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Benign metastasizing leiomyoma of bone and lung in postmenopausal women: two rare case reports and review of the literature

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Summary

Benign metastasizing leiomyoma (BML) is a rare disease that mostly occurs in women of reproductive age. Patients usually have a history of uterine leiomyoma and/or myomectomy. Although lung is the most common site of metastasis, bone involvement is rarely occurred. Here the authors report two rare cases of BML with lung and bone metastasis in postmenopausal women that were successfully treated with surgery and anti-estrogen approach.

Key words: Benign metastasizing leiomyoma; Lung metastasis; Aromatase inhibitors.

Introduction

Uterine leiomyomas are the most common gynecological tumor of premenopausal women. They are benign tumors of smooth muscle and vast majority of lesions are localized to uterine. Rarely, leiomyomas show extrauterine growth patterns, which are named as benign metastasizing leiomyoma (BML) and the most common site for BML is lung [1, 2]. Despite numerous distant metastatic lesions, no invasion is seen. BML are histologically benign and have low mitotic rate. Patients have mostly previous history of uterine myomas, and related surgeries. Immunohistochemically, estrogen (ER) and progesterone receptor (PR) expression are common [3]. The treatment for BML includes surgical removal of the appropriate metastatic lesions. For multiple lesions, which are not amenable to removal, conservative anti-estrogen manipulations such as oophorectomy, gonadotropin-releasing hormone analogue (GnRH), selective estrogen receptor modulator (SERM), and aromatase inhibitors show clinical benefit [4]. Here the authors report two rare cases of BML and review of the literature.

Case Report

Case 1

A 49-year-old woman was referred to the present department for multiple, bilateral lung nodules. She underwent total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) because of uterine leiomyomas three years ago. Since then, she was on oral hormone replacement therapy to prevent menopausal symptoms. Patient underwent whole-body ^{18}F-FDG positron emission tomography (PET)-computed tomography (CT) to evaluate potential metastasis and staging. PET-CT showed multiple bilateral lung nodules and widespread bone nodules, which did not show 18F-FDG uptake (sclerotic nodules in bilateral head of humerus, corpus of T1, T11, L1, and L3 vertebras, bilateral iliac bones, anterior side of bilateral acetabulum, and greater trochanter of left femur) (Figures 1A, 2). To establish a diagnosis, a pulmonary wedge resection by video-assisted thoracoscopic surgery was performed. The histopathologic examination revealed that tumors consisted of well-differentiated spindle-shaped cells without hypercellularity, pleomorphism, and nuclear atypia. There was minimal mitotic activity (about three mitotic figures per ten high-power-fields (MF/10 HPF) (Figures 3A, B). Immunohistochemical (IHC) staining was negative for CD117, and CD34, strongly positive for smooth muscle actin (SMA) (Figure 3E), showing low expression for Ki67 (3%) (Figure 3F). To confirm the diagnosis of BML, the authors examined again the paraffin-embedded tissue specimens obtained from hysterectomy and resected adnexal mass. There was no difference between paraffin-embedded tissue specimens and lung nodules with respect to findings of histopathologic examination. IHC analysis also showed strong expression of ER and PR receptors both in the metastatic tumors and in the uterine leiomyoma (Figures 3C, D). The authors ruled out the possibility of leiomyosarcoma and other metastatic diseases, and confirmed diagnosis of BML. After precise diagnosis, they stopped the hormone replacement therapy and patient started aromatase inhibitor letrozole. After ten months of aromatase inhibitor, significant response was observed. An 18F-FDG PET-CT showed that the remarkable shrinkage of lung nodules, while skeletal sclerotic lesions were unchanged (Figures 1B, 2).

Case 2

A 55-year-old woman with history of TAH-BSO was admitted to the present hospital with right hip and leg pain and paraesthesia. Her routine blood tests and X-ray were normal. Magnetic resonance imaging (MRI) of the left femur showed intertrochanteric

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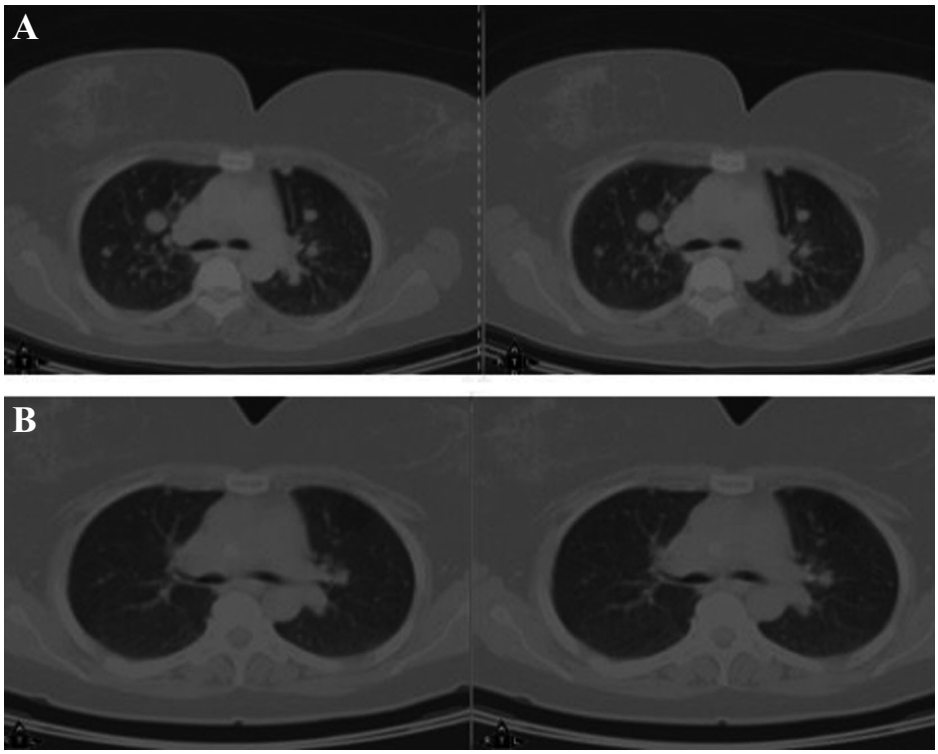

Figure 1. — A: PET/CT scan at the time of presentation shows multiple nodules in both lungs, which do not show 18F-FDG uptake. B: PET/CT scan taken after about ten months from treatment showed that nodules disappeared.

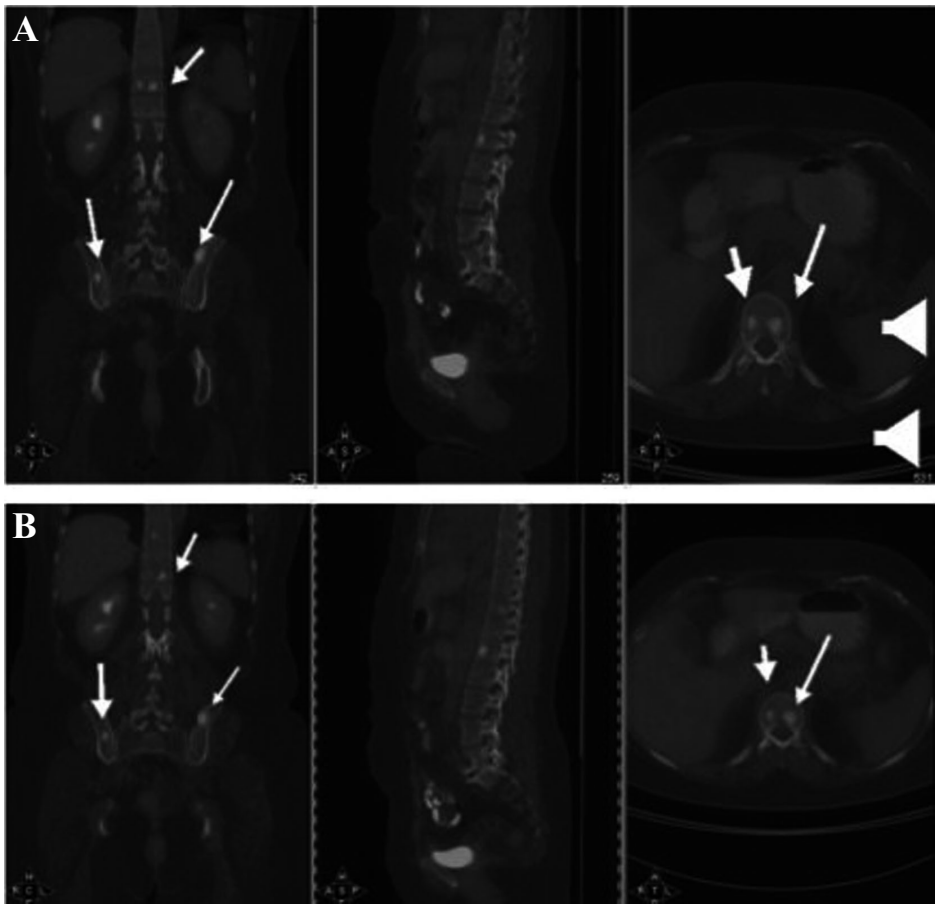

Figure 2. — A: PET/CT scan taken at the time of presentation shows bone nodules (vertebrae and iliac bones) which do not show 18F-FDG uptake. B: PET/CT scan taken after about ten months from treatment shows that nodules unchanged.

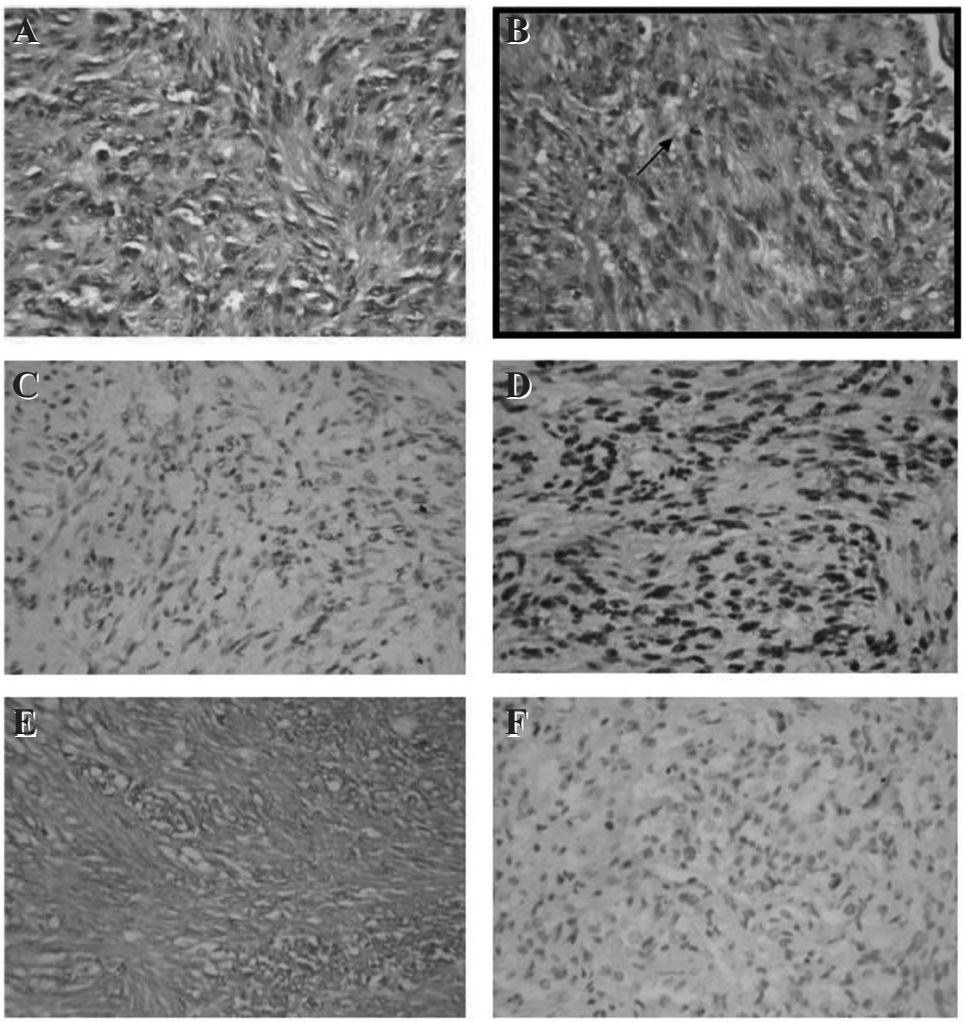

Figure 3. — A, B: H&E ×400, mitotically active leiomyoma (arrow) mitosis. C: Immunohistochemistry, ×400, estrogen receptor nuclear positivity. D: Immunohistochemistry, ×400, progesterone receptor nuclear positivity. E: Immunohistochemistry, ×400, Smooth muscle actin positivity. F: Immunohistochemistry, ×400, Ki-67 proliferation index 3%.

mass with the largest being 90×50 mm in size. Further MRI was also revealed that well-circumscribed right adnexal mass with extension into the aorta and vena cava inferior with the largest size of 92×59 mm. PET/CT showed left femoral and right para-aortical mass. The SUVmax (maximum standardized uptake value) were 8.6−9.7 and 5.5−5.9, respectively. Biopsies of both lesions were performed. Both were morphologically similar lesions and diagnosis of BML was confirmed with positive testing for desmin and ER and negative staining with actin, S100, CD34, myogenin, DOG1, and PR. The Ki-67 proliferation index was 3%. Since patient had significant pain and increased risk of fracture, ten days left femoral irradiation of total 30 Gy was done. Additionally, letrozole 2.5 mg PO, daily and monthly goserelin acetate 3.6 mg and zoledronic acid four mg were initiated on January 2014. Clinical and radiological partial response was obtained and patient is still on treatment without any disease progression and significant toxicity by May 2015.

Discussion

BML is a very rare disease that is detected as a solitary nodule or as multiple nodules in the various tissue and organs in patients with history of hysterectomy for uterine leiomyomas. In 1939, Steiner *et al.* reported the first case in which tissues similar to leiomyoma with benign histological appearance transferred from the uterus to the lung. It was termed "metastasizing fibroleiomyoma" [5]. BML is predominantly disease of premenopausal women. Unlike the present two cases, BML is rarely observed in postmenopausal women [2, 6]. Case 1 had surgical menopause after three years from TAH-BSO. Since this case had more widespread metastases than previously reported cases, hormone replacement therapy might have led to metastatic spread.

The pathogenesis and etiology of BML are still unclear. Uterine leiomyoma has been reported to depend on sex hormones [4]. ER and PR usually are highly expressed in BML, and anti-estrogen manipulations such as SERMs, progesterone, and aromatase inhibitors or oophorectomy show clinical benefit. Theories on its pathogenesis include a metastatic low-grade uterine leiomyosarcoma, a BML colonizing the tissues, and primary leiomyomatosis [7]**.** Patton *et al.* reported that it was clonally derived and

hematogenous spread from benign-appearing uterine leiomyomas [8].

Pathological diagnosis of BML is challenging, and it requires strict pathological diagnostic criteria. The diagnosis is based on the results of IHC staining and the history of hysterectomy for uterine leiomyoma. Pathologically, the present authors showed spindle-shaped cells with minimally mitotic activity without nuclear atypia. There were no hypercellularity, pleomorphism, and high mitotic activity as observed in leiomyosarcoma. In addition to these features, IHC staining was negative for CD117, and CD34, strongly positive for SMA, which shows smooth muscle origin of this benign tumor, demonstrating low expression for Ki67. The present authors ruled out the extra-gastrointestinal stromal tumors, lymphomas, and tumors of neuronal origin with negative CD117, CD34, and S100, respectively. Moreover, positive immunoreactivity for ER and PR in the present cases supported that the origin of spindle-shaped cells were uterine smooth muscle cells. Additionally, leiomyosarcoma was also ruled-out.

There are currently no standard treatment guidelines for this rare clinical entity. Reported treatment options include careful observation, surgical resection, hysterectomy and bilateral oophorectomy, and anti-estrogen. However, combined surgery and hormonal manipulation are believed to be the best choices of treatment for BML. If possible, a radical surgical resection has been advocated as the primary treatment for BML The use of GnRH analogs, which suppress the endogenous gonadotropin secretion, has been suggested as the best option for unresectable cases. The present case 1 was treated with letrozole monotherapy, while case 2 was given combination of letrozole, goserelin acetate, and zoledronic acid. Clinical and radiologic response was observed and very good symptomatic relief was achieved.

In conclusion, BML is rare disease of premenopausal women but should be also in differential diagnosis of postmenopausal women with lung and bone metastases, especially who having history of TAH-BSO. Although the standard treatment is not clear, surgery and hormonal manipulation should be attempted.

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