomyoma and the expression of estrogen and progesterone receptors in pulmonary nodules [8], BML is considered to originate from estrogen stimulation. Natural regression of pulmonary nodules after menopause and pregnancy has been observed [9]. Thus, control of estrogen level is the key to successful treatment. Hysterectomy and bilateral oophorectomy are very effective. In our case, the pulmonary nodules showed significant regression seven months after surgery (Figure 5).

Nonetheless, the possibility of medical castration attracts much more interest due to its reversibility, and its potential to obviate the need for a surgical procedure, or to allow symptom control when surgical management is not possible. The most commonly used drugs include luteinizing hormone-releasing hormone analogues (LHRHA), progesterone, aromatase inhibitors (AI) and selective estrogen receptor modulators (SERM).

LHRHA induce tumor regression by suppressing the synthesis of estrogen. However, in some cases, LHRHA alone cannot prevent tumor progression. A combination with other medicines may be a better strategy [10]. The mechanism of progesterone treatment is to suppress the hypothalamic-pituitary-gonadal axis, thereby reducing ovarian estrogen synthesis. Progesterone also acts to increase the rate of enzymatic inactivation of estradiol by increasing its conversion to estrone, through an increase

in the activity of an oxidative type 17 β -hydroxysteroid dehydrogenase enzyme. In addition, progesterone reduces aromatase activity. Aromatase-P450 is the key enzyme for estrogen synthesis. Over-expression of aromatase-P450 by uterine leiomyomas may contribute to their growth. Aromatase inhibitors, such as anastrozole, lower estradiol concentrations by acting both on the gonads and on the peripheral and tumor tissues. They are effective and increasingly used to treat ER-positive metastatic breast cancer [11].

Raloxifene, a synthetic non-steroidal SERM, acts as an estrogen agonist on the skeleton, cardiovascular system, and central nervous system, but exhibits only weak estrogenic antagonist effects on the breast and uterus. Additional administration of raloxifene to patients treated with an LHRH agonist for uterine leiomyomas results in higher reduction of leiomyoma size. However, there is still little data published regarding the combination of AIs and SERMs to treat BML.

In summary, a diagnosis of BML should be considered when a reproductive-aged women presents with multiple pulmonary nodules and has a prior history of hysterectomy. The prognosis of BML is good if estrogen levels are well controlled.

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