Novel hormone treatment of benign metastasizing leiomyoma: an analysis of five cases and literature review

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Objective: To evaluate novel hormonal therapies in patients with unresectable benign metastasizing leiomyoma (BML) disease.
Design: Case series.
Setting: National Institutes of Health (NIH).
Patient(s): Five subjects with the diagnosis of BML based on imaging and/or histopathologic diagnosis.
Intervention(s): Four patients were treated with single or combination therapy of leuprolide acetate and/or an aromatase inhibitor. One patient was treated with an antiprogestin (CDB-2914).
Main Outcome Measure(s): Response to therapy was measured by tumor burden on cross-sectional imaging employing RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 guidelines.
Result(s): Four patients treated with single or combination therapy of leuprolide acetate and/or an aromatase inhibitor demonstrated stable disease with reduction in tumor burden. The fifth patient treated with antiprogestin (CDB-2914) had degeneration of her tumor, progression of its size, and an improvement in symptoms.
Conclusion(s): Hormone treatment with GnRH agonist and/or aromatase inhibition may be a therapeutic option to reduce tumor burden in unresectable BML disease or for those patients who wish to avoid surgical intervention. RECIST 1.1 guidelines, while traditionally used to evaluate tumor response to cancer therapeutics, may be useful in evaluating BML tumor burden response to hormone therapy. (Fertil Steril® 2013;■:■–■. ©2013 by American Society for Reproductive Medicine.)
Key Words: Benign metastasizing leiomyoma, uterine leiomyoma, hormone therapy, intravenous leiomyomatosis, leiomyomatosis peritonealis disseminata

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Since Steiner first described benign metastasizing leiomyoma (BML) in 1939, there have been over 150 cases documented in the literature (1). This rare disease is characterized by well-differentiated smooth muscle tumors occurring outside the uterine corpus in women who have a history of histologically benign leiomyomas. Most often these smooth muscle tumors are seen in the lungs, but they are also found in the lymph nodes, abdomen, deep soft tissues, heart, bone, and central nervous system (2). A majority of those afflicted are premenopausal women, more than 50% presenting after the third decade of life (3). Almost all have had a history of uterine surgery, on average 10 years before presentation. Not infrequently, diagnosis of BML has been found on routine imaging of an asymptomatic patient, while some patients present with dyspnea and respiratory distress (4).

Received January 6, 2011; revised and accepted January 30, 2013.
E.I.L. has nothing to disclose. R.J.C. has nothing to disclose. A.H.D. has nothing to disclose. A.A. has nothing to disclose. J.E. has nothing to disclose. A.M.V. has nothing to disclose.
This research was supported in part by the Intramural Research Program of the National Institutes of Health; the Program in Reproductive and Adult Endocrinology, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; and the National Institutes of Health Clinical Center.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2013 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2013.01.147

The pathogenesis of BML remains controversial and may overlap with other benign smooth muscle neoplasms such as intravenous leiomyomatosis (IVL) and leiomyomatosis peritonealis disseminata (LPD), which are characterized by macroscopic smooth muscle tumorlets found intravenously and diffuse peritoneal and omental implants, respectively (5, 6). Three theories have been proposed regarding metastatic spread: metastatic uterine leiomyoma with invasive implants, implantation of smooth muscle tumors by IVL or mechanical means, and multifocal but independent proliferation of smooth muscle tissue (2). Despite being associated with distant metastases, BML lesions are distinct from more aggressive leiomyosarcomas, demonstrating low mitotic counts and lack of nuclear pleomorphism, which are characteristic of benign leiomyomas. The cytogenetic profile of BML lesions has been found in 3% of normal uterine leiomyomas, indicating that BML arises from a minority of uterine leiomyomas that have metastatic potential (7). There is convincing evidence that BML lesions are of uterine origin given that clonality analysis of pulmonary lesions and uterine tissue has demonstrated an identical monoclonal X-chromosome inactivation pattern (8). Furthermore, most BML lesions and uterine leiomyomas express estrogen receptors (ER) and progesterone receptors (PR) similar to uterine smooth muscle (9).

While traditionally surgical resection of metastatic lesions was the mainstay of treatment with variable long-term results, more recent management has revolved around surgical or medical castration (10–12). Clinical evidence of hormonal influence is suggested by reports of BML lesion regression during menopause (13) and after pregnancy (14, 15). Conversely disease progression has been observed in patients on hormone replacement therapy (HRT) and oral contraceptives (16). Surprisingly, a growing number of reports indicate that despite surgical castration, some lesions continue to progress, indicating that hormone therapy might be a vital adjunct or primary treatment of BML (3, 17, 18).

MATERIALS AND METHODS

We present a case series of five patients diagnosed with BML who were treated at the National Institutes of Health (NIH) between 2006 and 2012 with medical regimens, including an aromatase inhibitor, GnRH agonist, CDB-2914, or a combination of these medications. We report the response to therapy as measured by tumor burden on cross-sectional imaging employing RECIST 1.1 guidelines. All leiomyomatous lesions (up to a maximum of five lesions total) were recorded in at least one dimension. Complete response was defined as disappearance of target lesions, partial response was defined as at least a 30% decrease in the sum of diameters of target lesions, progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions, and stable disease was defined as insufficient regression or increase in disease to qualify as "response" or "progression" (18).

RESULTS

Case 1

In 2006, a 44-year-old nulligravid African American female presented with lower extremity edema, leg pain, and renal failure eventually requiring bilateral nephrostomy tube placement. At that time, she was found to have a large abdominal mass and new lung nodules on imaging. Past surgical history was notable for a hysterectomy at age 32, secondary to a symptomatic fibroid uterus. Histopathology of the computed tomography (CT)-guided biopsy of the abdominopelvic mass was ER/PR positive and consistent with benign leiomyoma. The patient was initially started on raloxifene and leuprolide (3.75 mg/4 weeks) with no decrease in tumor burden or symptoms over a 10-month period. Her therapy was subsequently changed to letrozole (2.5 mg/day). Approximately 8 months later, the patient underwent loop sigmoid colostomy for small bowel obstruction. At the time her abdominal mass was unable to be resected owing to the proximity of external iliac vessels. Subsequently, she had a series of uterine artery emoblizations performed but with continued abdominal and leg pain. Given her persistent symptoms, she was started on a new regimen of leuprolide (3.75 mg/3 weeks) and letrozole (1 mg/day) approximately 2 years after her last hormone treatment. While on this treatment, her abdominal mass and lung nodules have been stable by RECIST 1.1 criteria (9.2% decrease in total tumor burden size), and she has had no new symptoms for the last 2 years.

Case 2

In 2008, a 49-year-old Caucasian female presented with pelvic pain secondary to a palpable abdominal mass and was found to have multiple pelvic lesions and subpleural pulmonary nodules on imaging consistent with a diagnosis of BML. Her surgical history was notable for an abdominal myomectomy at age 30, followed by two cesarean sections, her last at age 41, where incidental "abdominal studding" was noted on the operative report. One month after diagnosis, she was started on leuprolide (3.75 mg/3 weeks) and anastrazole (1 mg/day). Three months later, repeat imaging showed decreased tumor burden. The leuprolide acetate dose interval was increased to 3.75 mg/4 weeks, and anastrazole (1 mg/day) was continued. Approximately 2 months later, she developed disabling arthritis, and following a consult with rheumatology, she discontinued anastrazole and her leuprolide acetate regimen was changed to 11.25 mg/3 months. Repeat imaging 2 months later showed a slight increase in mass size; therefore she was restarted on anastrazole (1 mg/day) and leuprolide (3.75 mg/3 weeks). Her large pelvic tumor has since demonstrated an interval decrease in mass size with a stable response by RECIST 1.1 (22.0% reduction in size of overall disease), and she reports improved symptoms of pelvic pain. She has continued on this hormone regimen to date, and although surgery has been recommended, she strongly desires to continue with medical management.

Case 3

In 2009, a 43-year-old Hispanic female with a long history of symptomatic uterine fibroids was diagnosed with BML after new pulmonary nodules were found on CT scan. The patient's surgical history was notable for an abdominal myomectomy at age 37, uterine artery embolization at age 39, and total