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A Randomized Clinical Study to Compare the Efficacy and Safety of Naftopidil Versus Tamsulosin in Symptomatic Benign Prostatic Hyperplasia

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ABSTRACT

Aim: To compare the clinical efficacy and tolerability of naftopidil versus tamsulosin in patients with LUTS due to BPH. Tamsulosin acts via α1A-receptor and naftopidil acts via α1D-receptor blocker. The latter is believed to be more efficacious with fewer side effects.

Settings and Design: A prospective, randomized, non-placebo clinical study.

Methods and Materials: 110 patients fulfilling our inclusion criteria were randomized (double-blinded) to receive naftopidil (50 mg) or tamsulosin (0.4 mg) once daily for 3 months after obtaining institutional ethical clearance and administering informed consent. The patients were followed for changes in International Prostate Symptom Score (IPSS), Sexual Function Inventory Score (SFIS), peak flow rate (PFR), average flow rate (AFR), post-void residue (PVR), episodes of acute urinary retention (AUR), and side effects, which were recorded and analyzed using appropriate statistical tools.

Statistical Analysis: Recorded data was analyzed using appropriate statistical tools including the unpaired Student *t* test, Tukey test, and the repeated measure ANOVA test.

Results: Naftopidil and tamsulosin both improved patient symptoms, uroflowmetry, and other parameters. Naftopidil appeared to have an earlier onset of action shown by significant change in values of IPSS ($P = 0.003$), PVR (0.041), storage subscore (SIPSS) ($P = 0.011$), and QoI ($P = 0.017$) at 2 weeks. A higher incidence of postural hypotension, headache, and drug failure were observed with tamsulosin (not statistically significant). SFIS was significantly lower in the tamsulosin group.

Conclusions: The management of symptomatic BPH, with either naftopidil or tamsulosin, appeared to be equally effective, safe, and well tolerated. Naftopidil appeared to have a faster onset of action with fewer side effects versus tamsulosin. All patients appeared to be equally compliant, and there was no treatment withdrawal due to observed side effects with either drug.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a progressive disorder of aging men that is associated with bothersome lower urinary tract symptoms (LUTS) [1]. The vast majority of BPH patients benefit from medical management as an initial therapy, with surgery reserved for select indications. Alpha (α)-blockers with or without 5 α-reductase inhibitors forms the current mainstay of medical management for LUTS due to BPH. It is believed that there is a dominance of α1D-adrenoreceptors (AR) in the prostate and smooth-muscle detrusor in patients with BPH [2].

The safety and efficacy of tamsulosin for LUTS due to BPH is attested by some randomized clinical trials (RCTs) in the

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Table 1. The mean initial values of salient patient parameters evaluated in 101 patients form both groups.

Initial Parameters	Naftopidil (N) 50	Tamsulosin (T) 51	*P* value*
Age	61.69 (48-88)	61.15 (46-78)	0.744
Body mass index	22.106 (18.2-29.1)	21.779 (17-27.8)	0.501
Mean prostate grade (DRE)	1.84	1.95	0.283
Average flow rate (ml/sec)	4.19 (1.2-11.2)	4.434 (1.9-14.3)	0.627
IPSS score	21.06 (10-35)	21.53 (10-35)	0.739
Storage SS of IPSS	10.46 (4-15)	10.49 (4-15)	0.963
Voiding SS of IPSS	10.72 (2-20)	10.75 (2-20)	0.979
Maximum flow rate (ml/sec)	10.62 (3.2-41)	9.41 (4.2-25.4)	0.273
Post void residue (mls)	64.4 (0-246)	72.34 (0-400)	0.549
Quality of life	3.68 (2-5)	3.78 (1-5)	0.46
SFIS**	38.27 (12-44)	38.42 (21-44)	0.927
Flow time (secs)	37.92 (14-70)	34.26 (12-105)	0.265
Hesitancy (secs)	4.934 (0-22)	5.814 (0-18.5)	0.344
Voided volume (CC)	148.02 (39-496)	128.55 (10-294)	0.197
Prostate volume (CC)	31.38 (15-65)	30.01 (18-64)	0.507

*Indicates both groups were similar, P value was not significant; **SFIS evaluated in 61/101 patients only (30 in N vs 31 in T); values in parenthesis represent the range.

literature [3,4]. Another uroselective alpha-blocker (naftopidil) has emerged that blocks α1D-AR and is believed to have a 17-fold higher selectivity for α1D-AR versus α1A-AR, with claims of fewer side effects according to some Japanese studies [5]. Certain published studies [6-8] have shown that naftopidil may be used as an alternative to tamsulosin for patients of LUTS due to BPH; however, there appears to be no published study in the English literature evaluating the efficacy and safety of naftopidil for BPH in the Indian population. This forms the basis for undertaking the current study. This study was conducted to compare the clinical efficacy and tolerability of naftopidil versus tamsulosin in Indian patients with LUTS due to BPH.

SUBJECTS AND METHODS

After obtaining ethics committee clearance and administering informed consent, the current study was conducted from October 2010 to April 2012 from the outpatient clinic of our institution. One hundred and ten eligible patients were consecutively enrolled as per protocol and randomized into 2 groups. The randomization table was generated on September 21, 2010 from http://www.randomization.com. The randomization/allocation of patient group(s) and patient data per protocol was recorded by a resident (second author) who was blinded to the study medication. The protocol, concept, design, and intellectual content for the current study was drafted, conceived, and contributed by the first author who was also blinded to relevant patient data at the time of its interpretation and statistical analysis.

Entry criteria as per protocol included symptomatic patients of BPH with an IPSS score of >8 or >3 points for frequency, nocturia, and urgency on IPSS score. Other criteria included patients with persistent bothersome LUTS due to BPH, or a prostate volume > 15 ml, or a peak flow rate of < 10 ml for a voided volume of > 150 ml due to BPH without desiring surgery. Patients with hypersensitivity to α–blockers; a history of prostatic or urethral surgery; those with absolute indications for prostate surgery, neurological disorders, neurogenic bladder, and cardiovascular, renal, or hepatic dysfunction; and those who did not consent their inclusion in this study were excluded. Patients receiving tricyclic antidepressants, anticholinergics, sympathomimetics, 5-ARI, or first-generation antihistamines in the previous 3 months were also excluded.

Patients were randomized per a randomization table generated into 2 groups: Group N (naftopidil group; N = 55) and Group T (tamsulosin group; N = 55). Enrolled patients of both groups were similarly subjected to counseling and work-up comprised of history, focused urological examination, baseline renal function tests (blood urea, serum creatinine), serum PSA, urine analysis/culture, an ultrasound assessment of prostate kidney, ureter, and bladder (KUB) post-void residue (PVR), and uroflowmetry. Patients in Group N were prescribed naftopidil (50 mg) while Group T patients were prescribed tamsulosin (0.4 mg) daily at bedtime after meals and were followed at 2, 4, 6, and 12 weeks. At each visit, patients were assessed for compliance to therapy, severity of symptoms (by recording the IPSS), and side effects. All patients underwent uroflowmetry and ultrasound examination

to assess peak flow rate (PFR), average flow rate (AFR), and PVR. Any incidence of AUR and the results of subsequent trials without catheterization (TWOC) were also documented. All interventions were similar in both groups. The basic principle of the clinical intent to treat all symptomatic patients as deemed necessary was firmly adhered to in this study. Tamsulosin and or naftopidil medication(s) were prescribed, and their generic counterparts were not available in our institution at the time of this study. In this study, we endeavored to use only the plain, generic version of both these drugs.

Considering a standard deviation of 7.78 and 6.23 in groups N and T, respectively, for a difference of 4 units in IPSS as significant, 49 cases was required in each group for a power of 80%. Data was recorded in a predesigned proforma and analyzed using appropriate statistical tools such as the unpaired Student *t* test, Tukey test, and the repeated measure ANOVA test. Compliance to the therapy was assessed by recording the number of patients who failed to take the prescribed medication or who withdrew from the study.

RESULTS

Of the 110 patients, 9 patients defaulted/were lost to follow-up. These were excluded from the analysis, leaving 101 evaluable patients. The salient mean parameters recorded are depicted in Table 1. The mean age, BMI, grade of prostate, average flow rate, IPSS total score, storage subscore IPSS, voiding subscore IPSS, maximum flow rate, post-void residue, quality of life (QoL), SFIS, flow time, hesitancy, voided volume, and prostate volume were comparable in both groups and there was no significant difference noted between the 2 groups (Table 1).

A comparison of changes in chosen parameters between groups N and T after 1 and 3 months of therapy are summarized in Table 2. Four and 5 patients belonging to groups N and T, respectively, developed AUR during therapy; however, the frequency of AUR episodes between the 2 groups was not statistically significant ($P = 1.0$). Of these 9 patients, 7 responded to a trial of micturition without a catheter within 2 weeks while 2 patients were planned for surgical intervention.

The side effects observed in groups N and T are depicted in Table 2 (B). Orthostatic hypotension was initially observed in both groups (not significant) but resolved on follow-up. None of the patients reported asthenia, fatigue, rhinitis, somnolence, impotence, or priapism. All patients were fully compliant to the administered therapy. None of these adverse effects necessitated withdrawal from treatment. Figure 1 and Figure 2 depict a graphical presentation of the change in the salient outcome parameters in patients of symptomatic BPH to the administered therapy over a 3-month period.

Figure 1. a) Trends in IPSS, SFIS, and PVR in patients of symptomatic BPH on naftopidil and tamsulosin therapy over a period of 3 months; b) Change in AFR, QoL, and MFR in patients with symptomatic BPH on naftopidil and tamsulosin therapy over period of 3 months.

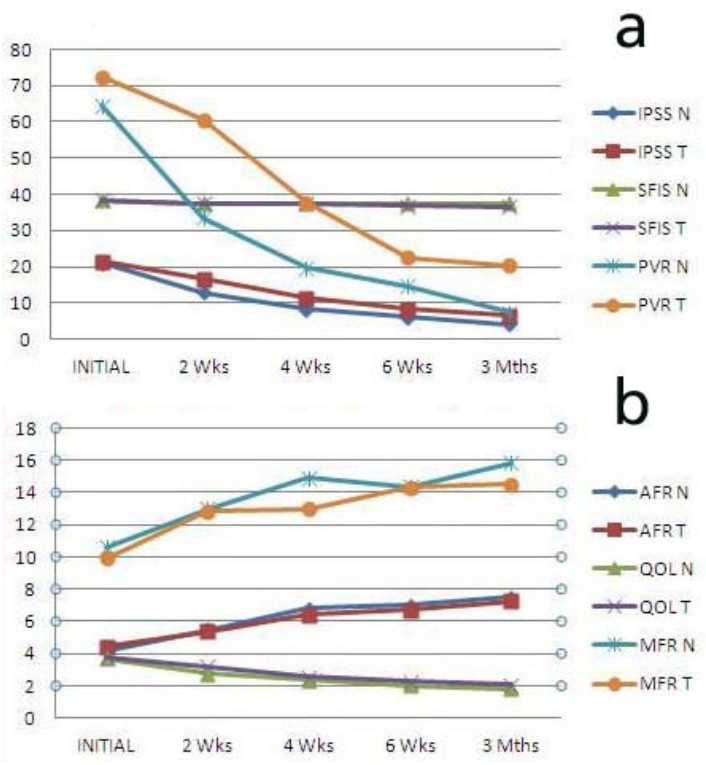
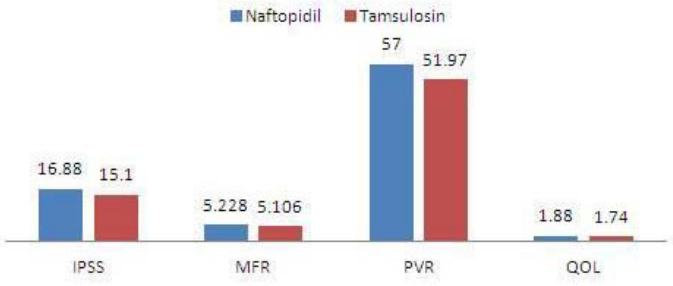


Figure 2. Change in the outcome parameters (from the initial values) in patients with symptomatic BPH on naftopidil and tamsulosin therapy at 2 months.



DISCUSSION

IPSS

Recent comparative Japanese studies [9-11] of naftopidil versus tamsulosin have demonstrated that naftopidil may be superior in efficacy in patients with BPH and predominant storage symptoms, nocturia, low compliance, and overactive bladder. Naftopidil has been well tolerated with some minor side effects that appear to be lower than with tamsulosin therapy [6,7,10]. In our study, both drugs decreased the IPSS score significantly ($P = 0.000$), and the mean change in IPSS was -16.88 and -15.10 for naftopidil and tamsulosin, respectively. In the current study, it appeared that the initial fall in IPSS at 2 weeks of therapy was greater with naftopidil than tamsulosin, which was statistically significant ($P = 0.03$), demonstrating that while both were comparable in decreasing IPSS, as shown in other similar comparative studies [9,10,12-14], the former had an earlier onset of action that may have been due to naftopidil's effect on α1D-receptors in the CNS, bladder, and spinal cord [15,16]. Differences in the α1D-receptor concentration between the Indian and Japanese population may be one of the reasons for greater naftopidil effectiveness in the Indian population compared to the Japanese population. The storage and voiding subscores of IPSS (Table 2) decreased significantly over a period of time, and none were statistically significant after 3 months of therapy. However, we did observe that the storage subscore after 2 weeks of therapy was significantly better with naftopidil ($P = 0.011$). Nevertheless, this data needs to be seen in light of the fact that the power factor for this study was perhaps inadequately powered to achieve validated results. Various studies have also shown that naftopidil may be superior in efficacy in patients with predominant storage symptoms, nocturia, low compliance, and overactive bladder [9-11].

Flow Rates

As depicted in Table 2a, both the drugs were effective in improving the MFR and AFR significantly over a period of time. While an observed change of 5.23 and 5.11 in MFR was noted with naftopidil and tamsulosin, respectively, the same was not statistically significant at any specific interval ($P = 0.349$ for MFR and $P = 0.783$ for AFR). Similar results were seen in the Japanese comparative studies [9,10,12,13].

PVR

There was an appreciable fall in the mean PVR in both groups (see Table 2a), which was comparable to other Japanese studies [9,10,17], but in our study this appeared to be slightly higher with naftopidil after 3 months of therapy, though this difference was statistically significant only at a 2-week interval ($P = 0.041$).

Table 2. a) The change in the outcome parameters of patients in both groups evaluated over 3 months and b) The adverse events recorded in the same patients.

2(a)

Parameter	Drug	Initial	2 Wks	4 Wks	6 Wks	3 Mths
IPSS†	N*	21	12.82	8.38	5.98	4.18
	T*	21.53	16.61	11.41	8.18	6.43
MFR	N*	10.62	12.99	14.91	14.35	15.85
	T*	9.91	12.81	12.99	14.29	14.518
PVR†	N*	64.4	33.42	19.66	14.6	7.4
	T*	72.34	60.59	37.6	22.61	20.37
AFR	N*	4.19	5.49	6.78	7.01	7.48
	T*	4.434	5.36	6.41	6.71	7.26
V-IPSS	N*	10.72	6.56	4.34	3.2	2.26
	T*	10.75	8.18	5.75	3.98	3.06
S-IPSS†	N*	10.46	6.32	4.16	2.78	1.92
	T*	10.49	8.47	6	4.2	3.39
QOL†	N*	3.68	2.74	2.36	2	1.8
	T*	3.78	3.18	2.57	2.27	2.04
SFIS	N	38.27	37.43	37.47	37.4	37.4
	T*	38.42	37.42	37.55	36.9	36.7

N: naftopidil; T: tamsulosin; IPSS: International Prostate Symptom Score out of 35; MFR: maximum flow rate; PVR: post-void residue; AFR: average flow rate; V-IPSS: voiding subscore of IPSS; S-IPSS: storage subscore of IPSS; QoL: quality of life; SFIS: Sexual Function Inventory Score out of 42; *: $P < 0.05$ (significant difference) within the group when initial parameters compared with 3-month parameters; †: $P < 0.05$ (significant difference) between N and T groups at 2-week interval. No parameters were significantly different at 3-month interval.

2(b)

Events	Group N	Group T	P value*
Orthostatic hypotension	8/50 (16%)	12/51 (24%)	0.342
Headache	1/50 (02%)	3/51 (06%)	0.617
Retrograde ejaculation	5/50 (10%)	10/51 (20%)	0.175

*Not Significant

Qol

Regaring Qol, we observed a significant improvement in Qol with both naftopidil and tamsulosin with no overall difference (significantly better at 2 weeks with nafopidil, $P = 0.017$). Various studies [9,10,12-14] show similar results, as found in both our study and another [17] that shows tamsulosin is significantly better than naftopidil in improving Qol.

Side Effects and Withdrawals

As depicted in Table 2b, though the tamsulosin group had more side effects compared to the naftopidil group, there was no statistically significant difference between Group N and Group T in respect to those side effects. None of the patients reported dizziness, asthenia, fatigue, rhinitis, or somnolence during the observed period of this study, and all patients were fully compliant to the administered therapy. According to a Cochrane Database, systemic review of adverse effects due to naftopidil occurred among 34 (15%) participants [18]. The most common adverse effects associated with naftopidil were dizziness and hypotension [18], while 1 study reported numbness of the tongue in some patients taking naftopidil [12]. The most commonly reported adverse effects in a Cochrane review due to tamsulosin were hypotension, dizziness, and headache [18]; furthermore, there were no significant differences in the incidence of adverse events in the control versus treated group [18], which was confirmed by pooled data from 3 other similar trials [12-14]. According to another well-cited study reported by Narayan et al [19], who reviewed the "Long-term efficacy and safety of Tamsulosin for BPH," reported that the most commonly met "treatment-emergent adverse events" were infection, accidental injury, rhinitis, pain, and pharyngitis; and other adverse effects included abnormal ejaculation (8.3%), syncope (1.7%), and postural hypotension (1.3%) [19].

SFIS

In a statistical evaluation of the SFIS, repeatedly measured ANOVA tests and Tukey tests revealed a significant change in SFIS in the tamsulosin group compared to the pretreatment values recorded over our study period ($P = 0.000$; $P < 0.001$). A Tukey test showed the critical difference of 0.930, which was observed in the tamsulosin group starting 2 weeks after starting the drug, thus showing that tamsulosin significantly decreases SFIS within 2 weeks of starting therapy. The naftopidil group had a total difference of -0.870 when comparing the initial value of SFIS to the 1- week value, which was not statistically significant. Another study [20] showed that 0.2 or 0.4 mg of tamsulosin for 3 days resulted in a reduced seminal volume, while 50 or 100 mg of naftopidil for 3 days did not. In another Japanese randomized control study by Masumori et al [17] that investigated the incidence of ejaculatory disorders caused by 50 mg of naftopidil (N = 48) and 0.2 mg of tamsulosin (N = 47)

Table 3. The comparison of the present study with other similar published trials of naftopidl versus tamsulosin for LUTS due to BPH.

Author	Group	Change from Initial				Salient Features of the Study
		IPSS	MFR	PVR	QOL	
Momose et al. (2007) [14]	N	6.7	NR	NR	0.6	RCT; SS-45 (N-20,T-25); 4-wk Rx; No parameter significantly different N vs T
	T	7.3	NR	NR	0.7	
Nishino et al. (2006) [10]	N	11.5	3.8	44.2	2.3	RCT; SS 34 (N-17, T-17);4 wks Rx; no parameter significantly different N vs T
	T	11.1	3.1	43.1	2.2	
Ikemoto et al. (2003) [13]	N to T	8.5	2.1	NR	NR	Crossover RCT; Sample size 96 (N to T-43, T to N-53); 16 weeks (8 x 2, no wash-out period); no parameters were significantly different N vs T
	T to N	9.2	2.1	NR	NR	
Ukimura et al. (2008) [9]	N	9.4	1.3	15.9	2.2	RCT; SS- 59 (N-31,T-28); 6-8-week Rx; N showed a significant early response to improved storage symptoms at 2 wks; no parameters were significantly different N vs T
	T	9.7	2.8	3.5	2	
Gotoh et al. (2005) [12]	N	5.9	2.1	13.6	1.3	RCT; SS-185 (N-69, T-75); 12-week Rx; no parameters were significantly different in N vs T
	T	8.4	2.1	9.6	1.4	
Current Trial	N	16.88	5.228	57	1.88	RCT; SS-101 (N-51,T-50); 12-week Rx; no parameters were significantly different in N vs T at 3 months. At 2 wks, storage symptoms were significantly better in N
	T	15.1	5.106	51.97	1.74	

SS: sample size; RCT: randomized clinical trial; N: naftopidil; T: tamsulosin hydrochloride.

among sexually active men during the 12 weeks, the proportion of patients who reported an abnormal feeling at ejaculation was higher in the tamsulosin group (16.7%) versus the naftopidil group (7.4%); however, they reported that this difference was not significant (P = 0.402). Men who reported reduced ejaculatory volume after treatment were significantly higher in the tamsulosin group (96.0%) compared to the naftopidil group (73.1%, P = 0.0496), although the improvement of erectile function by α1-blockers has reported [21,22]. No significant change in the International Index of Erectile Function (IIEF)-5 score caused by either drug was observed in this small study. On the other hand, Yokoyama et al [23] showed that the mean IIEF-5 score improved in a naftopidil group (7.0 at baseline to 7.6 at 3 months, P = 0.013) but not in the silodosin group (6.2 at baseline to 5.0 at 3 months, P = 0.682) or tamsulosin group (6.6 at baseline to 5.2 at 3 months, P = 0.342). Thus it appears that naftopidil may be more suitable for relatively younger and sexually active patients. According to a major randomised controlled study [24] with naftopidil, the authors observed that it improved storage and voiding symptoms. In another similar study [25], the authors found naftopidil also benefited patients of BPH with nocturia, improving their quality of sleep though this was not specifically evaluated in the current study.

There were certain limitations in the current study. Due to logistical constraints, the number of patients required for a power of 80 was not initially calculated for this study but was based on similar studies done in the past at our institution. A sample size of 50 in each group was considered while an additional 10 patients were recruited to compensate for 9 patients lost to follow-up. While this study was based on a small sample size wherein the possibility of type II statistical error(s) remains, we admit that a larger study is definitely required to establish the precise role of naftopidil in BPH. There was a no-dose escalation step incorporated in this study protocol for patients not benefitting from 0.4 mg of tamsulosin or 50 mg of naftopidil. According to a review by Masumori et al [26], it is probable that the optimal dosage of naftopidil may vary among individuals based on different α1A/α1D-AR subtype ratios [27]. Furthermore, this was a non-placebo, open-label study, and due to the logistical constraints of a public institution, all patients/physicians were not fully blinded to the administered therapy and the double blinding/allocation concealment in this study was not ideal. Finally, SFIS was evaluable in only 61/101 (60%) patients that were sexually active prior to therapy; therefore, the precise impact of the medication on sexual function could not be evaluated in all our patients.

While it is possible that many of the side effects may partly depend on the applied galenic formulation of the tamsulosin pill, and since we had used only the plain generic version of the tamsulosin pill in this study, it was not feasible for us to evaluate and comment on the difference, if any, in the observed side effects encountered with different galenic formulations of the tamsulosin pill.

CONCLUSION

Naftopidil and tamsulosin were both equally effective in relieving LUTS due to BPH, and patient groups appeared to be equally compliant with either of these drugs. Naftopidil appeared to improve IPSS, the storage subscore of IPSS, PVR, and QoL earlier than with tamsulosin. A higher incidence of postural hypotension and headache were observed in the tamsulosin group compared to the naftopidil group, but this perceived difference was not statistically significant. However, this data should be seen in light of the before-mentioned fact, that in this study the patient numbers needed to be adequately powered to achieve more consistent observations and validated results. Sexual function inventory score was significantly lower in the tamsulosin group while naftopidil group did not show a significant reduction in the SFIS score. While the prospect of apparently lower sexual dysfunction observed with naftopidil appears to be attractive, further comparative trials for evaluation of the same appear to be obligatory, and as mentioned before, this data again needs to be seen in light of the fact that sexual side effect(s) that appeared to be reduced in this study could not be decisively addressed due to several patients not providing data.

Patients of both naftopidil and tamsulosin groups were equally compliant, and there was no treatment withdrawal from our study on account of the side effects of the drugs being administered. Finally, prospective, large-scale, randomized clinical studies of naftopidil with tamsulosin for BPH as a whole with ample statistical power to draw authentic conclusions are needed.

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Bladder Tattooing in the Urological Armamentarium: An Experimental Study

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ABSTRACT

Objective: To evaluate the feasibility of tattooing of the bladder urothelium using different stains.

Methods: The study was performed on 20 healthy male and female dogs, which were divided into 4 groups according to the injected material. The first group (4 animals) was injected with hydrated iron (II) sulphate. The second group (4 animals) was injected with methylene blue added to hydrated iron (II) sulphate. The third group (8 animals) was injected with India ink, and the fourth group (4 animals) was injected with methylene blue. The procedure was performed under general anesthesia. The doses as well as the injection technique were standardized. Re-exploration with sacrifice of the dogs was performed after 40 days. The bladder was examined grossly for dye retention. Bladder, spleen, and liver specimens were sent for histopathological examination.

Results: Tattooing was performed successfully without any immediate reaction. Postoperative complications occurred in a single case in the form of vesicocutaneous fistula. At re-exploration, the dye was retained in both the first and second groups, and there was no difference in color intensity. Methylene blue increased the local inflammatory changes. The third and the fourth groups failed to retain the dye. Local reaction at the site of injection, as well as in the bladder, was present in all cases, being most severe in the third group. In cases of the first, second, and third groups the inflammatory reaction involved the liver with hepatic degeneration up to cirrhotic changes. Histopathological examination showed the presence of ferrous particles in the submucosa as well in the detrusor muscles. The presence of ferrous particles was also detected in the spleen.

Conclusion: In our study, tattooing the bladder urothelium was successful. Despite the side effects of the used materials, tattooing remains feasible; however, the type of material, dose titration, and long follow-up are needed to detect the most suitable material.

INTRODUCTION

DDermal pigmentation is a mark made by inserting pigment into the skin for decorative or other reasons. It is known in Egypt as "Al Washim" and used since ancient times for decoration of the face and arms in the villages of upper Egypt and the delta. Dermal pigmentation is also called tattooing. It is commonly believed that the original root word "tattoo" comes from the Tongan or Tahitian words "mark" or "strike twice" [1].

The body responds to pigment incursions in predictable and specific ways with an initial sloughing of the overlying epidermis, variable dermal inflammation, and gradual assimilation of the pigment into the macrophages. Eventually much of the pigment is carried to the regional draining lymph nodes, with a residue staining within macrophages localized to dermal perivascular regions [2]. A wide range of dyes and pigments can be used in dermal pigmentation, from inorganic and organic materials (e.g., titanium dioxide and iron oxides to carbon black, azo dyes, and acridine; quinoline, phthalocyanine, and naphthol derivatives; and dyes made from ash and other mixtures) [1].

KEYWORDS: Bladder tattooing, urothelial marking, Indian ink, ferrous sulphate

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Figure 1. Mucosal destruction with the presence of hydrated ferrous sulfate in the macrophages within the submucosal layer (H&E x 10).

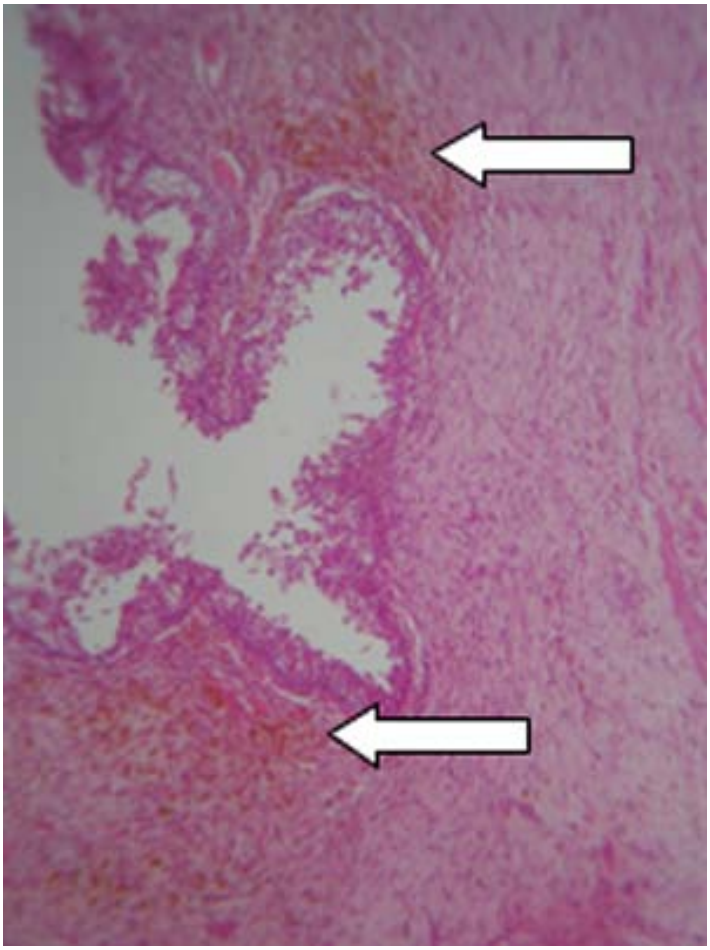
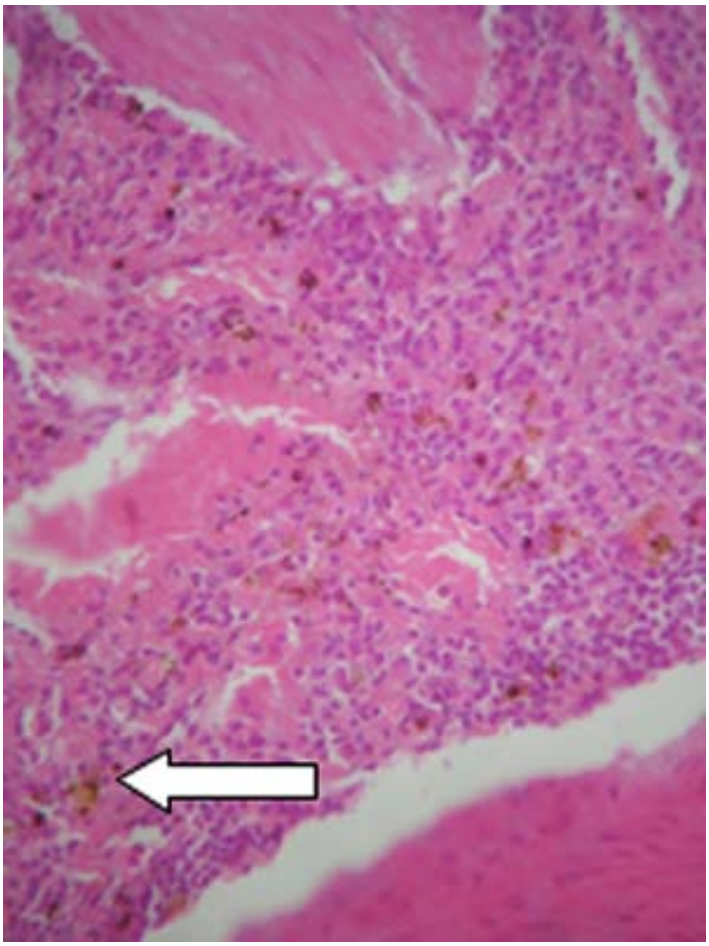


Figure 2. Hydrated ferrous sulfate in macrophages (H&E x 40).



India ink has been previously used in tattooing colonic tumors aiding in future identification of resection sites during colonoscopy [3-5]. Also, it is used in the esophagus of patients with Barrett's esophagus for marking the proximal squamocolumner junction [6]. Various India ink preparations were used whether unsterilized, autoclaved, or gas sterilized, as well as from undiluted to 1:100 (with 0.9% saline) [5].

Methylene blue is a thiazine dye. It occurs as dark green crystals or as a crystalline powder, having a bronze-like luster and a slight odor. Methylene blue is soluble in water and sparingly soluble in alcohol, and forms deep blue solutions. Methylene blue has a pH of 3 to 4.5 [7]. As a marking agent it has been used in the diagnosis of sentinel nodes [8-10], the marking of tumors during thoracoscopy via computed tomography (CT) guided injection [11], as well as laparoscopic colonic tumor identification [12,13].

Hydrated iron (II) sulfate can be found in various states of hydration and many of these forms exist in nature [14]: $FeSO_4 \cdot H_2O$, $FeSO_4 \cdot 4H_2O$, $FeSO_4 \cdot 5H_2O$, and $FeSO_4 \cdot 7H_2O$. Hydrated iron (II) sulfate is used in many fields [14].

METHODS

This study was performed in the animal laboratory in the Theodor Bilharz Research Institute (TBRI). Approval of the ethical committee was obtained for this research project.

This study was performed on 20 healthy dogs; 8 females and 12 males, respectively. Under general anesthesia, a midline transperitoneal incision was performed. The bladder was identified and held between 2 stay sutures. A stay suture was taken in the mucosa by means of 4-0 vicryl sutures, and the

tattoo material was injected submucosally via an insulin syringe injecting 0.2 ml of the tattoo material. The suture was tied during extraction of the syringe to prevent leakage of the injected material.

The dogs were divided into 4 groups based on the marking material used. The first group (4 animals) was injected with hydrated iron (II) sulfate (Chemie Lab), and FeSO4.7H2O dissolved as 43.5 grams/100 ml of distilled water. The second group (4 animals) was injected with hydrated iron (II) sulfate with the addition of diluted methylene blue, 1:1 (volume/volume). The third group (8 animals) was injected with undiluted India ink. The fourth group (4 animals) was injected with Methylene blue.

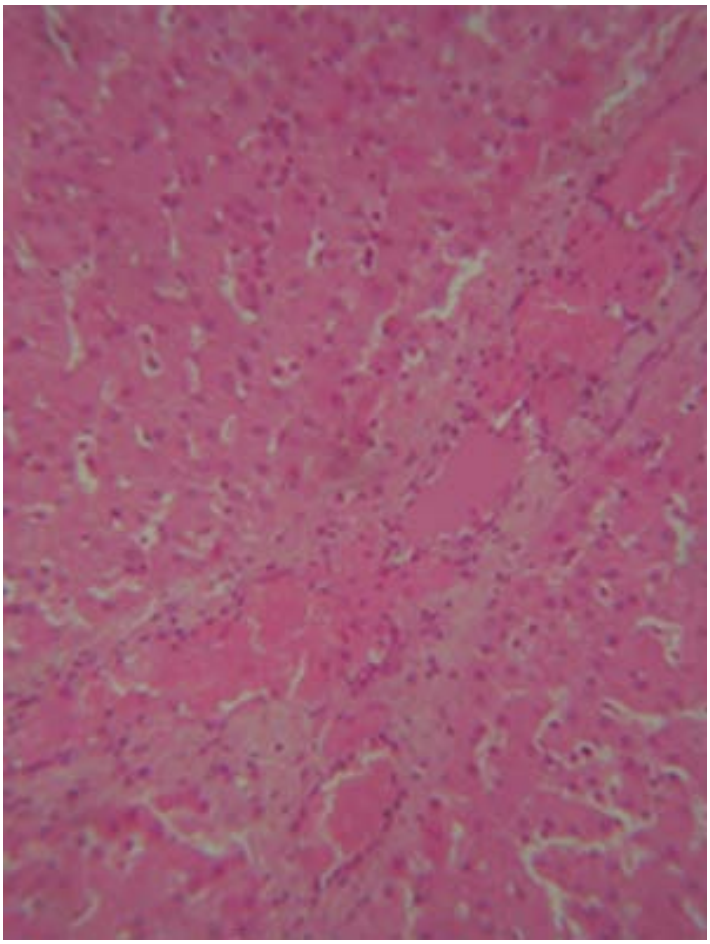
The bladder was closed by 4-0 vicryl, and the abdominal incision was closed en masse by using continuous 0 prolene sutures. Re-exploration and sacrifice of the dogs was performed after 40 days. The bladder was examined grossly for dye retention. Cystectomy, liver, and spleen specimens were sent for histopathology.

RESULTS

Tattooing was performed in 20 dogs. Four different materials were used in 4 groups. Tattooing was performed successfully in all cases without any immediate reaction to any of the injected materials. There was variable tissue staining caused by the injected material. There was minimal staining in the first group (pale yellow) and deep staining in all other groups (blue to black). Postoperative complications occurred in a single animal in the third group in the form of vesicocutaneous fistulae. Retention of the dye was observed in the first and second groups with no difference in color intensity. The third and fourth groups failed to retain the dye. Local site reaction was present in all 4 groups, being more severe in the third group. The additive effect of methylene blue to hydrated iron (II) sulfate increased the local reaction complications with no benefit in color retention.

Diffuse inflammatory reaction was present in all animals. Inflammatory reactions were limited to the bladder in the methylene blue group in the form of gross mucosal ulceration. Microscopically, there was marked urothelial sloughing with fibrosis and atrophy of the underlying muscle layer. In the groups with India ink and hydrated iron (II) sulfate there was additional involvement of the liver and spleen. Hepatic changes ranged from hepatic periportal degeneration with homogenizing degeneration around the blood vessels to bile duct hyperplasia with periportal fibrosis or cirrhotic changes. Hepatic affection was found in 16 animals (80%). Twelve animals (60%) showed microscopic splenic congestion with homogeneity around the large blood vessels. Pathological examination showed the yellow particles of hydrated iron (II) sulfate located both in the submucosa and the detrusor muscles.

Figure 3. The liver showing homogenizing degeneration around the blood vessels (H&E x 40)



DISCUSSION

Our objective in the current study was to investigate the possible use of urothelial tissue marking, and we examined 3 known substances that were used before in marking the colonic mucosa when doing polypectomy or tumor resection. We believe that it will be valuable in urologic practice for the follow-up of superficial bladder tumors after complete transurethral resection. Also, it may help in an easier identification of the ureteric orifice after sometimes-troublesome ureteroneocystostomy. Identification failure might lead to the abortion of some interventions or changing the treatment modality.

In the literature, tattooing of the colon was successfully performed to mark sites of colonic resection helping identify previously resected areas during follow-up as well as during open and laparoscopic surgery. Many dyes have been used such

Table 1. The results of the 4 groups.

Animal	Group	Color after injection	Complications	Retention of the dye	Retained color	Inflammatory reaction		
						bladder	liver	Spleen
1	1	pale yellow	negative	retained	pale yellow	present	present	present
2	1	pale yellow	negative	retained	pale yellow	present	present	present
3	1	pale yellow	negative	retained	pale yellow	present	present	negative
4	1	pale yellow	negative	retained	pale yellow	present	present	present
5	2	deep blue	negative	retained	pale yellow	present	present	present
6	2	deep blue	negative	retained	pale yellow	present	present	present
7	2	deep blue	negative	retained	pale yellow	present	present	present
8	2	deep blue	negative	retained	pale yellow	present	present	present
9	3	black	negative	not retained	negative	present	present	negative
10	3	black	negative	not retained	negative	present	present	present
11	3	black	negative	not retained	negative	present	present	negative
12	3	black	vesicocutaneous fistula	not retained	negative	present	present	present
13	3	black	negative	not retained	negative	present	present	present
14	3	black	negative	not retained	negative	present	present	present
15	3	black	negative	not retained	negative	present	present	negative
16	3	black	negative	not retained	negative	present	present	present
17	4	deep blue	negative	not retained	negative	present	negative	negative
18	4	deep blue	negative	not retained	negative	present	negative	negative
19	4	deep blue	negative	not retained	negative	present	negative	negative
20	4	deep blue	negative	not retained	negative	present	negative	negative

as India ink, methylene blue, and indocyanine green. India ink alone achieved persistence of the dye whereas both methylene blue and indocyanine green failed to persist [15,16].

In the current study, 3 different materials were used, namely hydrated iron (II) sulfate, undiluted India ink, and methylene blue. The injection technique was standardized. We want to emphasize the importance of suturing the injection site upon

withdrawal of the needle. This successfully controlled the dye leakage. Park et al., who studied the safety and efficacy of colonoscopic tattooing, reported a similar recommendation [17].

Upon injection, the pale yellow color of hydrated iron (II) sulfate was observed in the first group. A combination of methylene blue to hydrated iron (II) sulfate was used to benefit from its deep blue color as a marking agent in the second group. India ink demonstrated a black color in the third group, and there was a deep blue color of methylene blue in the fourth group. No complications occurred during injection or in the early postoperative period.

On re-exploration, the first and second group retained the pale yellow color of hydrated iron (II) sulfate with no difference in color intensity. The third and fourth group failed to retain the dye. The results of failure to retain India ink in the bladder submucosa are contradictory to other studies, which proved dye retention in colonic mucosa [3,18-21]. However, in the present study, dye retention failure can be explained by using undiluted India ink, which was responsible for the severe inflammatory reaction and ulceration.

Dye retention failure in the fourth group matches other studies [12,16] that reported methylene blue dye retention failure 7 days after colonic injection. Local reactions at the injected sites were observed in all 4 groups, with the most severe occurring in the third group, causing severe ulceration and vesicocutaneous fistulae in 1 case. These results are in line with other studies reporting colonic mucosal reactions in undiluted India ink as well as colonic perforation resulting from India ink injection [5,18,22-24].

Local inflammatory reactions to India ink and methylene blue were also reported [12]. Reactions to India ink included necrosis, edema, and neutrophilic infiltration in the submucosa and muscularis propria. Vessels were inflamed but without fibrinoid necrosis. Early reactions to methylene blue included ischemic ulceration, necrosis, and eosinophilic infiltration in the submucosa as well as fibrinoid necrosis of vessel walls. Later reactions due to methylene blue-induced injury showed obliterative intimal fibrosis. Such changes were absent in the colons injected with India ink.

In the present study, hydrated iron (II) sulfate in the first and second groups showed retention of the dye in both groups without changing color intensity; however, there was more severe tissue reaction at the injection site in the second group. This can be explained by the additive effect caused by a combination of both substances.

The pale yellow color of hydrated iron (II) sulfate particles was demonstrated histopathologically in both the submucosa and the detrusor muscles. The bladder mucosa showed severe inflammatory reaction in all 4 groups, both grossly and by histopathological examination. The reaction to the different materials was systemic and not localized to the bladder mucosa. Draining pelvic lymph nodes showed inflammatory reactions as well. The liver showed hepatic cell degeneration and portal tract fibrosis, which extended between the hepatic cells in 2 animals. The spleen showed the presence of deep orange/yellow to green substances in the macrophages in the first and second groups. This dye substance migration was also reported with Fu et al. [19] after the use of India ink during preoperative tattooing of the colon.

We noticed that there was some contradiction in our results and those done on the colonic mucosa. While the question may be raised about the histologic difference between the colonic mucosa and the urothelium, we believe that our pilot study is not enough to conclude study. Instead, we are proceeding toward a bigger study where we are planning to use different dilutions of the coloring substances and to examine for the long-term effect of using such a procedure.

CONCLUSION

In our study, the feasibility of tattooing the bladder urothelium was successful. Despite the side effects of the used materials, tattooing remains feasible; however, the type of material, dose titration, and long follow-up are needed to determine the most suitable material.

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Urodynamic Findings in Men Presenting with Incontinence After Open Versus Robotic Radical Prostatectomy

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ABSTRACT

Introduction: Urodynamic findings in patients with post-prostatectomy incontinence (PPI) following either an open radial retropubic prostatectomy or a robotic-assisted laparoscopic prostatectomy are not well described.
Methods: After IRB approval, we performed a retrospective review of urodynamic findings in patients presenting to our institution with PPI following either an open or robotic prostatectomy from 1985 through 2009.
Results: One hundred and twenty-six patients were identified for analysis (74 robotic, 52 open). Intrinsic sphincter deficiency was the cause of PPI in the majority of patients in both groups. Detrusor pressure at peak flow was significantly higher, and peak flow rate was significantly lower in patients who had undergone an open procedure. Anastomotic stenosis (AS) was also higher following an open procedure. Detrusor over- and underactivity were similar between the groups.
Conclusions: Following an open compared to a robotic prostatectomy, patients experienced elevated voiding pressures and decreased peak flows, presumably secondary to the increased incidence of AS observed in those patients.

INTRODUCTION

Radical prostatectomy (RP) continues to represent a gold standard in the treatment of localized prostate cancer. While providing excellent cancer control for patients, it has been consistently associated with urinary incontinence (UI) and erectile dysfunction [1-3]. Urodynamic findings in patients with UI following radical prostatectomy have been reported by several authors in an effort to characterize the nature of their incontinence. It is now widely accepted that intrinsic sphincter deficiency (ISD) is at least a contributing factor in the majority of men with post-prostatectomy incontinence (PPI) [4-10]. Chae and Mayo found sphincteric deficiency in 96% of men with PPI in their cohort, and it was the sole cause in over half [5].

Several other urodynamic findings following RP have been reported, including a decrease in bladder compliance (BC), a decrease in maximum cystometric capacity (MCC), and an increase in detrusor overactivity (DO) [6,8]. While improvements in these variables are seen over time in some patients, they often do not return to baseline on repeat urodynamic studies performed 3 years following RP [6,8].

More recently, detrusor underactivity (DU), or hypocontractility, has been reported on urodynamics in a number of patients following radical prostatectomy [11,6,9]. Damage to nerves innervating the bladder during prostatectomy has been suggested as a factor contributing to the decrease in contractility. Others have theorized that some of these men had dysfunctional bladders prior to surgery from years of benign prostatic hyperplasia and bladder outlet obstruction. These patients may have trained themselves over time to compensate with abdominal straining and therefore developed detrusor dysfunction and hypocontractility prior to RP.

While many have examined urodynamics in incontinent patients following RP, the difference in post-operative urodynamic

KEYWORDS: Post-prostatectomy incontinence, stress incontinence, urodynamics, bladder neck contracture

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parameters in patients who underwent radical retropubic (RRP) versus minimally invasive prostatectomy is not nearly as well reported. Here we report the results of urodynamic studies from patients who presented to us with PPI and compare findings from patients who underwent RRP to those who underwent a minimally invasive technique.

MATERIALS AND METHODS

Patients presenting to our institution with a chief complaint of persistent PPI undergo a standard evaluation, which includes a history and physical examination, urinalysis, office cystoscopy, and comprehensive urodynamic evaluation. Urodynamic assessment is performed in accordance with International Continence Society Standards [12]. Water cystometry is performed at room temperature with a fill rate of 10% of bladder capacity per minute based on a voiding diary. A 7 Fr dual lumen catheter is used for filling and intravesical pressure measurements, and a rectal catheter estimates abdominal pressure. At a fill of 200 ml, patients are asked to Valsalva and then cough to measure Valsalva leak-point pressure (VLPP). This is repeated at MCC and at several other time points during the fill, if necessary, to demonstrate incontinence. At capacity patients are asked to void to completion, during which the peak flow (Qmax) and detrusor pressure at peak flow (PdetQmax) are measured. Post-void residual (PVR) is then measured by catheter drainage after completion of voiding. The entire study is repeated at least once for each patient to ensure consistent results. Detrusor overactivity is defined as any uninhibited/inappropriate detrusor contraction during filling. Detrusor underactivity is defined as those patients with a Qmax < 15 ml/sec and a PdetQmax < 20 cm H_2O as previously described [11].

After approval from the local institutional review board, we identified patients with PPI presenting for evaluation between September 2006 and May 2011. Patients without complete urodynamic data and those with missing details regarding the surgical technique used for their prostatectomy were excluded. Data was obtained from a review of the office and inpatient medical records, and it included patient demographics, basic medical history, prostate cancer history, urodynamic parameters, and incontinence severity. The first urodynamic test obtained upon presentation was used for analysis. All urodynamic tests were performed at our institution with a single technician and a single physician interpreting each. All patients included in this analysis had either an open radical retropubic prostatectomy or a DaVinci robotic-assisted prostatectomy (DVP). Patients found to have an urethrovesical anastomotic stricture (AS) had their urodynamics obtained following treatment of the stricture.
Statistical analysis was performed using SPSS v 20 software. Continuous variables were compared using the Mann-Whitney U test, and categorical variables were compared with the chi-square test. Results were considered statistically significant if they had a P value ≤ 0.05 with a 2-tailed test.

RESULTS

One hundred and twenty-six patients presenting with PPI to our institution with available prostate cancer history and urodynamic results were included in the analysis. Of the 126 patients, 74 underwent a DVP from April 2001 through September 2009. The remaining 52 patients had a RRP performed between January 1985 and August 2008. As expected, given our transition from open to robotic prostatectomies, significantly more open procedures were performed early and more DVPs performed later in the series (P = 0.0005, Table 1). The average age at prostatectomy was 62.1 compared to 61.6 years in the robotic versus the open cohort (P = 0.3). The 2 groups were also similar in terms of race, body mass index, incidence of diabetes mellitus, tobacco use history, and history of prior pelvic radiation (Table 1). Significantly more patients in the open group had a history of an AS that was treated prior to undergoing urodynamic evaluation (6.8% versus 36.5%, P = 0.005), and pad use at presentation was higher in the open cohort (3.4 versus 4.6 pads per day, P = 0.006).

Urodynamics were obtained on each patient when they presented with a complaint of persistent PPI and were considering treatment options. On average, the study was performed 2.7 years following prostatectomy in the robotic cohort and 8.8 years following prostatectomy in the open group (P = 0.005). Urodynamic comparisons between the 2 groups are outlined in Table 2. Incontinence secondary, at least in part, to ISD (stress incontinence with VLPP < 100 cm H_2O) was demonstrated in 93.5% versus 93.7% (P = 0.62), and a VLPP of < 60 cm H2O was found in 59.4% and 65.2% (P = 0.34) of patients open and robotic groups, respectively. Patients with a history of an open procedure on average had higher detrusor pressure at peak flow (22 versus 27.8 cm H2O, P = 0.05) and a lower peak flow rate (18.7 versus 14.9 ml/sec, P = 0.016). When stratified further, a history of a previously treated AS was associated with higher detrusor pressures and lower peak flows in both the open and robotic cohorts (Table 3), suggesting AS as a contributing factor in those urodynamic findings. There were no significant differences between any of the other urodynamic variables tested, though there was suggestion of a trend towards higher rates of DO in the open group. Rates of DU were not statistically different between the open and robotic cohorts (18.9% versus 19.2%, P = 0.57).

DISCUSSION

Radical prostatectomy has been shown to have characteristic changes on urodynamics post-operatively. These urodynamic findings include an increase in the incidence of ISD, a decrease in cystometric capacity and bladder compliance, and an increase in both detrusor overactivity and detrusor under activity [5-11]. Some of these variables have been shown to improve with time, but even 3 years following prostatectomy, they may not

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Table 1. Patient demographics.

	DVP	RRP	*P* value
Age at prostatectomy (years ± SD)	62.1 ± 7.0	61.6 ± 6.7	$P = 0.3$
Year of prostatectomy			
Before 1990	0	2 (4%)	
1990-1995	0	11 (22%)	
1996-2000	0	10 (20%)	$\chi^2 = 49.53$, $P = 0.0005$
2001-2005	28 (38.4%)	20 (40%)	
2006-2009	45 (61.6%)	7 (14%)	
Race			
White	55 (74.3%)	37 (71.2%)	
Black	17 (23.0%)	10 (19.2%)	$\chi^2 = 2.87$, $P = 0.24$
Other	2 (2.7%)	5 (9.6%)	
Body mass index, kg/m^2 (mean ± SD)	28.5 ± 4.1	27.7 ± 3.5	$P = 0.29$
Diabetes mellitus	16 (21.9%)	12 (23.1%)	$\chi^2 = 0.023$, $P = 0.52$
Current tobacco use (pack/day ± SD)	0.04 ± 0.2	0.1 ± 0.34	$P = 0.37$
Former smoker	33 (45.2%)	29 (55.8%)	$\chi^2 = 1.36$, $P = 0.16$
History of pelvic radiation	11 (14.9%)	13 (25%)	$\chi^2 = 2.03$, $P = 0.12$
History of anastomotic stricture	5 (6.8%)	19 (36.5%)	$\chi^2 = 17.57$, $P = 0.0005$
Pad use at presentation, pads/day (mean ± SD)	3.4 ± 2.0	4.6 ± 2.4	$P = 0.006$

Mann-Whitney U: 2-tailed significance
Chi square: χ^2, 2-tailed significance

Table 2. Urodynamics.

	DVP	RRP	*P* value
Detrusor overactivity	19 (25.7%)	21 (40.4%)	$\chi^2 = 3.05$, $P = 0.06$
Detrusor underactivity	14 (18.9%)	10 (19.2%)	$\chi^2 = 0.002$, $P = 0.57$
VLPP, cmH_2O (mean ± SD)	55.9 ± 29.7	52.4 ± 32.8	$P = 0.35$
VLPP < 60 cmH_2O	38 (59.4%)	30 (65.2%)	$\chi^2 = 0.39$, $P = 0.34$
VLPP > 100 cmH_2O	4 (6.3%)	3 (6.5%)	$\chi^2 = 0.003$, $P = 0.62$
PdetQmax, cmH_2O (mean ± SD)	22.0 ± 17.3	27.8 ± 19.4	$P = 0.05$
Peak flow, ml/sec (mean ± SD)	18.7 ± 11.4	14.9 ± 11.2	$P = 0.016$
Post-void residual, ml (mean ± SD)	10.2 ± 30.7	13.6 ± 35.8	$P = 0.21$
Post-void residual > 50 ml	5 (6.8%)	3 (5.8%)	$\chi^2 = 0.05$, $P = 0.57$
Normal compliance	69 (93.2%)	51 (98.1%)	$\chi^2 = 1.57$, $P = 0.21$

Mann-Whitney U: 2-tailed significance
Chi square: χ^2, 2-tailed significance

have yet returned to baseline [6,8].

In this study we compared post-operative urodynamics in men presenting with PPI who had undergone an open or robotic prostatectomy. Our goal was to clarify whether a different surgical approach had variable effects on post-operative voiding patterns seen on urodynamics. Our data have echoed what many others have shown—that ISD contributes to PPI in the majority of patients.

In those patients who had undergone RRP, we demonstrated significantly higher voiding pressures and lower peak flow rates compared to their robotic counterparts. This phenomenon is at least partly explained by an increased incidence of treated anastomotic strictures in the RRP group. When these patients were excluded from the analysis, both of these urodynamic differences lost statistical significance. Additionally, patients with a history of AS all had significantly higher detrusor voiding pressures and lower peak flow rates compared to those without an AS history, regardless of the type of prostatectomy performed. Despite treatment, AS may continue to cause some increased outflow resistance as illustrated in these urodynamic findings. Given the extended follow-up in the open compared to the robotic cohort, it is difficult to make many inferences regarding the relative rates of AS in the 2 groups. Strictures may have developed in a higher proportion of patients undergoing a DVP if followed longer. That being said, others have also reported a higher rate of AS in men undergoing open compared to minimally invasive prostatectomy; therefore, we can speculate that this finding would remain significant regardless of extended follow-up.

Another objective of this study was to evaluate the relative rates of DU in these 2 groups, as previous studies have shown a higher incidence of DU in patients who had undergone a minimally invasive procedure [11]. Contrary to the work by Chung et al., our data did not show increased rates of DU in patients following DVP compared to men who had undergone an open procedure. We also found a lower rate of DU than previously reported, with less than 20% of either group having this urodynamic finding. There are several potential

explanations for these disparate results. There was a significant time passage in both groups following prostatectomy before undergoing their urodynamic testing. As demonstrated by Giannantoni and colleagues, DU may improve with time, and had the urodynamics of our sample been performed earlier we may have seen higher rates [6]. However, Chung and associates did not show time lapse from prostatectomy to urodynamics to be predictive of risk for DU [11]. Further research to clarify this discrepancy is worthwhile.

Matsukawa and colleagues showed a significantly increased rate of DO in patients undergoing an open compared with a laparoscopic prostatectomy, which also accounted for some increased incidence of PPI in their series [7]. We did not find a statistically significant difference in DO between the 2 groups in our study, but we did have a *P* value approaching significance, suggesting that trend. It is possible that this is a true difference that may have been statistically significant with a more balanced follow-up between the groups. Similar to the discussion surrounding DU, it is plausible that open prostatectomy has a larger effect on bladder innervation, which leads to these changes in detrusor function.

There are several limitations to this study. First, it is retrospective in design and suffers from those inherent biases. Data on the surgical approach for prostatectomy and urodynamic results were not available on all patients, and therefore we were unable to evaluate the entire cohort of patients referred for PPI. This may have inadvertently biased our results by including more recent patients that have charts in the new electronic medical record that are often more complete. Additionally, more time passed in the open group prior to undergoing urodynamics, and robotic procedures were performed more frequently in more contemporary patients. This has the potential to inadvertently bias the findings on urodynamics between the 2 groups. Finally, many of the patients included in this analysis were referred from outside institutions, some of them specifically referred to undergo a male sling procedure as opposed to an artificial urinary sphincter. This could potentially have excluded patients with poor detrusor function, severe incontinence, or urgency and urge incontinence if those patients were not referred secondary to concerns by their primary urologist that these findings would preclude them from sling placement.

CONCLUSIONS

Stress urinary incontinence from ISD is the primary etiology of post-prostatectomy incontinence. Patients undergoing an open prostatectomy were more likely to have higher voiding pressures and lower peak flow rates, presumably, at least in part, due to a higher incidence of anastomotic strictures.

Table 3. Voiding pressure and flow in patients with versus without a history of a treated anastomotic stenosis following radical prostatectomy.

	PdetQmax	Peak Flow
DVP, AS	38.7	10.3
DVP, no AS	21.8	17.4
P value	0.003	0.025
RRP, AS	38.5	7.24
RRP, no AS	20.7	19.5
P value	0.025	0.019

Mann-Whitney U: 2-tailed significance

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The Profound Impact of von Hippel-Lindau Gene Mutations in Renal Cell Cancers: A Study of the Kashmiri Population

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ABSTRACT

Introduction: The primary aim of this study was to evaluate the incidence of von Hippel-Lindau (VHL) gene mutations among a group of Kashmiri patients diagnosed with renal cell tumors. Correlation of these mutations was explored with clinical pathological status of the illness.

Methods: PCR-SCCP and DNA sequencing evaluated the DNA samples of both the tumor and adjacent normal tissue for the occurrence of VHL gene mutations. In addition, blood samples were used from all the cases to rule out any germ-line mutation.

Results: Mutations of the VHL gene identified in renal-cell cancer (RCC) patients were 52.5% (21 of 40), including 9 missense, 10 frame shift, and 2 non-sense mutations. Of the mutations, 52.38% were detected in exon 1, 38.1% in exon 2, and 9.52% in exon 3. Nineteen out of 23 (82.6%) cases of the clear-cell type and 2 out of 2 (100%) of angiomyolipomas of RCC were positive for VHL gene mutation. No correlation was found between tumor grade and/or stage and the presence of VHL mutation.

Conclusions: In conclusion, sporadic RCC shows mutations in the VHL gene, which mainly appear in the clear-cell subtype in our patients. Thus alteration in the VHL gene has been implicated in the pathogenesis of renal-cell sporadic cancer of the patients in our population.

INTRODUCTION

Renal-cell carcinoma (RCC) is the most common malignant kidney tumor in adults. It accounts for 2 to 3% of all human malignancies [1]. Among cancers of the urinary system, RCC is associated with the worst clinical outcome [2]. The incidence of RCC is increasing, and it is estimated that RCC accounts worldwide for 95 000 cancer-related deaths per year [3]. Overall, 8.9 new cases are diagnosed per 100 000 per year, with a male-to-female predominance of 3:2 [4]. In this region, urinary tract cancers comprised 9.5% of all cancers in which renal-cell carcinoma comprised about 1.5% of all cancers. The age-standardized rate (ASR) incidence in the case of RCC is 0.4 cases/100 000/year [5].

The development of RCC from normal renal epithelium may also involve alterations in genes that control cell division. These include genes that participate directly in controlling the cell cycle, such as the retinoblastoma (Rb) gene, the Tp53 tumor-suppressor gene, and the RAS gene family [6,7]. RCC is a morphologically and genetically heterogeneous tumor that includes, among several rare entities, 4 major subtypes, namely clear-cell, papillary, chromophobe, and collecting duct (Bellini duct) carcinomas [8-10]. The clear-cell subtype accounts for 70 to 80% of all RCCs [10]. Clear-cell RCC is thought to arise from the proximal tubule and presents as both a hereditary and a sporadic form. Hereditary clear-cell RCC occurs in patients with von Hippel-Lindau (VHL) disease because of germ-line mutations in the VHL tumor suppressor gene located on the short arm of chromosome 3 [11]. Clear-cell carcinomas make up 75 to 85 percent of tumors and are characterized by a deletion of one or both copies of chromosome 3p [12]. Biallelic von

KEYWORDS: Renal cell carcinoma, PCR, sporadic, angiomyolipoma

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Table 1. A sequence of primers used for amplification of exon 1, 2, and 3 of the VHL gene.

Primer	Primer Sequence*	AT (° C)	Product Size (bp)
MA2A-F MA2A-R	f 5'- GGCCCGTGCTGCGCTCGGTGAACT -3' r 5'CCCAGCTGGGTCGGGCCTAAGCGCCGGGCCCGT-3'	55	141
TK-F TK-R	f 5' GGCCCGTGCTGCGCTCGGTGAACT 3' r 5' CGGCCCGTGCCAGGCGGCAGCGTTGGAT 3'	57	190
VHL-3 F VHL-3 R	f 5' CCGAGGAGGAGATGGAGGCC 3' r 5' GACCGTGCTATCGTCCCTGC 3'	62	250
VHL-4 F VHL-4 R	f 5' CGGTGTGGCTCTTTAACAACC 3' r 5' CAAGTGGTCTATCCTGTACTT 3'	55	230
VHL- 5F VHL-5R	f 5' TTCCTTGTACTGAGACCCTAGT 3' r 5' TACCATCAAAAGCTGAGATGAAACAGTGTAAGT 3'	55	280

AT: annealing temperature

Hippel-Lindau (VHL) gene defects, a rate-limiting event in the carcinogenesis, occur in approximately 75% of sporadic clear-cell RCC. The disease is caused by mutations of the VHL gene on the short arm of the third chromosome (3p26 to p25).

Together with the loss of the homologous chromosome 3p allele (3p LOH), VHL mutations are rate-limiting events in the carcinogenesis of clear-cell RCC [13,14]. Mutations have been observed in the entire gene and usually lead to a truncated inactive protein [15]. The VHL gene is involved in cell cycle regulation, the regulation of hypoxia inducible genes, and proper fibronectin assembly in the extracellular matrix [16,18]. In approximately 19% of sporadic clear-cell RCC, methylation of the VHL gene promoter appeared to be involved [16,18]. In approximately 10 to 20% of sporadic clear-cell RCC no alteration in the VHL alleles was detected, indicating that other genes are involved in clear-cell RCC carcinogenesis, possibly affecting the same signaling pathway as VHL.

Owing to the fact that there is no data on genetic alterations on RCC available in our population or given the backdrop of a significant presence of RCC patients, the highest among males, it is the first initiative to study the gene alterations in RCC patients of Kashmir Valley by DNA sequencing.

METHODS AND MATERIALS

Specimen

A total of 40 histologically confirmed, previously untreated renal-cell cancer patients attending the Department of Urology of the Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Srinagar were included in this study. Blood samples were taken from all cases to rule out the possibility of germ-line mutation in the VHL gene to confirm the sporadic nature of mutation in our RCC cases.

Information on tumor grade and stage was obtained for all patients. The diagnostic slides were reviewed by a panel of 2 expert pathologists to confirm the diagnosis and insure uniformity of the classification criteria. We reviewed all cases and classified them according to the 1987 version of the TNM classification. Written pre-informed consent was obtained from all cases and controls. The demographic and clinic-pathological characteristics of each patient were recorded in a questionnaire. This study was approved by the ethical committee of the SKIMS. $\chi 2$ was applied to calculate the *P* value of VHL gene mutation with clinico-pathological characteristics. A P value < 0.05 was considered significant.

DNA Extraction

In this study, single-strand conformation polymorphism and DNA sequencing were used to analyze the regions of VHL genes harboring the point mutations in a series of 40 renal carcinoma samples. Tumor samples (both tumor and adjacent normal tissue) collected after radical nephrectomy of renal-cell tumors were immediately snap-frozen and stored at -70° C. DNA from tissues, as well as blood, was extracted using a DNA easy tissue kit (Qiagen GmbH; Hilden, Germany) according to the enclosed protocol.

Polymerase Chain Reaction

Exons 1, 2, and 3 of the VHL gene containing hotspot codons were amplified using previously described specific primers (Table 1). PCR amplification was carried out in a 50 µL volume container with 25 ng of genomic DNA; a 1X PCR buffer containing 1.5 mM

Table 2. Clinicoepidemiological variables of patients with a renal tumor used for mutational analysis

Variable	Parameter	Cases N = 40, %
sex[a]	males females	25 (62.5%) 15 (37.5%)
age	≤ 50 > 50	31 (77.5%) 9 (22.5%)
dwellingb	rural urban	27 (67.5%) 13 (32.5%)
smoking status[c]	smokers nonsmokers	22 (55%) 18 (45%)
differentiation guide	I II III IV	13 (32.5%) 22 (55%) 4 (10%) 1 (2.5%)
histological type[d*] (TNM)	clear-cell pappillary oncocytoma angiomyolipoma leomyoma	23 (57.5%) 10 (25%) 3 (7.5%) 2 (5%) 2 (5%)
sitee	upper pole middle lower	14 (35%) 17 (42.5%) 9 (22.5%)
lymph node status	no yes	36 (90%) 4 (10%)
stage	stage I stage II stage III stage IV	21 (52.5%) 5 (12.5%) 13 (32.5%) 1 (2.5%)

[a]age/sex: M = male, F = female; [b]rural/urban: R = rural, U = urban; [e]smoking status: S = smokers, NS = nonsmokers

MgCl2; 100 µM each of dATP, dGTP, dTTP, dCTP; 1.5 U of Taq DNA polymerase (Biotools; Madrid, Spain); and 1 µM of forward and reverse primers (Genescript; Piscataway, NJ, USA). The PCR and thermal conditions are given in Table 1. The PCR products were run on 2% agarose gel and analyzed under an ultraviolet illuminator. The single-strand conformation polymorphism (SSCP) analysis of the amplicons of exon 7, 10, and 15 was performed on 6% non-denaturing polyacrylamide gel (PAGE) utilizing nonradioactive silver staining [17]. The purified PCR amplicons of the tumor samples showing mobility shift on SSCP analysis, and randomly chosen normal samples were used for direct DNA sequencing using the automated DNA sequencer ABI PRISM® 310 Genetic Analyzer (Applied Biosystems, Life Technologies; Carlsbad, CA, USA).

RESULTS

Table 2 contains the clinicoepidemiological characteristics of the patients with RCC. The number of cases in the age group of ≥ 50 (N = 31; 77.5%) exceeded < 50 years (N = 9; 22.5%). Histological breakup of the RCC cases were stage I, 21 (52.5%); stage II, 5 (12.5%); stage III, 13 (32.5%); and stage IV, 1 (2.5%). All the cases after surgical resection were subjected for histopathological examination (HPE), and all of the samples resected were histologically confirmed as renal-cell carcinomas of different types, as depicted in Table 2.

Overall mutations in exon 1, 2, and 3 of VHL identified in this study aggregated to 52.5 % (21/40) (Table 3). In all, there were 8 missense mutations (6 transitions and 2 transversions), 6 were C > T transitions, and 2 G > T transversions. We detected 10 frame shifts in which 4 were insertion mutations of AGGT > AGAGT (insertion A) in exon 1 and six insertion mutations of GTTG > GTATG (insertion A) in exon 2. We found 3 nonsense mutations of GGA > TGA resulting in Gly > stop codon in exon 2 (Table 3).

Among 21 mutations detected in our study, 20% were seen in exon 1, 20% in exon 2, and 5% in exon 3 (Table 4). Representative partial electropherogram of few mutations are given in Figure 1, Figure 2, Figure 3, and Figure 4. Among 21 mutations found in this study, 5 (38%) were found in grade I and 12 (54.5%) in grade II, whereas 4 (75%) and 1 (100%) were detected in grade III and grade IV, respectively (Table 3).

Figure 1. Partial reverse sequence of exon 1 showing mutation (above) in codon 246 CCC > CAC and a normal sequence (below).

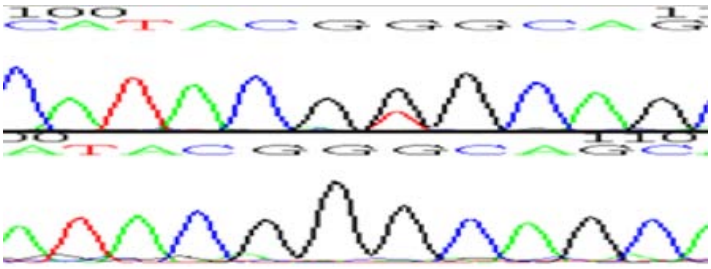
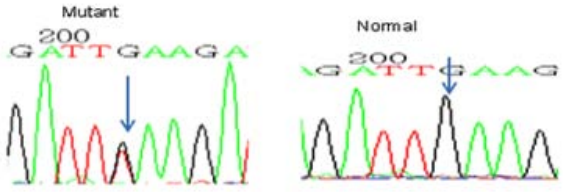


Table 3. Clinicoepidemiological characteristics and mutational status of patients with a renal tumor

Characteristics	Cases (N = 40)		Mutant		Wild		*P*
	N	N%	N	N%	N	N%	
	40	100%	21	52.5%	19	47.5%	0.327
sex							
male	25	62.5%	14	56%	11	44%	0.567
female	15	37.5%	7	46.7%	8	53.5%	
smoking status							
smoker	18	45%	10	55.6%	8	44.4%	
nonsmoker	22	55%	11	50%	11	50%	0.726
histopathological grade							
grade I	13	32.5%	5	38.5%	8	61.5%	0.427
grade II	22	55%	12	54.5%	10	45.5%	
grade III	4	10%	3	75%	1	25%	
grade4	1	2.5%	1	100%	0	0%	
histopathological type							
clear cell							
pappillary	23	57.5%	19	82.6%	4	17.4%	0.000
oncocytoma	10	25%	0	0%	10	100%	
angiomyolipoma	3	7.5%	0	0%	3	100%	
leomyoma	2	5%	2	100%	0	0%	
	2	5%	0	0%	2	100%	
stages							
stage I	21	52.5%	11	52.4%	10	47.6%	
stage II	5	12.5%	1	20%	4	80%	0.327
stage III	13	32.5%	8	61.5%	5	38.5%	
stage IV	1	2.5%	1	100%	0	0%	

This difference showed a non-significant correlation with VHL mutation patterns ($P > 0.05$). Mutations in 11 of 21 (52.4%) were detected in stage I tumors and 1 of 5 (20.0%) in stage II, and 8 out of 13 (61.5%) were detected in stage III while 1 mutation was found in stage IV (100%; $P > 0.5$). Nineteen of 21 (82.6%) mutations were found in clear-cell RCC while as 2 of 2 (100%) were found in angiomyolipoma. This difference in mutation frequency between different histological tumor types was seen as statistically significant in clear-cell RCC ($P < 0.05$).

Figure 2. Partial forward sequence of exon 3 showing mutation (left) in codon 614 TGA > TTA and a normal sequence (right).



DISCUSSION

In the present study, the mutational spectrum of the VHL gene (exon 1, 2, and 3) were studied in 40 cases of RCC. The VHL

Table 4. Characteristics of patients with RCC showing VHL gene mutations.

ID	Age	Sex	SS	G	St	L.N.	HPE	Cdn.	NC	Base Change	AA	Mut
KT3	65	M	S	2	III	yes	CC	246	C > T	CCC > CTC	Pro > Leu	M
KT5	45	M	NS		III	No	CC	246	C > T	CCC > CTC	Pro > Leu	M
KT10	45	M	NS	3	III	yes	CC	614	G>T	TGA > TTA	SC > Leu	M
KT1	50	M	S	1	I	No	CC		Ins T	AGGT > AGAGT		FS
KT19	60	F	S	2	I	No	CC		Ins T	AGGT > AGAGT		FS
KT25	60	M	S	1	I	No	AM	424	G>T	GA > TGA	Gly > SC	NS
KT33	80	M	S	2	II	No	AM	424	G > T	GGA > TGA	Gly > SC	NS
KT6	55	F	N.S	2	III	No	CC	422	Insertion A	GTTG > GTATG		FS
KT28	50	M	S	1	I	No	CC	422	Insertion A	GTTG > GTATG		FS
KT39	60	F	NS	2	I	No	CC	422	Insertion A	GTTG > GTATG		FS
Kt29	75	M	S	1	III	No	CC	246	C > T	CCC > CTC	Pro > Leu	MS
KT8	55	F	NS	2	I	No	CC	246	C > T	CCC > CTC	Pro > Leu	MS
KT17	50	M	S	2	I	No	CC	246	C > T	CCC > CTC	Pro > Leu	MS
KT26	45	M	NS	1	I	No	CC	614	G > T	TGA > TTA	SC > Leu	MS
KT11	42	F	S	2	III	No	CC		Ins T	AGGT > AGAGT		FS
KT23	65	M	NS	4	I	No	CC		Ins T	AGGT > AGAGT		FS
KT40	55	M	NS	2	I	No	CC	422	Insertion A	GTTG > GTATG		FS
KT20	45	M	S	2	III	No	CC	422	Insertion A	GTTG > GTATG		FS
KT37	50	M	NS	3	I	No	CC	422	Insertion A	GTTG > GTATG		FS
KT17	60	F	NS	3	III	No	CC	246	C > T	CCC > CTC	Pro > Leu	MS
KT13	70	F	NS	2	IV	yes	CC	246	C > T	CCC > CTC	Pro > Leu	MS

SS: Smoking status; G: Grade; St: Stage; Ex: exon; Cdn: Codon; AA: Amino acid change; NC: Nucleic acid change; Mut: mutation; M: Missense; FS: Frame shift

gene is a tumor suppressor gene predisposed to both sporadic clear-cell (conventional) RCC and VHL disease. The frequency of mutations in this series aggregated to 52.5%. No germ-line mutations were detected in the VHL gene in extracted DNA from peripheral blood of the studied patients. The most common mutations found in our study were frame shifts, missense, and nonsense mutations from all the 3 exons of the VHL gene. Individuals with VHL disease carry 1 wild type VHL allele and 1 inactivated VHL allele. In other words, VHL patients are VHL heterozygotes. Tumor or cyst development in VHL disease is linked to somatic inactivation or the loss of the remaining wild type VHL allele. Approximately 20 to 37% of VHL patients have large or partial germ-line deletions, 30 to 38% have missense mutations, and 23 to 27% have nonsense

Figure 3. Partial reverse sequence of exon 1 showing insertion (left) resulting in AGGT > AGAGT and a normal partial sequence (right).

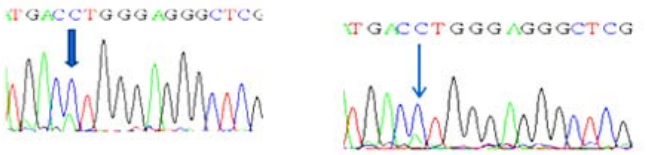
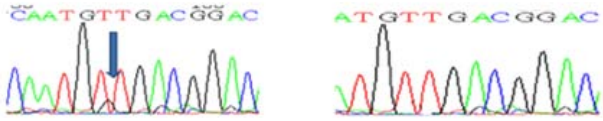


Figure 4. Partial reverse sequence of exon 2 showing insertion of A in codon 422 (left) resulting in GTTG > GTAGT and a normal partial sequence (right).



or frame-shift mutations [15,19]. In general, VHL mutations are extremely heterogeneous and are distributed throughout the coding sequence, except that intragenic missense mutations are rarely seen within the first 50 codons. With 12 in total, more than 150 different germ-line VHL mutations linked to VHL disease have been reported [20]. VHL seems to be mutated somatically in approximately 50%, and hypermethylated in another 10 to 20% of sporadic clear-cell renal carcinomas. However, mutation of the VHL gene is rarely detected in other histologic subtypes of RCC. This shows that mutational frequency detected in RCC in our study is in accordance with most of the studies that have been done to date (our study: 52.5%, vs Gnara et al. [20]: 57%, vs Gallou et al. [21]: 56%, vs Kondou et al. [22]: 51%). Some of the studies were not in conformity with our report in terms of the frequency of the mutations seen in the VHL gene (our study: 52.5%, vs Foster et al. [23]: 42%, vs Whaley et al. [24]: 33%, vs Brauch et al. [25]: 42%, vs Igarash et al. [26]: 66%). This difference in the observed proportion of mutations in the VHL gene may be attributed to the use of different techniques; e.g., SSCP vs direct sequencing, to contamination with normal tissue components, or to the type of material analyzed (fresh or archival paraffin material). In keeping with the Knudson 2-hit model, biallelic VHL inactivation (as a result of mutation or hypermethylation) is common in both sporadic hemangioblastomas and sporadic clear-cell renal carcinomas [27]. VHL seems to be mutated somatically in approximately 50%, and hypermethylated in another 10 to 20% of sporadic clear-cell renal carcinomas. However, mutation of the VHL gene is rarely detected in other histologic subtypes of RCC. The percentage of frame-shift mutations was approximately 50% in most studies [28,29], comparable to the 48% observed in the current study. The percentage of in-frame deletions/insertions was higher in our study (12%) as compared to the percentage in other studies (< 5%) [28]. These frame-shift mutations may cause the altered 11 function of VHL protein, which leads to the abnormal tumor suppressor activity of the VHL gene. The present study found VHL mutations in 19 of the 23 cases (82.6%) of clear cell renal carcinoma, and presentation of a higher number of mutations in this tumor type was found to be statistically significant ($P < 0.05$). In this study we found 42.8% (9 of 21) mutations were of missense in nature compared to the distribution of mutation data present in the universal VHL. With mutation data based on 747 mutations [30], the relative amount of point mutations is much higher (64%) compared to the percentage of point mutations we observed (42.8%). Our observations of missense mutations are in accordance with Kjeld et al. [30]. The percentage of nonsense mutations is somewhat similar as thouse found in the Universal VHL Mutation Database (11% vs 9.5%). The missense mutations in sporadic cases of RCC that have already lost 1 allele may impair VHL protein function, resulting in the loss of tumor suppressor function of the VHL gene. The distribution of histological subtypes was comparable to the distribution described before. Surprisingly, our study also found VHL mutations in one of the non-clear-cell RCC samples that were collected. In angiomyolipoma, we found 2 mutations out of 2 samples (100%). These results are in contrast with the current opinion that VHL mutations are exclusively restricted to clear-cell RCC. In this study however, we did not find any mutation in any other non-clear-cell renal cancer. Our results and results from others [25,32] showed no association with nuclear grades. We did not observe a difference in stages between mutated and wild type tumors, as was confirmed by 2 other studies [32]. In a small number of tumors analyzed, which is also a limitation in this study, our results showed that VHL gene mutations were observed irrespective of pathological grade or stage. This finding suggests that VHL gene mutation may be an early event in the development of renal-cell carcinoma. Furthermore, our study could not find any association with age, tumor location, tumor size, or any other clinicopathological characteristics.

CONCLUSION

We conclude that sporadic RCC shows mutations in the VHL gene, which mainly appear in the clear-cell subtype in our patients. Thus alteration in the VHL gene has been implicated in the pathogenesis of renal-cell sporadic cancer of the patients in our population. Such alterations result in severe disturbances in the protein, likely disturbing its tumor suppressing function, and is then implicated in the development of RCC because the protein functioning was not evaluated in this study.

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Balanitis Xerotica Obliterans, the Topical Application of Tacrolimus Ointment, and the Result: An Institutional Study

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ABSTRACT

Background: Balanitis xerotica obliterans (BXO) is a well-known chronic disease affecting male genitalia. There are several treatment options available for this. This study was performed to establish the efficacy of tacrolimus ointment as a mode of nonsurgical management of early BXO changes.

Introduction: BXO is a chronic, lymphocyte-mediated skin disease causing glandular urethral stricture of unknown origin. Exact incidence of the disease is obscure; there are several surgical and nonsurgical treatment options available. Among the nonsurgical management, the use of tacrolimus (immunomodulator) ointment is being considered.

Methodology: This study was performed at our institution among the patients attending the outpatient department with typical clinical features of BXO during the year 2011. Thirty cases were studied.

Results and Discussion: The majority (63.33%) of cases presented during the third to sixth decade of life. Symptomatic relief occurred in 16 cases (53.33%) treated with tacrolimus ointment. There are several modes of nonsurgical management, including steroid ointment usage, carbon dioxide laser therapy, topical tacrolimus application, etc. Among these therapies, the use of topical tacrolimus has promising results with better symptomatic relief and fewer side effects, as seen in our study.

INTRODUCTION

Balanitis xerotica obliterans (BXO) was first described by Stuhmer in 1928 in Munster, Germany [1,2]. BXO is the other name of the disease Lichen sclerosus et atrophicus (LSA). It is basically the male genital form of LSA and is the most common chronic, lymphocyte-mediated skin disease causing glandular urethral stricture [1-4] of unknown origin. BXO is a rare disease that affects only 6 of 1000 males (0.06%) [5,6]. It can affect males of any age, especially in the third to fifth decade of life [7]. The traditional treatment has been radical circumcision when the disease is affecting the penile skin and at a young age [7]. However, many conservative treatment options are now available [6]. True incidence is obscure, but it is more common in the white population and has been reported as uncommon in other ethnicities [8].

The exact etiology is unknown. Chronic infection with borrelia burgdorferi [9] has been proposed, and other researchers showed it to be autoimmune in etiology [7]. On medical management of the disease, long-term antibiotic therapy or topical corticosteroid or immunomodulator therapy have been proposed. Tacrolimus is an immunomodulator currently used systemically in transplant medicine and has been recently licensed for treating atopic dermatitis. Topical therapy with tacrolimus in cases of BXO has been reported with varying efficacy [10,11].

This study was performed to assess the efficacy of the topical application of tacrolimus as a non-surgical modality of treatment in early BXO involving the meatus and fossa navicularis, and relapsed cases of meatal stenosis after surgical procedures.

KEYWORDS: Balanitis xerotica obliterans (BXO), topical, tacrolimus, treatment

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Table 1. Agewise distribution of cases.

Age Group Affected	No. of Patients	% of Distribution
10 - 20 years	5	16.67%
21 - 30 years	6	20%
31 - 40 years	7	23.33%
41 - 50 years	4	13.33%
51 - 60 years	2	6.67%
61 years and up	6	20%

MATERIALS AND METHODS

After approval from the institutional ethical committee, the present study was performed in Bankura Sammilani Medical College for a period of 1 year (January 2011 to December 2011), and 30 cases have been included in this study. All the patients attending in our outpatient department with typical clinical features of BXO have been included in the study; a detailed history was taken, patients underwent some tests (uroflowmetry, basic blood investigations, and urinalysis), and patients were treated with topical tacrolimus for a period of 6 weeks. Patients aged more than 75 years were excluded from the study. All the patients gave consent to be included in the study. The statistical tests were performed using IBM SPSS® Statistics 20 software.

RESULT AND ANALYSIS

Among the study population of thirty patients, 5 patients were bellow 20years of age, 6 patients were above 60 years of age and rest 19 patients (63.33%) were in the age group 30 to 59 years. Youngest boy in this study was 14 years old and oldest was 71 years old (Table 1). All patients were male. All had sufficient urinary obstructive symptoms such as straining, the splaying of their urinary stream, prolonged voiding time, and had glans and meatal appearances highly suggestive of BXO (Figure 1). Eighteen of them had a history of minimal surgical treatment with meatal dilatation or meatotomy and a topical application of the steroid-like clobetasol or mometasone, but none of them had long-term relief of symptoms so they frequently visited the outpatient department and needed dilatation without effective symptom relief.

Two middle-aged (39 years and 44 years) men had buccal mucosal urethroplasty for long, segmented anterior urethral strictures; 2 years after the surgery they developed meatal stenosis and demonstrated persisting BXO symptoms during

Figure 1. A clinical presentation of BXO changes seen at different stages of treatment in 2 different patients; a,b) the appearance of the glans and external urethral meatus of one patient before and after treatment; c,d) the apppearance of the glans and external urethral meatus of another patient before and after treatment.

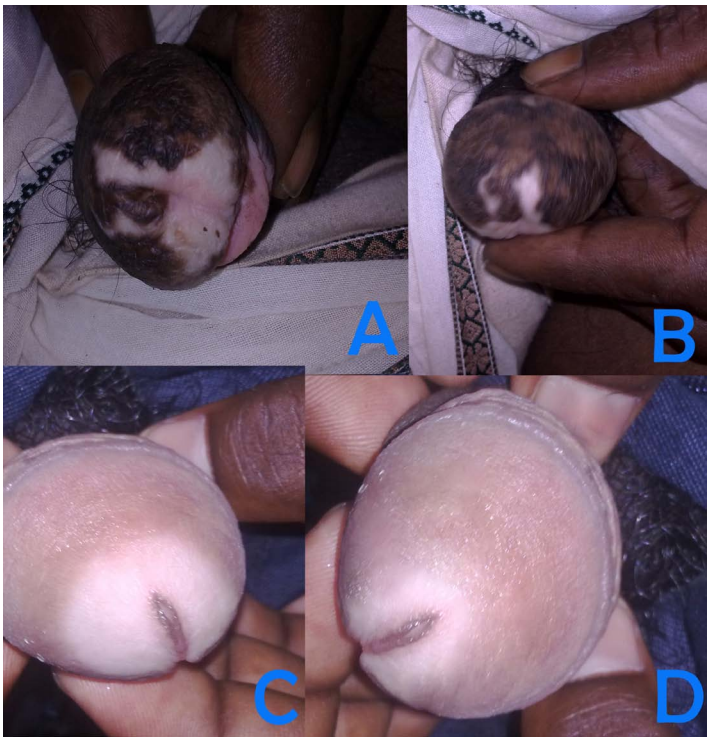

Figure 2. Uroflometry graphs of 2 patients; above – before treatment, below – after treatment.

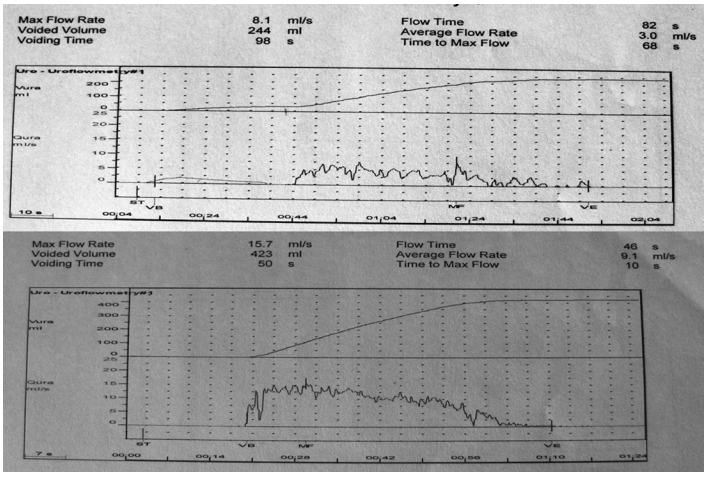

Figure 3. Histopathological characteristics of BXO changes: (original magnification X100, H/E Stain) hyperkeratosis, an absence of rete ridges, a pale upper dermis, band-like lymphocytes infiltrating to the dermis, and cleft-like space separating the epidermis from dermis.

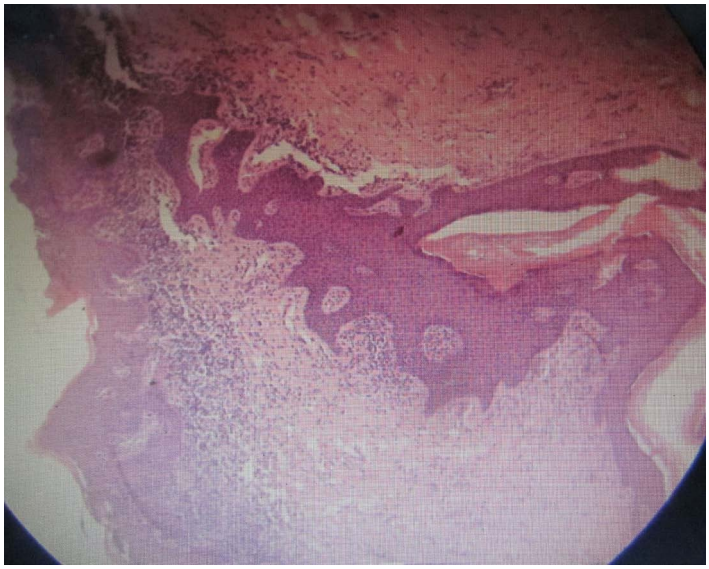

Table 2. Observed histopathological changes.

No. of Cases	Histopathological Report
9	early BXO changes
20	BXO changes
1	Zoon balantis

this period of study.

Uroflowmetry was performed in all cases except the case with suprapubic cystostomy, and the average flow was less than 4 ml per second in most cases (24 cases, 80%) before the application of tacrolimus ointment (Figure 2). Retrograde urethrography and urethroscopy were performed routinely to assess the length of urethral involvement. Long segment strictures were excluded from this study. A glans biopsy was done in all cases. Nine cases had early lichenoid reactions suggestive of early BXO, 20 cases had fully developed BXO (histopathological changes) (Figure 3), and 1 case where the clinical appearance was BXO with obstructing urinary symptoms, but the histopathological report came to be Zoon balanitis (Table 2).

All patients were treated with a local application of 0.03% tacrolimus twice daily for 3 weeks and then 0.1% tacrolimus for the next 3 weeks. The dosage schedule is controversial as there are not enough studies yet to determine the exact dosage, which depends on a) the few earlier studies, b) the availability of the ointment in these strengths, and c) a higher dose that may cause allergic reactions as stated by the manufacturer. In this study, the previously mentioned dosage was used. All patients tolerated the drug well, except for the complaint of a transient burning sensation at that site and pruritus in 6 cases. There were no other side effects noted during this study period.

Symptomatic relief of symptoms occurred in 53.33% (16 cases) of the total population studied, evidenced by the subjective improvement of urinary flow and the reduced frequency of urethral dilatation compared to earlier tests. These were supported by objective studies as well. Seventeen cases (56.67%) showed improved maximum flow rate at uroflowmetry (Qmax), and an average flow rate at uroflowmetry (Qavg) after the application of tacrolimus ointment at a 2-month follow-up during the study period (Figure 2). In 1 patient, there was objective improvement in urine flow but no subjective symptomatic relief. The cause may have been psychological, resulting from prolonged suffering with the disease. This improvement in uroflowmetry was statistically significant also (a Wilcoxon signed-rank test was performed on the uroflometry values before the start of therapy and at the end of therapy at a 6-week follow-up visit; the *P* value calculated was 0.002).

The appearance of the glans after the application of tacrolimus was better (16 cases, 53.33%) and less dry (Figure 1). However, histopathological changes after the use of tacrolimus were not confirmed via biopsy. Patients with early BXO changes responded more. The patient with suprapubic cystostomy with a narrow and rigid meatus, which was difficult to dilate, became pliable and amenable to dilatation. Suprapubic cystostomy catheter was removed after 1 month and the patient started voiding with a narrow stream.

It was also noted that the patient with Zoon balanitis did respond to the tacrolimus therapy; at presentation, the Qmax and Qavg were 13 and 7.3 ml a second, respectively, and at the end of therapy at a 2-month visit, those values became 22 and 11.5 ml a second, respectively.

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DISCUSSION

BXO is a chronic, debilitating, and inflammatory condition that impairs urinary flow, affects sexual function, and alters the aesthetic appearance of the glans, affecting the psychosocial status of patient. It is a chronic inflammatory disease of the skin of unknown etiology [7]. It is the male variant of lichen sclerosus et atrophicus [3,7,12]. The name BXO was derived from 3 components of the disease, which are balanitis (chronic inflammation of the glans), xerotica (abnormally dry appearance of the lesion), and obliterans (the association of occasional endarteritis) [7]. The exact etiology is unknown. Different causes have been postulated, including infection by spirochetes, autoimmune disease, a genetic predisposition (human leukocyte antigen, HLA association), reactive oxidative stress, or some carcinogenic process [7,12].

It has no racial predisposition. It can affect any age group but is more prevalent in the third to fifth decade of life [2,5,7], as seen in our study. It is usually asymptomatic in the early course of the disease, and physical changes occur over months or years and may include color or textural changes at the prepucal skin and the glans only [12,13]. Symptoms are more dominant in uncircumcised men. They range from pruritus, a burning sensation at the glans, hypoesthesia, a painful erection, recurrent features of urinary tract infection, a decrease in urinary flow, features of urethritis, phimosis and paraphimosis, and squamous cell carcinoma may develop at the area of involvement [7,13]. There may be extragenital features such as lichen sclerosis affecting other parts of the body. Usually the area affected looks like a whitish patch, the superficial skin is thickened, and it is dry [10]. Though the typical clinical appearance is enough to diagnose the case, other differential diagnoses must to be ruled out, such as venereal diseases by serological tests. It may be confirmed by histopathological examination. In some studies, it has proved to be a precancerous lesion leading to carcinoma of the penis on a long-term basis [7]. Histologically, BXO is characterized by hyperkeratosis, epidermal atrophy, vascular alteration of basal keratinocytes, subepidermal edema, sclerosis of the subepidermal collagen, and lymphocytic infiltration [1,8,12].

Early treatment is necessary to delay or prevent the long-term complications of the disease. For this, several medical managements are used, such as topical or intralesional steroid usage, topical steroids with skin stretching, topical tacrolimus, and carbon dioxide laser treatments [12,14-16]. Windahl et al.[17] has shown encouraging results in his study after the application of carbon dioxide laser therapy (CO_2 settings: output = 15 to 20 watts, in defocus mode; wavelength = 10000 nanometers) for BXO changes for an average of 30 months both in terms of cosmetic and functional improvement. But they did not clearly mention objective outcomes and the timing of CO_2 laser therapy [18]. CO_2 lasers cause heat vaporization of cells, thus causing the death of BXO cells. However, we don't have any experience with CO_2 laser therapy in this study. Different types of surgical procedures may be done in advanced cases.

Kiss [14] and Ebert et al. [19] questioned the use of topical steroids as they may cause epithelial atrophy and its side effects. Tacrolimus is an immunomodulator and works by inhibiting the production of interlukin 2 and subsequent T-cell activation. This reduces or delays the process of balanitis and heals BXO [12,14,20]. The topical application of tacrolimus (0.03 to 0.1%) appears promising in early lesions, as seen in this study by the symptomatic relief and increase in urinary flow rates. The need for dilatation had also decreased. However, further studies, preferably with a control arm, are needed to know the exact dosage schedule, adverse effects, contraindications, etc., of topical tacrolimus usage in early BXO changes, and usage after circumcision and urethroplasty in cases of BXO diseases.

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Short-term Change in Renal Function in Patients Undergoing Continent vs Noncontinent Urinary Diversions

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ABSTRACT

Introduction: Despite good supporting evidence, the dogma still exists that patients with renal insufficiency are not good candidates for continent diversions. In this paper, we attempt to evaluate this relationship and investigate the short-term effects of continent and noncontinent diversions on patients with both normal renal function and preexisting renal insufficiency.

Methods: From Sept 2004 to June 2009, 212 adult patients underwent radical cystectomy and intestinal urinary diversion by a single surgeon (SD). Forty-four were excluded secondary to inadequate follow-up (41) or other factors leading to renal compromise (3). Continent diversions were performed either with a Studer orthotopic ileal neobladder (ONB) or a catheterizable stoma with right colon pouch. Evaluation of renal function included pre- and postoperative serum creatinine, bicarbonate, and estimated glomerular filtration rate (eGFR) using the National Kidney Foundation (MDRD) equation. A multivariable linear regression model was used to assess the influence of different urinary diversions on the change in renal function.

Results: Median follow-up for the 168 patients was 18.7 months (3 to 60 months). Forty-four patients underwent ileal conduit and 124 underwent continent diversion (109 ONBs; 15 continent cutaneous diversions). The mean preoperative eGFR between the conduit and continent groups was 63.8 and 73.3, respectively ($P < 0.001$). The mean decrease in eGFR between the 2 groups was -4.1 and -10.3, respectively ($P = 0.41$). In patients with preexisting renal insufficiency, the mean change in eGFR was 1.7 and -0.49, respectively ($P = 0.49$).

Conclusions: The mean change in eGFR, creatinine, and bicarbonate levels following urinary diversion with either conduit or continent diversions were not statistically different in patients with normal or preexisting renal insufficiency at short-term follow-up. This data suggests that mild preexisting renal insufficiency may not be a contraindication to continent diversion.

INTRODUCTION

Patients with lower urinary tract cancers or severe functional or anatomic abnormalities of the bladder often require urinary diversion to prevent pathological complications of the upper urinary tract and/or malignancy progression [1]. The type of urinary diversion selected for each patient depends on several clinical factors, as well as the patient's preference and understanding of the short-term and long-term complications of each. Adequate renal function is necessary to blunt the potential metabolic side effects of urinary diversion (i.e., hyperchloremic metabolic acidosis), and patients with poor renal function are thought to be less capable of handling the sequelae from these derangements (e.g., bone demineralization, impaired growth, infection, and urolithiasis) [2-4]. This relationship may be exacerbated in continent diversions given the longer urine retention time and the potential for even greater reabsorption of normally excreted products (e.g., NH4+).

There is now a growing body of evidence suggesting that

KEYWORDS: Ileal conduit, orthotopic neobladder, renal function, urinary diversion

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patients with adequate baseline renal function can tolerate both continent and non-continent urinary diversions without significantly different declines in renal function [2,5-8]. However, in patients with renal insufficiency, the long-term effects of continent versus non-continent diversions on renal function have not been well characterized. Despite this, the 2007 World Health Organization (WHO) consensus conference on bladder cancer concluded that renal compromise (whether due to long-standing obstruction or chronic renal failure), defined as serum creatinine of > 150 to 200 umol/L (~1.7 to 2.3 mg/dL), is an absolute contraindication to continent urinary diversion [2].

Conversely, other sources state that patients with normal urine protein levels and a preoperative serum creatinine of < 2.0 mg/dL usually do well with intestinal urinary reservoirs [9], and that some patients may actually have reversible renal impairment secondary to the removal of obstruction, inferring that a SCr of < 2 mg/dL may not be a necessary prerequisite.

The intent of this study is a retrospective review of renal function following urinary diversion in a single institution. We attempt to evaluate the short-term differences in renal function in patients undergoing continent vs non-continent urinary diversions in order to assess the capacity to handle continent urinary diversions in patients with renal insufficiency. Our cohort is somewhat unique in that patients with mild renal impairment were allowed to undergo a continent diversion.

METHODS

We conducted a single-center, retrospective chart review of 212 consecutive patients who underwent radical cystectomy and urinary diversion by a single surgeon (SD) between September 2004 and July 2009 at Oregon Health Sciences University in Portland, OR (IRB#00004701). This cohort represents 99% of urinary diversions performed at OHSU during this time period. Clinical variables reviewed included age, gender, race, indications for surgery, the type of urinary diversion performed, the length of follow-up, evidence of preoperative urinary obstruction (via CT, MRI, or chart-note verification as appropriate), whether patients underwent perioperative chemotherapy, and preoperative and postoperative plasma creatinine and bicarbonate levels. For assessing renal function, labs at the most recent follow-up visit at the time of data analysis were included. Continent diversions were performed either with a Studer orthotopic ileal neobladder (ONB) using a 60 cm segment of distal ileum or a cutaneous diversion with a right colon pouch via Monti or appendicoumbilicostomy. Ureteroileal anastomoses were performed individually using the Leadbetter-Clarke method with interrupted absorbable sutures.

Indications for cystectomy and urinary diversion included bladder cancer (203, 96%), prostate cancer (2, 0.01%), and other assorted causes (7, 3%). Evaluation of renal function included pre- and postoperative serum creatinine (SCr), bicarbonate (HCO3), and estimated glomerular filtration rate (eGFR, calculated using the Modification of Diet and Renal Disease (MDRD) equation, which incorporates age, gender, race, and serum creatinine). Subgroup analyses included short-term (3 to 12 months) versus longer-term follow-up (> 1 year) (N = 58 vs N = 110, respectively), continent versus noncontinent diversion (N = 124 vs N = 44, respectively), and the presence of preexisting renal insufficiency (58 with RI vs 110 with normal renal function). For the purposes of this study, we chose an eGFR between 40 to 59 (mild to moderate, stage III CRF) as our definition of "renal insufficiency" and any patients with eGFR > 60 as "normal."

Each patient undergoing urinary diversion was given extensive preoperative counseling and a standardized presentation of available options, including a 12-page illustrated handout describing the different diversions in detail. Contraindications for continent diversion included SCr of > 1.8 mg/dL (159.12 umpl/L) or an eGFR of < 40 mL/min 1.73 m2, unforeseen pelvic spread of disease (clinical stage T4bNx or TxN3), preexisting urinary incontinence, a history of pelvic irradiation, positive urethral margin at intraoperative frozen section analysis, urethral stricture, hepatic dysfunction, and neurological disease.

Multivariable analysis was used to assess the influence of different urinary diversions on renal function change while controlling for potential confounding effects of clinical factors, including age, preoperative renal function, preoperative obstruction, and perioperative chemotherapy using statistical software SAS (version 9.2). Differential analysis between groups was performed using the Fisher's exact test. The Tukey-Kramer adjustment for multiple comparisons was used to compare the effects of chemotherapy on postsurgical outcomes.

RESULTS

General Results

The mean follow-up for conduit and continent procedures was 17.5 and 19.9 months, respectively. Forty-four patients were excluded, 41 due to inadequate follow-up (< 3 months) and 3 due to other factors leading to unrelated renal compromise. The resulting 168 cases were made up of 44 ileal conduits, 109 ONBs, and 15 continent cutaneous diversions. Of those patients eligible for continent urinary diversion, 9 (6%) chose ileal conduit for personal reasons, which varied significantly and included fear of any incontinence, unwillingness to self-catheterize, belief it was "too complicated," and concern that catheterizing a continent cutaneous pouch would interfere with outdoor activities. A total of 11 patients from the cohort

Table 1. Clinical characteristics of cohort. eGFR of patients with preexisting renal insufficiency (defined as eGFR < 60 mL/min/1.73 m^2) calculated using MDRD equation.

	Conduit (44)	Continent (124)	Significance
Average age	71.4	65.3	*P* < 0.001*
Mean preop eGFR	63.8	73.3	*P* < 0.001*
Preop hydronephrosis (54)	16 (36%)	38 (31%)	*P* = 0.6
Periop chemotherapy (44)	11 (25%)	33 (75%)	*P* = 0.52
Preexisting RI (58)	24 (41%)	34 (59%)	*P* = 0.02*
Mean preop eGFR with RI	41	48.5	*P* < 0.009*
	Conduit	Continent	
Mean f/u for all	17.5 months	19.9 months	*P* = 0.10

RI = renal insufficiency; * denotes significance

Table 2. Renal function changes after surgery in the 2 general diversion types (ileal conduit vs ONB or continent cutaneous diversion with a right colon pouch). Serum creatinine shown in mg/dL and (umol/L).

		Changes after Surgery		
Patients	Markers	Conduit	Continent	P value*
All	Creatinine	0.2 (17.7)	0.2 (17.7)	0.56
(N = 168)	HCO_3	-0.4	-1.3	0.18
	eGFR	-4.1	-10.3	0.41
Short term f/u (N = 58)	Creatinine	-0.1 (8.8)	0.2 (17.7)	0.054
(3-12 months)	HCO_3	0.3	-1.3	0.27
	eGFR	1.6	-4.5	0.35
Longer term f/u (N = 110)	Creatinine	0.4 (35.4)	0.2 (17.7)	0.48
(> 1 year)	HCO_3	-1	-1.3	0.58
	eGFR	-9.3	-12.7	0.96
Normal renal function	Creatinine	0.1 (8.8)	0.3 (26.5)	0.18
(N = 110)	HCO_3	-0.1	-1	0.61
	eGFR	-11.1	-14	0.65
Preop insufficiency	Creatinine	0.2 (17.7)	0.1 (8.8)	0.98
(eGFR < 60)	HCO_3	-0.6	-2.1	0.13
(N = 58)	eGFR	1.7	-0.4	0.49

*Multivariate analysis corrected for age, renal insufficiency, preoperative obstruction (hydronephrosis), and follow-up time (when appropriate).

underwent an ileal conduit solely based on renal insufficiency (SCr of > 1.8 mg/dL (159.12 umpl/L)) and 3 based on surgeon discretion due to comorbidities [10]. Looking at all patients undergoing conduit procedures, this group was significantly older than those undergoing continent diversions (71.4 vs 65.3, P < 0.001) and had lower mean preoperative eGFRs (63.8 vs 73.3, P < 0.001). Fifty-four patients presented with preoperative obstruction (hydronephrosis) and 44 underwent perioperative chemotherapy. In the patients with renal insufficiency (RI), there was a significant difference of a mean preoperative eGFR between conduit and continent diversions (41 vs. 48.5, P < 0.009), and significantly more patients with renal insufficiency underwent conduit diversions (P = 0.02) (Table 1).

Postoperative Analysis

For postoperative analysis, we examined the length of follow-up in relation to the type of diversion to evaluate whether there was an initial decline followed by stabilization or the possibility of improved renal function after obstruction correction. Of the 168 cases, there were 58 with short-term follow-up (3 to 12 months) and 110 with longer-term follow-up (> 1 year). The patients with conduit diversion in the short-term group experienced a small increase in renal function (eGFR: +1.6) while the continent group experienced a decline (eGFR: -9.3). These differences, however, were not statistically significant (P = 0.35). The longer-term group experienced a decline in renal function for both conduit and continent diversions but these were also not significant changes (P = 0.96). None of the changes in serum HCO3 were statistically significant (Table 2). The ureteroileal anastomotic stricture rate was ~2% (3/168), each of which was repaired at an average of 6 months from initial surgery, all without significant loss of renal function.

Renal Insufficiency

There were 58 patients with mild to moderate renal insufficiency with mean preoperative eGFRs of 41 and 48.5 for ileal conduit and continent diversion groups, respectively. There was no

statistically significant difference in functional renal decline in either group with an 18-month follow-up. The conduit group experienced a small increase in renal function (eGFR: +1.7) while the continent group experienced a negligible decline (eGFR: -0.4) (P = 0.49). Both groups showed a decline in serum HCO3 with a trend toward a steeper decline in the continent group (P = 0.13) (Table 2).

Confounding

We also analyzed the potential confounding effect of renal function improvement secondary to obstruction release. There was no significant difference between conduit and continent diversion in terms of preoperative hydronephrosis (16 conduit and 38 continent diversions, P = 0.6). Multivariable analysis corrected for age, renal insufficiency, and follow-up time (when appropriate), and did not show any significant differences when controlled for these variables (Table 2).

Chemotherapy

Of the total 168 patients, there were 146 who had complete data regarding the use of perioperative chemotherapy, and of those, 44 patients underwent neoadjuvant or adjuvant chemotherapy (11 conduit, 33 continent, P = 0.52). Blood samples were drawn preoperatively, after neoadjuvant chemotherapy, and at the most recent clinical follow-up. When controlling for age, preoperative eGFR, and preoperative obstruction and chemotherapy, there were again no significant differences seen in terms of SCr, eGFR, and HCO3 in the 2 diversion groups (using the Tukey-Kramer adjustment for multiple comparisons). Repeating the analysis of this cohort in terms of normal preoperative eGFR versus the renal-insufficient groups again yielded no significant differences using the same test (data not shown).

DISCUSSION

Urinary diversion is a vital component of treating lower urinary tract malignancies and other anatomic or functional urologic problems. The advancement of surgical techniques combined with increasing surgeon experience has provided several diversion options that can now be offered with few contraindications.

In this study, we measured overall decline in function relative to the type of urinary diversion performed. Our data shows, with relatively short-term follow-up, this type of diversion did not adversely affect renal function in any significant way. These findings are consistent with other recent studies. Osawa et al. [8] studied 70 patients (45 continent, 25 conduits) with a mean follow-up of 47 months and found no difference in renal deterioration between the types of diversion. Hofner et al. [6] examined 224 patients (131 conduits, 94 ONBs) and calculated a 5-year probability of freedom from new onset decline in renal function (de novo eGFR < 60) calculated as 47.8% of conduits and 44.8% of ONBs (P = 0.73). Bazzi et al. [5] studied 109 patients (25 continent, 84 noncontinent) with a mean follow-up of 25.6 months, which also showed no significant difference in overall renal decline. Xiao-Dong et al. [11] retrospectively examined a cohort who survived > 10 years after surgery (50 ileal conduits, 111 ONBs), defining renal deterioration as > 10 ml/min eGFR loss in 10 years, and found no significant difference in decline relative to the type of diversion performed. Our data combined with these other studies yields a compelling argument that there is, in fact, no differential adverse effect on renal function when comparing continent and noncontinent diversions in the short term.

This still does not answer the question of whether preexisting renal insufficiency should, in fact, be an absolute contraindication. Many experts quote an SCr of 150 to 200 umol/L (~1.7 to 2.3 mg/dL) as an absolute contraindication to continent diversion despite the paucity of data in the literature. This roughly equates to an eGFR of ~30 to 43 ml/min/1.732 in a 65-year-old Caucasian male (stage III CRF). The rationale behind this recommendation is that when poor renal function exists the body will be less capable of handling the additional acid load and metabolic abnormalities, leading to increased comorbidity and possibly mortality. The question remains whether urinary diversion in and of itself leads to further renal function loss. One could argue that patients with poor renal function are much more vulnerable to renal insults, and a continent procedure may be the tipping point into fulminant renal failure. However, this is difficult to isolate given age-related decline (which has been estimated at 1 ml/min/yr in those > age 50) [12] as well as numerous other contributing insults over a lifetime (i.e., HTN, DM).

Patients in this study with mild to moderate renal insufficiency showed no statistically significant difference in renal functional decline in either cohort with an 18-month follow-up. This finding suggests that patients with mild to moderate renal insufficiency may be acceptable candidates for continent diversion. While it is true that patients with continent diversion surgeries are generally younger and need to be motivated, committed, and have the necessary dexterity to care for continent diversion, all else being equal, continent procedures in appropriately selected patients may preserve renal function as well as noncontinent procedures.

While we did not show any significant trends toward adverse effects of continent diversions, the follow-up is still relatively short, and it is perhaps too early to discern whether these observations will stand the test of time. This study was not intended to extrapolate the short-term findings to the long-term results given the fact that so many factors can contribute to functional renal decline over time (age, HTN, DM, infections, etc.). However, the type of diversion does not appear to be

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the sole reason for long-term functional decline considering several studies have described functional deterioration with both conduit and continent diversions over the long-term (2,7,11,13-16). In fact, some long-term studies have shown a beneficial effect of continent versus conduit diversion in relation to decline [14] and that other underlying problems (postoperative obstruction, DM, HTN) may be more pertinent to declining renal function rather than the type of diversion performed [11]. Certainly, longer-term follow-up is necessary to assess whether preexisting renal insufficiency affects the outcome of continent diversion surgeries, although up to 40% of patients die from either disease or secondary causes within 5 years following cystectomy, precluding robust long-term studies on renal function [17].

One limitation to this data is that we are using discrete points in time to assess renal function and did not take into account confounding factors such as hydration. Additionally, since this was not a prospective study, there was no assessment protocol for renal function after surgery, and patients had routine follow-up with the most the recent labs at the time of analysis included.

Using the MDRD equation is helpful in establishing an accurate eGFR, but the SCr incorporated into that calculation does not take into account hydration status or other variables out of our control. One could also argue that the MDRD equation is not the most accurate for calculating renal function. However, for this type of analysis, which evaluates the change in values as long as the same equation is used both pre- and postoperatively, the results should be consistent.

We also did not account for hypertension and diabetes within our sample (data unavailable), which certainly plays a role in renal functional decline. However, the sequelae of these comoribidities are better appreciated over the long-term (years) and may not affect short-term data significantly. Additionally, one could also argue that patients who underwent chemotherapy should not be included in an analysis with those who did not. To evaluate this, multivariate analysis was performed (using the Tukey-Kramer adjustment for multiple comparisons), and showed no statistical difference between the 2 groups. Therefore, we felt it was reasonable to include these patients in the analysis.

The number of subjects used in this study is also relatively small, and it is possible there is not enough power to show differential effects on renal function between the 2 surgeries. This is particularly important in regards to the subgroup of renal-insufficient patients (N = 58). As described previously, patients with poor renal function are often considered ineligible for continent diversion and therefore it can be difficult to accrue large numbers of patients for this type of analysis. It is important to keep this in mind while interpreting this data. However, our results are similar to other published data, albeit also with low numbers for analysis, which lends credence to the assertion regarding preexisting renal insufficiency and continent urinary diversion.

Finally, this is retrospective data, with inherent selection bias for patients undergoing continent diversion. This bias we believe is minimized given that only 11 patients from the entire cohort underwent an ileal conduit solely based on renal insufficiency and 3 based on surgeon discretion [10].

CONCLUSION

In this study, the mean change in eGFR, creatinine, and bicarbonate levels following urinary diversion with either an ileal conduit or continent diversion were not statistically different. This was true even with evidence of preexisting mild to moderate renal insufficiency. Although follow-up is relatively short, this data suggests that mild preexisting renal insufficiency may not be a contraindication to continent diversion. In the future, a multi-institutional study with long-term follow-up may be necessary to truly and definitively evaluate the nature of this relationship.

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A Giant Capsular Leiomyoma of the Kidney Complicating Pregnancy: A Case Report

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ABSTRACT

Capsular leiomyoma of the kidney is a rare benign tumor. Usually they are very small tumors and do not produce symptoms. We report a case of a huge renal capsular leiomyoma in a pregnant woman, which led to premature delivery of the baby.

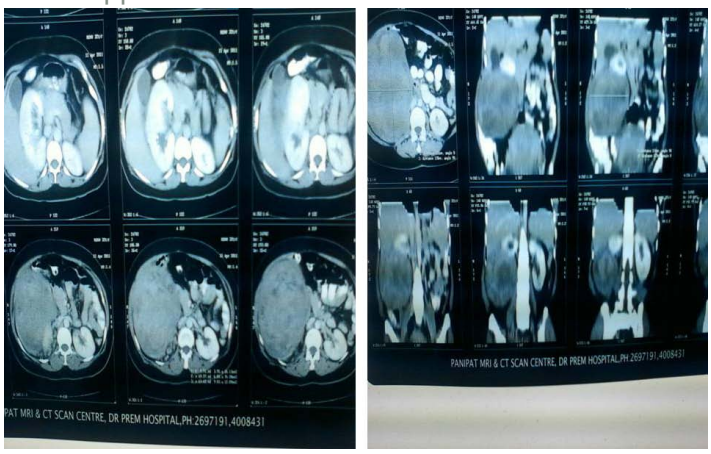
INTRODUCTION

Leiomyoma of the kidney is a rare benign tumor, usually asymptomatic, and mistaken as malignant. Diagnosis is made only on histopathology. They are usually less than 1 cm in diameter, and large ones are rare. Less than 100 cases of renal leiomyomas are reported in the literature [1], but to the best of our knowledge, none have been reported with a pregnancy.

CASE REPORT

A 30-year-old primigravida female was referred to our department 3 days after delivering a premature male baby, with a globular abdominal mass occupying the right hemi abdomen, crossing the midline. She was referred with a computed tomography- (CT) documented huge, lower pole renal tumor, possibly benign (Figure 1). She did not reveal any previous history of an abdominal mass. An intraoperative frozen section revealed features of leiomyoma kidney and, therefore,
lower polar partial nephrectomy was performed. She was discharged on the seventh postoperative day in a stable condition. Histopathology showed a leiomyoma arising from the renal capsule (Figure 2 and Figure 3).

Figure 1. Computed tomography showing a giant solid tumor arising from right kidney, lower pole, and crossing to the opposite hemi abdomen.



DISCUSSION

Leiomyomas usually present between the second and fifth decade of life, with a female preponderance (66%) [2]. These tumors are commonly seen in relation to the lower pole of the kidney (74%), with equal incidence in both kidneys. They can develop from the renal areas that normally contain smooth muscles, such as the renal capsule (37%), the renal pelvis (17%), renal cortical vasculature (10%), and indeterminate areas

KEYWORDS: Leiomyoma, kidney, pregnancy

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Figure 2. Specimen of the leiomyoma after lower polar partial nephrectomy. It is around 17 centimeters in its length.

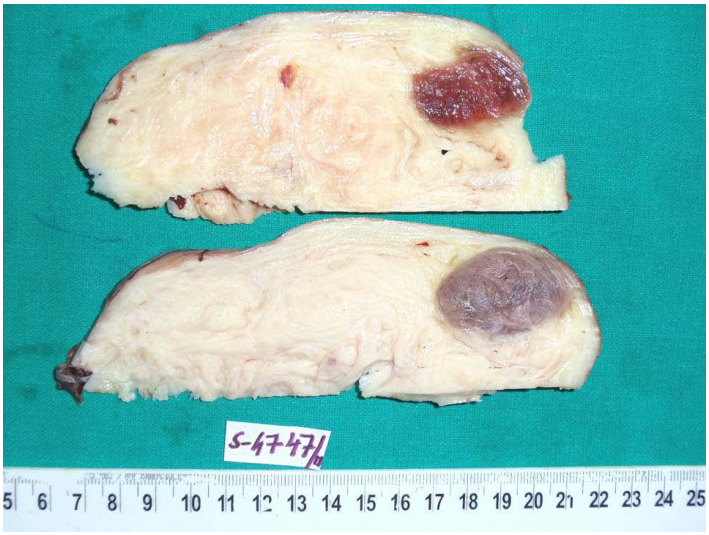
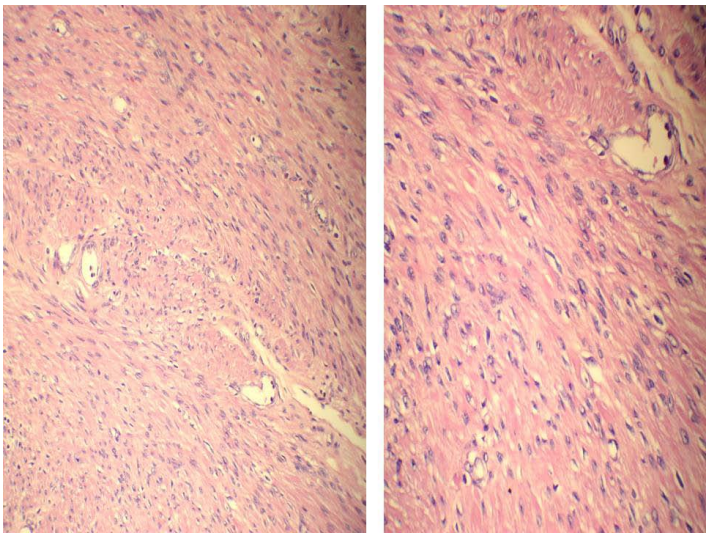


Figure 3. Histopathology of the specimen; the right side shows bundles of spindle cells arranged in fascicles (H&E, 20 X). The left side shows compressed renal parenchyma in the periphery, with few glomeruli and atrophied tubules (H&E, 10 X).



[2]. Their average size is less than 5 mm [3], they are usually asymptomatic, and when symptomatic they present as a large palpable mass (57%), with pain (53%), and with microscopic hematuria (20%). Diagnosis cannot be established by imaging alone. Small renal capsular leiomyomas typically appear as well circumscribed masses with homogenous enhancement on CT imaging and an occasional cleavage plane between the renal cortex and the tumor [4]. Irregular calcification may be seen in up to 20% of cases [4,5]. In large leiomyomas, the loss of fat planes makes it difficult to differentiate it from leiomyosarcomas, large exophytic renal carcinomas, and angiomyolipomas. Total nephrectomy is indicated for large leiomyomas to avoid the risk of necrosis, infection, and malignant degeneration; however, the exact risk is not known [5].

CONCLUSION

Giant leiomyomas of the kidney are rare tumors, which can grow rapidly in pregnancy, leading to premature termination of the pregnancy along with diagnostic difficulties.

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A Large Staghorn Calculus in Cross-Renal Ectopia: A Rare Presentation

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ABSTRACT

Crossed renal ectopia is a rare congenital malformation and is the second most common fusion anomaly after a horseshoe kidney. Crossed ectopic kidneys are fused to their ipsilateral mate in 90% of cases. crossed fused renal ectopia is usually diagnosed when other disease states are being investigated. It rarely causes significant clinical problems. Treatment is only indicated for the complication of the anomaly rather than for the anomaly itself.

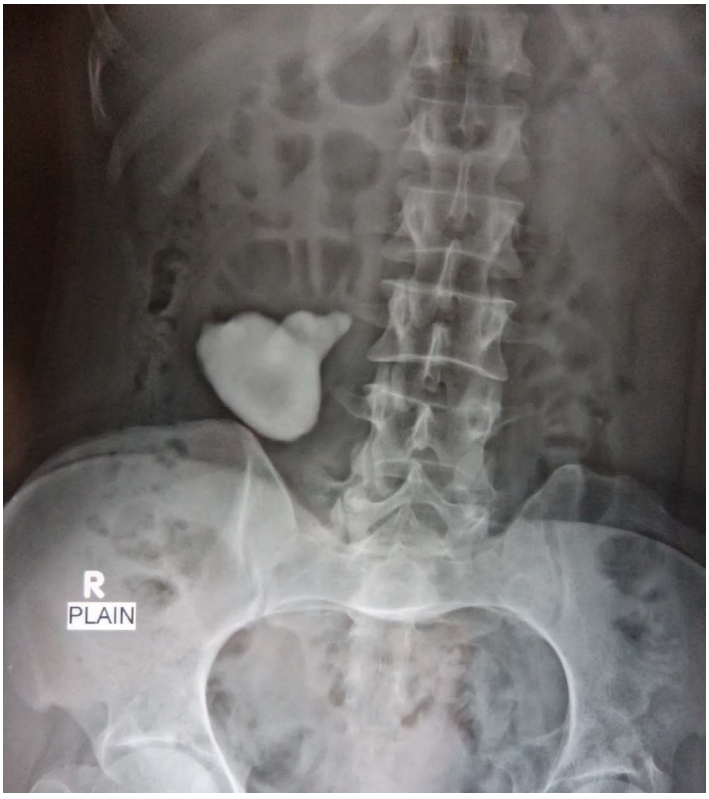
INTRODUCTION

Crossed renal ectopia is a rare congenital malformation and is the second most common fusion anomaly after a horseshoe kidney. Crossed ectopic kidneys are fused to their ipsilateral mate in 90% of cases. A case of crossed-fused, left-to-right renal ectopia with a staghorn calculus is reported herein.

CASE REPORT

A 30-year-old male presented with a 6-month history of intermittent, dull, right lower abdominal pain. There was no history of hematuria, graveluria, increased urinary frequency, urgency, or weight loss. Physical examination revealed a tender palatable lump of 7 cm x 6 cm in size without guarding and rigidity. Urinalysis revealed microscopic hematuria, while the urine culture was sterile. His hematological and biochemical profile was normal. Abdominal ultrasound revealed a large calculus in the left-to-right crossed-fused kidney measuring 5 cm maximum, casting a posterior acoustic shadow with dilatation of the pelvicalyceal system. A plain abdominal X-ray showed a large radio-opaque shadow at the level of L3-L4 (Figure 1). Intravenous urography revealed a normally functioning, malrotated, orthotopic right kidney with a nondilated pelvicalyceal system and laterally deviated ureter. Figure 2 shows the left-to-right crossed ectopic kidney showed a large staghorn calculus with a dilated pelvicalyceal system.

Figure 1. A plain abdominal X-ray showing a large radio-opaque shadow at the level of L3-L4.



KEYWORDS: Crossed-fused renal ectopia, staghorn, nephrolithiasis

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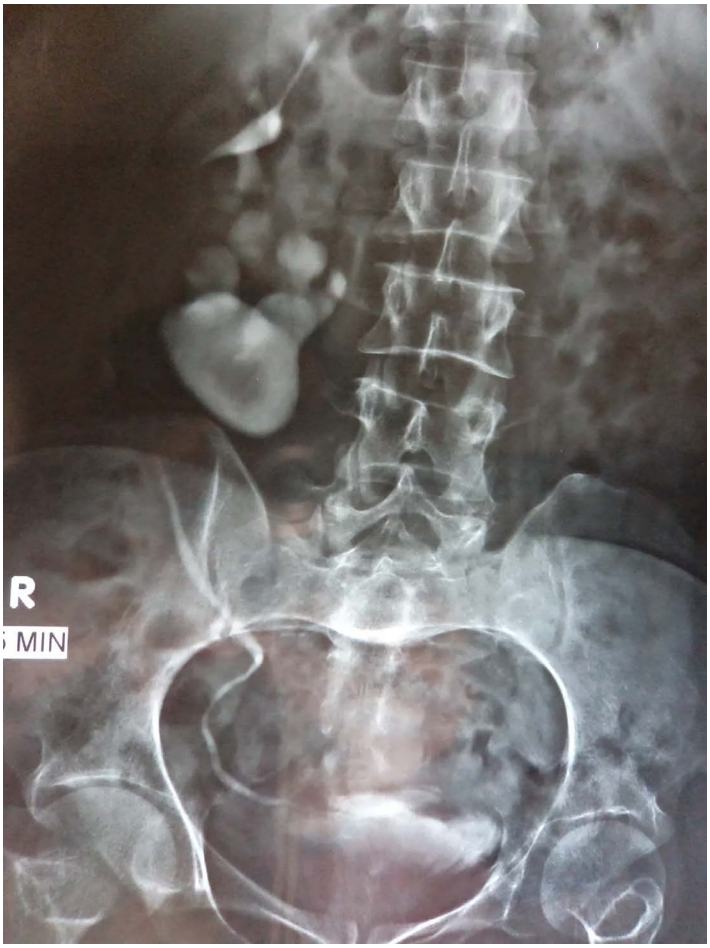
Figure 2. The left-to-right crossed ectopic kidney shows a large staghorn calculus with a dilated pelvicalyceal system.



A micturating cystourethrogram showed no reflux. Cystoscopy showed normal bilateral ureteric orifices. Bilateral ureteric catheterization was done.

A right pyelolithotomy was done in the flank position with an extraperitoneal approach. The Gerota fascia was opened by sharp dissection, and peripelvic dissection was carried out. No significant vessels crossing the pelvis were noted. A liberal pyelotomy was done. The pelvic and calyceal part of the stone (approximately 6 cm x 5 cm x 4.5 cm) was delivered with little manipulation (Figure 3). The postoperative period was uneventful.

DISCUSSION

Ectopic kidneys are thought to occur in approximately 1 in 1 000 births but only about 1 in 10 of these cases is ever diagnosed.

Figure 3. The pelvic and calyceal part of the stone (approximately 6 cm x 5 cm x 4.5 cm) was delivered with little manipulation.

Some of these cases are discovered incidentally, when a child or adult is having ultrasonography for a medical condition unrelated to renal ectopia [1]. Simple renal ectopia refers to a kidney that is located on the proper side of the abdomen but is abnormal in position. Crossed renal ectopia, on the other hand, refers to a kidney that has crossed from left to right or vice-versa and was first described by Pamarolus in 1964 [2,3].

Crossed-renal ectopia was classified by Mcdonald and McClellan into 4 types: 1) crossed renal ectopia with fusion, 2) crossed renal ectopia without fusion, 3) solitary crossed renal ectopia, and 4) bilaterally crossed renal ectopia. Those with fusion were further classified by the nature of the fusion and position [4]. The last significant review of the subject was conducted in 1959 and reported 500 cases of crossed renal ectopia with or without fusion that presented primarily with clinical symptoms [5].

Embryology of crossed renal ectopia is unclear. Some have suggested that the developing kidney crosses to the opposite side [6]. According to others, the ureteral bud alone is responsible for crossing. This is based on the fact that ureteral pain from stones is felt on the side of the ureteral orifice, where renal pain is felt on the side of the kidney [7].

In 20 to 30%, the pathology is an incidental finding. In the rest, the most common symptoms reported are abdominal or flank pain, a palpable mass, hematuria, urinary tract infection, and dysuria [7]. The urological conditions associated with crossed renal ectopia are hydronephrosis, reflux or tumors, and

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nephrolithiasis [8].

The simultaneous occurrence of bilateral multiple calculi leading to acute on chronic renal failure has been reported [9]. Stubbs and Resnick reported 2 cases of staghorn calculi in crossed fused ectopic kidney, which were treated by anatrophic nephrolithotomy [10].

Modi, Goel, and Dodia reported a laparoscopic pyeloplasty and pyelolithotomy performed on an 8-year-old boy who had calculi in the lower pole of the right kidney coexisting with crossed fused renal ectopia [11]. Gupta, Yadav, and Singh described a similar procedure in a child with a similar presentation [12]. Mishra et al. reported supine percutaneous nephrolithotomy for bilateral complete staghorn calculi in an L-shaped crossed fused renal ectopic anomaly. [20]. The diagnosis is made by ultrasonography and intravenous urography. Ultrasound can detect concomitant urinary pathology and cystic changes [13].

Anatomic delineation is best achieved by intravenous urography. Besides showing function, it can give an idea of ureteric displacement [14]. Other imaging modalities such as retrograde and intraoperative antegrade ureterography, renal cortical scintigraphy using 99mTc dimercaptosuccinic acid, computed tomography, and magnetic resonance imaging have been shown to be useful in the diagnosis of renal ectopia and ectopic ureters [15].

Generally, no treatment is needed for an ectopic kidney if renal function is normal and no complication, such as a UTI, stones, or obstruction, is found. Even in the absence of any of these, patients need to be followed up closely [3]. Renal ectopia complicated with calculi could be managed conservatively or with a number of endoscopic and other procedures, including shock-wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy, laparoscopic guided percutaneous lithotomy, and laparoscopic pyelolithotomy.

In conclusion, crossed fused renal ectopia is usually diagnosed when other disease states are being investigated. It rarely causes significant clinical problems. Treatment is only indicated for the complication of the anomaly rather than for the anomaly itself.

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Chordee without Hypospadias with a Communicating Symptomatic Epidermoid Cyst: An Unusual Presentation

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ABSTRACT

We present an unusual case of chordee without hypospadias with a communicating, symptomatic epidermoid cyst. A 12-year-old boy presented with painful erections, especially early in the morning, over the last year and a watery discharge from swelling located near the meatus for 2 months. On examination, ventral chordee was present, the meatus was orthotopic, the prepuce was normal, and a ~0.5X0.5 cm swelling was present near the meatus on the ventral aspect with watery discharge. During operation, it was found that this swelling had communication with the urethra, and it was an epidermoid cyst on histopathologic examination.

INTRODUCTION

Ventral penile curvature, or chordee, is common in hypospadias but is much less frequent when the meatus is orthotopic [1]. It rarely presents in isolated form, and its association with a symptomatic epidermoid cyst is very rare and has not been reported. The etiology and management of this condition continues to be a subject of debate in the literature.

CASE REPORT

A 12-year-old boy presented with chief complaints of painful erections, especially early in the morning, over the last year and a watery discharge from swelling located near the meatus for 2 months. There was no history of fever, nausea, vomiting, or voiding difficulty. He attained all developmental milestones normally. There was no other comorbid illness. His general and systemic examination revealed no abnormality. On local examination, ventral chordee was present, the meatus was orthotopic and normal, the prepuce was normal, and a ~0.5X0.5 cm swelling was present near the meatus on the ventral aspect and had a watery discharge. Both testes had normally descended. A testicular and renal ultrasound was done to rule out any other associated malformation, and imaging results were normal.

After a proper pre-anesthetic check-up, he was taken for definitive surgery. A circumcising incision 5 mm behind the corona was made dorsally, and then the swelling communicating with the urethra was excised ventrally, and chordee correction was done. A transverse preputial island flap was made to cover the short urethra. Closure was done after a dorsal incision on the penile skin. The postoperative period was satisfactory. The histopathologic diagnosis of the swelling was an epidermoid cyst.

DISCUSSION

Isolated chordee without hypospadias is rare, and its association with a symptomatic, communicating epidermoid cyst is very rare. The etiology and management of this condition continues to be a topic of debate in literature. Penile epidermoid cysts are uncommon. They are lined by well-developed, stratified epithelium without skin appendages. Although the etiology is unknown, some reports have suggested that it may originate from a median raphe cyst, possibly arising from abnormal embryological closure of the median raphe or, rarely, may be acquired after mechanical implantation, such as that involving injection of epidermal fragments. They usually do not communicate with the urethra. This type of presentation of

KEYWORDS: Chordee, hypospadias, congenital, preputial

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Figure 1. Ventral chordee without hypospadias with an epidermoid cyst.

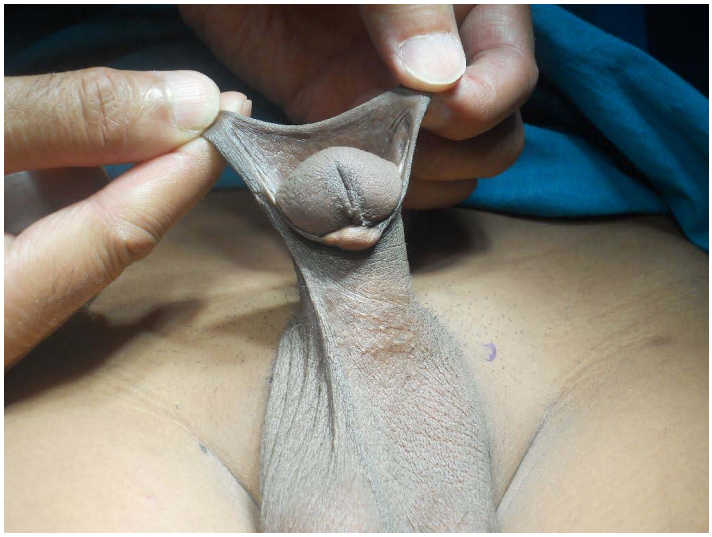
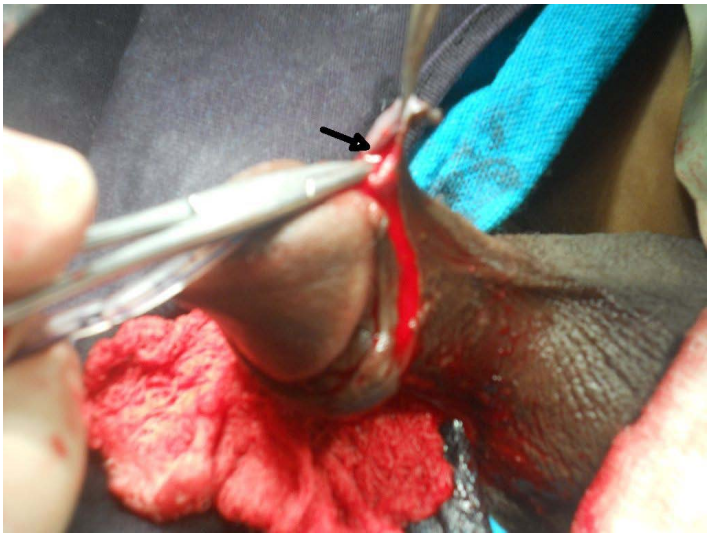


Figure 2. A cyst communicating with the urethra (black arrow).

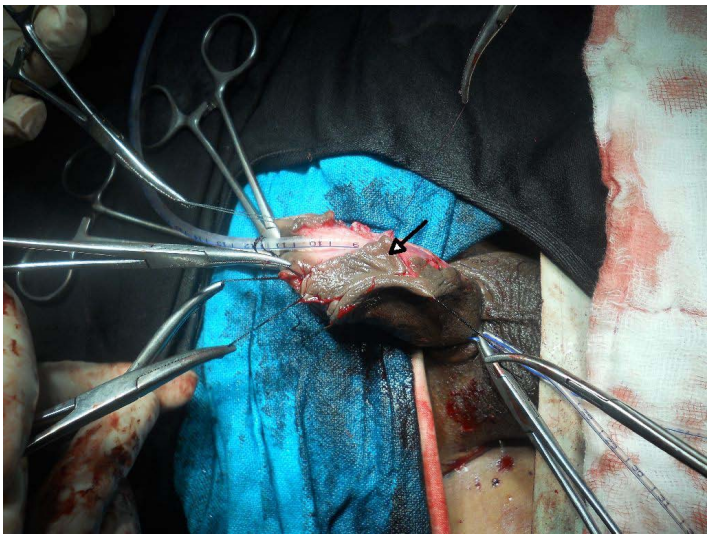


a communicating, symptomatic epidermoid cyst has not been reported in published literature to the best of our knowledge [2]. Developmental arrest is a presumed cause of hypospadias and often results in curvature with a relative shortening of ventral structures.

In 1973, Devine and Horton classified chordee without hypospadias into groups based on the different etiologies involved. Type I is considered the most serious defect. This comes about when the corpus spongiosum, dartos, and Buck's fascia are deficient in the portion of the urethra that is involved. Therefore, the urethra is located directly below the skin, and the fibrous tissue under the urethra causes the chordee. In type II, the corpus spongiosum is normal while the dartos and Buck's fascia are dysgenetic. In type III, only the dartos is deficient, causing penile curvature. Kramer subsequently recognized that corporal disproportion is an additional cause of penile curvature and classified this type as type IV chordee without hypospadias. Congenital, short urethra is also recognized as a rare cause of congenital chordee. In 1937, Young proposed that chordee without hypospadias was due to congenital, short urethra and suggested transection and reconstruction of the curved ventral urethra. In 1973, Devine and Horton proposed that chordee without hypospadias was due to abnormal development of the fascial layers surrounding the urethra. In their experience, the majority of patients were successfully treated by fibrous tissue resection while urethral transection was rarely required to straighten the penis [3].

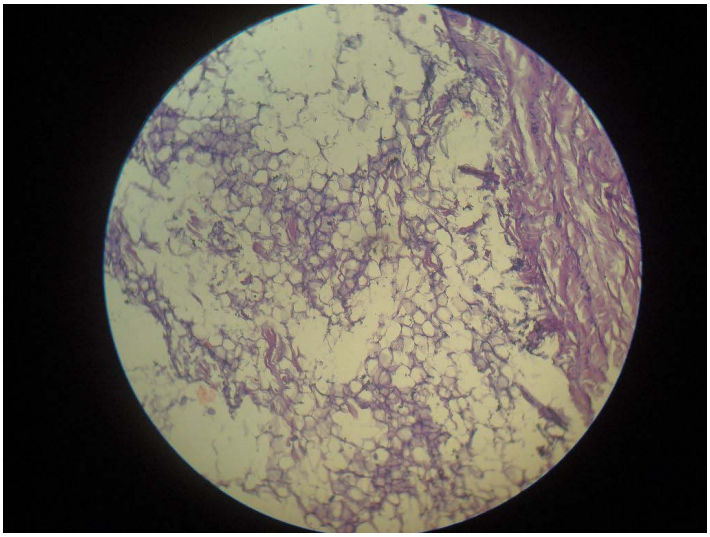
In 1982, Kramer recognized that corporal disproportion was

Figure 3. Transverse preputial island flap (black arrow).



an important cause of isolated chordee and recommended carrying out dorsal plication following the Nesbit principle to correct this type of chordee without hypospadias [4]. However, others suggest that elongating ventral corporal organs with graft material is superior to plication of the ventral corporal organs in severe penile curvature [5-7]. Successful repair of chordee without hypospadias should produce a straight phallus with a urethral meatus that permits normal urination.

Figure 4. Histology of the cyst showing a lipodermoid (H&E x 10).



CONCLUSION

Congenital, isolated chordee is a rare entity, especially when it presents in association with a symptomatic, communicating, epidermoid cyst. It can negatively affect the urination mechanism and cause alterations in genital aesthetics. There are multiple techniques for correcting this pathology but each case should be individualized. It is important to first define which structures are involved to avoid carrying out extensive unnecessary procedures. Preschool age is the ideal age for correcting this pathology.

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Complete Isolated Transection of a Distal Female Urethra Following a Bull Horn Injury: A Rare Urological Emergency

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ABSTRACT

Complete transection of the female urethra without associated pelvic fracture is a very rare presentation. We report a case of isolated rupture of the distal female urethra causing complete transection due to a bull horn injury for the first time in the literature. A 42-year-old woman presented to the Emergency Department immediately following a bull horn injury with complaints of severe bleeding via her vaginum and lower abdominal pain. A detailed examination revealed full laceration of the anterior vaginal wall with complete transection of the urethra 1 cm proximal to the external meatus with no signs of pelvic trauma on imaging. A primary repair was completed in layers with an excellent outcome, and there was no long-term morbidity during her 1-year follow-up. Female urethral injuries may be difficult to identify but early detection and primary repair provide the best chances of a cure. End-to-end repair is the gold standard for management in such cases.

INTRODUCTION

Urethral injury in females is an uncommon presentation and, unlike male urethral injury where pelvic trauma is a common etiological factor, these injuries are usually complications of vaginal and obstetric surgeries or instrumentation. Apart from being overlooked, these injuries have been inadequately reported in literature and their management is poorly outlined.

CASE REPORT

A 42-year-old lady presented to the Emergency Department 2 hours following a bull horn injury with complaints of profuse vaginal bleeding and pain in the perineum and lower abdomen. The patient had a pulse rate of 92/min and a blood pressure of 104/70 mm Hg. Local examination revealed a thick laceration of the anterior vaginal wall along with a complete tear of the distal urethra 1 cm proximal to the external urethral meatus (Figure 1). Patency of the proximal urethra was assessed by a gentle attempt at catheterization. Her abdominal examination was normal, and her digital rectal and vaginal examinations did not reveal any sign of associated rectal injury. Her pelvic compression test was negative. A computed tomography (CT) scan of the lower abdomen and pelvis was performed, which did not show any associated pelvic fracture or visceral injury. The routine laboratory workup was also within normal limits.

The patient was taken for emergency repair after initial resuscitation with fluids, antibiotics, and tetanus toxoid. The patient was operated on under spinal anesthesia in a lithotomy position. Both ends of the urethra were identified, mobilized, spatulated, and anastomosed in an end-to-end fashion over a 16 Fr Foley catheter in a single layer. Laceration of the anterior vaginal wall was repaired as a second layer using interrupted full-thickness absorbable sutures (Figure 2), and a vaginal pack was applied.

The postoperative period was uneventful and the patient was able to void spontaneously after removal of the catheter 1 week after surgery. The patient had no difficulty in voiding, and there was no incontinence or fistula formation during the 1 year of follow-up.

KEYWORDS: Isolated urethral injury, female urethral injury, bull horn injury, complete urethral transection

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Figure 1. Complete transection of the distal female urethra with anterior vaginal wall injury.

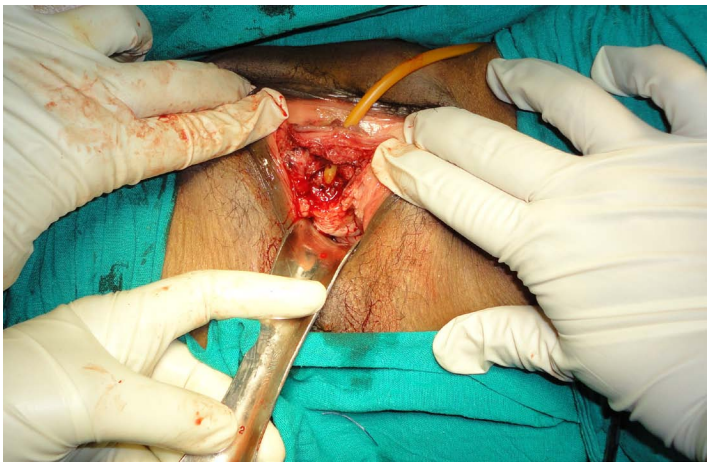
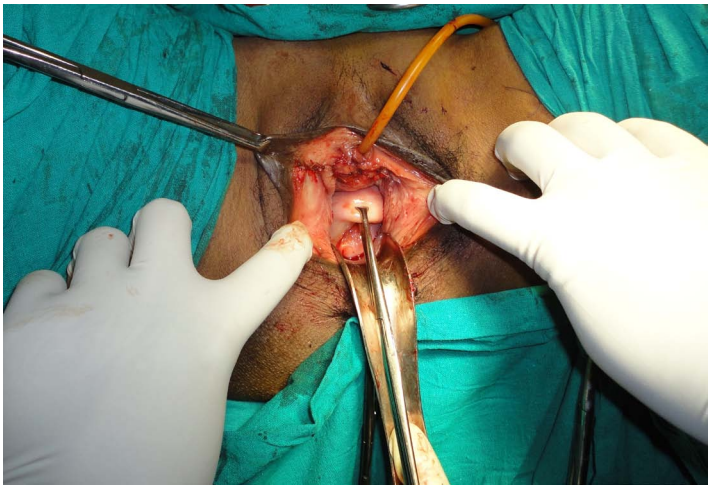


Figure 2. Completed primary repair in 2 layers.



DISCUSSION

Among female patients with pelvic fracture, concomitant urethral injury is rather rare [1], with an incidence of only 4 to 6% [2]. However, many of the female urethral injuries are associated with pelvic fractures. Isolated female urethral injury leading to complete disruption is a very uncommon presentation [3].

The typically encountered female urethral injury consists of a partial tear of the proximal anterior wall, while complete disruption is rare and usually associated with severe vaginal lacerations [4], as in this case. Most of these complete disruptions occur at the level of the bladder neck and proximal urethra, compared to the distal urethral injury in this case. Injuries have been found to be more common in children compared to adults. Injuries due to bull horns are common in rural India [5], but only an isolated case of urethral trauma could be found in the literature following bull horn injury occurring in a male, leading to urethrorectal fistula.

A review of literature reveals few small series on female urethral trauma and some isolated case reports. There is a lack of consensus on the management of female urethral injuries due to their relatively rare occurrence. Urethral injuries in females are more commonly found in association with pelvic trauma, and their management includes urinary diversion by a suprapubic cystostomy and delayed reconstruction for complex injuries [6]. Occasionally, simple urethral disruptions have been repaired. A similar case of isolated urethral transection following blunt trauma has been reported by Takayama et al. [7] but was managed by initial cystostomy and delayed repair.

In our experience, a transvaginal primary repair offers excellent results when the injury is promptly recognized and repaired. Due to the short length and accessibility of the female urethra, simple isolated urethral injuries can be subjected to early and successful repair.

CONCLUSION

Isolated urethral injury in females is a very rare entity, and it is often not subjected to immediate evaluation following trauma. Early diagnosis and prompt transvaginal repair is the best approach to isolated complete transection of the female urethra.

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Ileovesical Fistulae: A Rare Complication of Crohn Disease

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ABSTRACT

An ileovesical fistula is a rare complication of Crohn disease. It presents with recurrent abdominal pain, pneumaturia, fecaluria, recurrent urinary tract infection, and dysuria. A 13-year-old girl presented with an ileovesical fistula, which was diagnosed by clinical history, micturating cystourethrogram, and computed tomography (CT) cystography. Exploratory laparotomy, an excision of the fistulous tract, bladder repair, and ileostomy were performed. The histopathological examination of a resected, affected ileal segment showed the classical non-caseating granuloma, characteristic of Crohn disease. The restoration of bowel continuity was done later on. The patient is doing well after 3 years of follow-up.

CASE REPORT

A A 13-year-old girl presented with recurrent abdominal pain for 3 years along with pneumaturia, fecaluria, recurrent urinary tract infection, and weight loss for 6 months. Her general physical examination showed moderate pallor, and and examination of the abdomen was unremarkable. Her urine culture showed the growth of E. coli sensitive to ciprofloxacin. Her hemogram showed Hb% of 8 gm% and her serum albumin was 2.8 gm%. The renal parameters were normal. The ultrasound of the abdomen showed the normal bilateral renal units. The cystoscopy showed the presence of a 2 cm x 2 cm opening over the dome of the bladder, discharging fecal matter with bullous edematous reaction surrounding the opening (Figure 1a). The left ureteric orifice was normal, and the right orifice was not appreciated because of the bullous edematous reaction. A 15 Fr cystoscope entered easily inside the lumen of the intestine (Figure 1b). The cold-cup biopsy from the margins of the fistulous orifice was suggestive of chronic, non-specific inflammation. A micturating cystourethrogram (MCU) showed the contrast entering into the small bowel loop (Figure 2a). The computed tomography (CT) cystography with 3D reconstruction showed the presence of an ileovesical fistula (Figure 2b, Figure 2c). A urine specimen for the AFB stain, microscopy, and a culture were negative for acid-fast bacillus.

On exploratory laparotomy, bowel loops were adhered to each other and the fistula was about 1 feet proximal to the ileocecal region. The bladder was opened in the midline anteriorly and extended superiorly up to the fistulous opening. The bladder side of the fistulous margin was excised completely, ureteral orifices were stented, and the bladder was repaired in 2 layers by 3-0 polygalactin. A urethral catheter and a suprapubic catheter were inserted. About a 10 cm ileal segment on either side of the ileal fistulous opening was resected. The ileal loops were exteriorized as ileostomy.

The postoperative period was uneventful. The histopathological examination of the resected ileal loops near to the fistula showed chronic, nonspecific inflammatory infiltrate with non-caseating granuloma (Figure 3a). The histopathological examination of the bladder wall near the fistulous site also showed chronic, nonspecific inflammation (Figure 3b). A cystogram, performed at 4 weeks just following catheter removal, showed no evidence of contrast extravasation. The bladder biopsy was suggestive of chronic cystitis. Postoperatively on the enzyme immune assay, the anti-saccharomyces cerevisiae antibody (ASCA) IgG serum level was 26.3 IU/L and the ASCA IgA serum level was 76.3 IU/L, with perinuclear antineutrophil cytoplasmic antibody (P-ANCA) and cytoplasmic antineutrophil cytoplasmic antibody (C-ANCA)

KEYWORDS: Ileovesical fistulae, pneumaturia, Crohn disease

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Figure 1. a) Cystoscopy showing an opening on the dome of the bladder, with fecal material (left). b) An endoscopic view of the ileal lumen (right).

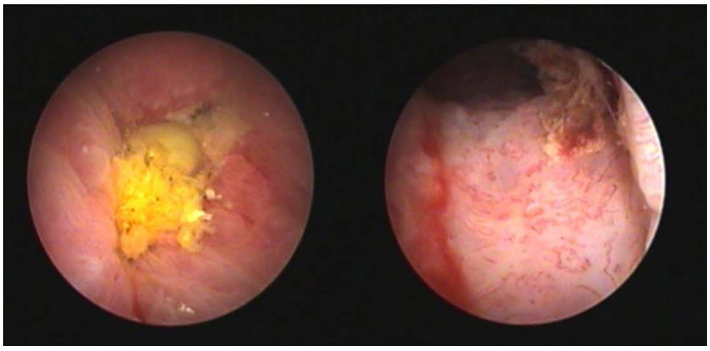
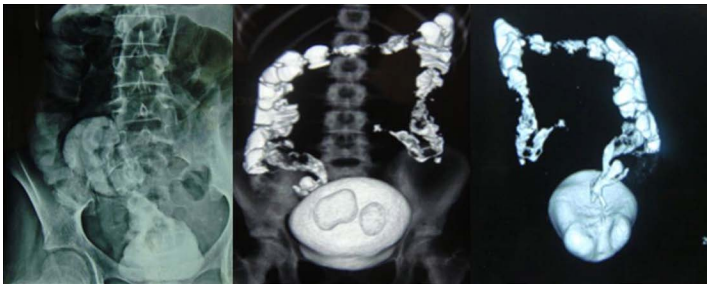


Figure 2. a) An MCU showing contrast entering in the lumen of the ileum (left). b) A CT cystography with 3D reconstruction in AP view showing ileovesical fistulae (middle). c) A CT cystography with 3D reconstruction in PA view showing ileovesical fistulae (right).



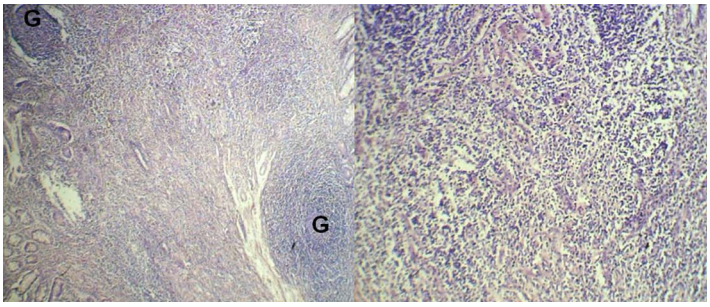
being negative. The patient was put on a low-dose steroid (prednisolone, 10 mg once a day, tapered and stopped after 6 weeks). The patient's general condition improved with weight gain (3 kg in 6 weeks). Ileostomy closure was done after 3 months of the initial laparotomy. The postoperative period was uneventful. The patient is doing well in 3 years of follow-up.

DISCUSSION

An ileovesical fistula is a rare complication of Crohn disease [1]. There was a time when Crohn disease was considered extremely rare in India, but in the last 10 years, there are case reports that suggest that it is no longer very rare [3,4]. The ileovesical fistula could be due to tuberculosis, malignancy, and ulcerative colitis. From India, Crohn disease has also been reported in pediatric age groups [4]. The diagnosis is based on clinical history, cystoscopy, cystography, and biopsy. The classical histopathology in the affected intestine reveals typical non-caseating transmural granulomas with skip lesions [1-3]. There are serological markers such as ASCA and ANCA, which help in making the diagnosis [5]. The treatment of small, unrecognized fistulae could be conservative using corticosteroids and 5-aminolevulinic acid [1-3,5]. The conservative treatment leads to improvement in the symptoms and closure of the fistula. The larger fistula needs surgical intervention.

In exploratory laparotomy for ileovesical fistulae, another concomitant internal fistulae such as an ileosigmoid fistula must be ruled out [1,2]. In our preoperative patient, we diagnosed the fistulae by cystoscopy and cystography suggestive of ileovesical fistulae. The preoperative biopsy from the fistulous margin in the bladder revealed chronic, nonspecific inflammation. The histological examination of the resected ileal segments showed the transmural, non-caseating granuloma typical of Crohn disease. The postoperative serological markers (ASCA and PCNA) were done to strengthen this rare diagnosis. The ASCA (raised titre) is more specific to Crohn disease [5]. Steroids should be given to patients, which is beneficial in such patients. In our patient, her general condition improved following steroid treatment, and the patient showed weight gain.

Figure 3. a) A microphotograph showing the transmural, non-caseating granuloma (left). b) A microphotoraph showing inflammatory cell infiltrate in the bladder biopsy (right).



CONCLUSION

Ileovesical fistulae in Crohn disease is a known but rare complication. For larger fistulae, surgical intervention in the form of exploratory laparotomy, excision of the fistulous tract, bladder closure, and, finally, restoration of bowel continuity are the treatments of choice.

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Perinephric Urinoma in a Woman During the Postpartum Period: A Case Report

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ABSTRACT

A urinoma is a continued perinephric or peripelvic extravasation of urine leading to the formation of encapsulated retroperitoneal urine collection due to the disruption of the urinary collecting system. Non-obstetric urinomas are usually the result of trauma, a urologic procedure, infection, and nephrolithiasis. We report a case of perirenal urinomas that were detected during the postpartum period.

INTRODUCTION

Urinomas are a continued perinephric or peripelvic extravasation of urine leading to the formation of an encapsulated retroperitoneal urine collection due to the disruption of the urinary collecting system [1]. A non-obstetric urinoma is usually the result of trauma, a urologic procedure, infection, and nephrolithiasis [2]. We report a case of perirenal urinomas that were detected during the postpartum period.

CASE REPORT

A 25-year-old female presented with the complaint of swelling on the right side of the abdomen and a dull, aching pain. The patient gave birth 5 weeks before via vaginal delivery. There was no history of trauma or stones, and no documented urinary tract infection during her pregnancy. The physical examination showed a soft lump on the left side of the abdomen. The lump was dull on percussion and had a smooth surface. The urinalysis yielded normal results, and the urine culture was negative. Her serum creatinine level was 0.6 mg/dL. Ultrasonography showed echo-poor collection around the kidneys. An abdominal computed tomography (CT) scan revealed poor attenuation with a large amount of collection around the left kidney. Perinephric collection was seen on the right side but less than the left. However, there was no evidence of hydronephrosis. Percutaneous drainage was performed on the left side. Approximately 4 000 ml of amber colored fluid was drained. After 7 days, the ultrasonography showed that the urinoma had resolved. There was no longer any urinary leakage via the drainage catheter, which was consequently removed. The patient was asymptomatic at the 6-week follow-up.

DISCUSSION

Hydronephrosis during pregnancy is quite common and is often associated with mechanical obstruction of the ureters at the pelvic brim [3]. Although this is present in over 80% of pregnant women, the ureter and bladder are usually restored to normal within several weeks postpartum [4]. Usually, the right ureter is much more affected than the left ureter, which is somewhat protected by the sigmoid colon and its mesentery [4].

Maternal urinoma is thought to develop secondary to a rupture of the calyceal fornix [5]. It occurs when renal pelvic pressure exceeds a critical level between 20 and 75 mm Hg due to ureteral or renal compression [6-9]. Urinomas in postpartum women may be due to acute or chronic retention [2].

Urinomas during pregnancy are an acute event, which is triggered by acute obstruction of both ureters during pregnancy and childbirth. Forniceal rupture secondary to ureteral obstruction and hydronephrosis is an established route of urinoma formation. In our case, the absence of hydronephrosis

KEYWORDS: Urinoma, postpartum, perinephric

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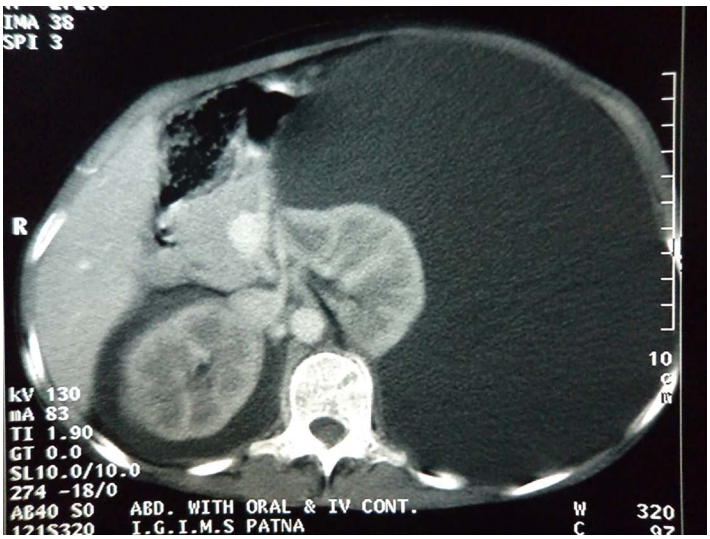
Figure 1. Urinoma imaging.



on imaging is presumably due to a time gap between the acute event of obstruction and the clinical presentation of the patient (6 weeks) during which hydronephrosis probably cleared.

The clinical presentation of hydronephrosis is flank pain and tenderness associated with gastrointestinal distress. These symptoms are similar to those of other obstetric and surgical emergencies such as appendicitis, cholecystitis, nephrolithiasis, and/or acute hydramnios [10]. Occasionally, increasing hydronephrosis can lead to retroperitoneal urinary extravasation and urinoma formation. Such a complication may lead to a perinephric abscess, peripelvic urine granuloma, or retroperitoneal fibrosis [11,12].

Reports of bilateral urinoma in connection with pregnancy are very rare in the literature [13]. Prompt diagnosis and management of urinary extravasation is very important and urgently requires measures to prevent such complications. Ultrasonography is indispensable for a diagnosis, and CT scanning may also aid in the diagnosis [14,15].

A perinephric urinoma appears on sonography as a homogenous collection of anechoic fluid. The treatment of a urinoma depends on the urinary extravasation cause and the degree to which the functioning of the kidney is affected. The treatment goals are to preserve renal function, relieve pain, and allow the ruptured site to heal [16].

In most cases, small urinomas will reabsorb without intervention. If urinomas are large or persist for several days, drainage of the urinoma should be considered. If a urinoma does not diminish despite an adequately positioned percutaneous drainage catheter, decompression of the pelvicalyceal system must be done in order to prevent continuous enlargement [15].

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Two Cases of Adult Disorders of Sexual Differentiation Presenting as Hematometra and Adenexal Masses

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ABSTRACT

Disorders of sex differentiation (DSDs) are defined as congenital conditions associated with atypical development of chromosomal, gonadal, or anatomical sex. It presents as a medical emergency at the time of birth, requiring correct gender assignment. In developing countries, adult presentation with incorrect gender assignment is not uncommon. The aim of this paper is to report 2 rare presentations of DSD in adulthood. The first patient presented with hypospadias and a non-palpable right testis while the second patient presented with cyclical abdominal pain and abnormal external genitalia. Both patients were 46,XX on karyotyping, and the computed tomography (CT) of the abdomen showed female internal genitalia with hematometra and gonadal cysts. The delayed adult presentation of DSD, with incorrect gender assignment, is a not a rare occurrence in the developing world. It is a challenging situation, and most of the time management has to be based on psychological and social factors rather than pure scientific principles.

INTRODUCTION

Disorders of sex differentiation (DSDs) are defined as congenital conditions associated with atypical development of chromosomal, gonadal, or anatomical sex [1]. To the best of our knowledge, we are reporting, for the first time, 2 rare cases of adult presentation of DSD as unsuspected hematometra and adenexal cysts.

CASE REPORT

Case 1

A 28-year-old unmarried male presented with a complaint of cyclical suprapubic pain every 2 to 3 months over the past 6 months and abnormal external genitalia since birth. The patient had a history of erections of the phallus upon stimulation without ejaculation. The physical examination revealed a masculine built phenotypic male with a short penis and penoscrotal hypospadias (Figure 1). The scrotum appeared well formed with a small left testis and an absent right testis, which was non-palpable anywhere. The abdominal examination was unremarkable. The contrast-enhanced computed tomography (CT) scan showed a hematometra with a heterogeneously enhancing right adenexal mass and a large cyst (Figure 1). The uterus appeared to be communicating with the posterior urethra with a fistulous tract. His hormonal profile was normal for a male with serum testosterone on the low/normal side. An evaluation of congenital adrenal hyperplasia was negative. After karyotyping, the diagnosis of 46,XX DSD was made. The patient underwent a laparoscopic hysterectomy with an excision of the right adenexal mass (Figure 1). The histopathology confirmed benign right-sided ovotestes with a cystic component, along with hematometra and endometritis. Since the patient wanted to continue with his male phenotype, he was counseled regarding impotence and infertility. Later, the patient was planned for the correction of his hypospadias.

Case 2

KEYWORDS: Hermaphroditism, hematometra, DSD

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Figure 1. a) Adult male phenotype; b) A short penis with a small left testis and a non-palpable right testis; c) Female internal genitalia; d) Gross specimen of the uterus with a right adenexal mass.

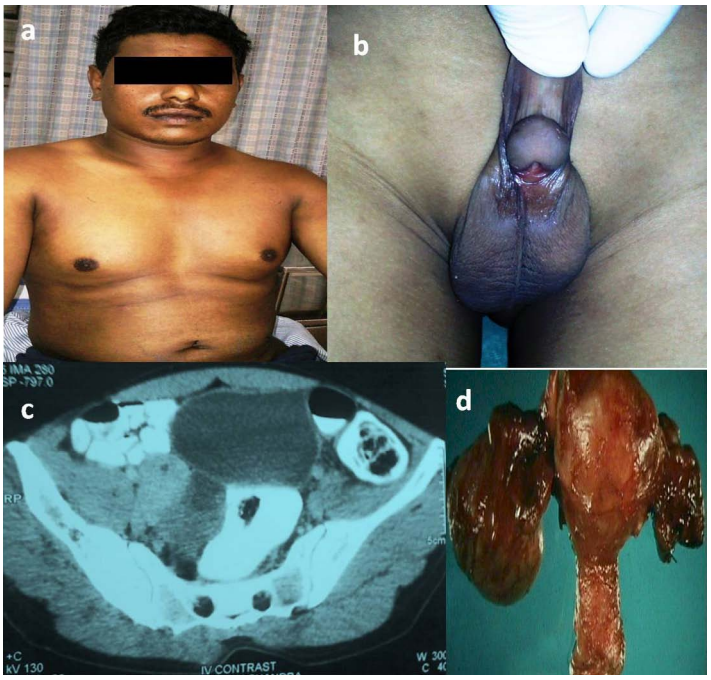
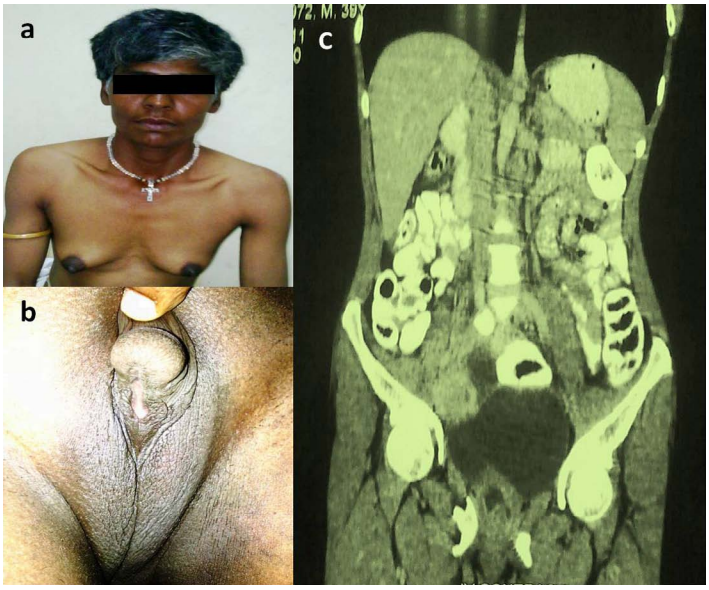


Figure 2. a) Adult female phenotype; b) Ambiguous external genitalia; c) The uterus with a hematometra and an adenexal mass.



A 24-year-old mentally challenged male presented with complaints of abnormal external genitalia. An examination showed a thinly built phenotypic female with well developed breasts, hirsute facies, and female-pattern distribution of hair (Figure 2). External genitalia revealed a small phallus with a dorsally hooded prepuce with penoscrotal hypospadias. The scrotum was bifid and hypoplastic with absent testicles and no vaginal opening (Figure 2). The patient was brought up as a male child with no prior medical consultation for his condition. A radiological evaluation revealed the presence of a hematoma in the uterus and a thickened endometrium with a cyst in the left adenexa (Figure 2). A biochemical evaluation showed serum FSH, LH, and progesterone levels were normal while his serum testosterone levels were high for a female. Karyotyping confirmed the diagnosis as 46,XX DSD. The patient was brought in with an expectation of converting the appearance of his external genitalia to that of a male. After counseling regarding the prospective usefulness of his extensive surgical correction, relatives chose against any intervention.

DISCUSSION

The word intersex has conventionally been used to refer to the appearance of the external genitalia but it is now considered inappropriate [2]. The Chicago consensus in 2005 established revised nomenclature and treatment recommendations in individuals with the newly defined term "disorders of sex differentiation" (DSDs), replacing terms such as intersex, hermaphroditism, and pseudohermaphroditism [1,3,4].

Criteria of physical findings suggestive of DSD include: 1) overt genital ambiguity (e.g., cloacal extrophy); 2) apparent female genitalia with an enlarged clitoris and posterior labial fusion (e.g., CAH); 3) apparent male genitalia with bilateral undescended testes, hypospadias, or micropenis; and 4) discordance between genital appearance and a prenatal karyotype [1]. Most DSDs are diagnosed in the neonatal period. Later presentations in older children often include: 1) previously unrecognized genital ambiguity, 2) inguinal hernia in a girl (e.g., complete androgen insensitivity), 3) delayed or incomplete puberty, 4) primary amenorrhea or virilization in a girl, 5) breast development in a boy, and 6) gross or cyclic hematuria in a boy [1]. Given the spectrum of findings and diagnoses, no specific single protocol could be used in the evaluation of DSD patients.

Adult presentation is significantly challenging as in mentioned cases because of incorrect assignment of sex at the time of birth. Unawareness about the need of seeking medical help is one reason and desire of a male child, hence tagging anything ambiguous accordingly, which affected our second case. Not surprisingly, in both cases correction to male phenotypes was desired, which was justifiable in the first patient who had a

male psychological orientation but not advisable in the second patient who lacked sexual understanding.

Initial gender uncertainty is distressful news for families. Influencing factors to consider when discussing gender assignment include diagnosis, genital appearance, fertility potential, therapeutic/surgical options, and familial views or circumstances relating to cultural biases. The general recommendations are to raise infants with 46,XX CAH or 46,XY CAIS as females, whereas infants diagnosed with 5-alpha reductase deficiency or 17-beta hydroxysteroid dehydrogenase 3 deficiencies, a male assignment should be considered [5].

But in adult presentations, psychological orientation plays the pivotal role in decision-making. The surgical correction technique and the timing of the operation need to be individualized according to medical conditions, experience of the surgeon, and the complexity of each case. The general trend is toward early reconstruction with subsequent early and long-term management of the patient.

CONCLUSION

Current recommendations emphasize sensitive, supportive interactions with families, and full disclosures of the risks, benefits, and potential outcomes of intervention to allow them to participate as fully as possible in decision-making and in the continued care of their child.

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