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Aromatase Inhibitor for Treatment of a Recurrent Abdominal Wall Endometrioma in a Postmenopausal Woman

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Summary

We present a case of a post-menopausal woman with an exceedingly large, recurrent abdominal wall endometrioma. The incidence of these clinical conditions is uncommon and a report of the combination of all of them has not previously been published. The patient was managed with the combination of an aromatase inhibitor, a progestin, and serial cyst aspiration. A successful response to treatment was determined via a novel method of measuring serum and cyst estradiol levels as well as sonographically demonstrating resolution of the cystic space. Taken together, this case demonstrates a novel approach for managing and monitoring medical therapy for unusual clinical presentations of endometriosis. Furthermore, it illustrates that endometriotic implants can be a source of circulating estrogen in postmenopausal women, and that this source of estrogen is generated by increased aromatase activity.

Keywords

Endometriosis; Endometrioma; Abdominal Wall; Aromatase Inhibitors

Endometriosis is a chronic gynecological condition defined as the presence of endometrial glands and stroma outside the uterine cavity. The most common sites of endometriosis are the ovaries, the pouch of Douglas, rectovaginal septum, the bowel and bladder, and when associated with formation of a mass lesion is described as an endometrioma. While the majority of patients have their disease limited to the pelvis, ectopic endometrial tissue has been identified at distant sites that include the abdominal wall, the pleural of the lungs and even the brain (1).

Endometriosis is an estrogen-dependant disease process, and as such, most commonly affects women between the ages of 25 and 45 years old who have menstrual cycles. Classically, it is believed that estrogens produced in the ovary during the menstrual cycle stimulate growth of the ectopic endometrium in a hormonal fashion and the cyclic pattern of symptomatology. However, there is a growing body of laboratory and clinical observations indicate that the endometriotic implants may themselves be a site of estrogen synthesis(2); thereby suggesting an autocrine and paracrine effect of estrogen on these ectopic tissues. Furthermore, this

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mechanism would account for patients with endometriosis that persists after surgical or physiologic menopause.

Treatment of endometriosis progresses through a step-wise pathway aimed at decreasing ovarian estrogen production. Initial treatment incorporates medical management and minimally invasive surgical treatment aimed at reducing the burden of ectopic endometrial tissue. Symptoms recur in more than 50% of patients after surgery or with cessation of medical therapy. Subsequent management strategies focus on a functional reduction in circulating estrogen either by supporting a woman medically until physiologic menopause is complete or by pursuing a surgical menopause with a total hysterectomy and bilateral salpingo-oophorectomy (3).

Case Presentation

We present the case of a 61-year-old G4P3103 postmenopausal woman who presents for evaluation and management of a recurrent, abdominal wall endometrioma. She has no significant gynecological history. She reports an unremarkable menstrual history with menarche in her early teens, regular cycles until menopause 16 years prior to presentation at age 45. She denies any history of dysmenorrhea, dyspareunia, dysuria, dyschezia, endometriosis, infertility, or chronic pelvic pain. Her obstetric history is remarkable for 4 vaginal deliveries including a single preterm delivery and subsequent neonatal demise.

Her past surgical history is significant for a bilateral tubal ligation approximately 30 years ago and an incarcerated ventral hernia that was repaired with mesh 6 years prior to presentation. She has no other significant past medical history. She uses no medications and has no known drug allergies. Her social and family histories are non-contributory.

The patient initially presented to a general surgeon two years prior with complaints of an abdominal wall soft tissue mass in her right lower quadrant increasing in size over an eight-month period and resulted in mild, intermittent discomfort. The mass was resected, and gross description demonstrated a well-encapsulated, multiloculated, cystic mass superficial to the rectus sheath measuring $10 \times 7 \times 6$ cm, containing hemorrhagic fluid and debris. Histopathology was consistent with a benign hemorrhagic cyst of the anterior abdominal wall of endometriotic origin.

Eighteen months after her primary resection, she presented with a recurrence of a right lower quadrant soft tissue mass that had been increasing in size over a one-year period. CT scan demonstrated a well-defined loculated, collection superficial to the rectus muscles measuring $20 \times 7.6 \times 8.7$ cm in largest dimension. Again, surgical resection was performed. Operative findings included a large cyst involving the entire infraumbilical, anterior abdominal wall. The mass was adherent to the surgical mesh that had been used to repair a ventral hernia six years prior. The mass, the mesh, and overlying skin were removed en-bloc, and the anterior abdominal wall was reconstructed. Exploration of the cyst revealed a multiple loculations with chocolate fluid. Histopathology was consistent with a subcutaneous endometriotic cyst composed of a fibrous wall without a lining epithelium. The cyst wall demonstrated scattered foci of endometrial glands and stroma. No evidence of malignancy was identified.

Ten months after her second resection, she presented with a new left lower quadrant soft tissue mass. CT scan demonstrated a 12.5×8 cm mass within the subcutaneous fat of the anterior abdominal wall. Considering her history, she was referred to our practice for evaluation and management. Her initial lab values were remarkable for an estradiol of 39 pg/ml, FSH of 44 mIU/ml, LH of 24 mIU/ml. Testosterone, complete metabolic panel, liver function tests, and complete blood count were normal. The tumor markers CA125 and CEA were 6.8 U/ml and 0.5 ng/ml, respectively, both of which are within the normal range.

Physical exam revealed an obese female (BMI=38.2kg/m²) with a tense, non-tender 12 cm cystic mass in the left lower quadrant. Transabdominal sonography demonstrated a multiloculated cystic mass measuring 12.7 × 8.2 × 10.0 cm. Approximately 200cc of chocolate colored fluid was aspirated under ultrasound guidance and cytology showed fibrinous material and hemosiderin laden macrophages with no evidence of malignancy, consistent with an endometrioma. Transvaginal sonography demonstrated no evidence of malignancy with a thin endometrial stripe, no uterine or adenexal masses were noted. Review of her recent CT failed to identify abnormalities in her pelvic viscera.

Within one week of the initial aspiration, the fluid reaccumulated and the cyst returned to its original size. A repeat aspiration was performed and an estradiol level of the cystic fluid was measured at 89 pg/ml with a serum estradiol of 39 pg/ml. The patient was started on letrozole 2.5mg PO daily. She returned every two weeks for a repeat cyst aspiration and determination of estradiol levels in the serum and cystic fluid (Fig.1).

After two weeks of aromatase inhibitor therapy, her circulating estradiol level decreased to 24 pg/ml with minimal change in the cystic fluid. Her dose of letrozole was increased to 5mg daily with a subsequent drop in the estradiol level in the cystic fluid to 28 pg/ml. She was started on medroxyprogesterone acetate (MPA) 10mg PO daily. After 4 weeks of aromatase inhibitor therapy and 1 week of MPA the size of the cystic mass decreased to 6.6 × 8.5 × 4.2 cm and could be completely decompressed after the last aspiration. The estradiol levels in the serum and cystic fluid decreased to <20 pg/ml and 22 pg/ml, respectively (Fig. 1).

Discussion

Extra-pelvic Endometriosis in Post-Menopausal Women

The prevalence of endometriosis in post-menopausal females has been reported to range from 2-4% of women but is often associated with hormone therapy. The patient described here has no history of hormone therapy but nonetheless made her initial presentation with endometriosis in the post-menopausal period. It is possible that this woman previously had undiagnosed or asymptomatic pelvic endometriosis.

Extrapelvic endometriosis can occur in as many as 14-26% of women with endometriosis but is less common as the solitary manifestation of the disease (4-6). Endometriosis of the skin and soft tissue is estimated to be 3.5% of extrapelvic endometriosis (1). The abdominal wall endometrioma is a well-described clinical entity. The true incidence of incisional scar endometriosis is difficult to determine and is likely related to the indication for the original surgery. It has been estimated to range from 0.03-0.47% of scars following cesarean section (7). The average time between the index surgery and clinical manifestation of scar endometriosis ranges from 6 months to 20 years (8-13). Interestingly, abdominal wall endometriomas have also been shown to arise *de novo* without any previous abdominal surgery (8,14,15).

Since the endometrial tissue, both eutopic and ectopic implants, proliferates in response to estrogen stimulation, affected patients often present with cyclic pelvic pain as a consequence of the hormonal changes across the endometrial cycle. By contrast with pelvic endometrial implants which presents with cyclic pain that correlates with the menstrual cycle, scar endometriosis can present with an abdominal mass and non-cyclic symptoms since the pain from the lesions results from distension of the cyst and thus the abdominal wall. In non-cycling, post-menopausal patients, such as the woman presented in this case, pain is likely to be continuous without a predictable pattern.

Recurrent Abdominal Wall Endometriosis

While the pathogenesis of abdominal wall endometriosis is unknown, it is speculated to result from iatrogenic transplantation of endometrial tissue, either from the uterine cavity at the time of hysterotomy, or from endometriotic peritoneal implants residing with the peritoneal cavity. In the patient presented here, the cellular origin of her abdominal wall endometrioma is unknown. While her previous laparoscopic tubal ligation and ventral hernia repair are risk factors for developing abdominal wall endometriosis, the patient had no history of pelvic endometriosis that would have been transplanted to the abdominal wall. Nonetheless, the recurrent endometrioma in this patient was likely the consequence of an inadequate surgical resection.

Aromatase Inhibitors for Management of Endometriosis

Aromatase (estrogen synthase), a cytochrome P450 enzyme encoded by the CYP19 gene, is the rate-limiting step in conversion of the androstenedione and testosterone to the estrone and estradiol (16). Letrozole, a competitive inhibitor of the aromatase enzyme has approved for the treatment of advanced breast carcinoma in postmenopausal woman (17). The use of aromatase inhibitors alone, or in combination with other hormone modulating therapies, for the treatment of endometriosis has been an area of active research (18). Preliminary reports suggest that this combination may be effective at treating severe or recurrent postmenopausal endometriosis (19-21).

By contrast with majority of medical therapies that impact ovarian estrogen production, aromatase inhibitors can inhibit both gonadal and peripheral production of estrogens. In postmenopausal women where estrogen production is derived from a non-gonadal source, aromatase inhibitors have been shown to suppress circulating estrogen levels to 95% of their pretreatment values (22). Recent trials have explored the use of aromatase inhibitors in combination with a progestin for treatment of advanced stage endometriosis (23-26). Ultimately, this medical regimen was employed in combination with serial cyst aspiration, to reduce the stored estrogen burden, as an effective, minimally invasive treatment strategy for the patient presented here. Furthermore, this case illustrates that endometriotic implants can be a source of circulating estrogen in postmenopausal women, and that this source of estrogen is generated by increased aromatase activity. Additionally, it suggests a novel approach for managing and monitoring medical therapy for unusual clinical presentations of endometriosis.

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Figure 1.

Quantification of estradiol levels (pg/ml) in blood and cystic fluid throughout treatment. Letrozole 2.5mg daily was initiated on day 0. On day 14, letrozole was increased to 5mg daily. A final measurement was collected 34 days after initiating medical therapy.