**Benign Metastasizing Leiomyoma of the Lung: A Case Report**

Po-Chi Huang, Jung-Ta Chen, Chou Chia-Man, Po-Cheung Kwan, and William L Ho

**Abstract:** Benign metastasizing leiomyoma (BML) refers to benign pulmonary neoplasm associated with a previous or coincident history of uterine leiomyomata. We report the case of a 56-year-old postmenopausal woman with a 4-year history of multiple benign leiomyomatous lesions in bilateral lungs and the uterus. The tumor cells from the lungs and uterus were focally immunoreactive for HMB-45 antibody and progesterone receptor. Immunoreactivity to HMB-45 is well known in smooth muscle cells of hamartomatous neoplasms, such as angiomyolipoma and lymphangioleiomyomatosis, but has not been reported in BML previously. These features suggest a multifocal hamartomatous histogenesis rather than metastasis in the present case.

Benign leiomyoma is an uncommon tumor of the pulmonary parenchyma. It accounts for less than 2% of all benign lung tumors [1], with a slight female predominance (M:F ratio, 1:1.6) [2]. Benign metastasizing leiomyoma (BML) is a term used to describe multiple benign pulmonary leiomyomatous lesions occurring in patients with a previous or coincident history of uterine leiomyomata [3]; the pathogenesis remains unclear. We report the case of a 56-year-old postmenopausal woman with multiple intrapulmonary and uterine leiomyomata. The possible histogenesis of the tumor is discussed.

**Case Report**

A 56-year-old postmenopausal woman was admitted to our hospital in 1997 for evaluation of asymptomatic bilateral lung tumors that had been first noted in 1995 during routine chest roentgenogram examination. The lung nodules had enlarged slowly and multiple new lesions had grown in the bilateral lungs during the 2 years since the previous roentgenogram (Fig. 1A). She had no history of chest pain, dyspnea, or cough. However, multiple uterine tumors had been discovered in 1994. On admission, a complete physical examination, laboratory examination, and gastroenteroscopy revealed no abnormalities. Metastatic lesions or pulmonary tuberculosis were suspected from the clinical presentation.

A wedge resection of the lung was performed. Grossly, the pulmonary tumors were round well-demarcated grayish white masses, measuring up to 1.5 x 1.5 x 1.2 cm (Fig. 1B). Histologically, there were multiple round satellite nodules composed of spindle cells arranged in whorl or storiform patterns. The tumor cells had cigar-shaped nuclei with evenly dispersed chromatin. The mitotic count was less than 5/50 HPF (high-power field). Some cuboid or columnar epithelium was entrapped in the tumor, forming clefts or cysts. The tumors showed a hypervascular growth pattern and occasionally encompassed the pulmonary vessel (Fig. 2). No necrosis, true vascular invasion, or intravenous tumor emboli was found. A diagnosis of benign smooth muscle tumor was made.

Abdominal total hysterectomy and bilateral salpingooophorectomy were performed 2 weeks later. The operative findings showed multiple tumors in the uterus and the broad ligament. Grossly, the tumors had the ordinary florid appearance of cutaneous lesions. The maximal diameter of the tumors was 7 cm. Bilateral ovaries and fallopian tubes were unremarkable. No lymphadenopathy or other intra-abdominal lesions were identified. Microscopically, all of the tumors were composed of spindle-shaped smooth muscle cells showing benign histologic features with rare mitosis (less than 1/10 HPF). The tumors were hypervascular and grew around the vessels of the broad ligaments.

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**Key words:**
- benign metastasizing leiomyoma
- progesterone receptor
- HMB-45
- hamartoma

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Tamoxifen and medroxyprogesterone were prescribed for control of postmenopausal syndrome and the residual pulmonary tumors. The postoperative course was uneventful and the patient remained in a stable condition at 2 years’ follow-up. The residual lung tumors showed minimal changes in size and number.

Immunohistochemical studies of the resected specimens from this patient were performed with a standard streptavidin-peroxidase complex method. The sources and dilutions of antibodies used were as follows: smooth muscle actin M-851 (Dako, Glostrup, Denmark; 1:50), monoclonal mouse anti-human melanosome clone HMB-45 (Dako, Real Carpinteria, CA, USA; 1:30), estrogen receptor (Dako, Denmark; 1:50), progesterone receptor (Dako, USA; 1:50), and factor VIII (Dako, Denmark; 1:200). All tumor cells from pulmonary, pelvic, and uterine areas were diffusely and strongly positive for smooth muscle actin M-851. The immunoreaction to HMB-45 was focally positive in the tumor cells from the lung (Fig. 3A) and the pelvic parauterine area, and in the perivascular cells in the tumors (Fig. 3B). The HMB-45 immunostains revealed conspicuous intracytoplasmic granular deposition, especially in the perinuclear area. The hormone immunostains showed that the tumor cells of the lung and uterus had intranuclear immunoreaction to progesterone receptor but were negative for estrogen receptor. Factor VIII immunostain confirmed a hypervascular stroma in the tumor from both sites.

Discussion

The term “benign metastasizing leiomyoma” was first introduced by Steiner in 1939 to describe the condition of an adult woman who died of cor pulmonale and whose autopsy demonstrated leiomyomatous tumors involving both lungs, the tracheobronchial lymph nodes, and the uterus [4]. Clinically, the disease affects women at reproductive age (average, 47 years) [5]. Most patients are asymptomatic and tumors are incidentally found by imaging studies, presenting as multiple, unilateral or bilateral, distinct pulmonary nodules without calcification. The images are usually difficult to distinguish from metastasizing malignant tumors, other benign tumors, or granulomatous inflammation [1]. The diagnosis of BML may be achieved by bronchoscopic sono-guided needle biopsy or cytological aspiration [6], or by intraoperative frozen section during exploratory thoracoscopy [1]. Histologically, these tumors are composed of smooth muscle cells with scant mitosis and little atypia. Alveolar pneumocytes or bronchoepithelium may be entrapped by the slowly growing tumors [5, 7]. The differential diagnosis includes primary or metastatic leiomyoma, leiomyo-sarcoma, intrapulmonary fibrous tumor, and lymphangioleiomyomatosis (LAM).
To date, the pathogenesis of BML is still confusing and undetermined [3, 4, 8-11]. Some authors consider these neoplasms to be metastatic leiomyomatous tumors [5, 9, 10], while others consider them to be primary hamartomas with a predominant leiomyomatous or adenomyomatous component [11]. The main controversy centers on the recognition of mitosis, vascular invasion, vascular emboli, hormone sensitivity, and the prolonged benign clinical course [5, 9-14].

On immunohistochemical study, the tumor cells from the present case were immunoreactive not only to progesterone receptor but also to HMB-45, while leiomyosarcomas have no such immunoreactivity. A recent chromosome study of patients with BML revealed cytogenetic changes different from those in non-BML leiomyomas and leiomyosarcomas [15], supporting a different histogenesis of BML.

Immunopositivity to HMB-45 for BML has never been reported in the literature. HMB-45 is an immunohistochemical antibody sensitive to tumors of melanocytic lineage, but also to hamartomatous smooth muscle cells in the angiomyolipomas and LAM [16, 17], and renal capsular leiomyomas [18]. Histologically, pulmonary LAM is characterized by smooth muscle proliferation along cystic dilated lymphatic spaces, arranged in a fascicular or nodular pattern, which is usually distinct from BML. However, an intermediate histologic picture could still confuse a pathologist [19]. In fact, there are many similarities between BML and LAM, such as female gender predominance, hormone sensitivity, multicentricity, and HMB-45 immunoreactivity. It is possible that these two tumors are closely related or share a common histogenesis associated with perivascular mesenchymal cells [17]. Thus, we postulate a benign multicentric histogenesis in BML rather than metastasis.

Treatment of these pulmonary tumors can include bronchoscopic resection, conservative pulmonary surgery, and surgical or medical hormonal manipulation [1, 2, 5, 19]. Hormonal manipulation can include bilateral oophorectomy and administration of luteinizing hormone-releasing hormone analogue, tamoxifen, and progesterone. The prognosis of this disease is usually favorable. Few tumors are located near the main bronchus or grow too large, resulting in hemoptysis, dyspnea, repeated pneumonia or atelectasis, or compression of other organs in the thoracic cavity.

In summary, our patient had the typical clinical, imaging, and histopathologic pictures of BML. The reactivity to HMB-45 in the tumor cells of our patient suggest that they may also have been derived from hormone-sensitive perivascular mesenchymal cells, like other hamartomatous myoid tumors [16], which reasonably explains why BML tumors have a grossly benign appearance, are hypervascular and multicentric, and respond well to hormone therapy.

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References

Immunohistochemical Study of Pulmonary Benign Metastasizing Leiomyoma