Original Article

The Role of l-Methionine in the Reduction of Recurrences of Chronic Bacterial Prostatitis: A Pilot Study

Konstantinos Stamatiou, Gianpaolo Perletti[1], Kurt Naber[2]

Department of Urology, Tzaneion Hospital, Piraeus, Greece, [1]Department of Biotechnology and Life Sciences, Section of Medical and Surgical Sciences, University of Insubria, Varese, Italy, [2]Department of Urology, School of Medicine, Technical University of Munich, Munich, Germany

Abstract

Introduction: L-methionine has been used for many years as an aid in the treatment of urolithiasis and as a prevention of further occurrence of struvite crystal formation by the acidification of the urine. Acidification of urine has been also used as a technique to treat and prevent symptomatic urinary tract infections. The current pharmacological research in the field of bacterial prostatitis focuses on the combinations of available antibiotics with prostatic microenvironmental modifiers for the prevention and treatment of chronic bacterial prostatitis (CBP) clinical recurrences. We aimed to study whether, in addition to antibiotic therapy, acidification of urine and prostatic microenvironment decreases CBP recurrences. **Materials and Methods:** This study was conducted between February 01, 2019, and December 20, 2020. The patient population included subjects with a confirmed diagnosis of CBP (National Institutes of Health [NIH] category II), history of CBP recurrences, and prostate calcifications confirmed on the transrectal ultrasound (TRUS) examination of the prostate. Symptom severity was self-estimated with the NIH-Chronic prostatitis Symptom Index (CPSI) and the International Prostatic Symptom Score (IPSS) questionnaires. Participants were randomly assigned to two groups. All underwent TRUS and the Meares–Stamey "four-glass" test. Patients of both groups received antimicrobial treatment (according to the results of susceptibility tests) for 30 days, while patients of Group 2 received additionally l-methionine 500 mg b. i. d for 2 months. After 4 weeks of therapy, the NIH-CPSI and IPSS tests were repeated. Follow-up included also interview, physical examination, TRUS, and "four-glass" test. Patients were followed for 6 months. **Results:** A total of 10 patients (5+5) were investigated in both groups. No significant differences were found between groups regarding median age, prostate volume, and bacterial susceptibility. Microbiological eradication occurred in similar proportions between the two groups. Similarly, the resolution of clinical symptoms occurred in equivalent numbers of patients belonging to Groups 1 and 2. Analysis showed in both groups highly significant improvements of symptoms, assessed with both the NIH-CPSI and IPSS tests. No difference in the number and location of calcifications after treatment between groups was also found. One patient of Group 1 experienced a clinical recurrence within 6 months after conclusion of treatment. **Conclusion:** No clear recommendations can be made from this pilot study. Thus, the preventive effect of l-methionine remains unknown and evidence for its use in this setting is lacking, but randomized trials with large numbers of participants would help to determine the role of urinary acidification in the treatment or prevention of recurrent CBP.

Keywords: *L-methionine, prostate, prostate calcifications, prostatitis, prostatitis recurrences*

Introduction

Chronic bacterial prostatitis (CBP) is a condition characterized by frequent clinical recurrences which have been associated with incomplete pathogen eradication and transition of planktonic bacteria (free-living bacteria that usually grow in nonorganic surfaces in low numbers) to sessile, chemoresistant, quorum sensing-activated biofilms. When biofilms are developing on the surface of prostatic calculi, biofilm extracellular material forms a barrier hindering the penetration and action of antibacterial agents. Therefore, the probability of attaining a cure decreases substantially.[1] Thus, the current pharmacological research in the field of bacterial prostatitis focuses on the investigation of new prostatotropic antibacterials or on the combinations of available antibiotics with prostatic microenvironment modifiers.[2] Driven by the limited number of previous studies addressing this topic, we designed a pilot study to investigate whether acidification of urine and prostatic microenvironment decreases CBP recurrences.

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Address for correspondence:
Dr. Konstantinos Stamatiou, 2 Salepoula Street, 18536 Piraeus, Greece.
E-mail: stamatiouk@gmail.com

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Materials and Methods

This ethically approved pilot study was conducted between February 01, 2019, and December 20, 2020. The patient population for this study included subjects with a confirmed diagnosis of CBP (National Institutes of Health [NIH] category II), history of CBP recurrences, and prostate calcifications confirmed on the transrectal ultrasound (TRUS) examination of the prostate.

Inclusion criteria

Patients suffering from conditions that influence bacterial virulence or host response (e.g., immunodeficiency and abnormalities of the urogenital system) and patients who received antibiotics or immunosuppressive treatments within 4 weeks of the recorded visits were excluded from the study. Patients diagnosed with prostatic diseases other than CBP (NIH category I acute bacterial prostatitis, NIH category III chronic prostatitis/chronic pelvic pain syndrome, overt symptomatic benign prostatic hyperplasia, and prostatic neoplasia) as well as patients exhibiting confounding factors (e.g., indwelling catheters, cystostomy, ureterostomy, ureteral stents, previous prostatic surgery or radiotherapy, and incomplete compliance to antibacterial therapy assessed by interviewing patients at the end of treatment) were also excluded.

Patient assessment

Participants underwent a brief interview with complete clinical history. Symptom severity was measured using the NIH-Chronic Prostatitis Symptom Index (CPSI) and the International Prostatic Symptom Score (IPSS). All participants underwent the Meares and Stamey ("four glass") test. Microbiological evaluation included the (i) first voided urine sample (VB1), (ii) midstream urine sample (VB2), (iii) expressed prostatic secretion (EPS) and the (iv) post prostatic massage urine sample (VB3). An abdominal ultrasound, and post-void residual urine measurement was also performed to all participants.

Calcification evaluation

A TRUS scan was performed on the eligible patients in order to provide both axial and sagittal images, thus improving the evaluation of the number and location of calcifications. TRUS was performed using an 8.0-MHz rectal probe (GE Healthcare, LOGIQ 3). The prostate volume (PV) was measured by TRUS using the formula for an elliptic volume. Besides larger, more echogenic foci that caused acoustic shadowing, also linear calcifications – mainly located between transitional and peripheral zones of the gland – were assessed. A single radiologist performed all TRUS procedures and measured calculi. A detailed description of our prostate calculus evaluation protocol is presented in details in previous publications from our group.[3]

Microbiological evaluation

Eligible patients underwent the Meares–Stamey "four-glass" test, based on cultures of first-void (VB1), preprostatic massage/midstream (VB2), postprostatic massage urine (VB3) specimens, and EPSs obtained during prostatic massage. Appropriate antimicrobial agents – according to susceptibility tests – were administered to confirmed cases of CBP for a period of 4 weeks (mainly fluoroquinolones).

Microbiological tests were considered positive when: (1) bacteria grew in the culture of EPS and VB3 specimens and did not in VB1 and VB2 and (2) bacterial colonies in VB3 were higher in number compared to VB1 and VB2 specimens. Given that no standard cutoff levels of the number of bacteria in both urine and prostate secretion samples are defined by consensus for the diagnosis of CBP, we did not define a lower threshold for such specimens. Cultures, identification, and semi-quantitative assays for *Mycoplasma hominis* and *Ureaplasma urealyticum* were performed using the *Mycoplasma* IST2 kit (bioMerieux, City, France). *Chlamydia trachomatis* was detected by direct immunofluorescence, using monoclonal antibodies against lipopolysaccharide membranes (Kallestad Lab., TX, USA). Urine samples were cultured undiluted in blood and MacConkey agar plates (Kallestad, USA) and subjected to centrifugation for microscopic examination of the sediment. Evaluation of culture results was performed by two specialist microbiologists, who were blinded to patient records. Identification of traditional pathogens was performed by conventional methods and the Vitek-2 Compact system (bioMerieux, France), and susceptibility testing was performed by disc diffusion and/or the Vitek-2 system. Interpretation of susceptibility results was based on Clinical and Laboratory Standards Institute guidelines.[4]

Treatment

Selected patients were randomly assigned to two groups using an online random sequence generator (https://www. randomizer. org/). Patients of both groups (Groups 1 and 2) received antimicrobial treatment according to the results of susceptibility tests (mainly fluoroquinolones and fosfomycin or minocycline in a few cases) for 30 days, while patients of Group 2 received additionally l-methionine 500 mg b. i. d for 2 months.

Therapy outcome evaluation

After 4 weeks of therapy, the NIH-CPSI and IPSS tests were repeated. Follow-up included also interviews, physical examination, TRUS, and the "four-glass" test. The microbiological response to antibacterial therapy was defined in a manner similar to that of Naber *et al*.: (i) eradication: baseline pathogen was eradicated; (ii) persistence: baseline pathogen was not eradicated; (iii) superinfection: baseline pathogen was eradicated with the appearance of a new pathogen.[5] Patients were followed up for 6 months.

Statistical analysis

The *t*-test was used to analyze differences between means. An alpha error inferior to 5% ($P < 0.05$) was set as a significance level for each comparison. The statistical analysis program used in the study was the SPSS Data Analysis software, version 15 (IBM Co., 1 New Orchard Road, Armonk, New York, United States).

Results

A total of 10 patients were included in this pilot trial. All patients reported chronic pelvic discomfort and genital pain, with or without lower urinary tract symptoms and sexual dysfunction. No significant differences were found between groups regarding mean age and PV [Table 1]. The most common symptom in both groups was scrotal/testicular pain (reported by 5 and 4 patients of Group 1 and Group 2, respectively). The most common pathogen in both groups was *Escherichia coli* (found in 3 and 4 patients of Group 1 and Group 2, respectively; $P > 0.05$). Data regarding patient demographics, clinical symptom presentation, and microbiological profiles are listed in Tables 1 and 2.

Microbiological eradication occurred in similar proportions between the two groups. Similarly, the resolution of clinical symptoms occurred in equivalent numbers of patients belonging to Groups 1 and 2. Analysis showed in both groups highly significant improvements of symptoms, assessed with both the NIH-CPSI and IPSS tests. No difference in the number and location of calcifications after treatment between groups was also found. One patient of Group 1 was referred with clinical recurrence within 6 months after conclusion of treatment. Data regarding treatment outcome comparisons are listed in Tables 3 and 4.

Discussion

The use of urine pH modifiers for the symptomatic treatment and prevention of urinary tract infections (UTIs) is a very old and common practice. It is described in some national formularies and is also widely promoted by primary health-care practitioners.[6] The most commonly used are urinary Alkalizers such as potassium citrate, sodium citrate, and sodium bicarbonate. In contrast, urinary acidifiers are less commonly used although they have been widely recommended for the prevention and treatment of UTIs since 1965.[7] The mechanism of action suggested for both urinary alkalizers and acidifiers in UTI is that changing urine pH directly reduces symptom severity on bladder and urethral mucosae while rendering the microenvironment of the affected organ hostile for the bacteria. Moreover, evidence suggests that both urinary alkalizers and acidifiers might be a beneficial therapeutic supplement to patients who have or have been treated for uric acid and struvite renal stones, respectively.[8,9] L-methionine is an amino acid with reported acidificating and biofilm-inhibiting properties.[10] This dual mechanism of action renders methionine ideal for the treatment of patients with CBP recurrences. In fact, biofilms are an aggregate of microorganisms in which cells

Table 1: Demographics and microbiological findings

	Group 1	Group 2	*P*
Demography			
n	5	5	>0.05
Mean age (years)	44.2	45.8	>0.05
Mean prostate volume (ml) (minimum-maximum)	42.58 (25.9-55)	42.4 (23-68)	>0.05
Main symptom			
Scrotal/testicular pain	3	4	
Frequency and suprapubic pain	1	0	
Perineal pain and SD	1	0	
Obstructive LUTS	0	1	
Microbiological presentation			
E. coli	1	2	
E. coli + CoNS	1	1	
E. coli + *Enterococcus* sp.	1	1	
Enterococcus sp.	1	0	
CoNS	1	1	

SD: Sexual dysfunction, LUTS: Lower urinary tract symptoms, CoNS: Coagulase-negative *Staphylococcus, E. coli: Escherichia coli*

Table 2: Bacterial isolates from expressed prostatic secretion and post massage samples

Bacteria	*n*	Any resistance, *n* (%)	Full sensitive, *n* (%)
Monoinfection			
E. coli	3	2 (66.6)	1 (33.3)
Staphylococcus CoN	2	1 (50)	1 (50)
E. faecalis	1	1 (100)	0
Mixed			
E. coli	2	2 (100)	0
Enterococcus		2 (100)	0
E. coli	2	0	2 (100)
CoNS		0	2 (100)

E. coli: Escherichia coli, E. faecalis: Enterococcus faecalis, CoNS: Coagulase-negative *Staphylococcus*

Table 3: Clinical outcome at the end of therapy

Scores (mean)	Group 1	Group 2	*P*
Pretreatment CPSI	22.4	21.7	>0.05
Posttreatment CPSI	8.6	7.8	>0.05
Difference between mean pre- and posttreatment CPSI	13.8	13.9	>0.05
Pretreatment IPSS	14.6	15.1	>0.05
Posttreatment IPSS	8.4	9.2	>0.05
Difference between mean pre- and posttreatment IPSS	6.2	5.9	>0.05

CPSI: Chronic Prostatitis Symptom Index, IPSS: International Prostatic Symptom Score

Table 4: Microbiological outcome at the end of therapy and follow-up

	Group 1	Group 2	*P*
Pathogen eradicated, *n* (%)	5 (100)	5 (100)	>0.05
Superinfection	1	0	>0.05

are frequently embedded within a self-produced matrix of extracellular polymeric substance and adhere to each other and/or to a surface. The development of biofilm greatly increases the tolerance of pathogens to antibacterial agents. Up to 80% of human bacterial infections are biofilm associated to various extents.[11] Since biofilms contribute to refractory CBP, dispersal of biofilms can turn microbial cells into their more vulnerable planktonic phenotype and improve the therapeutic effect of antimicrobials as they lead to antibiotic resistance and failure of effective clinical treatment.[12] It is not known whether and in what extend l-methionine can acidify the microenvironment within the prostate gland, though according to our anecdotal experience, a slight-to-moderate acidification of total ejaculate occurs following L-methionine administration. It should be mentioned that few studies examined the role of acidification of urine in UTI prevention. According to some studies, ascorbic acid and l-methionine are non-inferior to the standard antibiotic therapy in alleviating the symptoms, eliminating bacteriuria, and reducing the incidence of uncomplicated UTI recurrences. However these studies are limited by small sample size and/or lack of control for confounding dietary factors that might alter urinary pH.[13-15] In contrast, robust studies showed that l-methionine is noninferior to the standard antibiotic therapy in alleviating the symptoms, in eliminating bacteriuria, and in reducing the incidence of uncomplicated UTI recurrences.[14,15]

This study failed to demonstrate any benefit from the addition of L-methionine to conventional antimicrobial treatment in CBP patients. The reason remains unknown, however, the small size of sample on the referral of prostatitis patients owed to the impact of the COVID-19 disease and the relatively short follow-up may be the primary causes. Although zwitterionic fluoroquinolones used to treat these patients are effective either in alkaline and acid conditions, since we defined no cutoff value for the urine pH, it is possible that an excess acidification following l-methionine administration might have reduced the effectiveness of the methionine–quinolone combination.[15] It is also possible that the used dosage of l-methionine was insufficient to achieve drastical alterations in the intraprostate microenvironment.[16]

Conclusion

No clear recommendations can be made from this pilot study. Thus, the preventive effect of l-methionine remains unknown, and evidence for its use in this setting is lacking. Randomized trials with large numbers of participants, however, may help to determine the role of urinary acidification in the treatment or prevention of recurrent CBP.

Ethical considerations

The authors state that the protocol for the research project has been approved by the Ethics Committee of the institution within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo 2008).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Review Article

A Review of the Impact of COVID-19 Pandemic on Urology Residence Training

Abstract

Introduction and Objective: Since March 11, 2020, when the World Health Organization declared COVID-19 as a pandemic, a significant strain was placed on the worldwide health-care system. Although urology does not stand at the frontline of care for patients with COVID-19, every practicing urologist has been affected by the global outbreak. The impact of the COVID-19 pandemic on urology residency training was evaluated taking into account the residents' point of view regarding these unprecedented circumstances. **Evidence Acquisition:** We performed a literature review on the current evidence based on urology residency training during the COVID-19 pandemic. Relevant databases (MEDLINE, Scopus, and Cochrane Library) were searched (until June 2021), and the main inclusion criterion was the presence of residents' or directors' opinion on their residency training program during the COVID-19 pandemic. **Evidence Synthesis:** The search identified 72 articles. A total of 14 studies reporting on more than 2500 residents were eligible for inclusion. The articles were analyzed, and the results are presented in the current review. **Conclusions:** This unprecedented situation has critically affected urology residency training. A decrease in operation volume, especially those in which residents were directly involved as well as in the majority of academic activities, has been reported by many studies. Furthermore, the COVID-19 pandemic has generated a significant impact on trainees' mental well-being and lifestyle. On the other hand, the lockdown stressed the opportunity to implement innovative training tools, such as smart training programs and surgical skill development activities monitored by expert urologists.

Keywords: *Coronavirus and urology residency training programs, COVID-19 and urology residency training, urology residency training and COVID-19, urology residency training during the pandemic*

Panagiotis Velissarios Stamatakos, Ioannis Glykas, Charalampos Fragkoulis, Athanasios Dellis[1]

Department of Urology, General Hospital of Athens "G. Gennimatas", [1]Department of Surgery, School of Medicine, Aretaieion Hospital, National and Kapodistrian University of Athens, Athens, Greece

Introduction

The COVID-19 pandemic has dramatically transformed urologic training worldwide. A massive reduction of face-to-face medical consultations as well as of many elective surgical procedures have been reported recently.[1] Several hospitals have reassigned their residents to provide critical care to COVID-19 patients.[2] This caused a major reduction of residents' involvement in medical visits and surgeries and a decrease of many educational and scientific activities.[3,4] Moreover, trainees' mental health and well-being suffered a forced modulation with social distancing and the fear of contamination and/or transmitting the disease to relatives and patients to be some of the problems and concerns that affected urology residents worldwide. Therefore, many studies indicate that a significant proportion of urology residents have been experiencing anxiety and depression disorders during the pandemic period.[5,6] The objective of this review is to evaluate and depict the impact of the COVID-19 pandemic on clinical and surgical training, educational activities, health, and quality of life of urology residents worldwide taking into account the residents' point of view regarding these unprecedented circumstances.

Evidence Acquisition

Data retrieval-literature search

This is a narrative review. Two authors (IG, PV) performed a literature search independently using PubMed/MEDLINE, Scopus, and the Cochrane Library until June 2021, with no language restriction. Search algorithm was constructed using the following terms and their associated MeSH terms and

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

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Boolean operators: "training," "urology," "residency," and "COVID-19."

Duplicate studies were identified and removed. Review of citations within the articles identified additional relevant articles. Any disagreements were resolved on consensus with a third reviewer (CF).

Eligible studies

We considered eligible for inclusion studies which contained data from the resident's or the director's point of view on the topic. The main inclusion criterion was the presence of residents' or directors' opinions on their residency training program during the COVID-19 pandemic. Therefore, all studies in which online resident and director surveys were conducted were included in the analysis.

Study selection

Record evaluation and article selection were performed and based on the previously defined inclusion criteria. The reports were analyzed, and the articles to be included in the review were selected.

Evidence Synthesis

Search results

Literature search revealed a total of 72 reports. From this, a total of 14 articles that complied with the previously defined inclusion criteria were selected for analysis. These articles represent a total of more than 2500 residents. Table 1 summarizes information on the 14 included articles.

Study analysis

The article by Rosen *et al*. was based on a 35-item questionnaire which was distributed to urology residency program directors by the Society of Academic Urologists. The survey was distributed to 144 residency programs in the USA and had a response rate of 45% among the heads of the training programs (65 responses). The results of this study indicated that programs in states with higher incidence of COVID-19 were more likely to report resident redeployment (48% vs. 11%, $P = 0.002$) and exposure to COVID-19 positive patients (70% vs. 40%, $P = 0.03$), and were less likely to report concerns regarding residents' exposure (78% vs. 97%, $P = 0.02$) and personal protective equipment availability (62% vs. 89%, $P = 0.02$). Due to COVID-19, 60% of the residency programs reported concerns that residents will not meet case minimums while all programs had begun to use video conferencing and the majority planned to continue.[3]

Amparore *et al*. designed a 25-item online survey which was sent to all Italian residents evaluating residents' routine involvement in "clinical" (on-call duty, outpatient visits, and diagnostic procedures) and "surgical" (endoscopic, open, and minimally invasive surgery) training activities before and during the COVID-19 period. Overall, 351 of 577 (60.8%) residents completed the questionnaire. The study reported a severe reduction (>40%) or complete suppression (>80%) of training exposure ranged between 41.1% and 81.2% for "clinical" activities and between 44.2% and 62.1% for "surgical" activities during the pandemic. This reduction was even more pronounced for senior residents attending their final year of training.[4]

The study by Khusid *et al*. was based on an anonymous, voluntary, 47-question survey which was sent to all the certified urology residency programs in the United States. Three hundred and fifty-six of the approximately 1800 residents in the USA (20%) responded. Results of the study showed that the perception of access to personal protective equipment, local COVID-19 severity, and perception of vulnerable household members were important risk factors regarding mental health outcomes. Risk factors, for declination of redeployment, included current redeployment, having children and concerns regarding the ability to reach case minimums; and for concerns regarding achieving operative autonomy included cancellation of elective surgeries and postponement of surgical activities of higher training level.[7]

On the other hand, Busetto *et al*. designed an anonymous online survey with 36 items sent through e-mail to Italian Urology residents with a response period of 72 h. Three hundred and eighty-seven of the 577 residents in Italy responded (67.1%). Three geographical areas were created based on the prevalence of COVID-19, and participants were categorized as those working only in COVID hospitals, as well as "junior" and "senior" residents. The study reported that clinical and learning activities were significantly reduced for the overall group, whereas working only in a COVID hospital and having "senior" resident status were independent factors associated with a higher decrease of outpatient activity. Although that, the study report that the COVID era can offer an opportunity to implement new innovative training techniques.[8]

Rasyid *et al*. designed a cross-sectional study based on a web questionnaire (Survey Monkey) with an e-questionnaire link sent to all practicing urologists in Indonesia. Among residents, the response rate was 220/220 (100%) whereas trainees reported high rates of using personal protective equipment. The study concluded that the COVID-19 pandemic has caused a decline in urology services in both outpatient clinics and surgery services.[9]

The article by Paesano *et al*. was based on a multiple-choice nonvalidated survey answered online by residents from 18 countries coming from Latin America and Spain. A total of 148 responses participated in the study. Of the total, 82% mentioned that their urology department's activity was significantly reduced, whereas 15% stated that the urology activity has been closed completely and 3% continue their regular clinic activity. At the same time, 75% and 65% of the participants answered that their surgical

Table 1: Article information on urology residency training programs during the pandemic

Author	Month/year of publication	Country	Number of participants	Comments
Rosen GH *et al*.	11/2020	USA	65 residency programs in the USA	35-item questionnaire distributed to urology residency program directors, exploring residency program changes related to the COVID-19 pandemic
Amparore D *et al*.	8/2020	Italy	351 residents	25-item online survey to compare clinical and surgical training activities before and during the COVID-19 period
Khusid JA *et al*.	9/2020	USA	332 residents	47-question survey on educational and well-being issues
Busetto GM *et al*.	11/2020	Italy	387 residents	36-item online survey concerning clinical/surgical activities, social distancing, distance learning, and telemedicine
Rasyid N *et al*	11/2020	Indonesia	369 urologists and 220 residents	Cross-sectional questionnaire distributed to all practicing urologists and the chief resident in each center distributed the e-questionnaire to urology residents
Paesano N *et al*.	7/2020	18 countries from Latin America and Spain	148 residents	Cross-sectional designed, multiple-choice, nonvalidated, online survey Questionnaire was developed through the CAU EDUCACION platform
Fero KE *et al*.	9/2020	USA	64 program directors and 106 residents	27-question cross-sectional survey of program directors and residents at accredited US urology residencies
Campi R *et al*.	1-2/2021	58 countries worldwide	501 residents from 58 countries	Cross-sectional, 30-item, web-based survey conducted through Twitter, evaluating the urology residents' perspective on smart learning modalities
Abdessater M *et al*.	6-7/2020	France	275 residents	Anonymous questionnaire evaluating the pandemic added stress, and its negative impact on work and training quality sent to all the members of the French Association of Urologists in Training
Teixeira BL *et al*.	1/2021	Portugal	43 residents	A 30-question online survey was sent to all urology residents in Portugal to evaluate the reduction of clinical workload and its impact on residency training programs
Yee CH *et al*.	2/2021	Hong Kong	33 residents	Institutional data from all urology centers in the Hong Kong public sector during the COVID-19 pandemic were obtained. An online anonymous questionnaire was used to evaluate the impact of COVID-19 on resident training
Prezotti JA *et al*.	7-8/2021	Brazil	468 residents	Web-based survey sent to Brazilian urology residents from postgraduate years 3 to 5 to collect data on clinical practice, training, and behavioral changes after 4 months of COVID-19
Rajwa P *et al*.	9/2020	Poland	229 urologists and urology residents	28-question online survey. The questionnaire evaluated basic demographic and professional characteristics, and the impact of the COVID-19 pandemic on everyday work, mental status, and private life
Degraeve A *et al*.	12/2020	Belgium	62 residents	Self-administered anonymous questionnaire evaluating the risk of burnout in a pandemic situation and its impact on the quality of training sent to the members of the European Society of Residents in Urology of Belgium

and academic training has been partially or completely affected, respectively. As a result, the COVID-19 pandemic affected negatively the residency programs, and most of the surveyed residents supported that the period of residency should be extended.[10]

Another cross-sectional survey designed by Fer *et al* conducted among program leaders and residents at accredited United States (US) urology centers. Total cohort responses were reported and compared between those in high versus low COVID-19 geographic regions and between program leaders versus residents. The majority of participants reported decreased surgical volume (83%–100%) and decreased size of inpatient resident teams (99%). Regarding new technologies, 99% and 95% of participants reported increased use of telemedicine and a transition to virtual educational models, respectively. Nevertheless, the article draws attention to the downstream effects of the COVID-19 pandemic on urology residents' surgical and clinical training.[11]

Smart learning modalities and contents were studied in detail by Campi *et al*. A 30-item web-based survey was conducted through Twitter with 501 urology residents from 58 countries participated. More than half of the participants considered prerecorded videos (78.4%),

interactive webinars (78.2%), podcasts (56.9%), and social media (51.9%) as highly useful tools of smart learning. The preferred combination of smart learning included prerecorded surgical videos, interactive webinars, and prerecorded videos on guidelines.[12]

From another point of view, Abdessater *et al*. assessed the psychological impact of the pandemic on young French urologists in training. An anonymous questionnaire was sent to the members of the French Association of Urologists in Training with a total of 275 (55.5%) members responded. Study concluded that the COVID-19 pandemic had a negative impact on the psychosocial well-being of participants as more than 90% of responders felt more stressed by the pandemic. Independent factors associated with worsening of psychological condition were past medical history of respiratory disease and taking in charge of COVID-19 patients.[5]

The paper by Teixeira was based on a 30-question online survey sent to all urology trainees in Portuguese with a response rate of 54.4%. Of all, 81% stated great suppression (more than 75%) of outpatient clinical activity as well as decreased diagnostic procedures by 48.8%. The same proportion of participants reported that laparoscopic/robotic, endoscopic, and major open surgery was suppressed by 67.5%, 29.3%, and 17.5%, respectively. As a result, COVID-19 had a major impact on urology residency and many residents (32.6%) consider prolonging their residency.[13]

Similarly, Yee *et al*. examined the changes in urology practice during the COVID-19 pandemic and its impact on residency with a perspective from the SARS period in 2003. Authors declared reduced numbers of clinic attendance and operating sessions, with benign prostatic hyperplasia-related surgery (39.1%) and ureteric stone surgery (25.5%) be the most commonly delayed surgeries. Study conclude that pandemic has led to changes in every aspect of practice.[14]

In addition, a massive impact on Brazilian urology residents' training, health, and lifestyle behavior is pointed out in Prezotti *et al*. research. A web-based survey was sent to 468 urology trainees from postgraduate years 3–5. Massive reductions in every aspect of urology daily practice were reported, whereas the median damage to urological training was 6.0 (on a scale from 0 to 10). Meanwhile, modifications in health and lifestyle resulted in high percentage of sadness or depression among participants (48,2%). The authors state that new studies should confirm these findings to help developing strategies to mitigate residents' losses.[6]

More than that Rajwa *et al*. designed a 28-question online national survey to examine the COVID-19 pandemic's impact on Polish urologists. The response rate was 28.63% with 229 urologists and urology residents participated. Most of the residents (62.0%) claimed that the pandemic will harm their training, whereas 51.4% of trainees wanted telemedicine to permanently replace some of the consultations after the pandemic. In conclusion, the paper claim that there was significantly negative impact of the pandemic on Polish urologists' work, mental health, and private life.[15]

Finally, a different perspective is highlighted in Degraeve *et al*. survey. A self-administered anonymous questionnaire based on the Copenhagen Burnout Inventory score was e-mailed to the members of the European Society of Residents in Urology of Belgium with a response rate of 50% (62 participants). Although that 93% of the responders mentioned a negative impact of the crisis on their practical training, the majority of participants reported a positive impact on their life (56.%) and their theoretical training (61.7%) with a significantly reduced burnout risk score. Therefore, the lockdown did not have a negative psychological impact on Belgian residents in urology.[16]

Discussion

The COVID-19 pandemic has formed a challenging environment both for trainers and for residents in training, especially if we consider the uncertainty generated by not knowing this pandemic's duration.[17] The most obvious impact of COVID-19 on urology practice has been the reduction of different diagnostic procedures and training operations.[18] Urology has to review surgical activities based on the actual urgency of each procedure and the tradeoff between the available resources and the risks of deferring elective interventions.[19] In this setting, several national and international urological associations or societies, as well as panels of experts from the USA and Europe, have released a series of recommendations to guide the prioritization of clinical and surgical activities.[20] As a result, many centers reserved operation sessions for cancer cases and complicated stones while the number of cystoscopy sessions and prostate biopsy was reduced.[10,21] In addition to the decrease in urology surgical procedures, the European Association of Urology clinical recommendations suggest that the few nondeferrable surgical procedures that are performed during the pandemic must be carried out by experienced doctors resulting in further decrease of resident's participation in surgical operation.[22] Common goal of the measurements is to reduce surgical times, risks of infection, and complications as well as minimize spread and free up nursing staff, anesthetists, ventilators, personal protective equipment, and beds.[23]

Regarding inpatient and outpatient care, residents and fellows were redeployed to pathology and intensive care units, areas that their level of expertise could be utilized.[24] This had significant impact on residents' case logs, with mandatory training requirements at risk of being unfulfilled.[25] Meanwhile, university laboratories were closed and trainees in Ph.D. programs have been

asked to return to clinical practice.[23] As a result, curricular and face-to-face academic activities were put on hold and these delays are likely to have consequences for both clinical and basic science research.[13] Furthermore, many residency examinations along with plenty of congresses, meetings, and national conferences were delayed.[17] As such, residents from the last year had their consultant examination postponed while admissions examinations to residencies were deferred and many residents consider prolonging their residency.[6]

At the same time, several modifications in trainees' lifestyle during the pandemic included higher rates of anxiety, increased alcohol and cigarette consumption, and worsening of sexual life were noted.[6] Numeral independent factors associated with worsening of residents' mental health have been reported such as inadequate access to personal protective equipment, redeployment to a "frontline" COVID-19 service, resident's past medical history of respiratory disease as well as the presence of a household member who was susceptible to COVID-19.[1,5] From another point of view paper by Degraeve *et al*. reported a positive impact on residents' life and on their theoretical training during pandemic with a significantly reduced burnout risk score.[16]

In contrast to the abovementioned, this unexpected period has provided an opportunity to explore different virtual learning options and alternative resident education activities.[18] Initially, most urologic residency programs converted their standard conferences to digital platforms.[26] Meanwhile, urologic educators from across the world have joined forces to create daily didactic lectures, whereas several urologic oncologists have held interactive virtual viewings of their robotic surgeries.[21,27] By combining the collective virtual resources of various institutions worldwide, residents may be exposed to a higher quality and more varied cross-institutional education.[28] Furthermore, through the use of laparoscopic and robotic simulators and 3D printing of models, experts in surgical simulation may lead residents through guided surgeries. This curricular component would help residents to develop their surgical skills and learn how to perform cases that might not be performed at their institution.[29] As a result, telemedicine, prerecorded surgical videos, interactive webinars on clinical cases, and prerecorded videos on guidelines should be considered as highly useful smart learning modalities during the pandemic.[12]

Although these modalities do not replace the learning process in operating rooms, they represent a challenge and encourage new educational technology strategies generation that could be incorporated in educational programs in future. Simulation is especially valuable with the uncertain duration of the COVID-19 pandemic, as surgical volume is limited at most academic centers.[27] Even though it should be noted that distance teaching is still far from considered a daily routine.

Conclusions

The COVID-19 pandemic has a negative impact on urology residency programs worldwide. Residents' surgical and clinical training as well as trainees' well-being were severely impaired. On the other hand, online modalities such as webinars and virtual courses were widely used and hopefully COVID-19 pandemic could be the momentum to develop such consultation tools.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Percutaneous Nephrolithotomy as Minimally Invasive Treatment of Urinary Calculi

Themistoklis Ch. Bellos, Georgios S. Makris[1], Nikolaos A. Chatzikrachtis, Michael Chrisofos[1]

Department of 2nd Urology, Sismanogleio Hospital, [1]Department of 3rd Urology, University Hospital 'Attikon', Athens, Greece

Abstract

The management of urolithiasis has radically changed over the past two decades. Open surgery has been almost completely replaced by minimally invasive procedures. Percutaneous nephrolithotomy (PCNL) is considered to be the first line of treatment for large renal stones. Its use is associated with a multitude of complications. A thorough bibliographic search was performed for this review. Although PCNL comes with higher morbidity, its efficacy is unbeaten by other minimally invasive modalities. Improved skills and modifications of the procedure may reduce the probability of adverse outcomes. However, it is still associated with complications, even life-threatening ones. Since its introduction more than 30 years ago, PCNL has claimed its position as the minimally invasive procedure of the first choice for the treatment of large and complex renal stones. PCNL numbers are rising in recent years.

Keywords: *Complications, percutaneous nephrolithotomy, urinary lithiasis*

Introduction

In the last years, the surgical management of the stone disease has been transformed from an invasive treatment with inpatient hospitalization and long convalescence to a minimally invasive treatment with little or no hospital time and a short recovery period since open surgery now represents <1% of stone procedures.[1,2]

Treatment guidelines have not supported the superiority of one treatment option over another. However, the European Association Guidelines advice ureteroscopy (URS) or Extracorporeal Shock Wave Lithotripsy (ESWL) for stones in the ureter and Percutaneous nephrolithotomy (PCNL), retrograde intrarenal surgery (RIRS) or ESWL for kidney stones Table 1.[3]

The choice of specific treatment will be influenced by stone size and location, stone composition, previous stone history, patient habitus, patient and surgeon preference, and previous surgical treatments.

Evidence Acquisition

In this nonsystematic review, PubMed and MEDLINE databases were thoroughly searched from 1990 to the submission of this manuscript, using the terms: 'PCNL' and 'Percutaneous Nephrolithotripsy'. The results were screened independently by one author and rechecked by the other two authors. Any disputes were solved by a fourth author. The articles included are the most representative and innovative according to the authors' opinions. Due to the extent of the subject at hand and how easy is to get off topic a small number of articles were included.

Percutaneous nephrolithotomy

Since the first creation of a percutaneous tract for stone removal reported in 1976,[4] specific indications for PCNL have emerged, including the treatment of large, hard infected stones, obstruction-related stones, extracorporeal lithotripsy failures, and stones related with anatomic variations.[5] The usual indications for PCNL are stones larger than 20 mm, staghorn calculi and partial staghorn calculi, large stones in the lower pole, and calyceal diverticular stones. The contraindications for PCNL include pregnancy, bleeding disorders, and uncontrolled urinary tract infections.[4-6]

PCNL attains stone-free rates of up to 95%. Data from meta-analysis suggest that larger lower polar stones have lower clearance rates and higher retreatment rates. However,

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Address for correspondence:
Dr. Themistoklis Ch. Bellos, Department of 2nd Urology, Sismanogleio Hospital, Kassandras 8, Marathon 19007, Athens, Greece.
E-mail: bellos.themistoklis@gmail.com

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Table 1: Stone location and size, Suggested treatment

Proximal ureteral stone (mm)	
>10	URS (ante-or retrograde)
	ESWL
<10	ESWL or URS
Distal ureteral stone (mm)	
>10	URS
	ESWL
<10	ESWL or URS
Kidney stone (mm) (all but lower pole 10-20 mm)	
>20	PCNL
	RIRS or ESWL
10-20	ESWL or endourology
<10	ESWL or RIRS
	PCNL
Lower pole stone	
As for the upper pole	

URS: Ureteroscopy, ESWL: Extracorporeal shock wave lithotripsy, PCNL: Percutaneous nephrolithotomy, RIRS: Retrograde intrarenal surgery

there is some controversy about the optimal procedure for the management of lower polar stones of <2 cm. Based on the literature, PCNL seems to have higher stone-free rates and lower auxiliary procedures rates but with the cost of slightly increased complication rates.[7]

However, according to others, PCNL has similar recurrence rates and complication rates in comparison to ESWL.[7] In the pediatric population, stone-free rates after first- and second-look PCNL are 70.1%–97.3% and 84.6%–97.5%, respectively, with an overall complication rate of 20%.[8] In the general population, PCNL has overall complication rate of up to 83%, with minor complications being urine extravasation (7.2%), transfusion (11.2%–17.5%), and fever (21%–32.1%).[9] Major complications such as septicemia (0.3%–4.7%), colonic injury (0.2%–0.8%), or pleural injury are less common.[9]

The preoperative evaluation involves a close study and analysis of imaging which includes a computerized tomography (CT) urography.[10]

The choice of puncture either fluoroscopic or ultrasound (US) guided is dictated by the calyceal anatomy and the surgeon's expertise in a particular technique. Regardless of the choice of access ureteric catheter is placed in all cases.[11,12] The conventional PCNL is done in a prone position. This allows direct access to the posterior calyx. In the prone position, the bowels do not come in the line of puncture.[11,12] PCNL can also be done in the supine position which has the advantages of combined antegrade and retrograde approaches, easier switch of regional to general anesthesia, and usefulness in patients with cardiac comorbidities. However in the supine position, we would not be able to establish multiple channels and the space is limited. The Bart's modified of Valdivia position uses both X-ray and US guidance in combination.[13]

The advantages of US-guided access include the nonuse of radiation, minimal chance of visceral injury and proven safety in pregnancy. The downside of using US as an access modality are need for expertise, need for fluoroscopy in the dilatation stage of the procedure.[11]

In fluoroscopic-guided puncture (FGA), there is the ability to gain access to the kidney through an end on the posterior calyx.[11] The obvious disadvantage of this approach is the increased risk of radiation to the operator, patient as well as surgeon. Further, unlike the US-guided access there is no real-time visualization of visceral organs such as the kidney or the liver, thus potentially adding to the risk of injury to these organs.[11] The kidney should be approached from below the 12th rib to reduce the risk of pleural complications. The site of entry on the skin is usually just inferior and several centimeters medial to the tip of the 12th rib. The triangulation technique is the most common technique used for achieving FGA.[11]

Endoscopic guided renal access (EGA) involves the use of a flexible ureteroscope for identifying the ideal calyx for puncture and the calyx entry. Once the guide wire is passed in the rest of the steps which include dilatation are done either under endoscopic vision or under fluoroscopic guidance. In a study, the endoscopic-guided access (EGA) was compared with FGA. EGA was found to be better in terms of fluoroscopy time and the need for secondary procedures.[12]

The operating time is limited to 90 min because it has been shown in the number of studies of the risk of fluid absorption with prolonged surgery.[14-16] Complications such as hemorrhage and higher infection rates are associated with longer operation times. If it is decided that the procedure is to be staged the 14 Fr malecot tubes are inserted in the secondary access tracts.[14-16] These serve the dual purpose of achieving mature tracts and providing a conduit for subsequent intervention. The primary tracts are dilated up to 26 Fr while the secondary tracts are dilated until 20 Fr.[14]

A single tract with the use of flexible instrumentation can be performed and involves the creation of a strategic tract which clears majority of stones. Once the bulk is cleared, stones present in inaccessible calyces are approached with flexible instruments. The disadvantage of this approach is the additional cost for instrumentation.[17]

Standard PCNL is performed with the use of 24–30 Fr instrumentation. Continuous technological advancement has led to the miniaturization of endoscopic instrumentation, leading to newer concepts in percutaneous surgery such as the microperc and miniperc.[16]

Miniperc

Miniperc is PCNL done with sheath size ≤20 Fr. Miniperc was originally devised for handling stones in children, but it has been widely used in adults because of its ability to minimize blood loss and hasten recovery and with similar clearance rates.[15]

In miniperc, the scopes used range from 8 Fr to 16 Fr and the tract size varies from 12 Fr to 20 Fr. Both pneumatic lithotripsy devices and laser can be used for stone breaking modalities in mini PCNL. Mini-PCNL can also be used in situations where the infundibulum is narrow, and the smaller size of the scope can be used to navigate through the narrow infundibulum. Miniperc is ideally suited for treating stones of sizes varying from 1 to 2.5 cm. Stones of slightly larger sizes can also be tackled via miniperc by using modalities such as additional tracts.[18]

In a prospective study conducted by Mishra *et al*., the authors were able to prove that Miniperc has equal efficacy in clearing stones when compared to standard PCNL, whereas it has an advantage of less bleeding and tubeless procedure as well in some cases. They also noted that miniperc has a drawback of lengthy operative time.[16]

Microperc

Microperc uses 16G all seeing needle and a 0.9 mm flexible microperc telescope (8 Fr microsheath with 4.8 Fr shaft) and the stone is fragmented with laser. The ureteric catheter drains the pelvicalyceal system continuously. Intermittent manual suction through the ureteric catheter further reduces the intrarenal pressure.[16]

Microperc is currently used to manage single renal calculus or multiple renal calculi, which can be accessed with a single puncture and cumulative diameter of <1.5 cm in diameter.[16]

In a comparative study done by Sabnis *et al*., it was proved that microperc is similar to RIRS in terms of stone clearance and complications for small renal calculi.[19]

Complications of percutaneous nephrolithotomy

Most of the complications post-PCNL are minor.[9] Minor complications include fever and nephrostomy leak.[21] Major complications can either be related to access or stone removal.

The pleura might be injured more during supracostal access than infracostal. We usually use the infracostal approach for routine access unless special indications such as the requirement of upper pole access.[20]

Injury to the liver during PCNL is rare. If there is severe bleeding, angioembolization can be done.[9,21]

Splenic injury is also a rare during PCNL. Intraoperatively, one should suspect splenic injury if the patient is hemodynamically unstable and there is no visible bleeding. In case of uncontrollable hemorrhage, splenectomy may be required. This is usually confirmed by intraoperative US guidance.[9,21]

Injury to the colon, can occur in 0.2%–1%. The factors associated with increased risk are female gender, low body mass index, previous bowel surgery, and left side access. Symptoms include rectal bleeding, fever, pain, ileus elevated counts, and gas or feces from the percutaneous nephrostomy (PCN) tube. Intraoperative diagnosis is usually made after injection of contrast reveals colonic enhancement. Post-operative diagnosis can be made by CT or contrast study. The treatment of colonic injury is antibiotics and bowel rest. In case of delayed diagnosis, the PCN tube should be removed and a drain kept after consulting a general surgeon.[9,21,22]

Duodenal and jejunal injury is extremely rare in PCNL. CT scan helps in diagnosing duodenal injury in the postoperative period. The preferred treatment is open surgical approach, whereas, nonoperative management with bowel rest, nasogastric suction, with or without percutaneous duodenal drainage, and renal collecting system drainage has also been described. Mild fever post-PCNL occurs in about one-third of the patients, but the incidence of sepsis is much lower, in patients treated with appropriate perioperative antibiotics. Postoperative sepsis can be prevented by preoperative antibiotics, low-pressure irrigation, and use of drainage when required. Intravascular fluid overload can occur if there is injury to vessels, increased duration of surgery, hypotonic solutions, high-pressure irrigation, patients with cardiac comorbidities such as congestive cardiac failure. Extravasation of fluid during PCNL occurs due to injury to the collecting system. Systemic absorption leads to volume overload and electrolyte abnormalities. If fluid extravasation is identified in the post-operative period, then it should be aspirated percutaneously under US guidance.[9,21,22]

Post-PCNL bleeding is the most dreaded complication following PCNL. Most of the post-PCNL bleeds subside with conservative management. The causes of post-PCNL bleed are mainly multiple punctures and increased intraoperative time.[21] Superselective angioembolization (SAE) is an efficacious and safe method of controlling post-PCNL bleeding. Pseudoaneurysm is the most common finding on SAE responsible for post-PCNL bleeding.[21]

Residual stone fragments following PCNL can occur in up to 8% of the patients. When left untreated, approximately half of these patients will experience a stone-related event, for which more than half will require a secondary surgical intervention.[23] For these reasons, urologists should take all these measures to prevent their creation, carefully identify their existence postoperatively, and actively deal with them by a second look at flexible nephroscopy and/or flexible ureterorenoscopy.[24]

Prevention of complications

Appropriate training and adequate surgical skills, proper patient selection, recognition and correction of associated comorbidities, and thorough knowledge of renal anatomy and its vasculature are mandatory to prevent PCNL complications. Surgical skills and surgeons' learning curves influence PCNL outcomes, especially the complication rate.[24,25] When PCNL is performed in a dedicated stone center, a decreased operative time, a higher rate of uncomplicated access and stone extraction, and a shorter hospitalization is noted.[26]

Conclusion

Even if PCNL is associated with the increased number of complications, the percentage of the procedures used for calculi management is increasing. The reasons are several: limitations of the competitors ESWL and URS, new technological and surgical developments, but as well expansion of indications, justified by smaller instruments, and the use of flexible instruments. Proper patient selection and preparation as well as meticulous operative techniques may prevent the occurrence of complications. Prompt diagnosis of the complication and institution of appropriate measures to correct the problem will also limit its magnitude. The majority of complications can be treated conservatively and only some may require intervention.

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Review Article

Urinary Bladder Microbiome Identification Protocol with Proteomics in Bladder Cancer Patients and Review of the Literature

Abstract

Urine was conventionally thought to be sterile. However, recent evidence about the presence of microorganisms residing the urinary tract has led to an emerging field of investigation about the potential role of urinary microbiome in the pathogenesis of urinary bladder cancer. Urinary microbiota refers to the different microbe populations present in the urinary tract while a variety of genetic, environmental, and experimental parameters have been investigated as predisposing factors of microbial composition. Different methods of urine collection as well as experimental methodology on microbiome's characterization consist of well-defined factors that may alter the microbial composition. Few preliminary data have been reported so far implicating microorganisms as causative and prognostic factors of bladder tumorigenesis, examining mostly midstream-voided urine samples while the most commonly used analyzing technique was 16S rRNA sequencing method. In the present study, a protocol of microbiome identification using proteomics is reported analyzing differences in microbial composition between bladder cancer patients and healthy controls while a review of the current evidence is presented. To the best of our knowledge, proteomics has not been described as a possible method of microbiome characterization before.

Keywords: *Bladder cancer, urinary microbiome, urobiome*

Panagiotis Velissarios Stamatakos, Charalampos Fragkoulis, Ieronymos Zoidakis[1], Konstantinos Ntoumas, Athanasios Dellis[2]

Department of Urology, General Hospital of Athens "G. Gennimatas," [1]Department of Biotechnology, Biomedical Research Foundation, Academy of Athens, [2]2nd Department of Surgery, School of Medicine, Aretaieion Hospital, National and Kapodistrian University of Athens, Athens, Greece

Introduction

The microbiome consists of a wide complex set of microorganisms as a unique part of human beings, and it has been described many years ago. However, the presence of microbial population that resides in the urinary tract was unknown as urine was thought to be sterile. Recent studies discovered urinary microbiota while a few reports have been published attempting to evaluate a possible correlation between urinary microbiota and genitourinary tract malignancies. Particularly, urinary microbiota has been studied as a causative and prognostic factor in the tumorigenesis of urinary bladder cancer as well as a possible therapeutic target.

Most of the published data examining the correlation between urinary microbiota and bladder cancer have been performed with clean catch and/or catheterized urine samples. Meanwhile, 16S rRNA gene sequencing techniques were the most common approach of sample analyzing and microbiota identification while enhanced urine cultures have been rarely reported. In this study, we present a novel research protocol of urinary microbiota characterization based on proteomics analysis of the urine samples along with a review of the literature.

Evidence Acquisition

Data retrieval-literature search

This is a narrative review. Two authors (PV, CF) performed a literature search independently using PubMed/MEDLINE, Scopus, and the Cochrane library until June 2021, with no language restriction. The search algorithm was constructed using the following terms and their associated Mesh terms and Boolean operators: "urinary microbiome," "urinary microbiota," "bladder cancer."

Duplicate studies were identified and removed. A review of citations within the articles identified additional relevant articles. Any disagreements were resolved upon consensus with a third reviewer (ID).

Eligible studies

We considered eligible for inclusion studies identifying and comparing urinary

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Address for correspondence:
Dr. Panagiotis Velissarios Stamatakos, Department of Urology, General Hospital of Athens "G. Gennimatas," Athens, Greece.
E-mail: pvstamatakos@gmail.com

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microbiome among bladder cancer patients and healthy control group. The main inclusion criterion was the characterization of microbial profile of the bladder cancer group.

Study selection

Record evaluation and article selection were performed and based on the previously defined inclusion criteria. The reports were analyzed and the articles to be included in the review were selected.

Evidence Synthesis

Search results

Literature search revealed a total of 2053 reports; from this, a total of 7 articles that complied with the previously defined inclusion criteria were selected for analysis. These articles represent a total of about 200 bladder cancer patients [Table 1].

Study analysis

The association of urinary bladder microbiota in the tumorigenesis of urothelial bladder cancer was first described by Xu *et al*. in 2014. They compared the voided urine of 6 controls to 8 Urothelial cell carcinoma (UCC) patients using 16S sequencing technique. They reported that *Pseudomonas* and *Anaerococcus* were more commonly identified in UCC patients where they pointed out that the voided urine specimen may be unreliable for detecting the urinary bladder's microbiome as it can be contaminated by urethral micro-organisms.[1]

Bučević Popović *et al*. designed a study to characterize and compare the bacterial communities present in urine specimens among 12 male patients with bladder cancer and 11 healthy controls using 16S sequencing. Regarding While microbial diversity and overall microbiome composition were not signifcantly diferent between groups, authors identified operational taxonomic units (OTUs) belonging to genus Fusobacterium that were more abundant in the bladder cancer group.[2]

The study by Wu *et al*. collected 31 mid-stream urine specimens from male patients with bladder cancer and 18 specimens from nonneoplastic controls. Taxa of *Acinetobacter, Anaerococcus, Rubrobacter, Sphingobacterium, Atopostipes,* and *Geobacillus* were in abundance in bladder cancer patients compared with the control group. Furthermore, the authors reported distinct differences in microbial profile among groups with different risks of recurrence and progression.[3]

In 2019, another study by Bi *et al*. was published comparing the urinary microbiome composition of 29 bladder cancer patients with 26 noncancer control groups. All voided urine samples were obtained midstream and clean-catch and were analyzed using 16S rDNA sequencing techniques. The species *Actinomyces europaeus* was enriched in urine from patients with bladder cancer. Further examination of the relative abundance of specific genera in subgroups of cancer and control groups according to age and gender did not demonstrate any discrepancies between them.[4]

At the same time, the study by Liu *et al*. analyzed the differences in the composition of bacterial flora among mucosal tissue samples of bladder carcinoma gathered intraoperatively from bladder cancer patients and nearby normal tissues situated approximately 5 cm from the cancerous tissues. A total of 22 neoplastic mucosal samples and 12 noncancerous samples were examined using 16S rRNA gene sequencing. The study showed the enrichment of noncancerous sites by Lactobacillus and Prevotella_9, while *Acinetobacter* and *Escherichia-Shigella* were significantly increased in cancerous tissues. The researchers further analyze differences in microbiota composition between low- and high-grade disease, as well as between muscle-invasive and nonmuscle-invasive bladder cancer.[5]

Furthermore, potential differences in urinary microbial composition between men with or without bladder cancer were surveyed by Oresta *et al*. Midstream-voided urines, bladder washouts, and catheter-collected samples were processed for 16S rRNA gene sequencing. The authors reported that the urinary microbiome associated with

Table 1: Article information on urinary microbiome identification

Author	Year of publication	Number of bladder cancer group	Number of control group	Comments
Xu *et al*.	2014	8	6	*Pseudomonas* and *Anaerococcus* were more commonly identified in UCC patients
Popovic *et al*.	2018	12	11	Genus *Fusobacterium* that were enriched in the bladder cancer group
Wu *et al*.	2018	31	18	Taxa of Acinetobacter, *Anaerococcus, Rubrobacter, Sphingobacterium, Atopostipes, and Geobacillus* were in abundance in bladder cancer patients
Hai Bi *et al*.	2019	29	26	The species *Actinomyces europaeus* was enriched in urine from patients with bladder cancer
Liu *et al*.	2019	22	12	*Acinetobacter* and *Escherichia-Shigella* were significantly increased in cancerous tissues
Oresta *et al*.	NA	NA	148 residents	*Veillonella* and *Corynebacterium* were enriched in bladder cancer patients

NA: Not available, UCC: Urothelial cell carcinoma

catheter-collected urine samples by bladder cancer patients was enriched by *Veillonella* and *Corynebacterium*. Meanwhile, differences in microbiome composition were reported among different ways of sampling strategy.[6]

The first sex-specific microbiome characterization in the urine and bladder tissue of bladder cancer patients was conducted by Pederzoli *et al*. in 2020. In this study, 16s rDNA microbiome analysis on 166 samples (urine and paired bladder tissues) from therapy-naïve bladder cancer patients undergoing radical cystectomy and healthy controls was performed. Regarding urine samples, the genus *Klebsiella* was in abundance in the urine of female patients versus healthy controls, while no clinically relevant bacteria were found differently enriched in men. In tissue samples, the genus *Burkholderia* was more abundant in the neoplastic versus the nonneoplastic tissue in both sexes. In addition, researchers examined the reliability of midstream urine collection as a sampling method compared with tissue samples. They concluded that midstream-voided urine is a reliable sampling method.[7]

Protocol Description

Collection of urinary samples will be performed by urinary bladder catheterization under local antiseptic conditions from three different patients' group. The first will be consisted of patients with a history of muscle-invasive bladder cancer while the second group will be included patients previously diagnosed with nonmuscle-invasive bladder cancer and the last group will be composed of persons without previous history of urothelium malignancy. Each sample will be combined with trichloroacetic acid solution for protein precipitation. The protein extract will be mixed with urea buffer and proteins will be separated using polyacrylamide gel electrophoresis. Alkylation and tryptic digestion of proteins will be performed, and the peptides will be eluted. The peptides will be separated by liquid chromatography to be followed by their electrospray ionization and injection into the mass spectrometer.

Last but not least, identification and quantification of the peptides will be performed using DIA-NN v 1.8.1 (software for data-independent acquisition processing by Demichev, Ralser and Lilley labs) and Perseus software platform (https://maxquant.net/perseus/). Statistical analysis of the results will be performed during the last phase of our study.

Discussion

For many decades, the urinary bladder has traditionally been considered sterile based on conventional culture-dependent methods of bacterial detection. However, recent studies revealed the colonization of the urinary tract and the bladder by micro-organisms using both enhanced culture- and molecular-based techniques for microbial characterization. The microbial population (and their genes) that resides in the urinary tract has been termed "urinary microbiome." The term "microbiome" refers to the collection of genomes from all the microorganisms found in a specific region while the term "microbiota" refers to the different microbe populations present in a specific region. Although the two terms are often used interchangeably in the literature, there are small differences between them.[8]

Advances in new approaches to microbial detection have led to rapid progress in urinary microbiome knowledge. The most used methods are 16S rRNA sequencing and enhanced or expanded quantitative urine culture (EQUC). The last refers to a wide variety of culture media, aerobic and anaerobic conditions, and different growth temperatures to isolate specific living bacteria that could not grow under conventional cultures conditions. On the other hand, 16s rRNA sequencing is a molecular-based method used to characterize the urinary microbiome. Comparisons between the two methods revealed that 16S rRNA sequencing and EQUC detected similar but not identical microbiome profiles. A possible explanation for these differences is that certain bacterial genera do not grow under EQUC conditions while 16S rRNA sequencing methodology does not differentiate between living, dead, and ruptured bacteria. Nevertheless, *Lactobacillus* and *Streptococcus* have been the genera most frequently reported for the Urinary Microbiome (UM). Meanwhile, other bacterial genera such as *Alloscardovia, Burkholderia, Jonquetella, Klebsiella, Saccharofermentans*, *Rhodanobacter*, and *Veillonella* were found in the UM less frequently.[9]

However, data collected by the characterization of the microbiota of the gastrointestinal tract suggest that a great proportion of the microbes cannot be identified. As a result, the range of methods used for microbiota identification should be expanded. The rapid growth of genomic analyses such as metagenomics and nongenomic analyses including proteomics and metabolomics, coupled with bioinformatics tools, is generating large amounts of data helpful to decipher the secrets of the human microbiome.[10] Proteomics is described as the investigation of the complete protein complement expressed in a cell at a given time under specific environmental conditions.[11] These technologies are able not only to identify the human microbiome but also to uncover new genes, microbial metabolic pathway, and functional dysbiosis. However, metagenomics, although it is a powerful tool, is not a panacea. It is impossible to identify microbial expression products as well as it does not discriminate between bacteria that are active, dormant, or dead, as all microbial cells will be sequence.[12]

Knowledge of the human microbiome expanded rapidly after 2007, the year of the Human Microbiome Project (HMP) – an international effort to characterize the microbial communities in the human body and to identify each microorganism's role in health and disease. It has been shown that the human microbiome plays an important role

in host metabolism and physiology. However, HMP did not include investigation of the bladder microbiome.[13] One of the reasons for this was that it was considered unethical to obtain bladder biopsies or suprapubic aspirates from healthy individuals to characterize the bladder microbiome while avoiding sample contamination with microorganisms from the urethra. Moreover, the bladder and urine have long been considered sterile in healthy individuals. Advances in molecular biology techniques and culture methods have allowed the definition of a specific microbiome associated with several body sites previously believed to be sterile, including the urinary tract.[9]

Despite the fact that the microbiome is thought to benefit human health, micro-organisms have also been implicated in the pathogenesis of numerous malignancies such as association of *Helicobacter pylori* and human papillomavirus virus with gastric and vaginal carcinoma, respectively. While the role of the gastric microbiome in the pathogenesis of adenocarcinoma of the stomach has been thoroughly studied, few reports currently exist exploring the role of the urinary microbiome in urinary bladder cancer. One hypothesis is that the bladder microbiome may alter the extracellular matrix, which may promote or inhibit urothelial carcinogenesis.[14] Interestingly, secreted protein acidic and rich in cysteine glycoprotein located in the extracellular matrix has been implicated in bladder carcinogenesis by modulating the inflammatory response to cancer cells.[15] Another potential mechanism through which local bacteria may induce urothelial transformation includes chronic inflammation, release of genotoxic factors, and bacterial virulence. Regarding chronic inflammation and production of inflammatory factors, there is evidence that members of the urinary microbiome that mediate the formation of N-nitrosamines may contribute to schistosomiasis-induced bladder cancer. Finally, whether the urinary microbiome influences the development or progression of bladder cancer or alternatively whether bladder cancer impacts the composition, diversity, or abundance of bladder-associated microorganisms remains to be determined.[14]

At the same time, local microbiomes in BCa may influence and modulate the response to intravesical and systemic therapies. Possible mechanisms include destruction or inactivation of bacillus Calmette–Guérin (BCG) in the bladder lumen or modulation of urothelial sensitivity to BCG activity by attachment to fibronectin. Interestingly, various microorganisms such as *Lactobacillus* enable binding fibronectin and may compete BCG action. Other bacterial strains exhibit the ability to attenuate mucosal inflammation through inhibition of the NF-kB pathway, as well as interleukin (IL)-6 and IL-8.[16] It is then conceivable that the bladder microbiome might represent an important, modifiable, noninvasive biomarker in the management of BCa patients. Therefore, the role of the microbiome in modulating systemic immunotherapeutic agents will need to be evaluated.[17]

Conclusion

Urinary microbiota consists of a new era in bladder cancer research while the current literature reports indicate a possible correlation between urobiome and bladder cancer pathogenesis and prognosis. However, a variety of parameters should be addressed to increase the reliability of urinary microbiota reports. Proteomics may promote the identification of urinary microbiota constitution and reduce significant microbial diversity reported in the studies so far. We propose a urinary bladder microbiome identification protocol based on proteomics analysis of urine samples in bladder cancer patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Inflammatory Pseudotumour Post - Hernia Repair: An Unusual Cause of a Right Groin Mass

Abstract

Inflammatory pseudotumors (IPTs) are rare benign lesions resulting from unregulated growth of inflammatory cells and can be found in different anatomical locations. They are most commonly reported in the lungs or head-and-neck region, and less commonly in the genitourinary system. We report a case of an 85-year-old male with a history of hernia mesh repair presenting with a right groin mass. Radiological investigations revealed a solid inguinal mass without intrascrotal extension. The mass was excised *en bloc*, and postoperative histopathological examination revealed an IPT.

Keywords: *Hernia mesh repair, immunoglobulin G 4 disease, inflammatory myofibroblastic tumor, inflammatory pseudotumor*

Long Jiahuan Xanicia

MBBS, MRCS, Ministry of Health Holdings, 1 Maritime Square, Singapore

Introduction

Inflammatory pseudotumors (IPTs) are rare benign masses commonly located in the lungs and orbit, and less commonly in the genitourinary, gastrointestinal, heart, adrenals, and central nervous system.[1] Possible etiological factors include infection, trauma, prior surgery, and immune-autoimmune conditions.[2] Despite being regarded as benign, tumor recurrence[3] and malignant transformation[4] have been reported. While IPTs were conventionally grouped with inflammatory myofibroblastic tumors (IMTs), the authors feel that a distinction should be made between the two – whereby IPTs refer to a spectrum of reactive benign masses, while IMTs specifically refer to a distinct neoplastic myofibroblastic proliferation with possible malignant potential. Here, we discussed the clinical presentation and management of IPT involving the genitourinary region and conducted a literature review.

Case Report

An 85-year-old male presented to the Emergency Department for painless right groin mass with progressive enlargement and irreducibility. He had a past medical history of hypertension and hyperlipidemia and had previously undergone laparoscopic bilateral transabdominal preperitoneal herniorrhaphy 10 years ago with the usage of a polypropylene (Parietene™, Covidien) mesh for bilateral direct inguinal hernia. On clinical examination, there was a firm and mobile right groin mass. Hematological and biochemical investigations of a complete blood count, serum electrolytes, and creatinine were within normal reference ranges.

Ultrasonography of the groin mass [Figure 1] showed a 6.2 cm × 5.1 cm × 2.5 cm hypoechoic lesion with internal vascularity, located along the right spermatic cord, superficial to the pubic bone. Further, characterization of the mass with a computed tomography of the abdomen and pelvis [Figure 2] showed a 3.3 cm × 5.3 cm × 5.3 cm heterogeneously enhancing subcutaneous solid mass, with no intrascrotal or intra-abdominal extension. There were no inguinal, common iliac, and intra-abdominal lymphadenopathy. Some differentials at this point included a cord lipoma or tumor based on the location of the mass on scans.

Preoperative biopsy of the mass revealed a bland spindle cell lesion with positive for CD138 staining [Figure 3a and b].

He subsequently underwent a right inguinal exploration and excision biopsy of the mass for definitive diagnosis and treatment, with informed consent for possible right orchiectomy in the same

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Address for correspondence:
Dr. Long Jiahuan Xanicia, Ministry of Health Holdings, 1 Maritime Square, 099253 Singapore.
E-mail: xanicia@hotmail.com

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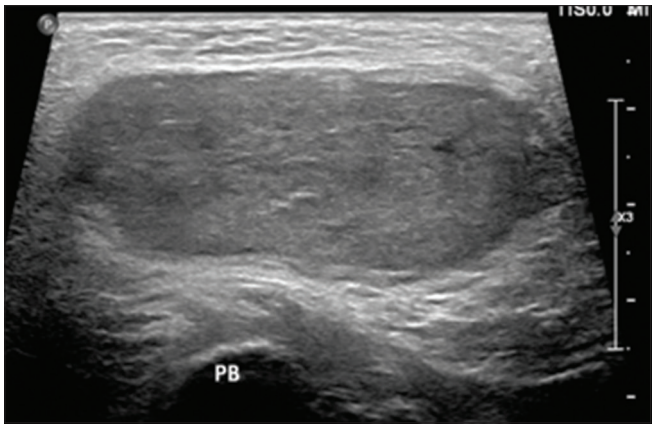

Figure 1: US right groin showing a 6.2 cm X 5.1 cm X 2.5 cm hypoechoic lesion

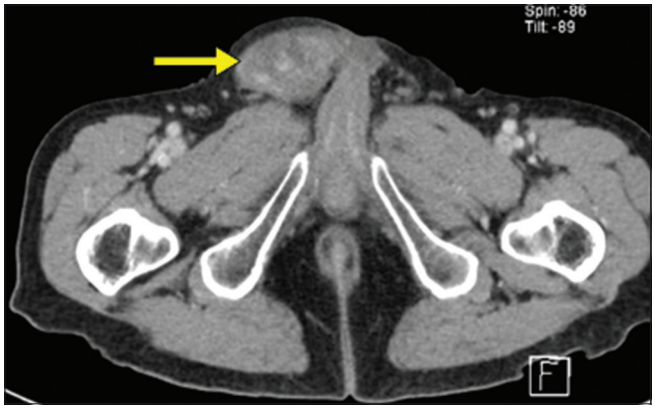

Figure 2: CTAP showing 3.3 cm × 5.3 cm × 5.3 cm subcutaneous mass (yellow arrow)

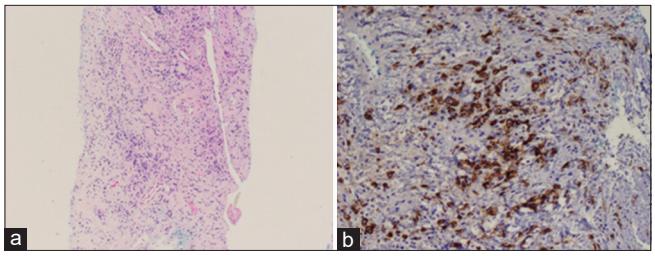

Figure 3: (a) Preoperative biopsy specimen showing a bland spindle cell lesion. (b) CD138 highlights increased numbers of plasma cells

setting. Intraoperatively, the biopsy tract was excised and sent separately for histology. The right spermatic cord was separate from and deep to the mass. There was no invasion of surrounding structures, no extension up to the inguinal canal, and no involvement of the right testes. A single feeding vessel and vein seen at the medial aspect of the mass were ligated [Figure 4b and c]. The right groin mass [Figure 4a] was excised en bloc [Figure 5a] with preservation of the right spermatic cord, and sent for histology.

Histology sections of the excised mass showed a bland spindle cell lesion, within a collagenous and edematous stroma [Figure 5b]. On immunohistochemistry, CD20 and CD3 highlighted reactive B- and T-lymphocytes – there was no light chain restriction on kappa and lambda-ISH to support the diagnosis of lymphoma. Anaplastic lymphoma kinase (ALK) expression was negative. Up to 45 immunoglobulin G (IgG) 4-positive plasma cells per high-powered field showed up in very focal areas of the mass specimen [Figure 5c and d], with an IgG4+/IgG+ ratio exceeding 40% in three hotspots. Other characteristic features of IgG4-related disease such as storiform fibrosis or obliterative phlebitis were not identified on extensive sampling. An IPT was favored as the diagnosis.

The patient remained well 1 year postoperatively while on surveillance, with no recurrence or systemic disease.

Discussion

IPT is a benign lesion resulting from the unregulated growth of inflammatory cells. The first case was described in the lungs by Brunn in 1939,[5] but it was Umiker and Iverson who coined the term "IPT" to describe these lesions in 1954.[6] They are located predominantly in the lungs and orbits, but less commonly in the genitourinary tract. Specific to the genitourinary tract, they manifest as benign growths in the bladder, kidneys, adrenal glands, or retroperitoneum.[7] Rarer locations include the ureter, prostate, urethra, scrotum, or inguinal lymph nodes.[7]

Genitourinary IPTs occurring as sequelae posthernia mesh repair are rare. To the best of our knowledge, only one case of IPT post laparoscopic hernia mesh repair has been reported to date by Dubbeling and Ramesh.[8] Our case of a groin IPT may or may not be related to the prior inguinal hernia repair performed. While one may argue that IPTs can arise secondary to an inflammatory reaction to a foreign body, for example, mesh, the hernia repair performed for our patient was 10 years ago, and therefore, it can be argued that these two events are independent of each other.

The diagnosis of IPT is obtained based on characteristic histological findings of spindle cell proliferation in a myxoid to collagenous stroma with inflammatory infiltrate composed primarily of plasma cells, lymphocytes, and/or eosinophils.[9] IMT, a neoplastic entity, can also have a similar histological appearance. While conventionally some authors regard IPT and IMT as the same entity, we feel a distinction should be made to reflect the reactive inflammatory nature of IPT, and the neoplastic nature of IMT. ALK and AE1/3 are oncogenic markers and the positivity for these markers suggests a neoplastic growth. Approximately 50% of IMT patients have ALK gene rearrangements,[10] and these are more common in younger patients with aggressive tumors.[10] The negativity for ALK and AE1/3 expression, coupled with the positive history of surgery to the region, renders a reactive inflammatory lesion IPT as the more likely diagnosis than a neoplastic lesion IMT in our patient.

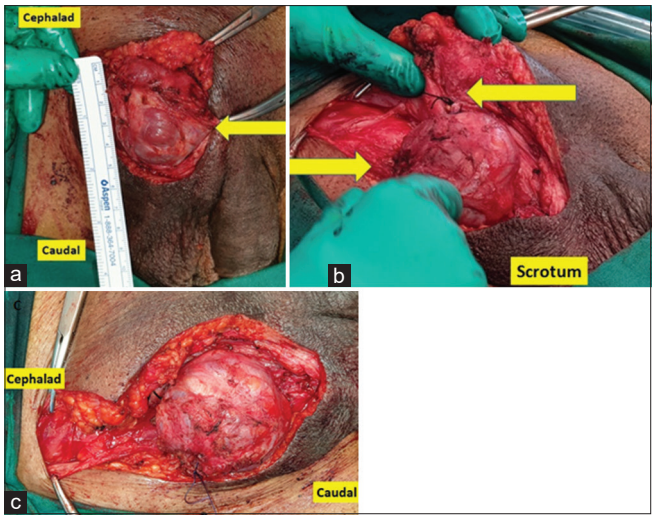

Figure 4: (a) Location of mass within the right groin; yellow arrow depicts mass. (b) Inguinal mass with feeding vessels ligated; yellow arrows depict ligated feeding vesses. (c) Close-up appearance of right inguinal mass; yellow arrows depict ligated feeding vessels

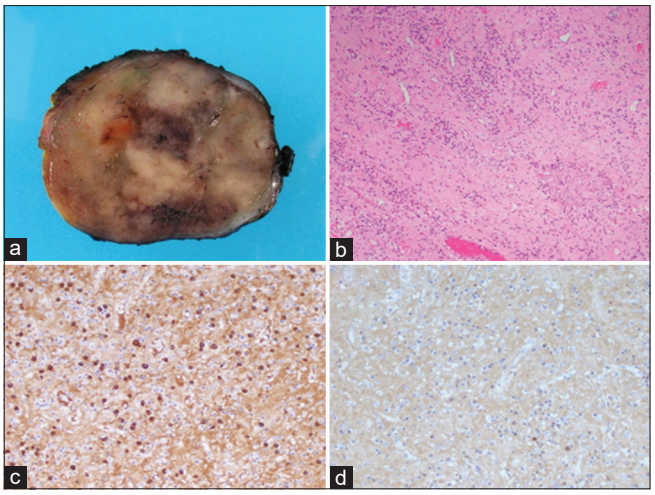

Figure 5: (a) Gross picture of mass with a solid tan-yellowish cut surface. (b) Low-grade spindle cell lesion within a fibrocollagenous stroma, with a patchy lymphoplasmacytic infiltrate. (c) IgG4 and (d) IgG immunostains showed an increased proportion of IgG4 plasma cells. This increase was seen only focally

IgG4 related disease was considered a differential for our patient due to focally increased IgG4 positive plasma cells. However, the lesion lacked the other important diagnostic features of IgG4 such as storiform fibrosis and obliterative phlebitis, and the increase in IgG4 cells was only focal. Elevated serum levels of IgG4 are not specific to the disease as they are also found in other autoimmune disorders such as Castleman disease, Churg-Strauss, and sarcoidosis.[11] Our patient displayed no evidence of systemic disease and remained well postoperatively without recurrence or need for immunosuppressive therapy.

Surgical resection remains the mainstay of treatment for IPTs in almost all anatomical locations, with exception of orbital lesions. Other treatment modalities such as chemotherapy, radiotherapy, and steroid therapy are used as adjuncts in recurrences, or when incomplete resection occurs.

Conclusion

Genitourinary IPTs, while uncommon, should be considered as a differential for groin masses in patients who have had surgery or indwelling foreign bodies. Diagnosis should be made based on histology and immunohistochemistry staining of the excision biopsy specimen. When in doubt, surgical resection should always be undertaken for curative treatment and to rule out the presence of malignancy.

Consent

Consent was obtained from the patient for the usage of radiographs, intraoperative images, and histology images.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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A Cautionary Tale of an Unfortunate Testis: Testicular Infarction and Rupture as a Rare Complication of Acute Epididymitis

Long Jiahuan Xanicia[1], Welras Long[2]

[1]Department of Emergency Medicine, Khoo Tech Puat Hospital, [2]Department of Family Medicine, National University Hospital, Singapore

Abstract

Epididymo orchitis is a common cause of unilateral scrotal pain. Infection is caused by retrograde ascent of pathogens to the epididymitis and extension to the testis. This condition typically follows an indolent course and responds well to a course of culture directed antibiotics along with analgesiaand scrotal support. Albeit rare, more severe complications such as abscess formation, testicular infarction, and testicular loss are still possible despite receiving appropriate extended antibiotic therapy. A high index of suspicion of these complications should be maintained in any presentation of acute scrotum, as early recognition could allow for salvage of the testis. We hereby present a rare case of acute epididymo-orchitis progressing to testicular infarction and rupture in a 50 year old male.

Keywords: *Epididymo-orchitis, orchiectomy, scrotal exploration, testicular infarction, testicular rupture*

Introduction

Acute epididymo-orchitis is a commonly encountered cause of unilateral scrotal pain in the emergency department and it typically follows an indolent course, with clinical resolution after antibiotics and analgesia. Complications of abscess formation, testicular ischemia, and necrosis are exceedingly rare with an incidence of 1%–2%. We report an unfortunate case of acute epididymo-orchitis progressing to testicular infarction and rupture requiring orchiectomy and discuss the workup and management of this unprecedented complication.

Case Report

A 50-year-old Chinese male presented to the emergency department with complaints of progressive pain and swelling over the left hemiscrotum over 2 months. He had a significant history of left epididymitis 1 month ago, for which he was managed with a 2-week course of ciprofloxacin. He was febrile, but other vitals were stable on arrival. On examination, his left hemiscrotum was tender, fluctuant, and swollen with a 1 cm × 1 cm defect expressing purulent discharge noted along the base [Figure 1]. Both testes were in normal lie. The left testis and left epididymal body were, however, significantly tender on palpation. Digital rectal examination revealed a 3-fingerbreadth prostate that was not tender or boggy on palpation. Laboratory markers revealed a raised white cell count of 15.57 × 10^9/L and C-reactive protein level of 15 mg/L. Renal panel was unremarkable. Urine microscopic analysis showed an elevated white cell count with positive leukocytes and nitrates. An indwelling catheter was inserted for the patient.

The initial impression was that of a left scrotal abscess with slight extension to the midline, given the physical examination findings. The patient was offered incision and drainage (I and D) keeping in view scrotal exploration. However, the patient initially declined I and D as he was averse to the idea of surgery and instead opted for a conservative approach of treatment with intravenous antibiotics. The patient was admitted for initiation of intravenous ceftriaxone.

On day 3 of admission, the patient remained febrile with uptrending temperature despite intravenous antibiotics, with increasing tenderness over his left hemiscrotum. Decision was made to further evaluate with an ultrasound Doppler of the testis [Figure 2], which showed an avascular

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Address for correspondence:
Dr. Long Jiahuan Xanicia, Department of Emergency Medicine, Khoo Tech Puat Hospital, Singapore.
E-mail: xanicia@hotmail.com

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Figure 1: Left hemiscrotum with erythematous swollen appearance and 1 cm × 1 cm defect expressing pus

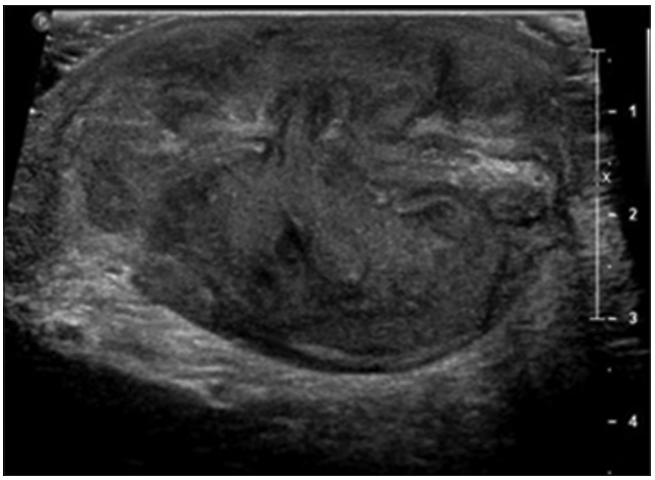

Figure 2: Ultrasound of the left testis in longitudinal view showing an anterior defect in tunica albuginea with extrusion of testicular contents

left testis with absent flow and extrusion of intratesticular contents through an anterior defect in the tunica albuginea. This was suggestive of testicular infarct complicated by testicular rupture.

Antibiotic was escalated to intravenous tazocin as urine culture returned positive for *Pseudomonas aeruginosa* at this point. The patient was immediately recounseled for surgery as a form of source control. He subsequently underwent left scrotal exploration. Intraoperative findings included an edematous scrotal wall and a 1-cm defect over the anterior aspect of the tunica albuginea with extrusion of necrotic intratesticular tissue. The left testicle was dusky and necrotic with little viable tissue remaining. A left orchidectomy and hemiscrotectomy was performed, with the placement of a lantern drain. His drain was removed on postoperative day (POD) 4 and he was discharged on POD 7 with a 2-week course of ciprofloxacin. The patient made a good recovery when reviewed in the clinic 1 month later.

Discussion

Acute scrotal pain is often encountered in the emergency department. The differentials include but are not limited to acute epididymo-orchitis, scrotal or testicular abscess, testicular torsion, torsion of appendix testis, Fournier's gangrene, hernia, and malignancy. Due to the broad list of differentials, it is impertinent to identify those that require urgent intervention. Fournier's gangrene and torsion require immediate surgical intervention, while epididymo-orchitis can be treated with antibiotics at first presentation.

Neisseria gonorrhoeae and *Chlamydia trachomatis* are the most common pathogens in epididymo-orchitis in sexually active males below 35 years old, *Escherichia coli* being the most common in elderly males.[1,2] Infection starts off with a lower urinary tract infection followed by retrograde ascent of pathogens to the epididymitis and extension to the testis. Epididymo-orchitis typically follows an indolent course, and complications of abscess development, testicular infarction, and rupture are rare,[3] and the incidence of testicular necrosis is 1%–2%.[4] In the context of epididymitis, the pathogenesis of infarction is secondary to compression of testicular vasculature by inflamed epididymal tissue.[5] Bacterial toxins causing endothelial damage leading to vascular thrombus are another mechanism.[6]

On ultrasound, epididymo-orchitis necrosis can be recognized by a juxta-epididymal string-of-bead sign (which may or may not be present), in contrast to the whirlpool sign seen in testicular torsion. The reduction of color Doppler signaling with high intratesticular resistive indices and negative diastolic flow increases the likelihood of testicular necrosis and infarct associated with epididymo-orchitis.

Delayed diagnosis of testicular infarct can lead to sepsis, atrophy, rupture, chronic pain, and infertility.[7] In our case, the patient presented with complications of testicular rupture with extrusion of intratesticular contents, eventually giving rise to a collection beneath the scrotal skin overlying the direct site of rupture, therefore exhibiting pus-pointing on examination. While it is easy to mistake this as a straightforward case of scrotal abscess which requires incision and drainage, the management of a testicular abscess is much more complex as it requires debridement of nonviable testicular tissue and a simple orchiectomy if there is extensive involvement of the testis. One-third of patients with testicular infarct may be managed nonoperatively with antibiotics, although approximately half will eventually require orchiectomy.[7]

Conclusion

Epididymo-orchitis does not always follow an indolent course and can develop complications such as abscess, testicular infarct, and rupture. Hence, a repeat ultrasound of the testes should be performed for nonresolving cases.

A high index suspicion is required for patient who do not respond to intravenous antibiotics and who turn acute ill or septic, as this might suggest a more sinister pathology requiring urgent surgical intervention.

Declaration of patient consent

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Conflicts of interest

There are no conflicts of interest.

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Testicular Torsion with Synchronous Adrenal Rest Tumors in a Patient with Congenital Adrenal Hyperplasia

Abstract

This is the case report of a 20-year-old male patient who was admitted to our clinic with a sudden onset of severe left testicular pain. Color Doppler ultrasonography revealed normal vascular supply of both testes nevertheless, but when compared with the right testis, the axis of the left testicular cord was located more posteriorly and along with swelling of the epididymis made the diagnosis of partial torsion highly probable. Bilaterally hypervascularized testicular and epididymal solid masses (up to 20 mm) were also present. Reposition of the left testicle followed by warm sponge compress was performed. The patient was suffering from congenital adrenal hyperplasia (CAH) and he was in steroid replacement therapy all his life. Testicular adrenal rest tumor is an important complication of classical CAH due to 21-hydroxylase deficiency that can potentially lead to gonadal dysfunction and infertility in adulthood. If the presence of enlarged testicular rest tumor deteriorates the stability of the testicular cord stability and renders the testis more vulnerable to torsion is a hypothesis that is hard to prove since these tumors are rare and torsion in these patients is even rarer. Nevertheless, the physicians must be aware of this condition and its benign course in order to correctly differentiate it from other diseases and avoid more radical procedures.

Keywords: *Adrenal rest tumors, congenital adrenal hyperplasia, testicular torsion*

Mustafa Bilal Tuna, Tunkut Doganca[1], Panagiotis Mourmouris[2], Neslihan Kurtulmus[3], Omer Burak Argun, Ali Riza Kural

Department of Urology, Acibadem Maslak Hospital, Acibadem Mehmet Ali Aydınlar University, [1]Department of Urology, Acibadem Taksim Hospital, [3]Division of Endocrinology and Metabolism, Medical School, Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey, [2]2nd Department of Urology, Sismanogleio General Hospital, National and Kapodistrian University of Athens, Athens, Greece

Objective

The objective of this study was to report a rare case of testicular torsion with synchronous adrenal rest tumors in a patient suffering from congenital adrenal hyperplasia (CAH).

Case Report

A 20-year-old male patient was admitted to our clinic with a sudden onset of severe left testicular pain. The patient was suffering from CAH and he was in steroid replacement therapy all his life. Physical examination revealed an edematous, swollen, and painful left testicle. Color Doppler ultrasonography revealed normal vascular supply of both testes nevertheless, but when compared with the right testis, the axis of the left testicular cord was located more posteriorly and along with swelling of the epididymis made the diagnosis of partial torsion highly probable. Bilaterally hypervascularized testicular and epididymal solid masses (up to 20 mm) were also present [Figures 1 and 2]. In addition, testicular magnetic resonance imaging (MRI) revealed bilateral testicular and epididymal masses with well-defined margins, isointense on T1-weighted and hypointense on T2-weighted images and bilateral enlarged epididymis [Figure 3]. Preoperative serum lactate dehydrogenase, beta-human chorionic gonadotrophin, and alpha fetoprotein (AFP) levels were normal. The patient's serum dehydroepiandrosterone sulfate, androstenedione, and adrenocorticotropic hormone (ACTH) levels were elevated. Immediate testicular exploration for suspicion of testicular torsion was performed. Left scrotal incision under general anesthesia in supine position was performed. 180° medial twisting of the left spermatic cord was noticed indicating partial testicular torsion. Reposition of the left testicle followed by warm sponge compress was performed. Intraoperative color Doppler ultrasound was performed to confirm the vascular supply of the organ. Both testes were fixed in the scrotum wall with 3/0 polyglactin monofilament sutures. Postoperative course of the patient was uneventful, and the patient was discharged on postoperative day 1.

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Address for correspondence:
Dr. Panagiotis Mourmouris, 2nd Department of Urology, Sismanogleio General Hospital, National and Kapodistrian University of Athens, Sismanogleiou 1 Str., Marousi, Athens, Greece.
E-mail: thodoros13@yahoo.com

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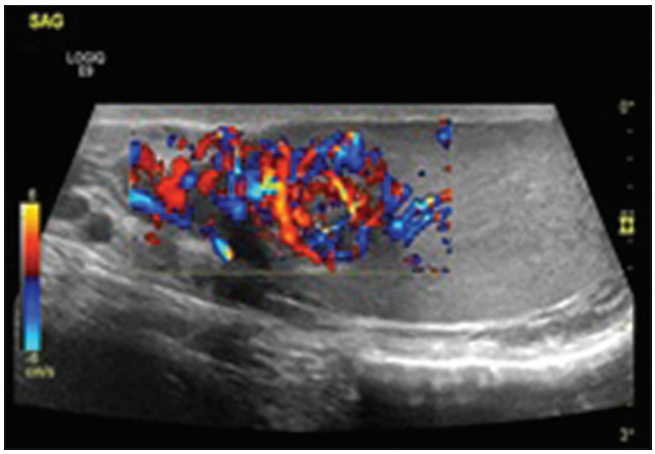

Figure 1: Scrotum Doppler (hypervascularized testicular mass)

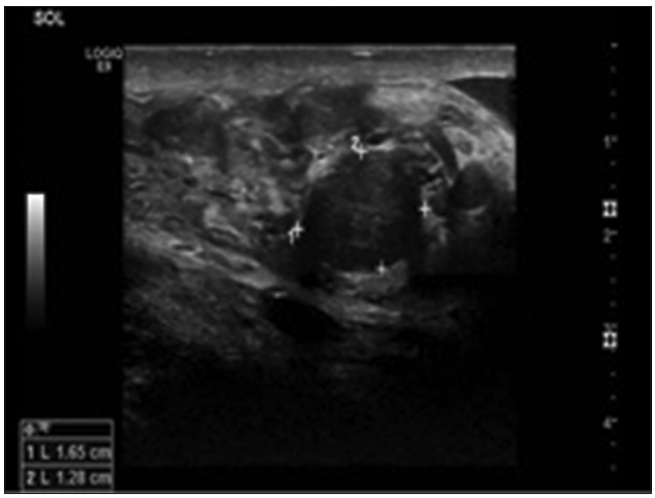

Figure 2: Scrotum Doppler (testis mass)

Figure 3: Scrotum magnetic resonance imaging (bilateral testis masses)

Discussion

CAH is a group of inherited autosomal recessive potentially life-threatening disorders characterized by enzymatic defects in steroid pathways.[1] This complex syndrome of adrenal steroid synthesis, that affects approximately 1 of 15,000 individuals, leads to cortisol, aldosterone, and epinephrine deficiency with compensatory high ACTH concentrations, adrenal hypertrophy, and accumulation of adrenal sex steroids.[2,3] Testicular adrenal rest tumor (TART) is an important complication of classical CAH due to 21-hydroxylase deficiency that can potentially lead to gonadal dysfunction and infertility in adulthood.[4] Testicular adrenal rest tissues are ACTH responsive, and they become hyperplastic under continuous ACTH stimulation. Their prevalence is reported between 0% and 94%, and most of the cases become visible during childhood.[5] These lesions can lead to tubular obstruction, oligo/azoospermia, irreversible damage of the surrounding testicle tissue, and consequently infertility by compression effect. They may also have a paracrine effect via local steroid production which may be toxic to the Leydig and/or germ cells.[6,7] Small TARTs might not be noticed in clinical examination, and imaging modalities are required for a correct diagnosis. On ultrasonography, small TARTs (<2 cm) are generally hypoechoic when compared with the normal testis parenchyma.[8] On MRI, these tumors have well-defined margins, typically isointense on T1-weighted and hypointense onT2-weighted images.[8]

The pathophysiology of these lesions is not well known. The updated hypothesis states that these tumors originate from a more steroidogenic cell type that it is already present *in utero* (like fetal Leydig cells or adults Leydig precursors).[9] It is assumed that overstimulation of ACTH and angiotensin receptor (in salt-wasting form) receptors of testicular adrenal rests in CAH may lead to these lesions in patients with poor hormonal control.[10,11]

Since these tumors are benign and they do not usually result in disease-specific complications,[12] the current treatment focuses or restores fertility in adult patients even though there are no specific guidelines.[13] To our knowledge, this is the first report of a testicular torsion in a patient suffering from TART. Testis rotation <360° is defined as incomplete torsion.[14] In incomplete torsion, the arterial flow is not completely interrupted and can be detected as far as the mediastinum testis.[15,16] If the presence of enlarged testicular rest tumor deteriorates the stability of the testicular cord stability and renders the testis more vulnerable to torsion is a hypothesis that is hard to prove since these tumors are rare and torsion in these patients is even rarer. Nevertheless, the physicians must be aware of this condition and its benign course in order to correctly differentiate it from other diseases and avoid more radical procedures.

Declaration of patient consent

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Conflicts of interest

There are no conflicts of interest.

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