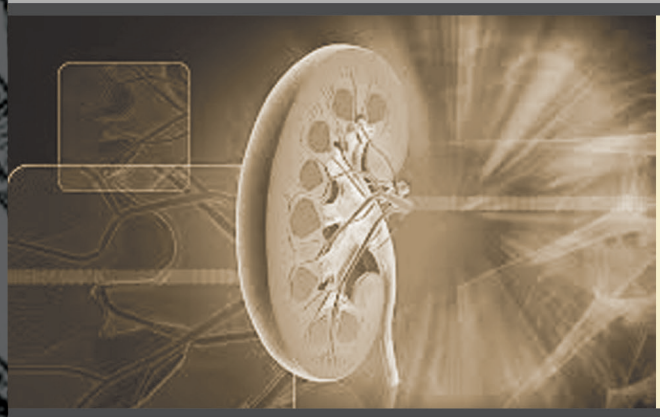
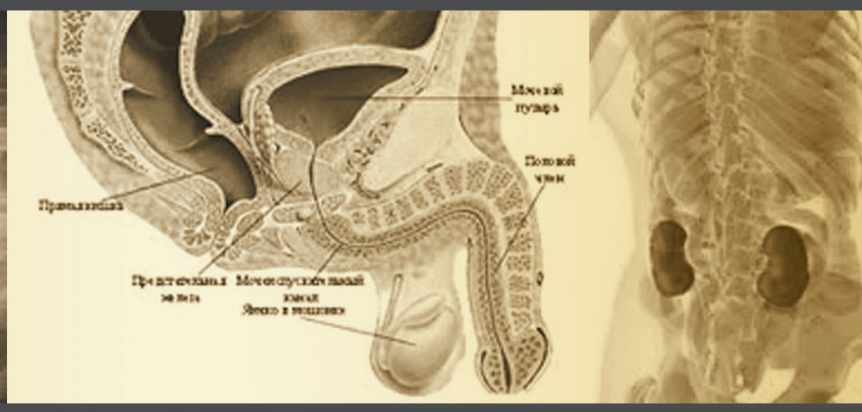
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Technical and other assistance should be provided on the title page.

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Conclusion: The study's new and important findings should be highlighted and interpreted.

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Abstract length: Not to exceed 250 words. "What is known on the subject and what dos the study add" not exceed 100 words.

Article length: Not to exceed 3000 words.

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Statistics: Describe the statistical methods used in enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. Statistically important data should be given in the text, tables and figures. Provide details about randomization, describe treatment complications, provide the number of observations, and specify all computer programs used.

Results: Present your results in logical sequence in the text, tables, and figures. Do not present all the data provided in the tables and/or figures in the text; emphasize and/or summarize only important findings, results, and observations in the text. For clinical studies provide the number of samples, cases, and controls included in the study. Discrepancies between the planned number and obtained number of participants should be explained. Comparisons, and statistically important values (i.e. p value and confidence interval) should be provided.

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1. List All Authors

Ghoneim IA, Miocinovic R, Stephenson AJ, Garcia JA, Gong MC, Campbell SC, Hansel DE, Fergany AF. Neoadjuvant systemic therapy or early cystectomy? Singlecenter analysis of outcomes after therapy for patients with clinically localized micropapillary urothelial carcinoma of the bladder. Urology 2011;77:867-870.

2. Organization as Author

Yaycioglu O, Eskicorapci S, Karabulut E, Soyupak B, Gogus C, Divrik T, Turkeri L, Yazici S, Ozen H; Society of Urooncology Study Group for Kidney Cancer Prognosis. A preoperative prognostic model predicting recurrence-free survival for patients with kidney cancer. Jpn J Clin Oncol 2013;43:63-68.

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, 2012, 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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ORIGINAL RESEARCH
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Comparison of Retrograde Intrarenal Surgery and Percutaneous Nephrolithotomy in the Treatment of 2-3 cm Multicalyceal Kidney Stones

Multikalisiyel 2-3 cm Böbrek Taşlarının Tedavisinde Kullanılan Retrograd İntrarenal Cerrahi ve Perkütan Nefrolitotomi Yöntemlerinin Karşılaştırılması

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

Considering the guidelines for the treatment of 2-3 cm multicalyceal kidney stones, the primary treatment is percutaneous nephrolithotomy, but when we considered possible multiple accesses, similar success rates, and higher rates of possible complications, retrograde intrarenal surgery can be used as the primary method that can be used in these patients.

Abstract

Objective: To demonstrate the feasibility of retrograde intrarenal surgery (RIRS) in the treatment of 2-3 cm multicalyceal kidney stones considering the possible complications and unsuitable situations. Multiple kidney stones are observed among 20-25% of patients seen in urology clinics. Percutaneous nephrolithotomy (PNL) is the primary method for treating kidney stones larger than 2 cm. Despite the high success rate achieved, life-threatening complications associated with PNL may arise. Multiple accesses may be required for multiple stones. RIRS has become increasingly widely used. In our study, we aimed to compare these two methods in the treatment of 2-3 cm multicalyceal stones.

Materials and Methods: We retrospectively evaluated data of patients who presented with multicalyceal kidney stones measuring 2-3 cm between 2012 and 2016. A total of 64 patients who underwent surgery (36 RIRS, 28 PNL) were included in the study.

Results: Major complications were more common, operative time, fluoroscopy time and length of hospital stay time were longer in PNL group than in RIRS group. The number of stones was statistically higher in RIRS group. There was no statistically significant difference in other parameters. No statistically significant difference was found between the two groups in operation success rates.

Conclusion: In the literature, the primary treatment option for 2-3 cm multicalyceal stones has been reported to be PNL. RIRS should be used in appropriate patients who have risks of complications related to anesthesia, bleeding disorder and patients with anatomic abnormalities who are not suitable for PNL. This method is also used to reduce the potential complications and it is more reliable.

Keywords: 2-3 cm, Kidney, Multicalyceal, Percutaneous nephrolithotomy, Retrograde intrarenal surgery, Stone

Öz

Amaç: Retrograd intrarenal cerrahi (RIRC) gelişen teknolojiyle beraber kullanımı yaygınlaşmakta olan bir yöntemdir. 2 cm'den büyük boyutlu böbrek taşı tedavisinde önerilen ilk yöntem olan perkütan nefrolitotomide (PNL) yüksek başarı oranlarına rağmen hayatı tehdit edebilen komplikasyonlar görülebilmektedir. Anestezi açısından riskli olan, kanama bozukluğu olan, vücut bütünlüğü anatomik olarak PNL'ye uygun olmayan hastalarda veya

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gözlenebilecek komplikasyonların azaltılması için RIRC tedavide kullanılabilecek bir yöntemdir. Çalışmamızda 2-3 cm boyutta taş yükü bulunan multikalisiyel taşların tedavisinde uygulanan RIRC ve PNL yöntemlerinin etkinlik ve güvenilirliklerini karşılaştırmayı amaçladık.
Gereç ve Yöntem: Çalışmada 2012-2016 yılları arasında multikalisiyel ve 2-3 cm boyutlarında böbrek taşı olan hastaların verileri retrospektif olarak değerlendirildi. Çalışmaya multikalisiyel ve 2-3 cm boyutunda taşı olup opere edilen toplam 64 hasta dahil edildi (36 RIRC, 28 PNL).
Bulgular: PNL grubunda majör komplikasyonlar, skopi, operasyon ve hastanede yatış süresi istatistiksel olarak daha yüksek bulundu. RIRC grubunda taş sayısı istatistiksel olarak daha yüksekti. Diğer parametreler arasında istatistiksel bir fark yoktu. Operasyon başarı oranlarında iki grup arasında istatistiksel olarak anlamlı bir fark bulunmadı.
Sonuç: Literatürde 2-3 cm multikalisiyel böbrek taşlarında primer tedavi seçeneği PNL'dir. RIRC, anestezi riski yüksek olan, kanama bozukluğu olan ve vücut bütünlüğü PNL için anatomik olarak uygun olmayan hastalara uygulanabilir. Bu yöntem ayrıca potansiyel komplikasyonları azaltmak için kullanılır ve daha güvenilir bir seçenektir.
Anahtar Kelimeler: 2-3 cm, Böbrek, Multikalisiyel, Perkütan nefrolitotomi, Retrograd intrarenal cerrahi, Taş

Introduction

With the improvements in technology and techniques, retrograde intrarenal surgery (RIRS) has gained considerable popularity in the treatment of renal calculi. Initially, it was used for the management of small-sized (<2 cm) stones (1). Its usage has been widened with the growing experience and the innovations achieved in laser technology. Stones larger than 2 cm began to be treated with RIRS in suitable conditions (2).

Multiple kidney stones are observed in 20-25% of patients (3). Percutaneous nephrolithotomy (PNL) is the primary method for treating kidney stones larger than 2 cm (4). Despite the high success rate achieved, life-threatening complications associated with PNL may arise. Multiple accesses may be required for multiple stones (5). Accordingly, renal parenchymal injury and bleeding might be seen and the postoperative comfort of the patient might decrease (6). RIRS can be used in patients having risk related with anesthesia, bleeding disorder and in patients with anatomic abnormalities who are not suitable for PNL. This method is also used to reduce the potential complications.

In our study, we aimed to compare the efficiency and reliability of RIRS and PNL methods which are employed in the treatment of multicalyceal stones larger than 2-3 cm in our clinic.

Materials and Methods

Data of the patients, who underwent PNL and RIRS procedures for kidney stones between 2012 and 2016 in the Urology Clinic at the University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital were retrospectively evaluated. A total of 64 patients with multicalyceal stones measuring 2-3 cm were included in the study (36 RIRS, 28 PNL). Patients with bilateral kidney stones, ureteral stones accompanied by kidney stones and those who did not have computed tomography (CT) images were excluded from the study. The patients were informed about the treatment methods. The council, which consisted of the authors of this study, decided to apply RIRS (group 1) and PNL (group 2). While making this decision, history of antiplatelet treatment, presence of obesity which makes prone positioning of the patient difficult, and preferences of the surgeon and the patient were taken into consideration.

Demographic and operative data of the patients were examined. Preoperative complete blood count, serum biochemistry, coagulation profile, urinalysis and urine culture as well as sensitivity tests of all patients were obtained. All the patients had preoperative sterile urine culture. Stone burden was calculated in all patients using the longest diameter of each stone on kidney ureter bladder (KUB) graphy and ultrasonography (US) for opaque and non-opaque stones, respectively. The total stone burden was calculated as the sum of each stone size. If any, intravenous urography and CT of the patients were also taken into account. Prior to the procedure, written informed consent was obtained from all patients. The operations were performed by the same surgical team in the same clinic.

A 7.5 French (Fr) flexible uretero-renoscope (Flex-X2; Karl Storz, Tuttlingen, Germany) was used in RIRS procedure. A semi-rigid uretero-renoscope was inserted into the ureter and a 0.035-0.038 inch hydrophilic safety guidewire was placed under fluoroscopic guidance with the patient under general anesthesia in a modified supine position. This procedure also helped us achieve urethral dilation. Later, a 9.5-11.5 Fr or 11-13 Fr access sheath (Elit Flex, Ankara, Turkiye) was placed over a hydrophilic guidewire. When an access sheath was not placed, the flexible uretero-renoscope was moved using the safety guidewire and the kidney was accessed. When the stone was reached, fragmentation was performed via a 200 mm holmium:yttrium-aluminum-garnet laser probe (Dornier Medilas H20; Medtech, Munich, Germany). During the procedure, 8-10 hertz frequency and 1.2-1.5 joule power were used. Fragmentation or dusting methods were used according to the preference of the surgeon. In line with the intraoperative conditions, a JJ stent was placed. The time from the beginning of the endoscopy until the placement of the JJ stent was calculated as the operative time.

In PNL procedure, a 5 Fr open-end ureteral catheter was placed into the ureter under fluoroscopic guidance with the patient under general anesthesia in a modified supine lithotomy position. Later, the patient was taken to the prone position. Under fluoroscopic guidance, percutaneous access was achieved

with 18-gauge needles. A 0.035 inch J ended guidewire was introduced to the collective system via a needle. Dilation was achieved up to 30 Fr via Amplatz dilators. Later, a rigid nephroscope (26 Fr, Karl Storz®) was placed. Upon accessing the stone, fragmentation was achieved via a pneumatic lithotripter (Lithoclast; EMS, Nyon, Switzerland). The stones broken via the lithotripsy method were removed via forceps. According to the decision of the surgeon, due to intraoperative conditions, a JJ stent was placed intraoperatively. Percutaneous nephrostomy was performed until the end of the procedure. The time from the beginning of the endoscopy until the placement of the percutaneous nephrostomy was calculated as the operative time.

The success of the operation was assessed via fluoroscopy in the operating room at the end of the operation, and via KUB and US on the 1st postoperative day. Detection of no stone or a residual fragment of <3 was considered success. JJ stents were removed three weeks later. Second session operation was performed in patients whose stones were not fragmented at the end of the operation or patients who had residual stones. Complications were assessed according to the Clavien-Dindo classification (7).

Statistical Analysis

The data were analyzed with SPSS for Windows 16.0 package program. Numerical measurement values were tested for normal distribution using the one sample Kolmogorov-Smirnov test. The difference in parameters, including gender, kidney anomaly, stone laterality, location, JJ stent usage, opacity, success and complications, between the two groups was analyzed using the Pearson chi-square test. The difference in age between the two groups was tested using Student's t-test. The difference in parameters, including stone number, stone burden, operative time, fluoroscopy time and length of hospital stay, between two groups was analyzed using the Mann-Whitney U test. A p value of less than 0.05 was considered statistically significant.

Results

When the demographic data and stone characteristics of the groups were examined, no statistically significant difference was detected in age, gender, stone radiopacity, stone laterality and stone burden between patients who underwent RIRS and PNL. When the groups were compared for body mass index (BMI), it was observed that the BMI value in RIRS and PNL groups was 26.4 and 25.9, respectively. The number of stones was statistically significantly higher in the RIRS group (Table 1). Three patients had a BMI value of >30, five patients had a high operative risk according to the American Society of Anesthesiologists physical status classification system and four patients had a history of antiplatelet use. Therefore, RIRS was performed in these patients.

Operative time, fluoroscopy time and length of hospital stay were significantly shorter in RIRS group than in PNL group. The mean access number per procedure was found to be 1.39 in PNL group. Eleven patients required double access. The stone-free rate was higher in PNL group than in RIRS group. However, there was no statistically significant difference (Table 2).

Table 1. Demographic data and stone characteristics

	Group 1 (RIRS) (n=36)	Group 2 (PNL) (n=28)	p value
Age (mean ± SD) (years)	44.91±11.54	50.25±12.75	0.640
Gender (male/female) (n)	20/16	19/9	0.828
Body mass index, mean	26.4	25.9	0.386
Anomalous kidney, n (%)	1 (2.8)	1 (3.6)	0.856
Radiopacity of stone, n (%)	33 (91.6)	26 (92.8)	0.894
Stone laterality			0.481
Right/left (n)	16/20	10/18	-
Number of stones (mean ± SD)	2.69±0.70	2.17±0.61	**<0.001**
Stone burden (mean ± SD) (mm)	24.97±3.89	25.39±3.85	0.728

SD: Standard deviation, *Significant at 0.05 level, RIRS: Retrograde intrarenal surgery PNL: Percutaneous nephrolithotomy

Table 2. Perioperative and postoperative data

	Group 1 (RIRS) (n=36)	Group 2 (PNL) (n=28)	p value
Operation time (mean ± SD) (minute)	56.11±10.89	82.32±34.06	**<0.001**
Fluoroscopy screening time (mean ± SD) (minute)	0.91±1.14	3.94±3.17	**<0.001**
Hospitalization time (mean ± SD) (day)	1±0	4±1.44	**<0.001**
Double-J placement, n (%)	31 (86.1)	8 (28.6)	**<0.001**
Stone-free status, n (%)	25 (69.4)	22 (78.6)	0.412
Stone free	25 (69.4)	22 (78.6)	0.412
CIRF	0	1	-
Rest	11	5	-
Success rates, n (%)	25 (69.4)	23 (82.1)	-

RIRS: Retrograde intrarenal surgery, PNL: Percutaneous nephrolithotomy, CIRF: Clinically insignificant residual fragments, SD: Standard deviation

Table 3. Postoperative data

	Group 1 (RIRS) (n=36)	Group 2 (PNL) (n=28)	p value
Complication rates, n (%)	3 (8)	7 (25)	-
Minor (Clavien 1-2) complications, n (%)	3 (8)	4 (14.2)	0.449
Fever	2	1	-
Blood transfusion	0	1	-
Urinary tract infection	1	2	-
Major (Clavien 3-5) complications, n (%)	0	3 (10.7)	**0.044**
JJ placement for urine leakage	0	3 (10.7)	-
Death	0	0	-
Auxiliary procedure, n (%)	11 (30.6)	6 (21.4)	-
SWL	2	0	-
RIRS	4	2	-
PNL	0	0	-
Observation	5	4	-

RIRS: Retrograde intrarenal surgery, PNL: Percutaneous nephrolithotomy, SWL: Shock wave lithotripsy

When the complications were examined, the rate of minor complications was higher in PNL group. No statistically significant difference was observed between the groups. In PNL group, the number of major complications was statistically significantly higher than in RIRS group (Table 3).

In RIRS group, as an additional intervention, shock-wave lithotripsy was performed in 2 patients after an unsuccessful RIRS. Also 2nd-session RIRS was performed in 4 patients. Additionally, five patients were followed up. In PNL group, as an additional intervention, RIRS was performed in 2 patients following an unsuccessful PNL. Four patients were followed up (Table 3).

Discussion

In urology practice, multiple kidney stones are seen among patients with a rate of 20-25%. Studies on the employment of PNL and RIRS methods in multiple kidney stones are available in the literature (8,9,10). However, there is no study comparing the efficiency or reliability of these two methods in the treatment of multicalyceal stones. Although the number of patients was low, this is the first study to compare these two methods in the management of multicalyceal stones measuring 2-3 cm.

The primarily recommended method in patients with a stone size larger than 2 cm is PNL (4). In a study which compared PNL and laparoscopic pyelolithotomy methods, PNL was performed in 39 patients with ≥2 cm kidney stones and the duration of operation and length of hospital stay was reported to be 110±54.6 minutes and 4.76±1.60 days, respectively. The success rate was 64.1% (8). In another study, the stone-free rate in single access PNL for multiple kidney stones was found to be 94.1% (11). In a study including 149 patients who underwent multiple access PNL, Singla et al. (12) reported a stone-free rate of 70.7%. In our study, in PNL group, the mean operative time and length of hospital stay were found to be 82.32±34.06 minutes and 4±1.44 days, respectively. Indwelling ureteral catheterization and turning the patient into the prone position caused longer operative time and removing percutaneous nephrostomy before the patient's discharge caused longer hospitalization periods. Group 1 patients had a higher number of stones, but when the stone burden was compared between the groups, group 2 had a higher stone burden even though it was not statistically significant. Therefore, we assume that the operative time in the group 2 was longer because the time to the entry into the collecting system was longer in group 2.

The overall stone-free rate was 78.6% and the success rate was 82.1%. No statistically significant difference was found in success rate between the PNL and RIRS groups. In their study including 48 patients with multiple kidney stones who were treated with RIRS, Alkan et al. (9) reported a stone-free rate of 100% and 84% in 23 patients with a stone burden less than 2 cm and 25 patients with a stone burden greater than 2 cm, respectively. Minor complications were observed in 6 patients (9). A study conducted by Breda et al. (10) RIRS method was used in 27 patients with multiple kidney stones ≥2 cm. After the first treatment, stone-free rate was reported as 52% and after two procedures, the total stone-free rate was reported as 85.1%. The overall complication rate was 13.6%. Takazawa et al. (13) reported a stone-free rate of 69% and 84.6%, respectively following the 1st and 2nd sessions in patients with ≥2 cm multiple kidney stones. We found a stone-free rate of 69.4% and complication rate of 8% in RIRS group. While double J stent placement rate was 86.1% in RIRS group, this rate was found to be 28.6% in PNL group.

Serious complications are observed in patients undergoing PNL. This method requires multiple accesses for multiple stones, which increases the risk of complications. A study in the literature indicated that fever (21-32.1%), blood transfusion (11.2-17.5%), extravasation of urine (7.2%), sepsis (0.3-4.7%), colon injury (0.2-0.8%), pleural injury (0.3-1%), perioperative mortality (0.3-0.78%) can be seen during and after PNL (14). In our study, minor complications were seen in 4 patients and major complications were seen in 3 patients in PNL group. The complication rate was statistically significantly higher in PNL

group. This was the result of the need for multiple access in PNL operation.

In RIRS, the rate of complication is between 6% and 16% (15,16). The most commonly reported complications include urinary system infection, minor ureteral injury, hematuria and postoperative renal colic (10,15,16). In our study, no major complication was observed in RIRS group. However, minor complications were seen in 3 patients. Two patients had fever and 1 patient had urinary tract infection.

In our study, operative time, duration of fluoroscopy and length of hospital stay were found to be longer in PNL group than in RIRS group. In the literature, there is only one study available reporting shorter operative time in RIRS than PNL for stones larger than 2 cm (17). However, in comparison of RIRS and PNL, multicaliceal stones 2-3 cm in size were not distinguished in other studies. The time required for multiple percutaneous accesses in multicalyceal stones extended the duration of fluoroscopy and operative time in PNL group. Advances in flexible renoscopy and laser technology and growing experience have also shortened operative time in RIRS. In our study, the time required for the withdrawal of percutaneous nephrostomy extended the length of hospital stay in PNL group.

Study Limitations

Our study has some limitations. Retrospective design and the low number of the patients included in the study are among the limitations. Our clinic is a center that works intensely for urolithiasis. However, the number of patients was limited due to the retrospective design of the study and the patients in the study were a specific subgroup under the title of urolithiasis. Further prospective studies with larger sample size are needed.

Conclusion

As a result, in the treatment of 2-3 cm multicalyceal stones, PNL is the primary method to be selected. In patients with comorbidity who have higher risks associated with anesthesia and, bleeding disorder and, those with anatomic abnormalities who are not suitable for PNL, in order to reduce the number of potential complications, RIRS is a method that should be used. In addition, considering the greater rate of major complications associated with PNL, as well as multiple access, we observed that RIRS was a more reliable method in the treatment of 2-3 cm multicalyceal kidney stones.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: The informed consent form of the patients regarding the procedure was taken preoperatively.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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Cost of Healthcare-associated Infections Developing After Endourologic Surgery and the Efficacy of Control Measures in a Turkish University Hospital

Türkiye'deki Bir Üniversite Hastanesinde Endoürolojik Cerrahi İşlem Sonrası Gelişen Hastane Enfeksiyonlarının Maliyeti ve Kontrol Önlemlerinin Etkisi

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

Besides posing a big threat to patient safety, healthcare-associated infections (HAI) cause serious additional costs and they are important cause of mortality in developed countries. While it is not possible to prevent all the cases of HAIs, it is probable to decrease HAI frequencies, high extra costs, high levels of mortality and lengthy bed-days through continuous monitoring and feedback of HAI, use of simple but extremely effective, evidence-based infection control systems and education and trainings. Therefore, the current study will provide additional information to the literature and will guide the surgeons willing to reduce HAIs.

Abstract

Objective: The study aimed to determine additional costs of healthcare-associated infections (HAIs) in patients undergoing endourologic surgery. It also aimed to evaluate the effect of infection control measures on costs of HAIs.

Materials and Methods: This interventional study carried out in patients admitted to the Department of Urology at Osmangazi University Hospital between January 2014 and October 2015. All surgeries were examined in the pre-intervention period for six months and then, a prevention package and education period, which intended to reduce hospital infections, were implemented. In the post-intervention period, all endourological operations were examined for 2 months.

Results: The prevalence of HAIs in the pre-intervention and post-intervention periods was 10.1% and 4.9%, respectively. Patients who had healthcare-related infections before or after the intervention had higher costs compared to those who did not get infections. It was found that HAIs decreased by 51% after the intervention (relative risk: 0.49, 95% confidence interval: 0.28-0.86). Thus, an additional cost of 146.332.8±139.29 TL was saved.

Conclusion: It is concluded that monitoring and reporting of HAIs regularly by using a simple but effective and evidence-based infection control practices and education programs could decrease the frequency of infection, high additional costs and length of hospital stay.

Keywords: Cost, Healthcare-associated infections, Control measures, Turkiye

Öz

Amaç: Bu çalışma endoürolojik cerrahi girişim yapılan hastalarda oluşan sağlık hizmeti ilişkili enfeksiyonların (SHİE) getirdiği ilave maliyetleri belirlemek ve yapılan müdahale ile alınan enfeksiyon kontrol önlemlerinin maliyet üzerine etkisini değerlendirmek amacı ile yapılmıştır.

Gereç ve Yöntem: Çalışma Eskişehir Osmangazi Üniversitesi Hastanesi Üroloji Anabilim Dalı Dalında, Ocak 2014-Ekim 2015 tarihleri arasında yürütülen bir müdahale araştırmadır. Müdahale öncesi dönemde tüm endoürolojik cerrahi girişimler 6 ay süre ile incelendi ve SHİE'yi azaltmaya yönelik hazırlanan önlem paketinin uygulanması ve yapılan eğitimler tamamlandı. Müdahale sonrası dönemde de 2 ay süre ile tüm endoürolojik işlemler incelendi.

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Bulgular: Müdahale öncesi dönemde çalışma grubundakilerin %10, SHİE tespit edilirken, müdahale sonrasında ise %4,9 olarak saptandı. Yapılan müdahale programı ile SHİE görülme sıklığının %51,0 oranında azaldığı saptandı (relatif risk: 0,49, %95 güven aralığı: 0,28-0,86). Müdahale öncesi ve sonrası SHİE tespit edilen bireylerin toplam maliyeti SHİE tespit edilmeyen bireylerden daha yüksek idi. Müdahale ile yıllık toplam 146,332,8±139,29 TL ek maliyetin önüne geçildi.

Sonuç: SHİE'nin izlenmesi ve sürekli geri bildiriminin sağlanması, basit ama son derece etkili kanıta dayalı enfeksiyon kontrol önlemlerinin kullanılması ve yapılan eğitimler ile enfeksiyon sıklıklarının, SHİE'ye bağlı yüksek ek maliyetinin ve uzamış yatış sürelerini azaltmanın mümkün olduğu sonucuna varıldı.

Anahtar Kelimeler: Maliyet, Sağlık hizmeti ile ilişkili enfeksiyonlar, Kontrol önlemleri, Türkiye

Introduction

Although many developments have been observed in the field of medicine, healthcare-associated infections (HAI) have become an important health problem all over the world due to high rates of mortality and morbidity as well as economic losses (1,2). According to the studies carried out in developing countries between 1995 and 2008, while the prevalence of HAIs was 5.7-19.1%, the incidence rate was reported as 1.7-23.6% (3). It has been ascertained that HAIs extend the length of hospital stay for 4 days on average and leads to 60.000 deaths in a year and, the USA spend up to 10 billion dollars more on it (4).

Although all the HAIs cannot be avoided, in a systematic review by Aboelela et al. (5), it has been reported that the interventions containing prevention packages are effective in reducing the HAI frequency. After a training program containing multidimensional infection control approaches, such as bundle of infection control interventions, education, surveillance, and performance feedback, carried out in 15 developing countries, including Turkiye, the incidence rate of HAIs decreased by 37% (6,7).

The prevention attempts against HAIs are cost-effective initiatives (3). In a study examining the cost of HAIs for 4 years after an infection prevention and control program carried out on 82.046 patients in 6 intensive care units in Canada, it has been reported that HAI was prevented in 4.739 patients in total and an additional cost of 9.1 billion dollars was avoided (8). Scarce resources allocated for the offering of health services will be fairly used by reducing the infection frequency through HAI prevention and control efforts by the adaptation of health professionals (9).

The aim of the study was to determine the extra costs brought by HAIs after endourological surgery in the Department of Urology at Eskişehir Osmangazi University Hospital and to evaluate the effects of the infection prevention and control measures on costs.

Materials and Methods

Study Design and Study Population

This intervention study was carried out on patients who underwent an endourologic surgery in the Department of Urology at Eskişehir Osmangazi University Hospital between January 2014 and October 2015. In this study, data was gathered by active surveillance based on patient and laboratory records. This study design was approved by the Eskişehir Osmangazi University Ethics Committee (80558721/27). Consent form was filled out by all participants. All endourologic surgeries were examined in the pre-intervention period for six months (1st January, 2014 to 30th June, 2014) and post-intervention period for two months (1st February, 2015 to 31st March, 2015). Between July 2014 and January 2015, the seven-month interventional study was carried out.

Patients included in the study were those aged 15 years and older and diagnosed with any infection upon questioning about symptoms of the urinary system infection and via physical examination. Neutropenic, pregnant and immunosuppressed patient, and those, who had any infection, urinary catheter inserted for any reason in the last 2 months and stayed in hospital less than 24 hours, were excluded from the study. In the pre-intervention period, of the 1384 endourological surgical procedures, 1095 (79.1%) were examined in accordance with the inclusion criteria. In the post-intervention period, of 595 endourological surgical procedures, 461 (78.5) were examined.

Baseline Period

Patient age, gender, diagnosis, chronic diseases, hospital admission and discharge dates, the order in the queue for the operative room and presence of HAI were recorded. Following the collection of the data, the patient's billing information was taken from the hospital information system and recorded with the permission of the hospital management.

The cost of the treatment was included in the study. The billing information was examined in detail and the treatment costs were calculated. Costs were analyzed in four groups as service cost, drug cost, medical equipment cost and total cost.

Following the completion of the pre- and post-intervention periods, patients having HAI and those without HAI were matched. Age, gender and primary diagnosis of patients were used as matching variables.

Patients who met the matching criteria with no HAI were matched with each patient with HAI. With a simple random number generating algorithm, a patient with no HAI was

selected for each patient with HAI. Thus, it was aimed to reduce the confounding effect of other causes that increases cost. With this new dataset, the additional cost of HAI was determined.

Intervention Period

Determination of Possible Causes that Increase Infection Incidence

At this stage of the study, a questionnaire consisting of 6 open-ended questions was prepared based on the the aim of determining the HAI prevention packages (10,11). This questionnaire was administered to the urology department lecturers, research assistants, operating room team and inpatient care nurses.

After analysing the questionnaire, it was realised that inadequate number of staff, improper sterilization, inadequate medical supplies, inadequate education and inadequate physical environment of the healthcare workplace lead to nosocomial infections.

Developing the Prevention Package

A prevention package was developed to reduce HAIs by evaluating the results of the feedbacks. Implementation of the prepared prevention packages and trainings were completed in January 2015.

The prevention package consisted of the following items;

- Assigning a specialised nurse for the urology operating room by the chief physician,
- Use of ethylene oxide for the sterilization of the device and sterilization system renewed by the chief physician,
- Training of nurses, research assistants and operating room personnel to prevent HAIs; while the objective of the training was to prevent and control HAIs, the goal of the education was to provide patient and employee safety and to promote and protect the awareness of health. The trainings included the definition of HAIs, the frequency of HAIs in the world and our country, the standard measures (hand washing, barrier precautions, medical waste management, isolation, sterilization and disinfection, etc.) to be taken to prevent HAI, the purpose of the infection control program and the effectiveness of package measures (face-to-face by using visuals, 4 sessions, 80 minutes in total, by the main author),
- Distribution of informative brochures prepared to prevent HAIs; the brochure emphasizes that all individuals could play a role in the prevention of infections and indicate what can be done to keep patients and their relatives healthy while receiving health care (face-to-face, 1 sessions, 10 minutes, by the main author). In addition, the brochure included the correct hand washing steps with visual supports suggested by the World Health Organization (WHO), five-stepped, and objective tasks to teach the right hand washing behavior. These steps were one of the most important steps in preventing HAIs (12).

Definition of Healthcare-associated Infections

In terms of urinary system infection; at least one of the following sign or symptoms should be present: fever (>38 °C), urgent need for urination, frequent urination, dysuria, suprapubic tenderness, pain or tenderness at the costovertebral angle, and positive urine cultures (>105 cfu/mL) which are the main criterion for HAIs with the presence of at least one of the laboratory findings such as positive dipstick test for leukocyte esterase and/or nitrite, pyuria, and microorganisms in gram examination (13). Relative risk (RR) was also calculated in groups with and without HAIs. The incidence density was used to determine the HAIs dimension.

Statistical Analysis

The data was analysed using IBM-SPSS (version 22.0) statistical package program. For descriptive statistics, the frequencies, percentage, mean ± standard deviation, median, minimum (min), maximum (max) and interquartile range (25-75) values were used. A chi-square test and the Kolmogorov-Smirnov test were used to compare the frequency between the groups. For the analysis of the costs, the Shapiro-Wilk test was performed and the Mann-Whitney U test was used for the comparison of the groups because the normality test did not fit the normal distribution. EPI Info V7 (CDC, Atlanta, Georgia, USA) package program was used to calculate the risk ratio. For statistical significance, $p \leq 0.05$ was accepted.

Results

At the pre-intervention period, a total of 1.095 (79.1%) endourological surgeries were performed in 673 patients with a total of 2.428 bed-days. The average age of the patients was 57.2±15.1 (min: 15.0, max: 91.0) years. 26.6% (n=179) of the patients were female and 73.4% (n=494) were male. At the post-intervention period, a total of 461 (78.5%) endourological surgeries were performed in 306 patients with a total of 1.089 bed-days. The average age of the patients was 55.5±15.3 (min: 15.0, max: 91.0) years. 77.5% (n=237) were male. There was no difference between the pre- and post-intervention groups in terms of gender (p=0.177) and age (p=0.583).

At the pre-intervention period, 10.1% of patients had nosocomial infection. At the post-intervention period, the nosocomial infection rate decreased to 4.9%. The incidence density of nosocomial infection was 28.0‰ at the pre-intervention group, however, this value was measured as 13.7‰ after the intervention. There was no difference between the pre- and post-intervention groups in terms of nosocomial infection with regard to gender, age group, physician-diagnosed diabetes, and

the presence of multiple chronic diseases (p>0.05 for each) (Tables 1, 2).

The risk of nosocomial infections was increased in patients with a later order in the operation queue, and the number of bed-days in patients having nosocomial infection was higher in both pre- and post-intervention period (p<0.001 for each) (Table 3).

Table 1. The distribution of healthcare-associated infections presence in terms of study stages

HAIs	Pre-intervention period		Post-intervention period		Total	
	n	%	n	%	n	%
No	605	89.9	291	95.1	896	91.5
Yes	68	10.1	15	4.9	83	8.5
Total	673	100.0	306	100.0	989	100.0

HAIs: Healthcare-associated infections
X^2: 7.336; p=0.007

After matching the data set, the costs of patients with nosocomial infection were higher than those of without nosocomial infection for both pre- and post-intervention period (p<0.001 for each). Although the total cost of the patients without nosocomial infection at the post-intervention period was higher than the costs at the pre-intervention period, this value did not change for the patients with nosocomial infection (p=0.012 and p=0.287, respectively) (Table 4).

The study groups were designed following matching; cost difference was calculated by subtracting the cost of patients with nosocomial infection from that of patients without nosocomial infection at the pre- and post-intervention period. While the difference in the median cost between patients with and without nosocomial infection before intervention was 1.002.9 TL, this value increased to 1.288.3 TL after intervention. After the matching, the difference in cost between patients with nosocomial infection and those without nosocomial

Table 2. The distribution of healthcare-associated infections presence in terms of study stages with regard to some characteristics

Some characteristics		HAIs (Pre-intervention period)						HAIs (Post-intervention period)					
		No		Yes		Total		No		Yes		Total	
		n	%	n	%	n	%	n	%	n	%	n	%
Gender	Male	445	90.1	49	9.9	494	73.4	227	95.8	10	4.2	237	77.5
	Female	160	89.4	19	10.6	179	26.6	64	92.8	5	7.2	69	22.5
Test (p)					0.791						0.305		
Age (years)	15-39	78	87.6	11	12.4	89	13.2	49	94.2	3	5.8	52	17.0
	40-49	85	86.7	13	13.3	98	14.6	45	97.8	1	2.2	46	15.0
	50-59	146	93.0	11	7.0	157	23.3	65	92.9	5	7.1	70	22.9
	60-69	159	90.3	17	9.7	176	26.2	75	98.7	1	1.3	76	24.8
	≥70	137	89.5	16	10.5	153	22.7	57	91.9	5	8.1	62	20.3
Test (p)					0.510						0.287		
Physician-diagnosed diabetes*	No	382	89.3	46	10.7	428	87.2	115	92.7	9	7.3	124	75.2
	Yes	59	93.7	4	6.3	63	12.8	40	97.6	1	2.4	41	24.8
Test (p)					0.281						0.262		
Presence of multiple chronic disease*	No	338	90.9	34	9.1	372	75.8	114	92.7	9	7.3	123	74.5
	Yes	103	86.6	16	13.4	119	24.2	41	97.6	1	2.4	42	25.5
Test (p)					0.176						0.247		

HAIs: Healthcare-associated infections
*Data from patients whose information was confirmed were evaluated

Table 3. The distribution of the queue number for the surgery and the number of bed-days in terms of the presence of healthcare-associated infections according to study stages

	HAIs (Pre-intervention period) Mean ± SD (Minimum-maximum)		HAIs (Post-intervention period) Mean ± SD (Minimum-maximum)	
	No	Yes	No	Yes
Queue number for the surgery	4.2±3.2 (1.0-21.0)	5.2±3.5 (1.0-19.0)	4.9±3.1 (1.0-16.0)	6.5±2.1 (3.0-11.0)
Test (z; p)	**8.824; <0.001**		**4.712; <0.001**	
Number of bed-days	3.2±2.8 (1.0-29.0)	7.2±5.3 (2.0-33.0)	3.3±2.7 (1.0-25.0)	8.7±5.0 (1.0-21.0)
Test (z; p)	**8.824; <0.001**		**4.712; <0.001**	

SD: Standard deviation, HAIs: Healthcare-associated infections

Tablo 4. The distribution of total costs of new study group after matching with and without healthcare-associated infections

		Without HAIs infection		With HAIs infection		Test z; p	
		Pre-intervention period	Post-intervention period	Pre-intervention period	Post-intervention period	Pre-intervention period	Post-intervention period
Service cost (TL)	Median	424.9	555.1	1.216.9	1.605.2		
	IQR 25-75	308.8-687.1	432.9-1.085.4	873.0-1.767.2	876.3-2.134.5	**8.230; <0.001**	**3.629; <0.001**
	Test (z; p)	**2.225; 0.026**		**1.018; 0.309**			
Drug cost (TL)	Median	54.3	70.4	183.8	275.9		
	IQR 25-75	36.2-80.3	23.1-87.9	113.8-481.1	157.1-496.7	**7.956; <0.001**	**3.754; <0.001**
	Test (z; p)	0.438; 0.661		0.864; 0.388			
Medical equipment cost (TL)	Median	17.2	103.7	102.1	180.8		
	IQR 25-75	7.5-67.2	65.2-201.9	76.7-125.5	22.1-379.9	**6.942; <0.001**	1.182; 0.237
	Test (z; p)	**4.343; <0.001**		0.604; 0.546			
Total cost (TL)	Median	532.0	779.54	1.651.2	2.180.1		
	IQR 25-75	375.1-836.7	589.18-1.201.05	1.124.9-2.595.7	1.408.1-2.796.0	**8.426; <0.001**	**4.003; <0.001**
	Test (z; p)	**2.521; 0.012**		1.065; 0.287			

HAIs: Healthcare-associated infections, IQR: Interquartile range

infection was not changed with intervention at all the fields of intervention (p>0.05 for each) (Table 5).

The infection frequency was decreased from 10.1% to 4.9% after the intervention carried out in the study. It was determined that with this intervention programme, a 51.0% decrease was observed in the incidence rate of nosocomial infection [RR: 0.49; 95% confidence interval (CI): 0.28-0.86; p<0.001]. Two months after the intervention, nosocomial infection was seen in 15 patients out of 306. If the intervention was not carried out, 31 patients would have had nosocomial infection by taking infection incidence rate before the intervention into consideration.

As a result, nosocomial infection was prevented by our intervention in 16 patients. When the post-intervention costs were considered, 146.332.8±139.29 TL were saved by preventing the development of the infection.

Table 5. The distribution of cost differences of the patients with nosocomial infection with regard to that of the patients without healthcare-associated infections

Cost differences		Median	IQR 25-75	Test (z; p)
Total cost (TL)	Pre-intervention period	1.002.9	745.7-1.774.1	-0.284; 0.776
	Post-intervention period*	1.288.3	294.8-1.889.8	
Service cost (TL)	Pre-intervention period	754.8	497.7-1.114.3	-0.651; 0.515
	Post-intervention period*	519.2	248.2-1.737.6	
Drug cost (TL)	Pre-intervention period	135.8	57.8-360.9	0.710; 0.478
	Post-intervention period*	189.8	71.4-427.1	
Medical equipment cost (TL)	Pre-intervention period	78.6	25.0-163.1	-0.635; 0.523
	Post-intervention period*	61.5	-56.4-297.9	

IQR: Interquartile range
*A 5% discount was applied for the post-intervention period

Discussion

Today, HAIs are the most common complications affecting hospitalized patients in the world (1,2). Besides posing a big threat to patient safety, HAIs are important cause of mortality. The incidence rate varies from 5.7% to 19.1% in low and middle income countries (3). In their one-day prevalence study performed in a university hospital, Metintaş et al. (14) found a hospital infection prevalence of 13.4%.

It has been put forward that HAIs cause serious extra costs in both developed countries and in Turkiye. Due to HAIs, the annual financial losses in the USA and Europe are approximately 6.5 billion US dollars and 7 billion euros, respectively (15). Extra cost for an infected patients has been reported to be 1.963 US dollars by Erbay et al. (16), and 2.026 US dollars by Esatoğlu et al. (17). In our study, the total cost of patients with nosocomial infection at the pre- and post-intervention period was higher than that of patients without nosocomial infection ($p<0.001$ for each). It has been reported that the costs increase owing to extended length of bed-days for patients with HAI, additional diagnostic tests and in particular, high-cost of antibacterial medicines used for treatment (5).

Reducing health-care costs and control of expenditures are the priority of many developing countries. While the share of health expenditures of the gross domestic product in the USA was 8.8% in 1980s, it increased to 15.2% in 2003 (18). Likewise, the share of health spending of the gross domestic product in France, Switzerland, Germany, Belgium, Austria, and Canada is above 10%, while the Organisation for Economic Co-operation and Development average is 9.3% (19). Although the share of health expenditures in general budget is increasing every year, it was 5.4% in Turkiye in 2013 (20). Many countries work on strategies for controlling and minimizing medical errors like HAIs. The USA has not been paying the additional costs of HAIs since 2008 (21,22). It is being discussed whether hospitals with high levels of HAI should receive their reimbursement with 5% deduction on the basis of the Health Practices Statement (20).

Aboelela et al. (5) reported that interventions containing prevention strategies were effective in decreasing HAI frequency. It is possible to obtain such potential gains as reducing HAI loads, mortality rates and health expenditures through changing health-care workers behaviors, adoption of infection control practices and and ensuring the continuation of prevention measures (23). It has been demonstrated that use of prevention measures in adult intensive care units of International Nosocomial Infection Control Consortium member hospitals have decreased the incidence rates of HAI by 37-58% and HAI mortality by 58% (23,24,25).

In this study the infection frequency has decreased from 10.1% to 4.9% through the intervention which equals to 51.0% decrease in rates (RR: 0.49; 95% CI: 0.28-0.86; $p<0.001$). In a prospective study carried out in Argentina through an intervention executed (phase 1: surveillance without an education and performance feedback; phase 2: addition of the education; phase 3: addition of performance feedback) HAI rates were decreased by 75% (RR: 0.25; 95% CI: 0.17-0.36; $p<0.0001$) (26). In analogy to our work, it has been shown in this article that education and training of healthcare workers can result in significant reduction in the rates of HAI. Similarly, in another study carried out in Mexico, an intervention (phase 1: active surveillance; phase 2: control of surveillance period and performance feedback) have made it possible to reduce the HAIs rate by 58% and the mortality rate from 48.5% to 32.8% (RR: 0.68; 95% CI: 0.50-0.31; $p<0.01$) (27).

Health systems, both private and publicly funded, face with the problem of providing cost effective and quality care. In Turkiye, the cost of many infection control measures is directly financed by the own budget of hospitals, while the extra costs caused by HAIs are paid by social security institutions (20).

Due to limited resources, it is important to make economically rational decisions in determining the measures to be taken for infection control. In this way, the limited resources are not only wasted and can be used more effectively. Measures for controlling infections and savings will enable individuals to reach health services more fairly (9).

In the study conducted by Esatoğlu et al. (17), the extra cost of HAI was reported to be 202.670 US dollars and it was stated that 30.754 US dollars could be saved in 4 months for 57 patients. Similary, a study carried out on 82.046 patients in 6 intensive care units in Canada which examined the HAI costs after infection prevention and control programs, 4.739 cases of HAI were avoided and a total of 9.1 million Canadian dollars was saved (8).

After the matching, the difference in cost between patients with and without nosocomial infection did not change with the intervention in all the fields of intervention ($p>0.05$ for each). The reason for this issue could be that the purpose of the intervention was decreasing HAI frequency rather than reducing the costs of offered services. As a result, 16 cases of nosocomial infection were prevented through the intervention carried out within the study period. When the post-intervention costs were considered, it was observed that 146.332.8±139.29 TL were saved through preventing the development of the infection.

In a systematic review by Bell et al. (28) investigating the cost-efficiency analyses published between 1976 and 2001, it was reported that only 9% (130 out of 1433) of the studies saved money and improved health simultaneously. According to the report by WHO, any intervention which provides saving three times more than gross national product per capita in a country could be counted as a cost-effective intervention (29). When gross national product per capita in Turkiye in 2014 (22.753 TL) is taken into consideration, the intervention carried out within the study could be counted as a cost-effective intervention on annual-basis.

Study Limitations

In this study, only direct cost was calculated, but indirect cost was not included.

Conclusion

While it is not possible to prevent all the cases of HAIs, it is possible to decrease the frequency of HAIs, high extra costs, high levels of mortality and lengthy bed-days through continuous monitoring and feedback of HAIs, use of simple but extremely effective evidence-based infection control systems and education and trainings. In order to realize all these developments, it is necessary to spend vigorous efforts; however, these efforts will contribute not only to decreasing HAI rates but also to eliminating economic losses.

Ethics

Ethics Committee Approval: This study was approved by Ethics Committee of Eskişehir Osmangazi University Faculty of Medicine (approval number: 80558721/27).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.E.G., B.I., B.B., Design: M.E.G., B.I., B.B., Data Collection or Processing: M.E.G., B.I., Analysis or Interpretation: M.E.G., B.I., Literature Search: M.E.G., Writing: M.E.G.

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Is Routine Measurement of Post-operative Hemoglobin and Electrolytes Necessary in Every Patient After Transurethral Resection of the Prostate?

Transüretral Prostat Rezeksiyonu Sonrası Her Hastada Postoperatif Hemoglobin ve Elektrolitlerin Rutin Ölçümü Gerekli midir?

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

Although subject is not new but little scientific evidence available, most urologists practice based on their preference and experience. Results will have positive impact on cost and other issues related to this subject.

Abstract

Objective: To evaluate the importance of post-operative hemoglobin and electrolyte monitoring after transurethral resection of the prostate (TURP) and establish the parameters to be considered for monitoring.

Materials and Methods: Data of patients who underwent TURP between 2007 and 2017 were reviewed. Data regarding prostate size, irrigation fluid volume, resection time, pre- and post-operative electrolytes, hemoglobin levels taken within 48 hours before and after surgery, and blood transfusion information were collected. In order to establish parameters for post-operative laboratory monitoring, we categorized prostate size, resection time, and irrigation fluid into groups i.e. (<45 g, 45-60 g, 61-80 g and >80 g), (<30 min, 31-60 and >60 min) and (<20 L, 21-40 L and >40 L) respectively.

Results: A total of 1.000 patients were included. The median age was 66 years with the minimum of 46 years and maximum of 98 years. The median prostate size was 54.26 g. Among all pre- and post-operative laboratory parameters, only hemoglobin and sodium showed a significant change, which were analyzed further. Drop in hemoglobin was significantly associated with increasing prostate size and volume of irrigation fluid. Patients with a prostate size of >80 g had 27.3 times higher chance of significant (>2 g) drop in hemoglobin while 5.1 times higher when irrigation volume exceeded 40 liters. Low levels of sodium were strongly associated with prostate size, irrigation fluid volume, and resection time. However, all these factors become insignificant ($p \geq 0.05$) for their effect on low sodium, when these variables were adjusted with each other. Blood transfusion was performed in 27 patients. All these patients belonged to a group of patients with prostate size of more than 80 g with high resection time and irrigation fluid volume. Three patients had TUR syndrome. Post-operative hemoglobin and electrolytes monitoring contributed to a change in the management of only 14% of patients.

Conclusion: Routine post-operative hemoglobin and electrolyte measurement is not required in every patient undergoing TURP. Use of risk stratification approach will help us to decide which patient needs post-operative lab testing.

Keywords: Transurethral resection of prostate, Post-operative, Hemoglobin, Electrolytes, Benign prostatic hyperplasia

Öz

Amaç: Transüretral prostat rezeksiyonu (TURP) sonrası, hastalarda postoperatif hemoglobin ve elektrolit izleminin önemini değerlendirmek ve izlem için dikkate alınması gereken parametreleri belirlemektir.

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Gereç ve Yöntem: 2007-2017 yılları arasındaki TURP hastalarının verileri gözden geçirildi. Prostat büyüklüğü, irrigasyon sıvısı hacmi, rezeksiyon zamanı, ameliyat öncesi ve sonrası elektrolitler, 48 saatlik hemoglobin seviyeleri ve kan transfüzyonu bilgileri ile ilgili veriler toplandı. Ameliyat sonrası laboratuvar izlemi için parametreler belirlemek amacıyla sırasıyla; prostat büyüklüğü (<45 g, 45-60 g, 61-80 g ve >80 g), rezeksiyon zamanı (<30 dk., 31-60 dk. ve >60 dk.) ve irrigasyon sıvısı (<20 L, 21-40 L ve >40 L) vb. kategorize edildi.
Bulgular: Çalışmaya toplam 1,000 hasta dahil edildi. Ortalama yaş 66 yıl iken; minimum 46, maksimum 98 yıl idi. Ortalama prostat büyüklüğü 54,26 g idi. Tüm ameliyat öncesi ve sonrası laboratuvar parametreleri arasında sadece hemoglobin ve sodyum anlamlı bir değişim göstermiştir. Hemoglobin düşüşü, prostat büyüklüğünün artması ve irrigasyon sıvısının hacmi ile anlamlı olarak ilişkili idi. Prostat büyüklüğü >80 g olan hastalar, hemoglobinde 27,3 (>2 g) kat daha yüksek anlamlı düşüşe sahip iken; irrigasyon hacmi 40 L'yi aştığında bu düşüş 5,1 kat daha yüksek olmuştur. Prostat büyüklüğü, irrigasyon sıvısı hacmi ve rezeksiyon zamanı multinominal lojistik regresyon analizinden sonra düşük sodyum etkisi nedeniyle önemsiz (p≥0,05) hale gelmiştir. Postoperatif hemoglobin ve elektrolit izlemi, hastaların sadece %14'ünün yönetiminde bir değişikliğe katkıda bulunmuştur.
Sonuç: TURP uygulanan her hastanın, postoperatif rutin hemoglobin ve elektrolit ölçümleri gerekli değildir. Risk sınıflandırma yaklaşımının kullanımı, postoperatif laboratuvar testlerine hangi hastanın ihtiyaç duyduğuna karar vermede bizlere yardımcı olacaktır.
Anahtar Kelimeler: Transüretral prostat rezeksiyonu, Postoperatif, Hemoglobin, Elektrolit, Benign prostat hiperplazisi

Introduction

Transurethral resection of the prostate (TURP) is one of the most common urological procedures. It has been the gold standard procedure for benign prostatic hyperplasia (BPH) with symptomatic bladder outlet obstruction (BOO) (1). Despite introduction of newer procedures, such as holmium laser enucleation, GreenLight laser and diode laser ablation, TURP still retains its position (2). Previously, post-procedure complications occurred quite frequently, with early complications of bleeding, sepsis, electrolytes imbalance, TUR syndrome, incontinence, and urinary retention (3). In the past few decades, there has been considerable decrement in the incidence of these early complications mainly due to standardization of the procedure, and improvement in equipment, perioperative management, and anesthetic techniques (4). Although bleeding is the most important complication of TURP (5), a combined data from 10654 procedures reported that only 2.9% cases required transfusion due to bleeding (6). Later, it was recommended that routine blood testing was not necessary (7). After bleeding, the next most important complication is electrolyte imbalance, due to the significant risk of developing TUR syndrome (8). However, it has also become rare with time. The risk of developing electrolyte imbalance is less than 1.1%, and this is attributable to a better understanding of its pathophysiology and advances in technology (9).

Despite considerable reduction in complications, major urological associations have not been specified by the guidelines for which patients require post-TURP hemoglobin (Hb) and electrolyte monitoring. Although such testing is performed routinely in many centers, it varies amongst different centers, usually not taking into account risk factors associated with electrolyte imbalance. Routine testing in all patients irrespective of risk factors is costly and burdensome. A study from an academic institute shows that out of a total of 24482 laboratory tests performed in 426 patients admitted for different diseases, 67.9% of the tests were irrelevant or unnecessary and the test results did not contribute towards the effective management of the patient (10).

At a time when a practice is both evidence-based and economical, we set out to establish certain parameters that can be considered before going for routine post-operative Hb and electrolytes measurement.

Materials and Methods

We retrospectively reviewed data of patients who underwent TURP between 2007 and 2017. The cases were performed by all urologists within the unit. Ethical review committee approval was taken before commencement of the study from the Kidney Centre Ethical Review Committee, under the Auspices of Dorab Patel Post Graduate Training and Research Centre (reference number: 26-URO-062015). All patients, who had normal pre-operative clotting profile and negative urine cultures, were included in the study. Patients excluded were those who were taking diuretics, antithrombotic, and anticoagulant drugs. The pre- and post-operative electrolytes, Hb levels taken within 48 hours before and after surgery and blood transfusion information were collected from the hospital's medical record department. Information regarding prostate size, irrigation fluid volume and resection time were also collected. A consultant or senior resident under supervision of a consultant carried out TURP using a 26 Fr continuous flow resectoscope with monopolar diathermy. During the procedure, the bladder was irrigated with 1.5% glycine. After the surgery, 0.9% saline was used for irrigation.

In order to establish parameters for post-operative laboratory monitoring, variables were categorized into groups. Prostate size was categorized in 3 groups i.e., <45 g, 45-60 g, 61-80 and >80 g. Similarly, resection time and irrigation fluid volume were also categorized into 3 groups: (<30 min, 31-60 and >60 min) and (<20 L, 21-40 L and >40 L). Drop in Hb was considered mild if <1

g/dL, considered moderate and severe if the drop was 1-2 g/dL and >2 g/dL, respectively. To see electrolyte derangements, post-operative serum sodium and potassium values were analyzed in all groups.

Statistical Analysis

Data analyses were performed by using software IBM SPSS version 21. Mean and standard deviation were reported for normally distributed continuous variables while for skewed data medians with interquartile range were described. At the stage of inferential analysis, continuous variables were categorized and association was obtained between different variables by the chi-square test. Two predicted model using binary and multinomial logistic regression analyses were established to evaluate the effect of factors leading toward low sodium and drop in Hb. A p value of less than 0.05 was considered statistically significant.

Results

A total of 1.005 patients had TURP in the study period. Five patients were excluded due to incomplete data. A total of 1.000 patients were included. The median age was 66 years with the minimum of 46 years and maximum of 98 years (Table 1). The median prostate size was 54.26 g. Among all pre- and post-operative laboratory parameters, only Hb and sodium showed a significant change (Table 2), which were analyzed further. For drop in sodium levels, prostate size, resection time and quantity of irrigation fluid were analyzed with post-operative sodium levels. A prostate size of >80 g (49.6%), more than 40 liters of irrigation fluid used (50.4%) and a resection time of longer than 60 minutes (55.8%) were most strongly associated with low sodium post-operatively (Table 3). On further analysis,

Table 1. Descriptive analysis of clinical variables

	Median with IQR	Minimum	Maximum
Age (years)	66.13	46	98
Prostate size (grams)	54.26	34	120
Irrigation fluid (liters)	20.15	5	60
Resection time (minutes)	43.30	20	92

IQR: Interquartile range

Table 2. Pre- and post-operative differences of laboratory parameters

	Median with IQR	Minimum	Maximum	p value
Pre-operative serum creatinine (mg/dL)	1, 0.4	1	3	0.024
Post-operative serum creatinine (mg/dL)	1, 0.4	1	2	
Pre-operative hemoglobin (g/dL)	12.7, 2.3	8	16	<0.001
Post-operative hemoglobin (g/dL)	11.8, 2.2	7	16	
Pre-operative sodium (meq/L)	140, 4	134	150	<0.001
Post-operative sodium (meq/L)	139, 5.7	123	148	
Pre-operative potassium (meq/L)	3.9, 0.4	3	5	0.22
Post-operative potassium (meq/L)	3.8, 0.5	3	6	

IQR: Interquartile range

Table 3. Association of post-operative decrease in sodium with different variables

		Post-operative sodium (meq/L)			p value
		≥134 meq (n with %)	<134 meq (n with %)	Total	
Prostate size	>80 grams	95 (59.7)	64 (40.3)	159	<0.001
	61-80 grams	180 (89.1)	22 (10.9)	202	
	45-60 grams	347 (93.3)	25 (6.7)	372	
	<45 grams	249 (62.4)	18 (37.6)	267	
Irrigation fluid	>40 liters	108 (62.4)	65 (37.6)	173	<0.001
	20-40 liters	325 (90.3)	35 (9.7)	360	
	<20 liters	438 (93.8)	29 (6.2)	467	
Resection time	>60 minutes	137 (65.6)	72 (34.4)	209	<0.001
	31-60 minutes	444 (92.5)	36 (7.5)	480	
	30 minutes	290 (93.2)	21 (6.8)	311	
	Total	871	129	1000	

the odds ratio for >80 g of size of the prostate was 9.3 times higher than <45 g for low sodium (p<0.001). Similarly, when >40 L of irrigation fluid was used, the patients suffered 9.1 times more with low sodium than with the use of <20 L of fluid (p<0.001). In the same manner, a resection time of >60 minutes was associated with 7.3 times greater risk for low sodium as compared to 30 minutes (p<0.001). When all these variables were adjusted with each other, we found that all these factors become insignificant (p≥0.05) for their effect on low sodium (Table 4). For drop in Hb, cross tabulation analysis among four categories of post-operative Hb drop with different variables was performed. We observed that a Hb drop of greater than 2 g was significantly associated with the size of the prostate, quantity of the irrigation fluid used and resection time. 46.3% of patients with a prostate size >80 g had a Hb drop greater than 2 g as compared to 4% in those having <45 g of size. On the other hand, <1 g drop in Hb mostly occurred in patients who had a prostate size of <45 g (40.5%). Similar pattern can be seen with irrigation fluid and resection time (Table 5). On further analysis by multinomial logistic regression analysis, patients with a prostate size of >80 g had 62.4 times higher chance of significant (greater than 2 g) drop in Hb while those with a prostate size 61-80 g and 45-60 g had 11 times and 8.8 times greater risk, respectively, as compared to those with a prostate size of <45 g (p<0.001). After adjustment of other confounding variables, the risk was reduced but remained

Table 4. Univariable and multivariable binary logistic regression analysis for effects of factors on post-operative serum sodium

Unadjusted analysis					Adjusted analysis			
	Odds ratio	95% CI for exp(B)		p value	Odds ratio	95% CI for exp(B)		p value
		Lower	Upper			Lower	Upper	
Prostate size >80 grams	9.3	5.3	16.5	<0.001	3.0	0.9	10.5	0.069
Prostate size 61-80 grams	1.7	0.9	3.2	0.114	1.3	0.5	3.0	0.59
Prostate size 45-60 grams	0.98	0.5	1.9	0.99	0.9	0.1	1.9	0.81
Prostate size <45 grams	1.0	-	-	-	-	-	-	-
Irrigation fluid >40 liters	9.1	5.6	14.8	<0.001	1.9	0.6	6.0	0.260
Irrigation fluid 20-40 liters	1.6	1.0	2.7	0.063	1.4	0.7	2.8	0.34
Irrigation fluid <20 liters	1.0	-	-	-	-	-	-	-
Resection time >60 minutes	7.3	4.3	12.3	<0.001	1.7	0.6	4.9	0.360
Resection time 30-60 minutes	1.1	0.6	2.0	0.691	0.9	0.4	1.9	0.79
Resection time 30 minutes	1.0	-	-	-	-	-	-	-

CI: Confidence interval

Table 5. Association of post-operative hemoglobin drop with different variables

		Drop in hemoglobin (g/dL)				p value
		<1 gram (n with %)	1-2 gram (n with %)	>2 gram (n with %)	Total	
Prostate size	>80 grams	40 (25.2)	509 (31.4)	69 (46.3)	159	<0.001
	61-80 grams	95 (47)	78 (38.6)	29 (14.4)	202	
	45-60 grams	184 (49.5)	143 (38.4)	45 (12.1)	372	
	<45 grams	217 (81.3)	44 (16.5)	6 (2.2)	267	
Irrigation fluid	>40 liters	42 (24.2)	61 (35.3)	70 (40.5)	173	<0.001
	20-40 liters	164 (45.6)	147 (40.8)	49 (13.6)	360	
	<20 liters	330 (70.7)	107 (22.9)	30 (6.4)	467	
Resection time	>60 minutes	61 (29.2)	79 (37.8)	69 (33)	209	<0.001
	31-60 minutes	235 (49)	179 (37.3)	66 (13.8)	480	
	30 minutes	240 (49)	57 (18.3)	14 (4.5)	311	
	Total	536	315	149	1000	

significantly higher at 27.3, 6.7 and 6.1 times, respectively (Table 6). Figure 1 shows the mean Hb drop with the increase in the size of the prostate. Regarding resection time, a significant drop (>2 g) in Hb occurred, in those patients with resection time >60 minutes (p<0.001) as compared to those with 30 minutes (19.4 times more). However, the effect of resection time on Hb drop became insignificant when adjusted with other variables (p≥0.05). On the other hand, the volume of irrigation fluid for significant drop (>2 g) in Hb remained significant even after adjustment of confounding variables. The adjusted odds ratio decreased from 18.3 times to 5.1 times for >40 liters (Table 6). Out of 1000 patients, blood transfusion was done in 27 patients, and 11% of patients, who needed further treatment like water restriction and diuretic therapy, had low sodium levels post-operatively. Three patients developed TUR syndrome. Therefore, post-operative Hb and electrolyte monitoring contributed to a change in the management of only 14% of patients. All these patients belonged to a group of patients with a prostate size of more than 80 g, long resection time and high irrigation fluid volume. Considering these results, a more practical risk stratification approach is suggested (Table 7).

Discussion

TURP is the gold standard surgical treatment for patients with moderate to severe lower urinary tract symptoms associated with BPH, and is most effective in relieving BOO due to large prostate size (11). Although perioperative mortality and morbidity rates have declined over time, they still remain at 0.1% and 11.1%, respectively, mainly due to bleeding, acute kidney injury, and TUR syndrome (12,13).

Table 6. Univariable and multivariable multinomial logistic regression analysis for effect of factors on drop in hemoglobin after surgery

		Unadjusted multinomial analysis				Adjusted multinomial analysis			
Drop in hemoglobin		Odds ratio	95% confidence interval for exp(B)		p value	Odds ratio	95% confidence interval for exp(B)		p value
			Lower bound	Upper bound			Lower bound	Upper bound	
1-2 gram	Prostate size >80 grams	6.2	3.6	10.4	<0.001	**1.1**	**0.39**	**3.16**	**0.85**
	Prostate size 61-80 grams	4.1	2.6	6.3	<0.001	2.0	1.2	3.4	0.011
	Prostate size 45-60 grams	3.8	2.6	6.3	<0.001	2.5	1.6	3.9	<0.001
	Prostate size <45 grams	1.0	-	-	-	-	-	-	-
>2 gram	Prostate size >80 grams	62.4	25.4	153.2	<0.001	27.3	5.8	129.0	<0.001
	Prostate size 61-80 grams	11.0	4.4	27.5	<0.001	6.7	2.4	18.5	<0.001
	Prostate size 45-60 grams	8.8	3.7	21.2	<0.001	6.1	2.4	15.6	<0.001
	Prostate size <45 grams	1.0	-	-	-	-	-	-	-
1-2 gram	Resection time >60 minutes	5.5	3.5	8.5	<0.001	2.0	0.9	4.2	0.080
	Resection time 31-60 minutes	3.2	2.3	4.5	<0.001	1.6	1.1	2.5	0.047
	Resection time 30 minutes	1.0	-	-	-	-	-	-	-
>2 gram	Resection time >60 minutes	19.4	10.2	36.8	<0.001	0.6	0.2	1.9	0.350
	Resection time 31-60 minutes	4.8	2.6	8.8	<0.001	1.5	0.7	3.1	0.28
	Resection time 30 minutes	1.0	-	-	-	-	-	-	-
1-2 gram	Irrigation fluid >40 liters	4.5	2.9	7.0	<0.001	3.7	1.4	9.4	0.007
	Irrigation fluid 20-40 liters	2.8	2.0	3.8	<0.001	1.7	1.1	2.4	0.011
	Irrigation fluid <20 liters	1.0	-	-	-	-	-	-	-
>2 gram	Irrigation fluid >40 liters	18.3	10.7	31.3	<0.001	5.1	1.6	16.9	0.008
	Irrigation fluid 20-40 liters	3.3	2.0	5.4	<0.001	1.7	0.9	3.0	0.078
	Irrigation fluid <20 liters	1	-	-	-	-	-	-	-

The reference category is: <1 gram

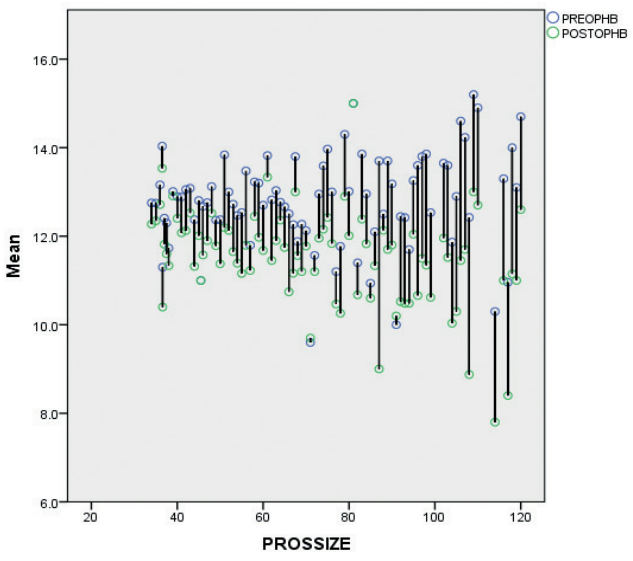


Figure 1. Change in mean hemoglobin pre- and post-transurethral resection of the prostate in relation to prostate size

PREOPHB: Preoperative hemoglobin, POSTOPHB: Postoperative hemoglobin, PROSSIZE: Prostate size

Table 7. Risk stratification strategy

Low risk group Prostate size: <45 mL	Post-operative Hb and electrolytes monitoring not required
Intermediate group Prostate size: 45-80 mL	Post-operative Hb and electrolytes monitoring is optional. Consider age, comorbid, and general condition of patients
High risk group Resection time >60 minutes Irrigation fluid >40 L Prostate size >80 mL	Post-operative Hb and electrolytes monitoring should be done in all cases

Hb: Hemoglobin

Bleeding has many contributing factors, which include acetylsalicylic acid intake, activation of fibrinolysis system, size of the prostate gland, weight of the resected gland, duration of the procedure, histologic presentation of the gland, and presence of urinary tract infection (14,15).

Regarding irrigation fluid used during TURP, it has been proven that 1.5% glycine and 2.7% sorbitol have not shown significant impact on the result (16). Therefore, glycine 1.5% was used in the present study. A resection time of longer than 60 minutes was related to an increase in loss of blood in two studies (17), but was refuted by another study (18). Mebust (19) has reported that the incidence of blood loss was higher in patients with a resected prostate tissue greater than 45 g. In this study, blood loss was also strongly associated with prostate size. The mean change in Hb in our study was 0.9 g/dL, which appears to be slightly lower as compared to other studies (20).

Studies have used different methods for estimating blood loss after TURP, but these require additional resources and hence have added costs and a margin of error of 4-5% (20,21). Post-TURP, maximum blood loss occurs within 2 days, with time to 50% blood loss at 16 hours. Hence, testing of Hb levels within 48 hours TURP is a practical and widely used method of determining blood loss (22). Although post-operative Hb is a useful guide to the need for transfusion and it is included in the TURP integrated care pathway at many centers, but routine testing of post-operative Hb in every patient is questionable. Often these results are overlooked or not documented, as discovered during this study. In addition, unnecessary blood testing raises ethical concern and discomfort to the patient. This testing should only be done where indicated, as in patients with large vascular glands, who have undergone long resections, ongoing blood loss or symptomatic anemia.

Another important complication of TURP is electrolyte imbalance. This includes TUR syndrome. The amount of fluid absorbed is directly related to the number and size of opened venous sinuses. This hypervolemic hyponatremic state may lead to mental confusion, bradycardia, hypertension, nausea, vomiting, and visual disturbances associated with hyponatremia (23).

Recent advancements in technology and with better understanding of pathophysiology, TUR syndrome has become a rare condition (less than 1.1%). These include development of continuous flow resectoscopes, utilization of non-hemolytic solutions, such as glycine, sorbitol, and mannitol, limited resection time and advances in training techniques (9,24). Hydrostatic pressure at the prostatic bed is an important factor for fluid absorption during TURP. This is dependent on the height of irrigating fluid column, and pressure inside the bladder during surgery (25). For good vision during resection, 60 cm is the suggested ideal height of irrigating fluid to obtain around 300 g of fluid per minute. In this study, the irrigation fluid column height was constant so that other determinants could be assessed.

In patients with deranged electrolytes, a higher volume of irrigant was found to be used in previous studies (26). Several proposed strategies are present for reduction in risk of fluid absorption during TURP, but none has been completely successful. Resection time is suggested to be kept below 60 min for minimal fluid absorption (27). In our study, three patients developed clinical TUR syndrome (0.3%), and the value of <135 mEq/L was used to define hyponatremia. In relation to potassium, post-operative hyperkalemia may result due to cell lysis and release of intracellular potassium, or due to acute

kidney injury secondary to sepsis or obstruction. A significant change in serum potassium levels was not encountered post-operatively, which can be explained by the fact that absorption of irrigation fluid causes hemodilution and offsets any changes in potassium. Also with the use of 1.5% glycine as an irrigant, hemolysis is comparatively minimal (28). Few studies have investigated the usefulness of routine electrolyte testing following TURP (29). Most of them focused on post-TURP Hb monitoring (30). It was concluded that post-operatively, routine blood testing is unnecessary and should only be sought on clinical need or after technically demanding surgery. Newer techniques, such as bipolar resectoscopes and vaporizing of tissue instead of resection, have caused reduction in absorption of fluid and hence electrolyte imbalance. Therefore, routine monitoring of fluid absorption has been abandoned in many hospitals. However, no guideline on routine monitoring of post-operative electrolytes is present. It has been shown in this study that post-operative Hb and electrolyte monitoring contributed to a change in the management of only 14% of patients as only 2.7% patients needed blood transfusion and 11% patients needed treatment for hyponatremia. Therefore, routine Hb and electrolyte measurements post-operatively are not required in every patient.

In view of the above findings, a more practical approach is suggested. A risk stratification strategy should be implemented, which will help decide which patients need post-operative lab testing. As a result, elimination of unnecessary investigations will be more cost effective and comfortable for patients.

Study Limitations

There are a few limitations in this study. As this is a retrospective study, information related to resected volume of the prostate was not available. Lack of uniformity in terms of expertise of different surgeons was another limitation.

Conclusion

Routine Hb and electrolyte measurements post-operatively are not required in every patient. Use of risk stratification approach will help us decide which patient needs post-operative lab testing.

Ethics

Ethics Committee Approval: Ethical review committee approval was taken before commencement of this study from the Kidney Centre Ethical Review Committee, Under the Auspices of Dorab Patel Post Graduate Training and Research Centre (reference number: 26-URO-062015).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.H.A.M., S.E.K., Concept: M.H.A.M., Design: M.H.A.M., Data Collection or Processing: M.H.A.M., S.A.K., I.S., A.S.A., Analysis or Interpretation: M.H.A.M., S.A.K., I.S., Literature Search: M.H.A.M., S.E.K., A.S.A., Writing: M.H.A.M., S.E.K.

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Are the Complication Rates for the Open Approach in the Surgical Treatment of Bladder Stones Higher Than Rates for Endoscopic Approaches? A Comparative Multivariate Analysis Study

Mesane Taşlarının Cerrahi Tedavisinde Açık Yaklaşımın Komplikasyonları Endoskopik Yaklaşımlardan Yüksek midir? Karşılaştırmalı Bir Multivaryan Analiz Çalışması

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

The complication rates for open surgical approaches are significantly higher than the rates for endoscopic approaches in the management of bladder stone disease.

Abstract

Objective: To compare the effectiveness, safety and complication rates of open vs endoscopic approach for bladder stone surgery and investigate the predictive factor for success and complication rate in patients with bladder stone.

Materials and Methods: The records of 128 patients, who underwent stone surgery between November 2010 and June 2017, were analyzed. The patients were divided into two groups according to surgical approach as endoscopic or open group. Duration of surgery and catheterization and length of hospital stay were recorded. Multivariate analyses were done using logistic regression test to determine the risk factors for complications.

Results: A total of 130 procedures were performed in 128 patients included in the study. Of them, 93 were treated via endoscopic approach and 37 via open approach. The overall success rate in endoscopic and open groups was 92.5% and 100%, respectively (p=0.44). Increased age, type of surgical approach and using lithotripsy were found to be risk factors for complications in univariate analysis. Only the type of surgery was found to be an independent risk factor for complications in multivariate analysis (p=0.006).

Conclusion: Open and endoscopic approaches showed similar effectiveness in patients with bladder stone. The only significant risk factor for complications was the type of surgical approach.

Keywords: Bladder, Stone, Endoscopic, Open, Surgery

Öz

Amaç: Mesane taşı cerrahisinde açık ve endoskopik yaklaşımın etkinliğini, güvenliğini ve komplikasyon oranlarını karşılaştırmayı ve mesane taşı olan hastalarda başarı ve komplikasyon oranı için öngörü faktörünü araştırmayı amaçladık.

Gereç ve Yöntem: Kasım 2010 ve Haziran 2017 arasında 128 hastanın kayıtları analiz edildi. Hastalar, endoskopik veya açık grup olarak cerrahi yaklaşıma göre iki gruba ayrıldı. Operasyon süresi, kateterizasyon ve hastanede yatış süreleri kaydedildi. Multivaryan analizle komplikasyonlar için risk faktörleri lojistik regresyon testi kullanılarak belirlendi.

Bulgular: Çalışmaya dahil edilen 128 hastaya toplam 130 işlem uygulandı. Bunlardan 93'üne endoskopik yaklaşım ve 37'sine açık yaklaşım uygulanmıştır. Her iki grubun genel başarı oranı, endoskopik ve açık gruplar için sırasıyla %92,5 ve %100 idi (p=0,44). Artmış yaş, cerrahi yaklaşım tipi ve litotripsi kullanımı komplikasyonlar için univaryan analizde risk faktörleri olarak bulundu. Multivaryan analizde sadece cerrahi yaklaşım tipi komplikasyonlar için bağımsız risk faktörü olarak bulundu (p=0,006).

Sonuç: Açık ve endoskopik yaklaşımlar, mesane taşı tedavisinde benzer etkinlik göstermiştir. Komplikasyonlar için tek anlamlı risk faktörü cerrahi yaklaşım tipi olarak tespit edildi.

Anahtar Kelimeler: Mesane, Taş, Endoskopi, Açık, Cerrahi

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Introduction

Bladder stones are the most common lower urinary tract stones and constitute about 5% of all urinary tract stones (1). Bladder stones usually occur as bladder outlet obstruction, diseases causing urinary stasis such as neurogenic bladder dysfunction, or as a factor secondary to the formation of stones such as foreign bodies (2).

Bladder stones are surgically treated with an open or endoscopic approach such as percutaneous and transurethral techniques. Cystolithotomy is a very old operation that has been practiced for thousands of years. Hippocrates found that suprapubic approach was dangerous for bladder stones. He refered to bladder stones, "I will not cut even for the stone" (3).

Open surgery was the gold standard treatment in the past, but it has fallen from grace with rapidly evolving minimally invasive techniques (4). Developments in pneumatic and laser energy sources, which allow lithotripsy intracorporally, have made percutaneous and transurethral access increasingly common.

The aim of this study was to investigate the presence of independent risk factors predicting the outcome and complications of different surgical approaches in the treatment of bladder stones.

Materials and Methods

We retrospectively reviewed data of patients who underwent surgery with bladder stone diagnosis between 2010 and 2017 in our department. A total of 128 patients enrolled in 130 approaches were included in the study. Demographic data, such as age and sex, and pre-operative and peri-operative data were recorded. The patients were divided into two groups according to surgical approach as endoscopic group and open group.

The patients were also divided into two groups according to the presence of complications. Peri-operative complications were classified according to the Satava classification (5) and the post-operative complications according to the Clavien classification (6).

This study was executed in a retrospective design and all patients provided written informed consent. Ethics committee approval was not applied because of the retrospective design of the study.

Statistical Analysis

Multivariate analysis was performed to investigate independent predictive factors for complications. A chi-square test and the Fisher's exact test were used for the difference between the categorical variables, while the Kruskal-Wallis and Mann-Whitney U tests were used for the difference between the means. The data were analyzed using the Statistical Package for the Social Sciences version 16 (SPSS Inc., Illinois, USA). A p value of less than 0.05 was considered statistically significant.

Results

The mean age of the patients was 53.02±24.15 years. Endoscopic approach was used in 93 (71.5%) patients and open approach in 37 (28.5%) patients. The demographic data is given in Table 1. The overall success rate was 92.5% and 100% in endoscopic and open groups, respectively (p=0.44). Patients with residual stones were treated with endoscopic approaches and 4 with transurethral and 3 with percutaneous cystolithotripsy. The

Table 1. Characteristics of patients and demographic datas

Characteristic	All	Endoscopic			Open	p value
		Transurethral	Percutan	T+P		
Number	130	62 (47.7%)	31 (23.8%)	93 (71.5%)	37 (28.5%)	-
Age (year, mean)	53.02±24.15	50.4±25.5	49.7±23.6	50.16±24.1	60.2±21.2	**0.012***
Gender						
Male	119 (92%)	54 (45.4%)	29 (24.4%)	83 (69.7%)	36 (30.3%)	0.17
Female	11 (8%)	8 (72.7%)	2 (18.2%)	10 (90.9%)	1 (9.1%)	
Stone burden (cm^2)	5.88±5.72	3.33±0.50	8.41±1.36	4.98±1.22	8.05±0.76	**0.006***
Primary disease						
BPO/urethra str.	87 (67%)	38 (29.3%)	19 (14.6%)	57 (44%)	30 (23%)	-
Neurogen bladder	16 (12.4%)	6 (4.6%)	6 (4.6%)	12 (9.3%)	4 (3.1%)	-
Upper UT Stone	21 (16.2%)	15 (11.6%)	4 (3.1%)	19 (14.7%)	2 (1.5%)	0.21
Foreign body	1 (0.8%)	0 (0%)	1 (0.8%)	1 (0.8%)	0 (0%)	-
Other	5 (3.8%)	3 (2.28%)	1 (0.76%)	4 (3.04%)	1 (0.76%)	-

BPO: Benign prostatic obstruction, Urethra str.: Urethral stricture, UT: Urinary tract, T: Transurethral, P: Percutan
* Student's t-test, other p values from chi-square test, all p values for T+P vs open data

Table 2. Peri- and post-operative complications

Variable	Grade	All	Endoscopic	Open
Post-operative complications according to the Clavien classification	1	2 (18%)	0 (0%)	2 (29%)
	2	8 (73%)	3 (75%)	5 (71%)
	3	1 (9%)	1 (25%)	0 (0%)
	4	0 (0%)	0 (0%)	0 (0%)
Post-operative complications	-	**11 (8.5%)**	**4 (4.3%)**	**7 (19%)**
Peri-operative complications according to Satava classification	1	3 (43%)	3 (75%)	0 (0%)
	2A	2 (28.5%)	0 (0%)	2 (66.7%)
	2B	2 (28.5%)	1 (25%)	1 (33.3%)
	3	0 (0%)	0 (0%)	0 (0%)
Peri-operative complications	-	**7 (5.4%)**	**4 (4.3%)**	**3 (8.1%)**
Overall complications (patients)	-	18 (14%)	8 (8.6%)	10 (27%)

Table 3. The univariate analysis outcomes

Characteristic	Complication +	Complication -	p value
Number	18 (13.8%)	112 (86.2%)	-
Age (year, mean)	62.5±21.2	51.8±23.8	**0.021***
Approach			
Endoscopic	8 (8.6%)	85 (91.4%)	**0.006**
Open	10 (27%)	27 (73%)	
Lithotripsy			
Yes	7 (8.4%)	76 (91.6%)	**0.018**
No	11 (23.4%)	36 (76.6%)	
Stone burden (cm^2)	4.78±2.92	6.06±6.04	0.771*
Primary disease			
Non-neurogen	16 (14%)	98 (86%)	0.868
Neurogen	2 (12.5%)	14 (87.5%)	
Concurrent procedures			
Yes	10 (16.1%)	52 (83.9%)	0.472
No	8 (11.8%)	60 (88.2%)	
Anesthesia type			
Generel	15 (13.8%)	94 (86.2%)	0.949
Regional	3 (14.3%)	18 (85.7%)	

mean stone burden (3.33±0.5 cm^2) in patients undergoing transurethral cystolithotomy was lower than in the other two groups (percutaneous-8.41±1.36 cm^2 and open-8.04±0.76 cm^2). The difference was statistically significant (p=0.001).

The peri-operative and post-operative complication rates in our patients were 5.4% and 8.5%, respectively (Table 2). In the peri-operative period, according to the Satava classification, urethral injury occurred in 3 patients (grade 1) and transurethral resection (TUR) syndrome occurred in 1 patient (grade 2B) in endoscopic group. In open group, 3 patients had peri-operative complications. One patient developed respiratory distress (grade 2B) and 2 patients had bleeding (grade 2A). In the post-operative period, according to the Clavien classification, two patients had high fever (grade 1) and urinary tract infection occurred in 8 patients (grade 2). After the necessary conservative treatment, all 10 patients were discharged without any problems. We performed internal urethrotomy in 1 patient at the post-operative period due to the urethral stricture (grade 3). There were statistically significant differences between the groups in terms of age, approach and lithotripsy (p=0.021, p=0.006 and p=0.018, respectively) in the univariate analyses by separating the two groups according to complications (Table 3). The patients with complications were older. There was no significant difference between the two groups in terms of stone burden, primary disease (neurogenic and non-neurogenic), concomitant procedure, and anesthesia (spinal and general anesthesia). The type of surgical approach was found to be independent risk factor for complications in multivariate analysis (Table 4). The open surgical approach was associated with more complications than the endoscopic approach (p=0.006).

Table 4. The multivariate analysis outcomes

Variables	Number	Odds ratio	Adjusted odds ratio (95% CI)		p value
			Lower	Upper	
Age	130	1.02	0.99	1.04	0.248
Gender					
Male	119	-	0	-	0.999
Female	11				
Method					
Endoscopic	93	1	-	-	**0.009**
Open	37	3.94	1.41	10.97	
Lithotripsy					
No	47	1	-	-	0.699
Yes	83	1.45	0.22	9.45	

CI: Confidence interval

Discussion

There are several surgical techniques for treating bladder stones including open surgery and endoscopic surgeries such as percutaneous and transurethral approaches (7,8). The stone burden, experience of the surgeon and concomitant surgery are the main factors to determine the type of treatment modality (9). Nowadays, new surgical techniques have taken the place of the open approach. Especially, developments in endoscopic and lithotripsy equipment in the last 20 years have achieved

the treatment of most bladder stones by minimally invasive procedures. Nevertheless, open approach is most commonly considered when transabdominal prostate surgery is planned. The aim of any procedure is to provide complete stone free status in the optimal surgery duration with no complication. In our study, the primary outcome showed that the satisfaction rates were similar both with open or endoscopic approaches (p=0.44). As a secondary outcome; both univariate and multivariate analyses showed that the open approach was an independent predictive factor for increased complication rates for bladder stone surgery (p=0.009).

After introducing endoscopic methods for the treatment of bladder stone, effective fragmentation with various energy sources made the transurethral method more preferred. However, transurethral access may not always be easy. When the duration of transurethral procedure is prolonged, the risk of iatrogenic urethral injury will increase. In addition, the risk of fibrosis and urethral stricture will also increase, leading to impairment of urethral perfusion. As a result, in late 1980s, percutaneous cystolithotripsy practices began to be an alternative to open surgery (10,11,12). The absence of urethral injury and no injury to mucosal unit, short operative duration and low complication rates have made the method popular (5). The method is also used in patients with concomitant benign prostatic obstruction (BPO); it can provide simultaneous TUR of the prostate without increasing complication and operation time (13). In this study, endoscopic approach was performed in 93 (71.5%) patients and, transurethral and percutaneous methods were used in 62 (47.7%) and 31 (23.8%) of them, respectively. Residual stone was detected in 7 patients. Four of them were in transurethral group and 3 in percutaneous group.

In a study comparing percutaneous and transurethral approaches in patients with secondary bladder stones >2.5 cm, following BPO; the duration of transurethral method was longer (14). In addition, residual stones and urethral stricture were reported to be more frequent at the post-operative period. Aron et al. (13) reported similar findings in their retrospective study. It is also possible to draw a conclusion from the data of these studies that urologists prefer percutaneous approach in larger stones (13,14). On the other hand, the results of a recent randomized clinical trial are not similar (15). It has been reported that percutaneous cystolithotripsy was associated with a longer hospital stay and more post-operative complications, as the duration of operation was similar in percutaneous and transurethral approaches (15). There are also authors who argue that the transurethral approach can be performed as an outpatient procedure under local anesthesia (16,17). In our study, lesser complications were seen in patients with intracorporeal fragmentation of the stone with laser and pneumatic energy sources, compared to that in patients in whom the stone was removed without fragmentation (cystolithotomy-23.4% and cystolicotripsy-8.4%). In addition, the mean stone burden (3.33±0.5 cm^2) in patients undergoing transurethral approach was lower than in those who were treated with percutaneous and open approaches (percutaneous-8.41±1.36 cm^2 and open-8.04±0.76 cm^2). The difference was statistically significant (p=0.001).

Bladder stone surgery is often performed with prostate surgery. In fact, the type of prostate surgery mostly determines the type of the approach for bladder stone in these cases. For instance, surgeons prefer open prostatectomy with open cystolithotomy in patients with a large prostate. In our study, 87 patients underwent bladder stone surgery with prostate surgery. In this patient group, 57 (65.5%) of them were in endoscopic group and 30 (34.5%) in open group. It was thought that high complication rates in open group may be due to additional open approaches such as open prostatectomy made in the same session. However, we have not enough evidence.

A significant proportion of bladder stone patients are also neurogenic. A retrospective study done by Bartel et al. (18) in 2014 presented long-term results of bladder stone development in patients with spinal cord trauma. In a cohort of 2825 patients with bladder stones, the rate of spinal cord trauma was reported to be 3.3%. In that study, persistent urethral catheter was emphasized to be the most common risk factor for stone formation, the fastest stone formation and frequent recurrence. In another study, the relationship between bladder stones development and persistent urethral catheterization lasting one month in the acute period after spinal cord trauma was established (19). In our series, 6% of patients were with spinal cord injury. The complication rate for cystolithotomy in patients with spinal cord injury and other neurogenic cases with secondary bladder stones was similar to that in other patients in our study (p=0.868).

In this study, the peri-operative and post-operative complication rates were found to be 5.4% and 8.5%, respectively. In the peri-operative period, according to the Satava classification, urethral injury occurred in 3 patients (grade 1) and TUR syndrome occurred in 1 patient (grade 2B) in endoscopic group. Also, 3 patients in open group had peri-operative complications; 1 patient developed respiratory distress (grade 2B) and 2 patients had bleeding (grade 2A). Concomitant prostatectomy was performed in both patients with bleeding. In the post-operative period, according to the Clavien classification, 2 patients had high fever (grade 1), and urinary tract infection (grade 2) occurred in 8 patients (5 in open group, 3 in endoscopic group). After necessary conservative treatment, all the 10 patients were discharged without any problem. We operated one of our patients in endoscopic group at the post-operative period with internal urethrotomy, after development of urethral stricture (grade 3). Iatrogenic urethral stricture can be seen after transurethral approach. Okeke et al. (20) proposed pre-operative dilatation with transurethral Amplatz sheath to prevent urethral

injury. It has been reported that the rate of complications associated with percutaneous approach was lower than that with transurethral approach (21). In our study, the patients with complications were relatively older (p=0.021). There was no significant difference between open and endoscopic groups in terms of stone burden, primary disease (neurogenic and non-neurogenic), concomitant procedure and anesthesia (spinal and general anesthesia). However, the type of surgical approach was found to be an independent risk factor for complications in multivariate analysis. The open surgical approach was associated with more complications than the endoscopic approach (p=0.006).

Study Limitations

This multivariate analysis study showed that the complication rates for open approach in the surgical treatment of bladder stones were higher than that for endoscopic approaches. Both endoscopic and open approaches showed similar satisfaction rates. However, our study has some limitations. The data were collected longitudinally and were verified retrospectively. In fact, our results suggest that endoscopic and open approaches are safe and feasible treatment modalities in the management of bladder stone. Future prospective studies are warranted.

Conclusion

Open and endoscopic approaches showed similar effectiveness in the management of bladder stone. The only significant risk factor for complications was the type of surgical approach.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Effect of the Anesthetic Method on the Outcomes of Ureteroscopy for Proximal Ureteral Stones: A Multi-center Study of the Society of Urological Surgery Aegean Study Group

Proksimal Üreter Taşı Nedeniyle Üreteroskopi Uygulanan Hastalarda Anestezi Yönteminin Sonuçlara Etkisi: Ürolojik Cerrahi Derneği Ege Çalışma Grubu'nun Çok Merkezli Bir Çalışması

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

Ureteroscopy is an effective method for the treatment of proximal ureteral stones and provides high stone-free rates. Many factors affecting the success of ureteroscopy have been discussed extensively in the literature. The anesthetic method considered to be one of these factors is also discussed, but mostly general and spinal anesthesia were compared with local anesthesia. The purpose of this study was to compare the impact of spinal and general anesthesia on ureteroscopy performed for the treatment of proximal ureter stones and it concluded that both methods are safe and effective.

Abstract

Objective: To analyze the effect of the anesthesia method (spinal and general) on the outcome of ureteroscopy (URS) in patients treated for proximal ureteral stones.

Materials and Methods: Patients, who underwent URS for proximal ureteral stones at various urology clinics in Turkiye, were included in the study. The patients were divided into two groups according to the anesthesia method performed; the procedure was performed under spinal anesthesia (SA) in group 1 and general anesthesia (GA) in group 2. Patients' demographic, perioperative data and complication rates were compared between the two groups in a retrospective manner.

Results: There were 309 and 329 patients in groups 1 and 2, respectively. The mean stone area and Hounsfield unit in GA group were higher ($p<0.001$ and $p=0.007$, respectively). In the GA group, the need for double J stent was more frequent ($p<0.001$). In the SA group, the rate of push-back of stone into the collecting system was higher ($p=0.017$). According to the Clavien classification system and the others, complication rates were similar between the two groups ($p>0.05$). The rate of success of URS, which is accepted as complete stone-free status, was higher in the SA group ($p=0.041$).

Conclusion: URS, which is used in the treatment of proximal ureteral stones, has a high success rate, independent of the anesthesia method used. It is important to keep in mind the patient's comorbidities prior to selecting the anesthesia method and that the stone area and the Hounsfield unit are the important factors affecting the outcomes.

Keywords: Ureteroscopy, Ureteral stone, Spinal anesthesia, General anesthesia, Complication

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Öz

Amaç: Bu çalışmada, anestezi yönteminin (spinal ve genel) proksimal üreter taşı tedavisinde uygulanan üreteroskopi (URS) sonuçlarına etkisini değerlendirdik.

Gereç ve Yöntem: Türkiye'deki farklı üroloji kliniklerinde proksimal üreter taşı nedeniyle URS uygulanan hastalar, çalışmaya dahil edildi. Hastalar, uygulanan anestezi yöntemine göre spinal anestezi (SA) uygulanan birinci grup ve genel anestezi (GA) uygulanan ikinci grup olmak üzere iki gruba ayrıldı. İki grup arasında, hastaların demografik ve perioperatif verileri ve komplikasyon oranları retrospektif olarak karşılaştırıldı.

Bulgular: Birinci grupta 309 hasta, ikinci grupta 329 hasta vardı. GA grubunun ortalama taş alanı ve Hounsfield ünitesi daha yüksekti (sırasıyla, p<0,001 ve p=0,007). GA grubunda, double J stent gereksinimi daha fazlaydı (p<0,001). SA grubunda, taşın toplayıcı sisteme "push-back" oranı daha fazlaydı (p=0,017). Genel ve Clavien sınıflandırma sistemine göre, komplikasyon oranları iki grup arasında benzerdi (p>0,05). Tam taşsızlık olarak kabul edilen URS'nin başarı oranı, SA grubunda daha fazlaydı (p=0,041).

Sonuç: Proksimal üreter taşlarının tedavisinde kullanılan URS, kullanılan anestezi yönteminden bağımsız, yüksek başarı oranlarına sahip bir yöntemdir. Anestezi yönteminin seçiminde hastanın komorbiditelerini göz önünde bulundurmak ve taş alanı ve Hounsfield ünitesinin sonuçları etkileyen önemli faktörler olduğunu akılda tutmak gerekir.

Anahtar Kelimeler: Üreteroskopi, Üreter taşı, Spinal anestezi, Genel anestezi, Komplikasyon

Introduction

Urinary system stone disease is a common problem and its prevalence may be up to 20% with geographical, climatic, ethnic, dietary and genetic factors (1). Urinary stones can be classified according to their etiology, composition, risk of recurrence, X-ray features, size and location (2).

Important factors determining spontaneous stone passage are the size and location of the stone (3). While the spontaneous passage rate for stones smaller than 5 mm is high, this rate for larger stones is dramatically decreased; the rate is very low for stones over 10 mm. Proximal ureteral stones are less likely to pass spontaneously compared to those in other locations. The spontaneous passage rate for proximal ureteral stones is generally 48%, which is 79% for stones in the ureterovesical junction (4). Stones with a low chance of spontaneous passage, persistent pain despite adequate analgesic treatment, persistent obstruction and renal insufficiency constitute the indications for active ureteral stone removal (5). Currently, treatment options for ureteral stones are observation, medical expulsive therapy, shock wave lithotripsy (SWL), ureteroscopy (URS), percutaneous nephrolithotomy, laparoscopic surgery, and open surgery (6).

The stone-free rate (SFR) in URS and SWL, which are two commonly used treatment methods for ureteral stones, is similar. However, better rates can be obtained with URS in larger stones. With the advances in technical equipment, the formerly high complication rate has decreased significantly for URS (7). It has also been possible to achieve high SFRs with URS in proximal ureteral stones, and the current European Association of Urology (EAU) urolithiasis guideline recommend URS (ante- or retro-grade) as the first treatment option in stones larger than 10 mm, and SWL or URS in stones smaller than 10 mm, evenly (6). This suggestion was SWL as the first option for stones smaller than 10 mm and URS or SWL for stones larger than 10 mm in the previous guidelines (8). Undoubtedly, the effect of dazzling technical and technological progress in the field of endourology on this dramatic change is great.

In the literature, many factors affecting the success of URS have been evaluated. Technical equipment (endoscope type, ureteroscope type, fragmentation method, etc.), pre-stenting, stone size and location are the most commonly discussed factors. The effect of anesthesia method which is applied during the procedure is controversial. In the EAU guideline, it is stated that most procedures are performed under general anesthesia (GA), but local or spinal anesthesia (SA) is also possible. Intravenous sedation is also suitable for female patients with distal ureteral stones (9). In this multi-center study, we aimed to analyze the impact of anesthesia method (SA and GA) on the outcome of the patients treated with endoscopic ureteral stone treatment due to proximal ureteral stone.

Materials and Methods

Patients and Data Collection

Data of patients, who underwent URS due to proximal ureteral stones in different reference centers, were obtained from patient files. A total of 638 patients underwent ureteroscopic lithotripsy. Patients were divided into two groups according to the anesthesia method: group SA (n=309) and group GA (n=329). The anesthesia method was determined by the anesthesiologists of the relevant clinics. Anesthesiologists performed SA or GA according to their clinical and patient preferences. Stones located in the region between the ureteropelvic junction and the pelvic brim in the ureter were considered proximal stones and included in the study. The stones that were immobilized, embedded in the ureteric mucosa, and those with mucosal fold observed during endoscopic visualization were evaluated as impacted stones. URS was considered successful upon determination stone-free status with the imaging methods after treatment. All patients

were evaluated post-operatively by non-contrast computed tomography or abdominal radiography. The stone area was calculated in square millimeters by multiplying the longest two dimensions. Patients' perioperative double J stent requirement, gender, stone push-back status, general complication rate and Clavien classification and URS success rate (stone-free) data were collected. The relationship between the anesthesia method (SA or GA) and these variables were evaluated. Ethics Committee of Dokuz Eylül University has approved this study (approval number 2018/03-03). Written informed consent was not obtained from patients because this was a retrospective study. The principles of the Helsinki Declaration were followed during the study, and the confidentiality of the patients' data was guaranteed.

Surgical Technique

Sterile urine culture was provided prior to the procedure. 1 g intravenous cefazolin was administered following SA or GA. In the lithotomy position, 5% lidocaine gel was applied to the urethra. All the procedures were performed using semirigid or rigid ureteroscopes with 8 or 9 Fr distal tip. A guidewire with 3 cm flexible tip was used routinely to guide ureteroscope. If stone access achieved, a holmium laser or a pneumatic lithotripter was used for stone fragmentation. A 16 or 18 Fr Foley catheter was introduced into the bladder with the completion of the operation and was taken on the same day or one day later.

Statistical Analysis

Pearson's chi-square test was used to compare the difference in the anesthesia method between the two groups. If the smallest theoretical frequency was <5, Fisher's exact test was used to analyze the variables. An independent-samples t-test was conducted to compare outcomes for URS in SA and GA conditions. Data were analyzed using the SPSS (version 23.0) statistical program. A p value of less than 0.05 was considered statistically significant.

Results

The vast majority of patients were male (n=424, 66.5% vs 33.5%). Four hundred and thirty patients (67.4%) had no systemic disease. Approximately one third of the patients (n=188, 29.5%) had a chronic medication use. Approximately half of the patients had a history of stone disease (n=304, 47.6%), but SWL history was absent in the vast majority of the patients (n=455, 71.3%). 84.6% of the patients (n=540) had no previous history of stone surgery. There was no significant difference in terms of energy source used to fragment the stone (laser: 50.8% vs pneumatic: 49.2%) and side of the stone (right: 50.8% vs left: 49.2%). 51.6% (n=329) of the patients were operated with GA and 48.4% (n=309) with SA. The majority of the stones were not impacted (n=491, 77%). The great majority of patients required perioperative double-J stenting (n=396, 62.1%). Of the 638 patients whose data were evaluated, 527 (82.6%) had no residual stone after the procedure. The stones were "pushed-back" to the renal collecting system during the procedure in 15 (2.4%) patients. The overall complication rate was 11% (n=70). According to the Clavien classification, 586 patients (91.8%) had no complication, 36 patients (5.6%) had Clavien grade 1, 6 patients (0.9%) had grade 2, and 5 patients (0.8%) had grade 3 and 4 complications. The most common complication was post-operative fever in 24 patients (3.8%). Following that, lumbar pain (n=11, 1.7%), urosepsis (n=5, 0.8%), ureteral perforation (n=5, 0.8%), urinary tract infection (n=5, 0.8%), post-operative hematuria (n=1, 0.2%), and arrhythmia (n=1, 0.2%) were the most common complications, respectively. URS success rate was 82.6% (n=527). Demographic data and stone characteristics of the patients are summarized in Table 1.

In the SA group, stone area and the Hounsfield unit of the stone on computed tomography was significantly lower than in the GA group (p<0.001 and p=0.007, respectively). There was no statistically significant difference in the other variables between the groups (p>0.05). The relationship of demographic data and stone characteristics with the anesthesia method is summarized in Table 2.

Table 1. Demographic data and stone characteristics of the patients

	Mean	Range
Age (years)	44.9±14.4	15-87
BMI (kg/m^2)	26.2±3.6	17.3-39.6
Stone area (mm^2)	83.7±57.2	20-560
Hounsfield unit	883.7±380.3	240-3200
Operation time (minute)	45.1±19.1	10-135
Length of stay (day)	1.8±2.0	1-23

BMI: Body mass index

Table 2. Relationship of demographic data and stone characteristics with the anesthesia method

	Spinal n=309	General n=329	p value
Age (years)	45.0±14.1	44.7±14.7	0.790
BMI (kg/m^2)	26.3±3.5	26.2±3.7	0.711
Stone area (mm^2)	73.9±38.4	92.9±69.2	**<0.001**
Hounsfield unit	829.3±346.1	933.3±403.5	**0.007**
Operation time (minute)	44.2±20.4	46.0±17.8	0.240
Length of stay (day)	1.8±1.6	1.8±2.3	0.834

BMI: Body mass index

The need for a double J stent was significantly higher in the GA group than in the SA group (83.3% vs 39.5%, p<0.001). The rate of push-back to the collecting system was higher in the SA group (3.9 vs 0.9%, p=0.011). The general complication rate was slightly higher in the SA group, but not statistically significant (8.7% vs 7.6%, p=0.665). The rates of complications according to the Clavien classification were also similar between the two groups (p=0.789). URS success rate, which we regarded as complete stone-free status, was higher in SA group (85.8% vs 79.6%, p=0.041). The relationship of the variables with the anesthesia method is summarized in Table 3.

Discussion

There is a tendency to perform URS with regional anesthesia for the diagnosis and treatment of upper urinary tract pathologies. However, this trend is present largely among anesthesiologists, because in this way, they aim to accelerate the turnover in the operating room and reliably discharge the patients on the same day with easier post-operative care. However, this situation is controversial from the urologist perspective. It is a strongly believed opinion that the movement of the patient in the cases of regional anesthesia may lead to ureteral trauma and that reflexes, such as deep breathing and cough, can be better controlled by GA. However, no significant difference was found in the literature in terms of ureteral trauma in URS with or without GA. There are many studies in the literature about the safety and tolerability of URS with local anesthesia and intravenous sedation (10,11).

Table 3. The effect of anesthesia method on operation outcomes

	Spinal n=309	General n=329	p value
Double j stent			
Yes	122 (39.5%)	274 (83.3%)	**<0.001**
No	187 (60.5%)	55 (16.7%)	
Push-back to the collecting system			
Yes	12 (3.9%)	3 (0.9%)	**0.011**
No	297 (96.1%)	326 (99.1%)	
Complication			
Yes	27 (8.7%)	25 (7.6%)	0.665
No	282 (91.3%)	304 (92.4%)	
Clavien classification			
Clavien 1	20 (6.5%)	16 (4.9%)	0.789
Clavien 2	2 (0.6%)	4 (1.2%)	
Clavien 3	3 (1.0%)	2 (0.6%)	
Clavien 4	2 (0.6%)	3 (0.9%)	
No	282 (91.3%)	304 (92.4%)	
Ureteroscopy success rate			
Successful	265 (85.8%)	262 (79.6%)	**0.041**
Unsuccessful	44 (14.2%)	67 (20.4%)	

In a surgical procedure, the anesthesiologist and the surgeon have different objectives and expectations from the operation. While the surgeon expects to end the operation with minimal complications and the most successful outcomes, the anesthesiologist aims to awaken the patient in the safest and fastest manner, after surgery. These goals can conflict in a technical and specific operation like URS. Urologists believe that the proximal stones are more easily accessible under favour of more relaxation of the ureter with GA, and that prevention of involuntary reflexes, such as coughing and sneezing, is more possible. The underlying reason for this belief is that there is a longer way to go for proximal ureteral stones with a rigid or semi-rigid ureteroscope and fragmentation is more susceptible to complications with a longer URS device remaining in the ureter.

There are many studies in the literature that compared the anesthesia methods used in URS (10,11,12,13,14,15,16). However, most of these studies compared local anesthesia with SA and GA. In addition, the patients were carefully selected in most series (13). The patients were often female and stone location was mostly distal ureter. Less complicated stones were included and thinner caliber (6.9-7.5 Fr) ureteroscopes were used for the interventions.

Park et al. (17) evaluated the efficacy of URS and patient tolerability with local anesthesia and concluded that the procedure was effective and tolerable. However, only 6 of 200 stones were located in the upper ureter, and none were larger than 10 mm. Al-Naimi et al. (18) evaluated URS results in 1182 patients who underwent URS under SA or GA in a training hospital. They did not indicate an exact number, but most patients underwent GA and they found that stone location and stone impaction were predictive factors for an adverse outcome. Hollenbeck et al. (19) evaluated the outcomes of URS in ureteral stones above and below the pelvic brim (proximal-distal). The number of applied anesthesia methods (GA, SA and sedation) was similar between the two groups. The authors concluded that ureteroscopic stone therapy can be safely applied in stones at the pelvic brim and that patients with proximal ureteral stones were not at greater risk.

Although there is no head-to-head comparison of the impact of SA and GA on URS outcomes in the above mentioned studies, indirectly, it is understood that the anesthesia method has no

significant effect on the results. In our study, we found that the results of SA, rather than GA as we suspected, were slightly better. In the present study, URS success rate was high similarly to the above mentioned studies in both groups (85.8% in the SA group and 79.6% in the GA group). We also found that both methods could be performed safely and effectively with similar complication rates. Moreover, the rate of the double J stent implementation was significantly higher in the GA group, but we consider that the higher stone area and the Hounsfield unit of the stones in this group were the possible reasons for this outcome. In the SA group, the rate of push-back to the collecting system was higher (3.9% vs 0.9%). The fact that the stones in this group were smaller in area may be an important factor affecting this outcome. It would not be wrong to come to the conclusion that with GA, the ureter is not more relaxed as it is supposed to be. More relaxed ureter may be a factor that makes the stone more mobile and facilitates the push-back of the stone.

Regional anesthesia may also have undesirable effects such as postspinal headache requiring hospitalization and prolonged urinary retention. Due to these negative effects of block anesthesia, there has been an increase in the choice of GA for endoscopic ureteral stone treatment in recent years. Undoubtedly, the risk of further complications in proximal ureteral stones contributes to this increase. The faster onset of SA and leading to a more localized and dense block than epidural anesthesia, make it a necessary option in some cases. SA is often the preferred method of anesthesia in pregnant patients, because the amount of drug that passes through the fetus is minimized. Sometimes, anesthesiologists prefer GA in patients with serious cardiovascular and respiratory comorbidities. In such cases, especially in those with proximal ureteral stones, when regional anesthesia is preferred, the block should be made high enough to cover the pain fibers of the kidneys at the level of T8. In addition, epidural anesthesia or GA may be preferred to SA in patients with severe cardiac disease, where sudden hypotension must be prevented, because the block becomes fast and the level becomes fixed within a short time with SA. The settlement of the block may take 10-15 minutes with epidural anesthesia and sudden hemodynamic changes are less expected.

Study Limitations

Our study is not without limitations. First, this is a retrospective study. Complications of the anesthesia methods used are not available, and their inclusion may have a significant contribution to the comparison in terms of anesthesia. The present study is a multi-center study. For this reason, a complete standardization of surgical and anesthetic applications could not be achieved. However, the high number of cases, comparison of common results of multi-centers, and being the first study to compare the impact of anesthesia methods on URS for proximal ureteral stones in the literature, as well as providing data for routine daily practice are important aspects of the present study.

Conclusion

URS is a safe and effective treatment method for proximal ureteral stones, whether with SA or GA, regardless of the anesthesia method used. The cardiovascular and respiratory comorbidities of the patient are more important factors for determining the anesthetic method. It should also be kept in mind that stone size and the Hounsfield unit are significant components affecting the outcome of the procedure.

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The authors declare that they have no relevant financial interests and no conflicts of interest.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Dokuz Eylül University with number 2018/03-03.

Informed Consent: Written informed consent was not obtained from patients because this was a retrospective study.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.K., B.İ., V.Ş., O.E., Ş.O., A.Y., Ö.Ç., M.Ş., M.O.Ş., A.C., O.Ü., O.B., Concept: F.K., B.İ., V.Ş., M.O.Ş., O.Ü., O.B., Design: F.K., B.İ., V.Ş., M.O.Ş., O.Ü., O.B., Data Collection or Processing: F.K., B.İ., V.Ş., O.E., Ş.O., A.Y., Ö.Ç., M.Ş., M.O.Ş., A.C., O.Ü., O.B., Analysis or Interpretation: F.K., B.İ., Literature Search: F.K., Writing: F.K.

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Assessment of Serotonin Metabolite 5-hydroxyindoleacetic Acid Levels in Urine Sample for Diagnosis and Treatment Efficacy in Children with Dysfunctional Voiding and Their Interaction with Biofeedback Therapy

Disfonksiyonel İşemeli Çocukların Tanısında ve Tedavi Etkinliğinin Değerlendirilmesinde Serotonin Metaboliti İdrar 5-hidroksiindolasetik Asit Düzeyleri ve Biofeedback Tedavisi ile Etkileşimi

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

Dysfunctional voiding is one of the childhood urological problems that constitute a serious problem for families and children. We still do not know if a problem at the level of neurotransmitter metabolite in the central nervous system plays a role in the etiology of dysfunctional voiding. New studies are needed to get more information about the role of neuromodulators in the etiology and treatment of dysfunctional voiding. Therefore, this study will be beneficial for researchers in shaping the relationship between dysfunctional voiding and neuromodulators.

Abstract

Objective: Dysfunctional voiding (DV), which is explained as an incoordination between the external urethral sphincter and the bladder, is a situation developing in neurologically normal children. Serotonin has some effects on the lower urinary tract which cannot be fully explained. The selective 5-hydroxyindoleacetic acid (5-HIAA) agonist improves voiding efficacy in the rat model with voiding dysfunction as serotonin. Serotonin decomposes to 5-HIAA which excreted from urine. We considered that a problem in neuromodulator levels can lead to DV and evaluated the levels of 5-HIAA in urine.

Materials and Methods: Our study included 130 children aged 5-15 years who were diagnosed with DV and 48 children with no urological complaints as controls. Urine samples were taken only once in control group, and 3 times [before and after the biofeedback treatment (sixth month and twelfth month)] in the study group to determine the difference and the interaction between 5-HIAA and biofeedback therapy.

Results: Biofeedback therapy was found to be an effective method in the treatment of DV. However, there was no significant difference in the level of mean urine 5-HIAA/creatinine (u5-HIAA/Cr) between study (6.139±3.652) and control groups (6.374±4.329) (p=0.751). The mean u5-HIAA/Cr levels in the DV group at baseline and at the end of biofeedback therapy (6^{th} month) were 6.249±4.132 and 6.19±4.715, respectively (p=0.951). The mean u5-HIAA/Cr levels in the DV group at baseline and at 12 months were 5.901±3.291 and 6.644±4.206, respectively (p=0.557). There was no significant difference in u5-HIAA/Cr levels between pre-treatment and post-treatment in the DV group.

Conclusion: We still do not know if a problem at the level of neurotransmitter metabolite in the central nervous system plays a role in the etiology of DV. We evaluated this relationship, but we could not find a significant result. New studies are needed to get more information about the role of neuromodulators in the etiology and treatment of DV.

Keywords: Biofeedback therapy, Dysfunctional voiding, 5-hydroxyindoleacetic acid, Serotonin

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Öz

Amaç: Disfonksiyonel işeme (Dİ), nörolojik olarak normal çocuklarda gelişen bir durumdur ve dış üretral sfinkter ile mesane arasındaki koordinasyonsuzluk olarak açıklanmaktadır. Serotoninin alt üriner sistem üzerinde tam olarak açıklanamayan bazı etkileri vardır. Selektif 5-hidroksiindolasetik asit (5-HIAA) agonisti, serotonin gibi işeme disfonksiyonu olan sıçan modelinde işeme etkinliğini geliştirir. Serotonin 5-HIAA'ya parçalanarak idrar ile atılır. Nöromodülatör düzeylerindeki bir sorunun Dİ etiyolojisine yol açabileceğini düşünüyorduk ve idrardaki 5-HIAA düzeylerini değerlendirdik.

Gereç ve Yöntem: Çalışmamız Dİ tanısı konulan 5-15 yaş arasındaki 130 çocuk ile 2013 ve 2015 yılları arasında planlandı. İdrar numuneleri, kontrol grubunda sadece bir kez ve çalışma grubunda biofeedback tedavisi ile olan farkı ve etkileşimi belirlemek için 3 kez [biofeedback tedavisinden önce ve sonra (altıncı ay ve on ikinci ay)] alındı.

Bulgular: Biofeedback tedavisinin Dİ'de etkili bir yöntem olduğu bulundu. Ancak çalışma (6,139±3,652) ve kontrol grubu (6,374±4,329) arasında ortalama idrar 5-HIAA/kreatinin (u5-HIAA/Cr) düzeyinde anlamlı farklılık yoktu (p=0,751). Dİ grubunda, biofeedback tedavisinin başlangıcında ve sonundaki (6. ay) ortalama u5-HIAA/Cr düzeyleri sırasıyla 6,249±4,132 ve 6,19±4,715 idi (p=0,951). Dİ grubunda, biofeedback tedavisinin başlangıcında ve on ikinci ayda ortalama u5-HIAA/Cr düzeyleri sırasıyla 5,901±3,291 ve 6,644±4,206 idi (p=0,557). Dİ grubunda tedavi öncesi ve sonrası u5-HIAA/Cr düzeyleri arasında anlamlı fark yoktu.

Sonuç: Dİ etiyolojisinde merkezi sinir sisteminde nörotransmitter metaboliti seviyesinde bir sorun olup olmadığını hala bilmiyoruz. Bu ilişkiyi değerlendirdik, ancak önemli bir sonuç bulamadık. Dİ etiyolojisi ve tedavisinde nöromodülatörlerin rolü hakkında daha fazla bilgi edinmek için yeni çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Biofeedback tedavisi, Disfonksiyonel işeme, 5-hidroksiindolasetik asit, Serotonin

Introduction

Dysfunctional voiding (DV) is a situation that occurs in neurologically normal children during toilet training period and explained as an incoordination between the external urethral sphincter and the bladder (1). Actually, it occurs as a result of wrong voiding habits (2).

In the standardization article published by International Children's Continence Society in 2016, various sub-types regarding the storage and voiding phase of lower urinary tract dysfunction (LUTD) are determined (1). Accordingly, overactive bladder, underactive bladder, DV and bladder neck dysfunction included in the sub-types of LUTD. In addition, LUTD is present in more rare subtypes such as voiding postponement, vaginal reflux, Hinman syndrome, bladder outlet obstruction, and giggle incontinence. DV is a voiding phase disease. DV symptoms may include hesitancy, straining, intermittency, dysuria, holding maneuvers, increased voiding frequency, incontinence, urgency, nocturia, and constipation (1). There is a pelvic floor activity in DV, which is manifested by a staccato and/or interrupted pattern in uroflowmetry with simultaneous electromyography (UF-EMG) (3). DV can lead to recurrent urinary tract infection, vesicoureteral reflux and chronic renal failure in children (4). DV can be evaluated with detailed history, physical examination, 3-day-bladder diary, urinary ultrasonography, the DV and Incontinence Symptoms Score (DVISS), UF-EMG, and post-void residual urine (PVR) measurement without a need for invasive examinations (5).

In the central nervous system (CNS), serotonin and other neuromodulators have some effects on lower urinary tract storage and emptying, however, they could not be fully demonstrated till now (6,7). Serotonergic neurons in the CNS are located mainly in the raphe nuclei in the brain stem. Serotonin, which is synthesized in serotonergic nerve endings, is stored together with other substrates in vesicles (8). Serotonin decomposes to 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidase which is excreted via urine (9). Serotonergic neural transport is regulated by serotonin receptors (5-HT). Studies on voiding function are related to the $5HT_{1A}$ receptor. It has been shown that 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) injected in anesthetized rats with DV model activated the voiding reflex, increased the frequency of bladder contractions, increased the voiding volume, reduced bladder capacity, reduced intravesical pressure, and decreased PVR (10). The 5-HT_{1A} agonist 8-OH-DPAT administered to rats with spinal cord injury increased the external urethral sphincter relaxation period (11). Serotonin and 5-HIAA levels may be important in children with DV.

In this study, we consider that a problem in neuromodulator levels in CNS can lead to DV. We aimed to examine the the value of serotonin metabolite 5-HIAA levels in urine sample for diagnosis and assessment of treatment efficacy in children with DV and their interaction with biofeedback therapy.

Materials and Methods

This study was approved by the Gülhane Military Medical Academy Ethics Committee (approval number: 15, date: 3 April 2013) and followed the Institution's Review Board of Human Subject Guidelines. Consent form was filled out by all participants. Our study was designed as prospective, double blind and controlled study including 130 children aged 5-15 years who attended our urology department from April 2013 to April 2015. A thorough physical examination including the urogenital system and neurological system was conducted.

All patients were evaluated by urinalysis, urine culture, serum urea and creatinine, lumbosacral spine radiography, and urinary ultrasonography.

Thirteen patients, who were diagnosed with urolithiasis, persistent recurrent urinary tract infections and syringomyelia, were excluded from the study. Families of 117 children who participated in the study filled the DVISS questionnaire and 3-day-voiding diary. Forty-eight children had no urological complaints and the DVISS was below 9. In fact, these children consisted of those who attended the pediatric outpatient clinic for height and weight measurements and were directed to our study. DV was not considered in these children and were selected as the control group. Sixty-nine children with a DVISS of 9 or greater, who had a staccato voiding pattern and presence of EMG activity in UF-EMG test and a PVR greater than 20 cc, were evaluated as having DV. UF-EMG (MMS USA, Inc., 383 Central Ave., Suite LL40 Dover, NH 03820, USA) and PVR measurements were conducted for at least twice to confirm the diagnosis of DV in 69 children. UF-EMG was conducted by an experienced technician. PVR was measured with a BladderScan BVI 6100 (Diagnostic Ultrasound, Bothell, WA, USA). DV was evaluated in children without the necessity to use invasive urodynamic studies.

Any situation that would cause a decrease or increase in serotonin and 5-HIAA, such as carcinoid tumor, celiac disease, Whipple disease, cystic fibrosis, bronchial carcinomas, depression, ileum resection, phenylketonuria, Hartnup's disease, and migraine, was included in the exclusion criteria. No detailed diagnostic tests was done for diseases that cause an increase or decrease in serotonin and urine 5-HIAA. To exclude these diseases, the medical history of the family was questioned and a detailed physical examination was performed. Children with spinal cord injury or neurogenic bladder were also excluded from the study.

Children, who were admitted to our outpatient clinic with DV, were taken to biofeedback treatment. The biofeedback treatment protocol, which is well established in our clinical practice, was to take place once a week for the first month. The biofeedback treatment was scheduled for at least six sessions.

The success of biofeedback therapy was evaluated with questioning the patient's symptoms (subjective evaluation criteria) and recovery DVISS, UF-EMG, and PVR (objective evaluation criteria). Urine samples for 5-HIAA levels were taken only once in control group, and 3 times [before and after the biofeedback treatment (6^{th} month and 12^{th} month)] in the study group to determine the difference and interaction with biofeedback therapy.

Success was defined as an improvement of more than 90% in patients' symptoms.

A 24-hour urine sample is preferred for the measurement of serotonin metabolite and degradation product 5-HIAA in urine. If it is not possible to collect a 24-hour urine sample, a spot urine sample may be used as well as a urine creatinine level. Urine 5-HIAA levels can be normalized by dividing urine creatinine concentrations and the result can be determined as "mg/g creatinine". When urine is collected according to the 24-hour urine procedure, the normal value range for urinary 5-HIAA is 2-8 mg in adults (12). There is no clear data on this value for children. When we examined studies evaluating urinary 5-HIAA levels in children, we saw that they were planned with a spot urine sample (13). We preferred spot urine sample in our study because of the difficulty in collecting and storing 24-hour urine sample in children, parental non-compliance, risk of contamination with defecation, and it was quickly affected by the storage conditions during the molecular collection procedure. However, the spot urine 5-HIAA level (mg/L) was normalized to urine creatinine (mg/dL) and the result was reported as "mg/g creatinine" in order to achieve more accurate results and more valuable study.

Three milliliter urine samples were collected in the morning as the first urine and stored in the refrigerator at -80 °C until the end of the study. Only one urine sample was collected from the children in the control group and kept as in the patient group.

Urine 5-HIAA measurements were made by the high-performance liquid chromatography method (Shimadzu, Japan) in spot urine samples. Measurements were made using an Eureka (Italy) kit in this system. Analyzes were completed with a 50 µL sample injection and a 1.2 mL/min mobile phase flow.

Statistical Analysis

Statistical analysis was done using the Statistical Package for Social Sciences 15.0 software (SPSS 15.0 for Windows, Chicago, IL, USA). Descriptive statistics were noted with numbers: mean ± standard deviation with minimum-maximum. A t-test was used to compare the groups. Categorical variables, expressed as percentages, were analyzed using the McNemar test. We also performed comparisons using the Wilcoxon test for subgroup analysis. A p value of less than 0.05 was considerd statistically significant.

Results

Our study was conducted with a total of 117 children, 69 in the patient group and 48 in the control group. The mean age of the patients was 8.65±2.53 (range: 5-15) years and 16 (23%) of them were boys and 53 (77%) were girls. The mean age of the control group was 9.20±2.86 (range 5-15) years and 26 (54%) of them were boys and 22 (46%) were girls. The results of DVISS for the patient group and the control group are depicted in Figure 1.

The objective parameters such as voiding pattern, UF-EMG and PVR were improved with the success rates of 84% (p<0.001), 63% (p<0.001) and 72% (p<0.001), respectively. We found that in DVISS parameters such as daytime incontinence, enuresis, frequency, straining, dysuria, intermittency, incomplete emptying, urgency, making holding maneuvers, urgency incontinence, and constipation were improved with success rates of 63%, 41%, 56%, 90%, 73%, 68%, 62%, 42%, 58%, 81% and 62%, respectively (Table 1). The mean DVISS in 62 patients before and after biofeedback treatment was found to be 13.08±7.34 and 5.62±5.51 (p<0.001). Twenty-six (50%) of 52 patients whose quality of life was affected before biofeedback treatment had a complete improvement in quality of life (p<0.001).

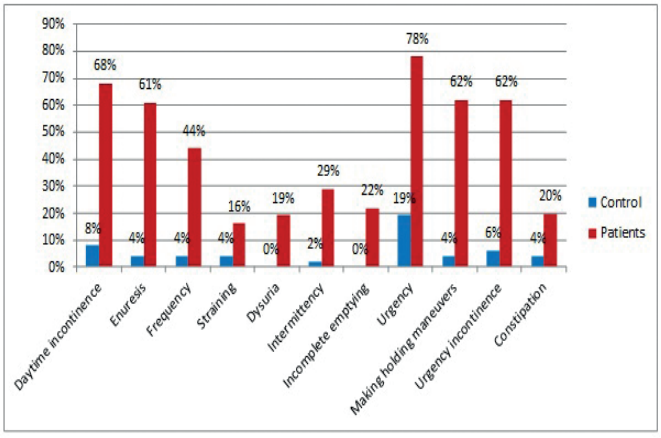


Figure 1. The answered Dysfunctional Voiding and Incontinence Symptoms Score questions for patient and control group

Table 1. Comparison of Dysfunctional Voiding and Incontinence Symptoms Score parameters before and after biofeedback therapies

DVISS questions	Before biofeedback therapy	After biofeedback therapy (6th month)	Success (%)	p*
Daytime incontinence	41	15	63	<0.001
Enuresis	37	22	41	0.001
Frequency	25	11	56	0.013
Straining	10	1	90	0.021
Dysuria	11	3	73	0.039
Intermittency	19	6	68	0.021
Incomplete emptying	13	5	62	0.109
Urgency	48	28	42	<0.001
Making holding maneuvers	36	15	58	<0.001
Urgency incontinence	37	7	81	<0.001
Constipation	13	5	62	0.039

DVISS: Dysfunctional Voiding and Incontinence Symptoms Score
*McNemar test

There was no significant difference in the level of mean urine 5-HIAA/creatinine (u5-HIAA/Cr) between the DV (6.139±3.652) and the control groups (6.374±4.329) (p=0.751) (Table 2).

The u5-HIAA/Cr values in patients in DV and control groups were evaluated in terms of gender. In DV group, the mean u5-HIAA/Cr levels in male and female patients were 7.353±3.044 (3.561-16.247) and 5.772±3.765 (0.84-25.011), respectively (p=0.039). When the pre-treatment u5-HIAA/Cr values were compared in DV group, pre-treatment u5-HIAA/Cr values in females were significantly lower than in males. In control group, the mean u5-HIAA/Cr levels in male and female patients were 6.57±4.752 (0.431-25.079) and 6.143±3.866 (2.235-19.174), respectively (p=0.725). There was no significant difference between genders in control group.

Table 2. Comparison of urine 5-hydroxyindoleacetic acid/creatinine levels between dysfunctional voiding and control groups

		n[a]	Mean[b]	SD	p[c]
u5-HIAA/Cr	DV	69	6.139	3.652	0.751
	Control	48	6.374	4.329	

DV: Dysfunctional voiding, u5-HIAA/Cr: Urine 5-hydroxyindoleacetic acid/creatinine, SD: Standard deviation
a: The number of children in dysfunctional voiding and control groups
b: Urine 5-hydroxyindoleacetic acid/creatinine (mg/g creatinine)
c: t test

Table 3. Comparison of pre-treatment urine 5-hydroxyindoleacetic acid/creatinine levels and those at the end of biofeedback therapy (6th month in completed the study)

		n[a]	Mean[b]	SD	p[c]
u5-HIAA/Cr	Baseline	45	6.249	4.132	0.951
	At the end of biofeedback therapy (6th month)	45	6.190	4.715	

u5-HIAA/Cr: Urinary 5-hydroxyindole acetic acid, SD: Standard deviation
a: The number of patients who completed the study
b: Urine 5-hydroxyindoleacetic acid/creatinine (mg/g creatinine)
c: Wilcoxon test

Table 4. Comparison of pre-treatment urine 5-hydroxyindoleacetic acid/creatinine levels and the levels at the 12th month (12th month in completed the study)

		n[a]	Mean[b]	SD	p[c]
u5-HIAA/Cr	Baseline	24	5.901	3.291	0.557
	12th months	24	6.644	4.206	

u5-HIAA/Cr: Urinary 5-hydroxyindole acetic acid, SD: Standard deviation
a: The number of patients who completed the study
b: Urine 5-hydroxyindoleacetic acid/creatinine (mg/g creatinine)
c: Wilcoxon test

There were 69 patients at the beginning for u5-HIAA/Cr levels, which declined to 45 and 24 patients at the 6th and 12th months, respectively. The mean u5-HIAA/Cr levels in DV group at baseline and at the end of biofeedback therapy (6th month) were 6.249±4.132 and 6.19±4.715, respectively (p=0.951) (Table 3). The mean u5-HIAA/Cr levels in DV group at baseline and at 12 months were 5.901±3.291 and 6.644±4.206, respectively (p=0.557) (Table 4). There was no significant difference in u5-HIAA/Cr levels between pre-treatment and post-treatment in DV group.

Discussion

DV is one of the childhood urological problems that constitute a serious problem for families and children. Any neurogenic or non-neurogenic disease that increases intrabladder pressure adversely affects the upper urinary tract (4). DV is a non-neurogenic lower urinary tract disease which can lead to recurrent urinary tract infection, vesicoureteral reflux and chronic renal failure in children (14).

In the CNS, transmitters and modulators have various effects on contraction and relaxation in the lower urinary system (15). When the literature is examined, it appears that there are a number of studies investigating the relationship between 5-HT and voiding functions in animals (10,11,15,16). Studies on voiding function are related to the $5HT_{1A}$ receptor. It has been shown that when injected in anesthetized rats with DV model, the $5\text{-}HT_{1A}$ receptor agonist 8-OH-DPAT activated the voiding reflex, increased the frequency of bladder contractions, increased the voiding volume, reduced the bladder capacity, reduced intravesical pressure and decreased PVR (10). It has been demonstrated that the selective $5\text{-}HT_{1A}$ agonist improved voiding efficacy in the rat model with voiding dysfunction. Serotonin which excreted with urine decomposes to 5-HIAA.

In the DV etiology, there is an inadequacy of complete relaxation of the pelvic floor muscles or urinary sphincter during voiding (17). We still do not know if there is a problem at the level of neurotransmitter or neurotransmitters metabolite in the CNS. There is no study in humans that evaluates this etiology.

We evaluated this relationship, but we could not find a significant result. We did not find significant differences in u5-HIAA/Cr levels between DV and control groups. There was no significant difference in u5-HIAA/Cr levels between pre-treatment and post-treatment in DV group.

Biofeedback therapy is a simple, effective, well tolerated and non-invasive treatment method for children with DV (18). Krzemiñska et al. (19) reported biofeedback therapy outcomes in children with DV. After 2 months of biofeedback therapy, children had a 50.7% improvement in daytime incontinence and 53.65% improvement in enuresis. Kibar et al. (20) reported results of biofeedback treatment in children aged 5-14 years with DV and vesicoureteral reflux. They reported significant, improvements in enuresis, daytime wetting, constipation, frequency and urgency (82%, 70%, 78%, 76% and 71%, respectively) in older children who received biofeedback therapy.

Shei Dei Yang et al. (21) reported outcomes of a short course biofeedback treatment in children with DV. They showed a 90% improvement in UF-EMG pattern. In addition, PVR decreased from 54.5 to 21.3 mL with biofeedback therapy. Biofeedback therapy has been applied successfully in our clinic for many years and we have many studies in this field (2,18,20). We found a significant improvement in DVISS, UF-EMG pattern and PVR as in other studies.

Study Limitations

In our study, we could measure the serotonin metabolite instead of serotonin. This situation can be regarded as the main limitation. We used urine specimens because it was difficult to get blood samples several times in children. Urine 5-HIAA results may be affected by the ingestion of tryptophan/serotonin-rich foods (avocados, bananas, kiwi fruit, melons, nuts, tomatoes, etc.) and certain medications and supplements (acetaminophen). It is important that these substances be avoided for 24 to 72 hours prior to urine sampling. We failed to comply with this rule.

Conclusion

Urine 5-HIAA has no place in the evaluation of the etiology and treatment success in childhood DV. New studies are needed to get more information about the role of neuromodulators in the etiology and treatment of DV.

Ethics

Ethics Committee Approval: This study was approved by the Gülhane Military Medical Academy Ethics Committee (approval number: 15, date: 3 April 2013).

Informed Consent: Consent form was filled out by all participants.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.T., G.E., Concept: B.T., Y.K., Design: B.T., B.K., T.E., Data Collection or Processing: B.T., G.E., Analysis or Interpretation: H.C.I., Y.K., M.M.D., Literature Search: B.T., B.K., Writing: B.T.

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Assessment of Voiding Dysfunction and Nocturnal Enuresis Rates in Primary School Children in an Anatolian City with a Validated Dysfunctional Voiding Scoring System Questionnaire

Bir Anadolu Şehrinde Valide Edilmiş İşeme Sorgulama Sistemi ile İlkokul Çağı Çocuklarındaki İşeme Bozuklukları ve Enürezis Oranının Belirlenmesi

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

Voiding dysfunction is a common problem in children which may affect families and children in terms of psychology, behaviour and financial burdens. There is no data about the prevalence of voiding dysfunction in many cities of our country. In this study, we investigated the prevalence of voiding dysfunction as well as related factors among primary school children in Karaman city using a validated dysfunctional voiding scoring system.

Abstract

Objective: To investigate the prevalence of voiding dysfunction (VD) and nocturnal enuresis (NE) in Turkish primary school children using a previously validated Dysfunctional Voiding Scoring System (DVSS) questionnaire and a self-administered questionnaire.

Materials and Methods: The previously validated DVSS questionnaire was completed by the parents of 3015 randomly selected children. Another questionnaire was also administered for studying VD and NE rates, demographic characteristics, and learning or behavioral problems of children.

Results: Of all children, 6.6% (n=199) had a score suggesting VD and 6.1% (n=185) had NE. No significant differences were found between children with and without VD in terms of age, gender, and fluid intake. Children with VD had significantly high rates of constipation (19.7% vs 5.2%; p<0.001) and fecal soiling (32.1% vs 5.1%; p<0.01) compared with children without VD. Children with a higher DVSS score had more frequent behavioral or psychological problems (20.7% vs 4.7%; p<0.01) and learning disabilities (14.7% vs 5.5%; p<0.01). VD had no correlation with overall maternal education level and the type of school (government or private).

Conclusion: VD and NE are highly frequent in early childhood and positively correlated with children's learning disabilities and psychological problems.

Keywords: Pediatric, Primary school, Symptom score, Voiding dysfunction

Öz

Amaç: Karaman il merkezindeki ilkokul çağı çocuklarındaki işeme bozukluğu (İB) prevalansının çocukluk çağı İB'leri Semptom Skoru (İBSS) sorgulama formu ile incelenmesi ve noktunal enürezis (NE) belirlenmesi amaçlandı.

Gereç ve Yöntem: İBSS formu, 21 farklı okuldan basit örnekleme ile belirlenmiş 3015 ilkokul çağı çocuğun ebeveynleri tarafından doldurduldu. İBSS 9 ve üzeri İB varlığı olarak temel alındı. Ayrı bir anket formu ile çocukların NE, kapsamlı demografik durumları, öğrenme ve davranış bozuklukları sorgulandı.

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Bulgular: Çocukların %6,6'sında İB düşündüren yüksek skor saptanırken, %6,1'inde NE saptandı. İB olan ve olmayan çocuklar arasında yaş, cinsiyet ve sıvı alımı açısından fark saptanmadı. İB olan çocuklarda anlamlı olarak daha yüksek oranda kabızlık ve iç çamaşırın dışkı ile kirlenmesi raporlandı. İBSS sorgulamasına göre İB düşünülen çocuklarda daha fazla davranış problemleri veya psikolojik problemler ile öğrenme güçlüğü bildirildi. Anne eğitim düzeyi ve okul tipi (devlet veya özel) açısından İB ile korelasyon saptanmadı.
Sonuç: Erken çocukluk döneminde İB ve NE oranı yüksek olup çocukların psikolojik ve öğrenme durumunu negatif olarak etkileyebilmektedir.
Anahtar Kelimeler: Çocukluk, İlkokul, Semptom skoru, İşeme bozukluğu

Introduction

Voiding dysfunction (VD) is a common cause for referral to urologists, pediatricians, and pediatric nephrologists. VD may present as urinary incontinence (UI), urinary tract infection (UTI), vesicoureteral reflux, overactive bladder, or constipation.

Nocturnal enuresis (NE), which is UI at night, affects both children's and parents' social and behavioral attitudes (1). Several classifications have been proposed according to clinical presentations of incontinence symptoms (2,3). Some classification systems are based on clinical presentations, whereas some on urodynamic parameters (2,4). NE is classified as monosymptomatic and non-monosymptomatic. Monosymptomatic NE is UI only at night and without any VD (5). As VD, NE is commonly seen and daytime lower urinary tract symptoms are frequent in children between 5 and 7 years of age; most of whom are primary school children (6).

The prevalence of NE usually varies by region and country. In Turkiye, the prevalence has been reported to be 9-16% (7,8,9,10). Detection and treatment of NE is of importance due to the high prevalence and the resulting effects on families and children in terms of psychological and behavioral aspects, as well as associated financial burdens.

Distinguishing between monosymptomatic NE and daytime UI as a medical conditions is essential for successful and appropriate treatment (2,3,4). The diagnosis of VD mainly depends on an accurate medical history reported by parents, physical examinations, and urine analysis (3,11). Questionnaires, as a non-invasive method, are useful for diagnosis and in treatment planning and follow-up for VD (3). For an objective diagnosis and treatment follow-up, the Dysfunctional Voiding Scoring System (DVSS), first reported by Farhat et al. (12), provides an exact quantitative tool. Akbal et al. (3) developed and validated the DVSS questionnaire, modified from van Gool et al. (13), for Turkish children. This validated version is commonly used for assessing VD. The use of the DVSS questionnaire in routine clinical practice has risen in recent years (14). In addition to our study, the DVSS questionnaire has been used in some epidemiological studies of Turkish children for detecting the prevalence of VD and UI (15,16).

We investigated the prevalence of VD in children by using the DVSS questionnaire, the associated factors affecting VD, and the prevalence of NE. The sample was drawn from primary school children living in a city in the central Anatolian region of Turkiye.

Materials and Methods

This was a random-selection based cross-sectional study involving 21 primary schools from March 2012 to May 2012 and employing a self-administered questionnaire and the DVSS questionnaire (Figure 1) (3). The children and parents were not informed about normal voiding and VD before completing the questionnaires. Parental consent and permission from the City Directorate of National Education and National Health were obtained. The DVSS questionnaire was administered to 4.477 parents, whose children were between 7 and 14 years of age. The questionnaires were completed particularly by the mothers and gathered after two weeks.

The first part of the questionnaire included demographic information, including questions on age, gender, school type (government or private), parents' education, family income, number of siblings, any incidence of NE, voiding habits, constipation, fluid intake, and any learning or behavioral problems. The second part was the DVSS questionnaire developed for Turkish children. A score of ≥9 indicated the presence of VD (3).

Statistical Analysis

The Statistical Package for Social Sciences, version 15.0, for Windows operating system was used to perform statistical analysis. Mean values are given as mean ± standard deviation. All individual and familial parameters were analyzed for significant risk factors associated with VD. Chi-square test and Student's t-test were performed to assess the differences in children with VD for categorical and continuous variables. A univariate regression analysis was performed to determine the independent factors correlating with VD. A p-value of less than 0.05 was considered statistically significant.

Results

The study population consisted of 3.015 children with a mean age of 10.2±2.2 years (range: 7-14 years). 6% (1.387) of subjects were boys and 54% (1.628) were girls. The response rate was 67.3%. Incomplete questionnaires were not assessed.

Does your child have urinary incontinence (peeing not on the toilet) during the day?	No	Sometimes	1-2 times/day	3 or more times/day
	0	1	3	5
If yes to Question 2	A few drops	Only underwear wet		Outer clothing layers wet
	1	3		5
Does your child have urinary incontinence (peeing not on the toilet) during the night?	No	1-2 nihgts/week	3-5 nights/week	6-7 nights/week
	0	1	3	5
If yes to Question 4	Underwear or pajamas wet		Bed wet	
	1		4	
My child goes to toilet to pee..	Less than 7 times/day		7 or more times/day	
	0		1	
My child has to strain to pee	No		Yes	
	0		3	
My child experiences pain when s/he pees	No		Yes	
	0		1	
My child pees intermittently when on the toilet	No		Yes	
	0		2	
My child has to go to revisit to toilet to pee soon after s/he pees	No		Yes	
	0		2	
My child has to run to the toilet when s/he feels the need to pee	No		Yes	
	0		1	
My child can hold his/her pee by crossing his/her legs, squatting, or doing the "pee dance".	No		Yes	
	0		2	
My child wets his/her clothes before reaching the toilet	No		Yes	
	0		2	
My child does not pass stool every day	No		Yes	
	0		2	
Quality of life				
If your children experiences any of the symptoms/issues mentioned above, does this affect his/her family life or social life?	Not at all	Not so much	Affects	Seriously affects
	0	1	3	5

Figure 1. The dysfunctional voiding scoring system questionnaire for children

The prevalence of VD, NE, and monosymptomatic NE was found to be 6.6% (199), 6.1% (185), and 2.6% (78), respectively. The highest incidences of VD (13.1%), NE (14.5%), and monosymptomatic NE (5.9%) were found at age seven years. The frequency of all the three conditions tended to decrease with age (Figure 2 and Table 1).

No statistically significant difference was found in terms of age, gender, or fluid intake between children with and without VD (Figure 3). As per demographic data, we found no significant difference in school type (government or private) or parents' education level but found statistically significant differences in the overall number of siblings (p=0.040) and family income (p=0.006). The subgroup analysis of parents' education level revealed that compared to the children of mothers in other subgroups, children of the university graduate mothers had lower rates of VD (p=0.002) (Table 2).

The overall rate of constipation was 9.6% (n=289); the rate was 19.7% (n=57) in children with VD and was statistically significant (p<0.001). The overall rate of fecal soiling was 5.5% (n=165); the rate was 26.6% (n=53) in children with VD and was statistically significant (p<0.001). Children with any congenital

Table 1. The distributions of voiding dysfunction, nocturnal enuresis and monosymptomatic nocturnal enuresis prevalence among age groups in our study

Age (year)	n	VD %, (n)	NE %, (n)	Monosymptomatic NE %, (n)
7	358	13.1 (47)	14.5 (52)	5.9 (21)
8	465	10.5 (49)	9.9 (46)	4.7 (22)
9	489	9.0 (44)	7.8 (38)	3.1 (15)
10	398	7 (28)	5.5 (22)	1.8 (7)
11	412	4.4 (18)	4.1 (17)	2.2 (9)
12	369	1.4 (5)	1.6 (6)	0.8 (3)
13	307	1.3 (4)	0.7 (2)	0.3 (1)
14	217	1.8 (4)	0.92 (2)	0 (0)
Total	3015	6.6 (199)	6.1 (185)	2.6 (78)

VD: Voiding dysfunction, NE: Nocturnal enuresis

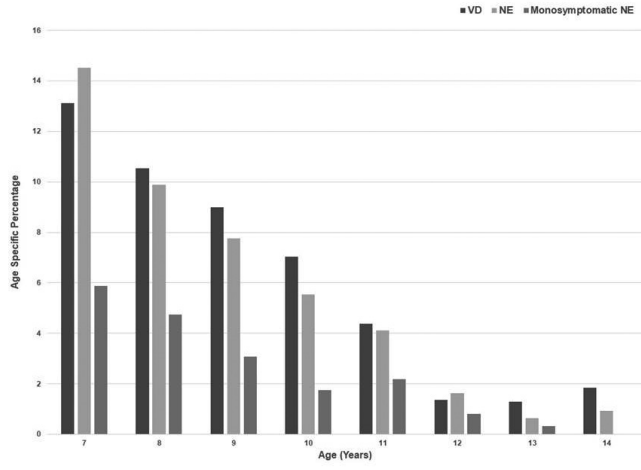


Figure 2. The distributions of voiding dysfunction, nocturnal enuresis and monosymptomatic nocturnal enuresis prevalence among age groups in our study

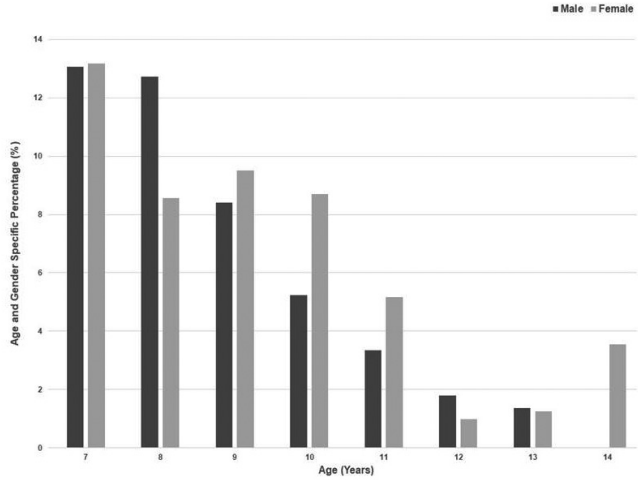


Figure 3. The distributions of voiding dysfunction prevalence according to gender

Table 2. Familial risk factors for voiding dysfunction

		DVSS <9 %, (n)	DVSS ≥9 %, (n)	Total %, (n)	p value
Mothers' education level					
	No education	0.7 (19)	1.5 (3)	0.7 (22)	0.140
	Elementary school	69.5 (1957)	68.8 (137)	69.5 (2094)	
	Junior high school	9.4 (264)	11.1 (22)	9.5 (286)	
	High school	12.4 (349)	14.6 (29)	12.5 (378)	
	University	8.1 (227)	4.0 (8)	7.8 (235)	
Number of siblings					
	0	7.6 (214)	9.5 (19)	7.7 (233)	0.040
	1	43.6 (1227)	51.3 (102)	44.1 (1329)	
	2	32.8 (925)	23.6 (47)	32.2 (972)	
	>3	16.0 (450)	15.6 (31)	16.0 (481)	
Family income					
	Low	13.1 (368)	20.6 (41)	13.5 (409)	0.006
	Medium	83.1 (2339)	77.4 (154)	82.7 (2493)	
	High	3.9 (109)	2.0 (4)	3.7 (113)	
Total		100.0 (2816)	100.0 (199)	100.0 (3015)	NA

DVSS: Dysfunctional Voiding Scoring System, NA: Not available

Table 3. Personal risk factors for voiding dysfunction

		DVSS <9 %, (n)	DVSS ≥9 %, (n)	Total %, (n)	p value
Gender	Male	46.1 (1299)	44.2 (88)	46.0 (1387)	0.602
	Female	53.9 (1517)	55.8 (111)	54.0 (1628)	
UTI history	Yes	14.0 (394)	32.7 (65)	15.2 (459)	0.000
	No	86.0 (2422)	67.3 (134)	84.8 (2556)	
Enuresis nocturnia	Yes	2.8 (78)	53.8 (107)	6.1 (185)	0.000
	No	97.2 (2738)	46.2 (92)	93.9 (2830)	
Habitual guarding or holding maneuvers (total)	Yes	25.2 (709)	56.3 (112)	27.2 (821)	0.000
	No	74.8 (2107)	43.7 (87)	72.8 (2194)	
Habitual guarding or holding maneuvers (male)	Yes	24.0 (312)	59.1 (52)	26.2 (364)	0.000
	No	76 (987)	40.9 (36)	73.8 (1023)	
Habitual guarding or holding maneuvers (female)	Yes	26.2 (397)	54.1 (60)	28.1 (457)	0.000
	No	73.8 (1120)	45.9 (51)	71.9 (1171)	
Congenital urinary anomaly	Yes	1.7 (49)	8.5 (17)	2.2 (66)	0.000
	No	98.3 (2767)	91.5 (182)	97.8 (2949)	
Constipation	Yes	8.2 (232)	28.6 (57)	9.6 (289)	0.000
	No	91.8 (2584)	71.4 (142)	90.4 (2726)	
Fecal soiling	Yes	4.0 (112)	26.6 (53)	5.5 (165)	0.000
	No	96.0 (2704)	73.4 (146)	94.5 (2850)	
Behavioral/psychological problems	Yes	9.9 (279)	36.7 (73)	11.7 (352)	0.000
	No	90.1 (2537)	63.3 (126)	88.3 (2663)	
Children with learning disability	Yes	10.3 (289)	25.1 (50)	11.2 (339)	0.000
	No	89.7 (2527)	74.9 (149)	88.8 (2676)	
Total		100.0 (2816)	100.0 (199)	100.0 (3015)	NA

DVSS: Dysfunctional Voiding Scoring System, UTI: Urinary tract infection, NA: Not available

urinary anomaly had a significantly high VD rate (25.8%), and children with any behavioral or psychological problem (20.7%) or learning disability (14.7%) had significantly high VD compared with children without such problems (Table 3). Family income and VD were inversely correlated, and children from low-income families had significantly higher VD rates than those from middle- (p=0.0039) and high-income (p=0.030) families (Table 2).

Univariate regression analysis did not reveal any statistically significant factor contributing to VD. However, multivariate analysis revealed a significant difference between VD-positive and -negative children when regarded as jointly on the variables of age and sibling number; Wilk's Λ=0.974, F (2, 3045)=40.2, p=0.000, partial η^2=0.026. A separate ANOVA was performed for each dependent variable, with each ANOVA assessed at an alpha level of 0.025. A significant difference was found between VD-positive and -negative children regarding age, F (1, 3046)=80.5, p=0.000, partial η^2=0.026, with VD-negative patients (M=10.3) scoring lower than VD-positive patients (M=8.9). No significant difference was found between VD-positive and -negative children regarding sibling number, F (1, 3046)=3.8, p=0.051, partial η^2=0.001.

Discussion

In our study, the response rate was 67.5%, which was significantly lower than that in studies by Yüksel et al. (15) (86%) and Bolat et al. (16) (91.9%). Incompletely answered questionnaires were not assessed, acknowledging that socioeconomic levels may be a factor for not completing questionnaires.

The overall frequency of VD was 6.6% in primary school children, compared with 9.3% in the study by Yüksel et al. (15), which was the first reported study evaluating VD with the DVSS questionnaire in an epidemiologic setting in an Anatolian city. Vaz et al. (17) reported a frequency of 21.8% for VD with a modified DVSS questionnaire in 739 healthy school-age Brazilian children. The population in both studies was younger than the population in our study, and the high rate of VD may be associated with rather low socioeconomic levels. However, our study population was urban.

The prevalence of daytime UI in children has been reported to be 4.4% to 19.2% and 2.1% to 6.3% in different European and Asian countries, respectively (18,19,20,21,22). Previous studies have reported prevalence rates between 0.5% and 8% in different Turkish cities (16,23,24,25,26,27). In our study, the overall daytime UI prevalence was 6.1%, which was in accordance with the overall NE rate and similar to the results of previous studies. However, most of these studies did not use a validated symptom score system, except for the study by Bolat et al. (16).

Mota et al. (28) reported a VD rate of 24.2% by using the scoring system of Farhat et al. (12)., Chung et al. (29) reported a VD rate of 46.4% with a different survey. Yüksel et al. (15) reported that if responders answered only the first question "Does your child have UI during daytime?" as a description of VD in the DVSS questionnaire, the VD rate was 25.4%. The authors concluded that only one question was sometimes related to an overestimation of frequency. By contrast, in our study, the frequency of VD was nearly the same. For previous studies reporting higher rates, the questionnaires may not have been validated in their country or region.

In this study, no difference in VD was found in the children with regard to age, gender, fluid intake, school type (government and private), or parents' overall education level. Yüksel et al. (15) reported that the prevalence of VD was significantly higher in girls than that in boys only in the age group of 12 to 15 years; in our study, girls had a higher frequency of VD than boys did but this difference was not statistically significant (Figure 3).

In our study, overall education level of the parents did not affect VD rates, but in the subgroup analysis, children of university graduate mothers had statistically lower VD rates than children of non-university graduate mothers (p<0.05). This difference was obvious in the study by Yüksel et al. (15). This difference may be related to the mothers' ability to teach or perform voiding training and mothers' close relationship with children for positive outcomes of VD. Another study reported that the degree of parental education level was inversely correlated with the prevalence of VD (29). Another study reported no statistically significant difference in parental education and VD in children (19).

Many reports have emphasized the association between NE and having more siblings but the association between VD and having more siblings has been considered less frequently (30,31). A study from Turkiye reported that risk factors for VD were having four or more siblings and having two or more persons per bedroom (15). Although we found a statistically significant difference in the overall number of siblings (p<0.05), the difference was not significant in the subgroup analysis.

In our study, the prevalence of VD was higher in children from low-income families than in those from middle- (p<0.01) and high-income families (p<0.05), in agreement with previous studies that evaluated NE and VD (10,16,32). Parents of with high income mostly had a high education level, therefore, this could be an advantage for voiding training and supporting children.

The total frequency of UTI history was 15% in this study. The children with a history of UTI had a significantly higher prevalence of VD than children without (p<0.01). Although we could not prove this association by using an objective tool or

test, such as urine culture, in our questionnaire, the previous studies have supported the association between VD and UTI (15,33).

According to previous studies, voiding positions and habits affect the voiding functions in children, especially in girls (34,35). In our study, children who had abnormal voiding positions had a higher prevalence of VD ($p<0.01$) than those who did not. We only asked parents about the existence of abnormal voiding positions, but a previous study used some pictures of abnormal voiding position to better explain the question (15). This approach might be more beneficial for patient understanding.

Constipation and bowel distension may affect the bladder and cause detrusor hyperactivity and UI (36). In our study, the prevalence of constipation and fecal soiling was significantly higher in children with VD. Many studies have reported higher prevalence rates of UI in children with constipation (15,16,17,21,37,38). In our study, as per univariate regression analysis, constipation was not a significant contributing factor.

Our study results showed that the prevalence of behavioral or psychological problems and learning disabilities were significantly higher in children with VD, which was also reported in previous studies (39,40). Particularly, inattentive presentation of attention-deficit hyperactivity disorder was demonstrated in children with monosymptomatic NE and nocturnal polyuria. According to teachers, the frequency of urination and a small voided volume might cause more attention problems and a high number of nights with nocturnal polyuria correlated with behavioral problems (40). Treatment of VD or monosymptomatic NE could have positive effects on taking care of behavioral or psychological problems and learning disabilities in children.

According to our study results, children with VD or NE did not seek any treatment or medical counseling before the study. Some myths about the treatment of NE in Anatolia may be a cause for parents' ignorance of VD and NE.

Study Limitations

Our study had some limitations. The questionnaires were not completed in an interview. We did not enquire about parents' voiding habits during their childhood, so we could not investigate the association between VD in children and VD in parents' childhood. In addition, we could not confirm the diagnosis of VD obtained from our questionnaire and the DVSS questionnaire by accurate clinical evaluation. Finally, we gave cursory information to teachers about VD and NE in children to guide children with VD and NE.

Conclusion

Our study shows comparable results of the prevalence of VD and NE in primary school children in an Anatolian city by using the DVSS questionnaire. VD has a high incidence in early childhood but children can spontaneously recover with age. However, children who have any behavioral or psychological problems and learning disabilities have significantly higher VD rates.

Ethics

Ethics Committee Approval: The permission from the City Directorate of National Education and National Health was obtained.

Informed Consent: Parental consent from the City Directorate of National Education and National Health was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.H.T., Concept: H.H.T., Y.T., C.A., Design: H.H.T., C.A., Data Collection or Processing: H.H.T., E.T., Y.T., Analysis or Interpretation: H.H.T., Y.T., Literature Search: H.H.T., Y.T., Writing: H.H.T., F.Ş., T.T.

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Clinical Relevance of Preoperative Neutrophil to Lymphocyte and Platelet to Lymphocyte Ratio in Renal Cell Carcinoma

Renal Hücreli Karsinomda Preoperatif Nötrofil/Lenfosit ve Trombosit/Lenfosit Oranının Klinik Önemi

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

Systemic inflammatory reactions cause alterations in full blood count parameters; with a particular decline in the lymphocyte count, and neutrophil and platelet count increments. Both neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are reproducible, simple and low-cost parameters highly effective in reflecting the inflammatory response. Recent analyses provide evidence that assessment of preoperative systemic inflammatory response contributes to prediction of stage-free cancer survival. Although not statistically significant, a positive correlation was observed between high tumor and nuclear grades and tumor-to-liver uptake ratio and platelet-to-lymphocyte ratio. It is concluded that, multi-center and prospective studies with more patients is needed for the achievement of meaningful results.

Abstract

Objective: The association of preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) with postoperative tumor stage and Fuhrman nuclear grade was investigated in patients with renal cell carcinoma (RCC).

Materials and Methods: Data of 123 patients, who were operated due to RCC, in our clinic was analysed. NLR and PLR were evaluated in patients who were classified according to tumor stage (T1 and T2 low stage, T3 and T4 high stage) and Fuhrman nuclear grade (grade 1 and 2 low-grade, grade 3 and 4 high-grade). NLR and PLR were compared using Levene's test between the groups.

Results: Sixty four patients were female (52.1%) and 59 were male (47.9%). All haematological parameters were expressed as 10^3/µL. Mean age, blood neutrophil, lymphocyte and platelet counts, and NLR and PLR values of the patients were 62.49±12.43 years, 6.27±2.8, 2.05±0.83, 263.72±89.03, 4.01±3.93, and 149.73±82.1, respectively. The most common histologic subtype was recorded as clear cell RCC (76.4%). NLR and PLR were 3.83±3.22 and 142.79±66.66, respectively in the low-stage group and 4.43±5.29 and 165.85±109.41, respectively in the high stage group. As for the Fuhrman nuclear grading, NLR and PLR were 3.81±3.45 and 146.63±87.36, respectively in the low-grade group and 4.61±5.387 and 159.32±63.42 in the high-grade group. There was no statistically significant difference between the groups (p>0.05).

Conclusion: Although not statistically significant, high tumor stage and nuclear grade were positively correlated with NLR and PLR. It is concluded that, further multi-center and prospective studies with larger samples are needed to derive meaningful results.

Keywords: Lymphocyte, Neutrophil, Platelet, Renal cell carcinoma

Öz

Amaç: Bu çalışmada renal hücreli karsinomlu (RHK) hastalarda operasyon öncesi nötrofil/lenfosit oranı (NLO) ve trombosit/lenfosit oranın (TLO), postoperatif tümör evresi ve Fuhrman nükleer derecesinin ilişkisi incelenmiştir.

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Gereç ve Yöntem: Kliniğimizde RHK nedeniyle opere edilen 123 hastanın verileri geriye dönük olarak incelendi. Tüm hastaların patolojik evreleri, histolojik tümör tipleri ve dereceleri, preoperatif tam kan sayımları değerlendirilerek kayıt edildi. Hastalar tümör evrelerine (T1 ve T2 hastalar düşük evreli, T3 ve T4 hastalar yüksek evreli) ve Fuhrman nükleer derecelerine (grade 1 ve 2 hastalar düşük dereceli, grade 3 ve 4 hastalar yüksek dereceli) göre sınıflandırılarak NLO ve TLO değerlendirildi. Levene testi kullanılarak grupların NLO ve TLO'su istatistiksel olarak karşılaştırıldı.
Bulgular: Hastaların 64'ü kadın (%52,1) ve 59'u erkek (%47,9) idi. Tüm hematolojik parametreler $10^3/\mu L$ olarak ifade edildi. Hastaların ortalama yaşları, ortalama kan nötrofil, lenfosit, trombosit sayıları, NLO ve TLO'su sırasıyla 62,49±12,43 yıl, 6,7±2,8, 2,05±0,83, 263,72±89,03, 4,01±3,93 ve 149,73±82,1 idi. En sık izlenen histolojik alt tip berrak hücreli RHK (%76,4) olarak kayıt edildi. Düşük tümör evreli grupta NLO ve TLO sırasıyla 3,83±3,22 ve 142,79±66,66 olarak ölçülürken yüksek evreli grupta 4,43±5,29 ve 165,85±109,41 olarak değerlendirildi. Düşük Fuhrman nükleer dereceli grupta NLO ve TLO sırası ile 3,81±3,45 ve 146,63±87,36 olarak ölçülürken yüksek dereceli grupta 4,61±5,387 ve 159,32±63,42 olarak değerlendirildi. Gruplar arasında istatistiksel olarak anlamlı farklılık izlenmedi (p>0,05).
Sonuç: İstatistiksel olarak anlamlı olmasa da yüksek tümör evresi ve nükleer derecesi ile TLO ve NLO arasında pozitif korelasyon olduğu görüldü. Anlamlı sonuçlara ulaşılması açısından daha fazla hasta sayılı, çok merkezli ve prospektif verilere ihtiyaç olduğu sonucuna varıldı.
Anahtar Kelimeler: Lenfosit, Nötrofil, Trombosit, Renal hücreli karsinom

Introduction

Among urogenital cancers, renal cancers are the third most common malignancies after prostate and bladder cancers (1). Renal cell carcinoma (RCC) is responsible for 80-85% of all primary renal neoplasms and constitutes 3% of all adult malignancies (2). RCC is one of the most lethal of the urogenital cancers (3). They are most prevalent in the 5th and 6th decades of life. The male-to-female ratio is 3/2 (4). RCC incidence has been shown to correlate with the level of development of a country (5). RCC has become more prevalent due to technological advancements in radiological imaging modalities and their introduction into clinical practice (6). RCC incidence has been reported to increase by 2-4% globally in the last decade (7).

Cancer is a multifactorial disease emerging with complex interactions between various environmental factors and genetic variants (8). The microenvironment of tumor formation and inflammatory reactions are associated with tumor development and progression (9). Systemic inflammatory reactions are held responsible for many cancer-related symptoms including anorexia, pain and cachexia as well as shorter life expectancy (10).

Systemic inflammatory reactions cause alterations in full blood count parameters with a particular decline in the lymphocyte count, and neutrophil and platelet count increments (11). Both neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are reproducible, simple and low-cost parameters highly effective in reflecting inflammatory response. Recent analyses provide evidence that assessment of preoperative systemic inflammatory response contributes to prediction of stage-free cancer survival (12).

This retrospective study investigates the association of preoperative NLR and PLR values with tumor and Fuhrman nuclear stage in patients who underwent radical or partial nephrectomy and received the diagnosis of RCC based on the pathological investigation of the surgical specimens.

Materials and Methods

Record of patients who underwent radical or partial nephrectomy in the Urology Clinic at Gaziosmanpaşa University Faculty of Medicine between 2011 and 2017 were analyzed retrospectively. A hundred twenty three patients, who received the diagnosis of RCC based on pathological investigation of the surgical specimens, were included in the study. The patients provided informed consent for use of their personal data in scientific studies. The study was conducted in compliance with ethical principles of the Helsinki Declaration. Age, clinical presentation, preoperative hemogram parameters and postoperative pathology results of patients were analysed. NLR and PLR were calculated for each patient after obtaining full blood counts preoperatively. NLR was obtained by dividing neutrophil count by lymphocyte count, whereas PLR was obtained by dividing platelet count by lymphocyte count. All surgical samples were staged according to the 2009 TNM classification (13). T1 and T2 patients were categorized as low-stage and T3 and T4 patients as high-stage. Then, pathology samples were assessed for tumor grades using the Fuhrman system (14). Grade 1 and 2 patients were classified as low-grade, and grade 3 and 4 patients as high-grade. Histological subtypes were evaluated according to the classification defined by the World Health Organization (15). Cut off values were set for tumor-to-liver uptake ratio and PLR as 2.61 and 128.75, respectively. NLR and PLR values were compared using Levene's test between the groups.

Statistical Analysis

Descriptive statistical work-up was conducted for the study in order to give insight on general characteristics. Data on continuous variables were given as arithmetic mean, standard deviation and standard error. The study provides frequencies and percentages of qualitative (discrete) data. Levene's test was used to check whether data pertaining to continuous variables matched with normal distribution or not ($p \leq 0.05$), and if ($p > 0.05$), data were accepted to be in the range of normal distribution. As for inter-group comparisons of variables

Table 1. Neutrophil/lymphocyte ratios according to tumor parameters

Parameters		NLR <2.61	NLR >2.61	p value
Tumor stage	Low stage (T1+2)	44 (51.2%)	42 (48.8%)	0.691
	High stage (T3+4)	18 (48.6%)	19 (51.4%)	
Nuclear grade	Low grade (grade 1+2)	48 (51.6%)	45 (48.4%)	0.674
	High grade (grade 3+4)	14 (46.7%)	16 (53.3%)	

NLR: Neutrophil-to-lymphocyte ratio

Table 2. Platelet/lymphocyte ratios according to tumor parameters

Parameters		PLR <128.75	PLR >128.75	p value
Tumor stage	Low stage (T1+2)	48 (55.8%)	38 (44.2%)	0.067
	High stage (T3+4)	14 (37.8%)	23 (62.2%)	
Nuclear grade	Low grade (grade 1+2)	51 (54.8%)	42 (45.2%)	0.083
	High grade (grade 3+4)	11 (36.7%)	19 (63.3%)	

PLR: Platelet-to-lymphocyte ratio

indicated with measurement, a t-test was used for independent samples to study inter-group differences. A p value of less than 0.05 was considered statistically significant. Calculations were made with available statistical software (IBM SPSS Statistics 21, SPSS Inc., an IBM Co., Somers, NY).

Results

The mean age of the 123 patients (64 female -52.1%- and 59 male -47.9%-) included in the study was 62.49±12.43 (16-86) years. Fifty three (43.1%) were symptomatic (diathesis, abdominal or flank pain, gross hematuria, palpable mass or paraneoplastic phenomena) and 70 (56.9%) were incidentally diagnosed. Eighty five patients (69.1%) underwent radical nephrectomy and 38 (30.9%) only partial nephrectomy. Sixty one (49.6%) patients were operated on the right side and 62 (50.4%) on the left side. According to histological subtypes, 94 (76.4%) patients had clear cell, 20 (16.3%)-papillary, 7 (5.7%)-chromophobe, 1 (0.8%)-renal medullary carcinoma and 1 (0.8%) had unclassified type RCC. Eighty six (69.9%) patients were reported to have low-stage tumor (T1 or T2), whereas 37 (30.1%) presented with high-stage tumor (T3 or T4). As for the Fuhrman nuclear grading, 93 patients (75.6%) presented with low-grade tumors (grade 1 or 2) and 30 (24.4%) with high-grade tumors (grade 3 or 4).

As regards to the classification per tumor stage, NLR and PLR were calculated as 3.83±3.22 and 142.79±66.66, respectively in the low-stage groups, while they were 4.43±5.29 and 165.85±109.41 in the high-stage group. According to the classification by the Fuhrman nuclear grading, NLR and PLR were calculated as 3.81±3.45 and 146.63±87.36, respectively in the low-grade groups whereas they were 4.61±5.387 and 159.32±63.42 in the high-grade group. Cut-off values calculated by receiver operating characteristic analysis for NLR and PLR were set as 2.61 and 128.75, respectively. The patients were categorized according to the cut off values. NLR was found to be less than 2.61 in 44 of 86 low-stage patients (51.2%), whereas it was above 2.61 in 19 of 37 high-stage tumor patients (51.4%). PLR was above 128.75 in 38 (44.2%) low-stage patients and 23 (62.2%) high-stage patients. In addition, when the patients were classified according to be Fuhrman nuclear grading, in 48 out of 93 low-grade patients (51.6%), NLR was found to be less than 2.61, whilst it was above 2.61 in 16 out of 30 high-grade patients (53.3%). In 42 low-grade patients (45.2%) and 19 (63.3%) high-grade patients, PLR was above 128.75. Although there was a positive correlation between high NLR and PLR values and both high-tumor stage and high Fuhrman nuclear grade, this correlation was not statistically significant (p>0.05). In conclusion, there was a statistically significant relationship of NLR value with pathological stage (p=0.691) and Fuhrman nuclear grade (p=0.674) (Tables 1 and 2). Likewise, there was no statistically significant relationship of PLR value with pathological stage (p=0.067) and Fuhrman nuclear grade of the tumor (p=0.083).

Discussion

As is the case in our country, cancer has become a global public health issue. Although its progression may vary according to

various factors including its histopathological nature, gender factors, life style, genetic factors, and geographical distribution, it is known as the second most common cause of mortality after cardiac diseases. It is estimated that 1.735.350 new cancer cases will emerge in 2018 in the USA with 609.640 cancer-related mortalities (16).

Many prognostic factors have been defined for RCC including tumor stage, nuclear grade, type of histology, surgical margin, patient complaints, and performance status (17). One of the main goals of RCC studies is to introduce molecular-based prognostic factors into daily medical practice for use in survival prediction (18). This has obliged clinicians to find new ways of preoperative prediction of potential pathology and cancer progression status data for RCC. For healthcare expenditures to be effectively sustainable, cost analyses should be kept in consideration at all times. In this context, the medical community has long been in a search for using preoperative blood hemogram parameters for prediction of postoperative data.

Although sources of inflammation generally contain bacterial and viral infections, it is known that many factors, including tobacco use, obesity, fatty liver, alcohol, chemical exposure and radiation, indeed cause inflammation. Inflammation is classified in two stages as acute and chronic inflammation. Acute inflammation is the first stage of inflammation mediated by activation of the immune system. On the other hand, chronic inflammation may be considered a predisposing factor for the host into many chronic diseases including cancer.

It is known that inflammation plays a critical role in many stages of carcinogenesis including tumor development, progression and prognosis (19,20). In particular, the tumor-infiltrating T-lymphocyte sub-types have a key role in cellular proliferation and metastases, in particular, in the tissue undergoing malignant transformation by playing a role in cellular viability and cytokine production (21). Another type of cells taking place in the inflammation and cancer association is the neutrophils. Neutrophils cause multiple and different types of cytokines. With such effects, neutrophils suppress the anti-tumor immunity system response resulting in tumor growth and progression by stimulating the angiogenesis (22). Although many links are yet to be made in the cancer and inflammation relationship, there are many studies discussing the use of hemogram parameters in prediction of tumor stage and grade and assessment of disease-specific survival.

As regards to the analysis of studies looking into urogenital system cancers and NLR and PLR, Wei et al. (23) in a meta-analysis of 17 studies and 3159 cases reported a potential association between high NLR and poor clinical outcomes in urinary system cancers and suggested that NLR could be used as a significant biomarker of prognosis. In another meta-analysis, Hu et al. (24) assessed 15 studies and 3357 cases and concluded that high NLR was an indicator of poor prognosis in patients with RCC. As far as the studies looking into NLR and PLR together are concerned, in their study on 127 patients diagnosed with urothelia carcinoma and 162 control subjects, Luo et al. (25) stated that high NLR and PLR might be an independent determinant in cancer patients. In a similar study, Fankhauser et al. (26) reported that systemic inflammatory response markers might contribute to prediction of prognosis in metastatic testicular germ cell tumors.

As for the studies conducted in our country, a study by Kaynar et al. (27) on 291 patients with bladder tumor reported a positive correlation between tumor size and invasion and preoperative NLR. Similarly, Otunctemur et al. (28), in their series of 432 patients where they assessed surgical specimens obtained from RCC patients found a statistically significant relationship of NLR values with high tumor stage and nuclear grade. Nevertheless, in a study by Yıldırım et al. (29), the researchers could not find a significant association between preoperative NLR and tumor stage. In another study by Hamidi et al. (30) including 67 patients with testicular tumors, no statistically significant result was reported between NLR and disease-specific survival. Likewise, Bolat et al. (31) concluded that preoperative NLR was not a useful marker for predicting prognosis in germ cell testicular tumor patients.

Study Limitations

Although it may be considered a large-scale study, its retrospective design was a limitation.

Conclusion

Although not statistically significant, a positive correlation was observed between high tumor stage and high PLR and NLR values ($p>0.05$). Similarly, a positive correlation was observed between high Fuhrman nuclear grade and high PLR and NLR values, but this association failed to reach the level of statistical significance ($p>0.05$). Our study could not demonstrate a statistically significant correlation between PLR and NLR values and RCC tumor stage and Fuhrman nuclear grade, however, multi-center, prospective and large-scale studies are warranted.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K., D.A., B.P., S.C., Concept: E.K., D.A., B.P., S.C., V.Ü., İ.E., Design: E.K., D.A., B.P., Ş.K., V.Ü., İ.E., Data Collection or Processing: D.A., S.C., B.P., Analysis or Interpretation: E.K., D.A., V.Ü., İ.E., Literature Search: E.K., Ş.K., Writing: E.K.

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ORIGINAL RESEARCH
Robotic

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Complications of Robotic Surgery in Urology: Our Experience of 342 Procedures Including the Learning Curve

Ürolojide Robotik Cerrahi Komplikasyonları: Öğrenme Eğrisini de Kapsayan 342 Hastalık Deneyimimiz

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

Like in every new technique, robotic surgery also has a learning curve and in order to reduce complications, surgeons need to approach each case carefully until they reach a certain level of experience.

Abstract

Objective: The aim of this study is to analyze the complications of all robot-assisted surgeries performed in our clinic and to investigate the effect of the learning curve on complications occurred.

Materials and Methods: Data on a total of 342 robotic surgeries performed in our clinic between March 2015 and February 2018 was retrospectively analyzed. Two surgeons, who performed the surgery, were experienced in urological laparoscopic procedures. Intraoperative and postoperative complications were evaluated. According to the experience of robotic surgery, the complications were divided into two groups as those occurred in the first 18 months (March 2015-August 2016) and in the second 18 months (September 2016-February 2018). The complications were classified according to the Clavien-Dindo classification.

Results: A total of 32 complications occurred in 31 of 342 patients undergoing robot-assisted surgery. The overall complication rate was 9.4%. The number of minor complications was 20 (62.5%), and the number of major complications was 12 (37.5%). Among all, 6.2% were intraoperative complications, 62.5% were postoperative complications, and 31.3% were medical complications. It was observed that the number of complications was plateaued after August 2016 and there was a statistically significant difference between the first and the second 18 months ($p<0.05$).

Conclusion: Laparoscopic surgery experience alone is not enough to reduce complications in robot-assisted surgery and learning continues with every case. An experienced surgeon and robotic surgery team are needed for complex robotic surgeries.

Keywords: Complication, Robotic surgery, Urology

Öz

Amaç: Bu çalışmanın amacı kliniğimizde uygulanan tüm robot yardımlı ameliyatlardaki komplikasyonları analiz etmek ve öğrenme eğrisinin komplikasyon gelişimi üzerine etkisini araştırmaktır.

Gereç ve Yöntem: Mart 2015 ile Şubat 2018 arasında kliniğimizde uygulanan toplam 342 robotik cerrahinin verileri analiz edildi. İki cerrah da ürolojik laparoskopik cerrahide deneyimliydi. İntraoperatif ve postoperatif komplikasyonlar değerlendirildi. Robotik cerrahi deneyimine göre ilk 18 ayda (Mart 2015-Ağustos 2016) ve ikinci 18 ayda (Eylül 2016-Şubat 2018) karşılaşılan komplikasyonlar olarak iki gruba ayrıldı. Komplikasyonlar Clavien-Dindo sınıflamasına göre kategorize edildi.

Bulgular: Robotik cerrahi yapılan 342 hastanın 31'inde, toplam olarak 32 komplikasyon gelişti. Toplam komplikasyon oranı %9,4 idi. Minör komplikasyonların sayısı 20 (%62,5), majör komplikasyonların sayısı 12 (%37,5) idi. Tüm komplikasyonların %6,2'sini intraoperatif komplikasyonlar, %62,5'ini postoperatif komplikasyonlar, %31,3'ünü medikal komplikasyonlar oluşturmaktaydı. Komplikasyon sayılarının Ağustos 2016'dan sonra plato çizdiği görüldü ve ilk 18 ay ile son 18 ay arasında istatistiksel olarak anlamlı fark bulundu ($p<0,05$).

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Sonuç: Laparoskopik cerrahi tecrübesi, robotik cerrahideki komplikasyonları azaltmakta tek başına yeterli değildir ve öğrenme her olguyla birlikte devam eder. Komplike robotik cerrahiler için, deneyimli bir cerrah ve robotik cerrahi ekibine ihtiyaç duyulmaktadır.
Anahtar Kelimeler: Komplikasyon, Robotik cerrahi, Üroloji

Introduction

The reason for the development of laparoscopic surgery was to achieve similar results to open surgery but with lower morbidity and shorter recovery period. Although laparoscopic methods and auxiliary instruments were developed over the years, laparoscopic surgery remained a complex surgery with a long learning curve (1). Despite being termed as minimally-invasive, most of the laparoscopic operations performed in urology clinics are major surgeries and have a significant likelihood of complications. Robot-assisted laparoscopic surgery was introduced to urology practice in the year 2000 and became a common method within the past seventeen years (2). Contrary to two-dimensional image provided by standard laparoscopic systems, robotic systems offer 3-dimensional image and sense of depth for the surgeon. In addition, while standard laparoscopic equipments provide the surgeon a mobility in four directions, robotic systems offer a freedom of movement in six even seven directions similar to the human hand and wrist (3). Despite all these advantages, complications also occurred in robot-assisted laparoscopic surgeries and reported in the literature mainly by using Clavien-Dindo classification system. The Clavien-Dindo classification relies on the type of treatment used to handle the complication and this classification system is widely used in all surgical branches (4).

We analyzed the complications of all robot-assisted surgeries performed in our clinic and investigated the effect of the learning curve on complications occurred.

Materials and Methods

The data on 342 robotic surgeries performed in our clinic between March 2015 and February 2018 was retrospectively analyzed. The distribution of the operations was as follows: 240 radical prostatectomies, 52 partial nephrectomies, 28 radical cystectomies and urinary diversions, 6 pyeloplasties, 5 ureteroneocystostomies, 3 radical nephroureterectomies, 3 retroperitoneal lymph node dissections, 2 partial ureterectomies, 1 radical nephrectomy, 1 ureterolysis and 1 cystoplasty (Mitrofanoff). All operations were performed with a transperitoneal approach. The operations were performed by two surgeons and both surgeons were experienced in urological laparoscopic procedures. However, these surgeons had no prior robotic surgery experience, therefore, patients who were within their learning curves were also evaluated. Intraoperative and postoperative complications were recorded and they were divided into 2 groups depending on the robotic surgery experience, as complications in the first 18 months (March 2015-August 2016) and complications in the second 18 months (September 2016-February 2018).

The complications were categorized according to the Clavien-Dindo classification. According to this classification, grade 1 complications are the conditions that are deviated from normal postoperative course, however, do not require any endoscopic, surgical or radiological intervention and pharmacotherapy except for antiemetic, analgesic, antipyretic, diuretic or physiotherapy. Any pharmacotherapy necessity other than the medication allowed in grade 1 complications are classified as grade 2 complications. Blood transfusion, parental nutrition and infections requiring antibiotic treatment are also in this group. All complications that require surgical, endoscopic or radiologic intervention are classified as grade 3 complications. This group divided into two subgroups; interventions without general anesthesia are classified as grade 3a and interventions performed under general anesthesia are classified as grade 3b complications. Life-threatening conditions that require intensive care are classified as grade 4 complications and divided into subgroups; single organ failure is classified as grade 4a and multiple organ failure is classified as grade 4b complications. Death of the patient is grade 5 complication. To summarize briefly; grade 1 and 2 complications are minor; grade 3, 4, and 5 complications are major complications (5).

Data and complications related to the operations were prospectively recorded in the database. Written informed consent was obtained from each patient and our study was conducted in accordance with the principles of the Helsinki Declaration. Ethics committee approval was not gained as the study also included retrospective data.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics software version 22.0 (IBM Corp., Armonk, NY). Differences between two groups were assessed by Student's t-test. A p value of less than 0.05 was considered statistically significant.

Results

A total of 32 complications had occurred in 31 of 342 patients. The total complication rate was 9.4%. There were 20 (62.5%) minor complications and 12 (37.5%) major complications.

None of the patients required switching to open surgery and no mortality was observed. The number of operations, difficulty levels and complication rates are shown in Table 1.

Intraoperative complications represented 6.2% of all complications. Ureteral injury that occurred in a radical prostatectomy procedure was repaired with ureteral stent placement and uretero-ureterostomy. In another patient, ileal injury that occurred during trocar placement was repaired intraoperatively with primary closure and robotic surgery was continued.

Postoperative complications account for 62.5% of all complications. One of the patients, who underwent radical cystectomy and neobladder surgery, was admitted to the emergency room with acute abdomen on the postoperative 25th day. The patient was explored and neobladder rupture was detected. The blood supply of the neobladder was intact, therefore, the defect was closed with primary closure. When we explored the patient's story, we thought that the rupture could have been caused by the clean intermittent catheterization. Bladder neck contracture, which was developed in 5 patients, who underwent radical prostatectomy, was endoscopically treated. Lymphocele occurred in 6 patients and 3 of them required percutaneous drainage.

Medical complications were reported in 10 patients and represented 31.3% of all complications. Majority of these were urinary system infections. The types of all complications, incidence and Clavien-Dindo grade of the complications are shown in Table 2.

When the number of the complications was evaluated in six-months periods according to the surgical experience, the graphics showed a plateau after August 2016 and revealed a statistically significant difference between the first and the last 18 months ($p<0.05$), as shown in Figure 1.

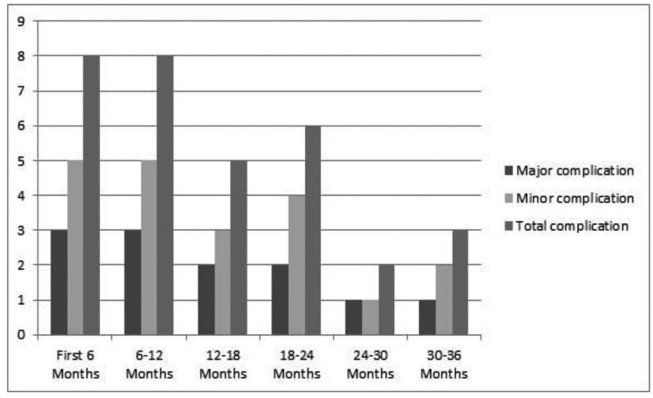


Figure 1. Distribution of the number of complications for 6-months periods

Table 1. Number of robotic cases, degree of difficulty and complication rates

Robotic operations	Technical difficulty	Number of cases	Complications, n (%) (342)	Minor complication	Major complication	Complications for individual robotic cases (%)
Radical prostatectomy	VD	240	22 (6.4%)	12	10	9.1%
Partial nephrectomy	VD	52	2 (0.6%)	2	0	3.8%
Radical cystectomy	ED	28	8 (2.4%)	6	2	28.5%
Pyeloplasty	D	6	0 (0%)	0	0	0%
Ureteroneocystostomy	D	5	0 (0%)	0	0	0%
Retroperitoneal lymph node dissection	ED	3	0 (0%)	0	0	0%
Nephroureterectomy	D	3	0 (0%)	0	0	0%
Partial ureterectomy	D	2	0 (0%)	0	0	0%
Cystoplasty (Mitrofanoff)	VD	1	0 (0%)	0	0	0%
Radical nephrectomy	E	1	0 (0%)	0	0	0%
Ureterolysis	D	1	0 (0%)	0	0	0%
Total	-	342	9.4%	20	12	-

E: Easy, D: Difficult, VD: Very difficult, ED: Extremely difficult

Table 2. Complication types, incidences and Clavien-Dindo grades

Complication	Number	Percent	Clavien-Dindo grade
Intraoperative			
Ureteral injury	1	0.3	Grade 4
Ileal injury	1	0.3	Grade 4
Postoperative			
Bladder neck contracture	5	1.5	Grade 3
Lymphocele (required drainage)	3	0.9	Grade 3
Lymphocele (not required drainage)	3	0.9	Grade 2
Ileus	2	0.6	Grade 2
Urethra-vesical anastomosis leakage	2	0.6	Grade 2
Incisional hernia	1	0.3	Grade 2
Rupture of neobladder	1	0.3	Grade 4
Ureteroileal anastomosis leakage	1	0.3	Grade 3
Ureteral catheter migration	1	0.3	Grade 1
Hematoma	1	0.3	Grade 2
Medical			
Urinary system infection	6	1.7	Grade 2
Wound infection	1	0.3	Grade 2
Blood transfusion	3	0.9	Grade 2
Total	32	9.4	-

Discussion

Robotic surgery has gained significant popularity within the last decade and included in the daily practice of urology (6,7,8,9). Also in our country, robotic surgery is widely used and series with high number of patients are contributing to the literature (10,11). In series with follow-up periods longer than five years, it was determined that there was no difference between open surgery and robotic surgery in terms of oncological results after radical prostatectomy, radical cystectomy and partial nephrectomy (12,13,14).

Although complications can occur in every surgical procedure, they are more frequent in complex surgeries. While some minor complications do not affect the course of the operation and the recovery period, major complications may risk the patient's life. Therefore, prevention of complications is very important especially during the learning curve. Like in every new surgical technique, robotic surgery has its own learning curve. This learning curve was defined as a longer curve for surgeons who make a direct transition from open surgery and as a shorter curve for surgeons who have laparoscopic experience (15,16).

In this study, we presented two surgeons process of transferring their laparoscopic skills to robotic surgery. It must be noted that, apart from the surgeons, a well-organized robotic surgery team also facilitates the operations. Despite all these positive factors, it took 18 months for us to plot a plateau for minor and major complications. Although the majority of the performed robotic operations were defined as "very difficult", none of the cases required switching to open surgery.

Although we began our robotic surgery experience with cases classified as "very difficult", such as partial nephrectomy and radical prostatectomy, our complication rate in the first 18 months was consistent with the literature (17,18). As the surgeons gained experience, they began to perform the cases classified as "extremely difficult" and their complication rates were decreased. In all these operations, the surgeons followed a standard procedure and did not change their techniques except for minor modifications. Previous studies also showed that surgical procedures with a standard course make positive contributions to oncological results and the learning curve of the surgeons (19). We also conclude that the decreased number of complications at the end of the 18th month was a result of following a standard surgical procedure.

In both robot-assisted and pure laparoscopic surgeries, reviewing the video records after the operation was reported to increase the surgical quality and decrease complication rates (20,21). We also recorded the videos of all our operations and performed reviews and self-criticism. We believe that this also can be a factor in decreasing the complication rate.

Among all cases 70% was radical prostatectomy, 15% was partial nephrectomy, 8% was radical cystectomy and urinary diversion. Fewer complications are expected in more frequent operations, but our complication rate in radical prostatectomy was higher than in partial nephrectomy. However, the operation-specific complication rate was higher for radical cystectomy and urinary diversion among others. This result reminds us that complex surgical procedures always carry a higher risk for complications. Therefore, it is emphasized that complex and risky procedures should be performed by experienced surgeons in reference hospitals (22).

Study Limitations

Our study has some limitations. First of all, data of a single surgeon could provide more accurate results for the determination of the learning curve. In addition, having a small number of patients and short follow-up period are other limitations.

Conclusion

Laparoscopic surgery experience alone is not enough to reduce complications in robot-assisted surgery and learning continues with every case. An experienced surgeon and robotic surgery team are needed for complex robotic surgeries. In order to

reduce complication rates in robotic surgery, surgeons need to approach each case carefully until they reach a certain level of experience.

Ethics

Ethics Committee Approval: Ethical committee approval was not gained as the study also included retrospective data.

Informed Consent: Written informed consent forms were obtained from each patient and our study was conducted in accordance with the Helsinki Declaration.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.İ., M.A., M.S., Concept: E.İ., M.S., Design: E.İ., M.S., Data Collection or Processing: H.A., K.K., Y.A., A.Y., Analysis or Interpretation: E.İ., H.A., K.K., Literature Search: Y.A., A.Y., Writing: E.İ., M.A., M.S.

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CASE REPORT
Urooncology

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Journal of Urological Surgery, 2018;5(3):199-201

Bilateral Torsion of Intra-abdominal Seminoma Presenting with Acute Abdomen and Intra-peritoneal Bleeding: A Case Report

Akut Karın ve İntraperitoneal Kanamaya Bağlı İntraabdominal Seminomun İki Taraflı Torsiyonu: Bir Olgu Sunumu

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Abstract

Seminoma is the most frequently reported tumor in patients with intra-abdominal testicles. In very rare cases, it might present with torsion or rupture. We report a 41-year-old man who presented with acute abdominal pain due to torsion of large bilateral intra-abdominal testicular tumors with rupture of the right-sided mass. Bilateral orchiectomy was performed and histopathological examination revealed bilateral seminoma. Postoperative staging imaging displayed no lymphadenopathy or metastatic lesions. No adjuvant treatment was required and the patient is clinically well and under regular follow-up. This case represents an extremely rare presentation of bilateral testicular cancer with a pleasant outcome.
Keywords: Bilateral cryptorchidism, Bilateral seminoma, Intra-abdominal testicle, Ruptured seminoma, Testicular torsion

Öz

Kriptorşidizm, testis tümörleri gelişme olasılığı yüksek, erkek cinsiyette görülen yaygın doğumsal anomalidir. Seminom, intraabdominal testisli hastalarda bildirilen en sık görülen tümördür. Genellikle abdominal kitlesi veya metastatik hastalığı bulunur, ancak nadir durumlarda torsiyon veya kopma olabilir. Akut karın ağrısı ve intraperitoneal kanama ile başvuran 41 yaşındaki erkek hasta üzerinde rapor veriyoruz. Resüsitasyondan sonra, cerrahi eksplorasyon, sağ taraflı kitle rüptürü ile geniş bilateral intraabdominal testis tümörlerinin torsiyonunu gösterdi. Bilateral orşiektomi yapıldı ve histopatolojik incelemede bilateral seminom tespit edildi. Postoperatif evreleme görüntülemesinde, tümör belirteçlerinin normalleştirilmesi ile birlikte lenfadenopati veya metastatik lezyon görülmedi. Hiçbir adjuvan tedavi gerekmemekteydi ve hasta klinik olarak iyi takip edildi ve düzenli takibe alındı. Bu olgu, bilateral testis kanserinin nadir görülen ve iyi sonuç veren bir sunumudur.
Anahtar Kelimeler: Bilateral kriptorşidizm, Bilateral seminom, İntraabdominal testis, Rüptüre seminom, Testis torsiyonu

Introduction

Cryptorchidism is the commonest congenital anomaly in male gender with overall incidence rate of 1-2% (1). Up to 23% of cases can present with bilateral disease, and the testicles can be located along the course of normal descent or in an ectopic position, including the abdominal cavity (2). The risk of malignant transformation is very high if orchiopexy was not performed before puberty (3). Seminoma is the commonest testicular tumor detected in uncorrected cryptorchidism (4). In this paper, we present an extremely rare case of bilateral intra-abdominal tumors which presented with acute abdomen and intra-peritoneal bleeding due to bilateral torsion and rupture of one of the tumors.

Case Presentation

A 41-year-old male patient presented to the emergency department with the complaint of severe abdominal pain for 48 hours. The pain started in the right iliac fossa then became generalized. On physical examination, the vital signs were

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unstable; heart rate, respiration, blood pressure were 126/min, 21/min, and 98/63 mmHg, respectively. Severe abdominal tenderness and guarding were detected mainly in the right iliac fossa. Genital examination showed absent bilateral testicles. Sonographic imaging revealed free fluid in the peritoneal cavity and a heterogeneous soft tissue lesion in the lower part of the abdomen. He was resuscitated with intravenous fluids, and analgesia was given. As the patient was unstable, after proper counseling, laparoscopic laparotomy was performed and then, was converted to lower midline laparotomy that revealed bilaterally twisted intra-abdominal gonadal tumors (Figure 1). No obvious metastasis was detected after careful inspection of the abdominal cavity and lymph nodes. Removal of the two tumors, followed by closure of the abdomen was performed.

Postoperatively, alpha fetoprotein (AFP) and beta-human chorionic gonadotropin (β-HCG) levels were not raised, however, lactate dehydrogenase (LDH) was high (1160 U/L). Seven days later, LDH was normalized. Contrast-enhabced computed tomography (CT) showed non-metastatic disease. Pathological reporting displayed seminoma, which infiltrated the tunica albuginea, without extension to any other structures. Until now, after 6 months of postoperative follow up, the patient still well with no detected tumor recurrence.

Written informed consent was taken for publication of the case report.

Discussion

The incidence of undescended testicles at the time of birth is up to 30% and 8% in premature and full-term boys, respectively (2). Due to the increased testosterone level around the age of 3 months, possibility of spontaneous descent is quit high (2). After 6 month of age, spontaneous descent is unlikely to be observed, therefore, orchiopexy is the standard treatment (5). The overall incidence at 1 year of age is 1-2% (1). Orchiopexy should be performed before 12 months of age to avoid the damage to germ cells (6).

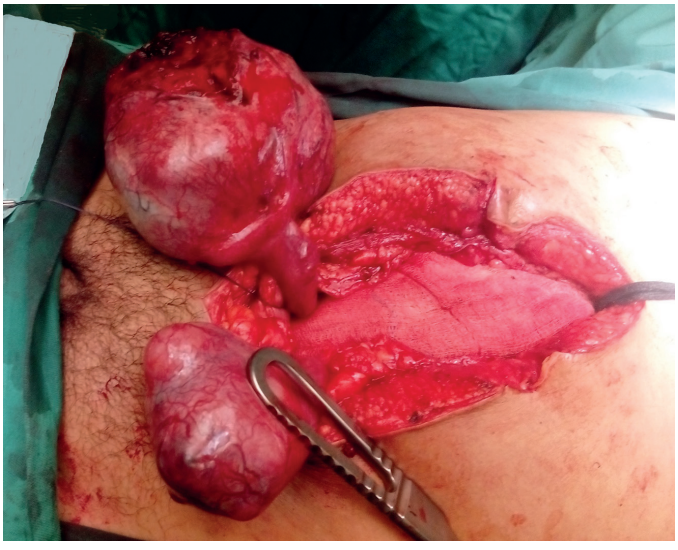


Figure 1. Bilateral testicular masses with rupture of the right sided tumor

It is well established that cryptorchidism increases the risk of testicular cancer. The possibility of cancer development is about 40 times higher than in people born with scrotal testicles (1). The pathogenesis of cancer development is still not completely understood, however, one of the theories is the destructive effect of increased temperature on the germ cells, which can be a source of carcinoma *in situ* after puberty (1). Orchiopexy after puberty does not decrease the risk of malignant transformation (7), yet it increases the possibility for earlier detection of the cancer. In adult patients with intra-abdominal undescended testicles, unfortunately the diagnosis of cancer at early stage is difficult and usually patients present with advanced disease or palpable mass.

Seminoma is the most frequently diagnosed tumor in undescended testicles, especially in patients who had not undergone orchiopexy (1). LDH, AFP, and β-HCG are the most commonly used tumor markers for testicular germ cell tumors. In seminoma, elevated LDH reflects a large tumor size and high tissue destruction level, yet its specificity is low (8). AFP and β-HCG levels are not usually elevated in seminoma. Only with mixed content, such as embryonic carcinoma or syncytiotrophoblast, AFP and β-HCG can be elevated, respectively. Elevated tumor markers might be associated with a poor prognosis, however, the curability of seminoma is high in general (8).

Torsion with subsequent severe pain due to ischemia is more common in undescended testicle than in the scrotal one (9). Bulky testicular tumors are vulnerable to rupture after complete twist of the spermatic cord with subsequent significant bleeding and hemorrhagic shock. Despite torsion might be life-threatening due to bleeding, it can be the leading cause to detect the tumor in an early stage before metastasis.

Clinical staging using contrast-enhanced CT and tumor markers is mandatory before surgical intervention in testicular tumors (10). In our case, the patient underwent urgent surgical intervention in view of the clinical instability. Contract-enhanced CT scan and analysis of tumor markers were performed postoperatively for staging and planning for any required adjuvant therapy. Fortunately, no metastatic lesion or persistently elevated markers was detected, thus, no adjuvant treatment was considered.

The take-home message is that cryptorchidism is best to detect immediately after birth to avoid further complications. The recommendation for orchiopexy of undescended testis in early childhood -ideally before 12 months of life- must be followed strictly. Prepubertal detected cryptorchidism should be corrected

with orchiopexy. Adult patients with cryptorchidism should be counseled for orchiectomy or orchiopexy which with allow regular self-examination without reduction of carcinogenesis (7). However, extremely rare, this case report highlights intra-abdominal seminoma as a cause for acute abdomen that should be considered in patients with a history of undescended testicles or accidently discovered during clinical examination. Scrotal examination should be included in clinical assessment of patients presenting with acute abdomen.

Ethics

Informed Consent: It was taken for publication of the case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.F., Concept: M.K.A., Design: A.R.S., Data Collection or Processing: S.H.S.M.H., Analysis or Interpretation: C.K.S.L., Literature Search: R.E., Writing: O.F.

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

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CASE REPORT
Urooncology

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Massive Inguinoscrotal Bladder Hernia and Bladder Tumor: A Very Rare Case

Masif İnguinoskrotal Mesane Hernisi ve Mesane Tümörü: Çok Nadir Bir Olgu

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Abstract

Here, we present a case of a 60-year-old male patient with inguinoscrotal bladder hernia and a bladder tumor who underwent cystoscopy and had no transurethral access. On the images, a massive inguinoscrotal hernia and a mass of 2.8 cm in diameter in the bladder were seen. First of all, hernia was repaired. Transurethral resection of the tumor was then performed. The tumor was in the posterior wall. High-grade T2 urothelial carcinoma was detected. The patient was offered radical surgery but he refused the operation. Multimodal therapy was recommended for the patient.
Keywords: Bladder, Bladder tumor, Urinary bladder, Prolapse

Öz

Bu raporda 60 yaşında inguinoskrotal mesane hernisi ve mesane tümörü olan, sistoskopi için başarısız üretral akses öyküsü olan bir erkek hasta sunulmaktadır. Görüntülemelerde masif bir inguinoskrotal herni ve 2,8 cm çapında mesane tümörü saptandı. Öncelikle herni tamiri yapıldı ve ardından tümör transüretral olarak rezeke edildi. Tümör posterior duvardaydı. T2 mesane kanseri saptanan hastaya radikal cerrahi önerildi fakat hasta tedaviyi reddetti. Bunun üzerine hastaya multimodal tedavi önerildi.
Anahtar Kelimeler: Mesane, Mesane tümörü, İdrar kesesi, Prolapsus

Introduction

Inguinoscrotal bladder hernia is a very rare condition (1). It usually causes scrotal swelling and lower urinary tract symptoms. In symptomatic patients, spontaneous urination following manual pressure over the hernia sac is typical of two-phase voiding (2). Most of the patients are male and the hernia is right-sided. Previous studies have reported that it was common in men aged 50-70 years (3). There is often a slight herniation towards the inguinal canal. Massive hernias in which the bladder is completely located in the scrotum are much less common. Treatment is surgical repair of the hernia.

Cases in which tumors are detected in the herniated bladder are very rare. In the literature, only 15 cases of malignancy originating from the herniated bladder have been reported. We present the case of a 60-year-old male patient who underwent cystoscopy for hematuria and had no transurethral access.

Case Presentation

A 60-year-old male patient was admitted to our clinic with scrotal swelling and intermittent hematuria. Scrotal swelling was present for 3 years and hematuria for 1 year. Cystoscopy was intended to be performed in the external center, but transurethral access was not achieved. Blood tests were normal and the kidney function was not impaired. The patient had no irritative or obstructive lower urinary tract symptoms. However, the patient was describing a two-phase voiding. The uroflowmetry test was normal (Q_{max}: 16 mL/sec). Repeated measurements with transabdominal and transscrotal bladder scans did not detect residual urine after voiding. Residual urine control was also performed with a urethral catheter. The prostate could not be palpated by digital rectal examination. The urine culture was sterile and the prostate-specific antigen value was normal (0.476 ng/mL). An advanced inguinoscrotal vesical hernia was seen on abdominopelvic computed tomography (CT).

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The bladder was completely in the scrotal sac (Figure 1). The distal parts of the bilateral ureters and the prostate were seen to be pulled toward the inguinal canal (Figure 2). In addition, a 1.4 cm lesion on the lateral side of the right adrenal gland was observed on CT scan. There were several millimetric calculations and multiple cysts in both kidneys. A mass of 2.8 cm in diameter extending from the wall to lumen was seen in the bladder located in the scrotum. First, the bladder hernia was repaired. Transurethral resection of the tumor was then performed. It was determined that the bilateral kidneys were free of stones in the patient who had stone dropping after repair of the hernia. The pathology of the bladder tumor was reported as high grade T2 urothelial carcinoma. Radical cystectomy + urinary diversion were recommended for the patient. However, the patient refused the operation, stating that his complaints had receded after the repair. The tumor was located in the posterior wall of the bladder. Since partial cystectomy was not an option, the patient was then offered multimodal therapy.

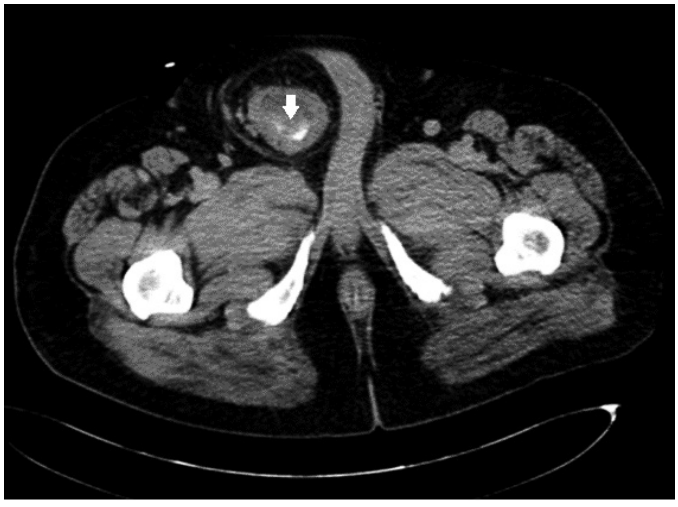


Figure 1. Hyperdense bladder tumor in the herniated bladder

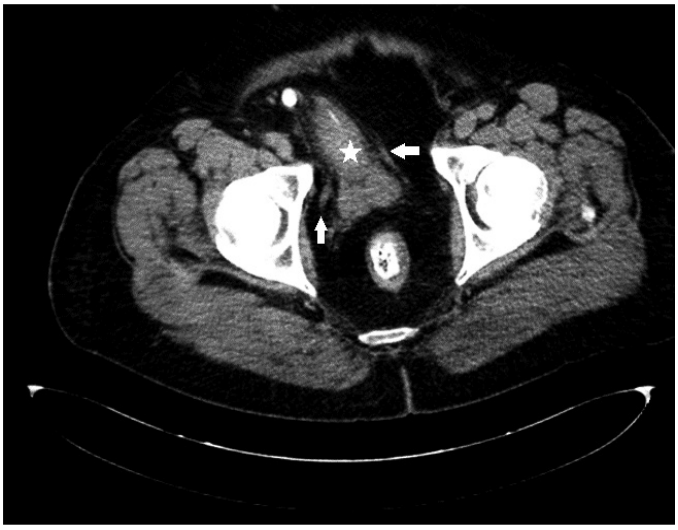


Figure 2. Herniated bladder accompanied by bladder neck and bilateral ureters

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Patient's approval was taken.

Discussion

Various studies have reported that 1-3% of inguinal hernias were associated with herniation of the bladder (4). As it can be understood, most of the bladder hernias are mild hernias limited to the inguinal canal. Advanced cases, where the entire bladder is placed in the scrotum, is rather rare.

Most cases are asymptomatic and diagnosed perioperatively (3). Some of them are diagnosed after the occurrence of postoperative complications. Very few are diagnosed with assessments of the symptoms. In our case, there were the complaints of scrotal swelling and hematuria related to the bladder tumor.

Hernia is evaluated in three groups according to its relationship with the peritoneum (5). Paraperitoneal hernias, where the outer part of the herniated bladder is wrapped with the peritoneum, are the most frequent group. Hernias that are all covered with the peritoneum are called intraperitoneal hernia. Hernias unrelated to the peritoneum are defined as extraperitoneal. Our case was classified as extraperitoneal hernia at perioperative evaluation.

Common etiologies of bladder hernia include obesity, pelvic wall failure, and bladder outlet obstruction (6). No evidence of other etiologies was found in the patient whose body mass index was 32 kg/m^2. Most of the cases reported in the literature were asymptomatic. In our case, the patient was admitted due to macroscopic hematuria. In addition, other common symptoms, such as two-phase voiding and scrotal swelling, were also detected.

Bladder diverticulum, mesenteric cyst hernia, hydrocele and spermatic cord cyst should be considered in the differential diagnosis (6). On ultrasonography, mild hydrocele in the right testis was observed. Hydrocele was thought to be due to bladder hernia, the ureters pulled toward the inguinal canal and cord pressure caused by the prostate.

Oruç et al. (7) reported that 11.2% of 190 cases of inguinal hernia were associated with urological malignancy. The association of a massive inguinoscrotal bladder hernia and bladder tumor is very

Table 1. Previously reported case reports

Author	Year	Number of patients
Oppenheimer GD	1943	1
Marcus R	1953	1
Elliott EG	1972	1
Tasca A et al.	1978	1
Lasaponara F et al.	1979	1
Epner et al. (4)	1993	1
Pardo Garcia et al. (8)	1997	1
Dario Casas J et al.	1997	1
Pareira Arias et al.	1998	1
Caterino M et al.	2001	1
Oruç et al. (7)	2004	1
Das CJ et al.	2007	1
Pastor Navarro H et al.	2010	2
Katsourakis et al. (6)	2014	1

rare (Table 1). In fact, this patient, who also had mild hydrocele, benign adrenal mass, bilateral renal cyst and stones, is a unique case that has not been reported in the literature before.

The main aims of the treatment are repair of the bladder hernia and endoscopic diagnosis and treatment of the tumor (6). However, there may be differences between the approaches of physicians. In 1993, Epner et al. (4) performed partial cystectomy for a tumor in a herniated bladder. In a case reported by Pardo Garcia et al. (8), bladder perforation and scrotal abscess occurred.

Massive inguinoscrotal bladder hernia is a very rare condition. Its association with bladder tumor has been reported less frequently. The main purpose of the treatment should be endoscopic diagnosis and treatment of the tumor.

Ethics

Informed Consent: Patient's approval was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.Ö., Ç.D., Z.T., Concept: O.Ö., Design: Ç.D., Data Collection or Processing: O.Ö., U.A., Analysis or Interpretation: O.Ö., S.Ç., Literature Search: O.Ö., Writing: O.Ö., Ç.D.

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
Urooncology

Doi: 10.4274/jus.1668
Journal of Urological Surgery, 2018;5(4):205-207

Adult Wilms' Tumor: A Rare Case Report

Erişkin Wilms Tümörü: Nadir Bir Olgu Sunumu

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Abstract

Wilms' tumor is one of the most common intraabdominal malignancies among children and treatment protocols have been well studied in this population. The clinical presentation differs between the pediatric and adult populations with adults presenting similar to patients with renal cell carcinoma. Diagnosis is usually made by surgical pathology as imaging cannot differentiate between Wilms' tumor and other kidney pathologies. In addition to surgical excision, treatment includes systemic chemotherapy and/or radiation. In this case report, we present a patient who underwent successful surgical resection of a 29x24x25 cm right-sided Wilms' tumor with subsequent chemotherapy and radiation.
Keywords: Wilms' tumor, Adult Wilms' tumor, Kidney malignancy

Öz

Wilms tümörü, çocuklar arasında en yaygın intraabdominal malignitelerden biri olup, bu popülasyonda tedavi protokolü iyi çalışılmıştır. Klinik görünüm çocuk hastalarla yetişkin hastalar arasında farklılık gösterir. Yetişkin hastaların semptom ve bulguları daha çok renal hücreli kanser hastaları gibidir. Tanı genellikle cerrahi patoloji ile yapılır, çünkü görüntüleme Wilms tümörünü diğer böbrek patolojisinden ayırmaz. Tedavi, cerrahi eksizyona ek olarak, sistemik kemoterapi ve/veya radyasyon içerir. Bu olgu sunumunda, 29x24x25 cm boyutlarında sağ renal taraflı bir Wilms tümörüne, kemoterapi ve radyasyon ile takip eden başarılı bir cerrahi rezeksiyon uygulanmış bir hasta sunulmuştur.
Anahtar Kelimeler: Wilms tümörü, Erişkin Wilms tümörü, Böbrek malignitesi

Introduction

Wilms' tumor, also known as nephroblastoma, is a common intraabdominal malignancy in young children with most cases occurring before age 5. The incidence of Wilms' tumor in adults is reported at 0.2 per million per year (1). As opposed to children, who usually present with a palpable abdominal mass, adults tend to present with flank pain and hematuria.

Adult Wilms' tumor has well known diagnostic criteria which include: 1) primary renal neoplasm, 2) presence of primitive blastemic spindle or round cell component, 3) formation of abortive tubules or glomerular structures, 4) no area of tumor diagnostic of renal cell carcinoma, 5) pictorial confirmation of histology, and 6) patient age >15 years (2). Due to the rarity of adult Wilms' tumor, the current standard of care regarding treatment is based on well-developed pediatric treatment protocols (3). We present a 41-year-old female who presented with a 29x24x25 cm right-sided Wilms' tumor.

Case Presentation

A 41-year-old Caucasian female presented with rapidly increasing abdominal girth and early satiety with a computed tomography (CT) scan demonstrating a 29x24x25 cm multicystic, multiloculated right-sided abdominal mass with extension into the pelvis (Figure 1). The patient was a non-smoker with a past medical history of obesity and no prior genitourinary problems. Past surgical history included laparoscopic hysterectomy and C-section. Oncologic family history was significant for leukemia and male breast cancer. Physical exam revealed a non-tender, protruding mass of the entire right abdomen. A screening chest CT showed no evidence of metastatic disease. The patient underwent an exploratory laparotomy with right nephrectomy and retroperitoneal mass excision. A multiloculated, cystic,

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friable mass arising from the collecting system of the right kidney was found intraoperatively with minimal invasion into the surrounding structures. Due to the friability of the tumor, spillage of cystic fluid occurred. The right ovary was found to be involved in the mass and was subsequently removed. The patient had an uneventful postoperative course and was discharge home on postoperative day 5 without requiring any blood transfusions. The patient had no major/minor complications related to the surgical intervention.

Intraoperative gross pathological review of the mass revealed a large pale solid and cystic mass originating from the right renal pelvis which was perforating through the lower pole of the right kidney (Figure 2). Microscopic pathological review revealed epithelial lined cystic spaces with a primitive population of cells resembling a cambium layer beneath the epithelium consistent with favorable histology, stromal predominant Wilms' tumor (Figure 3). The margins were noted to be positive for tumor and fluid cytology showed similar stromal predominant malignant-appearing cells. The right ovary removed during the procedure demonstrated a serous cystadenoma. Per pediatric staging, the patient was diagnosed with stage 3 Wilms' tumor due to positive tumor margins and tumor spillage intraoperatively (4).

Based on the diagnosis of stage 3, favorable histology, Wilms' tumor, the patient was started on multidrug chemotherapy that consisted of doxorubicin, dactinomycin, and vincristine. She also underwent whole abdomen radiation per the COGAREN0532 DD4A protocol set forward by the Children's Oncology Group which includes the National Wilms' Tumor Study Group (NWTS) (5). Repeat CT chest/abdomen/pelvis three months postoperatively showed no evidence of tumor recurrence.

Written informed consent was completed by this patient.

Discussion

Wilms' tumor is one of the most common intraabdominal malignancies in pediatric patients, but continues to be a rare occurrence in adult patients. The presentation between adults and children is variable. Unlike children who present with a palpable abdominal mass, adults present with painless hematuria, weight loss, decreased performance status and flank pain (6). The diagnosis of Wilms' tumor in adults is almost uniformly made from surgical pathology. CT imaging is non-specific and can mimic other forms of benign and malignant renal tumors including multicystic nephroma, renal cell carcinoma, sarcoma, liposarcoma, gastrointestinal stromal tumor, and other renal tumors.

The management and treatment of adult Wilms' tumor is customarily multimodal and includes surgical, multi-drug chemotherapy and/or radiation. Treatment protocols are

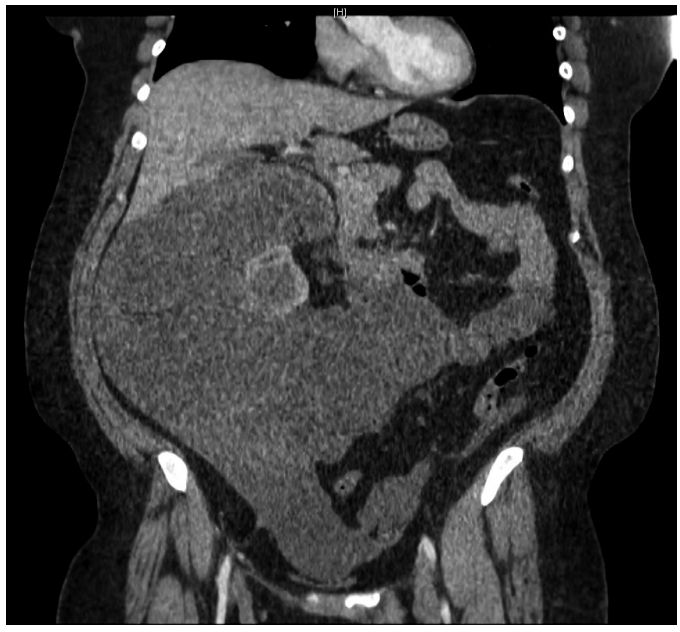


Figure 1. Coronal section of computed tomography abdomen demonstrating large mass arising from right kidney

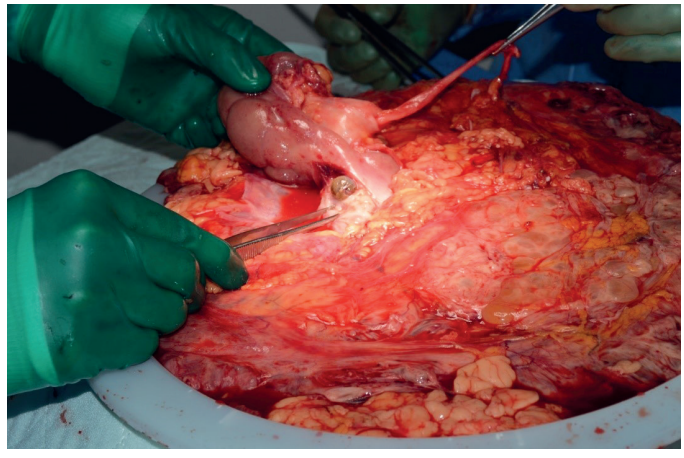


Figure 2. Gross examination of right sided kidney mass showing obliteration of lower pole of right kidney

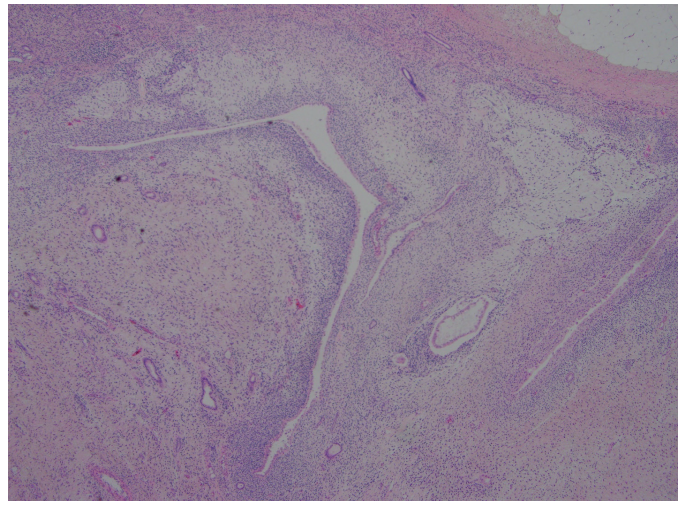


Figure 3. Microscopic specimen depicting stromal predominant wilms tumor

based on well-studied risk-based regimens developed for the pediatric population (6). The implementation of this approach to adult Wilms' tumor has been previously shown to improve the overall outcome in adult patients (7,8). Involvement of a pediatric oncologist can be an important step due to familiarity with such treatment protocols (9). Close monitoring and follow-up are essential in overall management of patients with adult Wilms' tumor. Treatment toxicity both from chemotherapy and radiation tends to be higher in adults (10). Cardiac, hematological and renal toxicity associated with chemotherapy is common and should be monitored during treatment. Patients may also suffer from infertility and secondary malignancies after radiation therapy (3).

Prior to the utilization of chemotherapy and radiation, the prognosis of adult Wilms' tumor was poor, with survival rates ranging from 18-27% (7). Studies found similar overall survival by both NWTS favorable histology Wilms' tumor when comparing pediatric and adult patients. For adults specifically, the NWTS found overall survival at 5 years based on stage of disease to be: stage 1-100%, stage 2-92%, stage 3-70%, and stage 4-73% (7). However, other case series have found that outcomes tend to be poorer for adults regarding overall survival. A recent study by Ali et al. (11) have found that, when comparing all stages, pediatric patients had much better 5-year overall survival when compared to adults. The author attributes this difference in survival to a combination of inadequate staging, treatment delay, and under treatment of adults in the general population (11).

Adult Wilms' tumor is a rare disease, in which diagnosis is dismal prior to the advent of pediatric treatment protocols for adult patients. The treatment of adult Wilms' tumor involves multi-drug chemotherapy with or without radiation, and adults tend to have higher rates of toxicity when compared to the pediatric population. The prognosis of adult Wilms' tumor has improved using pediatric protocols, however, in comparison to pediatric patients, conflicting data on outcomes is present when assessing the overall survival between the two populations. Further research is needed regarding treatment and prognosis of this rare disease process in the adult population.

Ethics

Informed Consent: Written consent was obtained from patient regarding use of case report for medical research.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.P., G.C., Concept: G.C., Design: G.C., S.P., K.C., Analysis or Interpretation: G.C., S.P., K.C., L.A., Literature Search: G.C., K.C., L.A., Writing: G.C., K.C., S.P.

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

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CASE REPORT
Urooncology

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Spermatocytic Seminoma with Sarcomatous Transformation: The First Brazilian Case Report

Sarkomatöz Dönüşüm ile Spermatositik Seminom: Brezilya'ya Özgü İlk Olgu Sunumu

Daniel Carvalho, Ronielly Bozzi, Aline Coltro, Bruno Reis, José Scheinkman

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Abstract

The cases of spermatocytic seminoma with sarcomatoid transformation are rare. When there is sarcomatoid transformation, the tumor takes an aggressive pattern, with high rates of metastasis and a worse prognosis. We present the case of a 42-year-old man with a slow enlargement of the left testicle over more than 18 months, which progressed to a pronounced and painful growth in the last six months. Computed tomography showed a left retroperitoneal mass in the renal area affecting the stomach. Total orchiectomy with partial scrotectomy was performed in the left testicle and the patient was referred to the oncology department for chemotherapy.
Keywords: Spermatocytic seminoma, Sarcoma, Testicular neoplasms, Orchiectomy

Öz

Sarkomatöz dönüşüm gösteren spermatositik seminom olguları nadirdir. Sarkomatöz dönüşüm olduğunda, tümör yüksek oranda metastaz ve daha kötü bir prognoz şeklinde agresif bir yol izler. On sekiz aydan fazla bir süredir sol testiste yavaş bir büyüme olan, son altı ayda ise bu büyüme belirgin ve ağrılı bir hale gelen, 42 yaşında bir erkek hastayı sunuyoruz. Bilgisayarlı tomografi, renal bölgede mideye etki eden sol retroperitoneal kitleyi gösterdi. Sol testiste parsiyel skrotektomi ile total orşiektomi yapıldı ve hasta kemoterapiye yönlendirildi.
Anahtar Kelimeler: Spermatositik seminom, Sarkoma, Testiküler neoplazi, Orşiektomi

Introduction

Testicular tumors account for approximately 1% of all neoplasms in men, with solid neoplasms more frequent in young adults (1,2). Primary testicular tumors are divided into germinal and non-germinal tumors. Germ cells comprise 90% of testicular neoplasms. Most are curable and have good prognosis. With various therapeutic approaches including surgery, chemotherapy and radiotherapy, 5-year survival rate can be increased to as much as 90%. However, spermatocytic seminoma (SS) with sarcomatous transformation, a rare testicular tumor, has a poor prognosis (1,3).

Case Presentation

A 42-year-old man presented to the Emergency Department at Antônio Pedro University Hospital on December 11th, 2016, with a slow enlargement of left testicle over the previous 18 months, which had progressed to a pronounced and painful growth in the last six months. The patient also complained of postprandial fullness. No other comorbidities were present.

Physical examination was unremarkable except for emaciation and hypocorous (+/++++). The left testicle presented as an enlarging testicular mass with a ten-fold increase in size, mobile, with stony consistency and pain. There was a palpable mass in the abdomen at the epigastric region, the umbilical region and the left flank. No other abnormalities were found on the exam.

Computed tomography of the abdomen and pelvis showed a left retroperitoneal mass in the renal area, which pushed the stomach and a heterogeneous testicular mass on the left side (Figure 1). Tumor markers were as follows: alpha-fetoprotein: 2.6 ng/mL; human chorionic beta-gonadotrophin: 7.36 mIU/mL; lactate dehydrogenase: 416 U/L and stadium: S1.

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Total orchiectomy and a partial scrotectomy were done in the left testicle due to the intimate and indissociable contact with the skin, with staging T3N3. Macroscobically, the tumor was measuring 13.5x8.0x7.0 cm in size, weighing 350 grams, capped with areas of necrosis and showed albuginea involvement and tunica vaginalis, and replacement of the entire testicular parenchyma. Histopathological analysis revealed SS in small focus and extensive high grade sarcomatoid component (Figure 2). The immunohistochemical stains S100 were positive in sarcomatous component. The surgical limit of the spermatic cord had neoplastic emboli. The patient was referred to the department of oncology for chemotherapy.

Written informed consent was taken from patient.

Discussion

SS is a rare germ cell neoplasm, accounting for about 1% of all testicular tumors, and mainly affects men in around the fifth decade of life (1,3). It was first described by Pierre Masson in 1946 as a variant of seminoma. However, SS and classical seminoma have distinct pathogens (1,2). For this reason, some authors prefer to use the term spermatocytoma, a term not widely accepted in the scientific community (2). SS also differs from seminoma by having a higher rate of cell differentiation, to the point of performing spermatogenesis. It has no association with cryptorchidism or other testicular neoplasm, as opposed to the classical seminoma (1,4).

The clinical presentation is in the form of an insidious and painless enlargement of testis (1). The possibility of metastasis is rare and the prognosis is favorable. Orchiectomy and surveillance of the contralateral testis is the appropriate therapy, without the need for adjuvant chemotherapy in most cases (2,3). The main differential diagnoses are classical seminoma and testicular lymphoma (1).

Approximately 6% of SS cases can develop from an anaplastic transformation of tumor cells into a sarcomatous differentiation (1,2). The risk of sarcomatous transformation increases mainly in cases of long-standing SS (3). It is a neoplasm that shows no ovarian equivalence and no association with intraepithelial testicular neoplasms (5). Possible differential diagnoses are: seminoma, lymphoma, teratoma, and primary testis sarcoma (1,4). There are less than 20 reports of SS with sarcomatous transformation in the literature, this being the first reported case of SS with sarcomatous differentiation from Brazil (3,4,6).

When there is sarcomatoid transformation, the tumor takes an aggressive pattern, with high rates of metastasis and worse prognosis (1,2,3). Thus, SSs that have metastasized normally present sarcomatous transformation (2). In these cases, distant metastasis or lymph node metastasis occurs.

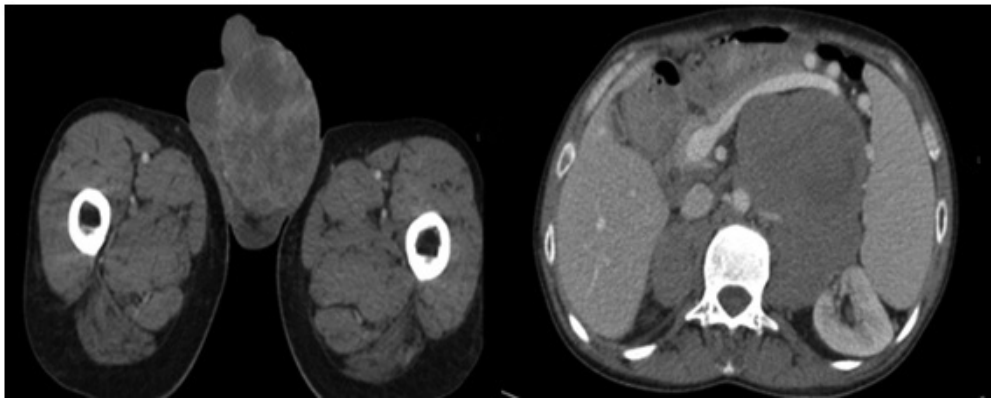


Figure 1. Computed tomography, which evidences tumor in the left testicle and voluminous retroperitoneal mass in the left that pushes away the adjacent structures

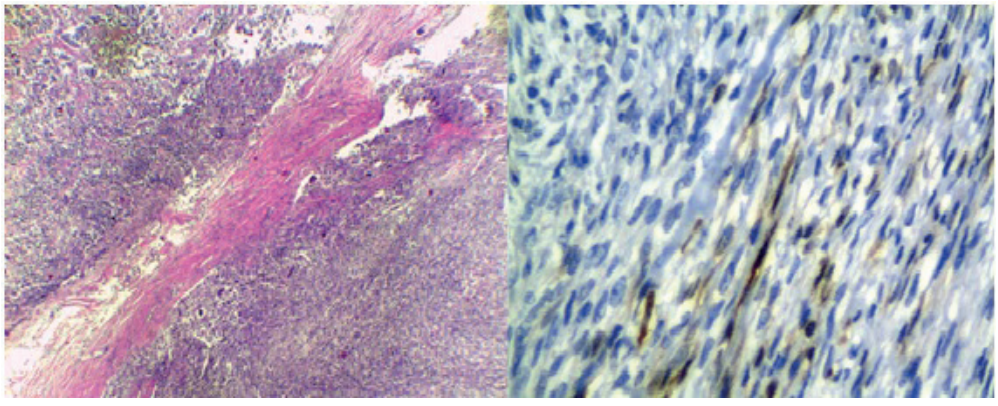


Figure 2. Spermatocytic seminoma histopathology (upper left) and sarcomatous transformation (lower right). On the right, immunohistochemistry stains S100 was positive for the sarcomatous component

In the literature, there are records of lung, bone and liver metastases, as well as retroperitoneal lymph node metastasis up to the level of the ipsilateral renal vein (2,6). The sarcomatoid components reported in the literature are rhabdomyosarcoma, chondrosarcoma, undifferentiated sarcoma or high-grade sarcoma (2,4). Undifferentiated sarcoma is the most commonly found component (4). All reported cases of rhabdomyosarcoma showed distant metastasis, although there is no significant evidence of difference in prognosis between histological types of sarcomatous transformation (6,7). Some studies have shown that only the sarcomatous elements of SS metastasize (2).

Histopathologically, SS is characterized by cells poor in cytoplasmic glycogen and with spherical nuclei (5). It is common for it to present a heterogeneous population of cells: small cells (6-8 µm) with dense and basophilic nuclei, medium cells (15-20 µm) with fine chromatin filaments and large cells (50-100 µm) which may be multinucleated (4). Unlike classic seminoma, SS has a sparse or simply absent lymphocytic infiltrate (5). It is common to find mitoses, including atypical forms (4).

The cases of SS with sarcomatous transformation are clinically characterized by a rapid increase in the size of pre-existing tumor, and may present with pain (3,4). It commonly affects only one testicle, being bilateral in about 10% of cases (3). Most patients have metastasis at the time of diagnosis (2). Differently from classic SS, where a sarcomatous component is present; greater benefits are obtained if the treatment includes radiotherapy and adjuvant chemotherapy in addition to radical inguinal orchiectomy (3,6). Thus, aggressive treatment with the combination of surgical approach and adjuvant chemotherapy is recommended in all cases, although the prognosis remains reserved despite chemotherapy (1,6). For some authors, the need for radiotherapy or chemotherapy is not clear in cases without radiological evidence of metastasis (4).

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Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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
Andrology

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Polyorchidism: A Case Report and Review of the Literature

Poliorşidizm: Bir Olgu Sunumu ve Literatür Derlemesi

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Abstract

Polyorchidism is defined by the presence of more than two testicles. It is a very rare anomaly. In this paper, we report a case of polyorchidism that presented as a painless scrotal mass. Undrained types require histological evaluation. Increased risk of malignancy should be taken into consideration in patients with nonscrotal supernumerary testes. We did not recommend any treatment to our patients who had scrotal supernumerary testicle and two children and decided to follow-up with scrotal ultrasound.
Keywords: Polyorchidism, Supernumerary testes, Painless scrotal mass

Öz

Poliorşidizm, ikiden fazla testisin varlığı olarak tanımlanır. Çok nadir görülen bir anomalidir. Bu yazıda ağrısız skrotal kitle ile ortaya çıkan poliorşidizmli bir olgu sunuldu. Drene olmayan fazladan testisler histolojik değerlendirme gerektirir. Nonskrotal yerleşimli poliorşidik hastalarda artmış malignite riski göz önünde bulundurulmalıdır. Skrotal poliorşidizmi ve iki çocuk sahibi olan hastamıza herhangi bir tedavi önermedik ve skrotal ultrasonografi ile takip etmeye karar verdik.
Anahtar Kelimeler: Poliorşidizm, Fazladan testis, Ağrısız skrotal kitle

Introduction

Polyorchidism is defined by the presence of more than two testicles. It is also named supernumerary testicle in the literature. It is a very rare anomaly. Only about 200 cases have been reported in the literature (1). In this paper, we report a case of polyorchidism that presented as a painless scrotal mass. The management of polyorchidism is controversial.

Case Presentation

We report a 29-year-old male patient who was referred to our urology clinic with scrotal pain and had no history of trauma or any previous history of urogenital complaints. The patient reported a subacute scrotal pain that continued for two weeks. He did not report any lower urinary tract symptom. Physical examination revealed that the left and the right testicles were normal in size and position and firm in consistency. No varicocele was palpable on either side. The vasa, epididymis and penis were normal. No lymphadenopathy was detected. In the left scrotum a mass that has smaller size and same consistency with the left testiscle was palpated. It was at the inferior of the left testicle.

A scrotal grayscale ultrasonography showed a rounded structure 2.9 cm in diameter with clear limits, located in the left hemiscrotum adjacent to the lower pole of the left testis (Figure 1). This showed the same echogenicity, Doppler intensity and normal flow signs with the testis in color Doppler ultrasound. Testicular tumor markers profile showed lactate dehydrogenase, alpha-fetoprotein and beta-human chorionic gonadotropin within normal levels (228 IU/L, 3.34 ng/mL and 0.28 mIU/mL, respectively). Magnetic resonance imaging showed normal right testicle measuring approximately 5.1 cm in diameter and normal epididymis. Two testicles were identified on the left side with the larger one measuring approximately 4.4 cm in diameter, and the second one, completely independent testicle, measuring 2.8 cm long, was found to be adjacent to the larger one. Each testicle was seemed having its own epididymis. All the three testicles had identical signal characteristics on T1- and

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T2-weighted images. On the basis of these imaging findings, the diagnosis was polyorchidism with duplication of the left testicle (Figures 1 and 2).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from the individual participant included in the study.

Discussion

Polyorchidism is a very rare testicular anomaly. Triorchidism, which refers to the presence of three testes, is the most frequent presentation and the supernumerary testis is often located in the left side of the scrotum (2,3). The most common location of the supernumerary testis is within the scrotum, superior or inferior to the ipsilateral testicle (4). In our case, the supernumerary testis was located in the left scrotum, inferior to the left testicle.

Leung classified polyorchidism into four groups based on testis embryology: 1) polyorchidism with no vas deferens or epididymis in the supernumerary testis, 2) testes sharing these two structures with the ipsilateral testicle, 3) testes with their own epididymis and sharing the vas deferens, and 4) supernumerary testes with their own annexes (5,6). The patient was considered to be in the group 4. Singer et al. (7) performed a polyorchidism classification according to the localization of the extra testis and the fertility status of the patient. Our patient was not infertile and had two children (group 1A).

In a meta-analysis performed by Bergholz and Wenke (8) in 2009, it was found that the median patient age was 17 years and most cases of polyorchidism were confined to the left side (65%).

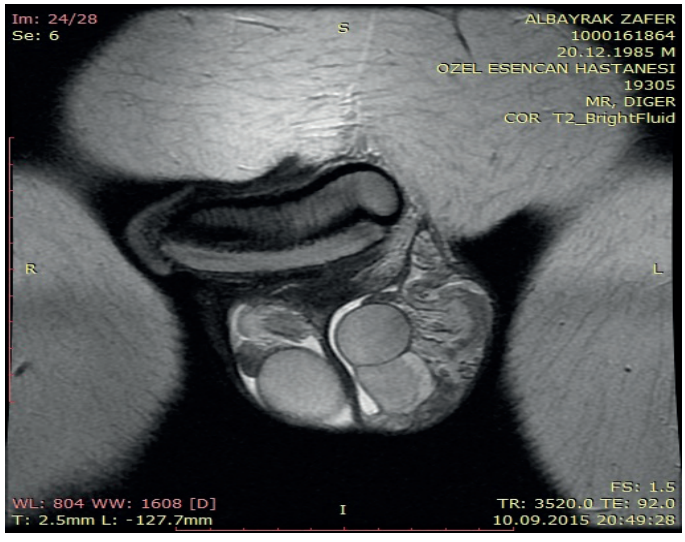


Figure 1. Right testicle and left testes in T2 weighted image

The etiology is still unclear. It is thought to be accidental division of the genital ridge before 8th week of gestation. Although there are many embryological theories in the literature, none are sufficient to explain the pathogenesis of polyorchidism alone (8).

The clinical signs and symptoms consist of scrotal pain, which may be intermittent. Many patients never experience clinical symptoms, and the diagnosis might be incidental (5). In our case, patient had a subacute scrotal pain, but it was in the right hemiscrotum and inguinal region and not associated with supernumerary testicle.

It is not clear whether or not polyorchidism is a clinical condition requiring treatment. Some authors suggest close follow-up to preserve spermatogenesis. On the other hand, excision of the supernumerary testis is recommended by some authors, taking into consideration the risk of malignancy (9). In their meta-analysis, Bergholz and Wenke (8) created a new classification for

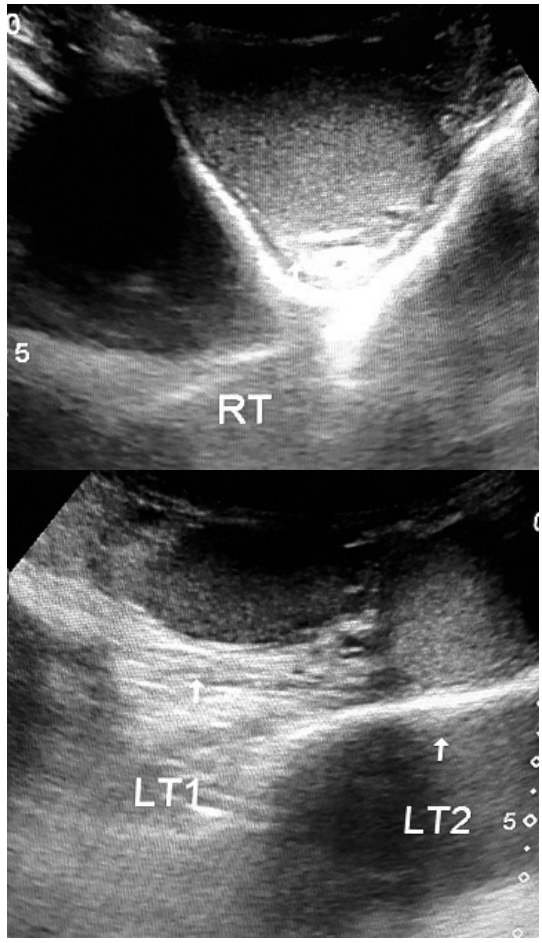


Figure 2. Single testicle in right hemiscrotum and two testes in left hemiscrotum, ultrasound images

RT: Right testicle, LT: Left testicle

statistical analysis and management recommendations. According to this report, undrained types require histological evaluation. The most important risk factor for malignancy is the nonscrotal location of the supranumerary testis. Patients with nonscrotal supernumerary testes should be informed about the increased risk of malignancy, and removal of the undescended testis must be discussed regardless of whether it is connected to a vas deferens. The majority of supernumerary testes are located in the scrotal (66%), inguinal (23%) or abdominal (9%) positions (8). Considering that the risk of malignancy was very low in our patient with scrotal placement of testis, we did not recommend any treatment and decided to follow-up with scrotal ultrasound.

Ethics

Informed Consent: Informed consent was obtained from the individual participant included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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
Andrology

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Journal of Urological Surgery, 2018;5(3):214-216

Penile Abscess Due to Intracavernosal Injection: A Case Report

İntrakavernozal Enjeksiyona Bağlı Oluşan Penil Apse: Olgu Sunumu

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Abstract

Penile abscess is a rare clinical entity. We present the case of a 45-year-old paraplegic male who developed penile abscess due to self-administration of intracavernous papaverine injections for erectile dysfunction treatment. Penile magnetic resonance imaging revealed an abscess of 5x4.5 cm in size, located at the right side of the penis and the penile corpus deviated to the left side. Penile exploration, incision and drainage were performed and the patient was treated successfully with intravenous antibiotics. A penile prosthesis was implanted 6 months after the initial surgery.
Keywords: Penile abcess, Intracavernosal injection, Erectile dysfunction

Öz

Penil apse ender görülen bir durumdur. Paraplejik ve erektil disfonksiyon nedeniyle intrakavernozal enjeksiyon kullanımına bağlı penil apse gelişen 45 yaşındaki erkek hasta anlatılmıştır. Penil manyetik rezonans görüntülemede penisin sağında olan ve penisi sola deviye eden 5x4,5 cm boyutlarında apse izlendi. Penil apse; eksplorasyon, insizyon, drenaj ve intravenöz antibiyotikler ile başarılı bir şekilde tedavi edildi. Operasyondan 6 ay sonra penil protez takıldı.
Anahtar Kelimeler: Penil apse, İntrakavernozal enjeksiyon, Erektil disfonksiyon

Introduction

Penile abscess is a rare clinical condition. Symptoms include swelling, pain and local increase in temperature. Among the causes of penile abscess, trauma, foreign body, perianal and perineal abscess drainage, extension of intraabdominal abscess, tuberculosis, priapism, and hematogenous dissemination of periodontal abscess may be listed. Penile abscess may also develop spontaneously (1,2). Diabetic patients are at greater risk for penile abscesses. *Staphylococcus aureus*, Streptococci, Bacteroides, and Enterococci are the most common microorganisms leading to formation of penile abscess.

Cavernosography, ultrasonography (US), magnetic resonance imaging (MRI) and computed tomography (CT) are useful diagnostic tools (3). Penile abscess can be successfully treated with incision and drainage combined with systemic antibiotics. Successful treatment with aspiration alone has also been described by some authors (1,3,4). We present a case of a paraplegic and parastetic patient who developed a penile abscess due to intracavernosal papaverine injections.

Case Presentation

A 45-year-old patient with spinal cord injury at T12 due to a car accident in 1998 is presented. He had lost both motor and sensory functions in the lower extremities. He was admitted with the complaint of penile swelling. His medical history revealed self-administration of intracavernous papaverine injections for the past 3 years due to erectile dysfunction (ED). At admission, his primary complaint was being unable to apply injections because of swelling. He noticed the swelling 2 months ago, but since he had no pain he did not seek any medical care. On physical examination, severe swelling was detected at the right side of the penis, shifting the corpus to the left side (Figure 1). A mass of 5 cm in size was palpated at the swollen area. In order to differentiate hematoma from abscess, penile MRI was performed. On the right side of the corpus cavernosum, beneath

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the tunica albuginea, there was an abscess measuring 50x45 mm in size. The abscess caused significant compression and edema in the corpus cavernosum and corpus spongiosum (Figure 1). After intravenous ciprofloxacin treatment was started, the patient was immediately taken into surgical intervention. A circular incision performed at the dorsum of the penis revealed the abscess and 20-25 mL of pus was drained (Figure 2). After pus specimen collection, the abscess region was irrigated with saline. A Minivac drain was inserted into the abscess area for drainage. *S. aureus* was isolated and the antibiotic treatment was continued. Following the removal of the drainage catheter, the patient was discharged at the 2nd postoperative day. Six months after the drainage of abscess, it was decided to implant a penile prosthesis in order to treat ED and to avoid further intracavernosal injections. A malleable penile prosthesis was preferred as there could be a risk of complications associated with abscess drainage surgery such as fibrosis and also it was the choice of the patient. Due to tissue fibrosis and adhesions, the process of malleable penile prosthesis implantation was more complicated and took longer than expected (Figure 2).

Written and signed informed consent was obtained from the patient.

Discussion

Penile abscess is a very rare clinical entity. It may occur either in the presence of predisposing factors or spontaneously (3,5). CT and US are good diagnostic tools (2). The management options for penile abscess consist of antibiotic therapy and either open surgical incision and drainage or radiologically guided needle aspiration.

Especially after the treatment of corpus cavernosum abscess, complications such as ED, penile deviation, and penile curvature could develop due to fibrosis and recurrence. Persistent cavernosal abscess may even lead to total penectomy and perineal urethrostomy (6). Penile abscess may be seen at any age. Up to the present, the youngest reported patient is a 24-day-old newborn who developed penile abscess after recurrent priapism (7).

Conditions causing immune suppression, especially diabetes mellitus, are among the most important predisposing factors. Besides these common underlying factors, rare causes such as intracavernous injection may also be listed. Bandi et al. (8) reported an unusual case of multiple retained needles in a 44-year-old man who presented with penile edema after

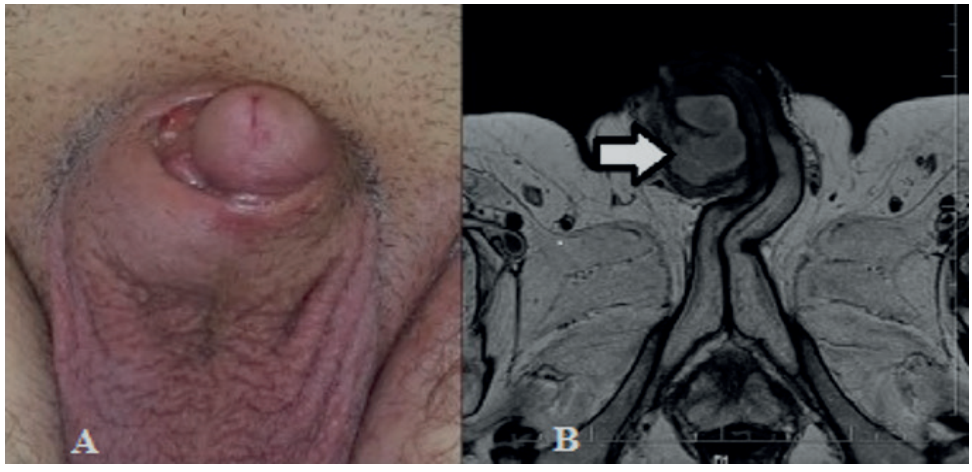


Figure 1. A) Penile abscess located at the right side of the penis, B) Penis is shifted to the left side and magnetic resonance image of the penile abscess

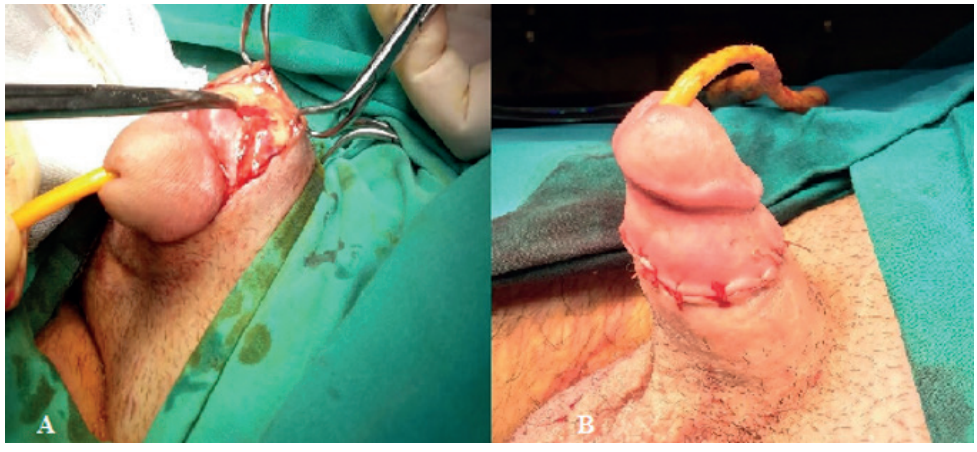


Figure 2. A) The insicion was performed at the dorsum of the penis for abscess drainage, B) Penile prosthesis implantation (6 months after the initial surgery)

intracavernous self-injection complicated by needle breakage. Tüzel (9) reported a case of a healthy bodybuilder with a corpus cavernosum abscess. In this case, development of the abscess is believed to be facilitated by long-term anabolic androgenic steroid abuse (9).

During the treatment of this rare condition, one could come across with rare complications. Jinga and Iconaru (10) reported a case of a 49-year-old male with penile abscess developed following intracavernous injection which was further complicated with urethrocutaneous fistula 12 weeks after the initial treatment. Kropman et al. (4) reported a successful treatment of a corpus cavernosum abscess with percutaneous aspiration and intravenous antibiotics in a paraplegic man on intracavernous papaverine injection therapy.

Penile abscess is a rare clinical entity. Surgical drainage is the most common mode of treatment but it has risks of ED and penile deviation. Drainage with US or CT guidance should also be considered when needed. Intracavernous self-injection for paraplegic or paraphasic patients with ED should be recommended with serious instructions including all details in order to avoid such complications.

Ethics

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.K., M.B.D., Ç.L.P., Concept: Y.K., M.B.D., Design: Y.K., M.B.D., Data Collection or Processing: Y.K., M.B.D., Analysis or Interpretation: Y.K., M.B.D., Literature Search: Y.K., M.B.D., Writing: Y.K., M.B.D., Ç.L.P.

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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Journal of Urological Surgery, 2018;5(4):217-220

Scrotal Tissue Necrosis in a Patient with Urethral Stricture Treated with Internal Urethrotomy and Mitomycin-C Injection

Üretra Darlığı Nedeniyle İnternal Üretrotomi ve Mitomisin-C Enjeksiyonu ile Tedavi Edilen Bir Hastada Gelişen Skrotal Doku Nekrozu

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Abstract

An 89-year-old male patient was admitted with open scrotal tissue wound. Approximately 4x4 cm scrotal necrotic tissue extending to the anal region was observed. It was learned that the patient underwent radical prostatectomy 9 years ago and then, internal urethrotomy was performed due to urethral stricture. Urethroscopy showed an anterior urethral stricture 2 cm in length. After internal urethrotomy, 20 mg of mitomycin-C (MMC) was diluted with 50 cc saline and injected as an intralesional injection (10 cc) and instillation (40 cc). In previous applications, our patients have tolerated this treatment during the process. In this case report, we present the case of scrotal tissue necrosis and treatment in a patient in whom internal urethrotomy and intralesional MMC application were performed.
Keywords: Collagen, Internal urethrotomy, Mitomycin-C, Necrosis, Urethral stricture

Öz

Seksen dokuz yaşında erkek hasta skrotal bölgede açık yara ile başvurdu. Skrotal bölgeden anal bölgeye doğru uzanan yaklaşık 4x4 cm'lik nekrotik doku izlendi. Dokuz yıl önce radikal prostatektomi olduğu ve sonra üretra darlığı nedeniyle internal üretrotomi olduğu öğrenildi. Üretroskopisinde 2 cm uzunluğunda anterior üretral darlık saptandı. İnternal üretrotomi sonrası, 20 mg mitomisin-C (MMC), 50 cc salinle dilüe edildi ve intralezyonel (10 cc) ve instilasyon (40 cc) tarzında uygulandı. Önceki uygulamalarda hastalar bu tedaviyi iyi tolere etmişlerdi. Bu olgu sunumunda, internal üretrotomi ve intralezyonel MMC uygulanan bir hastadaki skrotal doku nekrozunu ve tedavisini sunduk.
Anahtar Kelimeler: Kolajen, İnternal üretrotomi, Mitomisin-C, Nekroz, Üretra darlığı

Introduction

Urethral strictures are one of the most difficult urological problems in terms of treatment. Trauma and iatrogenic factors are more frequently observed in the etiology (1). Various treatment techniques have been developed for the treatment of urethral stricture, depending on the length of the stenosis, location and depth of scarring (2). According to the International Consultation on Urological Diseases and American Urological Association Guidelines, simple urethral dilatation, direct visual internal urethrotomy, laser urethrotomy, anterior urethral stenting or urethroplasty can be performed for bulbar urethral strictures of <2 cm (3,4). Urethral dilatation and cold knife urethrotomy are the safest therapy procedures for short urethral strictures, with a total success rate of 35-70% (3). The success rate for this treatment is very low when the size of the stenotic segment is longer than 2 cm (3). Urethral catheter can be safely removed within 24-72 hours following direct visual internal urethrotomy. Surgeons may offer self-catheterization schedules after direct visual internal urethrotomy for maintaining temporary urethral patency in candidates for urethoplasty (3). The success rate for resection and primary anastomosis of

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the stenotic segment is higher than for endoscopic treatment for bulbar urethral stricture (3). However, urethroplasty is a surgical procedure associated with high morbidity compared to endoscopic treatment. Urethroplasty should be performed for recurrent anterior urethral strictures following failed dilatation or endoscopic treatment (3). Surgeons should offer urethroplasty for a long (≥2 cm) bulbar urethral strictue. Urethral stenting may be performed in patients not suitable for urethroplasty (4). Injection of an antiproliferative agent injection, such as mitomycin-C (MMC), is a feasible method despite the conflicting data regarding the treatment of recurrent urethral stricture (3,4).

MMC is used in the treatment of superficial bladder cancer and it reduces tumor recurrence when administered intravesically after transurethral bladder resection (5). Recurrence of the stricture after internal urethrotomy is associated with poor prognosis in some patients. Therefore, MMC has been used as an instillation or intralesional injection during internal urethrotomy. It has been reported that submucosal injection of MMC during internal urethrotomy reduced stricture recurrence (6). In previous years, patients have endured adverse events associated with MMC administration.

In this case, we report a case of scrotal necrosis in a patient who was treated with MMC administration following cold knife urethrotomy for urethral stenosis.

Case Presentation

An 89-year-old male patient presented with tissue necrosis in the inferior hemiscrotum. It was seen that the lesion infiltrated into the subcutaneous tissue (Figure 1). The patient has been diagnosed with prostate cancer 9 years ago and open radical prostatectomy was performed. Internal urethrotomy and urethral dilatation had been performed several times within 1 year due to urethral stricture after radical prostatectomy.

In his urethroscopy, anterior urethral stricture 2 cm in length was determined. After internal urethrotomy, 20 mg of MMC was diluted with 50 cc isotonic solution and applied as an intralesional injection (10 cc) and instillation (40 cc). An 18-Fr Foley catheter was placed after the surgery. The catheter was removed on the postoperative 10th day and there was no problem during micturition. On the 15th postoperative day, epididymo-orchitis was detected and antibiotic treatment was planned.

On the postoperative first month, there was scrotal necrosis, but urethral stenosis was not detected in his urethroscopy. Debridement surgery was planned and the necrotic tissue was resected from the scrotal region. No necrotic tissue was observed in the testes and anal region. Postoperative hyperbaric oxygen treatment was considered but not applied because of claustrophobia. In postoperative 3rd month, there was no necrotic tissue in the scrotal area (Figure 2). The urethral stricture recurred about 1 year after the last operation and the perineal urethrostomy was performed and routine follow-up was planned.

Written informed consent was obtained from the patient.

Discussion

MMC is an alkylating drug preventing DNA synthesis and is known to be effective against gastrointestinal, lung, uterine, head-neck, and bladder cancers, and chronic leukemia. It is known that it reduces the risk of recurrence of bladder cancer. The most frequent adverse event is chemical cystitis after intravesical administration, which occurs in approximately 0-39% of patients (7). *In vitro* and animal model studies have shown that MMC decreases the collagen accumulation and scar formation by hindering fibroblast proliferation (8). MMC has been described as an anti-fibroblast effective agent and for this reason, MMC injection has emerged as a preferred treatment procedure for urethral strictures and bladder neck contractures (6,9,10,11).

In a study performed by Vanni et al. (9), favorable results were obtained with internal urethrotomy and intralesional MMC administration in recurrent bladder neck contractures. No complication was observed after MMC administration. Mazdak et al. (6) found that sub-mucosal injection of MMC resulted in a significant decrease in recurrence of stricture. They described MMC injection as a safe and easy method in the treatment of urethral stricture. Intralesional triamcinolone, MMC and hyaluronidase injections were performed with internal urethrotomy for the treatment of anterior urethral stricture in 2014 (10). Injection of these three agents increased the effectiveness of internal urethrotomy with no regional or systemic adverse events. Sourial et al. (12) performed MMC injection with urethral dilatation for the treatment of recurrent vesicourethral anastomotic stricture after radical prostatectomy and they did not notice any adverse effects. They found that MMC injection with urethral dilatation was a reliable, efficient, and minimally invasive treatment method. Redshaw et al. (13) reviewed data on 55 patients with bladder neck obstruction who underwent bladder neck resection with MMC injection. They reported that 7% of patients (n=4) experienced serious adverse effects, including osteitis pubis, necrosis of the trigone and genesis of rectourethral fistula. The exact mechanism of these adverse events associated with MMC injection was not understood. Moradi et al. (14) found that internal urethrotomy and application of MMC hydrogel might have an anti-fibrotic action preventing post-traumatic anterior urethral stricture recurrence with no adverse events. Kumar et al. (15) evaluated

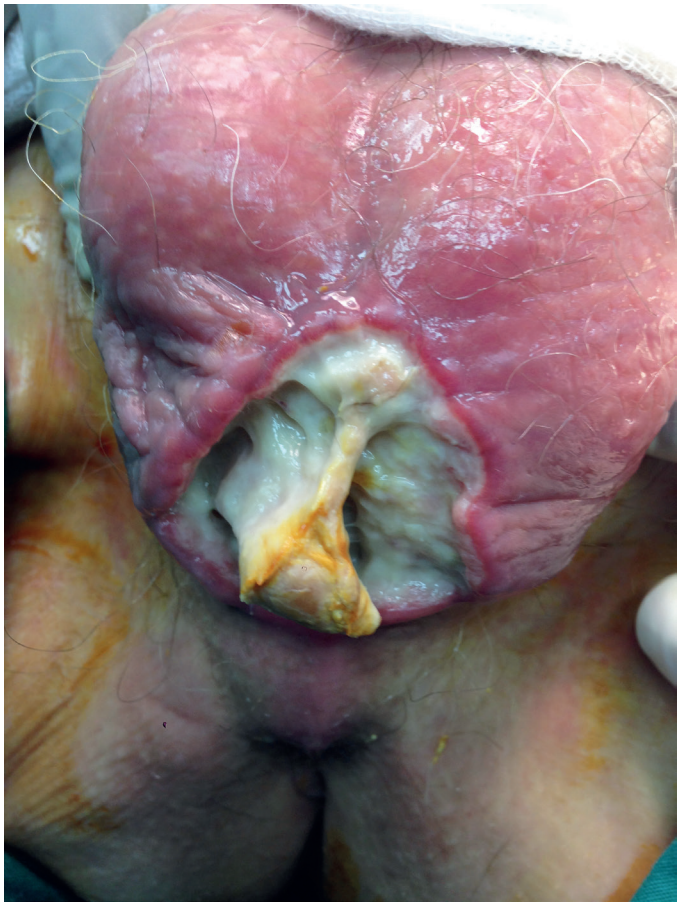


Figure 1. Approximately 4x4 cm scrotal necrotic tissue extending to the anal region was observed



Figure 2. In postoperative 3th month, there was no necrotic tissue in the scrotal area

the influence of holmium laser urethrotomy with intralesional administration of Santosh PGI tetra-inject (triamcinolone, MMC, hyaluronidase and N-acetyl cysteine) in 50 patients with urethral stricture. They reported a successful outcome in 41 patients (82%) (15). A total of 50 patients were cured with this method. No complications were observed after intralesional injection of Santosh PGI tetra-inject. Ali et al. (16) reported effectiveness of MMC in avoiding urethral stricture recurrence after internal urethrotomy without any major complications such as necrosis of the urothelium, extravasation, or systemic absorption.

The urethra is endoscopically incised in some operations such as internal urethrotomy. If the incision involves a deep or wide urethral segment, the integrity of the spongious body may be impaired and the irrigation fluid may leak into the tissues. Then the irrigation fluid passes through the tissues to the vascular area and can initiate an infective process in adjacent organs. In our case, MMC was applied as an intralesional injection and instillation after the urethral incision. After this procedure, the solution which contained MMC was probably spread into the tissues and initiated an infective process. The clinical situation was considered to be a late complication of urethral MMC administration.

Intralesional MMC injection has been described as an efficient and reliable treatment method with rare complications. However, although it has not been reported, our case gives an important message to the surgeons that MMC may cause tissue necrosis.

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

Doi: 10.4274/jus.1763
Journal of Urological Surgery, 2018;5(4):221-223

A Stranger in the Epididymis: Ectopic Spleen

Epididimde Bir Yabancı: Ektopik Dalak

Yelda Dere[1], İlker Akarken[2], Özgür İlhan Çelik[1], Hayrettin Şahin[2]

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Abstract

Splenogonadal fusion, which can be clinically confused with testicular neoplasms as they present with testicular swelling, is a rare abnormality in young adults. Intraoperative frozen section analysis can be helpful in diagnosing such cases and preventing unnecessary orchiectomies. We report a case in which frozen section analysis was done and testis-sparing surgery could be performed.
Keywords: Splenogonadal fusion, Ectopic spleen, Testis

Öz

Splenogonadal birleşme genç erişkinlerin testiste şişlik ile bulgu veren ve testis tümörleri ile klinik olarak karışabilen nadir bir anomalisidir. Operasyon esnasında patolojik olarak frozen kesit ile inceleme bu tip olguların gereksiz orşiektomiden korunması açısından yardımcı olabilir. Biz de operasyon esnasında frozen kesit ile incelenen ve bu sayede testis koruyucu cerrahi uygulanabilen bir olgumuzu sunduk.
Anahtar Kelimeler: Splenogonadal birleşme, Ektopik dalak, Testis

Introduction

Splenogonadal fusion (SGF), which is one of the rarest congenital abnormalities in the genital tract, is defined as the ectopic localization of the splenic tissue in/between the mesonephric tissues such as gonadal or perigonadal tissues. SGF is generally seen in men (1) as a scrotal mass or an incidental finding during other surgical procedures, such as hernia repair, but the real incidence remains a mystery (2).

SGF is classified into continuous and discontinuous types. In continuous type, the normal spleen is attached to the gonads, however, in the discontinuous type, ectopic splenic tissue is attached to the gonads showing no connection to the normal spleen.

Herein, we report a case of discontinuous type SGF presenting as a paratesticular mass in an 19-year-old patient.

Case Presentation

A 19-year-old patient with a history of crypthorchidism in the right testis presented with a palpable mass in the left scrotum. The patient stated that this mass was there since childhood. Ultrasonography showed a mass of 29x25 mm in the upper part of the left scrotum. Magnetic resonance imaging demonstrated an extra testicular, well defined solid mass measuring 25x28x45 mm in the upper part of the left scrotum.

Due to the presence of the medical history of cryptorchidism, testis-sparing surgery with intraperative frozen section analysis was planned. A small, well defined and semi solid mass was excised from the proximal part of the epididymis and sent to our pathology laboratory for frozen section analysis (Figures 1a, b). In macroscopic examination, the mass was measured as 4x2.5x2 cm, had a ruptured capsule and a brown cut surface. In the microscopic frozen section of the mass, we observed slit-like spaces with lymphoid cell aggregates dispersed in the parenchyma and reported as benign and the operation ended with no orchiopexy (Figures 2 and 3). In the paraffin-embedded (permanent) sections of the mass, the slit-like spaces were thought to be the glandular parts of an adenomatoid tumor or vascular structures and they stained negative for calretinin and CK7 and positive for CD34. When dispersed lymphoid aggregates

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were taken into account, the vascular structures were decided to be the sinusoids and the lymphoid aggregates were thought to be the white pulp of an ectopic spleen. Considering these findings, the final diagnosis of ectopic splenic tissue was established. The patient got no additional medication and was well after 3 months of follow-up.

Written informed consent was taken from the patient before the operation.

Discussion

SGF is a rare entity presenting as a swelling that can be seen in both females and males, however, more common in men and generally in the left testis (3).

Although many other congenital abnormalities, such as cardiac malformations, micrognathia, and spina bifida, have been reported in the literature, the most common abnormality is cryptorchidism. Duncan and Barraza (4) reported a case of SGF associated with bilateral cryptorchidism and hypospadias.

Testicular swelling is the most common symptom, however, incidental diagnoses have also been reported in addition to three cases of SGF associated with testicular tumors (3,5).

As many imaging studies can be performed for diagnosing these cases before surgery, 37% of cases need orchiectomy because of unpredictable diagnosis of testicular neoplasms (3). Intraoperatively, frozen section analysis can also be helpful in avoiding unnecessary orchiectomy (6).

In addition, in cases where the lesion is located around the testis and testis-sparing surgery is planned, frozen section analysis is very helpful as seen in our case.

In conclusion, SGF should be kept in mind especially in young adults with long-term testicular swelling and frozen section analysis can be used to prevent unnecessary orchiectomies.

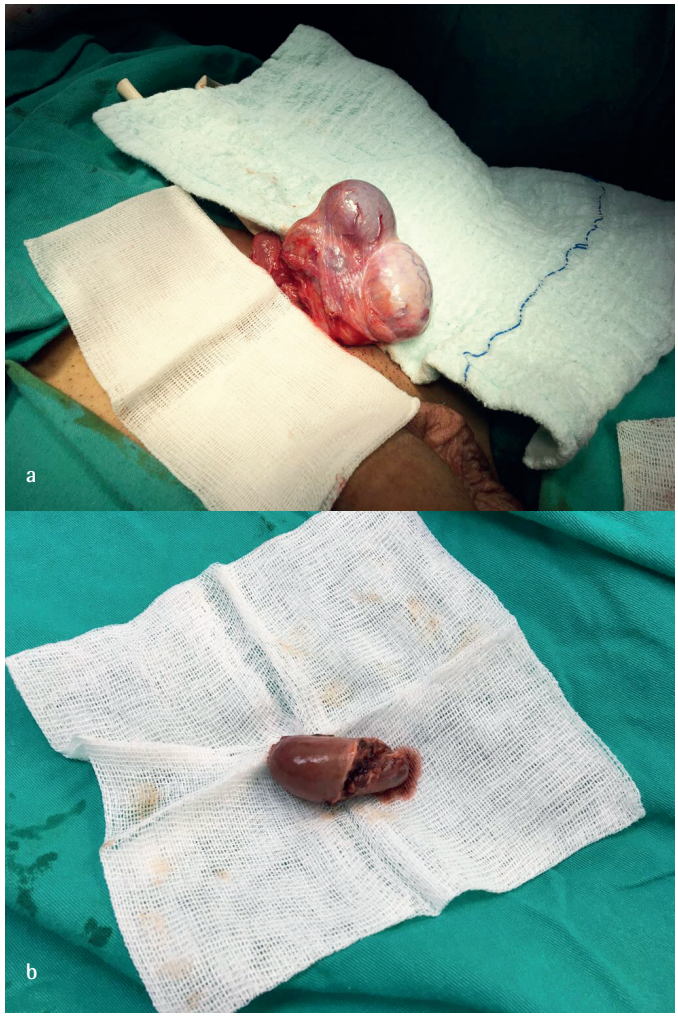


Figure 1. Macroscopic appearance of the mass in the operation (a) and after the excision (b)

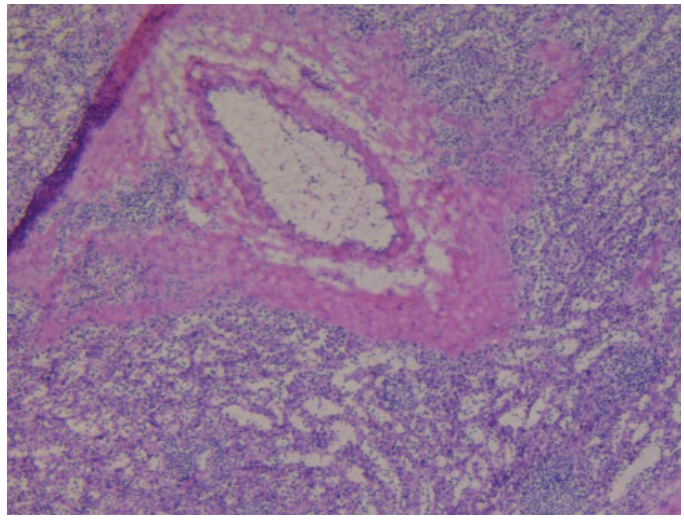


Figure 2. Frozen section of the mass showing slit like spaces and lymphoid aggregates (hematoxylin and eosin, 40x)

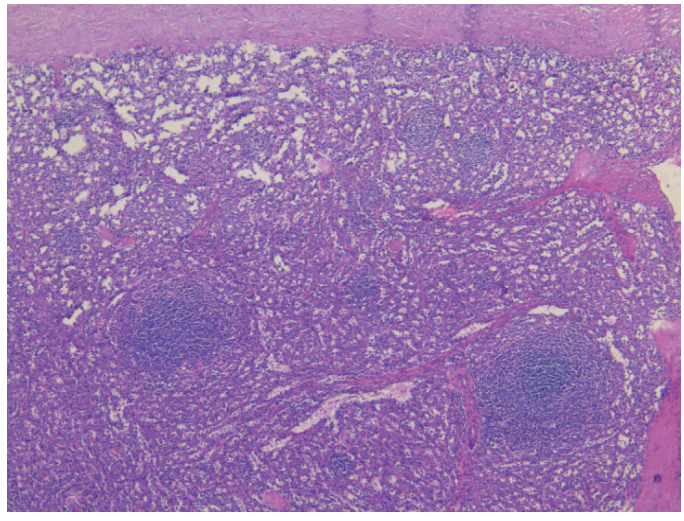


Figure 3. Permanent parafine sections revealing the sinuzoids and the white pulp (hematoxylin and eosin, 40x)

Acknowledgments

Special thanks to Prof. Dr. Kutsal Yörükoğlu for his contribution in this case.

Ethics

Informed Consent: It was taken from the patient before the operation.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.D., İ.A., Ö.İ.Ç., Concept: Y.D., Ö.İ.Ç., Design: Y.D., İ.A., H.Ş., Data Collection or Processing: İ.A., Analysis or Interpretation: Y.D., İ.A., Literature Search: Ö.İ.Ç., H.Ş., Writing: Y.D., İ.A.

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
Radiology

Doi: 10.4274/jus.1976
Journal of Urological Surgery, 2018;5(4):224-226

A Rare Mimicker of an Adrenal Carcinoma: Co-occurrence of Hemorrhagic Pseudocyst and Myelolipoma

Adrenal Karsinomun Nadir Bir Taklitçisi: Hemorajik Psödokist ve Miyelolipomun Birlikte Oluşumu

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Abstract

Adrenal collision tumors are rare tumors composed of two different benign or malignant tumors in the adrenal gland. Radiological features are very helpful in the diagnosis, however it is not always possible to make a definite diagnosis with imaging findings alone because the coexisting masses contain different tissue components. In this paper, we report the imaging findings of an adrenal lesion with pseudocyst and myelolipoma mimicking an adrenocortical carcinoma in a 42-year-old female patient. To the best of our knowledge, this is the first reported case of an adrenal lesion containing myelolipoma and hemorrhagic pseudocyst mimicking an adrenal carcinoma in the literature.
Keywords: Adrenal lesions, Adrenal pseudocyst, Myelolipoma, Computed tomography, Magnetic resonance imaging

Öz

Adrenal kollizyon tümörleri, adrenal bezde iki farklı benign veya malign tümörden oluşan nadir tümörlerdir. Radyolojik özellikler tanıda çok yardımcıdır, ancak farklı doku bileşenleri içerdiği için tek başına görüntüleme bulguları ile kesin bir tanı koymak her zaman mümkün değildir. Bu sunumda; 42 yaşında bir kadın hastada adrenokortikal karsinomu taklit eden psödokist ve miyelolipom içeren bir adrenal lezyonun görüntüleme bulgularını sunuyoruz. Bildiğimiz kadarıyla, literatürde ilk kez adrenal karsinomu taklit eden miyelolipom ve hemorajik psödokist içeren adrenal lezyon bildirilmiştir.
Anahtar Kelimeler: Adrenal lezyonlar, Adrenal psödokist, Miyelolipom, Bilgisayarlı tomografi, Manyetik rezonans görüntüleme

Introduction

Adrenal collision tumor is the simultaneous co-occurrence of two different benign or malignant tumors in the adrenal gland (1). It is often unilateral, asymptomatic and incidentally detected. It can cause symptoms related to compression to surrounding tissues when it enlarges. It may contain two different primary tumors or one primary tumor and a metastasis. Both tumors may be malignant, one may be malignant and the other may be benign, or both may be benign (2). Radiological findings are very helpful in the diagnosis. However, it is not always possible to make a definite diagnosis with imaging findings alone, because the coexisting masses contain different tissue components. In this paper, we report imaging findings of an adrenal tumor containing a pseudocyst and a myelolipoma which was confused with adrenocortical carcinoma.

Case Presentation

A 42-year-old female patient was admitted to the urology clinic at our hospital with the complaints of pain radiating from the left upper quadrant and epigastric region to the back. Physical examination revealed a palpable mass in the left lumbar

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Received: 09.03.2018 **Accepted:** 01.05.2018

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area. Complete blood count, hepatic and renal function tests, electrolytes, and urinalysis were all within the normal limits. Intravenous contrast-enhanced computed tomography (CT) scan was subsequently performed. CT revealed a well circumscribed, internally heterogeneous, progressively enhancing, 140x123 mm mass in the left adrenal gland with areas of fat attenuation and calcifications (Figure 1). The adrenal gland was indistinguishable from the tumor. Malignant adrenal masses, primary adrenocortical carcinoma, retroperitoneal teratomas and mesenchymal tumors were considered in the differential diagnosis. Twenty-four-hour urine vanillylmandelic acid, homovanillic acid and 5-hydroxyindoleacetic acid values were within the normal limits, ruling out pheochromocytoma. Blood adrenaline, noradrenaline, metanephrine, normetanephrine and adrenocorticotropic hormone levels were also normal. Magnetic resonance imaging (MRI) was performed to evaluate the internal structure of the tumor better and to make a differential diagnosis.

MRI showed a well circumscribed, heterogeneously enhancing 170x130x121 mm sized mass containing hemorrhagic foci and focal fat tissues (Figure 2). All imaging findings were suggestive of adrenal malignant tumors, primarily adrenocortical carcinoma, secondarily teratomas or mesenchymal tumors. With these findings, the patient underwent surgery and left adrenalectomy was performed. Pathologically, the material was reported to be composed entirely of large necrosis and bleeding areas with focal calcifications and multiloculated cysts without epithelium. In addition, a focus compatible with myelolipoma was observed in a limited area, and the diagnosis was interpreted as an adrenal hemorrhagic pseudocyst and concomitant myelolipoma. No malignant component was found.

All of the procedures described in this report were standard of care and the patient provided informed consent for the standard of care procedures according to hospital policy. No informed consent for this report was needed as this was not a research study.

Discussion

The pathogenesis of adrenal collision tumors is still controversial, because the limited number of cases in the literature prevents detailed analysis of the etiology. Two separate theories have been proposed to explain the pathogenesis (3,4). The first and simplest explanation is the simultaneous formation of two distinct primary tumor centers only by chance. The secondary hypothesis is that a carcinogenic stimulus permits two different tumors to form adjacent to each other by altering a specific region in the adrenal gland, or the first tumor provides a fertile ground allowing the secondary tumor to form, by affecting the local environment.

Adrenal collision tumors are most commonly composed of adenomas and metastatic components (5). This can be explained by the high incidence of adenomas and the high tendency of adrenal glands to metastases (6). More rarely, adenoma-pheochromocytoma, adenoma-hemangioma, adrenocortical carcinoma-metastasis, adrenocortical carcinoma-myelolipoma, carcinosarcoma-metastasis, and myelolipoma-Hodgkin's lymphoma have been reported in the literature. Collision tumors with cystic lesion component are rare and there is limited number of reported cases (2). According to our knowledge of the current literature, there has been no report of an adrenal lesion



Figure 1. Axial contrast-enhanced computed tomography image of the abdomen shows a large mass in the left upper quadrant which contains calcifications and fat-attenuated areas (curved arrows)

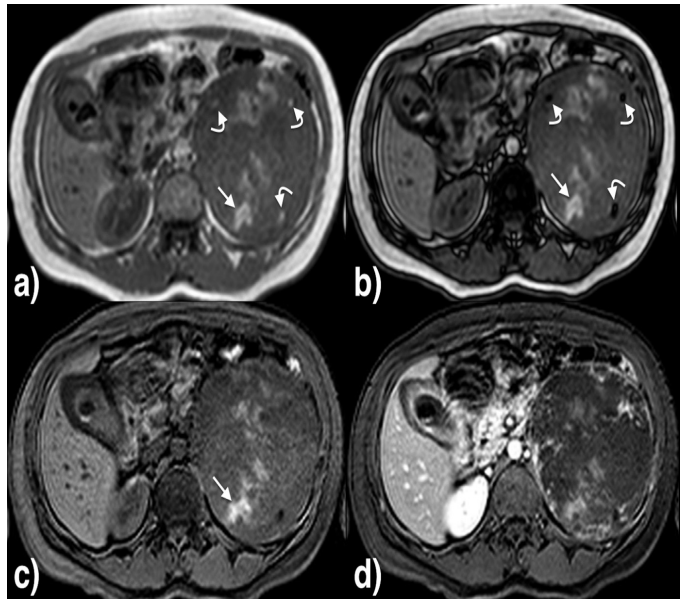


Figure 2. a) Axial T1-weighted in-phase, b) T1-weighted out-phase, c) non-contrast enhanced fat suppressed T1-weighted and d) contrast enhanced fat suppressed T1-weighted images of the mass are shown. The mass contains fat tissue which is demonstrated as signal dropped areas on T1-weighted out-phase and fat suppressed T1-weighted images (curved arrows). There is also significant amount of hemorrhage (arrows)

consisting of the combination of pseudocyst and myelolipoma as in our case. Like collision tumors, both neoplastic and non-neoplastic lesions can be seen together in adrenal lesions. This co-occurrence makes a definite diagnosis challenging as in our case.

Adrenal pseudocysts are rare, asymptomatic and mostly benign cysts. They are often seen after trauma or with a history of previous pancreatitis. Symptomatic cases may present with gastrointestinal symptoms, flank pain, and palpable mass depending on the lesion size (7,8). In the literature, the estimated risk of a pseudocyst being malignant has been reported to be 7%. The risk of malignancy increases with size especially for masses larger than 6 cm (9,10,11). Especially when hemorrhage occurs within the pseudocyst, the cyst enlarges and it can be confused with malignant lesions. In our case, due to bleeding into the pseudocyst, MRI findings were suggestive of an adrenocortical carcinoma. However, the presence of fat is not a common finding in adrenocortical carcinomas (12). Therefore, retroperitoneal teratomas or fat-containing mesenchymal tumors were considered in the differential diagnosis.

Pheochromocytoma should also be considered in differential diagnosis of adrenal masses. Radiologically, pheochromocytomas are unilateral, solitary, oval or round, well-circumscribed, heterogeneous cystic masses usually larger than 3 cm in diameter. On CT, they demonstrate vivid arterial enhancement and wash-out on delayed phase. On MRI, they are usually hypointense on T1-weighted images, markedly hyperintense on T2-weighted images and enhance heterogeneously after the administration of intravenous contrast agent. There is no signal loss on T1-out phase images since they do not usually contain intracellular fat (13). However, regardless of the lesion size, degeneration, necrosis, cystic changes and rarely microscopic or macroscopic fat can be seen (14,15,16). In these situations, it may be confused with adrenocortical carcinoma and metastasis. Pheochromocytoma was not considered in our case as clinical and laboratory findings ruled out pheochromocytoma and there was no wash-out on dynamic imaging.

In conclusion, pseudocyst with accompanying myelolipoma is very rare among adrenal tumors. The radiological findings of different histological components of hemorrhagic pseudocyst and myelolipoma make it difficult to distinguish from adrenocortical carcinomas and other retroperitoneal tumors occupying adrenal region.

Ethics

Informed Consent: All of the procedures described in this report were standard of care and the patient provided informed consent for the standard of care procedures according to hospital policy. No informed consent for this report was needed as this was not a research study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.K., S.A., İ.Ç., M.S.N., M.D., M.Ö., M.K., Concept: C.K., S.A., İ.Ç., M.S.N., M.D., M.Ö., M.K., Design: C.K., S.A., İ.Ç., M.S.N., M.D., M.Ö., M.K., Data Collection or Processing: C.K., S.A., İ.Ç., M.S.N., M.D., M.Ö., M.K., Analysis or Interpretation: C.K., S.A., İ.Ç., M.S.N., M.D., M.Ö., M.K., Literature Search: C.K., S.A., İ.Ç., M.S.N., M.D., M.Ö., M.K., Writing: C.K., S.A., İ.Ç., M.S.N., M.D., M.Ö., M.K.

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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Transplant Survey

Doi: 10.4274/jus.2018.05.023

Re: The Impact of Donor Body Mass Index on Outcomes After Deceased Kidney Transplantation-a National Population-Cohort Study

Arshad A[1], Hodson J[2], Chappelow I[1], Inston NG[3], Ready AR[3], Nath J[1,3], Sharif A[1,3]

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Transpl Int. 2018;31:1099-1109. doi: 10.1111/tri.13263. Epub 2018 May 9.

EDITORIAL COMMENT

The negative relationship between organ supply and demand has caused an increase in the acceptance of previously declined organs for transplantation including kidneys from obese donors. There are no clear guideline recommendations regarding acceptable body mass index (BMI) limits for kidney transplantation. As a result, there is wide variability in practice and heterogeneous acceptance criteria for deceased donor BMI across transplantation centers. In this population cohort study, the authors have evaluated the impact of donor BMI on a range of deceased donor kidney transplant outcomes by using UK Transplant Registry for all deceased donor kidney transplant recipients (n=17590) between January 2003 and January 2015. Donor BMI was found to be an independent risk factor for delayed graft function in recipients of kidneys from overweight [odds ratio (OR): 1.12, 95% confidence interval (CI): 1.00-1.23, p=0.022), obese (OR: 1.23, 95% CI: 1.08-1.39, p<0.001) and morbidly obese (OR: 1.38, 95% CI: 1.16-1.63, p<0.001) donors, when compared to normal donor BMI group. However, donor BMI did not appear to influence long-term graft survival or patient survival. Furthermore, donor BMI does not appear to be associated with a deleterious increase in either warm ischaemia time or functional warm ischaemia time. In the light of this information, in the context of increasing BMI in the deceased donor pool, acceptance of those kidneys from higher BMI donors should not be avoided.

Yarkın Kamil Yakupoğlu, MD

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Transplant Survey

Doi: 10.4274/jus.2018.05.024

Re: Safety of Dual Kidney Transplantation Compared to Single Kidney Transplantation from Expanded Criteria Donors: A Single Center Cohort Study of 39 Recipients

Mendel L[1], Albano L[2], Bentellis I[1], Yandza T[1], Bernardi C[3], Quintens H[1], Tibi B[1], Jourdan J[1], Durand M[1], Amiel J[1], Chevallier D[1]

[1]University Hospital of Nice, Department of Urology, Nice, France

[2]University Hospital of Nice, Department of Nephrology, Nice, France

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Transpl Int. 2018;31:1110-1124. doi: 10.1111/tri.13280. Epub 2018 Jun 5.

EDITORIAL COMMENT

Dual kidney transplantation (DKT) has been developed in order to compensate for nephron mass reduction and to use kidneys from very marginal donors that would have been discarded for single kidney transplantation (SKT). DKT is transplanting two kidneys from the same donor to a single recipient ipsilaterally or bilaterally. In this single center retrospective study, the authors compared the outcomes of DKT (n=39) with that of SKT (n=155) performed with grafts from expanded-criteria donors over an 8-year period and followed for a median of 36 and 26.5 months respectively, in recipients ≥65 years of age, focusing on surgical outcomes. Although the authors observed a higher venous thrombosis rate in the DKT group (12.8% vs 3.2%) (p=0.02), similar graft survivals and better glomerular filtration rate over 24 months posttransplant were observed in DKT group (45.0±16.3 vs 39.8±13.8 mL/min/1.73m^2; p=0.04). DKT seems to remain a promising strategy to address the growing graft shortage in elderly patients with shorter waiting time on the waiting list, however, these data need to be confirmed by larger randomized controlled studies.

Yarkın Kamil Yakupoğlu, MD

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Andrology

Doi: 10.4274/jus.2018.05.025

Re: Prevalence and Risk Factors of Infertility in Turkey: Evidence from Demographic and Health Surveys, 1993-2013

Sarac M, Koc I

Hacettepe University, Institute of Population Studies, Ankara, Turkiye

J Biosoc Sci. 2018;50:472-490. doi: 10.1017/S0021932017000244. Epub 2017 Jun 23.

EDITORIAL COMMENT

In recent years, in Turkish media and general population, infertility has gained increasing interest and, mostly, it is believed that the prevalence is increasing. In this study, the authors aimed to understand the changes in the prevalence of infertility in the last 20 years. They used the data of Demographic and Health Surveys (DHS) performed between 1993 and 2013. Three different approaches were used for this purpose: the DHS approach estimating infertility prevalence among women who have been married for at least 5 years; the constructed approach estimating infertility within the 12 months before the survey date; and the current duration approach focusing on the time from when a couple starts to attempt pregnancy until it occurs. Surprisingly, this study showed that the infertility rate in Turkey has declined from 15% in 1993 to 8.1% in 2013. However, the percentage of women who have used assisted reproductive technology (ART) at least once increased from 1.9% in 2008 to 4.2% in 2013. The authors believed that increasing number of ARTs in recent years was the result of incentives provided by the Turkish government for the treatment of infertility and a decline in taboos about infertility and its treatment.

Emre Bakırcıoğlu, MD

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Andrology

Doi: 10.4274/jus.2018.05.026

Re: Evaluation of the Azoospermic Male: A Committee Opinion

Practice Committee of the American Society for Reproductive Medicine in Collaboration with the Society for Male Reproduction and Urology:

Hwang K, Smith JF, Coward RM, Penzias A, Bendikson K, Butts S, Coutifaris C, Falcone T, Fossum G, Gitlin S, Gracia C, Hansen K, Jindal S, La Barbera A, Mersereau J, Odem R, Paulson R, Pfeifer S, Pisarska M, Rebar R, Reindollar R, Rosen M, Sandlow J, Stovall D, Vernon M

American Society for Reproductive Medicine, Birmingham, Alabama

Fertil Steril. 2018;109:777-782. doi: 10.1016/j.fertnstert.2018.01.043.

EDITORIAL COMMENT

Azoospermia, affecting approximately 1% of all men, is a definition for no sperm in the centrifuged pellet of two separate semen samples. Approximately 10-15% of all infertile men receive the diagnosis of azoospermia. In this document, the Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society for Male Reproduction and Urology published a very useful updated guideline for physicians who are mostly dealing with azoospermic men. The committee emphasized the importance of genetic evaluation in nonobstructive azoospermic patients and in those having no vas deferens. To my opinion, urologists working close to in vitro fertilization clinics should have more information regarding evaluation and genetic tests in azoospermic men and this document will be helpful for them.

Emre Bakırcıoğlu, MD

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Basic Research

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Re: Activated Omentum Slows Progression of CKD

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EDITORIAL COMMENT

Perinephric fatty tissue has been commonly used for the purpose of stopping bleeding especially during partial nephrectomy or nephrorrhaphy. In this study the authors reported that the omentum could be used also for preserving the remnant kidney and preserving its function. Especially the omentum contains a large amount of stem cells. Stem cells show promise in the treatment of acute kidney injuries but do not survive for more than a few days after injection. The authors aimed to examine whether fusing the omentum to a subtotally nephrectomized kidney could slow the progression of chronic kidney disease. They used two groups of rats: an experimental group undergoing 5/6 nephrectomy only and a control group undergoing 5/6 nephrectomy and complete omentectomy. After 12 weeks, they examined both groups via biochemical and histological analyses and it was observed that experimental rats had lower plasma creatinine levels; less glomerulosclerosis, tubulointerstitial injury and extracellular matrix, and reduced thickening of basement membranes compared with controls. A fusion zone formed between the injured kidney and the omentum contained abundant stem cells expressing stem cell antigen-1, Wilms' tumor-1, and CD34. Kidney extracts from experimental rats showed increases in expression levels of growth factors involved in renal repair. These results suggest that contact between the omentum and injured kidney slows the progression of chronic kidney disease in the remnant organ. These results should be remembered during the repair of injured kidney or partial nephrectomy.

Fehmi Narter, MD, PhD

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Basic Research

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Re: Biomarkers in Active Surveillance

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EDITORIAL COMMENT

Prostate cancer (PCa) is a common health problem and the majority of PCa's are accepted as an innocent cancer. Active surveillance (AS) is an approach for management of low-risk PCa. However, there remain challenges in patient selection and monitoring protocols for AS. Actual methods for AS are highly invasive, expensive or inadequate. For these reasons, there is substantial interest in identifying markers. In this review, the authors summarized the evidence on serum, urine and tissue markers in AS. Serum markers include prostate specific-antigen (PSA) kinetics during AS as PSA doubling time, PSA velocity, PSA density or the percent free PSA. Two new PSA-based blood tests incorporating free PSA are the Prostate Health Index and 4K score. Several urinary markers, such as PCa antigen 3 and the *TMPRSS2: ERG* gene fusion or DNA methylation patterns of urinary sediment, have also been explored for use in PCa detection and management. In addition to these methods, multiple tissue-based markers are available including the Oncotype DX Genomic Prostate Score, Prolaris Cell Cycle Progression Score, GenomeDx Decipher Score, etc. and immunohistochemical staining for inactivation of the *PTEN* gene. Very few markers have long-term results available for patients during AS. In addition to the actual AS protocols as PSA, digital rectal examination, rebiopsy or mp-magnetic resonance imaging, there is not yet well described unique protocol for patients under AS. In the near future, we believe that more accurate protocols will be suggested for patients under AS.

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Adenocarcinoma of the Urinary Bladder

Mesane Adenokarsinomu

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Introduction

Primary adenocarcinoma of the bladder is malignant tumor with histologically pure glandular differentiation. It accounts for 0.5-2% of all primary bladder malignancies. This tumor is more common in men than in women. Patients are usually in the sixth-seventh decade of life. The tumor is very aggressive and metastatic disease is reported in 40% of patients at the time of diagnosis. Although the pathogenesis is uncertain, several risk factors have been described. Since it is often seen in mucosa adjacent to primary adenocarcinoma of the urinary bladder, intestinal metaplasia is thought to be precursor lesion. However, recent studies have shown that intestinal metaplasia was not associated with an increased risk for adenocarcinoma (1).

Bladder adenocarcinoma may be primary or secondary; secondary adenocarcinomas are more common than primary adenocarcinomas in the bladder. The most common origin of the secondary bladder adenocarcinoma is the colon, prostate, endometrium, cervix, breast and lung. Secondary involvement of the bladder occurs either by direct extension or by metastasis from a distant site (2).

The diagnosis of primary adenocarcinoma of the bladder should only be made when carcinoma shows pure glandular differentiation (3). Morphologically, adenocarcinoma of the bladder can be divided into intestinal (enteric) type and non-intestinal (non-enteric) type. Primary bladder adenocarcinoma exhibits several different growth patterns, including enteric, mucinous, signet-ring cell, not otherwise specified, and mixed patterns (4). The enteric (intestinal) type of adenocarcinoma consists of tall columnar tumor cells with abundant eosinophilic cytoplasm containing necrosis (Figure 1).

Mucinous adenocarcinoma of the bladder is a specific subtype and characterized by large lakes of extracellular mucin containing tumor cells (Figure 2). These mucinous foci should constitute at least half of the tumor mass for diagnosis. The prognosis varies with stage and, survival is better in tumors confined to the urinary bladder. However, low stage tumors are less frequent than 30% of all tumors (5).

Signet ring cell adenocarcinoma is another rare morphological subtype of primary adenocarcinoma of the bladder. For establishing diagnosis, there should be at least focal signet ring cell differentiation with an adenocarcinoma without evidence of urothelial carcinoma. The signet ring cells within the tumor are characterized by plasmocytoid or monocytoid appearance or have the classic signet ring cell morphology (Figure 3). Pure signet ring cell adenocarcinoma is extremely rare and the prognosis is very poor (6,7).

The most important and difficult problem is to differentiate these tumors from metastatic adenocarcinoma from other organs such as colon, lung, prostate, breast and uterus. The most common secondary tumor to involve the urinary bladder is colon adenocarcinoma. Morphologically, it is similar to enteric type bladder adenocarcinoma. For this reason, for correct diagnosis, it is very important that pathologists obtain adequate clinical information. Immunohistochemical methods may help distinguish between these two tumors in some cases.

The immunohistochemical staining pattern of primary adenocarcinoma of the bladder is variable and usually similar to that of colon adenocarcinoma. Immunohistochemistry has limited utility in differentiating primary bladder adenocarcinoma from metastatic colon adenocarcinoma (8,9,10). Expression of cytokeratin 7 is variable and cytokeratin 20 is mostly stained with adenocarcinoma of the bladder. The CDX2 nuclear

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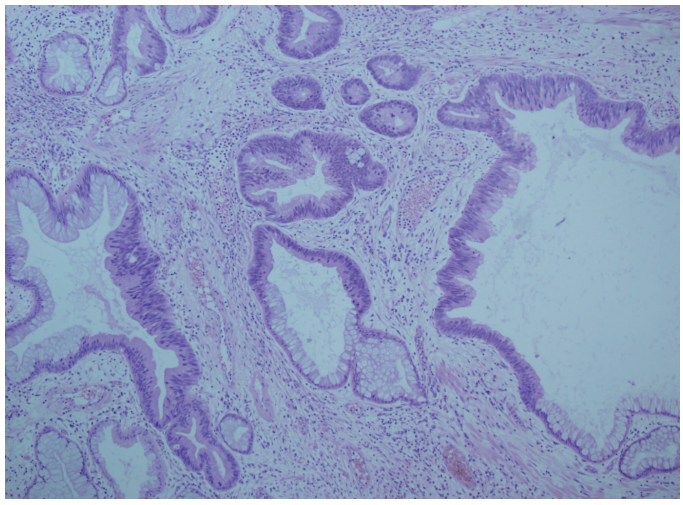


Figure 1. Enteric type primary adenocarcinoma of the bladder, which is often indistinguishable from colorectal adenocarcinoma (hematoxylin and eosin, original magnifications, 200x)

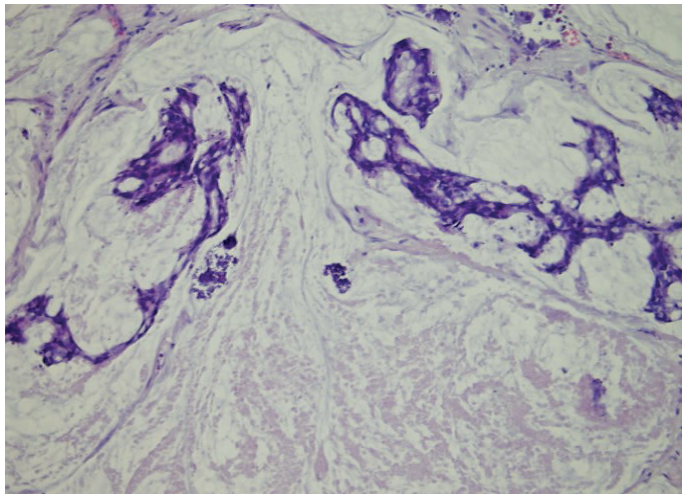


Figure 2. Mucinous-type bladder adenocarcinoma produces abundant extracellular mucin, pool of mucin with floating tumor cells (hematoxylin and eosin, original magnifications, 200x)

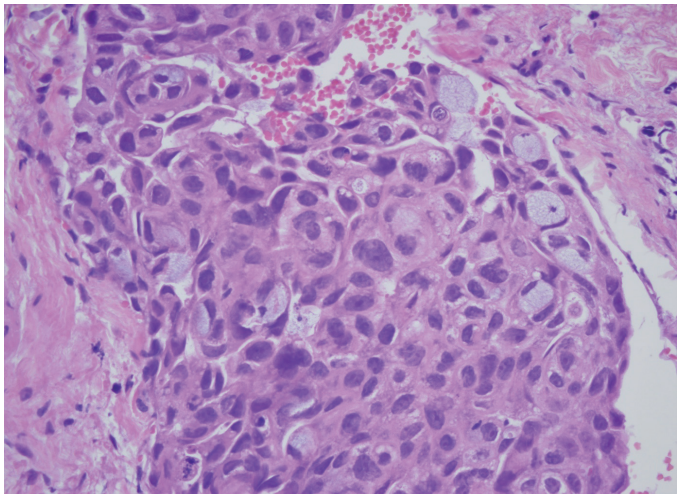


Figure 3. Signet ring cell-type bladder adenocarcinoma (hematoxylin and eosin, original magnifications, 200x)

transcription factor, which is an intestinal marker, may also be misleading because it also stains bladder adenocarcinomas. Nuclear ß-catenin staining is typical of colorectal carcinomas (81%), whereas primary bladder adenocarcinoma shows limited cytoplasmic staining.

Clear cell adenocarcinoma (CCA) is a very unique variant that forms 0.5-2% of all bladder carcinomas (11). The term CCA should be reserved for tumors resembling CCA of the female genital tract (12). Unlike other bladder adenocarcinomas, CCA affects women more than men. CCA is common in female urethra, but it can also be seen in men and in the urinary bladder. Hematuria and dysuria are the most common clinical findings. CCA may be associated with endometriosis or müllerianosis (11,13). It can also be seen within a urinary bladder diverticulum. CCA consists of cells with abundant clear cytoplasm containing glycogen in the form of tubules, cysts, papillary structures or diffuse sheets (Figure 4). The tumor cells lining tubules or cysts may be cuboidal, hobnail or flattened (Figure 5). It usually shows

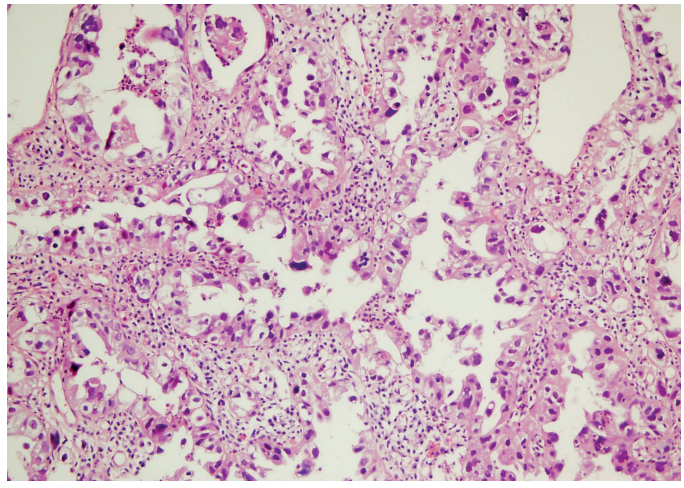


Figure 4. Clear cell adenocarcinoma exhibits tubulocystic and papillary growth patterns (hematoxylin and eosin, original magnifications, 200x)

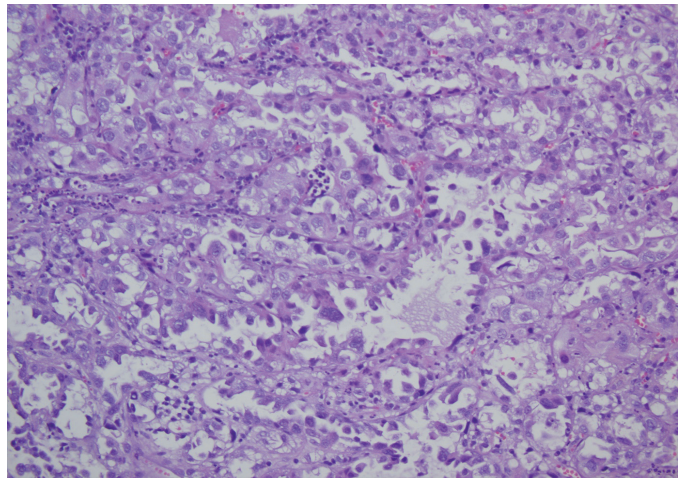


Figure 5. Hobnail or cuboidal tumor cells in clear cell adenocarcinoma (hematoxylin and eosin, original magnifications, 200x)

strong immunostaining for PAX8 (Figure 6). The differential diagnosis of CCA includes benign reactive processes, primary malign tumors and metastatic tumors of the bladder (14). The benign process which is the most common problem especially in biopsies is the nephrogenic adenoma. Nephrogenic adenoma, unlike bladder CCA, is more common in males and is usually small sized lesion.

CCA can also develop in other organs such as the prostate, lung, breast, uterus, ovary and vagina. Before establishing the diagnosis, metastatic melanoma, clear cell sarcoma and seminoma should be excluded. To exclude these possibilities, negative staining of tumor cells with S100, human melanoma black-45, CD117 and placental alkaline phosphatase and positive staining with cytokeratin 7 will support carcinoma diagnosis. Cancer antigen-125 expression is insufficient to show müllerian origin. As a result, bladder CCA has a different morphology, resembling clear cell carcinoma of müllarian origin (15).

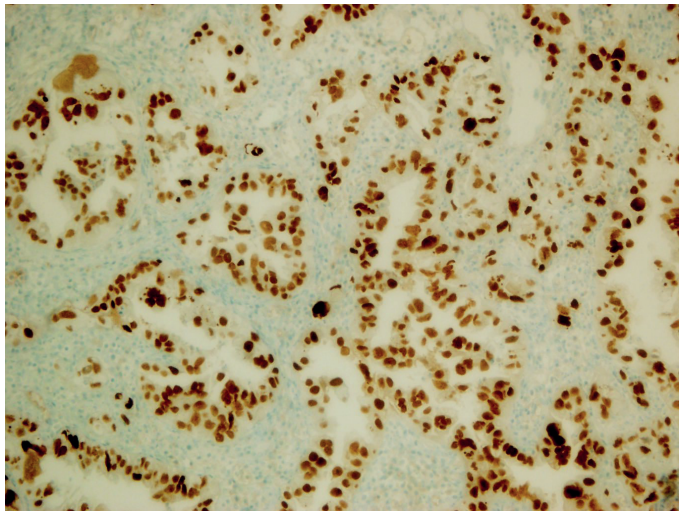


Figure 6. The carcinoma cells show nuclear immunreactivity with PAX8 (immunohistochemistry, original magnifications, 200x)

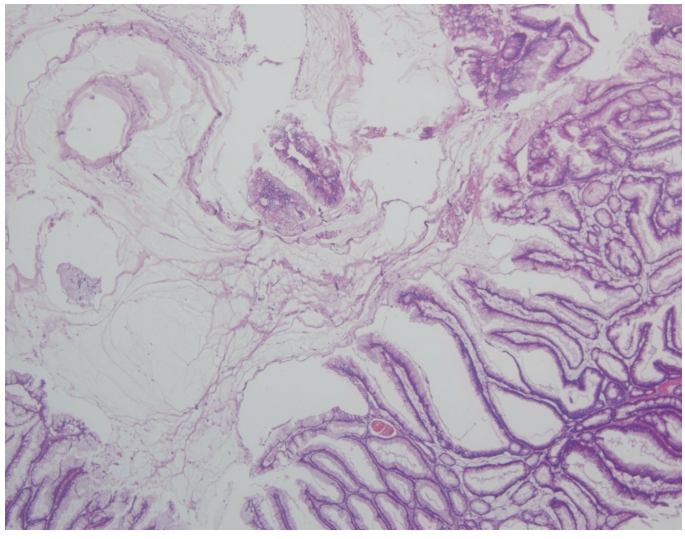


Figure 7. Urachal adenocarcinoma which is indistinguishable from non-urachal carcinoma (hematoxylin and eosin, original magnifications, 200x)

Urachal adenocarcinoma; primary adenocarcinoma of the bladder accounts for less than 1% of all bladder malignancies, of these 20-39% are of urachal origin (16,17). Urachal adenocarcinoma is a special tumor developing within the urachal remnants of the bladder dome. Bladder involvement is often a secondary occurrence. Urachal remnant is the residual tissues of the embryonic allantoic sac associated with umbilicus. Urachal adenocarcinoma is more common in men and tends to occur in the fifth and sixth decades of life. Common symptoms are hematuria, pain, symptoms of irritative voiding, and mucosuria (16). The diagnosis of urachal adenocarcinoma is a diagnosis of exclusion. The possibility of primary or secondary non-urachal adenocarcinoma should be excluded (18,19).

Urachal adenocarcinoma has various morphological features (Figure 7). However, none of these features are highly specific to distinguish urachal and non-urachal tumors (3,20). Different diagnostic criteria for urachal adenocarcinoma have been defined. The most practical diagnostic criteria include localization in the bladder dome, sharp transition between tumor and benign surface urothelium, and exclusion of the possibility of adenocarcinoma elsewhere in the bladder (20). The prognosis of urachal adenocarcinoma is not significantly different from non-urachal adenocarcinoma (16). The immunohistochemical staining pattern of urachal adenocarcinoma shows a significant overlap with metastatic colorectal adenocarcinoma as well as primary bladder adenocarcinoma. Almost all urachal adenocarcinomas express CK20 and CDX2. They also show variable expression of CK7, β-catenin and high-molecular-weight cytokeratin (HMWK) (18). Immunohistochemical markers are insufficient to distinguish between colorectal adenocarcinoma and urachal adenocarcinoma. Diffuse HMWK staining supports the diagnosis of urachal adenocarcinoma, whereas diffuse nuclear β-catenin staining supports that of colorectal origin. However, exclusion of colorectal metastases is a critical step in the diagnosis.

Secondary Adenocarcinoma

Secondary tumors of the bladder are rare and constitute less than 2% of all bladder tumors. Although bladder is not a common area for metastatic adenocarcinoma, secondary adenocarcinoma is more frequent than primary adenocarcinoma (20). The bladder is involved with various malignancies as a secondary tumor. It has been reported that the commonest sites of tumors spreading to the bladder were colon (21%), prostate (19%), rectum (12%), and cervix (11%) (2,21,22,23). Tumors that spread to the bladder are most commonly located on the bladder neck and trigon. It may be difficult to differentiate secondary adenocarcinomas from primary adenocarcinomas of the bladder. The histological

features combined with results of immunohistochemistry and clinical history help obtain accurate diagnosis. For this reason, knowledge of the history and clinical findings are particularly important in the diagnosis of non-urothelial carcinomas that are metastatic to the urinary bladder.

The most common secondary malignancy involving the urinary bladder is colorectal adenocarcinoma (Figure 8a). Although it has been suggested that immunohistochemical markers such as CK7, CK20, villin, CDX-2 and β-catenin help resolve the differential diagnosis of these tumors, sensitivity and specificity limitations have prevented any single marker or marker panel from appearing as superior (24,25,26,27,28). A panel of CK7, CK20, β-catenin and thrombomodulin has some value in distinguishing primary bladder adenocarcinoma from metastatic colorectal adenocarcinoma. Primary bladder adenocarcinoma is usually positive for CK7 and thrombomodulin and shows membranous staining for β-catenin, while a nuclear β-catenin and CK20 positive staining favor colorectal origin (20). However, the possibility of colonization of urothelial mucosa of the bladder with a well-differentiated colonic adenocarcinoma secondary to intestinal metaplasia/dysplasia should be kept in mind. In most cases, however, clinical history and colonoscopic findings are the most important for accurate diagnosis.

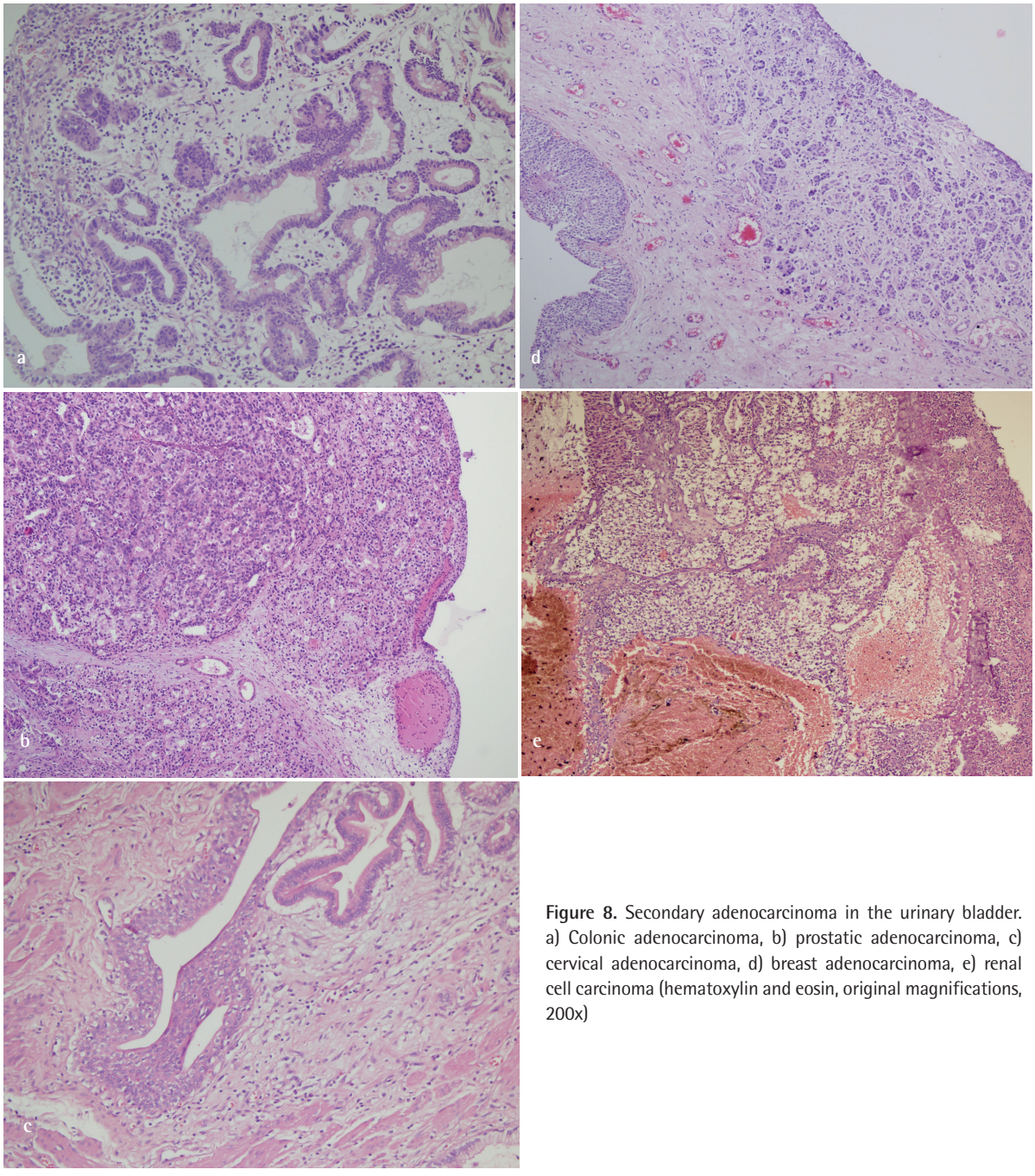


Figure 8. Secondary adenocarcinoma in the urinary bladder. a) Colonic adenocarcinoma, b) prostatic adenocarcinoma, c) cervical adenocarcinoma, d) breast adenocarcinoma, e) renal cell carcinoma (hematoxylin and eosin, original magnifications, 200x)

The second most common secondary malignancy involving the bladder is prostatic adenocarcinoma (Figure 8b). Prostatic adenocarcinoma often involves the bladder by direct invasion because of its close proximity. It is important to differentiate prostate adenocarcinoma from bladder adenocarcinoma because they are managed differently (20). In most cases, prostatic adenocarcinoma has distinct morphology and is easily identifiable by histology alone. However, in difficult cases, basal cell markers, such as 34βE12 cytokeratin (HMWK) and p63, are usually negative in prostate cancer, whereas prostate-specific antigen (PSA) immunostaining is positive in approximately 90% of prostate cancer cases. Although most of the prostate adenocarcinomas express PSA and prostate-specific acid phosphatase (PSAP), some poorly differentiated or previously treated prostate adenocarcinomas may not be positive for PSA and PSAP in immunohistochemical analysis. In these cases, other prostate-specific markers, such as prostate-specific membrane antigen, prostein (P501S) and NKX3.1, may also be used in differential diagnosis. It is proposed to use antibodies panel instead of a single antibody to distinguish prostatic adenocarcinoma from bladder adenocarcinoma, especially in poorly differentiated tumors (29,30,31,32,33).

Endometrial and cervical adenocarcinomas (Figure 8c) may involve the bladder by direct invasion. Endometrial carcinoma is usually positive for PAX8 and vimentin, whereas bladder adenocarcinoma does not express one or the other (32,33). Although most endocervical adenocarcinomas are positive for p16 in immunohistochemical staining, some bladder adenocarcinomas also express p16. Correlation with the clinical history is important in resolving the tumor origin. Although most endocervical adenocarcinomas are positive for p16, some bladder adenocarcinomas also express p16. Correlation with the clinical history is important to resolve the tumor origin.

Metastasis from other organs; metastasis to the bladder from breast (Figure 8d), lung, renal (Figure 8e) and other adenocarcinomas are rare. Since these metastatic adenocarcinomas show morphologic patterns overlapping with primary bladder adenocarcinoma, immunohistochemistry and clinical history will be necessary for definitive diagnosis (2,34). When estrogen receptor and progesterone receptor are coexpressed, breast adenocarcinoma is favored. Bladder adenocarcinoma usually does not express GATA3, whereas breast adenocarcinoma is positive for GATA3 (35,36).

Lung adenocarcinoma is positive for thyroid transcription factor-1, whereas bladder adenocarcinoma is negative. Rarely, renal cell carcinoma can metastasize to the bladder, which should be distinguished from CCA of the bladder. Since PAX2 and PAX8 are expressed in both tumors, they do not help in the differential diagnosis (37,38). CD10, vimentin, carbonic anhydrase 9 and renal cell carcinoma are expressed in clear cell renal cell carcinoma whereas CK7 and CK20 are usually expressed in bladder CCA (39).

Majority of patients with primary bladder adenocarcinoma have a muscle-invasive disease and they are usually treated with radical cystectomy and pelvic lymph node dissection. Primary radiation therapy may be considered for some patients who are not candidates for cystectomy. The efficacy of primary radiation therapy compared to surgery is unclear due to the limited experience with this rare disease.

Conclusion

The diagnosis of bladder adenocarcinoma is clinically important due to the fact that the diagnosis of bladder adenocarcinoma initiates a clinical effort to exclude the possibility of secondary adenocarcinoma of the bladder with a different adenocarcinoma from a different region.

Keywords: Urinary bladder, Adenocarcinoma, Primary, Secondary

Anahtar Kelimeler: Mesane, Adenokarsinom, Primer, Sekonder

Ethics

Peer-review: Externally peer-reviewed.

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