Ureteral Endometriosis: A Rare and Underdiagnosed Cause of Kidney Dysfunction

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Key Words
Renal failure • Endometriosis • Obstructive uropathy

Abstract
Little attention has been paid by the renal literature to ureteral endometriosis, a rare and silent disorder that can eventually lead to renal failure. In endometriosis, the ureteral involvement can be limited to a single ureter, more often the left one, or both ureters with consequent urine tract obstruction and ureterohydronephrosis. In most cases, the ureteral obstruction is caused by endometrial tissue surrounding the ureter (extrinsic ureteral endometriosis). In the remaining cases, endometrial cells are located within the ureter (intrinsic ureteral endometriosis). Progressive ureteral obstruction can be insidious in onset and can ultimately lead to renal failure if a correct diagnosis is missed. The true incidence of renal failure caused by endometriosis is completely unknown, although cases have been reported in the literature. The diagnosis of ureteral endometriosis is difficult since the disease may be clinically silent or associated with non-specific symptoms. Only a high index of suspicion and radiological support may help to obtain an early diagnosis. However, while renal imaging is useful in the cases of extrinsic endometriosis, the diagnosis of intrinsic endometriosis often requires ureteroscopy or laparoscopy. The prognosis of ureteral endometriosis depends on the time of diagnosis. In too many cases of bilateral obstruction, the patient is referred to the nephrologist because of an advanced, irreversible renal failure. Although some patients may benefit from progestin or anti-aromatase therapy, in most cases of ureteral endometriosis surgery is needed, laparoscopy surgery being preferred today to laparotomy.

Introduction and Overview

Very little has been reported in the nephrological literature on the possibility that ureteral endometriosis may lead to end-stage renal disease (ESRD). The true incidence of ureteral endometriosis is still unknown, but its association with renal obstruction is well recognized. The main problem is that bilateral ureteral endometriosis may be asymptomatic and many cases are discovered incidentally during laparoscopy for extensive endometriosis. On the other hand, while renal echography may show a pyelocaliceal dilation in cases of extrureteral endometriosis it is of little, if any, help for diagnosing patients with endoureteral endometriosis. Recent observa-
tion of 2 cases of young women with a history of pelvic endometriosis progressing to ESRD without any suspicion of the possible association from their nephrologists, prompted us to review the available data concerning ureteral endometriosis and ESRD.

Endometriosis is a clinical disorder in which functionally active endometrial cells are deposited in areas outside the uterus. The disorder is typically seen during the reproductive years occurring in 5–15% of women and is more common in nulliparous or infertile women. The pelvis is the main location of the endometrial tissue, however, extrapelvic locations have been found in lung, lymph nodes, scars, and, exceptionally, in the kidney [1, 2]. Symptoms depend on the site of implantation. Chronic pelvic pain more or less related to menses, dyspareunia and dysuria are frequent manifestations but can also be seen in other diseases. Extragenital endometriosis rarely involves the urinary apparatus, however, when it does occur, involvement of the bladder, ureter, kidney and urethra is 85, 10, 4, and 2%, respectively [3]. Ureters are rarely involved in endometriosis, however, the close anatomical proximity of the distal ureter to the female reproductive organs makes it an ideal target for the development of extrinsic compression of the ureter [4]. Deeply infiltrating endometriosis of the pelvis is often asymmetric and mainly involves the left pelvis: it may cause rectovaginal lesions and can involve other vital structures, including the bladder and ureters. When within the bladder, the lesion is usually situated in the posterior wall or at the dome; more rarely endometrial lesions involve the vesical base being proximal to ureteral hiatus. Ureteral endometriosis is classified as intrinsic and extrinsic with a 1:4 ratio and the ureter is usually involved below the pelvis brim [5, 6].

The ureteral involvement may lead to urine tract obstruction and ureterohydronephrosis which can happen with minimal or extensive disease. Involvement can be limited to a single ureter, more often the left one [7], or both ureters, particularly in patients with extensive pelvic endometriosis. Ureteral endometriosis is usually discovered in women aged between 30 and 35 years [4, 7–9]. It is uncommon and therefore even more likely to remain undiagnosed in postmenopausal women [10]. In the extrinsic form (about 75% of all cases), ureteral endometriosis is localized to the adventitia or surrounding connective tissue of the ureter. Pathologic and clinical studies report that most patients showed hydroureter hydronephrosis, with superimposed pyelonephritis in about one third of cases [11]. As many as 25–50% of nephrons are lost when ureteral endometriosis is present. Rare cases of renal failure caused by bilateral ureteral obstruction have been reported [12] but the true incidence of ESRD caused by endometriosis is completely unknown.

### Pathogenesis

The pathogenesis of deeply infiltrating endometriosis is still under discussion. A first hypothesis was that pelvic endometriosis might be a direct extension of endometrial cells outside the uterine wall favored by previous pelvic surgery [13]. This interpretation was supported by the fact that the diagnosis of ureteral endometriosis is preceded in most cases by hysterectomy and bilateral salpingo-oophorectomy, possibly because of prior symptoms related to adenomyosis or pelvic endometriosis, and that ureteral endometriosis has a strong predilection for involvement of the lower third of the left ureter. However, the available evidence rather suggests that deep infiltrating vesical and rectovaginal endometriosis result from intrauterine seeding of regurgitated endometrial cells, which collect and implant in the most dependent portions of the peritoneal cavity and the anterior and posterior cul-de-sac, and trigger an inflammatory process leading to adhesion of contiguous organs with creation of false peritoneal bottoms. Peritoneal, ovarian, and deep endometriosis may be diverse manifestations of a disease caused by regurgitated endometrium. According to these findings, the occurrence of ureteral endometriosis may be explained by the menstrual reflux theory with flow of peritoneal fluid and by the anatomic differences of the left and right hemipelvis [14]. However, further data are needed to demonstrate the validity and reliability of this hypothesis [15].

### Clinical Presentation

The clinical presentation of ureteral endometriosis may be variable. In most cases the disease is clinically silent [9]. In about one third of patients ureteral endometriosis is associated with non-specific symptoms such as dysmenorrhea, dyspareunia, pelvic pain, infertility, dysuria, frequency, recurrent urinary tract infections, or lumbar pain [16]. In women with chronic pelvic non-cyclic pain, the occurrence of endometriosis must be taken into account. In the differential diagnosis, the postoperative adhesions, pelvic varices, interstitial cystitis and irritable bowel syndrome must be considered.
A correlation between pain occurrence and uterine cyclic phase has not been clearly demonstrated. Hematuria is rare. Rarely, ureteral endometriosis is present with right lower quadrant pain giving rise to initial diagnostic possibility of acute appendicitis [18]. In rare cases the disease may present with arterial hypertension [19] or acute renal failure [20, 21]. In most cases ureteral endometriosis is not associated with bladder disease, however, it is often associated with retrocervical and rectum-sigmoid lesions [22]. For patients with associated ovarian endometrioma, deeply infiltrating endometrial lesions are more severe, with an increased rate of vaginal, intestinal, and ureteral lesions. About 30% of patients suffer from reduced kidney function at the time of diagnosis [11]. For the nephrologist it is important to recall that an undefined number of women silently progress to advanced renal failure due to bilateral obstructive uropathy. In other cases the loss of one kidney is discovered incidentally.

**Diagnosis**

Progressive ureteral obstruction can be insidious in onset and can ultimately lead to renal failure. The diagnosis of ureteral endometriosis should be considered in women with renal symptoms of non-calculous obstruction, particularly in premenopausal women with an anamnesis of polycystic ovary disease or severe menstrual related symptoms, although the disease is often strictly associated with silent renal obstruction. The diagnosis of ureteral endometriosis is difficult. Since endometriosis rarely involves mucosal membranes, exfoliative cytology is only occasionally able to detect endometrial and glandular cells in the urine [23]. Only a high index of suspicion and radiological support may help to obtain an early diagnosis. In one study, ureteral endometriosis was presumptively diagnosed before surgery only in 40% of patients [9]. Imaging techniques are of limited value in providing an accurate depiction of extension of ureteral lesions. Abdominal ultrasonography may raise suspicion that could be confirmed by further investigations. However, not in all women with ureteral endometriosis echography shows ureteral or calicopelvic dilatation. Intrinsic ureteral endometriosis can lead to uni-lateral renal atrophy without dilatation. Extensive unresectable periureteral fibroinflammatory thickening involving vascular or visceral structures may be associated with mild or absent dilatation. In other instances, ultrasonography may show moderate calico pyelic dilatation that can be confused with parapyelic cysts or sponge kidneys.

Intravenous urography and, more recently, spiral computed tomography still remain important diagnostic tools for ureteral endometriosis, as they may localize the level, degree and laterality of ureteral involvement. However, urography is unable to identify the cause of an extrinsic obstruction. In the case of intrinsic endometriosis, urography may show a filling defect within the lumen of the ureter, but again this finding is not specific as it can be caused by stones or transitional cell cancer.

Magnetic resonance imaging (MRI) is sensitive and specific, although the ureteral lesions may be underestimated [24]. Magnetic resonance urography is accurate in differentiating between intrinsic and extrinsic forms of ureteral involvement [25]. Ureteral endometriosis can be identified as a hypointense nodule on T2-weighted images and hyperintense foci on T1-weighted images. MRI can also detect periureteral involvement (extrinsic endometriosis) rather than ureteral wall lesions (intrinsic endometriosis). MRI is also a useful preoperative tool for directing towards better treatment [26]. Sometimes, diagnostic imaging may lead to some pitfalls. For example, radiographs may show "pulmonary metastases" together with hydronephrosis, mimicking a malignant metastatic gynecologic tumor of unknown primary origin [27].

Ureteroscopy is particularly useful to discover intrinsic endometriosis [5, 28]. A diagnostic tool often used for evaluation of a wide range of abnormalities, including ureteropelvic junction obstructions, ureteral and renal pelvic neoplasms, and obstructed ureter is two-dimensional endoluminal sonographic imaging of the ureter. It can demonstrate the periureteral anatomy, and can define the presence and the nature of lesions within the ureteral wall. Three-dimensional reconstruction of two-dimensional sonographic imaging is a new technique applicable to intraluminal imaging. It offers advantages over two-dimensional imaging by demonstrating the spatial relation of anatomic structures that cannot be appreciated using conventional imaging [29].

Laparoscopy allows direct localization of endometrial tissue around the ureter while its role in patients with intrinsic endometriosis is limited. Because the inflammatory process surrounding endometrial tissue is in close proximity to the ureter, adequate visualization of the ureter for proper diagnosis may require aggressive mobilization of the colon and ureter. The main advantage of laparoscopy – as a diagnostic tool – is to identify other foci of endoperitoneal endometriosis, especially in the region of...
the cul-de-sac. Laparoscopic adhesiolysis, ureteroureterostomy or ureteral reimplantation, although technically challenging, can be performed [5].

Ureteral endometriosis should be included in the differential diagnosis of obstructive ureteral lesions in women, particularly those involving the lower third of the left ureter, even in postmenopausal patients. The nature of invasive tissue may be confirmed by immunostains for cytokeratin-7 (CK7) and progesterone receptor (PR) which are positive in case of endometriosis, whereas immunostains for estrogen receptor (ER) are positive in 83% of cases and immunostains for CK20 are negative in all cases. CA125 immunostains are positive in 67% of cases. The stromal cells are positive for CD10, ER, and PR immunostaining [30]. Polypoid endometriosis is a rare manifestation of endometriosis that may be mistaken for a neoplasm on clinical, intraoperative, or pathologic assessment [31].

Outcome and Prognosis

The prognosis of kidney endometriosis is generally good [1, 2]. A single case of a large endometriotic cyst, arising from the left renal area and occupying almost the whole left side of the abdomen, has been reported [32]. The prognosis of ureteral endometriosis depends on the time of diagnosis. In too many cases of bilateral obstruction, often secondary to pelvic surgery, the clinical presentation is characterized by an advanced renal failure and shrunken kidneys or dilated kidneys with extremely thin cortices at ultrasonography. In case of an early diagnosis, an appropriate medical or surgical treatment may prevent renal function deterioration. However, recurrence can occur. Out of 30 patients with ureteral endometriosis treated with ureterolysis, ureter resection or ureterectomy and ureterocystotomy during a mean follow-up period of 14.6 months endometriosis recurred in 3 patients with no evidence of ureteral reinvolution [9].

Treatment

Drugs induce temporary quiescence of active endometrial deep lesions and may be useful in selected circumstances. Progestins should be considered as first-line medical treatment for temporary pain relief. Hormone therapy should be offered to patients of childbearing age who have the disease at an early stage and wish to have children. The aromatase inhibitor anastrozole which blocks conversion of aromatizable steroids to estrogen has also been used, but not all patients respond to this treatment [33]. Ureteral lesions secondary to endometriosis can be treated by cystoscopy and JJ stent [34]. However, in most cases of severely infiltrating disease, surgery is the final solution, particularly in case of intrinsic ureteral obstruction [11].

Surgical treatment may consist of ureteroneocystotomy, laparoscopic ureterolysis, with later ureteral resection and end-to-end anastomosis, or even autotransplantation in case of ureteral relapses. Traditionally, laparotomy has been the method of choice for ureteral injuries even when the injury is identified during a laparoscopic procedure. Today, however, some urologists feel that laparotomy should be avoided [34] as it shows a higher rate of infection and incisional hernias, longer hospital stay, and slower recovery compared with laparoscopy. It is still debated whether segmental resection and anastomosis or ureterolysis or minimal-access procedures are preferable. Recent studies suggest that laparoscopic ureterolysis can be an effective treatment option in most patients with ureteral endometriosis but that recurrence rates are not negligible [9]. Successful application of laparoscopic surgery, even for procedures that have traditionally necessitated laparotomy, has been reported. Extensive experience with endourological techniques is prerequisite for success [35]. Systematic ureteric stenting prior to surgical dissection of the pelvic wall is recommended in patients with posterior nodules and in the case of partial cystectomy for anterior nodules when the ureteric meati are adjacent to the lesion. Ureteric reimplantation onto a psoas hitch bladder must be performed when the endometrial lesions are extensive and partly resected or invade the ureteric wall. The frequency of associated lesions (urinary, gynecological gastrointestinal) justifies a multidisciplinary surgical approach [36].

Conclusions

Urinary tract endometriosis is an uncommon pathologic finding and a silent cause of monolateral or bilateral renal atrophy in an undefined number of patients. The nephrologist should carefully monitor renal function and renal ultrasonography in patients with a diagnosis of endometriosis. In patients with signs of dilation or hyperechogenicity at ultrasonography and/or signs of renal dysfunction, MRI and ureteroscopy may be indicat-
ed. Patients with previous pelvic surgery because of deeply infiltrating endometriosis are at high risk of ureteral endometriosis and should be carefully investigated and monitored over time. The upper urinary tract should be evaluated in patients with severe endometriosis, even in postmenopausal women. Surgery is the treatment of choice. Conservative laparoscopic surgery is a safe, feasible modality for management of ureteral endometriosis. However, the surgical technique depends on the location and depth of the lesion. As a form of adjuvant treatment to surgery, hormonal therapy is an appropriate option.

References


Ureteral Endometriosis and Renal Failure

Nephron Clin Pract 2010;114:c89–c94
Editorial Comment
M. El Nahas, Sheffield

This intriguing editorial draws the nephrologist’s attention to an unusual cause of ureteric obstruction and hydronephrosis in premenopausal women, namely ureteric endometriosis. It provides the reader with clues to diagnosis and recommends a high index of suspicion in those at risk. It also provides comprehensive monitoring, diagnostic and management recommendations. Most of all, this minireview points to an uncommon and probably underdiagnosed cause of ureteric obstruction in young women. Those who have come across similar cases are encouraged to report them to Nephron.