post-menopausal endometriosis with inferior vena cava invasion requiring surgical management

R. Flyckt, S. Lyden, A. Roma, and T. Falcone*
Department of Obstetrics, Gynecology and Women’s Health, Cleveland Clinic, 9500 Euclid Ave, A81, Cleveland, OH 44195, USA

*Correspondence address. Tel: +1-216-444-1758; Fax: +1-216-445-6325; E-mail: falcont@ccf.org
Submitted on March 16, 2011; resubmitted on June 22, 2011; accepted on June 28, 2011

Abstract: Post-menopausal endometriosis is rare after hysterectomy, and preliminary data support treatment with aromatase inhibitors (AIs). Sites for extrapelvic recurrent disease are wide-ranging; however, no previous case reports have described endometriosis invading the inferior vena cava. A 59-year-old woman status post hysterectomy and bilateral salpingo-oophorectomy for endometriosis developed a peri-aortic mass with ureteral obstruction. Computerized tomography-guided biopsy confirmed recurrent endometriosis and the lesion enlarged despite treatment with AIs. Vascular surgery, urology and gynecology were involved. The mass was resected surgically and pathology confirmed invasion of the inferior vena cava. Medical management with AIs can be attempted for extra-pelvic endometriosis status post hysterectomy; however, the efficacy in this setting is limited. Surgical management may be necessary for bulky or invasive disease.

Key words: post-menopausal endometriosis / aromatase inhibitors / inferior vena cava

Introduction

Endometriosis is a condition affecting up to 10% of pre-menopausal women which can result in pain, bowel and bladder dysfunction, and subfertility (Diwadkar et al., 2011). Multiple medical treatments for endometriosis are available, including progestin-only agents, combined oral contraceptives, danazol, GnRH agonists and aromatase inhibitors (AIs), although the latter is not approved by the Food and Drug Administration (FDA) for the treatment of endometriosis (Ruhland et al., 2011). The definitive surgical therapy remains total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO) (Berlanda et al., 2010). Recurrent endometriosis is especially rare after menopause or after TAHBSO, although the risk may be higher in women who have taken hormone replacement therapy (HRT) (Oxholm et al., 2007). Limited studies of AIs have shown promise in controlling post-menopausal endometriosis, perhaps due to reduced estrogen production within these estrogen-dependent lesions (Takayama et al., 1998; Mousa et al., 2007; Sasson and Taylor, 2009).

Recurrence of endometriosis in post-menopausal women or women who have undergone TAHBSO has been described in numerous sites. In rare cases, even after the removal of pelvic organs, thoracic endometriosis has been reported on the diaphragm or in the pleura or pericardium (Joseph et al., 1994). There has been one published case of endometriosis involving the thoracic aorta; however, this occurred in a pre-menopausal women who had undergone a patch repair of aortic coarctation 16 years before (Nötzold et al., 1998). Another case report described pathology-confirmed recurrent endometriosis involving the para-aortic lymph nodes during pregnancy (Beavis et al., 2011). No previous case reports have described endometriosis invading the inferior vena cava (IVC). The following is a report of our management of a very rare presentation of recurrent post-menopausal peri-aortic endometriosis with concurrent ureteral obstruction and IVC invasion.

Case

A 59-year-old G3P3 Caucasian woman presented as a referral for a peri-aortic mass. The patient had a past medical history significant for severe endometriosis, resulting in a TAHBSO at the age of 43. She received 15 years of continuously dosed hormone HRT with conjugated equine estrogen, and had been hormone-free for one year prior to her visit. She had a past obstetrical history of three uncomplicated vaginal births, and one of her adult daughters had been diagnosed with endometriosis.

The patient initially presented to an outside emergency room with left lower quadrant abdominal pain approximately 2 months prior to her visit with us. Workup of her pain led to a computerized tomography (CT) scan at an outside hospital, which revealed a complex cystic and solid mass within the retroperitoneum measuring 8.5 × 5.6 cm. The mass surrounded the aorta and aortic bifurcation and was notable for septations. A mild mass effect and encasement of the
IVC was noted. There was also right-sided hydronephrosis and hydro-ureter, which required a ureteral stent to relieve the obstruction. A diagnosis of cancer was presumed; however, a CT-guided biopsy revealed endometriosis on final pathology. The patient was started on a monthly intramuscular GnRH agonist by the referral physician, presumably as this medication is a common treatment for pre-menopausal endometriosis. She was referred to us for consultation and possible surgery.

At our initial visit, the patient’s BMI was 33 and her physical exam was benign, without any reported abdominal or flank tenderness on palpation. The patient stated that her pain was improved after two monthly doses of GnRH agonist. Despite this perceived benefit, the use of GnRH agonists in hypogonadal women is not indicated and therefore the agonist was discontinued and an AI was initiated. We prescribed 2.5 mg letrozole daily. Serum estradiol at the time of presentation was in the menopausal range at 19 pg/ml (lower limit of assay = 12 pg/ml). Serum FSH had been suppressed after 2 months of GnRH agonist treatment to 12.2 mU/ml. Vascular surgery and urology were consulted. Over the next 6 weeks, despite increasing the dose of letrozole from 2.5 mg daily to 5 mg daily, the mass continued to enlarge. A positron emission tomography/CT performed one month after presentation to our clinic demonstrated that the mass was encasing the distal aorta and aortic bifurcation, and had enlarged from 8.5 to 11.1 cm (Fig. 1). The lesion was intimately associated with inferior vena cava, surrounding, displacing and possibly invading into the vessel. There was also mild right hydronephrosis and hydrourerter, with proximal ureteral stenosis likely due to a mass effect from the lesion. The right kidney itself demonstrated multiple areas of cortical scarring.

In coordination with urology, vascular surgery performed a resection of the mass via laparotomy. Initially, the tumor was freed from the aorta; however, several smaller venous and arterial branches, the inferior mesenteric artery and nearby lymphatic tissue had to be divided to remove the mass. The lesion could not be separated from the IVC. The IVC appeared chronically scarred and showed occlusion in the area of the mass by Doppler. Several large collaterals had developed in the area of the occluded IVC; these collaterals as well as the renal vein and inferior mesenteric vein were spared. Resection and ligation of the IVC was then performed from the bifurcation of the common iliac veins to two centimeters below the renal vein.

Urology was present to perform the ureterolysis. The ureter was mobilized distally to the crossing of the iliac vessels and proximally to the area likely corresponding to the lower pole of the right kidney. This ureterolysis extended proximally and distally beyond the extent of the endometriosis. A ureteral resection was not performed due to the increased morbidity of this procedure and the near-complete reduction in disease accomplished at the time of surgery. At the conclusion of the procedure, the majority of the disease had been debulked and both the ureter and aorta were wrapped in omentum.

The patient was discharged home on post-operative Day 19. Her course was complicated by ileus requiring temporary placement of a nasogastric tube. She also required post-operative therapeutic paracenteses due to the accumulation of ascites, likely from venous outflow obstruction and lymphatic leak. She otherwise did extremely well given the involved nature of her surgery and she was maintained on letrozole 2.5 mg daily to prevent recurrences. She was advised to avoid any further HRT to reduce recurrence risk. The patient will be monitored in the future with office visits and serial CT scans. Our major concerns for long-term follow up are recurrence of disease or development of chronic venous insufficiency.

The final pathology report demonstrated extensive tissue involvement of polypoid endometriosis composed of crowded and irregular glands, consistent with complex non-atypical hyperplasia. Polypoid endometriosis is a subtype of disease that often presents as a large mass and can be differentiated from malignant neoplasms based on the lack of histologic atypia (Laird et al., 2004). Focal endometrial-type stroma was present along with the areas of recent and remote hemorrhage. Most glands showed atrophic features and the stroma showed extensive foamy type changes, consistent with the prior hormone

**Figure 1** T2-weighted CT images demonstrating association of the ureter, inferior vena cava, aorta and duodenum with the endometriotic lesion.

**Figure 2** Endometriosis composed of glands and foamy cells in the stroma and areas of hemorrhage involving the wall of the inferior vena cava. H&E. 40 x.
agreed on the final diagnosis. On our review of the literature, there was one prior case describing bulky endometriosis in a post-menopausal woman that required extensive retroperitoneal dissection but did not invade the wall of the inferior vena cava (Bailey et al., 2010). Medical management was not attempted before surgical intervention. In our case, the large volume of disease resulted in loss of ipsilateral renal function. There are several teaching points to be learned from our case.

First, and perhaps most importantly, a multidisciplinary approach is critical in managing patients who have extrapelvic non-gynecologic endometriosis. For example, despite the extensive surgical experience of gynecologic surgeons within our institution, urologic consultation was necessary for the management of the proximal ureteral disease. In this case, the patient required ureteral stenting for pre-operative management as well as ureterolysis at the time of her surgery. Vascular consultation was also required due to the vascular involvement of the lesion as well as the fibrosis and occlusion of the vein that necessitated extensive dissection, excision and ligation.

Secondly, AIs may be of limited utility in some post-menopausal women, as letrozole blocks the conversion of androgens to systemic estrogens in the peripheral tissues via reversible competition with the aromatase enzyme. In patients with endometriosis, local aromatase expression within the lesions themselves may be blocked using AIs. Although they are used in clinical practice, it should be noted that AIs are not FDA approved for this purpose. Lack of response in this case to the AI may have been due to the already low systemic estrogen levels. Local depletion of the estrogenic microenvironment by the AI is dependent on the extent of expression of aromatase. Although some previous studies have demonstrated aromatase expression in human endometriotic lesions, two recent studies have failed to detect significant aromatase activity in tissue samples (Colette et al., 2009; Delvoux et al., 2009). Colette et al. demonstrated a lack of aromatase expression at both the protein and mRNA levels in both glands and stroma of ectopic endometrial lesions (Colette et al., 2009). These findings were independent of menstrual cycle phase or concurrent hormonal treatments. It may be that reported benefits of aromatase treatment are mediated by a systemic rather than local response, or could perhaps inhibit estrogen production by peritoneal or adipose tissues rather than endometriotic lesions themselves. Other reports have also demonstrated the lack of effect of AIs on extensive pelvic endometriosis disease after TAHBSO (Bohrer et al., 2008).

In this case, poor perfusion to the mass may also have influenced the patient’s reduced response to AI treatment. On final pathology, there was extensive fibrosis encasing the lesion. In addition, this patient’s lesion measured at least 8 cm at the time of initial presentation. Although attempts to reduce the size of the lesion with medications were reasonable given the risky nature of surgical management, the likelihood of success with medical therapy for a lesion this large was probably slight. It is our hope that treatment with AIs post-operatively may have greater effect due to decreased tumor load and improved perfusion. In addition, we recommended that this patient avoid HRT in the future. A recent Cochrane database review concluded that HRT for women with post-menopausal women with endometriosis could result in disease recurrence, although the risk is low and the available data are extremely limited (Al Kadri et al., 2009).

Third, it should also be noted that GnRH agonists do not have value in treating endometriosis in hypogonadal women. GnRH agonists work via suppression of the hypothalamic-pituitary-ovarian axis to affect ovarian estrogen production; therefore, they would not be expected to achieve therapeutic benefit in patients who had their ovaries removed. Although a commonly used treatment for endometriosis, GnRH agonist therapy is not indicated in post-menopausal women and that there would be no indication for its use in our patient.

Finally, when medical treatment fails, many patients do ultimately require surgery for bulky or invasive disease. Surgical management of post-menopausal or post gonadectomy recurrence or persistence of endometriosis requires extensive experience and a multidisciplinary approach.

Authors’ roles
R.F. facilitated all aspects of patient care and subsequent case report, and was involved in drafting the manuscript and discussion. S.L. (primary surgeon), assisted with manuscript drafting and discussion of surgical aspects of case. A.R. was involved in pathology as well as preparation of figures and legends, and assisted with manuscript drafting of pathologic aspects of the case. T.F.(primary physician) took part in coordination of patient care and manuscript drafting, critical discussion and final review of manuscript.

Conflicts of interest
The above authors state that they have no biases of a financial, personal or professional nature which would affect this manuscript. These include financial competing interests, such as stock ownership, paid employment, board membership, patent application (pending and actual), research grants (from whatever source), travel grants and honoraria for speaking or participation at meetings and gifts; personal competing interests, such as membership of lobbying organizations and relationships with editors of Human Reproduction, or professional competing interests, such as acting as an expert witness, membership of Government advisory board and organizations and funding bodies.

References


