Title

Deep Phenotyping the Anterior Urethral Stricture: Characterizing the Relationship Between Inflammation, Fibrosis, Patient History, and Disease Pathophysiology

Journal

Journal of Urology, 212(1)

ISSN

0021-0005

Authors

Gutierrez, Wade R
Luo, Yi
Dahmoush, Laila
et al.

Publication Date

2024-07-01

DOI

10.1097/ju.0000000000003962

THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro

Check for updates

Reconstruction

JU Insight

Deep Phenotyping the Anterior Urethral Stricture: Characterizing the Relationship Between Inflammation, Fibrosis, Patient History, and Disease Pathophysiology

Wade R. Gutierrez, Yi Luo, Laila Dahmoush, et al.

Correspondence: Bradley A. Erickson (brad-erickson@uiowa.edu).

Full-length article available at https://doi.org/10.1097/JU.0000000000003962.

Study Need and Importance: The most common etiology of anterior urethral stricture disease (aUSD) is idiopathic. This gap in knowledge has been of little concern historically as surgical treatments for aUSD, especially in the bulbar urethra, rarely consider stricture cause. However, while urethroplasties have high anatomic surgical success rates, they are not benign procedures, with outcomes studies showing clinically significant rates of postoperative sexual dysfunction and persistent lower urinary tract symptoms that are of concern to our patients, both pre- and postoperatively. The recent addition of dilating balloons, capable of precisely delivering drugs to the urethra, to the treatment armamentarium has also generated a renewed interest in obtaining a better understanding of aUSD pathophysiology, as personalized, etiology-specific aUSD treatments appear to be getting closer to reality.

What We Found: Three aUSD cohorts were enrolled: traumatic (n = 33), idiopathic (n = 78), and lichen sclerosus (LS; n = 27). Deep phenotyping included patient-reported outcome measures, serum inflammatory/fibrosis markers, and histopathology. Our general hypothesis was that idiopathic and traumatic phenotypes would resemble each other given conventional wisdom that assumes idiopathic strictures are of subacute and/or forgotten urethral traumas. Instead, we found idiopathic strictures to more closely resemble LS strictures, with both having significantly higher rates of chronic inflammation in both the stricture (54% and 48% vs 27%) and in nonstrictured urethral tissue, vs traumatic strictures (Figure). All cohorts, regardless of etiology, had higher levels of circulating cytokines associated with inflammation (interleukin-9) and fibrosis (platelet-derived growth factor–BB and CCL5) vs controls, suggesting a possible shared aUSD predisposition.

Limitations: The antigen and/or organism responsible for the inflammation in idiopathic and LS strictures remains elusive, limiting our current ability to use histopathology to direct treatments.

Interpretation for Patient Care: Idiopathic strictures appear to be a unique subset of strictures with high rates of inflammation that extends beyond the visible stricture that is of unknown clinical significance. However, one might consider treating idiopathic strictures surgically and/or endoscopically beyond the visible stenosis if the entire field of pathology is to be managed. Urethral biopsy may eventually show pretreatment clinical utility.

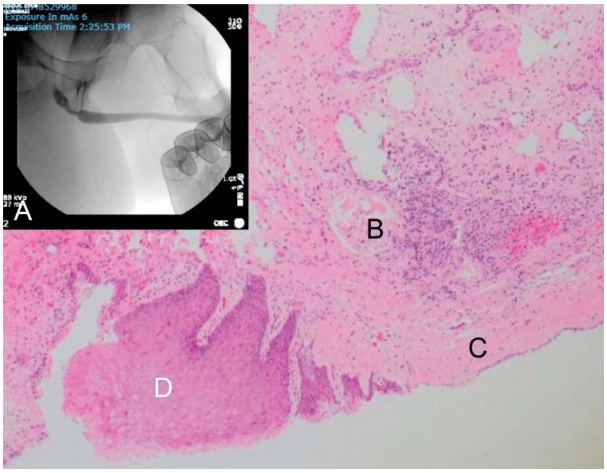

Figure. A, Retrograde urethrogram and histopathologic specimen in a nonstrictured (proximal) urethra segment in a study participant with idiopathic urethral stricture etiology. B, Lymphocytic subepithelial infiltration. C, Normal urethral epithelium. D, Urethral squamous metaplasia.

https://doi.org/10.1097/JU.0000000000003962
Vol. 212, 153-164, July 2024
Printed in U.S.A.

THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro

Deep Phenotyping the Anterior Urethral Stricture: Characterizing the Relationship Between Inflammation, Fibrosis, Patient History, and Disease Pathophysiology

Wade R. Gutierrez,[1] Yi Luo,[1] Laila Dahmoush,[2] Jacob J. Oleson,[3] Charles H. Schlaepfer,[1] Benjamin N. Breyer,[4] Sean P. Elliott,[5] Jeremy B. Myers,[6] Alex J. Vanni,[7] Denise Juhr,[1] Katherine N. Christel,[2] and Bradley A. Erickson[1]

[1]Department of Urology, Carver College of Medicine, University of Iowa, Iowa City, Iowa
[2]Department of Pathology, Carver College of Medicine, University of Iowa, Iowa City, Iowa
[3]Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, Iowa
[4]Department of Urology, University of California, San Francisco, San Francisco, California
[5]Department of Urology, University of Minnesota, Minneapolis, Minnesota
[6]Division of Urology, Department of Surgery, University of Utah, Salt Lake City, Utah
[7]Department of Urology, Lahey Hospital and Medical Center, Burlington, Massachusetts

Purpose: Anterior urethral stricture disease (aUSD) is a complex, heterogeneous condition that is idiopathic in origin for most men. This gap in knowledge rarely affects the current management strategy for aUSD, as urethroplasty does not generally consider etiology. However, as we transition towards personalized, minimally invasive treatments for aUSD and begin to consider aUSD prevention strategies, disease pathophysiology will become increasingly important. The purpose of this study was to perform a deep phenotype of men undergoing anterior urethroplasty for aUSD. We hypothesized that unique biologic signatures and potential targets for intervention would emerge based on stricture presence/absence, stricture etiology, and the presence/absence of stricture inflammation.

Materials and Methods: Men with aUSD undergoing urethroplasty were recruited from one of 5 participating centers. Enrollees provided urethral stricture tissue and blood/serum on the day of surgery and completed patient-reported outcome measure questionnaires both pre- and postoperatively. The initial study had 3 aims: (1) to determine pediatric and adult subacute and repeated perineal trauma (SRPT) exposures using a study-specific SRPT questionnaire, (2) to determine the degree of inflammation and fibrosis in aUSD and peri-aUSD (normal urethra) tissue, and (3)

Submitted November 3, 2023; accepted March 28, 2024; published April 9, 2024.

Recusals: Dr Elliott is a member of the urological survey editorial committee for *The Journal of Urology®* and was recused from the editorial and peer review processes. Dr Erickson is a member of the editorial board for *The Journal of Urology®* and was recused from the editorial and peer review processes.

Funding/Support: Funding for this study was provided by the NIH/National Institute of Diabetes and Digestive and Kidney Diseases grant 1R21DK115945-01.

Conflict of Interest Disclosures: The Authors have no conflicts of interest to disclose.

Ethics Statement: All human subjects provided written informed consent with guarantees of confidentiality (IRB No. 201806016).

Author Contributions:

Conception and design: Erickson, Myers.

Data analysis and interpretation: Erickson, Gutierrez, Luo, Schlaepfer, Christel, Dahmoush, Oleson, Breyer.

Data acquisition: Erickson, Gutierrez, Elliott, Myers, Vanni, Juhr, Breyer.

Drafting the manuscript: Erickson, Gutierrez, Breyer.

Critical revision of the manuscript for scientific and factual content: Erickson, Gutierrez, Luo, Schlaepfer, Elliott, Myers, Vanni, Juhr, Christel, Dahmoush, Oleson, Breyer.

Statistical analysis: Erickson, Gutierrez, Schlaepfer, Myers, Oleson.

Supervision: Erickson, Luo, Elliott, Vanni, Breyer.

Corresponding Author: Bradley A. Erickson, MD, Carver College of Medicine, University of Iowa, 3233 RCP, Iowa City, IA 52246 (brad-erickson@uiowa.edu).

https://doi.org/10.1097/JU.0000000000003962
Vol. 212, 153-164, July 2024
Printed in U.S.A.

to determine levels of systemic inflammatory and fibrotic cytokines. Two controls groups provided serum (normal vasectomy patients) and urethral tissue (autopsy patients). Cohorts were based on the presence/absence of stricture, by presumed stricture etiology (idiopathic, traumatic/iatrogenic, lichen sclerosus [LS]), and by the presence/absence of stricture inflammation.

Results: Of 138 enrolled men (120 tissue/serum; 18 stricture tissue only), 78 had idiopathic strictures, 33 had trauma-related strictures, and 27 had LS-related strictures. BMI, stricture length, and stricture location significantly differed between cohorts ($P < .001$ for each). The highest BMIs and the longest strictures were observed in the LS cohort. SRPT exposures did not significantly differ between etiology cohorts, with > 60% of each reporting low/mild risk. Stricture inflammation significantly differed between cohorts, with mild to severe inflammation present in 27% of trauma-related strictures, 54% of idiopathic strictures, and 48% of LS strictures ($P = .036$). Stricture fibrosis did not significantly differ between cohorts ($P = .7$). Three serum cytokines were significantly higher in patients with strictures compared to stricture-free controls: interleukin-9 (IL-9; $P = .001$), platelet-derived growth factor–BB ($P = .004$), and CCL5 ($P = .01$). No differences were observed in the levels of these cytokines based on stricture etiology. However, IL-9 levels were significantly higher in patients with inflamed strictures than in patients with strictures lacking inflammation ($P = .019$). Degree of stricture inflammation positively correlated with serum levels of IL-9 (Spearman's rho 0.224, $P = .014$).

Conclusions: The most common aUSD etiology is idiopathic. Though convention has implicated SRPT as causative for idiopathic strictures, here we found that patients with idiopathic strictures had low SRPT rates that were similar to rates in patients with a known stricture etiology. Stricture and stricture-adjacent inflammation in idiopathic stricture were similar to LS strictures, suggesting shared pathophysiologic mechanisms. IL-9, platelet-derived growth factor–BB, and CCL5, which were elevated in patients with strictures, have been implicated in fibrotic conditions elsewhere in the body. Further work will be required to determine if this shared biologic signature represents a potential mechanism for an aUSD predisposition.

Key Words: urethral stricture, pathophysiology, inflammation, fibrosis, phenotyping

Anterior urethral stricture disease (aUSD) is a relatively common urologic condition in males with an annual incidence of nearly 1%.[1,2] Though it is assumed that most cases of aUSD are acquired, an exact cause remains unknown in the majority of men. Remarkably, this detail has little impact on how the disease is currently managed. With rare exception, stricture etiology does not factor into aUSD treatment algorithms besides providing a moderate degree of assistance with predicting posttreatment recurrence risk.[3]

Despite this clear gap in aUSD knowledge, the field continues to evolve. Surgical techniques have advanced such that most men undergoing urethroplasty can expect a hospital stay of < 24 hours, a catheter for less than 2 weeks, and a functional success rate of > 90%.[4,5] These surgical improvements have undoubtedly increased awareness of the condition, and a concordant increase in fellowship training has expanded aUSD expertise outside of academic centers.[6] Still, true aUSD cures and preventative strategies remain elusive. As with urologic oncology, where the evolution from large extirpative surgeries to multimodal approaches with minimal surgery first required a basic understanding of disease pathophysiology, so too will aUSD if our goal is to view the condition as more than just urethral fibrosis.[7]

To reach this goal of personalized aUSD care, we must first obtain a better understanding of the stricture in the context of the patient with the stricture. The purpose of the current study was, thus, to evaluate the histopathologic characteristics of aUSD tissue along with patient-/stricture-specific systemic inflammatory and fibrotic profiles, and their stricture-specific medical history. Our overall hypothesis for this 3-aim, exploratory study was that phenotypic signatures would emerge that would provide insights into potential causative mechanisms and ultimately, treatment targets for specific stricture subtypes.

MATERIALS AND METHODS

Patient Cohort

Patients were enrolled at 5 academic centers in an NIH/National Institute of Diabetes and Digestive and Kidney (1R21DK115945-01)–sponsored study evaluating the role of inflammation in aUSD. All centers obtained individual Institutional Review Board approval and all patients signed consents agreeing to the study protocol outlined in Figure 1. Patients were included in the experimental group if they met the following criteria: males > 18 years old with aUSD who were undergoing anterior urethroplasty. Patients were excluded from the experimental group if they met any of the following criteria: aUSD recurrence at the site of a prior urethroplasty (category E3b per the LSE classification system described by Erickson et al[8]), aUSD associated with radiotherapy (category E3c), aUSD associated with a prior hypospadias repair (category E5), active intermittent catheterization at the time of urethroplasty, and performance of a transurethral dilation/incisional procedure within 3 months of the urethroplasty date. Patients were also excluded from

the study if, at the time of urethroplasty, the surgeon was not able to obtain stricture tissue or if the stricture was concerning for malignancy (in this scenario, the entirety of the stricture specimen was sent for surgeon/institutional-specific pathologic analysis). Notably, the inability to collect tissue proximal/distal to the stricture was not a criterion for study exclusion.

Two control groups were included: a serum control group and a urethral tissue control group. The serum control group (n = 10) was comprised of patients recruited from a general urology clinic who were undergoing vasectomy and who did not have any active urologic problems or history of aUSD. Serum and whole blood were collected from these patients. Demographic information was also collected; otherwise, the cohort was deidentified. No urethral tissue was obtained from the serum control group. The urethral tissue control group was comprised of recently deceased patients (n = 14) who were part of the hospital's deeded body program, which allows for the procurement of cadaveric tissue for research purposes at the time of autopsy. Consent was provided either by the patient prior to death or by their medical power of attorney. Complete anterior urethral specimens were obtained from these patients within 12 hours of death. Urethral tissue specimens were immediately stored in formalin at the time of collection.

Study Outline

Enrolled patients were asked to complete pre- and post-operative patient-reported outcome measures (PROMs),[9-12] provide serum/whole blood, and donate urethral stricture and nonstrictured urethral tissue proximal and distal to the stricture on the day of their urethroplasty. Enrollees then returned at 3 months and 12 months for routine posturethroplasty monitoring, which typically involved uroflowmetry and cystourethroscopy (3-month cystoscopy was considered routine clinical care; 12-month cystoscopy was performed only if uroflowmetry or PROMs suggested urethral pathology).[13]

Assessment of Subacute and Repeated Perineal Trauma

Among the series of validated PROMs provided to the patients at the time of enrollment was a nonvalidated, study-specific questionnaire that aimed to quantify the patient's history of subacute and repeated perineal trauma (SRPT; Supplemental Appendix 1, https://www.jurology.com). The hypothesis that was tested in this aim was that men with idiopathic urethral strictures, a diagnosis of exclusion but generally defined by the surgeon as aUSD without a known history of external/internal trauma, untreated urethritis, or lichen sclerosus (LS), will have higher frequency of SRPT history relative to patients with a documented acute urethral trauma or patients with LS-related aUSD, as subacute SRPT is often the presumed stricture etiology in these men.[14,15] Patients were asked about their recalled childhood voiding history; their recalled childhood/adult athletic activity, with a focus on activities that have a potential for perineal trauma (eg, bicycle riding); and their sexual histories.

Urethral Tissue Inflammatory Analysis

Urethral stricture tissue was excised in a routine manner and then stored immediately in formalin. When stricture excision was not appropriate (or necessary) for the repair as deemed by the surgeon, a 3-mm punch biopsy was used to obtain 2 samples from the midportion of the stricture. Nonstrictured tissue was obtained using the 3-mm punch biopsy a minimum of 1 cm proximal and 1 cm distal to the edges of the strictured tissue, when possible. Notably, urethral stricture and nonstrictured tissue were obtained only if the surgeon believed removal of this tissue would not significantly alter the urethroplasty outcomes. For control cadaver urethras, 2 samples were obtained from standardized locations in the proximal and distal bulbar urethra.

All urethral tissue was processed by a single pathology core at the primary investigator's home institution. All tissue underwent hematoxylin and eosin and trichrome staining and were reviewed by 2 pathologists who were blinded to stricture etiology or location (K.C., L.D.). Hematoxylin and eosin specimens were analyzed for inflammation severity using a previously described grading system, which rated inflammatory severity as none, minimal, mild, moderate, or severe based on the volume of inflammatory cells and the depth of epithelial inflammatory penetration (Supplemental

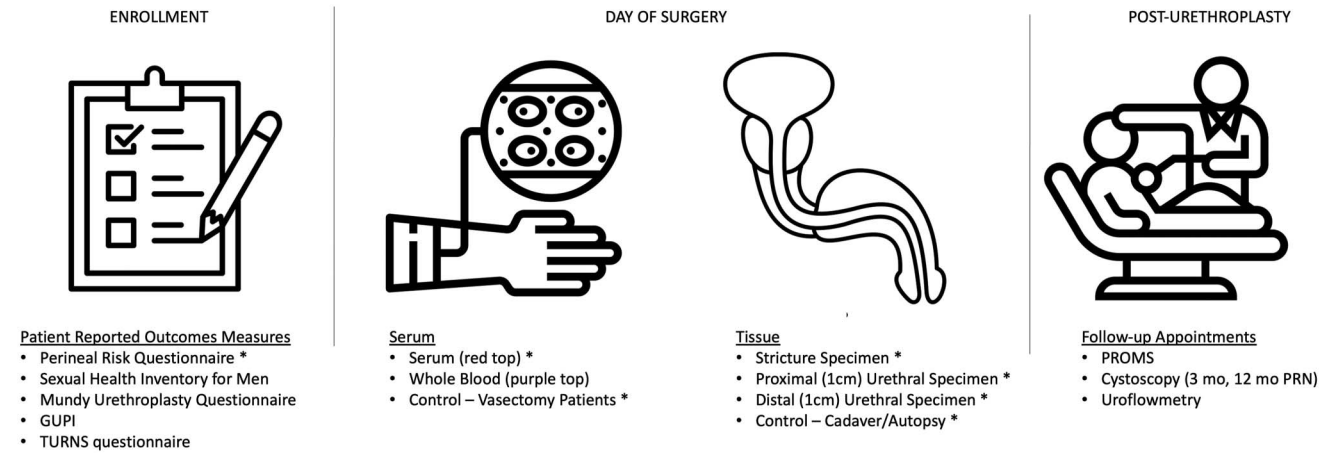

Figure 1. Study schematic. GUPI indicates genitourinary pain index; PRN, as needed; PROMS, patient-reported outcome measures; TURNS, Trauma and Urologic Reconstruction Network of Surgeons.

Table 1. *Demographics of Stricture Tissue Samples by Etiology*

	Trauma and iatrogenic n = 33	Idiopathic n = 78	Lichen sclerosus n = 27	*P* value
Age, median (IQR), y	52 (37-63)	41 (29-57)	50 (42-58)	.13
BMI, median (IQR), kg/m^2	29 (26-32)	29 (27-33)	37 (33-42)	< .001
CCI score, median (IQR)	0 (0-2)	0 (0-1)	0 (0-0)	.019
Diabetes, No. (%)	10 (30)	9 (12)	5 (19)	.057
Stricture length, No. (%)				
L1: ≤2 cm	15 (46)	44 (56)	7 (26)	< .001
L2: >2 cm, ≤7 cm	15 (46)	30 (39)	6 (22)	
L3: >7 cm	3 (9.1)	4 (5.1)	14 (56)	
Stricture location, No. (%)				
S1a[a]	23 (70)	63 (81)	0 (0)	< .001
S1b[b]	3 (9.1)	7 (9.0)	1 (3.7)	
S2a[c]	4 (12)	3 (3.8)	0 (0)	
S2b[d]	1 (3.0)	1 (1.3)	0 (0)	
S2c[e]	1 (3.0)	3 (3.8)	6 (22)	
S2d[f]	1 (3.0)	1 (1.3)	8 (30)	
S3[g]	0 (0)	0 (0)	12 (44)	
Prior stricture management				
≥1 procedure (either DVIU or urethral dilation), No. (%)	25 (76)	55 (71)	23 (85)	.4
No. of procedures (DVIU and urethral dilations), median (IQR)[h]	2.0 (1.0-3.0)	2.0 (2.0-3.5)	2.0 (1.0-2.0)	.4

Abbreviations: CCI: Charlson Comorbidity Index; DVIU, direct vision internal urethrotomy; IQR, interquartile range.
Kruskal-Wallis test used for analysis of age, BMI, CCI scores, and median number of procedures (DVIU and urethral dilations).
χ^2 test used for analysis of diabetes, stricture length, and prior stricture management ≥ 1 procedure (either DVIU or urethral dilation).
Fisher's exact test used for analysis of stricture location because > 25% of cells have expected counts less than 5.
[a] Proximal bulbar.
[b] Distal bulbar.
[c] Bulbar + penile without fossa/meatus.
[d] Penile only.
[e] Penile + fossa/meatus.
[f] Fossa/meatus.
[g] Bulbar + penile + fossa/meatus.
[h] Median and IQR of values ≥ 1.

Appendix 2, https://www.jurology.com).[16] The predominant inflammatory cell type within samples was assessed and categorized as acute (neutrophils) or chronic (lymphocytes, plasma cells, eosinophils). Trichrome-stained specimens were assessed for density and severity of subepithelial fibrosis, the degree of squamous metaplasia, and the presence/absence of a basal cell layer. The hypothesis being tested in this aim was that inflammatory cell density and type would differ by presumed etiology. Specifically, that LS strictures would have high inflammation, traumatic strictures would have low inflammation, and idiopathic would also show low levels of inflammation as they were presumed to have a similar etiology as traumatic strictures.

Serum Analysis

Serum was obtained on the morning of surgery at the time of peripheral intravenous catheter placement. Serum cytokines and chemokines were analyzed using a Bio-Plex Pro Human Cytokine 27-plex Assay (Bio-Rad, M500KCAF0Y). This kit assesses 27 proinflammatory, anti-inflammatory, and adaptive immunity cytokines that are relevant in a variety of physiologic responses and disease processes. Samples were processed per manufacturer instructions in triplicate. The hypothesis being tested in this aim is that serum cytokine profiles would differ by presumed stricture etiology.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics (version 28) and GraphPad Prism 9. Study question 1: Do demographic features differ between stricture etiology cohorts? Kruskal-Wallis test used for analysis of age, BMI, Charlson Comorbidity Index scores, and median number of procedures (direct vision internal urethrotomy and urethral dilations). χ^2 test used for analysis of diabetes, stricture length, and prior stricture management ≥ 1 procedure (either direct vision internal urethrotomy or urethral dilation). Fisher exact test used for analysis of stricture location because > 25% of cells have expected counts less than 5 (Table 1). Study question 2: Do demographic features differ between serum cohorts by presence/absence of stricture? Mann-Whitney *U* test used for analysis of age and BMI. χ^2 test used for analysis of diabetes (Supplemental Table 1, https://www.jurology.com). Study question 3: Do SRPT histories differ between stricture etiology cohorts? Fisher's exact test used for analysis of pediatric and adult perineal risk scores, pediatric and adult contract risk scores, and history of sexually transmitted disease because > 25% of cells have expected counts less than 5. χ^2 test used for analysis of all remaining categories (Table 2). Study question 4: Do stricture histologic features differ between stricture etiology cohorts? χ^2 test used for analysis (normal urethra tissue cohort excluded from statistical analysis; Figure 2; Supplemental Table 2, https://www.jurology.com). Study question 5: Do serum cytokine levels differ between stricture present/absent cohorts? Mann-Whitney *U* test used for analysis (Table 3). Study question 6: Do serum cytokine levels differ between stricture etiology cohorts? Kruskal-Wallis test used for analysis (Supplemental Table 3, https://www.jurology.com). Study question 7: Do serum cytokine levels differ between stricture inflammation

Table 2. *Subacute and Repeated Perineal Trauma History by Etiology*

	Trauma and iatrogenic n = 28	Idiopathic n = 77	Lichen sclerosus n = 27	*P* value
Pediatric				
History of pediatric UTI, No. (%)	5 (18)	10 (13)	3 (11)	.7
Memory of slow urination (relative to peers), No. (%)	7 (25)	26 (34)	6 (22)	.4
History of pediatric catheterization, No. (%)	6 (21)	12 (16)	0 (0)	.051
Age of nocturnal enuresis resolution, No. (%), y				
≥8	6 (21)	14 (18)	3 (11)	.8
Unknown	6 (21)	15 (20)	7 (26)	
Pediatric perineal risk score, No. (%)[a]				
Low	6 (21)	14 (18)	5 (19)	.8
Mild	11 (39)	34 (44)	12 (44)	
Moderate	1 (3.6)	4 (5.2)	3 (11)	
High	0 (0)	0 (0)	0 (0)	
Pediatric contact sport risk score, No. (%)[b]				
Low	15 (54)	44 (57)	14 (52)	> .9
Medium	12 (43)	31 (40)	12 (44)	
High	1 (3.6)	2 (2.6)	1 (3.7)	
Adult				
Presence of buried penis, No. (%)	1 (3.6)	9 (12)	9 (33)	.004
History of STD, No. (%)				
None	22 (79)	62 (81)	23 (85)	.17
Once	4 (14)	15 (19)	3 (11)	
>1	2 (7.1)	0 (0)	1 (3.7)	
Sexual partners, No. (%)				
<5	12 (43)	31 (40)	12 (44)	.11
5-10	9 (32)	25 (32)	14 (52)	
>10	7 (25)	21 (27)	1 (3.7)	
Adult perineal risk score, No. (%)[a]				
Low	17 (61)	47 (61)	19 (70)	.8
Mild	10 (36)	26 (34)	6 (22)	
Moderate	1 (4.0)	4 (5.0)	2 (7.4)	
High	0 (0)	0 (0)	0 (0)	
Adult contact sport risk score, No. (%)[b]				
Low	26 (93)	68 (88)	25 (93)	.6
Medium	2 (7.1)	8 (10)	1 (3.7)	
High	0 (0)	1 (1.3)	1 (3.7)	

Abbreviations: STD, sexually transmitted disease.
Fisher's exact test used for analysis of pediatric and adult perineal risk scores, pediatric and adult contract risk scores, and history of STD because > 25% of cells have expected counts less than 5. χ^2 test used for analysis of all remaining categories.
[a] Cumulative score for bike, motorcycles, and horseback riding. Max score of 9. Low = < 2; mild = 2 to 4 (no individual high exposures); moderate = 5 to 6 (max 1 high exposure); high = > 6 (or >2 high exposures).
[b] Scoring based on exposures to contact sports. Max score of 9. Low = < 3; medium = 3 to 5; high = > 5.

present/absent cohorts? Mann-Whitney *U* test used for analysis (Supplemental Table 4, https://www.jurology.com). Study question 8: Do serum cytokine levels correlate with stricture inflammation levels? Spearman correlation used for analysis. Estimation of SE based on the formula proposed by Fieller, Hartley, and Pearson (Supplemental Table 5, https://www.jurology.com).

RESULTS

Cohort Demographics

A total of 141 men with stricture enrolled in the study, of which 120 had both histopathologic and serum samples adequate for analysis. Additional men had tissue (18) or serum (3) only and were included in the analyses when appropriate.

Patient demographics and basic stricture characteristics are shown in Table 1 and Supplemental Figure 1 (https://www.jurology.com). Notable findings include significant differences in BMI, stricture length, and stricture location between cohorts ($P < .001$ for each). The highest BMIs and the longest strictures were observed in the LS cohort. Penile urethra strictures were also most frequently observed in the LS cohort. No other significant differences were observed in demographics or basic stricture characteristics.

SRPT Risk Questionnaire

The SRPT questionnaire results are shown in Table 2. Overall, there were no significant differences in patient-reported lifetime perineal trauma exposure or contact sport participation amongst cohorts. Nearly one-third of patients reported a history of "slow childhood urination" relative to their peers; 14% of patients reported a pediatric UTI; 14% reported pediatric catheterization; sexual and STI histories were similar amongst cohort.

Urethral Stricture Histopathology

Histopathologic analyses of the stricture are shown in Figure 2 and Supplemental Table 2 (https://www.jurology.com). Inflammatory cells were present in the majority (57%) of the 138 patients with aUSD

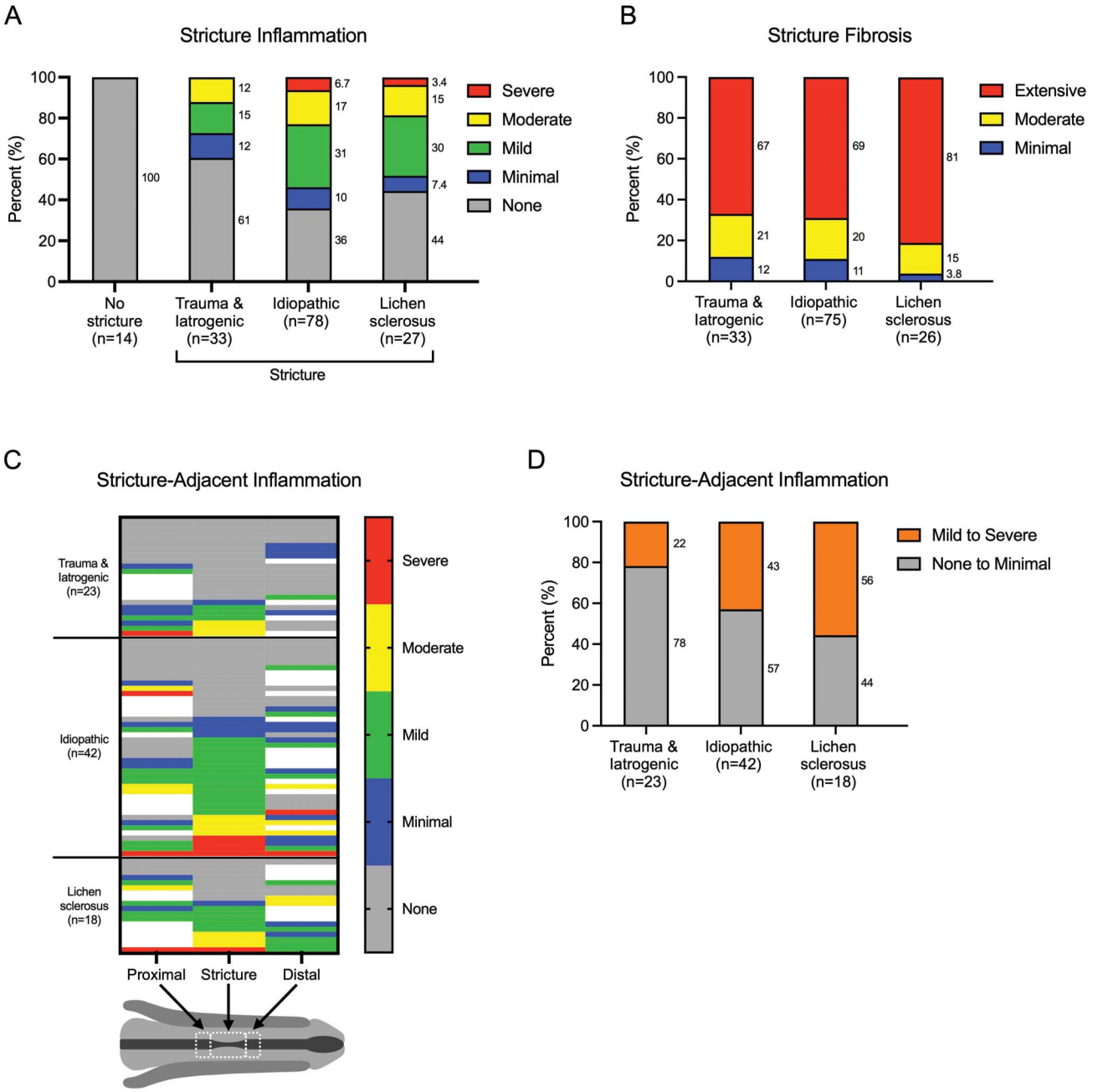

Figure 2. A, Distribution of inflammatory severity. B, Degree of fibrosis. C, Peri-stricture inflammation presence. D, Inflammation severity by stricture etiology.

tissue available for analysis and in 0% of the control urethral tissue segments. Stricture inflammation significantly differed between cohorts, with mild-severe inflammation present in 27% of trauma-related strictures, 54% of idiopathic strictures, and 48% of LS strictures ($P = .036$; Figure 2, A). Subepithelial stricture fibrosis did not significantly differ between cohorts ($P = .7$; Figure 2, B).

Stricture-adjacent urethral tissue (proximal, distal, or both) was available from 83 patients (60% of the cohort; Figure 2, C). Mild to severe inflammation was present in the proximal or distal stricture-adjacent tissue of 33 patients. There was no statistically significant difference in the prevalence of mild to severe inflammation in stricture-adjacent tissue between etiology cohorts when assessed by χ^2 test ($P = .076$; Figure 2, D).

Desquamation and basal cell layer degeneration were similar amongst all 3 cohorts (Supplemental Table 2, https://www.jurology.com). Squamous metaplasia significantly differed between cohorts ($P < .001$) and was present in 71% of trauma/iatrogenic cohort, 96% of the idiopathic cohort, and 100% of the LS cohort.

Table 3. *Cytokine Levels by Presence or Absence of Stricture*

Cytokine, median (IQR), pg/mL	No stricture n = 9		With stricture n = 123		*P* value
CCL2 (MCP-1)	33.3	(27.0-47.1)	32.6	(17.8-62.6)	.8
CCL3 (MIP-1α)	1.1	(0.1-2.8)	0.7	(0.1-2.2)	.8
CCL4 (MIP-1β)	372.5	(357.0-391.1)	384.6	(334.9-446.7)	.4
CCL5 (RANTES)	10,596.4	(7555.8-12,500.9)	16,696.3	(10,795.5-23,445.6)	.01
CXCL10 (IP-10)	358.6	(186.1-469.6)	333.3	(243.4-471.0)	.9
Eotaxin	49.9	(36.6-74.9)	52.3	(41.3-70.1)	.6
G-CSF	28.6	(17.4-67.1)	37.5	(16.3-73.2)	.6
IFN-γ	0.9	(0.7-6.4)	2.4	(0.7-4.5)	.6
IL-1Ra	237.5	(148.8-262.9)	262.9	(105.9-484.9)	.3
IL-4	4.0	(2.5-6.0)	3.8	(2.23-5.0)	.6
IL-8	3.4	(0.8-4.5)	2.1	(0.4-6.8)	.9
IL-9	615.5	(608.3-654.9)	769.1	(666.9-888.0)	.001
IL-13	0.6	(0.2-0.8)	0.9	(0.2-2.2)	.3
IL-17	15.4	(9.3-23.5)	16.4	(12.8-22.7)	.5
PDGF-BB	1416.1	(867.5-1816.5)	3064.8	(1704.6-4742.9)	.004
TNF-α	46.6	(37.3-52.8)	41.4	(29.6-53.9)	.5

Abbreviations: G-CSF, granulocyte colony-stimulating factor; IFN, interferon; IL, interleukin; IP, inducible protein; IQR, interquartile range; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; PDGF-BB, platelet-derived growth factor–BB; RANTES, regulated on activation, normal T-expressed, and secreted; TNF, tumor necrosis factor. Mann-Whitney *U* test used for analysis.

Anterior Urethral Stricture Disease Serum Cytokines

Of the 27 cytokines analyzed, 3 significantly differed between aUSD and control patients, 13 did not display statistically significant differences, and 11 were not statistically analyzed because > 50% of samples were below the limit of detection for the assay (Table 3). Interleukin-9 (IL-9), platelet-derived growth factor–BB (PDGF-BB), and CCL5 were significantly higher in aUSD patients than in controls ($P = .001$, $P = .004$, and $P = .01$, respectively). No statistically significant differences were observed in the levels of these cytokines based on stricture etiology (Supplemental Table 3, https://www.jurology.com). However, IL-9 levels were significantly higher in patients with inflamed strictures than in patients with strictures lacking inflammation ($P = .019$; Supplemental Table 4, https://www.jurology.com). Degree of stricture inflammation positively correlated with serum levels of IL-9 (Spearman's rho 0.224, $P = .014$; Supplemental Table 5, https://www.jurology.com).

DISCUSSION

This study had 3 aims supporting an overall hypothesis which stated that the clinical aUSD etiology would be associated with unique biological signatures. The questionnaire aim asked patients about their pediatric and adult history of perineal trauma exposure and was specifically designed to test the hypothesis, and conventional wisdom, that men with idiopathic strictures were likely to have had histories of SRPT leading to their stricture.[14,15] This hypothesis was not supported by these data. Instead, SRPT rates in idiopathic stricture patients were found to be equal to those in the traumatic and LS cohorts with low rates of moderate/high SRPT in all 3 cohorts. While this does not rule out SRPT as a causative mechanism in some of the cohort, it suggests a more complicated explanation in the majority.

Prior work on perineal trauma histories in idiopathic stricture patients has revealed only weak associations between subacute perineal trauma history and stricture development. Viers et al evaluated 215 idiopathic aUSD cases and found that only 24% reported SRPT.[15] However, acknowledging this percentage was unexpectedly low, the study instead used the morphologic similarities (length and location) between idiopathic and traumatic strictures to conclude that idiopathic strictures must also be of traumatic origin (if not always remembered or perceived by patients). Awad et al surveyed 5488 nonrandom males using Facebook and noted the odds of urethral stricture were higher among cyclists—a common activity associated with perineal trauma—vs noncyclists (odds ratio 2.5; $P = .04$).[14] However, the overall stricture rate in this sample was well under 0.5%, and importantly, a dose-response effect was not seen, with men in the lowest and highest quintiles of lifetime miles on a bicycle reporting similar stricture rates.

Our study confirmed the Viers et al findings that the lengths and locations of the idiopathic strictures are similar to traumatic strictures. However, the purpose of Aim 2 was to expand on the standard radiographic and surgical classifications and include stricture histopathology—and it was here that significant differences between the cohorts emerged. The prevalence of squamous metaplasia was higher in idiopathic and LS strictures compared to traumatic strictures. Furthermore, while most traumatic strictures could be described as fibrotic tissue with little to no inflammation, as might be predicted by a mechanism of acute injury and fibrotic repair, over 50% of idiopathic strictures contained mild to severe inflammation, suggesting the possibility of an

atraumatic pathophysiology with ongoing antigen-mediated repair processes in at least some of the idiopathic strictures. Additional support for this hypothesis is lent by the finding that in 40% of the idiopathic cohort, inflammation extended beyond the visible stricture into stricture-adjacent urethral tissue. A similar finding was observed in the LS cohort, in which stricture-adjacent inflammation was present in over 50% of patients. As has been suggested by others, this pattern of focal fibrosis amongst a more widespread, organ-specific inflammatory effect, potentially implicates immune modulation rather than trauma as the cause.[16-20]

The association of aUSD with systemic inflammation was evaluated in Aim 3 of the study, which hypothesized that higher levels of circulating inflammatory cytokines would be found in patients with inflammatory strictures, drawing upon previous studies that showed an association between systemic inflammatory conditions (eg, metabolic syndrome, diabetes) and inflammatory aUSD.[17] Cytokines are small proteins secreted by immune cells and the epithelium and are important in cell signaling. Their role in the body is primarily for healing purposes, and while many have been linked to disease states, their functions, and complex interactions, are vital to homeostasis.[21,22] Cytokine dysregulation will generally increase systemic inflammation, which can result in pathologic fibrotic states.[23]

Of the 27 cytokines tested, 3 were found to be significantly higher in patients with aUSD vs controls (IL-9, PDGF-BB, and CCL5), and 1 (IL-9) positively correlated with degree of stricture inflammation. While our methodology inhibits our ability to implicate these cytokine elevations as causative, elevations in other disease states can provide support to their potential role in aUSD pathophysiology. For example, PDGF-BB is a mitogen for mesenchymal cells, including fibroblasts, and has long been known to play a role in the formation of hypertrophic and keloid scars.[21,22] Similarly, CCL5 has been shown to play a role in hepatic fibrosis in both animal and human studies, with CCL5 mRNA levels positively correlating with degree of hepatic fibrosis in patients with hepatitis C infection.[24] Finally, IL-9 has been found to promote chronic inflammation by activating T helper cells and by impairing mucosal barrier function.[25] IL-9 also has context-dependent profibrotic activity.[26,27] Importantly, genetic variability in the production of proinflammatory cytokines in response to an external insult has been shown to affect disease penetrance,[28] and an elevated paracrine cytokine response to otherwise indolent insult (eg, perineal trauma, genital LS) is a potential mechanism for a 2-hit aUSD development hypothesis worthy of future study.

The implications of the findings from this study are many. First, idiopathic aUSD appears to have a distinct pathophysiology from traumatic strictures. While this may not affect surgical management in the short term, the fact that over 50% of strictures are idiopathic in nature suggests further work should focus on the anatomic uniqueness of the midbulbar urethra, especially as pertains to its aUSD susceptibility, and disease heritability and prevention. Second, chronic inflammation is a common feature in aUSD that should be explored as a potential target for intervention, in addition to a continued search for the source of the inflammation propagating antigen. Third, there were 3 pathologic findings that were consistent across each of the 3 cohorts—fibrosis, desquamation, and basal layer degeneration. This is pertinent because while the surgical focus in aUSD is on the removal and/or augmentation of fibrosis, the nonsurgical (endoscopic) focus will require targeting cells that have the potential to be chemically manipulated, eg, via a balloon delivery device. The obvious target would be the epithelium. However, the basal cell layer, which was preserved in over half of specimens, is another cell layer worth exploration. In the lungs, basal cells have been implicated in the pathogenesis of idiopathic pulmonary fibrosis by promoting the proliferation of fibroblasts and the deposition of extracellular matrix in response to injury.[29] Further studies are needed to understand whether urethral basal cells play a similar role in aUSD and if so, how they can best be therapeutically targeted.

This study should also be viewed in the context of recent advancements in the endoscopic management of aUSD, with the introduction of a paclitaxel-coated aUSD dilating balloons, which have been shown to have treatment outcomes superior to standard balloons.[30] These early studies present the proof of concept that dilating balloons can be used to precisely deliver drugs through microfissures in the strictured tissue. Still, while it was fortuitous that paclitaxel, a chemotherapeutic agent that stabilizes microtubules and decreases restenosis rates of cardiac stents after angioplasty, showed effectiveness in aUSD, this outcome was not inevitable. Instead, the known heterogeneity of aUSD, confirmed here, suggests that a multitude of drugs, including some with regenerative capabilities, will likely be necessary to treat the full diversity of aUSD subtypes with endoscopic techniques.

There are limitations to the study that deserve mention. In Aim 1, we used a nonvalidated questionnaire to assess SRPT and relied on patients' memory of trauma. Additionally, exposure comparisons were made between cohorts and not with exposure in the general population. In Aim 2, quantitative histopathologic staining of immune cell subtypes and cellular function assays such microRNA analyses were not included. In Aim 3, 11 of 27 cytokines were below the limit of detection for $> 50\%$ of samples, which precluded robust statistical analysis and interpretation, and serum from

only 9 controls was obtained, which increases the likelihood of a type 2 error. Additionally, the cytokine panel was exploratory and thus, only correlative conclusions could be made. The role of additional cytokines not included in the 27-cytokine panel and the timing and function of IL-9, PDGF-BB, and CCL5 in aUSD remain subjects for future exploration.

CONCLUSIONS

This deep phenotyping study of aUSD patients confirms significant disease heterogeneity and strongly suggests that our understanding of idiopathic bulbar strictures, the most common type of aUSD, is incomplete. Elevated profibrotic cytokines in all stricture cohorts suggests that some patients may have a predisposition to stricture formation after otherwise indolent insult. Though traditional surgical treatments rarely consider aUSD pathophysiology, the heterogeneity shown here suggests that as more creative endoscopic treatment solutions are explored, drug delivery to the stricture may benefit by tailoring to the unique stricture histopathology.

REFERENCES

1. Alwaal A, Blaschko SD, McAninch JW, Breyer BN. Epidemiology of urethral strictures. *Transl Androl Urol.* 2014;3(2):209-213. doi:10.3978/j.issn.2223-4683.2014.04.07
2. Santucci RA, Joyce GF, Wise M. Male urethral stricture disease. *J Urol.* 2007;177(5):1667-1674. doi:10.1016/j.juro.2007.01.041
3. Meeks JJ, Erickson BA, Granieri MA, Gonzalez CM. Stricture recurrence after urethroplasty: a systematic review. *J Urol.* 2009;182(4):1266-1270. doi:10.1016/j.juro.2009.06.027
4. Erickson BA, Elliott SP, Voelzke BB, et al; Trauma and Reconstructive Network of Surgeons (TURNS). Multi-institutional 1-year bulbar urethroplasty outcomes using a standardized prospective cystoscopic follow-up protocol. *Urology.* 2014;84(1):213-216. doi:10.1016/j.urology.2014.01.054
5. Cotter KJ, Hahn AE, Voelzke BB, et al; Trauma and Urologic Reconstruction Network of Surgeons (TURNS). Trends in urethral stricture disease etiology and urethroplasty technique from a multi-institutional surgical outcomes research group. *Urology.* 2019;130:167-174. doi:10.1016/j.urology.2019.01.046
6. Naud E, Rourke K. Recent trends and advances in anterior urethroplasty. *Urol Clin North Am.* 2022;49(3):371-382. doi:10.1016/j.ucl.2022.04.002
7. Sanmamed MF, Chen L. A paradigm shift in cancer immunotherapy: from enhancement to normalization. *Cell.* 2018;175(2):313-326. doi:10.1016/j.cell.2018.09.035
8. Erickson BA, Flynn KJ, Hahn AE, et al; Trauma and Urologic Reconstruction Network of Surgeons (TURNS). Development and validation of a male anterior urethral stricture classification system. *Urology.* 2020;143:241-247. doi:10.1016/j.urology.2020.03.072
9. Clemens JQ, Calhoun EA, Litwin MS, et al; Urologic Pelvic Pain Collaborative Research Network. Validation of a modified National Institutes of Health chronic prostatitis symptom index to assess genitourinary pain in both men and women. *Urology.* 2009;74(5):983-987. doi:10.1016/j.urology.2009.06.078
10. Raina R, Lakin MM, Thukral M, et al. Long-term efficacy and compliance of intracorporeal (IC) injection for erectile dysfunction following radical prostatectomy: SHIM (IIEF-5) analysis. *Int J Impot Res.* 2003;15(5):318-322. doi:10.1038/sj.ijir.3901025
11. Jackson MJ, Sciberras J, Mangera A, et al. Defining a patient-reported outcome measure for urethral stricture surgery. *Eur Urol.* 2011;60(1):60-68. doi:10.1016/j.eururo.2011.03.003
12. Baradaran N, Hampson LA, Edwards TC, Voelzke BB, Breyer BN. Patient-reported outcome measures in urethral reconstruction. *Curr Urol Rep.* 2018;19(7):48. doi:10.1007/s11934-018-0797-9
13. Amend GM, Nabavizadeh B, Hakam N, et al. Urethroscopic findings following urethroplasty predict the need for secondary intervention in the long term: a multi-institutional study from trauma and urologic reconstructive network of surgeons. *J Urol.* 2022;207(4):857-865. doi:10.1097/JU.0000000000002353
14. Awad MA, Gaither TW, Murphy GP, et al. Cycling, and male sexual and urinary function: results from a large, multinational, cross-sectional study. *J Urol.* 2018;199(3):798-804. doi:10.1016/j.juro.2017.10.017
15. Viers BR, Pagliara TJ, Rew CA, et al. Characteristics of idiopathic urethral strictures: a link to remote perineal trauma?. *Urology.* 2017;110:228-233. doi:10.1016/j.urology.2017.07.022
16. Grimes MD, Tesdahl BA, Schubbe M, et al. Histopathology of anterior urethral strictures: toward a better understanding of stricture pathophysiology. *J Urol.* 2019;202(4):748-756. doi:10.1097/JU.0000000000000340
17. Erickson BA, Elliott SP, Myers JB, et al; Trauma and Urologic Reconstructive Network of Surgeons (TURNS). Understanding the relationship between chronic systemic disease and lichen sclerosus urethral strictures. *J Urol.* 2016;195(2):363-368. doi:10.1016/j.juro.2015.08.096
18. Doersch KM, Barnett D, Chase A, Johnston D, Gabrielsen JS. The contribution of the immune system to genitourinary fibrosis. *Exp Biol Med (Maywood).* 2022;247(9):765-778. doi:10.1177/15353702221090872
19. Levy AC, Moynihan M, Bennett JA, et al. Protein expression profiles among lichen sclerosus urethral strictures-can urethroplasty success be predicted?. *J Urol.* 2020;203(4):773-778. doi:10.1097/JU.0000000000000610
20. Kohli H, Childs B, Sullivan TB, et al. Differential expression of miRNAs involved in biological processes responsible for inflammation and immune response in lichen sclerosus urethral stricture disease. *PLoS One.* 2021;16(12):e0261505. doi:10.1371/journal.pone.0261505
21. Zhang Y, Chen J, Zhong ZM, Yang D, Zhu Q. Is platelet-derived growth factor-BB expression proportional to fibrosis in the hypertrophied lumber ligamentum flavum?. *Spine (Phila Pa 1976).* 2010;35(25):E1479-E1486. doi:10.1097/BRS.0b013e3181f3d2df
22. Andrews JP, Marttala J, Macarak E, Rosenbloom J, Uitto J. Keloids: the paradigm of skin fibrosis—pathomechanisms and treatment. *Matrix Biol.* 2016;51:37-46. doi:10.1016/j.matbio.2016.01.013
23. Elenkov IJ, Iezzoni DG, Daly A, Harris AG, Chrousos GP. Cytokine dysregulation, inflammation and well-being. *Neuroimmunomodulation.* 2005;12(5):255-269. doi:10.1159/000087104
24. Katsounas A, Trippler M, Wang B, et al. CCL5 mRNA is a marker for early fibrosis in chronic hepatitis C and is regulated by interferon-α therapy and toll-like receptor 3 signalling. *J Viral Hepat.* 2012;19(2):128-137. doi:10.1111/j.1365-2893.2011.01503.x
25. Angkasekwinai P, Dong C. IL-9-producing T cells: potential players in allergy and cancer. *Nat Rev Immunol.* 2021;21(1):37-48. doi:10.1038/s41577-020-0396-0
26. de Lira Silva NS, Borges BC, da Silva AA, et al. The deleterious impact of interleukin 9 to hepatorenal physiology. *Inflammation.* 2019;42(4):1360-1369. doi:10.1007/s10753-019-00997-0
27. Yanaba K, Yoshizaki A, Asano Y, Kadono T, Sato S. Serum interleukin 9 levels are increased in

patients with systemic sclerosis: association with lower frequency and severity of pulmonary fibrosis. *J Rheumatol.* 2011;38(10):2193-2197. doi:10.3899/jrheum.110268

28. Vakil MK, Mansoori Y, Al-Awsi GRL, et al. Individual genetic variability mainly of proinflammatory cytokines, cytokine receptors, and toll-like receptors dictates pathophysiology of COVID-19 disease. *J Med Virol.* 2022;94(9):4088-4096. doi:10.1002/jmv.27849

29. Jaeger B, Schupp JC, Plappert L, et al. Airway basal cells show a dedifferentiated KRT17^{high}Phenotype and promote fibrosis in idiopathic pulmonary fibrosis. *Nat Commun.* 2022;13(1):5637. doi:10.1038/s41467-022-33193-0

30. Virasoro R, DeLong JM, Estrella RE, et al. A drug-coated balloon treatment for urethral stricture disease: three-year results from the ROBUST I study. *Res Rep Urol.* 2022;14:177-183. doi:10.2147/RRU.S359872

EDITORIAL COMMENT

This multi-institutional study of urethral stricture etiology aims to identify phenotypic signatures among variable presentations of the disease.[1] Using a combination of patient-reported characteristics, serum inflammatory profiles, and histology, the authors demonstrated an association between clinical etiology and biological profiles. Although all stricture patients had a background elevation in systemic inflammatory markers, the histologic signature of idiopathic strictures resembled that of inflammatory lichen sclerosus more often than traumatic strictures.

This undertaking represents an exciting look toward the future of investigation in reconstructive urology. While only 1% of National Institutes of Health grant funding of urologic research is awarded to male reconstruction and trauma, efforts in the reconstructive community, including the founding of the Society of Genitourinary Reconstructive Surgeons Multi-Institutional Trials Committee, seek to increase high-quality, and potentially fundable, research.[2] This manuscript offers a blueprint for others to follow in that endeavor. Just as we have seen remarkable advances in targeted therapies within urologic oncology, via the study of cellular signaling pathways and genetics, efforts to better understand the pathophysiology of benign conditions like stricture disease will allow for an expansion of our reconstructive armamentarium.

These findings also have potential implications for current management of urethral stricture disease. While idiopathic strictures have traditionally been compared to traumatic strictures, this work demonstrates that their biologic signature may often be more akin to inflammatory strictures. Armed with this knowledge, in addition to high-quality evidence favoring augmentation over excision, urologists may consider leaning more toward grafting idiopathic strictures when faced with borderline cases.[3] After proper validation in additional patient cohorts, it is intriguing to consider a future state in which pretreatment biopsy allows a precision approach to urethral stricture disease using targeted agents or techniques.

Kate Dwyer,[1] George E. Koch ,[2,3] and Hunter Wessells[2]

[1]Department of Urology, Vanderbilt University Medical Center Nashville, Tennessee

[2]Department of Urology, The University of Washington Seattle, Washington

[3]Early Career Editor, The Journal of Urology®

REFERENCES

1. Gutierrez WR, Luo Y, Dahmoush L, et al. Deep phenotyping the anterior urethral stricture: characterizing the relationship between inflammation, fibrosis, patient history, and disease pathophysiology. *J Urol.* 2024;212(1):153-164. doi:10.1097/JU.0000000000003962

2. Hakam N, Sadighian M, Nabavizadeh B, et al. Contemporary trends and end-results of National Institutes of Health grant funding to departments of urology in the United States: a 10-year analysis. *J Urol.* 2021;206(2):427-433. doi:10.1097/JU.0000000000001751

3. Nilsen OJ, Holm HV, Ekerhult TO, et al. To transect or not transect: results from the Scandinavian urethroplasty study, a multicentre randomised study of bulbar urethroplasty comparing excision and primary anastomosis versus buccal mucosal grafting. *Eur Urol.* 2022;81(4):375-382. doi:10.1016/j.eururo.2021.12.017

REPLY BY AUTHORS

As we continue to move forward in our understanding of anterior urethral stricture disease (aUSD), we must keep in mind that most aUSD looks like the retrograde urethrogram in the Figure when they first present to a urologist. In the Trauma and Urologic Reconstruction Network of Surgeons prospective database, the short (L1/L2), proximal/mid-bulbar (S1a) urethral strictures of idiopathic origin (E2) make up over half of the nearly 3000 strictures in the cohort.[1] While this area is certainly vulnerable

to straddle injury, the uniformity of the stricture appearance both on retrograde urethrogram and, shown in this manuscript,[2] histopathology, should make us rethink how these strictures truly come to be.

Fortunately for our patients, urethroplasty techniques have made strictures in this area essentially curable, seemingly regardless of the type of repair that is performed—that is, transection/nontransection, ventral/dorsal graft, excision/nonexcision all perform about the same when sound reconstructive techniques are applied. Unfortunately for clinicians and researchers, our successes surgically have prevented us from answering the most obvious question: why here and how? This study suggests that further work on our most common, and most surgically straightforward, aUSD may be the key to unlocking improved nonsurgical treatments and preventative strategies.

As suggested by the previous commentary, the pathophysiologic mechanism of inflammation and fibrosis is common to many nononcologic disease processes in urology, and a uniform approach to studying fibrosis in urologic organs is surely to benefit urologic disease processes beyond aUSD (eg, erectile dysfunction, ureteral stricture, radiation cystitis/fibrosis). Notably, while we have historically considered fibrosis to be an irreversible process, advances in cardiac and pulmonary fibrosis suggest that the cells responsible for "protecting" the organ after injury are manipulatable and phenotypes can be reversed under the right conditions.[3,4] With continued discovery, we may soon be innovating our way out of one of the most enjoyable, and successful, surgical procedures in all of urology.

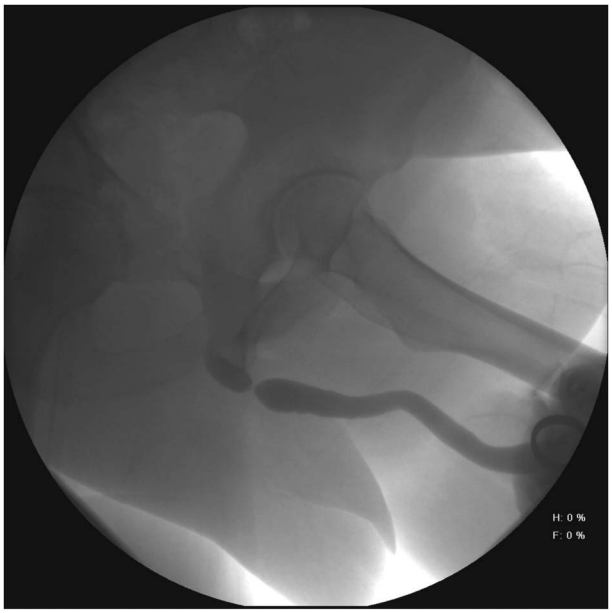

Figure. L1S1aE2 urethral stricture.[1]

REFERENCES

1. Erickson BA, Flynn KJ, Hahn AE, et al; Trauma and Urologic Reconstruction Network of Surgeons (TURNS). Development and validation of a male anterior urethral stricture classification system. *Urology.* 2020;143:241-247. doi:10.1016/j.urology.2020.03.072

2. Gutierrez WR, Luo Y, Dahmoush L, et al. Deep phenotyping the anterior urethral stricture: characterizing the relationship between inflammation, fibrosis, patient history, and disease pathophysiology. *J Urol.* 2024;212(1):153-164. doi:10.1097/JU.0000000000003962

3. Nagaraju CK, Robinson EL, Abdesselem M, et al. Myofibroblast phenotype and reversibility of fibrosis in patients with end-stage heart failure. *J Am Coll Cardiol.* 2019;73(18):2267-2282. doi:10.1016/j.jacc.2019.02.049

4. Ahangari F, Price NL, Malik S, et al. microRNA-33 deficiency in macrophages enhances autophagy, improves mitochondrial homeostasis, and protects against lung fibrosis. *JCI Insight.* 2023;8(4):e158100. doi:10.1172/jci.insight.158100