UIJ UroToday International Journal®

Table of Contents: December, 2013

ISSN 1944-5792 (print), ISSN 1944-5784 (online)

UroToday International Journal®

Elderly Men with Overactive Bladder: Maintenance of Satisfactory Therapeutic Effect of Administration of Combined High-Dosed Antimuscarinics

Kirill Vladimirovich Kosilov, Sergey Alexandrovich Loparev, Yuliya Igorevna Gainullina, Marina Anatolyevna Ivanovskaya, Liliya Victorovna Kosilova

Far Eastern Federal University (School of Humanities; School of Biomedical), Vladivostok, Russian Federation

Submitted October 5, 2013 - Accepted for Publication November 15, 2013

ABSTRACT

Objectives: The performance management of the long-term results of treatment of overactive bladder (OAB) in elderly men.

Patients and Methods: The focus of the study was a search for an optimal maintenance regimen that would secure the initial effect of treatment with double doses of antimuscarinics and decrease the risk of the recurrence of OAB. One hundred and ninety-seven men (average age 68.7 years, from 65 to 77 years of age), suffering from urodynamically and clinically confirmed OAB, were included in this study. All examined patients received the most effective treatment regimen according to the data of the initial study (60 mg trospium and 40 mg solifenacin daily for 6 weeks) with a positive result, and then were distributed into 4 groups based on the type of maintenance therapy. Group A (49 persons): trospium (60 mg daily) and solifenacin (40 mg daily) during 1 month. Group B (41 persons): electrical stimulation of the detrusor during 1 month. Group C (43 persons): laser puncture during 1 month. Group D (48 persons): placebo. The cycle of maintenance therapy was conducted in 2.5 months after primary treatment had been completed. The monitoring of patient conditions was performed through the OAB-q questionnaire (during 1 year) and urodynamic examination (sixth and twelfth month from the beginning of the study).

Results: A monthly course of treatment with 2 high doses of trospium and solifenacin, conducted in Group A in 2.5 months after a main cycle with similar content, enabled the maintenance of the initial clinical and urodynamic results for a long period of time (no less than 7 months). The average number of daily incontinence events decreased after an initial cycle of antimuscarinics from 5.2 (1.3) to 1.3 (0.4) and remained consistently low in the sixth month, 1.5 (0.5), the ninth month, 1.5 (0.5), and twelfth month, 1.9 (1.1), differing from the initial level, with $P < 0.05$. Indices reflex volume, bladder capacity, and detrusor compliance showed improvements after the first cycle; after the second cycle of antimuscarinics these indices remained stable during all periods of monitoring.

Conclusion: An additional cycle of treatment with a combination of high-dosed trospium and solifenacin, conducted 2 months after the primary treatment, significantly decreased the probability of recurring OAB in elderly men during 1 year, with low-level side effects.

KEYWORDS:Overactive bladder, elderly men, antimuscarinic, physiotherapy

CORRESPONDENCE: Kirill Vladimirovich Kosilov, PhD, MD, Far Eastern Federal University (School of Humanities; School of Biomedical), Vladivostok, Russian Federation (oton2000@mail.ru)

CITATION: *UroToday Int J*. 2013 December;6(6):art 67. http://dx.doi.org/10.3834/uij.1944-5784.2013.12.02

INTRODUCTION

Overactive bladder (OAB) in elderly men is a common abnormality affecting quality of life. At least 40.4% of men over 65 years report constant or occasional symptoms of neurogenic urinal bladder [1-4].

Most researchers agree about the significance of the disorder of afferent innervation in the pathogenic mechanism of neurogenic dysfunction in the urinal bladder. Studies of pathology of ascending innervation specify 2 main links forming adequate or excessive signals. It is the urothelial functional block, consisting of the urothelium, interstitial cells, and afferent nerve fibers. Initial level of activation is represented by mechanoreceptors and chemoreceptors of mucosa. Second, myogenic activation is represented by mechanoreceptors of the muscle membrane of bladder generating signals at the contractive activity of myocytes. The central nervous system receives excessive information from the bladder, which is generated by different receptors providing "afferent noise" effects [5-7].

An issue concerning proper management of OAB symptoms is still the focus of many articles. Antimuscarinic agents, which proved themselves to be effective, still remain the first-line pharmacological treatment of OAB because of the rapid positive effect and small quantity of side effects [8-10]. But their long-term effects are often unstable and result in a comparatively rapid recurrence of pathological signs [11,12]. Due to this, research of potential efficiency, safety, and the stability of the effects of recent drugs, such as mirabegron and onabotulinumtoxin A, and mechanisms of action of that differ from antimuscarinic agents, appear interesting [13-15]. On the other hand, the optimization of OAB treatment regimens with currently used drugs and physical therapy may be a promising direction in this search, especially considering data on significantly high level of refusals from long-term therapy with antimuscarinics [16].

Previously, we studied the efficiency and safety of management of OAB in elderly men and women with combined high-dosed antimuscarinics. The results let us conclude that the proposed therapeutic regimen provided good therapeutic effects with an allowable level of increased side effects [17]. Previous research was followed by this study in which we set objectives to compare the maintenance effect of different therapeutic methods in elderly patients with a good initial result from the administration of antimuscarinics.

Detrusor overactivity in elderly women often correlates with the functional inconsistence of pelvic floor muscles and pelvic organs [18-20], which is why, in this study, we focused on researching the possibility of the long-term management of OAB symptoms in men over 65 years old without symptoms of prostatic hyperplasia and chronic urological inflammatory pathology.

METHODS AND MATERIALS

We selected at random 197 men (average age 68.7 years; from 65 to 77 years of age) with OAB. All patients received the most rational treatment according to the data of initial study: 60 mg of tropsium plus 40 mg of solifenacin daily, during 6 weeks. Satisfactory results were received in 181 patients (91.9%), after that they were distributed into 4 groups. Patients of Group A (49 persons) received trospium (60 mg daily) plus solifenacin (40 mg daily) during 1 month—the same as during basic therapy. Elderly men from Group B (41 person) received electrical stimulation of the detrusor according to the following procedure: active electrode (50 - 70 cm2) was applied above the pubis, an indifferent electrode (150 cm2) was applied in the lumbosacral area, Bernard's currents, frequency 20 Hz, depth of modulation 50 (75%), strength 20 to 40 mA, exposure time 15 minutes, with 15 procedures every other day [21-25]. Patients from Group C (43 persons) received laser punctures using helium-neon lasers (632.8 nm) applied to the projection of acupuncture points RP 6, RP 9, VC 2 during 1 to 1.5 minutes, to each point daily. The output power of light guide was 2 mW, with 30 procedures [26-29]. Group D (48 persons) was a control group. The cycle of maintenance therapy was conducted in 2.5 months after primary treatment.

The monitoring of patient conditions was performed clinically, through OAB-q questionnaires (during 1 year) [30,31] and using cystometry (before enrollment, in 6 and 12 months after primary treatment). The urodynamic state of the lower urinary tract was evaluated in accordance with the International Continence Society (ICS) guidelines [32-35]. Cystometry was performed using the urodynamic system "Relief-01" (DALPRIBOR, Vladivostok, Russia) with a double catheter microtip (UROBAR, Helmbrechts, Germany). The following data was recorded and analyzed: reflex volume (ml), bladder capacity (ml), and detrusor compliance (ml/cm H2O).

In accordance with research protocol, all patients who took part in the examination, less than 3 months prior to its beginning, underwent endoscopic examinations (cystoscopy) in order to exclude organic pathology. On the basis of cystoscopy, 7 patients were eliminated from the study.

Initial data were collected and processed with Microsoft Excel (Microsoft, Redmond, Washington, United States). Analysis was performed using JMP SAS Statistical Discovery 8.0.2 (SAS Institute, Cary, North Carolina, United States). Wilcoxon and Kruskal-Wallis tests were used to compare results in each treatment group during monitoring. One-way analysis of variance (ANOVAs) with the Tukey-Kramer method was used to compare effects in the groups. Standard deviation P values of < 0.05 were considered statistically significant.

The study was performed in accordance with good clinical practice and the Declaration of Helsinki. Prior written informed

UIJ / Vol 6 / Iss 6 / December / http://dx.doi.org/10.3834/uij.1944-5784.2013.12.02
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

consent was obtained from each patient [32,33,35]. An examination and treatment diagram is shown in Figure 1.

RESULTS

Data on patient clinical and urodynamic indices in the course of basic and supportive treatment are shown in Figure 2 and Table 1 and Table 2. The best results among all groups were observed in Group A. The average number of daily incontinence events decreased after the initial cycle of antimuscarinics from 5.2 (1.3) to 1.3 (0.4) and remained consistently low at the sixth month, 1.5 (0.5), the ninth month, 1.5 (0.5), and the twelfth month, 1.9 (1.1), differing from the initial level with $P < 0.05$. Indices reflex volume, bladder capacity, and detrusor compliance showed improvements after the first cycle; after the second cycle of antimuscarinics these indices remained stable during all periods of monitoring. Also, a high correlation of main urodynamic and clinical indices (r - 0.6 ($P < 0.05$)) compared to IE with bladder capacity and detrusor compliance.

In Group B, satisfactory results were observed after 6 months of treatment; the clinical index of IE was at an allowably low level (2.0 (1.1)). The urodynamic indices also statistically differed from the initial. But by the ninth month almost all markers of the lower urinary tract showed reverse, negative development, and by the twelfth month they were close to initial indicators.

In Group C, the number of incontinence events by the sixth month was not statistically different from the initial level (3.4 (0.9)), and by the ninth month was almost identical to it. Urodynamic indicators of the lower urinary tract for patients of this group which, by the sixth month, differed from the initial level, though with minimal statistical significance they were somewhat unexpected.

In Group D, in which patients received a placebo, the number of incontinence events returned to the initial level by the sixth month of follow-up. Final urodynamic indicators were not different from the initial level as well.

As Table 1 shows, the tendency toward an increase of the indicator of post-void residual was observed in all monitored groups, but statistically significant differences were noted only between median values of the indicator in Group A compared before treatment and after the sixth month from its beginning.

In total, 31 patients reported side effects; among them 19 persons had poorly expressed side effects; therefore, the therapy was continued. The most common side effects included dry mouth (14), rash (2), flatulence (1), nausea (1), and dry and itchy skin (1).

Prior to examination all patients were informed orally and in writing about probable drug-related side effects (including

Figure 1. An algorithm of the examination and treatment of elderly men with OAB (before treatment: N = 197; after treatment: N =181).Note: The arrow shows the urodynamic tests (UDO); orange: the feature of reception solifenacin (40 mg) and trospium (60 mg); green: electrostimulation of the detrusor; pink: laser puncture; grey: receiving placebo.

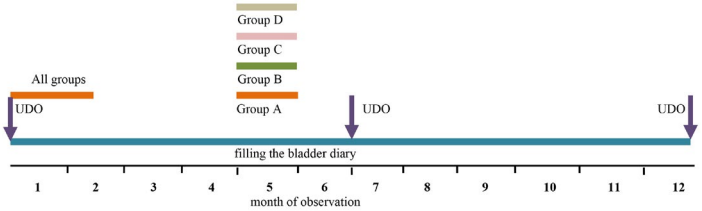
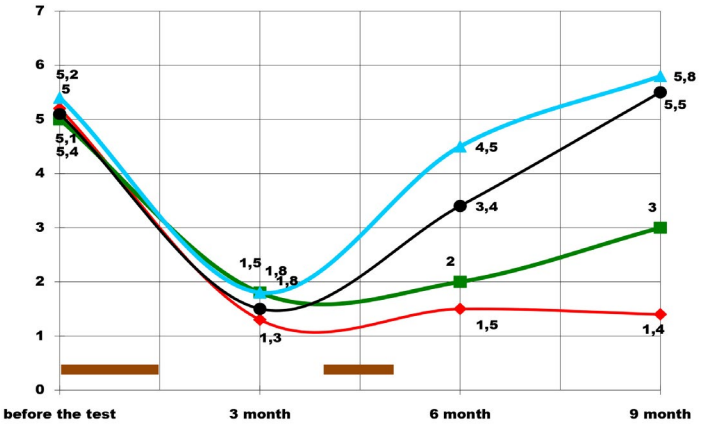


Figure 2. The frequency of episodes of incontinence in elderly men (before treatment: N = 197; after treatment: N = 181). Red: Group A (N = 49); Green: Group B (N = 41); Blue: Group C (N = 43); Black: Group D (N = 48). Horizontal lines indicate the time of the basic and supporting courses of treatment.



acute retention of urine), and the necessity to inform us immediately in case of the occurrence of side effects. During the follow-up period, acute urine retention events were observed in 3 cases (twice in the same patient). But at the time of consultation urine formation and urination function had restored spontaneously, and special drug therapy was not needed. After the examination of kidney functions and obtaining information about the absence of disorders, patients continued drug administration according to the schedule.

Table 1. Result of urodynamics (before treatment: N = 197; after treatment: N = 181).

Form of control	Indicators of urodynamics (± SD)											
Parameters of LUTS	Post-void residual (mL)			Reflex volume (mL)			Bladder capacity (mL)			Detrusor compliance (mL/cm H_2O)		
Time of study	Before	After[1]	After[2]	Before	After[1]	After[2]	Before	After[1]	After[2]	Before	After[1]	After[2]
Group A (N = 49)	17.5 (6)	29.5 (5.7)*	25.6 (7.9)	158.5 (37.6)	277.1 (44.2)**	266 (31.1)**	198 (25.6)	298.7 (45.6)**	293.4 (35.6)*	24.3 (3.4)	36.6 (5.4)*	33.9 (2.7)*
Group B (N = 41)	20.5 (7.9)	31.8 (11.8)	27.7 (5.3)	141.4 (30.5)	289.7 (34.5)**	196.4 (24.3)	185.6 (47.8)	301.5 (35.6)**	266,.7 (34.5)	19.8 (2.2)	33.6 (6.4)*	26.2 (2.6)*
Group C (N = 43)	2.,9 (4.9)	28.9 (9.1)	1.,8 (7.1)	148.2 (37.8)	267.6 (42.5)*	221.5 (76.5)	178.4 (47.4)	298.7 (34.3)*	187.6 (24.5)	20.5 (4.5)	34.4 (4.7)*	22.0 (7.3)
Group D (N = 48)	22.6 (6.6)	31.0 (6.3)	19.8 (8.5)	139.6 (35.6)	284.3* (34.4)	156.6 (32.3)	189.5 (34.6)	313.4 (47.3)*	199.8 (27.8)	25.2 (2.3)	35.6 (4.5)*	23.7 (4.8)

Remarks: SD, standard deviation; * < 0.05; ** < 0.001; Before, amounts taken at onset of study and considered baseline; After[1], 6 months from the start of the study; After[2], 12 months from the start of the study.

Table 2. Voiding diary data (before treatment: N = 197; after treatment: N = 181).

Form of control	Data diaries (± SD)					
Clinical parameters of LUTS	Incontinence events/day			Frequency of urination/ day		
Time of study	Before	After[1]	After[2]	Before	After[1]	After[2]
Group A (N = 49)	5.2 (1.3)	1.5 (0.5)**	1.9 (1.1)*	7.9 (1.3)	4.9 (1.1)*	5.3 (2.0)
Group B (N = 41)	5.0 (0.9)	2.0 (1.1)*	3.3 (1.0)	8.5 (0.7)	5.5 (1.3)*	7.5 (2.4)
Group C (N = 43)	5.1 (1.4)	3.4 (0.9)	4.7 (1.1)	8.1 (4.1)	6.4 (2.7)	7.9 (1.2)
Group D (N = 48)	5.4 (1.1)	4.5 (1.0)	5.5 (2.1)	6.9 (2.5)	6.0 (1.9)	6.8 (4.9)

Remarks: SD, standard deviation; * < 0.05; ** < 0.001; Before, amounts taken at onset of study and considered baseline; After1, 6 months from the start of the study; After2, 12 months from the start of the study.

During yearly follow-up study 12 patients (6.6%) stopped treatment and examinations: in 9 cases due to development of side-effects – intolerable dry mouth (7), flatulence (1), nausea, vomiting (1); in 3 cases treatment was discontinued due to circumstances not related to the treatment. In 4 cases treatment was discontinued in connection with lack of a positive effect.

DISCUSSION

We conducted a comparative analysis of the efficiency of several methods for maintenance therapy in elderly men having OAB who previously had demonstrated good therapeutic effects of treatment with combined antimuscarinics.

It was determined that the short cycle of treatment with 2 high-dosed antimuscarinics of different generations, conducted in 2.5 months after the main cycle, enables the maintenance of the initial clinical and urodynamic results for a long period of time (up to 1 year).

Positive results received in Group A, in our opinion, can be explained by the supposition that antimuscarinic agents synergistically activate suburothelial M2 and M3 receptors of the elderly male bladder with a "strengthening" effect and stabilization of their functional activity after repeated treatments after a small period of time [36-39].

Electrical stimulation of the urinary bladder and laser punctures as maintenance therapy, according to our data, proved to be less effective and cannot prevent the recurrence of the pathological symptoms of OAB. These methods, in particular, stimulate microcirculation and improve oxygenation of the detrusor, but it is insufficient for securing positive effects. Hypoxia of the urinary bladder wall tissue is not a leading mechanism in the development of OAB, and the absence of specific influences on receptors results in weak and short-term effects.

CONCLUSION

A short cycle of treatment with 2 high-dosed antimuscarinics (trospium and solifenacin), conducted in 2.5 months after

UIJ / Vol 6 / Iss 6 / December / http://dx.doi.org/10.3834/uij.1944-5784.2013.12.02
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

the main cycle, significantly decrease the probability of OAB recurrence during 1 year with a low level of side effects. An application of electrical stimulation of the detrusor and laser puncture does not ensure the maintenance of positive effects of pharmaceutical therapy. Further studies are required to determine necessary terms for repeated cycles of maintenance and pharmaceutical treatment of OAB in elderly men in the period exceeding 1 year.

MAIN CONCLUSION

Repeated treatment of OAB with a combination of high-dosed antimuscarinics is an effective method for reducing the risk of recurrence of the disease in elderly men.

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Does Limited Pelvic Lymphadenectomy in Low-Risk Prostate Cancer Patients Affect Biochemical Recurrence?

Joshua E. Logan, Bethany Barone Gibbs, Stephen B. Riggs, Robert W. Given, Michael D. Fabrizio, Paul F. Schellhammer, Raymond S. Lance

Department of Urology, Eastern Virginia Medical School, Norfolk, Virginia

Submitted November 20, 2013 - Accepted for Publication November 28, 2013

ABSTRACT

Introduction: Several studies have reported a very low incidence of lymph node metastasis in D'Amico low-risk prostate cancer. As a result, omission of the pelvic lymphadenectomy (PLND) has become more common in this group. We evaluated whether omission of a PLND in these patients was associated with increased rates of 5-year biochemical recurrence (BCR).

Materials and Methods: The study population included 535 patients with prostate cancer clinical stage T1-2, Gleason 3 + 3, and PSA < 10 ng/mL. Patients were divided into 2 groups, those with a limited PLND (+PLND) at the time of prostatectomy (N = 139) and those without (–PLND) (N = 396). BCR was defined as PSA > 0.2 ng/mL at any time following surgery. Univariate and multivariate Cox proportional hazards analyses were applied to evaluate the association between the omission of PLND and BCR.

Results: Median follow-up was 43 months (range 0.4 to 194.8). The mean number of lymph nodes obtained at PLND was 6.2 (range 1 – 38). Of these, 122 men had BCR during follow-up. Men who had PLND had earlier surgery dates and were more likely to have had open prostatectomy. They were also associated with higher preop PSAs, fewer biopsy cores but a higher percent of positive cores, and higher maximum cancer in any 1 core. Kaplan-Meier analysis revealed similar survival curves for both groups (log-rank test P = 0.723). Using the univariate Cox proportional hazards analysis, omission of PLND was not associated with a higher risk of BCR when compared to +PLND. Preoperative PSA, year of surgery, procedure type, pathologic Gleason score and stage, as well as margin status were all significantly (P < 0.05) associated with the risk of BCR, while African American race approached significance (P = 0.062).

Conclusion: With a 43-month median follow-up, D'Amico low-risk prostate cancers are no more likely to develop BCR when limited PLND is omitted than those who undergo limited PLND. A potentially confounding variable might be the variability in the extent of PLND.

INTRODUCTION

Several studies report a very low incidence of lymph node metastasis in low-risk prostate cancer, and pelvic lymphadenectomy (PLND) is decreasing in this group [1-3]. Evidence suggests that it can be safely omitted in patients who are D'Amico low-risk without putting the patient at risk for biochemical recurrence [4-6]. Based on commonly used nomograms, a patient with D'Amico low-risk prostate cancer has an approximately 2% chance of having lymph node

KEYWORDS: Prostate cancer, pelvic lymph node dissection, PSA

CORRESPONDENCE: Joshua E. Logan, MD, Eastern Virginia Medical School, Norfolk, Virginia, United States (joshuaelogan@gmail.com)

CITATION: *UroToday Int J*. 2013 December;6(6):art 73. http://dx.doi.org/10.3834/uij.1944-5784.2013.12.08

Table 1. Demographic, preoperative clinical, and pathological characteristics by pelvic lymph node dissection status.

	Pelvic Lymph Node Dissection		P Value
	Yes (N = 139)	No (N = 396)	
Age at surgery	59.1 ± 6.4	59.3 ± 6.8	0.785
Race			
- White	96 (69%)	289 (73%)	
- Black	36 (26%)	88 (22%)	
- Other/unknown	7 (5%)	19 (5%)	0.660
Year of surgery			
- 1990-1996	28 (20%)	8 (2%)	
- 1997-2000	41 (30%)	40 (10%)	
- 2001-2003	34 (24%)	110 (28%)	
- 2004-2006	36 (26%)	238 (60%)	< 0.001
Preoperative PSA (ng/mL)	5.6 ± 2.2	5.1 ± 1.9	0.009
Prostatectomy type			
- RARP	29 (21%)	199 (50%)	
- LRP	5 (4%)	38 (10%)	
- ORP	105 (76%)	159 (40%)	< 0.001
Clinical tumor stage			
- T1	113 (81%)	341 (86%)	
- T2	26 (19%)	55 (14%)	0.173
Pathological Gleason score			
- ≤ 6	98 (71%)	287 (72%)	
- 7+	41 (29%)	109 (28%)	0.656
Pathological tumor stage			
- ≤ T2	108 (78%)	319 (81%)	
- T3+	31 (22%)	75 (19%)	0.407
Positive margins	38 (28%)	96 (38%)	0.634
Number of cores (N = 437)	9.4 ± 4.1	11.0 ± 3.8	< 0.001
Percent of positive cores (N = 350)	32% ± 23%	26% ± 20%	0.018
Maximum cancer percent (N = 454)	32% ± 25%	27% ± 24$%	0.045

metastasis; however, there is the competing risk of simply undergoing PLND, which increases a patient's risk for venous thromboembolism, lymphocele, as well as ureteral, vascular, or nerve injury [7].

We sought to determine if omission of PLND in patients with D'Amico low-risk prostate cancer increased the risk for biochemical recurrence (BCR), where the general practice, over time, has evolved from PLND for all patients undergoing prostatectomy, primarily during the open prostatectomy era, to omission of PLND during the laparoscopic/robotic era.

MATERIALS AND METHODS

Data elements of all patients undergoing prostatectomy at our institution have been recorded in an institutional review board-approved, prospectively maintained database. This database was queried for all patients with cT1-2a, clinical Gleason 3 + 3, and prostate-specific antigen (PSA) < 10 ng/mL who had not received any adjuvant or neoadjuvant therapy from the years 1990 to 2006. Patients who had undergone perineal prostatectomy and those for whom follow-up PSA data was not available were excluded from the cohort. The study population included 535 patients who had undergone open radical prostatectomy (ORP), laparoscopic radical prostatectomy (LRP), or robot-assisted radical prostatectomy (RARP). Patients were divided into 2 groups: 139 (26%) patients had undergone PLND (+PLND) at the time of prostatectomy and in 396 (74%) patients the PLND was omitted (–PLND). See Table 1 for cohort characteristics.

Data elements analyzed were age, race, preoperative PSA, number of cores obtained at biopsy, percentage of positive biopsy cores, clinical tumor stage, year of surgery, procedure type, pathological Gleason grade, pathologic tumor stage, presence of positive surgical margins, number of lymph nodes obtained, and biochemical recurrence (BCR), defined as PSA > 0.2 ng/mL.

Regarding statistical analysis, all variables were assessed for normality, and type 1 error rate was set at $\alpha = 0.05$. Baseline characteristics of men with +PLND and -PLND were compared using independent t tests for continuous variables and chi-squared tests for independence for categorical variables. Data for biopsied number of cores (N = 457), percent positive biopsy cores (N = 350), and maximum percent of cancer in any core (N = 454) were not available in the full study population, but we included all patients with available data on these parameters. Next, the Kaplan-Meier method was used to estimate BCR-free survival by PLND status. Survival curves were compared using the log-rank test and used to estimate 5-year BCR-free survival in each group. The univariate Cox proportional hazards analysis was applied to evaluate the association between the omission of PLND and BCR. In addition, the other demographical, clinical, and pathological variables listed in Table 1 were examined for associations with BCR. Validity of the proportional hazards assumption was assessed for each variable using log-log plots. In a final multivariate model, the effect of PLND was evaluated and adjusted for all other variables, with the exception of the number of biopsy cores, percent positive cores, and maximum percentage of cancer in any core because they did not predict BCR and were not available in the full study sample. The statistical analysis was completed by a statistician (BBG).

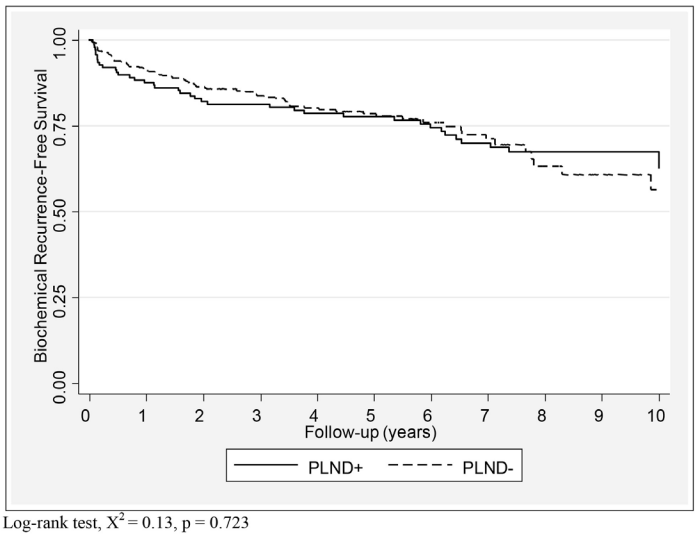
RESULTS

The median follow-up for the entire cohort was 43 months (SD 40.8 months). Men with +PLND (N = 139) and –PLND (N = 396) were similar at baseline with respect to demographics, clinical and pathological tumor stage, pathological Gleason grade, and positive margin rate (Table 1). Of note, primary pathologic Gleason 4 was diagnosed in a total of 12 of the patients (2% of the total cohort), 3 in the +PLND group, and 9 in the –PLND group. Primary pathologic Gleason 5 was diagnosed in 1 patient (0.2% of the total cohort) of the –PLND group.

Men with +PLND underwent surgery in the earlier years of the study period (P < 0.001), had a higher preoperative PSA (5.6 vs 5.1, P = 0.009), had a different distribution of prostatectomy type (more ORP, less RARP, P < 0.001), had less biopsy cores (9.4 vs 11.0, P < 0.001), a greater percentage of positive cores (32% vs 26%, P = 0.018), and a higher maximum percentage of cancer (32% vs 27%, P = 0.045).

The mean number of lymph nodes obtained at PLND was 6.2 (range 1-38). Two patients had positive nodes on pathologic analysis, both patients had 1 positive node each; both patients were pathologic Gleason 3 + 4, 1 patient was pT3a, and the other was pT3b; 1 of the patients was Caucasian, and race is not known for the other patient.

Figure 1. Biochemical recurrence-free survival by PLND group.



Log-rank test, $X^2 = 0.13$, $p = 0.723$

Kaplan-Meier BCR-free survival curves are presented in Figure 1. The curves are overlapping, suggesting similar BCR-free survival rates in both groups, which is reflected in the log-rank test (X2 = 0.13, P = 0.723). The five-year BCR-free survival rate for +PLND was 77.6% and for –PLND was 78.6%.

Univariate Cox proportional hazard ratios (HR) for BCR are reported in Table 2. –PLND did not predict BCR in unadjusted models (HR = 1.07, P = 0.723). Higher preoperative PSA, higher pathological tumor stage and Gleason score, as well as positive margins all predicted BCR. Year of surgery and type of prostatectomy also predicted BCR. Because of the numerous univariate predictors that were significantly associated with BCR, a multivariate model was completed; –PLND remained a non-significant predictor of BCR in the sample. Lastly, mean prostate volumes were statistically different at 52 mL and 45 mL for the +PLND and –PLND groups, respectively (P = 0.003), but volume was not associated with BCR (Cox HR = 1.00, P = 0.84).

DISCUSSION

Pelvic lymph node dissection has increasingly been omitted at the time of prostatectomy as the PSA era has led to a stage migration in which patients are routinely diagnosed with

UIJ / Vol 6 / Iss 6 / December / http://dx.doi.org/10.3834/uij.1944-5784.2013.12.08
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

Table 2. Cox proportional hazards ratios for factors predicting biochemical recurrence.

	Univariate HR	P Value	Multivariate HR	P Value
Pelvic lyphadenectomy Yes No	 1.0 1.07	 0.723	 1.0 1.37	 0.154
Preoperative PSA (ng/mL)	1.17	0.001	1.14	0.009
Year of surgery	0.91	< 0.001	1.03	0.348
Age at surgery	1.02	0.233	1.02	0.178
Race White Black Other/unknown	 1.0 1.45 0.91	 0.062 0.836	 1.0 1.40 0.81	 0.127 0.655
Prostatectomy type RARP LRP ORP	 1.0 3.57 7.95	 0.011 < 0.001	 1.0 3.71 9.96	 0.013 < 0.001
Clinical tumor stage T1 T2	 1.0 0.64	 0.117	 1.0 0.74	 0.307
Pathological tumor stage pT1 and pT2 pT3	 1.0 2.60	 < 0.001	 1.0 1.41	 0.120
Pathological Gleason Score ≤ 3 + 3 ≥ 3 + 4	 1.0 1.75	 0.002	 1.0 1.54	 0.032
Margins Negative Positive	 1.0 3.13	 < 0.001	 1.0 2.04	 < 0.001
Number of biopsy cores (N = 437) ≤ 12 12+	 1.0 0.98	 0.469	 - 	 -
Percent positive biopsy cores (N = 350)	1.37	0.570	-	-
Maximum percent cancer in any core (N = 454)	0.99	0.883	-	-

localized prostate cancer [8]. In addition, with the introduction of nomograms, the ability to preoperatively identify those at low-risk for lymph node metastasis enabled surgeons to rationally decide in whom to omit PLND [1,2]. Currently, the most recent NCCN prostate cancer guidelines allow for exclusion of PLND in patients with < 2% predicted probability of nodal metastases by nomograms. In the absence of prospective randomized data, information from large retrospective studies provide a reasonable basis for this practice [4,5].

The results presented here, similar to the 2 studies mentioned above, support that PLND can safely be omitted in patients who are low-risk by D'Amico criteria without putting the patient at increased risk for BCR [4,5]. Our results also suggest that in this cohort of clinically low-risk patients, by omitting the PLND, the patient risk stratification would not have been obscured, as shown by examining the characteristics of the 2 patients with positive lymph nodes in the +PLND group. One patient was pT3a and the other was pT3b; therefore, both patients would have both been considered high risk for BCR just based upon the pathologic stage of the prostate gland itself, irrespective of the nodal status.

Regarding the number of cores obtained at biopsy, there was a difference between the groups; on average, 9 cores were obtained in the +PLND group and 11 total cores were obtained in the –PLND group. It could be assumed that fewer cores obtained could lead to under-detection of higher-stage or

higher-grade cancer. However, this was not the case as there was no difference between the groups on pathological staging. The percentage of positive biopsy cores was significantly higher in the +PLND group. This is likely due to the smaller denominator (positive cores/total cores) in the +PLND group, reflecting that these patients had their biopsy in the era when less total cores were obtained at the time of biopsy.

The difference in the distributions of procedure type between the –PLND and +PLND groups throughout the years of surgery reflect the change from the open to the minimally invasive approach; patients who were treated with ORP were more likely to have had PLND.

A definite strength of this study rests in the fact that the cohorts had similar preoperative and postoperative characteristics; this provides confidence in interpreting the Kaplan-Meier curve. A shortcoming of this study is the median follow-up of 43 months. However, our endpoint, BCR, most often occurs in the first 2 to 3 years following radical prostatectomy and is shown in other previously published reports [9-11]. In addition, the duration of follow-up in this study is within the range of follow-up (32-89 months) that was reported in the 2 similar, previously discussed studies [4-6].

Our study is unique in its proportion of African Americans who represented 23% of the study population. This is in contrast to other studies discussed in which African Americans represented 4.5 to 7.7% of their respective populations [4-6]. Interestingly, African American race trended toward significance as a risk factor for BCR. Whether this is related to access to care issues or actual differences in biology cannot be determined.

We do note that BCRFS in this study is lower than what would be expected for a cohort of patients with clinically low-risk disease. The above-mentioned higher proportion of African Americans in this study compared to other studies, and the fact that race showed a trend toward increasing risk for BCR, may offer an explanation.

Because smaller prostate volume has been implicated to be a risk factor for BCR, we evaluated this in our cohort [12]. While there was a statistical difference in the prostate gland volume between the groups, the Cox hazard ratio showed no association between prostate volume and BCR.

An additional limitation of this study is the limited extent of the PLND. The mean LN yield was 6, and while we do acknowledge that this represents the low end of what is reported in the literature, this may be a reflection of variability of pathological processing and reporting between institutions [13,14]. Moreover, consideration of a more extended PLND in low-risk prostate cancer patients does not appear warranted given the increased risk for adverse outcomes without proven benefit [15].

CONCLUSION

For patients with low-risk prostate cancer who have chosen to proceed with prostatectomy, a limited PLND may be omitted without compromising their BCR-free survival.

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Early Imaging Improves the Performance of C11-Acetate PET/CT for Recurrent Prostate Adenocarcinoma

Fabio D. Almeida,[1,4] Chi-Kwan Yen,[1,4] Steven E. Finkelstein,[2,4] Larry L. Bans,[2,4] Mark C. Scholz,[3] Richard Y. Lam,[3] Gordon L. Grado,[5,6] Elisa Blackwell,[1,4] Carlos Patino[1,4]

[1]Arizona Molecular Imaging Center, Phoenix, Arizona, United States; [2]21st Century Oncology, Scottsdale, Arizona, United States; [3]Prostate Oncology Specialists, Marina Del Ray, California, United States; [4]Arizona Cancer Research Alliance (ACRA); [5]Southwest Oncology Centers, Scottsdale, Arizona, United States; [6]Department of Radiation Oncology, University of Minnesota, Minneapolis, Minnesota, United States

Submitted October 2, 2013 - Accepted for Publication November 10, 2013

ABSTRACT

Purpose: We evaluated the performance of C11-Acetate positron emission tomography/computed tomography (PET/CT) in recurrent prostate cancer patients with early and late imaging.

Patients and Methods: Forty-one patients with recurrent prostate adenocarcinoma as evidenced by a rising prostate-specific antigen (PSA) after prior definitive treatment where imaged with C11-Acetate PET/CT. Patients with prior initial prostatectomy and prior radiation were similar in number. Early post-tracer injection PET/CT imaging was performed (3 to 7 minutes, mean 4.25), with subsequent later pelvic/lower abdominal imaging (21 to 31 minutes, mean 26.6). Target lesions where identified visually and with quantitative measurements of maximal standardized uptake valve (SUV) and lesion-to-background (L/B) ratios obtained for each lesion. Analysis was performed to determine statistical significance.

Results: Twenty-eight patients had evaluable lesions in the pelvis, which could be compared across the imaging time points. Sixty lesions were detected with 12 in the prostate, 33 in lymph nodes, 7 in the peri-prostate soft tissues or seminal vesicles (SV), and 8 in the bone. Lesions involving the lymph nodes, peri-prostate soft tissues, and bone were all more visually conspicuous on the early imaging as compared to the later imaging, and demonstrated statistically significant higher maximal SUVs and L/B ratios ($P < 0.001$). Lesions in the intact prostate and seminal vesicles on the early images also demonstrated significantly higher maximal SUVs ($P < 0.001$), but the L/B ratios were similar or slightly higher on the later images with the difference not found to be statistically significant.

Conclusion: C11-Acetate positron emission tomography/computed tomography with early imaging post injection provides improved lesion detection both in terms of maximal SUV and lesion-to-background ratios for lesions involving nodes, peri-prostate soft tissues, and bone. Lesions in the prostate and seminal vesicles showed equal visual conspicuity and lesion-to-background ratios across early and later imaging. Early imaging appears optimal in the evaluation of recurrent prostate adenocarcinoma. In a larger application (300 patients) of early imaging in this patient population, C11-Acetate PET/CT demonstrates a consistently high detection rate.

KEYWORDS: C11-Acetate positron, PET/CT

CORRESPONDENCE: Fabio D. Almeida, M. D., Arizona Molecular Imaging Center, 4540 E. Cotton Gin Loop, #150, Phoenix, Arizona 85718, United States (falmeida@healthwestpartners.com)

CITATION: *UroToday Int J*. 2013 December;6(6):art 66. http://dx.doi.org/10.3834/uij.1944-5784.2013.12.01

INTRODUCTION

Prostate cancer is the second most common cancer in American men with the American Cancer Society 2011 estimating about 240,890 new cases of prostate cancer diagnosed and 33,720 deaths from prostate cancer. About 1 man in 6 will be diagnosed with prostate cancer during his lifetime, and death from prostate cancer in American men lags only behind lung cancer.

Regardless of the type of primary treatment, a significant proportion of patients will experience relapse of prostate adenocarcinoma, occurring approximately 35% after radical prostatectomy [1,2] and up to 40% after external beam radiotherapy [3-5]. In these patients, evidence of residual or recurrent disease is heralded by detectable or increasing serum prostate-specific antigen (PSA) [6-11], with many of these patients demonstrating no or minimal evidence of disease on standard imaging studies such as magnetic resonance imaging (MRI), CT, ultrasound, and technetium bone scans—also referred to as "biochemical relapse." Subsequent treatment decisions rely critically on distinguishing between loco-regional relapse in the prostate bed and adjacent soft tissues, loco-regional relapse in lymph nodes, and distant metastases. Imaging with F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is successful in most malignant diseases, but is not useful for prostate adenocarcinoma, primarily because prostate adenocarcinoma does not routinely exhibit a glycolytic phenotype [12,13]. Additionally, FDG tracer excretion through the kidneys into the bladder significantly obscures evaluation of the prostate bed.

Over the past few years, novel PET tracers have been introduced to assist with the evaluation of prostate adenocarcinoma. In addition to C11-choline and F18-choline, C11-Acetate (AC) appears to be highly promising. Various groups have tested the potential of AC PET imaging in prostate adenocarcinoma [14-20], providing encouraging results. Limitations in several of the previous studies, however, have been a lack of standardization of the imaging technique, primarily in terms of time to commence imaging post injection. Additionally, the majority of prior studies have been performed with PET only or separately co-registered morphologic and metabolic imaging techniques. It has been established that combined hybrid PET/CT imaging provides improved diagnostic accuracy and impact on clinical patient management [21]. Thus, we evaluated the performance of AC PET/CT at our institution in men with biochemically recurrent prostate cancer after definitive treatment, with an integrated PET/CT imaging system and multiple time-point imaging.

PATIENTS AND METHODS

Our institutional review board approved the study for all patients undergoing C11-Acetate PET/CT imaging at our institution. Forty-one male patients (ages 54 to 85, mean 71) with histologically proven prostate adenocarcinoma and biochemical recurrence (BCR) were imaged. Biochemical recurrence was defined as PSA 0.2 ng/mL or greater for a patient who underwent prior prostatectomy, nadir plus 2 ng/mL or a sequential increase in PSA for patients treated with radiation or cryotherapy, or a sequential increase in PSA for the patients treated with primary androgen deprivation therapy (ADT). The PSA range for these patients was 0.5 to 60.2 ng/mL (mean 8.6 ng/mL). Gleason scores (Gs) ranged from 5 to 9 (Gs5 N = 2; Gs6 N = 8; Gs7 N = 19; Gs8 N = 8; Gs9 N = 4). Prior primary therapy consisted of prostatectomy (N = 7), external beam radiation therapy (N = 18), external beam plus brachytherapy (N = 4), prostatectomy with subsequent salvage radiation therapy (N = 11), and ADT (N = 1).

C11-Acetate was produced by reacting methylmagnesium bromide with [11C]CO2. In brief, [C-11]CO2 gas was produced from the cyclotron (PETtrace series 800, General Electric) after a 45-minute, 60 micro-Amp target irradiation producing approximately 4 Curies of [C-11]CO2. [11C]CO(2) gas from the target was directed to the synthesis unit containing a column of methylmagnesium bromide in diethyl ether used for carbonation of the gas. The intermediate was then hydrolyzed under heat and unreacted [C-11]CO2 removed from the mixture, passed through C18 resin to remove ionic and organic compounds, and collected into a batch vial through a membrane filter. Our typical yield of C11-Acetate is 1.4 Curies with a total synthesis time of 10 minutes.

C11-Acetate PET/CT imaging was performed on an integrated PET/CT scanner (Siemans Biograph 6 TruePoint; Malvern, Pennsylvania, United States). Patients were positioned on the camera and then 740-1480 MBq C11-Acetate (half-life 20.4 minutes) was administered as a bolus intravenous injection. A CT topogram was obtained from the vertex through the pelvis. On the basis of the topogram, the tube current for the CT scan was adjusted utilizing a Care doseTM application to minimize exposure. The tube voltage was 130 kVp. Reconstructed images were 3 mm thick slices. After the CT scan, emission images beginning at the pelvis and proceeding cranially were obtained (3 to 7 minutes post injection, mean 4.25). After completion of the initial imaging sequence, delayed imaging (21 to 31 minutes post injection, mean 26.6) was performed of the pelvis and lower abdomen. PET imaging acquisition parameters were weight-based for bed stop and filter settings with an average of 2.25 minutes per bed stop with 6 to 8 bed positions. Images were reconstructed with iterative reconstruction (2 iterations, 8 subsets, matrix 168, Gaussian filter). The administration of C11-Acetate was well tolerated by all patients and no adverse events were encountered.

Detected lesions were defined as moderate to intense focal

UIJ / Vol 6 / Iss 6 / December / http://dx.doi.org/10.3834/uij.1944-5784.2013.12.01
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

areas of increased AC metabolic activity over background in the prostate, prostatic bed, nodes, and bone. Maximal standardized uptake values (SUVmax) were determined for each lesion with a spherical region of interest (ROI), with SUV representing the calculated ratio of tissue radioactivity concentration c (e.g., MBq/kg) at time point t and injected dosage (e.g., in MBq) at the time of injection, and then divided by body weight (e.g., in kg).

SUV = c(t)/injected activity(t)/body weight

Early and late imaging sequences for each study were anatomically fused on a PET/CT workstation (MIMFusion V5.6.2, MIMSoftware; Cleveland, Ohio, United States), allowing for precise measurement of the same location/lesion on each comparison imaging study. Background values were also obtained in the prostate, muscle, blood pool, bone, and urinary bladder. Lesion-to-background ratios where determined for each lesion, with background selected on the basis of the type of lesion. For lesions in the intact prostate, a contralateral area in the prostate was selected for the background. For lesions in the post prostatectomy bed or for lymph nodes, the lower abdominal aortic blood pool was selected. For bony lesions, background was selected in the intramedullary space of the L5 vertebral body. Data analysis was performed utilizing statistical software (SigmaXL, SigmaXL Inc.; Toronto, Ontario, Canada) and consisted of comparison of the difference in maximal SUV values utilizing a 2-tailed paired *t* test. Lesion-to-background ratios were also determined for each lesion and compared across early and late imaging studies utilizing the paired *t* test.

RESULTS

Of the 41 patients imaged, 28 patients were found to have evaluable lesions in the pelvis and lower abdomen, which could be compared across the different time-point sequences. A total of 60 lesions were detected in these patients (12 in the prostate, 33 in lymph nodes, 7 in the peri-prostate soft tissues or seminal vesicles, and 8 in the bone).

All of the evaluable lesions where visually detectable on both the early and late imaging sequences. In lesions involving lymph nodes, peri-prostate soft tissues, and bone, nearly all lesions appeared visually more prominent on the early images as compared to the late images. The maximal SUV values were also demonstrated to be higher on the earlier imaging sequence compared to later imaging, with a mean difference of 1.09 and maximum difference of 6.02. Data comparison across the imaging studies demonstrated the difference in SUV values to be statistically significant ($P < 0.001$). Lesion-to-background ratios (L/B) in the AC-positive lymph nodes, peri-prostate regions, and in bone were also found to be statistically higher on early imaging compared to delayed imaging ($P < 0.001$).

In lesions involving the prostate or seminal vesicles, AC accumulation in many cases appeared visually similar between the different imaging time points. The maximum SUV in these lesions was statistically higher on the early imaging, but ratios of lesion-to-background where similar or slightly higher on the later imaging in a few lesions. A difference in the L/B ratios for these lesions was not found to be statically significant (Figure 1, Figure 2, Figure 3, Figure 4, Figure 5).

Figure 1. 60 y/o, Gleason 7, treated with brachytherapy and EBRT 5 years previously. Rising PSA at the time of AC PET/CT imaging was 14.4 ng/mL. The left image shows a sub-centimeter focally metabolic lymph node in the proximal right common iliac region on early imaging (SUVmax 4.51, L/B 2.36). The right image shows the same finding in the lymph node on the later imaging but with this appearing much less conspicuous (SUVmax 3.44, L/B 1.67).

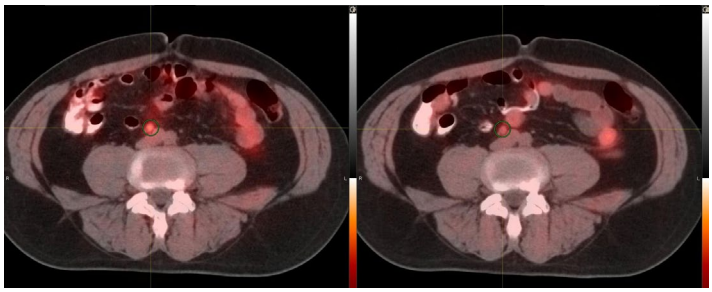


Figure 2. 59 y/o, Gleason 9 (4+5), treated with prostatectomy and subsequent salvage radiation therapy to the bed for rising PSA 1 year later. Rising PSA 1 1/2 years later, and at the time of AC PET/CT imaging, was 0.7 ng/mL. The left image shows a sub-centimeter focally metabolic lymph node in the left external iliac region on early imaging (SUVmax 3.22, L/B 2.73). The right image shows the same finding in the lymph node on the later imaging but with this appearing less conspicuous (SUVmax 2.36, L/B 1.92).

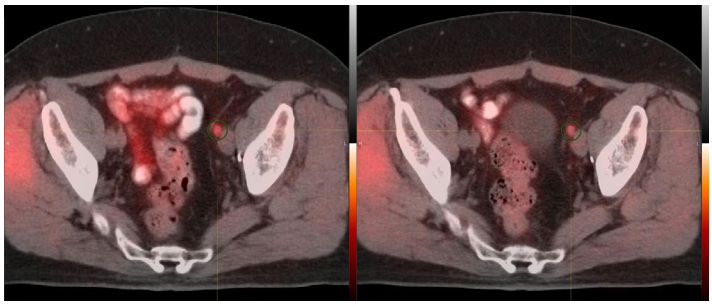


Figure 3. 71 y/o, Gleason 7, treated with prostatectomy 15 years previously. Rising PSA at the time of AC PET/CT imaging was 0.87 ng/mL. Multiple nodal and bony lesions were positive in this patient. Only 1 example node is shown. The left image shows a sub-centimeter focally metabolic lymph node in the left proximal common iliac region on early imaging (SUVmax 2.43, L/B 1.94). The right image shows the same finding in the lymph node on the later imaging but with this appearing less conspicuous (SUVmax 1.77, L/B 1.7).

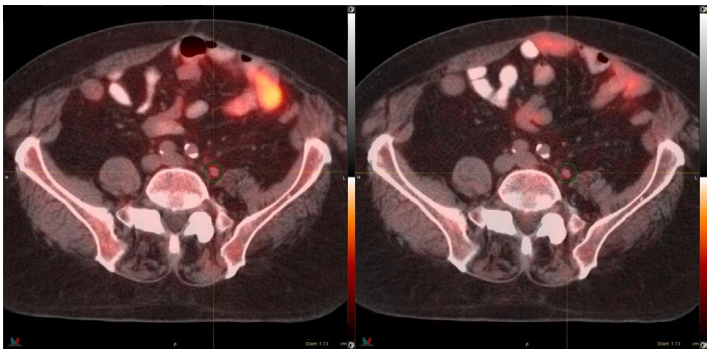


Figure 4. 75 y/o, Gleason 7, treated with brachytherapy and EBRT 11 years previously. Rising PSA at the time of AC imaging was 11.15 ng/mL. The left image shows a focal bone metastasis in the right ilium with early imaging (SUVmax 9.06, L/B 3.28). The right image shows the same finding in the bone but is much less conspicuous on later imaging (SUVmax 5.08, L/B 2.43).

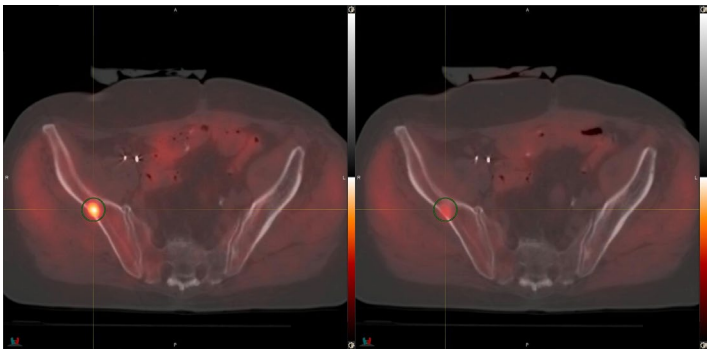


Figure 5. 70 y/o, Gleason 7, treated with EBRT 4 years previously. PSA nadir was 0.43 ng/mL. Rising PSA at the time of AC imaging was 3.9 ng/mL. The left image shows focal recurrent disease in the right aspect of the prostate gland with early imaging (SUVmax 6.14). The right image shows the same finding in the prostate gland on the later imaging (SUVmax 5.15). The L/B ratio was 2.74 for the early and 3.0 for the later imaging, respectively.

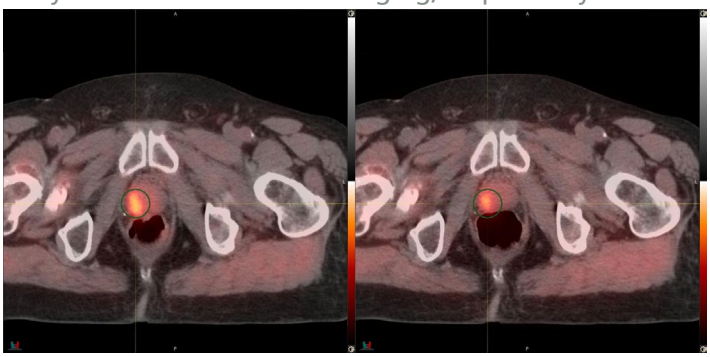
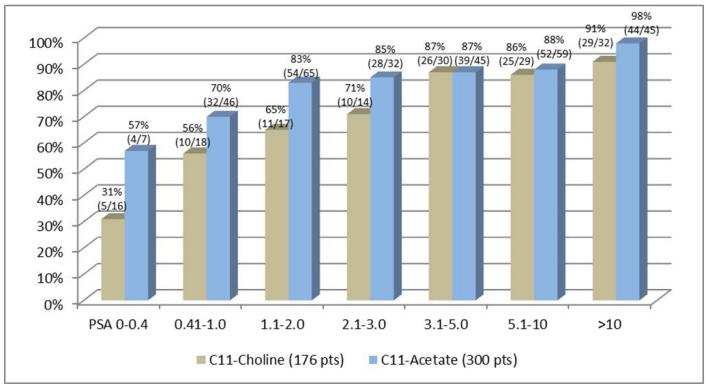


Figure 6. Detection rate of C11-Acetate PET/CT imaging across various PSA levels in 300 patients,[33] compared to C11-Choline PET/CT in 176 patients.[32]



DISCUSSION

The reported sensitivity for detection of recurrent or metastatic prostate cancer with C11-Acetate PET has varied widely in publications to date (55 to 100%) and is difficult to compare due to variations in camera technology, PSA levels, and timing [15,17,18,22-28]. A study by Vees et al. [23] showed only a 55% detection rate, but PSA was < 0.8 in all patients, and PET-only technology was used. In a study by Yu et al. [27], sensitivity was 100%, but all patients had documented bone lesions by technetium bone scans and much higher PSAs, ranging from 6.3 to 2,012 ng/mL. An early study by Frickle [18] showed a good detection rate, but the mean PSA (50ng/mL) was also higher than most other studies, which may have influenced performance. Most prior studies with shorter delay to imaging have additionally used "PET only" technology, which may also have contributed to lower detection rates [21]. With the PET-

Table 1. C11-Acetate PET imaging performance in BCR/metastatic prostate cancer. Prior studies have varied in terms of technology (PET versus integrated PET/CT), PSA levels, and timing for imaging post injection. Studies with earlier time to imaging generally show improved detection rates compared to later imaging.

Author	Year	Camera	N	Delay	PSA ng/mL	Detection Rate
Kotzerke[17]	2002	PET	31	5 min	0.1 - 150.6 (mean 10.4) < 2.0	83% 63%
Frickle[18]	2003	PET	25	2 min	0.3 - 400 (mean 50)	83%
Oyama[15]	2003	PET	46	10 - 20 min	0.3 - 47.5 (mean 5.2)	59%
Sandblom[22]	2006	PET	20	10 min	Median 2.0	75%
Vees[23]	2006	PET	11	2min	< 0.8	55%
Wachter[24]	2006	PET	50	15 min	0.5 - 24.9	64%
Albrecht[25]	2007	PET	17 (RT) 15 (RP)	2 min	2.6 - 30.2 0.08 - 4.8	82% 60%
Dusing[26]	2010	PET/CT	20	5 - 10 min	Unknown	85%
Yu[27]	2011	PET	8	2 min	6.3 - 2,012	100%
Haseebuddin[28]	2013	PET/CT	107	10 - 15 min	1.4-225.4	68%
Almeida[33]	2013	PET/CT	300	3 min	0.2 - 98 (mean 6.9)	84%

only studies, longer imaging acquisition times where generally necessary compared to modern PET/CT. Additionally, the detection of smaller lesions may have been less compared to higher-resolution, modern PET/CT. A recent meta analysis by Mohsen et al. [29] demonstrated a pooled sensitivity of 64% and specificity of 93%. In that analysis, included studies were generally small and highly heterogeneous. In 14 literature references evaluated in the meta analysis, 3 small studies were extreme outliers with very low detection rates (21 to 38%). Pooled sensitivity of the remaining 11 studies was significantly higher at 75% and likely more representative of the overall performance of prior studies. Our review of several publications where the timing of imaging could be ascertained demonstrates a trend of lower detection rates with longer delay from injection to imaging. See Table 1.

The differences in the early-to-late imaging findings in our study are not fully understood, as the kinetic molding work by Schiepers et al. [30] suggests pooling or trapping of AC for intracellular processes (for example, incorporation into mitochondria for energy metabolism, in the cytosol for enhanced lipid synthesis, and for building blocks for membranes, amino acids, and steroids). Time-activity curves from that study suggest rapid clearance from the blood pool with an early peak of AC uptake in prostate cancer cells, but then with a plateau after 5 to 10 minutes. In the meta analysis by Mohsen et al. [29], the authors indicated that time to imaging did not appear to influence sensitivity; however, their analysis did not distinguish between detection of local recurrence from detection of regional nodal and distant metastatic disease. Our data suggests, at least in sites of regional or distant metastatic disease, that a degree of AC washout or oxidation via the tricarboxylic acid cycle to CO2 and H2O may play a part after a 20-minute post-tracer injection. In conjunction with the rapid decay of C11 due to its short half-life, this may contribute to the lower levels of measured lesion tracer activity and L/B ratios in the later time-point imaging sequences.

Use of C11 choline PET imaging in patients with BCR prostate cancer has recently been approval by the U.S. Food and Drug Administration (FDA) for "in house" use at the Mayo Clinic. This has generated intense interest in the biomedical molecular imaging community. The primary experience with C11 choline in prostate cancer has been in Europe. Briefly, C11 choline has been found to be relatively insensitive in patients with BCR after surgery, with PSA values less than 2 ng/mL. In a study by Giovacchini et al. [31], C11 choline had a 5% detection rate for PSA levels of < 1 ng/mL, 15% for PSA levels of 1 to 2 ng/mL, and 28% for PSA levels of > 2 ng/mL. Data published on 176 patients by the Mayo Clinic, which formed a portion of the basis for FDA approval, demonstrated better imaging characteristics in the less than 2 ng/mL PSA range compared to the European data, but still performed poorly overall [32].

Based on our findings in this multiple time-point imaging study, early AC PET/CT imaging (3 minutes post injection) has been applied in an ongoing larger evaluation of performance characteristic in patients with biochemically recurrent prostate cancer [33]. Results in 300 patients (PSA 0.2 to 98 ng/mL, mean 6.9) thus far enrolled demonstrated an overall detection rate

UIJ / Vol 6 / Iss 6 / December / http://dx.doi.org/10.3834/uij.1944-5784.2013.12.01
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

of 84%, which was in concordance with other AC PET studies performed with shorter delay to imaging. When compared to performance data for C11 choline, AC demonstrates a superior overall detection rate (84% for AC versus 74% for choline). Additionally, AC performed better at nearly all levels of PSA. See Figure 6. In the PSA greater than 2ng/mL range, AC shows a 90% detection rate compared to 86% for choline. In the lower PSA range (0.4 to 2.0ng/mL), AC has a much higher overall detection rate of 77% compared with 60% for choline. Possible explanations for the higher performance of AC compared to choline may be the difference in imaging technique and patient characteristics, but also urinary tracer excretion may have contributed. Choline demonstrates some urinary excretion, while AC does not have significant urinary excretion. On AC studies, better evaluation and detection of lesions was likely afforded in the prostate bed, peri-prostate soft tissues, and lymph nodes along the ureters. Our study of AC PET/CT continues with more detailed analysis and publication pending. Further analysis of the impact of PSA kinetics and patient follow-up will be of significant importance to add to the understanding of the performance characteristic of AC PET/CT.

In conclusion, in patients with biochemically recurrent prostate cancer, early post injection C11 acetate PET/CT imaging utilizing modern hybrid PET/CT systems appears to demonstrate higher lesion tracer activity and higher lesion-to-background ratios compared to later imaging. This was found to be the case in the evaluation for nodal, peri-prostate, and bony metastasis, likely leading to the detection of small lesions that may otherwise have gone undetected on late imaging. Lesions in the prostate and seminal vesicles were detected, with higher tracer activity on earlier imaging but without statistically different early-to-late lesion-to-background ratios. Our findings are further confirmed by implementation of early imaging in a large series of patients (300), with generally superior detection rates of recurrent or metastatic prostate cancer when compared to studies performed with longer post-injection imaging times. The detection rate of AC PET/CT also appears to be generally superior to C11 choline PET/CT, particularly in the low PSA ranges (0.4 to 2.0ng/mL).

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Identification of Bleeding Sources During Removal of Inferior Vena Cava Tumor Thrombi: Multidetector Computed Tomography Study

Dmytro V. Shchukin,[1,2] Oleksiy O. Altukhov,[1,2] Ganna V. Lisova,[2] Yuriy A. Ilyukhin,[3]

[1]V. I. Shapoval Regional Clinical Center of Urology and Nephrology, [2]Kharkiv National Medical University, [3]Belgorod Regional Clinical Hospital of Saint Joasaph

Submitted October 29, 2013 - Accepted for Publication December 13, 2013

ABSTRACT

Objectives: The purpose of this study was to investigate the sources of bleeding from the lumen of the inferior vena cava (IVC) during removal of the tumor thrombus. We have studied the multidetector computed tomography (MDCT) anatomy of the posterior tributaries of the IVC, including variant lumbar veins and lumbar veins of the infrarenal IVC.

Materials and Methods: The retrospective study included 302 patients who underwent the bolus contrast-enhanced MDCT of the abdomen for various indications. We analyzed the anatomy of the variant lumbar veins and infrarenal IVC lumbar veins.

Results: Variant lumbar veins were detected in 50% of patients (151 out of 302). The diameter of these vessels ranged from 1 mm to 5 mm and averaged 2.5 mm. The distance from the upper edge of the right renal vein mouth to the variant vein mouth varied from 0 mm to 51 mm and averaged 13.7 mm. In 71% of cases the variant veins entered the subhepatic IVC. In 26.3% of cases it drained at the level of the upper edge of the renal vein mouths (cavarenal segment) and only in 2% of cases—to the retrohepatic IVC. Lumbar veins entered the IVC immediately next to the lower edge of the right renal vein mouth in 35 (11.6%) cases. Their average diameter was 4.7 mm. On the left side of the "risk zone" the lumbar veins drained only in 2 (0.7%) patients at a distance of 7 mm and 8 mm from the mouth of the left renal vein.

Conclusion: The variant lumbar veins rarely are the main source of bleeding during thrombectomy. From our point of view, the right upper lumbar veins of the infrarenal IVC draining into the inferior vena cava in close proximity to the mouths of the renal veins played the leading role in this matter.

INTRODUCTION

Modern surgical approaches to removal of tumor intravenous thrombi of the inferior vena cava (IVC) are based on the technique of vascular isolation, which prevents pulmonary embolism with tumor masses and reduces the risk of excessive bleeding from the lumen of the vein. This method involves applying clamps on the IVC above and below the thrombus, as well as on the contralateral renal vein (3 tourniquets technique) [1-3] (Figure 1). With "high" tumor extension, a Pringle's maneuver is used to stop hepatic blood flow. However, in some situations, with the use of classical vascular isolation during cavatomy, there is active discharge of blood from the lumen of the vena cava. This is due to blood inflow to the operation site from the other tributaries, which in most cases are lumbar veins [4,5].

KEYWORDS: Inferior vena cava, lumbar veins, variant lumbar vein, tumor thrombus, source of bleeding, MDCT

CORRESPONDENCE: Dmytro V. Shchukin, V. I. Shapoval Regional Clinical Center of Urology and Nephrology, 195, Moskovskyy Avenue, Kharkiv, 61037, Ukraine (shukindv@gmail.com)

CITATION: *UroToday Int J*. 2013 December;6(6):art 75]. http://dx.doi.org/10.3834/uij.1944-5784.2013.12.10

Figure 1. Vascular isolation of the subhepatic IVC segment with the tumor thrombus.

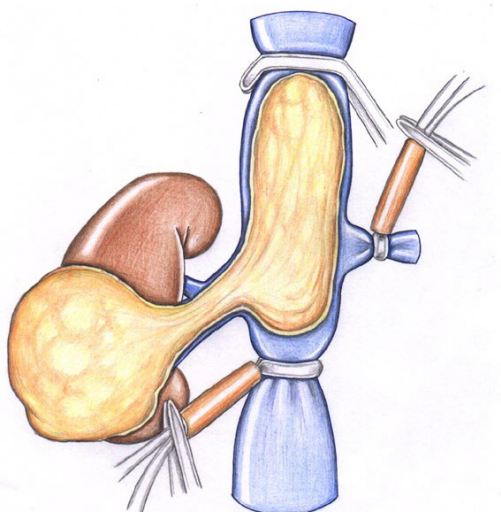
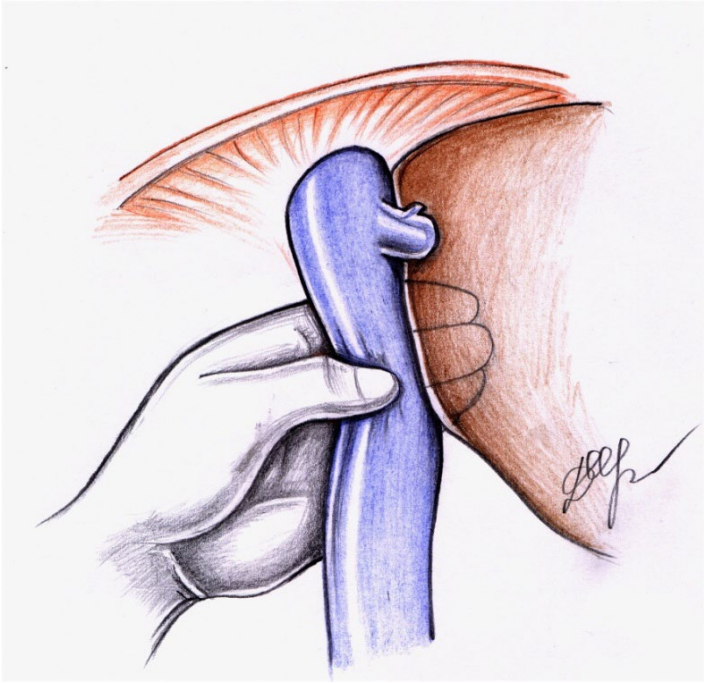


Figure 2. Mobilization of the posterior surface of the retrohepatic IVC before thrombectomy.



Incomplete vascular control can cause significant hemorrhage, which not only makes it difficult to view the internal surface of the IVC and prevents radical removal of the tumor, but is also accompanied by large blood loss.

A detailed study of surgical anatomy of the lumbar veins is presented in the paper by Baniel et al. [6]. At the same time there is significant variation in the number and topography of these vessels. However, this work is focused on the anatomy of infrarenal lumbar veins and the problems associated with retroperitoneal lymphadenectomy, but not vena cava thrombectomy.

Recently a group of American researchers examining 49 corpses for the first time has discovered an unpaired lumbar vein opening into the retrohepatic IVC in 38.8% of cases [7]. This anatomical feature was prevalent in men. The authors called this vessel the variant lumbar vein. The mean diameter of the mouth of the variant lumbar vein was 3.7 mm, and the mean distance from the mouth of the variant lumbar vein to the mouth of the right renal vein was 7.4 cm. In most cases the mouth of the vein was located between the 6 and 7 o'clock positions. The authors believe that it is the variant lumbar vessel that is the major cause of bleeding from the isolated area during IVC thrombectomy. Retrospective evaluation of our own experience of surgery on the inferior vena cava during radical nephrectomy demonstrated that bleeding from the lumen of the IVC occurred with the same frequency during removal of both retrohepatic and subhepatic tumor thrombi. In our clinical practice we apply the technique of thrombectomy described by Ciancio et al., which comprises "piggyback" mobilization of the liver and digital displacement of the thrombus below the mouths of the major hepatic veins [8-10]. In this case the use of posterior retrohepatic inferior vena cava mobilization is always required (Figure 2). However, during the operations we did not encounter large lumbar vessels in the area.

From our point of view, most frequently the main sources of hemorrhage were lumbar veins draining into the cavarenal or subrenal segment of the IVC (within 1.0 cm below the mouth of the renal veins). This assumption is also supported by frequent detection of large lumbar veins draining into the IVC just below its cavarenal segment during computed tomography (CT) scanning.

Considering these facts, in order to support the presented hypothesis, we performed MDCT examination of the anatomy of tributaries of the infrarenal, cavarenal, and subhepatic IVC segments, as well as nonhepatic tributaries of retrohepatic vena cava, including variant lumbar veins.

UIJ / Vol 6 / Iss 6 / December / http://dx.doi.org/10.3834/uij.1944-5784.2013.12.10
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

MATERIALS AND METHODS

The retrospective study included 302 patients who were examined and treated in the hospital of V. I. Shapoval Regional Clinical Center of Urology and Nephrology in the city of Kharkov. Patients underwent MDCT for various indications. The study was approved by the local ethics committee for V. I. Shapoval Regional Clinical Center of Urology and Nephrology (Protocol No. 3 dated May 17, 2012).

Patients with tumor thrombi of the inferior vena cava, as well as those who had undergone surgery, including retroperitoneal lymphadenectomy or vena cava thrombectomy, were not included in the study.

Among 302 patients there were 104 (34.4%) women and 198 (65.6%) men. Their average age was 57.5 (18 to 85 years). MDCT was performed using a CT scanner (Toshiba Aquilion S16, model TSX-101A, Japan). The examinations were performed with a section thickness of 1 mm, tube rotation time of 0.5s, voltage of 120V, and an electric current of 400 mA. As a contrast medium, 100 mL of a nonionic contrast agent (ultravist 300, 370 and tomogexol 300, 350) via the venous cubital catheter with the automatic bolus injector was administered at the rate of 3.0 to 3.5 mL using SureStart and with further multiplanar and 3-dimensional reconstructions.

The study protocol included the arterial (20 to 25s after administration of the contrast agent), venous (50 to 70s), and delayed (5 to 7 minute) phases. All received data was analyzed by 1 radiologist.

The venous vessels that drained along the posterior IVC at the level of its retrohepatic, subhepatic and cavarenal segments and which were neither adrenal nor lower diaphragmatic veins, were classified as the variant lumbar veins.

RESULTS

Variant Lumbar Veins

Variant lumbar veins were detected in 50% (151 of 302) of patients. The diameter of these vessels ranged from 1 mm to 5 mm and averaged 2.5 mm. In 85.4% of cases this parameter was not more than 3 mm (Table 1).

The distance from the upper edge of the right renal vein mouth to the mouth of the variant vein varied from 0 mm to 51 mm and averaged 13.7 mm (Table 2). In 40 (26.3%) cases the variant vein ran into the IVC at the level of the upper edge of the mouth of the renal veins (cavarenal segment); in 3 (2.0%) cases the variant vein ran into the retrohepatic IVC segment; in 1 (0.7%) case it was connected to the upper right lumbar vein of the infrarenal IVC (Figure 3).

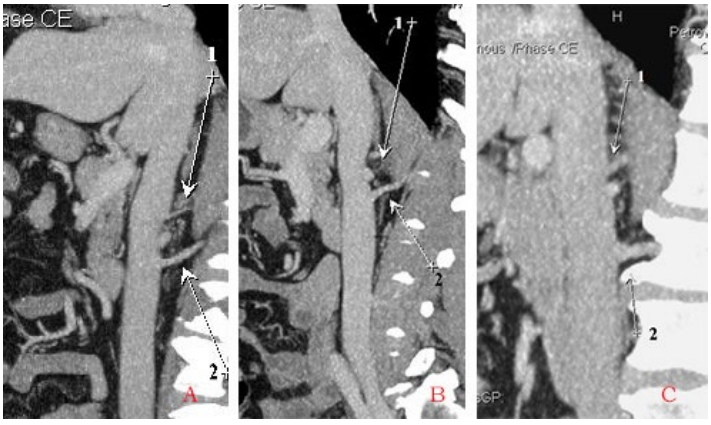
Table 1. Characteristics of the diameter of the variant lumbar veins.

Vein diameter	≤ 2 mm	> 2 mm ≤ 3 mm	> 3 mm ≤ 4 mm	> 4 mm
n/%	90/59.6	39/25.8	17/11.3	5/3.3

Table 2. Localization characteristics of the variant lumbar vein.

The distance from the mouth of the right renal vein to the mouth of the variant vein	0 to 10 mm	11 to 20 mm	21 to 30 mm	31 to 40 mm	41 to 51 mm	Total
n/%	75/49.7	34/22.5	27/17.9	10/6.6	5/3.3	151/100

Figure 3. MDCT of the variant lumbar veins: a, b, c) sagittal reconstruction. The variant veins opening into the subhepatic IVC (arrow 1) and the upper lumbar vein of the infrarenal IVC (arrow 2) are visualized.



The variant vein mouths opened into the IVC most commonly at the 4 to 5 o'clock position (Table 3).

Lumbar Veins of the Infrarenal IVC

In the infrarenal part of the inferior vena cava the lumbar veins were most often detected on the right side (833 vs. 633). On average, 2.8 veins were found on the right, and 2.2 veins were

Table 3. Localization characteristics of the variant lumbar vein using conventional zones in clockwise order.

Localization characteristics of the variant lumbar vein mouths with the use of conventional zones in clockwise order	2 o'clock	3 o'clock	4 o'clock	5 o'clock	6 o'clock	7 o'clock	Total
n/%	1/0.7	15/9.9	58/38.4	60/39.8	15/9.9	2/1.3	151/100

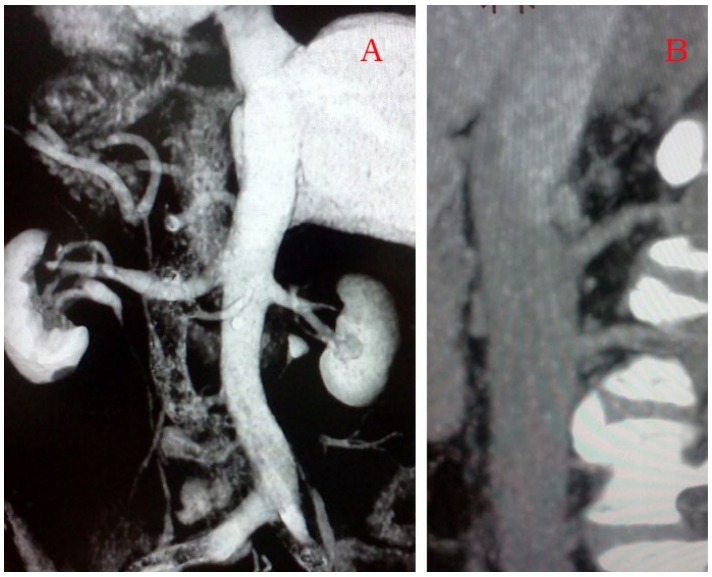
Table 4. Detailed distribution of the lumbar veins depending on their number and location.

Number of veins	1	2	3	4	5	Total
On the right	11 (3.6%)	109 (36.1%)	133 (44%)	40 (13.3%)	9 (3%)	302 (100%)
On the left	56 (18.5%)	157 (52%)	73 (24.2%)	14 (4.6%)	2 (0.7%)	302 (100%)

Table 5. Characteristics of the upper lumbar veins of the infrarenal IVC.

	All the upper right lumbar veins	All the upper left lumbar veins	Upper right lumbar veins of the "risk zone"	Upper left lumbar veins of the "risk zone"
The average diameter of the mouth	3.7 mm (1 to 10 mm)	2.7 mm	4 mm (2 to 8 mm)	3 mm (2 to 4 mm)
The distance from the mouth of the ipsilateral renal vein to the mouth of the lumbar vein	17.2 mm (0 to 98 mm)	53.0 mm (7 to 115 mm)	4,3 mm (0 to 10 mm)	7.5 mm (7 to 8 mm)
Localization of the lumbar vein mouth with the use of conventional zones in clockwise order	5.2 o'clock	3.9 o'clock	5.2 o'clock	3.5 o'clock

Figure 4. MDCT of the upper lumbar veins entering the "risk zone". a) Coronal reconstruction of the IVC (the rear view). The right upper lumbar vein flowing into the IVC at the level of the lower edge of the renal vein mouths is visualized. b) Sagittal reconstructions show the large upper lumbar veins draining into the IVC at the level of the right renal artery.



found on the left. The detailed distribution of the lumbar veins, depending on their amount, is presented in Table 4.

The mean diameter of all lumbar veins on the right did not exceed 3 mm, and on the left did not exceed 2.5 mm. The mean distance from the right renal vein to the first right lumbar vein reached 17.2 mm, and from the left renal vein to the first lumbar vein on the left was 53 mm.

Considering the problem of hemorrhage from the lumbar veins during thrombectomy, we have identified a conditional "risk zone" where the upper lumbar veins flow into the area of vascular isolation of a thrombus. This "risk zone" included an IVC portion of 10 mm long below the mouth of the ipsilateral renal vein. Therefore, the study assessed such parameters as the size and location of the lumbar vein mouths closest to the cavarenal segment of the IVC.

Drainage of the right side lumbar veins in the "risk zone" was identified in 116 (38.4%) patients. (Table 5). The lumbar veins ran into the IVC immediately next to the lower edge of the right renal vein mouth in 35 (11.6 %) cases (Figure 4). Their average diameter reached 4.7 mm. On the left side of the "risk

Table 6. Detailed distribution of the lumbar veins depending on their number and location.

Localization of the lumbar vein mouths of the "risk zone" with the use of conventional zones in clockwise order	2 o'clock	3 o'clock	4 o'clock	5 o'clock	6 o'clock	7 o'clock	Total
On the right	1/0.9	0	8/7	74/63.8	30/25.8	3/2.5	116/100
On the left	0	1/50	1/50	0	0	0	2/100

zone" the lumbar veins drained only in 2 (0.7%) patients at a 7 mm and 8 mm distance from the mouth of the left renal vein.

The mouths of right upper lumbar veins were more often located between the 5 and 6 o'clock positions, while on the left side they were located between the 3 and 4 o'clock positions (Table 5 and Table 6).

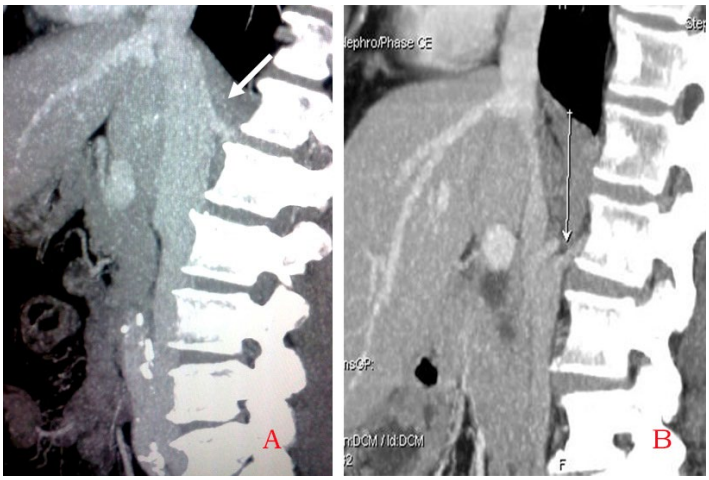
Fusion of infrarenal lumbar veins was found in 88 (29.1%) cases. At the same time a lot of variants of their junction were revealed (Figure 5). In most cases there was fusion of 1 pair of veins (88.7 %); in 9 (10.2%) cases it was 2 pairs; in 1 (1.1%) case there were 3 pairs. Mainly, the veins joined on the contralateral sides, but in 3 (3.4 %) patients fusion of the veins was detected on the ipsilateral side. In 4 (4.5%) cases the lumbar veins were joined with the renal veins (in 1 case there was fusion of the first right lumbar vein, the first left one, and the left renal vein). In 1 patient there was fusion of the first right lumbar vein with the variant lumbar vein.

DISCUSSION

The problem of bleeding from the lumen of the IVC during removal of the intravenous tumor thrombi is very important, as the operation can result in significant blood loss and cause problems with the examination of the endothelial surface after removal of the tumor mass. All of this ultimately can heavily deteriorate the radicality of the surgery.

Analyzing the sources of bleeding in a particular patient, it is necessary to take into account several factors, which include the degree of thrombus extension, anatomical parameters of the patient, and special aspects of thrombectomy technique.

Figure 5. MDCT of the inferior vena cava. a, b) Sagittal reconstruction. A large variant vein draining into the retrohepatic IVC is visualized.



During standard vascular isolation of the IVC thrombus, which includes placing clamps or tourniquets on the contralateral renal vein, as well as above and below the thrombus, the potential source of bleeding can be actually all venous tributaries draining into the IVC at this level (lumbar, infradiaphragmatic, and adrenal veins). The clinical significance of these vessels as sources of bleeding cannot be considered equivalent. If we consider the venous vessel mouth with the diameter of more than 3 mm as an important parameter for bleeding during thrombectomy, the lower right diaphragmatic veins can hardly be considered a source of significant blood loss. Typically, their diameter does not exceed 3 mm. However, in the presence of caval obstruction and development of collateral venous outflow, they can come to a larger diameter and be the source of bleeding during thrombectomy. In most cases the diameter of the right adrenal veins is much larger than the diameter of the lower phrenic veins; however, their importance as a source of bleeding is not high due to the low volume of blood flow in the adrenal gland. In addition, the role of the right lower phrenic and adrenal veins should be taken into account mainly during removal of the retrohepatic or "higher" thrombi.

There is no doubt that lumbar veins are the most important source of bleeding from the lumen of the IVC. Anatomical studies, including the authors' own work, demonstrate considerable variations of their number, size, and topography [6,11,12]. In particular, their mouths can be located not only

UIJ / Vol 6 / Iss 6 / December / http://dx.doi.org/10.3834/uij.1944-5784.2013.12.10
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

in the infrarenal vena cava segment, but in the retrohepatic, subhepatic, or cavarenal segments of the IVC. Taking into account the diameter of the lumbar veins, and a relatively high intensity of blood flow (due to the association with the vertebral venous plexus), it can be stated that these vessels play the leading role in the development of bleeding from the lumen of the IVC during thrombectomy.

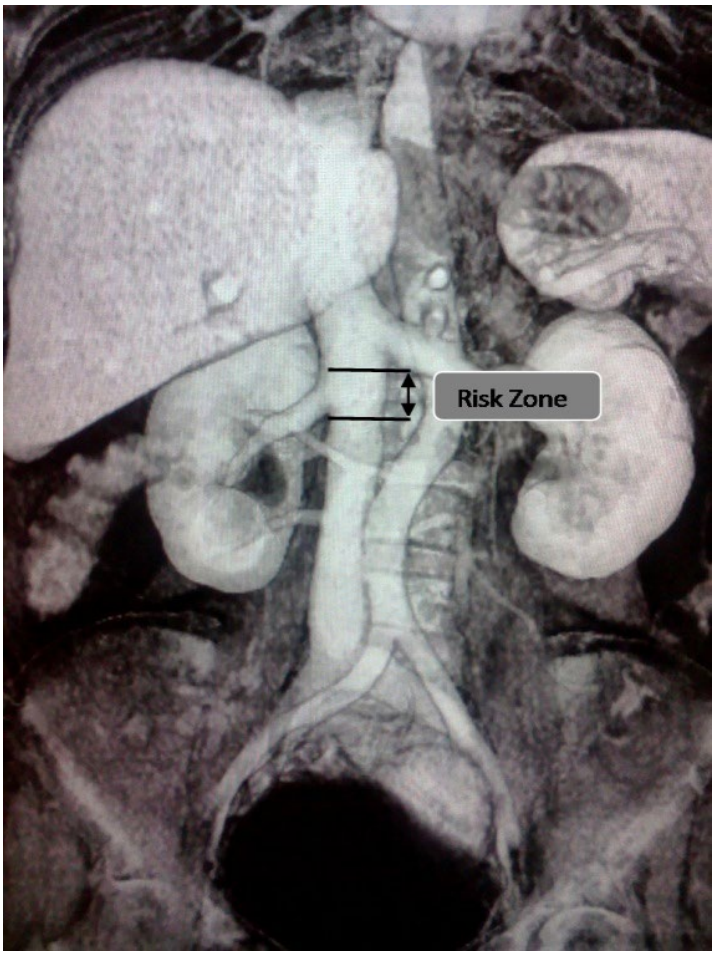
Recently Abbasi et al. have found a variant lumbar vein opening into the retrohepatic IVC [7]. These vessels were identified in 38.8% of cases in 49 observations that mainly occurred in men. The average diameter of a variant lumbar vein mouth was 3.7 mm, and the mean distance from the mouth of a variant lumbar vein to the mouth of the right renal vein was 7.4 cm. In most cases the mouth of this vein was located between the 6 and 7 o'clock positions. The authors believe that it is the variant lumbar vessel that is the major cause of bleeding from the isolated area during IVC thrombectomy.

In our investigation, the variant lumbar vein was detected in 50% of cases. In contrast to the results of Abbasi et al., draining of the variant lumbar vein into the retrohepatic IVC was found only in 3 cases (2%) [7]. In 40 (26.3 %) cases the variant vein ran into the IVC at the level of its cavarenal segment; in 1 (0.7 %) case it was connected to the upper right lumbar vein of the infrarenal IVC. In 71% of patients the variant veins drained into the subhepatic segment of the vena cava.

The distance from the mouth of the right renal vein to the mouth of the variant lumbar vein ranged from 0 mm to 51 mm and averaged 13.7 mm. Another difference between the results obtained in this study was that the average diameter of the mouth of the variant lumbar veins did not exceed 2.5 mm. Therefore, from our point of view, they are unlikely to be a significant source of bleeding during thrombectomy, except for the rare situations. These situations may include the diameter of a variant vein greater than 3 mm (7.3% of all patients) and localization of the mouth of the variant vein in the retrohepatic segment of the IVC (1% of all patients) (Figure 6).

To reduce the risk of bleeding from the lumen of the inferior vena cava, the surgeon before the operation should carefully plan the stage of vascular thrombus isolation and evaluate the anatomy of the variant lumbar vein on the basis of visual research methods; in particular, multispiral CT. On the other hand, the use of surgical technique proposed by Ciancio et al., which includes mobilization of the liver and manual displacement of the thrombus below the mouths of the major hepatic veins to remove the IVC tumor thrombus, greatly facilitates control of the lumbar veins at the level of subhepatic and retrohepatic vena cava [8-10].

Figure 6. MDCT. Frontal reconstruction. The right and left renal veins flow into the IVC at different levels.



Analyzing the anatomy of the lumbar veins of the infrarenal segment of the inferior vena cava, one should note the apparent variability in the number of these vessels and localization of their mouths. The results of our study have demonstrated predominance of the right lumbar veins in the infrarenal IVC (2.8 vs. 2.2), although in the work by Baniel et al. the left-side lumbar veins were more frequent [6].

Taking into account that during vascular isolation of the thrombus it is not always possible to place the lower clamp immediately under the mouths of the renal veins, we performed a detailed study of the upper (first) lumbar veins that flow into

UIJ / Vol 6 / Iss 6 / December / http://dx.doi.org/10.3834/uij.1944-5784.2013.12.10
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

the IVC closest to the renal veins, and may happen to be in the area of vascular isolation of the thrombus. At the same time, the "risk zone" where the upper lumbar veins may enter the area of thrombectomy while placing the lower clamp on the IVC was defined. The area included the IVC segment of 10 mm long below the mouth of the ipsilateral renal vein. By choosing this option we give reasons from several points of view:

In some situations the tumor thrombus extends not only in the antegrade direction, but also in the retrograde direction 5 to 7 mm downwards.

The right and the left renal veins in many cases flow into the IVC at different levels. These differences can amount up to 10 mm, so placing of a clamp under the lowest renal vein may result in the situation where the area of vascular isolation of the thrombus is entered by a lumbar vein from the contralateral side.

During placement of the upper clamp above the IVC thrombus, downward displacement of the thrombus is often performed (especially when the expansion of intraluminal tumor above the mouths of the hepatic veins takes place); therefore, the lower part of the thrombus may be displaced below the mouths of the renal veins.

During clamp placing under the mouth of the right renal vein, a "risk zone" occurs where the first lumbar vein may enter the area of vascular isolation of the thrombus. We discovered that the right upper lumbar vein drained into the "risk zone" in 38.4% of cases, and the left only in 0.7%. These differences can be explained by the fact that the upper left lumbar vein often flows not into the IVC but directly into the left renal vein. It is interesting that in 35 (11.6%) cases the lumbar veins drained directly into the IVC next to the lower edge of the right renal vein mouth. The average diameter of these vessels amounted to 4.7 mm.

The distance from the mouth of the ipsilateral renal vein to the mouth of the upper lumbar veins in the "risk zone" averaged 4.3 mm (0 to 10 mm) on the right and 7.5 mm (7 to 8) on the left. The mouths of the right lumbar veins opened in the IVC more often between the 5 and 6 o'clock positions, and the left ones between the 3 and 4 o'clock positions.

This data suggests the high prevalence of the upper lumbar veins, which may enter the area of vascular isolation of the thrombus during clamp placing 10 mm below the renal vein mouths. Taking into account that the average diameter of these vessels is more than 4 mm, it can be assumed that they are the main source of bleeding during removal of the IVC tumor thrombi.

Although control of the infrarenal IVC lumbar veins during thrombectomy is normally performed by most surgeons, it is quite difficult in some situations to complete this control since the right upper lumbar veins open into the IVC posteriorly at the 5 to 6 o'clock positions. In case of massive thrombi restricting the mobility of the vena cava and causing caval obstruction, these thin-walled veins can amount to large diameters and can be easily injured during their ligation or clamping. This maneuver is the most difficult to perform with the increased paracaval lymph nodes, as well as with large tumors expanding to the perinephric fat. In such situations we can control the upper lumbar veins after removal of the thrombus from the lumen of the inferior vena cava.

Taking into account the importance of the upper lumbar veins in the development of bleeding from the lumen of the IVC, during removal of the tumor thrombus, the surgeon must carefully examine the anatomy of these vessels before the operation with the use of multispiral CT or magnetic resonance imaging. This will enable us to plan the stage of vascular thrombus isolation properly and avoid serious complications associated with bleeding.

CONCLUSION

The results of our study have demonstrated that the variant lumbar veins occur in about 50% of patients and in most cases their mouths open in the subhepatic segment of the IVC. The average diameter of these vessels does not exceed 2.5 mm, so we believe that they are not the main source of bleeding during vena cava thrombectomy. From our point of view, the right lumbar veins of the infrarenal IVC, which flow into the inferior vena cava in the immediate proximity to the mouth of the renal veins, play the leading role in this matter. These veins have an average diameter of 4 mm and occur in 38.4% of cases. A surgeon before the operation should carefully plan the stage of vascular thrombus isolation and evaluate the anatomy of the lumbar veins with the use of the data presented with visual methods.

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A Model for Implementation and Sustainability of Urologic Services in the Developing World: Based on the 4-Year Experience of Knock Foundation Urologic Volunteers in Kenya and Ethiopia

Joel Cornfield, Mark Schacht, Craig Smith, Brien Keuer, Charles Durkee, Robert Wadman, F. Bruce Cohen, David Grossman

Submitted November 7, 2013 - Accepted for Publication December 13, 2013

ABSTRACT

The purpose of the Knock Foundation initiative in sub-Saharan Africa, to date in Kenya and Ethiopia, is to bring modern urologic procedures, specifically cystoscopy, transurethral resection/vaporization of the prostate, and visual internal urethrotomy to an underserved population in a sustainable and therefore accessible fashion. The article describes in detail the 4-year effort of the Knock Foundation and its volunteers in bringing these procedures to previously underserved areas of Kenya and Ethiopia, teaching techniques to local physicians and building sustainable, if nascent, programs in urology at distinct institutions.

PURPOSE

The purpose of the Knock Foundation [1] (Knock) program in urology is to bring modern urologic procedures, specifically cystoscopy, transurethral resection of the prostate (TURP), and visual internal urethrotomy (VIU) to an underserved population in a sustainable fashion.

BACKGROUND

In late 2009, the Knock Foundation, acting through 2 of its founders and directors, F. Bruce Cohen and David Grossman, contacted Susan Blaustein, director of the Millennium Cities Initiative [2] (MCI) of the Earth Institute of Columbia University, New York, New York, seeking its help in facilitating a medical mission to one of the 11 millennium cities located in sub-Saharan Africa. The MCI is, among other things, a facilitator for nongovernmental organizations (NGOs) via the employment of local representatives whose mission it is to serve as catalysts for change. Working in concert with MCI, its representative in Kisumu, Kenya, Beldina Opiyo-Omolo, and United Therapies LLC [3] (UT) of Park Ridge, Illinois, Knock successfully sponsored a medical mission trip to Nyanza Provincial General Hospital (NPGH) [4] in Kisumu, Kenya [5]. The initial purpose of that mission was to provide urologic services to the surrounding population and much-needed supplies to the local hospital.

Kisumu is situated on the western edge of the country on the northeastern shores of Lake Victoria, with its vast surface area of 69,000 square kilometers. With an estimated population of 500,000 [6], Kisumu is the fastest growing metropolis in Kenya and has grown to become the principal administrative, communication, commercial, and industrial center in the Lake Basin region, an area that traverses the whole of Nyanza, western Rift Valley, and western provinces in Kenya. Kisumu has gradually become one of the poorest areas of Kenya. While absolute poverty in Kenya is high, affecting 29% of the population, Kisumu's rate is estimated to be nearly double that figure. Fifty-three percent of Kisumu's population lack reliable access to food, as compared to 39% in the second largest city, Mombasa, and only 8% in Nairobi [7]. Unemployment is high (30%), with at least 50% of the population engaged in the informal sector [8]. In addition, Kisumu's HIV/AIDS infection rate is approximately 15% [9] and it has a high prevalence of

KEYWORDS: Cystoscopy, TURP, VIU

CORRESPONDENCE: Joel Z. Cornfield, Uropartners LLC dba York Urologic Associates, 950 N. York Road, Suite 208, Hinsdale, Illinois 60521(cornf5@yahoo.com; jcornfield@uropartners.com)

CITATION: *UroToday Int J*. 2013 December;6(6):art 76. http://dx.doi.org/10.3834/uij.1944-5784.2013.12.11

malaria and other infectious diseases. Like many other diseases, urologic disease, including benign prostatic hypertrophy (BPH) and urethral stricture (US) disease, are not uncommon disease states, but have been undertreated due to a lack of trained personnel and access to cystoscopy.

An acute public health area need is for further medical training, particularly in sub-specialty areas, including urology. Other than perhaps taking a 3-month urology course at KCMC Hospital in Moshi, Tanzania, there are very few urologists that go through the level of training found in the west. Following exhaustion of home remedies and the onset of urinary retention, available therapy for BPH has generally consisted of placement of a suprapubic tube followed by open prostatectomy performed, often incompletely and repeatedly, by general surgical staff. Treatment for US disease often consisted of rare dilation and/or suprapubic tube placement. Urethroplasty of any kind has been an uncommonly attempted procedure due to lack of training.

In 2010, the city itself was serviced by one solo private practice urologist Willis Oyeko, MD. A General surgeon by training, Dr. Oyeko transitioned to urology by virtue of such a 3-month residency at KCMC and functioned with a partial set of ACMI cystoscopic instruments, a resectoscope consisting of a single woven 24 Fr sheath, a solitary 30 degree lens, and 1 loop which he reused. Prior to Knock's arrival he had accomplished 1 TURP on his own. Because of the absolute unavailability of Glycine for irrigation, he was required to use sterile water.

An office visit with Dr. Oyeko cost the equivalent of about $1.50, in an economy where daily income is often in the range of $1 to $2 [10]. A significant percentage of the population was unable to afford this or any other service in the private sector and sought care via the public sector.

Nyanza Provincial General Hospital (NPGH) has been in existence for more than 100 years. Since then, it has grown to become the referral hospital for the province, serving over 12 district hospitals in Nyanza and the neighboring districts in the western province and Nandi. Its principal mandate is to provide curative and preventative health services and to perform other services, as provided for by the Kenya Ministry of Health. It serves a population of more than 5 million in 3 provinces: Nyanza, Western Valley, and Rift Valley. As a publicly funded hospital, patients are required to pay nominal fees for services, including radiologic services as well as operating room fees. Moreover, patients are required to purchase supplies that will be used for their elective surgeries from an outside pharmacy and bring these supplies to the operating room the day prior to the scheduled surgery; if they fail to do so the surgery is oftentimes cancelled. Many people are unable to afford even these costs and must wait and save, in some cases for years in order to undergo a procedure. Fortunately, these costs are waived in emergencies.

Prior to Knock's arrival, the hospital possessed no urologic equipment beyond a limited array of Foley catheters and a single set of Van Buren sounds. Moreover, the dearth of equipment meant that both TURP and visual internal urethrotomy (VIU) were unavailable. Our team found patients in retention from either BPH or stricture disease with suprapubic tubes that had been in place for almost 7 years. In 1 case, a gentleman had functioned without a change of tubing or a voiding trial for 6 years. We quickly realized that a simple 2-week mission would be little more than a Band-Aid and the goal of the mission evolved from the provision of limited services to one of building a urology service that would be useful long after our departure. Indeed the mission had evolved from that of just performing procedures to bringing (and leaving) enough equipment and training the general surgeons so they achieved a level of proficiency and were capable of performing such procedures long after we departed.

Consequently, Knock procured and donated functioning cystoscopic equipment and crafted a urology cart for organized instrument and consumable storage. An on-site C-arm was salvaged, repaired, and placed into use by Knock volunteer cysto/radiology tech, Robert Wadman that allowed for the performance of retrograde pyelograms and passage of ureteral stents. Knock trained operating room (OR) staff in the care and use of the cystoscopic equipment, and taught and supervised surgeons in the performance of TURP, VIU, and both end-to-end and 2-stage urethroplasty.

These accomplishments gelled during a second 2-week mission in 2011, during which Knock was able to provide a bipolar TURP device for use with sterile saline as well as the required training. Armed with knowledge gleaned from the prior mission to NPGH, and once again using the local MCI representative as a facilitator, Knock contacted Mekelle University in Mekelle, Ethiopia [11] to plan missions for 2012 and 2013.

Ethiopia, a country of some 90 million people, is served by a mere 60 urologists who have completed various stages of training, and possess variable and generally incomplete sets of cystoscopic equipment. Guide-wires and stents are rare commodities. Lithotripsy is available only in Addis Ababa, when the machine is functioning [12].

Mekelle, approximately 475 miles north of Addis Ababa, is a city of approximately 300,000 people. Mekelle, the capital of

UIJ / Vol 6 / Iss 6 / December / http://dx.doi.org/10.3834/uij.1944-5784.2013.12.11
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

the Tigray region, is one of the cities closest to the ports of Djibouti, which is used for most of Ethiopia's import and export trade on the Red Sea. The city is located at the hub of a road system connecting all of the region's urban centers.

To date, missions to Mekelle have been completed in 2012 and 2013; the 2013 mission was completed shortly before this writing. Knock Foundation urologists worked primarily at the university's Aydar Referral Hospital but also spent time at Mekelle Hospital, the equivalent of a public facility. Mekelle Hospital was built in 1962 to serve the then-20,000 people living in and around the city. Since then, there has been a 12-fold growth in the population.

Although the hospital has made efforts to increase its service offerings in response to the rapid urban expansion and mounting health needs, Ayder Referral Hospital, affiliated with Mekelle University, seems to be the pre-eminent facility in the region. Indeed, many of the shortages of equipment and supplies found at Mekelle Hospital were not in evidence at Ayder. Moreover, the facility itself was better maintained.

Learning from our experience in Kenya, and much like our second trip to Kenya, these missions mainly involved the training of 2 general surgeons in cystoscopy, retrograde pyelography, VIU, and TURP/BT. In addition, Knock also engaged in the supplementary training of a recent graduate of the nascent urologic residency program in Addis Ababa and provided fairly complete instrument sets for Ayder Referral Hospital, the recently graduated urologist, and supplemented the instrument set of the private practice urologist in Mekelle. We believe this should enable the physicians and the facilities to perform the procedures outlined above for years to come. Moreover, we are setting up a process for semi- or as-needed consultation with our Ethiopian counterparts. One of the general surgeons Knock helped train has matriculated in the new 3-year residency program in Addis Ababa, during which time he will be rotated periodically to the Ayder referral hospital.

DESCRIPTION OF THE PROGRAM

The goal of the Knock missions is the sustainable delivery of urologic services to an underserved population. In the Knock model, Knock directors work through MCI to identify an MCI city with an underserved population, hospital facility, cooperative administration, and eager medical staff.

Facilitated by the local MCI representative, arrangements are made for an approximately 2-week stay to provide surgical and cystoscopic services by volunteer urologists, solicited through Knock's relationship with physicians.

During the preparation phase, Knock actively solicits the donation and/or purchase of supplies, not limited to urologic use, and equipment, in particular new and/or used cystoscopic equipment.

Much of the equipment and supplies are shipped on ahead via container, a process which Knock discovered requires a minimum of 4 months to insure both timely arrival and customs clearance. This is a laborious process, which is unique to each country. Thus, the challenge is compounded when one considers that Knock moves from country to country every 2 years.

Selected equipment that can be transported by hand and is absolutely essential to the mission is usually transported by hand to ensure that even if the container is delayed, the primary purpose of the mission can continue unabated.

During the mission, volunteer urologists, working in teams of 2 and occupying 2 or 3 of the site's available operating rooms, actively engage in open and endoscopic procedures and intensive teaching of staff general surgeons, residents, and medical students motivated to learn how to use cystoscopic equipment. The local surgeons are introduced to diagnostic cystoscopy, retrograde pyelography, stent placement, visual urethrotomy, TURP/BT, 2-stage urethroplasty, end-to-end urethroplasty and the use of vascularized penile flaps. By the conclusion of the first 2-week mission, the local staff has been able to successfully demonstrate use of the equipment in both diagnostically related cystoscopy and VIU with minimal supervision. Facility in TURP has not been so easily accomplished and has required a second site visit in each case. Other less common procedures include pyelo- or ureterolithotomy, cystolithotomy, radical nephrectomy and hypospadias repair, penile reconstruction, and repair of 1 case of extrophy (Table 1).

Given the dearth of local urological specialists, Knock has made the decision to actively work with a limited number of local private urologists. It works with them by providing them with additional advanced training and also supplies them with specialized equipment to buttress the limited equipment currently at their disposal. The decision was made to support private practice physicians based upon the belief that they ultimately serve the targeted population as well. Knock and the physician volunteers maintain contact with the surgeons with whom we work through the use of e-mail and Facebook [13].

A second mission to the host country and facility(ies) is undertaken the following year to solidify and continue hands-on training, particularly in TURP, help with difficult, recalcitrant cases, provide additional equipment with particular attention to filling in gaps in equipment discovered during the first mission, and, perhaps most importantly, solidify the interpersonal relationships that have developed between the visiting urologists and the host physicians, which will be further reinforced by continued contact via e-mail, social media, and video conferencing.

UIJ / Vol 6 / Iss 6 / December / http://dx.doi.org/10.3834/uij.1944-5784.2013.12.11
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

Table 1. A chart of procedures.

Procedures Done	Kisumu	Mekelle
Diagnostic cystoscopy	25	23
Cystoscopy/retrograde	6	7 (2 ureteral caths placed)
VIU	12	14 (1 failure going on to urethroplasty)
TURP/TUIP	17 (bipolar)	22 (mostly TUIP)*
TURBT	2 (< 2 cm)	1 (extensive disease referred to Addis Ababa)
Open prostatectomy	6 (1 postop death due to hypothermia)	7
Radical nephrectomy	2 (1 Wilms tumor)	1
Pyelolithotomy	6 (1 bilateral)	7 (1 ureterocalycostomy)
Cystolithotomy	3	2
Ureterolithotomy	--	4
Patch/flap urethroplasty	1	6
End-to-end urethroplasty	2	1
Staged urethroplasty	3	1
Distal hypospadias	1	5
Midshaft hypospadias	2	2
Proximal hypospadias	--	1 (adult)
Urethrocutaneous fistula	2 (1 prostato-rectal)**	1 (post-circ)
Penile reconstruction	--	2 (1 electrical burn, 1 post-circ amputation)
Extrophy repair	1	--
Epispadias repair	1	1 (simple closure)
Orchiopexy	2	--
Bilateral orchiectomy	3 (subcapsular)***	1 (subcapsular)
Herniorrhaphy	2	2
Gastroschesis closure	1	--
Mitrofanoff valve	--	--

*due to lack of glycine and use of water as irrigant
**secondary to an ox goring
***patients declined simple orchiectomy

During the intervening year and beyond the second mission Knock continues to collect both durable and disposable equipment to provide to the selected sites.

Program Requirements

- Identification of an underserved population
- General surgeons with a desire for training
- Local facilitator
- Cooperative hospital administration
- Urologic volunteer preceptors
- Adequate OR suites to allow for multiple teams. Ideally, one team to work on particularly difficult cases while a second team occupies a different OR, which is used for working with and training local surgeons
- At least two urologists per team, one for teaching and one for supervision and assistance
- Cysto/radiology tech
- Equipment (ideally from a single manufacturer)

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ISSN 1944-5792 (print), ISSN 1944-5784 (online)

- Cystoscopic sheaths, lenses, bridges, biopsy forceps, grasping forceps, endoscopic scissors
- Urethrotome, zero degree lens, cutting elements
- Resectoscope Set, adaptors, cutting loops, Collins knife, vaporization Electrodes, roller ball electrodes
- Light cords, adaptors, light source
- Video equipment (if possible)
- Electrical adaptors and step-up transformer(s)
- Cautery unit
- Sterilization/soaking trays
- C-arm
- Table adaptable for use in cystoscopy
- Stirrups

- Supplies, including the following:
  - Stents
  - Wires
  - Open ended catheters
  - Y tubing
  - Cords
  - 3-way Foley catheters

RESULTS

Kisumu

Results in Kisumu have been mixed due to the untimely death of our lead surgeon, Dr. Joseph Wayiwu. While diagnostic cystoscopy and VIU continue to be performed, despite the presence of bipolar equipment, the use of TURP has declined. Fortunately Dr. Willis Oyeko has recently affiliated with Maseno University Medical School and will be working at Nyanza General Hospital in the Department of Surgery as the staff urologist. Because of this a third trip to Kisumu has been planned for April of 2014 in conjunction with Cure Cervical Cancer and their organization of a see-and-treat clinic at the facility in order to assist Dr. Oyeko's efforts.

Mekelle

Results in Mekelle have been better. Cystoscopy, TURP (mostly TUIP), and VIU continue to be performed on a regular basis. The surgeons there have also accomplished ureteroscopy and are now more comfortable with and regularly engaged in the successful use of pyelolithotomy. Unfortunately, the exact numbers of procedures accomplished since our visits are not available to us. As previously mentioned, one of the surgeons we trained, Dr. Tsegay G. Yohannes Reda, has matriculated in the new 3-year residency in urology at the referral hospital in Addis Ababa.

Program Follow-Up and Requirements for Sustainability

As discussed above, follow-up of the initial site visits has consisted primarily of a second visit to solidify Knock's relationships, supplement equipment, and provide additional hands-on training. A third visit to NPGH is planned for April of 2014. Ideally, visits should consist of a month long "rotation," but this has not proved to be logistically feasible given that the Knock team consists of actively practicing urologists. Knock volunteer urologists have been able to maintain contact with providers at both sites via e-mail and social media, including Facebook. and are in the process of making arrangements for video conferencing.

Knock believes long-term sustainability of a program like this is dependent upon a number of factors, including:

- A fertile environment
- Training for both cystoscopists and technicians
- Ongoing training and educational opportunities
- Supplementation of existing equipment to fill gaps and build on existing equipment
- Provision of new specialized equipment
- Mechanisms for repair and/or replacement of equipment, goals setting forth with specificity that can and should be accomplished, and what teaching should be undertaken

Translational Aspects of Program and Future Efforts

Knock believes the model of careful site selection, site visit, teaching, provision of equipment, and continuing education can serve as a blueprint for future efforts in accelerating permanent advancement in not only urologic care in the developing world but other disease states.

For instance, the equipment provided to Ayder Referral Hospital has proven instrumental in the development of a locally operated fistula clinic opened shortly after the first Knock site visit. Further, the recent mission to Mekelle was coupled with a visit by curecervicalcancer.org (Director Patricia Gordon, MD) [14] to implement a program of visual cervical inspection with acetic acid (VIA) [15] for HPV and CIS coupled with immediate treatment using cryotherapy for positive tests. Following the Knock model, one of the attending OB/GYNE staff and 2 nurses were trained in VIA, equipment was delivered and installed, and a commitment was made to continue to supply light sources and CO2 beyond Knock's departure. As of this writing, there is a new clinic in place, which inspects and treats anywhere from 20 to 30 patients per day.

Cure Cervical Cancer is, in fact, planning to duplicate this effort

UIJ / Vol 6 / Iss 6 / December / http://dx.doi.org/10.3834/uij.1944-5784.2013.12.11
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

at Knock's original site in Kisumu, and as mentioned above Knock has plans to piggyback a third site visit to NPGH on to this project.

CONCLUSION

In conclusion, Knock believes this model represents a blueprint for the future dissemination of modern urologic (and other) care to the developing world in situations where there is a cooperative hospital administration and an environment where local physicians have both general surgical training and a desire to deliver basic urologic care to their patients. Knock also believes this model is translatable to other medical specialties given the necessary resources and dedication to appropriate follow-up.

FINANCIAL, RESEARCH, AND WRITING CONTRIBUTORS

Funding was made possible by contributions to the Knock Foundation, a 503c corporation and by donations of the time and effort of the authors, all of whom were heavily involved in the planning and implementation of the project. The article was written by the corresponding author with editorial input primarily by Dr. Schacht and F. Bruce Cohen.

SPECIAL THANKS

The administration, physicians, and nurses of (i) Nyanza Provincial General Hospital, (ii) Ayder Referral Hospital, and (iii) Mekelle Hospital, Willis Oyeko, MD and Dedan Ogonga, MD of Kisumu, Kenya; Fasika Amdesalesie, MD and Tsegay G. Yohannes Reda, MD, of Mekelle, Ethiopia; Beldina Opiyo-Omolo and Aberash Abay of the Millennium Cities Initiative; Patricia Gordon, MD and Judy Laner of Cure Cervical Cancer

IN MEMORIAM

Joseph Wayiwu, MD of Kisumu, Kenya, an excellent surgeon, patient advocate, gentleman, and friend.

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UroToday International Journal®

A Novel Approach to Managing Intravesical Magnetic Beads

Ryan C. Hedgepeth

Center for Urologic Oncology, Gayle and Tom Benson Cancer Center, Ochsner Clinic, New Orleans, Louisiana, United States 70121

Submitted November 15, 2013 - Accepted for Publication December 1, 2013

ABSTRACT

Recent reports of magnetic beads inserted into the urethra have identified challenges for urologists during removal. Even moderate numbers of these beads in the bladder necessitate open removal due to their tendency to cluster tightly in a spherical formation. This case report describes a novel approach to using the magnetic property of the beads to aid in removal.

INTRODUCTION

Insertion of foreign objects into the urethra is a rare but serious problem that can often be resolved successfully with cystoscopic management. Recently, several reports have highlighted the phenomenon of the insertion of magnetic beads that become lodged in the bladder or urethra [1,2]. While this problem can sometimes be managed cystoscopically, the insertion of a large number of these beads can necessitate open surgical removal due to the magnetic properties of the beads [3]. The purpose of this case report is to describe a novel way that the magnetic properties of the beads themselves may be used to aid in removal.

CASE REPORT

A 23-year-old man arrived to the emergency room complaining of 48 hours of worsening urinary urgency, frequency, and hematuria. Vital signs were stable but his urinanalysis revealed large volume red blood cells and leukocytes. The patient refused further care by emergency staff and requested urology consultation stating he had accidently put something up his penis. During the urologic evaluation, the patient admitted that he had inserted magnetic beads into his urethra during masturbation following a discussion in an online chat room. The patient reported the beads were initially placed into a string conformation before insertion. At some terrible point, he realized that he had put in a very large number of beads. He attempted to remove them but was only able to pull out a much smaller number. Embarrassed, the patient waited in silent desperation hoping that he would spontaneously void the remaining beads out. After several hours, he began having difficulty urinating with urgency, frequency, and hematuria. He delayed medical evaluation for an additional day until he developed severe pain.

The patient was taken to the operating room after being consented to both cystoscopic and open management. Initial fluoroscopy revealed a large mass of dense objects in the bladder in a spherical conformation (Figure 1). Cystoscopy was then performed and confirmed that the magnetic beads were densely adherent in a ball shape. Multiple attempts were made to remove the beads cystoscopically using a variety of endoscopic baskets and graspers. The beads were noted to be strongly magnetized to one another and only 2 beads could be removed in this manner. A Foley was placed for bladder irrigation.

An 8 cm retropubic midline incision was made from the pubis and dissected down to the bladder wall. The bladder was irrigated with water and the dome was identified. A 2 cm cystotomy incision was made. In order to work through a small incision, the surgeon decided to try to use the magnetic property of the bead mass and pull it up to the bladder surface with

KEYWORDS: Urethra, bladder, magnetic beads, surgical management, foreign body

CORRESPONDENCE: Ryan C. Hedgepeth, MD, MS, 1514 Jefferson Highway, Center for Urologic Oncology, Gayle and Tom Benson Cancer Center, Ochsner Clinic, New Orleans, Louisiana, United States 70121 (rhedgepeth@ochsner.org)

CITATION: *UroToday Int J*. 2013 December;6(6):art 70. http://dx.doi.org/10.3834/uij.1944-5784.2013.12.05

Figure 1. Fluoroscopic X-ray of the pelvis revealing a foreign body.

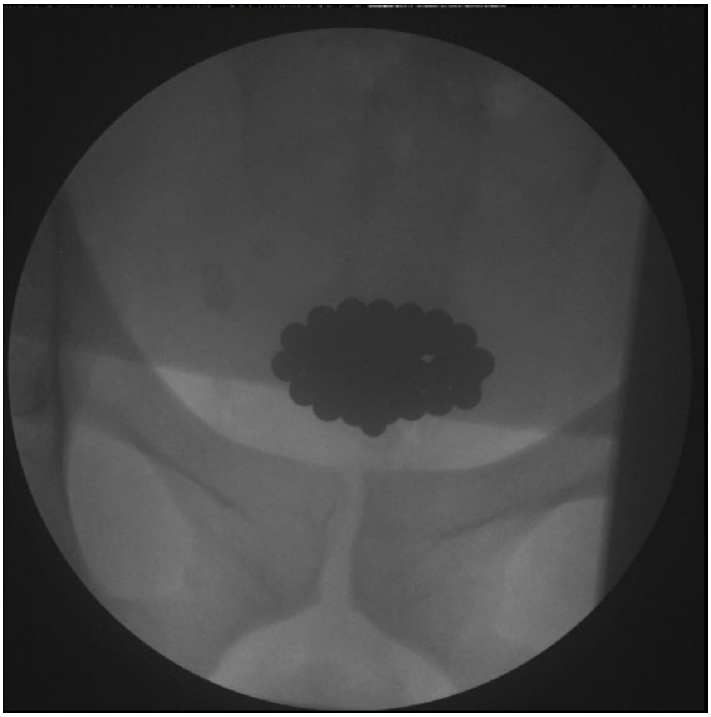
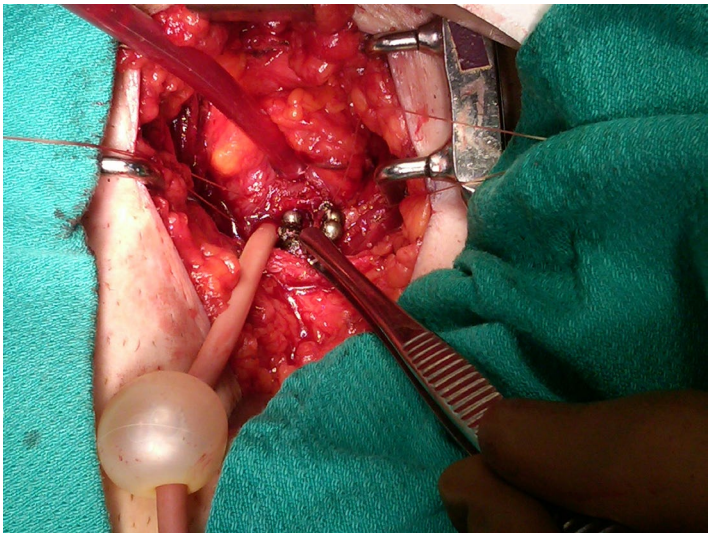


Figure 2. The magnet used to bring the bead mass to the cystotomy opening.

Figure 3. Magnetic beads being removed in singlets and clusters.



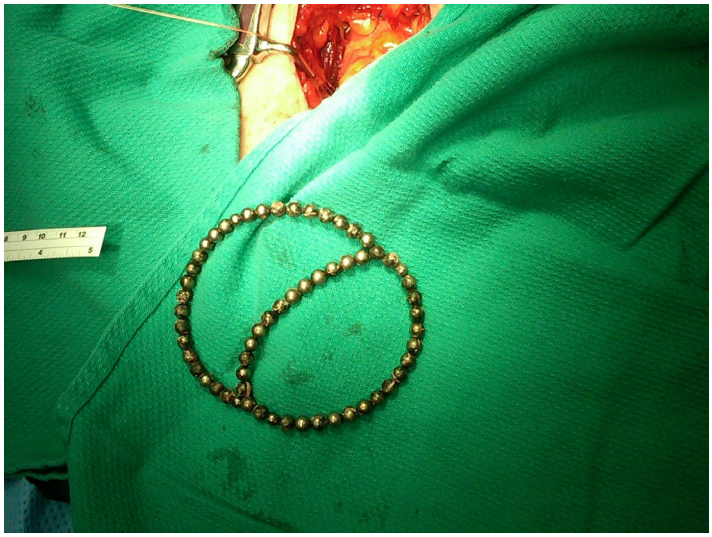
another magnetic material. A pacemaker magnet (Guidant, Boston Scientific, Natick, Massachusetts, United States) was sterilized (Figure 2) and placed over the cystotomy site. The magnet was then pushed down over the bladder and used to bring the magnetic bead mass up to the bladder dome. The beads were then grasped and removed individually and in small groups off of the bead cluster until all were removed (Figure 3). 62 beads in total were recovered—2 cystoscopically and 60 through the mini incision. The magnetic properties of the beads are demonstrated in Figure 4. Fluoroscopy was used to confirm no further beads were in the bladder. The bladder was closed in 2 layers and the incision was closed with a drain in place. The patient did well and was discharged the next morning on antibiotics and with Foley drainage. The Foley and drain were removed in 1 week. At a 3-month follow-up, the patient was voiding well with no complaints.

DISCUSSION

The inherent properties of magnetic beads make them especially challenging to remove cystoscopically when they are retained in the bladder after urethral insertion. Large numbers of these beads in the bladder almost certainly mandate the use of open surgery, as their magnetism leads them to condense into a densely adherent spherical shape [4]. This property of the beads, however, may also be used to aid in their extraction. In this case, we used a pacemaker magnet to bring the bead cluster close to the cystotomy opening, making them more easily accessible through the mini incision.

The novel management described in this report demonstrates one way we can use the magnetic properties of a foreign

Figure 4. Total bead volume removed through a mini incision and configured to highlight strong magnetic properties.



body in order to aid in removal. Another future target to aid in removal may be to alter or negate the magnetism of the beads. One of the approaches we deliberated on after initial cystoscopic management failed was to demagnetize the beads in order to facilitate removal. The possibility of using the magnetic resonance scanner to change the polarization or demagnetize the beads was discussed. However, the theoretical risk of creating a projectile in the bladder greatly outweighed our curiosity to try this approach. Instead, we decided to work through a small open incision and use a readily available magnet to see if we could bring the bead cluster close enough to a small cystotomy to allow for removal. This allowed for minimal additional damage to an already inflamed urothelium.

The ultimate endgame in managing a retained foreign body such as this is to remove the foreign body with minimal damage to surrounding structures. While cystoscopy remains the desired approach, it is unlikely to be successful when the foreign body is large and magnetic. The magnetic properties of the beads themselves, however, may be used to aid in open removal and may ultimately be a target for future management.

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UroToday International Journal®

Isolated Primary Megalourethra: A Case Report

Sanjay Kumar Gupta, Shashidharan, Khalid Mahmood, Ahsan Ahmed, Atul Khandelwal, Vijoy Kumar, Mahendra Singh

Department of Urology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India

Submitted November 20, 2013 - Accepted for Publication November 28, 2013

ABSTRACT

Megalourethra is a non-obstructive dilatation of the penile urethra. It is a rare congenital anomaly characterized by the congenital absence of the corpus spongiosum and/or corpus cavernosum, leading to dilatation of the urethra. Only 80 cases have been reported so far in English literature. Incidence is sporadic with no hereditary or racial predisposition. We report a case of six-year-old child who presented with ballooning of the phallus on micturition and post-void dribbling. The diagnosis of megalourethra was established on the basis of clinical and radiological findings. The patient was successfully managed by reduction urethroplasty. The patient is doing well after 4 years of follow-up.

CASE REPORT

A 6-year-old male child presented with ballooning of the phallus during micturition and post-void dribbling since birth. On physical examination, the phallus was swollen with diffuse sagging of the ventral aspect of the urethra, with dribbling of urine upon applying pressure. The meatus was adequate with normally developed scrotum and testes. An examination of the abdomen, chest, cardiovascular system, and musculoskeletal system was normal. On investigation, hemogram and renal function test was within normal parameters. Ultrasonography of the kidney, ureter, and bladder revealed normal sized kidneys with normal corticomedullary differentiation. The bladder was of normal capacity with no post-void residual urine. Retrograde cystourethrogram (Figure 1) demonstrated scaphoid dilation of the urethra, more marked in the penile region with a normal outline of the bladder. Cystourethroscopy showed marked dilatation of the anterior urethra with a normal posterior urethra and bladder. The patient was managed by 1 stage longitudinal reduction urethroplasty. After circumferential degloving of the penis, the redundant urethra was excised (Figure 2), and neourethra formation was done over a 10 Fr Foley catheter using vicryl 4/0 (Figure 3). The postoperative course was uneventful. The catheter was removed on the fourteenth day, with a normal cosmetic appearance of the penis (Figure 4). In the postoperative period, the patient voided with a good stream and without any cosmetic deformity and post-void dribbling. After 4 years of follow-up, the patient is doing well without any abnormality of the penile shaft.

DISCUSSION

Megalourethra was first coined by Nesbit (1955) who treated the first case of megalourethra at 9 months of age [1]. Embryologically, there is a congenital deficiency of mesodermal tissue of the phallus that leads to the absence or underdevelopment of the corpus spongiosum, and in extreme cases of corpus cavernosum, too. Exact etiology is not known. In megalourethra, urinary tract dilatation develops as a result of urinary stasis in the dilated penile urethra, which lacks adequate support and balloons during fetal micturition, thus causing passive obstruction of the urinary flow. This functional obstruction may also act as a valve-like flap mechanism in some cases, producing intermittent mechanical obstruction to the urine stream through the glandular urethra [2]. Although stricture or severe narrowing of the meatus may cause complete

KEYWORDS: Megalourethra, scaphoid, reduction urethroplasty

CORRESPONDENCE: Sanjay Kumar Gupta,\Department of Urology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India (sanjayssgtamkuhi@yahoo.co.in)

CITATION: *UroToday Int J*. 2013 December;6(6):art 74. http://dx.doi.org/10.3834/uij.1944-5784.2013.12.09

Figure 1. Retrograde cystourethrogram.

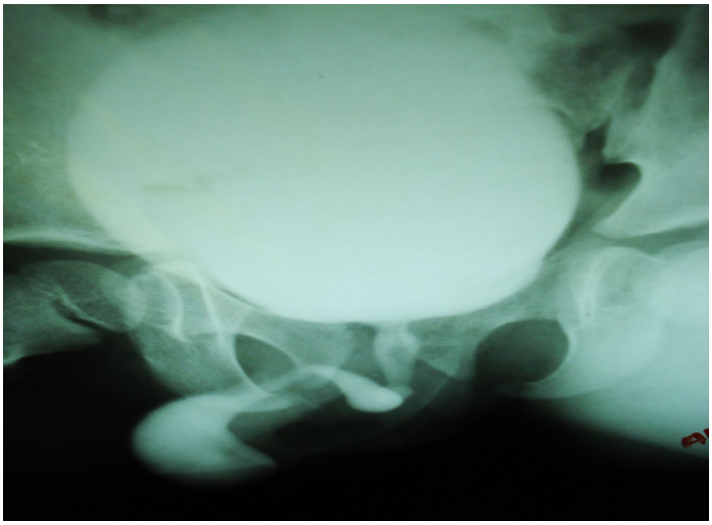


Figure 2. After circumferential degloving of the penis, the redundant urethra was excised.

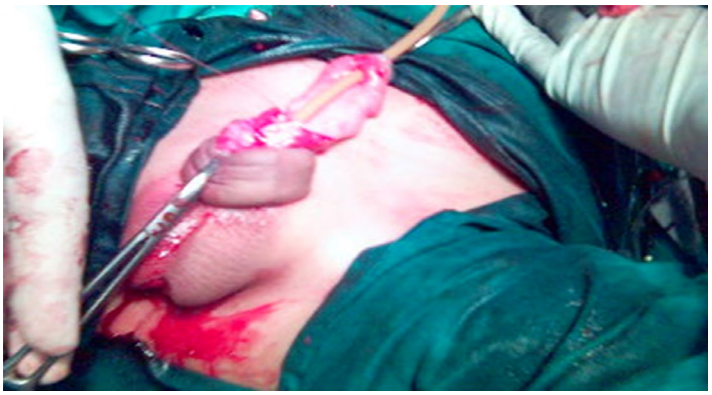


Figure 3. Neourethra formation was done over a 10 Fr Foley catheter using vicryl 4/0.

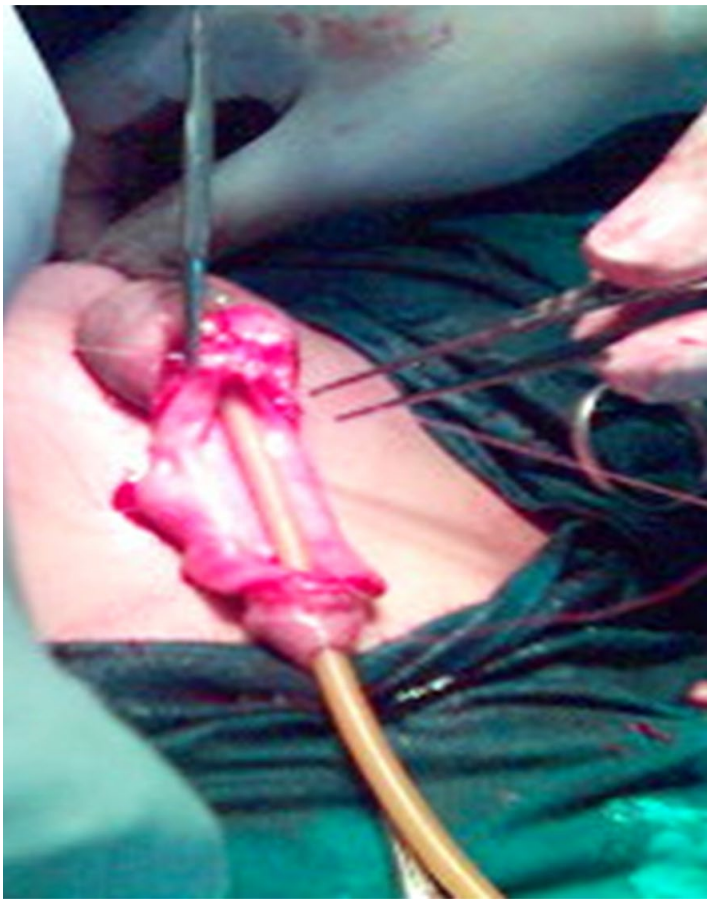
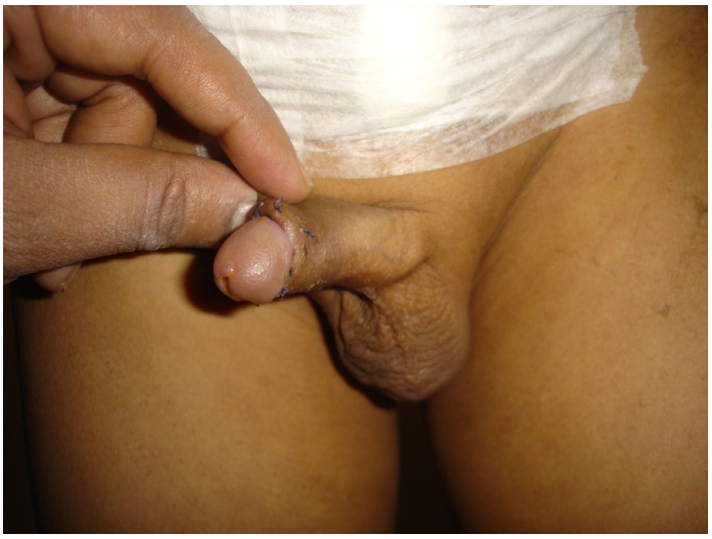


Figure 4. The catheter was removed on the fourteenth day, with a normal cosmetic appearance of the penis.



anatomic urethral obstruction, no true anatomic obstructive defect has been identified in cases of megalourethra [2,3]. Based on urethrography, there are 2 types of megalourethra [4]. First is the scaphoid type in which there is attenuation of the corpus spongiosum and thus bulging of the ventral urethra. The second is the fusiform type. The absence of both the spongiosum and the cavernosum leads to the circumferential expansion of the urethra. Of cases, 50% are associated with Prune Belly Syndrome [5]. There may be association with genitourinary or extra genitourinary anomalies, including vacteral syndrome. Associated anomalies are more common in the fusiform type and the prognosis is worse. Prenatal diagnosis of megalourethra

relies on sonographic dilatation of cystic dilatation of the penis with or without the presence of obstructive uropathy [6,7]. In neonates with severe fusiform deformity presenting with urosepsis, patients may need a diversion vesicostomy followed by definitive urethroplasty. Diagnosis after birth is mainly clinical. Urethrogram differentiates it from large anterior urethral diverticulum. Some workers diagnosed megalourethra antenatally by ultrasonography (USG).

Ardiet et al. reported a case of complete sequence of vacteral anomalies with megalourethra in one of the twins of antenatal pregnancy [8]. At birth, the penis was enlarged and covered with wrinkled skin. The testes were undescended and the anus was imperforate. Also noted were a single umbilical artery, a patent urachus, and a type-III esophageal atresia. Echocardiography was performed and interventricular communication was discovered. Transfontanellar echography appeared normal but the vertebral echography demonstrated a tethered spinal cord. Sindic et al. reported a complex case of complete urethral duplication with dorsal megalourethra that was severely stenotic in its bulbar part, and the meatus, with the ventral urethra atretic distally, and dilated proximally while missing the corpus spongiosum and cavernosum. Urethral patency was restored successfully by meatoplasty, staged buccal mucosa graft urethroplasty, and tailoring of the megalourethra [9]. Our case was of the scaphoid type with a large, thin, and baggy urethra with attenuated spongiosum. We managed the case by simple reduction urethroplasty. Rarity of the defect precludes any generalization with regard to surgical management. Every case must be considered individually.

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UroToday International Journal®

Management of Neobladder Vaginal Fistulae and Stress Incontinence Following Radical Cystectomy with Martius Flap Interposition and a Transobturator Sling

Francisco-Xavier Elizalde-Benito, Angel-Gabriel Elizalde-Benito, Maria Urra-Palos
Clinica del Pilar de Zaragoza, Zaragoza, Spain
Submitted October 27, 2013 - Accepted for Publication December 1, 2013

ABSTRACT

Objective: We report the case of the management of neobladder vaginal fistulae and stress incontinence following radical cystectomy with Martius flap interposition and a transobturator sling. We review the literature on the evaluation and treatment of these patients.

Methods: A 62-year-old patient required cystectomy and a Studer's neobladder, which presents a neobladder vaginal fistula and stress incontinence

Results: Those complications were successfully treated using a vaginal approach with the interposition of a Martius flap and a sling placed after the fistula was repaired.

Conclusions: A neobladder vaginal fistula is a devastating complication. In our experience, we believe that closure in 2 planes by a transvaginal approach with Martius flap interposition plays a crucial role in avoiding a therapeutic abdominal approach. The surgical treatment of stress incontinence in the neobladder has serious potential complications and requires the judicious use of slings, with obturator tape being important in this context.

INTRODUCTION

Orthotopic urinary tract reconstruction has revolutionized urinary diversion after radical cystectomy, and is an accepted treatment in appropriately selected women with bladder cancer [1]. Neobladder vaginal fistulae is a known, but relatively rare, complication of cystectomy and orthotopic diversion in women [2], and both its treatment and the stress urinary incontinence treatment of these patients are still under discussion. We report a case of neobladder vaginal fistulae and stress urinary incontinence, and review the literature on the evaluation and treatment of patients.

CASE REPORT

We report the case of a 62-year-old female patient. She was a former smoker with a history of hypertension, and had undergone surgery for radical cystectomy with Studer ileal neobladder reconstruction in November 2010 for extensive multifocal carcinoma in situ. Postoperatively, an early anastomotic dehiscence occurred, requiring a new urethra to neobladder anastomosis, and accidental traumatic Foley catheter avulsion also occurred. The patient reported continuous incontinence since cystectomy. Complete physical examination was performed, with negative urine culture result, a consultation on Incontinence Questionnaire-Urinary

KEYWORDS: Fistula, neobladder, incontinence, sling, Martius flap

CORRESPONDENCE: Francisco-Xavier Elizalde-Benito, MD, Clinica del Pilar de Zaragoza, Paseo Ruiseñores 22-24 pta. 12 50006, Zaragoza, Spain (jelizalben@hotmail.com)

CITATION: *UroToday Int J*. 2013 December;6(6):art 69. http://dx.doi.org/10.3834/uij.1944-5784.2013.12.04

Figure 1. Neobladder vaginal fistulae following radical cystectomy.

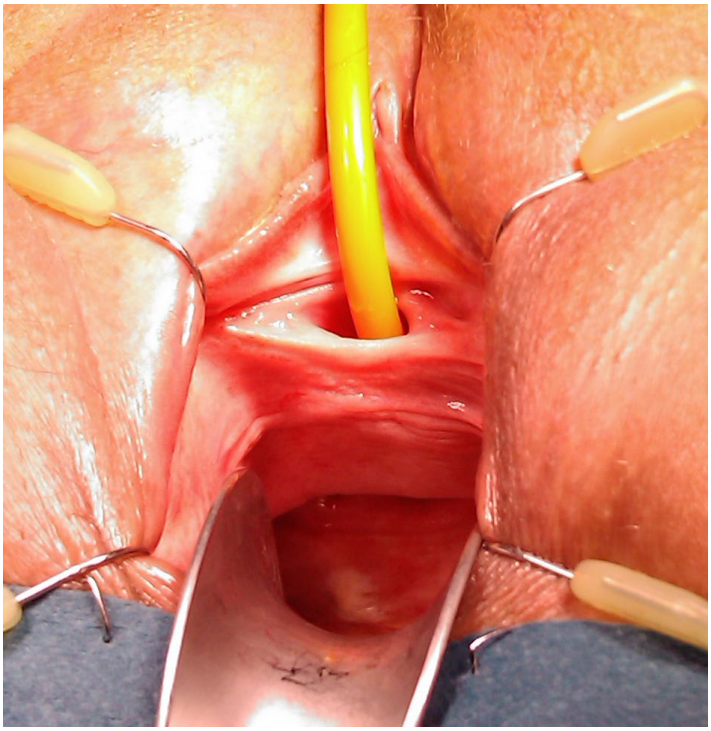
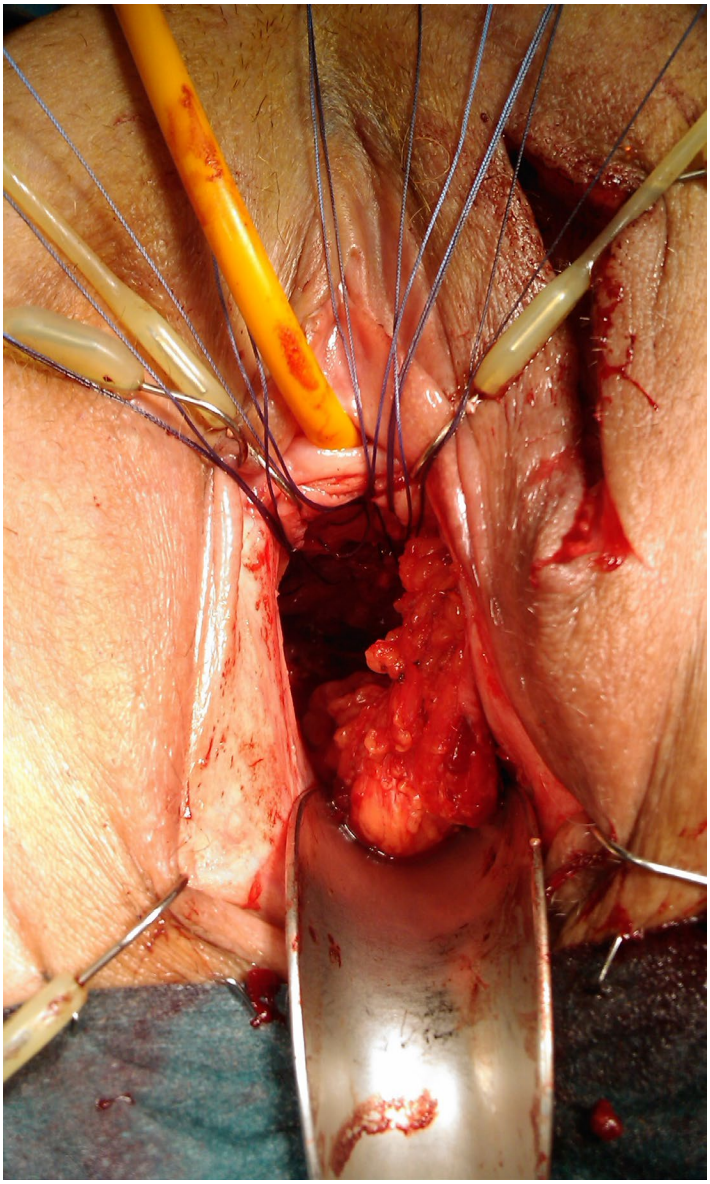


Figure 2. Management of neobladder vaginal fistula with Martius flap interposition.



Incontinence Short Form (ICIQ-UI SF) was performed showing continuous urinary incontinence with severe impairment in quality of life with a punctuation of 21 points. Computed tomography revealed no abnormalities. The physical examination confirmed a 4 centimeter neobladder vaginal fistula (Figure 1), and the cystoscopic study showed urethral integrity. The fistula was treated by Martius flap interposition in January 2011 (Figure 2); however, we observed total incontinence due to the loss of urethral tone and a traumatic increase in urethral diameter, which was treated with the transobturator sling Monarc® in April 2011 (Figure 3), improving the stress urinary incontinence with a follow-up of 2 years. During follow-up, physical examination and cystoscopy did not show recurrence of the fistulae at 2 years, with an improvement in quality of life and urinary incontinence in ICIQ-UI SF, with a score of 6 points. Pressure flow study showed minimal stress incontinence. Computed tomography did not show abnormalities.

DISCUSSION

Urinary diversion with an orthotopic neobladder after radical cystectomy has proven to be a viable option in women undergoing radical cystectomy. Despite excellent clinical results, in most women undergoing neobladder reconstruction, complications include functional neobladder urinary retention, requiring catheterization, stone formation, and persistent urinary incontinence, after radical cystectomy [3].

A neobladder vaginal fistula is a rare complication in these patients. Hari et al. conducted a review in 2004 collecting a total of 11 cases of neobladder vaginal fistula described in the literature [4].

Compared to the native bladder, the wall of the neobladder is much thinner, which may render it vulnerable to fistulization.

A vaginal wall lesion during dissection is the most important factor for the formation of a fistula [5]. All precautions should be taken to prevent injury in the vagina at the bladder-vaginal dissection plane, where the risk of damage to the vagina is greatest during the distal dissection of the bladder-vaginal plane at the urethra. Rapp et al. [5] minimized the risk, with blunt dissection near the bladder neck and posterior urethra. Possible risk factors for fistula formation are the proximity of the suture line between the vagina and the bladder neck, abnormal tissue between the posterior bladder neck and vagina leading to procedures for removal, and possible tissue vascularization due to surgical dissection [6], the poor vascularization of tissue after radiotherapy [7], and local recurrence [5].

Multiple techniques have been proposed to minimize this complication. Preservation of the anterior vaginal wall during cystectomy significantly decreases the risk of neobladder vaginal fistulae and improves functional outcomes [1]. Studies have shown that the preservation of the reproductive organs in radical cystectomy is possible without compromising the oncologic basis of the operation [8]. Ali El-Dein et al. promoted establishing an omental pedicle flap between the vaginal stump and urothelial anastomosis, providing a back up for the ileal pouch, and preventing posterior displacement and angulation of the urothelial union [2], although the effectiveness of these maneuvers has not been clearly demonstrated.

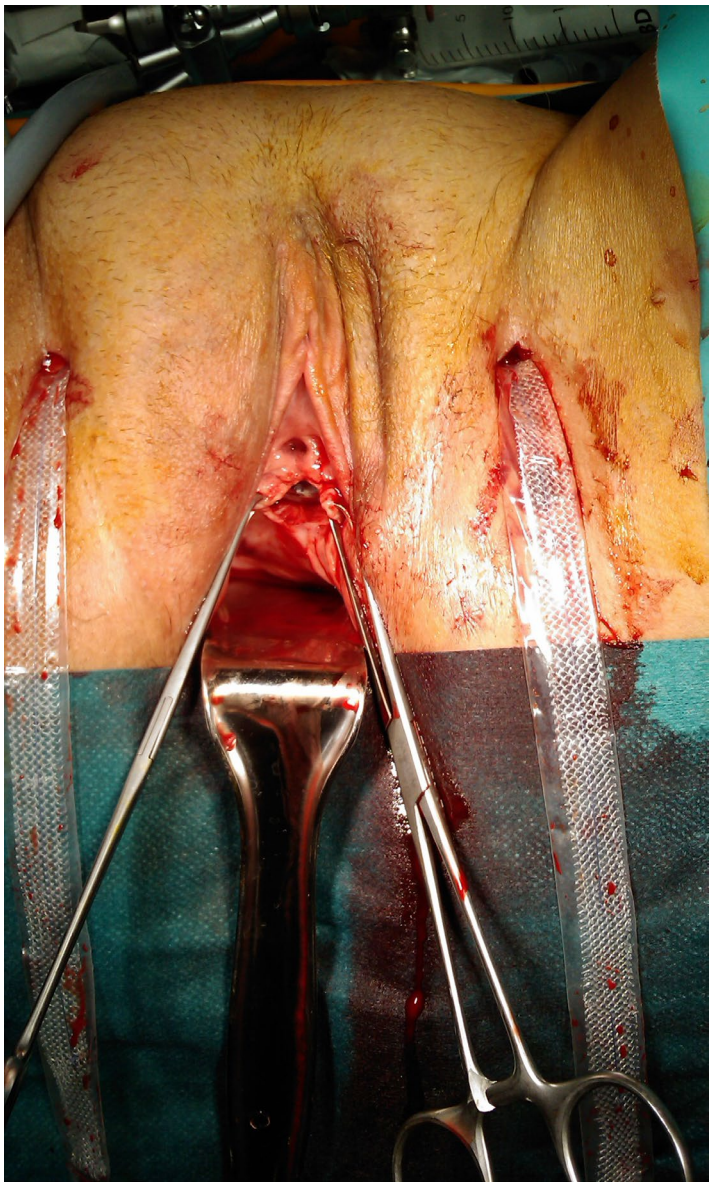
The Martius flap interposition is useful in protecting the fistula repair. Quek et al. [3] and Pruthi et al. [6] reported positive results after Martius flap interposition between a repaired neobladder vaginal fistula and the anterior vaginal wall.

Our patient underwent a transvaginal approach with Martius flap interposition because the treatment has been successfully used in complex bladder-vaginal fistulae, and avoids an abdominal approach in a previously operated abdomen. The interposition of the labia-major adipose tissue allows increased surface epithelization supplemented with lymphatic vascularization and better drainage, also avoiding the interposition of stitches [10].

Meticulous surgical technique is essential to preserve the function of the pelvic floor and urethra. The fibers of the inferior hypogastric plexus support the urethra and vagina. The preservation of these nerve fibers has been suggested to improve continence, and the preservation of an intact vagina is important for the functional integrity of the female striated urethral sphincter and the urethra-vaginal sphincter mechanism [9].

A pubo-vaginal sling should be used with caution for the treatment of stress urinary incontinence in patients with a neobladder because it may not be as effective and safe as in patients with a native bladder [6]. Hari et al. suggested that concomitant pubo-vaginal sling placement at the same time as the neobladder vaginal fistula is repaired cannot be completely safe [4], so the sling should be placed after the fistula is repaired, as in our case.

Figure 3. Management of stress incontinence with transobturator sling.



CONCLUSION

A neobladder vaginal fistula is a devastating complication that can be prevented by meticulous surgical technique and proper dissection. However, once it has developed, treatment

options are limited and may intensely affect the quality of life because of the need for a new reservoir. In our experience, we believe that closure in 2 planes by a transvaginal approach with Martius flap interposition plays a crucial role in avoiding a therapeutic abdominal approach. The surgical treatment of stress incontinence in the neobladder has serious potential complications and requires the judicious use of slings, with obturator tape being important in this context.

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Metanephreic Adenoma of the Kidney

Shankar Pradad Hazra, Nipun Awasti, Debojyt Gogoi, Debasis Chakrabortty, Dilip Kumar Pal
Institute of Postgraduate Medical Education & Research, Kolkata, Kolkata, West Bengal, India
Submitted November 24, 2013 - Accepted for Publication November 28, 2013

ABSTRACT

Metanephric adenoma is a rare benign tumor of the kidney. Macroscopically, the cut surface of the tumor shows a well-circumscribed mass of grey to yellow color. Here we have presented our experience with 2 cases of metanephric adenoma. Although it is very difficult to differentiate it from malignancy by clinical or radiological findings, the differentiation is mainly done by histopathology and immunohistochemistry. Complete surgical removal or polar nephrectomy is the proper treatment in almost all cases.

INTRODUCTION

Metanephric adenoma is a rare benign renal tumor [1-4] and only 80 cases have been documented till now [1]. The concept of metanephric adenoma was recognized as a different entity of adult-onset Wilms tumor [5]. If the tumor is characterized by proliferation of spindle cells surrounding multifocal nodules of epithelial cells, it should be designated as a nephrogenic adenofibroma or metanephric adenofibroma [6]. Argani and Beckwith have recently described another renal tumor designated as metanephric stromal tumor that consists purely of a mesenchymal component without an epithelial component [2]. Pathologists should consider that the spectrum of these 3 metanephric tumors is morphologically continuous [6]. Metanephric adenomas are usually encapsulated and are not associated with metastasis or recurrence [3]. Therefore, further studies on various aspects are needed to identify the gene responsible for the occurrence of metanephric tumors and, also, to clarify the association among the 3 types of metanephric tumors [6].

CASE REPORTS

Case Number 1

A 29-year-old female patient presented with a 6-month history of right-sided, localized, dull aching flank pain with no history of burning micturation or hematuria. On examination no mass was palpable in the right renal area. Ultrasonography revealed a 3.2 cm by 3 cm heterogeneous space occupying lesion (SOL) in the upper pole of the right kidney. The computed tomography (CT) scan showed a 4.2 cm by 4.2 cm mixed density heterogeneously enhancing mass in the upper pole of the right kidney (Figure 1) and the left kidney was normal. On metastatic workup, no metastasis was detected. Laparoscopic radical nephrectomy was done. During operation, no features of local metastasis were found. The cut surface showed a big tumor involving the upper pole up to the hilum, which was yellowish in color with hemorrhagic areas (Figure 2). Histopathological examination showed tiny tubules and papilla accompanied by very scanty stroma. The nuclear features were bland, and the overall features were similar to developing metanephric tubular epithelium. On immunohistochemistry, lectin, keratin, and epithelial membrane antigen (EMA) were positive.

Case Number 2

A 37-year-old female presented with complaints of left flank pain off and on, and had no history of dysuria or hematuria. On Ultrasonography, a heterogeneous solid renal SOL 3.2 cm by 2 cm in the upper pole of the left kidney was seen, and the other kidney was normal. Contrast-enhanced computed tomography (CECT) of the abdomen showed an enhancing

KEYWORDS: Metanephric adenoma, renal tumor, immunohistochemistry

CORRESPONDENCE: Dilip Kumar Pal, MS, FAIS, MCh (Urology), Institute of Postgraduate Medical Education & Research, Kolkata, Kolkata, West Bengal, India (drdkpal@yahoo.co.in)

CITATION: *UroToday Int J*. 2013 December;6(6):art 68. http://dx.doi.org/10.3834/uij.1944-5784.2013.12.03

Figure 1. CECT showing a heterogenous tumor in the upper pole of the right kidney.

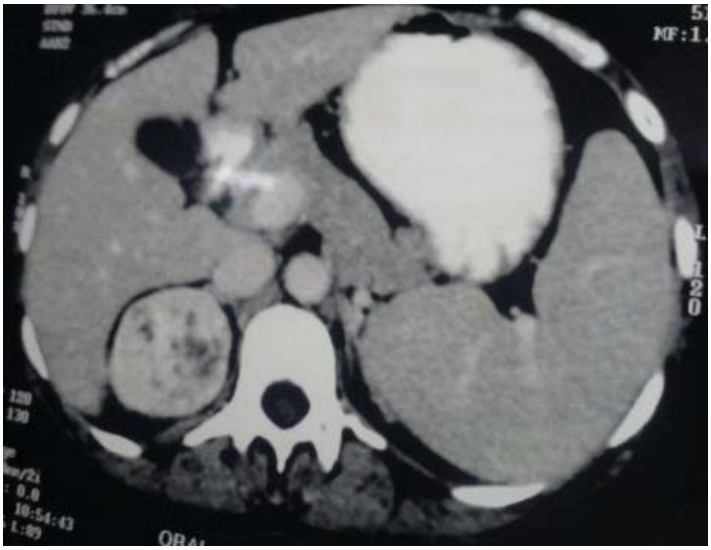
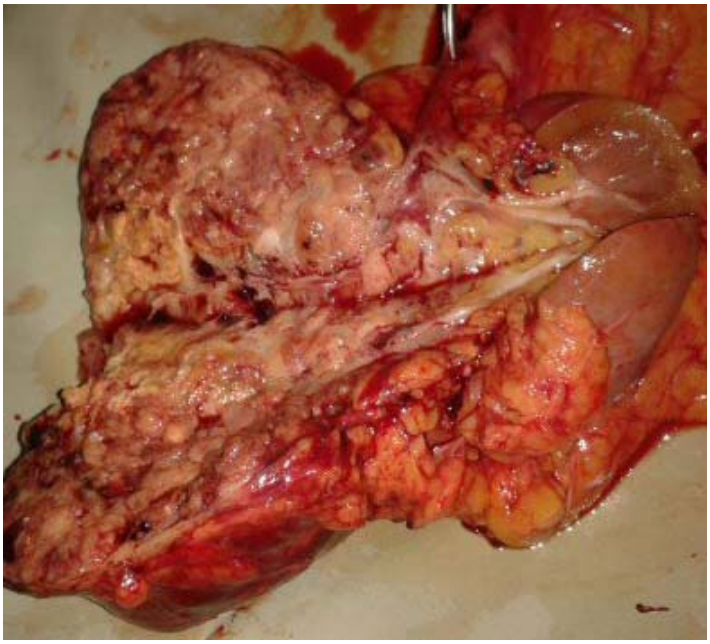
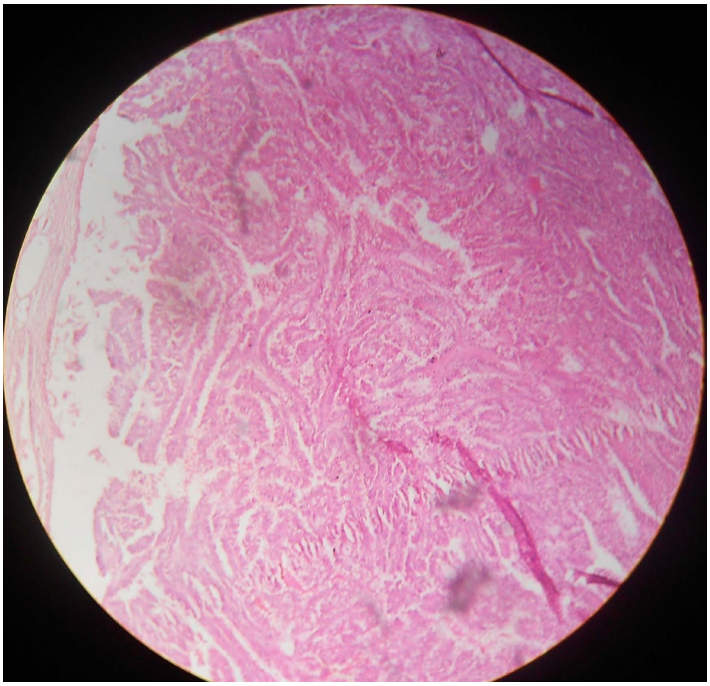


Figure 2. Cut surface of the tumor showing yellowish color in hemorrhagic background.



lesion of the same size with no evidence of metastasis or retroperitoneal lymphadenopathy. Metastatic workup was negative. She underwent left radical nephrectomy. On gross examination, the specimen was solid and white in color with no areas of necrosis. Histopathalogical examination showed a highly cellular, tightly packed small tubules and acini lined by monomorphic cells lying in a loose oedematous stroma. The tumor cells were bland in appearance and did not show significant mitotic activity. No lymphovascular invasion was found (Figure 3). On immunohistochemistry it showed lectin and EMA positivity.

Figure 3. Microphotograph showing tiny tubules and papilla with very scanty stroma (H&E X 400).



DISCUSSION

Metanephric adenoma is a very rare tumor and till now only few cases are reported [1-5]. As the kidney develops from metanephros, the remnants of this tissue remain within the renal parenchyma in post-natal life and often develop into Wilms tumor whether blastemal component remains and predominates. Metanephric adenoma develops when a blastemal component is absent or not predominant. So, metanephric adenoma and Wilms tumor are histologically related [7] though Wilms tumor is more common than metanephric adenoma.

It generally occurs in adult females but also occurs in children. Most of the patients suffer from dull aching flank pain, hematuria, or something asymptomatic. In some patients paraneoplastic syndrome like polycythemia and hypercalcemia is found. It is a benign and slow-growing tumor. They are usually

encapsulated and not associated with metastasis or recurrence. Tumor size is considered as the criteria to differentiate between malignant and non-malignant tumors, with 3 cm being the cut-off [4]. Treatment is usually radical nephrectomy as it is diagnosed only by histopathological examination. Partial nephrectomy is considered adequate for polar lesions.

Both metanephric adenoma and Wilms tumor have tubular, tubulo papillary structures, and glomeruloid bodies [7,8]. Metanephric adenoma lacks the large nuclei and other primitive components that are characteristics of Wilms tumor. The lining cells in metanephric adenoma are bland. Sometimes these two may coexist; so proper histological examination and immunohistochemistry are essential for the diagnosis [9]. Morphologically metanephric adenoma is often compact, showing compact tubules within much stroma, lined by bland cells. Immunohistochemistry positivity for metanephric adenoma are lactin, keratin, and EMA. S-100 protein expression is very high in metanephric adenoma, and they are also positive for vimentin and Leu7 [6], but negative for WT1, which is positive in Wilms tumor. So further studies on various aspects are needed to identify the gene responsible for the occurrence of metanephric adenoma and also to differentiate it from oncogenes for Wilms tumor.

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Nephron-Sparing Surgery in Renal-Cell Carcinoma in a Second Allografted Kidney: A Rare Case Report

Amit Kumar, Surya Prakash Vaddi, Chandra Mohan, Vijay Bhaskar, Vijay Kumar Vasanthu
Department of Urology and Renal Transplantation, Narayana Medical College, Nellore, Andhra Pradesh, India
Submitted October 4, 2013 - Accepted for Publication December 1, 2013

ABSTRACT

Renal cell carcinoma in a renal allograft kidney is a rare entity. We report a case of localized renal-cell carcinoma in a second allograft kidney, which we have managed successfully by nephron sparing surgery. The histopathology was clear-cell carcinoma with negative margins.

INTRODUCTION

Renal transplant recipients are at an increased risk of malignancy compared to the general population. This is thought to be due to the immunosuppressive therapy used in these patients. Renal-cell carcinoma (RCC) accounts for 4.6% of post-transplant malignancies, 10% of which occur in the allograft kidney [1,2]. Less than 45 cases are reported in the literature. There is no definite treatment consensus for the management of RCC in the renal allograft [3]. Nephron-sparing surgery, whenever feasible, should be attempted to preserve function in the allograft kidney. We report a case of renal-cell carcinoma in a second allograft kidney that was treated by partial nephrectomy.

CASE REPORT

A 48-year-old male patient presented with dull aching pain in the left lower abdomen over a 2-month duration. He had been hypertensive for 25 years and diabetic for 15. There were no other urinary complaints. Twenty years previously, he underwent live-related kidney transplantation for end-stage kidney disease (ESRD) secondary to interstitial nephritis. In the early postoperative period, allograft nephrectomy was done for renal artery thrombosis. Two months later he underwent a second live-related renal transplant, which was placed in left iliac fossa. At presentation he had a urine output of 1.5-2 liters/day. His serum creatinine was 2 mg% with an estimated glomerular filtration rate (GFR) of 35.1 mL/min. The reason for impaired allograft function could be due to chronic graft rejection.

On examination, an ill-defined, non-tender mass was palpable in the left iliac fossa. A plain computed tomography (CT) scan of the abdomen and pelvis revealed a well-defined heterogenous mass of 6 cm x 7 cm arising predominantly from the anterior cortex of the upper pole of the allografted kidney. Gadolinium-enhanced magnetic resonance imaging (MRI) showed a heterogeneously enhancing exophytic mass arising from the upper pole of the transplanted kidney. The patient was on single-drug immunosuppression (prednisolone, 40 mg once daily) before the diagnosis of the renal tumor. The same immunosuppression was continued after the diagnosis. With a diagnosis of a renal tumor in a transplanted kidney, nephron-sparing surgery was planned.

Intraoperatively, a 6 cm x 7 cm exophytic mass confined to the upper pole of the transplanted kidney was identified. Upper polar partial nephrectomy was done with a 0.5 cm margin without clamping renal vessels. Haemostasis was achieved by suture ligation of the bleeding vessels, and the opened calyceal system was repaired with an absorbable suture. Intraoperative frozen sections of the resected margins were tumor free. The operative time was 120 minutes, with blood loss of 150 mL. Histopathology of the tumor revealed clear-cell renal

KEYWORDS: Renal-cell carcinoma, nephron-sparing, allografted kidney

CORRESPONDENCE: Amit Kumar, MS, Department of Urology and Renal Transplantation, Narayana Medical College, Nellore, Andhra Pradesh, India (kumar.amit023@gmail.com)

CITATION: *UroToday Int J*. 2013 December;6(6):art 71. http://dx.doi.org/10.3834/uij.1944-5784.2013.12.06

Figure 1. MRI of the axial plane.

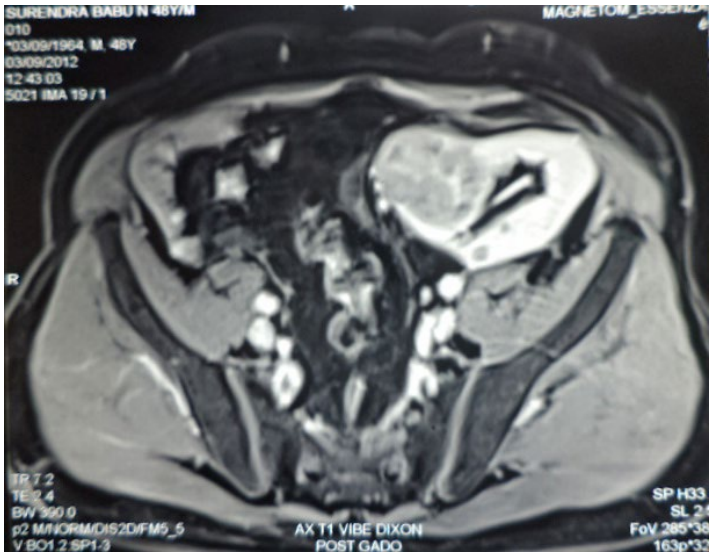


Figure 2. MRI of the saggital plane.

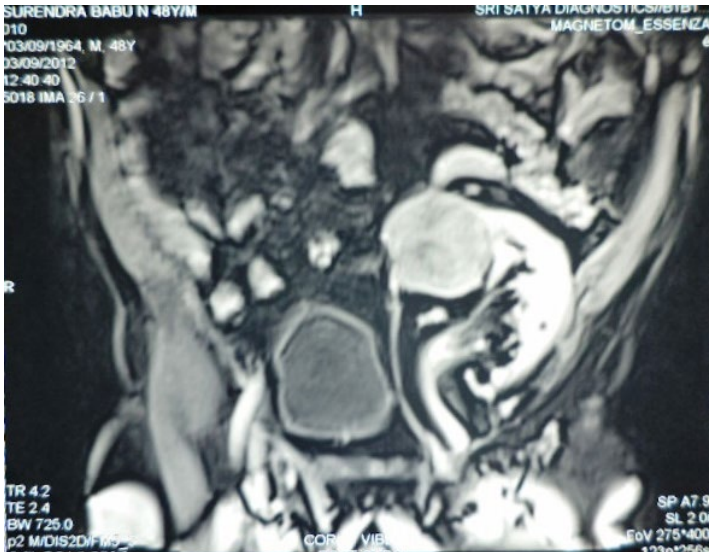


Figure 3. Perioperative photograph.

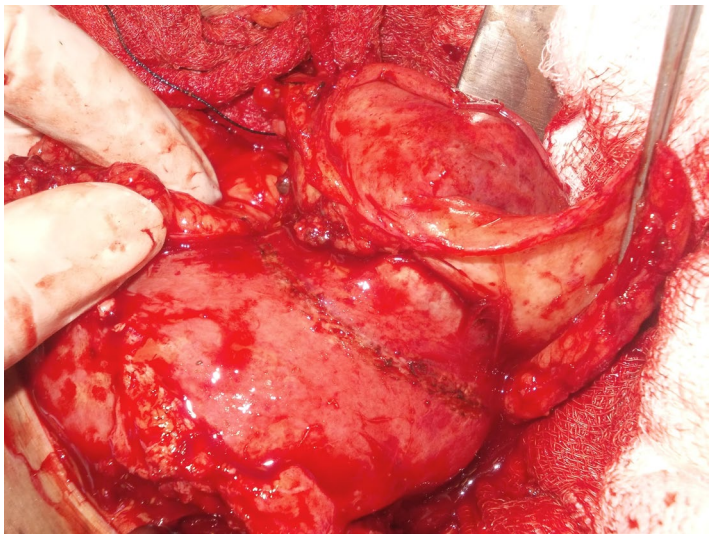
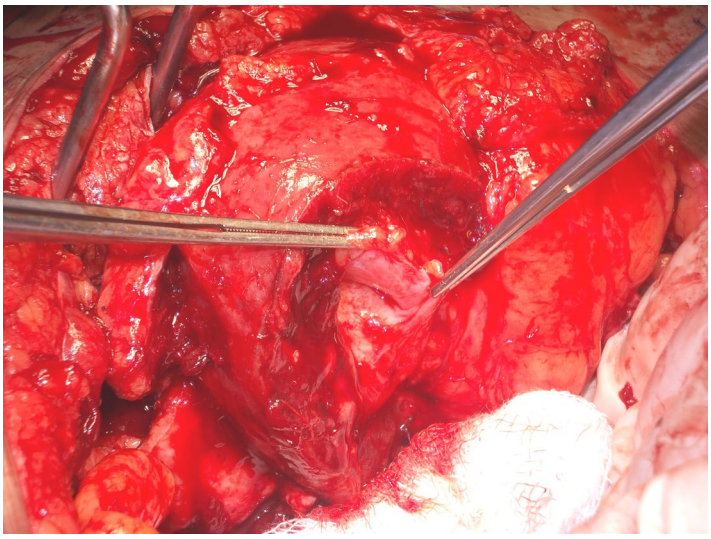


Figure 4. Perioperative photograph.



carcinoma PT1, Fuhrman grade II. The postoperative period was uneventful. Postoperative serum creatinine was 2.2 mg/dl, with a GFR of 31.9 mL/min.

In follow-up, his serum creatinine gradually increased to 4.8 mg% at 6 months. He was started on maintenance hemodialysis at 6 months. Ultrasound done at the 1-year follow-up showed no evidence of tumor recurrence in the allografted kidney and native kidney.

DISCUSSION

Renal transplantation requires prolonged immunosuppression, which increases the risk of infection and malignancies in transplant recipients. Renal-cell carcinomas in transplant recipients occur predominantly in native kidneys. Allografted

tumors are less common and can develop de novo or as consequences of transmission of occult malignancy from the donor [1-5].

Michael Leveridge et al. reported 8 cases of (0.2%) renal-cell carcinoma (RCC) in the allografted kidney in a total of 3,568 patients who underwent renal transplants between 1966 and 2009 [6]. Barama et al. reported 5 cases of RCC in renal allografts [7]. All tumors were less than 4 cm and were found incidentally on routine ultrasound. Chambade et al. reported 7 allograft cancers in their database of 2,050 recipients (0.34%) [8]. Our patient developed renal-cell carcinoma after the second renal transplant and, to our knowledge, renal-cell carcinoma in the second allograft is not reported in the literature.

A majority of the reported allografted kidney tumors are incidentally detected on routine ultrasound screening [7]. However, our patient presented with lower abdominal pain, which led to further investigation. In the literature, the time of diagnosis posttransplant varied from 4 to 20 yrs [6-8].

Regular screening of allografted and native kidneys by ultrasound will enable the diagnosis of renal tumors at an early stage. Graft evaluation by CT and/or MRI is necessary to confirm the tumor diagnosis and extent, and to evaluate the feasibility of nephron-sparing surgery [9].

As the role of partial nephrectomy in renal-cell carcinoma is established, the same indications can be applied for the management of tumors in allografted kidneys where it is essential to preserve graft function and thereby prevent/delay dialysis. Partial nephrectomy can be done without clamping the renal pedicle, as managed in our case. Barama et al. performed partial nephrectomy in 5 patients without clamping renal vessels [7]. Alternatives to partial nephrectomy are radiofrequency ablation and cryoablation [8].

The histopathology in our patient revealed clear-cell carcinoma. In the Michael Leveridge et al. and Chambade et al. series, the commonest histology was papillary renal-cell carcinoma [6-8]. In view of the small numbers published in the literature, it is difficult to comment on the predominant histology in this group of patients.

The immunosuppression protocols for transplant recipients found to have malignancy is controversial. mTOR inhibitors, which are used as targeted therapy in renal-cell carcinoma, are also used for immunosuppression in transplant recipients. The mTOR inhibitor rapamycin is an approved immunosuppressor in transplant patients. Unlike calcineurin inhibitors, rapamycin does not increase the risk of malignancy [8].

CONCLUSION

Nephron-sparing surgery is a safe and feasible option for renal-cell carcinoma in allografted kidneys. This will delay and/or prevent hemodialysis requirements in this group of patients. Regular follow-up by annual ultrasound is required to detect recurrence in the allografted kidney.

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Postangioplasty Infrequent Complication: A Page Kidney Case Report

Natalia Miranda-Utrera, José Medina-Polo, Manuel Pamplona-Casamayor, Rafael Díaz-González
Department of Urology, Hospital Universitario 12 de Octubre, Madrid, Spain
Submitted September 17, 2013 - Accepted for Publication November 28, 2013

ABSTRACT

Page kidney phenomenon (PK) is hypereninemic hypertension triggered by any compressive mechanism on the kidney. Since it was first described in human beings in 1955, multiple causes of extrinsic compression of the renal parenchyma have been reported. However, to our knowledge, no cases related to arteriography with angioplasty as the cause of PK in a transplanted kidney has been reported. Clinical suspicion is always essential in making an accurate diagnosis. Treatment should be individualized. Patients who suffer PK should be monitored due to the possibility of chronic hypertension.

INTRODUCTION

In 1939, Irwin Page [1] demonstrated experimentally that wrapping dog kidneys in cellophane caused constrictive perinephritis, favoring microvascular ischemia of the renal parenchyma, and juxtaglomerular cell hyperplasia, thereby stimulating the renin-angiotensin-aldosterone system and reabsorption of sodium and water, generating hypertension.

Page kidney (PK) is an uncommon and severe clinical disease. Since 1955, when Engel and Irwin Page [2] first described a PK in human beings, a rugby player who had received blunt trauma to the side, very few cases have been reported in the literature.

We are presenting a case of PK treated at our hospital after an angioplasty in a kidney transplant patient, which is an uncommon complication and to our knowledge not described in the literature until now.

CASE REPORT

A 38-year-old male who received his first kidney transplantation from a donation after circulatory determination of death with the graft implanted in the left iliac fossa, posttransplant serum creatinine was 2 mg/dl. A progressive stricture of the renal artery, which caused impaired renal function, was diagnosed 6 months after kidney transplantation, whereupon a scheduled arteriography and angioplasty were performed. At the time of the angioplasty, the serum creatinine was 3.74 mg/dl, with a creatinine clearance of 27.2 mL/min, a urine output of 2800 cc, and the proteinuria was 0.73 g/24 hours.

Seventy-two hours after the angioplasty, the patient presented sudden pain, mass effect in the left iliac fossa, anuria, impaired renal function (serum creatinine 7.8 mg/dl), hypertension (171/107 mmHg), and severe anemization.

An urgent ultrasound of the renal graft showed a heterogeneous collection of 3 cm x 8 cm deforming the contour of the upper pole of the kidney, consistent with subcapsular hematoma. A computed tomography (CT) scan was requested to provide a better assessment of possible active bleeding, which was not confirmed (Figure 1 and Figure 2). The nephrographic phase showed a heterogeneous uptake of the renal parenchyma, suggesting poor perfusion. In view of the patient's acute severe clinical situation, a capsulotomy and urgent surgical drainage of the hematoma was performed. In the days postoperation, the patient's renal function improved up to his baseline values

KEYWORDS: Hypertension, page kidney, renal artery stenosis, renal transplantation, subcapsular hematoma, ultrasound

CORRESPONDENCE: José Medina-Polo, Department of Urology, Hospital Universitario 12 de Octubre, Avda. Córdoba s/n, 28041, Madrid, Spain (josemedinapolo@movistar.es)

CITATION: *UroToday Int J*. 2013 December;6(6):art 72. http://dx.doi.org/10.3834/uij.1944-5784.2013.12.07

Figure 1. Computed tomography scan showing hematoma surrounding the transplanted kidney.

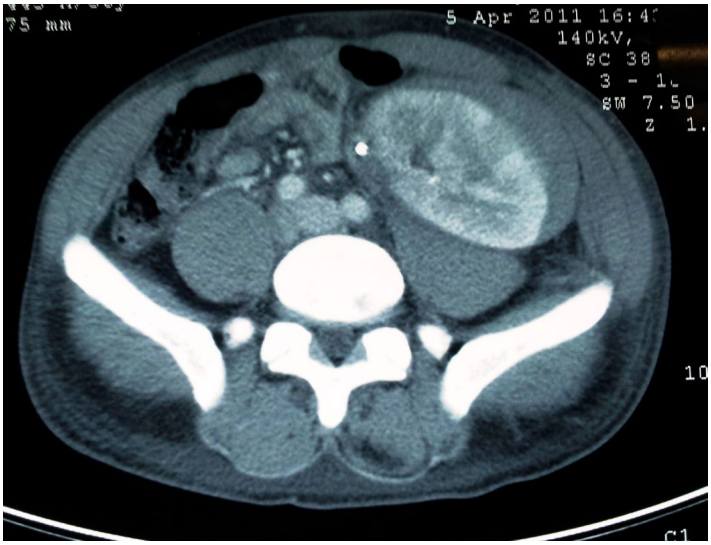
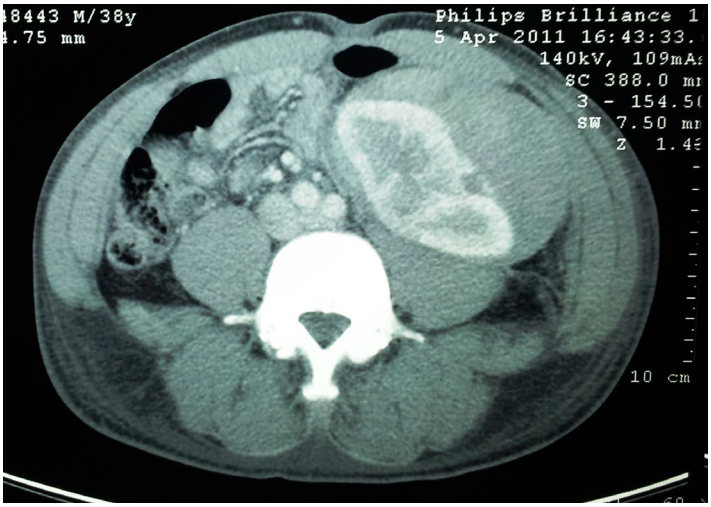


Figure 2. Computed tomography scan showing hematoma surrounding the transplanted kidney.



(creatinine 3.3 mg/dl 9 days after the capsulotomy) and to normal urine output. However, a certain degree of hypertension persisted, which required medical treatment to control it.

DISCUSSION

Page kidney phenomenon is hypereninemic hypertension triggered by any compressive mechanism on the kidney. Multiple causes of extrinsic compression of the renal parenchyma have been reported. Blunt trauma used to be the most common cause of subcapsular hematoma, but its incidence has tapered off in recent years and it currently accounts for only 30% (classic PK) [3]. In recent decades, the kidney biopsy is undoubtedly the main etiological agent of subcapsular hematoma [3-6] with an estimated incidence of 35% [3]. Many other less frequent causes of compression have been described in the literature: percutaneous nephrostomy, percutaneous radiofrequency ablation, partial nephrectomy, ureteroscopy, shock-wave lithotripsy, lymphoceles, renal cysts, pararenal tumors, urinomas, and unknown etiology [7-9]. To date, we have no knowledge of any reported case of arteriography with angioplasty on one of the main renal arteries as the cause of PK in a transplanted kidney.

The clinical manifestations of KP will depend on the patient characteristics and how rapidly the compressive effect on the renal parenchyma kicks in. Hypertension is the constant and characteristic sign of PK, mainly due to the pathophysiology of the phenomenon. In double-kidney patients, or those in whom the compressive effect is progressive and not acute, the hypertension may go unnoticed on being confused with essential hypertension, particularly if PK is not suspected. In single-kidney patients, the clinical manifestations are more striking because they have no other kidney to compensate for the functional deficit of the affected kidney. Thus, oligoanuria and acute renal failure with impaired creatinine and glomerular filtration rate will be more evident in these patients. Acute anemization presents mainly in cases in which the cause of compression is hemorrhage. In our case, and as the patient has a kidney transplantation, we observed all these clinical manifestations acutely: anemization, oligoanuria and impaired renal function, and sudden hypertension with poor drug control. Moreover, pain in the graft area and the mass effect in the left iliac fossa were observed.

Clinical suspicion is always essential in making the diagnosis. Ultrasound is the technique of choice because it is quick and harmless for the patient, and it is also highly sensitive and specific for identifying renal abnormalities [3]. Moreover, CT scan provides greater detail and precision of the compressive cause, its nature, and anatomical relationships. There are no guidelines or consensus-based recommendations on the procedure for the treatment of PK. Therefore, treatment should be individualized.

The different authors do seem to agree that one of the first measures is pharmacological control of hypertension. Drug treatment will only suffice in 18% of cases in which there is only hypertension [3,10]. Kidney decompression will be necessary in all other cases. The use of angiotensin-converting enzyme inhibitors is more than justified [11]. However, if they are

contraindicated, as was the case in our patient who presented renal artery stricture, diuretics, beta-blockers, and calcium channel blockers may be used. Decompression can be performed through percutaneous drainage or by surgical drainage and capsulotomy, as was necessary in our case due to its severity. In cases in which the cause of the extrinsic compression is not a hematoma, this cause can be treated specifically. Nephrectomy should only be considered in selected cases, as it has been proven that conservative management and adequate drainage of the hematoma can solve acute cases. These patients must be closely monitored, as it is known that up to one third of patients with PK, with no previous history of hypertension, will develop chronic hypertension despite receiving suitable initial treatment [11].

CONCLUSIONS

PK is a rare and serious condition that can lead to loss of the kidney. Clinical suspicion is essential in all patients with a history of kidney manipulation, like an arteriography with angioplasty. Diagnosis by imaging, ultrasound, or a CT scan is fast and accessible for most centers. Surgical drainage of the hematoma and capsulotomy are the most effective options, but treatment should be individualized because some cases could be subsidiary to drug treatment and percutaneous drainage. Patients who suffer PK should be monitored due to the possibility of chronic hypertension.

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Replacement of Both Tunica and Urethra by Inner Prepucial Flap in a Neglected, Old Case of Fracture of the Penis

Amilal Bhat,[1] Mahakshit Bhat,[2] Karamveer Sabharwal,[3] Manish Singla,[3] Vinay Kumar,[3] Ravi Upadhayay[3]

[1]Senior Professor and Head, Department of Urology, [2]Senior Demonstrator, Department of Preventive and Social Medicine, [3]Senior Resident, Department of Urology, S. P. Medical College, Bikaner, India 334003

Submitted October 20, 2013 - Accepted for Publication December 13, 2013

ABSTRACT

The present case is a rare complication of fractured penis involving the tunica leading to a large fibrous plaque and stricture urethra because of involvement of corpus spongiosum in the plaque. The fibrous plaque in the tunica was excised and distal urethra involved in plaque was resected. An inner preputial flap was divided into 2 and used successfully to cover the resultant tunica defect and for urethral replacement with good results.

INTRODUCTION

Fracture of the penis is not so uncommon but involvement of the urethra in fracture of the penis is rare, and the treatment of choice is immediate surgical exploration. Untreated or conservatively treated patients heal with fibrous plaque formation with or without calcification, and such patients present with chordee, painful erections, and painful coitus or impotence. If a small segment of the urethra is involved, the resultant stricture is amenable to visual internal urethrotomy. But sometimes both the corpora and urethra are involved in a large segment of fibrous plaque, leading to a large segmental loss of the urethra. Such cases are very rare and pose problems in management. We managed 1 case of old penile fracture with large fibrous plaque involving both the tunica and distal urethra. The objective of the case report is to highlight this rare complication of fracture of the penis and difficulty in its management.

PATIENTS AND METHODS

A 42-year-old male presented with a history of poor urinary stream, impotence, and swelling in the distal half of the penis for 6 months after penile trauma. The patient gave a history of penile bending during sexual intercourse followed by a loss of penile erection and swelling of the penile shaft, pain, and bleeding via the urethra. Bleeding via the urethra continued for 3 consecutive nights during nocturnal tumescence. He did not come to the hospital because of shyness. The pain disappeared in about 10 days but the swelling of penile shaft persisted with loss of erection. The patient gradually developed a thin stream and ultimately started passing urine in drops. Examination revealed a swelling of 5 cm x 4 cm on the right side of the distal shaft involving the urethra (Figure 1a). The urethrogram showed almost complete loss of lumen (Figure 2) in the distal 5 centimetres of the urethra. Ultrasonography (USG) showed a large echogenic area in the distal penile shaft on the right side (Figure 2). Penile degloving was done after circumferential circumcoronal incision. The plaque, which was starting from mid penis to the corona, was identified and dissected (Figure 1b, Figure 1c, Figure 1d). The plaque was excised, including the involved urethra, resulting in a gap in the tunica of about 4 cm x 3.5 cm and urethral loss of 4 cm (figure 1d). An inner prepucial flap was raised and divided into 2 (figure 1e, Figure 1f). One flap was used to cover the defect in tunica (Figure 1g) and another was used for distal urethral replacement by tubularizing the flap over a catheter (Figure 1i, Figure 1j, Figure 1k). Pressure dressing was done after applying skin sutures.

KEYWORDS: Penile fracture, Peyronie's, urethral stricture

CORRESPONDENCE: Dr. Amilal Bhat, C-15 Sadul Ganj, Bikaner (Rajasthan), India 334003 (amilalbhat@rediffmail.com, bhatamilal@gmail.com)

CITATION: *UroToday Int J*. 2013 December;6(6):art 77. http://dx.doi.org/10.3834/uij.1944-5784.2013.12.12

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Figure 1. Showing operative steps of resection of plaque and replacement of both tunica and urethra by inner prepucial flap.

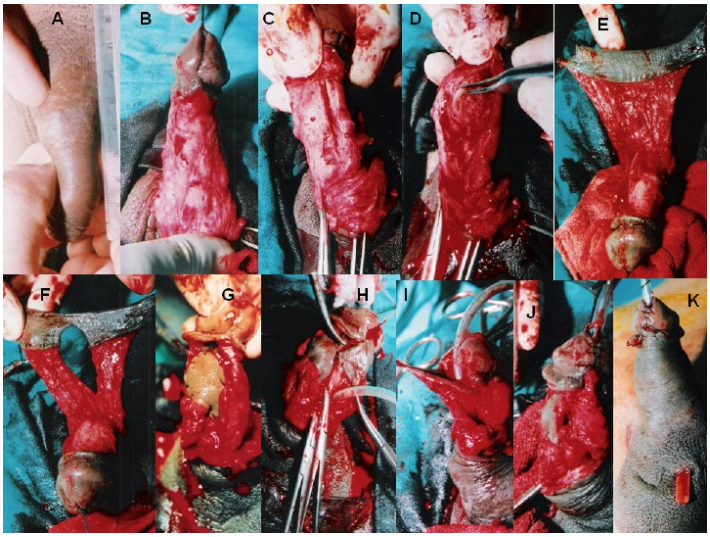
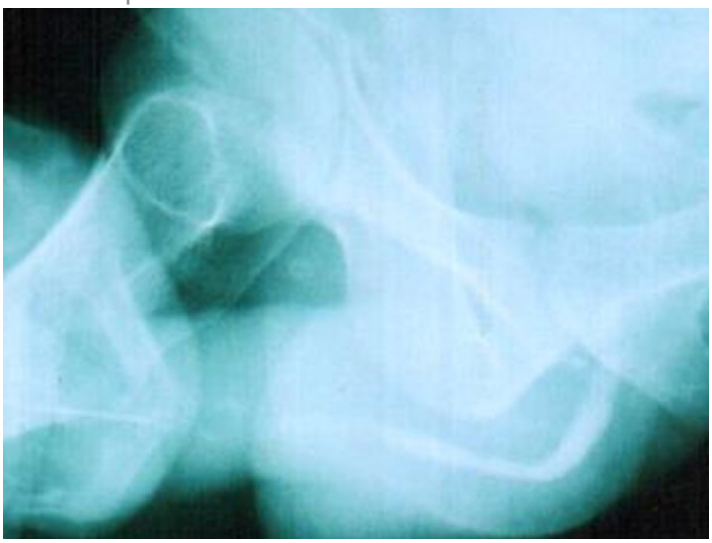


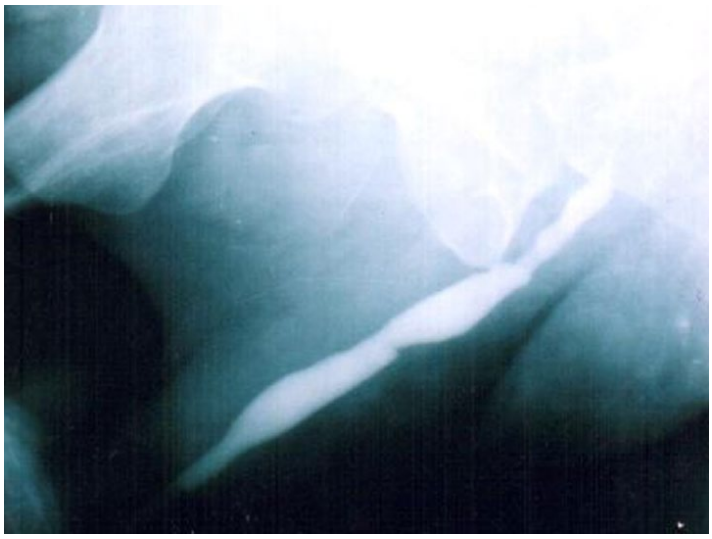
Figure 2. A preoperative urethrogram showing the loss of the distal penile urethra.



RESULTS

Postoperative progress was uneventful and the patient voided in a good stream after removal of the catheter at 2 weeks. The patient reported good penile erection and sexual intercourse at 3 months, but his urinary stream was thin. The Urethrogram revealed a normal distal urethra but proximal bulbar urethral stricture (Figure 3). Visual internal urethrotomy was done for the stricture 4 months after surgery. The patient reported having sexual intercourse and voiding well when last seen at 18 months of follow-up .

Figure 3. Postoperative urethrogram at 3 months showing a proximal urethral stricture.



DISCUSSION

Penile fracture with urethral trauma is a relatively rare urological emergency with a wide spectrum of injuries ranging from minor tears in the tunica albuginea to development of fibrous plaques in the long-term, causing penile curvature and pain during erection. The incidence of urethral trauma in fracture of the penis varies from 1 to 38% [1-5], with reported incidences higher in the United States and other western countries compared to Asia [6]. Classically, blood at the urethral meatus, painful voiding with hematuria, and inability to void with/without a distended bladder indicate a urethral injury. Some authors consider urethrography to be mandatory in such circumstances [7-9], whereas others consider routine urethrography to be unnecessary [3]. After excision of the plaque, provided the defect is small and the fibrosis isn't deep, resuturing the tunica albuginea is a reasonable alternative. If resection of the fibrous tissue produces a big gap in the tunica

albuginea, then a replacement graft is required to bridge the defect.

The outcome of trauma to the urethra in fracture of the penis is different when the urethra and corpus spongiosum are surrounded by the hematoma. If such patients are treated conservatively or remain untreated, then both tunica and urethral loss are likely to be larger due to involvement of the urethra in the plaque. This was the case with our patient who presented late and had developed a 5 cm stricture. Being a long segment in the anterior urethra with moderate to severe spongiofibrosis, such strictures are not amenable to visual internal urethrotomy and requires dorsal onlay graft or urethral replacement. Dorsal onlay is feasible only if the corpus spongiosum is available. End-to-end urethroplasty is not possible in such cases with extensive loss of the anterior urethra. Urethral replacement remains the choice available. Various tissues used for urethral replacement are bladder mucosa, buccal mucosa, penile skin, and inner prepucial flap. Among these, the best available option in such situations is the inner prepucial flap.

Various alternatives for tunica replacement described in the literature are a dermal graft, free fat graft, a tunica vaginalis graft, a temporalis fascia graft, mono filaments, knitted polypropylene or lyophilized human dura, a venous patch graft, and a dermabraded graft with variable results. The dermis is more vascular and has a higher metabolic demand, with a more random fiber arrangement that might contribute to its contraction when used as a free graft [10]. The tunica vaginalis lacks strength and might result in areas of aneurysmal dilatation [10]. Prosthetic materials have the disadvantage of promoting a capsule around the material, which may contract later, defeating the purpose of the procedure [11]. Fascia lata, dura mater, and temporalis fascia grafts require additional major surgery to harvest the graft. In dermabraided flaps, removal of the epidermis leads to potential weakness in the flap strength. Trauma to the epidermis will cause an inflammatory reaction, which may lead to fibrosis and contracture. Inner prepucial flap has the advantages of being well vascularized, so it has good strength.

Krishnamurti [13] used dermabraded skin flaps for the replacement of tunica after excision for Peyronie's disease with good long term results. The inner prepuce is also skin with similar tensile strength and is thus adequate replacement for the tunica. It has little chances of graft contracture, is hairless, has the advantage of easy take-up, and is taken from the same site of surgery [4]. Although there is a theoretical disadvantage of increased risk of inclusion of a dermoid due to a buried epidermis [12], in a previous series of use of inner prepuce for tunica replacement, we didn't encounter a dermoid on long-term follow up of up to 13 years [4].

CONCLUSION

This is a first case of extensive urethral involvement in fracture of the penis that was managed successfully with good results by excision of plaque, and replacement of both tunica and urethra by an inner prepucial flap.

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Urogenital Schistosomiasis: A Diagnosis to Consider in Patients with Hematuria in Europe

Lucas Regis,[1] Fernando Lozano,[1] Miguel A. Lopez-Pacios,[1] Juan Morote[1,2]

[1]Department of Urology, Vall d´Hebron Hospital, Universitat Autónoma de Barcelona, [2]Vall d´Hebron Research Institute, Universitat Autónoma de Barcelona

Submitted August 5, 2013 - Accepted for Publication September 20, 2013

ABSTRACT

Introduction: Over 100 million people worldwide are affected by urogenital schistosomiasis, a disease caused by Schistosoma haematobium. Here, we report our experience with urogenital schistosomiasis.

Materials and Methods: We retrospectively evaluated patients with urogenital schistosomiasis between 2004 and 2012. Clinical and demographic variables were analyzed.

Results: All cases (5) occurred in male patients with a median age of 33.8 years (range: 14-47). All patients resided in or had visited endemic areas. The average time from the onset of symptoms to diagnosis was 19.5 weeks (1-52). Hematuria was the most common initial clinical sign in 3 cases (60%), 2 of which arose in a monosymptomatic form. One case presented with sepsis and acute renal failure (ARF), and another case presented atypically and was diagnosed in an organ donor candidate. Four cases exhibited consistent bladder calcifications that were found through radiographic imaging at the time of diagnosis. The parasite was identified in urine in 1 case (20%), and cystoscopy results were suspicious for 2 of them (40%). The chosen standard treatment was pharmacological (Praziquantel) after anatomopathological confirmation.

Conclusions: Given the high prevalence of schistosomiasis in sub-Saharan countries, the emergence of macro- or microscopic hematuria in immigrants or travelers requires comprehensive study and the consideration of schistosomiasis as a probable cause. Accurate diagnosis and early treatment can prevent complications from tissue inflammation caused by the parasite.

INTRODUCTION

FOver 100 million people worldwide, particularly in rural areas, are affected by urogenital bilharziasis, a parasitic disease caused by Schistosoma haematobium [1]. Given the high prevalence of schistosomiasis in sub-Saharan countries and the subsequent clinical implications, the appearance of macro- or microscopic hematuria in immigrants or travelers requires comprehensive study and the consideration of schistosomiasis as the probable cause [2-4]. According to a literature review of articles indexed in PubMed, few cases have been published in Spain in the last 15 years. The aim of this study is to describe the clinical characteristics of patients with a diagnosis of urogenital schistosomiasis at the Hospital Universitari Vall d´Hebron (Vall d´Hebron University Hospital), Barcelona.

MATERIALS AND METHODS

We retrospectively identified all patients suffering from schistosomiasis who were admitted to the Vall d´Hebron University Hospital over a period of 93 months between June 2004 and April 2012. Five patients were identified, and their medical records, laboratory tests, and images were evaluated. The following variables were examined: age, sex, country of origin, travel to endemic areas, laboratory tests, imaging results, and treatment.

KEYWORDS: Hematuria, schistosomiasis, Schistosoma haematobium, urine cytology

CORRESPONDENCE: Lucas Regis, Vall d´Hebron Hospital, Department of Urology, Pg Vall d´Hebron 119-129, Barcelona 08035, Spain (lucasregis@gmail.com)

CITATION: *UroToday Int J*. 2013 December;6(6):art 78. http://dx.doi.org/10.3834/uij.1944-5784.2013.12.13

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Table 1. Demographic and clinical characteristics.

Parameters	
Patients nº	5
Age (years)	
Median (range)	33.8 (14-47)
Gender (%)	
Men/women	100/0
Nacionality (Spanish)	
Yes*	1 (20%)
No	4 (80%)
Time between onset of symptoms and diagnosis (weeks)	
Median (range)	19.5 (1-52)
Hematuria	
Yes	3 (60%)
No	2 (40%)
S. haematobium – orine analysis	
Ye	1 (20%)
No	4(80%)
Urine cultive	
Positive**	1 (20%)
Negative	4(80%)
IgG-serum	
Positive***	1 (20%)
Negative	4(80%)
Suspicious lesion on cystoscopy	
Yes	2 (40%)
No	3 (60%)
Suspicious calcifications – radiological examinations	
Yes	4 (80%)
Vesical	1
Ureteral	1
Vesical and ureteral	2
No	1 (20%)

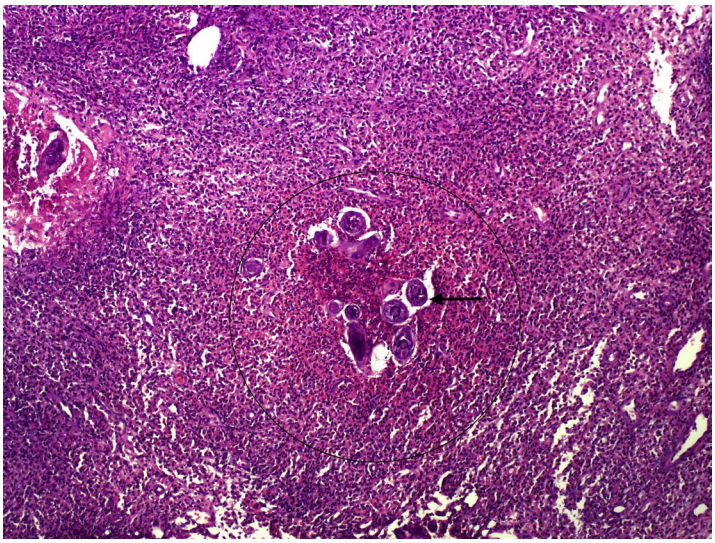
* patient with history of travel to endemic area
** E. coli isolated in urine culture
*** positive IgG S. mansoni especific

RESULTS

Demographic and clinical characteristics are presented in Table 1. All patients (5) were male, with a median age of 33.8 years (14-47); 80% were of African origin (2 from Senegal, 1 from Gambia, and another from Ghana). One patient was from Spain and had recently traveled to Mali. Of the cases (3), 60% presented with macroscopic hematuria: 2 cases in the monosymptomatic form and 1 case with associated lower back pain. One patient exhibited urinary sepsis with associated acute renal failure (ARF). An atypical case in an organ donor candidate was incidentally diagnosed by radiological imaging and biopsy. The mean time between the onset of symptoms and diagnosis was 19.5 weeks. The parasite was isolated in the urine in only 1 case (20%). Calcifications of the urinary tract (bladder or ureter) were observed in 80% of the cases; 2 patients exhibited bladder and ureteral calcifications, 1 patient exhibited only bladder calcifications, and another patient exhibited only ureteral calcifications. Approximately 40% of the patients exhibited suspicious lesions on cystoscopy (including 1 hypervascularized lesion and a verrucous lesion).

All of the patients received pharmacological treatment (Praziquantel) after definitive anatomopathological diagnosis (Figure 1), except for an incidental postmortem diagnosis. In 3 patients, the diagnosis was confirmed after transurethral resection (TUR), and in 1 other patient, the diagnosis was confirmed after nephroureterectomy. All patients exhibited complete remission of their symptoms and no evidence of the

Figure 1. Pathology. TURB, hematoxylin-eosin tecnic 10 x: eggs (black arrow) surrounded granuloma S. hematobium, intense inflammatory infiltrate (inside the bubble).



disease on later tests (urinalysis, cystoscopy).

DISCUSSION

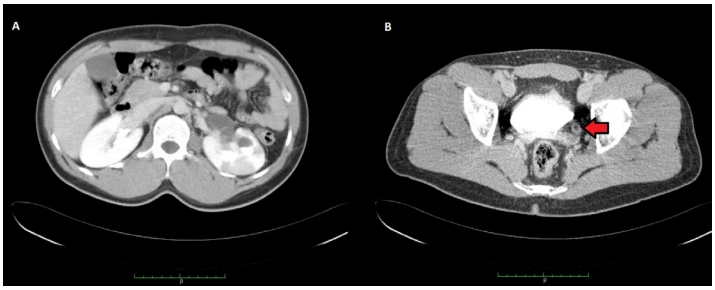
To date, this is the largest published case series of urogenital schistosomiasis in Spain. The parasite Schistosoma haematobium is widely distributed in the sub-Saharan African region, the East African coast, the Maghreb, Cyprus, and the Middle East [1]; all patients in our case series exhibited exposure to these regions.

The life cycle of this parasite is complex. The snail (Bulinus) is the intermediate host and releases the parasite's cercariae in the water. These larvae infect humans (main host) by penetrating the skin. The adult forms persist for decades within the venous plexus of the pelvic organs, bladder, rectum, pelvic ureters, and deep genital organs. Parasitic eggs result from sexual reproduction and migrate into these organs, causing mucosal microperforations. Repeated urothelial microlesions cause hematuria. After their elimination in the urine, the parasites become ciliated embryos or miracidium and infect snails, thus completing the life cycle [1,4].

Primary infection often goes unnoticed for years, as was the case in all of the patients in our series. All cases in our series exhibited a positive epidemiological history, including visits to endemic areas years before the appearance of the clinical signs. Occasionally, the initial infection causes irritation, itching, fever, or rash, producing the condition known locally as "swimmers itch" [5].

The active chronic phase of the disease is characterized by a significant increase in the egg population in the urothelium, causing hematuria. Hematuria was the most common symptom in our series and the reason for consultation in 60% of the patients. The only isolated case that did not exhibit hematuria was associated with lower back pain. A computed tomography (CT) scan revealed images suggestive of an upper urinary tract tumor, and a diagnosis of bilharziasis was established after nephroureterectomy, which is the standard treatment for a suspected malignancy of this type (Figure 2). Bladder lesions result in inflammation, sclerosis, calcifications, loss of bladder capacity, and bladder neck stenosis, which may subsequently favor the development of bladder neoplasia. Most bladder tumors associated with bilharzias are squamous cell carcinomas. In addition, there is also an associated increase in the incidence of transitional cell carcinoma, which are more aggressive, of high-grade, recur frequently, and affect younger people [1,6,7]. The intense granulomatous inflammatory response and irreversible fibrous lesions produced in response to the parasitic eggs can cause ureteral stenosis (3 patients) and consequent progressive loss of renal function, eventually causing terminal renal disease [1,5]. In our series, 1 patient exhibited an atypical form of urinary sepsis associated with ARF, and the patient exhibited a baseline creatinine of 1.6 mg/dL in subsequent control tests. This likely represents a case of chronic renal disease due to obstructive uropathy secondary to chronic schistosomiasis, diagnosed following urinary sepsis.

Figure 2. TAC: A. Globular left kidney with hydronephrosis. B. Left pelvic ureter with thickened walls (stenosis) causing secundary retrograde hydronephrosis.



Aberrant localization of the parasite has been described, typically in patients from endemic areas [8]. The diagnosis of schistosomiasis is based on the presence of parasite eggs in the urine. Based on the number of eggs identified, it is possible to classify the magnitude of the infection [1] (< 100 mild, 100-400 moderate, > 400 severe). Serological tests have little utility in screening for this disease. First, they are unable to differentiate the mild from severe infections. Second, cross-reactions with other parasites are common [1], as was observed in 1 patient in our series (positive IgG serology for S. mansoni). Radiology allows us to assess sequelae in the urinary tract. The images typically demonstrate a calcified bladder or "porcelain bladder," which constitutes a pathognomonic radiological finding of chronic urinary schistosomiasis [9]. CT scans are necessary in cases in which renal or upper urinary tract tumors are suspected. The cystoscopic findings are typical: erosions, mucosal congestion, nodules, and red sessile lesions. Cystoscopy is typically followed by transurethral resection of the suspicious area, and a definitive diagnosis is established after confirming the presence of the parasitic egg [1,4,8].

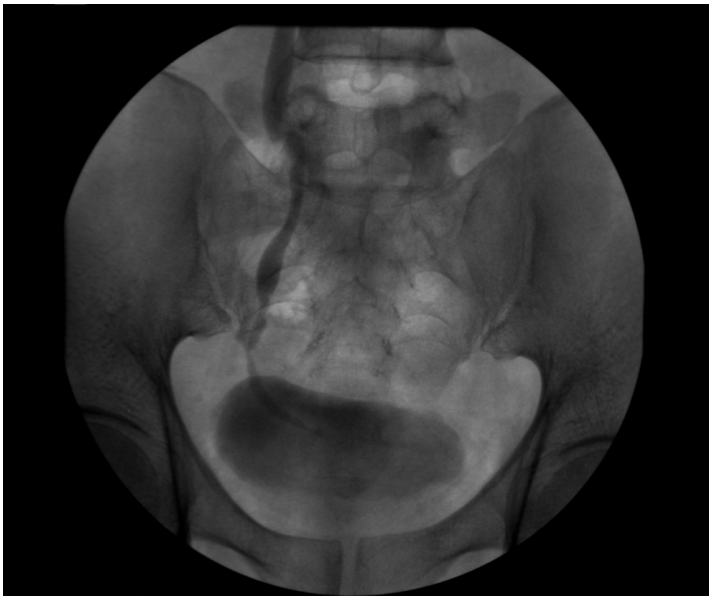
Treatment with Praziquantel usually induces remission of the inflammatory response caused by the oviposition and promotes healing of the infection in the majority of cases. Meanwhile, scar lesions persist despite eradication of the parasite (Figure 3) [1,5,10].

CONCLUSION

Given the high prevalence of schistosomiasis in sub-Saharan countries and the subsequent clinical implications, the appearance of macro- or microscopic hematuria in immigrants or travelers requires comprehensive study and the consideration

UIJ / Vol 6 / Iss 6 / December / http://dx.doi.org/10.3834/uij.1944-5784.2013.12.13
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

Figure 3. Intravenous urography 1.5 years following treatment with praziquantel: moderate pelvic dilatation up ureter chronic stenosis.



of schistosomiasis as a probable cause. Accurate diagnosis and early treatment can prevent complications from tissue inflammation caused by the parasite.

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