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Favorable Response to Antigonadal Therapy for a Benign Metastasizing Leiomyoma

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Abstract

Background—Benign metastasizing leiomyoma and lymphangioleiomyomatosis (LAM) are both characterized by abnormal proliferation of smooth muscle-like cells in the lung.

Case—A 32 year-old African woman with a diagnosis of LAM underwent myomectomy for uterine leiomyomas. An alternative diagnosis of benign metastasizing leiomyoma was made by a repeat lung biopsy. Treatment with leuprolide acetate decreased pulmonary infiltrates and improved lung function and exercise tolerance.

Conclusion—Accurately diagnosing benign metastasizing leiomyoma has important implications for clinical outcome. Since its clinical presentation may be misleading, immunohistochemistry techniques may assist in differentiating benign metastasizing leiomyoma from LAM. This is important because in benign metastasizing leiomyoma reduced tumor burden and improved pulmonary function may be achieved by suppressing gonadal steroids.

Introduction

Benign smooth muscle tumors, leiomyomas, commonly develop in the uterus and occasionally in adjacent pelvic structures. In rare cases however, tumors demonstrating a similar histological appearance may be found outside the pelvis, presenting as multiple nodular smooth muscle cell proliferation of uncertain etiology and known as benign metastasizing leiomyoma (1). The lungs are the most commonly affected organ (2).

Lymphangioleiomyomatosis (LAM) is a multisystem disease affecting women (3), which is characterized by cystic lung destruction, kidney angiomyolipomas, and lymphatic abnormalities (e.g., lymphangioleiomyomas, adenopathy) (3). Patients may present with dyspnea, pneumothorax, hemoptysis, pleural effusions and ascites (3).

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LAM lung lesions are characterized by proliferation of abnormal-appearing smooth muscle-like cells (LAM cells), expressing smooth muscle (e.g., α -smooth muscle actin [α -SMA]) and melanoma (e.g., gp100) cell antigens (3), in nodules located in the walls of the cysts, and within the lung interstitium. Immunohistochemistry of the lung nodules reveals epithelioid cells that react with HMB-45 (a monoclonal antibody that recognizes the premelanosomal protein gp100) (3).

Both benign metastasizing leiomyoma and LAM tumor cells express estrogen and progesterone receptors and are most commonly identified among reproductive-aged women. The vast majority of women with benign metastasizing leiomyoma report a history of previous surgery for uterine leiomyomas (i.e. hysterectomy or myomectomy) (4). A distinction between benign metastasizing leiomyoma and LAM is clinically important, as effective treatment regimens differ. Herein, we present the case of a woman with no prior history of surgical intervention for uterine leiomyomas who developed benign metastasizing leiomyomatosis which was difficult to distinguish from LAM. This report highlights the similarities and differences between these two conditions affecting reproductive-aged women (5). This report was approved by the NHLBI IRB (protocol 96-H-0100).

Case

In 1999, at age 32, a nulligravid African woman presented with recurrent pneumothoraces. A chest CT demonstrated cystic changes in upper lungs and bilateral smaller parenchymal cysts (Figure 1A). Lung biopsy showed proliferation of spindle cells (Figure 2) with a small focus reactive with HMB-45, consistent with LAM.

The patient gave a history of uterine leiomyomas diagnosed at age 28 but denied prior uterine surgery. During the first 8 years of follow-up at the National Institutes of Health, radiographic studies were consistent with uterine leiomyomas in varying stages of degeneration which were associated with abdominal pain, menometrorrhagia, and anemia. Therefore, the patient underwent a fertility-preserving abdominal myomectomy in 2006. The uterine tissue was compared with lung tissue from the biopsy performed prior to the myomectomy. Both tumors reacted with anti-SMA and anti-desmin antibodies and demonstrated estrogen and progesterone receptors. Additionally, these smooth muscle cells had no mitotic activity and reacted weakly with anti-h-caldesmon antibodies. These findings were consistent with the diagnosis of benign metastasizing leiomyoma. Further support for this diagnosis was the lack of reactivity with monoclonal antibody HMB-45. Over the course of the next year, the patient developed increased dyspnea, worsening pulmonary nodular infiltrates and pulmonary function, and recurrent uterine leiomyomas. A repeat lung biopsy was consistent with benign metastasizing leiomyoma; the smooth muscle-like cells did not show reactivity with HMB-45. The patient was started on leuprolide acetate (3.75 mg IM monthly) in January 2007. Twelve months after starting leuprolide acetate, CT imaging showed a moderate decrease in the size of the uterus and radiologic improvement of pulmonary infiltrates (Figure 1A and 1B)). Pulmonary function tests improved over time (Figure 1C).

Comment

Cystic pulmonary diseases may result from common causes, such as, emphysema, sarcoidosis and idiopathic pulmonary fibrosis and from more rare diseases such as LAM (4). Radiographically, LAM lesions appear as interstitial opacities (reticular, reticulonodular, or miliary) or well-circumscribed cystic lesions, giving a honeycomb appearance (3), consistent with the initial presentation of our case. In contrast, benign metastasizing leiomyoma is frequently asymptomatic and diagnosed incidentally upon routine imaging in

patients with a history of uterine surgery (4) but in our case surgical intervention for treatment of uterine leiomyomas had not been performed. In benign metastasizing leiomyoma, pulmonary imaging demonstrates single or multiple bilateral, nodular parenchymal lesions, measuring from a few millimeters to several centimeters (5), but, as in our patient, lesions may, rarely, be cystic (6). Pulmonary lesions in benign metastasizing leiomyoma are well-circumscribed and not associated with lymphadenopathy, pneumothorax, pleural effusions or other pulmonary findings because benign metastasizing leiomyoma tumors, unlike LAM, spare the lymphatics, blood vessels, and airway (5).

Both benign metastasizing leiomyoma and LAM seem to be hormonally regulated, as evidenced by observations that these lesions do not present prior to menarche, may worsen during pregnancy and at the time of menses, and tend to progress more slowly or regress after menopause (5). Further evidence supporting hormonal involvement in both disease processes includes the presence of estrogen and progesterone receptors (3,5). Histologically, tissue from both benign metastasizing leiomyoma and LAM have SMA, desmin, vimentin, type IV collagen expression by immunohistochemistry, and few mitoses (<5 mitoses/10 high-power fields) (2). With these similarities, it may be difficult to distinguish between these two different disease processes. A distinguishing histological feature of LAM cells is the positive immunoreactivity with HMB-45 (3), a monoclonal antibody recognizing gp100. In contrast to LAM, benign metastasizing leiomyoma lesions do not react with HMB-45 (5). This salient feature, after a second lung biopsy, led to a diagnosis of benign metastasizing leiomyoma.

The etiology of benign metastasizing leiomyoma remains speculative and several theories of the pathogenesis of this disease have been proposed: 1) hematogenous spread to extra-uterine sites precipitated by surgical interventions; 2) malignant behavior of benign appearing uterine tumors acting as low-grade sarcomas; 3) systemic leiomyomatosis manifesting as multi-focal smooth muscle proliferations (2); and 4) shared cytogenetic profile of a small subset of uterine leiomyomas (7).

The hypothesis of metastasizing leiomyomas as the cause of benign metastasizing leiomyoma has been supported by the fact that the majority of women present with a history of a surgical procedure (i.e. hysterectomy, myomectomy, dilation and curettage) for leiomyomas (2,4,5). Our patient, however, did not have uterine surgery prior to the diagnosis of pulmonary lesions. Suggesting microscopic vascular invasion as a mechanism for metastasis.

Another theory holds that metastases derive from well-differentiated leiomyosarcomas (1,5). Some distinguishing features between leiomyosarcomas and benign metastasizing leiomyoma include proliferation markers, such as ki-67 and apoptosis-related gene expression (bcl-2 and p53) (2,5). Benign metastasizing leiomyoma lesions demonstrate a lower ki-67 staining index when compared to leiomyosarcoma, while bcl-2 and p53 are expressed at higher levels in benign metastasizing leiomyoma (2). Complex and unbalanced karyotypic aberrations are commonly observed in leiomyosarcomas, while leiomyomas typically do not have these karyotypic aberrations.

Another suggested etiology of benign metastasizing leiomyoma includes multifocal proliferation of smooth muscle cells. However, analyses of clonality examining X-chromosome inactivation analysis and comparative genomic hybridization patterns have determined that the leiomyomas arising from the lung were identical in clonality to those from the uterus (1). However, the cytogenetic profile of benign metastasizing leiomyoma appears to be different from that of uterine leiomyomas as, 19q and 22q terminal and 1p

deletions are much more frequent in benign metastasizing leiomyoma than uterine leiomyomas.

Because of the few reported cases of benign metastasizing leiomyoma, there is no standard treatment algorithm. These tumors tend to be sensitive to ovarian hormones, as estrogen is thought to increase the expression of factors that inhibit cell death and suppress the expression of factors that inhibit growth (5,7). Gonadotropin releasing hormone agonists which suppress the endogenous gonadotropin secretion and reduce estrogen production have shown a clinical response (5,7). Other agents that reduce or modulate estrogen production include aromatase inhibitors and selective estrogen receptor modulator, such as raloxifene, which has estrogenic effects on skeleton but acts as a weak estrogen antagonist on uterine tissue. Gonadotropin releasing hormone agonists and raloxifene combined are effective in the treatment of uterine leiomyomas (8).

Because of the potential for long-term therapy on anti-estrogenic agents, we monitored bone mineral density and urinary N-telopeptide levels in our patient. We did consider estrogen-progesterone add-back therapy but this may induce proliferation of the lesions. Instead, we treated the patient with bisphosphonates, calcium and vitamin D and her bone density and urinary N-telopeptide levels have remained normal.

This case demonstrates that benign metastasizing leiomyoma may develop in patients without a history of uterine surgery. The unique features of this case made the diagnosis of benign metastasizing leiomyoma challenging. Indeed, the clinical presentation, initial imaging and lung biopsy favored a diagnosis of LAM. However, the lack of conclusive HMB-45 reactivity and the changes seen on lung CT scans lead to additional evaluation and a diagnosis of benign metastasizing leiomyoma. The importance of correct diagnosis is evident in this case where treatment with leuprolide acetate reduced the severity of the pulmonary lesions and improved pulmonary function and exercise tolerance.

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References

1. Tietze L, Gunther K, Horbe A, et al. Benign metastasizing leiomyoma: a cytogenetically balanced but clonal disease. *Hum Pathol.* 2000; 31:126–28. [PubMed: 10665925]
2. 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; 437:284–92. [PubMed: 11037349]
3. McCormack FX. Lymphangioleiomyomatosis: a clinical update. *Chest.* 2008; 133:507–16. [PubMed: 18252917]
4. Wentling GK, Sevin BU, Geiger XJ, Bridges MD. Benign metastasizing leiomyoma responsive to megestrol: case report and review of the literature. *Int J Gynecol Cancer.* 2005; 15:1213–17. [PubMed: 16343217]
5. Pitts S, Oberstein EM, Glassberg MK. Benign metastasizing leiomyoma and lymphangioleiomyomatosis: sex-specific diseases? *Clin Chest Med.* 2004; 25:343–60. [PubMed: 15099894]
6. Matsumoto K, Yamamoto T, Hisayoshi T, Asano G. Intravenous leiomyomatosis of the uterus with multiple pulmonary metastases associated with large bullae-like cyst formation. *Pathol Int.* 2001; 51:396–401. [PubMed: 11422800]

7. Nucci MR, Drapkin R, Cin PD, Fletcher CD, Fletcher JA. Distinctive cytogenetic profile in benign metastasizing leiomyoma: pathogenetic implications. *Am J Surg Pathol.* 2007; 31:737–43. [PubMed: 17460458]
8. Sankaran S, Manyonda IT. Medical management of fibroids. *Best Pract Res Clin Obstet Gynaecol.* 2008; 22:655–76. [PubMed: 18468953]

Figure 1. Computed tomography images of the lung before initiating anti-gonadal therapy (panel A) and 24 months after treatment with leuprolide acetate (panel B). Panel B shows a significant decrease in the density of the interstitial pulmonary infiltrates following anti-gonadal therapy. Panel C shows changes in lung function expressed as percent predicted of the normal total lung capacity, forced vital capacity, forced expiratory volume in the first second (FEV₁), and diffusion capacity for carbon monoxide, during 11 years of follow-up. After initiation of leuprolide acetate therapy (arrow), total lung capacity increased 10% (500 mL), forced vital capacity increased 15% (300 mL), forced expiratory volume in the first second increased 14% (270 mL), and diffusion capacity for carbon monoxide increased 4%.

Figure 2. Histologic sections of initial lung biopsy. Panel A shows a distinctive pattern of cystic lesions, along with multinodular proliferation of smooth muscle cells characteristic of lymphangioleiomyomatosis (hematoxylin-eosin staining; magnification $\times 50$, bar-graph 250 micrometers). Panel B: high magnification view of one nodule showing characteristic smooth muscle cells (hematoxylin-eosin staining; magnification $\times 200$, bar-graph 100 micrometers).