Original Article

Virtual Reality Simulator Face Validity for Topographic Real Situation of Inflated Abdomen

Tuncay Tas, Basri Çakiroğlu[1], Esra Akdeniz[2], Ismet Aydin Hazar[3], Can Balci[3]

Department of Urology, Istanbul Cerrahi Hospital, Nisantasi University College of Health Sciences, [1]Department of Urology, Hisar Intercontinental Hospital, Galata University, [2]Department of Medical Education, School of Medicine, Marmara University, [3]Department of Urology, Taksim Teaching and Research Hospital, Istanbul, Turkey

Abstract

Objective: The aim of this study is to investigate the face validity of LapSIM® (haptic feedback Xitact™ IHP, Mentice AB, Sweden) for the topographic real condition of the inflated abdomen in upper urinary tract laparoscopic interventions. **Materials and Methods:** The present study was conducted with 30 urologists with experience in transperitoneal laparoscopic renal surgery. Surgeons were divided into three groups: novices, intermediate experience, and experts. After performing the tasks, the participants were then asked to finish a five-item questionnaire regarding the face validity of the simulator. Participants answered questions with ratings from 1 (not realistic/useful) to 5 (very realistic/useful). **Results:** The mean age of the study group was 38.33 ± 5.45 (29–47) years. The mean years of experience of the doctors were 4.27 ± 1.89 (1–7) years. All the variables showed significant differences from the ideal value of 5. We also tested whether the medians differed from 3, and the restrained body posture of the surgeon, the monitor position, and the trocar position not show significance with one-sided P value of $P = 0.825$, $P = 0.992$, and $P = 0.265$, respectively. **Conclusion:** Although the LapSIM® virtual reality simulator provides face validity for the topographic real condition of the inflated abdomen, it should be improved.

Keywords: *Face validity, laparoscopy, LapSIM, simulator, surgeon*

Introduction

For competence in laparoscopic surgical practice, knowledge, reasoning, and training are required as well as skill.[1] Challenging urological laparoscopic interventions have created the need for training models as in other branches.[2-4] Simulators, animal models, and cadaveric models are used in laparoscopic manual skill training in urology.[5,6] Box trainers (BTs) and virtual reality simulators (VRSs) are frequently used in training centers.[7]

Virtual reality training has become one of the mainstays of surgical training outside the operating room.[8] Conventional BTs do not aim to simulate operations exactly. VRSs are created to simulate one to one. VRSs are designed as a virtual environment in which basic laparoscopic tasks can be performed. The use of video and instrumentation in laparoscopy training has provided VRS with a unique field as a teaching tool. After the developments in software technology in recent years, the reality in the image has been increased. The system has models with and without haptic feedback. Haptic feedback has been shown to improve the fidelity, realism, and thus the training effect of VRSs.[9]

LapSIM® is one of the VRSs with the most validation studies. The aim of this study is to investigate the face validity of LapSIM® (haptic feedback Xitact™ IHP, Mentice AB, Sweden) for the topographic real condition of the inflated abdomen in the upper urinary tract laparoscopic interventions.

Materials and Methods

The study was conducted with 30 urologists with experience in transperitoneal laparoscopic renal surgery. Surgeons were divided into three groups: novices with 20–50 primary surgeries ($n = 7$), intermediate experience with 50–100 primary surgeries ($n = 14$), and experts ($n = 9$) with more than 100 primary surgeries.

Simulator

The LapSIM® used in our study is a VRS that allows basic laparoscopic skills and some procedures to be applied.[10,11] LapSIM® basic skills module training

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Address for correspondence:
Dr. Basri Çakiroglu,
Saray Mah.Siteyolu
Cad. No. 7 34768,
Ümraniye, Istanbul, Turkey.
E-mail: drbasri@gmail.com

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program (Haptic LapSIM® Surgical Science AB, Sweden) was used in the study. The system consisted of an 18-inch Thin Film Transistor (TFT) monitor, a laparoscopic interface module (Immersion Inc., San Jose, CA), a box, and a foot pedal. The software was dual processor Pentium IV, Microsoft Windows XP operating system, and video card 256 MB RAM and Geforce [Figure 1]. The box system consisted of two systems for hanging the hand tool and an unrounded space. The system and all modules were compatible with haptic feedback.

Exercises

LapSIM® basic skills training system consists of 11 modules [Figure 2]. Each module of the simulator training has three phases as easy, intermediate, and difficult. It was requested to complete tasks involving 11 basic skill modules such as camera navigation, instrument navigation, coordination, grasping, cutting, clip applying, lifting and grasping, fine dissection, seal and cut, suturing, precision, and speed. The short course is completed approximately 60 min.

After performing the tasks, the participants were then asked to finish a five-item questionnaire regarding the face validity of the simulator. Participants answered questions with ratings from 1 (not realistic/useful) to 5 (very realistic/useful) [Table 1].

Statistical analyses

The variables were described with mean (standard deviation), median, first quantile (Q1), third quantile (Q3), and minimum and maximum values. The medians of restrained body posture of the surgeon, monitor position, trocar position, tissue distance, and limited field of movement and motional capability were tested whether they were less than the ideal (a perfectly realistic compared to real laparoscopic cases) value of 5 and also from 4 to 3 using the one-sample one-sided Wilcoxon-signed rank test. The boxplots for each variable were also displayed using the jittered observations. Kruskal–Wallis test was employed to compare doctors classified with respect to their experiences in terms of their opinions about the VRS. $P < 0.05$ was considered significant. R statistics program was used for all calculations.

Figure 1: LapSIM® virtual reality simulator (Surgical Science AB) with haptic feedback Xitact™ IHP, Mentice AB, Sweden. IHP: Instrument haptic ports

Results

Thirty doctors were included in the study. The mean age of the study group was 38.33 ± 5.45 (29–47) years. The mean years of experience of the doctors were 4.27 ± 1.89 (1–7) years.

The medians of restrained body posture of the surgeon (3.06 [0.45]), monitor position (3.23 [0.50]), trocar position (2.93 [0.52]), tissue distance (2.70 [0.47]), and limited field of movement and motional capability (2.63 [0.49]) were tested whether they were less than the ideal value of 5 and the results are given in table. All the variables showed significant differences from the ideal value of 5. We also tested whether the medians differed from 3 and the restrained body posture of the surgeon, the monitor position, and the trocar position did not show significance with one-sided P values of $P = 0.825$, $P = 0.992$, and $P = 0.265$, respectively [Table 2]. The table show whether the opinions of doctors about the properties of the VRS changed according to their experience level [Table 3].

The boxplots of each variable are given in Figure 3. From the boxplots, it was seen that monitor position, the

Table 1: Posttask questionnaire and questions: ratings from 1 (not realistic/useful) to 5 (very realistic/useful)

Is the restrained body posture of the surgeon representative for the real situation?
Is the position of monitor and devices representative for the real situation?
Are the trocars entry slots representative for the real situation?
Is tissue distance representative for the real situation?
Is limited field of movement and motional capability representative for the real situation?

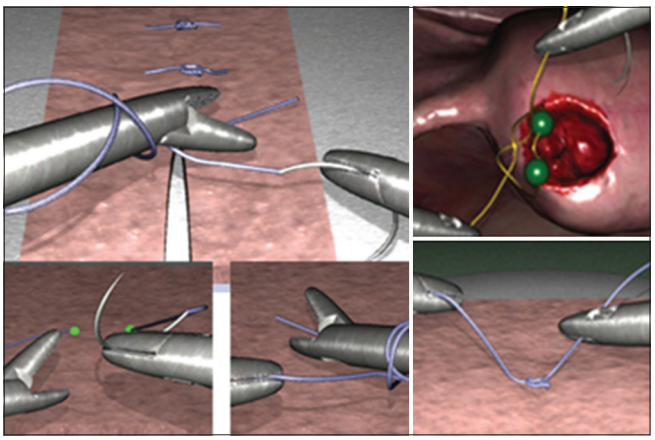

Figure 2: LapSIM® basic skills training suturing and knot models

Table 2: Descriptive statistics

	Mean±SD	Median	Minimum/maximum	Q1	Q3	P^a	P^b
Age (years)	38.33±5.45	37.5	29/47	34.25	43.5	-	-
Experience (years)	4.27±1.89	4	1/7	3	6	-	-
Restrained body posture of the surgeon	3.06±0.45	3	2/4	3	3	<0.001	0.825
Monitor position	3.23±0.50	3	2/4	3	3.75	<0.001	0.992
Trokar position	2.93±0.52	3	2/4	3	3	<0.001	0.265
Tissue distance	2.70±0.47	3	2/3	2	3	<0.001	0.002
Limited field of movement and motional capability	2.63±0.49	3	2/3	2	3	<0.001	0.001

[a]*P* values were obtained by testing the median was below 5, [b]*P* values were obtained by testing the median was below 3. SD: Standard deviation

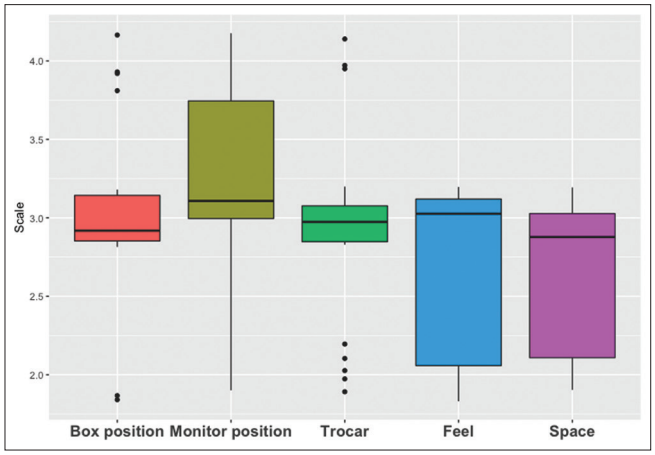

Figure 3: Boxplots for variables (Box position: Restrained body posture of the surgeon, feel: tissue distance, and space: Limited field of movement and motional capability)

restrained body posture of the surgeon and trocar position observations were centered around the median 3; however, for tissue distance and limited field of movement and motional capability, many observations are below the median level 3.

Discussion

The restrained body posture of the surgeon, the monitor position, and the trocar position were seen as close imitations of the real environment. LapSIM® showed face validity in 3 of 5 parameters evaluated in our study. Based on the participants; feedback, LapSIM® was considered to be moderately realistic. Doctors' opinions did not differ significantly due to their level of experience.

The restrained body posture of the surgeon representative

In our study, laparoscopists reported that LapSIM® is partially representative in terms of the surgeon's mandatory posture in transperitoneal laparoscopy of the upper tract procedures. The mean value in all three of novices, intermediate experience, and experts has been determined to be above 3. Surgeons generally stated that due to the more comfortable posture, it may partially give the same fatigue. LapSIM® partially presents the humanoid structure that can give this posture condition and the condition that muscle groups should be accustomed to.

The position of monitor and devices

In our study, it attracted attention as the closest imitation by taking the highest mean value. According to experience, the mean value was found to be above 3 in all three groups. Surgeons reported that the monitor position partially represents the actual situation.

The trocars entry slots

Surgeons reported that trocars entry slots were partially representative of the real situation. However, unlike the other two groups, expert surgeons have an average of <3. Depending on the type of surgery, the distance between the trocars and the angles they make during operation vary. In LapSIM®, the fact that the distances of the trocars cannot be adjusted to each other, and although the upper tract attempts make an angle close to parallel to the ground, working with an angle close to 45° may have been effective in this results.

Surgeons reported that tissue distance and limited field of movement and motional capability were not representative. It has been reported that the area to be studied and the trocars do not meet the support point, i.e., the tissue depth, in laparoscopic interventions, and that the manipulations are performed much more easily in LapSIM®, which has a larger working area.

Shetty *et al*. assessed the face validity of medical students, surgical residents (postgraduate years 1–5), fellows, and attending participants with a questionnaire. The curriculum improved my camera handling skills, the curriculum should be required for novices before assisting in the operating room, the feedback from the program is accurate, the curriculum is relevant to surgery, the curriculum is a valid training tool, and the curriculum is a valid testing tool. In this study, it was reported that LapSIM® camera navigation shows construct and face validity.[12] Schreuder *et al*. evaluated facial validity using a questionnaire consisting of 27 statements with novice (medical students), intermediate (residents), and expert (gynecologists and some senior residents who all performed more than 100 laparoscopic) participants. It

Table 3: Whether the opinions of doctors about the properties of the virtual reality simulator changed according to their experience level

Variables	Groups															*P*
	Novices (*n*=7)					Intermediate experience (*n*=14)					Experts (*n*=9)					
	Mean±SD	Median	Minimum; maximum	Q1	Q3	Mean±SD	Median	Minimum; maximum	Q1	Q3	Mean±SD	Median	Minimum; maximum	Q1	Q3	
Restrained body posture of the surgeon	3±0.58	3	2; 4	3	3	3.1±0.49	3	2; 4	3	3	3.1±0.32	3	3; 4	3	3	0.91
Monitor position	3±0	3	3; 3	3	3	3.3±0.63	3	3; 4	3	4	3.3±0.48	3	3; 4	3	3.75	0.32
Trocar position	3.14±0.69	3	2; 4	3	3.5	3±0.41	3	2; 4	3	3	2.7±0.48	3	2; 3	2.25	3	0.19
Tissue distance	2.57±0.534	3	2; 3	2	3	2.77±0.44	3	2; 3	3	3	2.7±0.48	3	2; 3	2.25	3	0.66
Limited field of movement and motional capability	2.57±0.534	3	2; 3	2	3	2.77±0.44	3	2; 3	3	3	2.5±0.527	2.5	2; 3	2	3	0.40

SD: Standard deviation

has been reported that there is a significant difference between subjects with different laparoscopic experience, and therefore, construct validity for the laparoscopic simulator can be established.[13]

Van Dongen *et al*. reported that LapSIM® provided construct validity by showing statistically significantly higher scores than novices for both overall score and efficiency, speed and precision parameters in experienced surgeons and surgical residents.[14] Woodrum *et al*. reported that LapSIM® showed construct validity, but some performance parameters did not differentiate between groups.[15] In a study conducted by Kovac *et al*. after completing 15 junior and senior residents and three skill tasks (lifting and grasping, cutting and clip application) in LapSIM®, construct validity could not be demonstrated for the total time, path length, angular path length, and tissue handling parameters.[16]

Although virtual reality training shows that it improves general skills such as suturing or cutting, there is limited predictive validity study evaluating whether they are ready to work on human subjects after training. Hogle *et al*. reported in their study with 21 surgical residents that basic LapSIM® training programs did not have predictive validity in many areas.[17] Radical nephrectomy performances of 12 urology residents in the pig model after LapSim training were evaluated by two surgeons and showed poor predictive validity.[18]

There is no widely accepted or recommended humanoid model for laparoscopic simulation. We think that the humanoid model pretentious VRS should simulate an inflated abdomen. In this state, it was wanted to be investigated in terms of face validity. Experienced surgeons were questioned by questionnaire, since it was thought that topographic measurements of the working area in VRS application could not be taken by us. Since easy and moderate cases such as cortical renal cyst resection, ureterolithotomy, and nephrectomy (benign) are the first operations recommended for those who start laparoscopy, the study was designed based on transperitoneal kidney intervention.

Although LapSIM® is one of the VRSs with one of the largest validation studies, literature is limited. In our study, the scenario in the real operation was evaluated with five parameters. It is aimed to present LapSIM® face validity new data to literature. Face validity is the extent to which the simulator is identical to real-life scenarios.[19] In our study, all the variables showed differences from the ideal value of 5 (all $P < 0.001$).

Conclusion

Although the LapSIM® VRS provides face validity for the topographic real condition of the inflated abdomen, it should be improved.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Endoscopic Treatment of Vesicoureteral Reflux with Macroplastique in Spinal Cord Injury Patients: A Comparison of Video-Urodynamic Parameters between Treated and Failed Cases

Vasileios Sakalis, Rachel Oliver[1], Peter Guy[1], Melissa Davies[1]

Department of Urology, Agios Pavlos General Hospital of Thessaloniki, Thessaloniki, Greece, [1]Department of Urology, Salisbury NHS Foundation Trust, Salisbury, England, UK

Abstract

Context/Objective: Vesicoureteric reflux (VUR) is a well-known complication of neurogenic lower urinary tract dysfunction. VUR results to progressive renal deterioration and eventually renal failure. Our aim was to assess the efficacy of Macroplastique bulking agent in managing VUR in spinal cord injury population and correlate the pre- and postintervention VUDS (Video-urodynamics) findings with the outcome. **Design:** Retrospective cohort study. **Participants:** Spinal cord injury patients with VUR, treated with Macroplastique, had pre- and postintervention VUDS and followed up for at least 12 months. **Interventions:** Macroplastique injection and video-urodynamics. **Outcome Measures:** The primary endpoint was the overall treatment rate of VUR at 3 months. The secondary outcomes were the overall treatment rate of VUR at 12 months, the success rate at 3 and 12 months, the need for additional treatments, and the comparison of VUDS parameters in treated versus failed cases. **Results:** Forty-eight patients and 62 refluxing ureteric units were studied. At 3-month follow-up, the overall treatment rate was 79.1%. The overall success rate (treated + improved) was 90.3%. There is a statistically significant difference in baseline cystometric capacity ($P = 0.047$), degree of reflux ($P < 0.01$), and bladder compliance ($P = 0.023$) between the treated and failed cases. **Conclusion:** Macroplastique is effective in the management of VUR in spinal cord injury population. It is minimally invasive, quick, with low complication rates. Care should be taken to treat the parameters of the neurogenic bladder that contributes to secondary VUR development such as detrusor overactivity and poor bladder compliance.

Keywords: *Macroplastique, neurogenic bladder, vesicoureteric reflux*

Introduction

Vesicoureteric reflux (VUR) is a well-known complication of neurogenic lower urinary tract dysfunction.[1] It is secondary to high bladder pressures and differs etiologically from primary VUR that is typical for pediatric population. VUR leads to progressive renal deterioration and eventually renal failure. Talbot and Bunts, in 1949, suggested that kidney damage in paraplegics results from the combination of pressure-related changes due to persistent hydronephrosis and ascending urinary tract infections.[2] Many studies have confirmed that VUR is not always simultaneous to involuntary detrusor contraction. Vírseda *et al.* suggested that in long-standing secondary VUR, it is possible that the antireflux mechanism is damaged and the reflux becomes primary.[3] The gold standard treatment is the open or laparoscopic surgical correction and has become nowadays less popular due to the new minimally invasive treatment options that show promising results.[4]

The use of Teflon for the endoscopic correction of VUR has been described in the early Eighties.[5] Since then, several bulking agents have been developed such as polydimethylsiloxane, polytetrafluoroethylene, dextranomer/hyaluronic acid, and glutaraldehyde cross-linked bovine collagen. Numerous investigators reported encouraging results mostly in pediatric population and primary VUR.[6] Macroplastique (polydimethylsiloxane) (Uroplasty Inc., Geleen, The Netherlands) is a solid, elastomeric silicone which is suspended in a hydrogel carrier.[6] Distant migration is limited by the particle sizes, which are greater than 100 μm.[7,8] Upon implantation, the hydrogel is substituted by body

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Address for correspondence:
Dr. Vasileios Sakalis, Department of Urology, Agios Pavlos General Hospital of Thessaloniki, Thessaloniki, Greece.
E-mail: vsakkalis@hotmail.com

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Website: www.hellenicurologyjournal.com

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fluids and host fibroblasts deposit collagen around the Macroplastique particles which hold them in place.[7,8] The hydrogel is later removed by the reticuloendothelial system and excreted unmetabolized from kidneys.[7]

There is evidence that Macroplastique is effective in the management of primary VUR in children, but data on secondary VUR in neuropathic bladder and especially in the spinal cord-injured population are limited.[8,9] The aim of this study was to assess efficacy of Macroplastique in this population and correlate the pre- and postinjection urodynamic findings with the outcome.

Methods

Participants

We conducted a retrospective review of all spinal cord-injured patients with unilateral or bilateral VUR who were managed with Macroplastique injection. The outcomes were recorded in prospective database over a 10-year period. The inclusion criteria were as follows: age >18 years, upper motor neuron lesion, baseline and follow-up video-urodynamic assessment, proved VUR, adequate follow-up (≥12 months), and at least 2 postinjection annual ultrasonographic assessments of urinary tract. Patients who were known nonattenders to clinic appointments and those whose medical records were not up-to-date were excluded. All patients with VUR who were treated with ureteric re-implantation, as well as those who had sacral anterior root stimulator implant, were excluded due to difficulties in assessing postoperative outcome.

Protocol

VUR was confirmed by video-urodynamics (VUDS) and graded as per the International Reflux Study Committee grading system.[10] VUDS were performed according to the Good Urodynamic Practice of the International Continence Society.[11] The examinations were carried out in supine position using standard urodynamic catheters (6Fr dual bladder catheter and 8Fr slit balloon rectal line), and the filling rate was set at 20 ml/min. Detrusor overactivity provocation by coughing, bending forward, and suprapubic tapping were standard maneuvers at filling phase. Voiding phase was recorded only when possible.

The Macroplastique procedure was performed in all patients under general anesthesia as a day case procedure. The details of the procedure are described elsewhere.[7] The injection is completed when the incompetent ureteric orifice achieves a crescent-shaped appearance. Those with bilateral reflux had their treatments in two sessions starting with the ureteric unit at risk (greater VUR grade and hydronephrotic changes).

All patients had a repeat VUDS at 3 months after injection and an annual US scan of the urinary tract.

Analysis

The primary endpoint was defined as overall treatment rate of VUR at 3 months. Treatment was defined as the complete resolution of VUR in the follow-up VUDS. The secondary outcomes included the overall treatment rate of VUR at 12 months, the success rate (treated + improved) at 3 and 12 months, the need for additional treatments, the comparison of VUDS parameters (pre- and postinjection), and the study of the management for those who failed or improved. Data were retrieved from patient records while unclear information was verified during a telephone consultation for this study purposes. The operative notes, clinical follow-ups, and urodynamic traces were reviewed.

For the statistical analysis, the statistic software SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) was used. The Shapiro–Wilk test was used for normality before any analysis. Inferential statistics were used for demographic characteristics and baseline calculations. The *t*-test was used for the intragroup variability and the nonparametric Mann–Whitney test to assess the variability between the two groups. The local ethics committee approved the study, and patients gave their verbal consent for data publication.

Results

From 2005 to 2015, a total of 74 SCI patients were diagnosed with VUR with complete follow-up data. We have identified 48 (64.9%) patients who fulfilled the inclusion criteria, and we studied 62 refluxing ureteric units. The mean age at the time of injection was 48.3 years (standard deviation [SD]: 15.4, range: 20–71), while the median time from the diagnosis of VUR since injury was 13 months (mean: 51.8, SD: 91.8, range: 2–396). There were 20 quadriplegics and 28 paraplegics. The mean follow-up was 56.2 months (SD: 34.9, range: 12–150). The basic demographics are shown in Table 1.

At the time of diagnosis, 45 (93.8%) patients were on anticholinergics, 5 (10.5%) were on regular botulinum toxin injections, and 2 (4.2%) had previous external sphincterotomies. Twenty-two (45.8%) patients had an additional procedure at the time of Macroplastique treatment. Twenty (41.7%) had Botox, the majority of whom continued on a regular basis. One (2.1%) had external sphincterotomy and one (2.1%) had suprapubic catheter insertion. The procedures were carried out in day surgery settings. There were no immediate postoperative complications, except one case (1/62) of ureteric obstruction that required temporary ureteric stent.

At 3-month follow-up, the overall treatment rate was 79.1% since 49/62 refluxing ureteric units showed radiographic resolution of VUR. The overall success rate (treated + improved) was 90.3%. Seven (11.3%) units improved and downgraded, while six (9.7%) failed. One

patient with unilateral VUR had successful outcome but developed contralateral VUR.

The results were similar at 12-month follow-up. The seven ureteric units that improved (downgraded) occurred in six patients. The patient with the bilateral VUR underwent augmentation cystoplasty as well as one who downgraded from grade 4–2. Three patients had a second injection with curative intent, which were successful. There was one complete resolution without any treatment (initially grade 2 and downgraded to 1). The six ureteric units that failed occurred in six patients. All underwent augmentation cystoplasty within 3–6 months.

There are limited data for long-term follow-up. At 48 months, 22 patients, who were initially considered as treated, did not show any signs of VUR recurrence; three of them underwent augmentation cystoplasty due to change in bladder behavior and worsening of compliance, eight remain on botulinum toxin injections, while the rest are still on surveillance.

Table 2 presents the baseline VUDS parameters between the two groups (treatment vs. failures). There is a statistical significant difference in baseline cystometric capacity ($P = 0.047$) [Figure 1], degree of reflux ($P < 0.01$), and bladder compliance ($P = 0.023$) [Figure 2]. The maximum detrusor filling pressure was higher in the failure group [Figure 3] without reaching statistical significance ($P = 0.077$). Baseline detrusor overactivity was more common in the failure group as compared to the treatment group (92.3% vs. 73.5%).

The postinjection video-urodynamics revealed a nonsignificant increase of mean detrusor filling pressure (48.8 vs. 63.2 cmH2O, $P = 0.11$) in the failure group while as compared to the treated group which was literally unchanged (36.6 vs. 37.5 cmH2O, $P = 0.808$).

There was no difference in postinjection cystometric capacity as compared to baseline in both groups. Postinjection compliance was reduced in the failure group (7.86 vs. 5.01 ml/cmH_2O, $P = 0.034$) as compared to baseline.

Table 3 presents the comparison of injury level and grade to outcome. There were no statistically significant differences between the groups on the outcome based on the level of injury. Based on the American Spinal Injury Association Impairment Scale (ASIA), patients with incomplete ASIA D type injury showed a significant response ($P < 0.001$).

Preinjection ultrasonography showed hydronephrotic changes only in 2/48 patients. Interestingly, both failed to improve after Macroplastique.

Table 1: Basic demographics of the study group

	All patients
Gender, *n* (%)	
Males	38 (79.2)
Females	10 (20.8)
Age at injury (years); mean, SD (range)	44.8, 16.9 (19-72)
Interval from injury since VUR treatment (months); mean, SD (range)	51.8, 91.7 (2-396)
Level of injury, *n* (%)	
C1-4	7 (14.6)
C5-8	13 (27.1)
T1-T12	23 (47.9)
L1-L5	5 (10.4)
ASIA score, *n* (%)	
A	32 (66.7)
B	4 (8.3)
C	6 (12.5)
D	6 (12.5)
Unilateral VUR, *n* (%)	34 (70.8)
Bilateral VUR, *n* (%)	14 (29.1)

SD: Standard deviation, VUR: Vesicoureteric reflux, ASIA: American Spinal Injury Association Impairment Scale

Discussion

We present our experience on the efficacy of Macroplastique for the treatment of secondary VUR due to neurogenic bladder in spinal cord injury population. We report an overall treatment rate 79.1%, and a success rate (treated + improved) 90.3% at 3rd and 12th month of follow‑up. Sugiyama *et al.* reported 79% success following Teflon paste injection in 16 patients with neurogenic bladder dysfunction.[12] Shah *et al*. reported 77.2% success after single or repeat injection in a similar population.[7] It is difficult to assess the long-term efficacy since, at 48 months, there were data available for only 22 patients who were initially considered as treated. None showed signs of VUR recurrence, but few patients had radical treatment of their poor compliance. Polackwich *et al*., in a series of 12 patients with neurogenic bladder, showed that the success reduced to 35% at 4.5 years (58% at 12 months).[13] Our complication rate is 1/48 (Clavien IIIb). Our results agree with previous publications.

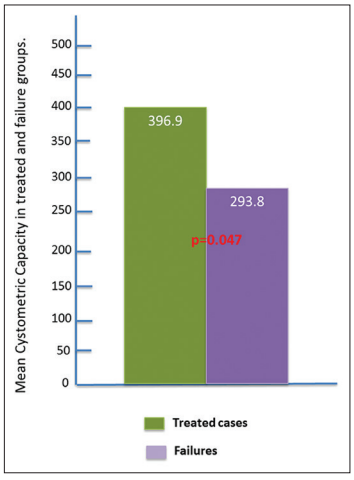

Figure 1: Postintervention mean cystometric capacity in treated versus failed cases

Although literature lacks evidence from randomized or sham-controlled trials, there are data from the pediatric literature regarding the efficacy of various bulking agents. Bae *et al*. reviewed retrospectively the efficacy of Macroplastique in 23 children versus Deflux (dextranomer/hyaluronic acid) in 48 children from a single center.[14] Both treatments were equally effective (80.6% vs. 78.6%) without significant difference ($P > 0.05$). Dodat *et al*. reported superiority of Macroplastique over Teflon and silicone (93.3% vs. 85.7% vs. 52.6%).[15] Chertin *et al*. compared the results of previous publications both and short and long terms.[6] Engel *et al*. compared the surgical versus the endoscopic correction of VUR in children with neurogenic bladder.[16] It was found that ureteroneocystostomy was superior to subureteral polytetrafluoroethylene (84.3% vs. 56.7%).

The efficacy of Macroplastique depends on the degree of reflux, bladder status, and type of injury. A hostile neurogenic bladder (small capacity, overactive, poorly compliant) is liable to Macroplastique failure. Lee *et al*. suggested that detrusor overactivity, high bladder filling pressures, and poor compliance are independent risk factors for secondary VUR in the neurogenic population.[17] VUR grade in the failure group is higher (2 vs. 3) as compared to the treated group. Even though we failed to show that level and completeness of injury might influence outcome, Macroplastique injection is more successful in incomplete (ASIA D) type injuries.

It should be noted that unlike primary VUR, the success rate of surgical correction of secondary VUR in thickened trabeculated bladders is small.[7] We have managed these patients with augmentation cystoplasty with excellent results. One had patient underwent ureteric re-implantation. The comparison between the treated group and the failure group shows that both bladder compliance and capacity significantly reduced in the latter (cystometric capacity: 396.9 mls vs. 293.8 mls, $P = 0.047$, and compliance: 18.06 vs. 7.86, $P = 0.023$). Filling detrusor pressures were higher in the failure group (36.6 vs. 48.8) without reaching statistical significance ($P = 0.077$). The treated group had more stable bladders (26.5% vs. 7.7%) and less overactivity (73.5% vs. 92.3%).

The complication rate after Macroplastique injection is low. In our study, there was one ureteric unit obstruction due to overcorrection. Similar are the results in the literature. Al-Hunayan *et al*. reported that ureteric obstruction occurred in less than 1%.[18] Puri *et al*. had 1 ureteric obstruction in a series of 11 patients with neurogenic bladders.[19] There is evidence that Macroplastique induces mucosal necrosis, erosion, and microscopic hematuria.[13] The safety of silicone is also a concern, but unlike breast implants which were silicon gels, Macroplastique is composed of solid particles.[7,14]

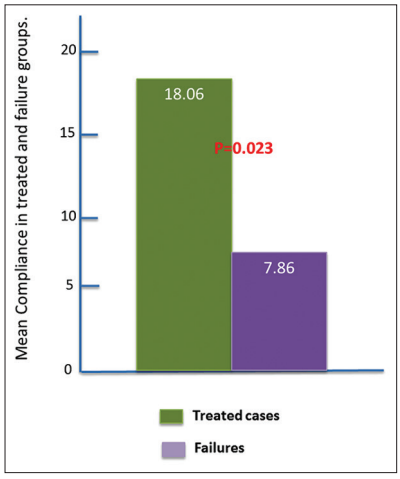

Figure 2: Postintervention mean compliance in treated versus failed cases

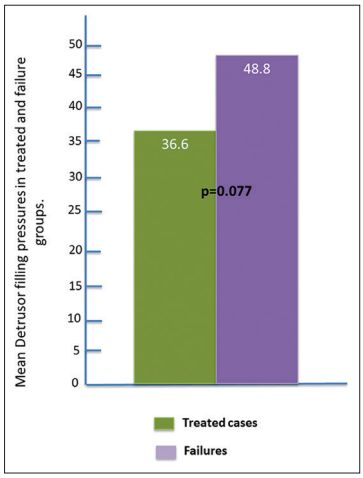

Figure 3: Postintervention mean detrusor filling pressure in treated versus failed cases

Table 2: Baseline video-urodynamic parameters and comparison between the groups

	Treated cases	Failures	*P*
Filling Pdet max (cmH_2O); mean, SD (range)	36.6, 24.6 (10-100)	48.8, 24.3 (20-90)	0.077
Cystometric capacity (ml); mean, SD (range)	396.9, 159.6 (100-700)	293.8, 145.7 (70-500)	0.047
VUR grade; mean, SD (range)	2.08, 0.49 (1-3)	3.0, 0.71 (2-4)	0.01
Compliance (ml/cmH_2O); mean, SD (range)	18.06, 15.7 (2.5-60)	7.86, 6.1 (1.2-22.5)	0.023
Detrusor, *n* (%)			
Stable	13 (26.5)	1 (7.7)	
Overactive	36 (73.5)	12 (92.3)	

SD: Standard deviation

Table 3: Injury details and comparison between the two groups

	Treated cases (ureteric units)		Failures (ureteric units)	
	Total, *n* (%)	Group specific (%)	Total, *n* (%)	Group specific (%)
Level of injury				
C1-4	9 (18.4)	90	1 (7.7)	10
C5-8	12 (24.5)	66.7	6 (46.1)	33.3
T1-12	25 (49)	83.3	5 (38.5)	16.7
L1-5	3 (6.1)	75	1 (7.7)	25
ASIA status				
A	32 (65.3)	78.1	9 (69.2)	21.9
B	3 (6.1)	60	2 (15.4)	40
C	7 (14.3)	77.8	2 (15.4)	22.2
D	7 (14.3)	100*	0 (0.0)	0*

*P<0.001. ASIA: American Spinal Injury Association Impairment Scale

To the best of our knowledge, this is one of the biggest series in the endoscopic management of VUR in neurogenic bladders due to spinal cord injury. We understand the limitation of the retrospective study and the lack of comparator, but we believe that we add more insight to the efficacy of this treatment as well as to the factors that contribute to VUR development.

Conclusion

Macroplastique is effective in the management of VUR in the spinal cord injury population. It is a minimally invasive procedure, quick, with low incidence of complications and high-resolution rate. Care should be taken though to treat the parameters of the neurogenic bladder that contributes to secondary VUR development like detrusor overactivity and poor bladder compliance.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Rare Histolopathologic Variants in Bladder Cancer

Eleftherios Tsiakoulas, Anastasios Zarkadas[1], Vasileios Tzortzis, Diomidis Kozyrakis[2]

Department of Urology, University General Hospital of Larissa, Larissa, [1]Department of Urology, "Achillopouleio" General Hospital of Volos, Volos, [2]Department of Reconstructive Urology and Surgical Andrology, Metropolitan General Hospital, Holargos Greece

Abstract

The heterogeneous spectrum of bladder cancer comprises the coexistence of conventional urothelial carcinoma (UC) with its variants as well as the non-urothelial carcinoma (including squamous and glandular tumors). Since the official classification of rare histologic subtypes, by the World Health Organization (WHO) in 2004, uropathologists and urologists are paying more attention to the role of these subtypes as potential prognostic markers. Most of these rare variants have been associated with increased risk of progression and poor prognosis. Therefore, patients diagnosed with some of the histologic subtypes, have been classified to "the very high risk group" of recurrence and progression, although it has not yet been clarified if this is due to advanced stages at presentation and underdiagnosis or due to the aggressiveness of each variant, as an independent factor. This review discusses the most common variants of bladder cancer (urothelial carcinoma with squamous and/or glandular differentiation, pure squamous carcinoma, pure adenocarcinoma, urachal carcinoma, nested pattern, microcystic, micropapillary, small cell carcinoma, plasmacytoid, sarcomatoid, and lymphoepithelial like carcinoma), outlining the recent advances regarding the diagnosis, differential diagnosis, treatment and clinical significance for each one. High index of suspicious is required by the uropathologists for detection of these variants and well-designed multi-institutional studies are necessary in order the specific treatment strategies for these patients to be established.

Keywords: *Adenocarcinoma, glandular, histologic variants, lymphoepithelial-like, micropapillary, nested microcystic, plasmacytoid, sarcomatoid, small cell, squamous*

Introduction

Bladder cancer (urological cancer or urinary bladder cancer) is the 10th most common cancer in the world (and the 6th most common cancer among men) with a continuously rising incidence worldwide, especially in developed countries, according to the Global Cancer Statistics-GLOBOCAN 2020.[1] Risk factors such as chemical exposure, including tobacco smoke (polycyclic aromatic hydrocarbons) and occupational exposure, have been highly associated with conventional urothelial bladder cancer, which represents more than 90% of bladder malignancy.[2,3] Unusual architectural, cytological, and immunohistochemical divergences, others from the conventional urothelial carcinoma (UC), have been noted in the rest 10% of pathologic reports and have lately been characterized as "histological variants" of bladder cancer, after being first added to the World Health Organization classification in 2004. Moreover, conventional urothelial malignancy with concurrent squamous or glandular differentiation may be encountered at rates as high as 20%–25%.[4] According to the more recent WHO classification of 2016,[5] divergent differentiations including pure squamous carcinoma (e.g., due to schistosomiasis in Africa) need to be individuated from UC with squamous differentiation; glandular neoplasm (including primary adenocarcinoma) also needs to be distinguished from UC with glandular differentiation. Apart from the aforementioned, other more rare variants include the nested and large nested variant of UC (NVUC), the microcystic, micropapillary, plasmacytoid, sarcomatoid, and lymphoepithelial-like carcinoma (LELC).[3-5]

According to the most recent EAU guidelines (2021), some forms of variant histology are considered prognostic factors and are used to substratify high-risk group patients and identify those at the highest risk of disease progression, to whom early

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Address for correspondence:
Dr. Diomidis Kozyrakis, 264 Mesogeion Ave., 15562, Holargos, Attiki Greece.
E-mail: dkozirakis@yahoo.gr

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cystoprostatectomy is indicated.[3] The detection of these variants may be used as prognostic indicator affecting the overall response to therapeutic treatment and therefore the patient's prognosis and survival.[4] Effective multimodal approaches concerning each variant of bladder cancer are expected to be determined by future studies.

Urothelial Carcinoma with Divergent Differentiation Nested and Large Nested Variant of Urothelial Carcinoma

The NVUC, first reported by Stern,[6] is a rare variant of UC with a reported incidence of 0.3% of all invasive bladder tumors.[7] The bland-appearing invading nests of cells are very similar with the von Brunn's nests and therefore can be easily misinterpreted as benign lesions, especially in case of absence of invasion of muscularis propria of the bladder.[8] Small- or large-packed nests, consisting of urothelial cells with focal-to-mild atypia and mild pleomorphism, that infiltrate or not the lamina propria or muscularis propria, are the usual characteristics of NVUC.[8,9] At presentation, the NVUC is usually diagnosed at locally advanced or metastatic stages, often with the involvement of the ureteric orifices.[9] Large nested variant (LNVUC) consists of a combination of the NVUC (with larger cell nests) and the inverted growth pattern of NMIBC UC. NVUC was first reported as an aggressive entity with poor prognosis, but recently, it was found to have similar clinical outcome with that of conventional UC, probably because of its frequent misclassification in the past.[8] Differential diagnosis includes von Brunn's nests, cystitis glandularis, cystitis cystica, inverted papilloma, and nephrogenic adenoma, alone or in combination. Immunohistochemically, loss of p27 expression is common between NVUC and conventional UC,[9] but the presence of TERT promoter mutation can be suggested as a promising biomarker to distinguish NVUC and LNVUC from benign urothelial lesions.[10] Early radical cystoprostatectomy is recommended in the presence of NVUC-LNVUC variant.[11]

Squamous Differentiation and Pure Squamous Cell Carcinoma

Two categories of malignancies relevant with the squamous pattern (characterized by the presence of intracellular keratin, intercellular bridges, and/or keratin pearls) have been reported: the UC with squamous differentiation and the pure squamous carcinoma.[5] In the former case, the predominant urothelial pattern is accompanied by squamous differentiation at a lesser percentage albeit no official thresholds have been established so far as to determine the extent of the squamous counterpart. Usually, in mixed carcinomas, the squamous pattern corresponds up to 40% of the total extend of the malignancy. Noteworthy, tumors with squamous differentiation may be associated with advanced stages of the disease. There is uncertainty about the way the squamous differentiation can affect prognosis, survival, and response to chemotherapy and radiotherapy, in comparison with the UC.[12,13]

Pure squamous malignancy is rarely reported in developed countries (1%–7% of the new cases in the United States), but it is the main (almost 60%) cause of bladder cancer in North Africa (due to schistosomiasis caused by *Schistosoma haematobium* infection). Apart from schistosomiasis, other causes such as chronic inflammation (production of cyclooxygenase COX-2) due to recurrent urinary tract infections,[13] bladder calculi, long-term catheterization, or prior exposure to cyclophosphamide chemotherapy have been recognized as risk factors of squamous carcinoma in developed countries.[12]

Radical cystoprostatectomy remains the treatment of choice for pure squamous carcinoma and UC with squamous differentiation, although the effect of neoadjuvant chemotherapy (NAC) has not been determined yet (NAC has been reported to be beneficial against mixed, but not against pure squamous carcinoma at several studies).[14] A recent study, based on the use of immune checkpoint inhibitors (e.g., pembrolizumab) in patients with mixed or pure squamous bladder carcinomas and PD-L1 expression, reported comparable results with those of patients with pure UC.[15]

Urothelial Carcinoma with Divergent (Glandular) Differentiation

Glandular differentiation–pure adenocarcinoma–urachal carcinoma

Similar to squamous differentiation, a distinction should be made between mixed UC with divergent (glandular) differentiation, pure adenocarcinoma, and urachal carcinoma, all of which have histological similarities with colorectal adenocarcinoma.[12,16] UC with glandular differentiation is encountered in 16% of conventional UC, while pure adenocarcinoma has an incidence of only 0.5%–2% representing the third most common bladder cancer after urothelial and squamous carcinomas.[17] Urachal carcinoma, corresponding to 10% of all bladder adenocarcinomas, is the subset of primary bladder adenocarcinomas that arises from the urachal remnant to the bladder dome.[12]

The presence of small tubular or gland-like spaces with extracellular or intracellular mucin in conventional UC usually indicates the diagnosis of UC with glandular differentiation, whereas bladder tissue with complete glandular differentiation is diagnosed as pure adenocarcinoma (associated with bladder exstrophy, intestinal metaplasia, and chronic obstruction as risk factors) and a differential diagnosis between primary and metastatic tumors from gynecologic or colon malignancies must be made.[18] Enteric, clear cell, signet ring cell, mucinous, hepatoid, and mixed types are included as subcategories of pure bladder adenocarcinoma.[18]

The presence of UC with glandular differentiation classified the patients in the very high-risk subgroup of

disease recurrence and progression, so immediate radical cystectomy is strongly recommended.[19] In these patients, the administration of NAC may also be beneficial.[12] Partial cystectomy (resection of urachal ligaments and umbilicus with lymph node dissection) is recommended to urachal carcinomas. Encouraging results emerge from several studies investigating the benefits of 5-fluorouracil-based chemotherapy and immune checkpoint inhibitors.[20]

Microcystic urothelial carcinoma

Microcystic UC is a very rare variant, with an incidence of 1%, characterized by microcysts, macrocysts (whose shape varies from round to oval and size up to 2 cm).[9] This variant can be easily misinterpreted as benign lesion and must be differentially diagnosed from cystitis cystica, cystitis cystica glandularis, and nephrogenic adenoma but also from bladder adenocarcinoma, especially in the presence of tubules and cysts with glandular structures. The overall survival seems similar to that of conventional UC although more robust evidence is required.[18]

Micropapillary urothelial carcinoma

Micropapillary UC is a variant associated with an incidence of almost 6%, male predominance (male-to-female ratio of 5:1 to 10:1 compared with the estimated ratio of UC which is 3:1) and with papillary configuration (tight small or larger nests of neoplastic urothelial cells gathered in lacunae or stromal retraction spaces).[12,21,22] This variant may resemble the papillary serous carcinoma of the ovary although the presence of psammoma bodies, a usual finding in ovarian tumors, is rarely encountered in micropapillary malignancy.[22] The variant seems to progress through the luminal pathway and the chromatin-remodeling complex RUVBL1 and mi-RNA-296 seem to play a crucial role in its pathogenesis; these targets can be used for treatment in future research.[21] At presentation, the higher percentage of this variant seems to indicate poorer outcomes and it is usually associated with aggressive behavior, advanced stages, lymphovascular invasion (50%), early lymph node metastasis, wide metastatic spread and therefore, decreased survival and prognosis.[22] in a review of 100 patients the 5-and 10-year survival have been estimated to be 51% and 24% respectively.[23] Intravesical BCG therapy appears ineffective in T1 patients with the micropapillary variant (very high risk of disease recurrence and progression group), so early cystoprostatectomy is recommended.[24] Moreover patients with muscle-invasive micropapillary varant treated with cystoprostatectomy and platinum based chemotherapy in neoadjuvant or adjuvant settings had no survival benefit, in comparison to conventional UC with NAC of the same stage.[25,26]

Small cell carcinoma

The presence of any percentage of small cell histology on bladder tissue provokes the pathologist to diagnose the primary small cell carcinoma of bladder, rather than UC with small cell differentiation. This happens because it is the small cell histology that determines the aggressiveness, the poor prognosis and the brief survival of this rare disease (<1% of all bladder cancers).[12] Histopathologically, it is similar to other small cell malignancies, such as the undifferentiated small cell lung carcinoma; it is characterized by scant cytoplasm, nuclear crowding, necrosis and frequent mitosis without any specific pattern of diffuse growth. At the time of diagnosis, almost 95% of the patients have MIBC, 65% have metastasis and the 5-year survival does not exceed the rate of 40%.[22] The majority of the cases is positive for chromogranin and synaptophysin and must be differentially diagnosed from malignant lymphoma, inflammation, UC with scant cytoplasm and alveolar rhabdomyosarcoma.[22] Cisplatin and etoposide agents, which are used in small cell lung cancer, are also recommended against small cell bladder carcinoma in neoadjuvant settings. Radical cystectomy should be offered to the patients, including those with earlier stages (cT1), although multimodal treatment could also be considered, as there is no standard care for these patients.[27]

Plasmatocytoid urothelial carcinoma

The plasmatocytoid variant of UC is a rare, aggressive variant, in which histologically infiltrative tumor cells with abundant eosinophilic cytoplasm, resembling plasma cells with eccentric nuclei set in a myxoid stroma, create patterns similar to lobular carcinoma of breast and gastric signet-ring carcinoma.[28] The coexistence with conventional UC or sarcomatoid carcinoma histology is usual. Same histological features can be found at malignant lymphomas, plasmacytomas, melanoma, metastatic carcinomas including lobular and gastric adenocarcinoma, paraganglioma, rhabdomyosarcoma and UC.[22,28] Lack of E-cadherin expression, due to mutation in gene coding *CDH1*, is a characteristic of this variant only and is very helpful at the differential diagnosis.[29] At the time of diagnosis, up to 90% of the cases curry at least a pT3 disease and 5-year survival is <30%.[28] Because of its poor prognosis and the suboptimal results reported with NAC in plasmatocytoid variant compared with conventional UC, upfront early cystoprostatectomy is recommended.[30] Recent evidence suggests that PD-1/PD-L1 targeted immunotherapy might be a promising treatment option for patients with advanced disease although more studies are required.[28] Similar to other variants, it has not yet been identified if poor prognosis is due to the variant itself or due to advanced stage at presentation.

Sarcomatoid urothelial carcinoma

Sarcomatoid UC is another very rare variant, representing the 0.3% of all bladder carcinomas, in which both the epithelial and the mesenchymal sarcomatoid features emerge from a common monoclonal cell origin.[31,32] Others propose that this biphasic variant is the result of

two monoclonal tumors emerging at the same time.[33] The term has been registered in the WHO classification and the presence of urothelial malignant cells or *in situ* helps the very difficult distinction between this variant and a primary (pure) sarcoma.[22] In the sarcomatoid variant pattern, obvious sarcomatoid overgrowth with usually a myxoid background may appear which may be accompanied by urothelial or squamous or small cell carcinoma. The sarcomatoid component can be represented by osteosarcoma, chondrosarcoma, rhabdomyosarcoma, liposarcoma, angiosarcoma or a mixture of sarcoma histologies.[22] Pseudosarcomatous myofibroplastic proliferations and primary sarcomas are included in differential diagnosis and positivity for pancytoceratin, p63, CK5/6, HMW cytokeratin or mutation in TP53, RB1 and PIK3CA can be used as diagnostic markers.[31] Moreover, overexpression of PD-L1 genotype has been revealed in sarcomatoid component of mixed tumors.[34] At presentation, the majority of sarcomatoid carcinomas is in advanced stages with development of nodal or distant metastasis (even after surgery) and a very poor prognosis. However, there is much controversy whether the poor prognosis is due to the presence of the variant or to the advanced stage of the disease at time of diagnosis. Although there are not specific treatment strategies for patients with this variant and they are treated with radical cystoprostatectomy, studies show that the benefit of neoadjuvant or adjuvant chemotherapy is debatable and almost 70% of patients succumb 2 years following diagnosis.[35]

Lymphoepithelioma-Like Carcinoma

LELC corresponds to a very rare variant of bladder carcinoma, with a high resemblance to non-keratinizing nasopharyngeal carcinoma (lymphoepithelioma). However, testing for Epstein-Barr virus is uniformly negative and therefore this variant is designated as lymphoepithelioma-*like*.[36] Syncytial undifferentiated malignant cells, large pleomorphic nuclei, indistinct cytoplasmic borders, lymphoid infiltration and dense inflammation are usual histological features of this variant. The histopathologic characteristic of this variant is the dense infiltration of T-and B-cells, occasionally accompanied by the presence of other inflammatory cells (e.g., eosinophils, plasma cells).[12,22] Most cases present with muscle invasion, but usually without metastasis. Pure, predominant and focal subgroups have been proposed for this malignancy with more favorable prognosis for the predominant subgroup, compared to the focal.[37,38] A head to head comparison of cystoprostatectomy in LELC versus cystoprostatecromy in conventional UC has shown similar survival. Due to the variant's chemosensitivity to platina, bladder preservation treatment with chemotherapy has been proposed by some authors but it was associated with higher recurrence rate in the LELC group compared with the conventional MIBC.[37,38] Future studies are required to define whether the amount of LELC component can be used as a prognostic indicator and whether these patients will benefit by immunotherapy, since the presence of PD-L1 expression is has already been revealed.[39]

Conclusions

Although each one of the presented histologic variants is rare, they overall represent up to one out of four cases of all bladder malignancies; therefore the early identification, quantification and accurate report by pathologists are imperative due to lack of data concerning these patients. Squamous, glandular, sarcomatoid and micropapillary are the most common urothelial variants while pure squamous, adenocarcinoma and small cell carcinoma are the most common non-urothelial counterparts. Small number of patients, poor prognosis and advanced stages at presentation can be considered as obstacles in determining if and how the early and accurate diagnosis of these variants can have therapeutic or prognostic implications. Well-designed multi-institutional studies are necessary in order to clarify the prognostic role of each variant, to define specific biomarkers and to establish specific treatment strategies that will be beneficial for the patients.

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Conflicts of interest

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Review Article

Guidelines and Medical Management of Stone Disease: Do we have a Consensus?

Lazaros Tzelves, Panagiotis Mourmouris, Andreas Skolarikos

Department of Urology, National and Kapodistrian University of Athens, Sismanogleio General Hospital, Athens, Greece

Abstract

Medical management of the stone disease is a topic of controversy even between worldwide guidelines. With this review, we attempt to clarify the disparities that exist in the literature and provide to the clinical urologist a tool for battling this common disease. The search was based on current Guidelines from national and international urological Associations including European and American guidelines and the guidelines of Societe d"Urologie. The use of a-blockers is highly indicated by most Guidelines as medical expulsion therapy, whereas nonsteroidal anti-inflammatory medication for pain relief. Fluid intake of 2 lit/day, controlled dietary calcium consumption and sodium restrictions are universal dietary modifications from urological Associations on the prevention of stone disease. Despite methodological heterogeneity and subjective rating of recommendations, an acceptable degree of consensus was noted on Guidelines regarding medical management of the stone disease.

Keywords: *American Urological Association, European Urology Association, guidelines, medical management, prevention, urolithiasis*

Introduction

Urinary lithiasis tends to recur even after successful surgical treatment, with reported rates of recurrence of 50% within a decade after the first stone event,[1] with 10% of them experience more than one recurrent episode.[2] Considering their disease, a chronic condition, many patients often seek measures to prevent future stone episodes. Lifestyle changes, dietary modifications, and pharmaceutical interventions have been studied to aid toward that direction. International scientific committees publish guidelines with the goal of helping clinical decision evidence-based guidance. The variations of methodology often lead to discrepancies between existing guidelines and so the objective of our study is to find points of consensus or ambiguities between them and provide an overall quality assessment of these clinical tools.

Methods

Two authors (L. T., A. S.) performed an independent search of existing Guidelines from international/national societies. The search was confined to a membership list of Societe International d' Urologie (SIU),[3] along with the list of international Associations in the American Urological Association (AUA) website.[4] A search in PubMed/MEDLINE until June 30, 2020 using the following terms: " Guideline OR guide OR recommendation OR algorithm" AND "urolithiasis OR kidney stone disease OR lithiasis OR calculi OR calculus OR nephrolithiasis" and associated MesH terms, was performed. Discrepancies were resolved on consensus between the two authors.

We evaluated each one of the included Guidelines with the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument.[5] The reviewer using AGREE II assesses each Guideline on six different domains, namely: scope and purpose, stakeholder involvement, the rigor of development, clarity of presentation, applicability, and editorial independence with a total of 23 questions.[6]

Results

Our search revealed a total of 82 urological Associations across six continents. Sixty-nine of these Associations either provided no recommendations or they provided links for relevant European Urology

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Address for correspondence:
Dr. Panagiotis Mourmouris, Department of Urology, National and Kapodistrian University of Athens, Sismanogleio General Hospital, 1st Sismanogleiou Str, Marousi, Athens, Greece.
E-mail: thodoros13@yahoo.com

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Association (EAU) or AUA Urolithiasis Guidelines. Recommendations from eight urological committees were eligible: EAU,[2] AUA,[7-9] SIU/International Consultation on Urological Diseases (ICUD),[10] National Institute for Health and Care Excellence (NICE),[11] Urological Association of Asia (UAA),[12] Canadian Urological Association (CUA),[13,14] French Urological Association (AFU),[15] and German Urological Association (DGU).[16] An outdated review released by AFU was also excluded.[17]

EAU publishes a yearly updated Guideline on Urolithiasis, which is based on the highest level of existing literature. AUA Guideline on medical management of stones was published in 2014 and reviewed-validated in 2019 by the Panel members.[7] SIU/ICUD Guideline contains recommendations based onOxford Centre for Evidence-Based Medicine (OCEBM) definitions of level of evidence (LOE)/grade of recommendation (GOR) and information after reviewing EAU/AUA Guidelines.[10] UAA developed the Guideline on urolithiasis after literature review between 1966 and 2017 with a combined search in EAU and AUA Guidelines.[12] GOR was assessed after a literature search, while LOE was based on a system modified from OCEBM.[12]

NICE produces evidence-based recommendations after literature review on a specific topic, performed by experts.[11] Update is planned every 3 years, except an urgent circumstance requires a faster renewal.[11]

There seems to be a consensus between guidelines (EAU, NICE, UAA, AFU, and DGU) for the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as 1st line treatment in renal colic, except in patients with contraindications (pregnancy, renal insufficiency, ischemic heart disease). The most commonly recommended drugs are diclofenac, metamizole, indomethacin, and ibuprofen, UAA also recommends NSAIDs/steroids for increased stone passage, while DGU for further pain episodes prevention. Alternatively, paracetamol is the drug of choice when NSAIDS cannot be used, while it is also suitable for pregnant/lactating women. Opiates are considered a 2nd line treatment option.

Almost all guidelines rate the recommendation of a-blockers as medical expulsion therapy with a high LOE, while the cut-off stone size is yet to be determined. EAU and UAA recommend the drug for stones >5 mm, while AUA and NICE for stones ≤10 mm. In addition, a-blocker is recommended after shock-wave lithotripsy (SWL) or Ho: YAG laser lithotripsy (EAU) to increase the stone-free rate and decrease analgesic needs, while its use is advised as beneficial for stent-related symptoms by EAU and AUA.

For medical management of recurrent lithiasis, both thiazide and potassium citrate in patients is a universal recommendation even if urine metabolic abnormalities are not detected (AUA, SIU/ICUD). Allopurinol is also strongly recommended by AUA and SIU/ICUD in patients with hyperuricosuria while in the opposite CUA advises against its use. In patients with cystine lithiasis, urine alkalization with alkaline citrates is the first recommended measure nevertheless the recommendation comes with a low LOE. If urine alkalization fails, most of the guidelines proposed in favor of the use of tiopronin.

As for the quality assessment EAU, AUA, and NICE Guidelines were the most highly rated. NICE Guideline was assessed with a higher score at stakeholder involvement (75%), whereas UAA, CUA, SIU/ICUD, and DGU Guidelines were rated with average scores 55%–75%.

Discussion

Despite the heterogeneity, most of the recommendations on acute renal colic management were similar, with 1st line treatment proposed being NSAIDs/paracetamol and opiates the next option. Similarly, MET is recommended for distal ureteral stones, usually ≤10 mm, and also after SWL/ laser lithotripsy and stent-related symptoms. Prevention of stone recurrence in high-risk patients is crucial since high-relapse rates are noticed.[18,19,20,21] All guidelines contained information on dietary modifications and medical interventions to decrease relapse rates. In general, dietary interventions proposed were similar, with differences noted in LOE/GOR ranking. This is the first study to review and compare urological guidelines on medical management of stone disease. A detailed search was performed, while two independent reviewers assessed all the recommendations/processes of development and ranked each one off the Guidelines with AGREE II instrument. A limitation of the study was the fact that some of the Guidelines overlap with others, most commonly with AUA and EAU recommendations and this could be a confounding factor.

Conclusion

This review highlights an acceptable degree of consensus on most aspects of medical management of the stone disease. Most differences were detected on GOR/LOE, which is partially explained by the average heterogeneity and the probable subjectivity of the author of each guideline.

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Case Report

Mucinous Adenocarcinoma of the Prostate Found Incidentally in Adenomectomy Specimen Complicated with Vesicocutaneous Fistulae

Spinos Theodoros, Lardas Michail, Kotoulas Grigorios, Thanos Anastasios, Kyriazis Iason

Ygeias Melathron Hospital, TYPET, Palodeia, Cyprus

Abstract

Primary mucinous tumors of the prostate gland are rare, including mucinous adenocarcinoma, prostatic adenocarcinoma with mucinous features, and mucinous adenocarcinoma of the prostatic urethra. In this report, we present a case of a locally advanced mucinous variant of prostatic ductal adenocarcinoma, found incidentally during pathology examination of an adenomectomy specimen, after bladder outlet obstruction surgery. Recent large studies indicated that mucinous adenocarcinoma of the prostate, treated by radical prostatectomy, is not more aggressive than ordinary nonmucinous prostatic adenocarcinoma. In our case, the rapid deterioration of our patient, the return of tumor in its initial size soon after surgery, in addition to its distal metastatic spread should be attributed not only to the mucinous variant of prostatic adenocarcinoma but also to the advanced stage during initial diagnosis and the noncompliance of the patient with the suggested treatment after surgery, omitting radiotherapy, and hormonal maneuvers.

Keywords: *Adenocarcinoma, fistulae, mucinous, prostate, vesicocutaneous*

Introduction

Primary mucinous tumors of the prostate gland are rare, representing approximately 0.2%–0.4% of prostatic adenocarcinomas.[1-3] The primary mucinous tumors involving the prostate include mucinous adenocarcinoma, prostatic adenocarcinoma with mucinous features, and mucinous adenocarcinoma of the prostatic urethra. Mucinous adenocarcinoma of the prostate is characterized by the presence of at least 25% of the tumor consisting of glands with extraluminal mucin. However, this diagnosis can only be made in radical prostatectomy specimens, because the whole tumor must be present to report that the extraluminal mucinous component is more than 25%. In cases of radical prostatectomy specimens, where extraluminal mucinous component represents <25% of the tumor, the diagnosis of prostatic adenocarcinoma with mucinous features is set. It is worth noting that, all cases of prostatic adenocarcinoma with extraluminal mucinous components, found in prostate needle core biopsies and in transurethral resection of the prostate specimens, are characterized as prostatic adenocarcinomas with mucinous features. Up to one-third of prostatic adenocarcinomas include intraluminal mucin. These cases should not be considered mucinous adenocarcinomas or prostatic adenocarcinomas with mucinous features.[4] Concerning the molecular basis and pathogenesis of prostatic mucinous adenocarcinomas, these tumors have been found to express MUC2 (goblet-type, secretory-type, or gel-forming-type mucin). MUC2 forms strong bonds with the stroma and contributes to the morphology and the slow growth of mucinous adenocarcinomas.[5,6] Mucinous prostatic adenocarcinomas and prostatic adenocarcinomas with mucinous features have also been shown to express PTEN. Loss of PTEN expression is associated with aggressive high-grade prostatic adenocarcinoma.[4,7] Recently, there has been increased interest in the magnetic resonance (MR) features of prostatic mucinous adenocarcinoma, enabling its noninvasive diagnosis. Mucinous adenocarcinomas of the prostate have been shown to differentiate from the usual characteristics of nonmucinous tumors on T2-weighted magnetic resonance imaging (low-signal intensity) and MR spectroscopy (increased choline and decreased citrate peaks), as a result of

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Address for correspondence:
Dr. Spinos Theodoros, Apollonos 57 ,Pallini, Greece.
E-mail: thspinos@otenet.gr

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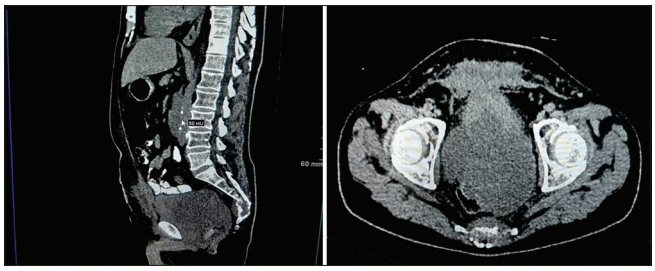

Figure 1: A computed tomography evaluation of the patient confirmed the presence of a vesicocutaneous fistula due to an infiltrating prostatic mass of 400 ml size running through the bladder wall toward the anterior abdominal wall. Large retroperitoneal lymph node masses were also evidenced in the computed tomography scan

the extracellular mucin which they include. Nevertheless, these imaging studies carry many limitations and thus no conclusion can be safely drawn.[8] In this report, we present a case of a locally advanced mucinous variant of prostatic ductal adenocarcinoma, found incidentally during pathology examination of an adenomectomy specimen, after bladder outlet obstruction surgery. The bad progression of this patient's health condition, in combination with the extremely rare nature of mucinous prostatic adenocarcinoma, raised questions as to whether these tumors are more aggressive and associated with worse prognosis.

Case Report

A 62-year-old male patient presented to the emergency department of our hospital with bilateral hydronephrosis and acute kidney injury with concomitant urinary retention. The radiological evaluation identified an extremely large prostate of 420 ml and an overdistended urinary bladder with more than 1 l of urine. A urinary catheter was inserted and renal function gradually returned to normal. Prostate-specific antigen (PSA) levels were 10.26 ng/dL 1 month after catheterization and digital rectal examination was unremarkable. Subsequently, the patient was subjected to laparoscopic adenomectomy.

Surgical technique

After the establishment of an extraperitoneal access with the use of a balloon, 5 trocars were inserted into the extraperitoneal space under direct vision. A midline bladder incision was made and the bladder trigone was exposed. A vertical incision of the mucosa above ureteral orifices was made and enucleation of the adenoma was performed. Since the beginning of enucleation an atypical behavior of the adenoma was evident with the presence of large intraprostatic cavities that were breaking open during laparoscopic maneuvers. Opening of one of these cavities at the posterior aspect of the intracapsular dissection plane led to entrance into the underlying bowel, as evidenced by retrograde infusion of saline in the rectum returning saline into the operative field. A general surgeon was called into the theater and assisted into the suturing of the bowel defect in two layers. A urinary catheter was inserted into the bladder and the bladder wall opening was closed in a single layer using Vlock 2/0 sutures. Postoperative course was uneventful. The patient stayed fasten for 2 days and was discharged with the catheter in place for 10 days on postoperative day 4. A low-fiber diet was advised for 1 week time.

Pathology examination of the 300 ml specimen, revealed the presence of mucinous variant of prostatic ductal adenocarcinoma infiltrating the underlying bowel wall.

Three months after surgery, PSA levels were 14.92 ng/dL and no evidence of distant metastases was documented in scintigraph and radiological evaluation. Androgen deprivation treatment was initiated with SC leuprorelin 11.25 mg every 3 months and PSA levels dropped to 0.38 ng/dL 1 month later. While immediate radiotherapy would be a suitable treatment option for this patient, it was decided to delay treatment for 6 months, due to the bowel perforation observed during surgery. After 3 sessions of radiotherapy, the patient was lost to follow-up.

Two years later, he presented to the emergency department of our hospital due to urine leakage through his anterior abdominal wall. A computed tomography (CT) evaluation confirmed the presence of a vesicocutaneous fistula due to an infiltrating prostatic mass of 400 ml size running through the bladder wall toward the anterior abdominal wall. Large retroperitoneal lymph node masses were also evidenced in the CT scan [Figure 1]. After a multidisciplinary team meeting including oncologists, general surgeons, and urologists-bilateral nephrostomies were placed and a docetaxel regimen chemotherapy was initiated. The patient returned home after the first cycle of chemotherapy but passed away 10 days later at home.

Discussion

Traditionally, most mucinous adenocarcinomas of the prostate were considered to be aggressive tumors.[9-11] Nevertheless, recent large studies indicated that mucinous adenocarcinoma of the prostate, treated by radical prostatectomy, is not more aggressive than ordinary nonmucinous prostatic adenocarcinoma. Surprisingly, data from these studies demonstrated that it may potentially even be less aggressive.[12-17] It is very possible that the extracellular mucin, accumulated in the stroma of these tumors, surrounding cancer cells, and interferes with their ability to spread.[6] Similarly, some pathologists in the past, were convinced that all of these tumors should get a high Gleason score. Moreover, whether these tumors should be graded with a Gleason score was an object of debate. Recent data suggest assigning prostatic mucinous adenocarcinomas a Gleason score based on their underlying architectural pattern, like common prostatic adenocarcinomas, rather than hypothesizing that all of these tumors are aggressive.[12,16,17] In our case, the rapid

deterioration of our patient, the return of tumor in its initial size of 400 g soon after surgery in addition to its distal metastatic spread should be attributed not only to the mucinous variant of prostatic adenocarcinoma but also to the advanced stage during initial diagnosis (as evidenced by bowel infiltration) and the noncompliance of the patient with the suggested treatment after surgery, omitting radiotherapy and hormonal maneuvers.

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There are no conflicts of interest.

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Isolated Adrenal Gland Hematoma after Blunt Abdominal Trauma: A Case Report and Literature Review

Abstract

Isolated traumatic adrenal gland hematoma is a very rare condition. Our aim is to present a case of an isolated traumatic hematoma of the adrenal gland after a low-speed motorcycle accident without other associated injuries. A 30-year-old Caucasian male presented to the emergency department complaining of intense upper abdominal pain associated with shortness of breath. Trauma ultrasonography assessment, focused assessment with ultrasonography for trauma, was negative; emergency computed tomography (CT) imaging revealed a well-defined 3.8 cm × 2.8 cm mass in the location of his right adrenal gland. He was hospitalized for 48 h and was discharged hemodynamically stable, with normal hemoglobin levels. CT imaging at 1-month follow-up revealed a decrease in hematoma size and complete resolution of symptoms. Conservative treatment may be the method of choice for adrenal trauma, provided that patients remain hemodynamically stable and closely monitored.

Keywords: *Adrenal gland, close monitored, conservative approach, isolated traumatic hematoma*

Savvas Tsakiris, Spyridon Paparidis, Maria Zerva, Antonios Katsimantas, Konstantinos Bouropoulos, Nikolaos Ferakis

Department of Urology, Korgialenio-Benakio Hellenic Red Cross Hospital, Athens, Greece

Introduction

Isolated traumatic adrenal gland hematoma is a rare condition. The incidence rate of adrenal gland injury ranges from 0.03% to 4.95% of all trauma cases. Isolated adrenal hemorrhage is a very rare subset of this type of injury.[1,2] It is very difficult to diagnose this condition because it has a nonspecific clinical presentation, and there are no specific diagnostic biomarkers.[3]

Case Report

A 30-year-old Caucasian male presented to the emergency department (ED) complaining of intense upper abdominal pain associated with shortness of breath after a low-speed motorcycle accident. On presentation, the patient's Glasgow coma scale score was 15/15. Blood pressure was 148/102 mmHg, heart rate 128 beats/min, respiratory rate 23 breaths/min, temperature 37°C, oxygen saturation 98%, and FiO_2 of 21%. He had no previous medical record except daily tobacco use. A physical examination revealed normal bilateral lung auscultation. Bowel sounds were present, and the abdomen examination showed mild tenderness in deep palpation of his right upper quadrant and right lower back area, without visual evidence of lacerations on his abdomen or his chest. White blood cell count was 157,000/μΛ (77.1% segmented neutrophils). Hemoglobin level was 16.3 mg/dL, with 48.4% hematocrit. Only hepatocellular liver enzymes were elevated (aspartate transaminase: 125 U/l and alanine transaminase: 106 U/l) without an increase in bilirubin, alkaline phosphatase, and gamma-glutamyl transferase. The rest of his blood examinations were within normal limits. Trauma ultrasonography evaluation and focused assessment with ultrasonography for trauma (FAST), performed in the ED, were negative for trauma

Emergency abdominal contrast-enhanced computed tomography (CE-CT) was performed due to the persistence of pain and abnormal liver examinations, which set high level of clinical suspicion. Abdominal CT revealed a well-defined, oval-shaped mass in his right adrenal gland, sized 3.8 cm × 2.8 cm, with 70–80 HU density, without active extravasation of contrast agent [Figure 1]. Neither no musculoskeletal trauma was identified nor injuries to his liver or kidneys. CT confirmed the diagnosis of isolated right adrenal injury. The patient was subsequently admitted to the urology clinic for close monitoring.

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Address for correspondence:
Dr. Savvas Tsakiris, Ampelokipoi 11526, Athens, Greece.
E-mail: savvasts11@hotmail.com

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During hospitalization, his clinical condition remained stable [Table 1]. Right upper quadrant pain gradually subsided, along with abdominal tenderness after administration of low-dose intravenous analgesia with paracetamol and tramadol. The patient was discharged 48 h later with oral antibiotics and analgesia prescribed for 7 days. Restriction on physical activities for 1 month was also recommended. A follow-up CT scan 7 days after discharge showed no size reduction of the adrenal gland hematoma. Right upper quadrant pain and tenderness were reduced 1 week after discharge. Follow-up CT scan at 1 month after discharge revealed a small reduction in hematoma size [Figure 2] and complete resolution of symptoms.

Discussion

Adrenal hematoma is rare because of the anatomical location of the adrenal gland, which is found deep in the retroperitoneal cavity, surrounded by protective soft-tissue structures that act as a natural protective environment. The incidence of adrenal gland injury ranges from 0.03% to 4.95% of all trauma cases. Isolated adrenal hemorrhage is a very rare subset of this type of injury.[1-3]

It is very difficult to diagnose an isolated traumatic adrenal gland hematoma because it has nonspecific clinical presentation without any sensitive or specific diagnostic biomarkers.[3] FAST is the most frequently used imaging modality for trauma patients in the ED. However, FAST ultrasonography may fail to identify many traumatic lesions such as adrenal gland hematoma due to limitations in the size of the injury and variable experience of the examiner. The method of choice for the diagnosis of adrenal trauma and synchronous identification of associated injuries is CT with intravascular contrast agent infusion (CE-CT).[4,5] In this case, diagnosis, set with CE-CT, was based on high level of clinical suspicion due to the persistence of pain, along with mild liver enzyme elevation.

Management of patients with isolated adrenal gland hematoma depends mainly on the patient's comorbidities and the severity of trauma. There is an increasing trend toward conservative management or minimally invasive procedures such as angiography instead of surgical exploration. In most of the cases, stable patients with isolated adrenal trauma are treated conservatively with monitoring, analgesic drug administration, and avoidance of activities that may increase intra-abdominal pressure.[6] If the patient becomes hemodynamically unstable with active extravasation of contrast agent, there is the choice of minimally invasive procedures such as angiographic embolization to control bleeding. However, there are no guidelines concerning monitoring and the definite timing for angiography and embolization.[7,8] The decision on whether to proceed to more invasive treatment depends on symptom severity. In case of uncontrolled bleeding or lack of angiography, surgical exploration should be performed. There are no current guidelines about follow-up for an isolated traumatic adrenal hematoma, although follow-up imaging is necessary to reassess the size of the lesion.[9]

Table 1: Hemoglobin and hematocrit

	Reference range	Admission	4 h	16 h	32 h and units
Hemoglobin (g/dl)	13.5-17.0	16	15.6	15.5	15.9
Hematocrit (%)	41-53	47.2	47.1	46.8	47.5

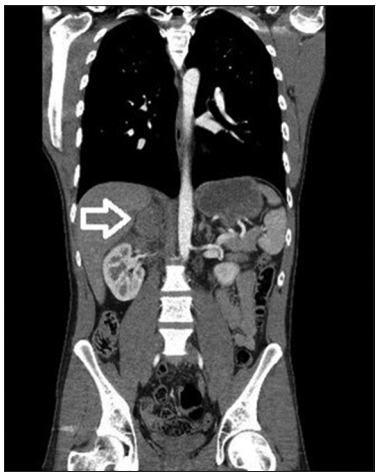

Figure 1: Right adrenal hematoma depicted in CE-CT scan, 2 hours after presentation in the Emergency Department (arrow)

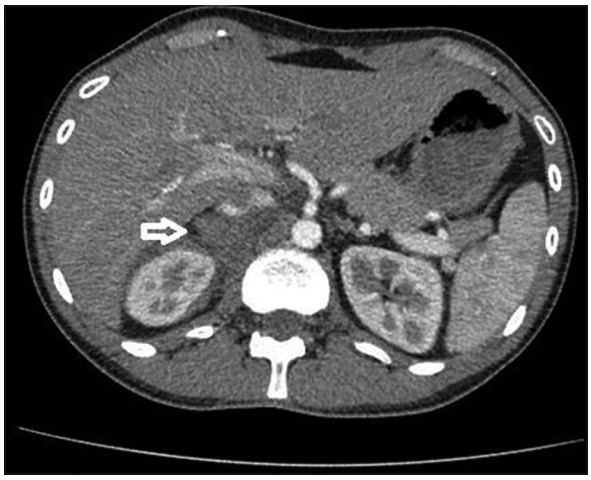

Figure 2: CE-CT follow up scan, one month after discharge shows reduction in adrenal hematoma size, with no active contrast agent extravasation

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Bladder Metastasis of Renal Cell Carcinoma. A Case Report and Review of the Literature

Abstract

Renal cell carcinoma (RCC) metastasis to the urinary bladder is an exceedingly rare entity. In this paper, we present a case of a 78-year-old male presented in our department with painless gross hematuria, 2 years after he underwent a left open nephrectomy that revealed a clear cell RCC. Imaging examination revealed a sessile mass on the bladder wall. The patient underwent a transurethral resection of the bladder tumor with the histological diagnosis of clear cell RCC. Pathogenesis and possible routes of such a metastasis are not well-documented and no treatment of choice has been established yet.

Keywords: *Bladder metastasis of renal cell carcinoma, rare metastasis of renal cell carcinoma, rare sites of metastasis of renal cell carcinoma, renal cell carcinoma bladder metastasis, urinary bladder metastasis of renal cell carcinoma*

Panagiotis Velissarios Stamatakos, Loannis Glykas, Charalampos Fragkoulis, Georgia Theodoropoulou[1], Sofia Pappa[1]

Departments of Urology and [1]Pathology, General Hospital of Athens, "G. Gennimatas", Athens, Greece

Introduction

Worldwide, kidney cancer is the third most common urological cancer, while renal cell carcinoma (RCC) constitutes approximately 70% of all primary malignant renal tumors. About 20%–25% of patients with RCC present with advanced disease at the initial diagnosis. The most common metastatic sites are lungs, lymph nodes, bones, and liver, while rare metastatic sites include the testis and the urinary bladder.[1] Urinary bladder metastasis from RCC is extremely rare with few cases reported in the literature so far.

Case Report

A 78-year-old male with multiple comorbidities was referred to our department in October 2018 due to an accidentally found left renal tumor located in the upper pole. The computer tomography (CT) scan identified a 5 cm left renal tumor located in the upper pole of the kidney. There was no evidence of metastatic disease nor lymphadenopathy. A successful left open nephrectomy was performed by a retroperitoneal approach. The postoperative course was uneventful, and the patient was discharged 7 days after surgery. The pathology report revealed a well-delineated, solid, and elastic, white to orange mass of 4 cm × 5 cm × 4.5 cm, and the tumor was classified as pT1b clear cell RCC of Grade 3 according to ISUP 2012 and the 8th edition of the TNM Classification. The patient underwent the follow-up protocol of a chest and abdomen CT scan at 6 and 12 months which revealed no sign of recurrence or metastasis.

Two years after the operation, the patient presented to our department with painless gross hematuria. An ultrasound was performed which revealed a hyperechoic mass of 1 cm at the posterior wall of the urinary bladder. The patient underwent a flexible cystoscopy that revealed a sessile mass on the left lateral bladder wall. Transurethral resection of the bladder tumor was performed, and the histologic examination revealed a metastasis of the known patient's clear cell RCC [Figure 1]. A chest and abdominopelvic CT scan was followed for staging purposes. No sign of another metastatic lesion was described. The patient decided to undergo an open radical cystectomy within the rationale of a solitary metastasectomy. He had a good postoperative course. No systemic treatment was administered before or after surgery. The pathology report revealed the already known solitary, localized clear cell RCC metastasis of the urinary bladder.

Discussion

Bladder metastasis of RCC is an uncommon condition that accounts <2% of all bladder tumors. The mean age of the patients at diagnosis is 60 ± 12 years.[2] Bladder

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Address for correspondence:
Dr. Panagiotis Velissarios Stamatakos,
Krevvata 44, Piraeus, Athens, Greece.
E-mail: pvstamatakos@gmail.com

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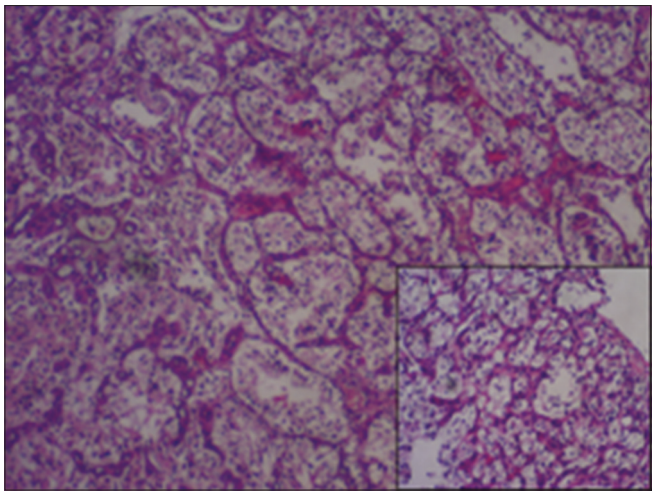

Figure 1: H and E stain original magnification ×50 and ×100 in the lower right quadrant. Section from the bladder tumor showing infiltration of the clear cell renal cell carcinoma

metastasis may occur either in a synchronous or metachronous setting with the primary renal cancer. The average period between primary RCC diagnosis and metastasis to the bladder ranges from 2 to 131 months in literature.[3]

Routes of metastatic spread of RCC to the bladder remain unclear. Several underlying mechanisms have been proposed including hematogenous, lymphatic, and metastasis via the urinary stream. Hematogenous metastasis may occur through either systemic circulation or retrograde venous route. The last indicates the formation of tumor thrombus in the renal vein and the retrograde dissemination of malignant cells through the venous system. Infiltration of the muscular layer of the bladder wall without contact to the urothelial layer indicates a hematogenous spread. Another theory suggests tumor cells spread through lymphatic blood vessels. The synchronous finding of widespread disease including multiple metastatic sites is thought to result from these hematogenous or lymphatic metastatic pathways. The last mechanism of bladder metastasis is the direct extension of renal tumor to the ureter and bladder, as well as the transition of tumor cells through urine with implantation at the distal urothelium ("drop metastases").[4]

Clinical presentation of bladder metastasis consists of asymptomatic gross hematuria and symptoms of urinary obstruction. CT scan and cystoscopy reveal a sessile mass with spherical protuberances into the bladder lumen which is well enhanced after the use of intravenous contrast. Transurethral resection of the mass and pathology examination of the specimens establish the diagnosis of bladder metastasis of RCC.[5]

Clear cell variant of RCC is the most common histopathologic subtype associated with bladder metastasis. Histologically, metastatic lesions must be differentiated from clear cell adenocarcinoma of the urinary bladder, lipoid-cell variant of urothelial carcinoma as well as clear cell carcinomas arising from other organs such as the prostate, lung, and breast. At last, pathologists should also consider the possibility of metastatic melanoma, clear cell sarcoma, and seminomas.[6]

Due to the lack of evidence, there are no guidelines regarding the treatment of bladder metastasis of RCC. So far, transurethral resection of the tumor, partial or radical cystectomy, and systemic chemotherapy have been used. A suggestion of treatment in cases with solitary bladder metastasis is to perform transurethral resection as a part of cytoreductive management and to provide systemic therapy as soon as other metastatic sites are detected.[7] In our case of a solitary bladder clear cell RCC metastasis, a radical cystectomy was performed in the rationale of a metastasectomy.

Conclusion

Bladder metastasis of RCC is a rare medical entity that medical community should be aware of it. More data should be obtained about its pathogenesis to provide the best therapeutic utilities to these patients.

Statement of ethics

The study complied with the principles of Declaration of Helsinki for the protection of human rights. The patient was informed in detail by the treating physician for inclusion in the case presentation and signed an informed consent before participation. In the form the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published.

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Conflicts of interest

There are no conflicts of interest.

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