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Observational study on histopathology of male anterior urethral stricture: Toward better understanding of stricture pathophysiology

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ABSTRACT

Background: Stricture urethra is generally limited to anterior urethra. At present, there are only a few studies which focus exclusively on the histopathology of stricture urethra disease. **Aims and Objectives:** The aims of this study were to assess the urethral stricture pathology specimens for determining the severity of chronic inflammation and characteristics of stricture, demographics, and patient-reported outcome measures in patients with inflammatory and non-inflammatory strictures. **Materials and Methods:** This was a prospective and observational study done on 60 male patients of anterior urethral stricture disease who underwent excision biopsy of stricture during urethroplasty. Pre-operative urinary symptoms assessment was done with a questionnaire provided to all patients and data maintained to assess patient-reported outcomes in inflammatory and non-inflammatory stricture urethra. Cohorts comprising strictures with no inflammation, mild, and moderate to severe inflammation were developed and stricture, the patient characteristics were compared. **Results:** In a total of 60 histopathological stricture specimens, there was no inflammation in 40%, mild and moderate inflammation was in 28% and 3.3%, respectively. Lichen sclerosis-related strictures had moderate to severe inflammation and most of the strictures were in bulbar urethra (51.6%). Patients with BXO changes showed more inflammation. In patients with inflammatory strictures, hesitancy, straining, and stream were statistically more compared to non-inflammatory strictures. Idiopathic is the most predominant etiology for stricture which showed no inflammation. **Conclusion:** Histopathological analysis of urethral stricture showed significant tissue heterogeneity in clinically similar strictures. Chronic inflammation was commonly found in stricture specimens indicating active antigen presentation for underlying pathology and patients with inflammatory strictures reported worse health outcomes.

Key words: Anterior urethral stricture; Lichen sclerosis; Inflammation; Histopathology

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INTRODUCTION

In males, urethral stricture is defined as a narrowed segment of the anterior urethra due to fibrosis and cicatrization of urethral mucosa and surrounding spongiofibrosis.[1] Stricture urethra is generally limited to the anterior urethra. There is a development of secondary scarring into the corpus spongiosum.[2] Posterior stricture urethra is a fibrotic process, in which narrowing of the bladder neck occurs, and usually, it results from distraction injury due to surgery or trauma.[2] When it comes to disorders that directly affect organs, evaluating histopathology is usually the first step. At present, there are only a few studies which focus exclusively on the histopathology of stricture urethra disease (USD). Lately, the development of chronic inflammation is linked to an increasing number of systemic and chronic diseases. The impact of inflammation in the development of stricture urethra is also being explored.[3] Lichen sclerosis (LS) is an inflammatory genital disorder which causes stricture formation in the urethra and the

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pathophysiology of it reveals chronic inflammation. Inflammation is now seen in non-LS strictures also suggesting that USD is a dynamically more active process than previously thought.[4,5]

Aims and objectives

This study was assessment of male urethral stricture pathology specimens in the context of determining the severity of chronic inflammation for baseline heterogeneity and to determine characteristics of stricture, patient demographics, and patient reported outcomes measures (PROMs) in patients with inflammatory and non-inflammatory strictures.

MATERIALS AND METHODS

This was a prospective observational study, carried out in the Department of Urology at a tertiary care center. Taking the prevalence of male urethral stricture as 0.6% (P), 80% as the power of the study, 95% confidence interval, and absolute error 2% (L), the sample size is calculated with the following formula $n=4PQ/L^2$ (Q=100-P), n=59.4. Hence, 60 male patients of anterior urethral stricture disease attending our department over a period of 3 years who underwent urethroplasty were included in the study, in all these patients stricture site, biopsy was obtained at the time of surgery. Patients with stricture urethra due to trauma, patients actively performing clean intermittent self-catheterization, and female patients with stricture urethra were excluded from the study. After obtaining informed consent from patients, data regarding demographic details, presenting complaints, systemic risk factors, stricture urethra etiology, and diagnosis by RGU for stricture position and average length, were collected. All men who underwent anterior urethroplasty in whom tissue biopsy at the stricture site was obtained at the time of surgery were sent to the department of pathology for histopathological analysis. In histopathological analysis, the presence of dysplasia or malignancy was ruled out. Characteristics of LS are hyperkeratosis, epithelial thinning or thickening, basal cell layer degeneration, dermal collagen homogenization, and lichenoid plasmacytic or lymphocytic infiltrate selected for diagnosis of lichen sclerosus (LS).[6] The presence of two or more of these characteristics represented a diagnosis of LS. The presence of inflammation noted, if inflammation is present, it is graded as mild, moderate, and severe (based on a grading system used in BPH literature). Predominant cellular infiltrates (neutrophils, lymphocytes, plasma cells, or eosinophils) are determined in slides. A prospectively maintained database was used to obtain information on patient, stricture characteristics. Pre-operative urinary symptoms assessment was done with a questionnaire provided to all patients and data maintained to assess patient-reported outcomes in inflammatory and non-inflammatory stricture urethra. Cohorts comprising strictures with no inflammation, mild inflammation, and moderate to severe inflammation were developed and, stricture and patient characteristics were compared.

RESULTS

In the present study, 60 male patients of anterior stricture urethra underwent urethroplasty. The pathological specimens at stricture sites are obtained and sent for histopathological analysis over a period of 3 years. There was no dysplasia or malignancy noted in any of the histopathological analyses. Out of 60 patients, 25 (41.6%) patients were in the age group of 41–50 years and 17 (28.3%) patients were in the age group of 51–60 years. The mean age group was 48.5 years (SD - 8.9). The mean body mass index (BMI) of patients in the current study was 31.9 Kg/m^2 (SD - 4.4). In a total of 60 patients, 20 (33%) were hypertensive, 13 (21%) were diabetic, 7 (11%) were having coronary artery disease (CAD), and 5 (8%) were having chronic obstructive pulmonary disease (COPD). Fifteen (25%) patients in the study were not having comorbidities. Out of 60 patients, 39 (65%) were addicted to tobacco use, as shown in Table 1 below.

Maximum number of patients in the study were having idiopathic (n=29, 48.3%) and iatrogenic (n=13, 21.6%) etiology for stricture urethra. Nine (15%) patients in the study had clinically changes of balanitis xerotica obliterans. In the present study, the maximum site of stricture urethra was in the bulbar region (n=31, 51.6%) followed by the bulbomembranous location (n=17, 28.3%). In the present study, 28 (46.6%) patients were having intraoperative stricture length <2.5 cm, 30 (50%) patients were having stricture length between 2.5 cm and 5 cm and 2 (3.3%) patients were having stricture length >5 cm, Mean– 2.6 cm, and SD – 0.73, as shown in Table 2 below.

In a total of 60 histopathologies of the stricture site, there was no inflammation in 24 (40%) samples, mild (Figure 1) and moderate (Figure 2) inflammation was 17 (28%) in each sample and 2 (3.3%) samples showed severe (Figure 3) inflammation. In total 36 of inflammatory strictures histopathology, the predominant inflammatory cells were lymphocytes (n=30, 83%) followed by plasma cells (n=5, 14%). In a total of 19 inflammatory strictures (moderate to severe), 9 (47%) histopathology slides showed the presence of LS. There were no LS in mild inflammatory strictures. In nine histological slides of LS, hyperkeratosis (n=7, 77%) and lichenoid lymphocytic infiltrate (n=8, 88%) characteristics were predominant. In the etiology of stricture urethra, idiopathic and iatrogenic factors were more, which were 18 (75%) and 3 (12%) in non-

Table 1: Age and comorbidities

Patient characteristics	Range	Frequency (n=60)	Percentage
Age	Age group (in years)		
	21–30	2	3.3
	31–40	6	10
	41–50	25	41.6
	51–60	17	28.3
	61–70	9	15
	71–80	1	1.6
	Mean	48.56 years	
	SD	8.9	
BMI	BMI range (Kg/m^2)		
	<18.5	2	3.3
	18.5–24.9	3	5
	25–29.9	16	26.6
	30–34.9	34	56.6
	35–39.9	3	5
	>40	2	3.3
	Total	60	100
	Mean	31.9 Kg/m^2	
	SD	4.4	
Patient comorbidities	Risk factors		
	No comorbidity	15	25
	Hypertension	20	33
	CAD	7	11
	Diabetes	13	21
	COPD	5	8
TOBACCO use	TOBACCO use		
	Present	39	65
	Absent	21	35

BMI: Body mass index, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease

Table 2: Stricture position and length

Characteristics	Location and size	Frequency (n=60)	Percentage
Stricture position	Stricture position		
	Penile	10	16.6
	Bulbar	31	51.6
	Bulbomembranous	17	28.3
	Multiple	2	3.3
	Total	60	100
Stricture length	Stricture length		
	<2.5 cm	28	46.6
	2.5–5 cm	30	50
	>5 cm	2	3.3
	Total	60	100
	Mean	2.6 cm	
	SD	0.73	

inflammatory strictures, respectively. Patients with BXO changes showed more inflammatory grades as 2 (11.7%) with mild inflammation and 7 (36.8%) with moderate to severe inflammation. Maximum sites of stricture were at the bulbar region of urethra (n=36.60%), among which maximum were non-inflammatory strictures (n=18.75%). In LS, grades of inflammation were mild in 2 (11.7%) and 7 (36.8%) were moderate to severe inflammation. Out of nine, each bulbar and bulbomembranous strictures, severe and mild

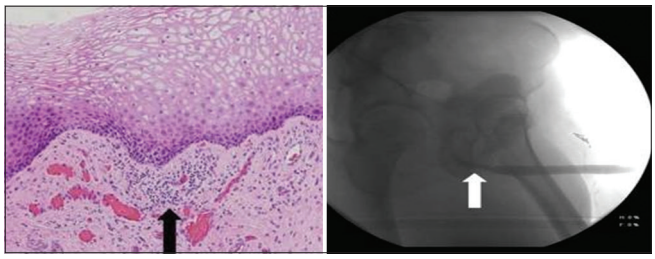

Figure 1: Mild inflammation (arrow) with no epithelial infiltration by inflammatory cells

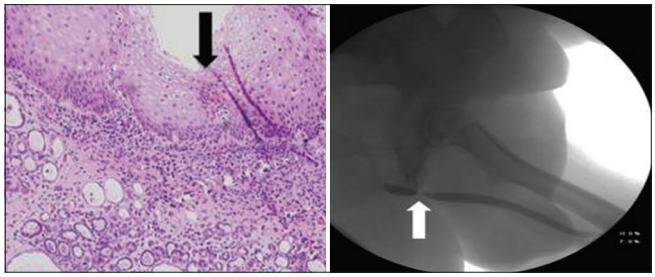

Figure 2: Moderate inflammation with focal epithelial infiltration by inflammatory cells (arrow)

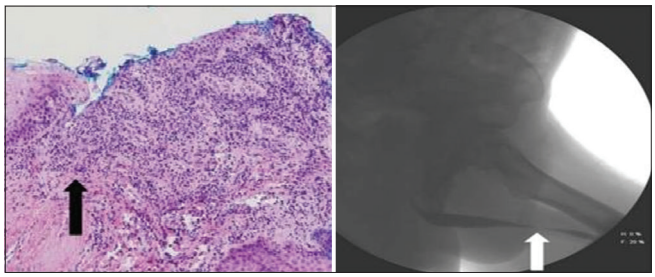

Figure 3: Severe inflammation with mucosal ulceration (arrow)

inflammation grade was noted in seven and two cases of LS, respectively, as shown in Table 3 below.

In patients with inflammatory strictures, hesitancy, straining, and stream strength were statistically more compared to non-inflammatory strictures with P value of 0.001, 0.002, and 0.02, respectively. No significant statistical difference in other urinary symptoms was noted, as shown in Table 4 below.

DISCUSSION

This study of 60 consecutive stricture urethra specimens showed several important findings regarding the histopathology of stricture. Routine pathological examination of USD specimens fails to detect stricture polymorphism, particularly when it comes to urethral inflammation. A pathological chronic inflammation was found in nearly 50% of the stricture specimens. Patients with inflammatory strictures had significantly worse overall health.[3] The estimated prevalence of stricture urethra in

Table 3: Cohort of stricture urethra inflammation

Stricture characteristics	No inflammation (n=24, %)	Mild inflammation (n=17, %)	Mod. to severe inflammation (n=19, %)
Etiology			
Idiopathic	18 (75)	7 (41.1)	4 (21)
Iatrogenic	3 (12)	4 (23.5)	6 (31.5)
Infectious	1 (4.1)	1 (5.8)	1 (5.2)
Failed Hypospadias	1 (4.1)	1 (5.8)	1 (5.2)
Radiation	0	1 (5.8)	0
BXO	0	2 (11.7)	7 (36.8)
Penile	3 (12.5)	2 (11.7)	5 (26.3)
Bulbar	18 (75)	9 (52.9)	9 (47.3)
Bulbomembranous	3 (12)	5 (29.4)	5 (26.3)
Multifocal	0	2 (11.7)	0
LS	0	2 (11.7)	7 (36.8)

Table 4: Patient reported outcome measure in inflammatory and non-inflammatory strictures using urinary symptoms assessment

S. No.	Symptoms	No inflammation (n=24)							Inflammation (n=36)							P value
		Range					Mean	SD	Range					Mean	SD	
		0	1	2	3	4			0	1	2	3	4			
1.	Hesitancy	0	1	8	12	3	2.7	0.7	0	0	6	11	19	3.3	0.7	0.001
2.	Straining	0	0	10	12	2	2.6	0.6	0	0	8	13	15	3.0	0.7	0.002
3.	Interrupted urinary stream	0	3	8	8	5	2.6	0.9	0	0	10	17	9	2.9	0.7	0.15
4.	Incomplete emptying	0	1	12	9	3	2.6	0.6	0	0	18	18	0	2.5	0.5	0.48
5.	Post-void dribbling	0	0	13	9	2	2.5	0.6	0	0	18	17	1	2.5	0.5	1.00
6.	Stream strength	0	0	8	14	2	2.7	0.5	0	0	5	24	7	3.0	0.5	0.02
7	Symptom interference	0	0	0	9	15	3.6	0.5	0	0	0	12	24	3.6	0.4	1.00

males is 0.6% and it has bothersome and painful chronic conditions causing significant urological problems.[3] The mean age of this study group is 48.5 with SD = 8.9 years. This correlated to the mean age in similar studies conducted by Liu et al.,[7] Erickson et al.,[8] and Hofer et al.,[9] where the mean age was 47.5 years, 46.7 years, and 46.6 years, respectively. The mean age in this study is lower than those recorded in other studies done by Matthew.[3] The mean BMI of patients in this study was 31.9 Kg/m$^{2.}$ (SD – 4.4). This correlated to the BMI in similar studies conducted by Grimes et al.,[3] Erickson et al.,[8] and Hofer et al.,[9] where the mean BMI was 30.2 Kg/m^2, 34.5 Kg/m^2, and 31.6 Kg/m$^{2\ year}$s, respectively. In a total of 60 patients in this study, 20 (33%) were hypertensive, 13 (21%) were diabetic, 7 (11%) were having CAD, and 5 (8%) were having COPD in patients with stricture urethra. A study by Fergus et al.,[10] demonstrated an association between LS and higher mean (BMI) (31.0 vs. 28.1, P=0.001), diabetes mellitus (OR=2.04, P=0.03), and a weaker association with CAD.[10] A similar study done by Grimes et al.,[3] showed that systemic illness has a role in local or focal urethral inflammation leading to stricture pathology and patients were reported to have the worst health outcome. However, they concluded that these factors are not causative but chronic inflammation in the urethra is a local manifestation of it. A study done by Erickson et al.,[8] on the relationship between chronic systemic disease and LS on urethral strictures showed that hypertension, hyperlipidemia, CAD, and DM were more common in men with LS USD than in non-LS USD. The study by Hofer et al.,[9] on LS in men with elevated BMI, diabetes mellitus, CAD, and smoking concluded that men with LS have a higher BMI, a higher prevalence of CAD, diabetes, and tobacco use. Systemic or vascular impairment from disorders of CAD, DM, and smoking may be related to the development and chronicity of LS, rather than being a solely dermatologic issue.

In this study, mean stricture length was 2.6 cm (SD – 0.73). The mean length of stricture in our study correlated with the studies done by Grimes et al.,[3] Erickson et al.,[8] and Hofer et al.,[9] which was 2.6 cm, 3.4 cm in non-LS stricture, and 2.9 cm, respectively. The mean stricture length of LS-related strictures in studies done by Erickson et al.,[8] was 5.30 cm. In this study, the mean stricture length was 2.6 cm with the maximum number at the bulbar and bulbomembranous urethra including LS-related strictures. A similar study done by Grimes et al.,[3] had that the mean length of the stricture urethra was 2.6 cm and the maximum site of the stricture urethra was at the penile and bulbar region. The LS-related strictures were maximum at the bulbar and bulbomembranous region. In a study by Erickson et al.,[8] the mean stricture length was 3.36 cm in non-LS stricture and it was 8.4 cm in LS-related stricture with significant statistics and LS-related more stricture

in penile and penobulbar urethra. Whereas one study by Barbagli et al.,[11] contradicted with our findings, where LS was documented in the meatus in 91.5% of cases, in the navicularis in 84.4% and in the penile urethra in 70.6%. All biopsies from the bulbar urethra were negative.[11]

In this study maximum, histopathological reports were suggestive of mild-to-moderate grading of inflammation (56.6%) in the stricture urethra with predominant inflammatory cells being lymphocytes (50%). In a similar study by Grimes et al.,[3] in review, histological analysis noted maximum mild-to-moderate inflammation (56%) with lymphocytes being the predominant inflammatory cells. In this study, the maximum number of patients were having idiopathic (n=18) and iatrogenic (n=3) etiology for stricture urethra, in which the maximum number of cases showed no inflammatory changes. Patients with BXO (n=9) changes were having moderate to severe inflammation (n=7). The maximum number of strictures at bulbar and bulbomembranous urethra showed no inflammation (n=21). Out of nine cases of LS related stricture, the maximum number were having moderate to severe inflammation (n=7) of which the maximum was at bulbar urethra. In a similar study by Grimes et al.,[3] idiopathic (n=43) etiology was predominant with more cases showing no inflammatory changes (n=24). Most of the strictures were in the bulbar region (n=78) of the urethra with no inflammatory changes (n=42). PROM was defined previously in studies by Jackson et al.,[12] in which pre-operative questionnaire was provided to all patients in the study for urinary symptom assessment and data were maintained. This obtained information, then, correlated with the corresponding histopathological report. In patients with inflammatory strictures, the urinary symptoms (hesitancy, straining, and stream strength) grading was more than in non-inflammatory strictures. Rest urinary symptoms did not show a significant statistical difference in both inflammatory and non-inflammatory strictures. The overall PROM was worse in inflammatory Strictures.[11] In a similar study by Grimes et al.,[3] no statistically significant difference was noted among symptoms in both inflammatory and non-inflammatory strictures. However, they concluded that patients with inflammatory stricture report worse health outcome.

Limitations of the study

There are limitations to the study that we will address here. This series is biased towards shorter strictures amenable to excisional repair. Second, pathologic analysis was limited to the strictured urethra itself and did not include surrounding urethral mucosa. This limits our ability to determine if all pathologic tissue was excised and may have an impact on surgical outcome. Lastly, no standardized consensus criteria for the pathologic analysis of urethral strictures exist and in lieu of this, histologic criteria associated with LS were utilized which are also not standardized. Despite these limitations, what this study does confirm is that urethral strictures are much more heterogeneous, and complex, than has previously been reported.

CONCLUSION

Metabolic and lifestyle factors may have a contributory role in the development and chronicity of the stricture urethra. Histopathological analysis of urethral stricture showed significant tissue heterogeneity in clinically similar strictures. Chronic inflammation was commonly found in stricture specimens indicating active antigen presentation for underlying pathology. Patients with inflammatory strictures reported worse health outcomes.

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Authors' Contributions:
KVT- Definition of intellectual content, Concept, Design of study, statistical Analysis and Interpretation, implementation of study protocol, data collection, data analysis; **TMMR-** clinical protocol, editing, and manuscript revision; **AK-** Writing**,** Literature survey, editing, Prepared first draft of manuscript, and preparation of Figures, manuscript preparation and submission of article; **IAQ-** Review Manuscript; **VMRP-** Coordination and Manuscript revision **MSP-** Literature survey.

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