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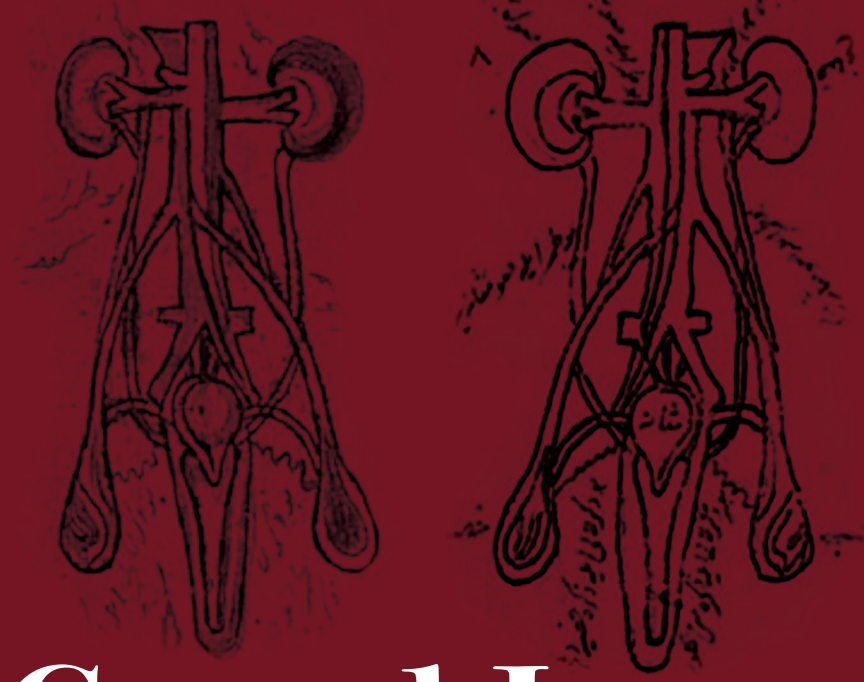

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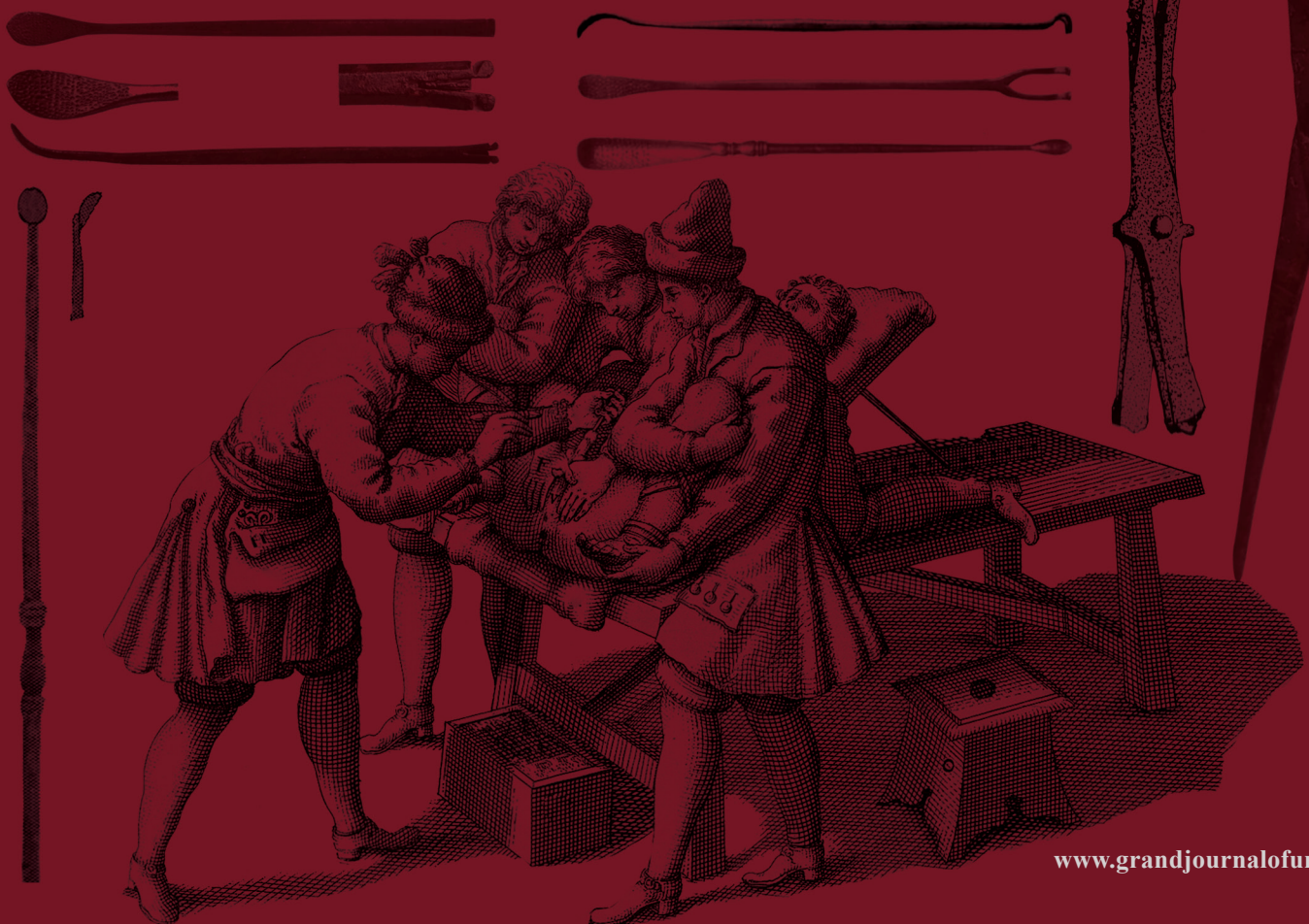

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Editorial

Dear Colleagues,

I am honored to share with you the second issue of the Grand Journal of Urology (Grand J Urol) with the contributions of valuable researchers and scientists. The journal is an open access, peer-reviewed journal and is published online in English three times a year (January, May and September).

The Grand Journal of Urology (GJU) brings written and visual scientific urology studies to academic platforms and makes significant contributions to the science of urology. In addition, GJU adds a new momentum to academic activities with its unique style.

After the first issue of our journal, valuable academicians from Autria, Germany, France, Italy and China joined the article review and advisory boards. In the meantime, I would proudly like to state that our journal has started to be indexed in the SCILIT database (an open-access scholarly database, Basel, Switzerland) and ScienceGate.

In this second issue of our journal, there are many valuable articles under the subheadings of Genitourinary Radiology, Urological Oncology, General Urology, Andrology and Pediatric Urology. I hope these articles will provide important contributions to our dear readers and researchers.

On this occasion, I would like to express my heartfelt gratitude to our authors who have contributed to our journal with their articles, to our reviewers who have meticulously evaluate the articles, to our designers and to our publisher.

Respectfully yours
May 2021
Assoc. Prof. Ekrem GUNER, MD
Editor-in-Chief

Original Article – Urological Oncology

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Is There a Relationship Between Biochemical Recurrence and Insulin-like Growth Factor-1 in Patients with Surgical Border Negative Radical Prostatectomy?

Cerrahi Sınır Negatif Radikal Prostatektomili Hastalarda Biyokimyasal Nüks ile İnsülin Benzeri Büyüme Faktör-1 Arasında İlişki Var mıdır?

Yusuf Kasap, Emre Uzun, Bugra Bilge Keseroglu, Sedat Tastemur, Cavit Ceylan, Muhammed Emin Polat

Department of Urology, University of Health Sciences, Ankara City Hospital, Ankara, Turkey

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Corresponding Author: Yusuf Kasap / University of Health Sciences, Ankara City Hospital, Department of Urology, Ankara, Turkey / dryusuf85@hotmail.com ORCID ID: 0000-0001-5313-2611

Abstract

Objective: Levels of insulin-like growth factor 1 (IGF-1) have been associated with prostate carcinoma. We have investigated whether IGF-1 level has an early predictive value for the biochemical relapse in the prostate carcinoma patients with a negative surgical margin who underwent curative surgery.

Materials and Methods: We retrospectively analyzed 82 patients who were followed-up regularly and did not receive neoadjuvant or adjuvant chemotherapy. We classified patients as having Gleason scores ≥7 and <7, PSA values ≥10 ng/ml and <10, biochemical relapse positive or negative, T stages ≥T2 and <T2, tumor burden in less or more than 50% pathologic specimens, respectively. PSA cut-off value accepted was as 0.2 ng/ml. According to average values in the literature, time to PSA relapses was considered early if it was less than 18 months and late if more than 18 months. We measured PSA and IGF-1 levels at each routine control visit.

Results: During 60-month follow-up, 66 (80.4%) patients had no relapse, while in 8 (9.8%) patients had early, and other 8 (9.8%) patients had a late biochemical relapse. There was no statistically significant difference between these 3 groups of patients according to their age, tPSA levels, and BMI parameters. We compared IGF-1 levels with tumor burden, tPSA levels, tumor grade, and Gleason scores without any significant difference between these parameters. When we accepted IGF-1 cut-off values as 60 ng/ml, we observed higher Gleason scores (≥ 7 and more) in these patients. There was a weak relationship between IGF-1 levels of non-relapse and early relapse patients (p:0.078). However, when we evaluated IGF-1 levels among patients with relapse, the early relapse group had significantly higher IGF-1 levels (p: 0.006). When the cut-off value of IGF-1 was accepted as 60 ng/ml, which was found to be significant for Gleason score, the early relapse group had significantly higher IGF-1 levels compared to the non-relapse group (p:0.023).

Conclusions: According to our study, the IGF-1 level has a predictive value for showing biochemical recurrence after surgery. Nevertheless, considering the number of patients, we need randomized controlled trials with a large number of patients.

Keywords: retropubic prostatectomy, prostate-specific antigen, insulin-like growth factor, prostate cancer

Öz

Amaç: İnsülin benzeri büyüme faktörü (IGF-1) seviyeleri prostat kanseri ile ilişkilendirilmiştir. Biz IGF-1 in prostat kanseri gelişimi üzerinde etkisi dışında küratif cerrahi geçirmiş ve cerrahi sınırı negatif olan hastalarda biyokimyasal nüksün önceden tahmininde katkısı olup olmayacağını araştırdık.

Gereçler ve Yöntemler: Neoadjuvan ve adjuvan tedavi almamış ve takibi yapılabilmiş 82 hasta geriye dönük incelendi. Hastalar biyopsi ve patolojik spesmenlerin Gleason skorları ≥7 ve <7, PSA değerleri ≥10 ng/ml ve <10, biyokimyasal nüks olanlar ve olmayanlar, T evreleri ≥T2 ve <T2 olanlar, patolojik spesmende tümör yükü %50 altında ve üzerinde olanlar şeklinde ayrıldı. PSA kestirim değeri 0,2 ng/ml kabul edildi. PSA relaps süresi literatür ortalaması alınarak 18 ay altında erken, 18 ay üzerinde geç relaps olarak kabul edildi. Rutin kontrollerde PSA ve IGF-1 düzeyleri ölçüldü.

Bulgular: 60 aylık takipte 66 (%80,4) hastada nüks izlenmezken, 8 (%9.8) hastada erken biyokimyasal nüks ve 8 (%9.8) hastada geç biyokimyasal nüks izlendi. Üç gruptaki hastaların arasında yaş, tPSA ve vücut kitle indeksi parametreleri arasında istatiksel olarak anlamlı fark yoktu. Tümör yükü, tPSA düzeyi, tümör evresi, gleason skorları ile IGF-1 düzeyleri karşılaştırıldı. Anlamlı fark izlenmedi. IGF-1 düzeyi için kestirim değeri 60 ng/ml alındığında bu değer üzerindeki hastaların yüksek gleason skorlarına (7 ve üstü) sahip olduğu izlendi. Nüks olmayan hastalar ile erken nüks gösteren hastalar arasında IGF-1düzeyleri açısından istatiksel olarak zayıf bir ilişki saptandı (p:0.078). IGF-1 seviyeleri nüks gösteren hastalar arasında değerlendirildiğinde erken nüks grubunda IGF-1 düzeyinin anlamlı olarak yüksek olduğu saptandı (p=0.006). Gleason skoru için anlamlı bulunan IGF-1 60 ng/ml değeri kestirim değer alındığında IGF-1 düzeyi erken nüks grubunda, nüks göstermeyen gruba göre anlamlı olarak yüksek olduğu izlendi (p=0.023).

Sonuç: IGF-1 düzeyi cerrahi sonrası biyokimyasal nüksü göstermede bizler için prediktif bir değeri vardır. Fakat hasta sayısı göz önünde bulundurulduğu zaman, daha geniş çaplı hasta sayısına sahip randomize kontrollü çalışmalara ihtiyacımız vardır.

Anahtar kelimeler: retropubik prostatektomi, prostat spesifik antijen, insülin benzeri büyüme faktörü, prostat kanseri

ORCID ID: **E. Uzun** 0000-0002-3005-2122 **B.B. Keseroglu** 0000-0003-1124-2462 **S. Tastemur** 0000-0003-0534-2520
C. Ceylan 0000-0001-5159-1291 **M.E. Polat** 0000-0003-0271-0746

Introduction

Prostate carcinoma (PCa) is one of the significant health issues in the male population. In Europe, 2.6 million people are diagnosed as cancer every year, and PCa accounts for 11% of all male cancers. Its incidence has increased rapidly after 1970 with the help of practical and accessible screening methods [1].

In carcinogenesis, inflammation, genetic, and multiple growth factors play an important role. Insulin is essential for both energy metabolism and glucose regulation. Also, it may have a role in PCa development because of its potent mitogenic and growth factor-like effects [2].

Insulin has a suppressive effect on insulin-like growth factor binding protein (IGFBP-1) secretion. Moreover, according to this relation, IGFBP-1 levels might be an essential factor for insulin activity on the target tissue [3]. Besides the effect of insulin on tissues, IGFBP-1 binds to insulin-like growth factor (IGF-1) with high affinity and decreases its level and effect [4]. In epidemiologic studies, low-risk PCas, are mostly related to high IGF-1 plasma levels. However, it is not definite whether IGF-1 and insulin interrelation causes PCa development or not [5].

Positive surgical margin (PSM) detected in pathology specimens after radical prostatectomy (RP) was accepted as a poor prognostic factor and has been reported as 10% in articles about RP. Both pathologic and biochemical findings have been investigated for estimation of biochemical recurrence in noninvasive cases after RP. According to recent studies, total tumor volumes and maximum tumor diameters are not enough to predict biochemical recurrence [6].

In this study, we aimed to find the contribution of IGF-1 levels in predicting biochemical relapse of RP patients with negative surgical margins (NSM).

Materials and Methods

In this study, we analyzed RP patients operated for PCa between May 2009 and June 2014 in Turkiye Yuksek Ihtisas Training and Research Hospital after obtaining approval from Education Plan and Coordination Board (Approval Number: 2014/B.10.4.ISM.4.06.00.15). RP was applied to 240 patients in this period, and positive surgical margins (PSMs) were detected in 14 of them. We analyzed 82 patients who had negative surgical margins (NSM) in pathology specimens and continued their prostate-specific antigen (PSA) controls regularly. Also, these 82 patients were not treated with neoadjuvant or adjuvant chemoradiotherapy.

PCa patients were classified as having Gleason scores ≥7 and <7, PSA values ≥10 ng/ml and <10, biochemical relapse positive or negative, T stages ≥T2 and <T2, and tumor burden in pathologic specimens less and more than 50%, respectively. PSA cut-off value was accepted as 0,2 ng/ml. According to average values in the literature, time to PSA relapse was considered early if it was less than 18 months and late if more than 18 months. All control PSA tests of the patients were studied and analyzed with Human PSA ELISA Kit, 96 tests, Quantitative. We also measured free IGF-1 levels with ELISA tests in Yildirim Beyazit University, Laboratory of Biochemistry Department.

Statistical Analysis

For statistical analyses, IBM SPSS version 22.0 (SPSS Inc, Chicago, IL) for Windows was used. Descriptive data were defined as number, percentage, mean ± standard deviation. Normal distribution of data was tested with the Kolmogorov-Smirnov test. Mann-Whitney U test was used for the analysis of quantitative data that did not show normal distribution. Kruskal-Wallis Test was used to analyze quantitative data of more than 2 groups that did not show normal distribution. For qualitative data, chi-square test, and when chi-square assumptions were not met, Fisher's exact test was used. The ability of IGF-1 to predict the presence of relapse was evaluated by receiver operating characteristic (ROC) curve analysis and area under curve (AUC) values of the analysis were presented. Cut-off values were calculated according to Youden index. $p<0.05$ was considered statistically significant.

Results

Eighty-two RP patients with NSM were evaluated in this study. In the 60-month follow-up, 66 (80,4%) patients had no relapse, while in 8 (9,8%) patients early, and in other 8 (9.8%) patients late biochemical relapses were observed. We evaluated patients in 3 groups according to their relapsing times. There was no statistically significant difference between these 3 patient groups according to their age, total PSA (tPSA) levels, and body mass index (BMI) parameters **(Table 1)**.

We compared IGF-1 levels with tumor burden, tPSA levels, tumor grade, Gleason scores detected in biopsy materials, and tumor specimens (GSs), without any significant difference between these parameters. When we accepted IGF-1 cut-off value as 60 ng/ml, we detected higher Gleason scores (≥ 7) (specimen GS p=0.011; biopsy GS p=0.017) in these patients **(Table 2)**. There was statistically weak relationship between non-relapse and early relapse patients in terms of IGF-1 levels (p: 0.078) **(Table 3)**.

However, when we compared IGF-1 levels between the relapse groups, the early relapse group had higher IGF-1 levels significantly (p: 0.006) and also, this association had high

Table 1. Distribution of age, PSA, BMI of all study patients

	No Relapse	Early Relapse	Late Relapse	P value
Age (years)	64.8±7.8	65.2±6.4	65.5±7.5	0.33
Total PSA (ng/mL)	9.9±5.7	10.1±5.9	9.1±3.7	0.49
BMI (kg/m^2)	27.4±3.3	28.2±4.2	27.3±3.2	0.21

sensitivity and specificity in ROC analysis **(Figure 1)**.

The non-relapse and relapse groups were compared again using a cut-off value of 60 ng/ml. IGF-1 levels of most of the patients in the early relapse group were more than 60 ng/ml (p: 0.023). We did not observe a significant difference between the late relapse and the non-relapse groups in terms of IGF-1 levels (p=0.12) **(Table 3)**.

Finally, a statistically significant difference existed between early relapse and non-relapse groups in terms of IGF-1 levels with high degrees of sensitivity and specificity **(Figure 2)**.

Discussion

PCa is one of the most prevalent tumors in the male population. While it's incidence increases with age, it constitutes 15% of carcinomas seen in male population [7]. Although the incidence of PCa has increased 4 times in the last 30 years, mortality rates have decreased significantly in the last 20 years thanks to detection of the disease at an early stage using disgnostic markers such as PSA [8].

RP a curative treatment for localized PCa patients. Surgical technique has improved with the help of technologic developments during the last 10 years. But biochemical relapse still a problem in 27-53% of these patients [9]. Although biochemical relapse is mostly seen as local recurrence, it can also manifest as symptomatic or asymptomatic systemic disease. Increase in biochemical values indicate PCa recurrence but may not have an effect on quality of life and overall survival. The purpose of biochemical relapse control is to prevent development of metastatic disease and decrease metastasis-related morbidity and mortality rates. Also, we can avoid unnecessary adjuvant therapy in PCa patients with low risk of disease progression [10].

There are many reasons directly or indirectly related to PCa development [11]. IGF-1 and its binding proteins are produced in healthy and carcinomatous prostate tissues, and stimulate cellular proliferation with IGF-1 receptor activation [12]. While some studies report that IGF-1 levels are high in PCa patients [13], there are also studies that do not support this [14,15].

In a study investigating IGF-1 levels in PCa patients, the

Table 2. Distribution of IGF-1 values , tumor burden, stage, tPSA, and GS

	IGF-1 mean (ng/ml) (n)	**P value**	**IGF-1 <60ng/ml (n)**	**IGF-1 ≥60 ng/ml (n)**	**P value**
TM Burden ≤50%	63 (40.8)	0.65	58	5	0.2
TM Burden >50%	19 (47.2)		15	4	
T2 ≤	54 (41.6)	0.96	50	4	0.26
> T2	28 (43.5)		23	5	
tPSA ≤10 ng/mL	58 (41.1)	0.43	50	8	0.19
tPSA> 10 ng/mL	24 (44.2)		21	3	
Biopsy GS 7<	52 (40.9)	0.75	49	3	**0.011**
Biopsy GS ≥ 7	30 (46.6)		8	22	
Specimen GS 7<	51 (41.9)	0.99	46	5	**0.017**
Specimen GS ≥ 7	31 (43.8)		11	20	

TM: tumor; GS: Gleason score; tPSA: total prostate specific antigen; IGF-1: insulin-like growth factor -1; n: number of patients

Table 3. Comparison of patient groups according to IGF-1 levels

	IGF-1 mean (ng/ml) (n)	**P value**	**IGF-1 <60ng/ml (n)**	**IGF-1 ≥60 ng/ml (n)**	**P value**
No Relapse	66 (41.1)	0.078	60	6	**0.023**
Early Relapse	8 (63.9)		1	7	
No Relapse	66 (41.1)	0.177	60	6	0,12
Late Relapse	8 (31.2)		5	3	
Early Relapse	8 (63.9)	**0.006**			
Late Relapse	8 (31.2)				

IGF-1: insulin-like growth factor -1; n: number of patients

patients were grouped according to their specimen GSs. PCa patients with low-grade GSs (GS<7) had significantly higher IGF-1 levels than the control group, but any significant difference was not detected in terms of IGF-1 levels between PCa patients with low-, and high-grade GSs (GS≥7) PCa patients did not have a significant difference. Also, in localized PCa patients, IGF-1 levels were correlated with the disease grade. However any difference was not detected between locally advanced and metastatic PCa patients as for IGF-1 levels in this study [16].

When we did not specified the cut-off value for IGF-1 in our study, there was no significant correlation between IGF-1 levels and GSs of specimens or biopsy materials. However, if we specified the cut-off value as 60 ng/ml, both biopsy material and specimen GS's were significantly higher in patients with IGF-1 levels above 60 ng/ml (specimen GS p=0.011; biopsy material GS p=0.017).

Koliakos et al. investigated 147 patients with PCa and benign prostate hyperplasia (BPH) for the effect of IGF-1 levels on the early diagnosis of PCa patients. There was no difference between IGF-1 levels, but the free/total (f/t) PSA ratio was lower in the PCa group. They used this result for its correlation with PSA/IGF-1 level. PCa patients had significantly higher PSA/IGF-1 levels (p=0.002). But, for the BPH group, the correlation was weak (P=0.042). According to ROC analysis, as a screening test for PCa, PSA/IGF-1 level had higher sensitivity and specificity than PSA and f/t PSA ratio [17].

Nam et al. measured IGF-1 levels in precancerous prostatic patients. High-grade prostatic intraepithelial neoplasia (HGPIN) detected in biopsy materials was accepted as a precancerous pathology. Their IGF-1 levels were significantly higher than the control group (p=0.01) [18].

In our study, in addition to the effect of IGF-1 levels on the PSA relapse in cured PCa patients, we also calculated correlations of IGF-1 levels with T stage, total PSA levels, and tumor burden in specimens in the same group. As a result, IGF-1 values higher than 60 ng/ml had a weak correlation with increased tumor burden and high T stage. However, any statistically significant correlation with total PSA levels was not detected.

Many studies have investigated the relationship between pathogenesis of PCa, and IGF-1. However, there are few studies on biochemical relapse after RP and its relationship with IGF-1. Guidelines have determined the cut-off value of biochemical relapse after RP as 0.2 ng/ml. Times to early or late relapse have not been standardized in the literature. Various studies accept this period as 3 to 36 months [19].

Shahabi et al. have searched risk factors for biochemical relapse in 2262 RP patients. These patients had not received any neoadjuvant or adjuvant treatment (pT2-3N0M0) [20]. In this study, they accepted the first 35 months after RP as early relapse and more than 35 months as late relapse. They found an association between early relapse, GS≥7, PSM, and ≥pT3a stages. Besides, late relapse was associated with GS 7 (4 + 3), high preoperative PSA level, and ≥pT3a stage in the same study.

According to the literature, we accepted the relapse time classification limit as 18 months. IGF-1 levels in non-relapse and late relapse groups were not statistically different. There was a weak correlation between the early relapse and the non-relapse group. However, when the early and the late relapse groups were compared a significantly higher IGF-1 levels were found in the early relapse group (p=0.006).

Also, we investigated cut-off IGF-1 levels for biochemical relapse risk factors. When we accepted 60 ng/ml for a cut-off value for IGF-1 which was significant as for GSs, IGF-1 levels were higher in the early relapse group compared to the non-relapse group (p=0.023).

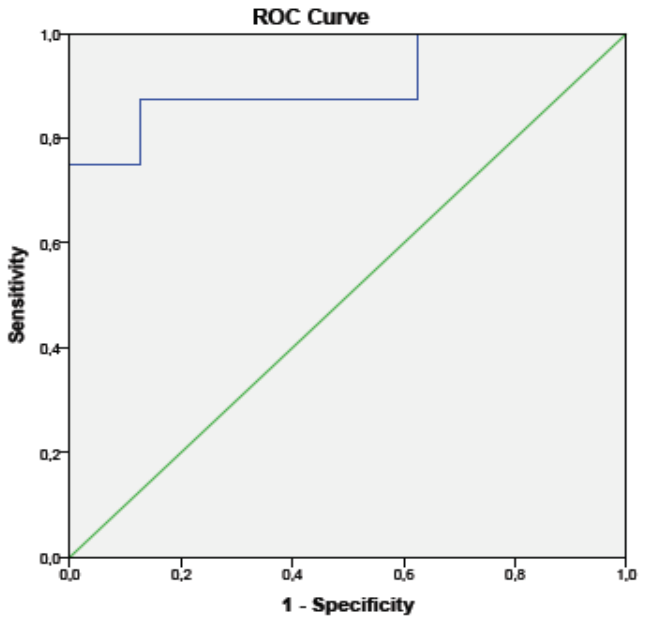

Figure 1. Relationship between early, and late relapse groups as for IGF-1 levels

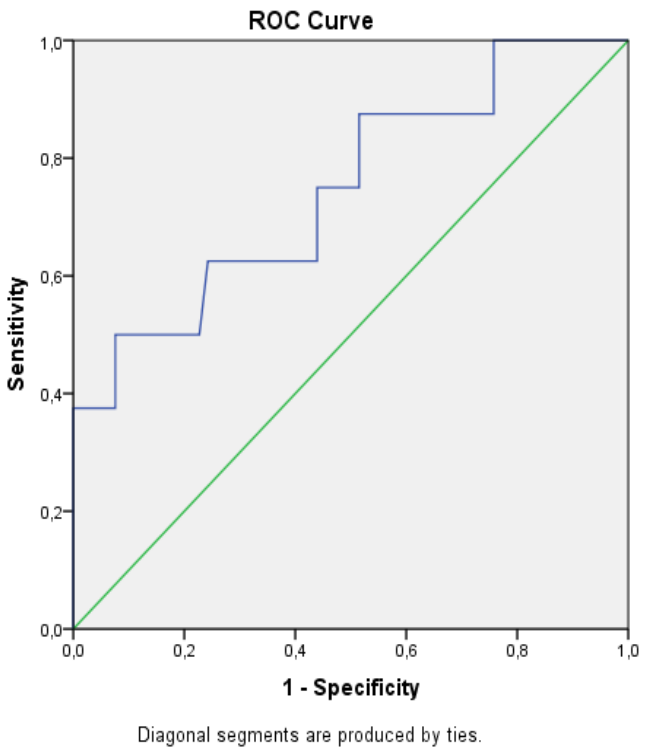

Figure 2. Relationship between early, and late relapse groups as for IGF-1 levels (cut-off for IGF-1 60 ng / ml)

Our study also has limitations. First of all, our study was designed retrospectively. In addition, the small number of patients is one of the limitations.

Conclusion

In conclusion, success rates of localized PCa treatment increase with the development of surgical techniques and medical technology. Evaluation of biochemical relapse after surgery also affects the success of treatment. Lots of biochemical parameters, hormonal and genetic risk factors have been evaluated in terms of treatment success. In our study, PCa patients with NSMs who underwent RP were analyzed. The relationship between IGF-1 levels and biochemical relapse was investigated. We observed that if the IGF-1 level was high, risk of early biochemical relapse increased. According to this result, IGF-1 is valuable for predicting biochemical relapse in the patients' follow-up.

Ethics Committee Approval: The study was approved by Turkey Yuksek Ihtisas Training and Research Hospital Education Plan and Coordination Board, Cankaya, Ankara, Turkey (Decision No: 03 July 2014/B.10.4.ISM.4.06.00.15).
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – Y.K., E.U.; B.B.K, M.E.P.; Design – Y.K., E.U., B.B.K, M.E.P.; Supervision – Y.K., E.U., C.C., M.E.P.; Resources – Y.K., E.U., B.B.K, M.E.P.; Materials – Y.K., E.U., B.B.K, M.E.P.; Data Collection and/or Processing – Y.K., E.U., B.B.K, M.E.P.; Analysis and/or Interpretation – Y.K., E.U., B.B.K, S.T., C.C., M.E.P.; Literature Search – Y.K., E.U., B.B.K, M.E.P.; Writing – Y.K., E.U., B.B.K, S.T.; Critical Review – Y.K., S.T., C.C., M.E.P.
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Original Article – Andrology

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The Comparison of Penile Doppler Ultrasonography Findings with Serum Lipid Parameters in Hyperlipidemic Patients with Erectile Dysfunction

Erektil Disfonksiyonlu Hiperlipidemik Hastalarda Penil Doppler Bulgularının Serum Lipit Parametreleri ile Karşılaştırılması

Mustafa Tasdemir[1], Unal Oztekin[2], Mehmet Caniklioglu[3], Hafize Aktas[4]

[1]Department of Radiology, Kayseri Memorial Hospital, Kayseri, Turkey
[2]Department of Urology, Kayseri System Hospital, Kayseri, Turkey
[3]Department of Urology, Yozgat Bozok University Faculty of Medicine, Yozgat, Turkey
[4]Department of Radiology, Ankara Numune Training and Research Hospital, Ankara, Turkey

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Corresponding Author: Unal Oztekin / Kayseri System Hospital, Department of Urology, Kayseri, Turkey / dr_unal@hotmail.com ORCID ID: 0000-0001-9568-9442

Abstract

Objective: The aim of this study is to investigate the effect of hyperlipidemia on the development of erectile dysfunction (ED) in hyperlipidemic patients with ED.
Materials and Methods: Twenty-five patients who applied to the radiology clinic were included in the study. All patients have only hyperlipidemia as a risk factor of ED. The patients were evaluated in terms of ED by using International Index of Erectile Function (IIEF) form. Before and after oral treatment with daily doses of 10 mg atorvastatin, all parameters were measured. Paired t-test was used to compare vascular velocities between lipid profiles and Erectile Function Domain Scores (EFDS) and IIEFs, before and after treatment separately.
Results: Cholesterol levels of 96% of patients were higher than 200 mg/dl and 52% of them had abnormal penile Doppler ultrasonography (PDU) findings. Patients with abnormal PDU findings had lower cholesterol levels than those with normal PDU findings. Significant differences existed between patients with normal and abnormal PDU in the high triglyceride group as for pre-, and post-treatment values . Pre-, and post-treatment EFD and IIEF scores were comparable.
Conclusion: It can be said that a relationship exists between hyperlipidemia and erectile dysfunction. Therefore, lipid profile of a patient admitted with ED may be analyzed routinely

Keywords: hyperlipidemia, statin, erectile dysfunction, penile Doppler

Öz

Amaç: Bu çalışmanın amacı, erektil disfonksiyonlu (ED) hiperlipidemik hastalarda erektil disfonksiyon gelişiminde hiperlipideminin etkisini araştırmaktır.
Gereçler ve Yöntemler: Bu çalışmaya 25 hasta dahil edildi. Tüm hastalarda ED risk faktörü olarak sadece hiperlipidemi mevcuttu. Hastalar Uluslararası Erektil Fonksiyon Endeksi (IIEF) formu kullanılarak ED açısından değerlendirildi. Atorvastatin 10 mg tedavisinden önce ve sonra tüm parametreler ölçüldü. Lipid profilleri ile Erektil Fonksiyon Alan Skorları (EFDS) ve IIEF'ler arasındaki vasküler hızları tedaviden önce ve sonra ayrı ayrı karşılaştırmak için paired t-testi kullanıldı.
Bulgular: Hastaların %96'sının kolesterol düzeyleri 200 mg/dl'nin üzerinde ve % 52'sinde anormal penil Doppler ultrason (PDU) bulguları vardı. Anormal PDU bulguları olan hastalar, normal PDU bulguları olanlara göre daha düşük kolesterol seviyelerine sahipti. Yüksek trigliserid seviyesine sahip olan grupta, anormal ve normal PDU'lu hastaların arasında, tedavi öncesi ve sonrası anlamlı farklılık mevcuttu. Hem EFDS hem de IIEF değerleri tedaviden önceki ile benzerdi.
Sonuç: Hiperlipidemi ile bozulmuş erektil fonksiyon arasında bir ilişki olduğu söylenebilir. Bu nedenle ED ile başvuran hastalarda lipit profili değerlendirilmesi rutin olarak uygulanabilir.

Anahtar kelimeler: hiperlipidemi, statin, erektil disfonksiyon, penil Dopler

ORCID ID: M. Tasdemir 0000-0002-8368-7463 **M. Caniklioglu** 0000-0003-2216-5677 **H. Aktas** 0000-0001-9759-0753

Introduction

Erectile dysfunction is defined as the failure to create and/or maintain the necessary rigid erection for a satisfactory sexual intercourse [1].

There is usually a multifactorial etiology. Many psychological, neurological, endocrinological, vascular, pharmacological, traumatic, iatrogenic factors have been described as etiologic factors. Potential risk factors are smoking, advanced age, alcohol addiction, hypertension, hyperlipidemia, diabetes mellitus (DM), depression, vascular diseases, some drugs and some surgical procedures and operations.

Penile erection is a complex physiologic and hemodynamic process that requires an intact arterial blood flow and a venocclusive mechanism in the corpus cavernosum. This process is related to the integration between central and peripheral nervous systems as well as the ratio of the trabecular smooth muscle to the connective tissue in the corpus cavernosum [2].

The most important and most common diagnostic test used in vascular ED is penile color Doppler ultrasonography (US). After an intracavernosal injection of a vasoactive substance (papaverine, prostaglandin E1, etc.), increase in penile artery diameter, blood flow velocity, systolic velocity and end-diastolic velocity can be measured and especially arterial and indirectly venous system can be evaluated in penile color Doppler US.

Penile erection is achieved thanks to adequate arterial distribution. The main cause of arteriolar insufficiency is atherosclerosis but it can also be caused by trauma or congenital anomalies. Atherosclerotic lesions are characterized by smooth muscle proliferation and accumulation of lipid in the vessel wall. Hypercholesterolemia, smoking, DM, exposure to radiation and perineal trauma are risk factors that can be associated with ED [3]. The presence of hypercholesterolemia increases lipid storage in vascular lesions, resulting in atherosclerosis and consequent blockage of blood flow.

Use of high-resolution ultrasonography and quantitative Doppler spectral analysis technique in the evaluation of vasculogenic ED was first described by Lue et al. in 1985 [4]. The cavernous artery exhibits very pronounced gray scale changes after injection of an intracavernosal vasoactive agent. The leading change among these alterations is the increase in arterial diameter. As reported in many studies, the expected increase in the diameter of cavernous arteries varies between 70-100% [5]. Measurements of maximal systolic velocity (MSV), end- diastolic velocity (EDV), acceleration (A), acceleration time (AT) and resistive index (RI) (RI= MSV-EDV / MSV) have been used to demonstrate the hemodynamic status of the cavernous artery.

Post-injection MSV measurement in arteriogenic ED are the most commonly used parameter in assessing arterial insufficiency. Collins and Lewandowski found average MSV as 26.8 cm/sec in patients responding to intracavernous papaverine injection [6]. Most of the studies have accepted MSV values above 30-40 cm/sec as normal [7–10].

In cases of venogenic ED excessive venous leakage occurs from corpus cavernosum, In a patient with increased diastolic velocity, venocclusive mechanism is presumably insufficient. The EDV value, which can be considered significant for the assessment of venous leakage, has been reported to be over 5 cm/sec in many studies [8,11].

The aim of this study is to compare PDU, IIEF, EFDS results before and after atorvastatin treatment in hyperlipidemic patients with ED.

Material and Methods

Local ethics committee approval was obtained prior to study. Undersigned informed consent forms were obtained from all patients before the procedure. Twenty-five patients who applied to the 2nd Radiological Clinic of Ankara Numune Training and Research Hospital between April 2005 and August 2005 were included in the study. All patients had only hyperlipidemia as a risk factor of ED. The reference values of total cholesterol , and triglyceride were 112-200 mg/dl and 50-179 mg/dl, respectively. The patients were questioned regarding the risk factors of ED including history of smoking and alcohol usage urogenital system and/or spinal cord trauma, operation, diabetes, hypertension, atherosclerosis or coronary heart disease, psychiatric disorders, drug usage and hyperlipidemia. Only hyperlipidemia was detected among these risk factors.

Threshold levels of total cholesterol (200≤ mg/dl), and triglyceride (179≤ mg/dl) were as indicated. The patients whose cholesterol or triglyceride values were higher than the determined levels were evaluated as hyperlipidemic cases.

The patients were also evaluated in terms of erectile function. IIEF form which was validated by Turkish Andrology Association, was used in face to face interview sessions. By this means, EFD and IIEF scores were estimated for each patients. Sum of the scores obtained from all questions in the IIEF form was accepted as the IIEF score, and the total score of the 1,2,3,4,5 and 15 questions as the EFD score.

After intracavernosal injecting 60 mg papaverine HCl, all patients underwent Doppler US at 0, 5th, 10th, 15th and 30th minutes, and MSV and EDV values were estimated for each patient. MSV of ≥ 30cm/sec and EDV of ≥ 5 cm/sec were evaluated as normal threshold values . The patients with MSVs, and EDVs lower than these threshold values were evaluated as having arterial failure and venocclusive deficiency, respectively.

Erectile response was evaluated as below:

Grade 0: No erectile response

Grade 1: Elongation in penile shaft

Grade 2: Mild tumescence

Grade 3: Enough tumescence and erection angle is less than 90 degrees

Grade 4: Enough tumescence and erection angle is greater than 90 degrees (rigid erection)

After oral 10 mg atorvastatin treatment for a month, all parameters were measured again. Paired -t test was used to make comparisons between vascular velocities, lipid profiles, EFDS and IIEF, before and after treatment separately. For statistical analysis IBM SPSS Statistics v25 software is used.

Results

The mean age of the study participants was 53.7±10.5 years, and mean duration of ED twas 37.2±40 months. Mean

Table 1. The comparison of average total cholesterol levels in both normal and abnormal PDU groups, before and after atorvastatin treatment.

Patients with	Average total cholesterol levels (mg/dl)	
	Before atorvastatin treatment	After atorvastatin treatment
Normal PDU findings	249.3	166.6
Abnormal PDU findings	235.8	198.3

PDU: Penile Doppler Ultrasound

Table 2. The comparison of average triglyceride levels in both normal and abnormal PDU groups, before and after atorvastatin treatment.

Patients with	Average triglyceride levels (mg/dl)	
	Before atorvastatin treatment	After Atorvastatin
Normal PDU findings	197.3	110.1
Abnormal PDU findings	238.6	152.6

PDU: Penile Doppler Ultrasound

Table 3. The comparison of average EFD scores in both normal and abnormal PDU groups, before and after atorvastatin treatment.

Patients with	Average EFD scores	
	Before atorvastatin treatment	After atorvastatin treatment
Normal PDU findings	11.6	17.9
Abnormal PDU findings	11.0	17.7

EFDS: Erectile Function Domain Scores; PDU: Penile Doppler Ultrasound

Table 4. The comparison of average IEF scores in both normal and abnormal PDU groups, before and after atorvastatin treatment.

Patients with	Average IIEF scores	
	Before atorvastatin treatment	After atorvastatin treatment
Normal PDU findings	36.4	51.4
Abnormal PDU findings	36.8	53

IIEF: International Index of Erectile Function; PDU: Penile Doppler Ultrasound

cholesterol, and triglyceride levels were 242.8±36.4 mg/dl and 217.5±73.3 mg/dl., respectively After treatment these laboratory parameters were 181 and 130 mg/dl, respectively. EFDS was calculated as 11.3±2.7 before treatment. After atorvastatin treatment it was 17.8±2.5. The average IIEF scores before and after treatment were was 36.6 , and 52 points, respectively. So, we can say that the treatment was clearly effective.

Cholesterol levels of 96% of the patients were higher than 200 mg/dl and 52% of them had abnormal PDU findings. Interestingly, patients with abnormal PDU findings had lower cholesterol levels than those with normal PDU resuls, without significant differences between these patients ($p>0.05$) **(Table 1)**. Even so, both groups responded to the treatment perfectly.

Ninety-seven percent of the patients had higher triglyceride levels, and as is the case with hypercholesterolemia patients 52% of the patients had abnormal PDU findings. Before treatment there was a significant difference between the groups ($p<0.05$). They significantly responded to the treatment **(Table 2)**.

Both EFD and IIEF scores were similar before treatment, in both patient groups with normal and abnormal PDUs. However, atorvastatin treatment improved their erectile functions **(Table 3-4)**.

Discussion

Etiology of ED still remains unclear. Most of the cases are related to psychological disorders and lipid profile or non-related vascular problems. In rest of the cases, neurogenic problems, smoking, iatrogenic causes, DM, hypertension are the most commonly confronted risk factors [12–14]. It is a fact that ED is more frequent in hyperlipidemic individuals. Some studies have investigated the relation between lipid profile and ED. In a study on 215 patients, Roumegure et al. determined that high-density lipoprotein (HDL) levels and triglyceride/HDL ratios were important on the development of ED [15]. Kendirci et al. stated that ED was the first signal about endothelial damage in patients with atherogenic risk factors [16]. However, the mechanisms haven't been fully clarified yet.

Rogers JH and Kaiser FE, emphasized the similar changes

in the vessels of ED patients with coronary artery disease and/or hyperlipidemia. Similar obstructive lesions starting from the aortic bifurcation to the distal internal pudendal artery were more common. Hyperlipidemia and its resultant macrosvascular atherosclerosis were also more frequent in patients with ED [17,18]. Gholami SS et al. determined that a high fat diet causes ED with accompanying neurological and vascular changes in hypercholesterolemic rats. All rats had less nerve content and endothelial cells but higher smooth muscle cells than rats with normal cholesterol levels. In rats treated with colosterol plus phosphate buffered saline electron microscopy showed; denuded andothelial lining of sinusoids covered by multiple platelets, hypermyelination and severe atrophy of axons, a significant decrease in the number and size of nonmyelinated axons, dysregulation of smooth muscle cells with insufficient myofilaments and foamy cytoplasm. [19]. Li R et al. investigated this issue in 14 rats. They found decreased smooth muscle/collagen ratio, increased fibrosis, increased apoptosis and decreased autophagy in penile tissue of hyperlipidemic rats in as little as six months. As a conclusion they said that hyperlipidemia might decrease erectile function in rats by causing cavernosal fibrosis [20]. Qiu X et al. showed reduced nitric oxide synthase (nNOS) positive nerves, reduced endothelium, and increased cavernous smooth muscle in penile tissues of hyperlipidemic rats. They interpreted the results and associated the mechanism of ED with, decreased number of nNOS-positive nerves and an attenuated endothelium all of which can adversely affect erectile function due to reduced bioavailability of nitric oxide. They also added that the attenuated endothelium causes smooth muscle to lose their contractile ability as the cells become synthetic. According to this study, both structural changes could possibly explain why men with hyperlipidemia, have higher risk of ED [21]. Kobat M et al. stated that , in men without coronary artery disease, circulating soluble oxidized low-density lipoprotein receptor levels play a role in oxidized LDL-induced damage, which is associated with ED [22].

Both statistical frequency and the above-mentioned literature above make hyperlipidemia important for the ED etiology. Now, we have some relevant histopathologic and laboratory data. Some structural changes that diminish the elasticity of penil micro tissue and structural and/or physiologic deficits of neurons seem responsible for the lack of erection.

We aimed to investigate the correlation between the lipid profile and penile vascular Doppler US findings of ED patients. In our results, we were not able to find any effect of total cholesterol level on ED. However, Saltzman et al. administrated atorvastatin treatment to ED patients, and decrease in lipid levels occurred, the patients improved and showed a good dissese progression [23]. In addition, Wei M et al. calculated that each 1 mmol/L increase in total cholesterol levelss was associated with 1.32-fold greater risk of ED. Likewise, every 1 mmol/L decrease in high-density lipoprotein levels resulted in a 2.6-fold increase in ED risk [24]. Discordance of our results with the literature may be related with our lower patient counts. It is hard to say "there is no relation between total cholesterol level and ED development" before performing a similar study in a larger group.

In our study triglyceride levels, were significantly higher among the patients with abnormal PDU findings. In the literature, the main trend is accepting risk factors of triglyceride and coronary artery disease (CAD) as predictors of ED. In a study on 3390 male participants, Corona G et al. found that high triglyceride levels were related with ED [25]. Atahan et al. determined that lipoprotein A and triglyceride levels were higher in both peripheral and cavernosal samples of vasculogenic ED group than in non-vasculogenic ED group. However, there weren't any significant differences in other groups [26]. Kim SC et al. found that low-density lipoprotein (LDL) was higher in ED patients, however, triglyceride and cholesterol levels didn't significantly change [27]. Pinnock et al. interpreted high cholesterol and triglyceride levels as the predictor of ED [28]. So, increased triglyceride levels in our study are correlated with the literature data. Also, response of the patients to the atorvastatin treatment, supports that triglyceride and cholesterol levels are related to ED. Both in normal and abnormal PDU groups, there was significant resolution of symptoms after atorvastatin treatment. EFD and IIEF scores were significantly elevated. However, in recent studies long- term statin usage has been held responsible for ED as a result of decreased testosterone levels in hyperlipidemic patients. Corona et al. determined in statin users that testosterone levels were getting lower while follicle stimulating hormone levels were getting higher. They presumed that statin usage might trigger primary hypogonadism and they suggested the clinicians should query the ED patients with low testosterone levels, in terms of statin usage [29]. In contrast, Mondul AM et al. could not determine any negative effect of statin usage on serum sex steroid levels [30]. Further studies are needed to reveal this issue.

Conclusion

It can be said that a relation exists between hyperlipidemia and erectile dysfunction. When a clinician meets an ED patient, the most confronted etiological factors are psychogenic and vascular disorders, and vascular disorders may be related to hyperlipidemia. Therefore, lipid profile of an ED patient should be routinely assessed at admission. Triglyceride levels appear to be more important than total cholesterol levels. It has been definitely seen that assessment of the ED patients with IIEF forms ensures healthier monitorization of the patients' ED and acquisition of useful quantitative data from them.

Ethics Committee Approval: The study was approved by Ankara Numune Training and Research Hospital Ethical Committee, Cankaya, Ankara, Turkey.
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
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Original Article – General Urology

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Retrospective Evaluation of the Performance of Leukocyte Parameter of the Automated Urine Analyzer and Its Concordance with Urine Culture

Otomatik idrar analizörü lökosit parametresi performansının retrospektif değerlendirmesi ve idrar kültürü ile uyumu

Murat Koser[1], Nilgun Isiksacan[2], Ramazan Korkusuz[3], Gulcin Sahingoz Erdal[4], Pinar Atar[2], Fatih Akkas[5], Ekrem Guner[6]

[1]Department of Biochemistry, Silivri State Hospital, Istanbul, Turkey
[2]Department of Biochemistry, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
[3]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
[4]Department of Medical Oncology, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
[5]Department of Urology, University of Health Sciences, Regional Training and Research Hospital, Erzurum, Turkey
[6]Department of Urology, Dr. Sadi Konuk Training and Research Hospital, Health Sciences University, Istanbul, Turkey

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Corresponding Author: Nilgun Isiksacan / University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Department of Biochemistry, Istanbul, Turkey / nisiksacan@gmail.com ORCID ID: 0000-0002-0230-6500

Abstract

Objective: Complete urinalysis (CUA) is one of the indispensable screening tests of clinical laboratories. The compatibility of this test with urine culture is of indispensable importance in the diagnosis and treatment of urinary tract infections. We aimed to evaluate the suitability of the leukocyte parameter measured in the microscopic units of the fully automated urine analyzers which replace traditional methods, by grouping them according to the results of chemical analysis.
Materials and Methods: Leukocyte counts in the reported CUA results of 4685 outpatients and the results of 113 urine cultures studied on the same day were analyzed. Noncentrifugated urine samples were included in the analysis. Cells were digitally imaged by flow microscopy. Chemical analyzes were performed using dual wavelength reflectance method. Urine samples were evaluated after 24 hours of incubation.
Results: High power field (HPF) values were recorded by grouping the leukocyte counts as negative, trace, 1+, 2+ and 3+. The arithmetic means of HPF values of the groups were calculated as 1.2, 2.1, 5.0, 11 and 208 white blood cell (WBCs/HPF). Bacterial growth was detected in 19 of 113 patients and no reproduction was observed in the remaining 94 cases. When results of microscopic examinations and chemical analysis were compared with the culture results, the analytical sensitivity, specificity, positive, and negative predictive values for microscopic urinalysis were 25%, 86%, 61.3%, and 58.3%, respectively. While, the analytical sensitivity, specificity, positive, and negative predictive values for chemical analysis of urine were 25.8%, 87.7%, 69.7%, and 51.4%, respectively.
Conclusion: The workload of medical laboratories is increasing, and the use of urine autoanalyzers may be preferred for busy laboratories. In the diagnosis and follow-up of urinary tract infections, complete urinalysis by autoanalysers in which the harmony of their microscopy and chemical units are closely monitored, may reduce the need for unnecessary requests for urine culture, but it cannot replace urine culture.

Keywords: complete urinalysis, automated urine analyzer, urine culture, HPF, leukocyte

Öz

Amaç: Tam idrar tahlili (TİT), klinik laboratuvarların vazgeçilemez tarama testlerinden biridir. Bu testin idrar kültürü ile olan uyumu, idrar yolu infeksiyonlarının tanı ve tedavisinde vazgeçilemeyecek bir önem taşır. Geleneksel metodların yerini alan tam otomatik idrar analizi yapan cihazların mikroskobik ünitelerinde ölçülen lökosit parametresinin kimyasal analiz sonuçlarına göre gruplandırılması yapılarak aynı gün yapılan idrar kültürleri ile olan uygunluğunun değerlendirilmesi amaçlanmıştır.
Gereçler ve Yöntemler: Ayaktan başvuran 4685 hastanın raporlanmış TİT sonuçlarındaki lökosit değerleri ve aynı gün çalışılmış 113 idrar kültürü sonuçları incelenmiştir. İdrar örnekleri santrifüj edilmeden dahil edilmiştir. Hücreler flow mikroskobi ile dijital olarak görüntülenmiştir. Kimyasal analizler dual dalga boyu reflektans metodu kullanılarak yapılmıştır. İdrar örnekleri ise 24 saat inkübasyon sonrası değerlendirilmiştir.
Bulgular: Lökosit ölçümleri negatif, eser, 1+, 2+ ve 3+ olarak gruplandırılarak yüksek güç alanı (HPF) değerleri kaydedilmiştir. Gruplara ait aritmetik ortalama HPF değerleri ise 1.2, 2.1, 5.0, 11 ve 208 HPF olarak hesaplanmıştır. 113 hastanın 19'unda üreme saptanmış, 94'ünde ise üreme olmamıştır. Mikroskopi ve kimyasal analiz sonuçları kültür sonuçları ile karşılaştırıldığında, idrar mikroskopisi için duyarlık %25, özgüllük %86, pozitif prediktif değer %61,3, negatif prediktif değer %58,3 bulunmuştur. İdrarın kimyasal analizi için duyarlık %25,8, özgüllük %87,7, pozitif prediktif değer %69,7, negatif prediktif değer %51,4 olarak saptanmıştır.
Sonuç: Tıbbi laboratuvarların iş yükü giderek artmakta olup yoğun laboratuvarlar için idrar otoanalizörünün kullanımı tercih nedeni olabilir. İdrar yolu enfeksiyonu tanı ve takibinde, mikroskobi ve kimyasal ünitelerinin uyumunun sıkı takip edildiği otoanalizörlerle TİT yapılması, gereksiz idrar kültürü istenmesini ve idrar kültürüne olan ihtiyacı azaltabilse de idrar kültürünün yerini almamaktadır.

Anahtar kelimeler: tam idrar tahlili, otomatik idrar analizörü, idrar kültürü, HPF, lökosit

ORCID ID: **M. Koser** 0000-0001-7102-0875 **G. Sahingoz Erdal** 0000-0001-5815-5847 **F. Akkas** 0000-0002-4560-7426
R. Korkusuz 0000-0002-9988-9596 **P. Atar** 0000-0003-1703-2204 **E. Guner** 0000-0002-4770-7535

Introduction

Urinary tract infection (UTI) is one of the most common infections. Most women experience UTI at least once in their lifetime [1]. The most common microorganisms are gram- negative enteric bacteria. Most prevalently Escherichia coli is grown in urine cultures. Bacterial growth due to contamination in urine culture is seen at a rate of 29-32% which is one of the problems that complicate clinical evaluation [2,3].

Complete urinalysis (CUA) is one of the fast, reliable, easy, cheap and sensitive screening tests of clinical laboratories. The compatibility of this test with urine culture is very important in both children and adults. CUA is used often especially in the diagnosis of urinary tract infections, selection of treatment and monitoring recovery. CUA also helps in the differential diagnosis of diseases and it is necessary to be able to initiate treatment as early as possible [4].

Today, as a result of the increasing workload and technological developments, traditional methods are replaced by fully automated urine analyzers. In this study, we aimed to group the leukocyte parameter measured in microscopic units of fully automated urine analyzers according to the results of chemical analysis and to evaluate its compatibility with urine cultures performed on the same day.

Materials and Methods

Local ethics committee approval was obtained prior to study (approval number: 2019/506). Outpatients who were admitted to our hospital whose urinalyses were requested from different polyclinics with different pre-diagnoses between November 2010 and February 2011 were included in the study.

Results of 113 urine cultures, and 4685 leukocyte counts performed using an automated urine analyzer on the same day were retrospectively analyzed and evaluated. Noncentrifuged urine samples were included in the analyses. Cells were digitally imaged by flow microscopy method. Chemical analyzes were made using the dual wavelength reflectance method. (IRIS IQ200, Beckman Coulter, USA).

High Power Field (HPF) is the microscopy reference unit of the region under the maximum magnification power of the lens used, and the leukocytes in the microscopy unit of the autoanalyzer were measured in HPF (the area under the maximum magnification power of the lens used, generally expressed as 400x magnification) unit.

Microscopic leukocyte values of the groups defined as negative, trace, 1+, 2+ and 3+, respectively, according to the leukocyte results in chemical analysis were recorded as HPF units. HPF values were plotted under chemical grouping. The arithmetic means of the leucocyte counts of each group were calculated respectively. The areas of the patients under the graphics were accepted as 100% in total. Charts were divided into percentiles. Percentiles were selected among the percentiles used in standard deviation and cut-off values were determined. Then, the ratio to fit the percentiles was multiplied by the total number of patients in that group, and the number of patients in that percentile was found. All HPF values were listed in each chemical group from minimum to maximum. The number of patients with the same HPF values was plotted against that HPF value. HPF values were matched so as to reach the total number of patients entering the percentile. Thus, the minimum and maximum HPF values of the patients were found. Percentages of 2.5% and 97.5% were used for minimum and maximum values.

Urine samples collected for culture were inoculated onto chromogenic medium with a 10 µl loop, and evaluated after a 24-hour incubation at 37◦C.

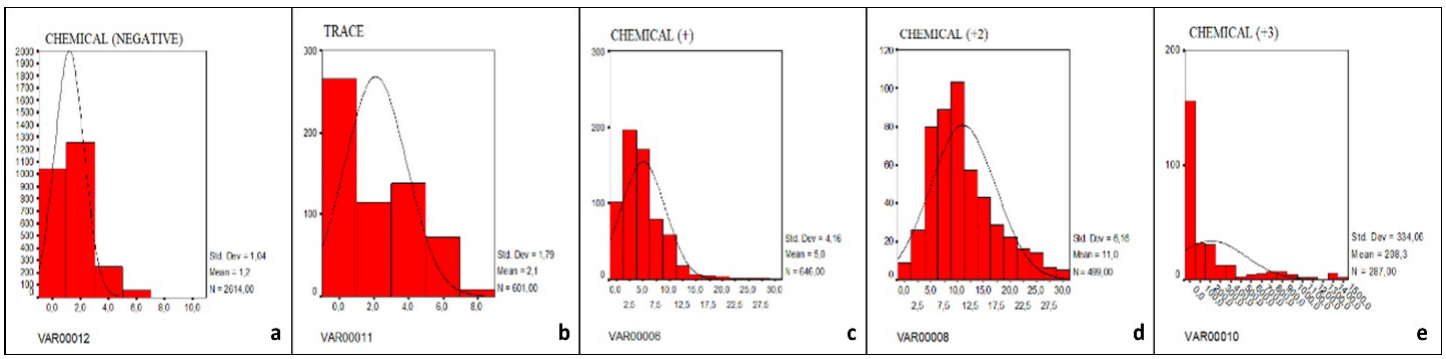
Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) program was used for statistical analysis. Mann-Whitney U test was used for intergroup comparisons of quantitative variables that did not show normal distribution, Spearman correlation analysis was used to evaluate the relationships between quantitative variables. Statistical significance was accepted as $p<0.05$.

Results

Most frequently, obstetric outpatient clinic requested complete urinalysis (24%), followed by outpatient clinics of internal diseases and pediatrics **(Table 1)**. In chemical analysis, leukocyte measurements were grouped as negative, trace, 1+, 2+ and 3+, and their respective HPF values were recorded **(Table 2)**. HPF values were plotted under chemical grouping **(Figure 1a,b,c,d,e)**.

Figure 1. Distribution of leukocyte microscopy values in chemical analysis groups



a) Negative, b) Trace, c) Positive (+), d) ++, e) +++

Table 1. Distribution of requests for complete urinalysis among polyclinics

UNITS	%
Gynecology	24
Internal Diseases	22
Pediatry	19.2
Urology	13.6
General surgery	6.6
*Others	6.4
Infectious Diseases	6.1
Emergency Medicine	2.1

*Dermatology, dentistry, physical therapy and rehabilitation, ophthalmology, otorhinolaryngology, neurology, orthopedics and psychiatry units are combined in the group named "others"

Leukocyte averages of each group were determined as 1.2, 2.1, 5.0, 11 and 208 white blood cells per high power field (WBCs/HPF). HPF values corresponding to 2.5% and 97.5% percentiles were used for the minimum and maximum values, respectively. These HPF values were found as 0-4 WBCs/HPF for negative, 0-6 WBCs/HPF for trace, 0-16 WBCs/HPF for 1+, 1-38 WBCs/HPF for 2+ and 1-1367 WBCs/HPF for 3+ according to the leukocyte counts under microscope (**Table 3)**.

Leukocytes were evaluated together with the culture results **(Table 4)**. Bacterial growth was detected in only 19 (16.8%) out of 113 patients whose urine cultures were requested, and no reproduction was observed in the remaining 94 (83.2%) patients. Correlations between the results of microscopy, chemical analysis and culture were found as r = 0.143 and 0.211, respectively ($p > 0.05$, $p = 0.006$).

WBC counts of all analysis (culture, microscopy and chemical) were classified as positive and negative. Microscopy and chemical analysis values were compared with urine culture values. When the results of microscopic and chemical analyses were compared with the culture results; the analytical sensitivity, specificity, positive, and negative predictive values for urine microscopy were 25%, 86%, 61.3%, and 58.3%, respectively. Analytical sensitivity, specificity, positive, and negative predictive values of chemical analysis of urine were 25.8%, 87.7%, 69.7%, and 51.4%, respectively **(Table 5)**.

Discussion

Complete urinalysis (CUA) has been used as the oldest analytical test in clinical laboratories since the 19th century. Today, it is still accepted as one of the most valuable screening tests [5].

CUA is a combination of chemical and microscopic analysis. Chemical analyzes are evaluated using strips and cells are assessed visually under microscope. Chemical strips are standardized and day by day highly sensitive strips are produced. Microscopic analyzes have been carried out manually for years. Based on the experience of the laboratory staff, highly different results have been reported among laboratories or between different personnel in the same laboratory vaeying with the brand of the strip used [5-6].

Microscopic examination of the urine sediment, although not standardized, gives important clinical information concerning the characteristic features of leukocytes, epithelial cells and erythrocytes. Microscopic examination requires considerable time allocation by laboratory staff [5-6].

Since the second half of the 20th century, it has been aimed to minimize the errors stemming from the individual differences of materials, instruments and laboratory workers in order to provide accurate and reliable results in complete urinalysis. Thus, automated urine autoanalyzers have been used in clinical laboratories with higher patient potential. To deal with the disadvantages of manual microscopy, automated urine analyzers using several analytical techniques have been developed [7]. Currently, these devices are frequently used in medical laboratories to minimize the work force lost during manual microscopic examination.

In this study, we aimed to take a closer look at the microscopic WBC/HPF measurements of automated urine analyzers. Since it is more standard, HPF values were grouped according to the chemical strip results. In addition, the compatibility of leukocytes with urine culture was examined. Finally, it was planned to set a cut-off value or a reference range for WBC/HPF so as to classify and standardize WBC/HPF as is the case with chemical analysis values. In the study, we noticed that 0-4 WBCs/HPF range found for the chemical leukocyte negative result was compatible with the 0-5 WBCs/HPF range provided by the manufacturer **(Table 3)**. The ranges for other chemical leukocyte values were 0-6 WBCs/HPF for trace, 0-16 WBCs/HPF for 1+, 1-38 WBCs/HPF for 2+ and 1-1367 WBCs/HPF for 3+.

Urinary tract infections are one of the most common infections and the first diagnostic test is complete urinalysis. Urine culture is still the 'gold standard' for detecting pathogens of urinary tract infections. However, many requested but unnecessary urine cultures cause loss of time and labor in laboratories. It is not uncommon for empirical antibiotic therapy to be applied while waiting for urine culture results of the patients. Rational treatment approaches should be applied to reduce costs and prevent development of antimicrobial resistance [8].

The HPF classification can help doctors identify real patients with urinary tract infections before requesting a culture. Since the CUA results are obtained within a short time after the sample is given, it can shorten the time to start treatment and reduce the number of requests for urine cultures. So, urinalysis is needed to support the diagnosis of UTI.

In our study, no correlation was found between results of culture and microscopic examination. Leukocyte values in chemical analysis correlated with urine culture results which may be due to the standardization of chemical analysis. Chemical analysis by automated urine analyzer, and microscopic examination correlate with urine culture results with analytical sensitivity rates of 25.8% and 25%, respectively. These results show that positive chemical values do not support actual growth rates which suggests that it would be more appropriate for doctors to request a urine culture after clinical evaluation of the patient.

Microscopic and chemical analysis have respective analytical specificity rates of 86% and 87.7% in patients without growth in their urine cultures. These results support the fact that there will be no growth in urine cultures of patients with CUA devoid of WBCs. This finding may allow the doctor to monitor the patient without

Table 2. HPF values in the grouping made according to the number of patients and leukocyte values

neg	n=2668	+	n=644	**2+**		n=511		**3+**				n=286			
HPF	**Freq**	**HPF**	**Freq**	**HPF**	**Freq**	**HPF**	**Freq**	**HPF**	**Freq**	**HPF**	**Freq**	**HPF**	**Freq**	**HPF**	**Freq**
Rare	1046	0.5	24	1	9	39	1	Rare	1	160	1	322	1	912	1
1	1119	1	77	2	14	42	1	1	7	165	1	351	1	935	1
2	307	2	105	3	12	43	1	10	20	167	1	352	1	969	1
3	107	3	90	4	19	44	1	11	19	169	2	366	1	976	1
4	42	4	53	5	17	45	2	12	23	170	1	370	1	1027	1
5	31	5	46	6	42	50	1	13	23	174	1	380	1	1027	1
6	6	6	73	7	48	54	1	14	29	178	1	386	1	1064	1
7	1	7	47	8	40	55	1	15	30	184	1	388	1	1064	1
8	1	8	31	9	32	68	1	100	1	188	1	394	1	1247	1
9	3	9	29	10	34	74	1	101	2	197	1	416	1	1247	1
11	1	10	15	11	36	88	1	102	2	198	1	441	2	1358	1
13	1	11	14	12	34	97	1	103	1	199	1	442	1	1358	1
14	1	12	9	13	23			104	1	202	1	444	1	1367	1
28	1	13	8	14	14			106	1	210	1	464	1	1367	1
172	1	14	4	15	14			107	1	212	1	473	1	1375	1
		15	1	16	14			112	1	216	1	488	1	1375	1
Trace	n=576	16	2	17	17			113	1	218	1	573	1	1483	1
HPF	**Freq**	17	4	18	12			114	1	221	1	616	1	1483	1
Rare	57	18	1	19	6			115	1	223	1	620	1	2488	1
1	208	19	2	20	9			116	1	228	1	635	1	2685	1
2	114	21	1	21	6			118	2	234	1	653	1	3340	1
3	90	22	1	22	10			125	1	236	2	686	1		
4	46	23	1	23	5			127	1	240	1	689	1		
5	27	26	1	24	5			132	1	245	1	701	1		
6	15	27	1	25	1			134	1	249	2	721	1		
7	4	28	1	26	7			136	1	253	1	750	1		
8	5	30	1	27	2			138	2	254	1	766	1		
9	1	51	1	28	4			139	1	256	1	772	1		
11	2	86	1	29	3			140	1	264	1	787	1		
12	2			30	2			144	1	268	1	797	1		
14	2			31	1			145	2	277	1	810	1		
16	1			32	1			146	2	283	1	834	1		
18	1			34	2			149	2	284	1	863	1		
36	1			35	1			151	1	295	1	869	2		
				37	1			152	1	306	2	884	1		
				38	1			157	1	315	1	908	1		

HPF: reported HPF values of patients; Freq: frequency; number of patients with the same HPF value; n: total number of patients belonging to the leukocyte group

using antibiotics and requesting a urine culture. Lesser use of antibiotics will also have a decreasing effect on the development of resistance to antibiotics. In studies with similar results, Lunn et al. determined the agreement between positive urine culture and chemically positive leukocyte results as 27%, and suggested that this difference was due to the number of samples used [9].

In various publications, the presence of a good correlation has been demonstrated between automated device and microscope as for the detection of erythrocytes and leukocytes [10-12]. Any significant difference does not exist between the automated urine analyzer and the microscope. Nevertheless, it was determined that the automated analyzer overestimated cell counts in the presence of greater number of erythrocytes and leukocytes in the sample compared to the manual method. In the manual method,

Table 3. Lower and upper reference values by percentiles in leukocyte grouping

Negative leukocyte	n	%	%	%	%	%
	2668	2.5	68	95	97.5	99
	(*)	67	1814	2535	2601	2641
	HPF (**)	**0**	<1	3	**4**	5
Trace leukocyte	n	%	%	%	%	%
	567	2.5	68	95	97.5	99
	(*)	14	386	539	553	561
	HPF (**)	**0**	2	5	**6**	7
(+1) leukocyte	n	%	%	%	%	%
	644	2.5	68	95	97.5	99
	(*)	16	438	612	628	638
	HPF (**)	**0**	6	12	**16**	23
(+2) leukocyte	n	%	%	%	%	%
	511	2.5	68	95	97.5	99
	(*)	13	347	485	498	506
	HPF (**)	**1**	13	28	**38**	54
(+3) leukocyte	n	%	%	%	%	%
	286	2.5	68	95	97.5	99
	(*)	7	194	272	279	283
	HPF (**)	**1**	178	1064	**1367**	1483
Total patients	4676					

(*): Number of patients entering the percentile; (**) Maximum HPF value of the relevant patients

Table 4. Distribution of the groups made in consideration of WBC counts according to the culture results

	Negative (n)	**Trace (n)**	**1+ (n)**	**2+ (n)**	**3+ (n)**	**Total (n)**
Gram- Negative Growth (10^5 CFU)	0	2	1	0	3	**6**
Gram- Positive Growth (10^5 CFU)	1	0	0	0	0	**1**
10^3 – 10^5 CFU Growth	1	1	0	1	3	**6**
Contamination	1	1	0	1	3	**6**
*Non-pathogenic Growth	39	6	3	7	16	**71**
Sterile	15	2	2	0	4	**23**
Total	**57**	**12**	**6**	**9**	**29**	**113**

* presence of non-infectious factors

Table 5. Comparison of urine culture and WBC counts with microscopic and chemical analysis

URINE CULTURE				URINE CULTURE			
	1	13	19		1	10	23
	0	80	57		0	70	66
		0	1			0	1
MICROSCOPY				CHEMICAL			

0: Negative; 1: Positive

many steps such as centrifugation, pouring the supernatant and resuspension can cause lysis and loss of cells. Budak et al. found that leukocyte counts were overestimated with automated urine analyzers compared to the manual method [13]. The automated analyzer automatically resuspends the particles by injecting air into each sample before testing. This procedure can separate clusters of cells which may result in higher cell numbers than those recorded by manual counting methods under microscope. Therefore, underestimations due to leukocyte aggregates are less common in the manual method [13].

There were some limitations in the study, and because of inadequate number of positive cultures, generalizations about the urine cultures could not be made. In daily practice, since urine culture is requested after the result of CUA is seen, the patient gives two separate urine samples, and the urine becomes more concentrated or diluted depending on the amount of fluid taken, even on the same day, causing differences in results. The exclusion of urine density and nitrite values of the samples in this study did not allow the evaluation of the correlations among urine density, bacterial growth in culture and nitrite values. In cases where leukocytes are found in urinalysis without detection of bacterial growth in culture, presence of non-infectious factors, and microorganisms that do not proliferate in culture media should be kept in mind.

Complete urinalysis is not sufficient to diagnose UTI, and the urine culture is essential. Nevertheless, in the future, the use of chemical reactions of microorganisms on strips and different magnification techniques such as HPF in microscopic units may make it easier to diagnose UTI.

Conclusion

The workload of medical laboratories is gradually increasing, and the use of urine autoanalyzers may be preferred for busy laboratories. The compatibility of the microscopy and chemical units of these devices can be closely monitored through quality control studies. Complete UA using autoanalysers in the diagnosis and follow-up of urinary tract infections may reduce unnecessary requests, and requirements for urine culture. This approach can reduce the cost burden and ease the workload of the laboratories. In addition, it can shorten the waiting time of patients and doctors for the results of the examinations by ensuring standardization of CUA results. This process can become more practical, especially in places such as emergency outpatient clinics, where a quick decision is required and faster patient circulation is desired.

Ethics Committee Approval: The study was approved by University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital Ethical Committee, Bakirkoy, Istanbul, Turkey (Decision No: 2019/506).
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
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Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – M.K., N.I., R.K.,E.G., Design – M.K., N.I., R.K., Supervision – M.K., N.I.,E.G., Resources – R.K., G.S.E., P.A., F.A., Materials – R.K., G.S.E., P.A., F.A., Data Collection and/or Processing – R.K., G.S.E., P.A., F.A., Analysis and/or Interpretation – M.K., N.I., R.K., G.S.E., P.A., F.A., Literature Search – R.K., G.S.E., P.A., F.A., Writing– M.K., N.I., R.K., G.S.E., Critical Review – M.K., N.I., E.G.
Conflict of Interest: The authors declare that they have no conflict of interest.
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Original Article – Pediatric Urology

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Evaluation of Risk Factors in Children with Hypospadias

Hipospadiaslı Çocuklarda Risk Faktörlerinin Değerlendirilmesi

Eda Celebi Bitkin[1], Alper Bitkin[2], Ender Cem Bulut[2], Oguz Tuncer[3]

1 Department of Pediatrics, Division of Pediatric Endocrinology, Van Yuzuncu Yil University Faculty of Medicine, Van, Turkey
2 Department of Urology, University of Health Sciences, Van Training and Research Hospital, Van, Turkey
3 Department of Pediatrics, Van Yuzuncu Yil University Faculty of Medicine, Van, Turkey

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Corresponding Author: Alper Bitkin / University of Health Sciences, Van Training and Research Hospital, Department of Urology, Van, Turkey / alperbitkin@gmail.com ORCID ID: 0000-0003-4724-3053

Abstract

Objective: Hypospadias is one of the most common congenital defects in boys. Multifactorial factors such as genetic predisposition and environmental factors play a role in the etiology of hypospadias. In this study, we investigated the risk factors of patients diagnosed with hypospadias.
Materials and Methods: Thirty-six patients who applied to the pediatric endocrinology and urology outpatient clinics with the diagnosis of hypospadias were evaluated retrospectively. Risk factors were evaluated by recording the parental ages, exposure to environmental factors, the maternal BMI, history of pregnancy, drug use, and the father's fertility status.
Results: The mean age of the patients was 3.5 ± 2 years. The patients had anterior (n:27 : 75%), middle (midshaft) (n:8 ; 22.2%), and posterior (n:1 ; 2.8%) hypospadias. The mean body mass index (BMI) of the mothers was 24 ± 4.1 kg/m2. Eight (22.2%) mothers were overweight and six (16.6%) mothers were obese. There was a history of hypospadias in the family of 4 (11%) patients.
Conclusion: Although combinations of environmental and genetic factors play a role in the etiology of hypospadias, many unexplained factors are responsible for this disease.

Keywords: hypospadias, risk factors, etiology, family history

Öz

Amaç: Hipospadias, erkek çocuklarda en sık görülen doğumsal kusurlardan biridir. Genetik yatkınlık ve çevresel etkenler gibi multifaktöriyel etkenler hipospadias etyolojisinde rol oynamaktadır. Biz bu çalışmada hipospadias tanısı konulan hastaların risk faktörlerini araştırdık.
Gereçler ve Yöntemler: Çocuk endokrinoloji ve üroloji polikliniğine hipospadias tanısı ile başvuran 36 hasta retrospektif olarak değerlendirildi. Ebeveyn yaşları, çevresel etkenlere maruz kalma, annenin vücut kitle endeksi (VKİ), gebelik öyküsü, ilaç kullanımı, babanın fertilite durumu kayıt altına alınarak risk faktörleri değerlendirildi.
Bulgular: Hastaların ortalama yaşı 3,5 ± 2 yıl idi. 27 (%75) hastanın anterior, 8 (%22,2) hastanın orta, 1 (%2,8) hastanın ise posterior hipospadiası mevcuttu. Annelerin ortalama VKİ 24± 4,1 olup, 8 (%22,2)'i fazla kilolu, 6 (%16,6)'sı obez idi. Hastaların 4 (%11)'ünün ailesinde hipospadias öyküsü mevcuttu.
Sonuç: Hipospadias etyolojisinde çevresel ve genetik etkenlerin kombinasyonları rol oynamakla birlikte henüz açıklanamamış birçok faktör de bu hastalıktan sorumludur.

Anahtar kelimeler: hipospadias, risk faktörleri, etiyoloji, aile öyküsü

ORCID ID: **E. Celebi Bitkin** 0000-0002-6586-7305 **E.C. Bulut** 0000-0002-5002-5471 **O. Tuncer** 0000-0003-3706-414X

Introduction

Hypospadias is a congenital anomaly due to inadequate virilization of the genital tubercle, characterized by insufficient tissue formation in the ventral aspect of the penis and urethra, and in which the urethral meatus opens more proximally than it should be in the ventral aspect of the penis [1]. It is a common disease affecting one in every 200 to 300 newborn males [2]. The total prevalence of hypospadias in Europe is 18.6 new cases per 10,000 births [3]. The most commonly used classification is formulated as anterior or distal hypospadias, midshaft, middle or penile hypospadias, and posterior or proximal hypospadias, depending on the position of the external meatus [4]. It has been suggested that genetic factors, maternal-placental factors, insufficient hormonal stimulation and environmental factors are involved in the etiology of hypospadias. Therefore, hypospadias etiology is thought to be multifactorial [5–7]. Studies conducted to evaluate the etiology of hyposypadiac have focused on different components with resultant lots of confusing information [8]. The aim of our study is to contribute to the etiology of hypospadias and to evaluate the risk factors associated with it.

Materials and Methods

Thirty-six patients who applied to pediatric endocrinology and urology outpatient clinics due to hypospadias were included in our study. Children diagnosed with hypospadias were classified according to the location of the external meatus. Birth weights, presence of hypospadias in other siblings and father, obesity status of the mother, medications used before and during pregnancy, occupational exposure to various agents, use of assisted reproductive techniques, the course of pregnancy and the father's spermatogenesis status were recorded and evaluated retrospectively. Patients with additional congenital anomalies were excluded from the study. Written consent was obtained from the parents of the patients for the publication of the study data. Ethics committee approval was not obtained due to the retrospective nature of the study.

Results

The mean age of 36 patients with hypospadias included in the study was 3.5 ± 2 years. The patients had anterior (n:27; 75%), middle (n: 8 ; 22.2%), and posterior hypospadias (n:1 ; 2.8%). The mean maternal, and paternal ages of the patients were 23.9 ± 3.6, and 25.7 ± 4.1 years, respectively. The mean BMI of the mothers was 24 ± 4.1 kg/m2. Eight (22.2%) mothers were overweight and six (16.6%) mothers were obese. There was a history of hypospadias in the family of 4 (11%) patients including 3 patients with anterior and 1 with middle hypospadias. Two (5.5%) patients had been delivered as low birth weight newborn. Oligospermia was present in the father's spermiogram of 3 children. None of the parents had a history of occupational exposure. The data of the patients and their parents are given in **Table 1**.

Discussion

Although hypospadias has a multifactorial etiology, there are many studies showing that heredity is an important factor in the etiology [9,10]. It has been shown that 7% of the children with hypospadias have a history of hypospadias in their relatives [10]. The chance that a brother of an affected boy will also have hypospadias is 9–17% [9,11]. Anterior and middle forms are more common in children with family history of hypospadias than posterior forms [10,12]. In our study, family history of hypospadias was reported for 4 (11%) children with hypospadias including 3 cases with anterior, and one patient with middle hypospadias. It has been proven by histochemical studies that androgen and estrogen receptors are intensely expressed on the urethral plate during normal fetal development [13]. Male sexual differentiation is generally dependent on testosterone, its metabolite dihydrotestosterone, and the expression of androgen receptors by target cells and the balance between androgens and estrogens. Disruption of this balance by endogenous or exogenous factors may cause hypospadias [14]. The use of oral contraceptives after conception has increased the risk of hypospadias (especially middle and posterior hypospadias). However, the use of oral

Table 1. Risk factors for hypospadiasis associated with the patient and his parents

Parameters	N
Number of patients	36
Patient's age (years)(mean .± SD)	3.5 ± 2
Paternal age (years)(mean .± SD)	25.7 ± 4.1
Maternal age (years)(mean .± SD)	23.9 ± 3.6
Maternal BMI kg/m^2 (mean .± SD)	24 ± 4.1
Obese mothers, n (%)	6 (16.6 %) 8 (22.2 %)
Overweight mothers, n (%)	
Family history n (%)	4 (11%)
Oral contraceptive use after conception n (%)	1 (2.7%)
Low birth weight (n) (%)	2 (5.5%)
Parents using assisted reproductive techniques n (%)	3 (8.3%)
Number (%) of subfebrile fathers	3 (8.3%)

contraceptives before pregnancy has not been found to be associated with hypospadias [12,15,16]. The mother of one of the patients in our study used oral contraceptives for 2 months after conception. This patient had posterior hypospadias.

Assisted reproductive technologies are widely used for couples who apply to health institutions for infertility. Hormonal treatment is often applied during these methods. Many studies have shown that the use of assisted reproductive techniques increases the risk of hypospadias [8,17]. The risk is increased frequently after the intracytoplasmic sperm injection (ICSI) method [18,19]. In our study, assisted reproduction techniques with ICSI method were applied to the parents of 3 (8.3%) patients diagnosed with hypospadias.

It is known that some maternal factors are effective in the development of hypospadias. It has been shown that the presence of obesity in the mother is associated with hypospadias [20]. Endogenous levels of free estradiol increase with increasing BMI which may play a role in the development of hypospadias [21]. Many studies have shown that the risk of hypospadias increases in children of overweight or obese mothers [22,23]. However, Rankin et al. showed that obesity was not associated with hypospadias [24]. In our study, the mothers of 8 (22.2%) patients were overweight, and the mothers of 6 (16.6%) patients were obese.

It has been found that the risk of hypospadias is higher in children with low birth weight [12,15]. It is known that human chorionic gonadotropin (hCG) secreted from the placenta in the fetus stimulates fetal testicular steroidogenesis. Placental insufficiency may result in inadequate provision of fetal hCG and fetal nutrients, possibly explaining the association between hypospadias and low birth weight [25]. In addition, several studies have shown that preterm birth may be associated with late placental dysfunction and cause hypospadias [26,27]. In 2 (5.5%) of the patients in our study, history of low birth weight was elicited, and none of the mothers of the patients had a history of premature delivery.

Lower sperm count, sperm motility and higher abnormal sperm morphology were found in fathers of children with hypospadias [28]. It is stated in the testicular dysgenesis syndrome (TDS) hypothesis that hypospadias and male subfertility may share the same genetic and environmental factors [29]. In this way, subfertile fathers may transmit a certain predisposition to their children. Oligospermia was present in the fathers of our 3 (8.3%) patients.

When occupational exposures are evaluated, although there are conflicting results in terms of the relationship between exposure to pesticides and hypospadias, it has been shown that fathers exposed to pesticides are more likely to have children with hypospadias [30,31]. There was no occupational pesticide exposure in the parents of any of our patients.

Our study has some limitations. Since it is a retrospective study, we could not obtain data about some etiologic factors responsible for the development of hypospadias.

Conclusion

As a result, there is no single factor responsible for the development of hypospadias. The combination of both genetic and environmental factors play a role in etiology. However, since the development of the disease is multifactorial, there are many factors that have not yet been revealed. Avoiding proven risk factors can reduce the incidence of the disease. We think that prospective studies with greater number of patients may help to find the factors responsible for the development of the disease.

Ethics Committee Approval: Ethics committee approval was not obtained due to the retrospective nature of the study. Informed consent forms were obtained.
Informed Consent: An informed consent was obtained from the parents of all patients.
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Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – E.C.B., A.B., E.C.B.; Design – E.C.B., A.B., E.C.B.; Supervision – E.C.B., A.B., O.T.; Resources – E.C.B., A.B., E.C.B., O.T.; Materials – E.C.B., A.B., E.C.B., O.T.; Data Collection and/or Processing – E.C.B., A.B., E.C.B., O.T.; Analysis and/or Interpretation – E.C.B., A.B., E.C.B., O.T.; Literature Search – E.C.B., A.B., E.C.B., O.T.; Writing– E.C.B., A.B.; Critical Review – E.C.B., A.B., O.T.
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Original Article – Urological Oncology

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D-dimer in the Diagnosis of Prostate Cancer

Prostat Kanserinin Tanısında D-dimer

Hasan Salih Saglam, Haci Ibrahim Cimen

Department of Urology, Sakarya University Faculty of Medicine, Training and Research Hospital, Adapazari, Sakarya, Turkey

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Corresponding Author: Hasan Salih Saglam / Sakarya University Faculty of Medicine, Training and Research Hospital, Department of Urology, Adapazari, Sakarya, Turkey / ssaglam@sakarya.edu.tr ORCID ID: 0000-0002-8904-1612

Abstract

Objective: To investigate the value of D-dimer, a marker of fibrinolysis, in metastatic and non-metastatic prostate cancer.
Materials and Methods: A retrospective analysis was performed on 138 male patients including 52 patients with prostate cancer and 86 with benign prostatic hyperplasia. Participants who had factors that altered D-dimer levels were excluded. The mean ages of the groups were similar (70 ± 8 vs 68 ± 8, p= NS). In addition, data regarding biochemical findings, prostate-specific antigen and hemostatic markers, including D-dimer, were retrieved from the database of our hospital. The cut-off point of D-dimer was 0.5 mg/L. Data from scintigraphy and magnetic resonance imaging (MRI) scans related to metastasis were also considered. Patients who showed findings of metastasis according to scintigraphy and lumbosacral MRI were accepted as having metastases. Positive findings in only scintigraphy in any area were considered suspicious for metastasis.
Results: Patients with prostate cancer had higher D-dimer levels than benign prostate hyperplasia patients (p= 0.024). Sixteen patients with metastatic prostate cancer and suspicious for metastasis had markedly high D-dimer levels compared to benign prostate hyperplasia and non-metastatic prostate cancer patients.
Conclusion: prostate cancer, especially when metastatic, may increase D-dimer levels.

Keywords: D-dimer, prostate cancer, metastasis.

Öz

Amaç: Fibrinolizin bir belirteci olan D-dimerin metastatik ve metastatik olmayan prostat kanserinde değerini araştırmak.
Gereçler ve Yöntemler: 52'si patolojik prostat kanseri ve 86'sı benign prostat hiperplazisi olan 138 erkek hasta retrospektif olarak analiz edildi. D-dimer düzeylerini değiştiren faktörlere sahip katılımcılar dışlandı. Grupların ortalama yaşları benzerdi (70 ± 8'e karşı 68 ± 8, p= NS). Hastanemizin veri tabanından rutin biyokimyasal bulgulara ek olarak prostat spesifik antijen (PSA) ve D-dimer içeren hemostaz belirteçleri toplandı. D-dimerin cut-off noktası 0.5 mg/L idi. Metastaz için sintigrafi ve manyetik rezonans görüntüleme araştırmalarından elde edilen veriler de dikkate alındı. Sintigrafi ve lumbosakral manyetik rezonans görüntülemesine göre metastaz bulguları gösteren hastalar metastazlı olarak kabul edildi. Herhangi bir bölgede sadece sintigrafide pozitif bulgular metastaz için şüpheli kabul edildi.
Bulgular: Prostat kanserli hastaların D-dimer düzeyleri benign prostat hiperplazili hastalara göre daha yüksekti (p= 0.024). Metastatik prostat kanseri olan ve metastaz şüphesi olan 16 hasta, iyi huylu prostat hiperplazisi ve metastatik olmayan prostat kanseri hastalarına kıyasla belirgin şekilde yüksek D-dimer seviyelerine sahipti.
Sonuç: prostat kanseri, özellikle metastatik olduğunda D-dimer düzeylerini artırabilir.

Anahtar kelimeler: D-dimer, prostat kanseri, metastaz.

ORCID ID: H.I. Cimen 0000-0002-0824-3926

Introduction

Prostate cancer (PCa) has been shown to be the second-most common malignancy and the fourth leading cause of death in men worldwide. Epidemiological studies have revealed that its incidence is rising in the era of the prostate-specific antigen (PSA) [1].

Although PCa can be managed in the early stages by surgical intervention or radiation, over time, approximately 7.0% of cases of PCa metastasize and progress to castration-resistant cancer, even with aggressive hormone deprivation therapy [2–4]. The prognosis is poor in men with distant metastases of PCa, in which bone is the most common site of involvement [4].

Today, the routine diagnostic screening tests for PCa include measurement of PSA in the blood, digital rectal examination and, ultimately, a systematic transrectal ultrasound-guided biopsy [5,6]. However, despite the rapidly growing number of candidate biological markers of prognosis and/or response to specific treatments in PCa, to date, none have shown the ability to give a complete understanding of prognosis for PCa in evidence-based urology. Many tools have been used to determine advanced stages of PCa in addition to PSA, comprising C-reactive protein, ceruloplasmin, beta-2-microglobulin, fibronectin and calcitonin etc. [7–9]. In this context, D-dimer, which is another biomarker, has been associated with advanced and metastatic cancers.

D-dimer is produced as a result of cleavage of cross-linked fibrin by the fibrinolytic enzyme plasmin. Therefore high levels of D- dimer indicate activation of coagulation and fibrinolysis [10]. Although not extensively studied, it has also been suggested that PCa increases serum D-dimer levels. However, conflicting data exist regarding the association of D-dimer levels with the stage of the disease [11]. In this study, we aimed to exhibit a presumptive relation of D-dimer levels with PCa.

Materials And Methods

The data were retrieved retrospectively from the database of Sakarya University Medical Faculty Training and Research Hospital which provides tertiary health care. Information regarding male inpatients aged ≥ 50 years who were hospitalised with lower urinary tract symptoms (LUTS) for surgery, cases with increased PSA levels scheduled for transrectal prostate biopsy, and patients with the diagnosis of PCa interned for treatment between May 2011 and October 2020, were used. The patients who had pretreatment or preoperative biochemical tests including D-dimer, and pathologic diagnoses after operation or biopsy, were enrolled in the study. The patients with pathologic diagnosis of BPH who were of a similar mean age were used as a control group. The criteria for exclusion were as follows: presence of active infection including urinary system infection, any malignancy other than PCa, any chronic inflammatory disease such as chronic obstructive pulmonary disease or rheumatoid arthritis, indwelling urethral catheter, any recent operation or trauma, and any record or diagnosis of thromboembolism. Additionally, patients who had taken antithrombotic/antiaggregant agents for other indications were also excluded.

Besides, information were retrieved from the database regarding age, international prostate symptom score (IPSS), the international normalised ratio of prothrombin time (INR), activated partial thromboplastin time (aPTT), scintigraphic and radiologic imaging results. The cut-off point of D-dimer was 0.5 mg/L. The results of the scintigraphic and radiological (magnetic resonance imaging [MRI]) examinations of the patients who had been diagnosed with PCa were used to exhibit metastasis. Patients who showed findings of metastasis according to both lumbosacral skeletal scintigraphy and lumbosacral MRI results were accepted as having metastasis. Radioactive substance uptake in scintigraphy only in areas beyond the lumbosacral region or in the lumbosacral area but not confirmed by MRI was considered "suspicious" for metastasis. The patients could not be detailed regarding stage of PCa retrospectively but dichotomised as metastasis- positive or metastasis- negative cases based on the presence of metastasis.

Statistical Analysis

Because the data regarding D-dimer did not have a Gaussian distribution, Spearman's rho correlation test was used to measure strength and direction of association between nonparametric variables. The Mann-Whitney U test was applied to compare independent groups that did not have sufficient participants for parametric tests. A paired t-test was used for dependent groups who had sufficient number of participants and normal distribution. In this study, statistics were performed using the software package SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Values of $p < 0.05$ were used to reject the null hypothesis.

Results

A total of 138 consecutive male patients were recruited. Eighty-six patients were pathologically diagnosed with benign prostatic hyperplasia (BPH), and 52 with PCa. The basic characteristics of the two groups are presented in **Table 1**. Median D-dimer levels of the BPH and PCa patients were 0.32 mg/L (0.10-6.40) and 0.49 mg/L (0.02-7.29), respectively with a a significant intergroup difference ($p = 0.011$) **(Table 1)**.

Twenty-two (42%) out of 52 PCa patients had D-dimer values above the cut-off value. Ten of these 22 patients were found to have metastatic disease according to scintigraphy and MRI findings. In all metastatic patients (median D-dimer 1.66 mg/L, range 0.60-7.29) D-dimer values were above the cut-off point. The remaining 12 patients also had D-dimer values over the cut-off point including 6 cases suspicious for metastasis, and the remaining 6 patients had not any findings suggesting the presence of metastasis. Thus, 31% of the PCa patients with higher D-dimer levels had significant or suspicious evidence of metastasis. None of the patients had MRI -positive and scintigraphy- negative findings suggestive of metastasis **(Table 2)**.

On the other hand, 17 (20%) patients with BPH had D-dimer levels above the cut-off point, versus 22 (42%) patients with PCa. The ratio of individuals having D-dimer levels above the cut-off value was significantly greater in the PCa patients than in the BPH patients ($p = 0.021$). Among BPH patients, a subgroup with higher D-dimer levels was similar to the other subgroup with normal D-dimer levels regarding age ($p > 0.05$).

Table 1: Basic characteristics of the patients with BPH and PCa

Variables	BPH(n=86)	PCa(n=52)	*p*
D-dimer (mg/L) Median (min-max)	0.32(0.10-6.40)	0.49(0.02-7.29)	0.011
Age years (mean±SD)	67±8	70±8	NS
IPSS Median (min-max)	19(4-33)	15(3-30)	0.009
INR (%) Median (min-max)	1.06(0.81-3.12)	1.19(0.82±9.96)	NS
aPTT (sec) (mean±SD)	26.04±3.50	27.20±3.76	NS

SD: standard deviation; NS: nonsignificant; Pca: prostate cancer; BPH: benign prostatic hyperplasia

Additionally, D-dimer levels were shown to be associated with PSA (rs= 0.287; p= 0.001) and age (rs= 0.362; p= 0.024). Taken Gleason score into consideration for grading PCa, no significant association has been detected between PCa and D-dimer levels (rs= 0.214, p> 0.05) **(Table-2)**.

Discussion

This study showed that D-dimer levels were higher in patients with PCa than in patients with BPH, which is in line with data encountered in the literature [12–14]. Although some BPH patients revealed D-dimer values above the cut-off value, the median value of D-dimer levels was below the cut-off point in patients with BPH. Approximately 31% of PCa patients who were metastatic or suspicious for metastasis had higher D-dimer values than non-metastatic PCa and BPH patients. Similarly, in their study of 49 BPH and 55 PCa patients, Geenen et al. found that levels of D-dimer, as a marker of fibrinolysis, were elevated in the metastatic group compared to the non-metastatic PCa and BPH groups. They also noted that fibrinolysis might not play a prominent role in PCa, since there was no significant intergroup difference regarding another marker of fibrinolysis, plasmin-a2-antiplasmin [13].

D-dimer is a degradation product of cross-linked fibrin. Its presence in plasma is an indirect marker of activation of coagulation followed by reactive thrombolysis. High D-dimer levels combined with other factors were proposed as independent predictors for venous thromboembolism (VTE) in patients with cancer, allowing an overall risk assessment [10,15]. Blom et al. concluded that in the presence of distant metastasis, cancer patients had a highly increased risk of VTE after diagnosis [16]. In our study, all D-dimer levels in 10 patients with distant metastasis and six patients suspicious for metastasis, were above the cut-off point. These results were in accordance with the results reported by Adamson et al., who concluded that high D-dimer levels might have some predictive value in determining bone scan status in untreated PCa patients [12]. In our study, in each of the 22 patients (42%) of the PCa group, D-dimer levels were above the cut-off point, suggesting activation of the hemostatic system This finding is in line with Adamson's conclusion that up to 40% of patients with untreated PCa showed evidence of activation of hemostatic system [12].

On the other hand, Adcock observed evidence of distant metastasis in up to 40% of cases with cancer and concomitant VTE [17]. In our study, 10 out of 22 (46%) patients with PCa and higher D-dimer levels showed strong evidence of metastasis. In contrast, Hong studied antithrombin-III (ATIII), plasminogen, fibrinogen and D-dimer, and concluded that subjects with organ-confined disease and those with an extraprostatic extension of a tumour had not demonstrated any significant differences in the preoperative levels of the four coagulation factors analysed [11].

The methods we used (scintigraphy and MRI) have some limitations, despite their relatively high sensitivity and different specificity in determining PCa metastasis [18–21]. Since a precise diagnostic confirmation method for detecting metastasis is lacking, we could not be sure if the cases with higher D-dimer levels, which were assumed as suspicious or non-metastatic, harbour distant metastasis. Other routine laboratory studies also did not rule out such conditions in these cases.

The hemostatic system seems to play a role in the metastatic capacity of solid tumours [16]. However, the actual mechanism of this coagulopathy in cancer patients is not precise [14]. Tissue factor (TF) is a cell procoagulant found in normal cells, including endothelial cells, macrophages, and -monocytes. Although normal endothelial cells express TF only in response to an inflammatory stimulus, malignant cells constitutively express TF [17]. Tumour cells interact with all parts of the hemostatic system and activate the coagulation cascade with procoagulant factors, such as TF and cancer procoagulant factor. The coagulation cascade eventually results in thrombosis comprising blood cells, such as platelets, monocytes or macrophages [22]. In addition, previously reported studies

Table 2: Distribution of D-dimer values in patients with PCa

D-dimer (mg/L)	Met. (+), (n)	Met. Susp.,(n)	Met. (-), (n)	Total (n)
D-dimer>0.5 (n)	10	6	6	22
D-dimer<0.5 (n)	0	0	30	31
Total (n)	10	6	36	52

Met. (+): metastasis- positive; Met. Susp.: suspicious for metastasis; Met. (-): metastasis- negative.

have shown that D-dimer, a fibrinogen degradation product, is involved in tumor progression due to the ability of tumor cells to transform fibrinogen to fibrin. The rising plasma D-dimer levels may display fibrinogen metabolism within the tumor stroma that is actively remodeling [23]. Also fibrin creates a protective layer on tumor cells, providing resistance to endogenous defense mechanisms, which can facilitate angiogenesis, invasion and metastasis [24].

In this study, D-dimer levels were also shown to be weakly but significantly associated with PSA, which may be due to a relation between D-dimer and PCa. D-dimer was found to be more strongly associated with age when compared to PSA. Although D-dimer levels gradually increase with age, its specificity for venous thromboembolism decreases accordingly [25,26]. This condition increases the frequency of false positive test results in the elderly [27]. Thus D-dimer cut-off points were suggested separately for each decade after 50 years of age [28,29]. Accordingly, although the mean D-dimer levels of BPH patients were below the cut-off point, 17 of 86 BPH patients (20%) had D-dimer values above the cut-off point. However, the mean ages of the 17 patients and the remaining patients were similar (p> 0,05).

The data in this study seem somewhat confusing. One may encounter difficulties when attempting to use D-dimer values for the estimation of metastasis. D-dimer level above the cut-off value may not point to any significant evidence regarding metastasis. But its negative predictive value may be valuable, as shown in **Table 2**.

This study has many limitations. First of all, this is a retrospective study. Secondly, we studied a small number of PCa patients. Another possible limitation is the issue of clinically asymptomatic VTE. These asymptomatic cases could appear in both groups and could not be excluded from the study. No further investigation regarding the elevated D-dimer levels was possible. If any asymptomatic VTE exists, we have assumed it to be distributed among all the patients randomly. The lack of an exact method for confirmation of metastasis presents a challenge regarding metastatic cases.

Conclusion

D-dimer levels are higher in PCa patients than in BPH patients. Patients with skeletal metastasis may have markedly elevated D-dimer levels; furthermore, in conditions of elevated D-dimer levels, the patients may have a higher probability of metastasis compared to a non-metastatic group. In addition, in PCa cases, a D-dimer value below the cut-off point may refer to a non-metastatic condition. We believe that the results of this study justify the need for further investigation of coagulation factors, including D-dimer levels in PCa.

Ethics Committee Approval: We did not obtain ethical approval as the study was retrospective. Informed consent forms were obtained from all patients before the procedure.
Informed Consent: An informed consent was obtained from all the patients.
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Case Report – General Urology

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Acute Proximal Tubular Necrosis Due to Cidofovir Usage in BK Virus Related Hemorrhagic Cystitis in an Allogeneic Stem Cell Transplanted Patient

Allojenik Kök Hücre Nakli Yapılan Bir Hastada BK Virüsüne Bağlı Gelişen Hemorajik Sistitte Kullanılan Cidofovire Bağlı Olarak Ortaya Çıkan Akut Proksimal Tübüler Nekroz

Sebnem Izmir Guner[1], Mustafa Teoman Yanmaz[2], Ekrem Guner[3], Pinar Seymen[4], Melike Nalbant Moray[5], Isin Kilicaslan[5]

[1]Department of Hematology, Istanbul Gelisim University, Memorial Sisli Hospital Hematology and Bone Marrow Transplantation Center, Istanbul, Turkey
[2]Department of Medical Oncology, Arel University, Memorial Bahcelievler Hospital, Istanbul, Turkey
[3]Department of Urology, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
[4]Department of Nephrology, Halic University, Medicana Kadikoy Hospital, Istanbul, Turkey
[5]Deparment of Pathology, Istanbul University, Faculty of Medicin, Istanbul, Turkey

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Corresponding Author: Sebnem Izmir Guner / Department of Hematology, Istanbul Gelisim University, Memorial Sisli Hospital Hematology and Bone Marrow Transplantation Center, Istanbul, Turkey / sebnemizmirguner@gmail.com ORCID ID: 0000-0002-6326-9424

Abstract

Hemorrhagic cystitis (HS) is a frequently seen complication of bone marrow transplantation. This condition occurs depending on the preparatory regimen of bone marrow transplantation. The BK virus (BKV), a human polyomavirus, is a small double helix DNA virüs belonging to the Papovaviridae family. It is commonly found in societies as an occult infection. Whereas, cidofovir (CDV), an acyclic nucleoside phosphonate, is used as a proven antiviral agent against polyomaviruses. In this case report, acute proximal tubular necrosis due to cidofovir used in hemorrhagic cystitis caused by BK virus, and its treatment in a patient diagnosed with T-lymphoblastic lymphoma in remission, and underwent allogeneic stem cell transplantation, was presented.

Keywords: hemorrhagic cystitis, BK virus, T-lymphoblastic lymphoma, acute proximal tubular necrosis

Öz

Hemorajik sistit (HS), kemik iliği transplantasyonun sık görülen bir komplikasyonudur. Bu durum, kemik iliğinin hazırlık rejimine bağlı olarak ortaya çıkmaktadır. Bir insan poliomavirüsü olan BK virüsü (BKV), küçük bir çift sarmal DNA virüsüdür. Papovaviridae ailesine ait bir virüsdür. Genellikle toplumlarda latent bir enfeksiyon olarak bulunur. Bunlarla birlikte, bir asiklik nükleosit fosfonat olan cidofovir (CDV), poliomavirüslere karşı kanıtlanmış bir antiviral ajan olarak kullanılır. Bu olgu sunumunda allojenik kök hücre nakli yapılan remisyondaki T-lenfoblastik lenfoma tanılı hastada BK virüsüne bağlı olarak gelişen hemorajik sistitte kullanılan cidofovirin yapmış olduğu akut proksimal tubuler nekroz ve tedavi yönetimi anlatılmıştır.

Anahtar kelimeler: hemorajik sistit, BK virüs, T-lenfoblastik lenfoma, akut proksimal tübüler nekroz

ORCID ID: **MT. Yanmaz** 0000-0002-8680-1006 **E. Guner** 0000-0002-4770-7535 **P. Seymen** 0000-0003-4988-9253
M. Nalbant Moray 0000-0002-1896-986X **I. Kilicaslan** 0000-0002-4206-9941

Introduction

The BK virus (BKV), a human polyomavirus, is a small double helix DNA virus belonging to the Papovaviridae family. It is commonly found in societies and forms a latent infection. However, it can lead to serious clinical findings in patients with immunosuppression such as patients who had undergone bone marrow or solid organ transplantation or patients with cancer [1]. Hemorrhagic cystitis (HS) is seen as a frequent complication of bone marrow transplantation. This condition occurs depending on the conditioning regimen of bone marrow transplantation. Hematuria, dysuria, pollakiuria, and suprapubic pain are the most common findings and symptoms of its clinical presentation. Its emergence is not only limited to cases where bone marrow transplantation is performed. It can also occur during the treatment of some other neoplastic diseases where cyclophosphamide (CY) or ifosfamide is used.

Hematuria occurs two weeks after the administration of bone marrow transplantation preparatory regimens where cyclophosphamide (CY) or ifosfamide is used. In contrast, hemorrhagic cystitis has also been reported to occur immediately or in the long term, three months after the administration of cyclophosphamide. Hemorrhagic cystitis (HS) is defined in two groups as early- or late-onset HS, taking into consideration the differences in the etiologies. Early-onset hemorrhagic cystitis is more commonly associated with chemoradiotherapy used in conditioning regimens of bone marrow transplantation. Late-onset hemorrhagic cystitis occurs weeks or months after the transplantation. Multiple factors are accused in the etiology. A previously emerged HS is considered a risk factor in itself for this type of HS. In addition, viruses and Graft-Versus-Host Disease (GVHD) are also accused in the etiology. The major accused viruses are BK virus (BKV), adenovirus and cytomegalovirus [2–5]

The BK virus, which remains latent in renal and uroepithelial cells after primary infection, reactivates after transplantation in which immunosuppressive agents are used and the cellular immunity is weakened [6]. The most common pathology caused by the reactivation of BKV is HS, and supportive therapies such as hyperhydration, alkalinization, and bladder irrigation are usually applied in the treatment. Cidofovir (CDV) which is an acyclic nucleoside phosphonate in antiviral drugs used in the treatment against polyomaviruses has been reported as an agent with confirmed efficiency [7–10] 19 of 71. Cidofovir, a nucleotide analog, exerts its effect by inhibiting viral DNA polymerase and preventing chain elongation. Unlike nucleoside analogs, it contains a phosphatase group. Cidofovir (CDV) is given to patients infected with BKV at a dose of 5 mg/kg per week during the first 2 weeks. After that, the treatment is repeated every 2 weeks. Its most important side effect is renal failure manifested by proteinuria, which can be prevented by using probenecid [11–13]. Renal failure is the main toxicity of CDV, and therefore serum creatinine and urine protein levels should be measured before each CDV application. To reduce its side effect, CDV should be used with oral probenecid and intravenous physiological saline solution [11–13].

In this case report, the management of acute proximal tubular damage due to the use of cidofovir in hemorrhagic cystitis caused by BK virus in a patient with T-lymphoblastic lymphoma in remission, in whom allogeneic stem cell transplantation was performed, was presented.

Case Presentation

For a 22-year-old male diagnosed with T-lymphoblastic lymphoma in October 2014, stem cells were collected with cyclophosphamide + G-CSF (granulocyte colony-stimulating factor) regimen under partial response obtained after chemotherapy and radiotherapy, then autologous stem cell transplantation was performed on the patient in December 2015 with BEAM stem cell conditioning regimen. The patient who showed recurrence in the follow-up received the FLAG-IDA chemotherapy protocol; and hematopoietic peripheral stem cells were transplanted from the HLA 9/10 compatible haploidentical unrelated donor in October 2016 using the reduced intensity conditioning (RIC) stem cell conditioning regimen. The patient was suspected of hemorrhagic cystitis infection related to the reactivation of BKV due to the development of macroscopic hematuria on the 50th day after transplantation. In the urinalysis, BKV: 3, 444.359.614 copy/ml was detected, so the patient was treated with 5 mg/kg i.v. cidofovir per week, then the treatment continued at 2-week intervals. To protect against renal failure, probenecid was given orally at doses of 1.25 mg/m^2 3 hours before and 1 and 8 hours after the administration of CDV. In addition to CDV, cyclosporine treatment was also started for GVHD prophylaxis, and cyclosporine levels and renal functions were followed in the patient once in two days. BKV levels were measured weekly. Since BK virus disappeared in the urine and blood, and hematuria disappeared after 4 doses of CDV, the cyclosporine dose was reduced to 25 mg daily after the 75th day of stem cell transplantation. Remission was detected in PET/CT taken on the 90th day after stem cell transplantation. In the patient who reduced the intake of fluids due to nausea and hid it, the blood urea and creatinine levels were 139 mg/dl and 6.78 mg/dl, respectively, on the 122th day of stem cell transplantation due to insufficient fluid intake. In the evaluation, the patient with normal anion gap metabolic acidosis was urgently interned and intravenous hydration was started. However, he was hemodialyzed due to the absence of improvement in their values. The patient, whose creatinine level could not be

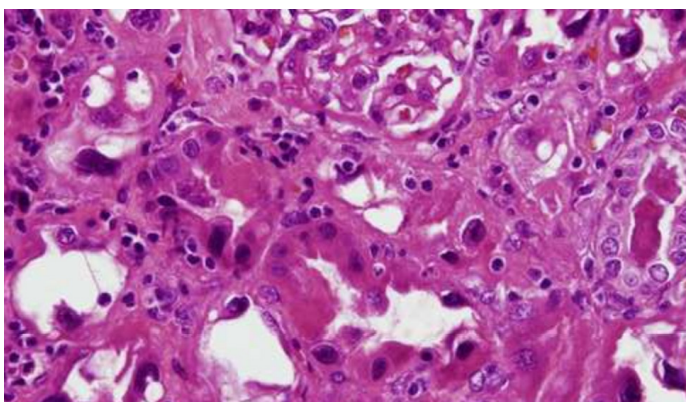

Figure 1. Histopathologic findings of tubular epithelial cell necrosis (renal biopsy specimen)

reduced despite all the treatments, underwent US-guided kidney biopsy. In the histopathological examination of renal biopsy specimen, nucleomegaly, hyperchromasia, and atypia, as well as, interstitial mixed inflammatory cell infiltration were detected in tubular epithelial cells due to CDV **(Figure1)**. The patient who entered chronic renal failure continued with bicarbonate hemodialysis treatment 2 times a week with the recommendation of nephrology consultation.

Discussion

After transplantation, the frequency of hemorrhagic cystitis varies between 5-70 percent [4]. In some patients with bone marrow transplantation, asymptomatic microscopic hematuria may be detected clinically. In contrast, a small number of patients have resistant and long-term macroscopic hematuria, dysuria and bladder-induced pain that indicate hemorrhagic cystitis (HS). The diagnosis is usually based on clinical data, and the urinary infection due to other agents should be excluded. For this purpose, the mid-stream urine culture should be made. With cytological examination of urine, abnormally shaped urinary epithelial cells with hyperchromatic nuclei can be seen in one third of the cases. In the presence of BKV, intracellular inclusions stained with Papanicolaou dye may be noted. The presence of BKV can also be revealed by electron microscopy, ELISA or by the demonstration of the genomic structure of the virus. It is not easy to show BKV in the culture media. In our case, the presence of the BK virus in urine was detected by the PCR method.

Renal failure is the main toxicity of CDV, therefore serum creatinine and urine protein levels should be evaluated before each CDV administration. CDV should be used along with oral probenecid and intravenous physiological saline solution. In the present case, in the treatment of hemorrhagic cystitis caused by the BK virus with cidofovir, acute proximal tubular damage developed, and hemodialysis treatment had to be initiated in spite of prophylaxis with probenecid. In this case report, the management of acute proximal tubular damage due to the use of cidofovir in hemorrhagic cystitis caused by BK virus in a patient with T-lymphoblastic lymphoma in remission who underwent allogeneic stem cell transplantation, was presented. Although hemorrhagic cystitis caused by chemotherapy protocol is frequently seen in the preparatory stage of bone marrow transplantation, acute proximal tubular damage and renal failure due to CDV used in the treatment of serious HS cases have attracted attention as a relatively rare complication.

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Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – S.I.G., M.T.Y., E.G.; Design – S.I.G., M.T.Y., E.G.; Supervision – S.I.G., I.K.; Resources – S.I.G., P.S., M.N.M.; Materials – S.I.G., P.S., M.N.M.; Data Collection and/or Processing – S.I.G., E.G., P.S., M.N.M.; Analysis and/or Interpretation – S.I.G., E.G., P.S., M.N.M.; Literature Search – P.S., M.N.M.; Writing– S.I.G., M.T.Y., E.G.; Critical Review – S.I.G., I.K.
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Case Report – Andrology

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Testicular Torsion and Contralateral Torsion of the Appendix Testis

Testis Torsiyonu ve Kontralateral Apendiks Testis Torsiyonu

Oguzhan Yusuf Sonmez, Mehmet Sevim, Halil Ibrahim Ivelik, Burak Isler, Bekir Aras

Department of Urology, Kutahya Health Science University Faculty of Medicine, Kutahya, Turkey

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Corresponding Author: Halil Ibrahim Ivelik / Department of Urology, Kutahya Health Science University Faculty of Medicine, Kutahya, Turkey / halib_ive@hotmail.com ORCID ID: 0000-0001-5298-0045

Abstract

Testicular torsion is a urological emergency that results in deterioration of the blood supply of the testicle and ischemia as a result of the rotation of the spermatic cord around itself. It may show a wide clinical variety with inflammatory manifestations varying from mild abdominal pain to severe scrotal pain. Orchiectomy may be required in cases which are delayed and cannot be operated urgently. Torsion of the testis and epididymis are other frequently seen causes of acute scrotum in children. Growth of masses and hormonal stimulation in the adolescent age cause an increase in the tendency of the torsion of appendix testis which have a small pedicle and epididymis. In the presence of sudden scrotal pain, testicular torsion should be considered, if there is clinical suspicion, patients should be evaluated with color doppler ultrasound (CDUS) and scrotal exploration should be performed immediately. A 20-year-old male whose clinical picture, and scrotal ultrasonography suggested the presence of testicular torsion is presented in this case report.

Keywords: acute scrotum, testicular torsion, torsion of the appendix testis

Öz

Testis torsiyonu; spermatik kordun kendi etrafında dönmesi sonucu testisin kanlanmasının bozulması ve iskemi ile sonuçlanan bir ürolojik acildir. Hafif karın ağrısından, şiddetli skrotal ağrıya kadar enflamatuar bulguların olduğu geniş bir klinik çeşitlilik gösterebilir. Gecikmiş ve acil tedavi edilemeyen vakalarda orşiektomi gerekebilir. Apendiks testis torsiyonu ve epididim torsiyonu çocuklarda sık görülen bir diğer akut skrotum nedenidir. Adelösan çağda kitlelerinin büyümesi ve hormonal stimülasyon, küçük bir pediküle sahip appendiks testis ve epididimisin torsiyone olma eğiliminin artmasına sebep olur. Ani gelişen skrotal ağrı varlığında testis torsiyonu akla gelmeli, klinik şüphe duyulursa Doppler ultrason ile değerlendirilmeli ve skrotal ekplorasyon vakit kaybetmeden yapılmalıdır. Bu vaka sunumunda kliniği ve skrotal ultrasonografisi testis torsiyonu düşündüren 20 yaşındaki olgu sunulmaktadır.

Anahtar kelimeler: akut skrotum, testis torsiyonu, apendiks testis torsiyonu

ORCID ID: O.Y. Sonmez 0000-0003-1538-867X **M. Sevim** 0000-0002-7571-7669 **B. Isler** 0000-0002-6536-0619 **B. Aras** 0000-0002-7020-8830

Introduction

Testicular torsion (TT) is one of the urological surgical emergencies. Failure to receive adequate treatment in time may result in the loss of the testicle. TT is divided into extravaginal and intravaginal torsions. Extravaginal torsion is frequently seen in prenatal period and newborn infants [1,2]. It may present with a firm and a non-transilluminating bluish scrotal mass. color doppler ultrasonography (CDUS) usually does not show signs of vascular torsion. Detorsion cannot be applied manually. It is generally not possible to achieve detorsion surgically which usually requires orchiectomy. Although orchiopexy can be performed on the contralateral testicle during orchiectomy the evidence-based logic of this practice is controversial. Intravaginal torsion; is most common between the ages of 12-18 years. Its sudden onset clinic is usually accompanied by moderate or severe scrotal pain which must be treated urgently. In suspicious cases, clinical examination is performed with or without anesthetic block and scrotal palpation should be tried to see whether the lower pole of the epididymis is separated from the lower pole of the testicle. In doubtful cases, testicular blood flow should be evaluated by CDUS. Scrotal exploration should not be delayed in the presence of clinical uncertainty.

Torsion of the appendix testis and appendix epididymis occurs in adolescents due to their small pedicles as they turn around more easily. It is generally observed in the patient group above the age of 16. The clinical picture is in the form of a palpable painful mass in or on the testicle. In the torsion of appendix testis, a blue dot sign can be observed on the scrotum skin [3]. Scrotal exploration should be performed, if the torsion of the spermatic cord is suspected.

Case Presentation

Our case was a 20-year-old male patient who referred to our clinic with pain in both testicles (more severe in the right testicle) for three days. In the examinations that were performed on the patient, no abnormalities were found in the complete urinalysis, biochemistry parameters, and hemogram. In the physical examination of the patient who was diagnosed as acute scrotum both testicles were painful. Additionally the pain increased with elevation of the testis. Scrotal color doppler ultrasonography was performed, which revealed that the contours of both testicles were normal, the parenchyma was homogeneous, and torsion was detected in the distal part of the left spermatic cord. The blood supply of the left testicle was decreased compared to the right.

After pre-diagnosis of left testicular torsion, scrotal exploration was performed. Torsion of the left spermatic cord was detected, so detorsion was performed **(Figure 1)**. During follow-up, improvement in the left testicular blood flow was observed with colour change on superficial testicular tissue and testis was fixed to a left scrotal dartos pouch which was prepared priorly during the procedure. Right scrotal exploration performed priorly because of patient had significant right scrotal pain. On the other hand ischemic and thrombosed right appendix testicle was observed **(Figure 2)**. The appendix of the testis was excised from its ischemic pedicle, and right testicle was fixed to the scrotum.

Discussion

Torsion of the spermatic cord is a rare disease commonly seen in adolescent males. Its incidence is 1/4000 in the male population under 25 years old. Although sudden scrotal pain is usually seen in the torsion of the spermatic cord, some children may experience less pain with slow onset [4]. The differential diagnosis includes traumatic epididymitis, acute hydrocele, inguinal hernia, testicular tumours, and Henoch-Schönlein purpura. One of the helpful tools in the differential diagnosis is "Prehn's sign". The Prehn's sign is the change in the intensity of pain with the elevation of the testicle. During the elevation of the testicle, the pain increases in torsion, while it is relieved in epididymitis and orchitis. In these cases, scrotal exploration should be performed as soon as possible in case of evidence of torsion in the clinical history and physical examination.

Definitive diagnosis of testicular torsion is made with color doppler ultrasound, while blood flow is visualized on the normal side but is absent on the affected side. In less than 360 degrees of torsion, scrotal color doppler ultrasonographic examination may show a small amount of blood flow in the symptomatic testicle which can be a misleading false- negative result. In orchitis, parenchymal echoes decrease heterogeneously; in the rare presence of parenchymal hemorrhage, an increase in echogenicity may be observed [5].

Torsion of the appendix testis is the most common cause of scrotal pain in children [6]. Spontaneous recovery may be achieved non-operatively. Scrotal color doppler ultrasonography is an imaging method that can be used in clinically suspected cases. If there is a suspicion of torsion or an increase in

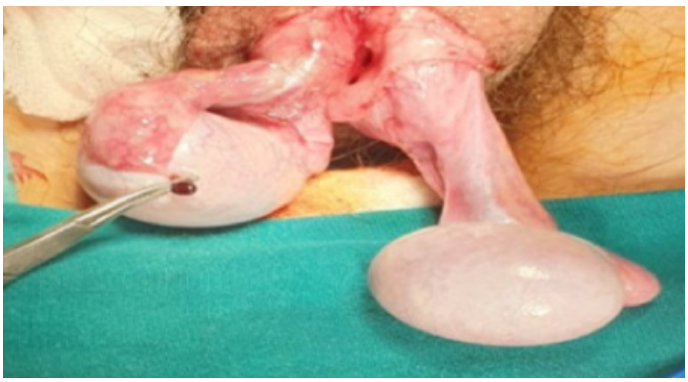

Figure 1. The left testicle and detorsioned right appendix testis and visually improved blood flow

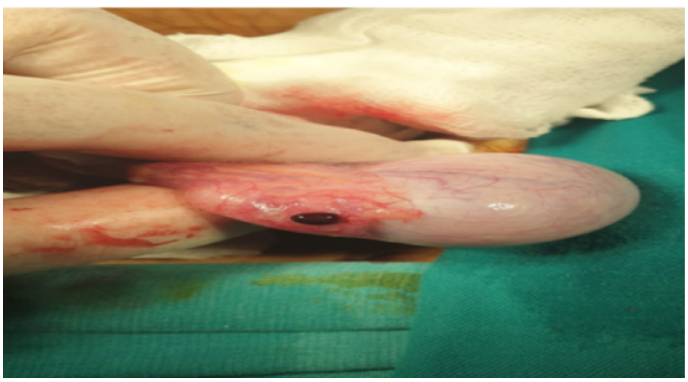

Figure 2. Torsion of the right appendix testis

inflammatory findings, immediate exploration should be performed and the torsioned appendix testis should be excised away from its ischemic pedicle [7].

In our case, after the patient presented with acute scrotal pain and the absence of left testicular blood flow detected in doppler ultrasonography, emergency scrotal exploration was performed. Torsion of the left testis and the right testicular appendix are rare causes of the acute scrotum, which were contralaterally observed in our case. It should be kept in mind that the torsion of the appendix testis is more common in the pediatric age, however it may be present in adolescents and rarely it is accompanied with testicular torsion as was in our case.

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

Publication: The results of the study were not published in full or in part in form of abstracts.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – O.Y.S., M.S.; Design – O.Y.S., M.S.; Supervision – B.A.; Resources – M.S., H.I.I., B.I.; Materials – M.S., H.I.I., B.I.; Data Collection and/or Processing – O.Y.S., M.S., H.I.I., B.I.; Analysis and/or Interpretation – O.Y.S., M.S., H.I.I., B.I.; Literature Search – M.S., H.I.I., B.I.; Writing – O.Y.S., M.S., H.I.I.; Critical Review – O.Y.S., B.A.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Case Report – Urological Oncology

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Tumor Surgeries Delayed Due to the COVID-19 Pandemic; Renal Cell Carcinoma Progressing from Stage T1b to T3b: A Case Report

COVID-19 Pandemisi Döneminde Geciken Tümör Cerrahileri; Evre T1b'den T3b'ye İlerleyen Renal Hücreli Karsinom: Olgu Sunumu

Kadir Karkin, Hakan Ercil, Umut Unal, Guclu Gurlen, Ferhat Ortoglu, Ediz Vuruskan

Department of Urology, University of Health Sciences, Adana City Training and Research Hospital, Adana, Turkey

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Corresponding Author: Kadir Karkin / University of Health Sciences, Adana City Training and Research Hospital, Department of Urology, Adana, Turkey / kadir_karkin@msn.com ORCID ID: 0000-0002-4324-3032

Abstract

COVID-19 is a highly contagious disease. This condition affects the decision of both the patient and the surgeon about the surgery of newly diagnosed cancer patients and it may also result in delays in cancer surgeries because of the limitations in healthcare applications. In our particular case, it was aimed to present the transition of the cancer from the localized stage to distant spread stage cancer since the patient who was pre-diagnosed with RCC and who was recommended surgery, did not want to undergo surgery due to COVID-19 pandemic and its risks. Our case was a 49-year-old female patient. In her computed tomography, a 58x70 mm heterogeneously enhancing solid lesion which showed exophytic extension from the middle zone of the right kidney to the lower pole was observed. Surgery was recommended for the patient but the patient claimed that she did not want to undergo surgery due to the risk of COVID-19 pandemic. The patient made an application for the surgery 8 months later. The new magnetic resonance imaging of the patient showed that there was a mass lesion of approximately 76x76x80 mm in size, which involved middle-lower part of the right kidney and extended into the opening of the renal vein VCI by invading the renal vein. Radical nephrectomy and thrombectomy procedure was applied to the patient with RCC? tumor. Due to psychosocial problems caused by the pandemic, surgeries are delayed and an acceleration of the cancer progression from the localized stage to the distant spread stage occurs indispensably.

Keywords: pandemic, COVID-19, renal cell carcinoma, renal tumor surgery

Öz

COVID-19 oldukça bulaşıcı bir hastalıktır. Bu durum, hem hasta hem de cerrahın yeni teşhis konmuş kanser hastalığının ameliyatı konusundaki kararlarını etkilediği gibi, sağlık uygulamalarındaki kısıtlamalar nedeniyle kanser ameliyatlarında gecikmelere de neden olabilmektedir. Bu olgumuzda RCC ön tanısı alan ve cerrahi önerilen hastanın COVID-19 pandemisi ve getirdiği riskler nedeniyle ameliyat olmak istememesi sonucunda hastalığın lokal evreden ileri evre kansere geçişini sunmayı amaçladık. Olgumuz 49 yaşında kadın hastaydı. Bilgisayarlı tomografisinde sağ böbreğin orta bölgesinden alt pole doğru ekzofitik uzanım gösteren, 58x70 mm boyutlarında ve heterojen kontrastlanan solid lezyon izlendi. Hastaya ameliyat önerildi ancak hasta, COVID-19 salgını riski nedeniyle ameliyat olmak istemediğini ifade etti. Hasta operasyon için 8 ay sonra başvurdu. Hastanın yeni manyetik rezonans görüntülemesinde sağ böbreğin orta-alt kısmını kaplayan ve renal pelvisi dolduran, renal veni invaze ederek renal venin VCI'daki açılma yerine kadar uzanan, yaklaşık 76x76x80 mm boyutlarında kitle lezyonu olduğu görüldü. RCC? tümörü olan hastaya radikal nefrektomi ve trombektomi işlemi uygulandı. Pandeminin neden olduğu psikososyal sorunlar nedeniyle ameliyatlar gecikmekte ve kanserin lokalize aşamadan uzak yayılma aşamasına ilerlemesinde bir artış kaçınılmaz olarak ortaya çıkmaktadır.

Anahtar kelimeler: pandemi, COVID-19, renal hücreli karsinom, böbrek tümör cerrahisi

ORCID ID: **H. Ercil** 0000-0001-7103-7597 **U. Unal** 0000-0003-4040-0044 **G. Gurlen** 0000-0002-7830-5010 **F. Ortoglu** 0000-0002-1986-5181 **E. Vuruskan** 0000-0002-3446-0430

Introduction

Novel coronavirus of 2019's (2019-nCoV) infection has rapidly spread to China and many other countries since it was first emerged in Wuhan Province of China in December 2019 [1] and it has become a major global health issue. The virus was named 2019-nCoV first temporarily by the International Virus Taxonomy Committee but then it was renamed as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [2]. Hyperinflammation and immunosuppression are the two most important entities in COVID-19 disease [3]. Fever, cough, shortness of breath, myalgia, headache and diarrhoea are the most common symptoms. The most common underlying diseases are reported as cardiovascular diseases, hypertension, and diabetes mellitus [4].

Renal cell carcinoma (RCC) is one of the deadliest urological tumors, accounting for 2-3% of all adult malignancies [5]. RCC is the one of the risk factors which pose a higher risk for Covid-19 infection followed by age >60, arterial hypertension, diabetes, obesity and smoking [6]. Therefore, many patients who were diagnosed with RCC during this pandemic period are at risk of developing this viral infection and its life-threatening complications if they were treated surgically [7]. In newly diagnosed cases with cancer, moreover, Covid-19 affects the decision of both the patient and the surgeon as it is a high contagious disease and the cancer surgeries are delayed due to limited healthcare applications and resources [8,9].

In this particular case, we aimed to present the transition of the disease from the localized stage to distant spread stage cancer as the patient who was pre-diagnosed with RCC and who was recommended surgery did not want to undergo surgery due to the Covid-19 pandemic and the risks it brought.

Case Presentation

Our case in this study was a 49-year-old female patient. The patient was under follow-up due to left kidney cyst causing right flank pain and weight loss 10 kg in the previous 6 months. In the ultrasonography of our case, a heterogeneous solid mass of 5 cm in the right kidney was observed. The patient had hypertension and struma history, but she did not have undergone any surgical intervention before. The patient was taking levothyroxine sodium and perindopril arginine for the treatment of these diseases. Complete blood count and serum biochemistry values were normal at the time of application. Karnofsky performance scale index was 90% (ECOG-WHO performance scale index score corresponds to 0). Contrast-enhanced thorax and abdominal computed tomography (CT) were requested. Thorax CT of the patient was unremarkable, but a sharply demarcated, and heterogeneously enhancing 58x70 mm solid lesion (PADUA score 8) with exophytic extension from the middle zone of the right kidney to the lower pole was observed. Abdominal aorta, vena cava inferior (VCI) and other major abdominal vessels were normal . No pathological lymph nodes were reported in the abdomen **(Figure 1)**. Laparoscopic radical nephrectomy was recommended for the patient with a stage T1b tumor. However, the patient stated that she did not want to undergo surgery due to the COVID-19 pandemic. The patient was informed that the tumor could progress aggressively and that surgery had to be performed. The patient, who wanted to take some time to think, did not apply to our clinic to undergo surgery for 8 months. She

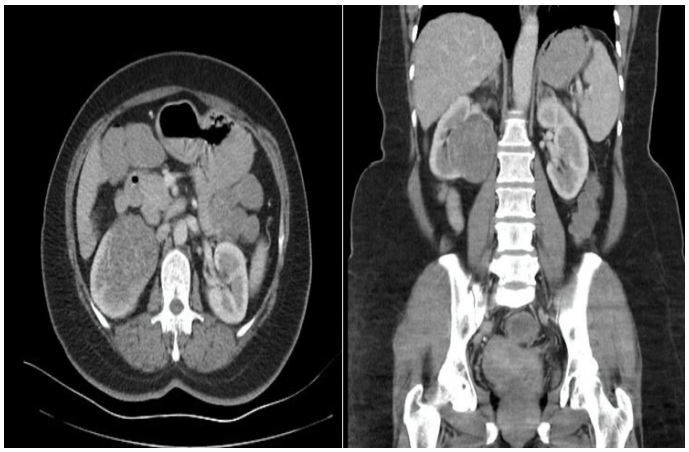

Figure 1. CT revealed a solid lesion which showed exophytic extension from the middle zone of the right kidney to the lower pole and which was sharply demarcated, 58x70 mm in size

was admitted with an abdominal MRI taken in a public hospital in his province 8 months later. Her MRI revealed a heterogeneous mass lesion of approximately 76x76x80 mm in size, with irregular lobulated contours involving middle-lower part of the right kidney and renal pelvis and extending into the opening of the renal vein into the VCI by invading the renal vein. After intravenous injection of the contrast agent, a heterogeneous enhancement in the mass lesion was observed. Renal parenchyma got thinner due to the mass lesion (PADUA score 11). Based on radiological findings, the patient was informed that RCC was suspected, and clinical evaluation or excision was recommended **(Figure 2)**. In this stage, open radical

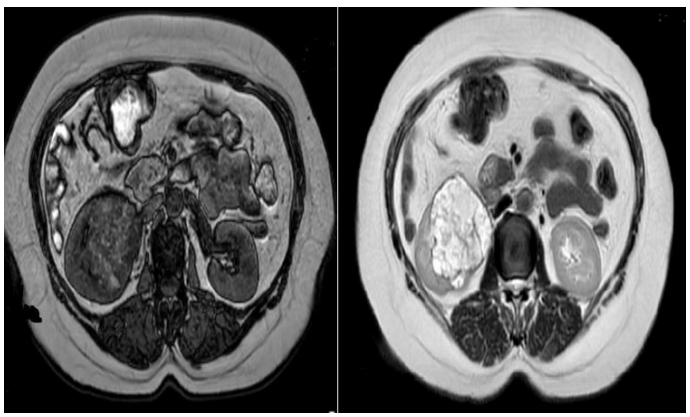

Figure 2. MRI revealed a heterogeneous mass lesion of approximately 76x76x80 mm in size, with irregular lobulated contours, invading middle-lower part of the right kidney and renal pelvis and extending to the opening of the renal vein into VCI

nephrectomy and thrombectomy procedure was performed upon the approval of the patient with stage of T3b RCC tumor. The patient was discharged from the hospital when pathological diagnosis was reported as Fuhrman grade 2 clear cell RCC. No recurrence was observed in control thorax and abdominal CT images obtained in the 3rd month follow-up.

Discussion

In COVID-19 pandemic, it has become too difficult to provide care for immunocompromised patients and patients suffering from cancer. Even during a pandemic, cancer patients need timely diagnosis, evaluation and treatment. It was revealed that

cancer patients who were infected with COVID-19 are 3.5 times more likely to be admitted to the intensive care unit (ICU) or mechanical ventilation when compared with general population. Concurrently, limited resources in treatment environments, including administrative staff and specialists, hinder the routine care of these patients [8,10]. In addition, the current focus on the spread of COVID-19 infection around the world draws all the attention of the public and this may push aside the psychosocial consequences of the outbreak in individuals who were affected by the disease and the general population. Psychological problems emerging in connection with this global issue may turn into long-term health problems, isolation and stigmatization of patients. Health precautions in the global dimension should be taken to deal with psychosocial stress factors which are associated with the use of isolation, and quarantine measures, fear, and defencelessness, particularly among the general population [11]. These psychosocial problems have led the oncology community to experience unprecedented challenges, especially during the extraordinary period. Therefore, other specialty fields which are regularly involved in the diagnosis, active treatment and long follow-up of cancer patients, as well as oncologists, should consider how to balance the delay in cancer diagnosis or treatment against a potential risk of COVID-19 and plan the process accordingly. They should also reduce the risks of the disruptions in the patient care in line with social distancing and properly manage the appropriate distribution of limited healthcare resources [6]. When we consider this situation regarding RCC, these patients consist of a heterogeneous population. While some of the tumor treatments can be delayed safely, some others are aggressive and need emergent surgery. For example, patients with cT1a tumors (and complex cysts, Bosniak III/IV) should be taken under active surveillance and delayed intervention. The cases of cT1b-T2a/b should be treated with partial or radical nephrectomy (in some selected cases of T1b-T2a ≤7cm, surgery may be delayed for 60-90 days). Locally progressive tumors progressed (≥cT3 and or N +) should be resected immediately. If possible, minimally invasive surgery and early hospital discharge should be encouraged [12].

It is quite difficult to manage cancer patients during the pandemic considering their vulnerable situations and the aggressive nature of their underlying diseases. When the psychosocial problems caused by the pandemic accompany this situation, surgeries are delayed and the progression of cancers from the localized stage to the distant spread stage accelerates.

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Clinical Image – Genitourinary Radiology

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Multipl Masses Diagnosed as Oncocytoma in Both Kidneys

Her İki Böbrekte Onkositom Tanılı Multipl Kitleler

Mustafa Orhan Nalbant, Omer Yildiz, Elif Hocaoglu, Ercan Inci

Department of Radiology, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey

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Corresponding Author: Mustafa Orhan Nalbant / University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Department of Radiology, Bakirkoy, Istanbul, Turkey / m.nalbant@saglik.gov.tr ORCID ID: 0000-0002-5277-9111

A 67-year-old male patient who had multiple solid masses in both kidneys in another center ultrasound examination was referred to our clinic for further examination. He had no known chronic or syndromic disease. The patient was evaluated with dynamic contrast enhanced upper abdominal magnetic resonance imaging (MRI). In MRI, homogeneous enhancing solid lesions with hypointense central stellate scar and non-enhancing cysts was seen in both kidneys. Diffusion restriction was observed in the periphery of the solid lesion in the lower pole of right kidney which was considered suspicious for malignancy and biopsy was performed from this lesion **(Figure 1)**. Pathology result reported as oncocytoma so follow-up decision was made for the patient. In the follow-up, the masses in the left kidney increased in size and diffusion restriction developed in the upper pole of the left kidney **(Figure 2)**. This lesion was also biopsied because of suspect imaging finding, the result was reported as oncocytoma as well. At the same time, the patient was evaluated for tuberous sclerosis and Birt-Hogg-Dube syndrome as they associated with multiple bilateral oncocytomas. There was no similar signs, semptoms and imaging findings related to these genetic syndromes in the family members of the patient. Informed written consent was obtained from the patient for this report.

Renal oncocytoma is a benign renal tumor and up to three-quarters of patients with a renal oncocytoma are asymptomatic [1]. So its diagnosis is incidental on abdominal imaging. Possible signs and symptoms of a renal oncocytoma include hematuria, flank pain and an abdominal mass [2].

Both oncocytomas and renal tumors show similar enhancement but the central scar and the inversion pattern of enhance-

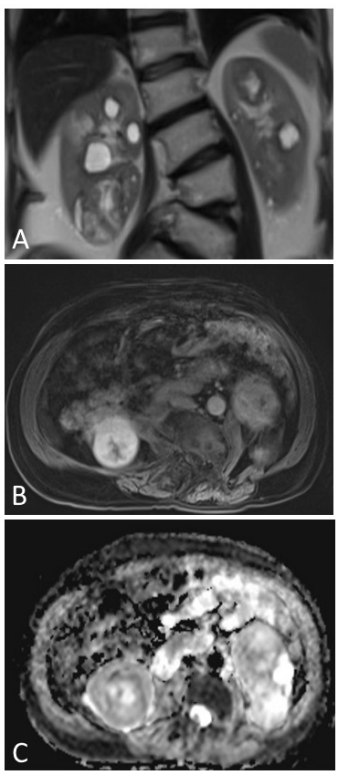

Figure 1. A-Homogeneous enhancing, B-Multipl solid lesions with hypointense central stellate scar and non-enhancing cysts in both kidneys, C- Diffusion restriction was observed in the periphery of the solid lesion in the lower pole of right kidney (Coronal and axial view of enhanced abdominal MRI)

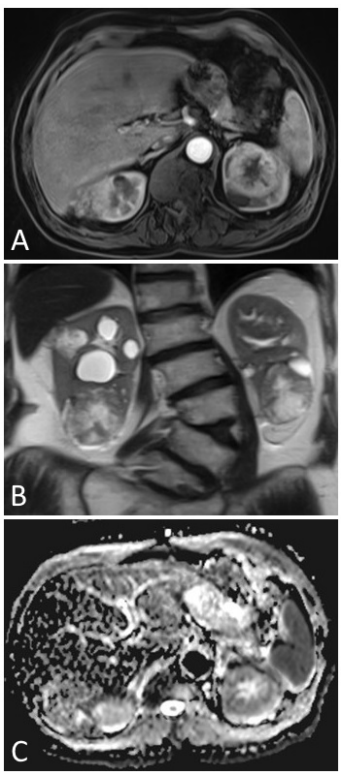

Figure 2. A- Although having homogeneous enhancement with hypointense central stellate scar, B- Solid lesions in the left kidney increased in size, C- Peripheral diffusion restriction developed in the upper pole of the left kidney on follow-up MRI (Coronal and axial view of enhanced abdominal MRI)

ORCID ID: O. Yildiz 0000-0003-4774-9281 **E. Hocaoglu** 0000-0002-2506-4794 **E. Inci** 0000-0002-3791-2471

ment have been associated with oncocytomas [3]. The "central stellate scar" sign refers to a central zone of fibrous connective tissue, with the bands of fibrosis radiating toward the periphery of the lesion is a characteristic radiological finding described of renal oncocytoma [4]. Central scar cannot be distinguished on imaging from the necrosis commonly found in renal cell carcinoma [5].

The underlying cause of most isolated renal oncocytomas is unknown; however, multiple oncocytomas can occur in people with certain genetic syndromes such as tuberous sclerosis and Birt-Hogg-Dube syndrome. Isolated oncocytomas usually seen as a single tumor affecting one kidney, on the other hand renal oncocytomas that are part of a genetic syndrome often affects both kidneys with multipl tumors [6,7].

Renal oncocytomas which are part of a genetic syndrome are associated with mutations. Birt-Hogg-Dube syndrome is caused by mutations in FLCN gene while tuberous sclerosisis caused by mutations in the TSC1 or TSC2 genes [8].

It can be hard to distinguish oncocytoma from renal cell carcinoma with only imaging studies. Biopsy is often needed to confirm the diagnosis [9]. Most patients are treated with surgery to confirm the diagnosis since the distinction between oncocytoma and renal cell carcinoma can not be made with imaging methods alone. Whether oncocytoma is strongly considered, partial nephrectomy can be done as a more conservative method [10].

Keywords: central stellate scar, magnetic resonance imaging, oncocytoma, renal mass

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