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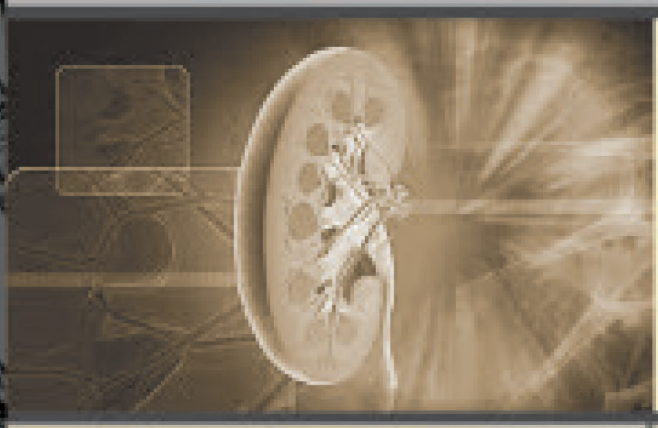

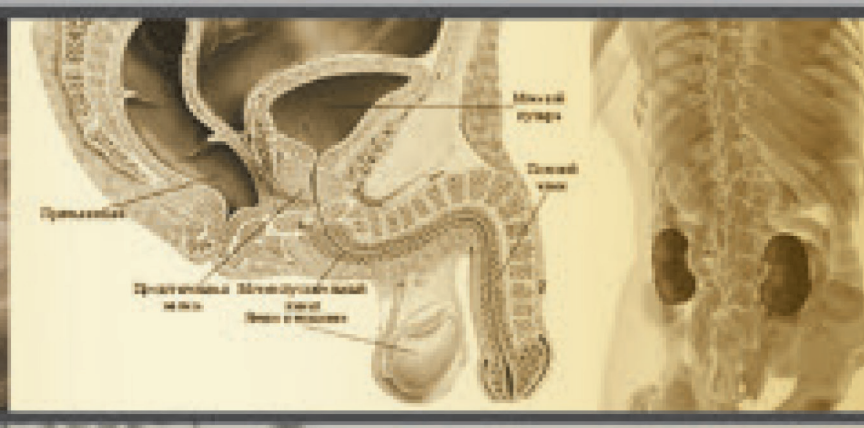

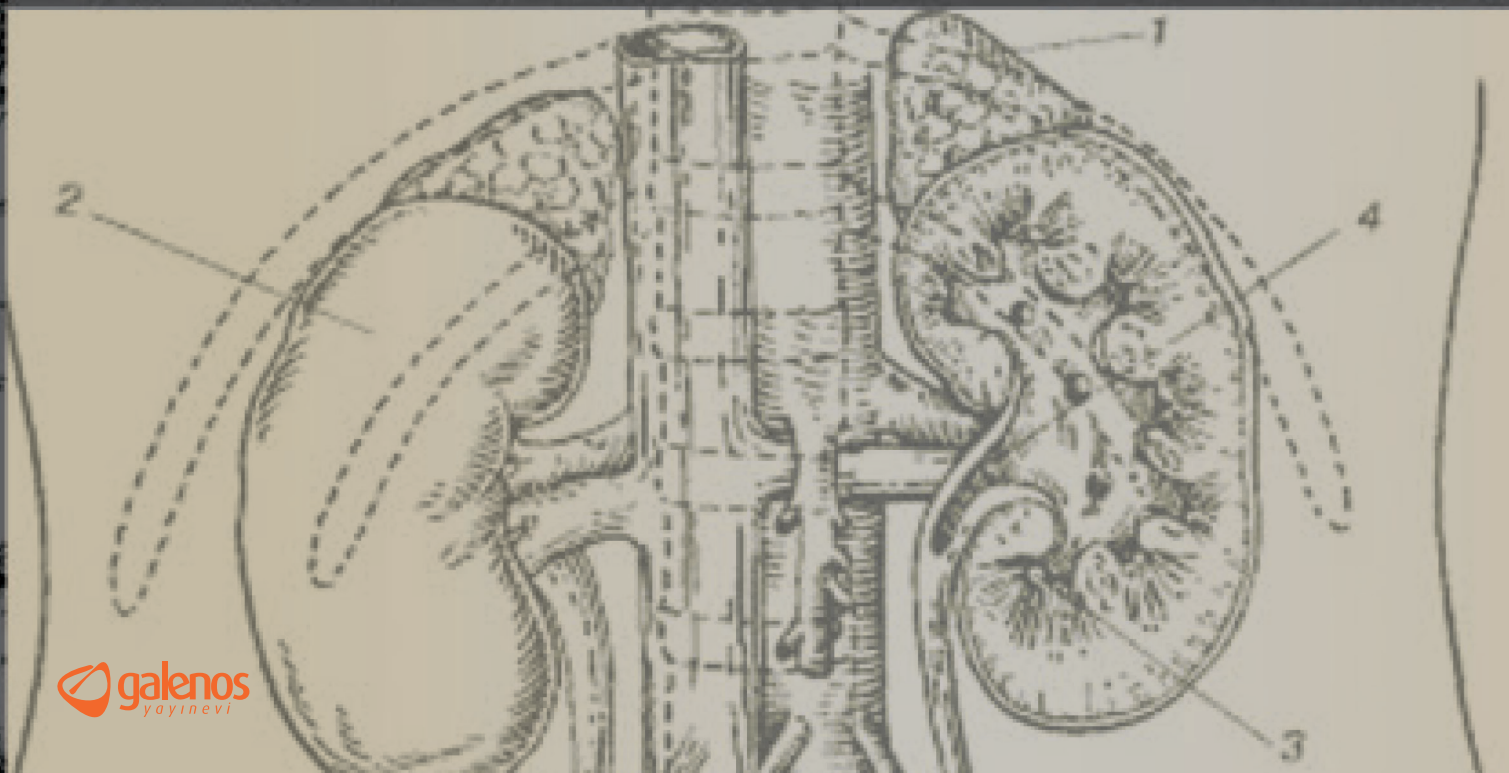

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3. Complete Book

Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012.

4. Chapter in Book

Pearle MS, Lotan Y Urinary lithiasis: etiology, epidemiology, and pathogenesis. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 201, pp 1257-1323.

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5. Abstract

Nguyen CT, Fu AZ, Gilligan TD, Kattan MW, Wells BJ, Klein EA. Decision analysis model for clinical stage I nonseminomatous germ cell testicular cancer. J Urol 2008;179:495a (abstract).

6. Letter to the Editor

Lingeman JE. Holmium laser enucleation of the prostate-If not now, when? J Urol 2011;186:1762-1763.

7. Supplement

Fine MS, Smith KM, Shrivastava D, Cook ME, Shukla AR. Posterior Urethral Valve Treatments and Outcomes in Children Receiving Kidney Transplants. J Urol 2011;185(Suppl):2491-2496.

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CONTENTS

ORIGINAL RESEARCH
Urooncology

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The Effect of Transurethral Resection and BCG Therapy on Cytokine Levels in Non-Muscle Invasive Bladder Cancer

Oktay Üçer[1], Gökhan Temeltaş[1], Talha Müezzinoğlu[1], Zeki Ari[2], Funda Kosova[3]

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What's known on the subject? and What does the study add?

In this study, we found that in non-muscle invasive bladder cancer cases, transurethral resection of bladder tumor decreased the tumor weight and accordingly, cytokine levels decreased.

Abstract

Objective: The present study investigated the effect of treatment on interleukin (IL)-1, IL-6, IL-8, and neopterin levels in patients with non-muscle invasive bladder cancer (NMIBC).

Materials and Methods: Thirty patients with NMIBC and 30 age-matched controls were included in the study. Preoperative, postoperative first control [at two weeks after second transurethral resection of bladder tumor (TURBT)] and the second control (at the end of intravesical immunotherapy) blood samples were analyzed using ELISA to determine IL-1, IL-6, IL-8, and neopterin levels. The mean cytokine levels of the patients were statistically compared and comparing the patients' and controls' levels.

Results: There were no statistically significant differences between the mean IL-1, IL-6, IL-8, and neopterin levels of the patient and control groups before initial TURBT. In the patient group, there were no statistically significant differences in the IL-6 and IL-8 levels after both TURBT and intravesical Bacillus Calmette-Guérin (BCG) therapy. The mean of preoperative IL-1 and neopterin levels significantly decreased after TURBT ($p<0.05$). However, this reduction does not continue after intravesical BCG instillation.

Conclusion: The findings of this study showed that the IL-1, IL-6, IL-8, and neopterin levels of the patients with NMIBC were similar to the levels of healthy controls. IL-1 and neopterin levels significantly decreased after TURBT. But these reduction did not continue after intravesical BCG instillation. These findings demonstrate that IL-1 and neopterin levels decrease after TURBT due to the reduction in tumor weight or tumor removal.

Keywords: Bladder cancer, IL-1, IL-6, IL-8, neopterin

Introduction

Bladder cancer is the seventh most commonly diagnosed cancer in men, in whom it is approximately four times more common than in women. At the time of diagnosis, approximately 75% of patients present with non-muscle-invasive bladder cancer (NMIBC), which are confined to the mucosa (Ta, carcinoma *in situ*) or submucosa (T1) (1). Many meta-analyses have confirmed that intravesical Bacillus Calmette-Guérin (BCG) immunotherapy after transurethral resection of bladder tumor (TURBT) is superior to TURBT alone for preventing the recurrence and/or progression of NMIBC (2-5). Therefore, the European Association of Urology (EAU) Guidelines on NMIBC recommend intravesical BCG immunotherapy after TURBT in patients with intermediate- or high-risk NMIBC (1).

Some studies have investigated the effect of intravesical BCG immunotherapy on some angiogenetic factors and cytokines

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such as interleukin (IL)-8 in patients with NMIBC (6,7). They suggested that these factors and cytokines might be used for follow-up after intravesical BCG immunotherapy in NMIBC. The antitumor features of intravesical BCG immunotherapy primarily depend on the BCG-induced inflammatory response (8) that is impaired in NMIBC as reflected by an imbalanced production of immuno-modulating cytokines (9). It is important to more fully understand the significance of these cytokines for predicting the outcome of intravesical BCG immunotherapy in NMIBC. Some studies have shown that proinflammatory cytokines, including IL-1, IL-6, IL-8 and neopterin played an important role in the active immune response in cancer (10-12). Therefore, these cytokine levels may decrease after treatment of cancer (surgical resection and medical therapy). The present study compared IL-1, IL-6, IL-8, and neopterin levels of the patients with NMIBC and healthy controls, and investigate the changes in these cytokines and neopterin levels after TURBT and intravesical BCG immunotherapy.

Materials and Methods

Study Population

Patients with newly diagnosed bladder cancer (n=41) who underwent initial TURBT and 30 age-matched controls were enrolled in the study. The inclusion criteria were newly diagnosed intermediate or high-risk NMIBC who received a second TURBT and 6 doses of BCG. Exclusion criteria were low-risk NMIBC, T2 and BCG toxicity. Three patients with low-risk NMIBC and 3 patients with MIBC (T2) after initial TURBT were excluded from the study. Thirty-five patients underwent the second TURBT at 4-6 weeks after the initial TURBT. Three patients with MIBC after the second TURBT were excluded from the study. Thirty-two patients received intravesical BCG therapy once a week for 6 weeks. Two patients were excluded from the study because of BCG toxicity. The patients' enrollment algorithm is illustrated in Figure 1. The study group comprised 30 patients with intermediate- or high-risk NMIBC and 30 age-matched controls. IL-1, IL-6, IL-8, and neopterin levels were measured by enzyme-linked immunosorbent assay (ELISA) in the blood samples of the patients before initial TURBT (preoperative group), at 2 weeks after the second TURBT (postoperative first control group) and at 2 weeks after the end of induction intravesical BCG immunotherapy (postoperative second control group). These cytokines were also measured by ELISA in the blood samples of controls. Informed consent was obtained from all the patients and controls who participated in the study and The Local Ethics Committee (Celal Bayar University Ethic Committee) approved the study protocol (decision number: 20478486/243).

Statistical Analysis

Statistical analysis was performed using "Statistical Package for Social Sciences 22.0 software (SPSS 22.0 for MAC)". Descriptive statistics were presented as mean ± standard deviation, frequency and percentages. The Shapiro-Wilk test was used to determine whether the data showed a normal distribution. It was observed that all parameters we examined conformed to a normal distribution. Student's t-test (t-test in independent groups) was used to compare normally distributed continuous variables between the control and patient groups before initial TURBT. Mann-Whitney U test was used to compare not normally distributed continuous variables between the control and patient groups before initial TURBT. The comparison between the patient and control groups for sex was performed using the chi-square test. In the patient group, repeated measures analysis of variance (ANOVA) was used to compare variables between the preoperative, postoperative first control and postoperative second control. When appropriate, a Bonferroni t-test was used as a Post-hoc test. $P<0.05$ was defined as the statistical significance level.

Results

The mean age of the patient (22 males and 8 females) and control (21 males and 9 females) groups were 57.3±7.8 and 55.8±9.0 years, respectively (p=0.33). There were no statistically significant differences between the mean IL-1, IL-6, IL-8, and neopterin levels of the patient and control groups before initial TURBT (Table 1). In the

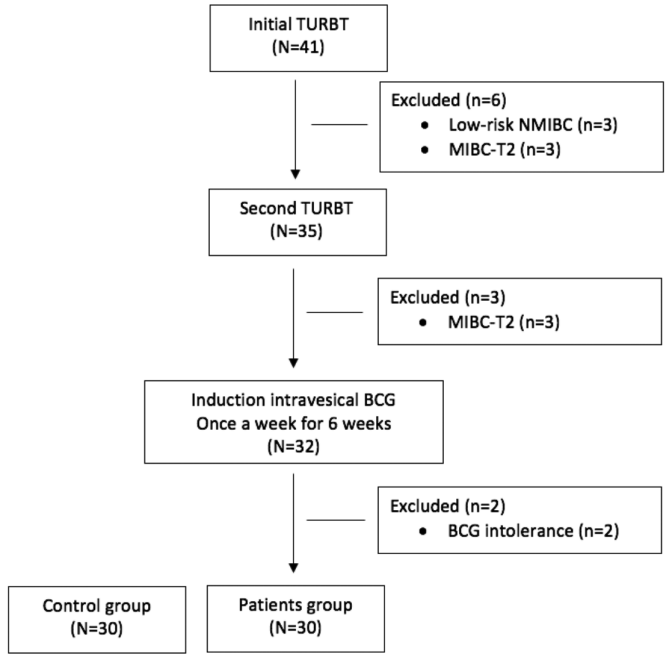

Figure 1. Flow diagram of the study participants

TURBT: Transurethral resection of bladder tumor, NMIBC: Non-muscle-invasive bladder cancer, MIBC: Muscle-invasive bladder cancer, BCG: Bacillus Calmette-Guérin

patient group, there were no statistically significant differences in the preoperative IL-6 and IL-8 levels after both TURBT and intravesical BCG therapy [respectively, $X^2(2)=1.333$, p=0.513, and $X^2(2)=2.778$, p=0.249]. The mean IL-1 levels of the preoperative, postoperative first control and postoperative second controls were 4.09±2.43, 3.99±2.49 and 3.95±2.30, respectively [$X^2(2)=10.500$, p=0.005]. In the pairwise comparison analysis, there was a significant decrease between the IL-1 levels in the preoperative and postoperative first controls (p<0.05) (Figure 2). The mean neopterin levels in the preoperative, postoperative first control and postoperative second controls were 3.31±1.18, 2.89±1.60 and 2.89±1.35, respectively [$X^2(2)=14.941$ p=0.001]. In the pairwise comparison analysis, there were decreases between neopterin levels in the preoperative and postoperative first controls (p<0.05), in the preoperative and postoperative second controls (p<0.05) (Figure 3).

Discussion

This study demonstrated that the IL-1 and neopterin levels of the patients with NMIBC significantly decreased after TURBT, however these decreases did not continue after intravesical BCG immunotherapy (Figures 2 and 3). Although the IL-1 levels of the patients were higher than the levels of the controls, this difference was not statistically significant. According to our best knowledge, there has been no study in literature to examine IL-1 levels in the blood samples of patients with NMIBC. Some studies have evaluated IL-1 levels in urine samples of patients with NMIBC in hours after intravesical BCG therapy (13,14). They found that the urine IL-1 levels increased after intravesical BCG therapy and reported that the result reflected the local inflammatory response to BCG. They also suggested further studies that would evaluate the possible role of IL-1 against NMIBC (14). We investigated the effect of treatment (TURBT and intravesical BCG) on the IL-1 levels in the blood of the patients with NMIBC and our results showed that TURBT caused a significant decrease in the IL-1 level. This finding is novel to the literature. This reduction may be related to the decrease in tumor weight or tumor removal.

Similar to the reduction of the IL-1 level, the neopterin levels of the patients with NMIBC decreased after TURBT in our study. According to the best of our knowledge, only one study examined neopterin levels in the blood samples of patients with NMIBC (15). In this study, the authors measured the neopterin levels before, at 4th, 24th, 48th and 96th hour after intravesical BCG and investigated the role in the immune response of neopterin after BCG. They found that the highest blood neopterin levels were found 48 hours after intravesical BCG therapy and were significantly higher than levels before BCG, 4 hours and 24 hours after BCG. They also suggested that neopterin in serum might be used as a parameter for monitoring the treatment course. We differently measured neopterin levels after TURBT. Similar to the decrease in IL-1, the reduction of neopterin levels after TURBT may be related to the decrease in tumor weight and tumor removal.

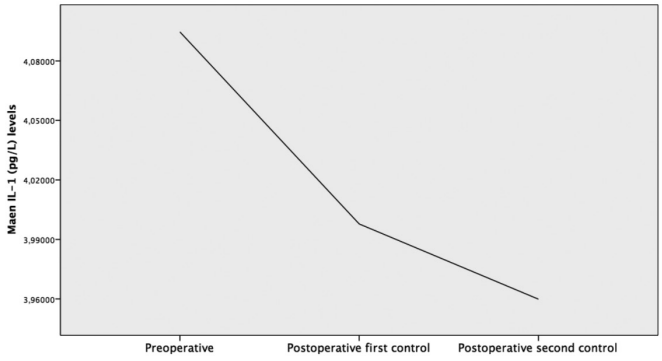

Figure 2. The maen IL-1 levels of the patients in preoperative, postoperative first control and postoperative second control

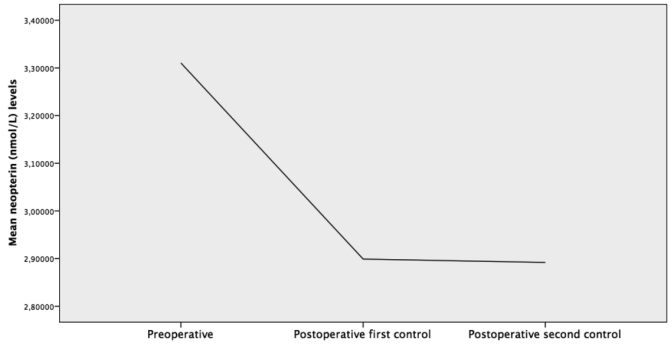

Figure 3. The mean neopterin levels of the patients in preoperative, postoperative first control and postoperative second control

Table 1. Mean IL-1, IL-6, IL-8 and neopterin levels of patient and control groups

	Patient group (preoperative) Mean ± SD	Control group Mean ± SD	p-value
IL-1 (pg/L)	4.09±2.43	3.65±1.30	0.96
IL-6 (ng/L)	4.13±2.13	3.82±1.24	0.58
IL-8 (ng/L)	5.37±2.81	4.32±1.50	0.05
Neopterin (nmol/L)	3.31±1.21	3.70±1.31	0.34

P<0.05 is defined a statistically significant, SD: Standard deviation, IL: Interleukin

There have been some studies that examined IL-6 levels in patients with bladder cancer (16-20). Only one (20) of these studies evaluated this cytokine in the blood samples of patients. In the other studies, it was measured either in urine samples (18,19) or in tumor issues (16,17). Kumari et al. (20) evaluated serum the IL-6 levels in 72 patients with bladder cancer (52 NMIBC and 20 MIBC). They divided the patients into 2 groups according to the presence of recurrence and found that the IL-6 levels of the patients with recurrent were higher than the patients with non-recurrent. They also reported the association of high concentrations of some cytokines, such as IL-6, with poor recurrence-free survival in the patients with bladder cancer. However, in their study, the IL-6 levels were not compared before and after the treatment of bladder cancer. Therefore, we do not know the change in IL-6 levels after the treatment in their study. We differently examined the IL-6 levels before and after TURBT and intravesical BCG instillation in only NMIBC. The results of our study showed that the before IL-6 levels before the treatment did not change statistically after both TURBT and intravesical BCG therapy. Therefore, according to our outcomes, IL-6 is not a proper biomarker to follow patients with NMIBC.

Similar to IL-6, there have been some studies that examined IL-8 levels in the urine of patients with NMIBC (19,20). The results of these studies showed that there was a significant relationship between high IL-8 levels and poor prognosis in the follow-up of NMIBC. However, they did not investigate the IL-8 levels in the blood of the patients. We compared the IL-8 levels in the blood of the patients with NMIBC with the healthy controls and found that there was no significant difference. We also compared the preoperative IL-8 levels with the IL-8 levels after TURBT and intravesical BCG therapy. We found that the preoperative IL-8 levels did not change after treatment with NMIBC. Therefore, although the previous studies suggested that urinary IL-8 levels in patients might be used to predict the prognosis of NMIBC, the findings of our study showed that serum IL-8 levels are not an appropriate cytokine to use in patients with NMIBC.

Study Limitations

There were some limitations to our study. The first one was that we did not follow the patients after intravesical BCG therapy. Therefore, we could not assess the progression and recurrence status of the patients. The other limitations were the small sample size and choice of cut-off times for blood sampling. The last limitation was that we measured the cytokines only in blood samples and did not perform urine tests.

Conclusion

The findings of this study showed that IL-1, IL-6, IL-8, and neopterin levels in the blood of patients with NMIBC were similar to the levels of healthy controls. Although the IL-6 and IL-8 levels did not change after TURBT and intravesical BCG instillation, the IL-1 and neopterin levels significantly decreased after TURBT. But these reductions in the IL-1 and neopterin levels did not continue after intravesical BCG instillation. In conclusion, our findings demonstrated that the IL-1 and neopterin levels decrease after TURBT due to the decrease in tumor weight or tumor removal. We suggest further studies that will investigate IL-1 and neopterin in long-term follow-up after TURBT.

Ethics

Ethics Committee Approval: The Local Ethics Committee (Celal Bayar University Ethic Committee) approved the study protocol (decision number: 20478486/243).

Informed Consent: Informed consent was obtained from all the patients and controls who participated in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.Ü., Z.A., F.K., Concept: O.Ü., T.M., Design: O.Ü., Data Collection or Processing: O.Ü., G.T., T.M., Z.A., F.K., Analysis or Interpretation: O.Ü., G.T., Literature Search: O.Ü., Writing: O.Ü.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial.

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ORIGINAL RESEARCH
Urooncology

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Evaluation of Risk Groups for the Prediction of Biochemical Progression in Patients Undergoing Radical Prostatectomy

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What's known on the subject? and What does the study add?

According to previous studies, preoperative and postoperative prostate specific antigen level measurements, pathological stage, Gleason score, extraprostatic extension, positive surgical margins and seminal vesicle invasion could be the predictors of biochemical progression and biochemical progression-free survival in prostate cancer patients undergoing radical prostatectomy. In our study, we showed that postoperative prostate specific antigen level higher than ≥0.2 ng/dL is the most important predictor of biochemical progression and biochemical progression-free survival in prostate cancer patients undergoing radical prostatectomy.

Abstract

Objective: The aim of this study was to investigate the potential relationship between biochemical progression and prognostic risk factors in patients with prostate cancer (PCa) patients undergoing radical prostatectomy (RP).

Materials and Methods: After inclusion/exclusion criteria were applied, 216 patients who underwent RP were included in this study. Follow-up protocol included prostate specific antigen (PSA) measurements; every 3 months for the first year, every 6 months for the second year, and an annual check after 2 years. Preoperative and postoperative PSA measurements, pathological stage, Gleason score (GS), extraprostatic extension, positive surgical margins and seminal vesicle invasion were evaluated. Uni- and multivariable analyses were used to detect the relationship between biochemical progression, biochemical progression-free survival (BPFS) and prognostic risk factors.

Results: Median follow-up was 29 months. Biochemical progression was observed in 39 (18.1%) patients, in 18 (9.7%) of 185 patients with first postoperative PSA level of <0.2 ng/dL, and 21 (67.7%) of 31 patients with first postoperative PSA level of ≥0.2 ng/dL. Patients with first postoperative PSA level of ≥0.2 ng/dL had a statistically significant higher risk of biochemical progression and shorter BPFS (odds ratio: 2.41; 95% confidence interval: 1.84-3.10; p<0.001), in univariate and multivariate analyses. Patients with GS ≥8 or T3-4 or positive surgical margins had a statistically significant higher risk of biochemical progression (p<0.001, p=0.003, p<0.001).

Conclusion: Postoperative PSA level higher than ≥0.2 ng/dL was the most important predictor of biochemical progression and BPFS after RP. GS ≥8, T3-4 stages, and positive surgical margins are also related to biochemical progression.

Keywords: Prostate cancer, radical prostatectomy, biochemical progression

Introduction

Prostate cancer (PCa) is the most frequent malignancy and the fifth leading cause of cancer-related death in men worldwide (1). In 2016, 30.000 deaths occurred in the United due to PCa (2). Currently, the gold standard treatment for localized PCa is radical prostatectomy (RP) (3). Prostate specific antigen (PSA) levels are commonly used for the early detection of disease progression after RP.

In the urology guidelines (4,5), biochemical progression is defined as a PSA-level increase above 0.2 ng/mL in two

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consecutive determinations with a minimum two-week interval in PCa patients who underwent RP. Additionally, in a 10-year follow-up study, biochemical progression could occur in up to 30% of PCa patients (6). Preoperative and postoperative PSA measurements, pathological stage, Gleason score (GS), extraprostatic extension (EPE), positive surgical margins, and seminal vesicle invasion (SVI) are considered prognostic factors related to biochemical progression (7,8).

We hypothesized that prediction and early detection of biochemical progression might help clinicians be able to prevent and/or delay disease progression and thereby decrease PCa-specific mortality (9). Therefore, we investigated the biochemical progression status, predictors of biochemical progression and the potential relationship between biochemical progression and prognostic risk factors in PCa patients who underwent RP.

Materials and Methods

Between May 2007 and August 2017, 245 localized PCa patients who underwent RP, were evaluated retrospectively.

This study was approved by our institutional medical ethical committee (2018/145).

Patients with secondary malignancy (5 patients) missed postoperative PSA records (18 patients), and incomplete pathological data (6 patients) were excluded. Consequently, a total of 216 patients were included in the study. Also, none of the patients received neoadjuvant therapy, and surgical procedures were performed the open retropubic method.

All data were obtained from the patient file records of our urology and radiation oncology departments and the institutional electronic database. Preoperative and postoperative PSA measurements, prostate biopsy pathology findings, and RP pathology reports were considered.

Follow-up protocol included PSA measurements; every 3 months for the first year, every 6 months for the second year, and an annual check after 2 years. Biochemical progression was defined as a PSA-level increase above 0.2 ng/mL in two consecutive determinations. Preoperative and postoperative PSA measurements, pathological stage, GS, EPE, positive surgical margins, and SVI were evaluated with univariate and multivariate analyses in patients who had biochemical progression. Disease-free survival and overall survival were defined as the period between the date of operation and progression and the date of diagnosis and last follow-up or mortality, respectively.

Statistical Analysis

Descriptive analyses were performed using the frequencies for the sociodemographic variables. The chi-square test was used to analyze the relationship between parametric values in comparison with categorical data, and Fisher's exact test was chosen to compare two nonparametric groups. The Mann-Whitney U test was used in the analysis of variables that did not show normal distribution. Kaplan-Meier analysis was used to calculate survival probabilities. Logistic regression analysis was applied to the independent variables affecting the dependent variable. The results were analyzed within the 95% confidence interval. A p-value of ≤0.05 was considered statistically significant. All statistical analyses were conducted using SPSS 24.0 for Windows (IBM, Chicago, IL, USA).

Results

The mean age of our patients was 63.1 years (range 47-75). The pathological T-stage was pT1c in 7 (3.2%) patients, pT2a in 9 (4.2%) patients, pT2b in 2 (0.9%) patients, pT2c in 92 (42.6%) patients, pT3a in 32 (14.8%) patients, pT3b in 73 (33.8%) patients and pT4a in 1 (0.5%) patient. 22 (10,2%) patients underwent lymph node dissection. Only 5 (2.3%) patients had lymph node metastasis. The median preoperative and postoperative PSA levels were 12.0 and 0.3 ng/mL, respectively. Pathological and biochemical characteristics are summarized in Table 1.

When classified according to the D'Amico risk classification, 7 (8.4%) of 83 low-risk patients, 21 (22.6%) of 93 medium-risk patients and 11 (27.5%) of 40 high-risk patients had biochemical progression.

The median follow-up was 29 months (range 7.1-128.9 months). The mean survival time for the whole population was 89.6 months, and the 3-year overall survival probability was 87.9%. The mean disease-free survival time was 22.9 months, and the 1-year and 2-year BPFS probabilities were 42.5% and 31.9%, respectively (Figure 1).

No significant correlation was found between overall survival and prognostic risk factors like GS, PNI, EPE, SVI, positive surgical margins, and postoperative first PSA levels. However, patients with first postoperative PSA level of <0.2 ng/dL had significantly longer BPFS than those with the first postoperative PSA level of ≥0.2 ng /dL in both univariate and multivariate analyses (hazard ratio: 2.41; 95% confidence interval: 1.84-3.10; p<0.001).

The first postoperative PSA level was <0.2 ng/dL in 185 (85.6%) patients and ≥0.2 ng/dL in 31 (14.4%) patients. Biochemical progression was observed in 39 (18.1%) patients. Of those, 18 (9.7%) patients had a first PSA level <0.2 ng/dL, and 21 (67.7%) patients had a first PSA level ≥0.2 ng/dL. The mean survival time was 99.2 months and 36.3 months for patients with first postoperative PSA level of <0.2 ng/dL and ≥0.2 ng/dL, respectively. Patients with the first postoperative PSA level of ≥0.2 ng/dL had a significantly higher risk of biochemical

progression compared to those with the first postoperative PSA level of <0.2 ng/dL (p<0.001) (Table 2). Patients with GS ≥8 or T3-4 or positive surgical margins had a statistically significant higher risk of biochemical progression (p<0.001, p=0.003, p<0.001). Mean survival time and biochemical progression according to different pathological risk factors are also shown in Table 2.

Discussion

Our study showed that a postoperative PSA level higher than ≥0.2 ng/dL was the most significant predictor of biochemical progression and BPFS after RP. This result can be interpreted as indicating that adjuvant radiotherapy can be considered for patients with a measurable postoperative PSA value in multidisciplinary councils, and patients can benefit from adjuvant radiotherapy rather than salvage radiotherapy. However, in a recent randomized phase 3 GETUG-AFU 17 study, no difference was shown in terms of progression-free survival between adjuvant and early salvage radiotherapy after RP, and side effects were more common in the adjuvant radiotherapy arm (10). But it should be kept in mind that this study was limited by the lack of statistical power to reach conclusions about efficacy. Therefore, it is still not wrong to say that uncertainties remain regarding the question of which patients can benefit from adjuvant radiotherapy or salvage radiotherapy after RP.

Currently, administering strict postoperative follow-up protocols, discussing these patients in multidisciplinary uro-oncology councils, and collaboration with urologists, especially

Table 1. Patients' characteristics

Parameter	**Value**
Patients	216
Median preoperative PSA (ng/mL)	12.0±15.2
Median postoperative PSA (ng/mL)	0.3±1.5
Biopsy GS	**n (%)**
≤6	127 (59.9%)
7	55 (25.9%)
8	18 (8.5%)
9-10	12 (5.7%)
Pathological GS	**n (%)**
≤6	97 (44.9%)
7	71 (32.9%)
8	22 (10.2%)
9-10	26 (12%)
Pathological tumour stage	**n (%)**
pT1	7 (3.2%)
pT2	103 (47.7%)
pT3	105 (48.6%)
pT4	1 (0.5%)
Surgical margin status	**n (%)**
Positive	111 (51.4%)
Seminal vesicle invasion	**n (%)**
Positive	36 (16.7%)
Perineural invasion	**n (%)**
Positive	159 (73.6%)
Lymph node metastasis	**n (%)**
Positive	5 (2.3%)
BCP	**n (%)**
Positive	39 (18.1%)
Time to BCP (months)	
From diagnosis	22.9
From operation day	19.6

PSA: Prostate specific antigen, pT: Pathological tumour stage, BCP: Biochemical progression, GS: Gleason score

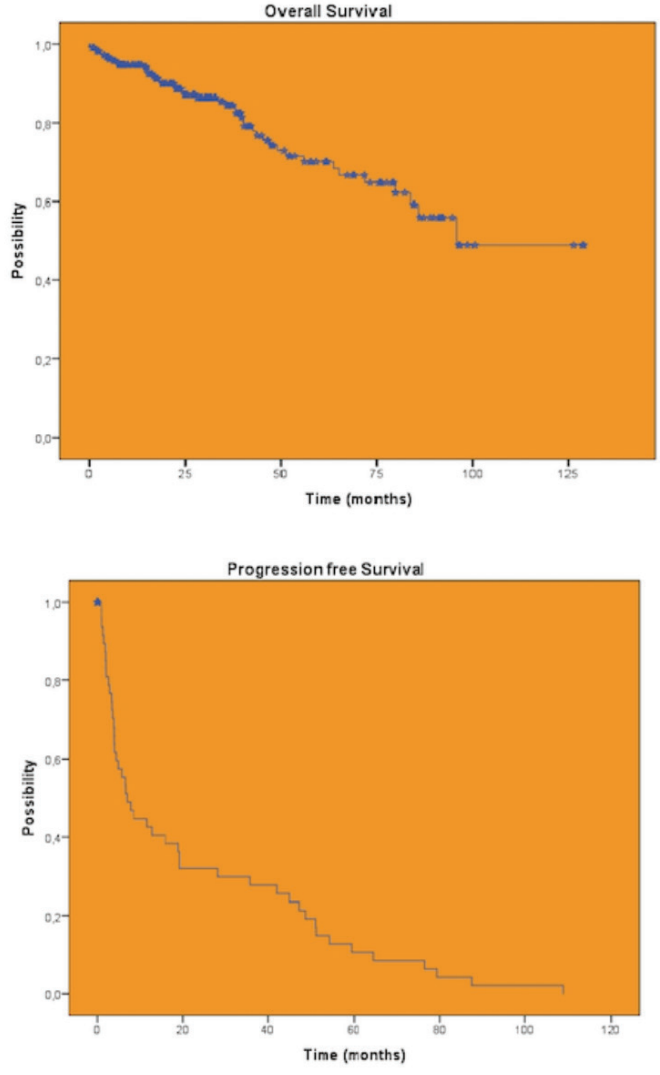

Figure 1. Kaplan-Meier survival analysis

with radiation oncologists, seem to be the most important strategies in daily clinical practice. The long-term outcomes of randomized phase 3 studies with strong statistical power may reduce uncertainties in this regard. Previous studies reported biochemical progression rates ranging from 8% to 30% after RP (11-13). In our study, a biochemical progression rate of 18.1% was found after RP, which is consistent with the literature.

Recent studies with median follow-up times between 15.7 and 26 months reported 2-year BPFS rates ranging between 79.6-86.5% after RP (14,15). Compared to both studies, despite the longer median follow-up time (29 months) that can be considered a strong aspect, we found a lower rate of 2-year BPFS for the whole study population. However, we believe that the high percentage of patients with positive surgical margins, detectable postoperative PSA level and/or pT3-4 disease, and who did not receive adjuvant radiotherapy may explain the low BPFS rate. Because of late recurrence risk, long-term follow-up can be required, especially for the patients with high-risk PCa (16).

In their study including 200 PCa patients who underwent RP, Doherty et al. (17) reported that biochemical progression was directly related to postoperative PSA levels, which should optimally undetectable. Our study, which included a similar number of patients, showed that having a first postoperative PSA level of <0.2 ng/dL was significantly associated with better progression-free survival and progression risk compared with having the first postoperative PSA level of ≥0.2 ng/dL (p<0.001). Additionally, a postoperative PSA level higher than ≥0.2 ng/dL was the most important predictor of biochemical progression and BPFS after RP compared to other parameters. Therefore, these results support the importance of regular PSA measurements after RP.

Epstein et al. (18) showed significant variability in recurrence rates regarding GS of 7, 8, and 9. The prognostic role of GS and the new group grade system was illustrated by Mathieu et al. (19) in a large series of 27,122 PCa patients. According to the new group grading system, the 4-year predicted BPFS rates of PCa patients with grades 1, 2, 3, 4, and 5 were 96.1%, 86.7%, 67.0%, 63.1%, and 41.0%, respectively. In our study, GS was not directly associated with overall survival, but patients with a total GS of ≥8 had a higher risk of biochemical progression compared to those with total GS of ≤7, which correlates with the literature. High total GS can be a predictor of biochemical progression and can be interpreted as the importance of the required collaboration between urologists and radiation oncologists in terms of recurrence and early treatment in PCa patients with high GS or new group grade.

Ball et al. (20) investigated the effect of EPE on biochemical progression and showed that EPE had a negative impact on recurrence-free survival. They also divided EPE into two groups as focal and non-focal, which can be determinants of BPFS. Compared to our findings, although we did not subdivide patients according to EPE, we could not find any correlation between EPE and BPFS. Although the incidence of pT3b cases may decrease with early diagnosis and treatment, it has been shown that SVI could be a precursor for progression (21). On the other hand, Freedland et al. (22) signified that SVI is not a predictor of poor prognosis and cancer-free survival alone without considering other risk factors. In this study, we found that patients with stage pT3-4 have a higher risk of biochemical progression than those with stage pT1-2. Therefore, EPE and SVI were interpreted as risk factors for biochemical progression. Nevertheless, BPFS and overall survival were not directly related to EPE or SVI.

The presence of positive surgical margins is known as a determining factor for recurrence, but it is not obvious that it increases the risk of cancer-specific mortality (23). A recent meta-analysis investigating the relationship between positive

Table 2. Results of uni- and multivariate analyzes in patients with biochemical progression

Variables	n: Patients number	Biochemical progression positive n (%)	Mean survival in months	Univariate analyzes OR (95% CI) p-value	Multivariate analyzes OR (95% CI) p-value
PSA <0.2 PSA ≥0.2	n=185 n=31	18 (9.7%) 21 (67.7%)	99.2 36.3	3.41 (1.81-6.10) <0.001	6.65 (2.16-21.96) <0.001
GS <8 GS ≥8	n=168 n=48	21 (12.5%) 18 (37.5%)	94 68.6	2.66 (1.24-5.48) <0.001	5.57 (1.77-14.42) <0.001
pT1-2 pT3-4	n=110 n=106	10 (9.1%) 29 (27.4%)	103.6 77.3	1.17 (1.08-1.28) 0.003	1.19 (1.08-1.33) 0.003
PSM- PSM+	n=105 n=111	8 (7.6%) 31 (27.9%)	95.4 77.8	2.44 (1.17-5.02) <0.001	5.11 (1.52-12.9) <0.001
PNİ- PNİ+	n=57 n=159	8 (14%) 31 (19.5%)	101.3 83.7	1.01 (0.97-1.07) 0.099	-

GS: Gleason score, pT: Pathological tumor stage, PSA: Prostate specific antigen, PSM: Positive surgical margin, PNI: Perineural invasion, OR: Odds ratio, CI: Confidence interval

surgical margins and biochemical progression showed that the presence of positive surgical margins was an independent risk factor for progression (24). Moreover, in a recent study, Lian et al. (25) reported that the location of positive surgical margins was a significant independent predictor of biochemical progression. Similarly, we found that the presence of positive surgical margins was significantly associated with a higher risk of biochemical progression, both in univariate and multivariate analyses. However, we did not investigate the relationship between biochemical progression and the positive surgical margin location.

The literature contains conflicting results regarding the effect of PNI on survival in patients who underwent RP. Merrilees et al. (26) observed that the presence of PNI does not predict biochemical progression. Similarly, Reeves et al. (27) reported that PNI is not an independent predictor of biochemical progression, whereas Loeb et al. (28) revealed that PNI was a dependent risk factor for biochemical progression. The authors stated that PNI should be evaluated with other risk factors like PSA, GS, and stage, together, as a predictor of progression. Our study also did not show any significant correlation between PNI and biochemical progression. Therefore, we agree that PNI, as a single parameter, might not be adequate to predict biochemical progression.

Study Limitations

The limitations of this study are as follows. Firstly, it was a retrospective study with a relatively small number of patients. Secondly, we did not consider/investigate factors such as PSA doubling time, PSA velocity, and PSA density, which can also help physicians be able to determine biochemical progression. Another limitation of our study is the limited number of lymph node dissections.

Conclusion

In conclusion, postoperative PSA level higher than ≥0.2 ng/dL is the most important predictor of biochemical progression and BPFS in PCa patients after RP. Besides, GS ≥8, T3-4 stages and positive surgical margins are also related to biochemical progression. However, further research with longer follow-up and larger sample sizes must evaluate more specific and precise predictors of biochemical progression.

Ethics

Ethics Committee Approval: This study was approved by our institutional medical ethical committee (Trakya University Faculty of Medicine Scientific Research Ethics Committee - 2018/145).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.M., G.T., E.A., V.Y.Ç., U.K., Concept: S.M., G.T., E.A., V.Y.Ç., U.K., Design: S.M., G.T., E.A., V.Y.Ç., U.K., Data Collection or Processing: S.M., G.T., E.A., V.Y.Ç., U.K., Analysis or Interpretation: S.M., G.T., E.A., V.Y.Ç., U.K., Literature Search: S.M., G.T., E.A., V.Y.Ç., U.K., Writing: S.M., G.T., E.A., V.Y.Ç., U.K.

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Effects of the COVID-19 Pandemic on Bladder Cancer Diagnosis and Treatment Processes; A Turkish Multicenter Study

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What's known on the subject? and What does the study add?

The COVID-19 pandemic adversely affects the health system and it is not known exactly when the pandemic will end. As with many diseases, the diagnosis and treatment of bladder cancer has been adversely affected by this process.

Abstract

Objective: The coronavirus disease-2019 (COVID-19) pandemic effect diagnosis and treatment of certain conditions, including bladder cancer (BC). This study aimed to evaluate the effects of the COVID-19 pandemic on BC diagnosis and treatment.

Materials and Methods: Following the approval of the ethics committee for the study, data of 869 patients who underwent surgery for BC in the 2-year period between March 1, 2019 and February 28, 2021 were analyzed retrospectively. The number of surgeries performed for BC, the time elapsed between symptoms and diagnosis, the treatments performed, and the operative pathologies were compared before and during the COVID-19 pandemic.

Results: During the COVID-19 period, there was a decrease in the total number of BC surgeries compared to the pre-COVID-19 period (p=0.004). It was observed that this decrease was due to a decrease in patients newly diagnosed with BC (p=0.001) as well as the decrease in the number of primary transurethral resection for bladder tumor procedures performed. There was no difference in the tumor stages of the patients at diagnosis (p=0.9). Intracavitary Bacillus Calmette-Guérin therapy use in high-risk non-muscle invasive bladder cancers (NMIBC) patients also decreased (p=0.008) during the pandemic period. It was observed that the time between symptom and diagnosis was longer in MIBC than in NIMBC during both periods (p<0.001).

Conclusion: Diagnosis and treatment of BC have been adversely affected by the ongoing COVID-19 pandemic. The decrease in the number of new diagnoses may not reflect a true decrease in BC incidence, meaning that BC cases that arose during the pandemic are likely to be diagnosed at a more advanced stage.

Keywords: Bladder cancer, COVID-19, diagnosis, treatment

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Introduction

Bladder cancer (BC) is the ninth most common cancer worldwide and 13th in cancer-related death rates (1). BC diagnosis is diagnosed by histopathological evaluation after transurethral resection for bladder tumor (TURBT). Approximately 75% of BCs are diagnosed as non-muscle invasive bladder cancers (NMIBCs) (2). In low-risk NMIBC, cystoscopy is performed to check whether a new tumor has formed following TURBT. In patients with high-risk NMIBC, cystoscopy should be performed periodically following intravesical instillation of the Bacillus Calmette-Guérin (BCG) vaccine to reduce progression and recurrence after TURBT (3). Muscle-invasive bladder cancer (MIBC) constitutes 25% of newly diagnosed BCs (4). Treatment of MIBC involves neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) or bladder-sparing modalities, including radiotherapy and chemotherapy as part of a multimodal treatment plan (5).

In December 2019, the World Health Organization (WHO) reported that pneumonia cases of a previously unknown etiology detected in Wuhan, China, were caused by a coronavirus (SARS-CoV-2), and the disease was named coronavirus disease-2019 (COVID-19). The WHO officially declared COVID-19 a pandemic on March 11, 2020 (6). Across the world, health workers were deployed to combat the pandemic. Intensive care and other units began to be used for COVID-19 patients. The European Association of Urology (EAU) formed a rapid working group to develop adaptive guidelines for dealing with various situations and priorities resulting from the pandemic. This organization defined 4 priority groups for the diagnosis and treatment of BC. Low-priority NIMBC cases could be deferred for up to 6 months, while intermediate priority cases could be deferred for up to 3 months. Cystoscopy with computed tomography urogram and urinary cytology should be performed within 6 weeks for patients with visible hematuria. Emergency diagnosis involving TURBT should be made within <24 hours in patients with clot retention requiring bladder catheterization. As for treatment guidelines, EAU recommendations stated that treatment for lower- priority NIMBC cases could be delayed for 6 months. Intermediate priority cases should be treated within 3 months, while high priority cases should be treated within 6 weeks. For MIBC treatment, the organization stated that delays of up to 12 weeks in the time to RC may be safe (7).

During the COVID-19 pandemic, numerous surgeries had to be postponed to reduce infection transmission, evacuate hospital beds, and allow healthcare workers to deal with the pandemic (8).

In this study, we evaluated the effects of the COVID-19 pandemic in terms of diagnosis and treatment of BC by comparing diagnosis and treatment of BC tumors in the year preceding the COVID-19 pandemic and in the first year of the pandemic.

Materials and Methods

Eight centers from different regions of Turkey and hospitals at different levels participated in the study. The data of 869 patients who underwent surgery for BC in the 2-year period between March 1, 2019 and February 28, 2021 were analyzed retrospectively. The pre-COVID-19 period was defined as the range from March 1, 2019 to February 28, 2020. The COVID-19 period was defined as ranging from March 1, 2020 to February 28, 2021. Patient age, gender, time between symptoms and diagnosis, post-operative pathologies, and treatments received were recorded. Patients were divided into two groups: NIMBC and MIBC. These groups were compared across the pre-COVID-19 period and the COVID-19 period. This study was authorized by the Afyonkarahisar Health Sciences University Research Ethics Committee with the decision number: 2021/293.

Statistical Analysis

Statistical analysis of the study data was done by computer with the IBM SPSS (Statistical Package for the Social Sciences) version 15.0 program. The conformity of the variables to the normal distribution was examined using the Kolmogorov-Smirnov (K-S) test. It was observed that all parameters except age showed abnormal distribution and were calculated using non-parametric tests. Student's t-test was used for age. The Mann-Whitney U test was used to compare paired groups in data that did not show normal distribution. Pearson's chi-square test was used for multivariate comparisons. The results were considered statistically significant when $p<0.05$.

Results

According to their pathology results, the patients included in the study were divided into either the NIMBC or the MIBC group. Of the 869 patients treated during the two-year period, 729 (83.89%) were treated with TURBT for NIMBC. RC due to MIBC was performed on 140 (16.11%) patients. Of the patients, 771 (88.72%) were male and 98 (11.28%) were female. While 473 (77.16%) of 613 patients who were primarily diagnosed with BC were treated with TURBT due to NIMBC, 140 (22.84%) patients underwent RC due to MIBC. Figure 1 shows the number of surgeries performed for BC before and during the COVID-19 period.

In the 1-year period before COVID-19, TURBT was performed on 471 patients. 274 (58.17%) patients received this procedure due to primary BC and 197 (41.83%) due to BC recurrence. The time elapsed between symptoms and the TURBT procedure in patients

diagnosed with primary BC was calculated as 63.19±52.9 (1-180) days. Of the patients with primary diagnosis, 142 (51.83%) were diagnosed with Ta, 132 (48.17%) with T1 BC. 132 (48.17%) high grade and 142 (51.83%) low-grade tumors were detected. 122 (92.42%) of 132 patients diagnosed with T1 BC received intracavitary BCG treatment, whereas 10 (7.58%) patients did not.

In the COVID-19 period, 383 patients underwent TURBT. TURBT was performed on 199 (51.96%) patients due to primary BC and 184 (48.04%) patients due to recurrence. The time elapsed between symptoms and the TURBT procedure in patients diagnosed with primary BC was calculated as 59.82±58.97 (1-180) days. Of the patients with primary diagnosis, 102 (51.3%) were diagnosed with Ta and 97 (48.7%) with T1 BC; 101 (50.76%) high grade and 98 (49.24%) low-grade tumors were detected. 82 (84.54%) of the 97 patients diagnosed with T1 BC received intracavitary BCG treatment, whereas 15 (15.46%) patients did not.

When the pre-COVID-19 and COVID-19 periods were compared in terms of NMIBC diagnosis and treatment, it was observed that 274 patients with primary BC underwent TURBT during the pre-COVID-19 period while 199 patients underwent the same procedure during the COVID-19 period. The number of patients with newly diagnosed NIMBC decreased significantly (p=0.001). As for patients with relapse, TURBT was performed on 197 patients in the pre-COVID-19 period and 184 patients during the COVID-19 period, a statistically insignificant decrease (p=0.5). When the two periods were compared, there was no statistical difference in terms of gender (p=0.15), age (p=0.64), time between symptoms and TURBT (p=0.07), tumor stages (p=0.9) and grade (p=0.72). When the patients who underwent primary TURBT and were diagnosed with T1 BC were compared in terms of intracavitary BCG treatment, it was seen that the rate of receiving treatment before COVID-19 was 92.42%, while the rate of receiving treatment after COVID-19 decreased to 84.54%, a statistically significant decrease (p=0.008). Table 1 shows the information of patients who underwent primary TURBT for NIMBC before and during the period of COVID-19.

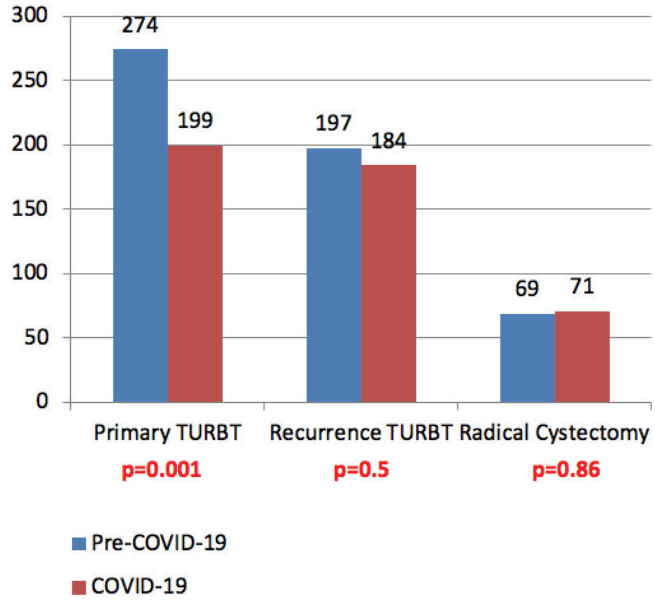

Figure 1. The number of surgeries performed for BC before and during the COVID-19 period

BC: Bladder cancer, COVID-19: Coronavirus disease-2019

During the study period, 140 patients with MIBC underwent RC. 69 of these patients (49.29%) underwent RC during the pre-COVID-19 period and 71 (50.71%) during the COVID-19 period. There was no difference between the two groups in terms of surgery period (p=0.86). The mean age of MIBC patients was 65.63±8.22 (39-88) years. The time between symptom presentation and TURBT was calculated as 91.55±87.40 (3-365) days. The time between TURBT or NAC and RC was calculated as 108.96±89.06 (8-365) days. While 122 (87.14%) patients with MIBC did not receive NAC before RC, 18 (12.9%) patients received NAC before RC. T2 RC was performed in 97 (69.28%) patients, T1 RC in 33 (23.57%) patients, and RC for carcinoma *in situ* (CIS) in 10 (7.15%) patients. RC pathology was T0 in 22 (15.7%) patients, CIS in 9 (6.4%) patients, T1 in 21 (15.0%) patients, T2 in 32 (22.8%) patients, T3 in 30 (21.5%) patients, and T4 in 26 (18.6%) patients. Lymph nodes were negative in 105 (75%) patients, and lymph nodes were positive in 35 (25%) patients. When the pre-COVID-19 period and the COVID-19 period were compared, no difference was found between the two groups in terms of gender (p=0.2), age (p=0.36), time between symptoms and TURBT (p=0.6), time between TURBT or NAC and RC (p=0.39), TURBT pathologies before RC (p=0.5), RC stage (p=0.74), lymph node positivity (p=0.770) and NAC administration (p=0.13). Although there was no statistical difference in NAC administration, there was a prominent decrease in the COVID-19 period compared to the pre-COVID-19 period (p=0.13). Table 2, the information of patients who underwent RC due to MIBC before and during the period of COVID-19 is given.

When patients with NIMBC and patients with MIBC were compared in terms of the time between the onset of symptoms and initial diagnosis during both periods, the MIBC duration was 91.55±87.40 (3-365) days, while the NIMBC duration was 58.66±52.41 (1-180) days, a statistically significant difference (p<0.001).

Discussion

The WHO declared COVID-19 a pandemic on March 11, 2020, and the first official case in Turkey was detected on the same day. Around the world, increasing numbers of beds and intensive care

units have begun to be used for COVID-19 patients. Healthcare workers and other resources were allocated to the fight against the pandemic, causing many non-urgent operations to be postponed. Curfews due to the COVID-19 pandemic, warnings to stay home unless absolutely necessary, and people's concerns about getting sick decreased the number of patients seeking diagnosis and treatment in hospitals. The number of cancers diagnosed during the COVID-19 period was significantly lower than that in the pre-COVID-19 period (9,10). Tulchiner et al. (11) reported that they observed a decrease in the diagnosis of newly diagnosed BC in the first six months of the pandemic, and that pre-pandemic diagnostic numbers were reached because of an increase in diagnoses in the following six months. It is known that men are more likely to contract COVID-19 than women and are more likely to become severely ill. COVID-19 is more severe in the elderly than in the young (12). Since BC is a cancer that is more common in men and people over the age of 55, it was expected that its diagnosis and treatment would be affected during the COVID-19 period.

Tulchiner et al. (11) compared the one-year period before COVID-19 with the first one-year period of COVID-19 and reported that there was a decrease in the number of surgeries for BC in the first 6-month period but no difference over the entire year due to an increase in the following 6-month period. In NIMBC patients, they found that tumor stage and grade increased during the COVID-19 period compared to before. To the best of our knowledge, this is the first study comparing the pre-COVID-19 period and the first one-year period of the COVID-19 pandemic with regards to BC (11). In our study, when the pre-COVID-19 period and the COVID-19 period were compared, we found that the total number of BC-related surgeries performed during the COVID-19 period decreased. It was observed that this decrease was due to a decrease in the number of primary TURBT procedures performed, especially for newly diagnosed BC. There was no difference in tumor stage and grade in NIMBC patients. Based on these results, we expect to see an increase in the number of newly diagnosed patients and the diagnosis of tumors of advanced stage and grade in Turkey.

Intravesical BCG induction and maintenance therapy in high-risk NMIBC is an effective treatment that reduces the recurrence and progression of BC (13,14). The latest urology guidelines for the COVID-19 pandemic period recommend that intravesical BCG therapy should not be delayed in high-risk NMIBC (7). In terms of reducing the number of hospital admissions during the COVID-19 epidemic, it has been reported as an expert opinion that two, rather than three, doses of BCG maintenance therapy can be administered for high-risk NMIBC patients and that the treatment can be terminated in patients receiving maintenance BCG therapy for more than 1 year (15). A lower incidence and mortality rate of COVID-19 has been reported in countries with high rates of BCG vaccination. It is unclear whether exposure to intravesical BCG is protective against COVID-19 (16). Akan et al. (17) compared the patient group receiving BCG treatment for BC during the COVID-19 epidemic with the same age group not receiving BCG treatment and reported that COVID-19 infection was more common in patients receiving BCG treatment. They stated that this may be due to recurrent hospital admissions during the pandemic period. Intravesical BCG therapy in high-risk NMIBC is an extremely effective treatment in reducing recurrence

Table 1. The information of of patients who underwent primary TURBT for NIMBC before and during the period of COVID-19

	Pre-COVID-19	COVID-19	p
Gender			
Male	247 (90.1%)	171 (85.9%)	p=0.15
Female	27 (9.9%)	28 (14.1%)	
Age	66.34±10.65	66.82±11.81	p=0.64
Time between symptoms and TURBT (day)	63.19±52.9 (1-180)	59.82±58.97 (1-180)	p=0.07
Primary TURBT stage			
Ta	142 (51.83%)	102 (51.26%)	p=0.9
T1	132 (48.17%)	97 (48.74%)	
Tumor grade			
Low grade	132 (48.17%)	98 (49.24%)	p=0.72
High grade	142 (51.83%)	101 (50.76%)	
Intracavitary therapy (T1 tumor)			
Yes	122 (92.42%)	82 (84.54%)	**p=0.012**
No	10 (7.58%)	15 (15.46%)	
Total patients	274	199	**p=0.001**

TURBT: Trans urethral resection of bladder tumour, NIMBC: Non-muscle-invasive bladder cancer, COVID-19: Coronavirus disease-2019

and progression, but it causes recurrent admissions of patients to the hospital which, during the COVID-19 outbreak, may be associated with a greater likelihood of exposure to COVID-19. In our study, an increase was observed in the number of patients who did not receive treatment during the COVID-19 period compared with the pre-COVID-19 period. This situation may have arisen because patients did not want to make repeated visits to the hospital during the pandemic period. This decrease in treatment may increase recurrence and progression. Intravesical BCG therapy should be continued with necessary precautions against COVID-19 being taken in patients with high-risk NMIBC. Patients should be adequately informed about the importance of treatment.

Tulchiner et al. (11) reported that the number of surgeries performed for MIBC and tumor stage was not affected by the COVID-19 period. Similarly, there was no change in the number of surgeries for MIBC and tumor stage in the pre-COVID-19 period and the COVID-19 period. Studies comparing RC after NAC and RC alone in MIBC found improved patient survival after NAC, and RC is recommended after NAC as a standard treatment (18,19). Griffiths et al. (20) reported that NAC increased 5-year survival by an average of 6%. In their meta-analysis, Li et al. (21) compared RC after NAC and RC alone and reported that there was no significant difference in average survival. Tulchiner et al. (11) it has been reported that the rate of NAC intake before RC was 50% before COVID-19 and decreased to 40% during the COVID-19 period, but there was no difference between the two periods. Only 18 (12.86%) of 140 patients treated for MIBC during the two-year period included in our study underwent RC after NAC. Twelve of these patients underwent the procedure during the pre-COVID-19 period, while 6 underwent the procedure during the COVID-19 period following NAC treatment. In our study, the number of patients who accepted NAC treatment in MIBC was found to be extremely low. Although not statistically significant during the COVID-19 period, the number of patients receiving NAC decreased by half. Although RC is the recommended treatment following NAC for MIBC, it was observed that its use was limited in practice due to its low effect on life expectancy and side effects related to NAC. It was thought that there was a decrease in the rate of NAC application due to the desire to

Table 2. The information of patients who underwent RC due to MIBC before and during the period of COVID-19

	Pre-COVID-19	COVID-19	p
Gender			
Male	58 (84.1%)	65 (91.5%)	p=0.2
Female	11 (15.9%)	6 (8.5%)	
Age	66.3±9.56	64.96±8.04	p=0.36
Time between symptoms and TURBT (day)	103.8±102.01	79.65±69.05	p=0.6
TURBT stage before cystectomy			
CIS	4 (5.8%)	6 (8.5%)	p=0.5
T1	19 (27.5%)	14 (19.7%)	
T2	46 (66.7%)	51 (71.8%)	
NAC			
Yes	12 (17.4%)	6 (8.5%)	p=0.13
No	57 (82.6%)	65 (91.5%)	
Time between TURBT or NAC and RC (days)	93.9±68.9	123.6±103	p=0.39
RC stage			
T0	10 (14.5%)	12 (16.9%)	p=0.74
CIS	6 (8.7%)	3 (4.2%)	
T1	10 (14.5%)	11 (15.5%)	
T2	16 (23.2%)	16 (22.5%)	
T3	16 (23.2%)	14 (19.7%)	
T4	11 (15.9%)	15 (21.2%)	
Lymph node positivity			
Yes	18 (26.1%)	17 (23.9%)	p=0.770
No	51 (73.9%)	54 (76.1%)	
Total patients	69	71	p=0.86

TURBT: Trans urethral resection of bladder tumour, NIMBC: Non-muscle-invasive bladder cancer, RC: Radical cystectomy, COVID-19: Coronavirus disease-2019, NAC: Neoadjuvant chemotherapy

reduce hospitalizations due to the COVID-19 pandemic or the infection concerns of the patients.

Boeri et al. (22) patients being studied with MIBC (cT2-T4) and reported that a delay of more than 10 weeks after the last NAC administration and RC resulted in worse outcomes for cancer-specific and overall mortality. Similarly, EAU guidelines recommend RC in MIBC to be performed within 12 weeks (7). The time between the last TURBT or NAC and RC of the patients included in our study was calculated as 108.96±89.06 days (8-365). When the two periods were compared, it was observed that the duration was longer in the COVID-19 period, although there was no statistically significant difference between the pre-COVID-19 period and the COVID-19 period. Note that the time between TURBT or NAC and RC in the patients included in the study is longer than in the existing literature, and this may have negative effects on progression and overall survival. Patients who are recommended to have RC due to MIBC should be given sufficient information about NAC and the importance of early intervention in terms of survival should be explained.

When the time elapsed between the onset of symptoms and diagnosis in all patients included in the study was compared, it was observed that the time between symptom onset and diagnosis was longer in MIBC than in NIMBC. This shows the importance of early diagnosis in a disease such as BC, where treatment changes according to the disease stage.

Our study is important because it is a multicenter study examining the effect of the COVID-19 pandemic on the diagnosis and treatment of BC in a 1-year period in Turkey and is the first Turkish study on this subject. A review of the literature shows that our study is the first to demonstrate that administration of intravesical BCG therapy in NIMBC is adversely affected by COVID-19.

Study Limitations

There were some limitations to our study. The study design was retrospective and patients whose file information could not be accessed were not included in the study. Therefore, prospective studies with large BC patient populations will be needed to understand the pandemic's effects on BC diagnosis and treatment.

Conclusion

In our study, a decrease was found in the number of TURBT procedures performed for primary BC due to the decrease in hospital visits during the COVID-19 period. A decrease was observed in the number of high-risk NIMBC patients receiving intravesical BCG therapy during the COVID-19 period. Although the guidelines recommended NAC before RC for MIBC, our results indicate that this recommendation was not followed sufficiently.

The COVID-19 pandemic is ongoing, and it is clear that it has adversely affected the diagnosis and treatment of BC in Turkey. We predict that BC will be diagnosed at higher stages and grades due to the ongoing pandemic situation.

Ethics

Ethics Committee Approval: This study was authorized by the Afyonkarahisar Health Sciences University Research Ethics Committee with the decision number: 2021/293.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.K., O.G., A.Ö., S.Z.S., B.Y.E., C.B., M.A.K., Concept: A.G., A.D., S.Z.S., A.E.D., Design: A.G., B.B., Ü.Ö., E.E., Data Collection or Processing: B.B., İ.K., O.G., Ü.Ö., A.Ç., Analysis or Interpretation: İ.K., A.Ö., A.E.D., Literature Search: A.D., İ.U., E.E., Writing: A.G., M.K., İ.U., A.Ç.

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ORIGINAL RESEARCH
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Comparison of Preoperative Urine Culture and Intraoperative Renal Pelvis Culture in Patients Who Underwent Flexible Ureterorenoscopy

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What's known on the subject? and What does the study add?

Urine culture was recommended before any type of stone surgeries. The urine culture generally collected from bladder and infectious complications could occurs even the bladder urine culture was negative. The studies suggested that bladder urine culture do not correlate with pelvic urine culture and pelvic urine culture were better predictors for infectious complications and sepsis. However, the pelvic urine culture could not collect routinely.

Our study demonstrated that preoperative bladder urine culture may not shows pelvic urine culture colonization and in patients with preoperative hydronephrosis and low tomographic pelvic urine density prone to positive pelvic urine culture. Our study suggest that preoperative antibiotic prophylaxis could be administered to patients who had preoperative hydronephrosis and low pelvic urine density.

Abstract

Objective: There is no correlation between the preoperative bladder urine culture (PBUC) sensitivity test and the results of the renal pelvic urine culture (RPUC) test.

Materials and Methods: A total of 129 patients who underwent f-URS included the study. Preoperatively, PBUC was collected in all cases, and RPUC was taken when starting the surgery.

Results: In PBUC, there was growth in 25 (19.4%) patients and in RPUC, there were only in 35 (27.1%) cases. Preoperative tomographic urine density at the renal pelvis [odds ratio (OR): 0.848, p<0.001], grade ≥2 hydronephrosis (OR: 18.970, p=0.001), and lower calyceal stone location (OR: 0.033, p=0.017) were determined as independent predictive factors for RPUC growth. The ability of tomographic urine density to foresee positive RPUC positivity was determined to be 0.858 (0.780-0.936). The tomographic urine density threshold for RPUC positivity prediction was 4.5, with 80% sensitivity and 77.7% specificity.

Conclusion: PBUCs do not necessarily mean accurate colonization. Obtaining renal pelvis urine samples is important for managing postoperative infectious complications. Patients that have preoperative hydronephrosis and nominal tomographic urine density could develop RPUC even if the preoperative bladder urine samples are negative.

Keywords: Bladder urine culture, Renal pelvic urine culture, RIRS

Introduction

The preoperative bladder urine culture (PBUC) test is a part of the generally applied procedure before any type of stone operation. Previous studies have shown that a positive PBUC indicates an increased possibility of postoperative infectious complication development (1). However, infectious complications can occur even in the presence of prophylactic antibiotics and a negative PBUCs (2,3).

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The results of the PBUC susceptibility test and pelvic urine culture (RPUC) analysis do not correlate well with each other (4). Growth in RPUC has been shown to be a significant signal of infection development following endoscopic operations (5). Despite antibiotic treatment or preoperative antibiotic prophylaxis (PAP), growth may occur in cultures taken intraoperatively, or postoperative urinary tract infection may develop depending on factors such as obstruction and antimicrobial resistance in the urinary system (6,7). If the type of the bacteria in the upper urinary system can be predicted before the operation using any method, patients can be treated with a more appropriate antibiotic or appropriate prophylaxis before the intervention/operation. While the American Urological Association (AUA) guidelines suggest that PAP should be applied to all patients to reduce urosepsis after flexible ureterorenoscopy (f-URS), the European Association of Urology (EAU) recommends that it should only be given to patients with a high risk of infection (8-10). The role of cultures taken during f-URS has not yet been fully revealed. Sepsis is the most terrifying infectious complication of f-URS that may result in intensive care unit hospitalization and even mortality. In case of post-operative fever and/or sepsis, a positive culture which was obtained from the renal pelvis is critical for arranging proper antibiotherapy.

In this study, we evaluated the disagreement between preoperative PBUC analysis and RPUC obtained at the outset of the f-URS operation and determined the predictability of a positive RPUC based on associated preoperative markers.

Materials and Methods

After obtaining the approval of the ethics committee (01.04.2021.01), a retrospective analysis was conducted based on a database that was prospectively collected from 129 patients who received f-URS on renal and proximal ureteral stones in two different medical facilities from 2017 to 2020. All the patients were evaluated preoperatively using 64-detector non-contrast computed tomography (NCCT). The renal pelvis urine density [hounsfield units (HU)] of the patients with hydronephrosis was measured using the technique described by Basmaci and Sefik (11). Wall thickness at the location of the stones in the proximal ureter and pelvis was measured and recorded as defined by Sarica et al. (12). Stone parameters evaluated consisted of number, size (measured as the longest diameter of the stone in NCCT in axial or reconstructed coronal planes), and CT attenuation value. Patient data obtained included age, gender, body mass index, history, physical examination findings, and specific comorbidities. PBUC and RPUC were performed using 5% sheep blood agar and eosin-methylene blue agar and incubated at 37 °C for 18-24 h. The results are evaluated (13,14). The bacterial growth of ≥105 cfu/mL was determined as positive.

PBUC was obtained from the patients, and if negative, intravenous cefazolin was administered as PAP with the induction of anesthesia according to the EAU guidelines (9). In the case of a positive PBUC, the operation was not performed until a negative PBUC was achieved with appropriate antibiotherapy. Patients with a previous history of urological operation, urinary system catheterization, or congenital urinary system anomalies, patients using corticosteroid drugs, and cases in which a Double-J (DJ) stent was placed for passive dilation were excluded from the study.

All operations were performed by experienced surgeons in the lithotomy position under general anesthesia. First, ureteroscopy was performed using a semirigid ureteroscope (8 Fr; Karl Storz, Tuttlingen, Germany) to provide active dilatation and place a guidewire. At this stage, approximately 10 cc of available urine sample was taken from the renal pelvis for the RPUC analysis. Cultures were obtained with a semi-rigid ureterorenoscopy for proximal ureter stones either after the stone was slightly broken or pushed into the pelvis. In other cases, cultures were obtained using a flexible ureterorenescope after it reached the pelvis. If the stone did not allow the progression of ureteroscopy or guide wire through the ureter, these patients were excluded from the study. Also, if the stone was only slightly broken, or if the stone could be pushed into the pelvis then, the culture was taken at that stage. Afterwards, according to the surgeon's preference for all procedures, a ureteral access sheath (UAS) (Flexor 9.5/11.5Fr or 12/14Fr, Cook Medical Bloomington, IL, USA, Navigator 11/13Fr, Boston Scientific, Natik, MA, USA) was placed over the guidewire under fluoroscopic control. However, we prefer not use UAS mostly. Also, in cases where UAS could not be placed, the flexible scope was back-loaded over a guidewire and procedure was performed. If the flexible ureteroscope could not reach the kidney, a DJ stent was placed and the procedure was postponed by 2 weeks. In all patients, f-URS was performed using a flexible ureteroscope (Flex-X2, Karl Storz Endoscope, Tuttligen, Germany) and a 200/273-micron Holmium laser lithotriptor. The procedure was terminated after stone-free status was confirmed by both ureteroscopic inspection and fluoroscopy (leaving only ungraspable gravel or fragments <2 mm), in cases of bleeding, or if deemed necessary by the surgeon. To minimize perioperative complications, the operation was stopped if 120 min. elapsed. At the end of the operation, a DJ stent or a ureteral catheter was placed according to the surgeon's preference. On the first postoperative day, the patients were discharged if there was no hematuria or fever.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 23 for Windows. Categorical data are presented as numbers and percentages. The compliance of continuous data with a normal distribution was evaluated

with the Shapiro-Wilk test. Continuous data conforming to non-normal distribution was presented as median and interquartile range (IQR) values. Pearson's chi-square or the exact test was used in the comparison of categorical data. The Mann-Whitney U test was used in the comparison of continuous variables. Univariate regression analysis was performed to evaluate the factors associated with a positive pelvis urine culture, and the parameters that were found to be significant at this stage were further examined using the multivariate analysis. A value of $p<0.05$ was considered statistically significant.

Results

Demographic Data

The characteristics of the patients and stones are shown in Table 1. The median age of the patients was 69 years, and the female/male ratio was 61 (47.3%)/68 (52.7%). The median stone size and median stone density (HU) were 90 mm^2 and 1,039, respectively. The most frequent primary location of the stones was the pelvis (35.7%) stones. The median operation time was 65 minutes. While postoperative stents were placed in 77.5% of the patients, a ureteral catheter was required in 9.3%. The stone-free rate was 69.7%. Seven (5.4%) patients had postoperative fever, and one (0.7%) developed sepsis.

Group Comparisons

The frequencies and rates of microorganisms grown in urine cultures are presented in Table 2. The PBUC analysis revealed positivity in 25 (19.4%) patients, and the most common microorganism was identified as *Escherichia coli* (9.3%). According to the perioperative RPUC, 35 (27.1%) patients had growth. *Pseudomonas aeruginosa* (10.1%) was the most common organism identified in the RPUC analysis. When the bacteriological analysis results of RPUC and PBUC were compared, it was observed that the same organism was isolated only from seven patients (14.3%). Growth was detected in both the pelvic and urinary cultures of 12 (24.5%) patients.

Table 3 presents a comparison of the factors associated with a positive RPUC. A higher rate of growth was seen in the RPUC of patients with preoperative hydronephrosis ($p<0.001$). The ureteral wall was found to be thicker in RPUC-positive patients ($p<0.001$). The presence or absence of growth was evaluated according to stone location, and the subgroup analysis revealed less growth in lower, middle and upper pole stones while multicalyceal stones had significantly greater growth ($p=0.011$). Increased stone size and decreased preoperative tomographic urine density (HU) were associated with a positive RPUC ($p<0.001$ for both).

The multivariate analysis of factors associated with a positive RPUC and postoperative fever is shown in Table 4. Multivariate logistic regression was used to evaluate potential signals for predicting a positive RPUC. Preoperative tomographic urine density [odds ratio (OR): 0.848, $p<0.001$], grade ≥2 hydronephrosis (OR: 18.970, $p=0.001$) and lower calyceal location (OR: 0.033, $p=0.017$) were found to be independent predictive markers for a positive RPUC. Receiver operating

Table 1. Demographic parameters

		Value
Age[a]		69.0 (66.0-72.0)
BMI[a]		25.4 (23.5-27.6)
Gender[b]	**Female**	61 (47.3%)
	Male	68 (52.7%)
History of ESWL[b]	**Absent**	100 (77.5%)
	Present	29 (22.5%)
Metabolic syndrome[b]	**Absent**	88 (68.2%)
	Present	41 (31.8%)
Stone location[b]	**Lower pole**	20 (15.5%)
	Middle pole	5 (3.9%)
	Upper pole	5 (3.9%)
	Pelvis	46 (35.7%)
	Proximal ureter	26 (20.1%)
	Multiple calyxes	27 (20.9%)
Preoperative Hydronephrosis[b]	**None**	45 (34.9%)
	Grade 1	59 (45.7%)
	Grade 2	22 (17.1%)
	Grade 3	3 (2.3%)
Ureteral wall thickness[a] (mm)		1.90 (1.7-2.4)
Preoperative tomographic urine density[a] (HU)		6.0 (-4.0-9.0)
Stone density[a] (HU)		1039.0 (751.0-1223.0)
Stone size[a] (mm^2)		90.0 (80.0-130.0)
Postoperative stent[b]	**None**	17 (13.2%)
	Ureteral catheter	12 (9.3%)
	Double-J stent	100 (77.5%)
Postoperative complication[b]	**None**	121 (93.7%)
	Fever	7 (5.4%)
	Perforation	0
	Sepsis	1 (0.7%)
	Death	0
Operation time[a] (min)		65.0 (50.0-70.0)
Hospitalization date[a] (day)		2.0 (2.0-3.0)
Residual fragment[b]	**Absent**	90 (69.7%)
	Present	14 (10.8%)
	CIRF	25 (18.6%)

[a]Data expressed as median and interquartile range.
[b]Data expressed as count and frequency, BMI: Body mass index, ESWL: Extracorporeal shock wave lithotripsy, HU: Hounsfield unit, CIRF: Clinically insignificant residual fragment, min: Minute

characteristic analysis was used to evaluate the predictive ability of tomographic urine density for determining positive RPUC. The threshold for tomographic urine density in predicting RPUC positivity was determined to be 4.5 with a sensitivity of 80%, specificity of 77.7% and an area under the curve of 0.858 (0.780-0.936) (Figure 1).

Additionally, in univariate analysis; increased age, prolonged operation time, decreased preoperative tomographic urine density in CT, increased hydronephrosis grade and stone size, multicalyxial stone location, positive RPUC and UAS usage were statistically significantly associated with postoperative fever. There was no significant correlation between PBUC and postoperative fever. In the multivariate analysis, only the operation time was found as an independent prediction factor (OR: 1.149, p=0.037).

Discussion

PBUC analysis is a standard procedure performed before any stone surgery and is very important for selecting patients undergoing f-URS to receive prophylaxis and for predicting the risk of postoperative infection complications (1,5). In a previous meta-analysis, a single preoperative antibiotic dose was shown to reduce postoperative pyuria and bacteriuria, but it did not statistically significantly reduce postoperative urinary tract infections (15). Theoretically, the effect of PAP is considered to prevent the spread of bacteria during the stone operation; however, the actual efficacy of this application remains uncertain. In our study, PBUC growth was present in 19.4% of the patients. Although there was no growth in the post-treatment control cultures of these patients, it was observed that bacteriuria persisted in RPUC in 27.1%. Considering this information, it has been deemed necessary to establish proper prophylaxis and treatment strategies in patients with a positive PBUC to prevent infectious complications. The AUA guidelines recommend PAP to all patients to reduce urosepsis after f-URS while EAU states that PAP is indicated only for those with a high risk of infection (8-10).

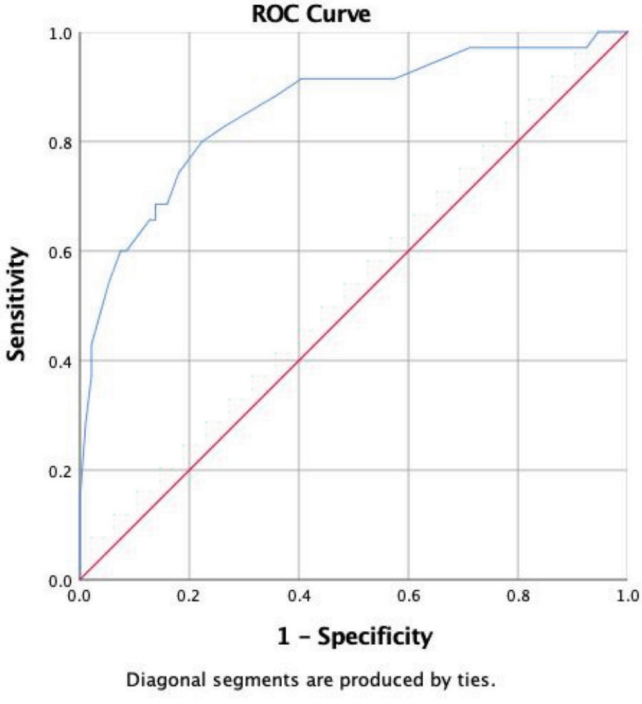

Figure 1. Receiver operating characteristic (ROC) curve plot of pelvis urine density in predicting pelvis culture positivity (AUC: 0.858)

In another previous study, the efficacy of PAP and preoperative antimicrobial treatment were compared using the cultures taken intraoperatively, and growth was found in intraoperative cultures in only 3.2% of the patients who were negative for PBUC and were administered PAP. In the same study, 43.3% of the cultures taken intraoperatively from patients with a positive PBUC had growth despite appropriate antibiotherapy; i.e., an existing or different microorganism managed to survive. That study demonstrated the efficacy of preoperative antimicrobial therapy to be 71.6% (16). In our study, we found that growth in pelvic urine culture in some patients is different from bladder urine culture. Previous studies, the reason for this is not fully explained. We think that the growth of different microbial cultures can be caused by urinary obstruction, biofilm, or antimicrobial resistance, inadequate or inappropriate antimicrobial and prophylaxis usage. Even though we sterilized our reusable f-URS before each operation, we believe that it is still possible that there can still be residual microorganisms that remain in the device and that may be the source of positive RPUC cultures that we examined in some patients.

Table 2. Bacteriological analysis of culture

Preoperative bladder urine culture[b]	**None**	104 (80.6%)
	Escherichia coli	12 (9.3%)
	Pseudomonas aeruginosa	6 (4.7%)
	Staphylococcus aureus	1 (0.8%)
	Enterecocus	4 (3.1%)
	Proteus mirabilis	0
	Klebsiella	1 (0.8%)
	Candida albicans	1 (0.8%)
Perioperative pelvis urine culture[b]	***None***	94 (72.9%)
	Escherichia Coli	6 (4.7%)
	Pseudomonas aeruginosa	13 (10.1%)
	Staphylococcus aureus	4 (3.1%)
	Enterecocus	9 (7.0%)
	Proteus mirabilis	1 (0.8%)
	Klebsiella	2 (1.6%)

Table 3. Comparison of the patients with and without a positive pelvis urine culture				
		Pelvis urine (Negative)	Pelvis urine (Positive)	p-value
Agea (years)		69.0 (66.0-71.0)	69.0 (65.0-74.0)	0.686#
BMI*		25.4 (23.1-27.5)	25.8 (23.9-29.0)	0.176#
Gender[b]	**Female**	48 (51.1%)	13 (37.1%)	0.159*
	Male	46 (48.9%)	22 (62.9%)	
History of ESWL[b]	**Absent**	72 (76.6%)	28 (80.0%)	0.680*
	Present	22 (23.4%)	7 (20.0%)	
Metabolic syndrome[b]	**Absent**	66 (70.2%)	22 (62.9%)	0.425*
	Present	28 (29.8%)	13 (37.1%)	
Stone location[b]	**Lower pole**	19 (20.2%)[a]	1 (2.8%)[b]	**0.010^**
	Middle pole	5 (5.3%)[a]	0[a]	
	Upper pole	5 (5.3%)[a]	0[a]	
	Pelvis	33 (35.1%)[a]	13 (37.1%)[a]	
	Proximal ureter	18 (19.1%)[a]	8 (22.8%)[a]	
	Multiple calyxes	14 (14.8%)[a]	13 (37.1%)[b]	
UAS usage	**No**	79 (84.0%)	25 (71.4%)	0.107*
	Yes	15 (16.0%)	10 (28.6%)	
Preoperative bladder urine culture[b]	**None**	80 (85.1%)[a]	24 (68.6%)[b]	**0.026^**
	Escherichia coli	9 (9.6%)[a]	3 (8.6%)[a]	
	Pseudomonas aeruginosa	3 (3.2%)[a]	3 (8.6%)[a]	
	Staphylococcus aureus	0[a]	1 (2.9%)[a]	
	Enterecocus	1 (1.1%)[a]	3 (8.6%)[b]	
	Proteus mirabilis	0[a]	0[a]	
	Klebsiella	0[a]	1 (2.9%)[a]	
	Candida albicans	1 (1.1%)[a]	0[a]	
Preoperative hydronephrosis[b]	**None**	43 (95.5%)	2 (4.5%)	**<0.001***
	Grade 1	45 (76.3%)	14 (23.7%)	
	>Grade 2	6 (24.0%)	19 (76.0%)	
Preoperative tomographic urine density* (HU)		8.0 (6.0-11.0)	-7.0 (-10.0-3.0)	**<0.001#**
Stone densitya (HU)		1092.0 (800.0-1250.0)	950.0 (728.0-1150.0)	0.078#
Stone size* (mm^2)		90.0 (80.0-110.0)	110.0 (90.0-190.0)	**<0.001#**
Postoperative complication[b]	**None**	92 (97.8%)	29 (89.2%)	**0.006^**
	Fever	2 (2.2%)	5 (14.3%)	
	Perforation	0	0	
	Sepsis	0	1 (2.9%)	
	Death	0	0	
Preoperative white blood cell count* ($10^3/\mu L$)		8.0 (6.7-9.8)	7.9 (6.3-9.0)	0.401#
Preoperative neutrophil count* ($10^3/\mu L$)		4.3 (3.6-6.1)	4.2 (3.8-5.8)	0.824#
Operation time* (min)		60.0 (45.0-70.0)	70.0 (60.0-75.0)	**0.003#**
Hospitalization date* (day)		2.0 (2.0-3.0)	2.0 (2.0-4.0)	0.379#
Residual fragment[b]	**Absent**	68 (72.3%)	22 (62.9%)	0.352*
	Present	8 (9.0%)	6 (17.1%)	
	CIRF	18 (19.1%)	7 (20.0%)	

[a]Data expressed as median and interquartile range.
[b]Data expressed as count and frequency, *Pearson chi-square test, # Mann-Whitney U test.
*Fisher's exact test, Bold values indicate statistical significance, BMI: Body mass index, CIRF: Clinic insignificant residual fragment, HU: Hounsfield unit

He et al. (17) administered cefuroxime PAP for three days preoperatively to patients without preoperative urine culture growth and observed reduced growth in RPUC. The authors emphasized that preoperative antibiotic administration should be adjusted according to the risk level and suggested that RPUC showed bacterial colonization more effectively. In our study, we determined that even if the patients with a positive PBUC were treated, some had growth RPUC. However, PBUC positivity is not an independent predictive factor for the possibility of growth in RPUC. The efficacy of PAP or antimicrobial treatment before surgery was limited against bacteria that we could not detect preoperatively. Therefore, we consider that even if PBUC is negative in patients scheduled to undergo f-URS, we should be prepared for the possibility of a positive RPUC in some patients to ensure that appropriate antibiotherapy is started promptly to prevent alarming complications, such as sepsis.

The literature shows that there is significant growth in intraoperative cultures in patients with renal stones and a history of obstructive pyelonephritis (16). In our study, a statistically significant relationship was found between stone location and the presence of hydronephrosis and RPUC positivity. If a stone is in a location that can cause hydronephrosis (e.g., pelvis and/or proximal ureter), it can explain a higher rate of growth in RPUC. In patients with urinary system obstruction, infection or bacterial colonization in the upper urinary tract may continue even in the presence of

Table 4. Factors affecting renal pelvis urine culture positivity and postoperative fever

[a]Renal pelvis urine culture positivity	OR	95% CI		p
		Lower	Upper	
PBUC	2.191	0.532	9.026	0.278
Stone size, mm²	1.003	0.994	1.014	0.494
Stone density, HU	0.999	0.997	1.001	0.425
Preoperative tomographic urine density, HU	0.848	0.782	0.919	**<0.001**
Stone location				
Other	Ref			
Lower calyx	0.033	0.002	0.543	**0.017**
Multiple calyxes	1.823	0.401	8.286	0.437
Preoperative hydronephrosis				
Grade 0	Ref			
Grade I	0.624	0.148	2.629	0.660
Grade II	18.970	3.406	105.657	**0.001**
[b]Postoperative fever				
Age, years	1.031	0.886	1.200	0.692
Preoperative tomographic urine density, HU	0.920	0.770	1.100	0.362
Preoperative hydronephrosis				
Grade 0	Ref			
Grade I	0.122	0.001	10.204	0.352
Grade II	0.408	0.019	8.535	0.563
Stone size, mm²	1.011	0.984	1.039	0.429
Stone location				
Other	Ref			
Multiple calyxes	1.205	0.064	22.526	0.901
Operation time, min	1.149	1.008	1.309	**0.037**
PBUC	0.168	0.004	6.609	0.341
RPUC	10.188	0.145	713.392	0.284
UAS usage	0.397	0.021	7.624	0.540

[a]: Variable(s) entered on step for Renal pelvis urine culture positivity: Preoperative urine culture, Stone size, Stone density, Preoperative pelvis urine density, Stone localization, Preoperative hydronephrosis , [b]: Variable(s) entered on step for Postoperative fever: Age, Preoperative tomographic urine density, Preoperative hydronephrosis, Stone size, Stone location, Preoperative urine culture, Renal pelvis urine culture, OR: Odds ratio, CI: Confidence interval, HU: Hounsfield unit, RBUC: Preoperative bladder urine culture, RPUC: Renal pelvic urine culture, UAS: Ureteral access sheath

a negative PBUC. Other studies have revealed that in addition to the degree of hydronephrosis, the thickness of the ureteral wall surrounding the stone may also increase. A significant association between ureteral wall thickness (UWT) and degree of obstruction has been demonstrated, and a possible predictive value has been presented (18,19). Sarica et al. (12) found the cut-off value of UWT to 3.35 mm and they were not unable to place a DJ stent in patients with a value over this threshold. The authors considered that if the guidewire required for the DJ insertion could not reach the proximal of the stone, the urine sample obtained preoperatively would also not be sufficient for the culture analysis. Impacted stones have indirect NCCT findings, including changes in UWT, degree of hydronephrosis, and fluid collection around the kidney (20). Another study revealed that the thickness of the wall immediately surrounding the stone depends on the time elapsed and the degree of inflammatory reactions that occur (21). In our study, the wall tissue thickness at the proximal ureter and/or pelvis was higher in patients with RPUC growth. However, due to being a confounding factor in the multivariate analysis, it was excluded in the model.

The literature demonstrates that 10.1% of the patients with a negative PBUC were positive for RPUC, but these patients also did not show any signs of infection (4). Basmaci and Sefik (11) reported that at a cut-off value of 0, renal pelvis HU had 100% sensitivity and 96% specificity for a positive RPUC. In our study, the HU value was found to be lower in the RPUC group. We certainly do not claim that it is possible to definitively determine the presence of RPUC growth by examining HU. However, we consider that in patients examined for stone disease and planned to undergo f-URS, pelvis HU can predict RPUC growth, and thus help identify those that require wider-spectrum PAP and a closer follow-up in the postoperative period. We think that a low HU value in patients with RPUC growth may be due to bacterial burden colonizing in that location, fragmented urine, and/or increased urine density.

In previous studies, the percentage of patients with fever and sepsis was reported as 4.4% and 0.7%, respectively, after f-URS (3,22). We observed postoperative fever in 7 patients (5.4%) and sepsis in 1 patient (0.7%) during the study. In the literature, high stone burden, long operation time, positive preoperative culture, presence of diabetes mellitus, presence of renal abnormalities were identified to influence the infection risk following f-URS (5,22,23). In our study, we found that the operation time was the only predictive factor for postoperative fever. Günseren et al. (23) showed that f-URS operations can be held safely for as long as 83 minutes. We think that as the operation time increases, intrarenal pressure protective mechanisms (pyelo-tubular, pyelo-venous, pyelo-sineous, and pyelo-lymphatic) might become less effective and give way to infections. However, it might be inaccurate to claim that the operation length is the only reason for infection. In our study, we only obtained RPUC perioperatively. We didn't find any correlation between that and fever in our multivariate analysis. However, we think that if we obtained stone cultures perioperatively, we might have found it to be a significant predictor of infection. Thatis because we think that there might be microorganisms colonized inside the stones, which might have spread after the fragmentation and caused an infection.

Study Limitations

This study has certain limitations. First, it was a retrospective study and had few patients. Another important limitation of our study is that we didn't compare intraoperative urine cultures with postoperative samples. The main goal of our study was to demonstrate that urine cultures obtained from obstructed upper urinary system obstruction cases may not always reflect an accurate picture. Therefore, we excluded postoperative urine cultures in our study. Second, the chemical analysis of the stones was not undertaken. Third, this study was not conducted with a single-use f-URS. The reason for PBUC and RBUC to show different microbial growth can be device contamination despite sterilization procedures. Fourth, stone cultures were excluded from the study. Although the effect of PAP and preoperative antimicrobial treatment remains uncertain, it is essential to identify high-risk patients, take an intraoperative culture and perform infection control more carefully according to the results to prevent serious infection complications. Therefore, well-designed prospective studies with larger case series must confirm the results of the current study.

Conclusion

Preoperative PBUC may not represent true colonization; therefore, preoperative PAP administration should be adjusted according to the individual risks of PBUC-negative patients. Obtaining renal pelvis urine culture is important for managing postoperative infectious complications. Even if PBUC is negative, it should be kept in mind that there may be growth in RPUC in cases where preoperative hydronephrosis and low tomographic urine density were present.

Ethics

Ethics Committee Approval: This study was conducted with the approval from the Ethics Committee of the Mustafa Kemal University (01.04.2021.01).

Informed Consent: An informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.G., Ö.K., S.P., M.Ş., A.E., D.B., İ.H.B., Concept: F.G., Ö.K., S.P., M.Ş., A.E., D.B., İ.H.B., Design: F.G., Ö.K., S.P., M.Ş., A.E., D.B., İ.H.B., Data Collection or Processing: F.G., Ö.K., S.P., M.Ş., A.E., D.B., İ.H.B., Analysis or Interpretation: F.G., Ö.K., S.P., M.Ş., A.E., D.B., İ.H.B., Literature Search: F.G., Ö.K., S.P., M.Ş., A.E., D.B., İ.H.B., Writing: F.G., Ö.K., S.P., M.Ş., A.E., D.B., İ.H.B.

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A Rational Solution for Megaureter in Infants with Solitary Kidney: Temporary Loop Cutaneous Ureterostomy

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What's known on the subject? and What does the study add?

In patients with solitary kidneys, it is essential to prevent further possible bladder problems in order to decrease the risk for renal insufficiency. By performing this technique in patients with ureterovesical obstruction and solitary kidney, we can protect the kidney from possible side effects and bring the patient to the last treatment age while maintaining the bladder cycle and development.

Abstract

Objective: To define and discuss the new concept which using loop cutaneous ureterostomy (LCU) in patients with obstructing megaureter and solitary kidney.

Materials and Methods: Two patients with solitary kidney with obstructive pattern were included. Both patients underwent LCU within the 1st month to reduce the obstruction and to relieve the pelvicaliceal system. Thereafter, parents were taught to dilate the ureter and irrigate the bladder with sterile saline by a disposable 6F catheter via antegrade fashion through the distal ureter. Initially, 10 cc saline was used once a day, then it was increased to 20 cc once a day after 2 months. When the bladder capacity was sufficient (50 mL capacity at the 6th month or by cystoscopic evaluation intraoperatively), we performed undiversion with ureteroneocystostomy and Double-J-stent placement.

Results: Ureterorenal dilatations were followed-up by ultrasonography and renal function tests. No bladder dysfunction and renal insufficiency were observed during follow-up. At the postoperative controls, patients' renal function tests were compatible with their ages and they had no voiding dysfunction.

Conclusion: Patients with solitary kidney and obstructing megaureter require urgent diversion. After diversion, bladder cycling is required to prevent bladder dysfunction by protecting and developing bladder capacity. Using this concept, the kidney can be protected from further damage and treatment can be finalized around 6 months of age with minimum morbidity.

Keywords: Megaureter, solitary kidney, bladder cycling, urinary diversion

Introduction

Ureteral reimplantation in patients with massive hydroureteronephrosis (HUN) has technical limitations infants due of low bladder capacity and carries the risk of deteriorating bladder development (1-3). Therefore, a temporary loop or end cutaneous ureterostomy (CU) is easy to perform and effectively provides the decompression of the system (4,5). If remains untreated, it can lead to end-stage renal failure; especially in patients with a solitary kidney.

By using loop CU in patients with obstructing megaureter and solitary kidney, we intended to protect the kidney from possible adverse effects and finalize the treatment earlier while maintaining bladder cycling and development. This article aims to define and discuss this new concept.

Materials and Methods

Two patients with a solitary kidney and megaureter with obstructive pattern were included. Patients were intervened

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after urosepsis. In both cases, we tried and failed to pass a guide wire up to the kidney using endoscopic approach. Both patients underwent loop CU (LCU) within the 1st month. Bladder irrigation was performed by professionals, on the first postoperative day and by the family under the supervision of professionals on the other days. After that, parents were taught to dilate the ureter and irrigate the bladder with sterile saline by a disposable 6F catheter via antegrade fashion through the surgically dissected and dilated distal ureter (Figures 1,2). We consider that we reached capacity as soon as the baby became restless and started crying. It was almost a rule that each time the baby reached that state he/she started to urinate. Initially, 10 cc saline was used once a day, then it was increased to 20 cc once a day after 2 months. When the bladder capacity was sufficient (50 mL capacity at the 6th month or by cystoscopic evaluation intraoperatively), we performed undiversion with ureteroneocystostomy (UNC) and Double J-stent (DJS) placement. The patient was followed-up by ultrasonography (USG) and renal function tests. urinary tract infection did not develop in either patient after surgery. No bladder dysfunction or renal insufficiency was observed during follow-up. This study was approved by the local ethical committee (GO-18/267).

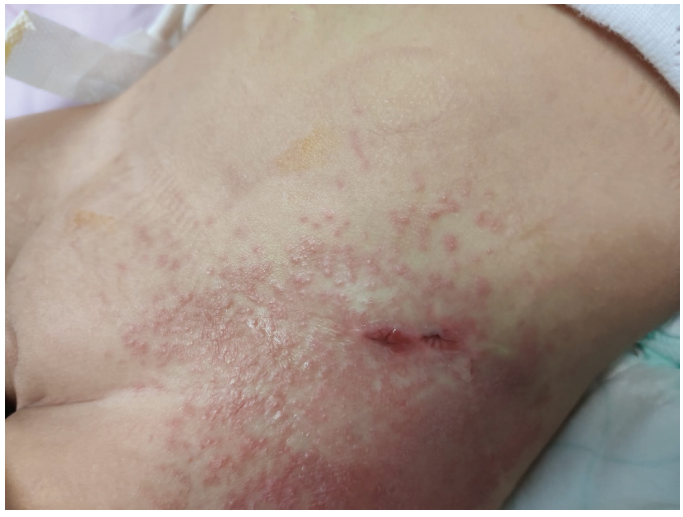

Figure 1. Loop cutaneous ureterostomy in first patient

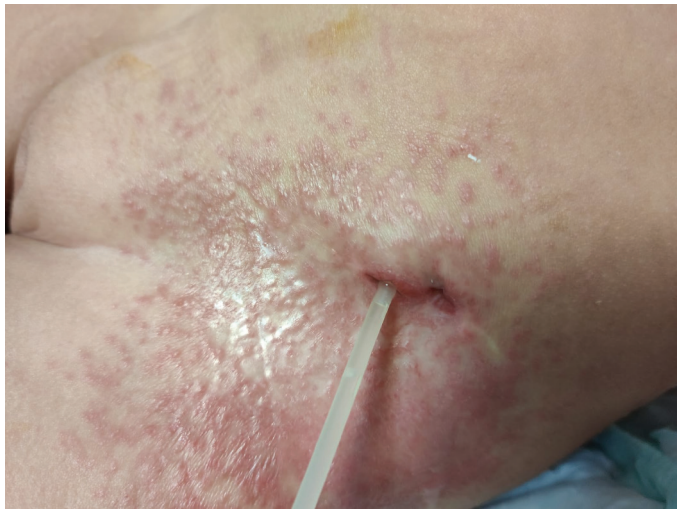

Figure 2. Bladder irrigation with sterile saline by a disposable 6F catheter via antegrade fashion through the distal ureter

1st patient: Female.

She was diagnosed with antenatal hydronephrosis (HN) before birth and uterine didelphys, right renal agenesis. Grade 4 HUN was detected by USG on the postnatal 4th day. We performed loop CU on the patient whose findings were compatible with ureterovesical (UV) stenosis on cystourethroscopy performed at the 4th week. After surgery, bladder cycling was initiated. At the age of 4 months, we performed undiversion with Cohen UNC and DJS placement. At the age of 1 year, serum creatinine level was 0.4 mg/dL and clinically asymptomatic grade 2-3 HN was present on USG. At the age of 3 years, serum creatinine level was 0.48 mg/dL, no reflux was detected on voiding cystourethrography and renal emptying was sufficient on retrograde pyelography.

2nd patient: Male

He was diagnosed with antenatal HN and right renal agenesis. Left HUN was detected by USG and serum creatinine level was 0.5 mg/dL on the 5th day after birth. After detecting the findings compatible with UV stenosis on cystourethroscopy performed at the 1st month, we performed loop CU. After surgery, bladder cycling was initiated. At the age of 6 months, we performed undiversion with Cohen UNC and DJS placement. At the age of 1 year, serum creatinine level was 0.5 mg/dL and clinically asymptomatic grade 3 left HN was present on USG. Grade 2 left HN was detected and serum creatinine level was 0.34 at the age of 2 years. İn the final control at the 13th year of age, serum creatinine was 0.48, and grade 3 residual left HN persisting. The patient is voiding without any residual urine and has no voiding dysfunction.

Discussion

The placement of a nephrostomy catheter is easy to perform and has low complication rates, keeping the nephrostomy tube for long-term is technically difficult and there is increased risk of infection (6). Cutaneous diversion of the ureter is the preferred method when prolonged drainage is required in patients with obstructed megaureters. CU is a safe and effective procedure to decompress the system (4).

The placement of a JJ stent is technically challenging and often impossible endoscopically in the infants, requires open intervention and carries a high risk of infection (7). Endoscopic treatment is also technically limited because of the size of the child and the ureter (8,9).

Jayanthi et al. (10) reported further bladder dysfunction in 25% of patients who underwent mandatory cutaneous diversion. In similar studies, bladder diversions reduce bladder capacity and compliance (11). The capacity begins to decrease in long-term dysfunctional bladders. Especially in infants who have immature and still-developing bladder dynamics, bladder dysfunction may lead to some voiding problems in older ages. Our method included regular cycling with saline to provide a bladder rehabilitation because of the disabled bladder. Similarly, the lack of fully developed bladder capacity makes the undiversion technically and functionally difficult.

Refluxing ureteral reimplantation technique for the obstructive megaureter was defined by Lee et al. (12). The technique is much more complex especially in a new born. Moreover, this technique is also not well defined and doing a reimplantation on the dome of the bladder is not only reflux persists but there is a risk of distal kinking when the bladder is full. Moreover, we are not sure which is better for bladder dynamics, as there is a continuous high grade reflux increasing the bladder load and therefore the volume. One can argue that this may actually have more long-term problems as there has been one surgery on the bladder much earlier in life and the bladder physiology could not yet be considered as normal.

Obstructed megaureter of a single system is a very rare condition, which requires some unique, challenging and often individualized management and both patients were clinically suitable candidates for this procedure. The main challenge is of course to maintain the bladder cycling and function once the single ureter is diverted. We performed undiversion as early as possible in our 2 patients to prevent the bladder capacity and compliance from reducing. Although bladder cycling prevents the bladder capacity from reducing, it is not completely sufficient because it is not permanent and natural. We did immeasure the pressure but monitored how baby reacted to the fillings while in discomfort or when crying. We consider that we reached capacity as soon as the baby became restless and started crying. It was almost a rule that each time the baby reached that state he/she started to urinate. Therefore, it was difficult and probably unreliable to measure of pressure and we relied on signs and occurrence of voiding when the capacity is reached. If the capacity is not sufficient the frequency of daily installations can be increased. In patients, particularly with solitary kidneys, it is essential to prevent further possible bladder problems order to decrease the risk of renal insufficiency.

The main advantage of this approach is that the initial procedure (LCU) is easy and later can be followed with another easy and standard procedure (reimplantation) after the ureteric diameter has down-sized. The second procedure can be performed as soon as the ureteric dilatation has gone down and the bladder capacity is within acceptable volumes. It is difficult to name what period is needed before reimplantation we could do that at 4 and 6 months. Therefore, based on this experience, we believe it can be done before or around 6 months as a definitive procedure.

The preservation of existing renal functional reserves is critical in patients with solitary kidney. After diagnosis, urinary diversion should be performed as soon as possible to reduce the system pressure. Prophylactic antibiotics should be administered to protect patients from possible infections. The frequent follow-up is essential after surgery to be alert for possible complications.

Study Limitations

The main limitations of this study are the retrospective nature, the lack of randomization and the small number of patients. It cannot be evaluated clearly that the capacities will be affected and whether the dysfunction will occur if cycling is not performed. However, we think that bladder cycling improves the bladder capacity and the patients, for this reason, are not adversely affected in their future life. Another limitation is the inability to perform a standard evaluation such as voiding cystourethrography and MAG-3 scan for the prenatal HUN because these patients were hospitalized with urosepsis in the neonatal period and urgent urinary diversion was planned.

Conclusion

Patients with solitary kidneys and an obstructing megaureter require urgent diversion. After a diversion, bladder cycling must prevent bladder dysfunction by protecting and developing bladder capacity. Using this concept, in clinically appropriate patients, the kidney can be protected from further damage and treatment can be finalized around 6 months of age with minimum morbidity.

Ethics

Ethics Committee Approval: This study was approved by the local ethical committee (GO-18/267).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.T., H.S.D., Concept: S.T., B.Ç., Design: S.T., B.Ç., H.S.D., Data Collection or Processing: B.Ç., T.C., Analysis or Interpretation: S.T., B.Ç., H.S.D., Literature Search: S.T., B.Ç., H.S.D., Writing: S.T., B.Ç., H.S.D., T.C.

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Do High-Power Lasers Reduce Operative Time for Ureterorenoscopy? A Comparison of Holmium Lasers in An Australian Tertiary Centre

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What's known on the subject? and What does the study add?

There is some laboratory-based evidence that high-powered laser systems destroy stones more effectively than low-power laser systems. However, whether this translates clinically is unknown, as direct clinical comparisons are absent from the literature. This study provides a direct comparison of the two laser systems.

Abstract

Objective: Holmium lasers are an effective endoscopic treatment for renal stones. Although laboratory studies have demonstrated reduced destruction times for high-power lasers, clinical evidence is lacking. Operative times for ureterorenoscopy (URS) were investigated by comparing high- and low power lasers in a general hospital setting.

Materials and Methods: An audited review was conducted of 354 patients who underwent URS over a two-year period at two hospital sites using high- or low power laser. Operative time, stone characteristics, disposable equipment, s use of dusting, complications and stone-free rates were recorded. Linear regression was used to model the relationship between laser type and theater time. Univariate analysis was performed to determine other factors associated with increased operative time.

Results: Mean operative time was 61.9 minutes. No significant difference between sites [0.40, p=0.88, confidence interval (CI) -4.9-5.8] was found, including following the exclusion of large stones (>20 mm). Stone size categories analyzed separately showed reduced operative times for larger stones when using high-power laser. Basket use (8.4, p=0.002, CI 3.06-13.65) and increasing stone size (6.9, p<0.005, CI 3.4-10.4) were associated with increased operative time. Complications and stone-free rates did not vary between sites.

Conclusion: High-power laser was not associated with reduced total operative time in this cohort, although there was a trend toward this for larger renal calculi. Further delineation by surgeon expertise would be useful to determine whether high power laser is generally advantageous in the clinical setting. In training hospitals, any differences may be obscured by other factors.

Keywords: Ureterenoscopy, endoscopy, operative time

Introduction

Holmium lasers came into use in the 1990's and have proven to be cost effective, safe and effective treatment of ureteric and renal stones (1). Endoscopic interventions currently account for the largest proportion of stone procedures conducted in Australia (2). Renal stone disease in Australia, as in other western countries, is a significant and increasing financial burden (3) that will need to be managed across public and private sectors in coming years. The use of equipment associated with fewer complications, maximal stone clearance and efficient utilization of theater time will be key to minimizing the cost of endoscopic stone treatments in coming years (3).

Holmium lasers come in various guises with wattage (W) representing the main point of difference. Laser settings for stone destruction are relatively limited when using low-powered lasers (4). 10-20 W systems can be used to fragment stones, resulting in multiple particles (5). Large fragments often require basket retrieval and access sheath insertion, both of which add to operative time, procedure cost and potential complications including ureteric damage (6).

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High-power lasers can deliver more energy (up to 120 W) at higher frequencies. This allows more variation in laser settings, including the ability to dust stones with low-power high-frequency settings (1,7). Dusted stones may result in fewer large fragments, increasing the likelihood of spontaneous passage without the need for multiple procedures to clear a single stone (8). Additionally, resulting in smaller fragments may not require basket retrieval, reducing costs and complications associated with baskets and access sheaths (1). Finally, high-power lasers allow pulse width variation, which can reduce retropulsion. Resulting improved control of renal stones during procedures could reduce operative time (1).

These combined advantages of high-power lasers may result in reduced total operative time. Time in theater is costly and associated with increased complications (9,10). There is some laboratory-based evidence that high-powered laser systems destroy stones more effectively (11). However, whether this translates clinically is unknown, as direct clinical comparisons are absent from the literature. Operative time comparisons must date been based on the results of individual arms of separate studies, with no differences identified (12). In practice, many factors contribute to increased time in theater, encompassing patient, stone, surgeon and anesthetic attributes. Many of these influences are unmodifiable, particularly in a public hospital setting. Given the deficit of clinical evidence supporting the adoption of high-power laser technology, this study compares operative times for high and low-powered lasers within the public hospital system. Secondary aims were to identify other factors associated with increased operative time and compare complication rates between these devices.

Materials and Methods

An audited review was undertaken of 354 consecutive patients who underwent ureterorenoscopy (URS) performed under general anesthetic for stone disease over a two-year period. Procedures were conducted at two hospital sites that utilized either the Lumenis Pulse 120 W (Lumenis, Israel) or 30 W laser (Dornier MedTech Gmbh, Germany) laser. Specific laser settings used for each procedure were not available. The two sites were training hospitals as part of the same metropolitan public hospital network and subject to similar operative conditions and patient population. Operative time was extracted from anesthetic records. Data describing stone burden, composition, location and use of disposable equipment (access sheath, baskets and stents) were collected, in addition to demographic data. Stone size was based on the maximum diameter from computed tomography scans and calculated cumulatively if there were multiple stones. Use of the dusting technique, the length of admission, complications and post-operative stone-free rates were recorded.

Statistical Analysis

Data were analyzed using Stata 16.0. Descriptive statistics of the cohort were obtained and compared to ensure no significant differences between sites. Linear regression was used to model the association between the mean operative time and laser type. Univariate logistic and linear regression analyzes were performed to determine other factors that may be associated with increased operative time. Logistic regression was used to model relationships between laser type and complications, use of baskets and dusting. The relationship between laser type and operative time was modeled for each category of stone size to assess for effect modification from stone burden, and the relationship between laser type and operative time for stones less than 2 cm in size only was modeled using linear regression.

This study was approved by the institution's Human Ethics and Research Committee (RES-19-0000-593Q).

Results

Cohort Characteristics

354 individual patients were identified Table 1. More procedures occurred at the high-power site (n=195, 55.08%) compared with the low power site (n=159, 44.92%). 81% (n=287) patients underwent one URS, 17% (n=6) went on to undergo a second procedure. There were no significant differences in baseline characteristics between the two sites other than an over-representation of large stones (>2 cm) at the high-power site (12.7% compared to 6.6%), although this difference was not statistically significant. Most stones were located intrarenally Table 2.

Table 1. Baseline characteristics of the cohort subdivided by laser

Baseline characteristics	High-power site		Low-power site	
	Mean	Range (standard deviation)	Mean	Range (standard deviation)
Age (n=354)	53.8	18.0-83.0 (14.9)	54.3	20.0-89.0 (6.9)
BMI (n=335)	30.1	18.8-58.4 (6.3)	28.4	17.2-65.8 (6.6)
Stone size (n=344)	10.7	3.0-65.0 (7.7)	11.2	4.0-37.0 (6.0)

BMI: Body mass index

Operative Time and Lasers

The mean operative time was 61.9 minutes. No significant difference in mean operative time was found between the two sites [difference 0.40 minutes, p=0.88, confidence interval (CI) -4.9 - 5.8]. Due to the over-representation of large stones (>2 cm) at the high-power site, mean time difference between sites was modeled excluding stones >2 cm; still, no significant difference was identified (0.03 minutes, p=0.99, CI -5.4 - 5.5). Across the cohort, stone size increased operative time, adding 7 minutes for each increase in size category (p<0.001, CI 3.4 - 10.4 minutes) (Table 3). The relationship between operative time and laser type was modeled for each stone size category separately, to assess for effect modification from varying stone burden. There was a trend toward high-power laser reducing operative time for large stones, but the relationship did not reach significance Table 4. Stone composition data were available for a third of the cohort. There was no relationship between operative time and stone composition. Calcium oxalate stones comprised 50% of stones for which composition data were available Table 5.

The reported use of dusting at the high-power site was associated with a reduction in operative time of almost 8 minutes (-7.8 minutes, p=0.05, CI -15.5 - -0.12). The reported use of dusting did not significantly affect operative time at the low-power site (1.05, p=0.80, CI -7.27 - 9.37). Dusting was reported more frequently in the high-power cohort [odds ratio (OR) 3.9, p<0.005, CI 2.5-6.1].

Table 2. Stone location	
Location	**% (n)**
Ureteric	13.4 (47)
Pelviureteric junction	5.7 (20)
Intrarenal	63.1 (222)
Multiple locations	17.9 (63)

Operative Equipment and Lasers

Laser type did not significantly affect basket use (OR 1.16, p=0.48, CI 0.76 - 1.78). Basket use decreased by 35% for procedures that reported dusting compared to those that did not (OR 0.65, p=0.05, CI 0.42 - 0.99), however, subdivided by site, this was only significant for the low-power laser (OR 0.48 p=0.055, CI 0.23 - 1.02)

Operative Time and Adjunct Equipment Table 5

Stone Clearance and Complications Table 6

There was a trend toward higher likelihood of adequate stone clearance post-URS (no fragments >4 mm) at the high-power site, although the relationship did not reach significance. This assessment was based on post-operative CT or XR KUB conducted usually 6-12 weeks post URS. Overnight stays were more likely at the high-power site, although numbers were low across the cohort (7.4%). There were fewer complications at the high-power site although again the difference did not reach significance. Across the cohort, there were 30 complications, including post-operative sepsis (11), mucosal trauma (7), intra-operative bleeding affecting vision (10), one pseudoaneurysm and one post-operative myocardial infarction (8.55% complication rate).

Discussion

Urolithiasis represents an increasing burden on healthcare systems throughout the western world (2). With significant financial implications associated with efficient use of operative

Table 3. Operative time for high-power compared to low-power laser for increasing stone size					
Stone size	**Total % of stones**	**HP site minutes**	**LP site minutes**	**Difference (min)**	**p-value (CI)**
<6 mm	11.3	49.6	51.7	2.08	0.73 (-14-4-10.8)
6-10 mm	53.8	61.6	61.2	0.40	0.92 (-7.06-7.87)
11-20 mm	28.8	60.6	64.2	-3.60	0.46 (-6.0-13.3)
>20 mm	6.1	49.5	65.0	-15.5	0.23 (-10.4-41.3)
CI: Confidence interval					

Table 4. Adjunct equipment used					
Item	**HP site (%, n)**	**LP site (%, n)**	**Total (%)**	**Effect on operative time**	**p-value (CI)**
Stent pre-ureterorenoscopy	61.0 (119)	78.6 (125)	68.9 (244)	-4.0 minutes	0.18 (-9.8-1.90)
Stent post-ureterorenoscopy	93.7 (178)	88.0 (140)	91.2	+8.3 minutes	0.09 (-1.2-17.90)
Basket	46.2 (90)	42.4 (67)	44.5 (157)	+8.4 minutes	0.002 (3.06-13.65)
Access sheath	82.6 (157)	82.4 (131)	82%	-1.6 minutes	0.66 (-8.7-5.54)
CI: Confidence interval					

time (13), identifying equipment associated with efficiency in theater is of great benefit. With various Holmium lasers available for use in Australia, we assessed the potential time-benefits of upgrading to a high-power laser system in the public hospital setting. To our knowledge, this is the only comparison of laser type and operative times in a public hospital setting in Australia.

No significant difference in operative times because of using the high-power 120 W Holmium laser compared to the lower-power laser was noted in the public hospital setting, although there was a trend toward shorter times for larger calculi. Basket use and increasing stone size were independently associated with increased operative time. The reported use of dusting was significantly associated with shorter operative time at the high-power site. Complications and overnight admissions did not vary significantly between laser type. This study benefited from access to complete medical, anesthetic and operative records for patients who underwent ureterenoscopy with one of two commonly used lasers, within the environment of a single hospital network. However, the retrospective nature of this study was in some ways limiting.

Study Limitations

Sufficient data describing the training level of the primary operator in addition to contributions and level of supervision from senior surgeons could not be obtained. At the consultant level, it is possible that high-power laser techniques could consistently reduce operative time. However, in training hospitals where surgeons have varied levels of confidence and familiarity with not only lasers but also adjunct equipment, any advantage of high-powered lasers may be overshadowed. A prospective study could delineate the benefits of high-power lasers further by using either a single surgeon or collecting data on the level of training.

Knowledge of laser settings would have improved accuracy and allowed more definite conclusions to be drawn from the results. It was assumed that those at the high-power site utilized settings unique to the 120 W laser when appropriate, but this may not have always been the case. Deciding factors on whether to "dust" or fragment were not recorded by surgeons. Use of "dusting" was more commonly reported at the high-power site, however it was also reported at the low power site suggesting some subjectivity in the use of the technique and term (1). Some definitions of dusting in the literature refer to the laser settings used to achieve "dust", typically low energy, and high pulse rate (7). Others refer to "dusting" in terms of the result -fine fragments able to be passed spontaneously (8). Both are variable in the literature with reference to the exact settings that will best achieve dusting and the acceptable size of residual fragments (1). This may explain why dusting was associated with decreased basket use at the low-power site only -perhaps views differed on acceptable size of residual fragments between sites. At the high-power site, reported use of dusting was less than 50%. The high-power laser capability of dusting stones may have been under-utilised, potentially increasing operative time in this group. Surgeon experience and confidence with the high -power laser and associated dusting techniques may have influenced this finding. In the training hospital settings where 120 W lasers are less commonly available, laser-specific training may be needed to ensure high-power laser settings are utilized where appropriate. A prospective study design ensuring appropriate utilization of high-power technology features could alleviate this issue in future studies.

Utilizing anesthetic time as a proxy for operative time, rather than directly recording lasering time, was a necessity of our retrospective study design that could also have potentially obscured time benefits of high-powered lasers in stone destruction. Although direct collection of lasering time would provide a more accurate comparison of the effects of high-powered lasers *in vivo*, our results show that even if this benefit exists, it is still obscured (and over-all operative time unaffected) by other factors. Some prospective studies have recorded operative time only until fragmentation was complete,

Table 5. Stone composition

Composition	HP site	LP site	Total %, n
Data unavailable	68.3%	68.8%	68.8, 225
CaOx	13.9%	18.1%	15.6, 51
CaOxPhos	5.6%	7.6%	6.4, 21
CaOxPhosMg	4.4%	2.1%	3.4, 11
Uric acid	1.7%	1.4%	1.5, 5
CaOx + uric acid	3.3%	1.4%	2.5, 8
Other combination compositions including cysteine and ammonia	2.8%	0.7%	1.8, 6

Table 6. Admission, stone clearance and complications

	Cohort (%, n)	HP site (%, n)	LP site (%, n)	Difference between sites
Overnight admission	7.4 (26)	8.8 (17)	5.7 (9)	OR 1.60, p=0.270, CI 0.69-3.70
Stone clearance*	41.6 (79)	43.6 (51)	38.4 (28)	OR 1.24, p=0.48, CI 0.68-2.26
Complications	8.55 (30)	6.7 (13)	10.8 (17)	OR 0.59, p=0.17, CI 0.28-1.26

*Data available for 54% of patients, OR: Odds ratio, CI: Confidence interval

or focused on time spent lasering (14). The absence of this data does not detract from the result that in the training setting, any time saving still does not significantly influence total operative time. This is important because the time spent in theater is the largest contributor to the cost of treating renal stone (15). Total theater time is the target of reduction. A reduction in lasering time that does not result in decreased operative time is arguably not particularly valuable.

Finally, confidence in conclusions drawn regarding stone-free rates was low due to a significant amount of missing data. No follow-up imaging was available for around 46% of the cohort. Despite this, data on repeat ureteroscopy was complete and reassuringly showed that 81% of the cohort had one procedure alone. Subdivided by stone size, 61% of those who had more than one procedure had stones in the larger two size categories. Assuming stone-free rates correlate with repeat procedures, this is consistent with stone-free rates for single stage URS procedures quoted in the literature (1).

Importantly, missing follow-up data did not vary significantly between sites, nor was the reason for attrition expected to vary between sites. Complications appeared to occur more frequently at the low powered site although again the relationship did not reach significance. This supports at least comparable safety of high-powered lasers with low powered technology, even if no safety advantage resulting from shorter operative time was demonstrable.

Conclusion

High-power Holmium laser was not associated with reduced operative times in this patient cohort, although there was a trend toward this for larger renal calculi. High-powered lasers allow more confidence when utilizing "dusting" settings, which was reflected in the shorter operative times observed in the high-power laser arm when dusting was used. Prospective research assessing laser settings associated with optimal stone fragmentation and dusting is required in order to maximally utilization high-powered lasers. Further delineation by surgeon expertise would be useful to determine whether using a high-power laser is advantageous in the clinical setting generally. However, in training hospitals, our results suggest that any time advantage gained using a high-power Holmium laser may be obscured by other factors.

Ethics

Ethics Committee Approval: This study was approved by the institution's Human Ethics and Research Committee (RES-19-0000-593Q).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: P.M., Concept: P.M., Design: P.M., Data Collection or Processing: R.F.M., C.Y.M.L., A.Y.Y.N., Analysis or Interpretation: R.F.M., C.Y.M.L., A.Y.Y.N., Literature Search: R.F.M., C.Y.M.L., A.Y.Y.N., Writing: R.F.M., C.Y.M.L., A.Y.Y.N., P.M.

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ORIGINAL RESEARCH
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The Effect of COVID-19 Phobia on the Time of Admission to the Hospital in Patients with Ureteral Stones

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What's known on the subject? and What does the study add?

It was observed that there was a decrease in hospital admissions of patients due to COVID phobia during the COVID-19 pandemic process. In our study, it was shown that the increase in COVID-19 Phobia reduced hospital admissions in patients with ureteral stones, which is an emergency.

Abstract

Objective: To investigate the effect of coronavirus disease-2019 (COVID-19) phobia in patients with ureteral stones.

Materials and Methods: Between August 2020 and March 2021, patients over the age of 18 who were diagnosed with ureteral stones were included in this study. The COVID-19 Phobia scale (C19P-S) was used to measure the COVID-19 phobia levels of the patients. Demographic and patients' characteristics were recorded. The time between the onset of the patient's complaint and the time of admission to the hospital was recorded and grouped as group 1 (≤7 days), group 2 (7-21 days), group 3 (>21 days).

Results: A total of 77 patients with a mean age of 45.8±14.8 years were eligible for analysis. Among these, 55 (71.4%) were male. According to the time between the onset of the patient's complaint and the time of admission to the hospital, there were 39 (50.6%) patients in group 1 (≤7 days), 17 (22.1%) patients in group 2 (7-21 days) and 21 (27.3%) patients group 3 (>21 days). The median C19P-S scores in these groups were 32.0 (15.0-46.0), 37.0 (26.0-62.0) and 56.0 (37.0-80.0), respectively. There were significant differences in terms of C19P-S between groups of the time between the onset of the patient's complaint and the time of admission to the hospital (p≤0.001).

Conclusion: COVID-19 phobia caused a delay in the hospital admission of patients with ureter stones. When patients have complaints, it is necessary to raise the awareness of society about applying to the hospital and to increase awareness of this issue.

Keywords: COVID-19, phobia, ureter stone, urology

Introduction

Coronavirus disease-2019 (COVID-19) began to spread around the world after it was first detected in Wuhan City, China in December 2019, and was named "pandemic" by the World Health Organization on March 11 (1,2). COVID-19, which affected the whole world in 2020, continues to increase its negative impact on 2021. The numbers of cases and deaths due to COVID-19 are still increasing, and the virus has not yet been fully controlled. The pandemic still affects the large population in various aspects including psychological, social, political, health and economic and has changed routine lives worldwide. As with other epidemics, COVID-19 usually causes various psychological difficulties in humans such as fear, panic or phobia (3-5). People may experience phobic avoidant reactions like not admitting to hospitals to prevent being infected during the pandemics (5).

Ureteral stone causing renal colic is a very common condition in daily urology practice and has been seen in more than 2

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million patients who present to the US emergency services with signs and symptoms of ureterolithiasis every year (6). The ureteral stone disease can be a problem-free condition, or if it is accompanied by infection and/or kidney failure, it can be a life-threatening situation. Treatments ranging from the follow-up of ureter stones to surgery are decided according to the size, location of the stone, pain infection, hydronephrosis (HN), and kidney function.

Acute pain due to obstruction in ureteral stones is a reason for admission to the hospital. Despite the acute pain during the pandemic process, we think that admissions to the hospital have decreased and treatment has been delayed due to COVID-19 phobia. Therefore, we investigated COVID-19 phobia and its results in patients with ureteral stones.

Materials and Methods

A total of 114 patients over the age of 18 who were diagnosed with ureteral stones signed an informed consent from August 2020 to March 2021. Patients who underwent only medical treatment (n=19), patients with kidney stones who underwent retrograde intrarenal surgery and/or percutaneous nephrolithotomy (n=11), patients who were diagnosed with psychiatric disease and/or who were using psychiatric drugs (n=7) were excluded from the study.

All patients admitted to the emergency or urology outpatient clinic with flank pain were examined, and all patients with clinically suspected ureteral stones were undergone non-contrast computed tomography (CT), urinalysis, complete blood count and biochemical tests. An operation [ureterorenoscopy (URS) and/or Double J stent (DJ)] was recommended according to the degree of pain, grade of HN, kidney function, location and size of the stone. Before the operation, urine culture was obtained in the patients. In patients with urinary tract infections, antibiotics were administered before the operation, and the operation was performed after the infection was taken under control. All patients signed a written consent form before the operation. Demographic and patients' characteristics were recorded. Pain severity was evaluated using the visual analog scale (VAS) (VAS 0 = no pain, VAS 10 = the most severe pain that could be seen). VAS was grouped as mild (0-3), moderate (4-6) and severe (7-10). Estimated glomerular filtration rate (eGFR) was calculated according to the modification of diet in renal disease formula based on the serum creatinine level of the patients (7). The time between the onset of the patient's complaint and the time of admission to the hospital was recorded and grouped as group 1 (≤7 days), group 2 (7-21 days), group 3 (>21 days).

The COVID-19 Phobia scale (C19P-S) questionnaire was used to measure the degree of COVID-19 phobia. The C19P-S is a 20-item questionnaire form to assess the levels of corona phobia (COVID-19) and all items in the scale are rated on a 5-point scale from "strongly disagree (1)" to "strongly agree (5)". Cronbach alpha for the overall scale was 0.926 (5).

In accordance with the Declaration of Helsinki, the study protocol was approved by the Regional Ethics Committee (IRB No. 110-21-2020).

Statistical Analysis

All analyses were performed using the IBM SPSS Statistics Version 20.0 statistical software package. Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviations and as median and minimum-maximum where appropriate. Chi-square test was used to compare categorical variables between the groups. Kolmogorov-Smirnov test was used to assess the normality of the distribution of continuous variables. For comparison of continuous variables between two groups, Mann-Whitney U test was used. For non-normal distributed data, Kruskal-Wallis test was used to compare more than two groups. Bonferroni adjusted Mann-Whitney U test was used for multiple comparisons of groups. To evaluate the correlations between measurements, Spearman Rank Correlation Coefficient was used. The statistical level of significance for all tests was considered 0.05.

Results

A total of 77 patients with a mean age of 45.8±14.8 years (range: 20-78 years) were eligible for analysis. Among them, 55 (71.4%) were male and 22 (28.6%) were female. Demographic and patients' characteristics are given in Table 1. The stones were located in the distal ureter in 23 (29.9%), in the middle ureter in 14 (18.2%), and in the proximal ureter in 40 (51.9%) patients. The mean stone size was 11.2±4.8 mm. Grade 1 HN was present in 40 (51.9%), grade 2 HN was in 27 (35.1%) and grade 3 HN was in 10 (13.0%) patients. The mean of VAS was 7.3±2.3. The median of time between the onset of the patient's complaint and the time of admission to the hospital was 7.0 (0-180.0) days. The mean of eGFR was 96.2±20.8 mL/min/1.73 m^2.

C19P-S scores according to patient characteristics are summarized in Table 2. According to the time between the onset of the patient's complaint and the time of admission to the hospital, there were 39 (50.6%) patients in group 1 (≤7 days), 17 (22.1%) patients in group 2 (7-21 days) and 21 (27.3%) patients group 3 (>21 days). The median C19P-S scores in these groups were 32.0 (15.0-46.0), 37.0 (26.0-62.0) and 56.0 (37.0-80.0), respectively. There were significant differences in terms of C19P-S between groups of the time

between the onset of the patient's complaint and the time of admission to the hospital (p≤0.001) (Figure 1). As the patient's C19P-S increased, the delay in the patient's admission to the hospital increased significantly (Figure 2). As the VAS scores and HN grade increased, the C19P-S score decreased significantly (p=0.003, and p=0.033, respectively) (Table 2). There was no significant difference between groups of age, gender, side, location and stone size in terms of C19P-S (p>0.05).

Table 1. Demographic and characteristics of the study population

	All patients (n=77)
Age, years[a]	45.8±14.8 45.0 (20.0-78.0)
Gender[b]	
Male	55 (71.4)
Female	22 (28.6)
BMI kg/m^2[a]	27.1±3.4
Hypertension[b]	
No	62 (80.5)
Yes	15 (19.5)
Diabetes mellitus[b]	
No	66 (85.7)
Yes	11 (14.3)
Smoking[b]	
No	44 (57.1)
Yes	33 (42.9)
Alcohol[b]	
No	61 (79.2)
Yes	16 (20.8)
Side[b]	
Right	29 (37.7)
Left	46 (59.7)
Bilateral	2 (2.6)
Stone size (cm)[a]	11.2±4.8
VAS[a]	7.3±2.3
Location[b]	
Distal	23 (29.9)
Middle	14 (18.2)
Proximal	40 (51.9)
Grade of HN[b]	
1	40 (51.9)
2	27 (35.1)
3	10 (13.0)
The time between the onset of the patient's complaint and the time of admission to the hospital (days)[a]	25.9±40.3 7.0 (0-180.0)
eGFR[a]	96.2±20.8

[a]Data are expressed as mean ± standard deviation, median (min-max); [b]Data are expressed as n (%), *VAS: Visual analogue scale

Characteristics of groups of the time between the time between the onset of the patient's complaint and the time of admission to the hospital are summarized in Table 3. As the degree of HN and stone size increases, the time of admission to the hospital decreases (p=0.014 and p=0.042). There was a significant difference between group 1 (≤7 days) versus group 3 (>21 days) and group 2 (7-21 days) versus group 3 (>21 days) in terms of VAS (p=0.010 and p=0.025, respectively). There was no significant difference between groups of the time between the onset of the patient's complaint and the time of admission

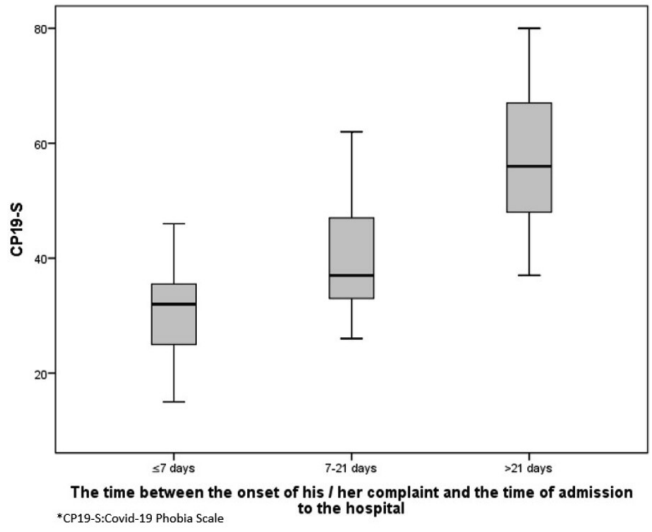

Figure 1. There were significant differences in C19P-S between groups of the time between the onset of the patient's complaint and the time of admission to the hospital (p<0.05 for each comparison)

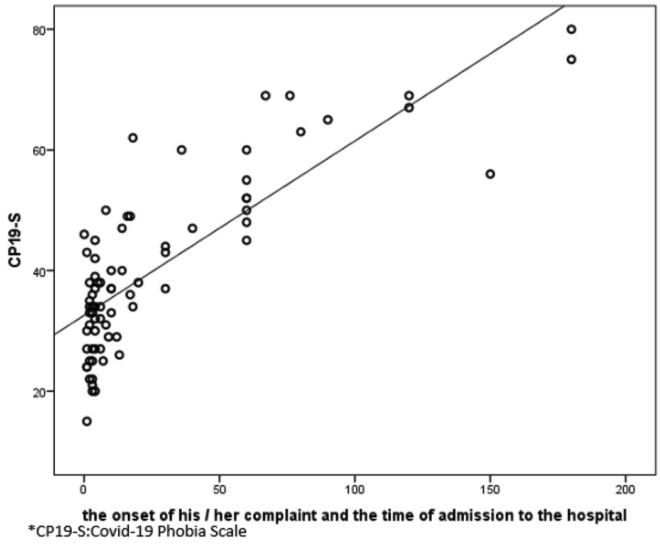

Figure 2. Correlation between the time between the onset of the patient's complaint and the time of admission and C19P-S (r=0.812, p<0.001)

Table 2. COVID-19 phobia (C19P-S) scale			
	n (%)	CP19-S Mean + SD Median (min-max)	p-value
Age			
18-35	24 (31.2)	37.7±10.4 37.0 (20.0-62.0)	0.594
36-54	29 (37.7)	42.4±16.2 38.0 (15.0-75.0)	
>55	24 (31.2)	39.5±15.3 33.5 (20.0-80.0)	
Gender			
Male	55 (71.4)	40.6±15.8 37.0 (15.0-80.0)	0.991
Female	22 (28.6)	38.6±10.1 36.5 (22.0-69.0)	
VAS			
Mild (0-3)	6 (7.8)	53.1±16.9 59.0 (22.0-69.0)	0.003*
Moderate (4-6)	22 (28.6)	46.4±16.2 45.5 (20.0-80.0)	
Severe (7-10)	49 (63.6)	35.5±10.9 34.0 (15.0-75.0)	
Side			
Right	29(37.7)	40.1±16.1 37.0 (20.0-80.0)	0.189
Left	46(59.7)	40.6±13.3 37.0 (15.0-75.0)	
Bilateral	2 (2.6)	26.0±1.4 26.0 (25.0-27.0)	
Location			
Distal	23 (29.9)	39.5±12.6 36.0 (20.0-69.0)	0.596
Middle	14 (18.2)	36.2±11.2 34.0 (22.0-63.0)	
Proximal	40 (51.9)	41.7±16.1 37.5 (15.0-80.0)	
Stone size			
<1 cm	40 (51.9)	42.2±15.5 39.0 (20.0-80.0)	0.190
>1 cm	37 (48.1)	37.6±12.7 34.0 (15.0-75.0)	
Grade of HN			
1	40 (51.9)	43.5±14.1 42.5 (15.0-75.0)	0.033*
2	27 (35.1)	37.3±15.6 34.0 (20.0-80.0)	
3	10 (13.0)	33.8±7.1 33.0 (25.0-49.0)	
The time between the onset of the patient's complaint and the time of admission to the hospital			
≤7 days	39 (50.6)	31.1±7.3 32.0 (15.0-46.0)	<0.001*
7-21 days	17 (22.1)	39.2±9.4 37.0 (26.0-62.0)	
>21 days	21 (27.3)	57.4±11.6 56.0 (37.0-80.0)	

Data are expressed as mean ± standard deviation, median (min-max); *In Post-hoc pair-wise comparison: for VAS mild versus severe p=0.018 and moderate versus severe p=0.037; for grade of HN 1 versus 2 p=0.025, 1 versus 3 p=0.054; for the time between the onset of the patient's complaint and the admission to the hospital ≤7 days versus 7-21 days p=0.048, ≤7 days versus >21 days p<0.001 and 7-21 days versus >21 days p=0.003, *VAS: Visual analogue scale

to the hospital in terms of age, gender, side, location, eGFR and urinary tract infection (p>0.05) (Table 3).

Discussion

Our study showed that the phobia caused the COVID-19 pandemic process caused a delay in the admission of patients with ureter stones to the hospital. We found that C19P-S positively correlated time between the onset of the patient's complaint and the time of admission to the hospital. We also found that when the VAS scores and HN grade increased, the C19P-S score and the time of admission to the hospital decreased significantly.

The COVID-19 pandemic strikes the whole world and causes radical differences in the habits of individuals. Health concerns, fear of transmission, changes in social relations, canceling travel plans and sports activities, being in a closed environment during quarantine days, and many other factors negatively affect mental health. Mental disorders such as post-traumatic stress disorder, major depressive disorder, acute stress disorder, and phobias can occur due to pandemics (8). Phobias are classified among anxiety disorders in the Diagnostic and Statistical Manual for Mental Disorders 5 (DSM-5) and are characterized by persistent and excessive fear of an object or a situation (9).

During the COVID-19 pandemic process, there may have been two reasons for the delay in patients' admission to the hospital. The first reason is the limitations and malfunctions in the healthcare system during this process. The second reason is that the patient may be afraid of getting COVID-19 infection in the hospital. Surveys show that even patients with life-threatening conditions may have avoided hospitalization, possibly out of fear of exposure to COVID-19

Table 3. Characteristics of groups of the time between the onset of the patient's complaint and the time of admission to the hospital

The time between the onset of the patient's complaint and the time of admission to the hospital				
	≤7 days (n=39)	**7-21 days (n=17)**	**>21 days (n=21)**	**p**
Age[a]	43.7±15.7	45.4±16.4	49.9±11.2	0.220
Gender (male)[b]	28 (71.8)	10 (58.8)	17 (81.0)	0.323
VAS[Φ,Ψ]	7.2±3.1	7.7±1.9	5.6±2.4	0.006
Side[b]				
Right	17 (43.6)	6 (35.3)	6 (28.6)	0.431
Left	20 (51.3)	11 (64.7)	15 (71.4)	
Bilateral	2 (5.1)	0 (0.0)	0 (0.0)	
Location[b]				
Distal	14 (35.9)	4 (23.5)	5 (23.8)	
Middle	9 (23.1)	3 (17.6)	2 (9.5)	0.371
Proximal	16 (41.0)	10 (58.8)	14 (66.7)	
Stone size (cm)[a,Φ]	12.5±5.1	10.5±3.4	9.5±5.0	0.042
Grade of HN[b]				
1	17 (43.6)	7 (41.2)	16 (76.2)	
2	15 (38.5)	7 (41.2)	5 (23.8)	0.014
3	7 (17.9)	3 (17.6)	0 (0.0)	
eGFR[a]	96.3±20.7	94.4±29.3	97.1±12.1	0.960
Urinary tract infectionb	24 (61.5)	10 (58.8)	8 (38.1)	0.203

[a]Data are expressed as mean ± standard deviation, median (min-max); [b]Data are expressed as n (%); [Φ]p<0.05 for ≤7 days versus >21 days; [Ψ]p<0.05 for 7-21 days versus >21 days, VAS: Visual analog scale

infection (10). De Filippo et al. (11) reported in their study that hospitalization of acute coronary syndrome decreased by 27.6-39.2% in Italy compared with pre-COVID-19 (11). Petrovic et al. (12) found a significant 44.3% reduction in the number of hospitalizations for acute coronary syndrome and an increase in an ST-elevation myocardial infarction during the COVID-19 outbreak in Serbia. They concluded that this situation contributed to increased complications and mortality in these patients. Also, they emphasized that the reason for this was the constraint in the healthcare system, as well as the fear of going to the hospital as a place where people could become infected (12). Our study showed that as the phobia of COVID-19 increased, the hospitalization of the patient with ureteral stones was delayed, and showed that the delay in the application decreased when the VAS and HN grade increased. We think that when the degree of HN increases, the severity of the pain increases, the patient applies to the hospital by reducing the COVID-19 phobia. Unlike other studies, in our study, we defined the patient-induced delay by measuring the COVID phobia score.

The emergence of COVID-19 has caused a dramatic change in the healthcare system and also affects daily urological practice. In a joint study by urology centers in Europe, participants reported that 37% of total hospital beds were occupied by COVID-19 patients. The main reason for the decrease in the bed occupancy was the ban on hospital administrations (13). In another study comparing the data of the early period of the pandemic to the same period in 2019, they reported that the pandemic had a significant negative impact on uro-oncologic surgery (14). In a study involving 51 urology centers, they reported a dramatic decrease in the number of urologically outpatients, inpatients, surgeries and daily interventions during the pandemic period and emphasized that the urology practice was given priority to urgent and non-postponable surgeries (15). In a multicenter study aimed at measuring changes in emergency urological care during the pandemic period, the authors reported a significant decrease in emergency urology practice and a reason being the fear of being infected by the virus in the hospital (16). Our study showed that in ureter stone disease, which is one of the urological emergencies, hospital admissions decreased when COVID-19 phobias increased. The European Association of Urology has published an updated version of the guidelines for guiding urologists for patient selection during the pandemic process (17-19). These guidelines were aimed at the urology practice of urologists, but were not aimed at raising the awareness of patients. Our study showed that even in an emergency, hospital admissions of patients decreased due to COVID-19 phobia. We think that the reason for this is that the society is not sufficiently informed

on television, social media and internet sites. In contrast, we think that these platforms increase the COVID-19 phobia in society.

Study Limitations

In our study, it was observed that a delayed admission to the hospital did not have negative effects on patients such as kidney function or urinary tract infection. However, our study had some limitations. These limitations that the study is from a single center and few patients. Multicenter studies investigating the effect of COVID-19 phobia on all urological practices, such as urooncology diseases, kidney stone diseases and urological emergencies are needed. The strengths of our study are that it is the first study investigating the effect of COVID-19 phobia on urological disease and that it shows the importance of raising the awareness the society about hospital admissions and emphasizes that awareness of this issue should be increased.

Conclusions

COVID-19 phobia caused a delay in the admission of patients with ureter stones to the hospital. Multicenter studies investigating the effect of COVID-19 phobia on all urological practices such as urooncology diseases, kidney stone diseases and urological emergencies are needed. When patients have complaints, it is necessary to raise the awareness of society about applying to the hospital and to increase awareness of this issue.

Ethics

Ethics Committee Approval: In accordance with the Declaration of Helsinki, the study protocol was approved by the Regional Ethics Committee (IRB No. 110-21-2020).

Informed Consent: All patients signed a written consent form before the operation.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Critical Review: İ.A.A., Surgical and Medical Practices: M.D., V.İ., Concept: M.D., M.E.D., Design: M.D., M.E.D., Data Collection or Processing: N.A., S.S., S.P.Y., Analysis or Interpretation: M.E.D., S.S., S.P.Y., Literature Search: M.E.D., Writing: M.D., S.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL RESEARCH
Functional

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The Anterior Vaginal Wall Suspension Procedure: Mid-Term Follow-Up of a Native Tissue Vaginal Repair for Stress Urinary Incontinence

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Abstract

Objective: To report the outcomes of the anterior vaginal wall suspension (AVWS) procedure for stress urinary incontinence (SUI).

Materials and Methods: Following institutional review board approval, a long-term pelvic organ prolapse database of non-neurogenic patients who underwent AVWS for bothersome SUI and ≤ stage 2 anterior vaginal compartment laxity was reviewed. Any patient with prior SUI surgery or < a 6-month follow-up were excluded. Preoperative evaluation included detailed history, validated questionnaires [Urogenital Distress Inventory-Short form, visual analog quality of life score (QoL)], physical examination, and standing lateral voiding cystourethrogram (VCUG). Follow-up included VCUG at 6-12 months postoperatively, yearly examinations, and questionnaires. Failure was measured by a Kaplan-Meier curve using time to reoperation for SUI.

Results: Between 1996 and 2016, 171 patients met the study criteria. The median follow-up was 4.2 years, with 26 (15%) patients having over a 10-year follow-up. Median (interquartile range): age 64 (53-70), body mass index 26 (22-30), and parity 2 (2-3). Ninety-one (53%) patients underwent AVWS with a concomitant procedure, hysterectomy being the most common. Aa and Ba points, questionnaire results, and QoL improved post-operatively and remained improved over time. VCUG findings also improved for urethral support and bladder base reduction. SUI reoperation occurred in 9 (5%) patients, including: fascial sling placement (3) or injectable agents (6).

Conclusion: The AVWS procedure can correct SUI secondary to urethral hypermobility by restoration of the vaginal anatomic support to the bladder neck and bladder base.

Keywords: Anterior vaginal wall suspension, native tissue repair, burch suspension

Introduction

There is an overall paucity of available literature on the long-term outcomes for native tissue repair in the setting of stress urinary incontinence (SUI). The anterior vaginal wall suspension (AVWS) procedure is a modification of the four-corner suspension technique described by Raz in 1989 and has been performed at our institution since 1996 (1-4). The central concept originally put forth by Raz is to address the vaginal wall laxity as a whole, thus restoring support to the anterior vaginal compartment prolapse, which in turn corrects SUI secondary to urethral hypermobility (4). The previously described procedures either addressed anterior vaginal wall prolapse (e.g. Kelly-type plication) or urethral hypermobility (e.g. Marshall-Marchetti-Krantz or Burch culposuspension, Raz bladder neck suspension, or sling), but not both (5).

Initial results of the four-corner suspension were promising, however longer follow-up revealed a significant cystocele recurrence rate (6). It was hypothesized that failure occurred due to inadequate anchoring of the suspension sutures or gradual tissue pull-through. In 1989, Bruskewitz et al. (7) reported that helical loops of suture material in the abdominal rabbit fascia-minimized tissue pull-through compared with other-anchoring methods. Based on this concept, Zimmern et al. (8) published on the AVWS technique using suture placement in a helical fashion to broadly incorporate the full thickness of the anterior vaginal wall supporting the bladder neck and bladder base. This modification improved the durability of the

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repair, which similar to the Burch suspension, depends on the retropubic scar formation. Previous publications reported the outcomes of AVWS for > stage 2 anterior prolapse, uterine preservation, and concomitant hysterectomy (1-3). This study describes our experience with AVWS for SUI secondary to urethral hypermobility induced by anterior vaginal wall laxity.

Materials and Methods

Study Criteria

Following IRB approval, a single-surgeon database was reviewed for patients who had undergone AVWS procedure for the past 20 years. Included patients had bothersome SUI and stage ≤2 anterior vaginal compartment laxity on Pelvic Organ Prolapse Quantification System (POP-Q). Patients with less than 6-months follow-up, prior SUI surgery, or neurogenic bladders were excluded. The database has been prospectively maintained since 2004; data before that year were collected retrospectively. The data were collected by a third-party reviewer not involved in the care of these patients.

Preoperative Evaluation

Preoperative evaluation included a detailed history, validated questionnaires [Urogenital Distress Inventory-Short Form (UDI-6), visual analog quality of life score (QoL)], physical examination (using Baden-Walker grading until the POP-Q was adopted in 1999), and standing lateral voiding cystourethrogram (VCUG) (9). During physical examination, the conversion from Baden-Walker to POP-Q for Aa/Ba points was made using the following scale: grade 0 = Aa/Ba -3, grade 1 = Aa/Ba -2, grade 2 = Aa/Ba -1 or 0.

Regarding VCUGs, a previously standardized protocol was used (10,11). At a fixed bladder volume of 125 mL, the lower edge of the pubic symphysis was used as a reference point to compare lateral views of the urethral angle at rest and during straining to assess for urethral hypermobility, which has previously been defined as approaching a 20-degree gradient (12). The VCUG was also used to measure the lateral height of the cystocele below the lower edge of the pubic symphysis. Grade 0 corresponded to a lateral height of 0 cm or any positive value, grade 1: 0 to - 2 cm, grade 2: <-2 to -5 cm, and grade 3: <-5 cm.

AVWS Procedure

The AVWS procedure is a vaginal native tissue repair that corrects the anterior vaginal wall laxity from the bladder neck to the vaginal apex. The indication for this procedure is women with SUI secondary to urethral hypermobility from anterior vaginal wall laxity. The procedure has been previously described in the literature in detail and has remained unchanged over time (5,13). It is a modified Burch procedure done vaginally. In brief, bilateral longitudinal vaginal incisions are start lateral to the bladder neck and extended to the vaginal apex or cervix. Typically, two sets of #1 Prolene suspension sutures are placed broadly into the vaginal wall, excluding the epithelium, proximally and distally on each side at the level of the bladder neck and cystocele base, respectively. Suture placement is performed in a helical fashion to provide an even distribution of suture tension and prevent suture pull-through. A short, <2 cm midline suprapubic incision is then made to gain access to the tendinous portion of the rectus fascia inserted on the pubis. Then through each vaginal incision, using a blunt and sharp dissection, the endopelvic fascia is perforated to gain access to the retropubic space. Once the retropubic space is freed, a double-pronged ligature carrier is passed under finger control from the suprapubic incision down to the level of the vagina where the suspension sutures are threaded into the eyes of the ligature carrier before being withdrawn back suprapubically. Cystoscopy with 30° and 70° lenses is performed to assess for suture entry anteriorly or ureteric injury. The vaginal incisions are subsequently closed with running absorbable sutures. The suspension sutures are tied 1.5-2 cm above the tendinous portion of the rectus fascia without tension to provide support, but avoid over-correction of the anterior vaginal wall laxity.

Postoperative Follow-up

Postoperative visits were scheduled at 6 weeks, 6 months, 1 year, and then annually. One standing VCUG was performed for 6-12 months postoperatively to determine the degree of improvement in the anatomic support of the urethra and bladder base achieved by AVWS. Were examined by various clinicians, including Female Pelvic Medicine and Reconstructive Surgery (FPMRS) faculty, fellows, or FPMRS-trained physician assistants. Patients not seen in the clinic within the last 2 years were contacted using a structured telephone interview by a third party not involved in the care of these patients. The telephone interviews used questionnaires (UDI-6, QoL), questions about recurrent SUI symptoms, and inquires about SUI reoperation elsewhere.

The primary outcome was AVWS failure, defined as the need for reoperation for SUI. Secondary outcomes included long-term POP-Q scores based on prospective examinations and functional outcome based on questionnaire results, specifically the UDI6-Q3 (SUI) scores. The safety of the procedure was examined in terms of peri-operative complications.

Statistical Analysis

Descriptive statistics are given for continuous measures with medians and interquartile ranges; and for categorical measures with frequencies and percentages. Differences in characteristics between women who underwent another SUI surgery after AVWS and women who did not were tested using the Fisher's Exact test for categorical variables and either the t-test (age,

body mass index, parity) or the Kruskal-Wallis test (years of follow-up, visits per year).

A Kaplan-Meier curve determined UDI-6 Q3 failure-free survival (failure for score of 3) and reoperation-free survival over time for this population, as well as for subgroup comparisons of AVWS with concomitant hysterectomy vs. AVWS alone, and elderly patient >65 years old vs. those younger. Success rates included a loss to follow-up (LTF) analysis (14) considering the patients lost to follow-up as all success, all failure, or comparable to the followed population.

Mixed model analysis was used to determine whether there were trends in physical examination and questionnaire responses over time while controlling for baseline values. The "baseline" p-values refer to baseline values compared to the values during follow-up visits. The "years since AVWS" p-values refer to trends in post-AVWS values over time. All tests were two-sided and completed at the 0.05 significance level using SAS 9.4 (SAS Institute Inc., Cary NC).

Results

Patient Characteristics

Between 1996 and 2016, 171 of 274 patients met the study criteria. Excluded patients had prior SUI surgery (n=53), prior autologous or synthetic slings (n=16), less than 6-month follow-up (n=31), or neurogenic bladder (n=3).

Of the 73 patients not seen in the clinic within the last two years, 29 (40%) were reached by telephone interview. For those, the average distance from our tertiary care facility was 65 miles (standard deviation ±94 miles). Overall lost to follow-up rate was 29% (n=49/171), including deceased (n=5) or unreachable by telephone (n=44).

The median follow-up was 4.2 years, with the median number of visits per year at 1.0. Those with reoperation (n=9) had slightly increased follow-up time (median: 9.8, IQR: 4.4-10.3) compared to those with no reoperation (n=162, median: 4.1, IQR: 1.7-8.0) (p=0.0495). Fifteen percent of the total patients had over a 10-year follow-up. Patient characteristics are summarized in (Table 1).

Outcomes

Perioperatively, the most common complication was intraoperative bleeding (3%), with no blood transfusions required. Early complications (<6 weeks) included suprapubic wound infection (1%) and temporary urinary retention (1%). Late complications (≥6 weeks) included wound infection (1%) and pain (1%). There were no incidences of bladder perforation, erosion of sutures into the vagina, or delayed cystocele recurrence.

Postoperatively, all physical examination points and questionnaire results improved and remained so over time (Table 2). Though the trends were significant for some outcomes, there were no meaningful changes between the 1,

Table 1. Patient demographics

	Total Patients (%) (n=171)	No Reoperation (n=162)	Reoperation (n=9)	p
Age at AVWS, years (median, IQR)	64 (53-70)	64 (53-70)	68 (57-72)	0.5800
Follow-up, years (median, IQR)	4.2 (1.7-8.2)	4.1 (1.7-8.0)	9.8 (4.4-10.3)	**0.0495**
Visits/year of follow-up (median, IQR)	1.0 (0.6-1.5)	1.0 (0.6-1.5)	0.8 (0.6-1.1)	0.8141
Race				
Black	5 (3)	5 (3)	0 (0)	1.0000
Hispanic	4 (2)	4 (2)	0 (0)	
White	156 (91)	147 (91)	9 (100)	
Other	6 (4)	6 (4)	0 (0)	
BMI (median, IQR)	25.6 (22.3-30.1)	25.5 (22.3-29.9)	30.1 (27.3-31.9)	**0.0354**
Parity (median, IQR)	2 (2-3)	2 (2-3)	3 (2-3)	0.3171
Hysterectomy status				
Uterine sparing	24 (14)	22 (14)	2 (22)	0.2403
Concomitant hysterectomy	60 (35)	59 (36)	1 (11)	
Prior hysterectomy	87 (51)	81 (50)	6 (67)	
Concomitant surgery	91 (53)	89 (55)	2 (22)	0.0844
Post-AVWS SUI surgery	9 (5)	0 (0)	9 (100)	

AVWS: Anterior vaginal wall suspension, IQR: Interquartile range, BMI: Body mass index, SUI: Stress urinary incontinence

3, and 5 years post-AVWS time points. Standing VCUG findings were also significantly improved when compared pre- versus post-operatively (Table 3).

The overall success rate was 93% (n=113/122). Nine of 122 patients who required reoperation: Urethral bulking agents (6) and autologous sling placement (3) had a successful SUI outcome. The success rate assuming the LTF patients (n=49) were all successes was 95%, but 66% when assuming all were failures. Assuming the LTF patients (n=49) had a similar success/failure rate as the patients with follow-up (n=122), the overall success rate would be 93%.

As a secondary outcome, UDI-6 question 3 (SUI) results at the last encounter indicated that over half (52%) who completed the questionnaire were completely dry (score=0), while three-quarters (79%) had a score of 0-1.

The Kaplan-Meier 5-year UDI-6 Q3 failure-free survival rate and the reoperation-free survival rate was 94.3% [95% confidence interval (CI) 89.1, 97.0] and 94.7% (95% CI 89.0, 97.5), respectively (Figure 1). There was no significant difference between the Kaplan-Meier curves of patients with concomitant hysterectomy, prior hysterectomy, and uterine sparing AVWS procedure (p=0.33) (Figure 2). The age at the time of AVWS did not affect the time to reoperation (p=0.48) (Figure 3).

Discussion

This study aimed to report the outcomes of AVWS for treatment bothersome SUI secondary to urethral hypermobility from anterior vaginal wall laxity. For 171 patients with a median follow-up of 4.2 years, the success rate was 93% (66% LTF all failures, 95% LTF all successes), with success defined as no reoperations for SUI. Based on post-operative well-supported urethra by VCUG and urodynamic findings, recurrent SUI was most often due to secondary intrinsic sphincteric deficiency (ISD).

Both objective and subjective outcome measures showed significant improvement after AVWS that were maintained over time. Objective outcomes included POPQ Aa, Ba points and VCUG data, which had statistically significant improvement after AVWS and at 1, 3, 5-year follow-up with linear mixed model analysis. Subjective outcomes included UDI-6 (with a

Table 2. Linear mixed model estimates for physical exam and questionnaire data over time, controlling for baseline values

	Mean estimate (standard error)				LMM p-values	
	Baseline	1 Year	3 Years	5 Years	Baseline value	Years since AVWS
Physical Exam	(n=171)	(n=171)	(n=66)	(n=59)		
Aa (-3, +3)	-0.9 (0.1)	-2.8 (0.0)	-2.8 (0.0)	-2.8 (0.0)	0.0001	0.0675
Ba (-3, +8)	-0.8 (0.1)	-2.8 (0.0)	-2.7 (0.0)	-2.7 (0.0)	<0.0001	0.0001
Questionnaires	**(n=99)**	**(n=99)**	**(n=54)**	**(n=40)**		
UDI total (0-100)	44.2 (2.2)	21.0 (1.6)	23.3 (1.4)	25.7 (1.6)	0.0076	0.0008
UDI Q2 (0-3)	1.6 (0.1)	0.7 (0.1)	0.9 (0.1)	1.0 (0.1)	0.0045	<0.0001
No OAB Tx	1.5 (0.1)	0.6 (0.1)	0.8 (0.1)	0.9 (0.1)	0.0363	<0.0001
OAB Tx	1.9 (0.3)	1.3 (0.2)	1.4 (0.2)	1.6 (0.3)	0.1685	0.2547
UDI Q3 (0-3)	1.7 (0.1)	0.6 (0.1)	0.7 (0.1)	0.8 (0.1)	0.0011	0.0043
UDI Q5 (0-3)	0.8 (0.1)	0.4 (0.1)	0.4 (0.0)	0.5 (0.1)	0.9195	0.1048
	(n=97)	**(n=97)**	**(n=54)**	**(n=40)**		
QoL (0 - 10)	6.1 (0.3)	1.9 (0.2)	2.2 (0.2)	2.5 (0.2)	0.0022	0.0080

AVWS: Anterior vaginal wall suspension, LMM: Linear mixed model, Aa, Ba: Points, POP-Q: Pelvic organ prolapse quantification system, UDI: Urinary distress inventory, OAB: Overactive bladder, Tx: Treatment, QoL: Visual analog quality of life score, 1 year, 3 year, and 5 year mean estimates were calculated from LMM model estimates at the mean baseline value

Table 3. Mixed model least square means for baseline versus post-AVWS mean score comparison

	Patients	Baseline vs. Post-AVWS		
		Baseline	Post	p
VCUG				
UAR (degrees)	123	33.5	16.9	<0.0001
UAS (degrees)	122	53.5	23.5	<0.0001
UAR-UAS (degrees)	122	20.2	6.5	<0.0001
Lateral height (cm)	125	-2.4	-0.3	<0.0001

AVWS: Anterior vaginal wall suspension, VCUG: Voiding cystourethrogram, UAR: Urethral angle at rest, UAS: Urethral angle during straining

focus on UDI-6-Q3 related to SUI) and QoL questionnaire scores, which also showed sustained improvement.

These favorable results are similar to the previously published long-term data on a different cohort of women undergoing AVWS for stage >2 anterior prolapse and uterine preservation (1-3).

Other groups have published comparable success rates with AVWS. The original Raz et al. (15) bladder neck suspension had a reported success rate of 90.3% (mean FU 15 months, n=206). A study (n=82) on the 2 or 4 corner Raz et al. (15) bladder suspension revealed an 88% improvement rate (mean FU 4 years, n=48) (16). Another study on AVWS with bone anchors (mean FU 2 years, n=20) reported a cure rate of 95% with no recurrent cystocele, paravaginal defects, or detrusor overactivity (17,18).

A comprehensive review of >10-year follow-up studies for all open anti-incontinence procedures (tension free vaginal tape, transobturator sling, retropubic suspensions, Burch, fascial sling, Stamey needle suspension) reported SUI reoperation rates of 2%-37% (19). Therefore, our rate of reoperation was consistent with other standard anti-incontinence procedures (20).

In addition to providing a durable repair, the AVWS procedure resulted in minimal complications. Intraoperatively, bleeding risk, bladder perforation [previously reported risk 1.6% (1)], or ureteric injury did not occur in this cohort. Postoperatively, urinary tract infection, urinary retention, and wound infection was also uncommon. Because this procedure does not directly affect the urethra or change the voiding dynamics, secondary detrusor over activity is seldom observed (21), as confirmed by relatively unchanged UDI-6 Q2 results over time. The *de novo* damage that occurred in 12 patients was treated with medications. Suture extrusion along the anterior vaginal wall (not encountered in this series) has been previously described post-operatively. An exposed suture can be easily cut with no changes in the anterior vaginal wall support once the retropubic scar has developed. There is a low risk of POP recurrence, consistent with previous reports (1-3).

Lastly, in this series, no information regarding sexual activity before or after AVWS was collected. However, in a previous study (n=56, mean follow-up 24 months), postoperative sexual function was not affected, as AVWS preserves the caliber and length of the vaginal canal (22).

The study strengths include a well-characterized population of women with bothersome SUI and early anterior compartment

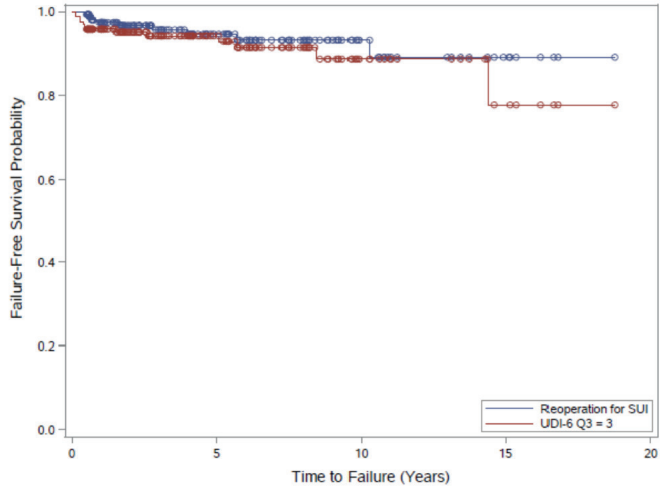

Figure 1. Kaplan-Meier Curve: UDI-6 Q3 failure-free survival and reoperation-free survival after anterior vaginal wall suspension

SUI: Stress urinary incontinence, UDI: Urinary distress inventory

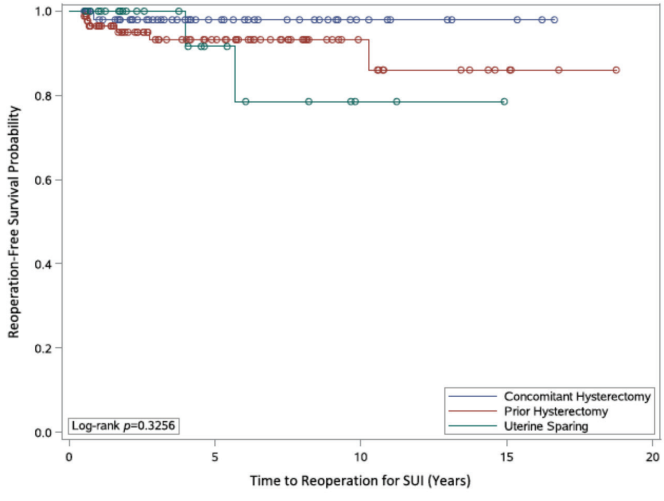

Figure 2. Kaplan-Meier Curve: Reoperation-free survival based on hysterectomy status during anterior vaginal wall suspension procedure

SUI: Stress urinary incontinence

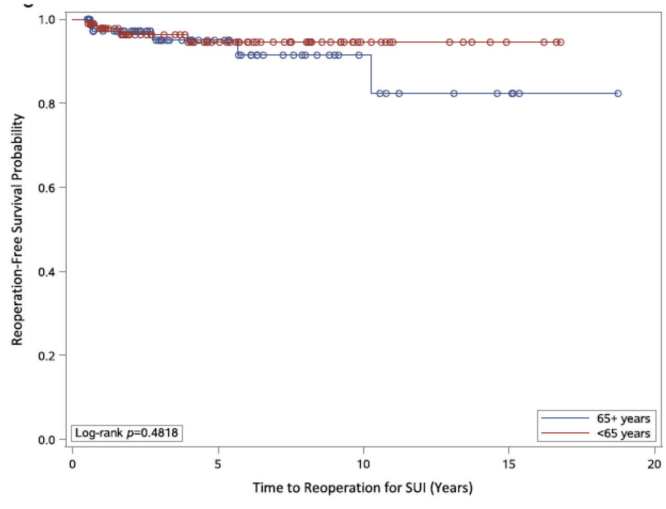

Figure 3. Kaplan-Meier Curve: Reoperation-free survival based on age at the time of anterior vaginal wall suspension procedure

SUI: Stress urinary incontinence

prolapse treated with AVWS with adequate median follow-up. The outcomes included objective and subjective parameters. The data were collected retrospectively before 2004, but since then has been prospective.

Study Limitations

Limitations to this study include being a single surgeon series and patients lost to follow-up. Travel for repeat follow-up appointments can be difficult in this aging population and may seem unnecessary to those doing well and satisfied with their operative results. Alternatively, LTF patients could have sought out care elsewhere for recurrent SUI management.

Additionally, defining failure as the need for reoperation secondary to recurrent bothersome SUI provides a definitive data point. It is our experience that, like in other long-term studies (23), patients who did not pursue reoperation were overall satisfied with their postoperative quality of life even if they had mild SUI recurrence.

Native tissue repair techniques for anterior POP should be part of the female pelvic surgeon's armamentarium, especially in the current state of synthetic vaginal mesh controversy (24). This study supports the that the AVWS procedure is an attractive management technique for surgeons and patients alike given its durability, simplicity, and low morbidity. It is a less than one-hour surgery which can be associated with other procedures (hysterectomy, apical suspension, posterior repair (25), with no negative effects on success rates. It is also very suitable for obese patients since a vaginal approach carries less morbidity than a retropubic approach. Lastly, AVWS is cost-effective compared with other vaginal anti-incontinence procedures (26).

Conclusion

In this mid-term follow-up study, the AVWS procedure was shown to be a durable, simple, and safe non-mesh repair alternative to treat SUI secondary to urethral hypermobility by restoring the vaginal anatomic support to the bladder neck and bladder base.

Ethics

Ethics Committee Approval: XX

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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Emphysematous Pyelonephritis: A Twelve-year Review in A Regional Centre

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What's known on the subject? and What does the study add?

It is known that emphysematous pyelonephritis is a severe and life threatening illness that does not have a clearly defined treatment algorithm. This paper shows the experience of treating this disease over 12 years and reinforces that there remains a role for both minimally invasive therapy as well as extensive surgical intervention, but further research into this condition is required.

Abstract

Objective: To examine outcomes and prognostic features of patients admitted with emphysematous pyelonephritis (EPN) at a regional tertiary centre.

Materials and Methods: Nineteen patients with EPN were identified between January 2007 and December 2019. Patients were grouped into two "mild" (grade I or II); and "severe" (grade III or IV) based on their Huang and Tseng classification. The two groups were compared using Fisher's Exact tests to determine prognostic features associated with poor outcome, defined as extensive surgical intervention or death.

Results: Thirteen patients had mild disease and six patients had severe disease. 69% of patients had ureteric obstruction, 58% were diabetic, 26% were thrombocytopaenic, and there was a female predominance (12:7). Poor outcomes were significantly more common in patients with severe disease (83%), versus mild disease (8%) ($p<0.0001$). Half of the patients managed with sole medical management died (two of four patients) and only two patients required escalation to extensive surgical management, both of whom survived. Overall mortality during admission was 19%; encompassing three of six patients with severe disease (50%) and one of thirteen patients with mild disease (8%).

Conclusion: EPN is dangerous, requiring prompt recognition and intervention, and is of increasing importance given the aging population and increased prevalence of comorbidities associated with the disease. This study of the largest recorded cohort of patients with EPN in Australia it was found that poor outcomes were significantly more common in patients with high radiological-grade disease, and severe thrombocytopaenia.

Keywords: Emphysematous pyelonephritis, urinary tract infections, nephrectomy, percutaneous nephrostomy, pyelonephritis

Introduction

Emphysematous pyelonephritis (EPN) is a rare but life-threatening infection, characterized by "necrosis of the renal and peri-renal tissues by gas-producing bacteria" (1). Patients with EPN usually present with fever, flank pain, pyuria, raised inflammatory markers and septic shock. Therefore, differentiating EPN from severe pyelonephritis on clinical features alone is challenging. Hence, computerized topography (CT) is necessary for diagnosis.

An example of a system for radiological grading for the severity of EPN has been described by Huang and Tseng (2) in 2000, and is displayed in Table 1.

The grading system described above is frequently described in two groups, mild disease, encompassing class I and II grades, and

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severe, including classes IIIA, IIIB and IV. Example images from the study cohort are shown in Figure 1, displaying severe disease (class IIIB, left frame) and mild disease with concurrent ureteric calculus causing obstruction (class I, right frame).

Because of the severity and high mortality rate of EPN, early diagnostic CT and appropriate treatment are critical to prevent morbidity and mortality (3).

It is necessary that clinicians are familiar with poor prognostic features and signs of EPN as the average age of the general population increases and comorbid conditions that elevate both the risk of developing EPN and the risk of a poor outcome become more prevalent (4).

The primary purpose of this study was to validate the prognostic value of the radiological grading system for EPN. Secondary purposes were to provide evidence regarding the risk factors for poor outcomes and assist with clinical decision making.

Materials and Methods

An ethical waiver to report these cases was obtained from Hunter New England Human Research Ethics Committee (authorisation number: AU202007-19) for a retrospective audit performed on all imaging requests and reports, and all discharge summaries issued in our institution between January 1, 2007 and December 31, 2019 that contained the term "emphysematous pyelonephritis", "emphysematous pyelitis", as well as all patients coded with an unspecified variant of "pyelonephritis" as per the Intentional Classification of Disease.

Patient demographics were retrieved electronically and clinical, laboratory, treatment and post-treatment variables were identified by analysis of relevant medical records.

Patients with radiological Huang class I or II were classified as mild, and Huang class IIIa/b and IV were classified as severe, consistent with previous studies (5-7). The groups were compared with Fisher's Exact and T-testing for independent variables.

"Good" outcomes were defined as a response to medical and/or renal decompression. "Poor" outcomes were defined as extensive surgical intervention or death, which is consistent with outcome reporting described in a previous series (2,8).

Table 1. Grading system described by Huang and Tseng (2)	
Class I	Gas in the collecting system only
Class II	Parenchymal gas only
Class IIIA	Extension of gas into perinephric space
Class IIIB	Extension of gas into pararenal space
Class IV	EPN in a solitary kidney or bilateral disease
EPN: Emphysematous pyelonephritis	

All imaging had previously been reviewed by consultant radiologists.

Results

Eighty-nine patients were identified from the medical records electronic review. Seventy patients were excluded: 62 with simple pyelonephritis, five with emphysematous cystitis, two with incomplete medical records, and one due to a pre-existing ureteric stent. Nineteen patients with EPN were identified for further investigation.

The demographics of the cohort are displayed in Table 2.

Twelve of the 19 patients (63%) were female and 11 patients had diabetes mellitus (DM) (58%). Median age was 65 years [interquartile range (IQR) 13] with no statistically significant difference in age between severity groups (p>0.1).

All cases were unilateral; 11 cases were left sided (58%), one of which was a left pelvic transplant kidney.

Fourteen (74%) patients presented with septic shock; nine of those had mild disease and five had severe disease. Septic shock was defined according to local guidelines as two or more of the following criteria; temperature >38 °C or <36 °C; heart-rate >90 bpm; respiratory rate >25 breaths/min or <10 breaths/min; white cell count >12.000 mm^3 or <3.000 per mm^3 and systolic blood pressure <90 mmHg (9). Six patients who presented with septic shock had poor outcomes (40%). All patients without evidence of septic shock had good outcomes.

The white cell count was elevated in 12 of the 19 patients (63%), and C-reactive protein (CRP) was elevated in all patients who were tested, with no significant difference in laboratory titer between the severity groups (p>0.1).

Table 2. Patients demographics, n (%)	
Median age in years (IQR)	**65 (IQR 13)**
Male	7 (37%)
Diabetic males	4 (57%)
Female	12 (63%)
Diabetic females	7 (53%)
Diabetic total	11 (58%)
Ureteric obstruction	13 (68%)
Left side EPN	12 (63%)*
Right side EPN	7 (37%)
Haematuria on presentation	15 (79%)
Septic shock on presentation	14 (74%)
Immunosuppressed	13 (68%)
Hypoalbuminaemia (<30 g/L)	13 (68%)
Thrombocytopaenia (<150x10^9/L)	5 (26%)
*Includes single case of transplanted kidney, EPN: Emphysematous pyelonephritis, IQR: Interquartile range	

Thrombocytopaenia was present in five of 19 cases (26%) and was more common in those with severe disease (n=3; 50%). Statistical significance was reached with the degree of thrombocytopaenia (p=0.041), but not with the frequency of thrombocytopaenia (p>0.1) between the severity groups.

Hypoalbuminaemia was present in 13 of the 17 patients tested (77%), and in all cases of severe disease tested (n=5) however, there was no statistically significant difference between the two groups (p=0.051).

Elevated blood sugar levels (BSLs) were detected in 12 of the 18 patients tested (67%). Hemoglobin A1c (HbA1c) was performed in 10/11 patients with diabetes and was >7% (indicative of poor glycemic control) in nine cases (90%). For mild disease median BSL on presentation was 8.3 mmol/L (IQR 4.4 mmol/L), with a median HbA1c of 9.5% (IQR 3.4%). For severe disease median BSL was 10.5 mmol/L (IQR 6 mmol/L), with a median HbA1c of 7.4% (IQR 0.5%). However, subgroup analysis revealed no statistically significant difference in HbA1c or BSL on presentation between the severity groups (p>0.1).

Microbiological testing revealed organisms similar to those seen in pyelonephritis/urinary tract infection. Sixteen of 18 urine cultures were positive (90%) and 14 of 16 blood cultures were positive (88%).

The organisms cultured from urine were *E. coli* in 13/16 (72%), *Klebsiella pneumoniae* in 2/16 (11%) and mixed *Enterococcus aurogenes* and *Enterococcus faecium* in 1/16. Blood cultures grew *E. coli* in 12/14 (86%), and *Klebsiella pneumoniae* in 2/14 (14%).

Table 3 shows the treatment received by patients graded according to the Huang and Tseng (2) classification. Obstruction was identified in 13 cases (68%); of which 10 cases were caused by ureteric calculi, two by ureteric stricture, and one by a displaced ureteric stent. Of the 13 patients in the mild group, 11 had identified causes of obstruction (85%), compared with two of the six patients in the severe group (33%).

Percutaneous nephrostomy (PCN) was performed in eight patients of whom none required further escalation, including a patient who had EPN of a transplant kidney (grade IV).

Table 3. Treatment based on radiological grading

Grading	Number (n=19)	Treatment	Outcome (Good vs. Poor)
Class I	5	3 x PCN	3 x Good
		1 x MM	1 x Good
		1x RS	1 x Good
Class II	8	3 x RS	2 x Good 1 x Poor*
		4 x PCN	4 x Good
		1 x MM	1 x Good
Class IIIA	3	2 x MM 1 x Palliation	2 x Poor 1 x Poor
Class IIIB	2	1 x SD	1 x Poor*
		1 x EN	1 x Poor*
Class IV	1	1 x PCN	1 x Good

MM: Medical management, PCN: Percutaneous nephrostomy, RS: Retrograde stent, EN: Emergency nephrectomy, SD: Surgical drainage, *Patient failed initial conservative/decompressive management, highest intervention required displayed.

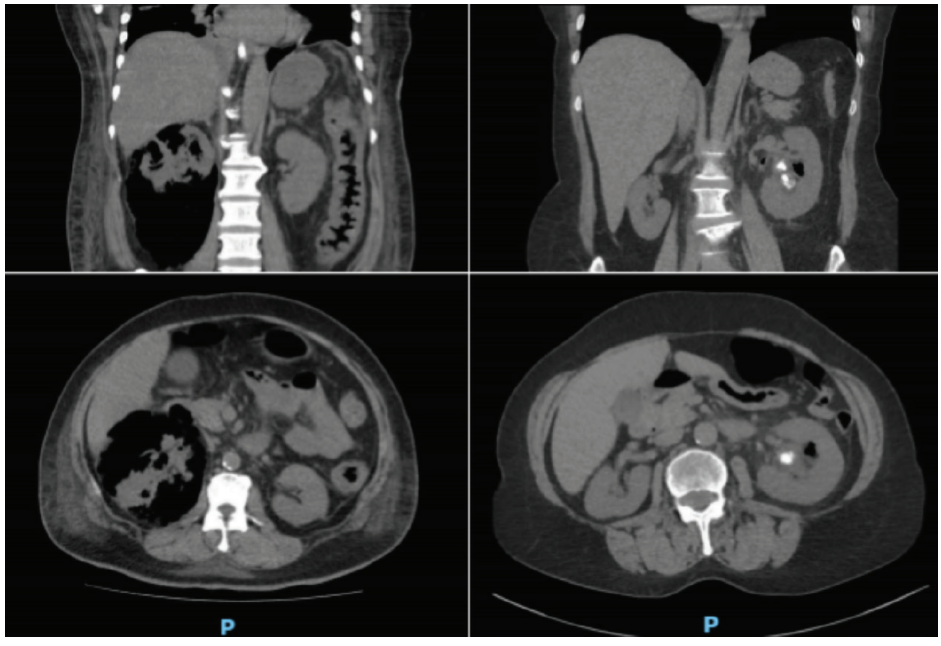

Figure 1. Severe disease (Class IIIB, left frame) and mild disease with concurrent ureteric calculus causing obstruction (Class I, right frame)

Double J (DJ) stents were inserted acutely in five patients. Of those, two patients responded without further intervention; one patient-required escalation to open surgical debridement; and one case required subsequent emergency nephrectomy after continued haemodynamic instability. The final patient who underwent DJ stent insertion elected to pursue palliative management after minimal response to renal decompression and subsequently died. Subgroup analysis of patients undergoing PCN vs DJ stent insertion was performed and there was a statistically significant difference (p=0.035) in favour of PCN. Four patients were treated with medical management only; two were treated successfully and two died.

58% of patients (n=11) required admission to the intensive care unit (ICU): 65% (n=8) of patients with mild disease and 50% (n=3) of patients with severe disease. However, of the three patients with severe EPN who were not admitted to the ICU; one died in the emergency department 2 hours after presentation; another declined admission and subsequently died. The final patient had class IV disease according to the classification, with a pelvic transplant kidney that had gas only within the collecting system, but that patient had no evidence of significant sepsis. Of the 14 patients who presented with septic shock, 10 (71%) required ICU, while one patient who did not fulfill criteria for septic shock on presentation required ICU after developing persistent hypotension following PCN.

The median hospital length of stay (LOS) was eight days (IQR 20 days) for mild disease, and 16 days (IQR 27 days) for severe disease. The median ICU LOS was 2 days (IQR 2 days) for mild disease, and 1 day (IQR 7.8 days) for severe. There was no statistically significant difference in the ICU admission rate, ICU LOS, or hospital LOS between the severity groups.

Six of 19 patients had poor outcomes (32%). Four died (21%), and two required extensive surgery (11%). Of the patients who died, one patient with evidence of ureteric obstruction elected for immediate palliative management due to concurrent comorbidities, and another chose palliative management after failing to respond to renal decompression. Two patients died after failing to respond to medical management alone; one died within two hours of presentation to the hospital before further intervention could be instituted, the other declined more intensive treatment. All patients who died or required extensive surgical intervention initially presented in septic shock but this was not found to be statistically significant (p>0.1), likely due to inadequate power. Fifteen patients (79%) were discharged home after successful treatment, two of whom had required extensive surgical intervention. The majority of patients with poor outcomes were patients with severe disease based on radiological grading (5/6; 83%; p<0.01).

Discussion

EPN is a rare but life-threatening infection, characterized by "necrosis of the renal and peri-renal tissues by gas-producing bacteria" (1). It was first reported in 1898 by Kelly (10), and less than 800 cases have been reported worldwide to date. With the increasing prevalence of risk factors for the condition, it is likely that the incidence of EPN will increase (4). The mortality rate of EPN ranges from 11-42% (11-13), with a recent international meta-analysis reporting overall mortality of 19% (7).

DM is the most common predisposing factor and is present up to 95% of patients with EPN (14,15). This is thought to be due to high glucose concentrations and poor perfusion in the microenvironment providing ideal conditions for the growth of gas-producing bacteria (16). Ureteric obstruction has been implicated in 25-40% of cases (17).

Other risk factors for mortality reported include age, shock on presentation, poor glycemic control (defined as HbA1c >7%), thrombocytopaenia, and need for emergency nephrectomy (2,8,11,16,18,19).

The initial management of EPN requires intravenous antibiotics, aggressive fluid, and electrolyte resuscitation. Renal decompression through either PCN, or retrograde DJ stent insertion is used in an attempt for renal preservation, is particularly important in patients with chronic renal failure, solitary kidneys and transplant allografts (20,21). However, there are still those who advocate emergency nephrectomy of the affected kidney immediately after clinical stabilization, or if no improvement is achieved with initial treatment (22-24).

A systematic review of 10 retrospective studies reported a mortality rate of 50% with medical management alone compared to 13.5% with renal decompression with PCN (5). Other studies have reported successful treatment of severe disease (Class IV) with medical management alone, including cases of bilateral disease (20).

Huang and Tseng (2) reported in their seminal paper an overall survival rate of 81% however, almost 20% of all patients required EN. Jain et al. (8) reported cure in 90% of 72 patients, with 80% renal preservation. However, of those that underwent nephrectomy (n=14), 14% died. Shoiker et al. (23) reported that conservative management was successful in 92% of patients, however 30% of their cohort required subsequent nephrectomy of the affected kidney within four years. This shows that although surgical management can be effective in severe cases, escalation to invasive measures should be used as a last resort (2,7,14,23-25).

In our cohort 58% of patients had DM and proportionally more were women (12:7). *E. coli* was the most frequently isolated causative pathogen, as expected (26). The rate of

both DM and female predominance were lower than the rates reported in previous studies. Obstruction was present in 13 patients (68%), which is higher than the previously reported rate of 25-40% (17). 83% of patients with severe disease were diabetic (n=5) compared with 46% of patients with mild disease, but neither the presence of DM nor glycaemic control correlated with severity or outcomes, consistent with current literature (5,7).

There were more poor outcomes in patients with severe thrombocytopaenia (p=0.041), but no difference in the prevalence of thrombocytopaenia between the two groups (p>0.1). The laboratory values measured, including albumin, CRP and white cell count did not correlate with the outcome, consistent with prior findings (6,7,16). ICU admission was required in 58% of patients, which was slightly higher than 36.5% reported in some other series (27). Unusually, the rate of ICU admission was higher in the mild group compared to the severe group-though this is likely due to one early death, and one patient electing to withdraw care and the limitations with sample size.

Renal decompression was sufficient for treatment in most cases, consistent with current literature (5,7,8). PCN was effective in the treatment of all cases, whereas patients who underwent DJ stent insertion required escalation in 40% of cases. 60% of patients who underwent DJ stent insertion had poor outcomes, statistically significantly higher than those undergoing PCN insertion (p=0.035). Two patients failing to respond to renal treatment with extensive surgical intervention recovered well postoperatively and were discharged home without complication.

Four patients died (21%); two patients elected to withdraw care; one patient died before significant intervention could be instituted. There was a 50% cure rate for patients treated exclusively with medical measures, however there were more mortality (n=2) compared to those treated with renal decompression (n=1) or operative measures (n=1), consistent with the outcomes reported in previous analyses (8,11,24). Perhaps patients with a higher chance of mortality due to poorer baseline health were offered less invasive treatment options, hence causality cannot be inferred.

The rate of poor outcomes was statistically significantly higher in patients with severe disease based on the radiological grading systems (p=0.0005). This supports the validity of the radiological grading system categorizing patients into severe and mild disease. We found that higher grade disease had a trend toward higher mortality, longer overall hospital stay, higher morbidity, and more invasive intervention, though these were not found to be statistically significant - potentially secondary to inadequate power.

Study Limitations

We acknowledge that there are limitations of this study; it is underpowered due to the rarity of the disease, and there are biases present secondary to the retrospective retrieval of data. However, given that EPN is a rare and dangerous disease with an increasing number of susceptible individuals, all additions to the worldwide literature are beneficial to assist with the development of evidence-based guidelines for managing such a dangerous condition.

Conclusion

EPN is a life-threatening disease, but there is an increasing body of evidence that early treatment with renal decompression and intravenous antibiotics is sufficient in most cases. There are no established management guidelines for treating EPN, and opinions conflict regarding the efficacy and timing of conservative versus aggressive intervention. This is of particular significance given that there is a marked increase in the prevalence of risk factors and comorbid conditions, such as diabetes and chronic renal disease, in the context of an aging population.

In our experience, the radiological grading system described by Huang and Tseng is an effective prognostic tool. We found that most patients with EPN can be safely managed with antimicrobial therapy and renal decompression, preferentially with PCN insertion, including patients with Grade IV disease. Patients who present in septic shock with concurrent thrombocytopenia warrant close observation and aggressive surgical intervention if they fail to progress. However, further multi-centre series must establish treatment guidelines for this disease state.

Ethics

Ethics Committee Approval: An ethical waiver to report these cases was obtained from Hunter New England Human Research Ethics Committee (authorisation number: AU202007-19).

Informed Consent: Retrospective study.

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CASE REPORT
Endourology

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J Urol Surg, 2022;9(3):209-211

Migration of LAPRA-TY Clips in Ureter and Collecting System Mimicking Urinary Stones Following Laparoscopic Partial Nephrectomy

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Abstract

We present a rare case of the clip migration after laparoscopic partial nephrectomy in which the clips were misdiagnosed as urinary stones. A 57-years-old female presented with right flank pain 3 months after the surgery. A computed tomography scan showed a 4 mm stone in the left upper ureter and hydronephrosis. Another 3 mm stone was also detected in the left upper calyx. Rigid ureteroscopy and flexible ureterorenoscopy revealed two LAPRA-TY clips, which were embedded in the upper ureter and calyx. The clips were fragmented by holmium laser lithotripsy and removed with stone basket. Pain and hydronephrosis are resolved at follow-up.

Keywords: Nephrectomy, clip, urinary stone

Introduction

Laparoscopic and robotic partial nephrectomy (PN), which are minimally invasive surgeries, have become popular and established as standard treatments for localized renal cancer. These surgeries are still technically challenging. Especially, renorrhaphy is a stressful part to shorten warm ischemic time. LAPRA-TY clip (Ethicon Endosurgery, Cincinnati, OH, USA) is used to reduce the ischemic time and make the surgery easier because it secures the sutures quickly, unlike the conventional knot tying during renorrhaphy. However, the clips may be moved into the renal parenchyma and misdiagnosed as urinary stones.

Case Report

A 57-years-old female presented with a sudden right flank pain in emergency room. She had undergone laparoscopic PN 3 months earlier. The operation was performed for a 1.5 cm sized, totally endophytic tumor at mid pole. The tumor had been excised with anterior segmental arterial clamping. A small defect in the collecting system was repaired using a 3-0 vicryl. Tightness had been achieved by Lapra-ty clipping. The absorbable fibrin sealant product had been applied to the parenchymal bed. Continuous running sutures with 2-0 vicryl have been used for parenchymal and capsular closures. Operation and warm ischemic time was 80 min and 21 min. The bleeding amount had been about 100 cc, and the postoperative course had been uneventful. Pathologic result had been a 1.2x1 cm sized renomedullary interstitial cell tumor. Her flank pain was radiating to the right groin. Urinalysis showed microscopic hematuria and pyuria. Abdominopelvic computed tomography (CT) scan showed a 4 mm stone in the left upper ureter (hounsfield unit: 159) and grade 2 hydronephrosis (Figure 1). Another 3 mm stone was also detected in the left upper calyx. The two stones were radiolucent on plain X-ray. Rigid ureteroscopy revealed LAPRA-TY clip, which were embedded in the upper ureter and misdiagnosed as urinary stones (Figure 2). The clip was fragmented using Holmium laser lithotripsy and removed with a stone basket. Additional flexible ureterorenoscopy revealed another LAPRA-TY clip in the upper calyx. It was also taken out using a stone basket. The removed clips were broken but not calcified. The operation time was 15 min. The pain and hydronephrosis were resolved at follow-up.

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J Urol Surg,
2022;9(3):209-211

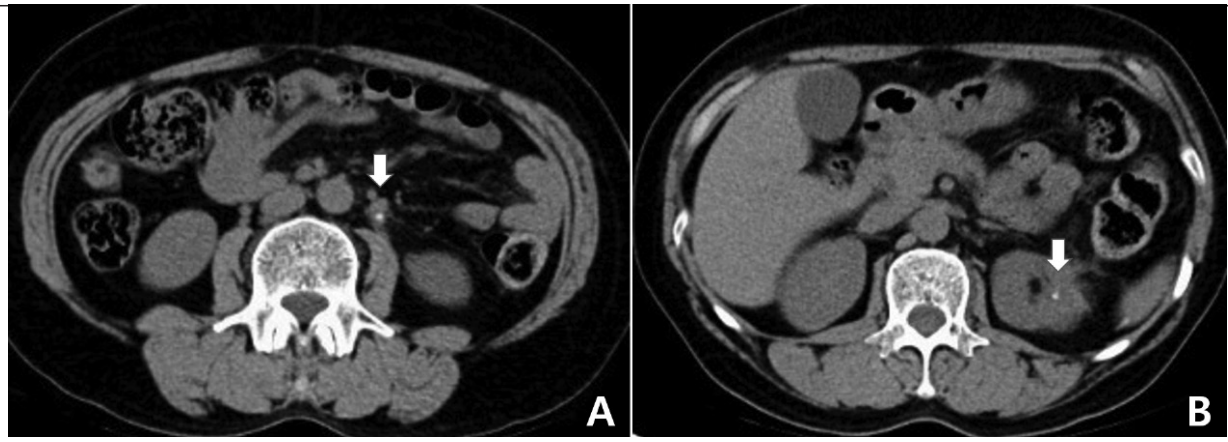

Figure 1. Abdominopelvic computed tomography scan showed a 4 mm stone (arrow) in left upper ureter (Hounsfield Unit: 159) (A). Another 3 mm stone (arrow) was also detected in left upper calyx (B)

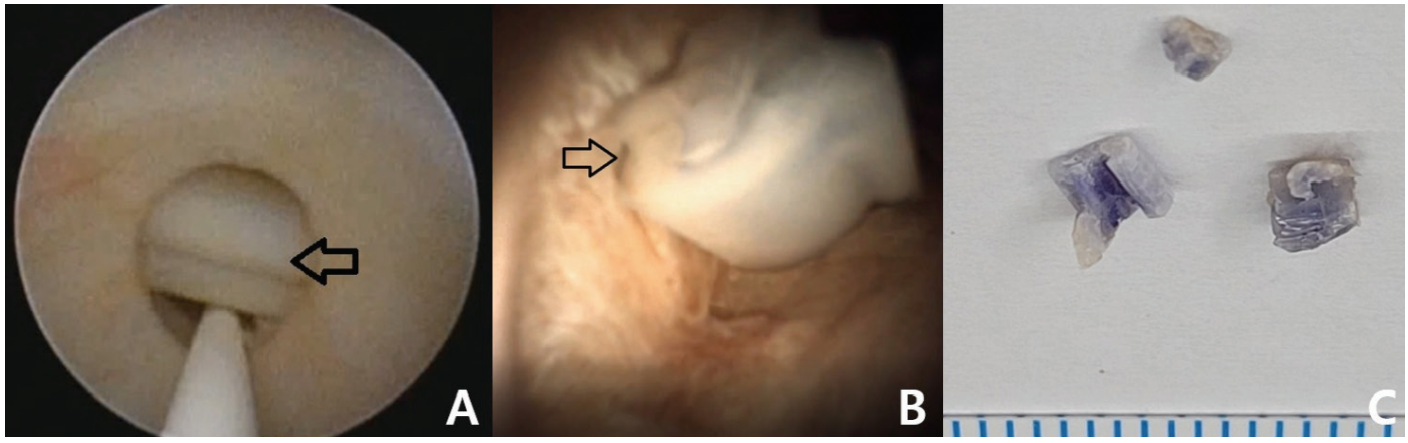

Figure 2. Ureteroscopy showed a white foreign body, LAPRA-TY clip, in the upper ureter (A). Flexible ureterorenoscopy found another clip in upper calyx (B). Removed clips were broken, and the size was seen in millimeter scale (C)

Discussion

Surgical clips may migrate to abnormal positions in urologic surgeries. Metal clips have been found in the bladder and urethra after radical prostatectomy in several cases (1). The clips might induce voiding difficulty and urinary infection (2). Furthermore, the clips may act as niduses for stone formation when they are in contact with urine (3). The migration of surgical clips into the collecting system is rare, but has been consistently reported after laparoscopic and robotic PN. Rare cases of ureteral migration of Hem-O-Lok clips (Teleflex, Research Triangle Park, NC, USA) after PN have been reported (4,5). The clips were misdiagnosed as urinary stones and removed with endoscopic surgery. A similar case with absorbable LAPRA-TY suture clips has been reported after PN. It was found in the collecting system and misdiagnosed as urinary stone (6).

Migrated surgical clips showed similar findings of urinary stones on imaging study. Hem-O-Lok clips are radiopaque on CT images with 223 to 570 HU (5,7). The clip can be suspected as it shows a curved design in the early stage after surgery, but as the calcification worsens, the shape of the clip disappears. In this study, it was initially diagnosed as a urinary stone because the patient complained of colicky flank pain and hyperdense lesions in the ureter and calyx on CT images. However, CT showed HU of 152, which was lower than that of stone and appeared radiolucent on plain X-ray. These migrated clips can be found in days or years after surgery (6,8). If there are no symptoms, it can be discovered incidentally on imaging studies and diagnosed as urinary stones. After symptoms develop, they can be passed spontaneously after conservative treatment, but they can also be removed through endoscopic surgery.

There are some hypotheses as to why the surgical clips migrated to the collecting system after PN. If the operative view during renorrphay is not secured due to severe bleeding, the clipping to knot will be inaccurate, and as a result, the clip will be deep into the collecting system. And excessive tension on the suture will also cause the clip to move (5). Therefore, if LAPRA-TY clipping is incorrectly performed in the renal bed, careful observation

and treatment are required. In this study, even after clamping the renal segmental artery, there was bleeding, so accurate operative view was unclear. And, clipping was performed while pulling excessively after the sutures.

Conclusion

Intrarenal movement of LAPRA-TY clip after PN is very rare, but it is possible. As in our case, the migrated clips into the collecting system can obstruct the ureter and induce similar symptoms and CT findings of urinary stone. During PN, clear operative view should be ensured, and excessive tension to the suture knot should be avoided to prevent migration of the clip.

Ethics

Informed Consent: Written informed consent was omittable and the omission was also approved.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: I.Y.S., T.H.O., Concept: I.Y.S., Design: I.Y.S., Data Collection or Processing: T.H.O., Analysis or Interpretation: I.Y.S., Literature Search: T.H.O., Writing: I.Y.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT
Reconstructive

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J Urol Surg, 2022;9(3):212-214

Free Ileal Flap: An Alternative Approach to Urethral Reconstruction

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Abstract

The scarred urethra remains a difficult reconstructive problem. Patients who have undergone multiple attempts at reconstruction lack the local tissue necessary for successful management using traditional techniques. In this report, we present two cases of urethral reconstruction performed at our institution with free ileal flaps. Both patients suffered from chronically strictured urethra, having failure multiple prior operative interventions. A joint plastic and genitourinary reconstructive surgical team excised all scarred native urethra, harvesting and inserted an ileal free flap for successful urethral substitution. Postoperatively, both intestinal neourethras remain patent. We offer this technique as a promising alternative solution to the reconstructive challenge.

Keywords: Urethral reconstruction, microsurgery, reconstructive

Introduction

Reconstruction of the scarred urethra remains a challenge. In the repeatedly operated patient, paucity of well-vascularized tissue often precludes the use of many described techniques, such as local skin flaps. Free flaps have been described as an option, with studies advocating the use of fasciocutaneous forearm flaps (1-3). However, these flaps carry significant donor site morbidity, including visible scarring and risk of vascular compromise to the hand. The use of intestinal flaps has been infrequently described, last in 2011, in which a transgender male patient's urethra was reconstructed with a free jejunal flap (4-6). We present the first two cases of anterior urethral reconstruction using free ileal flaps performed in cis-male patients with early postoperative results.

Case Reports

All patients undergoing ileal free flap urethral reconstruction were identified with pre-, intra-, and post-operative data collected.

Case 1

A 31-years-old-male presented with an obliterative bulbar urethral stricture. He sustained perineal trauma at age 11 and had undergone multiple reconstructive procedures with skin flaps. He initially presented to us with a suprapubic tube in place and underwent the first stage urethroplasty with a buccal mucosal graft and gracilis flap for the creation of a perineal urethrostomy. The urethrostomy closed with the contraction of the buccal graft. Given his extensive surgical history, reconstruction was planned with an ileal free flap.

Case 2

A 35-years-old-male presented with recurrent urethral stricture since the age of 15 secondary to perineal trauma. He had failed multiple attempts at reconstruction, most recently staged urethroplasty using a gracilis flap with perineal urethrostomy creation with subsequent stenosis of the urethrostomy. Cystoscopy revealed an obliterated membranous urethra. Reconstruction was planned with a free ileal flap.

Operative Techniques

The ileal flap harvest was approached via a lower midline laparotomy incision. The terminal ileum (TI) was identified, and a 17 centimeter (cm) and 15 cm segment of bowel located 15 cm proximal to the TI was marked in cases 1 and 2, respectively. The mesentery of this section of the bowel was transilluminated to identify the proximal ileal artery and vein along with distal arcades supplying the bowel. The bowel was stapled at each end;

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marginal arcades were divided and the mesentery was dissected down to the proximal artery and vein to adequate vessel size and length. A side branch of the ileal vein was maintained in each case as an option for secondary venous outflow.

The deep inferior epigastric vessels were chosen as recipient vessels and were dissected through the same laparotomy incision. These were divided and brought down to the groin through the external ring for anastomosis. The saphenous vein was harvested and tunneled to the groin with anastomosis to the deep inferior epigastric artery (DIEA) for the creation of an arteriovenous (AV) loop.

The AV loop was divided after the flap was fully harvested with anastomosis between the DIEA and ileal artery and the ileal vein and saphenous vein proper (Figure 1). In Case 1, an ileal vein side branch was anastomosed to the deep inferior epigastric vein using a vein graft. Fluorescent angiography confirmed excellent inflow and outflow to the flap, which was then inserted in an isoperistaltic direction into the defect.

The ileal segment was prepared for urethral anastomosis by stapling the bowel over a 24-French catheter on the antimesenteric side (Figure 2). Proximal urethral anastomosis proceeded with absorbable sutures. The ileal flap was then divided at the appropriate point for distal anastomosis, with the distal segment used as a monitoring limb. Distal urethral anastomosis was then completed. A suprapubic tube was retained for urinary diversion.

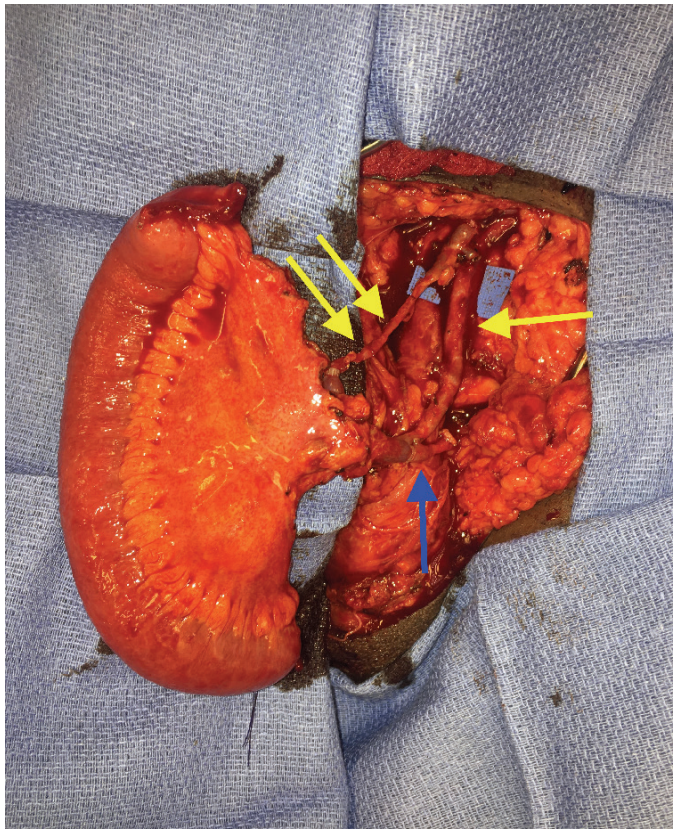

Figure 1. Free ileal flap after anastomosis between the ileal artery and the deep inferior epigastric artery via saphenous arteriovenous loop (yellow arrow), ileal vein proper and saphenous vein (blue arrow), and ileal vein side branch and deep inferior epigastric vein via vein graft (double yellow arrows)

Outcomes

Patient 1's postoperative course was uneventful, whereas Patient 2's course was complicated by an abdominal wall abscess requiring IR drainage and prolonged intravenous antibiotics. There were no flap-related complications.

After 3 weeks postoperatively, cystourethrogram performed in Patient 1 revealed no extravasation, and at 3-months follow-up, he demonstrated normal voiding per the neourethra. He returned to the operating room 4 months postoperatively for takedown of his suprapubic tract and monitoring of the ileal segment. He was found to have a patent ileal urethral anastomosis with high bladder capacity. Cystoscopy in Patient 2 six weeks postoperatively revealed concern for distal anastomotic leak; however, it resolved on repeat study 2 weeks later. He returned to the operating room 3 months postoperatively for excision of his monitoring ileal limb and cystoscopy, which revealed narrowing at the proximal urethral anastomosis, treated with

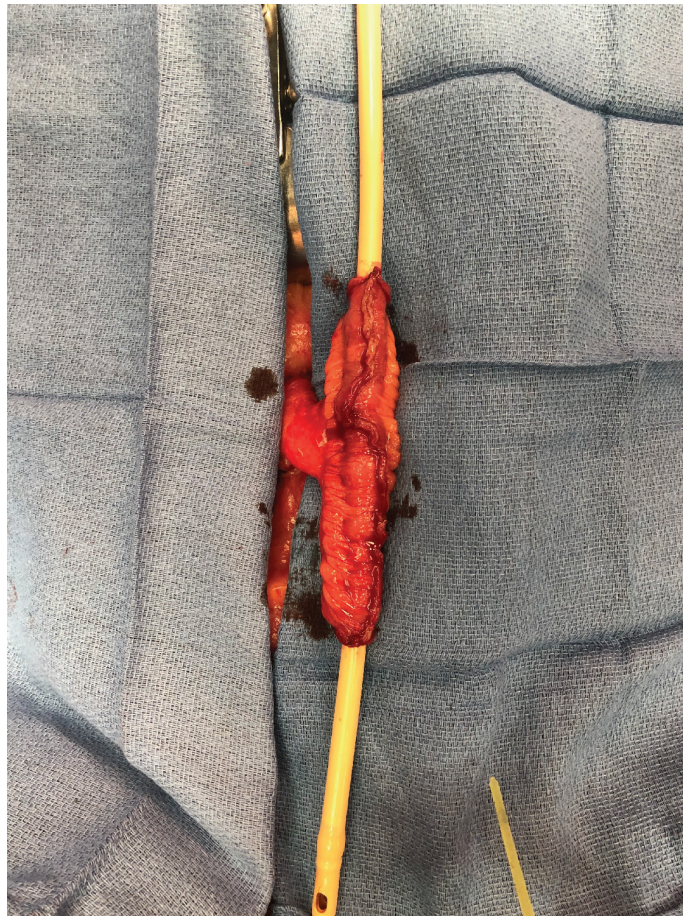

Figure 2. The free ileal flap is crafted into a neourethra by stapling the bowel on the anti-mesenteric side over a 24-Franch catheter

balloon dilation with good effect. At 4 months postoperatively, he is voiding well per the neourethra.

Discussion

The reconstructive armamentarium for treating severe urethral strictures remains limited. The addition of vascularized tissue in the form of a free flap can be beneficial to these patients (7). While the tubed forearm flap remains a viable option, no alternative flap has yet to be identified when this donor site is not available. The use of a jejunal flap for urethral reconstruction has been previously described in three patients (4,5). We prefer to use the ileum for multiple reasons. First, the identification of a usable bowel segment proximal to the ileocecal valve is simple. The luminal diameter is also smaller compared to the jejunum, better approximating that of the native urethra and requiring less manipulation for neourethral construction. Additional advantages include the fact that it is hairless; better providing a like-with-like reconstruction compared to forearm flaps; and can be used to reconstruct large segments of diseased urethra due to the availability of intestine.

Despite these advantages, several concerns exist. The need for a laparotomy and bowel manipulation for flap harvest is a significant consideration. Neither patient experienced a bowel-related complication. Additionally, while our short-term results yield promising outcomes, long-term follow-up is required.

In conclusion, we present our experience with free ileal flaps for urethral substitution in two patients who suffered traumatic perineal injuries and failed conventional methods of reconstruction. This technique represents an alternative for plastic and genitourinary reconstructive surgeons faced with end-stage urethral stricture, fistula, or obliteration of any etiology. Finally, the two-team approach with plastic and urologic surgery is invaluable in these cases.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: L.M.A., D.A.D., J.D.F., L.C.Z., J.P.L., Concept: L.M.A., D.A.D., J.D.F., L.C.Z., J.P.L., Design: L.M.A., D.A.D., J.D.F., L.C.Z., J.P.L., Data Collection or Processing: L.M.A., D.A.D., J.D.F., L.C.Z., J.P.L., Analysis or Interpretation: L.M.A., D.A.D., J.D.F., L.C.Z., J.P.L., Literature Search: L.M.A., D.A.D., J.D.F., L.C.Z., J.P.L., Writing: L.M.A., D.A.D., J.D.F., L.C.Z., J.P.L.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT
General Urology

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J Urol Surg, 2022;9(3):215-217

Testicular Torsion: Not Just in Young Men

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Abstract

Testicular torsion (TT) is a urological emergency, which requires a time-sensitive approach to diagnosis and management. TT predominantly presents with severe, sudden onset, unilateral testicular pain in men under the age of 21. It is a clinical diagnosis with assistance from a scrotal ultrasound or confirmation via scrotal exploration. Here we present an interesting case of a 67-year-old man with TT. This case demonstrates that medical professionals should have a high degree of clinical suspicion for men of all ages with unilateral scrotal pain.

Keywords: Testis torsion, scrotal pain, orchidectomy

Introduction

Testicular torsion (TT) is a urological emergency, occuring when the contents of the spermatic cord twist within the tunica vaginalis causing ischemia of the testis. TT has a bimodal incidence, it is seen in neonates and post pubescent boys between the ages of 12-18 (1,2). The incidence of TT is approximately 3.8 in 100.000 men under the age of 25 (3), with 6% of these occurring in men older than 31 (4).

Case Report

A 67-year-old man presented to the emergency department with a 24-hour history of acute, right-sided testicular pain radiating to the flank. The pain was described to be intermittent and episodic for over 50 years, often lasting for several hours at a time and it felt like his testicle was twisted. The pain would then gradually alleviated when lying flat. There was no other significant past medical or surgical history.

On examination, his right testis was swollen, tense and mildly tender. A testicular ultrasound (US) showed features consistent with right testicular and epididymal torsion with infarction (Figure 1). The US also showed arterial Doppler flow present in the left testicle and bilateral complex hydroceles. All other investigations were otherwise normal.

Upon urgent surgical exploration, the right testicle was torted to 900 degrees, with signs of associated ischemia/infarction (Figure 2). The testicle was not viable and orchidectomy was performed. His left testis demonstrated "Bell Clapper deformity" and testicular fixation was performed. Post-operative histopathology showed changes in keeping with hemorrhagic infarction.

Discussion

The most common diagnosis for adults with acute scrotal pain over the age of 25 years is epididymo-orchitis. In this age group, TT occurs less frequently and often with a worse prognosis due to a delay in diagnosis and management leading to a greater degree of torsion of the testis (5). The viability of a testis torted for more than 24 hours is less than 10% leading to severe testicular ischemia (6).

A diagnostic TT can be made with a high index of clinical suspicion after a thorough history and examination. Patients commonly present reporting severe, sudden onset, unilateral testicular pain. Physical examination findings may show a patient with a swollen testis, erythematous and be tender on palpation. Further findings may include a horizontal or high riding testicle and an absent cremasteric reflex (7). Imaging of a suspected TT is primarily conducted by Doppler US of the

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scrotum. US images are compared to the contralateral testicle and may indicate TT through findings such as a whirlpool sign or reduced flow seen as decreased or no waveform on colour Doppler (8). Complications of TT occur secondary to testicular ischemia and are closely related to the degree of torsion of the testis and ischemic duration. TT may lead to sub/infertility, testicular infarction, necrosis, and loss of the testis (9).

Goh et al. (10) found that men over the age of 50 years were being misdiagnosed on the first presentation, 53.8% of the time. 57% of these men required orchidectomy, with a salvage rate of 43%. On exploration, elderly men were also seen to have higher degrees of torsion of 585 degrees, compared with 431 degrees in men under the age of 21 (5).

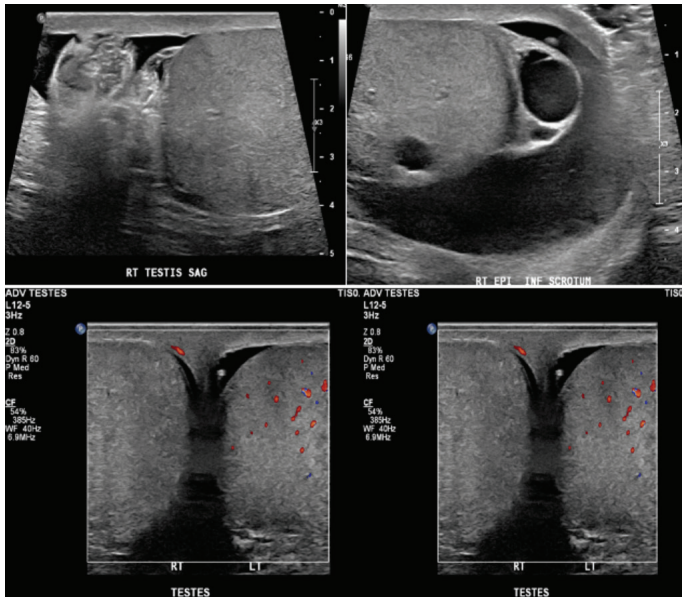

Figure 1. Preoperative ultrasound showing a loss of power doppler in the right testicle indicating ischemia (4 panel figure)

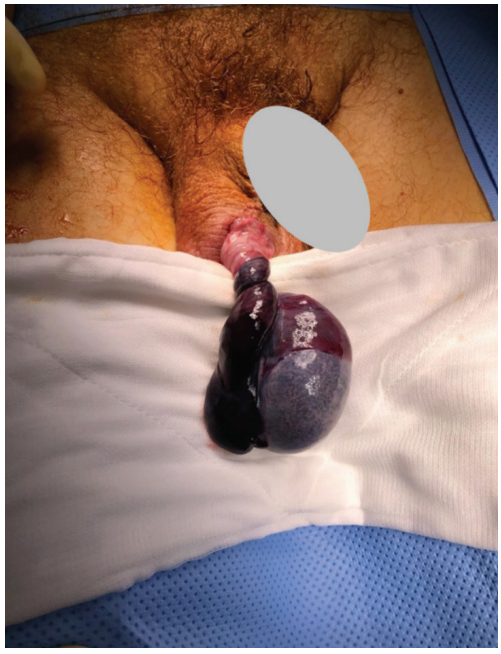

Figure 2. Intra operative image of the torted testis with signs of associated ischemia/infarction

Here, our patient also presented with Torsion-detorsion syndrome (TDS). TDS is defined as intermittent, sharp testicular pain with intervals in which the patient is asymptomatic (11). This occurs due to periods in which the testis is torted then deported causing ischemic and reperfusion injuries. Men with a long history of acute on chronic scrotal pain should be examined further for the risk of TDS. This could reduce the likelihood of TT later in life.

This case report highlights the importance of maintaining TT as a differential diagnosis for acute scrotal pain in older men. With the potential severity of TT, the need to diagnose and treat early is essential. Therefore, the treating doctor should keep a high degree of clinical suspicion of TT in men of all ages.

Ethics

Informed Consent: Written and informed consent from the patient was obtained for publishing.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.H., C.V., M.J.R., Concept: J.S., S.H., M.J.R., Design: J.S., M.J.R., Data Collection or Processing: J.S., R.S., M.J.R., Analysis or Interpretation: J.S., R.S., M.J.R., Literature Search: J.S., R.S., M.J.R., Writing: J.S., R.S., C.V., M.J.R.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT
Endourology

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J Urol Surg, 2022;9(3):218-220

Metastasis of Gastric Signet-Ring Cell Carcinoma to the Bladder: An Incidental Finding During Cystoscopy

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Abstract

Signet-ring cell carcinoma of the bladder is very rare pathology and can be seen as a primary disease or a metastatic manifestation. In this case report, we present the metastasis of gastric signet-ring cell carcinoma to the bladder, which was detected incidentally during follow-up of a 45-years-old male patient who had previous Ta low-grade urothelial cell carcinoma diagnosis.

Keywords: Signet-ring cell carcinoma, bladder metastasis, gastric metastasis

Introduction

Signet-ring cell carcinoma accounts for a very low rate of bladder neoplasms (0.5-2%) (1). If this histology, which is considered resistant to chemotherapy and radiotherapy, is detected in the bladder, the diagnosis of whether the disease is the primary bladder or metastatic becomes essential. In this article, we present the gastric plasmacytoid/signet ring/diffuse carcinoma metastasis detected during routine cystoscopy in a patient who is being followed up for primary bladder urothelial cell carcinoma.

Case Report

A 43-years-old male patient was evaluated for painless hematuria, and a 2 cm mass in the bladder was detected during the urinary ultrasonography. Cystoscopy was performed and a solitary papillary bladder mass was resected. The pathological diagnosis was low-grade non-invasive urothelial cell carcinoma (Ta). The patient was followed up in routine urological evaluation since this date. During the first cystoscopy control, there was no pathological finding in the bladder, but the next two cystoscopy revealed a recurrence of the bladder tumor with the same histological features (Ta Lowgrade). Due tu this recurrent behavior of the disease, intracavitary mitomycin-c chemotherapy is offered and started. After the 5th instillation of the therapy, the patient developed severe irritative symptoms and the treatment was terminated. During his follow-up, the patient never reported macroscopic hematuria.

In the ultrasonography performed 2 years after the initial diagnosis of the patient, a 2 mm lesion that was visible within the bladder wall and forming a slight bulge toward the lumen was detected (Figure 1). Cystoscopy was performed. Consistent with ultrasonography, a mild edematous, reddish area was detected in this region (Figure 2). Cold-cup punch biopsy was taken. According to the immunohistochemical staining performed, it was found as a signet-ring cell infiltrate under the urothelium, invading the entire lamina propria, containing intracytoplasmic mucin. There was an oncological burden in 3 relatives of the patient (2 lymphoma, one lung cancer). Because of this pathology, the patient underwent gastroscopy and colonoscopy. No pathological formation was detected in the colon. In gastroscopy, there was no significant mass formation in the stomach, but multiple ulcers were detected, predominantly in the corpus and antrum (Figure 3). Pathological analysis showed plasmacytoid/signet ring/diffuse carcinoma (weak cohesive type poorly differentiated adenocarcinoma) in biopsy samples which were obtained from

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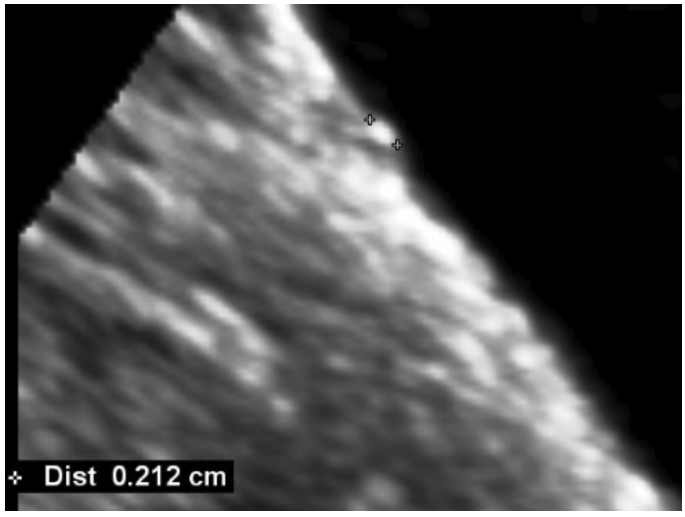

Figure 1. Ultrasonography image of the lesion

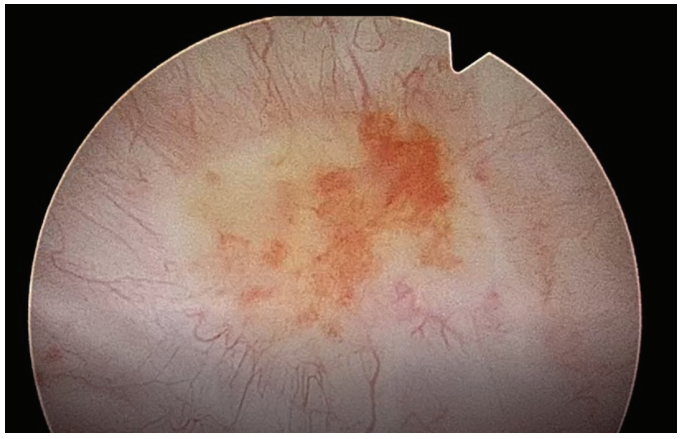

Figure 2. Cystoscopic image of the lesion

these ulcers. Immunochemistry study results were as this: CK20 +, CK7 +, CDX2 +, 0 PASAB +).

In the fluorodeoxyglucose positron emission tomography and abdominopelvic magnetic resonance imaging of the patient, no significant mass formation or metastatic lymph nodes were detected except for thickening in two areas in the bladder and loss of pili in one area of the stomach. The patient is referred to the medical oncology and systemic chemotherapy is initiated.

The patient received 4 cycles of FLOT (fluorouracil. leucovorin, calcium folinate, oxaliplatin) chemotherapy. It was then evaluated at the oncology board and the general surgery offered the option of gastrectomy. The patient underwent gastrectomy. The pathology of the gastrectomy specimen was consistent with primary gastric signet ring cell carcinoma: pT1a, plasmacytoid/signet ring/diffuse carcinoma, signet-cell 60%, cribriform 30%, undifferentiated 10%, with negative surgical margins and metastasis was detected in 34 of 64 lymph nodes removed. The patient's postoperative chemotherapy continues.

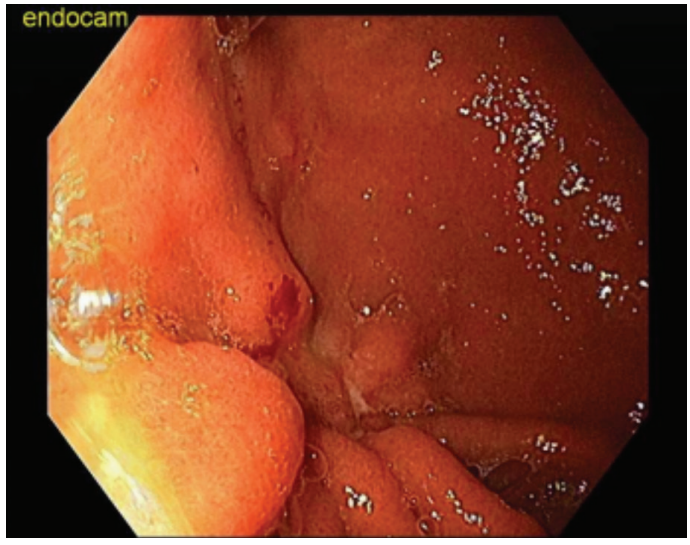

Figure 3. Gastroscopic image: Ulcers

Informed consent was obtained from the patient to share medical information.

Discussion

Although signet ring cell carcinoma is very rarely detected in the bladder, the diagnosis of primary signet-ring cell carcinoma of the bladder is even less so, when such a case is encountered, screening of the gastrointestinal tract becomes essential (2).

Adenocarcinoma of the bladder is usually in the form of invasion of adjacent organs such as the colon and prostate, sometimes primary bladder adenocarcinoma can be detected (3). In such cases, it is essential to correctly identify the carcinoma by immunohistochemical study. In our patient, the IHC studies showed positive results for CK20, CK7, CDX2, and 0 PASAB stains (4).

Generally, gastric signet ring cell carcinoma is detected in the advanced stages. In this patient, routine follow-up because to a previous diagnosis of urothelial carcinoma led to the relatively early detection of the disease, which did not yet cause any radiological or clinical symptoms. Although the appearance of a lesion during cystoscopy is not typical, it can be interpreted in favor of reactive changes in the patient with a history of severe irritation due to intracavitary mitomycin-c treatment, but biopsy was taken due to the possibility of a possible variant pathology or carcinoma *in situ*, and the approach was confirmed for detecting the patient's primary disease.

Ethics

Informed Consent: Informed consent was obtained from the patient to share medical information.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.D., A.R.K., Y.S., Concept: T.D., Design: T.D., Data Collection or Processing: T.D., M.B.T., Analysis or Interpretation: T.D., M.B.T., A.R.K., Y.S., Literature Search: T.D., M.B.T., Writing: T.D., M.B.T., A.R.K., Y.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT
Pathology

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Primary Renal Synovial Sarcoma

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Abstract

Primary renal synovial sarcoma is a rare malignancy that may present similarly to other renal neoplasms. The diagnosis of synovial sarcoma is performed through the identification of a *SYT-SSX* gene fusion. Here, we present a case of a primary renal synovial sarcoma in a patient who presented with renal mass initially thought to be renal cell carcinoma until further pathological characterization. After undergoing radical open nephrectomy, the patient developed pulmonary and psoas metastases and was treated with systemic therapy.

Keywords: Synovial sarcoma, kidney neoplasm, SYT-SSX

Introduction

A synovial sarcoma is a malignant mesenchymal tumor that notably presents adjacent to large joints. A primary synovial sarcoma arising from the kidney is rare with limited reports in the literature. As such, it is unlikely to be on the differential diagnosis list of most urologists (1). More likely, the diagnosis is made upon renal mass biopsy or after surgical extirpation.

Characterization of the synovial sarcoma is performed histologically and at the molecular level through the presence of a *SYT-SSX* gene fusion of t(X;18)(p11.2;q11.2) (2). Because of the rarity of this malignancy, reports outlining the most effective management are scarce (3). Furthermore, due to the rarity of primary renal synovial sarcomas, descriptive case presentations can provide valuable insight into the clinical presentation and management of this malignancy to improve medical and surgical management (1).

Here, we present a case of a primary renal synovial sarcoma in a 35-year-old female patient who presented with a renal mass initially thought to be renal cell carcinoma, but was determined to be a primary synovial sarcoma upon pathological investigation. Informed consent by the patient to publish the details of this case was obtained.

Case Report

A 35-year-old female patient presented to her family physician with sudden and severe right-sided flank and abdominal pain. She underwent computed tomography scans revealing a 5.2 cm heterogeneous enhancing right-sided renal mass with associated retroperitoneal hematoma (Figure 1). A prominent retroperitoneal lymph node adjacent to the right ureter was present and appeared stable in size (8 mm) compared to previous imaging. The left kidney was unremarkable. Bloodwork noted an acute decrease in serum hemoglobin, which was treated with 1 U of packed erythrocytes. The patient denied constitutional symptoms such as weight loss or fever and denied any history of hematuria.

The patient's medical history was unremarkable apart from morbid obesity. A right renal biopsy was performed and the specimen was sent to pathology that detected a SYT-SSX translocation through a multiplex real-time polymerase chain reaction assay. Pathological investigation determined the presence of a primary monophasic synovial sarcoma with a mitotic rate of 21 per 100 high power field and a pathologic staging (pTNM) of pT1b. Immunohistochemical analysis demonstrated strong positivity for BCL-2 and moderate positivity for CD99 (Figure 2). Liver lesions discovered upon imaging were biopsied

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and characterized as benign and not metastases associated with the renal synovial sarcoma. No other sites of disease were identified, and after multidisciplinary discussions with medical oncology, radical open nephrectomy and a paracaval lymph node dissection were recommended.

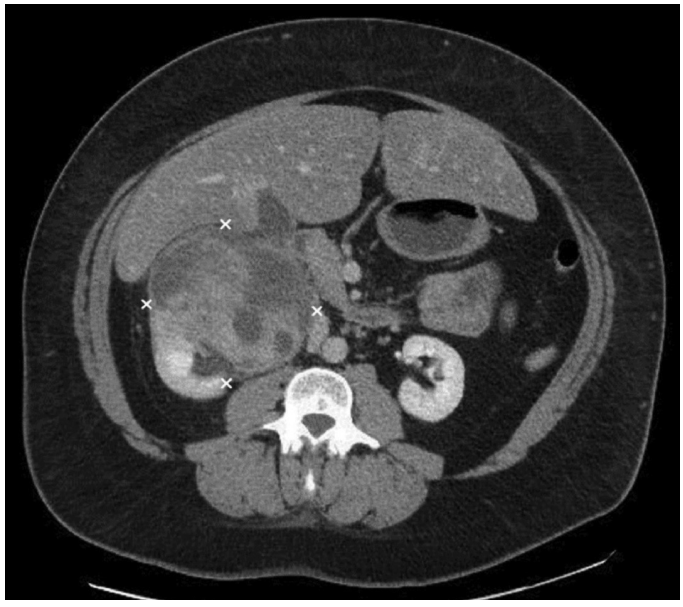

Figure 1. CT scan showing a right renal synovial sarcoma located within the collecting system of the upper, middle, and lower pole. A right perinephric hemorrhage with mass effect on the kidney and right ureter was also noted

A midline laparotomy approach was used with a full retroperitoneal exposure, including mobilization of the root of the mesentery and temporary evisceration of the bowel. A significant mass effect on the vena cava with dense adhesion was noted. At the level of the renal hilum, an excision of the renal vein os with primary closure of the inferior vena cava was performed. A paracaval lymph node dissection was then performed.

Tumor dimensions were 13.5 cm x 12.5 cm x 8.5 cm, showing rapid growth in the 3 months between initial imaging and surgery. Tumor involvement of the collecting duct region with extension into the perinephric fat and the renal vein was found. Surgical margins were negative for tumour involvement. The paracaval lymph nodes were negative for metastasis.

In hospital, the patient recovered uneventfully and was discharged home on post-operative day 5. Unfortunately, 6 months after surgery on the first surveillance imaging, multifocal pulmonary metastases developed and the patient was started on doxorubicin single-agent systemic therapy. After 5 cycles of doxorubicin treatment with an unsatisfactory response, the patient began single-agent ifosfamide treatment. Fifteen months after surgery, a right psoas metastasis developed and the patient was started on gemcitabine and docetaxel. Twenty-four months after surgery the patients remain alive and with stable disease.

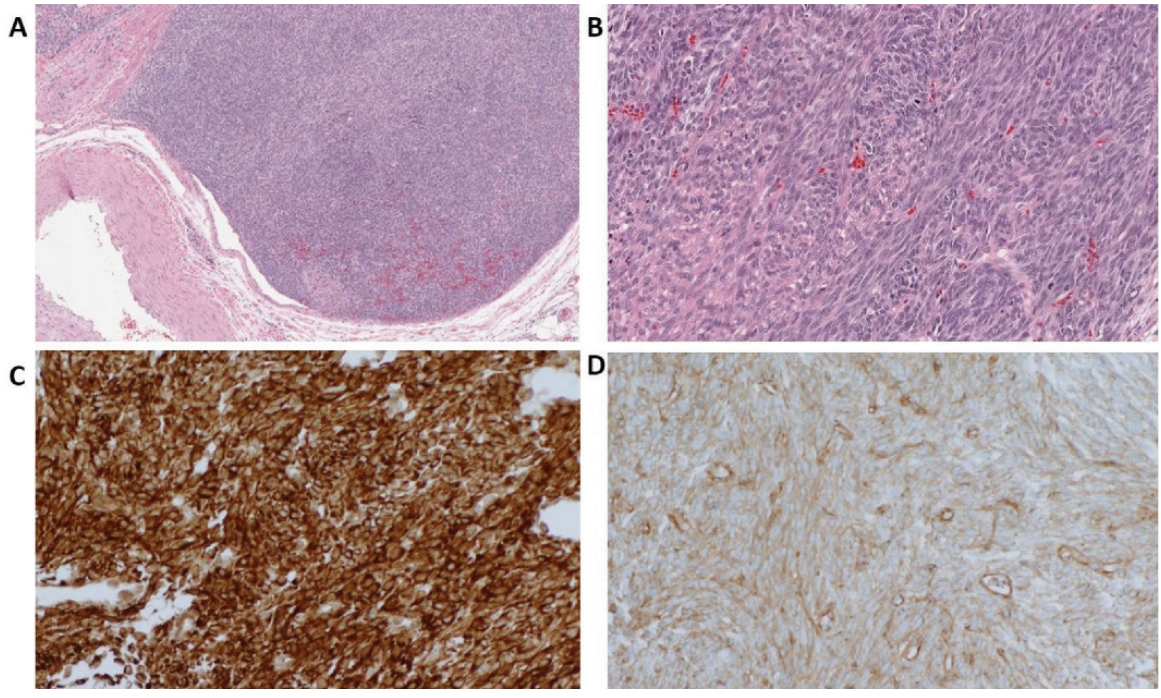

Figure 2. (A) Renal synovial sarcoma (4x HE Stain) showing interlacing fascicles of spindle neoplastic cells with high mitotic index and tumor invasion into a renal vein branch. (B) Dot-like keratin expression without distinct epithelial component, histologic (FNCLCC) grade of 3 (Differentiation score: 3, Mitosis score: 3, Necrosis score: 1) (20x HE Stain). (C) Strong BCL-2 expression (membranous and cytoplasmic pattern) detected in the tumor cells (100x magnification). (D) Moderate level of CD99 expression (membranous pattern) detected (100x magnification)

Discussion

Primary renal synovial sarcoma is a rare malignancy that presents similarly to a renal cell carcinoma and is associated with high rates of metastasis (3). The median age for diagnosis is 36.5 years with a male-to-female ratio of 1:1 (1,3). As this median age is approximately half that of renal cell carcinoma (61 years), there is an increased relative likelihood of renal synovial sarcoma being the cause of malignancy in younger patient presentations (4). The median overall survival in patients who underwent radical nephrectomy is 48 months (3).

The initial clinical presentation in cases of primary renal synovial sarcoma has been described to include abdominal or flank pain (67%) and hematuria (38%) (3,5). Here, our patient presented initially with abdominal and flank pain, which progressed to life-threatening hemorrhage.

As the clinical and radiological presentation of synovial sarcoma is indistinguishable from other renal malignancies, the gold standard for diagnosis is through pathologic examination demonstrating a *SYT* gene translocation (1). Metastatic disease upon diagnosis is rare (8%), although there is an increased incidence of metastasis post-nephrectomy (36%) with the median time of metastasis development occurring 33 months post-operation (3). Additionally, the most common sites of metastasis post-nephrectomy include the lung (42%), abdominal lymph nodes (29%), and liver (24%), highlighting the importance of follow-up investigations in patients with this malignancy (1,3).

For the treatment of primary synovial sarcoma without evident metastatic disease, radical nephrectomy is the first-line approach to attempt to achieve local control and reduce metastasis and recurrence risk. For metastatic cases, surgical resection and chemotherapy (ifosfamide and doxorubicin) has shown success, with meta-analyses highlighting the efficacy of doxorubicin in reducing overall recurrence, promoting remission and reducing tumour volume (6). Although studies have shown success in tumour-volume reduction, there is controversy regarding the impact of overall survival in patients undergoing adjuvant chemotherapy due to the sparsity of randomized controlled trials (7). Recently, immunotherapy has shown promise for the treatment of synovial sarcoma (8). For metastatic or surgically unresectable locally advanced sarcoma, pembrolizumab, an anti-PD-1 monoclonal antibody, has demonstrated a 10% objective response rate in a phase II trial (9). For patients with advanced synovial sarcoma who have progressed on other approved therapies, targeted therapies such as pazopanib have demonstrated non-inferior progression-free survival and similar overall survival compared with doxorubicin (10).

Conclusion

This case describes a rare primary renal synovial sarcoma in a 35-year-old female presenting with retroperitoneal hemorrhage that was initially thought to be renal cell carcinoma. These rare malignancies can pose surgical challenges and have a high potential for metastatic progression. Prompt extirpation of the localized disease provides the best chance for cure.

Ethics

Informed Consent: Informed consent by the patient to publish the details of this case was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.A.R., B.C., C.W., K.D.H., J.M., R.J.M., Concept: W.M., R.A.R., B.C., K.D.H., Design: W.M., K.D.H., Data Collection or Processing: W.M., C.W., K.D.H., Analysis or Interpretation: W.M., R.A.R., B.C., C.W., K.D.H., Literature Search: W.M., Writing: W.M., C.W., K.D.H.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT
General Urology

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J Urol Surg, 2022;9(3):225-227

Mobile Charger Cable in Urinary Bladder of a Patient with No History of Mental Disorder

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Abstract

Numerous reports have indicated a foreign body in the bladder. Various objects, or more precisely, everything in the human environment, have been found in the urinary bladder. In the current case study, the patient was a single 38-year-old woman who was referred to the emergency department with the complaints of lower urinary tract symptoms. The patient's history and radiological examination confirmed the presence of a foreign body (mobile phone charger cable) in the bladder. Since the patient was not mentally retarded and had no history of substance abuse, investigating other mental disorders and sexual abuse for her was recommended.

Keywords: Foreign body, bladder, mobile phone charger cable

Introduction

In the literature, many cases reported the insertion of foreign bodies in the bladder. The main causes may be either iatrogenic or self-inflicted for several reasons, such as sexual gratification, symptomatic self-medication, mental disorder, drug intoxication, and curiosity in children (1,2).

In this report, we intend to describe the presence of a rare foreign object (mobile phone charger cable) in the bladder and the possible causes of this issue.

Case Report

A young, 38-year-old unmarried woman with a history of surgical treatment of ovarian dermoid cyst presented to the emergency department with the complaints of dysuria, hematuria and suprapubic tenderness for the previous two weeks. According to her, the reason behind the delayed presentation was fear and embarrassment. The patient reported that to relieve lower urinary tract symptoms (LUTS) such as urinary frequency, urgency, dysuria, and lower abdominal pain; she had inserted a foreign body (i.e., mobile phone charger cable) in her bladder. She had no psychiatric or drug addiction history. Despite the patient's claim of good mood, depressive symptoms were clear.

Urinalysis showed plenty of erythrocytes and urine culture was reported negative after 48 hours of incubation. Physical examination was unremarkable except for suprapubic tenderness; consequently, pelvic radiography (Figure 1) and spiral computed tomography scan (Figure 2) were requested for her. In resulting reports, the foreign body was seen as a strongly coiled up wire-like structure that had created a mass-like area with the dimensions of 37x74 mm. Furthermore, the presence of gas in the bladder wall and lumen as well as thickening bladder wall (emphysematous cystitis) were also visible.

The patient underwent general anesthesia, was placed in the lithotomy position and prepped and draped sterilely. Then, under a cystoscope, the urinary tract and bladder were checked. No lumps or stones were seen. The bladder contained a lot of debris, and its mucosa appeared normal. The foreign body, a

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2022;9(3):225-227

mobile phone charger cable (Figure 3), was cystoscopically removed from the patient's bladder using a grasp. The surgical procedure was finalized by fully fixing the patient's direction and delivering her to the recovery room. She was discharged after being able to pass the urine normally.

The written informed consent was obtained from the patient. She was adequately informed about the purpose of this study, and she was also assured that her information and her anonymity would remain confidential.

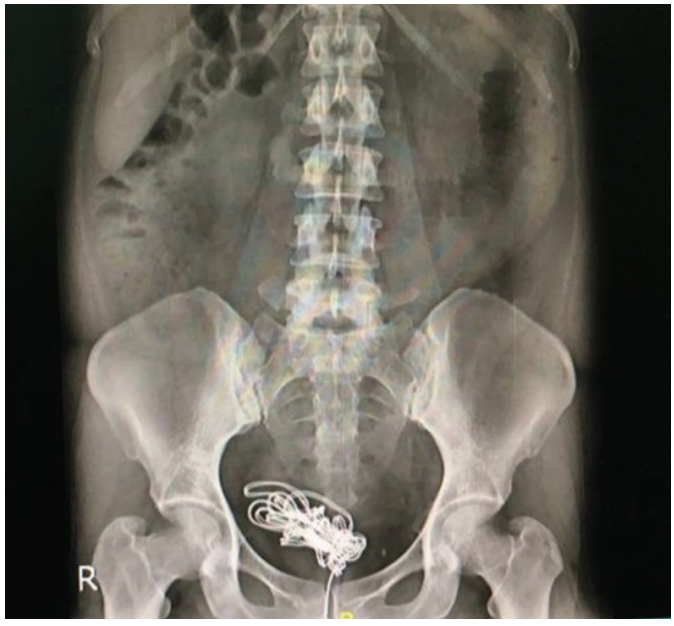

Figure 1. Pelvic X-ray showing coiled up radiopaque wire in urinary bladder

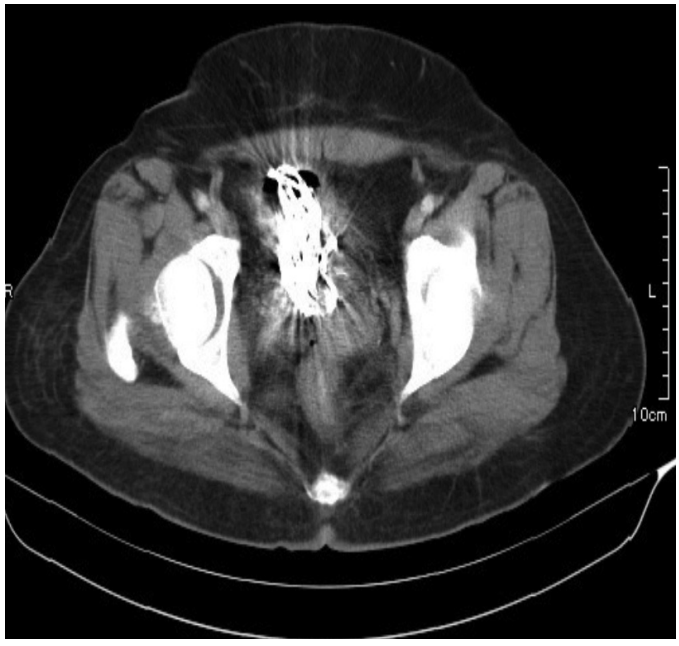

Figure 2. Pelvic spiral CT scan showing coiled up radiopaque wire in urinary bladder

Discussion

Foreign bodies in the lower urinary tract represent a relatively unusual condition, and the bladder is one of the most common organs in the urinary tract where the presence of a foreign body has been reported (3). The symptoms of a foreign body in the bladder include urinary frequency, urgency, and retention, decreased urine volume, painful erection, enuresis, hematuria, dysuria, and pain in the urethra and pelvis (4,5).

Various reasons for the occurrence of foreign bodies in the pelvis have been mentioned, including iatrogenic causes (such as the surgical staples, encrusted sutures, sponges, swabs, catheter, intra uterine contraceptive devices, or surgical gauze) (6), eroticism (masturbation or sexual gratification) (7), sexual abuse (2), penetrating trauma (8) (such as bullets, bullet casings or pieces of patient clothing) (9), migration from neighboring organs (5) curiosity in children (10), and mental disorders (such as schizophrenia and borderline personality disorder) (11).

The existence of almost anything found in the human environment has been reported as a foreign body (6). This spectrum varies from pencils, pens, pins and needles and swabs (12), tampons, paper clips (13), thermometers (14) to edible grains such as beans (15) and telephone cords (16).

The anatomy of female urethra facilitates the entry of foreign objects in terms of its short length and absence of twisting or obstruction of the prostate, as it is in the case with males (17).

According to the literature, masturbation and mental disorders can be considered the main reasons for a self-inflicted foreign body in females (18). The presence of foreign bodies in the patient's bladder can be due to migration from nearby organs. The root cause may be either iatrogenic or accidentally after treating discharge disorders such as catheterization or endoscopic treatment (10).

In an exceptional study in 1915 by De Tarnowsky (19), it has been reported that a patient colleague pushed solid tar into his urinary tract.

After the clinical examination, psychiatric counseling was strongly recommended. During the counseling, mental retardation and autoerotic reasons were rejected, and as the patient had no particular psychiatric, medical history and previous drug addiction; psychiatric counseling to examine other mental disorders such as depression, bipolar disorder, schizophrenia, and borderline personality disorder as well as sexual abuse were suggested. In line with the above-mentioned recommendations, a physical examination for the virginity test was also requested.

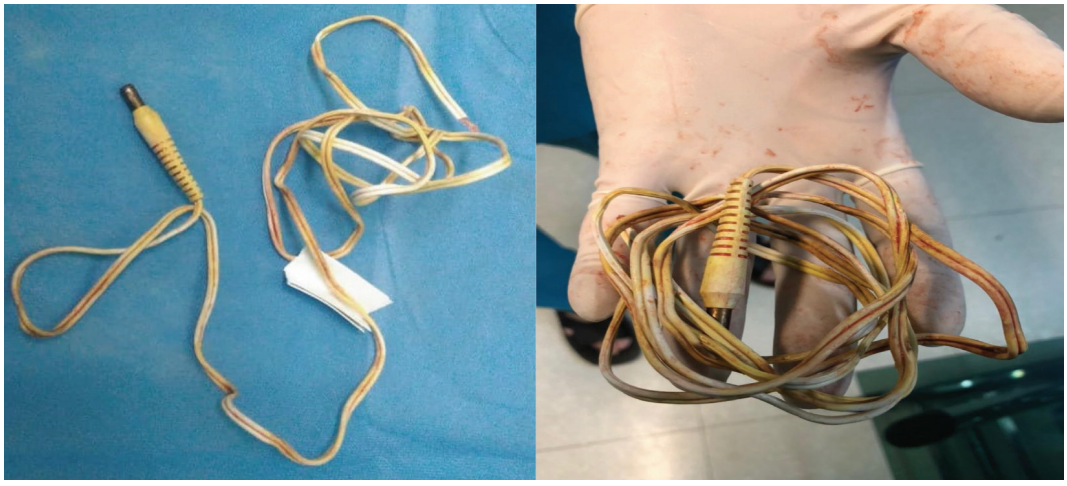

Figure 3. Retrieved mobile phone charger cable from the urinary bladder

Ethics

Informed Consent: The written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.P., N.H., T.N., A.A., R.M., Concept: F.P., N.H., T.N., A.A., R.M., Design: F.P., N.H., T.N., A.A., R.M., Data Collection or Processing: F.P., N.H., T.N., A.A., R.M., Analysis or Interpretation: F.P., N.H., T.N., A.A., R.M., Literature Search: F.P., N.H., T.N., A.A., R.M., Writing: F.P., N.H., T.N., A.A., R.M.

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