Vesicular Cystitis: A Chronic Cystitis Variant Often Unresponsive to Antibiotics and Electrofulguration

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Abstract

Objective: The aim of the study was to report on the presentation and outcomes of vesicular cystitis (VC), a chronic cystitis exhibiting translucent bladder mucosal vesicles, among women with antibiotic-refractory recurrent urinary tract infections (RUTIs). *Methods:* An analysis of our Institutional Review Board-approved series on antibiotic-refractory RUTIs was performed, selecting for documented VC lesions on cystoscopy. All patients had RUTIs defined as ≥3 urinary tract infections/year with positive urine culture. All patients were extensively treated with antibiotics with no resolution of RUTIs and were offered electrofulguration (EF) of VC lesions under anesthesia as a last resort. All patients had a 6-month post-EF office cystoscopy documenting persistence or resolution of the lesions, and a clinical outcome assessment based on RUTI frequency. *Results:* Of 482 patients, 18 (3.7%) treated during 2011–2017 met the study criteria. VC was most commonly found over the dome/anterior wall (7/18, 38%) and as pancystitis (7/18, 38%). There was often concomitant cystitis cystica of the trigone (8/18, 44%). At post-EF cystoscopy, persistence of VC was noted in 10/18 (56%) patients; 6/18 (33%) underwent repeat EF and an additional 3/18 (17%) were retreated due to new lesions after initial resolution. Two (11%) patients required simple cystectomy and urinary diversion due to RUTIs refractory to all interventions. Within a median follow-up of 2.8 years after EF, clinical cure was observed in 5/18 (28%), improvement in 10/18 (56%), and failure in 3/18 (17%) patients. *Conclusions:* Among women with antibiotic-refractory RUTIs, VC is an infrequent and persistent form of cystitis with a predilection for non-trigonal bladder surfaces, whose management is challenging.

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Introduction

Recurrent urinary tract infections (RUTIs) are common among adult women [1]. Murine models have suggested the persistence of bacterial pathogens in the bladder wall as a mechanism for RUTIs [2]. A recent multidisciplinary study on urine and bladder biopsies from postmenopausal women with RUTIs provided direct evidence, using targeted fluorescent markers, that bacteria reside in the bladder wall of these patients [3]. When antibiotic therapies fail to eliminate these deep-seated sites of infection, and inflammatory bladder wall lesions are

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identified on cystoscopy at the sites where these bacteria reside, electrofulguration (EF) can be considered as a last resort to disrupt these niches. This endoscopic procedure has produced satisfactory outcomes for many women with antibiotic-refractory RUTIs in the short and long term [4, 5].

Over years of experience with EF, we have noticed several endoscopic phenotypes, the most frequent being cystitis cystica of the trigone, with or without extension beyond the trigone. Beyond this common presentation, we have identified vesicular cystitis (VC), an infrequent and previously uncharacterized form of cystitis, among women undergoing EF for antibiotic-refractory RUTIs. A thorough search of the literature identified only 1 case report of VC [6]. Therefore, we report on a contemporary series of patients treated for this condition with emphasis on clinical presentation, antibiotic courses, and endoscopic features, along with outcomes after EF and antibiotic therapies.

Methods

Following Institutional Review Board approval, we queried a database of women with antibiotic-refractory RUTIs (defined as 3 or more symptomatic urinary tract infections (UTIs) treated with antibiotics over 1 year [7]) and an office cystoscopy demonstrating inflammatory bladder lesions, who subsequently underwent EF. Only patients who exhibited findings of VC on cystoscopy were included in this study. Women with neurogenic bladder, stage II or greater pelvic organ prolapse, upper urinary tract anomalies, uncontrolled diabetes, or immunodeficiency were excluded. VC was endoscopically defined as the presence of fields of small translucent bladder mucosal vesicles (Fig. 1a–c). It is important to note that the appearance of VC lesions was uniquely different from interstitial cystitis (Hunner's ulcer), cystitis cystica (Fig. 1f), or other previously described bladder mucosal lesions. The location of these clear vesicles was classified as involving the trigone, bladder base above the trigone, lateral walls, posterior wall, or dome/anterior wall, or as pancystitis (covering most bladder surfaces).

A striking presenting feature among these patients was the repeated failure of multiple courses of antibiotic therapy. Typically, patients had a negative thorough urological evaluation, including upper and lower urinary tract imaging and pelvic examination to exclude stage II or greater pelvic organ prolapse. Patients did not have voiding dysfunction or uncontrolled risk factors for infection such as immunosuppression or untreated diabetes. Many patients exhibited resistant bacterial strains and had allergies to several classes of commonly used antibiotics as confirmed by allergy testing. All had also exhausted traditional forms of antibiotic therapy, including prolonged suppression and, at times, intravenous (IV) courses. Therefore, as a last resort and because we had encountered favorable results by applying EF to other variants of antibiotic-refractory chronic cystitis, EF was also offered to these patients with the hope of eliminating their chronic VC lesions.

EF procedures were performed under general anesthesia with a female urethrocystoscope, a 30-degree lens, and a fine-tip Bugbee electrode on a low setting of 20–25, as previously described [8]. Recognizing that diverse bacterial species can be isolated from the bladder tissue of these women [3] and that fulgurating the bladder surface could unmask these strains, some patients were discharged home on daily low-dose antibiotic suppression whenever a suitable oral antibiotic class was available.

All patients had routine follow-up visits, including a 6-month follow-up visit with office cystoscopy to document resolution, persistence, or new VC lesions. These cystoscopies were performed by a female pelvic medicine and reconstructive surgery (FPMRS) faculty member or an FPMRS-trained physician assistant. All cystoscopies were accompanied by photographic documentation. Based on the electronic medical record, we recorded patient demographics, past UTI history, past surgical history, antibiotic exposure, EF findings, concomitant surgeries, and follow-up after EF, including courses of antibiotic treatment. In one of the 2 cases of VC eventually requiring cystectomy, a VC lesion was examined histologically by a genitourinary pathologist (Fig. 1d).

For clinical outcome evaluation, UTIs were counted beginning 6 months after the EF procedure because irritation and healing from the cauterization of the bladder surface can often be confused for UTI symptoms. After the cystoscopy at 6 months post-EF, any patient with a symptomatic UTI was treated with antibiotics whether she had UTI-like symptoms alone or also had a confirmatory positive urine culture. We classified patients as (1) clinically successful or *cured* if there were no further UTIs, (2) *improved* if there were 1–2 UTIs per year, or (3) *failed* if there were ≥3 UTIs per year. All patients had regularly scheduled follow-up in our clinic and were asked to call to document any new symptoms as well as positive cultures or antibiotic courses from outside providers. All known dates of antibiotic prescriptions and positive cultures were recorded along with the organisms grown, colony counts, and any antibiotic resistances. Fluoroquinolone-resistant, trimethoprim-sulfamethoxazole-resistant, and extended spectrum beta-lactamase-producing organisms were noted. We classified organisms resistant to more than 3 antibiotics based on the susceptibility report as highly resistant. The date of last follow-up was the last clinic visit or last correspondence regarding UTIs documented in the electronic medical record.

Results

Of 482 women with antibiotic-refractory RUTIs who underwent EF, 18 (3.7%) were identified who had VC and met the study criteria. Endoscopic findings of VC were confirmed on office cystoscopy during outpatient evaluation, and during subsequent EF procedures which were performed between 2011 and 2017. Demographic information is reported in Table 1. The cohort comprised predominantly older, postmenopausal women. Most patients were complex in that they had failed multiple courses of antibiotics, including suppressive antibiotic therapy, and some had prior genitourinary procedures. Several women had concomitant stress urinary inconti-
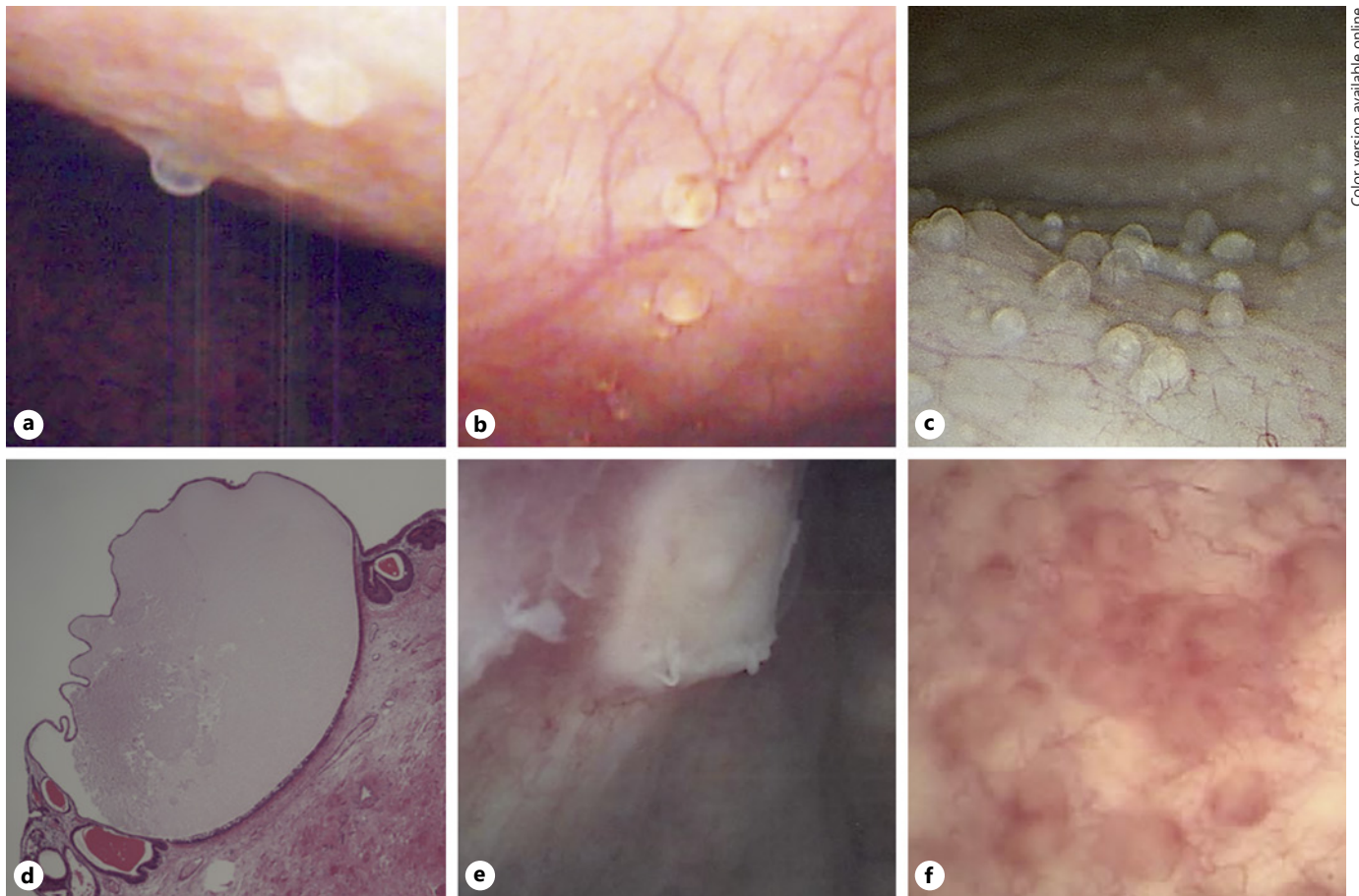
Fig. 1. a–c Cystoscopic views of VC lesions over the anterior and posterior bladder walls. **d** 100x view of a hematoxylin and eosin-stained lesion from a cystectomy specimen demonstrates a single cell-layered vesicle filled with proteinacious fluid. **e** Blanching of a VC lesion in response to EF. **f** Cystoscopic view of cystitis cystica, for comparison, demonstrating thick-walled cystic lesions with significant associated inflammation. EF, electrofulguration; VC, vesicular cystitis.

Table 1. Baseline characteristics of 18 women with antibiotic-refractory RUTIs and VC managed with EF

Demographic and past medical history		Past surgical history, n (%)	
Median age (IQR), y	66 (63–69)	Hysterectomy	13 (72)
Median BMI (IQR), kg/m²	27 (25–32)	Midurethral sling	7 (39)
Ever smoker, n (%)	6 (33)	Bladder neck suspension	3 (17)
Diabetes, n (%)	5 (28)	Sling removal	2 (11)
Median parity (IQR)	3 (2–3)	Vaginal mesh removal	2 (11)
Postmenopausal, n (%)	18 (100)	Urethral dilation	1 (6)
Hormone replacement, n (%)	13 (72)	Prolapse repair	1 (6)
Past UTI history, n (%)		Bulking agent	1 (6)
Suppressive antibiotics	11 (61)	Concomitant surgeries, n (%)	
Coital prophylaxis	1 (6)	Sling removal	5 (28)
Self-start antibiotics	8 (44)	Bulking agent	3 (17)
IV antibiotics	3 (17)	Urethral dilation	3 (17)
Pyelonephritis	3 (17)	Fascial sling	1 (6)

RUTIs, recurrent urinary tract infections; EF, electrofulguration; IQR, interquartile range; UTI, urinary tract infection; IV, intravenous; VC, vesicular cystitis.

Table 2. Lesion location prior to and 6 months after EF for the 18 women in this series

Location	Pre-EF		Post-EF	
	VC lesions, n (%)	other concomitant lesions, n (%)	VC lesions, n (%)	other concomitant lesions, n (%)
Trigone	0 (0)	8 (44)	0 (0)	1 (6)
Bladder base above trigone	1 (6)	0 (0)	1 (6)	0 (0)
Lateral walls	1 (6)	0 (0)	0 (0)	0 (0)
Posterior wall	2 (11)	0 (0)	1 (6)	1 (6)
Dome/anterior wall	7 (38)	0 (0)	7 (38)	0 (0)
Pancystitis	7 (38)	2 (11)	1 (6)	1 (6)

EF, electrofulguration; VC, vesicular cystitis.

Table 3. Endoscopic and clinical outcomes of 18 women with antibiotic-refractory RUTIs and VC managed with EF

	Endoscopic outcome	
	success (n = 8, 44%)	failure (n = 10, 56%)
Clinical outcome, n (%)		
Cure (n = 5, 28%)	2 (11)	3 (17)
Improvement (n = 10, 56%)	4 (22)	6 (33)
Failure (n = 3, 17%)	2 (11)	1 (6)

RUTIs, recurrent urinary tract infections; EF, electrofulguration; VC, vesicular cystitis.

nence or outlet obstruction, which was addressed at the time of EF. Such corrective procedures performed in the same setting as EF are also reported in Table 1.

During EF, we frequently observed the diffuse appearance of the VC lesions in fields of thin-walled, clear, or sometimes pus-filled vesicles originating from the mucosal surface but with no surrounding inflammatory reaction, and with typical size ranging from 0.1 to 1.0 mm in diameter (Fig. 1a–c). During EF, we also observed blanching of the VC lesions once the surface was fulgurated, and they tended to stay attached beneath the mucosal surface (Fig. 1e). A striking observation was their presence most commonly over the dome and anterior bladder wall, and sometimes involving the whole bladder as pancystitis; concomitant cystitis cystica of the trigone was also frequently noted (Table 2).

To study the evolution of VC lesions, Table 2 describes the pre-EF and 6-month post-EF endoscopic VC landscapes. Persistent VC lesions were noted in 10/18 (56%) patients on 6-month post-EF office cystoscopy, with

complete resolution seen in 8/18 (44%) patients. Among the ten endoscopic failures, 6 underwent repeat EF due to persistent symptomatic UTIs and failed additional antibiotic courses. Despite initial VC resolution at the 6-month follow-up cystoscopy, 3 additional patients experienced a delayed symptomatic VC recurrence and elected to undergo a secondary EF. Two patients required simple cystectomy and urinary diversion due to severe and persistent RUTIs refractory to all interventions, with nearly completely resistant bacterial strains (see histology in Fig. 1d). At a median follow-up of 2.8 years (interquartile range 1.9–4.0) after EF, clinical cure (no further UTI symptoms) was observed in 5/18 (28%), clinical improvement in 10/18 (56%), and clinical failure in 3/18 (17%) patients. Importantly, all UTIs during the follow-up period were microbiologically proven. Table 3 summarizes the clinical outcomes, stratified by endoscopic outcome.

The 4 most common uropathogens isolated in post-EF urine cultures are displayed in online suppl. Table 1 (see www.karger.com/doi/10.1159/000510320 for all online suppl. material). Nine (50%) patients had highly resistant organisms, 6 (33%) had fluoroquinolone-resistant organisms, 7 (39%) had trimethoprim-sulfamethoxazole-resistant organisms, and 2 (11%) had extended spectrum beta-lactamase-producing organisms. Pre-EF, intra-EF, and post-EF antibiotics and their frequency are listed in online suppl. Table 2. The median length of post-EF antibiotic daily suppression course prescribed was 44 (range 3–90) days.

Discussion

To our knowledge, this is the first contemporary series of women with VC. This description of VC was based on patients identified from a large database of women treat-

ed for antibiotic-refractory UTIs who subsequently underwent EF. We found that VC exhibited clear vesicles that can be difficult to detect when they are located anteriorly and can present in diffuse patches throughout large areas of the bladder wall. Our experience indicates that they are often resistant to short- and long-term antibiotic therapies, including suppressive antibiotic courses. Because of previously demonstrated efficacy of EF for other forms of chronic cystitis associated with RUTIs [4, 5], the procedure was considered to attempt to eradicate these chronic bladder lesions; however, as reported, this endoscopic approach was met with persistence and recurrence of VC lesions for several women. In fact, 2 patients ultimately underwent cystectomy due to RUTIs refractory to all other therapies, including several IV antibiotic courses. At the time of cystectomy, both women were left with only 1 IV antibiotic class for treatment. We were unable to identify a particular bacterial strain related to the VC pathotype, although highly resistant organisms were common among women in this series.

So far, we have found only one report of VC in the literature [6]. This report is of a patient with epidermolysis bullosa, a dermatologic blistering disease, who had longstanding cystitis, negative urine cultures, and likely autoantibody-induced inflammation of the bladder. This single case report is distinct from our series, as the patients all had a history of antibiotic-refractory RUTIs. None had a history of blistering diseases. To our knowledge, there are no other case reports or series in the literature describing bladder lesions with an endoscopic or histologic appearance comparable to the lesions in this series.

The basis for the gross and histologic features of VC and its association with antibiotic-refractory RUTIs in this series is unclear. While VC lesions are morphologically different from cystitis cystica lesions, the association of RUTIs with cystitis cystica is also incompletely understood [9, 10]. Other infectious etiologies of cystitis have been described. Herpes simplex, for example, which manifests as skin and mucosal vesicles, has been seen in association with hemorrhagic cystitis [11]. Inflammatory etiologies such as eosinophilic cystitis have also been extensively described [12]. We believe further microbiological and histological evaluation of urine and tissue from patients with VC will be required to better understand the underlying pathobiology. However, this may be hampered by the small size of these lesions and their easy collapse upon bladder biopsy. Additionally, as recently described for inflammatory lesions other than VC [3], pathogenic bacteria in the bladder wall can differ from bacterial culture findings, potentially explaining the failure of antibiotic therapies in some of these patients, as well as the prevalence of the resistant organisms observed in this series. Notably, direct evidence that VC lesions contain intracellular bacteria is currently not available, and this is a worthwhile topic for future investigation.

This study has several strengths, including the strict criteria defining VC based on endoscopic appearance and photographic documentation, detailed demographic analysis, charted courses of antibiotic therapies including oral and IV treatments, documentation of bacterial strain resistances, EF procedures performed by a single surgeon using a standardized technique, office cystoscopies performed 6 months after EF to document healing sites and areas of persistence or recurrence of VC lesions, and a median follow-up of 3 years after the EF procedures. This study is limited in that it is a preliminary series of an infrequent antibiotic-recalcitrant RUTI variant. We were unable to establish any predictors of outcomes for patients with VC, other than the marked resistance of VC to all forms of antibiotic therapy or endoscopic treatment in a number of cases. In fact, endoscopic success did not guarantee clinical improvement or cure, and endoscopic failure did not guarantee clinical failure. The incidence of particular cystitis symptoms was not measured in this study; future work focusing on symptomatology may help better define the clinical presentation of different cystitis variants. Although our urine culture data were broad, not all urine culture data were retrievable, as many patients had been on long-term suppressive antibiotics and had many of their UTIs diagnosed and treated outside our institution. Additionally, for a subset of women, the diagnosis of RUTI was made at initial evaluation at our tertiary referral center based on a thorough history if detailed records of culture-proven infections were not available. Finally, we recognize that concomitant surgeries such as sling removal or urethral dilation, which might impact voiding function, could have confounded the outcome of VC therapies. Indeed, for this reason, most patients in this cohort had been excluded from a prior study describing long-term outcomes of EF [5], although these concomitant procedures do reflect urological problems frequently observed in this age-group.

Conclusion

We report on an infrequent chronic cystitis variant, VC, found in association with antibiotic-refractory RUTIs most predominant among postmenopausal women. The endoscopic appearance is pathognomonic with a

cluster of small, mostly clear vesicles independently sitting on the bladder mucosa, oftentimes located anteriorly or throughout the bladder wall. Of note, the management of VC was found to be extremely challenging, involving antibiotic treatments including long-term suppression and IV courses, EF, and even cystectomy with urinary diversion in the most recalcitrant cases.

Statement of Ethics

This study involving human participants was in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Review Board of the University of Texas Southwestern Medical Center approved this study (ID#: STU 082010-016). Patients in this study provided informed consent for all surgical and office procedures. The Institutional Review Board of the University of Texas Southwestern Medical Center approved a waiver of consent for inclusion in the study, as it is a retrospective chart review.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Both authors contributed to project development, data collection, data management, data analysis, manuscript writing, and manuscript editing.

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