Benign metastasizing leiomyoma: 'a sheep in wolf's clothing'

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Benign metastasizing leiomyoma (BML) is a rare entity,[1-9] of which a small number of cases, about 75[1,4,6] to 120,[8-10] have been described in the literature since the condition was first described in 1939. It usually affects women of reproductive age with a history of uterine leiomyomatosis who have undergone a hysterectomy.[3,6] The lung is the most common site of involvement.[1-4,7-9] The pathologic features of this entity are described as having originated from the metastasis of the histologically benign uterine leiomyoma and are an uncommon lesion characterized by the presence of multiple smooth-muscle nodules that are often located in the lung, lymph nodes, or abdomen.[2] Although these lesions are slow growing and asymptomatic and are usually incidentally diagnosed, they may rarely cause debilitating symptoms.[1,6] Optimal treatment is controversial, but careful follow-up of these patients is recommended because the lesions show a low-grade clinical malignant behavior although their appearance is benign.[4] We describe here a rare case of pulmonary BML.

Case presentation

The patient in our report is a 37-year-old African American woman with a medical history that included hypertension treated with lisinopril and a surgical history of a total abdominal hysterectomy and left salpingo-oophorectomy (in July 2010) secondary to leiomyoma. At that time, the pathology of the leiomyoma was benign. The patient was a nonsmoker and denied any occupational exposures. There was family history of thyroid cancer (grandfather) and endometrial carcinoma (grandmother). She had no history of pulmonary diseases or respiratory symptoms.

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The patient had been well until January 2011 when she was evaluated in the emergency department for her complaint of stabbing, intermittent right lower quadrant abdominal pain for the past month but that did not interfere with her gastrointestinal function. A computed tomography (CT) scan of the abdomen and pelvis was done at that time and revealed a complex mass-like structure posterior to the right colon and measuring 4 cm × 5.5 cm, which did not appear to communicate clearly with the colon. In addition, the CT scan also showed multiple pulmonary nodules in the lower lung fields. A subsequent CT scan of the chest (Figure 1) revealed multiple bilateral small noncalcified lung nodules of 0.5-1 cm in size, without definite lymph nodes in the mediastinum.

The only other symptom that the patient manifested was difficulty in breathing. On examination, she seemed to be in no acute distress and her vital signs were normal. Her pulmonary and general physical examinations were normal, except for a mild abdominal discomfort on palpation. The results of laboratory tests, including complete blood count and chemistry panel blood tests and a thyroid stimulating hormone test, were all in the normal range, as were the results of a carcinoembryonic antigen test. Because of obvious concerns about metastatic disease, biopsies of the lung and the pelvic masses were recommended. Clinicians in the interventional radiology department performed a CT-guided lung nodule biopsy. The pathology of the specimen that was submitted as a lung nodule showed chronic inflamed lung tissue, fibroconnective tissue, and skeletal muscle and was negative for malignancy. A CT-guided biopsy was done to evaluate the pelvic mass, and the results were histologically consistent with benign ovary and fallopian tube tissue. A wedge resection of the left lower lung lobe was done to further evaluate

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FIGURE 1 A computed tomography scan showing multiple bilateral, well-circumscribed, small, noncalcified lung nodules. There were no definite lymph nodes in the mediastinum.

the lung nodules, and the pathology report showed multiple well-defined nodules consisting of a bland spindle cell population with less than 1 mitotic figure per 10 per high-power field, and there was entrapped benign bronchial mucosa (Figure 2).

Immunohistochemical stains (Figure 3) consisting of smooth muscle markers, as well as estrogen and progesterone receptors, all turned out strongly positive, leading to the diagnosis of pulmonary benign metastasizing leiomyoma. Those results were also confirmed by Mayo Clinic in Scottsdale, Arizona. Because of the patient's history of recurrent right lower quadrant abdominal pain and the previous finding of the pelvic mass from the right ovary, an appendectomy and right salpingo-oophorectomy were performed. The patient tolerated the procedure well. Pathology of the right fallopian tube and ovary showed benign ovarian and fallopian tube tissue.

A repeat CT scan of the chest (Figure 4) and pelvis in July 2011 showed a small increase in the size of the lung lesions, but the pelvic scan did not show any masses or lymphadenopathy.

Given that BML is a rare condition and that there is a paucity of literature about it, our treatment of the patient was based on anecdotal case reports. Because of the strong positivity of the estrogen and progesterone receptors and considering the mild difficulty the patient was having with breathing and the increase in the size of her lung nodules, it seemed reasonable to treat her with aromatase inhibitors. The patient tolerated the aromatase inhibitors

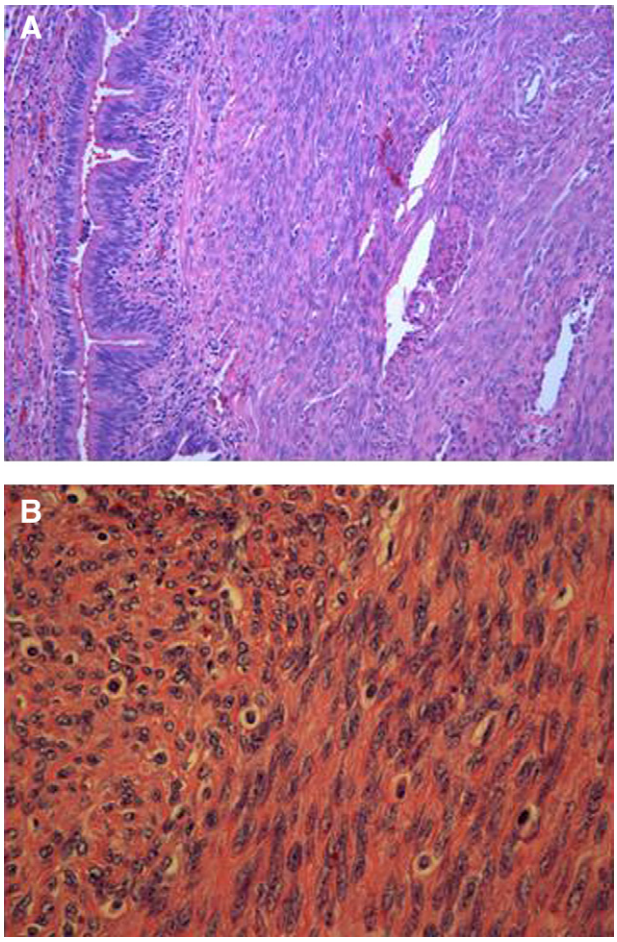

FIGURE 2 A, Low-power photomicrograph (hematoxylin–eosin stain) of a lung wedge resection showing smooth muscle spindle cell population with entrapped bronchiolar epithelium. B, High-power photomicrograph (hematoxylin–eosin stain) of a smooth muscle bland spindle cell population showing minimal atypia and no evidence of necrosis.

without problems. Repeated CT scans showed stable disease. A clinical and radiological follow-up was planned for the patient, and she currently follows up with the oncology and pulmonary departments.

Discussion

BML is characterized by multiple well-differentiated leiomyomas at sites distant from the uterus. The lesions are histologically identical to their uterine source.[3,8,9] BML most commonly metastasizes to the lungs,[1-4,7-10] and more rarely, can metastasize to other distant sites such as the skin, bone, mediastinum, lymph nodes, muscular tissue, heart, and retroperitoneum.[2,8,9]

The condition usually is detected incidentally as multiple pulmonary nodules. A previous diagnosis of uterine leiomyoma may point to the diagnosis in many cases. A

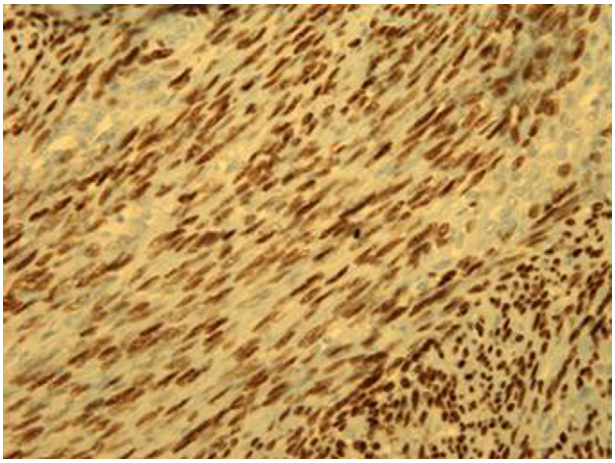

FIGURE 3 Immunohistochemistry of the lung nodule. The tumor cells were diffusely positive for smooth muscle actin, and the nuclei stained positive for estrogen and progesterone receptors.

FIGURE 4 A computed tomography scan showing multiple bilateral lung nodules slightly increased in size compared with images from the previous scan.

history of myomectomy or hysterectomy for histologically benign-appearing uterine leiomyomas may be suggestive. The interval between hysterectomy and the appearance of pulmonary nodules can range between 3 months and 20 years.[3,8-10]

Symptoms of chest pain, shortness of breath, and cough have been described. Although the clinical course of the condition is usually asymptomatic, a more rapid progression to severe, and even fatal, respiratory symptoms also has been reported.[1-3,6-9] The clinical course of patients with BML varies and seems to depend on the estrogen status of the patient and the course of the disease may be more progressive in premenopausal patients than it is in postmenopausal patients.[10]

There has been much debate about the nature of this lesion, a tumor with benign histological features but having biological behavior that suggests malignancy.[10] It is now largely accepted that the lesions arise as hematogenous metastases from benign tumors and it has been theorized that the tumor cells may enter the blood stream during the trauma of surgery and disseminate that way.[2,3] The radiologic imaging appearance of pulmonary nodules in benign metastasizing leiomyomas varies from solitary lesions to multiple lesions mimicking pulmonary metastases from malignant tumors. Cavitations of lesions occasionally takes place and rarely may be accompanied by pneumothorax.[7-9]

Both CT and magnetic resonance imaging may be used to show the pulmonary nodules in benign metastasizing leiomyoma, which have a nonspecific appearance and usually enhance homogeneously. The radiographic manifestations are usually well-defined nodules of 0.2-8 cm in size, which may be unilateral or bilateral and scattered among normal interstitium. Typically, these nodules are noncalcified and do not enhance with intravenous contrast administration.[8-10]

The inclusion of particular entities in the differential diagnosis depends on the size of the nodules, but the most commonly included are metastases from malignant tumors. Less common entities to consider are infectious granulomas, sarcoidosis, rheumatoid nodules, amyloidosis, and arteriovenous malformations.[8-10] BML of the lung has very rarely been associated with primary lung cancer.[11]

An image-guided core biopsy is frequently required to obtain a definitive diagnosis. Pathologically, pulmonary BML lesions are composed of benign smooth muscle cells that are similar to uterine leiomyoma. Estrogen and progesterone receptors have been identified in these metastatic foci. The primary uterine lesions are classified as smooth muscle tumors of unknown malignant potential because of the limitations of current histopathologic tests. It is not uncommon to find entrapped alveolar or bronchiolar epithelium, which sometimes can be prominent and cause diagnostic confusion.[8-10]

There are no guidelines or standardized therapy for treating BML because of the limited number of reported cases. The tumors tend to be hormonally sensitive.[2,3,8,9] There have been reports of successful treatment with aromatase inhibitors, progesterone, gonadotropin-releasing hormone analogues, luteinizing hormone-releasing hormone agonists, and selective estrogen-receptor modulators. The surgical removal of BML lesions has been successful.[3-5,12] In addition,

the spontaneous resolution of BML has been described.[8-10] However, because BML could recur, patients with the condition should have prolonged surveillance after surgical removal or hormonal suppression.[2]

In conclusion, BML is a rare tumor with benign histologic features, despite its biological behavior suggesting malignancy. It usually affects women who have a history of uterine leiomyomatosis and usually occurs after hysterectomy. The lungs are the most common site of metastatic involvement, so BML should be a differential diagnosis in any patient who presents with solitary or multiple pulmonary nodules and a history of uterine leiomyomatosis.

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