



Female chronic posterior urethritis is underestimated in patients with lower urinary tract symptoms

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Background: As one of the causes of urethral symptoms, female chronic posterior urethritis is a common and distressing disease; however, it is often neglected and misdiagnosed as overactive bladder (OAB) or interstitial cystitis/bladder pain syndrome (IC/BPS). Currently, little is known about the urothelium and lamina propria of the bladder neck and proximal urethra. Thus, identifying urethral lesions is necessary for the diagnosis and treatment of female chronic posterior urethritis. Transurethral electroresection is an effective and safe approach for treating female chronic posterior urethritis. This study sought to determine if urethral lesions are necessary for the diagnosis and treatment of female chronic posterior urethritis, and evaluate the efficacy and safety of the transurethral electroresection of mucosa and submucosa in treating female chronic posterior urethritis.

Methods: A single-center, retrospective, observational study was conducted at a teaching and referral hospital. A total of 147 female patients who had been diagnosed with chronic papillary urethritis underwent transurethral electroresection between 2015 and 2018. Each patient underwent a follow-up examination. A chart review was also performed.

Results: Patients had a mean age of 54 years (range, 23–82 years), and the average follow-up period was 54.8 months (range, 6–600 months). Urinary frequency and urgency (51.7%) were the most common clinical manifestations of chronic posterior urethritis. Forty-two-point two percent of patients had positive urine culture results, most commonly with *Mycoplasma genitalium*. The cystoscopic findings revealed that chronic posterior urethritis has tuft-like, pseudopodia-like, finger-like, and follicular-like polyps and villi, and a pebble-like appearance with mucosal hyperemia. The success rate of the transurethral electroresection was 88.6%, and patients showed no apparent or serious complications.

Conclusions: This study showed that female chronic posterior urethritis is a cause that contributes to LUT symptoms. Its characteristic cystoscopic appearance and biopsy play a vital role in its diagnosis. The transurethral electroresection of urethral lesions is simple, effective, and minimally invasive without any apparent complications.

Keywords: Chronic polypoid urethritis; lower urinary tract symptoms (LUT symptoms); female posterior urethritis; transurethral electroresection; urethral syndrome

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Introduction

Chronic posterior urethritis, which is a chronic non-specific inflammation condition of the intraurethral, results from a response to injury in the urethral mucosa (1). It has chronic posterior urethritis symptoms, including urethral pain, gross/microscopic hematuria, urinary frequency, urinary urgency, and dysuria and other lower urinary tract (LUT) symptoms (2-4). As these symptoms overlap with those of recurrent urinary tract infection, overactive bladder (OAB), and interstitial cystitis/bladder pain syndrome (IC/BPS) (5-7), chronic posterior urethritis can be misdiagnosed. Research has shown that the mucosal layer of the LUT is involved in mechanosensory functions that regulate both bladder contractile activity and the urethral sensation (8,9). Changes to the mucosa are usually associated with disorders, including IC/BPS and OAB (10). However, compared to the urinary bladder, much less is known about the urothelium and lamina propria of the bladder neck and proximal urethra.

Urologists have treated female chronic urethritis from the bladder neck to the distal urethra with oral antibiotics or operations, such as urethral dilatations, internal urethrotomy, and urethral-hymenal fusion surgery (11-13). However, studies on the diagnosis and treatment of female chronic urethritis are scarce. This study examined the clinical data on transurethral electroresections that were performed on female patients suffering from chronic posterior urethritis, and who had experienced antibiotic resistance or therapy resistance and had been misdiagnosed with OAB or IC/BPS. We aimed to draw the attention of urologists to the relationship between urethral lesions and LUT symptoms, and to demonstrate the efficacy and safety of transurethral electroresection in treating chronic urethral lesions. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/tau-21-550>).

Methods

Study population

A single-center, retrospective, observational study was performed at a teaching and referral hospital from January 2015 to December 2018. A total of 147 female patients, who had been diagnosed with chronic papillary urethritis and undergone transurethral electroresection, were included in the study. All patients were treated with antibiotics or other methods at other hospitals, and had developed treatment-resistant urethritis.

To be eligible to participate in the study, patients had to meet the following inclusion criteria: (I) have symptoms such as urinary frequency, urinary urgency, dysuria, urethral pain, or gross/microscopic hematuria; (II) be older than 18 years and have a disease duration of no less than 6 months; and (III) have been diagnosed with chronic papillary urethritis or chronic cystitis and have undergone cystoscopy. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had urinary tract cancer or traumatic urethral stricture; (II) were pregnant or giving childbirth; (III) had urethral diverticulum, refractory radio or chemotherapy-induced cystitis, and OAB or IC/BPS.

The clinical data were collected after this study was approved by the ethics committee of the Second Hospital of University of South China (No. 2020001). All data were collected by two people independently. All patients agreed to participate in this study and signed an informed consent form. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Preoperative evaluation

All patients underwent a standard preoperative assessment,

Table 1 Characteristics of all patients

Data item	Baseline data	First follow-up	Final follow-up	Baseline vs. first follow-up improvement rate ¹	Baseline vs. final follow-up improvement rate ²
Age	54.7±11.6				
Preoperative average diseases duration (months)	54.8 (6–600)				
Average follow-up period (months)	29.8±8.8				
Average urinary urgency (0–5)	4.6±0.5	1.3±2.0	1.2±2.0	74.6%	77.9%
Average urinary frequency (day)	11.4±2.9	6.9±2.3	6.8±2.3	64%	72.8%
Daily average number of nocturia events (night)	3.4±1.7	1.3±2.2	1.0±1.3	60.3%	62%
Quality of life (QoL) score (1–7)	5.8±0.7	3.9±1.7	3.5±1.7	54.4%	51.2%

^{1,2}, no improvement was defined as patients with symptom improvement of less than 50%. Conversely, symptom improvement of more than 50% (effective improvement) and 80–100% (significant improvement) represented overall improvement, and all patients were included in the statistical analysis.

including a medical history, physical examination, laboratory tests, a routine urine test, a urine culture, a cystoscopy. Patients were also asked to keep a urination diary (for 72 hours), and complete a questionnaire survey, and quality of life (QoL) survey.

Postoperative follow-up period

Data were collected via a telephone call on which a questionnaire was administered, and during outpatient visits at the 6-month and final (at least 24-month) follow-up appointments after transurethral electroresection. At the visit, a symptom assessment, physical examination, and cystoscopy were performed, and a urinary diary was kept. Patients' symptom scores, OAB activity, and QoL questionnaire results were used to assess symptoms, including urinary urgency, daily frequency of urination, daily number of nocturia, and QoL score. Any complications related to the procedure were also assessed.

Statistical analysis

The statistical analysis was performed using SPSS® (version 26) software. The continuous variables are presented as mean ± standard deviation (SD). The categorical variables are presented as median (range), and number (percentage). Handling missing values, we deleted the researchers directly. A paired *t* test was used to comparatively analyze the continuous variables. The interaction of time with treatment was examined using a 2-way repeated analysis

of variance (ANOVA) tests. If Mauchly's test of sphericity indicated a violation of the sphericity assumption for the repeated measure ANOVA tests, Greenhouse-Geisser sphericity correction was applied. A *P*<0.05 was considered statistically significant.

Results

A total of 147 female patients underwent surgery. Among these 147 patients, 11 were lost during the follow-up period. The remaining 136 patients had an average age of 54 years (range, 23–82 years). The mean follow-up period was 54.8 months (range, 6–600 months). Thirty-one patients received transurethral electroresection of the papillary urethritis only, and 105 underwent transurethral electroresection of both urethral and bladder lesions. The mean duration of patients' symptoms was 20 months. The results in relation to the short-term efficacy (baseline *vs.* improvement 6-month post-surgery) and long-term efficacy (baseline *vs.* improvement at least 24-month post-surgery) of the approach are presented in *Table 1*.

Among the 147 patients, the most common symptoms were urinary frequency and urgency [76 (51.7%); see *Table 2*]. Among the 146 patients with urine cultures, the results of 61 (42.2%) patients were positive for bacterial growth. Surprisingly, the most pathogenic microorganism was *Mycoplasma genitalium* [37 (25.2%)] and not *Escherichia coli* [13 (8.8%)]. Cystoscopic examinations were performed to detect urethral lesions in all patients. Among the 147 cases, 29 (19.7%), 85 (57.8%), 14 (9.5%),

Table 2 Clinical characteristics and cystoscopic findings

Clinical manifestation	Frequency	Urine culture	Frequency	Cystoscopic findings	Frequency
Urinary frequency and urgency	76/147 (51.7%)	Mycoplasma genitalium	37/146 (25.3%)	Finger-like polyps	29/147 (19.7%)
Hematuria	10/147 (6.8%)	Escherichia coli	13/146 (8.9%)	Multiple papillary polyps	85/147 (57.8%)
Pricking and burning pain during urination	15/147 (10.2%)	Streptococcus agalactiae	3/146 (2.1%)	Pseudopodia-like polyps	14/147 (9.5%)
Voiding difficulty	10/147 (6.8%)	Klebsiella pneumoniae	2/146 (1.4%)	Pebble-like appearance with mucosal hyperemia and edema	15/147 (10.2%)
Lower abdominal pain	34/147 (23.1%)	Proteus mirabilis	1/146 (0.7%)	Follicular-like polyps	4/147 (2.7%)
Pelvic pain	2/147 (1.3%)	Enterococcus faecalis	1/146 (0.7%)		
		Albicans Candida	1/146 (0.7%)		
		β -hemolytic Streptococcus	1/146 (0.7%)		
		Candida parapsilosis	1/146 (0.7%)		
		Albicans candida	1/146 (0.7%)		

15 (10.2%), and 4 (2.7%) were found to have finger-like polyps, tuft-like polyps and villi, pseudopodia-like polyps, a pebble-like appearance with mucosal hyperemia and edema, and follicular-like polyps, respectively. One hundred and five of the 147 patients suffered from bladder lesions at the trigone and bladder neck in addition to urethral lesions (see *Figure 1*).

2 operations were performed; that is, the transurethral electroresection of the urethra only, or the transurethral electroresection of the urethra and bladder. The efficacy of each operation in treating different LUT symptoms was calculated. Patients in the urethral surgery group had a mean age of 54.4 years. Statistically, there were significant differences in the number of urination events, urgency, nocturia events, and QoL scores before and after surgery (i.e., at the end of the last follow-up appointment post-surgery; $P < 0.001$; see *Figure 2* and *Table 3*). Patients in the urethra and bladder surgery group had a mean age of 54.0 years. Significant differences in the number of urination events, urgency, nocturia events, and QoL scores were found before and after surgery (i.e., at the end of the first or last follow-up appointment post-surgery; $P < 0.001$; see *Figure 2* and *Table 3*).

As of the last follow-up date, 15 patients (11%) had experienced complications, including urinary incontinence (5.1%), urinary tract infection (2.2%), urinary stricture (1.5%), hematuria (1.5%), and dysuria (0.7%). Most of the

adverse events were of short duration. 3 patients with stress urinary incontinence were treated by tension free vaginal tape (TVT), 4 patients with urgency urinary incontinence were symptom-free after inflammation was controlled.

Discussion

Chronic posterior urethritis is more difficult to diagnose in women than men, as its clinical symptoms are similar to those of OAB, primary cystitis, vaginitis, and cervicitis (14) involving the LUT. The urothelium in the region of the bladder neck and proximal urethra play a role in continence and sensation (9,15,16). The cause and pathogenic factors of female chronic posterior lesions are not yet completely known. It has been suggested that many factors, including non-specific infection, urethral obstruction, urethral-hymenal fusion, senile atrophy, traumatic causes, inflamm-ageing, and estrogen deficiency, may be implicated in its pathogenesis (4,12,17,18). Urethritis is classified as gonococcal or nongonococcal urethritis (NGU) based on its causative organisms that may be sexually and non-sexually transmitted. The major causes of NGU are Chlamydia trachomatis and Mycoplasma genitalium, which account for 75% of cases (19). However, other pathogenic organisms include Trichomonas vaginalis, anaerobes, herpes simplex virus, and adenovirus (20). In the present study, we identified Mycoplasma as the most common etiological agent.

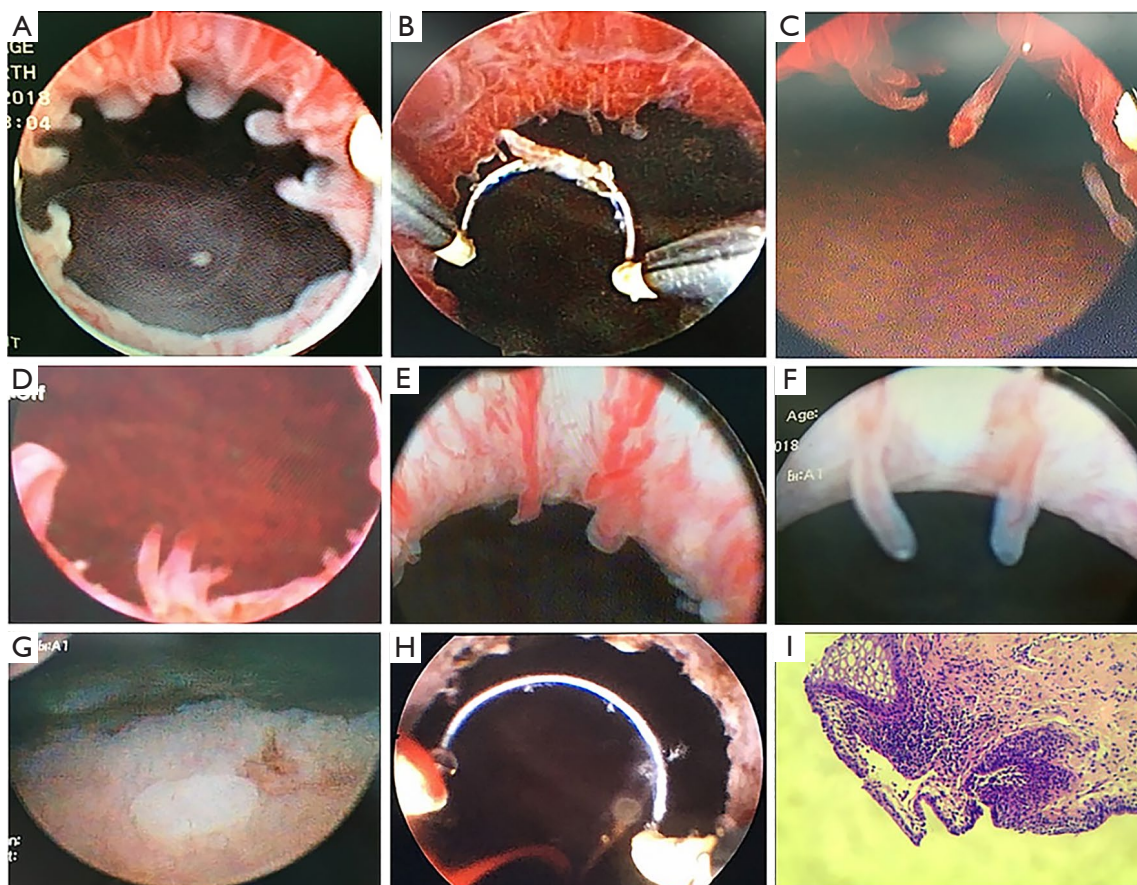


Figure 1 Cystoscopic appearance and biopsy. (A) Finger-like polyps. The locations were the posterior urethra and bladder neck. (B) Pebble-like appearance with mucosal hyperemia and edema. (C) Pseudopodia-like polyps. (D) Tuft-like polyps. (E) Follicular-like polyps. (F) Villous polyps. (G) Leukoplakia of bladder mucosa. Cystoscopic appearance of trigonitis. (H) Cystoscopic appearance after transurethral resection. (I) Hematoxylin and eosin-stained histopathology images of urethritis (10× by light-microscope).

As these posterior urethral lesions may be caused by infection or other injury, it is necessary for women with LUT symptoms to undergo a cystoscopy to rule out urethral and bladder inflammatory lesions. The endoscopic evaluation of the LUT provides more important information than an ultrasound or urethrocytography (21). In this study, women with chronic urethritis were leukocyte-negative, and exhibited only microscopic hematuria or an increase in the number of squamous cells in routine urine tests. Most urine cultures were negative for bacterial infections; however, urethral inflammatory changes were evident. The cystoscopies revealed that the center of lesions was located at the proximal urethra and bladder neck, which displayed hyperemia, edema, paler and granular changes, and polyp and villus formation(3). Posterior urethritis usually tended to be complicated by a bladder

lesion called trigonitis (22,23). Similar to keratinizing squamous metaplasia in the bladder, some researchers have conjectured that keratinizing squamous metaplasia is a normal variant in some conditions (24). We intend to conduct further research to determine whether such lesions exist in normal women, especially pre-menopausal women.

To identify whether lesions are the cause of female chronic posterior urethritis, we intervened by removing lesions by transurethral electroresection. Polyps and villi are the sites at which organisms persist and evade the immune response. Studies have suggested that uropathogenic bacteria can invade urothelial cells to form an intracellular bacterial community/quiescent intracellular reservoir in murine models, thus releasing strong pro-inflammatory factors that prompt an immune response and physiological changes in urothelial cells (25,26).



Figure 2 Efficacy evaluation of transurethral resection—entire population.

Transurethral electroresection, an effective and minimally invasive procedure with a low complication rate, can address the polyps and villus which are the sites where organisms to persist and evade the immune response. In the present study, we used the following surgical indications: (I) LUT symptoms that lasted at least 6 months; (II) urethral inflammatory changes (as observed by cystoscopy and biopsy); and (III) ineffective repeated courses of antibiotics and ineffective preventive strategies. Unlike electrofulguration (27), transurethral electroresection can perfectly resolve the mucosa and submucosa lesions of polyps and villi. In this study, we included 136 women who underwent transurethral electroresections at a single center.

The success rate of the transurethral electroresections was 88.6%. The reasons for the failure of transurethral electroresection, maybe uncleaned etiology, combined other diseases such as autoimmune diseases, depression, central nervous system disorders. In order to improve the success rate and prevent the recurrence of polyps, if possible, etiology-based and combined with other treatments should be administered at the same time. After a post-transurethral electroresection follow-up period of 24 months, all preoperative lesions were resolved, and no new lesions were found. We focused on the 2 major late complications; that is, urinary incontinence (5.1%) and urethral stricture (1.5%). Notably, urethral stricture failed to develop to the

Table 3 Analysis of transurethral resection of 2 groups' statistical data

Group	Indicator	F0	F1	F2	P total	P1	P2
G1	Average urinary frequency (day)	12.45±3.53	7.23±2.42	7.03±2.42	<0.001	<0.001	<0.001
	Average urinary urgency (0–5)	31 (100%)	11 (35.5%)	10 (32.3%)	<0.001	<0.001	<0.001
	Daily average number of nocturia events (night)	3.16±1.81	1.97±3.77	1.10±1.27	0.016	0.127	<0.001
	Daily urine leakage times	0 (0%)	5 (16.1%)	6 (19.4%)	0.012	0.062	0.016
	Quality of life (QoL) score (1–7)	5.61±1.145	3.9±1.758	3.68±1.815	<0.001	<0.001	<0.001
G2	Average urinary frequency (day)	11.10±2.73	6.78±2.21	6.7±2.19	<0.001	<0.001	<0.001
	Average urinary urgency (0–5)	105 (100%)	34 (32.4%)	30 (28.6%)	<0.001	<0.001	<0.001
	Daily average number of nocturia events (night)	3.44±1.76	1.06±1.35	0.96±1.28	<0.001	<0.001	<0.001
	Daily urine leakage times	0 (0%)	14 (13.3%)	14 (13.3%)	<0.001	<0.001	<0.001
	Quality of life (QoL) score (1–7)	5.85±0.533	3.92±1.674	3.54±1.593	<0.001	<0.001	<0.001

G1, transurethral resection of urethral lesion subgroup; G2, transurethral resection of urethral and bladder lesion subgroup; F0, baseline data; F1, first follow-up data; F2, last follow-up data; P total, overall differences between the 3 time points; P1 (F0 vs. F1), comparison of first follow-up and baseline data; P2 (F0 vs. F2), comparison of last follow-up and baseline data.

bladder neck contracture; rather, it was safely and effectively resolved by urethral dilatation. In the present study, transurethral electroresection did not increase the incidence of stress urinary incontinence unless it occurred before the operation.

This retrospective study had several limitations, including a potential bias, reporting errors, and the need for a longer follow-up period and high-quality trials. Based on the results of this retrospective study, while transurethral electroresection can ameliorate LUT symptoms effectively, we need to further verify whether a sham treatment (e.g., a cystoscopy without resection) would lead to symptom relief by conducting a random control trial in the future.

Conclusions

This study showed that urologists need to pay attention to the diagnosis and treatment of female chronic posterior urethritis, as it has LUT symptoms. Urethral lesions found in cystoscopy may be important in diagnosing the refractory disease of LUT. Further, transurethral electroresection is a simple, effective, minimally invasive approach for treating chronic posterior urethritis that does not give rise to any apparent complications.

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Footnote

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Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The clinical data were collected after this study was approved by the ethics committee of the Second Hospital of University of South China (No. 2020001). All data were collected by two people independently. All patients agreed to participate in this study and signed an informed consent form. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

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