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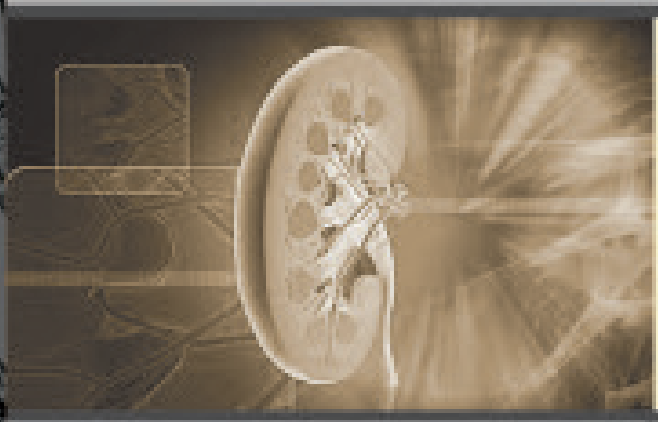

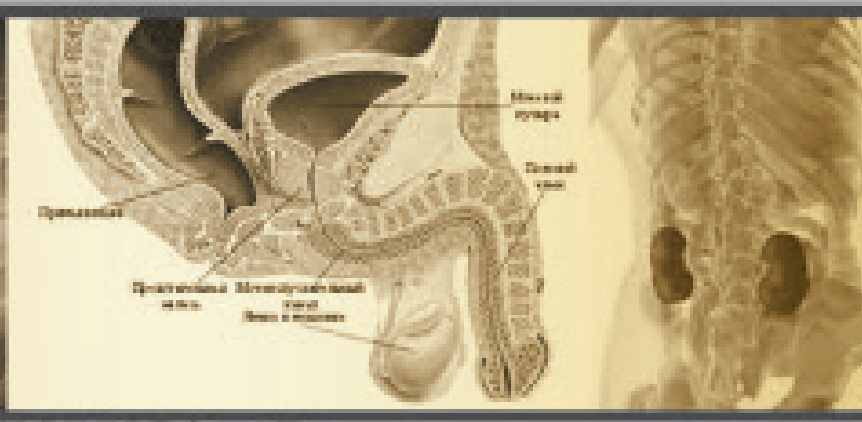

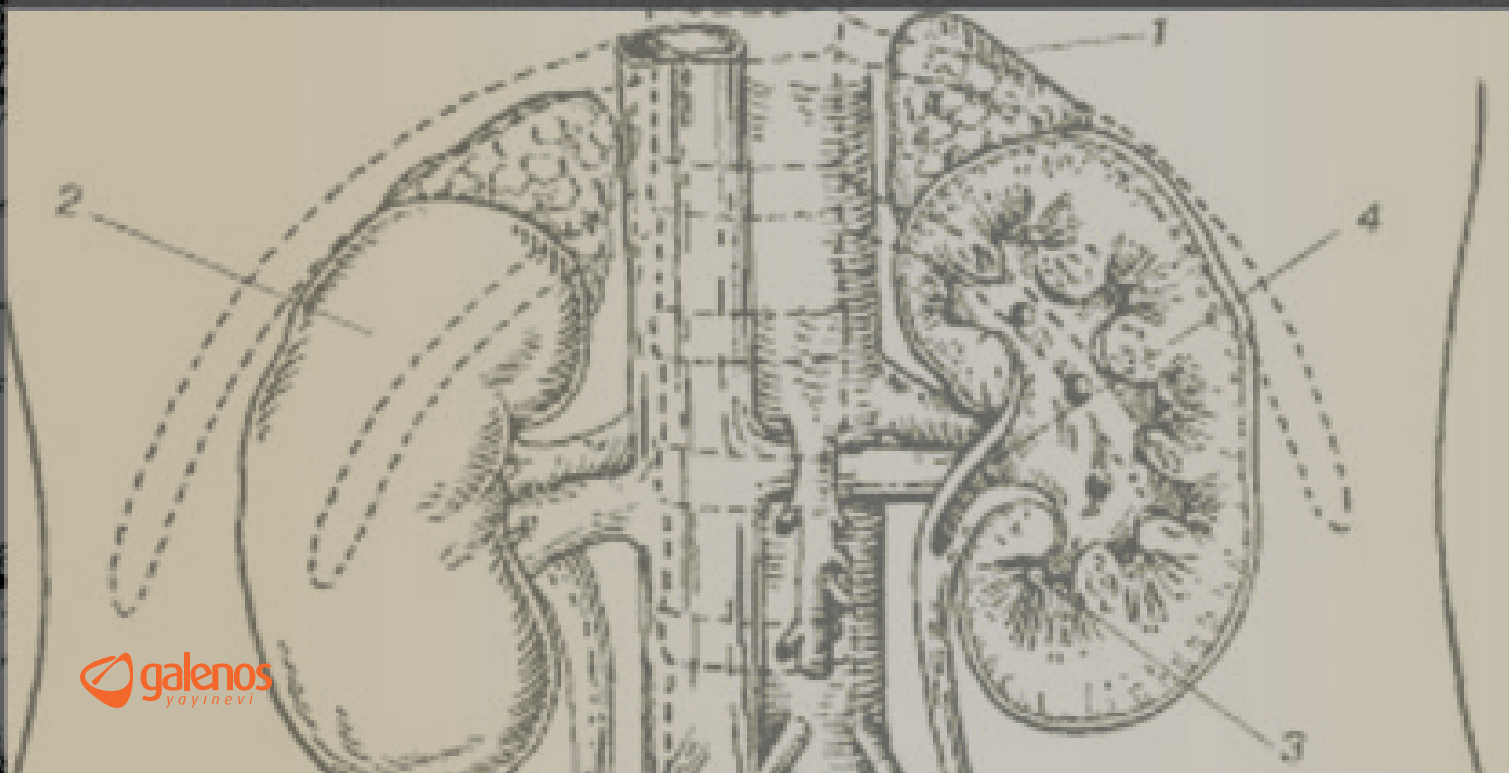

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Technical and other assistance should be provided on the title page.

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Objective: The abstract should state the objective (the purpose of the study and hypothesis) and summarize the rationale for the study.

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Results: Important findings and results should be provided here.

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

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Article length: Not to exceed 3000 words.

Original researches should have the following sections:

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Cite references in the text, tables, and figures with numbers in parentheses. Number references consecutively according to the order in which they first appear in the text. Journal titles should be abbreviated according to the style used in Index Medicus (consult List of Journals Indexed in Index Medicus). Include among the references any paper accepted, but not yet published, designating the journal and followed by, in press. Authors are solely responsible for the accuracy of all references.

Examples of References:

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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REVIEW

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How to Write and Publish a Scientific Article?

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Abstract

Today, writing and publishing scientific articles is amongst the most valid ways of scientific communication for scientists. They may also be written for academic advancement or to be appreciated by colleagues. The purposes of this review are to demonstrate the most frequent mistakes in scientific writing, to guide the authors in the preparation of appropriate articles, and to prevent waste of time in the process. Authors can make some errors during the preparation of the articles. Thus, a good article should be written with more attention to each section. Although several rules are published for article preparation, the author must have enough grammar knowledge to allow the reader to focus on what he/she wants to say. We consider that this review will help inexperienced authors prepare publishable scientific papers easily, and also will save the time during the publishing process.
Keywords: Scientific article, Publishing, Writing

Öz

Günümüzde bilim yapanlar arasında iletişimin en doğru yollarından biri bilimsel makale yazımıdır. Bilimsel makaleler akademik yönden yükselmek veya diğer bilim adamları tarafından tanınmak için de ele alınabilir. Bu çalışmanın amacı; yazar adaylarının bilimsel makale hazırlama aşamasında yaptıkları yanlışları göstermek, yazarlara uygun makale hazırlanmasında rota oluşturmak ve bu hazırlık zarfındaki istenmeyen zaman kaybını engellemektir. Bilimsel makale yazılırken birçok hata yapılabilir. Bir bilimsel makale her bölüme daha fazla dikkat edilerek hazırlanmalıdır. Makale için yayımlanmış bazı kurallar olsa da tam olarak ne ifade etmek istediğini makalede yeterince açıklayabilmek için yazarın iyi grameri olmalıdır. Bu çalışmamızın yeni yazarların nispeten daha iyi makaleler hazırlamasına yardımcı olacağını ve sıklıkla yapılan yanlışları belirterek makale hazırlanması esnasındaki zaman kaybını minimize edeceğini düşünmekteyiz.
Anahtar Kelimeler: Bilimsel makale, Yazma, Yayımlama

Introduction

The scientific article is the printed report that describes the outcomes of the authentic studies. Scientific progress can be achieved with studies. Sharing the results of studies and experiences by presenting rare cases is only possible through the articles published in scientific journals (1). Studies find their value only by publishing, if they reach conclusions. Thus, Gerard Piel's statement "Without publication, science is dead" explains this very well. Namely, if you do not publish your work, it has no meaning in the world of science (2). Turkish proverbs such as "Wisdom exists with the pen" and phrases like "Words fly away, writings remain" are the answers for "Why should science be published?".

One of the common problems encountered by young researchers is the subject of "How to prepare a scientific article?" (3,4). Hence, embalming the dead is easier than writing an article about it for some, as Paul Silvia stated (5). Before starting to write an article, setting up your daily plans and appointments are recommended. One-2 hours daily should be reserved for writing the article. First of all, it is necessary to ask the questions shown in Table 1 for the publication. Once these questions are answered, you can begin writing. References should be studied carefully for fundamentals and literature reviews. Today, the internet is frequently used for reference scanning. It is possible to reach references from many internet sites such as Pubmed, Google Scholar, Research Gate, IEEE Xplore, ISI Web of Knowledge, the

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ACM Digital Library, Scopus, CiteSeerX, arXiv, and DBLP (6).

Scientific articles consist of four sections (7). A widely accepted format "IMRaD" which is a scientific writing structure includes four or five major sections: introduction (I), methods (M), results (R), and (a) discussion (D) (8). However, not including the topic, abstract and authors' names is a drawback of this format. The IMRaD form should be able to respond to the questions listed in Table 2 (5). The simplicity and clarity in article writing require choosing the most suitable words to convey the right thought. Providing clarity makes it easier to understand. The use of simple and short words instead of complex words that have the same meaning increases the understandability of the article (9).

Writing Article

Title

It is important that the title is a label. Simple and clear words should be used when the title is being planned (10). Keep in mind that the best titles are short (11). A good title is a few words long (12). The title should not be in the form of question, if possible.

Writing and Sorting the Authors' Names

The preferred spelling for the authors' names is the first letters of the first and middle name then the surname. Scientific journals usually do not include the titles and grades after the author's name, but some medical journals may. Titles are often given following the name and grade or in the footnote on the title pages in medical publications (13). The first author should be designer and conductor of the study (14).

Table 1. Questions to ask before article preparation (5)

1. What is the issue and aim of my article?
2. Why is this article important?
3. How could I prepare the hypothesis?
4. What are the findings?
5. What is the most significant result?

Abstract

Abstract is considered as a looking-glass of the article. Certainly, the most viewed section of an article is abstract both in journals and electronic literature searches. The abstract should be organized in such a way as to draw the attention of the reader, especially to the objectives, design, outcomes, and conclusion (15). Two principles are important should the authors want to use concise language to sum up the article: first the summary needs to be apparent enough for those who will not view the rest, and second, it needs to be short; word restriction in journals differs (3). Indicating the keywords at the end of the summary briefly explains the concepts covered by the article.

Introduction

The introduction is a critical part as it establishes the approach of the reader and reviewer. It is better if the introduction has two segments, preferentially in two paragraphs. Of these paragraphs, the first one may clarify and sum up the background information that constitutes a basis and explanes the necessity for the study, and the new information that the study intends to demonstrate. The reader should be convinced that the study is established on a solid ground with reasonableness. The objective or hypothesis of the study may be described in the second paragraph (3).

Materials and Methods

"Materials and Methods" is traditionally reported to be the easiest to write. Even though it is known to be the easiest, it also causes nearly 30% of the rejections alone. The following must be specified at the beginning of this part (16):

1. The date on which the study was conducted,

2. The number of cases included in the study,

3. Whether or not ethics committee approval has been granted,

4. Whether it was a prospective or retrospective study.

After that, the questions listed in Table 2 should be answered (5). The choice of experimental or observational samples should be clearly defined; for example, the type, gender, sex, weight or physiological status of the experimental animal used in an experimental study should all be specified.

Table 2. Questions to ask in IMRaD format (5)

Introduction	Materials and methods	Results	Discussion and conclusions
1. Why is this research important?	1. Which materials should we use?	1. What are our major results or findings?	1. What are major results of the research?
2. What is known about the issue?	2. Who are the subjects of our research?	2. What are our supportive findings?	2. What is the implication or significance of our findings?
3. What are the hypotheses?	3. What is the design of our research?		
4. What are the aims?	4. Which ways should we follow?		

IMRaD: Introduction, methods, results and discussion

In clinical trials, details, such as the selected population of patients, the inclusion of patients, or the reasons for exclusions should be explained. If used, materials should be parameterized such as chemical composition, trade name, company name, and country of origin. It should be clearly stated how the study was designed and the procedures were followed (17,18).

Results

As shown in Table 2, initially the most important findings, then the supportive findings should be mentioned. All data should be presented in an understandable manner in this section. The results can be highlighted in tables, charts, or figures to make it more understandable. Data shown in a table does not need to be mentioned in detail in the text as well, which may make it harder for the reader and the reviewer to understand (19). However, it may be useful to mention the featured data in the text. In addition, statistical evaluation of the study should be covered here. Data interpretation is not for the results section but the discussion section (20,21). Only the data disclosed in this section may be addressed in the introduction or discussion section. If data is obtained using small numbers, exact numbers should be specified, not percent values. Additionally, unexpected results obtained in the study are often as valuable as expected findings; therefore, they should also be marked.

Discussion

Each study has its unparalleled findings and results; therefore, the discussion section may vary in its structure, shape or length. Placing your findings in the context of your study and explaining the meaning of these findings and their importance without appearing patronizing, condescending or arrogant should be the purpose of "discussion section" (22). Major findings of the study should be indicated. By the way, unexpected findings can be explained and discussed (23). According to the results of the study, implications must be made.

That is to say, the discussion section should roughly include the following (3):

1. Basic findings and new information presented by the current study need to be clearly stated,

2. The strengths and weaknesses need to be addressed,

3. Data of the study need to be compared with the findings of studies conducted previously,

4. Resemblances and discrepancies with the previous studies need to be described,

5. Possible explanations need to be made for different findings,

6. The study needs to be clearly and briefly concluded that it is related to clinic, practice, or future research,

7. Suggestions need to be made for future research.

Conclusion

Last paragraph should include brief summarizing or concluding sentences indicating the importance of the article. This way, at the end of the article, the reader may have a clear idea of what this information will do (24).

Acknowledgement

People and institutions assist in the conduct of the study or writing of the article (such as control, statistical or monetary contribution in terms of grammar and language) should be thanked in this section (1,25).

Disclosure

Since journals generally have hard rules about disclosure, if there is a suspicious data or contradiction in the study, it should be remarked. (18). By the way, authors should highlight the limitations of their study (26).

References

Scientific studies are ethically inclusive for they are based on authenticity and reliability. Only the published references can be cited. Although there are many ways of showing references, many journals give the references in one of three general models. They are usually categorized by number according to "name and year", "alphabetical list number" and "cited order" (13,20). The ideal number of references varies between 20 and 40, but many journals do not accept more than 25 references. The reference listing is an important part that will increase your paper's chances of being accepted. Because the editors often use authors listed here as commentators. This is normal because authors in references with similar works are considered expert (3). The sources from the journals indicated differently than the ones from congress paper, personal interviews, and internet sites. The lack of mention of the cited reference leads to plagiarism, one of the basic subjects of scientific ethics. Plagiarism is claiming someone else's article or thought as author's own. There is no place for plagiarism in an authentic and reliable scientific article (27).

Computer programs such as, Endnote, Zotero and Mendeley may help writing references (28). The most common reference styles are the Harvard and the Vancouver systems. The reference is indicated with author's name and year of publication and reference section is arranged alphabetically in the Harvard system. However, in the Vancouver system, references are arranged numerically and reference section arranged numerically. Medical journals and theses tend to use the Vancouver system and the Harvard system, respectively (29).

Publication of Article

Sending Manuscript and Choice of Journal

Ask someone with knowledge about the subject to review and, if necessary, edit your manuscript before submitting it. All co-authors should also examine the manuscript. Take their suggestion into account, but keep in mind that it is not a necessity to accept all. After these, you should decide which journal to send your manuscript to. It is useful to check previous issues of the journal to see if similar papers have been accepted. You should choose the journal with higher impact factor. The selected journal's instructions to the authors should be carefully followed (30). Reviewers pay particular attention to important criteria for acceptance of manuscripts. Therefore, importance and timeliness of the subject, writing style of the manuscript (well-written, apparent, simple to read and reasonable), design (appropriate, rigorous, and comprehensive), review of the previous data (cautious, focused, and contemporary) and a sufficient sample will play a substantial role in acceptance of your manuscript (31).

Revision and Resubmission

If your paper is declined, do not quit immediately, and plan to send it again (30,32). Less than 25% of the submitted papersare accepted in major scientific journals (33). Therefore, refusal of a paper does not always mean that it is poor. A rejection indicates that the reviewers did not give it a sufficiently high priority. Since you have received important suggestions on how to improve your manuscript, you should not get too disappointed (8). Before sending your paper to next journal, carefully examine the criticisms of the reviewers and try to answer them as much as possible.

According to the experiences of evaluated authors, the most common mistakes are (3):

Unsuitable results.

Power analysis failure.

Insufficient sample size.

Excessive confidence in the negative consequences of sample size.

Statistics performed inadequately.

Since finding one or more comparisons to be statistically significant is only possible by chance, the actual clinical symptom is not accepted when multiple comparisons are performed.

Improper use of the statistical terminology of "multi-variable" and "hypervariable" terms.

Inappropriately reporting of shares and ratios of the shares without any reference.

The possibility of manipulating the study target retrospectively according to positive findings.

Incorrect author names in references. If a writer's name is misspelled and the writer is one of those who originally reviewed, the reviewer can be "closed".

According to the reasons for refusal, the article may be submitted to another journal. If a revision is requested, after completing revisions, the paper may be sent to the same journal again or preferably another.

Conclusion

As a result, writing scientific papers is a laborious and patience-requiring process. However, usually, the effort pays off. Since contribution to science is a contribution to humanity, when the article is published and the journal is a popular magazine, feelings of happiness cannot be described.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.T.Ö., Y.Ö., Design: M.T.Ö., Y.Ö., Data Collection or Processing: M.T.Ö., Analysis or Interpretation: M.T.Ö., S.Ü.A., Y.Ö., Literature Search: M.T.Ö., S.Ü.A., Writing: M.T.Ö., S.Ü.A.

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Etiology and Treatment of Renal Forniceal Rupture: A Single Center Experience

Renal Forniks Rüptürü Etiyolojisi ve Tedavisi: Tek Merkez Deneyimi

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

Our study is one of the best series about the subject. It will also guide all urologists as their treatment modalities are assessed.

Abstract

Objective: To evaluate the clinical findings, treatment methods and outcomes of patients treated for renal forniceal rupture (RFR).
Materials and Methods: Files and records of the patients treated for RFR between January 2013 and November 2016 were evaluated retrospectively. In primary treatment; ureteroscopy and laser/pneumatic lithotripsy (URL) with stone fragmentation and double J (JJ) stent placement were performed in patients with no finding of sepsis. However, only JJ stent/percutaneous nephrostomy placement was performed in those with sepsis findings. The demographic characteristics, related symptoms, and the results of primary and secondary treatment of the patients were evaluated.
Results: We had 43 patients with a mean age of 48.6±16.6 years. No cause was found in 4 patients while a urological cause was identified in 39 of them by using anamnesis, physical examination, laboratory and imaging methods. Out of 43 patients, percutaneous nephrostomy catheterization was performed in 5 of 32 patients under primary treatment. URL and JJ stenting were performed in the remaining 11 patients. Additionally, due to giant retroperitoneal urinoma, a retroperitoneal drain was placed in 2 patients by interventional radiology clinic.
Conclusion: URL and stone fragmentation seem to be feasible treatment option in the primary treatment of patients with RFR without sepsis findings.
Keywords: Fornix rupture, Urinoma, Urolithiasis, Primary ureteroscopic treatment, Urology

Öz

Amaç: Renal forniks rüptürü (RFR) sebebi ile tedavi ettiğimiz hastaların klinik bulguları, tedavi yöntemleri ve sonuçlarını değerlendirmeyi amaçladık.
Gereç ve Yöntem: 2013 Ocak-2016 Kasım tarihleri arasında RFR sebebi ile tedavi ettiğimiz hastaların dosyaları ve bilgisayar kayıtları retrospektif olarak değerlendirildi. Hastaların tamamına öncelikle ampirik tedavi başlandı. İdrar kültürü-antibiyogram sonucuna göre gerekli görülen hastalarda seftriakson uygun olan başka bir antibiyotik ile değiştirildi. Sepsis bulgularının olmaması durumunda tedavi olarak üreteroskopi ve lazer/pnömotik litotriptör (ÜRL) ile taş fragmantasyonu ve double J (DJ) stent yerleştirilmesi ameliyatı yapılmıştı. Ancak; sepsis bulgularının olması durumunda tek başına DJ stent/perkütan nefrostomi yerleştirilmesi yapılmıştı. Hastaların demografik özellikleri, ilişkili semptomları, primer ve sekonder tedavilerinin sonuçları değerlendirildi.
Bulgular: Hastalarımız yaş ortalaması 48,6±16,6 (23-82) olan 22'si erkek 21'i kadın olmak üzere 43 hastadan oluşmaktaydı. Hastaların yapılan anamnez, fizik muayene, laboratuvar ve görüntüleme yöntemleri ile 4'ünde sebep bulunamazken, 39'unda ürolojik bir sebep saptandı. Kırk üç hastanın 32'sinde hastaya acil tedavide 5 hastaya perkütan nefrostomi kateteri konulurken, 27 hastaya lokal anestezi altında sistoskopi eşliğinde DJ stent takıldı. Geri kalan 11 hastaya ise ÜRL ile taş fragmantasyonu ve DJ stent yerleştirilmesi yapılmıştı. Ayrıca 2 hastaya dev ürinom sebebi ile retroperitoneal dren yerleştirilmişti.
Sonuç: Her iki grup tedavi başarısı ve komplikasyonlar açısından değerlendirildiğinde fark olmadığı düşünülürse, sepsis bulguları olmayan spontan RFR'si olan hastalarda öncelikli tedavide ÜRL ve taş fragmantasyonu uygulanabilir bir tedavi gibi görünmektedir.
Anahtar Kelimeler: Forniks rüptürü, Ürinom, Taş hastalığı, Öncelikli üreteroskopik tedavi, Üroloji

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Introduction

Renal forniceal rupture (RFR) is a potential urological emergency, although it is a rare result of obstructive uropathy. It often emerges as a secondary to obstruction of the ureter or ureteropelvic junction and generally occurs in the upper and lower renal pole calyces (1,2). Extravasated urine may accumulate in the extraperitoneal area, inside the peritoneal cavity, or both. The extraperitoneal collection can be formed as two types: subcapsular and perirenal. Subcapsular urinomas occur between the renal parenchyma and the renal capsule whereas perirenal urinomas are between the renal capsule and the Gerota's fascia.

Retroperitoneal urinoma can lead to a clinical picture that is indistinguishable from simple renal colic. Preoperative diagnosis becomes more difficult due to blood loss and generally lack of urinary symptoms (3,4). One of the major clinical findings is sudden pain relief due to decreased pressure in the collecting system (5). Prognosis varies according to underlying pathology, renal injury, place of rupture and presence of infection (6). If this formed urinoma is not treated, it may result in perirenal abscess formation, sepsis, retroperitoneal fibrosis, loss of renal function, and even death (7,8,9,10).

When urological literature related to RFR is examined, it can be seen that there are many case reports except two studies. In this study, we aimed to evaluate the clinical findings, treatment methods and outcomes of the patients treated for RFR.

Materials and Methods

Following the approval (decision number: 175/2018) from the Ethics Committee of Adana City Training and Research Hospital, the files and records of patients treated for RFR between January 2013 and November 2016 were evaluated retrospectively. A consent form was completed by all participants. The patients who were assessed and hospitalized in our clinic were referred by the emergency department or urology outpatient clinic. RFR diagnosis was made by radiological imaging methods. Primarily, kidney-ureter-bladder X-ray and abdominal ultrasonography (USG) were performed in all patients and abdominal computed tomography (CT) was performed to confirm the diagnosis and determine the etiology. Following the hospitalization, all patients were evaluated with vital signs, urine analysis, urine culture-antibiogram, serum blood urea nitrogen and creatinine levels, white blood cell count (WBC) and C-reactive protein (CRP). All patients primarily received empirical treatment (analgesia, intravenous fluids, empiric ceftriaxone, and bed rest). Ceftriaxone was switched to another antibiotic when necessary according to the results of urine culture-antibiogram. In primary treatment, ureteroscopy and laser/pneumatic lithotripsy (URL) with stone fragmentation and double J (JJ) stent placement were performed; in patients with no findings of sepsis (e.g. fever, increased WBC, increased CRP, etc.) (group 1). However, only JJ stent/percutaneous nephrostomy placement was performed in those with findings of sepsis (group 2). Additionally, the secondary treatment was applied to the patients of group 2 in a separate surgical session according to their RFR etiology.

The laboratory tests were repeated at every 48-72 hours until normal levels were reached. During the patients' hospitalization, the size of urinomas was monitored by USG at every 48 hours following surgical treatment. The patients followed up with USG every 15 days after discharge.

The demographic characteristics, related symptoms, and the results of primary and secondary treatment of the patients were evaluated.

Results

Demographic Characteristics and Clinical and Diagnostic Findings

A total of 43 patients (22 men and 21 women) with a mean age of 48.6±16.6 (23-82) were included in the study. RFR was on the left side in 24 patients and on the right side in 19 patients. Flank pain occurred in all patients (100%), fever in 15 patients (34.8%), emesis in 7 patients (16.3%) and hematuria in 4 patients (9.3%).

No cause was found in 4 patients (9.3%) while a urological cause was identified in 39 of them by using anamnesis, physical examination, laboratory and imaging methods. Ureteric stones were found in 32 of these 39 patients (74.4%), stones were found in the uretero-pelvic region in 6 patients (14%) and bladder tumors were found in one patient (2.3%). The number of patients with ureteric stones within the upper, middle and lower ureter was 6, 3, 23, respectively. Twenty six (81.2%) of these ureteric stones were impacted stones. Of the 4 patients in whom the cause of RFR could not be determined, 3 had a medical history of stone surgery or passing stones.

When all patients were evaluated; it was found that 3 patients had a solitary and the other kidney was atrophic in 5 patients. It was detected that 26 patients had elevated WBC (>103/µL), 26 patients had CRP elevation (>5 mg/L) and 16 patients had elevated creatinine (>1.2 mg/dL). The demographic characteristics and clinical and laboratory findings of the patients are shown in Table 1. In group 1 patients, all urine analyses were unsuggestive for possible infection. Urine culture was negative in all the group 1 patients, however, it was positive in 15 patients of group 2 (46.8%). The microorganisms identified in the urine culture are shown in Table 2.

Treatment

Out of 43 patients, percutaneous nephrostomy catheterization was performed in 5 of 32 patients (group 2) under primary treatment. JJ stents were implanted in 27 patients under local anesthesia with cystoscopy. URL and JJ stenting were performed in the remaining 11 patients (group 1). Additionally, due to giant retroperitoneal urinoma, a retroperitoneal drain was placed in 2 patients by the interventional radiology clinic (Figure 1).

Table 1. Demographic, clinical and diagnostic findings

Parameters	Group 1	Group 2	Result
Number of patients	11	32	43
Male/female	5/6	17/15	22/21
Right/left kidneys involved	7/4	17/15	24/19
Symptom			
Pain	11	32	43
Fever	2	13	15
Emesis	1	6	7
Hematuria	1	3	4
Underlying cause of fornix rupture	11	21	32
Ureter stones	0	6	6
Kidney stones	0	1	1
Bladder tumors	0	4	4
Unknown			
C-reactive protein elevation	3	23	26
Leukocytosis	4	22	26
Creatinine elevation	4	12	16

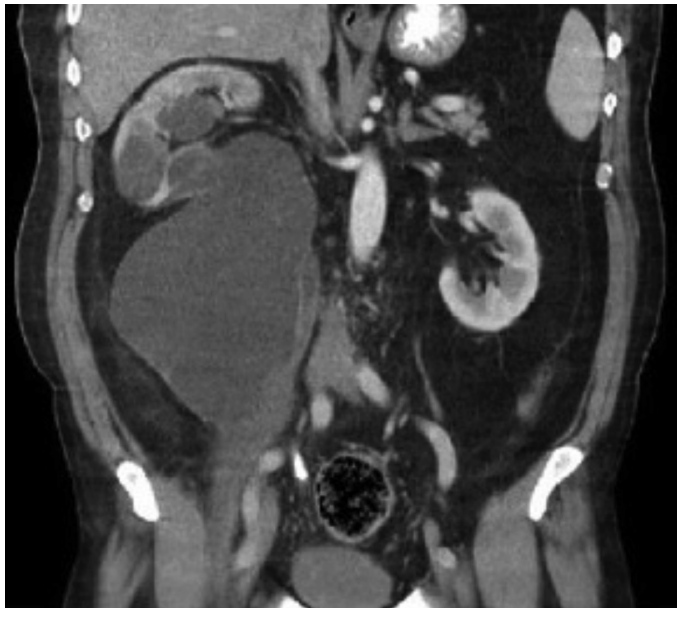

Figure 1. The computerized tomography image of fornix rupture

In the secondary treatment of 32 patients, who underwent JJ stent or percutaneous nephrostomy catheter placement in the primary treatment, ureteroscopic stone fragmentation and JJ stent placement were performed in 20 patients, percutaneous nephrolithotomy in 4 patients, flexible ureteroscopy in 2 patients, extracorporeal shock wave lithotripsy in 1 patient and radical cystectomy in 1 patient. In 4 patients with no cause of RFR, only JJ stenting was performed. Retroperitoneal urinary retention and kidney functions were found to be preserved these 4 patients in the follow-up period. The mean time to transition from the primary treatment to the secondary treatment was calculated as 29.5±6.7 days (20-42). The mean duration of hospital stay was 7.6±4.7 (2-25) days. The treatment methods are shown in Table 3.

During the follow-ups of patients, no major complication occurred in the early and late periods.

Discussion

RFR is a very rare clinical diagnosis and the most common cause of obstructive uropathy due to urethral stones (1,3). Rarely, it can occur due to blunt trauma or sharp object injuries, invasive urinary procedures, tumor obstruction and pregnancy (11,12,13). There are many opinions about the physiopathology of urinoma, most of which are chronic ureteral obstruction resulting in pyelosinus back-flow, renal sinus extravasation with pyelolymphatic and pyelovenous back-flow by 35-40 cm H_2O and/or more increase in intrapelvic pressure, and therefore the resultant perirenal extravasation (14).

Table 2. Microorganisms breeding in urine culture

Microorganisms	Number of patient
Escherichia coli	8
Pseudomonas aeruginosa	4
Proteus mirabilis	2
Enterococcus faecalis	1

Tablo 3. Treatment options

Primary treatment	Number of patient
Sole DJ stent or percutaneous nephrostomy	32
URL+DJ	11
Seconder treatment	32
URL+DJ	20
Flexible-ureteroscopy	1
Percutaneous nephrolithotomy	4
Extracorporeal shock wave lithotripsy	2
Sole DJ stent removal	4
Radical cystectomy	1

DJ: Double J, URL: Ureteroscopy and laser lithotripsy

The clinical diagnosis of RFR is difficult because its symptoms are rare and vary from asymptomatic to acute renal colic (15). Diagnosis is confirmed by serial USG or CT following the evaluation of symptoms. However, USG has low sensitivity in distinguishing urinoma from abscess and detecting the location of urinoma. Contrast-enhanced CT is highly sensitive for visualization of the location of the urinoma, its size and the demonstration of its the relationship with the kidney and the ureter, and, therefore, it provides additional information contributing to treatment planning. Contrast-enhanced CT should be considered by the emergency department physician in patients with obstructive uropathy and flank pain since RFR patients usually come from emergency departments (16). 69.8% of our patients were transferred from the emergency department.

In a study by Doehn et al. (5) evaluating 162 patients with RFR, it was found that the cause of RFR was ureteric stones in 59.9% of subjects while no other cause was found in 27.8% and other reasons were detected in 12.3%. In a study including 51 patients performed by Kalafatis et al. (1) ureteral stones were detected as an etiological cause of RFR in 100% of patients (5). In our patient group, 88.4% of the patients had ureteral or kidney stones, 2.3% had bladder tumor and 9.3% had no cause. In this context, the most common etiology of RFR is ureteric and kidney stones while other causes can be detected as well, even though rarely.

The primary goal in RFR treatment should be reducing pressure in the upper urinary system (1,5,16). JJ stent or percutaneous nephrostomy implementation is a reliable method for the treatment of patients with RFR due to URL obstructed ureteric stones combined with endourological maneuvers. However, since these patients are at risk of serious infections, it is suggested that antibiotic treatment should be initiated following the diagnosis (1,5), because in these patients, the rate of reproduction in urine culture is considerably high. This rate was found to be 34.9% in our study and as 27.4% in a study by Doehn et al. (5). For that reason, we think that patients who will undergo URL for stone treatment in addition to JJ stent implantation should be evaluated in a detailed manner for pre-operative infection findings.

In the study performed by Doehn et al. (5), the basic criteria for endoscopic treatment such as URL in which the stone was removed or not were reported as the patient's status (e.g. additional co-morbidities), presence of systemic infections, size and location of stone versus JJ stent placement only, and consequently showed more tendency to apply UR compared to JJ stent implantation only (5). When the results that were obtained in our clinic were evaluated, our treatment tendency in order to treat patients with septicemia findings (fever, leukocytosis, CRP elevation) was to reduce urinary pressure and implement JJ stent or percutaneous nephrostomy to enable drainage. However, if there is no evidence of septicemia in a patient, we think that URL combined with endourological maneuvers can be performed. However, in this group of patients, it has been reported that the operating team should work in strict coordination in order to avoid increasing the risk of complications due to prolonged intervention period, and the low flow irrigation fluid should be used in order to avoid an increase in extravasation (1). Although the treatment with JJ stent or percutaneous nephrostomy provides a solution in acute phase, the secondary treatment for RFR may be needed. In the studies by Doehn et al. (5) and Kalafatis et al. (1), the rate of secondary treatment was reported to be 75.9% and 56.8%, respectively. In our study, the rate of secondary treatment was 74.4%.

If RFR is not treated at the time of diagnosis or appropriately, it may lead to serious consequences such as perirenal abscess formation, sepsis, retroperitoneal fibrosis and loss of renal function (7,8,9,10). 10% of perirenal abscesses is a delayed complication of RFR (17). In the follow-up of the patients of our study, no major complications were detected in the early and late periods.

Conclusion

Although our study was retrospective, when the clinical findings are evaluated, it can be seen that we applied URL in the primary treatment in patients without sepsis findings while we applied only JJ stent or percutaneous nephrostomy in the primary treatment in patients with sepsis findings. However, prospective randomized studies are required in order to confirm this interpretation accurately.

Ethics

Ethics Committee Approval: Our study has been approved by the Ethics Committee of Adana City Training and Research Hospital with decision number 175/2018.

Informed Consent: A consent form was completed by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.E., E.A., E.T., Y.K.E., Concept: H.E., Design: H.E., E.T., E.A., Data Collection or Processing: H.E., E.T., M.E.D., Analysis or Interpretation: Z.G.G., Y.K.E., A.B.Ş., Literature Search: E.A., U.Ü., M.E.D., Writing: H.E., E.T.

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

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Supracostal PCNL-Standard Nephrostomy with Day Long Pain Versus Painless Tubeless

Gün Boyu Ağrılı Standart Nefrostomiye Karşı Ağrısız Tüpsüz-Suprakostal PNL

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

Supracostal access during percutaneous nephrolithotomy has become a fear factor among the urological fraternity. leaving a drainage tube postoperatively has become a beacon of safety. But the evidence proving this notion is feeble. This study adds to the evidence which proves that drainage is not necessary in supracostal access during a very common urological procedure of percutaneous nephrolithotomy. Hopefully after getting replicated by other researchers, this study will shape future guidelines pertaining to treatment modalities in stone disease management.

Abstract

Objective: To determine the scope of tubeless (TL) supracostal percutaneous nephrolithotomy (PCNL) in terms of safety through a randomized controlled trial.

Materials and Methods: Adult patients (>14 years) undergoing supracostal PCNL were randomized into two groups (25 patients each), by randomizing odd number for supracostal PCNL with tube (WT) as group A and for TL supracostal PCNL as group B. Both groups received injectable analgesia on operative day and oral analgesia from the first post-operative day. Pain severity was objectively assessed by a visual analogue scale (VAS). Chest X-ray and kidney ultrasonography were done to detect any pleural effusion and perinephric collection. These complications along with thoracostomy and endotracheal intubation were compared between the groups.

Results: The mean (VAS) score in group A and B was 7.88±0.83 and 4.12±0.83, respectively (p=0.01). Four of 25 (16%) patients in group A and 1 of 25 (4%) patients in group B developed pleural effusion. Two patients (8%) in group A and 1 patient (4%) in group B required tube thoracostomy (p=0.56). One patient (4%) in group A and 2 patients (8%) in group B developed perinephric collection (p=0.56). A single patient in each group (2%) developed respiratory distress needing elective intubation and ventilation (p=1.00).

The mean hospital stay in group B (4.12±0.52 days) was shorter than in group A (4.68±0.85 days) (p=0.01).

Conclusion: Tubeless supracostal PCNL is less painful than supracostal PCNL WT, without difference in complication rates. Supracostal PCNL (TL) has a shorter hospital stay.

Keywords: Percutaneous nephrolithotomy, Supracostal, Pleural effusion, Thoracostomy

Öz

Amaç: Tüpsüz suprakostal perkütan nefrolitotominin (PNL), randomize kontrollü çalışma ile güvenlik açısından kapsamını belirlemek.

Gereç ve Yöntem: Suprakostal PNL uygulanan erişkin hastalar (>14 yıl), tüplü suprakostal PNL için A grubu olarak ve tüpsüz suprakostal PNL için B grubu olarak iki gruba tek sayı randomize edildi (her biri 25 hasta). İki grup ameliyat günü enjektabl analjezi ve operasyon sonrası ilk günden itibaren oral analjezi aldı. Ağrı şiddeti görsel analog ölçeği (GAÖ) ile objektif olarak değerlendirildi. Plevral efüzyon ve perinefrik koleksiyonu saptamak için göğüs X-ray ve böbrek ultrasonu yapıldı. Torakostomi ve endotrakeal entübasyon ile birlikte bu komplikasyonlar gruplar arasında karşılaştırıldı.

Bulgular: Grup A ve B ortalama GAÖ skoru sırasıyla 7,88±0,83 ve 4,12±0,83 idi (p=0,01). Grup A'da 25 hastanın 4'ünde (%16) ve grup B'de 25

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Öz

hastanın 1'inde (%4) plevral efüzyon gelişti. Grup A'da 2 (%8) hasta ve grup B'de 1 (%4) hasta torakostomi yerleştirilmesini gerektirdi (p=0,56). Her bir grupta 1 hastada (%2) elektif entübasyon ve ventilasyona ihtiyaç duyan respiratuvar distres gelişti (p=1,00). B grubu (4,12±0,52 gün) için ortalama hastanede kalış süresi A grubundan (4,68±0,85 gün) daha kısa idi.

Sonuç: Tüpsüz suprakostal PNL, komplikasyon oranlarında fark olmaksızın tüplü suprakostal PNL'den daha az ağrılıdır. Tüpsüz suprakostal PNL daha az hastanede kalış süresine sahiptir.

Anahtar Kelimeler: Perkütan nefrolitotomi, Suprakostal, Plevral efüzyon, Torakostomi

Introduction

Percutaneous nephrolithotomy (PCNL) is known to provide best stone-free rate among all available treatments for renal stones (1,2) and it has been recommended as "standard" for stones larger than 20 mm. Safety of PCNL has been established on the basis of various studies and resources (3).

On most of the occasions, access into the kidney is acquired subcostally. However, in case of bulk stone or multiplicity, for better clearance of stones, pelvicalyceal system is accessed through upper calyceal system supracostally because of large stone size and anatomical alignment with other calyces and pelvis (4,5). Since the tube in supracostal PCNL is likely to move with every breath, more pain is expected leading to higher and frequent doses of analgesia. In the literature, there are several studies supporting the safety and efficacy of tubeless (TL) and totally TL PCNL with shorter hospital stay compared to standard PCNL with nephrostomy (6,7).

Literature regarding TL supracostal PCNL is not only sparse but also the recent guidelines have not established practices of such an entity. The major concern in TL supracostal PCNL is increased thoracic complications, such as pleural effusion, need for thoracostomy and endotracheal intubation with mechanical ventilation, but the limitedly literature available has not shown any major difference between two approaches in terms of pulmonary complications (TL 9.3% vs. standard 9.6%) (8,9).

Though the superior calyx is one of the preferred puncture sites for PCNL for its shortest course from the skin to the system and maximal maneuverability (10,11,12), increased risk of pulmonary complications has been concerning for many. Historically, the safety against pulmonary complications in supracostal PCNL has been improved with the use of nephrostomy tube but that notion is still debatable and there exists a strong need for prospective trials to evaluate the safety of this procedure without leaving a nephrostomy tube *in situ*. Such future studies will not only improve our knowledge of supracostal PCNL, but will also shape and strengthen the current urological guidelines.

Materials and Methods

This randomized controlled trial took place at the Kidney Centre Postgraduate Training Institute, Karachi, Pakistan from September 2013 to February 2015. Native ethical review board approval was taken prior to the study (Kidney Centre Ethical Review Committee reference # 01-URO-032013).

Sample size calculation was based on historical cohort of one of the previously performed and published similar trials (9) due to the sparse data. This yielded a sample size of 50 patients (25 patients in each arm). All adult patients (>14 years), who were electively admitted for PCNL, were informed about the trial in detail and, after obtaining informed consent, were proviionally enrolled in the study. Final decision for enrollment in the study was performed on the operating table once retrograde urography was performed and decision for supracostal access was established. Patients who did not require supracostal access were excluded from the study. After enrollment, the patients were randomized into two groups (25 patients each) by stratifying odd number for supracostal PCNL with tube (WT) as group A and for supracostal TL PCNL as group B.

Access was acquired in the prone position and puncture was performed with a spinal needle using the Bull's eye or triangulation technique under fluoroscopic guidance. Urologists of at least 10 years' experience performed the procedures with grossly similar operative technique. Patients, who underwent more than one puncture or severe bleeding, were excluded from the study (only one patient in group A underwent double puncture and was excluded with random replacement by another patient to maintain equal number arms). Age, gender, punctured calyx, visual analogue scale (VAS) score and hospital stay were recorded in all patients.

Both groups received post-operative injectable analgesia on operative day and oral analgesia from first post-operative day. Pain severity objectively assessed by a VAS. Chest X-ray and ultrasonography of the kidney were done to detect any pleural effusion and perinephric collection. Patients, who demonstrated respiratory distress clinically and with radiological evidence of fluid, underwent thoracostomy. Few patients, who did not resolve after thoracostomy, needed endotracheal intubation and mechanical ventilation. These complications along with

thoracostomy and endotracheal intubation were compared between the groups.

This study required two additional investigations consisting of postoperative day chest X-ray and ultrasonography of the kidney for perinephric collection other than the routine ones. Furthermore, the cost of thoracostomy and ventilatory support was also to be reimbursed through institutional grant. Therefore, this grant was also approved along with the ethical review board approval for the additional investigations and thoracostomy with or without ventilation, if needed.

Statistical Analysis

The results were described in terms of mean and standard deviation for continuous variables (age, punctured calyx, VAS score and duration of the procedure). Categorical variables, such as gender and punctured calyx, were described in terms of percentage and were compared between the 2 groups using a chi-square test. Data was analyzed using SPSS (Statistical Packages of Social Sciences) version 20. effect modifiers/ confounders (size of stone and duration of procedure) were analyzed through stratification and a chi-square test was applied. A p value of less than 0.05 was considered statistically significant.

Results

The mean (VAS) score in groups A and B was 7.88±0.83 and 4.12±0.83, respectively (p=0.01), as shown in Table 1.

Four (16%) patients in group A and 1 (4%) patient in group B developed pleural effusion, as shown in Table 1.

Two patients (8%) in group A and 1 patient (4%) in group B required thoracostomy (p=0.56), as shown in Table 1.

One patient (4%) in group A and 2 patients (8%) in group B, developed perinephric collection (p=0.56), as shown in Table 1.

A single patient in each group (2%) developed respiratory distress needing elective intubation and ventilation (p=1.00), as shown in Table 1.

The mean hospital stay in group B (4.12±0.52 days) was shorter than in group A (4.68±0.85 days) (p=0.01), as shown in Table 1.

Discussion

Supracostal PCNL is considered to be the easiest and most maneuverable puncture because of the distinct anatomy of the superior calyx and the alignment with other calyces and the pelvis. Nearly every part of the calyceal system is accessible through this route. However, the close proximity with pleural reflection makes urologists cautious against pulmonary complications. The present study was conducted to prove the widely unaccepted notion that supracostal PCNL is a very useful, yet quite safe procedure, such that it becomes part of future guidelines. Weighing the risks and benefits surely gives

Table 1. Baseline demographics and clinical characteristics

Group-A (Supracostal PCNL WT)	Group-B (Supracostal PCNL TL)		
Number of patients (n)	**Number of patients (n)**	**p value (p)**	
Gender			
Male	18	17	p=1.000
Female	07	08	
Age groups			
15-29	09	05	p=0.310
30-39	06	06	
40-49	05	03	
50-59	05	09	
60-75	0	02	
Stone clearance			
Complete	19	23	p=0.382
Residual <1cm	05	02	
Residual >1cm	01	0	
VAS scoring for pain			
Mild pain (Score: 1-4)	0	18	p=0.000
Moderate pain (Score: 5-7)	07	07	
Severe pain (Score: 8-10)	18	0	
Hospital stay			
3 days	0	01	p=0.013
4 days	12	21	
5 days	11	02	
6 days	0	01	
7 days	02	0	
Perinephric collection			
	01	02	p=0.500
Pleural effusion			
Mild effusion (Conservatively treated)	02	0	p=0.282
Significant effusion (Thoracostomy needed)	02	01	
Endotracheal intubation & mechanical ventilation			
	01	01	p=1.000

PCNL: Percutaneous nephrolithotomy, WT: With tube, TL: Tubeless, VAS: Visual analogue scale

us a winner. However, as every guideline needs more evidence, this study is aimed to strengthen that evidence.

In their study including 840 patients who underwent PCNL between 2004 and 2007, Shah et al. (7) compared demographic and perioperative data of 454 patients who underwent TL PCNL with 386 patients who underwent PCNL. They found out that decrease in hemoglobin, transfusion rate, complications and stone-free rate were comparable between the groups. They reported that analgesia requirement was less (p=0.000) and hospitalization duration was shorter (p=0.000) in the TL PNCL group.

Efficacy of supracostal PCNL is also supported by Sekar et al. (12) In their study including 376 patients who underwent PCNL from July 2012 to Dec 2015, 92 needed supracostal puncture. Complete stone-free status was achieved in 83% of patients after initial PCNL. They concluded that supracostal PCNL was a safe and effective option in selected patients.

Between March 2005 and February 2012, 243 patients had a supracostal access in a study performed by Kara et al. (13) in which PCNL was performed by making the puncture through either 11th or 10th intercostal space. The stone-free rate was 86.8% in 11th intercostal group and 84.6% in 10th intercostal group. Twenty patients (8.2%) encountered grade-1 complications, 38 patients (15.6%) showed grade-2 complications, 13 patients (5.3%) faced grade-3a complications, only 2 patients (0.8%) had grade-3b complications, while grade-4a was recorded in only 1 (0.4%) patient. No grade-4b or grade-5 complications were recorded. Overall complication rate was recorded to be 30.9% in 11th intercostal and 28.2% in 10th intercostal group.

Gonen et al. (14) performed a similar study including 10 patients as study group who underwent supracostal PCNL without nephrostomy tube between March 2005 and June 2007. These 10 patients were compared with 10 patients of control group who underwent supracostal PCNL with nephrostomy tube. The patients undergoing TL and stentless PCNL required less analgesia (p=0.001) and were discharged earlier (p=0.000) than those in the control group. Mean fall in hemoglobin and thoracic complications were insignificant and comparable between the 2 groups in this study.

Study Limitations

The present study supports the hypothesis of few of the internationally published articles with inference that nephrostomy tube is not needed to prevent the pulmonary complications in supracostal PCNL. The level of puncture (supra 11th or supra 12th rib) (15) also has a great impact on the outcome of safety, but due to limited scope of patients requiring supracostal access, this confounder was not assessed in the current study and turns out to be a single limitation of this study. Perinephric collection seemed to be the only preventable complication in the supracostal PCNL (WT) group, but the number of such patients was insignificant. Furthermore, this complication is self-limiting and trivial, seldom causing progression. Pulmonary complications hold the major attention in urology fraternity, and the fear is so substantial that supracostal access is reserved as a last resort by some urologists.

Another possible limitation of the study could be the use of 30 Fr Amplatz sheath in all patients, which could have given different outcomes if a smaller sized access sheath was used, however, published literature also has limited data about this fact.

Conclusion

Supracostal TL PCNL is less painful than supracostal PCNL WT, without difference in complication rates in terms of pleural effusion, perinephric collection, thoracostomy and endotracheal intubation. Furthermore, the TL group had a shorter hospital stay than the PCNL WT group. This study is likely to add to strength of evidence on the subject and will highlight the issue to be incorporated into guidelines for standardization in stone treatment.

Ethics

Ethics Committee Approval: This study was approved by the Kidney Centre Ethical Review Committee (approval number: 01-URO-032013, date: March 2013).

Informed Consent: Contained brief description about the study and disclosure about possible long term benefits of study, along with patient confidentiality policy. It was present in English and Urdu languages.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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Percutaneous Nephrolithotomy in Patients with Positive Urine Cultures: Do Complications Increase?

İdrar Kültürü Pozitif Hastalarda Perkütan Nefrolitotomi: Komplikasyonlarda Artış Var mı?

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

Regardless of the stone type, there are stone patients with persistant bacteriuria that can not be treated by antibiotherapy. It is known that the presence of uncontrolled bacteriuria in percutaneous nephrolithotomy (PNL) can increase sepsis and similar infectious complications. In this study, it was demonstrated that PNL during antibiotheraphy in patients with persistant bacteriuria is safe in terms of infectious complications. Our study is valuable because it provides information on a topic that is unclear in the literature

Abstract

Objective: Our aim in this study to determine whether positive urine culture is a risk factor for infectious complications in patients undergoing percutaneous nephrolithotomy (PNL).
Materials and Methods: A total of 958 patients, who underwent PNL in our clinic between 2008 and 2015, were included in the study. The patients were divided into two groups with respect to preoperative urine culture results. Group 1 included 126 patients with nonsterile urine culture. As the control group, 130 patients were randomly selected among patients with preoperative negative urine culture and named as group 2. The groups were compared in terms of demographic data, postoperative complications and additional interventions.
Results: The mean age was 51.4±1.05 years in group 1 was and 48.7±1.08 years in group 2. On postoperative 1st month computed tomography, postoperative residual stone fragments were observed in 27 patients (21%) in group 1 and 26 patients (20%) in group 2. The groups were similar in terms of treatment success (p=0.878). No significant difference was found between the groups in terms of postoperative fever (p=0.46), sepsis development and intensive care need (p=0.733).
Conclusion: PNL would not increase infectious complications in patients with positive urine culture
Keywords: Urolithiasis, Percutaneous nephrolithotomy, Urine culture

Öz

Amaç: Bu çalışmada amacımız, PNL olan hastalarda pozitif idrar kültürünün enfeksiyöz komplikasyonlar açısından risk faktörü olup olmadığını araştırmaktır.
Gereç ve Yöntem: 2008-2015 yılları arasında kliniğimizde PNL olan 958 hasta çalışmaya dahil edildi. Preoperatif idrar kültürü sonuçlarına göre hastalar iki gruba ayrıldı. Kültüründe üreme saptanan 126 hasta grup 1 olarak adlandırıldı. Kontrol grubu olarak 130 hasta idrar kültürü steril hastalar arasından rastgele seçildi. İki grup demografik veriler, postoperatif komplikasyonlar ve ek girişim gerekliliği açısından karşılaştırıldı.
Bulgular: Grup 1'deki hastaların yaş ortalaması 51,4±1,05, grup 2'deki hastaların yaş ortalaması ise 48,7±1,08 yıldı. Postoperatif 1. ayda istenen bilgisayarlı tomografide grup 1'de 27 hastada (%21), grup 2'de ise 26 hastada (%20) rezidü taş saptandı. Operasyon başarısı açısından iki grup benzerdi (p=0,878). Yine gruplar arasında Postoperatif ateş (p=0,46), sepsis gelişimi ve yoğun bakım ihtiyacı açısından fark izlenmedi (p=0,46).
Sonuç: Pozitif idrar kültürü olup da antibiyotik alırken yapılan PNL enfeksiyöz komplikasyonları artırmamaktadır.
Anahtar Kelimeler: Ürolithiazis, Perkütan nefrolitotomi, İdrar kültürü

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Introduction

Percutaneous nephrolithotomy (PNL) is the first treatment option for kidney stones that are 2 cm and larger in diameter (1). Postoperative fever is the most common complication occurring in 21-39% of patients and sepsis may develop in 0.3-9.3% (2). The value of preoperative urine culture in predicting postoperative infection has been investigated (3). Nevertheless, it is currently controversial whether urine culture positivity is a risk factor for infectious complications such as postoperative fever and sepsis (3). In this study, the results of PNL performed in patients with positive urine culture were reviewed and evaluated with a view to determine whether positive urine culture can be recognized as a risk factor for infectious complications.

Materials and Methods

Data of patients who underwent PNL between 2008 and 2015 were reviewed. Patients younger than 18 years of age and those with urinary tract anomaly were excluded from the study. Study groups were formed with respect to preoperative urine culture results. Group 1 included 126 patients with positive urine culture and antibiogram results. In these patients, appropriate antibiotic treatment was initiated 72 h before the operation and continued until postoperative fourth day (3). As the control group, 130 patients were randomly selected among patients with preoperative negative urine culture and named as group 2. Intraoperative single dose prophylaxis with 2nd generation cephalosporin was performed in patients of Group 2. All patients underwent preoperative non-enhanced computed tomography (CT) of the whole abdomen. Patients with only one calyx or a pelvic stone were classified as having simple stones, those with one or more calices and pelvis stones or those with staghorn stones were classified as having complex stones (4). The time from the administration of the contrast medium to the patient while in the prone position until the insertion of the nephrostomy catheter was recorded as the operation time. We also recorded the data such as fluoroscopy and operation time, access number and intraoperative complications if occurred. At the end of the operation, a 14 Fr re-entry Malecot catheter was placed in all patients. The Malecot catheter was removed on the postoperative day 1-3. The groups were compared with respect to demographic data, postoperative complications and additional interventions. At postoperative 1st month, all the patients were reassessed routinely by non-enhanced CT. The presence of residual fragments ≤4 mm or a complete clearance of the stones was accepted as treatment success (5). Stone analysis is not covered by the social security institution in our country; therefore, we have insufficient information about stone types in this study. Informed consent was obtained from all patients before surgery.

Statistical Analysis

In the comparison of two or more groups, the number of subjects in each group should be equal or close to each other. For this reason, we used simple random sampling to determine 130 subjects in the culture-negative group. SPSS package program was used for sampling. A chi-square test was used to evaluate the differences in categorical variables between the groups. The Mann-Whitney U test was used to compare the differences between two independent groups. A p value of ≤0.05 was considered significant. IBM SPSS (Statistical Package for the Social Sciences) software (version 15.00) was used for statistical analysis.

Results

The data of 958 patients who met the study criteria were reviewed and groups were established. According to demographic data, 39 were male (31%) and 87 (69%) were female in group 1; eighty five were male (65%) and 45 were female (35%) in group 2. The number of females was significantly higher in group 1 (p=0.001).

The mean age in group 1 and group 2 was 51.4±1.05 years and 48.7±1.08 years, respectively. There was no significant difference in mean age between the groups (p=0.07). In group 1, 68 patients were operated on the left kidney and 58 on the right kidney. In group 2, 84 patients were operated due to kidney stones on the left side while 46 patients on the right side. There was no difference between the two groups in terms of the operation site (p=0.08). Of the patients in group 1, 82 (65%) had simple stones and 44 (35%) had complex stones. In group 2, 74 patients (56.9%) had simple stones and 56 patients (43.1%) had complex stones. In terms of stone burden, the groups were found to be similar (p=0.2). The mean duration of operation was 60.6±3.1 minutes in the urine culture-positive group and 65.3±4.4 minutes in the urine culture-negative group. There was no significant difference between groups in terms of the duration of operation (p=0.08). The mean duration of fluoroscopy was 151.9±15.4 seconds in group 1 and 160.8±12.2 seconds in group 2. The groups were similar statistically in terms of the mean duration of fluoroscopy (p=0.65). The number of accesses performed during the operation was also analyzed between the groups. In the culture-positive group, 111 patients had single access, 13 had two accesses, and 2 patients had three accesses. In the culture-negative group, 117 patients had single access, 11 had two, and 2 patients had three accesses. The two groups were alike in terms of the number of accesses (p=0.87).

Evaluation of the groups in terms of access site revealed that 103 (81.7%) patients in group 1 had subcostal and 23 (18.3%) had intercostal access. In group 2, 111 (85.3%) patients had

subcostal and 19 (14.7%) had intercostal access. The groups were found to be similar in terms of access side (p=0.5) (Table 1).

Blood transfusion was performed in 2 patients in group 1 and 1 patient in group 2 due to hemorrhage resulting in intraoperative low blood pressure. The two groups displayed no difference regarding need for intraoperative blood transfusion (p=0.618). No other intraoperative complication except hemorrhage was detected.

In addition, 12 patients (9.5%) in group 1 and 2 patients (1.5%) in group 2 received blood transfusion due to postoperative hemodynamic instability. Need for postoperative transfusion was considered grade 2 surgical complication according to the Modified Clavien Classification System. Therefore the two groups showed some difference in the way of postoperative blood transfusion requirement (p=0.005). Fever over 38 °C was detected before discharge in 19 patients with positive urine culture and in 15 patients with negative urine culture. The groups were similar in the way of fever (p=0.46). Fever was classified as grade 1 complication. Three patients in group 1 and 4 patients in group 2 required intensive care due to sepsis. They were closely monitored in the intensive care unit and discharged uneventfully. The need for intensive care was considered as Clavien grade 4a and there was no statistically significant difference in sepsis development and intensive care need between the groups (p=0.733). Residual stones were observed in 27 patients (21%) in group 1 and 26 patients (20%) in group 2. The groups were similar in terms of treatment success (p=0.878). The groups were also evaluated regarding postoperative additional interventions. In the urine culture-positive group, 7 patients (5.5%) required additional interventions after discharge, 3 patients received a double J stent (DJS) due to discharge from the wound site and severe colic pain, 3 patients underwent ureterorenoscopy (URS), and one patient was kept under observation because of postoperative intermittent hematuria. In one patient, selective angiography revealed arteriovenous fistula and subsequent superselective embolization was performed, and the patient was discharged after embolization without any additional treatment. In group 2, 12 patients required additional interventions. Three patients received a DJS due to discharge from the wound site. URS was performed in 9 patients (9.2%) because of ureteral calculi (p=0.924). Additional intervention requirement was classified as grade 3 complication and no significant difference was found between the groups regarding any need for additional intervention (p=0.342) (Table 2).

Table 1. Significant preoperative and intaoperative data of the patients

	Group 1 (n=126)	Group 2 (n=130)	p
Mean age (years)	51.4	48.7	0.07
Gender (%)			0.001
Male	39 (31)	85 (65)	
Female	87 (69)	45 (35)	
Stone burden (%)			0.2
Simple	82 (65)	74 (85.3)	
Complex	44 (35)	56 (14.7)	
Operation time (minutes)	60.6	65.3	0.08
Fluoroscopy time (seconds)	151.9	160.8	0.65
Access site (%)			0.5
Subcostal	103 (81.7)	111 (88.6)	
Intercostal	23 (18.3)	19 (11.4)	
Number of access			0.87
One	111	117	
Two	13	11	
Three	2	2	
Stone free status (%)	99 (79)	104 (80)	0.878

Discussion

Since Wickham's (6) first series published in 1981, PNL has replaced open stone surgery today almost completely, with high success rates and low complication rates. It is a widely used method which is recognised as minimally invasive and its complications are well known (1). Although post-PNL fever is the most common complication, sepsis and related mortality are rare (1). The CROES study group identified preoperative urine culture positivity as an independent risk factor for postoperative fever (3). Again, el Nahas et al. (7) reported that preoperative positive urine culture is a significant predictor of infectious complications. In their study, Mariappan et al. (8) reported that positive urine culture was not related to the development of infection in the postoperative period. In another study, it was

Table 2. Intraoperative and postoperative complications of the groups

	Group 1 (n=126)	Group 2 (n=130)	p
Intraoperative transfusion (%)	2 (1.5)	1 (0.7)	0.618
Postoperative transfusion(%)	12 (9.5)	2 (1.5)	0.005
Postoperative fever (%)	19 (15)	15 (11.5)	0.46
Sepsis and requirement for ICU (%)	3 (2.3)	4 (3)	0.733
Additional intervention			
URS	3	9	0.342
DJS	3	3	
Embolisation	1	-	

ICU: Intensive care unit, DJS: Double J stent, URS: Ureterorenoscopy

pointed out that mid-stream urine cultures did not reflect the presence and type of bacteria in the upper tract while positive stone culture was significant for postoperative infectious complications and for sepsis (9). Apparently, the predictive value of preoperative urine culture positivity in PNL for postoperative complications is still controversial. The aim of our study was to compare infectious complications such as fever and sepsis between patients who had positive urine culture and accordingly received antibiotherapy 72 h before the operation until 4th day postoperatively (group 1) and patients who had negative urine culture and received a single dose of prophylaxis (group 2). In accordance with the literature (10), we observed that there were more females than males in urine culture-positive group. Other demographic data of the patients showed no difference between the two groups (Table 1). Postoperative fever was detected in 19 patients of group 1 and in 15 patients of group 2, and these patients were treated with broad spectrum antibiotics. Sepsis was detected in 3 patients of group 1 and 4 patients of group 2, and they were treated in the intensive care unit and none of them died from septic shock. There was no statistically significant difference between the groups in terms of fever and sepsis. When the groups were compared in terms of additional interventions, no difference was found between the groups regarding to complications URS, DJS insertion and angioembolization (Table 2). Hemorrhage in PNL is classified as intraoperative, immediate, postoperative, and delayed. Although hemorrhage is common, transfusion need is rare. The rate of transfusion requiring hemorrhage was reported to be 7% (0-20%) in a study (11). In our study, however, it was 9.5% in group 1 and 1.5% in group 2. Although our rates of transfusion were not significantly different from the cases in the literature, group 1 displayed a significantly higher rate (Table 2). The rate of treatment success in PNL has been reported to be between 76% and 84% (12). In our study, however, it was found to be 79% in group 1 and 80% in group 2. There was no difference between the groups in this regard. In addition, our success rates were compatible with the literature (Table 1).

Study Limitations

The groups could not be compared in terms of co-morbidity because of the retrospective design of the study and the operations were not performed by the same surgeon. Relatively low number of patients was another limitation of our study.

Conclusion

We may speculate that PNL operations did not increase infectious complications when performed in patients with positive urine culture and treated with relevant antibiotics starting from preoperative 3rd day until postoperative 4th day. Prospective studies with larger patient series are required to conclude with definite judgments on this subject which is still being discussed in the literature.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Diode 980 nm Laser Vaporesection of the Prostate: A Comparison of 150 to 250 Watt

Diode 980 nm Lazer ile Prostat Vaporezeksiyonu: 150 ve 250 Watt Karşılaştırılması

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

To the best of our knowledge, there are no large studies showing the efficacy and morbidity for 250 Watt diode laser for endoscopic prostate vaporization or vaporesection. We showed that it is more efficient than 150 Watt and it can be used safely for large prostates.

Abstract

Objective: The aim of this study is to compare the efficacy and morbidity of the diode 980 nm laser at two different power settings for vaporesection of the prostate.

Materials and Methods: A retrospective evaluation of patients who were operated for benign prostatic enlargement by the same surgeon at two different laser power settings. A hundred thirty six patients included in the study were consecutively randomized into 2 groups by certain time periods. The first group consisted of 57 patients with benign prostatic hyperplasia who were treated with 150 Watt and the remaining 79 treated with 250 Watt. International Prostate Symptom Score (IPSS), IPSS-quality of life (QoL), prostate volume, postvoid residual urine, maximum flow rate (Q_{max}) and prostate specific antigen (PSA) levels were recorded preoperatively and at 3 and 12 months postoperatively. Total energy consumption, lasing times and complications were noted.

Results: IPSS, Q_{max} and IPSS-QoL improved significantly in both groups in accordance with the decrease in prostate volume, postvoid residual and PSA levels. IPSS, Q_{max} improvement and prostate volume reduction were greater in the second group at the 12^{th} month. Early postoperative irritative symptoms such as dysuria and urge incontinence were significantly more common in the first group ($p<0.05$). Infravesical obstruction due to necrotic prostate tissue, which required secondary intervention, solely occurred in 5 patients of the second group.

Conclusion: Both power settings provided adequate patient satisfaction and significant improvements in objective outcome parameters in the long term, however, high power settings would be preferred for bigger glands for greater volume reduction.

Keywords: Diode laser, Prostatectomy, Vaporisation, Vaporesection, Prostate, Benign prostate hyperplasia, Infravesical obstruction

Öz

Amaç: Bu çalışmanın amacı, iki farklı güç seçeneği kullanılarak yapılan 980 nm diode lazer ile prostat vaporezeksiyonu operasyonlarını etkinlik ve morbidite açısından kıyaslamaktır.

Gereç ve Yöntem: Benign prostat büyümesi tanısı ile lazer prostatektomi uygulanan 136 hastanın ameliyat sonrası takiplerindeki bulgularının retrospektif olarak incelendiği bir çalışmadır. Hastalar ameliyat oldukları tarih aralıklarına göre gruplara iki farklı lazer güç seçeneği ile opere olmuş ve buna göre iki gruba ayrılmıştır. İlk grup 57 hastadan oluşmaktadır ve bu hastalar 150 Watt güç kullanılarak opere edilmiştir. İkinci grup ise 79 hastadan oluşmaktadır ve 250 Watt ile opere edilmiştir. Tüm hastaların Uluslararası Prostat Semptom Skoru (IPSS) ve IPSS-yaşam kalitesi (QoL) skorları, prostat hacimleri, maksimum akış hızı (Q_{max}) değerleri ve prostat spesifik antijen (PSA) seviyeleri preoperatif ve postoperatif 3. ve 12. ayda kayıt edilmiştir. Toplam harcanan enerji, lazer kullanım süreleri ve komplikasyonlar da kayda alınmıştır.

Bulgular: IPSS, Q_{max} ve IPSS-QoL parametreleri her iki grup için de prostat hacmi, postvoid rezidü ve PSA seviyelerindeki azalmayla uyumlu olarak belirgin olarak düzelmiştir. On ikinci ay kontrolünde IPSS skor artışı, Q_{max} değerlerindeki artış ve prostat hacim küçülmesi 2. grup için daha belirgin olmuştur. Erken postoperatif irritatif semptomlar ise ilk grupta daha yüksek oranda görülmüştür ($p<0,05$). İkincil müdahale gerektiren nekrotik prostat dokusuna bağlı infravezikal obstrüksiyon 5 hastada görülmüştür.

Sonuç: Uzun vadede her iki güç seviyesinde de hasta memnuniyeti ve objektif parametrelerde belirgin gelişmeler elde edilmekteyse de, yüksek güç seviyesi özellikle daha büyük prostat hacimlerinde daha etkili olmuştur.

Anahtar Kelimeler: Diode lazer, Prostatektomi, Vaporizasyon, Vaporezeksiyon, Prostat, Benign prostat hiperplazisi, İnfravezikal obstrüksiyon

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Introduction

Various lasers at different wavelengths and power settings have been used for benign prostatic hyperplasia (BPH) as proven alternatives to the gold standard transurethral resection of the prostate (TURP) (1). Laser vaporization and vaporesection are more widely used due to a relatively short learning curve compared to enucleation. TURP has its own drawbacks despite still being considered as the gold standard for the surgical treatment of BPH. Size of the gland (i.e., greater than 80 g) and high risk in patients with bleeding tendency in whom anticoagulant use is a must, are among the primary limitations (2,3,4). Since the introduction of 80 Watt potassium-titanyl-phosphate (KTP) 532 laser, both the fiber durability and the laser power have been among the major concerns despite successful initial short term results (5). Therefore, the power of KTP 532 has been increased from 80 to 180 Watt, and more durable fiber was concomitantly developed (6,7,8). Similar attempts have also been made for 980 nm wavelength diode lasers. While the power has been increased from 100 Watt to 300 Watt, side firing fiber was completely replaced by the Twister™ fiber, which allows working in the contact mode as the easiest way of resection or vaporization (9). According to our earlier experience obtained from KTP 532 and 980 diode lasers, higher power increases the speed of vaporization as well as possibility of higher complication rates particularly in the hands of an inexperienced surgeon (10). Considering the fact that men use more anticoagulants as they get older as most of BPH patients who need surgical intervention in an increasing manner, lasers, with no distinction among them, constitute better alternatives for such patients (11,12). The size is not a contraindication for laser enucleation, however, vaporization or vaporesection works as a function of time depending upon the fiber durability (13). Long and steep learning curve of enucleation prevents its worldwide use contrary to the easier vaporization or vaporesection techniques (14). Although successful reports appeared in the literature, even with the powers as low as 80 Watt, higher reoperation rates in the long term have led to the new developments both in power as well as fiber technology. KTP 532 reached up to 180 Watt power, with self-cooling fiber, on the other hand, 300 Watt 980 nm diode lasers are now in use with uniquely designed fiber. Twister™ fiber allows working in the contact mode, being capable of both resection and vaporization, not requiring special expertise as long as the surgeon is familiar with TURP. We have been able to speed up the vaporization parallel to the increasing power, however, it is not known what should be the uppermost energy level, which is adequately effective while keeping the patients out of the harm's way. Enucleation using holmium laser at the power as low as 50 Watt has been successful (15). Therefore, high powers may only be necessary when vaporization or vaporesection is attempted. Hence, we compared the two different power settings at the same wavelength to seek an answer to this question. In this study, we compared the data obtained from a 3-year period of laser vaporization with 980 nm diode using Twister™ fibers at two different powers, 150 and 250 Watt, regarding their efficacy as well as complication rates.

Materials and Methods

Patients who were operated for benign prostatic enlargement at two different laser power settings were retrospectively evaluated. The patients were selected consecutively by a certain time period which they were operated. The first treatment arm (180 Watt) consisted of patients who were operated between January 2014 and December 2015. The second treatment arm (250 Watt) consisted of patients who were operated between January 2015 and December 2016. All the operations were made by the same surgeon.

A total of 136 patients, who underwent laser prostate vaporesection, were included in the study. Digital rectal examination (DRE), urinalysis, International Prostate Symptom Score (IPSS), quality of life (QoL) assessment, uroflowmetry, prostate volume and postvoid residual (PVR) urine volume measurement via transabdominal ultrasound were performed, and serum prostate specific antigen (PSA) levels were evaluated prior to the operation. The possibility of prostate cancer was excluded in patients with suspicious DRE findings and/or a high PSA level by prostate biopsies. The patients on warfarin were switched to a low molecular heparin when possible, whereas aspirin use was not a contraindication. An informed consent was obtained from each patient prior to the operation. Data were analyzed after approval of the İstanbul Bahçeşehir University Ethics Committee (number: BAU- 2013/U1).

Patients were elected for surgery if they had urinary retention or a maximum flow rate (Q_{max}) <12 mL/sec, PVR >150 mL, IPSS >8 and IPSS-QoL score >3 despite medical therapy. IPSS was considered 35 if the patient had a chronic indwelling catheter. Exclusion criteria were previous lower urinary tract surgery (i.e., urethral stricture, TURP for BPH or bladder tumor), prostate cancer, bladder overactivity, urinary tract infection, and bladder stone.

The first 57 patients (group 1) underwent prostate vaporesection using an older version of 980 nm diode laser (Evolve® laser, Biolitec AG, Germany) with a maximum power of 180 Watt. Since it was replaced by the current version with 300 Watt maximum power, prostate vaporesection was performed at 250 Watt continuous power using the same Twister™ large fiber (Twister™ SF, Biolitec AG, Germany) in the second group of 79 patients (group 2). Twister™ is a recently developed laser fiber with its own angle at the tip, but devoid of internal reflective

mechanisms, which makes it possible to work in the contact mode due to less vulnerability to the reflected beams. There is no energy limit up to a 3.5 hours lifespan.

Urethral catheters were removed on the next day. Prostate volumes, IPSS, Q_{max}, IPSS-QoL score, PVR and serum PSA levels were recorded at 3 and 12 months postoperatively. Total energy consumption and lasing times were noted. Complications were also recorded.

Statistical Analysis

The distribution of variables was tested with the Kolmogorov-Smirnov test. The independent samples t-test and Mann-Whitney U test were used for the comparison of quantitative data. The Wilcoxon test was used for the repeated measurement analysis. Chi-square test was used for the comparison of the qualitative data. SPSS 22.0 was used for statistical analysis. A p value of less than 0.05 was considered statistically significant.

Results

The groups were found to be similar in terms of age (group 1: 72.4±8.2, group 2: 73.8±1, p=0.444) and the number of patients with an indwelling catheter (group 1: 38.2%, group 2: 39.2%, p=0.902) and the American Society of Anesthesiologists physical status (group 1: 2.04±0.90, group 2: 2.47±1.02, p=0.028), however, the number of patients on anticoagulant medications was significantly higher in group 2 than in group 1 (49.1% vs 77.2%, p<0.001).

Preoperative IPSS, Q_{max}, the mean prostatic volume, PVR and PSA levels were similar in both groups as the mean IPSS-QoL score (group 1: 4.6±0.9, group 2: 4.7±0.1, p=0.892). Objective outcome parameters were significantly improved in both groups throughout the follow-up. IPSS improvement was significantly greater in group 2 at 3rd and 12th month. However, Q_{max} value was significantly higher in the second group only at 12 months after surgery (Table 1). Prostate volume reduction was greater in the second group at 3rd and 12th month (p=0.002 and p=0.004).

The mean energy consumption in the first group was 32% lower than the second group (p=0.003), also indicating 17.4% less energy usage per gram of prostatic tissue (p=0.004). Nevertheless, higher power was faster than lower power when the lasing time required per gram of tissue was taken into account (p=0.055) (Table 2). The overall lasing time did not differ significantly (p=0.159).

Of the 79 patients in the group 2, one was unable to void at the first attempt and needed recatheterization and one necessitated a longer catheterization due to hematuria. No transfusion was required. Urinary tract infection and stress urinary incontinence rates were similar. One patient from each group required urethral dilatation due to urethral or bladder neck stricture. Early dysuria and urge incontinence were seen more frequently in group 1 than in group 2 (p=0.016 and p=0.044, respectively) (Table 3). An unexpected complication of high power laser was obstructive necrotic tissue remnants which required re-operation and removal of necrotic tissues in 5 patients of the group 2 who had midsized prostates (<60 g) (Figure 1).

Discussion

In our study, we were able to show that both lasers have equally been effective in terms of objective outcome parameters throughout the follow-up. However, the low power caused

Table 1. Preoperative and follow-up comparative data in each group

Parameter	Follow-up	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	p value
IPSS	Preoperative	27.7±6.7	27.4±7.4	0.742
	3 months	4.6±2.2*	3.7±1.4*	0.011
	12 months	2.9±1.3*	2.3±1.1*	0.003
Q_{max} (mL/sec)	Preoperative	8.0±2.5	7.7±3.5	0.380
	3 months	20.5±5.9*	18.8±3.6*	0.114
	12 months	21.6±5.9*	18.7±3.4*	0.006
Prostate volume (cc)	Preoperative	67.8±32.4	75.3±34.5	0.162
	3 months	32.4±14.6*	32.2±18.3*	0.499
	12 months	29.3±12.9*	28.6±16.3*	0.390
PVR (mL)	Preoperative	127.6±45.1	154.1±67.9	0.747
	3 months	16.7±12.2*	20.8±34.1*	0.394
	12 months	12.5±14.3*	12.8±10.0*	0.876
PSA (ng/mL)	Preoperative	3.5±1.9	5.0±6.9	0.789
	3 months	2.0±1.9*	1.5±0.9*	0.155
	12 months	1.7±1.3*	1.5±0.9*	0.887
IPSS-QoL score	Preoperative	4.6±0.9	4.7±0.1	0.892
	3 months	1.1±0.6*	1.0±0.6*	0.445
	12 months	1.1±0.6*	1.0±0.7*	0.406

IPSS: International Prostate Symptom Score, Q_{max}: Maximum flow rate, PVR: Postvoid residual, PSA: Prostate specific antigen, QoL: Quality of life, SD: Standard deviation
*Highly significant to baseline (p<0.001)

Table 2. Comparison of laser data

Variables	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	p value
Lasing time (min)	45.6±23.5	38.7±19.2	0.159
Energy consumption (kJ)	333±166	440±214	0.003
Lasing time per tissue weight (min/g)	0.45±0.23	0.38±0.19	0.055
Energy consumption per tissue weight (J/g)	4969±1405	6015±2339	0.004

more irritative symptoms in the short term, probably due to shallower coagulation depth at the surface rendering the nerves more susceptible to stimuli in the early postoperative period.

Using side firing fibers for vaporization is somewhat challenging, because the distance between the fiber tip and the tissue should be kept stable during vaporization, working either too close or far from the tissue, may result in fiber damage or coagulation. Contrary, Twister™ fiber obviates the reflected or scattered beams and creates a smaller spot size due to working in the contact mode regardless of the surgical technique. The 980 nm wave length tends to penetrate deeply, however, the power setting and lasing time are the other important determinants with regards to vaporization efficacy and the depth of coagulation as reported by Takada et al. (9) recently. They used bovine prostate as an experimental model to investigate the effects of diode (980 nm) laser at various power settings up to 300 Watt and irradiation times. They concluded that the speed of vaporization and depth of coagulation were correlated with the power and irradiation times up to 250 Watt. Conversely, increasing the power from 250 Watt to 300 Watt did not increase vaporization efficiency but the depth of coagulation. Therefore, limiting the uppermost energy level at 250 Watt seems reasonable, considering the fact that the animal model was devoid of blood circulation.

Table 3. Comparison of postoperative complications

Complications	Group 1	Group 2	p value
Significant hematuria	0	1 (1.3%)	0.418
Retention during hospital stay	0	1 (1.3%)	0.418
Dysuria	11 (20.0%)	5 (6.3%)	0.016
Urge incontinence	6 (10.9%)	2 (2.5%)	0.044
Stress incontinence	0	3 (3.8%)	0.269
Urinary tract infection	0	2 (2.5%)	0,512
Bladder neck contracture	1 (1.8%)	1 (1.3%)	0.788
Obstructive necrotic tissue	0	5 (6.3%)	0.059

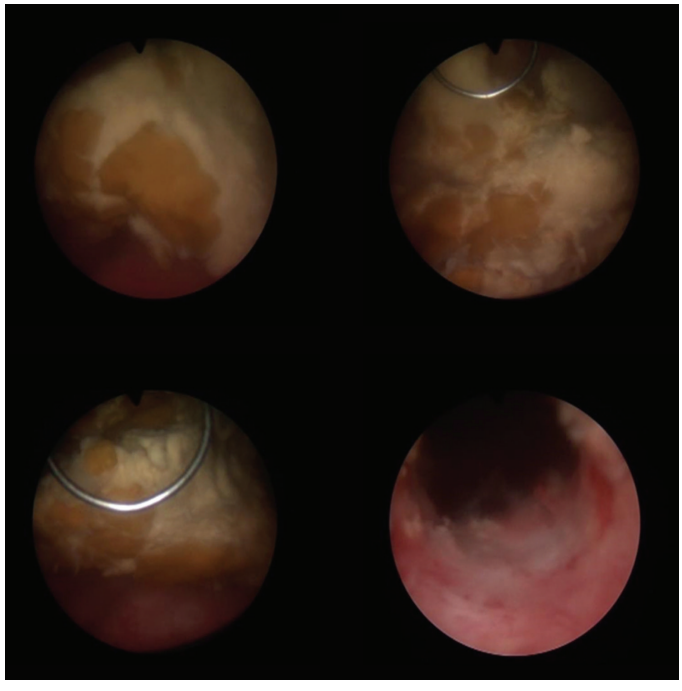

Figure 1. Removal of obstructive necrotic tissue remnants

A more recent study from Turkey by Cetinkaya et al. (16) showed that vaporization of the prostate with a diode laser was as safe and effective as TURP, and both had similar complication rates and functional results. Diode laser has the advantage of shorter hospitalization and catheter indwelling times and there is no need for discontinuation of anticoagulant therapy (16). Bipolar endoscopic enucleation of the prostate was recommended by the 2016 European Association of Urology guidelines as the first choice of surgical treatment in men with a substantially enlarged prostate and moderate-to-severe lower urinary tract symptoms and it is getting more popular in the last few years. In their randomized controlled study, Zou et al. (17) from China demonstrated that diode laser prostate enucleation was non-inferior to bipolar enucleation regarding Q_{max} and IPSS at 12 months postoperatively.

Our data revealed 17.4% faster speed with 250 Watt at a cost of 32% more energy consumption. This suggests that a substantial amount of energy may go deeper leading to a larger coagulation zone, which may be followed by a larger tissue sloughing or even a total transitional zone necrosis, albeit rare. A deep vascular compromise may also be responsible for this phenomenon apart from homogenous deep coagulation. Patients usually describe the evacuation of necrotic pieces during micturition, which may not be possible in case of poor bladder contractility or in the presence of big pieces of necrotic tissue. Timing of obstruction due to necrotic tissues is variable. It may develop a couple of months after the operation. Urinary difficulties or complete urinary retention may suggest obstructive necrotic tissue, which requires re-intervention. Fortunately, the necrotic tissues were well demarcated facilitating removal without using energy in most cases. Simply pushing the necrotic tissues towards the bladder followed by irrigation is enough, however, forceful maneuvers should be avoided if a resistance is encountered. Suprapubic methylene blue injection into the bladder may be useful as a guide in cases with severe obstruction. Patients may require cystostomy due to complete obstruction prior to the surgical intervention. We prefer 5 and 7 o'clock bladder neck incision in case of bladder neck stenosis after removal of the necrotic tissues. No recurrent obstruction has occurred in these patients. Fortunately, the external sphincter has always remained intact even in cases with total necrosis and obstruction. Necrotic tissue remnants tended to occur in the older and diabetic patients with relatively small prostates (<60 mL), who supposedly had

poorer bladder contractility not enough to completely wash out the large necrotic tissues. These tissues attracted calcium salts thereby frequently calcified in case of long lasting.

Study Limitations

The main limitation of this study was the retrospective and non-randomised design. We did not focus on the complications including retrograde ejaculation and erectile dysfunction and we encourage further studies concerning about these.

Conclusion

Both power settings at 250 or 150 Watt using Twister™ fiber are capable of relieving the symptoms of BPH in a safe manner. High-power 250 Watt 980 nm diode laser is faster and it may be preferred for big sized glands. It also cause less irritative symptoms during the early postoperative period, however, necrosis of the remaining tissue may lead to secondary intervention as far as smaller prostates are concerned (i.e.,<60 mL). Therefore, the power may be adjusted to a lower level accordingly as the prostate gets smaller.

Ethics

Ethics Committee Approval: The approval was taken from the İstanbul Bahçeşehir University Ethics Committee (number: BAU-2013/U1).

Informed Consent: All patients included signed an informed consent form.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Evaluating Knowledge of Autonomic Dysreflexia Among Physicians in a Tertiary Hospital

Bir Üçüncü Basamak Hastanesindeki Hekimler Arasında Otonomik Disrefleksinin Bilinirliğinin Değerlendirilmesi

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

Autonomic dysreflexia is a potentially life-threatening emergency status in patients with spinal cord injury involving the level of T6-T8 or above. Therefore, prevention and early diagnosis of autonomic dysreflexia is of vital significance. However, previous studies revealed that health care workers, patients and their families, and caregivers had inadequate knowledge about autonomic dysreflexia. Studies focusing on the physician' knowledge of autonomic dysreflexia are very limited. This is the first study investigating the knowledge of autonomic dysreflexia among physicians of the relevant departments in the literature.

Abstract

Objective: To evaluate the level of knowledge of autonomic dysreflexia among physicians practicing in different disciplines namely anesthesia and reanimation, emergency, neurology, neurosurgery, urology, and physical medicine and rehabilitation departments.
Materials and Methods: The study was conducted using a questionnaire consisting of seven questions, which was completed in a prospective manner by 95 physicians (residents and consultants) in our tertiary care hospital.
Results: None of the questions asked in the questionnaire could be replied by 38 (40%) of 95 physicians in the hospital. Only one physician did reply all the questions completely. The mean value of the mark given was 2.00±2.04 for consultants and 1.10±1.37 for residents (p=0.039). Our data showed that while only 27% of the physicians have received training on autonomic dysreflexia; 18% of physicians had a previous experience with patients having autonomic dysreflexia.
Conclusion: Taking the potential serious complications of autonomic dysreflexia into account, necessary information on this emergency status should be given to physicians. We believe that to reach a more precise conclusion about awareness of physicians on autonomic dysreflexia, multicenter studies with larger number of participants are certainly necessary.
Keywords: Autonomic dysreflexia, Spinal cord injury, Physician, Knowledge

Öz

Amaç: Farklı branşlarda (anestezi ve reanimasyon, acil tıp, nöroloji, beyin cerrahisi, üroloji, fizik tedavi) çalışan hekimlerin otonomik disrefleksi hakkındaki bilgi düzeylerini değerlendirmek amaçlandı.
Gereç ve Yöntem: Yedi sorudan oluşan ölçme ve değerlendirme anketi hastanemizde çalışan uzman ve asistanlardan oluşan 95 hekime uygulandı.
Bulgular: Hekimlerin %40'ı hiçbir soruyu yanıtlamadı. Sadece bir hekim tüm soruları tam olarak yanıtladı. Uzmanların ortalama puanı 2,00±2,04, asistanların ise 1,10±1,37 idi (p=0,039). Hekimlerin %27'si otonomik disrefleksi hakkında eğitim almıştı ve %18'i daha önce otonomik disrefleksi atağı geçiren hastayı görmüştü.
Sonuç: Otonomik disrefleksinin potansiyel ciddi komplikasyonları dikkate alındığında hekimlere bu konuda daha yoğun bir eğitim verilmelidir. Kesin sonuca varmak için çok merkezli, daha fazla katılımcıyı içeren çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Otonomik disrefleksi, Spinal kord yaralanması, Hekim, Bilgi

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Introduction

Autonomic dysreflexia is a potentially life-threatening emergency status in patients with spinal cord injury involving the level of T6-T8 or above. An uncontrolled reflex sympathetic discharge occurs as a result of loss of the autonomic response that coordinates heart and vascular tone to sensorial stimuli (1,2,3). Distal cord viability is a prerequisite (1).

Autonomic dysreflexia may occur in patients with complete or incomplete spinal cord injury, tumors and autoimmune-induced myelodysplasia (3,4,5). The frequency of autonomic dysreflexia has been reported to be 20% to 70% in cases with chronic spinal cord injury at the level of T6 or above (6). Usually, the symptoms start after the spinal shock period but it may take several years after injury to observe this pathology (1,2,3).

Autonomic dysreflexia is triggered by a massive discharge of the sympathetic preganglionic neurons. Stimuli from the urinary bladder, intestine, striated muscle, and skin cause this sympathetic discharge (3). Genitourinary organ-originated stimuli are the most common causes (81%-87%) (7). The second source of stimuli is the gastrointestinal tract (20%) (6,7,8).

Early diagnosis of autonomic dysreflexia is of paramount importance and physicians should remember the pathology in the presence of minimal symptoms or sometimes even in the absence of characteristic symptoms. Characteristic symptoms of autonomic dysreflexia are paroxysmal hypertension, pounding headache, bradycardia and sweating and flushing above the level of the lesion, and piloerection below the level of the lesion (1,2,3). The classical symptoms triad including severe headache and sweating and vasodilatation of the skin above the level of the lesion may be detected in around 85% of patients (3). Symptoms may be atypical or minimal (silent autonomic dysreflexia) (2,3,6). Migraine, pheochromocytoma, cluster headache, and posterior cranial fossa tumors should be considered in the differential diagnosis (3).

In this study, we aimed to evaluate the level of knowledge of autonomic dysreflexia among physicians working in the relevant departments (anesthesia and reanimation, emergency medicine, neurology, neurosurgery, urology and physical medicine and rehabilitation departments) in our hospital.

Materials and Methods

This study was performed in a training and research hospital. A measurement and evaluation questionnaire previously used in a study of the knowledge of autonomic dysreflexia (9) was utilized. The questionnaire consists of seven questions about description, clinics, treatment, and complications of autonomic dysreflexia. Additionally, all participant physicians were asked if they had evaluated any patient with autonomic dysreflexia attack and undergone training about autonomic dysreflexia.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. The study did not have approval of the ethics committee but, informed consent was obtained from all participants for being included in the study.

A hundred five physicians worked in the different clinics of the hospital where the study was conducted. Ten of them did not participate in the study. The questionnaire was administered to 49 residents and 46 consultants, totally 95 physicians. The questionnaire was distributed to the physicians working in the anesthesia and reanimation (residents n=19, consultants n=16, total: 35), emergency medicine (residents n=14, consultants n=8, total: 22), neurology (residents n=4, consultants n=3, total: 7), neurosurgery (residents n=4, consultants n=7, total: 11), urology (residents n=8, consultants n=8, total: 16), and physical medicine and rehabilitation (consultants n=4) departments at our hospital and the participants were asked to fill out the questionnaire in fifteen minutes during consecutive two days. Subsequently, a review of autonomic dysreflexia was delivered to all participants and they were informed about autonomic dysreflexia (10). The responses were evaluated and compared with the standardized answers. One point was scored for each correct response for a maximum of 7 points (Table 1).

Statistical Analysis

Descriptive data were presented as percentage and mean ± standard deviation. Normality of the data was assessed using the Kolmogorov-Smirnov test. Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared by a chi-square test. The Kruskal-Wallis test was used to compare three or more unmatched groups. A p value of less than 0.05 was considered statistically significant. Statistical analyses were performed using the GraphPad Prizm 5.0 software.

Results

Ninety-five physicians (64% men and 36% women) responded to the questionnaire with a response rate of 91%. The mean age of the respondents was 37.9±9.2 years.

The training and experience rates in consultant and residents are shown in Table 2. Twenty-six physicians (27%) had previously received training about autonomic dysreflexia and 17 of them (18%) reported to evaluate a patient referred with an autonomic dysreflexia attack. While the rate of education among the residents was the lowest in the neurosurgery clinic (0%), the highest rates were obtained in the urology (63%) and anesthesia clinics (37%); at the same time, the rate of education

among consultants was the lowest in the neurologist and neurosurgeons (0%), and the highest in the physical medicine and rehabilitation consultants (75%). The rates of experience on autonomic dysreflexia attacks among residents were the lowest in the neurosurgery clinic (0%), and the highest in the neurology clinic (50%). These rates among consultants were the lowest among the neurologists and the brain surgeons (0%), and the highest in the physical medicine and rehabilitation consultants (75%).

Thirty-eight physicians (40%) participating in this study could not answer any question. Only one consultant answered all the questions correctly. There was no statistically significant differences in these parameters between consultants and residents (p>0.05) (Table 2).

Table 1. Questions and answers about autonomic dysreflexia (10)

Question 1	**What is the autonomic dysreflexia?** Sympathetic outflow, noxious stimuli below lesion, unopposed
Question 2	**What are the signs and symptoms of autonomic dysreflexia?** Flushing and sweating above injury, nasal stuffiness, goosebumps and paleness below injury, hypertension, bradycardia, pounding headache, blurred vision and spots invisual fields, arrhythmias, anxiety
Question 3	**Who is at risk of autonomic dysreflexia?** Spinal cord injury at or above T6
Question 4	**What are the common causes of autonomic dysreflexia?** One each for bladder distension, bowel distension, then 1/2 for any others
Question 5	**What is the treatment for autonomic dysreflexia?** Recognize signs, sit up, check blood pressure, loosen clothing, treat cause, and check catheter, check bowel, pain relief, and glyceryl trinitrate spray
Question 6	**What are the potential complications of autonomic dysreflexia?** Intracranial hemorrhage, convulsions, death
Question 7	**What is the normal systolic blood pressure in tetraplegic patients?** 90-110 mmHg

Table 2. Training, experience, null and full response rates of physicians

	Consultant (n=46) n (%)	Resident (n=49) n (%)	Total (n=95) n (%)	p value*
Training	11 (24)	15 (31)	26 (27)	0.498
Patient experience	11 (24)	6 (12)	17 (18)	0.183
No response	14 (30)	24 (49)	38 (40)	0.093
Full response	1 (2)	0 (0)	1 (1)	0.484

*Chi-square test

The rate of correct answer to the 1st question among was lower among the consultants (22%), and higher to the 3rd question (50%). However, the rate of correct answer to the 4th question was lower among the residents (8%) and higher to the 3rd question (37%).

Scores of consultant and resident physicians are given in Table 3. There was a statistically significant difference in scores between consultants and residents (p=0.039). Although consultants in the physical medicine and rehabilitation department had the highest score, those in the urology clinic had the lowest score. There was a statistically significant differences in scores between consultants from different sections (p=0.020). The scores of residents were the highest in the anesthesia clinic and the lowest in the urology clinic. There was no statistically significant differences in scores between residents from different sections (p=0.386) (Table 3).

Discussion

Being first reported as a case report by Hilton in 1860 and then by Bowlby in 1890 (2); autonomic dysreflexia represents a fatal complication of spinal cord injury. The pathology has been defined in several forms namely autonomic hyperreflexia, spinal poikilopiesis, neurogenic paroxysmal hypertension, autonomic dysreflexia, sympathetic hyperreflexia, mass reflex, and neurovegetative syndrome (3,7).

The basics of effective treatment principles for this pathology are the recognition of symptoms and signs along with the prevention the precipitating causes. Related with this subject, early identification and elimination of triggering factors followed by an immediate pharmacological treatment are very important to prevent complications including intracranial and retinal bleeding, convulsions, cardiac arrhythmias and death (3,7)

Table 3. Scores of consultants and residents from different sections (mean ± SD)

Department	Consultant (n=46)	Resident (n=49)
Anesthesia and reanimation	1.16±1.48	1.55±1.75
Emergency medicine	3.14±2.34	1.21±1.17
Neurology	3.25±1.77	0.50±1.00
Neurosurgery	1.93±1.64	0.63±0.75
Urology	1.00±1.54	0.38±0.52
Physical medicine and rehabilitation	4.88±2.02	-
Total	2.00±2.04	1.10±1.37
p value*	0.020	0.386

SD: Standard deviation
*Kruskal-Wallis test

This study demonstrates that physician awareness of this condition is inadequate. Additionally, there are differences in knowledge of autonomic dysreflexia between physicians from different departments. This may be due to lack of experience and training in this regard. As a matter of fact, doctors who were trained and experienced, such as physical medicine and rehabilitation consultants, had higher scores.

It is vital that all patients and caregivers of patients with spinal cord injury must be properly educated about autonomic dysreflexia. Clinicians are responsible for educating patients and caregivers of patients with spinal cord injury. Therefore, lack of their knowledge will lead to inadequate awareness of autonomic dysreflexia among patients and their caregivers. The reason for lack of awareness of this issue which may result in extremely serious consequences was lack of appropriate training programs for the related physicians in this regard. Our findings indicate that the knowledge of autonomic dysreflexia should be well instituted with appropriate and adequate educational programs.

It has been reported by several studies that knowledge of autonomic dysreflexia among physicians was very limited. Jackson and Acland (9) found that health care workers (doctors and nurses) practicing in emergency department and spinal unit had limited information about autonomic dysreflexia. While Sullivan et al. (11) emphasized the actual need for training for dentists about autonomic dysreflexia, in another study, McGillivray et al. (12) have shown that patients with spinal cord injury and their families had poor awareness of autonomic dysreflexia. Schottler et al. (13) also found that patients with spinal cord injury and their caregivers had inadequate knowledge of autonomic dysreflexia.

This is the first study investigating the knowledge of autonomic dysreflexia among physicians from the related departments only. In our study, to outline the level the knowledge of autonomic dysreflexia; a questionnaire-based study was performed among physicians practicing in different disciplines that may provide care to patients suffering autonomic dysreflexia. Additionally all physicians participated in the study were asked to reply if they had any training on autonomic dysreflexia and/or they had any experience with a patient presenting with autonomic dysreflexia attack. Data obtained in our study demonstrated that, knowledge of autonomic dysreflexia was inadequate among residents as well as consultants.

Many unintended consequences may arise since spinal cord injuries are not known well enough by physicians of the departments other than the relevant ones. Therefore, the patients should carry a card containing information related to the likelihood of autonomic dysreflexia problem and patients, patient' families and caregivers as well as medical staff are also needed to be informed and educated on this aspect.

Study Limitations

Our study did not include physicians working in all departments. This issue is the main limitations of this study.

Conclusion

A well programmed training for physicians dealing with patients suffering from spinal cord injury is necessary to prevent serious complications of autonomic dysreflexia. We believe that to reach a more precise conclusion about awareness of autonomic dysreflexia among physicians, multicenter studies with larger number of participants are certainly necessary.

Ethics

Ethics Committee Approval: The study did not have approval of the ethics committee.

Informed Consent: A consent form was completed by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.T., A.C., Concept: F.T., Design: F.T., A.C., Data Collection or Processing: A.C., B.E., Analysis or Interpretation: F.T., A.C., Literature Search: F.T., Writing: F.T., A.C., B.E., K.S.

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ORIGINAL RESEARCH
Urooncology

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Clinical Value of Core Lenght in Saturation Prostate Biopsy

Kor Uzunluğunun Saturasyon Prostat Biyopsisindeki Klinik Önemi

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

To our best knowledge, our study is the first to evaluate the clinical value of total core length in saturation prostate biyopsy. Mean and total core length may not have significant impact on prostate cancer detection in patients receiving saturation prostate biopsy.

Abstract

Objective: To investigate the effect of core length on cancer detection in saturation prostate biopsy. We hypothesized that increasing mean and total core length in saturation prostate biopsy may allow more tissue sampling, thus, may increase the prostate cancer detection rate.
Materials and Methods: We retrospectively analyzed medical records of 145 patients who underwent 24-core transrectal ultrasound-guided saturation biopsy at our institution. We evaluated the clinopathological factors, including age, prostate specific antigen (PSA), prostate volume, mean core length and the total biopsy core length. The patients were divided into 3 groups according to their total biopsy core length; group 1: <20 cm, group 2: 20-30 cm and group 3: >30 cm. These groups were compared according to age, PSA value, prostate volume and cancer detection rate.
Results: The mean age, core length and total core length were 62.4±7.0 years, 10.91±1.8 mm, and 26.2±4.7 cm, respectively. The overall cancer detection rate was 33.8%. There was no statistically significant difference in mean core length and total core length between patients diagnosed with prostate cancer and those without it. The cancer detection rates in group 1, 2 and 3 were 25%, 37.4% and 23.1%, respectively. When these 3 groups were compared with each other, group 2 had a statistically significantly higher cancer detection rate relative to group 1 (p=0.001). Multivariate analysis showed no statistically difference in cancer detection rate between the groups (p=0.302).
Conclusion: Mean and total core length may not have any significant effect on prostate cancer detection in patients undergoing saturation prostate biopsy.
Keywords: Saturation biopsy, Core length, Prostate cancer

Öz

Amaç: Kor uzunluğunun saturasyon prostat biyopsisinde kanser saptamaya etkisini araştırmaktır. Hipotezimiz, ortalama ve toplam kor uzunluğunun artırılması ile daha fazla doku örneği sağlıyacağı için prostat kanseri saptama oranında artış gözleneceğidir.
Gereç ve Yöntem: Kurumumuzda 24 kadran transrektal prostat biyopsisi olan 145 hastanın medikal verilerini retrospektif olarak analiz ettik. Hasta yaşı, prostat spesifik antijen (PSA) değeri, prostat hacmi, ortalama kor uzunluğu, toplam kor uzunluğunu değerlendirdik. Hastalar toplam biyopsi kor uzunluğuna göre üç gruba ayrıldı. Grup 1: <20 cm, grup 2: 20-30 cm ve grup 3: >30 cm. Bu gruplar yaş, PSA değeri, prostat hacmi ve kanser saptama oranlarına göre karşılaştırıldı.
Bulgular: Ortalama yaş, kor uzunluğu ve toplam kor uzunluğu sırasıyla 62,4±7,0 yıl, 10,91±1,8 mm, 26,2±4,7 cm idi. Toplam kanser saptama oranı % 33,8'di. Prostat kanseri olan ve olmayan hasta grupları arasında ortalama kor uzunluğu ve toplam kor uzunluğu açısından istatistiksel anlamlı farklılık yoktu. Grup 1, 2 ve 3'ün kanser saptama oranları sırasıyla %25, %37,4 ve %23,1'di. Üç grup birbirleriyle karşılaştırıldığında grup 2'de kanser saptama oranı grup 1'e göre istatistiksel anlamlı yüksekti (p=0,001). Çok değişkenli analiz ile gruplar karşılaştırıldığında gruplar arasında kanser saptama oranı açısından istatistiksel anlamlı farklılık gözlenmedi (p=0,302).
Sonuç: Ortalama ve toplam kor uzunluğunun prostat saturasyon biyopsisi olan hastalarda prostat kanseri saptamaya anlamlı bir etkisi yoktur.
Anahtar Kelimeler: Saturasyon biyopsisi, Kor uzunluğu, Prostat kanseri

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Introduction

Prostate cancer (PCa) is the most common cancer among men (1). PCa is generally suspected in the presence of abnormal digital rectal examination (DRE) and/or elevated prostate specific antigen (PSA) levels. The definitive diagnosis of PCa depends on histopathological confirmation of carcinoma in prostate biopsy cores (2). The PCa detection rate has been reported to vary between 20% and 25% in the initial biopsy (3). Saturation biopsy involves extensive sampling of the prostate. Saturation techniques do not provide increased cancer detection when used for initial biopsy, but may provide increased sensitivity when repeat biopsies are performed (4). It has been reported in a meta-analysis that the saturation prostate biopsy technique has provided an important advantage in the diagnosis of PCa (5). The PCa detection rate is 30-43% in saturation biopsy and depends on the number of cores sampled during the biopsy; therefore, it may be considered that the amount of prostate tissue obtained in a biopsy may increase PCa detection rate (6,7). We hypothesized that increasing the mean and total core length in saturation prostate biopsy may provide more tissue sampling, thus, this may increase the PCa detection rate.

Materials and Methods

Medical records of 1240 patients, who underwent prostate biopsy in our hospital between June 2013 and August 2016, were retrospectively evaluated. Among these, 145 patients aged 40-80 years, who had a PSA value of less than 30 ng/mL and underwent a second transrectal ultrasound (TRUS)-guided prostate biopsy, were included in the study. These patients had undergone a second prostate biopsy due to elevated PSA values over 4 ng/mL. All second biopsies were performed using the 24-core saturation biopsy scheme. Patients were excluded if at least one biopsy core did not include prostate tissue (containing only rectal mucosa, blood, or periprostatic tissue). Patients were also excluded if they had a prior diagnosis of PCa, abnormal DRE findings, or previous anti-androgen or radiation therapy. Cores with the diagnoses of atypical small acinar proliferation and prostatic intraepithelial neoplasia were classified into benign category.

After having obtained informed consents from the patients, all biopsies were carried out transrectally with ultrasonography guidance using a 25 cm 18-gauge, side-notch cutting (Tru-cut) needle. The biopsies were performed using periprostatic nerve blockage with the patient in the lateral decubitus position. All zones of the prostate were sampled. Each sample was carefully pulled away from the needle and core quality was macroscopically evaluated by the urologist. In case of a poor core quality, another biopsy was obtained from the same site of the prostate. Each sample was transferred to a container including 10% formaldehyde for histopathological examination. Each prostate biopsy core was measured by the pathologist and we summed up these measurements and achieved the total biopsy core length.

After histopathological assessment, we evaluated the clinopathological factors, including age, PSA, prostate volume, mean core length and total biopsy core length. The patients included in the study were assigned into 3 groups according to their length of total biopsy cores. Group 1: <20 cm, group 2: 20-30 cm and group 3: >30 cm. These groups were compared according to age, PSA value, prostate volume and cancer detection rate.

Statistical Analysis

Compliance of the variables to the normal distribution was evaluated using the Shapiro-Wilk test. The descriptive statistics for normally distributed variables and the categorical variables were expressed as mean ± standard deviation and percentages (%). Student's t-test and chi-square test were used for the inter-group analysis of the continuous variables. More than two independent averages were compared with the ANOVA test, Kruskal-Wallis test and the post-hoc Dunn's test. The data analysis was carried out using the Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) version 22.0 and a p value of <0.05 was considered statistically significant.

Results

The biopsy records of 1240 patients were evaluated. Among these 1240 patients, saturation biopsy (24-core) was performed in only 145 patients.

The mean age of the patients was 62.4±7.0 years, the mean total PSA value was 10.5±7.5 ng/mL, the mean total core length was 26.2±4.7 cm, the mean core length was 10.91±1.8 mm, the mean prostate volume was 52.1±29.7 mL and the overall cancer detection rate was 33.8% (Table 1).

Pathological investigation revealed PCa in 49 of the 145 patients (33.8%), and a benign result in the remaining 96. The mean total core length was 25.9±3.9 cm in patients who had cancer and 26.4±5.1 in patients who had no cancer. The difference was not statistically significant (p=0.617). The mean core length in the cancer and benign group was 10.79±1.7 mm and 10.95±1.8 mm, respectively. This difference was not statistically significant (p=0.815). The clinical variables of the cancer and the benign groups are presented in Table 1.

The patients included in the study were assigned into 3 groups according to the length of the total biopsy cores; group 1: <20 cm, group 2: 20-30 cm and group 3: >30 cm. The number of patients in group 1, 2 and 3 was 22, 88 and 35, respectively. The cancer detection rate in group 1, 2 and 3 was 25%, 37.4% and

23.1%, respectively (Table 2). Comparison between the groups revealed a significantly higher rate of cancer in group 2 than in group 1 (p=0.001). However, when the cut-off value for the total core length was accepted as 20 cm, it was concluded that this core length was not sufficiently sensitive or specific for the diagnosis of PCa (p=0.465, odd ratio=1.002, 95% confidence interval=0.369-0.562) (Figure 1). After comparing the three groups with the multivariate analysis, there was no statistically significant difference in the cancer detection rate between the groups (p=0.302). We performed multivariate analysis in order to identify if any cut-off value for total core length was predictive for the PCa diagnosis and we could not detect any cut-off value.

When the groups were compared with each other, there was no statistically significantly difference in mean age, total PSA value and prostate volume (Table 2).

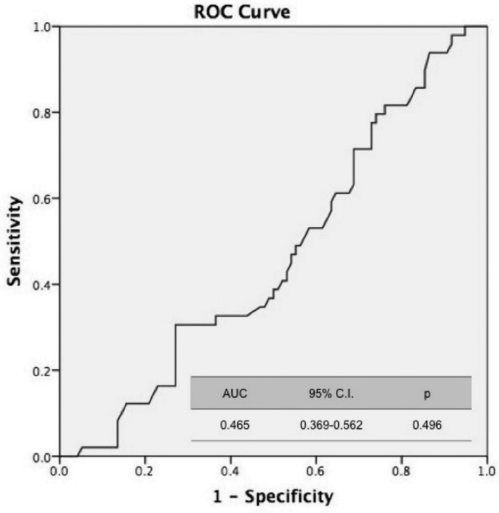

Figure 1. The receiver operating characteristic curve for total core lenght for diagnosing prostate cancer

Table 1. Clinical variables of cancer group and no cancer group

	Entire study	Cancer	No cancer	p value
Age (years)	62.4±7.0	64.7±6.7	61.3±6.9	0.006
PSA (ng/mL)	10.5±7.5	9.1±6.8	11.2±7.8	0.072
Prostate volume (mL)	52.1±29.7	52.1±24.7	57.2±30.8	0.161
Mean core lenght (mm)	10.91±1.8	10.79±1.7	10.95±1.8	0.815
Total core lenght (cm)	26.2±4.7	25.9±3.9	26.4±5.1	0.617

PSA: Prostate specific antigen

Table 2. Comparison of patients according to their total biopsy core lengths

	Group 1	Group 2	Group 3	p value
	(<20 cm)	(20-30 cm)	(30< cm)	
Age (years)	63.0±8.0	62.9±6.4	60.1±8.3	0.173
PSA (ng/mL)	11.6±6.1	10.3±8.2	10.6±4.8	0.176
Prostate volume (mL)	53.2±31.3	50.1±29.0	50.3±29.2	0.318
Cancer detection rate (%)	25.0	37.4	23.1	0.302

PSA: Prostate specific antigen

Discussion

In this study, we found that mean core length and total core length in saturation prostate biopsy were not correlated with PCa detection rate. Although we could not confirm our hypothesis, the results of our study will contribute to the literature regarding the importance of core lengths obtained in prostate biopsy.

Despite efforts made to identify new serum and biological markers and refinement of imaging modalities for the diagnosis of PCa, prostate biopsy performed with the guidance of TRUS is still the most important diagnostic method (8). In order to increase the cancer detection rate of prostate biopsy, various schemes have been applied in time such as sextant biopsy, extended biopsy and saturation biopsy (9). Treatment of patients, who are diagnosed not to have cancer in the first prostate biopsy despite persistently elevated levels of PSA, is a common problem for the urologist. Recently, various investigators have demonstrated that a higher diagnostic rate could be achieved via the saturation biopsy technique, which aims at increasing the number of samples obtained and to make sampling from multiple sites of the prostate (10). Borboroglu et al. (11) used an extensive saturation technique to obtain an average of 22.5 cores/patient, and achieved a cancer detection rate of 30%. In a study by Stewart et al. (12), a different scheme of saturation biopsy was used, and a cancer detection rate of 34% was achieved with a larger sample size. Walz et al. (6) used the 24-core saturation biopsy scheme and observed a cancer detection rate of 41%. In our institution, we prefer the 24-core saturation biopsy scheme for a second prostate biopsy. Consistent with the literature, we found the cancer detection rate of 33.8% in our study.

Although many studies have been published on the number and localization of the cores in the literature, very few have investigated the effect of core length as an indicator of the quality of prostate biopsy (13). This may be affected by many factors, including the length of the core obtained in a biopsy, the biopsy technique performed by the urologist, the diameter of the biopsy needle, the rigidity of the site the sample obtained, and the method of sample collection (14). Although there are studies

that have revealed that a greater core length increased the rates of PCa diagnosis, there have also been studies suggesting that the diagnosis of PCa was not affected by core length (15). A positive correlation was observed between mean core length and PCa detection in a study by Iczkowski et al. (16) conducted on patients who underwent sextant prostate biopsy, however, this outcome was significant for biopsies obtained from the apex only. According to the literature, the sextant prostate biopsy scheme is not currently recommended. Contrary to Iczkowski et al. (16), we determined that there was no correlation between mean core length and PCa detection rate.

In a single-center study by Öbek et al. (17) evaluating the medical data of 245 patients who underwent prostate biopsy via the extended sextant 12-18 cores biopsy scheme, all biopsies were performed by the same urologist and nurse, and the same biopsy gun was used in all biopsies. They found a mean core length of 12.3±2.6 mm in patients with cancer, and that of 11.4±2.4 mm in those with benign pathological results. The difference was determined to be statistically significant (17). The mean core length detected by these authors was longer than our mean core length. In our study, the biopsy sampling was performed by different urologists, thus, the homogenization of the data obtained in our study was limited. Ficarra et al. (18) reviewed the medical data of 509 prostate biopsies obtained through the transperineal approach, and reported that the mean length of cores diagnosed with PCa was similar to those with benign pathological results. They demonstrated that the transperineal prostate biopsy technique provided better and more sensitive sampling compared to the prostate apex, midgland and the base (18). In contrast to this study, we use the transrectal prostate biopsy technique in our clinics, which is easier, cost-effective and provides a better quality.

Lee et al. (14) reported that 3479 patients with a PSA level of <10 ng/mL were evaluated after multi-core prostate biopsy, and the mean core length for patients with and without cancer was the same (16.1 mm), and hence, they claimed that PCa detection rate was not affected by the core length. Similar to this study and that by Ficarra et al. (18), we did not observe a correlation between mean core length and the cancer detection rate in our study.

To the best of our knowledge, our study is the first to investigate the importance of total core length in prostate biopsy, in the literature. Our results did not support our hypothesis. We found no relationship between total core length and PCa detection rate in saturation biopsy. We thought, as reported by Lee et al. (14), that the outcomes of our study may be explained by a hypothesis similar to that suggested as 'saturation' in physical chemistry. Accordingly, if the total core length in prostate biopsies has reached a plateau for the diagnosis of PCa, longer core lengths obtained would no further contribute to the diagnosis of PCa.

Study Limitations

Our study has some limitations. The first limitation is that our study had a retrospective design. We did not separately assess the cores with and without cancer. The second limitation was not assessing the whole prostate gland after radical prostatectomy. Another limitation of our study was its small sample size. Further multi-center studies with larger sample sizes will provide more accurate insight into the subject.

Conclusion

Mean and total core lengths may not have significant effect on PCa detection in patients undergoing saturation prostate biopsy. The outcomes obtained in our study will provide information regarding the importance of core lengths obtained in a prostate biopsy. Multi-center, prospective studies with larger sample sizes will provide a more accurate picture for the clinical significance of the core length in prostate biopsy.

Ethics

Ethics Committee Approval: Ethics committee approval was not applied because of retrospective design.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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ORIGINAL RESEARCH
Andrology

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Pre-emptive Use of Riboflavin in a Rat Model of Bilateral Cavernous Nerve Injury

Bilateral Kavernozal Sinir Hasarı Sıçan Modelinde Preemptif Riboflavin Tedavisinin Etkileri

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

Penile rehabilitation is an important approach for patients after nerve-sparing radical prostatectomy. Many treatment strategies are being applied aiming rapid healing for erectile function. Riboflavin has never been used for penile rehabilitation before. This study supports riboflavin use for penile rehabilitation, especially in preemptive approach.

Abstract

Objective: Erectile dysfunction is commonly encountered after radical prostatectomy due to cavernous nerve injury (CNI). We investigated the effects of riboflavin (Rb) on bilateral CNI in a rat model.

Materials and Methods: Twenty-four male rats were divided into four groups: control (C), patients with bilateral CNI, those with CNI receiving postoperative Rb treatment (CNI+Rb), and those with CNI receiving pre- and post-operative Rb treatment (Rb+CNI+Rb). Bilateral CNI was performed in all groups except for C. The CNI+Rb group was treated with 30 mg/kg Rb daily after CNI for two weeks; the Rb+CNI+Rb group was treated with 30 mg/kg Rb daily one week before CNI and then for two weeks after injury. Mean arterial pressure (MAP) and intracavernosal pressure (ICP) were measured 14 days after CNI in all groups. Tissue malondialdehyde, cyclic guanosine monophosphate, nerve growth factor, superoxide dismutase and total nitric oxide synthase (NOS) activities, neuronal NOS (nNOS) and inducible NOS (iNOS) were analyzed.

Results: ICP/MAP ratio was significantly lower in the CNI ($p<0.01$) and CNI+Rb groups ($p<0.05$) compared to the control group, however, the Rb+CNI+Rb group had results comparable to the C group in terms of nNOS and iNOS expression in the Western Blot analysis.

Conclusion: Rb exerted anti-oxidative and anti-inflammatory effects on CNI in a CNI rat model. Rb can be a potential beneficial agent to improve erectile function in nerve-sparing radical prostatectomy patients as a preemptive penile rehabilitation strategy, although further clinical studies are needed.

Keywords: Cavernous nerve injury, Erectile dysfunction, Oxidative stress, Riboflavin

Öz

Amaç: Çalışmamızın amacı radikal prostatektomi modelinde erektil disfonksiyon tedavisinde riboflavinin (Rb) olası etkilerinin araştırılmasıdır.

Gereç ve Yöntem: Yirmi dört erkek sıçan kontrol (K), bilateral kavernoz sinir hasarı (KSH), KSH+Rb ve Rb +KSH+ Rb olmak üzere 4 gruba ayrıldı. Ön-tedavili KSH grubunda cerrahiden 1 hafta önce başlayarak toplam 3 hafta ve KSH+Rb grubuna ise cerrahiden sonra 2 hafta süreyle 30 mg/kg dozunda Rb uygulandı. Deney sonunda intrakavernosal basınç (İKB) ve ortalama arteryel basınç (OAB) ölçümü yapıldı. Kavernoz doku örneklerinde malondialdehit (MDA), siklik guanozin monofosfat (c-GMP) ve sinir büyüme faktörü (NGF) düzeyleri ile süperoksid dismutaz (SOD) ve total nitrik oksit sentaz (NOS) aktiviteleri ölçüldü. Dokuların indüklenebilir NOS ve nöronal NOS protein ekspresyonları Western blot yöntemi ile tayin edildi.

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Öz

Bulgular: KSH, İKB/OAB değerlerinde anlamlı azalmaya (p<0.01) neden olurken preemptif Rb tedavili grupta bu değerler kontrol grubu değerlerine yaklaşmış olarak bulundu. KSH grubunda doku MDA düzeylerinin ve NOS aktivitesinin anlamlı olarak arttığı, c-GMP ve NGF düzeyleri ile SOD aktivitesinin anlamlı olarak azaldığı belirlendi. KSH sonrası uygulanan Rb tedavisi bu parametrelerdeki değişimleri geri çevirirken preemptif Rb tedavili gruplarda bu değerler kontrol gruba benzer düzeylere geldi.
Sonuç: Çalışmamızda Rb, hasarlı kavernoz dokuda antioksidan ve anti-enflamatuvar etki göstermiş ve böylece dokuyu koruyarak erektil fonksiyon kaybında iyileşme göstermiştir. Özellikle preemptif Rb kullanımının faydalı bir tedavi yaklaşımı sağlayabileceğini düşündürmekte olup insan çalışmalarıyla bu yaklaşım desteklenebilir.
Anahtar kelimeler: Kavernoz sinir hasarı, Erektil disfonksiyon, Oksidatif stres, Riboflavin

Introduction

More than one million men are diagnosed with prostate cancer worldwide, leading to more than 300.000 deaths each year (1). Many patients who had radical prostatectomy (RP) for prostate cancer experience side effects, one of which is the post-operative erectile dysfunction (ED) (2). Cavernous nerve injury (CNI) is the reason behind ED after RP (3). Even though different surgical techniques and modifications of RP have been studied to maintain erectile function (EF), the cavernous nerve (CN) is often injured by manipulations such as traction, compression or thermal damage. Regeneration of neural tissues after neural injury following RP is limited and happens over a very long period of time. Moreover, only a very small proportion of men who were preoperatively potent have spontaneous erections after RP (4).

Nitric oxide synthase (NOS), nitric oxide (NO), soluble guanylyl cyclase (sGC) and cyclic guanosine monophosphate (cGMP) have major roles in penile erection physiology. NO is synthesized in the CN via neuronal NOS (nNOS) (5). NO, which is a ubiquitous neurotransmitter, consists of L-arginine and is released by nerve terminals. It then spreads into the neighboring smooth muscle cells and induces sGC, and this process increases the intracellular level of cGMP. Hence, the relaxation of smooth muscle in the corpus cavernosum as well as the penile arterioles is triggered by L-arginine. Meanwhile, phosphodiesterase type 5 inhibitors (PDE5i) prevent the catabolism of cGMP, which is the major supporting agent for penile erection (6). The pathophysiology behind CNI is not only nerve damage but also the accompanying oxidative stress (7), as the main cause of nerve damage is the increase in reactive oxygen species due to a decrease in NO. Superoxide radicals augment apoptosis, cause formation of peroxynitrite and can lead to dysfunction of the endothelium (5,8,9). Peroxynitrite, which stimulates superoxide dismutase (SOD), produces ineffective relaxation of smooth muscle and can stimulate adhesion of platelets to endothelium. Thus, endothelial dysfunction and increased NO destruction result in corporal veno-occlusive dysfunction and impairment of EF (5,6).

The nerve-sparing RP technique, which aims to protect the CNs and thereby provide penile innervation via regulation of the vascular homeostasis of the penis, maintains EF effectively (10). Other techniques or approaches include nerve grafting (11), nerve reconstruction (12), pharmacological neuromodulation using immunophilins (13), neuroprotection using erythropoietin (14), electro-stimulation of the CN or pelvic ganglion (15), regulation of FK506-binding protein (16) and transferring of the herpes simplex virus vector (17). Studies seeking to preserve EF peri-operatively have examined tissue healing procedures such as muscle-derived cell injection (18), neuronal embryonic stem cell injection (19), intracavernous injection of adipose-derived stem cells (20), inhibition of neuronal inflammation or neuronal cell death using neurotrophic and growth factors (21,22), and penile rehabilitation with PDE5i (4).

Riboflavin (Rb) is water-soluble B-complex vitamin that plays a role in various metabolic pathways and redox reactions via active coenzymes, flavin adenine dinucleotide and flavin mononucleotide (23). Rb protects tissues against neurotoxicity by alleviating oxidative stress, mitochondrial dysfunction, neurologic inflammation, glutamate and homocysteine toxicity (24).

The aim of this study was to investigate the essential role of Rb as an antioxidant and anti-inflammatory agent against ED in a bilateral CNI model in rats.

Materials and Methods

Animals and Experimental Design

Adult male Sprague-Dawley rats (250-300 g) were housed at a temperature-controlled room (22±2 °C) with a 12-hour light-dark cycle. Marmara University Animal Experiments Ethics Committee approved the study (number 78.2015.mar).

The rats were randomly divided into four groups with 6 rats in each: group 1, control (C) group, in which the rats underwent sham surgery and received carboxymethylcellulose (CMC) 0.5% as vehicle/solvent for intraperitoneal dosing; group 2, in which the rats underwent surgery to induce CNI and received CMC

0.5% only; group 3, CNI+Rb group, in which the rats underwent surgery for CNI induction and received Rb (30 mg/kg/day ip) for two weeks (25); and group 4, Rb+CNI+Rb group, in which the rats received Rb (30 mg/kg/day ip) before CNI induction then received Rb again (30 mg/kg/day ip) following the surgery. For the CNI and C groups, in which the sham operation was performed, CMC solvent was applied for 15 days following the operation. In the pre-treatment CNI group, Rb was applied at a dose of 30 mg/kg/day ip for a total of three weeks starting one week before surgery and continuing for two weeks after the surgery in the CNI+Rb group. Rb was dissolved in 0.5% CMC. Rb and CMC were purchased from Sigma Aldrich (St. Louis, MO, USA).

At the end of the experiment, under general anaesthesia, intracavernosal pressure (ICP) and mean arterial pressure (MAP) were measured and then cavernosal tissue samples were obtained for biochemical and histological analyses.

Cavernous Nerve Stimulation and Intracavernosal Pressure/ Mean Arterial Pressure Measurement

To induce CNI, in all surgical procedures, the animals were anaesthetized with ketamine (100 mg/kg) and xylazine (6-9 mg/kg). After the animals were anaesthetized, following the shaving of the abdominal wall, a lower midline incision was made. The major pelvic ganglion and the CN, a distinct structure arising from the ganglion and running caudally along the prostate in a groove between the urethra and rectum, were detected as previously described (26). A vascular bulldog clamp was applied to each CN, 5 mm distal to the ganglion. It was applied for 30 seconds, removed for 30 seconds, and then reapplied for an additional 30 seconds. Two weeks after the induction of CNI and sham operation, all animals were anaesthetized as described previously, and they underwent an operation during which electro-physiological erection assessment was conducted. With a transverse neck incision, subcutaneous layers and the underlying muscles were separated. Dissection and subsequent cannulation of the left internal carotid artery with a heparinized polyethylene-50 tube, connected to a pressure transducer and an amplifier unit (COMMAT Pharmacology & Physiology Instruments, Ankara, Turkey) were performed. The amplifier which was connected to a module for data acquisition (MP 35 data acquisition system, Ankara, Turkey) allowed the MAP to be recorded using Biopac Student Lab PRO recording software (Biopac Systems Inc., Goleta, CA, USA). At the junction of the penis and pubic arch, dissection of the ischiocavernous muscle was performed and the penile tunica albuginea was visualized. ICP measurement was performed with a 24-gauge needle placed into the left penile crus which was connected to a transducer by a heparinized polyethylene-50 tube. The laparotomy incision was extended below until the penile root. The CN was located bilaterally which is situated on both sides of the prostatic tissue. Following CN dissection with a micromanipulator, a stainless steel bipolar electrode with 1 mm-apart parallel hooks was placed distally to the major pelvic ganglion. The electrode cable was connected to a STPTO2-A stimulator (COMMAT Pharmacology & Physiology Instruments, Ankara, Turkey). The stimulation parameters were 1.5 mA, 20 Hz, pulse width 5 milliseconds, 35 milliseconds delays and 7.5 volts for 60 seconds each. Stimulation of the CN was performed and the data were individually recorded. The maximum ICP/MAP ratio was calculated and reported as percentage (26,27).

Biochemical Analysis

Measurement of Tissue Malondialdehyde Levels

Corpus cavernosal tissue samples were homogenized with ice-cold potassium chloride (150 mM) to determine MDA levels which shows the level of lipid peroxidation by monitoring thiobarbituric acid reactive substance formation as previously described. The results were expressed as mmol MDA/mg protein (24).

Measurement of Superoxide Dismutase Activity

SOD activity was measured according to the method described by Tavukcu et al. (28). A standard curve was prepared with bovine SOD (3000 U; S-2515; Sigma, St. Louis, MO, USA) as a reference. Absorbance readings were taken at 0 and 8 minutes of illumination, and the net absorbance was calculated (27).

Measurement of Cyclic Guanosine Monophosphate Levels

Amounts of cGMP in frozen tissue were determined in duplicate using an ELISA kit, according to the manufacturer's instructions (Enzo Life Sciences, Farmingdale NY, USA). A total protein assay was performed using the Bradford method. cGMP values were given as pmol/mg protein (27).

Measurement of Nerve Growth Factor Levels

Measurement of nerve growth factor (NGF) was detected by sandwich-ELISA according to the manufacturer's instructions (Chemicon International Inc., Temecula, CA, USA). A total protein assay was performed using the Bradford method (29). NGF values were given as pg/mg protein (27).

Measurement of Tissue Nitric Oxide Synthase Activities

Tissue samples were homogenised with phosphate-buffered saline (PBS) (pH 7.4) and centrifuged at 10.000 x g at 40 ^{0}C. Supernatant was used for the NOS activity assay to determine the levels of NOS activity (EnzyChrom, BioAssay Systems, Hayward, CA, USA), following the manufacturer's protocol. According to the assay, one unit of NOS catalyzes the production of 1 µmole of NO per minute under the assay conditions (pH 7.5 and 37 ^{0}C). NOS activity was given as U/mg protein (27).

Western Blot Analysis for Inducible Nitric Oxide Synthase and Neuronal Nitric Oxide Synthase

Western blot analysis and measurement was performed for inducible NO synthase (iNOS) and nNOS release as previously described (30). The Bradford assay was used to detect protein concentrations in homogenized samples (29). Afterwards, 25 µg of protein was resolved in 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and was transferred to nitrocellulose membrane (sc-3718, Santa Cruz Biotechnology) which was blocked with 5% non-fat skim milk powder (Sigma, 70166) in Tris-buffered saline (TBS) and which was washed twice in (TBS+tween) TBST (TBS containing 0.1% Tween-20) and incubated overnight with primary antibody (1:500 monoclonal rat anti-iNOS, sc-651 anti-nNOS, sc-648, anti-b-actin, sc-47778, Santa Cruz Biotechnology). The membrane was incubated with horseradish peroxidase (HRP)-conjugated secondary antibody (1:1000 goat anti-mouse IgG1-HRP, sc-2060 and goat anti-rabbit IgG-HRP sc-2004, Santa Cruz Biotechnology) for 2 hours. Chemiluminescence reagents (sc-2048, Santa Cruz Biotechnology using a Chemiluminescent Imaging System, Syngene, USA) were used to detect the blot. Data were analyzed using the ImageJ OD analysis software. Signals were normalized with respect to β-actin.

Statistical Analysis

GraphPad Prism 5.0 (GraphPad Software, San Diego; CA; USA) was used for the statistical analyses. All data were expressed as means ± standard error of mean (SEM) Data groups were compared using an analysis of variance followed by Tukey's multiple comparison tests. A two-tailed p value of less than 0.05 was considered statistically significant.

Results

ICP/MAP ratio was significantly lower in the CNI ($p<0.01$) and CNI+Rb groups ($p<0.05$) compared to that in the C group, however, the Rb+CNI+Rb treated group showed similar results to the C group (Figure 1).

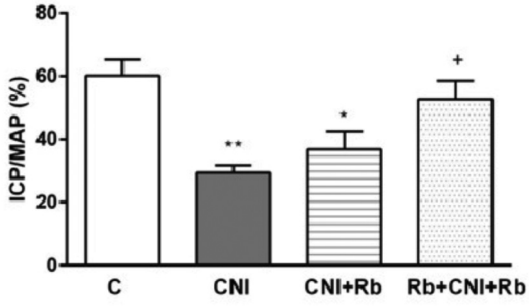

Figure 1. Intracavernosal pressure/mean arterial pressure results of all groups

*C: Control, CNI: Cavernosal nerve injury, Rb: Riboflavin. *p<0.05, **p<0.01: compared to group C, +p<0.05: compared to CNI*

MDA levels were significantly higher ($p<0.01$) in the CNI group, while treatment with Rb significantly reduced the MDA levels in the CNI+Rb and Rb+CNI+Rb groups, which achieved similar levels to that in the C group (Figure 2a).

SOD activity was significantly lower ($p<0.05$) in the CNI group when compared with the C group, while the Rb+CNI+Rb group showed no significant difference from the C group. However, SOD levels were significantly higher ($p<0.01$) in the Rb+CNI+Rb group than in the CNI group (Figure 2b). The total NOS activity was significantly higher ($p<0.001$) in the CNI group than in the C group, while NOS activity in the treatment groups was comparable to that in the C group and significantly lower than in the CNI group (Figure 3a). cGMP and NGF levels were significantly lower ($p<0.001$) in the CNI group when compared with the C group; moreover, the treatment groups had significantly higher levels ($p<0.001$) than the CNI group (Figure 3b, 4). Another important finding was that the Rb+CNI+Rb group demonstrated significantly higher NGF levels than the CNI+Rb group ($p<0.05$).

In the Western blot analysis for iNOS and nNOS, the Rb+CNI+Rb group demonstrated results similar to that in the C group, while the CNI group had significantly higher levels of iNOS and lower levels of nNOS (Figure 5).

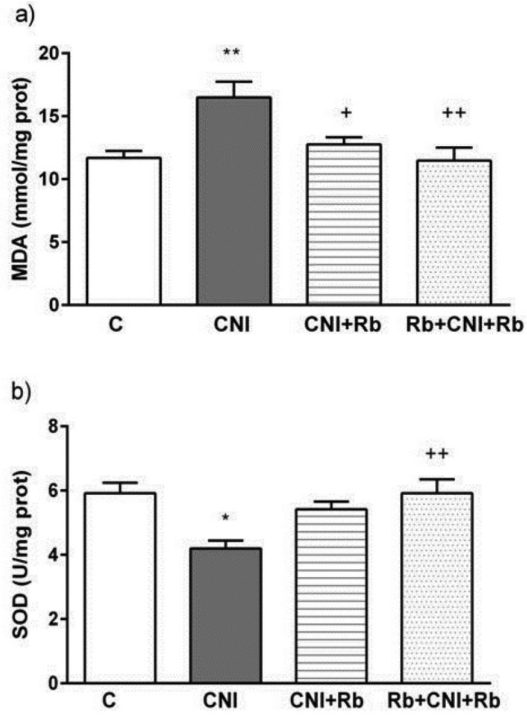

Figure 2. Cavernosal tissue analysis of; a) Malondialdehyde levels, b) Superoxide dismutase activity

*C: Control, CNI: Cavernosal nerve injury, Rb: Riboflavin. *p<0.05, **p<0.01: compared to group C, +p<0.05, ++p<0.01: compared to group CNI*

Histological analysis of cavernosal tissues revealed that the C group demonstrated good alignment of smooth muscle bundles and the endothelium (Figure 6a), whereas in the CNI group, endothelial deterioration was prominent in addition to mild accumulation of leukocytes (Figure 6b). In the CNI+Rb group, the endothelium showed moderate regression of degeneration (Figure 6c), whereas the Rb+CNI+Rb group demonstrated good regeneration of the endothelium (Figure 6d).

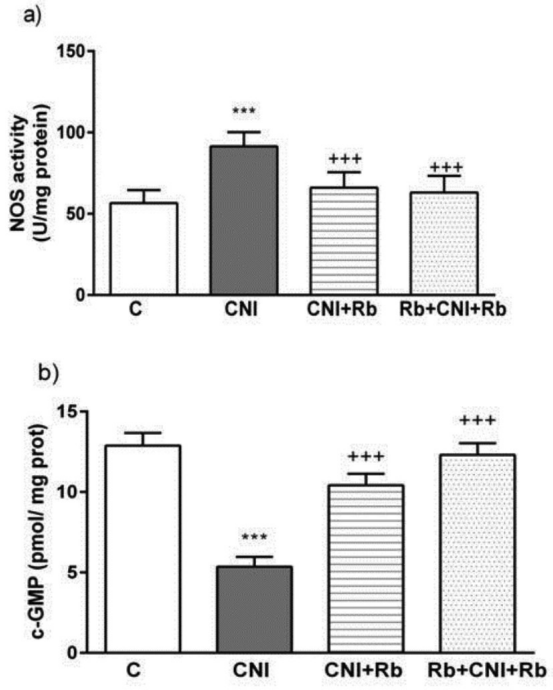

Figure 3. Cavernosal tissue analysis of; a) Nitric oxide synthase activity and, b) c-GMP levels

*C: Control, CNI: Cavernosal nerve injury, Rb: Riboflavin, cGMP: cyclic guanosine monophosphate, ***p<0.001: compared to group C, +++p<0.001: compared to group CNI*

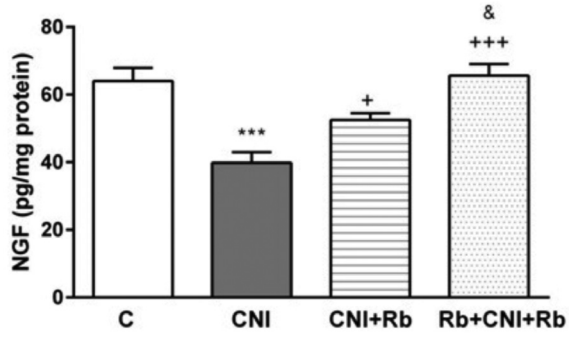

Figure 4. Nerve growth factor levels in cavernosal tissue

*C: Control, CNI: Cavernosal nerve injury, Rb: Riboflavin, NGF: Nerve growth factor, ***p<0.001: compared to group C, +p<0.05, +++p<0.001: compared to group CNI, &p<0.05: compared to group CNI+Rb*

Discussion

The current study indicates that CNI leads to inflammatory and oxidative damage in erectile tissue, with increased MDA levels in the cavernous tissue and decreased SOD activity. The elevated oxidative injury results in a reduction of the tissue anti-oxidant enzymes (7). In addition, while cGMP levels decreased, NOS activity increased, and both parameters are important for EF. Furthermore, the findings of the study clearly demonstrate that Rb reverses these changes to the C level and protects cavernous tissues against CNI-mediated tissue damage.

We also determined NOS activities and cGMP levels, which are the main components of the NO/cGMP signaling pathway in

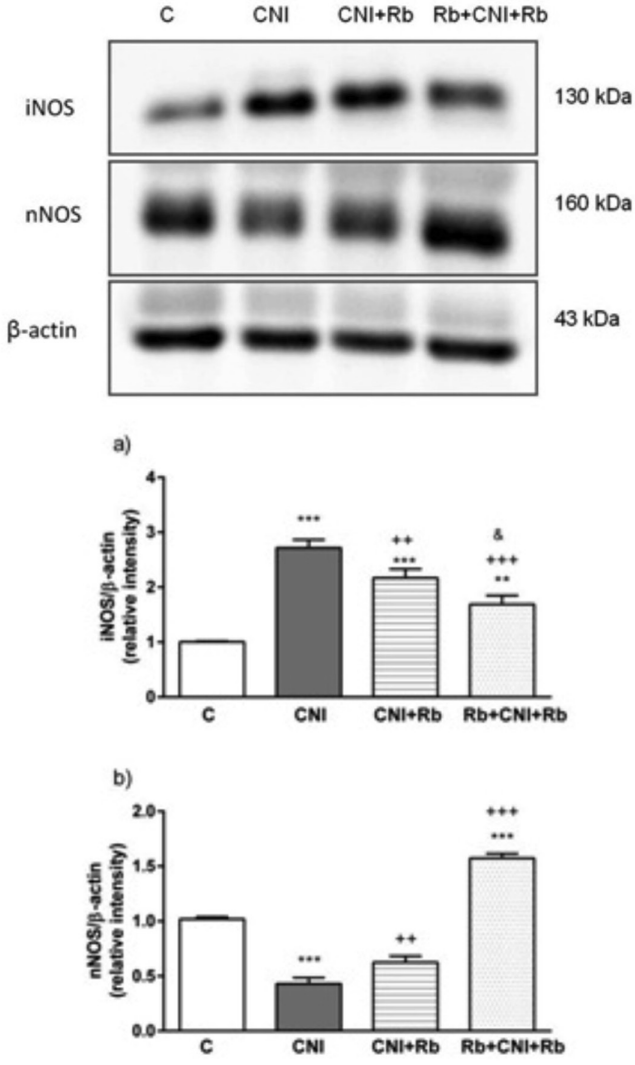

Figure 5. Western blot analysis in cavernosal tissue, a) inducible nitric oxide synthase ve b) neuronal nitric oxide synthase protein expressions

*C: Control, CNI: Cavernosal nerve injury, Rb: Riboflavin, nNOS: Neuronal nitric oxide synthase, iNOS: inducible nitric oxide synthase, **p<0.01, ***p<0.001: compared to group C, ++p<0.01, +++p<0.001: compared to group CNI, &p<0.05: compared to CNI+Rb group*

the cavernous tissue. We observed increased total NOS activity in CNI rats (Figure 3a). As shown by Western blot analysis, the drop in nNOS expression was associated with nerve fiber injury, compatible with previous studies (Figure 5) (16,19,31,32). Besides an elevation in iNOS expression, NGF levels also decreased, indicating that there was an apoptotic process in the CN fibers (Figure 4, 5) (12). With regard to a previous study, the increase in iNOS expression was normalized nearly to the C group by Rb, which was prominent in the Rb+CNI+Rb group (6). There was also a significant difference in iNOS expression between the Rb+CNI+Rb and CNI+Rb groups (Figure 5a; $p<0.05$). The increase in total NOS activity could be related to the elevated iNOS expression in the CNI group.

NGF, which is the first discovered neurotrophic factor and signaling molecule, has important neuroprotective effects against several diseases (12,33). We showed that NGF levels were significantly decreased after CNI, which could result in the development of ED. The current study showed that the Rb-treated pre-injury group (Rb+CNI+Rb) had significantly higher NGF levels than the CNI and CNI+Rb groups.

Similar to previous studies, the ICP/MAP values in CNI rats significantly decreased in our study (7,31). Furthermore, the Rb-treated groups had higher ICP/MAP values than the CNI group. The Rb+CNI+Rb group showed statistically significant differences from the CNI group and had values comparable to the C group (Figure 1). These data support the use of Rb for penile rehabilitation before CNI, as proven through biochemical analysis.

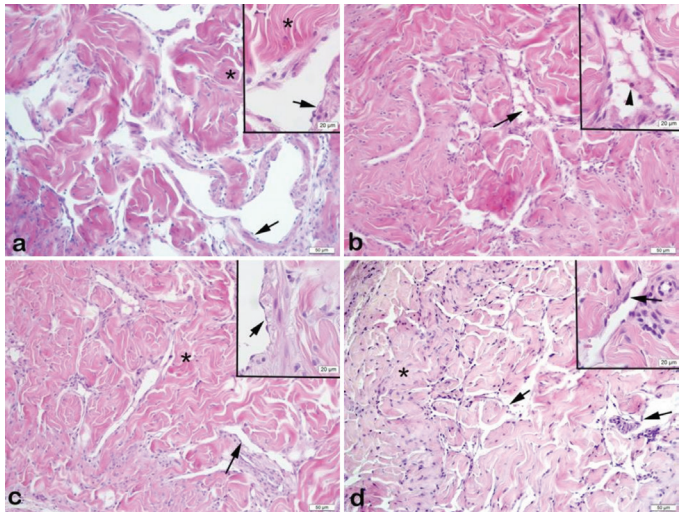

Figure 6. Histological analysis of cavernosal tissues, a) C group; smooth muscle bundles (*) surrounding vascular spaces, regular endothelial alignment (arrow). b) Cavernous nerve injury group; the prominent deterioration of vascular spaces and endothelium (arrow), sparsely observed leukocyte (arrowhead). c) Cavernous nerve injury + riboflavin group; the vascular endothelial cells have foamy cytoplasm (arrowhead) but vascular spaces were cleared away from deterioration (arrow), regular muscle bundles (*). d) Riboflavin + cavernous nerve injury + riboflavin group, clearly observed vascular spaces with regular endothelium cells (arrows), well-organized smooth muscle bundles (*)

Nevertheless, all penile rehabilitation strategies with PDE5i suggest the use of these agents after RP, following daily or on-demand protocols (34). No reported data was found except our previous study on the pre-injury treatment and pre-emptive penile rehabilitation, which is the first reported study on the data of pre-emptive penile rehabilitation before bilateral CNI in rats (35). According to these study results, pre-emptive penile rehabilitation with sildenafil (low- and high-dose) before bilateral CNI did not show a significant change in EF outcomes. Thus, our present study is the first one to demonstrate significant differences due to pre-emptive penile rehabilitation with Rb in CNI rats. Moreover, this is the first study in which Rb has been used for penile rehabilitation in a CNI rat model. The results of the current study show that Rb has protective effects on cavernous tissue after CNI.

Study Limitations

We only evaluated the effects of Rb in a CNI model; one arm of the study might be ordered with PDE5i and alone.

Conclusion

According to the results of this study, pathogenic CNI-induced ED causes oxidative stress to the cavernous tissue, and Rb can prevent injury to the erectile tissue. Furthermore, the results of this study suggest that preemptive use of Rb has a positive effect on oxidative parameters and improves all parameters towards the control levels. Rb can be considered a potential preventive agent in subjects undergoing RP, if supported with further studies, alone or with PDE5i.

Ethics

Ethics Committee Approval: Marmara University Animal Experiments Ethical Committee approved the study (number 78.2015.mar).

Informed Consent: None (Animal experiment).

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.E., H.H.T., T.E.Ş., G.Ş., Concept: M.E., H.H.T., T.E.Ş., G.Ş., Design: M.E., H.H.T., T.E.Ş., G.Ş., Data Collection or Processing: Ö.Ç., N.B., Ö.A., Ş.Ç., G.Ş., Analysis or Interpretation: Ö.Ç., N.B., Ö.A., Ş.Ç., G.Ş., Literature Search: H.H.T., T.E.Ş., M.E., Writing: H.H.T., T.E.Ş., G.Ş.

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

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CASE REPORT
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Bladder Sarcomatoid Carcinoma in an Adolescent: 10-Year Survival After Aggressive Surgical Management

Bir Ergende Mesane Sarkomatoid Karsinomu: Agresif Cerrahi Yönetimi Sonrası 10 Yıllık Sağkalım

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Abstract

Bladder cancer is a rare entity in the pediatric population. Sarcomatoid carcinoma is considered a variant histology of bladder urothelial carcinoma and is exceedingly unusual in children. We present a case of a 14-year-old black female who presented to the pediatric urology clinic with hematuria. Her history was notable for acute lymphocytic leukemia treated with cyclophosphamide, which had been in remission for four years. Subsequent workup demonstrated a large, complex bladder mass, consistent with sarcomatoid carcinoma following transurethral resection. She underwent a radical cystectomy with bilateral pelvic lymphadenectomy and ileal conduit and remains disease free 10 years after diagnosis.
Keywords: Bladder cancer, Adolescent, Radical cystectomy, Sarcomatoid

Öz

Pediatrik popülasyonda mesane kanseri nadir bir oluşumdur. Sarkomatoid karsinomda, mesane üroteliyal karsinomunun değişken histolojisi dikkate alınır ve çocuklarda son derece olağan dışıdır. Burada, pediatrik üroloji kliniğine hematuri ile başvurmuş 14 yaşındaki siyahi bir kadın olgusu sunulmuştur. Dört yıldır remisyonda olan, siklofosfamid ile tedavi edilen akut lenfositik lösemi için olgunun öyküsü kayda değerdi. Transüretral rezeksiyonu takiben yapılan tetkikler, sarkomatid karsinomu ile birbirini tutan büyük bir kompleks mesane kitlesini kanıtlamıştır. Hastaya, radikal sistektomi ile iki taraflı pelvik lenfadenektomi ve ileal konduit uygulanmıştır, tanıdan sonra 10 yıldır hastalıksız bir şekilde hayatını sürdürmektedir.
Anahtar Kelimeler: Mesane kanseri, Ergen, Radikal sistektomi, Sarkomatoid

Introduction

Sarcomatoid carcinoma is a rare variant histology of bladder urothelial carcinoma, accounting for less than 0.5% of all bladder tumors (1,2). This entity represents a biphasic tumor with epithelial and mesenchymal malignant components and is often considered synonymous with carcinosarcoma, a primary spindle cell neoplasm with epithelial elements (3). Both are rare, aggressive neoplasms typically presenting at advanced stages (1). Pathological stage is the best predictor of survival and even with aggressive treatment, the prognosis is dismal (1).

In a 2010 analysis of 221 cases, the mean age at diagnosis was 75 years, 65.2% were male, and 89.1% were Caucasian (2). We present a case of, to our knowledge, the youngest patient diagnosed with this rare histology. Diagnosed after four years of acute lymphocytic leukemia (ALL) remission and following aggressive surgical management and adjuvant chemotherapy, this patient remains disease-free 10 years after diagnosis.

In children ages 10-14, the incidence of cancer from 2003 to 2012 was 13.25 per 100.000 and the incidence of ALL was 2.14 per 100.000 (4). Childhood survivors of pediatric malignancies are at increased risk of secondary neoplasms, and the relative risk of secondary neoplasm ranges from two to eight times greater than the general population (5,6). Increased risk was also found in females and those treated with radiation or certain types of

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chemotherapy (4,7). One study reported that 7.7% of patients in remission of ALL develop second malignant neoplasms (8). The most common second malignant neoplasms present later in life and include breast, thyroid, and central nervous system tumors (8,9).

Case Presentation

A 14-year-old African-American female presented to the pediatric urology clinic with a two-month history of recurrent urinary tract infections with intermittent hematuria, dysuria and frequency. She denied recent weight loss, malaise, bone pain or other constitutional symptoms. Her past medical history was significant for ALL and family history was unremarkable. Her ALL was treated with protocol CCG 1961, consisting of vincristine, cytosine arabinoside, pegylated-asparaginase, doxorubicin, methotrexate, and cyclophosphamide. She was well hydrated per protocol, but her cyclophosphamide regimen (3 g/m^2 of cyclophosphamide given in 1 g/m^2 doses) did not necessitate the use of mesna (10,11). Additionally, she underwent cranial irradiation during the consolidation phase of her treatment. Following an uncomplicated chemoradiation course, she remained in ALL remission for four years at the time of pediatric urology consultation.

Diagnostic imaging included a renal/bladder ultrasound, first visualizing the bladder mass, followed by intravenous-contrasted computed tomography (CT) of the abdomen and pelvis demonstrating a complex, lobulated bladder mass with no evidence of hydronephrosis, lymphadenopathy, local extension or metastatic disease (Figure 1a). After obtaining informed consent, she underwent a transurethral resection of the bladder tumor, final pathology of which was sarcomatoid carcinoma. Metastatic workup included a positron emission tomography-CT, which was negative. After multidisciplinary consultation, discussion with the patient and family, and obtaining informed consent, the patient underwent a radical cystectomy with bilateral pelvic lymphadenectomy and ileal conduit. After 2 years with no evidence of disease, the patient made the decision to keep the conduit versus re-diversion to a neobladder. No gross extravesical involvement was noted and the urethra and reproductive organs were spared.

Pathology demonstrated a 7.1x6.5x3.9 cm tumor (Figure 1b). Histologic analysis revealed pure sarcomatoid carcinoma with heterologous mesenchymal elements in the form of chondrosarcoma. Hematoxylin and eosin staining exhibited morphologic features ranging from epithelioid to spindle to giant multinucleated cells (Figure 2a, b). Although invasion of the lamina propria was microscopically evident, no invasion of the muscularis propria was observed. Pancytokeratin staining was positive for epithelioid cells and the specimen showed

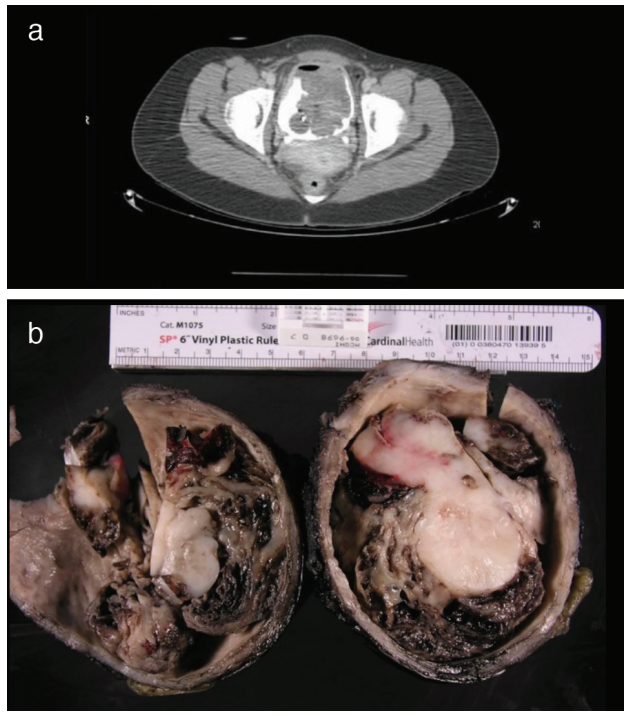

Figure 1. a) Computed tomography with intravenous contrast (transverse section), demonstrating a large volume, complex bladder mass; b) Anatomic gross representation of the bladder (bivalved) showing necrotic and viable portions of tumor, measuring 7.1x6.5x3.9 cm

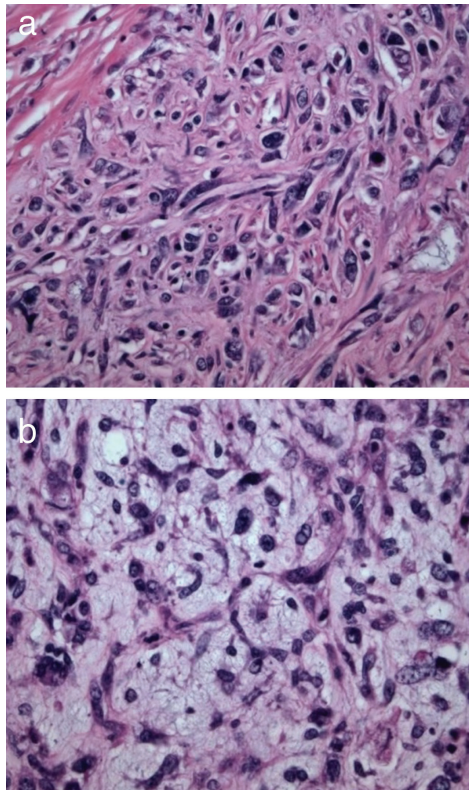

Figure 2. Hematoxylin and eosin stains of tumor at 10x, a) demonstrating T1 lamina propria invasion (muscle layer, left upper corner), spindle, and multinucleated cells. b) 40x representation demonstrating large multinucleated sarcomatoid malignant cells

diffuse positivity with vimentin staining. The final pathologic staging of the tumor was pT1N0MX with 0 of 8 lymph nodes positive.

Secondary to the patient's age and aggressive nature of the tumor, after further multidisciplinary discussion it was decided to administer adjuvant adult-dose chemotherapy (four cycles of standard adjuvant gemcitabine and cisplatin). Ten years following the aggressive management, surveillance imaging remains free of disease recurrence. Although at last follow-up she has not attempted to become pregnant, she expresses a desire for children in the future.

Discussion

This case represents the first report of an adolescent with bladder sarcomatoid carcinoma, an aggressive and rare neoplasm. The largest case series reported to date, reports the mean age at diagnosis to be 75 years (2). Given the dismal 1-, 5-, and 10- year survival rates of patients, 53.9%, 28.4%, and 25.8% respectively, aggressive surgical management and adjuvant chemotherapy are typically required and have remarkably allowed this patient to remain disease-free for 10 years post-treatment (2).

The initial treatment protocol for this patient's ALL included cyclophosphamide, which is metabolized to acrolein, a known urotoxin associated with hemorrhagic cystitis and bladder cancer. Mesna can be added to the cyclophosphamide treatment regimen to reduce associated urothelial toxicity. Mesna is classically reserved for patients receiving high-dose cyclophosphamide, typically defined as 50 mg/kg or 3 gm/m^2 (10,11,12,13). Based upon this recommendation, our patient's cyclophosphamide dose did not necessitate the use of mesna (10,11). Given the inherent risks of secondary bladder malignancy with cyclophosphamide use, readdressing the minimum cyclophosphamide dose requiring concomitant mesna administration may be necessary, especially in children.

Although rare in children and adolescents, bladder cancer outcomes are poorer in females than males and surgical management traditionally includes bladder, reproductive organ, and anterior vaginal vault removal (14,15). This patient's sarcomatoid carcinoma, age, and gender highlight the importance of considering the risks and benefits of disease recurrence versus subsequent fertility, particularly when assessing the aggressive nature of this tumor and benefits of radical extirpative surgery. This compels urologists to consider reproductive organ sparing extirpative surgery for invasive bladder cancer in appropriate young females desiring preservation of fertility. Further follow-up of this patient will be enlightening to assess reproductive capabilities, particularly in the setting of two previous aggressive chemotherapy regimens.

This case demonstrates a rare, aggressive bladder sarcomatoid carcinoma secondary malignancy following ALL that was treated aggressively with reproductive organ sparing surgery, adjuvant chemotherapy and long-term survival. An increased index of suspicion for secondary malignancies allows timely diagnosis, aggressive treatment and the best opportunity for long-term survival.

Ethics

Informed Consent: A consent form was completed by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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CASE REPORT
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Anterior Urethral Valve and Anterior Urethral Diverticulum with an Intradiverticular Stone: A Case Report and a Literature Review

Divertikül İçi Taş ile Birlikte Anterior Üretral Valv ve Anterior Üretral Divertikül: Olgu Sunumu ve Literatür Gözden Geçirmesi

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Abstract

Anterior urethral valve (AUV) is a rare but well-defined congenital anomaly. AUV can be isolated or occur in association with anterior urethral diverticulum (AUD). Here, we present the first pediatric case report of AUV and AUD which is complicated with an intradiverticular stone. We also review the literature involving AUV with AUD cases.
Keywords: Anterior urethral valve, Anterior urethral diverticulum, Intradiverticular stone

Öz

Anterior üretral valv (AÜV), az görülen fakat iyi tanımlanmış bir konjenital anomalidir. AÜV, izole veya anterior üretral divertikül (AÜD) ile birlikte görülebilmektedir. Biz bu yazıda divertikül içi taş ile komplike olmuş ilk pediatrik AÜV ve AÜD olgusunu raporladık. Ayrıca literatürdeki AÜD ile birliktelik gösteren AÜV olgularını da gözden geçirdik.
Anahtar Kelimeler: Anterior üretral valv, Anterior üretral divertikül, İntradivetiküler taş

Introduction

Anterior urethral valve (AUV) is a rare but well-defined congenital anomaly. AUV is a crescent-shaped fold that arises from the base of the urethra. AUV narrows the urethral lumen and may result in obstruction and serious effects on the proximal urinary system (1). AUV frequency is 15 to 30 times lower than posterior urethral valve frequency (2). A small number of AUV cases, both separately and in association with anterior urethral diverticulum (AUD), have been described. We present the first pediatric case report of AUV and AUD which was complicated with intradiverticular stone. We also review the literature involving AUV with AUD cases.

Case Presentation

A 14-year-old male patient was admitted to our clinic with dysuria, pollakiuria and pain on the tip of the penis during voiding. The patient also had nocturnal and diurnal urinary incontinence. Macroscopic haematuria had been seen only once, two years earlier. Bilateral grade 2 hydroureteronephrosis, 700 cc bladder capacity and 300 cc postvoiding residual (PVR) urine volume were observed on abdominopelvic ultrasonography. Laboratory testing revealed a serum creatinine level of 0.64 mg/dL and blood urea nitrogen level of 11.8 mg/dL. Recurrent bacterial growth was found in the urine cultures. Uroflowmetry showed a maximal flow rate (Q_{max}) of 5.1 mL/s, average flow rate (Q_{ave}) of 1.6 mL/s, voiding volume of 200 cc, PVR of 380 cc, and plateau voiding pattern. Detrusor overactivity was observed on videourodynamic study. Before the voiding phase, fluoroscopy revealed 2 cm opacity in the penile urethra. On voiding phase, anterior urethral stenosis and poststenotic dilatation were observed. Vesicoureteral reflux (VUR) was not observed (Figure 1). Cystourethroscopy confirmed the presence of the AUV and a stone within the AUD (Figure 2a). The AUV was incised by a cold knife and laser (Figure 2b). Following

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open surgery for intradiverticular stone extraction and urethral diverticulum excision, reduction urethroplasty was performed. On the postoperative first month, uroflowmetry showed a Q_{max} of 14.4 mL/s, Q_{ave} of 4.8 mL/s, voiding volume of 389 cc, and PVR of 52 cc as well as improved voiding pattern. The patient signed informed consent and anonymity has been preserved.

Discussion

AUV is a rare congenital anomaly that causes lower urinary tract obstruction. AUVs may be located at the distal segment of the membranous urethra. AUVs are most frequently observed in the bulbous urethra segment (40%) and are seen with similar rates in the penile (30%) and penoscrotal regions (30%). There are few cases described in the fossa navicularis (3). The clinical presentation of AUV is highly variable depending on the age of the patient and the degree of the obstruction. AUV is difficult to diagnose unless the practitioner suspects the condition. It is possible to miss the diagnosis of AUV until adulthood. Common complaints include difficulty in voiding, pollakiuria, urinary incontinence, low urine flow, and recurrent urinary tract infections (4). In the neonatal period and in infancy, AUVs may cause severe obstruction resulting in megacystis, bladder rupture, bilateral hydroureteronephrosis, urinary ascites, and azotaemia (5). VUR is detected in one-third of AUV patients, and renal scarring is observed in half of AUV patients with VUR (6).

AUV can be isolated or may occur in association with AUD. Several theories have been described for the aetiology of AUV and AUD. Some authors suggest that AUV is an incomplete form of urethral duplication, while others suggest that both AUV and AUD are the result of ruptured cystic dilatation of Cowper's gland or other periurethral gland ducts (7). Similarly, it is unclear whether AUV and AUD coexist embryologically or are part of a continuum. The rarity of these lesions and the difficulties in diagnosing them make it challenging to establish a definite aetiology. Urinary tract infection, fistulas and stone formation in the diverticulum are the most common complications associated with urethral diverticulum (8). As a result of urinary stasis and infection in the diverticulum, a stone may form therein or a renal stone may get trapped in the diverticulum after descending into the bladder (9). In the literature, only one adult case of AUV and AUD, which was complicated with intradiverticular stone, has been reported (10). Our patient is the first pediatric case in the literature. Children with low flow rate and recurrent urinary tract infections should be evaluated carefully. AUV or AUD should be kept in mind during the differential diagnosis of obstructive pathologies. Voiding cystourethrogram (VCUG) is the gold standard imaging method for detection of urethral anomalies (1). For AUV diagnosis, it is necessary to view and evaluate the moment of voiding. In VCUG, dilated or extended posterior urethra, dilated anterior

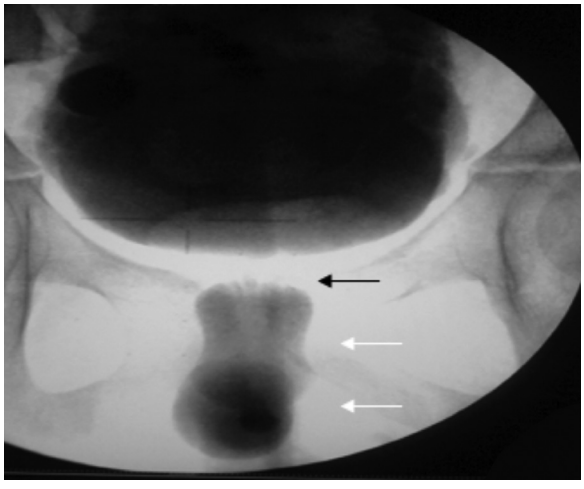

Figure 1. Anterior urethral stenosis (black arrow) and poststenotic dilatation of urethra (white arrows) on voiding phase of voiding cystourethrogram. Vesicoureteral reflux was not observed

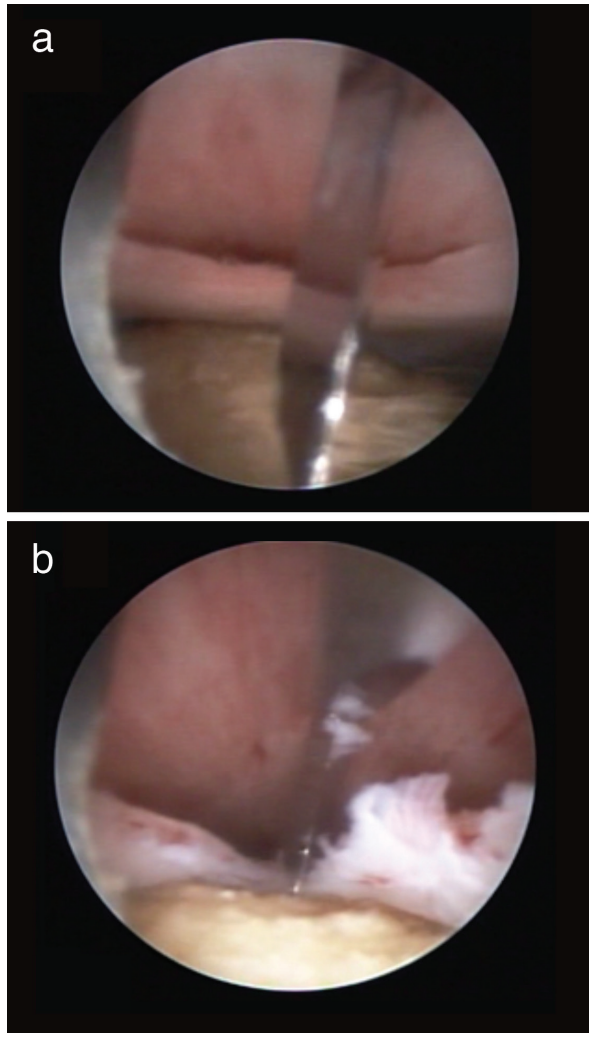

Figure 2. Cystourethroscopic view of the anterior urethral valve and a stone within the anterior urethral diverticulum, (a) anterior urethral valve incision by cold knife (b)

urethra, thickened and trabecular bladder, VUR, hypertrophic bladder neck, and urethral diverticulum can all be observed. The presence of retrograde fluid flow on the cystourethroscopy complicates the diagnosis by closing the crescent-shaped valves in isolated AUVs. When a patient is admitted with diagnosed or suspected AUV, the first procedure should be the placement of a permanent urethral catheter to allow urine drainage and reduce the risk of urosepsis and renal injury. The definitive treatment for AUV is surgery. Laser, electrocautery and hot or cold knife valve transurethral ablation are highly effective methods to treat AUV. In patients with very low birth weight, in whom endoscopic instrumentation is difficult, a temporary cutaneous vesicostomy may be required. AUD cases can be treated in a single surgical session that includes diverticulectomy and urethroplasty. AUD can also be treated with a two-session procedure. The urethrostomy can be opened from the proximal end of the valve before diverticulectomy and urethroplasty session. Urethrostomy preserves bladder functions better rather than vesicostomy (6). In our case, the AUV was first ablated with laser and cold knife. The diverticulum was excised, the stone was extracted and urethroplasty was performed. In conclusion, AUV with AUD is a rare cause of lower urinary tract obstruction and renal failure. All patients with low urine flow and recurrent urinary tract infections should carefully be evaluated, and AUV and AUD should be kept in mind during the differential diagnosis.

Ethics

Informed Consent: The patient signed informed consent and anonymity has been preserved.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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CASE REPORT
Reconstructive Urology

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Complete Urethral Rupture Related with Penile Fracture Occurring during Sexual Intercourse: A Case Report and Review of the Literature

Cinsel İlişki Nedeniyle Oluşmuş Penil Fraktür ile İlişkili Tam Üretral Rüptür: Olgu Sunumu ve Literatür Taraması

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Abstract

Complete disruption of the urethra due to penile fracture is a very rare occurrence. Herein, we report a case of a 39-year-old man who presented with penile fracture and complete disruption of the urethra as a result of sexual intercourse and present a review of the literature on penile fracture. Surgical exploration at presentation was performed and primary repair was done. In follow-up, the patient reported moderate erectile dysfunction which over time responded to phosphodiesterase-5 inhibitor drugs. Early surgical repair and evaluation for concomitant urethral injury in case of penile fracture is highlighted in this report.
Keywords: Penile fracture, Complete urethral rupture, Erectile dysfunction

Öz

Penil fraktür nedeniyle üretranın tam kopması nadiren görülür. Burada, cinsel ilişki sonucu üretra tam kopma ile beraber penil fraktür ile başvuran 39 yaşındaki bir erkek olguyu literatür eşliğinde sunuyoruz. İlk başvuruda hastaya cerrahi eksplorasyon yapıldı ve primer onarım uygulandı. Takipte, hasta fosfodiesteraz-5 inhibitör ilaçlarına cevap veren modarete erektil disfonksiyon bildirdi. Bu olguda, penil fraktür durumunda eşlik eden üretral hasarın değerlendirilmesi ve erken cerrahi onarım vurgulanmıştır.
Anahtar Kelimeler: Penil fraktür, Tam üretra yırtılması, Erektil disfonksiyon

Introduction

Penile fracture is characterized by tear in the tunica albuginea of any degree resulting from the abrupt bending of the erect penis (1). It may be accompanied by urethral trauma, which can be partial or complete, in up to 38% of cases (1). Penile fracture can cause some physiological and psychological consequences when therapeutic management is inadequate. On the other hand, with right diagnosis and sufficient surgical management outcomes remain excellent and complications are minimal. Our objective was to present a patient with penile fracture associated with complete urethral rupture due to sexual trauma in light of the literature.

Case Report

A 39-year-old Turkish man presented to the emergency department 3 hour after blunt trauma to the penis as a result of sexual intercourse. The patient reported a cracking sound and severe penile pain followed by immediate detumescence after striking his erect penis against his partner's perineum. He could not void at presentation though he did not describe blood at the urethral meatus. Physical examination revealed swelling and subcutaneous hematoma throughout the penis and the scrotum. He also had a dorsal-right deviation of the penis. The typical "rolling sign" was present in the right side of the penile shaft. There were painless scrotal swelling and palpable testicles on scrotal examination. Abdominal

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examinations showed swelling of the lower abdomen due to inability to void. Urethral catheterization could not be made despite gently insertion. Hematoma in the ventral penile shaft with a rupture of the tunica albuginea of the left cavernosal body and subcutaneous edema was revealed by penile ultrasound. Finding of blood at the urethral meatus suggested a urethral injury which was also demonstrated by urethrography (Figure 1). We informed the patient about the potential complications and took his written consent then he underwent immediate emergency surgery. Under spinal anesthesia, when degloving of the penile skin and evacuation of hematoma was done, partial disruption of both cavernosal bodies and complete urethral disruption were identified (Figure 2). Cavernosal defects were repaired by 3-0 polydioxanone (PDS) suture and a tension-free end-to-end anastomosis of the urethra was performed with 5-0 PDS sutures over an 18 Ch urethral catheter (Figure 2). As prophylaxis, ceftriaxone 1 g was given until discharge. On the second day following surgical intervention, the patient was discharged with urethral catheter. Foley catheter was not withdrawn for 1 week. Four months later, the patient reported normal voiding function and moderate erectile dysfunction; on physical examination, a little scar tissue was palpable on the dorsal side of the penis shaft. Six months later, the patient was evaluated with uroflowmetry and validated questionnaires. The maximum flow rate was 22 mL/s and international prostate symptoms score was 3, quality of life score was 0, and international index of erectile function-5 score was 10. A phosphodiesterase-5 (PDE-5) inhibitor was started on demand. In the 8th month of follow-up, penile magnetic resonance imaging was performed showing a normal penile integrity and a thickening of skin-subcutaneous tissue in the ventral and dorsal sections (Figure 3). It was observed that erectile dysfunction was responsive to PDE-5 inhibitors.

Figure 1. Urethral injury demonstrated by urethrography

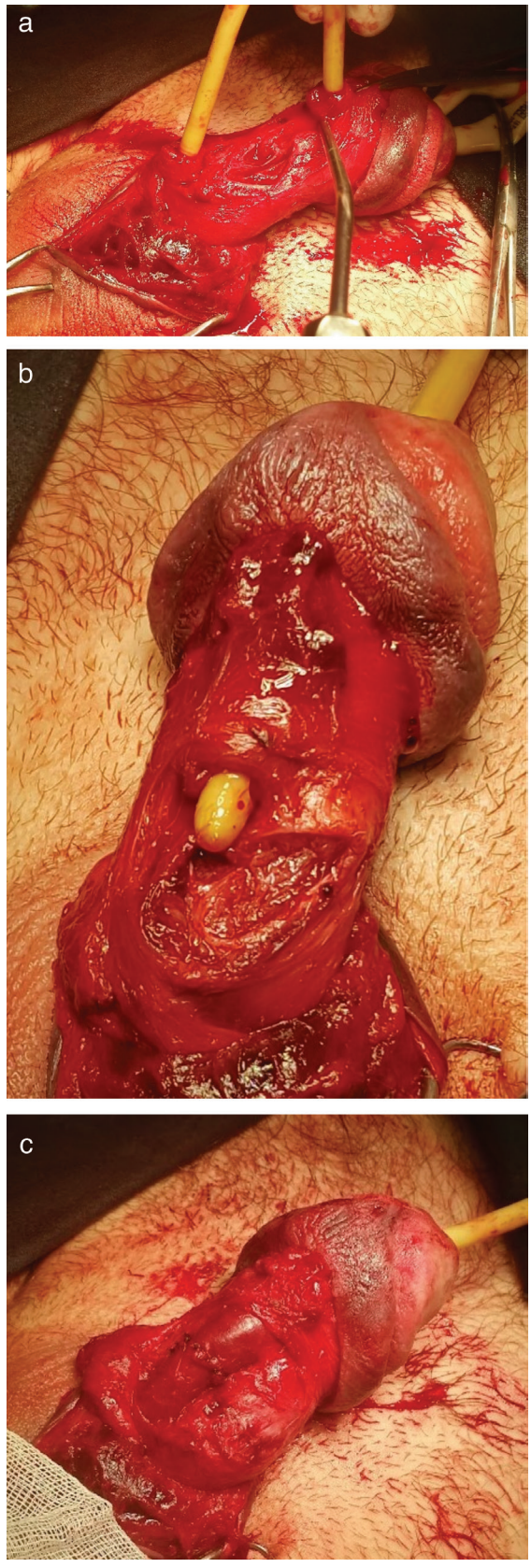

Figure 2. (a) Complete urethral disruption (b) Partial bilateral cavernosal body injury (c) Repaired cavernosal bodies and tensionfree end-to-end anastomosis of the urethra

Figure 3. Magnetic resonance imaging of the penis eight months later

Discussion

Penile fracture is an uncommon situation because of well-preserved location of the penis and high degree of genital mobility (2). However, during erection, the penis gets rigid and the tunica albuginea gets thinner, predisposing to penile fracture (2). Generally, the laceration is unilateral though bilateral rupture accounts for 2% to 10% of cases (3). Penile fracture with urethral injury is a rare situation. Urethral injury should be considered in patients with bilateral corporeal rupture (4). Among the causes of penile fracture, sexual intercourse is at the forefront. Due to this condition which is a cause of high-energy trauma, urethral injury is relatively more common which is generally partial in nature (5). A complete disruption of the urethra is a much less common condition (5). In a series of 312 cases published by Lynch et al. (8), there was also urethral injury in 10 patients. This is the 24rd case of penile fracture with total urethral disruption described in the English literature. There are many studies comparing surgical approach with conservative approach. Shorter duration of hospital stays and improved physiological and functional outcomes, including reduced erectile dysfunction, are associated with immediate operative intervention (6).

In their study including 155 patients with penile fracture, Ibrahiem et al. (9), reported that normal erectile function was observed in 77% of patients who were treated surgically. Venoocclusive dysfunction, arterial insufficiency, and continuous venous leakage are shown to be the causes of erectile dysfunction after penile fracture (7). Thus, some patients perform sexual acts with extreme fear of recurrence of trauma which may interrupt spontaneity and normality of the act (7). In our case, despite immediate surgical intervention, the patient had moderate erectile dysfunction which responded to PDE-5 inhibitors by time. However, since response to medication was obtained in our patient and there was no need for additional intervention, we did not need further investigation with penile color Doppler ultrasonography.

In about half of the partial anterior urethral disruptions, urethral luminal recanalization will occur (8). Optic urethrotomy or urethral dilatation can treat short strictures. Anastomotic urethroplasty is required in complicated strictures shorter than 1 cm in length. However, strictures longer than 1 cm in diameter should be repaired by flap urethroplasty in order to prevent chordee formation. Urethroplasty should be performed at 3th to 6th months in almost all complete disruptions of the anterior urethra in which urethral injury associated with penile fracture is an exception.

A subcoronal or circumferential incision is the best described surgical approach, thus the surgeon can explore all the corporeal bodies and repair if injured (9). Therefore, in our case, we did circumferential incision and repaired all the corporeal defects at the same time. In cases of complete urethral injury, urethral catheter was maintained until 2-3 weeks after the surgical operation (10,5). In our case, the urethral catheter was withdrawn on the 7th postoperative day and no voiding problem developed. Nevertheless, further case studies are needed for more information. In conclusion, this case supports the available data that early surgical intervention reduces the risk of complications.

Ethics

Informed Consent: Informed consent form was taken from the patient.

Peer-review: Internally peer-reviewed.

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

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CASE REPORT
Urooncology

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Huge Renal Angiomyolipoma with Life-threatening Bleeding into Itself Spontaneously

Kendi İçine Spontan Kanayarak Hayatı Tehdit Eden Büyük Renal Anjiyomiyolipom

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Abstract

Renal angiomyolipoma (R-AML) is one of the most common benign neoplasms of the kidney. It is usually asymptomatic and rarely becomes symptomatic. Management of R-AML is still controversial. Generally, follow-up is enough for the management of the disease but rarely, life-threatening complications may develop. Here, we would like to present a case of huge R-AML with life-threatening bleeding with literature review.
Keywords: Benign renal neoplasm, Nephrectomy, Angiomyolipoma

Öz

Renal anjiyomiyolipom (R-AML) böbreğin sık görülen benign tümörlerindendir. Genellikle asemptomatik olup nadiren semptomatik hale gelirler. Günümüzde halen R-AML'lerin nasıl tedavi edilmesi gerektiği açıklık kazanmamıştır. Genel yaklaşım bu hastalarda izlemdir fakat nadir de olsa hayatı tehdit edebilmektedir. Bu makalede devasal boyuta ulaşıp spontan kanayarak hayatı tehdit eden R-AML olgusunu ve uygulanan tedaviyi literatür eşliğinde sunduk.
Anahtar Kelimeler: Benign böbrek tümörü, Nefrektomi, Anjiyomiyolipom

Introduction

Renal angiomyolipoma (R-AML) is a benign mesenchymal neoplasm composed of smooth muscle cells, adipose tissue and thick-walled blood vessels in different compositions. It is usually asymptomatic and found incidentally by routine imaging techniques and rarely becomes symptomatic. The prevalence of R-AML in the general population is between 0.3% and 3% and females are 4 times more at risk than males (1,2). It develops sporadically in 80% of cases and might be a clinical sign of tuberous sclerosis.

We would like to present a patient with giant R-AML which was complicated by life-threatening bleeding into itself spontaneously.

Case Presentation

A 59-year-old male patient presented to the emergency department with abdominal distension, swelling, pain and confusion. There was no trauma or any anticoagulant drug use in the past medical history. Skin color was pale and a solid mass was palpated in the right upper and lower quadrant of the abdomen. His blood pressure was 100/60 mmHg, heart rate - 108 beats/min, hemoglobin (Hb) - 7.1 gr/dL, hematocrit (Htc) - 24%, platelet count - 124000, urea - 45 mg/dL and creatinine was 1.5 mg/dL.

Computed tomography (CT) of the abdomen revealed a 30x25 cm massive lesion originating from the hilum of the right kidney and extending inferiorly and laterally to the right lower quadrant of the abdomen, and including vascular parts in fat

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tissue. It was considered as a bleeding AML. One hour after the admission to the emergency department, Hb dropped to 6.4 g/dL and Htc dropped to 20.9%. The patient underwent emergency laparotomy due to suspicion of bleeding and the exploration revealed bleeding giant AML originating from the right kidney. Right radical nephrectomy was performed with administering 8 units of erythrocyte suspension and 2 units of fresh frozen plasma. After transferring him to the intensive care unit for 5 days, he completely recovered and was discharged from the hospital pathology showed that the lesion was composed of adipose tissue with proliferative vascular structures and fusiform-cheroot-shaped cells (Figure 1). Immunohistochemical staining for smooth muscle actin showed that fusiform-cheroot-shaped cells were smooth muscle fibers (Figure 2). These areas were also subjected to human melanoma black-45 staining. Vascular structures were stained with CD34. The diagnosis was AML based on the findings.

Written informed consent was obtained from the patient.

Discussion

The term "angiomyolipoma" was first used by Morgan et al. (3) for defining a renal tumor composed of smooth muscle and adipose tissue with different proportions. AML arises sporadically in 80% and accompanies tuberous sclerosis in 20% of cases. Sporadic cases usually seen in females aged 40-70 years and mostly manifest as a large, single and unilateral massive lesion (4). It may also be related with von Hippel-Lindau disease, von Recklinghausen syndrome and polycystic kidney disease (5).

In our case, we evaluated the central nervous system, skin and retina and we did not find any sign related with tuberous sclerosis. Therefore, our case was diagnosed as sporadic AML.

The most important complications seen in patients with AML are retroperitoneal hemorrhage, hematuria and renal failure caused by tumor compression. Sporadic AML is usually asymptomatic and found incidentally as a single mass by renal visualization techniques (6). In our case, the diameter of the mass was 30 centimeters, and this is one of the largest tumors reported in the literature. Renal cell carcinoma, oncocytoma or any other metastatic cancers must be considered in the differential diagnosis. The classical presentation of AML on ultrasonography (USG) is hyperechoic lesion with acoustic ghosting (2,6,7). The most echogenic tumors in all renal tumor types seen on USG are AMLs. CT is the most commonly used imaging technique for the diagnosis of AML (7,8). It is difficult to diagnose AMLs

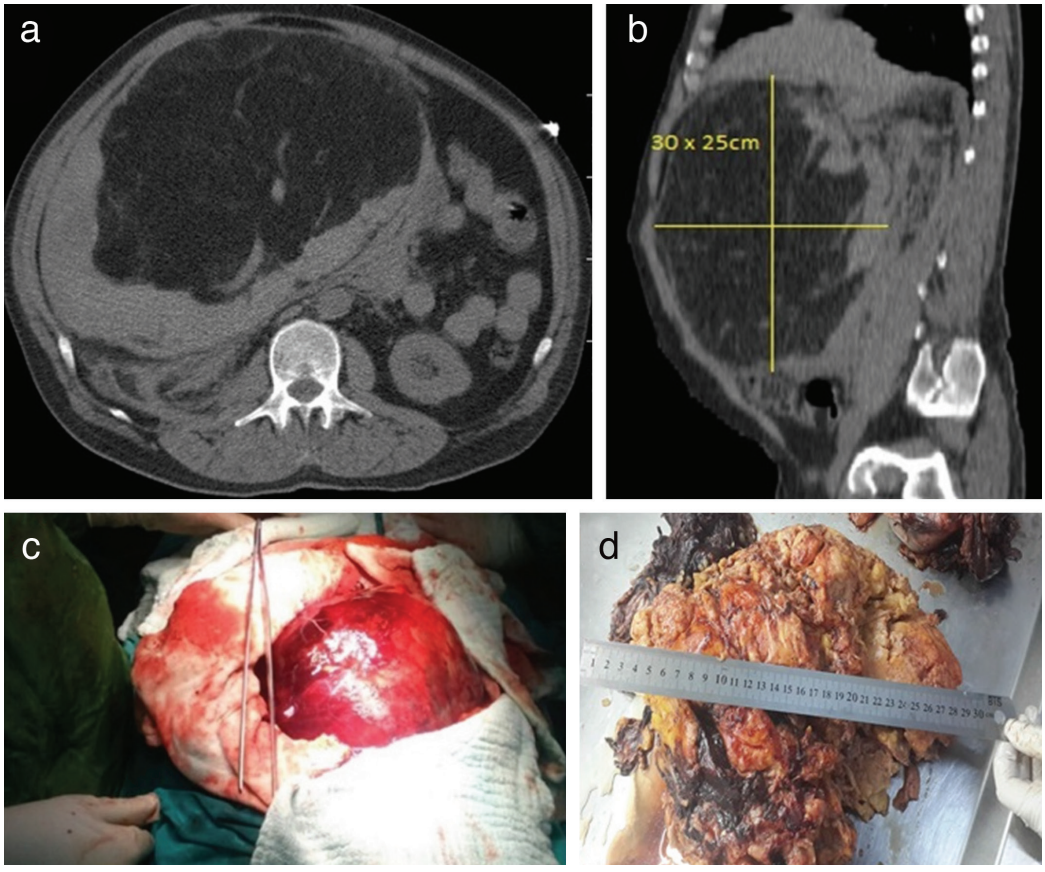

Figure 1. (a) Giant pathological mass on the transverse cross section computed tomographic scans, (b) mass size on sagittal sections, 30x25 cm (c) intraoperative photograph of angiomyolipoma, (d) specimen showing renal angiomyolipoma

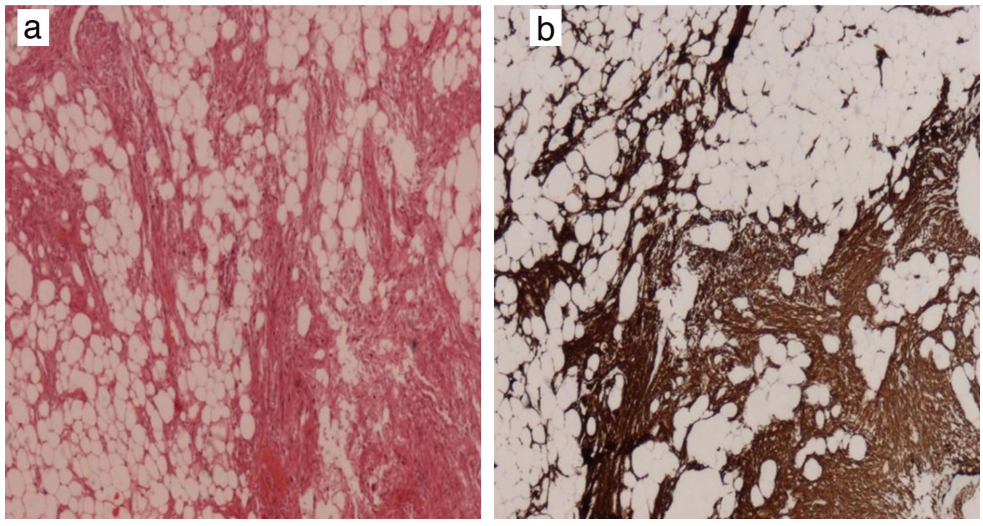

Figure 2. (a) Angiomyolipoma composed of lipocytes, smooth muscle bundles and vascular structures (hematoxylin and eosin 40x), (b) smooth muscle bundles of angiomyolipoma positive for smooth muscle actin (smooth muscle actin 40x)

with a small amount of fat using CT or USG (8). In our case, we observed a mass lesion composed of adipose density with vascular structures on CT and it was diagnosed as AML.

The treatment of renal AML is still controversial. For asymptomatic small lesions, follow-up is recommended. Surgical treatment options for AML are radical or partial nephrectomy, selective arterial embolization and ablative methods including cryoablation and radiofrequency ablation. Moreover, a new medical treatment, mechanistic target of rapamycin (mTOR) inhibitors are used for AML related with tuberous sclerosis. Oesterling et al. (9) suggested prophylactic surgery for renal AMLs larger than 4 cm, concomitant with aneurysms larger than 5 mm and AMLs with excessive vascularization due to spontaneous bleeding risk. Selective renal artery embolization or total nephrectomy may be an appropriate option for tumors which are inappropriate for nephron-sparing surgery because of tumor size and location. Following with USG once a year is enough for AMLs which are asymptomatic and smaller than 4 cm (10). Follow-up intervals must be shorter in pregnant patients and those receiving estrogen therapy because there is increased spontaneous rupture risk of AML due to increased estrogen and progesterone receptor expression, maternal circulation and intraabdominal pressure (11). Surgery may be suggested before pregnancy for patients with AML larger than 4 cm or a history of bleeding AML (12).

According to the European Association of Urology guidelines, the most favorable approach to asymptomatic renal AMLs is active follow-up. The first option is selective arterial embolization when any intervention is needed. When the option is surgery, most patients can be treated with nephron-sparing surgery but in some exceptions complete nephrectomy might be a choice. Furthermore, surgery may be delayed if tumor size decreases by mTOR inhibitors (everolimus and sirolimus) (13). In our case, we performed total nephrectomy instead of nephron-sparing surgery because the mass was huge and there was excessive perioperative blood loss.

In fact, our patient received the diagnosis of AML 5 years ago in another clinic but he was not followed. He would not have spontaneous bleeding if the patient had appropriate treatment for 5 years. Prophylactic surgery is the option for AMLs larger than 4 cm or concomitant with aneurysms larger than 5 mm because of the spontaneous bleeding risk (9). We believe that our patient's hemorrhage was due to an aneurysm rupture because there was no history of trauma or anticoagulant medication use.

As a result, we believe that huge AMLs should be electively treated before the symptoms occur.

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Ç., H.D., Ö.E., Concept: M.Ç., H.Ş., Ö.İ.Ç., Design: M.Ç., Ö.E., H.D., H.Ş., Data Collection or Processing: M.Ç., H.Ş., Ö.E., Literature Search: M.Ç., Ö.E., Writing: M.Ç., Ö.E.

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

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CASE REPORT
Pathology

Doi: 10.4274/jus.1454
Journal of Urological Surgery, 2018;5(2):120-122

Primary Localized Amyloidosis of the Bladder Mimicking Neoplasia

Neoplaziyi Taklit Eden Mesanenin Primer Lokalize Amiloidozisi

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Abstract

A 63-year-old woman was admitted to our hospital with macroscopic hematuria in 2013. On computed tomography, the bladder wall thickness was 2 cm, suspicious for malignancy. Cystoscopy showed irregularity in the posterolateral side of the bladder. Transurethral resection was performed. Histopathological examination revealed a dense homogeneous eosinophilic material in the lamina propria which showed positive orange-red staining with apple-green birefringence under polarized light. There were no signs of systemic amyloidosis at the time of diagnosis and during the 36 months of follow-up. Differential diagnosis of amyloidosis in the bladder includes urothelial carcinoma due to its appearance on imaging and cystoscopy. Histopathological evaluation is a requirement for accurate diagnosis.
Keywords: Primary, Amyloidosis, Bladder

Öz

Altmış üç yaşında kadın hasta 2013 yılında makroskopik hematüri ile hastanemize başvurdu. Bilgisayarlı tomografide, mesane duvarının posterolateral ve superior kısmının, tümör açısından şüphe uyandıracak şekilde 2 cm kalınlığında olduğu görüldü. Sistoskopik bakıda mesanenin posterolateral tarafında düzensiz alanlar görüldü. Transüretral mesane rezeksiyonu ile kürete materyal elde edildi. Biyopside lamina propriada turuncu-kırmızı boyanma gösteren, yoğun, homojen eozinofilik materyal izlendi ve polarizasyonda elma yeşili çift kırılımı gösterildi. Olguda tanı anında ve 36 aylık takiplerinde sistemik amiloidoz bulguları saptanmadı. Mesanenin amiloidozu, görüntüleme yöntemlerinde ve sistoskopide ürotelyal karsinom ile kolayca karışabilen nadir bir durumdur. Kesin tanı için histopatolojik inceleme şarttır.
Anahtar Kelimeler: Primer, Amiloidoz, Mesane

Introduction

Amyloidosis is a disorder caused by extracellular deposition of insoluble fibrils composed of misaggregated proteins (1). Primary amyloidosis of the urinary bladder is an extremely rare entity with less than 200 cases reported worldwide (2). The lesion can easily mimic malignancy because of its appearance on radiological examination and cystoscopy (3,4,5). Histopathological evaluation is necessary to exclude malignancies. We report a 63-year-old female who was admitted to our hospital with hematuria and received the histopathological diagnosis of amiloidosis.

Case Presentation

A 63-year-old female patient was admitted to our hospital with macroscopic hematuria. Computed tomography showed urinary bladder wall thickness of 2 cm in the posterolateral and superior wall of the bladder, suspicious for malignancy. Cystoscopy showed irregularity in the posterolateral wall of the bladder. Transurethral resection was performed. Histopathological examination revealed a dense homogenous eosinophillic material in the lamina propria showing positive orange-red staining with Congo-red with apple-green birefringence under polarized light (Figure 1). There was no evidence of urothelial neoplasia or precursor lesion. There was no sign of systemic amyloidosis at the time of diagnosis and during the 36 months

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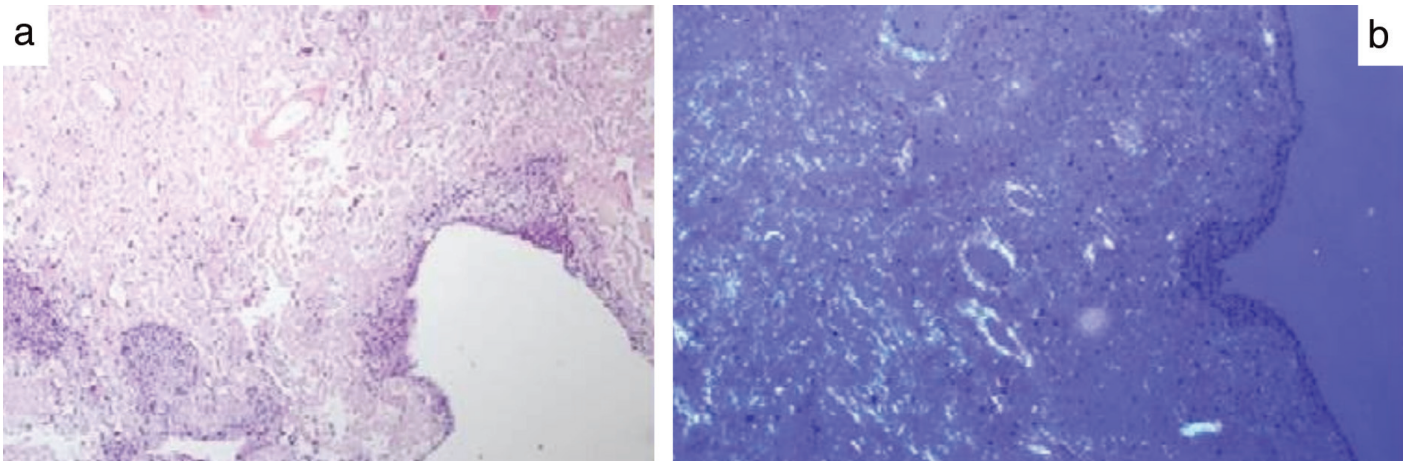

Figure 1. (a) Deposits of eosinophilic, acellular material in the lamina propria beneath urothelial epithelial layer (hematoxylin and eosin stain, 400x). (b) Apple green birefringence of amyloid deposits under polarized microscopy (congo red stain, 400x)

of follow-up. However, 36 months later, she presented with a second episode of macroscopic hematuria and underwent transurethral resection. Histopathological examination showed amiloid deposition in the lamina propria of the bladder wall.

Informed consent was obtained from the patient.

Discussion

Amyloidosis is a benign, non-neoplastic disease characterized by extracellular deposition of eosinophilic fibrillar proteins in various tissues and organs (6). In the urinary tract, amyloid deposition may occur in the kidney, renal pelvis, ureters, urinary bladder, urethra and even in the penis (4).

Both sexes are equally affected, most commonly during the fifth and seventh decades of life (4). The most frequent symptom of amyloidosis in the bladder is gross haematuria (7). Irritative voiding symptoms have been reported in 23% of cases in various studies (8). Since it predominantly involves the submucosal and muscular layers, massive hemorrhage is a rare occurrence (4).

Cystoscopic examination of bladder amyloidosis often shows yellowish plaques or tumor-like structures (9).

Histopathological examination demonstrates a dense acellular homogenous eosinophillic material showing positive orange-red staining with Congo-red with apple-green birefringence under polarized light.

Amyloidosis is classified as primary amyloidosis (AL), secondary amyloidosis (AA) and transthyretin-related amyloidosis (ATTR) (9,10,11). Amyloidosis can be either localized or systemic (9,10,11). Localized deposition of amyloid may occur in any organ in the absence of systemic involvement (12). Primary localized amyloidosis of the urinary bladder is uncommon, however, the bladder is the most common site of involvement (3,4). Primary amyloidosis is also the most common form of localized amyloidosis in the bladder (11).

The treatment modality in primary bladder amyloidosis is usually conservative with transurethral resection, but high recurrence rate of almost 50% has been described (7). In some patients with irritative symptoms or gross haemeturia, cystectomy is necessary (7). Medical treatment, such as colchicines, nitrofuazone and dimethylsulfoxide as primary or adjuvant therapy, has been tried for symptomatic relief (4).

Amyloidosis of the bladder is a rare condition which mimics urothelial carcinoma because of its appearance on imaging as well as cystoscopy. Histopathological evaluation is essential for definitive diagnosis and management.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.E., Ü.K., E.Ç., Ö.Ç., Concept: S.E., Ü.K., E.Ç., Design: S.E., Ü.K., Data Collection or Processing: S.E., Ü.K., E.Ç., E.E.P., S.A., Ö.Ç., Analysis or Interpretation: S.E., Ü.K., Literature Search: S.E., Ü.K., E.Ç., E.E.P., S.A., Ö.Ç., Writing: S.E., Ü.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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CASE REPORT
General Urology

Doi: 10.4274/jus.1406
Journal of Urological Surgery, 2018;5(2):123-125

Urethral Squamous Cell Papilloma: A Rare Case Report and Review of the Literature

Üretranın Skuamöz Hücreli Papillomu: Nadir Bir Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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Abstract

Urethral squamous cell papilloma is a benign lesion commonly presenting with lower urinary tract symptoms, such as dysuria and intermittent poor urinary flow. Surgical excision and careful pathological investigation are required for definite diagnosis and treatment. The probability of recurrence is fairly low. These lesions are generally observed in the urethra in post-menopausal women. This paper presents a case of squamous cell papilloma in the male anterior urethra in an 18-year-old male patient, who underwent surgical excision, and a literature review.
Keywords: Papilloma, Tumor, Urethra

Öz

Üretranın skuamöz hücreli papillomu genellikle dizüri ve aralıklı idrar akış hızında azalma gibi alt üriner sistem semptomları ile bulgu veren benign lezyonlardır. Kesin tanı ve tedavi için cerrahi eksizyon ve dikkatli bir patolojik inceleme gerekmektedir. Nüks riski oldukça düşüktür. Bu lezyonlar genellikle menopoz sonrası kadınların üretrasında gözlenmektedir. Fakat, bu yazıda literatür eşliğinde erkek anterior üretrası kaynaklı skuamöz hücreli papillomu olan ve cerrahi eksizyon yapılan 18 yaşında erkek hasta sunulmaktadır.
Anahtar Kelimeler: Papilloma, Tümör, Üretra

Introduction

Squamous cell papilloma is a benign epithelial tumor rarely observed in the distal urethra in both sexes (1). The majority of lesions are seen in women in the external meatus. Urethral caruncle, urethral prolapse, urethral diverticulum and periurethral gland abscess are included in the differential diagnosis (2). Generally, these lesions are observed in hypoestrogenic state in post-menopausal women and are reported to develop from urethral caruncle background (3). Careful histological investigation is important for diagnosis (2). The clinical importance of these non-invasive lesions is unknown, though some case reports are available in the literature.

In this paper, we aimed to present an 18-year-old male patient with the diagnosis of squamous cell papilloma in the distal urethra and a literature review.

Case Presentation

An 18-year-old male patient admitted to our clinic with the complaints of intermittent dysuria and occasional reduction in urine flow rate in recent times. Physical examination revealed a polypoid lesion protruding from the external meatus (Figure 1). There was no other pathology identified in the external genital area. Due to the possibility of multifocality, urethrocystoscopy was planned. Urethrocystoscopy showed a solitary polypoid lesion in the distal fossa navicularis, protruding from the external

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meatus. Urethroscopy of the anterior and posterior urethra appeared to be normal, and cystoscopy revealed no additional pathology in the bladder. Surgical excision was performed for the polypoid lesion. Histologically, it was composed of papillary cores with overlying benign squamous epithelium (Figure 2). Immunohistochemical staining was negative for human papillomavirus (HPV) and p16, thus, pathological diagnosis of squamous cell papilloma was made.

In the postoperative 12th month after surgical excision, the patient had no complaints and was monitored by our clinic with no recurrence.

This study is retrospective designed study.

Figure 1. Appearance of squamous cell papilloma sourced in the anterior urethra, protruding from external meatus before surgical excision

Discussion

Squamous cell papilloma is a rarely observed benign lesion presenting with irritative urinary symptoms, generally identified in women over the age of 40 years (4). The patient may have symptoms, such as dysuria, intermittent hematuria, difficulty in voiding, low urinary flow rate and residual urine sensation after voiding (4). In women, lesions are generally observed in the distal urethra protruding from the external meatus (4). Evaluation with cystoscopy is an appropriate approach. Urethral caruncle, condyloma accuminatum, urethral prolapse, urethral diverticulum and periurethral gland abscess are important pathologies in the differential diagnosis (2). There is no information related to male cases in the literature, however, for differential diagnosis, anterior urethral pathologies are important. When anterior urethral pathologies are examined, congenital urethral polyp in the anterior urethra, fossa navicularis pathologies (stenosis, Guerin's sinus), anterior urethral valve, syringocele (dilatation of Cowper's gland ducts), congenital bulbous urethral stricture, condyloma accuminatum, and especially botryoid sarcoma polyps should be taken into the consideration in the differential diagnosis (5,6,7,8). Definite diagnosis of squamous cell papilloma is made by careful pathological investigation. In a study investigating the correlation of squamous cell papilloma with HPV evaluated verrucous carcinoma, condyloma acuminata and urethral squamous cell papilloma cases, no correlation was observed (8). As a result, to exclude HPV and p16 immunostaining, clear definition of squamous cell papilloma is important. Microscopic investigation of the lesion demonstrates koilocytotic alterations and wrinkled hyperchromatic nuclei of squamous cells (8,9,10). In our patient with a polypoid lesion in the distal fossa navicularis and protruding from the external meatus, urethrocystoscopy was performed to aid differential diagnosis and to research the presence of additional pathologies. When additional pathologies were not identified, surgical excision was performed. Pathological investigation was negative for HPV and p16 in accordance with the literature and the diagnosis of squamous cell papilloma was made. Recurrence after surgery in urethral squamous cell papilloma is rare,

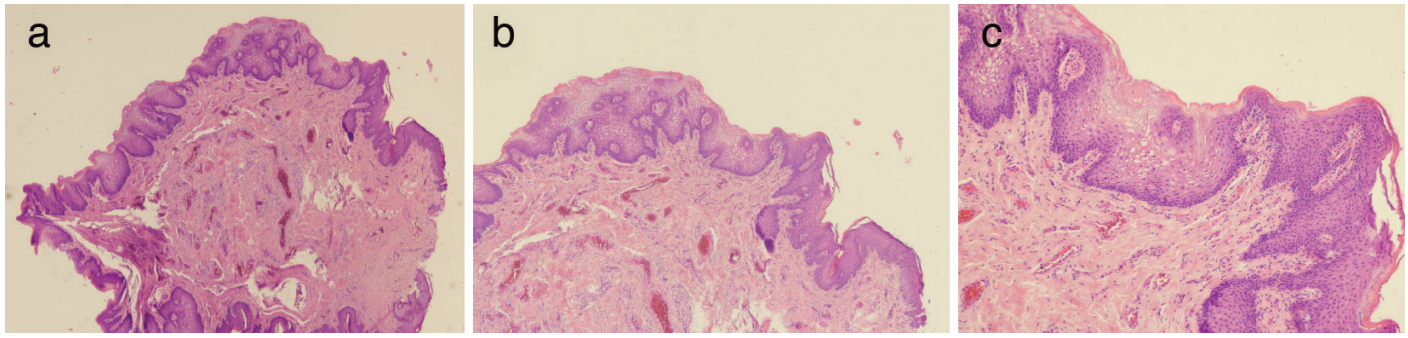

Figure 2. Classical squamous papilloma with a stalk devoid of inflammatory infiltration, without koilocytotic and nuclear atypia and keratinization (hematoxylin & eosin, a: 4x, b: 10x, c: 20x)

however, as there is a limited number of case reports in the literature, definite information cannot be given (8). The largest series in the literature comprises 5 patients. Two of these 5 cases could not be monitored so they were not assessed. Two patients did not have recurrence during follow-up and one patient was reported to have a lesion accompanied by low-degree urothelial carcinoma (11). However, when squamous cell papilloma cases are examined, the majority of patients appear to have a low risk for both urothelial carcinoma and HPV infection (4). There is no clear follow-up plan after surgical excision in the English literature; as a result, it is recommended that a follow-up plan can be determined based on physical examination and presence of symptoms (4). As recommended, we monitored our patient with physical examination and questioning of symptoms; and no recurrence was detected in the postoperative 12th month. In conclusion, urethral squamous cell papilloma is usually a benign lesion, generally occurring in the urethra in women above the age of 40 years and presenting with irritative urinary symptoms. Diagnosis can be made by urethrocystoscopy which is the accepted treatment with surgical excision. The probability of recurrence is usually low. In some cases, these lesions may be found in the female middle urethra and the male anterior urethra; other important anterior urethral pathologies and botryoid rhabdomyosarcoma polyps must be kept in mind for differential diagnosis.

Ethics

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.H.Ö., K.Y., M.U.M., Concept: S.Ç., Design: S.Ç., Data Collection or Processing: S.Ç., Analysis or Interpretation: S.Ç., H.H.Ö., K.Y., M.U.M., Literature Search: S.Ç., Writing: S.Ç.

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.2018.05.009

Re: Risk of ESRD in Prior Living Kidney Donors

Wainright JL[1], Robinson AM[1], Wilk AR[1], Klassen DK[2], Cherikh WS[1], Stewart DE[1]

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Am J Transplant 2018;18:1129-1139. doi: 10.1111/ajt.14678.

EDITORIAL COMMENT

Every year more living kidney donors (LKDs) are requiring renal replacement therapies due to end-stage renal disease (ESRD). In this retrospective observational study, the authors have evaluated the association between characteristics at donation and development of ESRD for LKDs who have donated between 1994 and 2016 (n=123.526) in the United States by using Organ Procurement and Transplantation Network and Centers for Medicare and Medicaid Services data. Of those, 218 LKDs developed ESRD, with a median of 11.1 years between donation and ESRD. Although the overall absolute 20-year risk of ESRD was low for LKDs, it was not uniform either. In multivariable analysis, being male, black race, having lower estimated glomerular filtration rate, having higher body mass index at donation, being first-degree relative of the recipient and full sibling were identified as significant risk factors for ESRD. There was also a strong age and race interaction, with older age at donation conferring higher risk for white donors, but younger age at donation resulting higher risk for black donors. Interestingly LKDs from low socioeconomic levels had a higher risk of ESRD compared to those living in higher income neighborhoods. It is important for the potential living donors to understand their absolute risk at the time of decision making for donation. Also, it is crucial to build national donor follow-up programs for calculating the absolute and relative risks for donors.

Yarkın Kamil Yakupoğlu, MD

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Transplant Survey

Doi: 10.4274/jus.2018.05.010

Re: Effects of Recurrent Urinary Tract Infections on Graft and Patient Outcomes After Kidney Transplantation

Britt NS[1], Hagopian JC[1,2], Brennan DC[2], Pottebaum AA[1], Santos CAQ[3], Gharabagi A[2], Horwedel TA[1,2]

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Nephrol Dial Transplant 2017;32:1758-1766. doi: 10.1093/ndt/gfx237.

EDITORIAL COMMENT

In this retrospective single center study at a large-volume center, the authors have investigated association between post kidney transplant (KT) urinary tract infections (UTIs) and graft and patient outcomes, with a focus on recurrent (R)-UTIs (≥2 UTIs in any 6-month period or ≥3 UTIs in any 12-month period). Of 2469 patients included, 1835 (74.3%) had no UTI, 465 (18.8%) had non-recurrent (NR)-UTI (urine sample containing $>10^5$ bacterial colony-forming units/mL) and 169 (6.8%) had R-UTI. The authors have found that patients with R-UTI had significantly worse graft function and graft survival compared with both those with no UTI as well as NR-UTI. R-UTI, but not NR-UTI, was associated with poorer patient survival compared with no UTI. Therefore, the association between UTI and worse patient outcomes in the KT population appears to be driven by recurrent cases. R-UTIs were more likely to be caused by multi drug resistant organisms, posing unique treatment challenges. Also, some risk factors, which have not been previously described, were found in this study for R-UTIs; increased age, African-American race and deceased donor status were also reported besides female gender, diabetes mellitus, ureteric stenting, re-transplantation, lack of antimicrobial prophylaxis and prolonged urinary catheterization which have been linked to R-UTI in the literature.

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Basic Research

Doi: 10.4274/jus.2018.05.011

Re: Oxytocin Effects on Experimental Skin Wound Healing

Sorg H[1], Grambow E[2], Eckl E[2], Vollmar B[2]

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Innov Surg Sci 2017;2 https://doi.org/10.1515/iss-2017-0033.

EDITORIAL COMMENT

Oxytocin (OXY) is a powerful hormone acting as a neurotransmitter in the brain. OXY has significant effects on mammalian behaviors including social interaction, love and sexual reproduction, lactation, parturition, uterine contraction and orgasm. As a possible new idea, wound healing effect of this hormone was suggested. In this study, the authors examined the effects of OXY and an OXY receptor antagonist [atosiban (ATO)] on skin wound healing, considering epithelialization and neovascularization. In this study, skin wound healing was evaluated using intravital fluorescence microscopy in a model of full dermal thickness wounds in mice. The animals received low or high doses of intraperitoneal injection of OXY or ATO daily. Morphological and cellular characterization of skin tissue repair was performed by histology and immunohistochemistry, *in vitro* cell proliferation and cell migration assays in this study. The evaluation of skin tissue repair due to this protocol showed that there was no major effects of OXY and ATO on epithelialization, neovascularization, wound cellularity, or inflammation. As a result of this animal study, it was reported that OXY had no significant effects on physiological skin wound healing *in vivo*. However, further well designed researches on especially local application of OXY are needed.

Fehmi Narter, MD, PhD

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Basic Research

Doi: 10.4274/jus.2018.05.012

Re: Larval Therapy from Antiquity to the Present Day: Mechanisms of Action, Clinical Applications and Future Potential

Whitaker IS, Twine C, Whitaker MJ, Welck M, Brown CS, Shandall A

Morriston Hospital, Clinic of Burns and Plastic Surgery, Swansea, United Kingdom

Postgrad Med J 2007;83:409-13.

EDITORIAL COMMENT

Non-healing chronic wounds present a major health problem despite medical and technological advances in the management of atherosclerotic or diabetic wounds. There are many well described methods such as vacuum pump therapy, hyperbaric oxygen therapy, ozone therapy, and growth factor injection. On the other hand, some ancient therapies have been reevaluated for their efficacy in the treatment of non-healing chronic wounds. One of these alternative and complementary methods is maggot therapy [maggot debridement therapy (MDT), biodebridement, biosurgery or larval therapy]. MDT is the intentional application of live, "medical-grade" and sterile fly larvae (*Lucilia sericata*) to wounds for debridement, disinfection, and ultimately wound healing. In the United States, medicinal maggots are approved by the Food and Drug Administration as a prescription-only, single-use medical device since 2004. There are many scientific reports on this topic in the medical literature. These larvae make an excellent debridement for necrotic tissues in the wound area in addition to antibacterial effect and production of substances to induce wound healing. There is evidence in the literature on the successful use of larval therapy for traumatic wounds that fail to heal; postsurgical wound infections and perineal gangrene (Fournier's gangrene) have also been treated with maggot therapy after unsuccessful antibiotic and surgical treatments. In our opinion, next generation transgenic larval therapies will be reliable treatment options for chronic non-healing wounds in the near future.

Fehmi Narter, MD, PhD

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Urooncology

Doi: 10.4274/jus.2018.05.013

Re: Clinical and Genomic Characterization of Low-Prostate-specific Antigen, High-grade Prostate Cancer

Mahal BA[1], Yang DD[2], Wang NQ[3], Alshalalfa M[3], Davicioni E[3], Choeurng V[3], Schaeffer EM[4], Ross AE[5], Spratt DE[6], Den RB[7], Martin NE[8], Mouw KW[8], Orio PF[8], Choueiri TK[9], Taplin ME[9], Trinh QD[10], Feng FY[11], Nguyen PL[12]

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Eur Urol 2018 Feb 22. pii: S0302-2838(18)30098-8. doi: 10.1016/j.eururo.2018.01.043.

EDITORIAL COMMENT

Prostate-specific antigen (PSA) is typically elevated in high-grade prostatic adenocarcinoma. However, some patients present with high-grade disease and low PSA. Patients presenting with neuroendocrine prostate cancer, which is an aggressive entity that does not respond to hormone therapy also typically have low PSA values. In order to investigate the clinical implications and genomic features of low-PSA, high-grade disease, the authors performed a retrospective study of clinical data from the National Cancer Data Base, Surveillance, Epidemiology and End Results program, and genomic data from the Decipher Genomic Resource Information Database.

For Gleason 8-10 disease, using PSA 4.1-10.0 ng/mL (n=38.719) as referent, the distribution of PCSM by PSA was U-shaped, with an adjusted hazard ratio of 2.70 for PSA ≤2.5 ng/mL (n=3862, p<0.001) versus 1.97, 1.36, and 2.56 for PSA of 2.6-4.0 (n=4199), 10.1-20.0 (n=17.372), and >20.0 ng/mL (n=16.114), respectively. For Gleason 8-10 tumors, PSA ≤2.5 ng/mL was associated with higher expression of neuroendocrine/small-cell markers compared to >2.5 ng/mL (p=0.046), with no such relationship for Gleason ≤7 disease.

These results show that low-PSA, high-grade disease is associated with a more than two-fold higher risk of prostate cancer death relative to NCCN high-risk/very high-risk disease, with a large number of deaths occurring within a short period after diagnosis. The authors argue that the clinical and genomic data from this study strongly suggest that low-PSA, high-grade prostate cancer is a clinically and biologically unique entity that is associated with poor prognosis and that may not respond well to androgen deprivation therapy. Thus, the findings of this study pave the way for further studies and possibly for developing modified risk classifications and alternative treatment approaches such as early chemotherapy for patients with low-PSA, high-grade prostate cancer.

Özgür Yaycıoğlu, MD, FEBU

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Andrology

Doi: 10.4274/jus.2018.05.014

Re: Fertility Outcomes After Extended Searches for Ejaculated Spermatozoa in Men with Virtual Azoospermia

Miller N[1], Biron-Shental T[2], Pasternak Y[3], Belenky M[4], Shefi S[5], Itsykson P[6], Berkovitz A[7]

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Fertil Steril 2017;107:1305-1311. doi: 10.1016/j.fertnstert.2017.04.005.

EDITORIAL COMMENT

Based on the World Health Organization 2010 recommendation, seminal fluid should be centrifuged at 3000 g for 15 minutes and the pellet should be detected for the presence of spermatozoa. If any sperm is observed in the pellet, the patient is considered as having cryptozoospermia. In this study, the investigators identified a group of men with cryptozoospermia and they searched centrifuged pellet around 2 to 4 hours to find sperm and called this group "virtual azoospermia" if they found a few. Using ejaculated sperm and testicular sperm for intracytoplasmic sperm injection, fertilization rates (56% vs 50%) were similar between the groups. Although the pregnancy rate was higher in the ejaculated group (64%) than in microsurgical testicular sperm extraction (microTESE) group (50%), it was not statistically significant. "Take-home baby" rates were higher in microTESE group (82%) compared to ejaculated sperm group (58%) but not statistically significant. This study shows that *in vitro* fertilization laboratory technicians have a very important role in extended spermatozoa search in the ejaculate as well as urologists working under the microscope to find viable sperm within the testes. In addition, finding motile sperm in ejaculate with extensive search, rescue the patient from surgical sperm recovery. However, this condition has no effect on the rates of pregnancy and live birth but significantly on high miscarriage rate in the first trimester (52% vs 8.6%).

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Andrology

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Re: Varicocelectomy to "Upgrade" Semen Quality to Allow Couples to Use Less Invasive Forms of Assisted Reproductive Technology

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EDITORIAL COMMENT

Varicocele is one of the most commonly seen and correctable anatomical pathology in infertile men. Although varicocele repair results in improvement of semen quality in most infertile men, the degree of improvement in semen parameters is not well studied. The authors aimed in this study to determine the magnitude of improvement in semen parameters and the fraction that have improvements after a varicocelectomy in order to pave the way for less invasive techniques for couples needing assisted reproductive techniques. The main outcome measurement is total motile sperm count (TMSC) before and after the varicocele repair. For natural pregnancy, more than 9 million, for intrauterine insemination (IUI)-5-9 million and for *in vitro* fertilization (IVF), less than 5 million TMSC are considered the cut off points. A total of 373 men underwent varicocele repair and the mean TMSC increased from 18 to 46 million which is statistically significant. The most pronounced increase was in the baseline TMSC less than 5 million group and 58% of men were upgraded from IVF candidacy to IUI of natural pregnancy. As a conclusion, the authors emphasized that even for low TMSC, a varicocelectomy may reduce the need for IVF and invasive ART techniques.

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Summary of the Changes in the 8th Edition of the Tumor-Node-Metastasis Staging of Urological and Male Genital Organs Cancers

Erkek Genital Organ ve Ürolojik Kanserlerde 8. Tümör-Nodül-Metastaz Evrelemesindeki Değişikliklerin Özeti

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Introduction

Cancer staging has an important role in combating cancer. The American Joint Committee on Cancer (AJCC) has recently published the 8th edition of the AJCC Cancer Staging Manual (8E AJCC) (1). Contributions from genitourinary pathology are evident in the AJCC classification from many of the International Society of Urological Pathology (ISUP) consensus conferences on prostate, renal, testicular, and penile neoplasms that addressed staging issues and the 4th edition of the World Health Organization (WHO) classification of urinary and male genital organ tumors, which was published in early 2016 and was incorporated as the histologic classification system in the 8E AJCC, but the revised form of staging was not encompassed by the WHO classification totally (2). Actual grading systems were adopted for renal, prostate and penile cancers. In fact, major changes are fixed in testicular, penile, and prostate cancer.

This review summarizes the changes for renal, bladder, urinary tract, prostatic, testicular and penile cancers in the 8th tumor-node-metastasis (TNM) staging systems.

Changes in the 8th Tumor-Node-Metastasis Staging of Renal Cancers

Resection of the primary tumor along with the overlying Gerota's fascia and perinephric fat is recommended to interpret pathological staging of renal cancers (3,4). Changes in kidney cancer staging were minimal compared with other sites of the male genital and urinary tract. T3a criteria in the 7th edition are based on the pathologist's gross inspection of the hilar vessels. Sometimes tumor involvement of the renal vein and, its branches are unrecognized at the time of gross examination of the specimen. This problem is more common in partial nephrectomy specimens. Microscopic evaluation is much reliable to determine renal vein invasion. Therefore, clarifications were made in T3 category especially in T3a disease classification involving renal vein and its branches (Table 1). The wall of the renal vein and its branches may be thin with minimal muscular wall, and it may be so difficult to identify these structures (5). Tumor nodules and cords within the renal sinus mostly reveals intravascular tumor (5). Thus, the word "grossly" has been excluded in the current pathological T3a (pT3a) staging, and also invasion of the pelvicalyceal system is added in T3a category (Figure 1). Perinephric/sinus fat invasion should be confirmed microscopically. Invasion into fat by tumor cells with or without desmoplastic reaction, and vascular invasion in perinephric soft tissue are all evidence of perinephric invasion. Modifications in T3a may have impact on clinical trials for adjuvant chemotherapy when defining locally-invasive disease. Especially for clear cell and papillary renal cell carcinoma subtypes, the new four-tiered WHO/ISUP nucleolar grading is adopted instead of the traditional Fuhrman nuclear grading (2,4,6).

Changes in the 8th Tumor-Node-Metastasis Staging of Urinary Bladder Cancers

The AJCC provides a staging system for bladder cancer and the 8th edition was updated in 2017 (1).

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Most changes are in the N and M categories, but some clarifications and recommendations were made in the T categories (8). Although not formally included in the new staging system, several experts have recommended substaging of pT1 disease. Categorization of pT1 appears to have a prognostic value, with early invasion (microinvasive disease) into the lamina propria showing better outcomes than more advanced pT1 disease. The method of pT1 substaging has not been optimized, but microinvasive disease has been defined by different groups as invasive tumor of <1 high power field, greatest invasive tumor diameter of 1 mm, or invasive tumor above the muscularis mucosa extending to a depth of 2 mm or less. Categorizing pT1 disease is strongly recommended, by using one of the mentioned methods (9,10,11). There is limited data on the best methodology to stage urothelial carcinoma that concurrently involves the urinary bladder and the prostatic urethra (PU). It has been shown by several studies that bladder cancer with intraurethral prostatic stromal invasion has a better outcome than with transmural prostatic stromal invasion (12,13,14). In fact, in the 7th TNM edition, intraurethral spread to the prostate was excluded from pT4a, with the support of a number of studies (15,16). However, staging of intraurethral prostatic stromal invasion was not addressed properly. The 8E AJCC clarified that intraurethral prostatic stromal invasion should be categorized as T2 (per urethral staging and not bladder staging) and the bladder proper tumor be given a separate T category (per bladder staging). Still it is unclear how a concurrent urethral T2 tumor will impact a >T2 bladder proper cancer; emphasis in reporting should be given to the higher stage between the two (Table 1).

Most of the bladder diverticula are acquired and do not contain a muscularis propria layer (17). Therefore, tumor directly invades from the lamina propria into the perivesical soft tissue and diverticular invasive cancer has no T2 category (Figure 2). There are limited studies on diverticular tumor T categories and for this reason, it is not possible to make further comments on the prognosis (18,19,20).

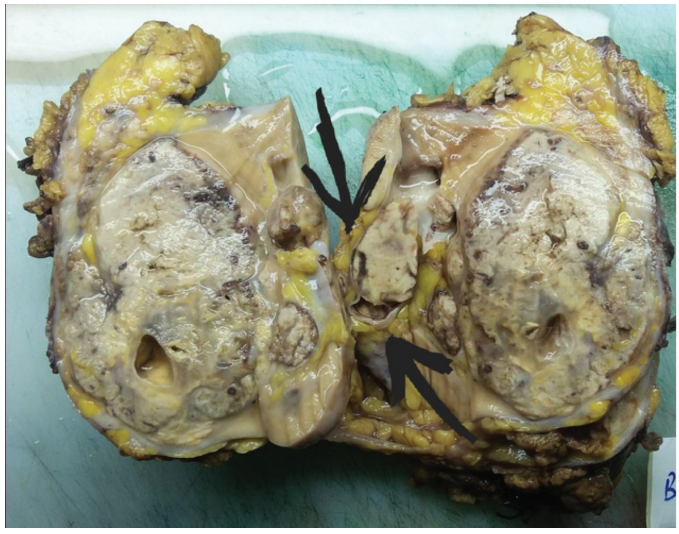

Figure 1. Renal vein invasion of the tumor

Based on contemporary mapping studies in which standard techniques were used to evaluate a pathologic specimen, excision of the primary nodal regions should result in an average of >12 lymph nodes (LNs) (21). Perivesical and non-perivesical LN involvements show no significant difference in survival (19). Therefore, in the revised form, perivesical LN among regional LNs is under the N category. By the way, 8E AJCC now classifies LN positivity beyond the common iliac as M1a and all other non-LN metastasis as M1b.

Changes in the 8th Tumor-Node-Metastasis Staging of Renal Pelvis and Ureteral Cancers

In fact, there is no obvious change in renal pelvis and ureteral tumors. In the 7th AJCC edition, metastatic LN greater than 5 cm was classified in the category of N3, however, in the revised form, it is now evaluated in N2 category (1).

Changes in the 8th Tumor-Node-Metastasis Staging of Urethral Cancers

Urethral staging criteria are used to classify carcinomas arising from the urothelial, glandular, or squamous lining of the PU, penile urethra or female urethra. Assignment of stage for urethral tumors is based on invasion into distinct regions, which is based on depth of invasion in the penile urethra and female urethra and into specified stromal elements in the PU. In the

Figure 2. Invasive cancer with diverticulum in the urinary bladder

revised form, non-invasive papillary carcinomas of the urinary tract are subdivided into low-grade and high-grade disease. For prostatic urothelial carcinoma, carcinoma *in situ* in PU (Tis PU) and ducts (Tis PD) are now gathered in a single Tis category. Prostatic acinar involvement is also in the same Tis category. As in bladder cancer staging, extension to other organs, including extraprostatic extension of the bladder wall, should be categorized as T4 disease.

Perivesical LN involvement is added to N category in the 8E AJCC for urethral cancers. Besides, in the N category, 2 cm metastasis size cut-off is revised with the number of LN involvement (Table 1).

Changes in the 8th Tumor-Node-Metastasis Staging of Prostate Cancer

TNM staging is the most important parameter in determining the treatment modality in prostate cancer (22). Prostate-specific antigen levels and tumor grade were mentioned in staging prostate cancer in the AJCC Cancer Staging Manual, 7th edition, for the first time. This practice continues with revisions in the 8th edition (1). There is no pT1 category for radical prostatectomy specimens. According to tumor spread and localization, the 7th edition of the AJCC TNM staging system subdivides pT2 disease into three categories as pT2a, pT2b, and pT2c. Up to several retrospective outcome data analyses, this subdivision has no prognostic value. No data exist to allow correlation of pT2 stage subgroupings with survival in localized prostate cancer due to the indolent and prolonged clinical course of the disease.

The pT3 disease is subdivided into two categories as pT3a and pT3b, evaluating the presence of extraprostatic extension and the presence of seminal vesical invasion with or without extraprostatic extention, in the 8E AJCC TNM staging system. Tumor cells in periprostatic fat are the most easily recognizable sign of extraprostatic extension. Tumor detected in the apex/distal margin sections is not considered as extraprostatic extension. Assessing the extraprostatic extension, the terms "focally" (a few neoplastic glands just outside the prostate or extraprostatic tumor occupying less than one high-power field in no more than two sections) and "extensively" (more than focal) are recommended to be used. In the 8E AJCC, microscopic bladder neck invasion is considered as pT3a, similar to the old version.

Periseminal vesicle soft tissue invasion, staged as pT3a (extraprostatic extension), should be distinguished from seminal vesicle invasion (pT3b) that keeps the tumor cells in the muscular wall of the seminal vesicle. In the revised version, there is no change for staging (pN) LN metastasis in prostate cancer. The tumor that is fixed or invades adjacent structures other than seminal vesicles, such as rectum, bladder, levator muscles or pelvic wall, is categorized as pT4 (Table 1).

Changes in the 8th Tumor-Node-Metastasis Staging of Testicular Cancer

Histologic evaluation of the radical orchiectomy specimen must be used for the pT classification. The gross size of the tumor should be recorded. The size of the largest tumor should be used for determining pT category, in the presence of multiple separated tumor nodules. Careful gross examination should determine whether the tumor extends through the tunica albuginea and whether it invades the epididymis and/or hilar soft tissue and/or spermatic cord. Tumors measuring 2 cm or smaller should be submitted entirely. In addition, the ISUP testicular tumor panel recommended that if the tumor is >2 cm in greatest dimension, 10 blocks or a minimum of 1 to 2 additional blocks/cm, whichever is greater, should be submitted (23). The junction of tumor and non-neoplastic testis and at least one block remote from the tumor should be obtained to determine whether germ cell neoplasia in situ (GCNIS) is present. These sections will allow assessment of either the presence or absence of vascular invasion. The clinical serum markers are needed for comparison when assigning the pathological stage S category, but levels after orchiectomy are used to complete the status of the serum tumor markers (S) for pathological staging. Size is an important prognostic risk factor for seminoma. Determination of GCNIS is essential because of two important situation; one is new terminology GCNIS is adopted in staging in Tis category, and second, changes in nomenclature of germ cell tumors require this finding.

In the revised form, seminomas, limited in the testis and without lymphovascular invasion (LVI) will be subclassified as pT1a and pT1b according to greatest dimension whether the tumor is smaller than (pT1a) or ≥3 cm (pT1b) in (1,24,25). Also, this subclassification only applies to pure seminomas, and other germ cell tumors are excluded. Upon showing that, it is unrelated to the usual postpubertal germ cell tumors; spermatocytic seminoma has been renamed as spermatocytic tumor and is excluded from the TNM staging because of its excellent prognosis.

Although rete testis stromal invasion does not alter the TNM stage 8, in most centers, its presence or absence in germ cell tumors is reported since it has impact on adjuvant radiation or carboplatin chemotherapy decision for stage 1 disease.

The hilar soft tissue is composed of adipose and loose fibrous connective tissue and is adjacent to the head of the epididymis. Differentiation between spermatic cord invasion and hilar soft tissue invasion is important to be certain about the location of the origin of the spermatic cord at gross dissection (29). Invasion of either epididymis or hilar soft tissue is adopted in pT2 category in the absence of spermatic cord (pT3) or scrotal (pT4) invasion, respectively. Therefore, the hilar soft tissue and epididymis should be sampled macroscopically to confirm the

Table 1. Summary box for changes in the 8th tumor-node-metastasis staging of urological and male genital organs cancers

Specimen	Summary of the changes
Kidney	WHO\ISUP histologic grading adopted changes in T3a category; - The word "grossly" excluded - Muscle containing changed to segmental vein - Pelvicaliceal system invasion added
Urinary bladder	T1: subcategorization in TUR materials as "microinvasive" and "invasive" T2: diverticular invasive cancer has no T2 category T4: prostatic stromal invasion must be transmural from bladder, subepithelial stromal invasion staged as T2 (urethral) N1: perivesical lymph node added in N1 category M: divided into non-regional LN only (M1a) and non-LN distant metastases (M1b)
Urethra	Tis: Tis prostatic urethra and Tis prostatic ducts changed to a single Tis category prostatic acini involvement without stromal invasion added T2: clarified for urothelial carcinoma of the prostate as involving the prostatic urethral subepithelial connective tissue T4: clarified that direct bladder extension is included N1: perivesical LN added in N1 category N1 and N2: divided only by the number of LN involved (single versus multiple); size cut-off removed
Prostate	Gleason score adopted to ISUP 2014 criteria; Histologic grade: grade group added in addition to Gleason score pT2: no longer subcategorized based on bilaterality and extent of involvement pT3 divided into two categories; -pT3a: the presence of extraprostatic extension in any location -pT3b: presence of seminal vesical invasion with or without extraprostatic extension
Testis	Tis: new terminology germ cell neoplasia in situ adopted pT1: subcategorized pT1a and pT1b for pure seminoma using 3-cm tumor size cut-off pT2: epididymal invasion upstaged from T1 hilar soft tissue invasion added LVI only in spermatic cord without parenchymal invasion M1: discontinuous involvement of spermatic cord by LVI added
Penis	Histologic grade: the three-tiered (WHO/ISUP) grading adopted Ta broadened to non-invasive localized squamous cell carcinoma T1a and Tlb have been separated by LVI, PNI and high histologic grade T1a or T1b are described by the site where they occur on the penis and are designated glands, foreskin, or shaft T2: confined to tumor invasion into corpus spongiosum T3: tumor invasion into corpus cavernosum Urethral involvement no longer the determinant and can be T2 or T3 pN1: increased to up to two unilateral inguinal LN metastases without extranodal extension pN2: increased to >2 unilateral or bilateral inguinal LN metastases without extranodal extension

ISUP: International Society of Urological Pathology, LN: Lymph node, LVI: Lymphovascular invasion, PNI: Perineural invasion, WHO: World Health Organization, TUR: Transurethral resection

findings (Figures 3, 4). Macroscopically, it may not be possible to evaluate invasion of these structures, thus, the hilar region should be sampled and microscopically examined in all cases. Direct infiltration of the spermatic cord results in a pT3 category. A block should be taken where the spermatic cord emerges above the head of the epididymis. If there is direct invasion by the tumor in this block, pT3 can be assigned. Microscopically, if the tumor surrounds or involves the vas deferens, then this is considered spermatic cord involvement (pT3). Discontinuous involvement of the spermatic cord via a vascular thrombus is currently considered a metastatic deposit (pM1) in the revised AJCC system, and a tumor thrombus within a vessel without

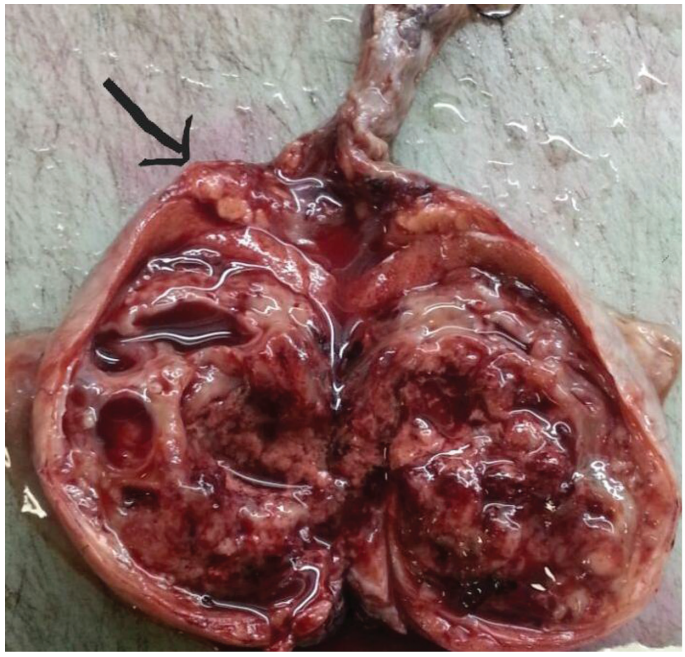

Figure 3. Mixed germ cell testis tumour with epididymis invasion

Figure 4. Seminoma with rete testis invasion

invasion is pT2. Epididymal invasion is now considered in pT2 category.

Changes in the 8th Tumor-Node-Metastasis Staging of Penile Cancer

The AJCC 7th edition referred to tissue layers between the skin and corpora as "subepithelial connective tissue". In the 8th edition, these areas are designated by their anatomical names to reflect the proper terminology and the levels of invasion prior to tumors reaching the corporal tissue (1). Complete resection of the primary lesion with tumor-free margins provides the greatest certainty that all histologic parameters in terms of grade, anatomic structures involved, and the presence or absence of prognostic factors important in assigning AJCC TNM stage are characterized subsequent to microscopic evaluation. In the current classification, in fact, the most changes are seen in penile cancer. The Ta category is expanded and applies to both pure verrucous carcinomas with no overt destructive invasion and non-invasive papillary, warty, basaloid, or mixed carcinomas (1).

In the previous editions, subepithelial tissue layer is used as a general definition, but the revised form includes precise definitions by glands, foreskin, or shaft regions allowing for more consistent categorization of T1 disease. T1 is also subcategorized into T1a and T1b as having different capacities for metastasis to inguinal nodes (10.5-18.1% vs 33.3-50%) (31,32). Some histomorphologic features such as perineural invasion, LVI and high-grade histology are used to differentiate T1a from T1b tumors (33,34). Invasion into corpus spongiosum is in T2 category while corpus cavernosum invasion is upstaged to T3. As accepted in the previous edition, pN1 and pN2 categories have been shown to have no significant difference in prognosis (35). In the light of some studies, it is determined that the laterality of LN metastasis is more important in predicting the outcome (36,37,38,39). Therefore, pN1 is now increased to up to two unilateral inguinal LN metastases, while pN2 is now modified as more than three unilateral or bilateral inguinal LN metastases. Tumor grading has traditionally been based on modifications of the Broder's grading system and consists of either a 3- or 4-grade system. The grade 3 category or presence of a sarcomatoid component is important in separating stage T1b from T1a primary tumors.

Conclusion

Staging is very valuable in the prognosis and treatment of cancer patients. Therefore, it should be revised at regular intervals so that new follow-up and treatment modalities can be identified. In this review, I tried to summarize the whole changes that were made in the 8th TNM staging. Although significant changes have been made in the T category, and there are new regulations in the N and M categories, still there are some points that have not yet been clarified and should be considered over time.

Keywords: Male genital cancers, Urological cancers, TNM, Staging

Anahtar Kelimeler: Erkek genital kanserler, Ürolojik kanserler, TNM, Evreleme

Ethics

Peer-review: Externally peer-reviewed.

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Magnetic Resonance Imaging Features of Prostate Mucinous Adenocarcinoma

Prostat Müsinöz Adenokanserinin Manyetik Rezonans Görüntüleme Bulguları

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Introduction

Prostate adenocarcinoma is the most common cancer and the second most common cause of cancer-related death among men in the Western world (1). It is more common in patients older than age 50 years. The mucinous subtype of prostate adenocarcinoma, also referred to as colloid adenocarcinoma, is extremely rare as a primary prostate lesion. The frequency of mucinous adenocarcinoma of the prostate, defined by the presence of more than 25% extravasated mucins, is approximately 0.2% (2).

The mucinous subtype of prostate adenocarcinoma has an aggressive clinical behavior (3). Surgical resection is the main therapeutic option (2). In this article, we describe the clinical and magnetic resonance imaging (MRI) features with histopathological correlation in a patient with mucinous adenocarcinoma of the prostate.

A 48-year-old man presented with urinary symptoms described as progressive urinary retention that was not associated with pelvic pain or fever. Physical examination was unremarkable. The prostate-specific antigen level was 2.55 ng/mL (normal range, <4.0 ng/mL), and all the other serum tumor markers were found to be normal.

MRI of the prostate was performed using a 1.5-T scanner and a pelvic phased array coil. MRI of the prostate revealed a tumor extending from the base to the apex of the prostate. The transitional zone of the prostate gland comprised a macrolobulated heterogeneous hyperintense mass with a hypointense capsule on T2-weighted images (WIs) (Figure 1) The prostatic mass exhibited central and peripherally hyperintense areas within the mass on T1-WIs, compatible with mucin lakes (Figure 2). After contrast administration, the lesion demonstrated strong heterogeneous enhancement (Figure 3). Diffusion-WIs revealed heterogeneous diffusion-restricted regions in the mass, compatible with solid portions of the mass (Figures 4a, b).

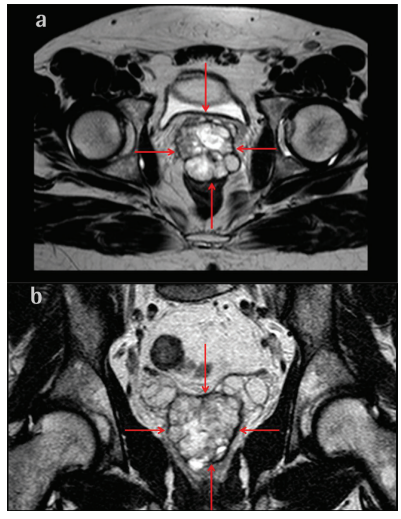

Figure 1. Axial and coronal turbo spin echo T2-weighted images reveal a well-defined, macrolobulated heterogenous hyperintense lesion with hypointense areas within prostate gland (red arrows)

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The mass invaded the serosa of the rectum, and fat tissue was obliterated in the pre-rectal region. No enlarged lymph node or metastasis was identified.

Surgery was performed using a retropubic approach. The patient underwent radical cystoprostatectomy and resection of the invaded rectum segment. Colostomy surgery was also performed. Histopathological examination confirmed the presence of prostatic adenocarcinoma with extraluminal mucinous pools involving >50% of the tumor volume (Figure 5). The final Gleason score was 4+4=8, and the stage was pathological T4. There was no recurrence detected in follow-up imaging studies after surgery. Lung metastasis was observed on computed tomography of the thorax 36 months after the diagnosis.

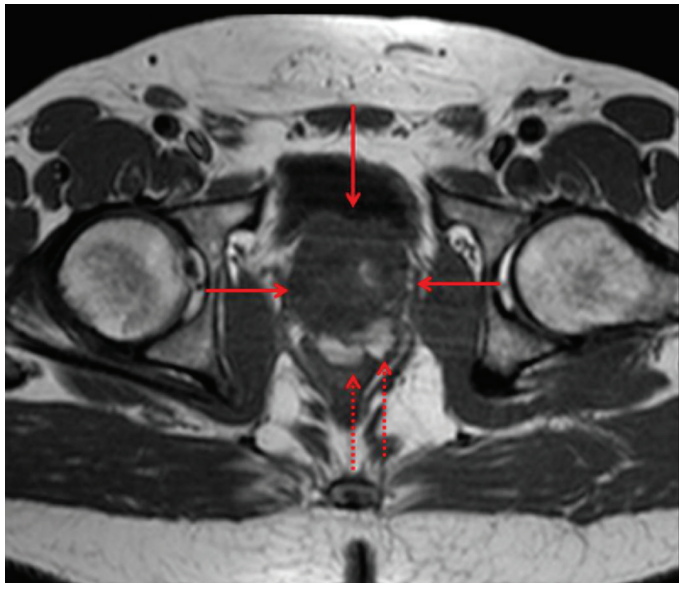

Figure 2. Axial turbo spin echo T1-weighted image reveals central and peripherally hyperintense areas (stippled arrows) within the mass (red arrows) compatible with mucin lakes

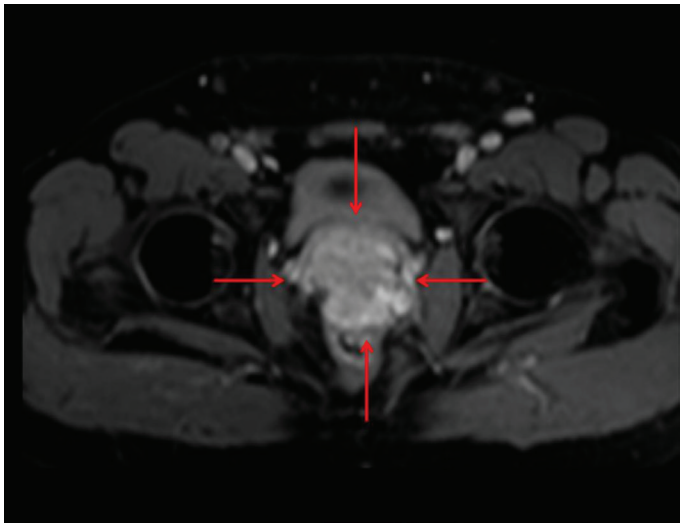

Figure 3. The prostate mass heterogenous enhanced on fat suppressed contrast-enhanced T1 weighted image (red arrows)

Mucinous adenocarcinoma of the prostate is a rare subtype of prostate cancer characterized by large pools of extracellular mucins, which by definition comprise at least 25% of the tumor

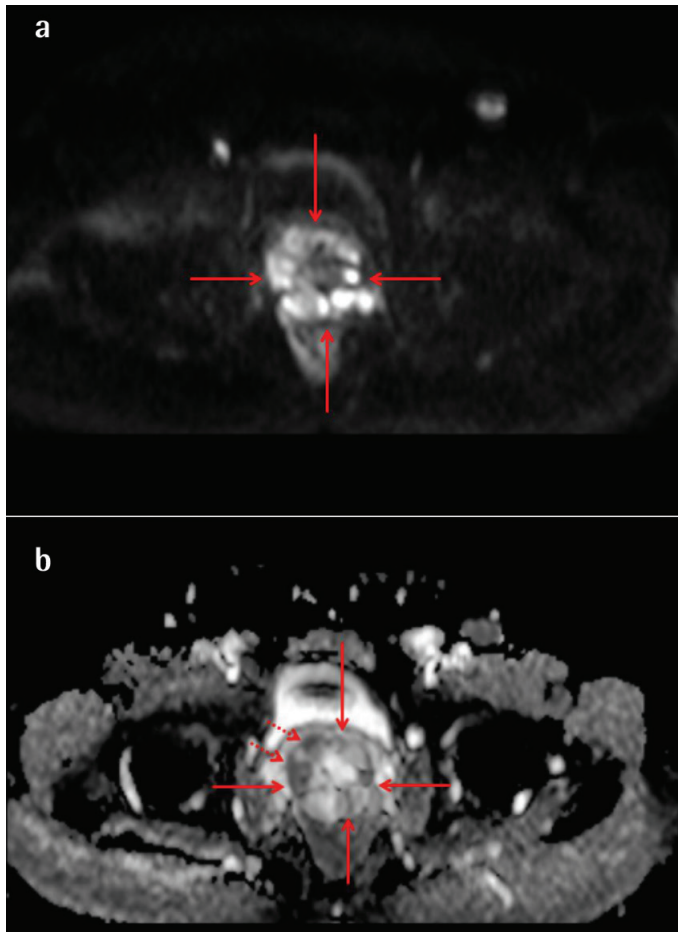

Figure 4. The prostate mass (red arrows) hyperintense on diffusion weighted image (a) and hypointense on apparent diffusion coefficient map (b) consistent with restricted diffusion (stippled arrows)

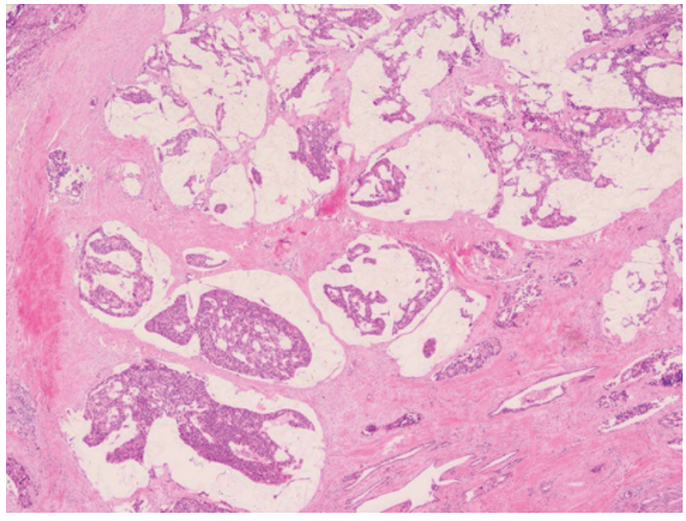

Figure 5. Mucinous carcinoma with cell nests embedded in mucinous lakes in radical prostatectomy specimen (Hematoxylin&eosin staining; original magnification 100x)

volume. Mucinous adenocarcinomas represent approximately 0.2–0.4% of all prostate adenocarcinomas (1,3).

The etiology of mucinous adenocarcinoma of the prostate remains unclear, and it is thought that the risk factors for mucinous adenocarcinoma of the prostate are similar to those for adenocarcinoma of the prostate, which are related to genetic, environmental, androgen, and other factors. The etiology of mucinous adenocarcinoma of the prostate may be related to the endocrine epithelium of the prostate (4).

Prostate involvement by mucinous adenocarcinoma of the intestine, the bladder or urethra is histologically similar to mucinous adenocarcinoma of the prostate. The infiltrating components of these extra-prostatic mucinous cancers contain mucin pools lined by columnar mucinous epithelium and show different degrees of nuclear atypia. Even then, mucinous adenocarcinoma of the prostate includes single bland and cribriform glands. Prostatic mucinous adenocarcinoma is only uncommonly associated with true intracellular mucin-positive "signet ring cells" (2).

Moreover, 60-90% of adenocarcinomas of the prostate secrete some mucoid material. Thus, these common tumors differ from true mucinous carcinoma primarily in degree. A criterion for the diagnosis of mucinous adenocarcinoma is a primary prostatic acinar tumor with the presence of at least >25% of an excised tumor consisting of tumor cells and clusters of cells floating in mucin lakes (5,6,7,8).

Mucinous adenocarcinoma of the prostate usually has no obvious symptoms during the early stages, and most of the symptoms are similar to those of benign prostatic hyperplasia. However, when the tumor invades the urethra and bladder neck, bladder irritation, and even acute urinary retention and hematuria, may occur (4). The main treatment option for mucinous adenocarcinoma of the prostate is radical prostatectomy. However, rarely, hormone therapy and/or radical radiotherapy have been used (7).

Multiparametric MRI is the best useful diagnostic tool for the pre-operative staging of prostate cancer (8). On MRI, mucinous prostate cancer appears as high-signal-intensity lesions on T1- and T2-WIs owing to the mucin component. However, in some cases, variable T2-weighted signal intensities may be observed because of a lower mucin content or different chemical composition, both of which induce shortening of the T2 relaxation time (5). An early small series of patients with mucinous adenocarcinoma of the prostate suggested that these tumors show high T2 signal intensity rather than the usual low T2 signal intensity of non-mucinous adenocarcinoma of the prostate (9,10). The differential diagnosis includes cystic prostatic hyperplasia, abscesses, and cystadenomas (5,9).

Conclusion

Primary prostatic mucinous adenocarcinoma is a rare and aggressive malignant tumor. The MRI features of mucinous adenocarcinoma are non-specific, however, hyperintense regions inside prostatic tumors are observed on T1- and T2-WIs because of the presence of mucin pools. MRI is also helpful for detecting invasion of adjacent tissues and for disease staging.

Keywords: MRI, Prostate carcinoma, Mucinous adenocarcinoma

Anahtar Kelimeler: MRG, Prostat kanseri, Müsinöz adenokanser

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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