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BANTAO Journal

Official Publication of the BANTAO Association

Incorporating Proceedings of the BANTAO Association

Published by: Balkan Cities Association of Nephrology, Dialysis, Transplantation and Artificial Organs

Printing: BANTAO, 2020

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BANTAO Journal 2020; 18(2): 47-53

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BANTAO Journal

Review

Is it Possible that Cadaver with Proven or Suspected Bacterial Infection be a Kidney Donor?

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Abstract

Kidney transplantation constitutes the primary treatment option in end-stage renal failure by offering advantages in terms of quality of life and survival. Considering that the prevalence of end-stage renal disease is rapidly increasing worldwide, the number of patients in need of kidney transplantation is also increasing. Additionally, organ transplantation comes to the fore with increasing frequency in potential donors to be patients in intensive care units who died due to different reasons. In such cases, the development of donor-derived infection in the recipient is the most important issue to consider. Donor-derived infection development puts the life of the recipient at significant risk. Also, there is no clear consensus on possible bacterial infections. In order to help prevent the development of donor-derived infection, the main theme of this article is the identification of which issues should be considered when accepting the deceased donor in terms of infectious conditions threatening the recipient and kidney.

Keywords: cadaver, kidney donor, infection

Introduction

Kidney transplantation is the primary treatment option in patients with end-stage renal failure. Successful kidney transplantation both increases the quality of life of patients and reduces the risk of mortality compared to other renal replacement therapies [1]. The available organ pool is declining, but the demand for kidney transplantation is not. To address this gap, an expanded donor concept has become popular in recent years, and marginal donors are being accepted. Individuals with risk factors for transmitting a range of infectious diseases are among these donors. Particularly, donors with multidrug-resistant (MDR) bacterial infections are encountered more frequently.

Although transplantation is a well-intentioned initiative, donor-derived infections can be associated with serious complications in kidney transplant recipients [2-4]. It is especially important to recognize potential disease transmission to recipients in terms of donor-derived infections during the deceased donor organ transplanttation period, where decision-making processes are shortened. Depending on the organ transplanted, the incidence of bacteremia varies between 8.6-26%, and it is considered to be the most important cause of morbidity and mortality. A major threat to this improvement has emerged from the progressive increase in the incidence of post-transplant infectious complications due to MDR microorganisms. These are known as the "ESKAPE pathogens," which are Vancomycin-resistant Enterococcus faecium, methicillin-resistant Staphylococcus aureus, extended-spectrum beta-lactamase-producing Klebsiella pneumoniae, carbapenem-resistant Acinetobacter baumannii, carbapenem- and quinolone-resistant Pseudomonas aeruginosa, and derepressed chromosomal beta-lactam and extended-spectrum beta-lactamase-producing Enterobacter species With the rise of MDR bacteria in hospital environments, an increasing number of potential donors are exposed to these kinds of bacteria in intensive care units. This exposure poses a significant risk for the development of donor-derived infections.

There is no clear consensus on possible bacterial infections. Two points are important in this regard: donors diagnosed and actively treated for bacterial infections and the presence of undiagnosed infections before organ procurement. In general, organs from individuals with diagnosed infection can be used with a low risk of disease transmission, since treatment is given beforehand. However, the main risk for recipients is donors with undiagnosed infection. If this situation is overlooked at first, complications may occur that are late for intervention and may cause high mortality of the recipient.

In this review, we aim to present what should be considered when accepting the deceased donor in terms of infectious conditions threatening the recipient and kidney due to immunosuppressive therapy after transplantation.

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We further seek to note the presence of undiagnosed latent infections in the donor by examining the international guidelines and case series through a literature search and provide suggestions that can be made in this regard.

Epidemiology and definitions

The term donor-derived infection is mostly used for deceased donors because if any infectious process is encountered in living donors, organ transplantation is mostly delayed, and the ideal time is expected. Donor-derived infections are defined as any infection present in the donor that is transmitted to one or more recipients [5]. Frequency of donor-derived infection is shown between 0.2% and 8% in all deceased donor organ transplantation [3,6-7]. Because of the lack of standardized reporting, the true incidence is not known.
Donor-derived infections are classified into two groups: expected and unexpected infections. Expected transmissions occur when the donor is known to have an infection, as demonstrated by positive serology or positive cultures in the donor at the time of donation. Unexpected transmissions occur when a donor is not known to be infected prior to donation [8]. In a systematic review, Rashmi *et al.* analyzed unexpected donor-derived infectious transmissions by kidney transplanttation from 139 donors. Twenty bacterial (14.4%), 21 fungal (15.1%), and 18 (12.9%) parasitic transmitted infections were reported. The most frequent bacterial infections were caused by *Mycobacterium tuberculosis* (10, 4.8%) and *Pseudomonas aeruginosa* (9, 4.3%). *Candida* species were the most frequent causes of fungal donor-derived infections (8, 3.9%) [9,10].

Helpful risk-mitigation tips

Risk assessment begins with the careful evaluation of the social and medical history of the deceased donor. Behavioral risk factors (IV drug abuse, high-risk sexual contacts) of the donor should be investigated. Terminal hospitalization period and cause of death may give an idea in terms of the presence of MDR bacterial infection. Culture and other serological tests sent during hospitalization should be reviewed in detail. Physical examination of the donor and explanted organ is also an important part of risk assessment. Additionally, the surgical team should evaluate abscesses, genital ulcers, lymphadenopathies, bowel perforation and intestinal contents in the peritoneal cavity, and the presence of granuloma in the explanted organ. Echocardiography and CT examinations may be required for any metastatic, granulomatous, or ongoing infection. Deceased donor characteristics and risk factors for donor-derived infections are summarized in Table 1.

Table 1. Deceased donor characteristics and risk factors for donor-derived infections

❖ High-risk sexual contacts
❖ Intravenous drug abuse
❖ Homelessness, incarcerated, prison more than 72 consecutive hours in preceding 12 months
❖ Travel to tropical/subtropical countries where sanitation conditions are substandard
❖ Extented length of stay in intensive care unit
❖ Follow up with open abdomen procedure
❖ Critical illness requiring vasopressor support and the need for cardiopulmonary resuscitation
❖ Unexplained eosinophilia
❖ Bowel perforation
❖ Contaminated preservation fluid
❖ Unexplained mental illnes or meningoencephalitis
❖ Unexplained fever, sweats, weight loss, pneumonia, non-calcified pulmonary nodules or lymphadenopathy
❖ Granulomas on explanted organ or unexplained organomegaly
❖ Genital ulcers

Bacteremic donors

Actively treated bacteremic donors with susceptible microorganisms may become eligible for donation. However, different data are available regarding unexpected donor infections. In a study by Freeman *et al*. from the USA in which bacteremic donors were evaluated between 1990-1996, bacteremic donor frequency was reported as 5%. *Staphylococcus*, *Streptococcus*, *Enterococcus*, gram-negative, and *Candida* species were found in the cultures of bacteremic donors. They further indicated that almost all recipients should receive a mean of 3.8±2.5 days' appropriate antibiotics postoperatively [11].
In another retrospective analysis, contaminated allografts were evaluated by Zibari *et al*. This study reviewed 599 organ transplants performed between 1993-1997 in a US state; positive blood culture was detected in 46 (7.5%), and positive urine culture was detected in 25 (4.5%) of the donors. A total of 179 recipients received organs from these contaminated donors. *Staphylococcus, treptococcus* and gram-negative microorganisms were found in the blood or urine cultures of donors. Both donors and recipients received prophylactic broad-spectrum antibiotics which were adjusted based on culture and sensitivity results. No disease transmission was observed in any of the 16 kidney recipients in their center [7].

Similar results have been reported in other case series. For example, successful liver and kidney transplantation (five kidney, two liver) from deceased donors with left-sided bacterial endocarditis (with *Staphylococcus epidermidis*, coagulase-negative *Staphylococcus, Staphylococcus hominis,* and *Streptococcus viridans*) from Spain, and five kidney, two liver, three lung, and two hearts transplantations from donors with *Acinetobacter baumanii* septic shock from Israel were performed, and donor-derived infections were not transmitted to any recipients [12,13].

Another report evaluated the effect of bacteremia that is not recognized before transplantation on the outcome of heart and liver recipients. Organisms such as *Staphylococcus aureus, Enterococcus faecalis, Acinetobacter baumannii, Streptococcus viridans, Streptococcus agalactiae*, coagulase-negative *Staphylococcus, Enterococcus faecium*, *Pseudomonas aeruginosa,* and *Serratia marcescens* were isolated from donors' blood cultures. Vancomycin and ceftazidime were administered to recipients as a surgical prophylaxis until the third day after transplantation. The study showed that unrecognized bacteremia in the donor does not have a negative clinical impact on the outcome of organ transplant recipients [14].

Essentially the question to be answered is, if the donor has a multidrug-resistant bacteremia (such as extended-spectrum β-lactamase or carbapenemase-producing *Enterobacteriaceae*, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* and multidrug resistant *Pseudomonas aeruginosa* or *Acinetobacter baumanii*) that was not cleared by standard antibiotic prophylaxis, should organs be procured?

There is no unity in the guidelines for this type of bacteremia. Experiences in the literature consist of case series and expert opinions. However, it is worth noting that different results from different cases have been reported in the literature.

As an example from Goldberg *et al*., a 36-year-old man with no significant medical background was admitted to the hospital after near drowning. Both lungs, both kidneys and the liver were recovered and transplanted into five recipients. Two days after organ procurement, sputum and bronchoalveolar lavage cultures were reported as positive carbapenem-resistant Klebsiella pneumoniae (CRKP). Antibiotic sensitivity was limited to gentamicin, colistin, and tigecycline. Regarding the two kidney recipients, no transplant infectious complications were noted, and graft functions were normal for both recipients at sixth months. Both patients received preoperative cefazolin treatment through the local protocol. However, the lung transplant recipient died. These experiences suggest that some respiratory colonized CRKB positive donors may be considered as candidate donors for organs other than the lungs [15].

In an experience from Italy, both kidneys from a donor who was an asymptomatic CRKP carrier were transplanted to a single recipient. Two days after transplanttation, the same bacteria were isolated in donor urine cultures. The recipient applied to the hospital with a high-grade fever 15 days after transplantation due to CRKP. The patient was started on meropenem, colistin, and tigecycline treatment. Antibiotic treatment was revised to ertapenem, meropenem, and colistin since bacteremia continued despite antibiotic treatment. The recipient died two months after transplantation due to resistant infection [16].

In an example reported from Brazil, a lung transplant was made from a donor who had only been in the hospital two days. Fever, hypotension, and respiratory failure developed in the recipient two days after transplanttation. The same day, A. Baumanii was isolated in the donor's bronchoalveolar lavage fluid. The recipient died on the 65th day of the lung transplant due to pneumonia and recurrence of infection at the surgical wound even though immunosuppression was stopped [17].

In another case, kidneys procured from a 21-year-old patient who was evaluated as a donor due to a gunshot were transplanted into two recipients. In the urine and peritoneal cultures taken during the transplant, MDR P. aeruginosa growth occurred three days after the transplantation. One of the recipients died shortly after transplantation due to pseudomonas infection. The other recipient was treated with colistin and amikacin for six weeks, and one year later was alive with normal kidney functions [18].

In another case presented for another resistant bacterium, methicillin-resistant S. aureus (MRSA), an intravenous drug abuser applied to the emergency department with confusion and fever. Antibiotic treatment was started, considering meningitis. Intracranial hemorrhage was detected on brain CT imaging. MRSA was isolated in blood cultures which were taken at the time of admission to the emergency room. The donor had been treated with vancomycin and remained afebrile for 48 hours. Lung, kidney, pancreas, and liver transplants were performed 36 hours after brain death. The patients with kidney and pancreatic transplantation continued with vancomycin, and no signs of infection were observed. The liver and lung recipients were successfully treated despite various MRSA infections such as cellulitis and pneumonia [19].

The lesson to be learned from these examples is that transplantation of the organ with infected or colonized with MDR bacteria poses a significant problem for transmission of donor-derived infections.

Although there are encouraging examples, there is insufficient evidence to use donors with multiple drug-resistant bacteremia. Management of donor-derived infections caused by MDR microorganisms is very difficult because of drug resistance, drug toxicities, and drug interactions with transplant medicine [20]. The results of virulent bacteremia, such as post-transplant

sepsis, graft artery rupture, or mycotic aneurysm, can be disastrous [21-23].

European guidelines recommend that organs from donors returning positive cultures for MDR bacteria may be considered for transplantation in well-defined circumstances provided there is close recipient follow-up, unless the organ to be transplanted is itself colonized [24].

Urinary tract infections (UTIs) and pyelonephritis are common among potential donors due to bacteria ascending along the urethral catheter. Any suspected UTI in potential donors should be confirmed by urine culture, and potential kidney donors with UTI should be investigated to rule out upper urinary tract infection. In case of a UTI restricted to the lower urinary tract, kidneys may be used, as they are not infected. All other organs can be safely used for transplantation [25]. European guidelines state that uncomplicated UTI/bacteriuria is not a contraindication for the utilization of kidneys, provided that adequate antibiotic treatment is given to the donor and recipient [24].

Organs from donors with bacterial meningitidis due to *Neisseria meningitidis*, *Streptococcus pneumonia*, *Haemophilus influenza*, and *Escherichia coli* can be transplanted safely [26-29]. It is important to note that not all infections carry the same risk for disease transmission; donors with meningoencephalitis with unknown etiology, *Listeria monocytogenes* meningitis, Mycobacterial meningitis, or metastatic virulent bacteremia have an unpredictable risk for donor-derived infections and mortality. Listeria species may cause a disseminated infection that is difficult to treat in the immunosuppressed patients with high-risk of relapse [30]. Similarly, meningitis caused by disseminated *M. tuberculosis* infection may be transmitted to the recipient with fatal consequences and is a contraindication for transplantation [31]. Donors with these type of infections should be avoided [3,5,32]. Also, donors with active tuberculosis infections should not be utilized [33].

To summarize international guidelines and expert opinions, it is recommended that the infected donor with readily treatable microorganisms receive appropriate antibiotic therapy for at least 24-48 hours, optimally with some degree of clinical response or improved inflammatory markers. In some cases, delaying organ procurement until the donor has received targeted antibiotics for at least 48 hours may be reasonable. After that, bacteremic donors with susceptible microorganisms may become eligible for procurement. Also, it is recommended that the recipient is treated with one or more weeks' course of antibiotics targeting the organism isolated from the donor [34,35]. General recommendations for deceased donors diagnosed with actively treated bacterial infections are reviewed in Table 2.

Table 2. Recommendations for deceased donors diagnosed with actively treated bacterial infections

❖ Important to define the isolate's resistance profile.
❖ Donor colonization should not constitute a contraindication to transplantation, except active infected kidney.
❖ Donors with a positive rectal swab for any MDR GN microorganism: all organs could be accepted for transplantation.
❖ Donors with MDR GN microorganisms isolated from airway secretions: organs other than lungs are appropriate for transplantation.
❖ Donors with a positive urine culture for MDR GN microorganisms: all organs could be accepted, except fort the kidneys.
❖ Donor with bacteremia with susceptible microorganisms who has received appropriate antibacterial treatment for at least 48 hours can be safely used as long as the same effective antibiotic therapy is continued in the recipients.
❖ There should be some evidence of a clinical response to the effective antibiotic therapy such as normalization of markers of ongoing infection before procurement.
❖ Donor should be assessed for disseminated foci of infections, this mas represent a higher risk of transmission of infection.
❖ Any meningitis caused by an unknown pathogen is an absolute contraindication for organ donation.
❖ If the donor has a positive urine culture for CRKP or CRAB, transplantation of their kidneys should be avoided unless the infection is eradicated.
❖ The organs from donors with highly resistant bacteria (ESKAPE pathogens) have rarely been used safely.
❖ Decisions regarding the use of organs that might be infected with antimicrobial resistant pathogens must be made on an indivudual basis.
❖ MDR GN: multi-drug resistant gram negative. CRKP: carbapenem resistant *Klebsiella pneumoniae*. CRAB: carbapenem resistant *Acinetobacter baumannii*.
❖ ESKAPE pathogens: vancomycin-resistant *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus*, extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*, carbapenem-resistant *Acinetobacter baumannii*, carbapenem- and quinolone-resistant *Pseudomonas aeruginosa*, and derepressed chromosomal beta-lactam and extended-spectrum beta-lactamase-producing *Enterobacter species.*

Fungal infections

Donor-derived fungal infections can be associated with serious complications, so a potential transmissible fungal infection in the donor is a contraindication for transplantation [36]. It is very important to recognize donors at risk of fungal infection. Blood and urine cultures should be taken in recipients with intestinal perforation in the donor or if *Candida* species are isolated from presservation fluids. Doppler ultrasound should be evaluated at intervals for a mycotic aneurysm that may develop in the vascular anastomosis line. Prophylactic antifungal therapy (fluconazole) should be initiated when yeast is visualized on stain or *Candida* species are isolated from preservation fluid or organs from donors with intestinal perforation [37].
C. neoformans should be considered in donors with unexplained mental illness or meningoencephalitis [38]. Also, cryptococcosis can be manifested as pulmonary nodules. Use of organs from untreated donors with cryptococcosis is not recommended. The standard regimen for the treatment of cryptococcosis is induction with lipid formulation of amphotericin B and flucytosine followed by consolidation and maintenance therapy with fluconazole. Antifungal treatment duration is 6-12 months [37].
Explanted organs that may have granuloma should undergo fungal culture and testing for antigen and antibodies to *Histoplasma capsulatum*, especially donors from the endemic regions for Histoplasma infections [37]. Positive antigen tests would be an indication for treatment for histoplasmosis, which is lipid formulation of amphotericin B for two weeks followed by itraconazole for at least one year [39].

Parasitic infections

Toxoplasmosis is caused by the intracellular protozoan parasite, *Toxoplasma gondii*. Toxoplasma seropositivity poses a great risk for the development of active toxoplasmosis in heart transplant recipients, but is rare in liver and kidney recipients [40,41]. Routine trimethoprim-sulfamethoxazole prophylaxis is effective in preventing toxoplasmosis transmission [42]. Screening for endemic infection, including *T. Cruzi* and *Strongyloides*, should be performed based on local epidemiologic guidelines [36].
As a future perspective, Yang and colleagues provide important clues to define donor-derived infections. They analyzed the non-human cell-free DNA to test for infections in the recipient's plasma. This method, which can be used to monitor broad-spectrum infections for recipients, provides comprehensive information for clinicians to optimize immunosuppression therapy [43]. Moreira *et al*. showed early increases of total cfDNA levels during acute rejection, systemic infection, and graft function after kidney transplantation [44]. Plasma dd-cfDNA levels have shown marked increases both during acute rejection and graft infection, pointing to the necessity of a combined pathogen monitoring strategy [45]. In this way, deaths due to donor-derived infections may decrease with the help of advanced laboratory techniques.

Conclusion

As a conclusion, transplantations with the expanded donors we have to consider due to the high requirements are very important for a successful transplant, while also not putting the patient at risk, especially for donor-induced infections. Therefore, all recipients of organs from suspicious donors should be informed of the risk of potential disease transmission. To minimize donor-derived infections, when obtaining deceased donor information, the entire history of the donor should be taken in great detail. Suspected or proven bacterial, viral and fungal infection status, culture results, infection sources, etc. should be thoroughly investigated. With this collected information, risk should be determined based on the severity of immunosuppressive treatment. In each transplant, the decision should be made individually according to the condition of the recipient and the donor. After the transplantation, the recipient should be followed up closely for infection; frequent monitorring of vital signs, and infection parameters such as WBC, CRP, procalcitonin and daily culture monitoring should be performed. Rapid inter-institutional communication and antibiotic prophylaxis based on in vitro susceptibility testing are crucial approaches.
The available organ pool is declining, but the demand for kidney transplantation is not. Of course, care must be taken to find the appropriate balance between minimizing the risk of disease transmission and organ wastage.
Respectfully submitted in memory of all the healthcare professionals who have died in the fight against Coronavirus all around the world.

Conflict of interest statement. None declared.

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BANTAO Journal 2020; 18(2): 54-59

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Original article

Outcomes Among Hospitalized Acute Kidney Injury - related COVID-19 Patients

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Abstract

Introduction. Although diffuse alveolar damage and respiratory failure are the key features of coronavirus disease 2019 (COVID-19), the involvement of other organs such as the kidney has also been reported. The reports of the incidence of acute kidney injury (AKI) in COVID-19 patients vary widely. In this study, we report our experience with AKI in COVID-19 patients and provide its incidence, risk factors, and prognosis to expand the current understanding of this complication.
Methods. In this single-center, retrospective observational study, we analyzed the data of 269 COVID-19 patients admitted to the Clinic for nephrology in Sarajevo, BH, from March 2020 through April 2021. Information regarding demographics, comorbidities, medications, clinical and laboratory data, and outcomes was collected from the electronic medical records. We excluded COVID-19 patients from our study if they were on maintenance dialysis or were kidney transplant recipients. The earliest day of the serum creatinine change that met the KDIGO criteria for AKI was selected as day 1 of AKI. Statistical analyzes were performed using SPSS 21 Windows (version 21.0).
Results. The median age of the patients was 64.2 years, and 59.85% of them were male. Most of these patients presented with dyspnea (96.65%), cough (92.19%), and fever (87.73%). Of all the patients studied, 69.88% were discharged, 16.73% died during hospitalization, and 13.38% were transferred to another institution. The incidence of AKI during hospitalization was 28.99% (n=78) and was significantly higher in patients who presented with eGFR <60 mL/min/1.73 m^2 (65.38 vs. 34.61%). The in-hospital mortality was significantly higher in patients with an eGFR <60 mL/min/1.73 m^2 (26 pts.) then in patients with an eGFR ≥60 mL/min/1.73m^2 (19 pts.) at presentation. Compared with patients without AKI, patients with AKI had higher levels of white blood cells (WBC), inflammatory markers, and had low pulse oxygen saturation at admission. The number of patients requiring renal replacement therapy (RRT) during hospitalization was 23. In the multivariable model, AKI (stage 3) is associated with a higher risk of hospital mortality during the follow-up period.
Conclusion. AKI in our hospitalized COVID-19 patients was common and carried high mortality, especially in patients with AKI stage 3. RRT did not improve survival.

Keywords: Coronavirus disease 19, Acute kidney injury, Renal replacement therapy, Hospital mortality

Introduction

Coronavirus disease 2019 (COVID-19) is associated with high morbidity and mortality [1]. Two other coronavirus infections, SARS 2002-03 and Middle East Respiratory Syndrome (MERS) in 2012 caused severe respiratory syndrome in humans. All three of these emerging infectious diseases are caused by coronaviruses. While COVID-19 is primarily an infection that can cause pneumonia and hypoxemia, other organs are involved, including the kidney, gastrointestinal tract, and heart. Reports are numerous, but the incidence of acute renal injury (AKI) secondary to COVID-19 (COV-AKI) is high, with a prevalence level of as much as 68% in critically ill patients in New York City, USA [2].
Most AKI cases are mild to moderate. However, dialysis rates may be as high as 30% and survival may be reduced when AKI occurs. Kidney failure appears to occur late in the course of the disease, so there may be a window for treatment. Treatment currently consists primarily of preventive measures as no directed treatment for AKI is available. This makes AKI in general, and in the current COVID-19 pandemic in particular, an essential condition to be addressed [3].
In this study, we report our experience with AKI in COVID-19 patients. The study's primary objective was to determine the incidence of in-hospital AKI in COVID-19 patients and to study baseline characteristics and la-

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boratory data associated with its development. The study's secondary objective was to identify risk factors and prognosis of AKI and thus provide a broader understanding of these complications in a hospitalized group of COVID patients at the Nephrology Clinic in the past year.

Material and methods

All adult patients >18 years of age admitted to the Clinic for nephrology with COVID-19 infection from March 2020 through April 2021 were studied in this retrospective analysis. COVID-19 infection was diagnosed based on clinical presentation, radiographic lung abnormalities, and a positive SARS CoV-2 of real-time PCR. We excluded COVID-19 patients from our study who were on maintenance dialysis or were kidney transplant recipients. We collected the demographics, prior medical history, including outpatient medications and prior level of kidney function, comorbidities, the presenting clinical symptoms when available, and in-hospital laboratory data from the electronic medical record. Laboratory data consisted of complete blood count, kidney and liver function, pulse oximetry, hemostasis parameters, creatinine kinase, lactate dehydrogenase, procalcitonin, and inflammatory markers: - C-reactive protein (CRP), ferritin, interleukine-6, and D-dimer. Our laboratory provided the normal range of these measures. The Kidney Disease Improving Global Outcome (KDIGO) (4) definition was used to identify AKI. The estimated glomerular filtration rate (eGFR) on admission was taken as baseline eGFR and was divided into <60 and ≥60 mL/min/1.73m^2. eGFR was estimated using the Modification of Diet in Renal Disease Study (MDRD) equation. The earliest day of the serum creatinine change that met the KDIGO criteria for AKI was selected as day 1 of AKI. The peak serum creatinine value was used to determine the stage of AKI, with an increase in the serum creatinine of 1.5-1.9, 2.0-2.9, and >3 times the baseline serum creatinine defined as AKI stages 1, 2, and 3, respectively.

Statistical Analysis

The distribution of baseline characteristics was summarized according to AKI status using mean ± standard deviation for normally distributed data or median and interquartile range (IQR) values for non-normal distribution. Categorical variables were presented as frequency and percentage. The mean of continuous variables was compared by using independent t-tests and the Kruskal-Wallis test (across the stages of AKI). We used the Cox proportional hazard (PH) regression to determine the association of kidney disease indicators and in-hospital mortality. Statistical analyses were performed using SPSS 21 Windows (version 21.0, SPSS Inc, Chicago, Illinois, USA). All tests were two-sided, and P values <0.05 or at a confidence level of 95% were considered significant.

Results

We pooled 269 in-hospital patients between March 2020 and April 2021. Five patients were excluded, three cases with chronic kidney disease (one case receiving regular maintenance dialysis, one with membranous glomerulonephritis, one with nephrotic syndrome), one case diagnosed with pericardial effusion after admission, one case missing the core medical record. Baseline characteristics of these patients are shown in Table 1.

The median age of the patients was 64.2 years, and 59.85% of them were male. Most of these patients presented with dyspnea (96.65%), cough (92.19%), and fever (87.73%). Of all the patients studied, were discharged 69.88%, 16.73% died during hospitalization, and 13.38% were transferred to another institution. On admission, eGFR was <60 mL/min/1.73 m^2 in 44.1% (n=107) of the patients. Patients with an eGFR <60 mL/min/1.73 m^2 at presentation were significantly older (mean age 68.03 vs. 61.22 years; p<0.0001), more likely to be males (54.03 vs. 45.96%), and have hypertension, diabetes, hyperlipidemia, and were higher smoker among other preexisting comorbidities. The incidence of AKI during hospitalization was 28.99% (n=78) and was significantly higher in patients who presented with eGFR <60 mL/min/1.73 m^2 (65.38 vs.34.61%). Twenty four, 4, and 29 of these patients had AKI stages 1, 2 and 3, respectively. Eleven out of 32 patients with documented chronic kidney disease (CKD) before admission developed AKI during the hospitalization. Overall, the in-hospital mortality was 16.73% in COVID-19 patients. The in-hospital mortality was significantly higher in patients with an eGFR <60 mL/min/1.73 m^2 (26 pts.) than in patients with an eGFR ≥60 mL/min/1.73m^2 (19 pts.) at presentation.

Table 2 shows the results of clinical and laboratory tests of the patients performed on admission. Compared with the patients without AKI, the patients with AKI had higher white blood cells (WBC) and neutrophil counts, higher levels of D-dimer, C-reactive proteins (CRP), procalcitonin, interleukine-6 (IL-6), creatine kinase, and had low pulse oxygen saturation at admission, also they appeared to have mild symptoms of dyspnea, possibly as a result of gradual deterioration of the condition to allow for adaption and compensation.

The number of patients requiring renal replacement therapy (RRT) during the hospitalization was 23 (Table 3). This represented 8.5% of all patients and 29.48% of those with AKI. All the patients who required RRT by definition had stage 3 AKI. The modalities of RRT were continuous RRT in 3 patients (13.04% of all those who required RRT) and intermittent hemodialysis in 20 patients (86.9%). One patient required both modalities of RRT.

Table 1. Characteristics of COVID-19 patients admitted in the hospital stratified by baseline eGFR

Characteristic	All patients *n* = 269	eGFR ≥60 mL/min/1.73 m^2 *n* = 162 (55.9%)	eGFR <60 mL/min/1.73 m^2 *n* = 107 (44.1%)	*p* value
Age, mean (SD)	64.2(±15.5)	61.22(±16.6)	68.03(±13.2)	<0.0001
Gender, male *n* (%)	161(59.85)	74(45.96)	87(54.03)	<0.001
BMI, median (IQR)	29(25.6-34.2)	29.2(25.7-34.3)	28.2(25.6-33.8)	0.2
Preexisting comorbidities, n (%)				
Hypertension	193(71.75)	67(34.72)	126(65.28)	<0.001
Diabetes	99(36.8)	27(27.27)	72(72.73)	0.002
COPD	24(8.92)	17(40.8)	7(29.16)	0.05
Cancer	11(4.09)	7(63.63)	4(36.36)	0.16
Smoker	121(44.98)	45(37.19)	76(62.8)	0.07
Hyperlipidemia	147(54.64)	70(47.61)	77(52.38)	0.02
Drugs, n (%)				
ACEi	138(51.3)	43(31.16)	95(68.84)	0.007
ARB	42(15.61)	24(57.14)	18(42.86)	0.2
Statin	171(63.57)	79(46.2)	92(53.8)	0.001
NSAID	48(17.84)	36(75)	12(25)	0.80
Aspirin	178(66.17)	56(31.46)	72(40.45)	0.001
Hemodynamic instability at presentation, *n* (%)	70(14.93)	31(11.89)	39(18.84)	0.03
Signs and symptoms, n (%)				
Fever	236(87.73)	143(53.16)	93(39.4)	0.04
Myalgia	118(43.86)	66(55.9)	52(44.06)	0.96
Nausea/vomiting	45(16.73)	25(55.5)	20(44.4)	0.96
Cough	248(92.19)	156(62.9)	92(37.09)	0.001
Dyspnea	260(96.65)	153(58.85)	107(41.15)	0.09
Diarrhea	52(19.54)	29(55.77)	23(44.23)	0.98
Chest pain	25(9.29)	19(76)	6(24)	0.04
AKI during hospitalization	78(28.99)	27(34.6)	51(65.4)	<0.001
Stage 1	33(12.3)	9(27.3)	24(72.7)	<0.001
Stage 2	7(2.6)	3(42.9)	4(57.14)	0.05
Stage 3	38(14.1)	9(23.7)	29(76.3)	<0.05
Disposition on discharge, n (%)				
Home	188(69.88)	114(60.63)	74(39.36)	<0.001
Transferred to other departments	36(13.38)	23(63.88)	13(36.11)	0.001
In hospital death	45(16.73)	19(42.22)	26(57.7)	0.04

Abbreviations: COPD - Chronic obstructive pulmonary disease; ACEi - Angiotensin-converting enzyme inhibitors; ARB - Angiotensin II receptor blocker; NSAID - Non-steroidal anti-inflammatory drugs

Table 2. Clinical and laboratory findings of the hospitalized patients positive for COVID-19

Characteristic	All patients	COVID-19 with AKI	COVID-19 and no AKI	p value
Initial vital signs, mean				
Temperature, °C	37.3±1.3	37.4±1.4	37.3±1.2	0.6
Respiratory rate, breaths/min	21.6±6.3	22.3±6.8	20.6±5.4	0.001
Pulse oximetry %	92.8	91.7	94.3	0.001
Pulse rate, beats/min	98.3±20	99.1±21.3	97.2±19.3	0.01
Initial laboratory dana				
WBC (10^9/L)	8.7±7.0	9.3±6.9	7.8± 7.1	0.001
Neutrophils (x10^9/L)	6.7±4.0	7.3±4.2	5.8±3.5	0.05
Lymphocyte (x10^9/L)	0.76(0.47-1.25)	0.68(0.47, 1.05)	0.91 0.63, 1.25)	0.03
PLT (x10^9/L)	138(118-190)	142(118-190)	171 130-190)	0.08
Creatinine (μmol/L)	113±65	184±342	93±73	<0.05
Procalcitonin(ng/mL)	0.06(0.03-0.15)	1.08(0.08-1.78)	0.05(0.03-0.12)	<0.05
CRP (mg/L)	78.8(4.8-19.1)	138.5±108	73.2(6.1-22.4)	0.001
D-dimer (mg/L)	1.7(0.9-3.8)	2.2(1.1-6.2)	1.1(0.7-2.3)	0.001
IL-6 (pg/ml)	15.57(3.07-39.62)	32.85(20.15-401.9)	11.61(2.71-37.82)	0.017
LDH (U/L)	403(300-546)	458(336-637)	350(270-451)	0.04
CK (U/L)	100(58-172)	118(69-223)	99(52-154)	0.03
Ferritin (ng/ml)	762.5(384-1420)	911(490.5-1667.5)	609.5(296-1086.5)	0.001

Abbreviations: WBC-white blood cells; PLT-Platelet count; CRP-C-reactive protein; IL-6-interleukin-6; LDH-Lactate dehydrogenase; CK-Creatine kinase

Table 3. SARS CoV-2 patients stratified by stages of AKI and demand for dialysis

Characteristic	Acute Kidney Injury					P value no RRT vs. RRT	P value stages AKI
	Stage 1 (33)	Stage 2 (7)	Stage 3 all pts. (34)	Stage 3 - no RRT (11)	Stage 3 – RRT (23)		
Age, median (IQR)	71(58-80)	65.5(54-74.5)	67(54-74)	71(60-77)	62(50–66)	0.19	0.005
Gender, male *n* (%)	19(57.57)	4(57.14)	26(76.47)	14(14.17)	12(35.29)	0.011	0.98
BMI, median (IQR)	27.9(25.8-32.5)	29.2(27.4-32.6)	31.5(27.5-35.5)	29.4(26.8-33.8)	34.4(27.7-40.3)	0.041	0.11
Preexisting comorbidities, n (%)							
Hypertension	26(78.78)	4(57.14)	30(88.23)	18(52.94)	12(35.29)	0.052	0.017
Diabetes	11(33.33)	4(57.14)	29(85.29)	9(26.47)	20(58.82)	0.42	0.53
COPD	4(12.12)	0	6(17.64)	5(14.70)	1(2.94)	0.56	0.65
Cancer	0	2(28.57)	4(11.76)	4(11.76)	0(0.00)	0.82	0.29
Smoker	28(84.84)	2(28.57)	17(50.0)	8(23.52)	9(26.47)	0.71	0.26
Hyperlipidemia	10(30.3)	7(100.0)	24(70.58)	12(35.29)	12(35.29)	0.46	0.04
Drugs, *n* (%)							
ACEi	23(69.69)	3(42.85)	26(76.47)	14(41.17)	12(35.29)	0.17	0.37
ARB	2(6.06)	0	2(5.88)	0	0	0.41	0.71
Statin	10(30.3)	7(100.0)	27(79.41)	17(50)	10(29.41)	0.85	0.035
NSAID	5(15.15)	5(71.42)	10(29.41)	7(20.58)	3(8.82)	0.04	0.71
Aspirin	23(69.69)	6(85.71)	29(85.29)	12(35.29)	17(50)	0.53	0.58
Hemodynamic instability at presentation, *n* (%)	7(21.21)	6(85.71)	20(58.82)	15(44.11)	5(14.7)	<0.001	0.52
Disposition on discharge, n (%)							
Discharged	18(54.54)	4(57.14)	13(38.23)	4(11.76)	9(26.47)	0.45	<0.001
Transferred to other departments	8(24.24)	1(14.28)	10(29.41)	3(8.82)	7(20.58)		
In hospital death	7(21.21)	2(28.57)	11(32.35)	4(11.76)	7(20.58)	<0.001	0.82
Recovery of kidney functions during hospitalization							
Full recovery	16(48.48)	2(28.57)	12(35.29)	9(26.47)	3(8.82)		<0.01
Partial recovery	10(30.3)	4(57.14)	11(32.35)	6(9.30)	5(14.7)		0.58

Abbreviations: COPD-Chronic obstructive pulmonary disease; ACEi-Angiotensin-converting enzyme inhibitors; ARB-Angiotensin II receptor blocker; NSAID-Non-steroidal anti-inflammatory drugs

Table 4. Association of kidney disease with in-hospital mortality in COVID-19 patients

Variables	95% CI	*p* value	HR
eGFR <60 mL/min/1.73m^2	1.31–1.91	0.01	1.58
Acute kidney injury	1.12–2.55	0.04	1.58
Stage 1	0.60-3.28	0.43	1.4
Stage 2	0.79-1.91	0.37	1.22
Stage 3	1.2–2.96	0.01	2.04

Abbreviations: eGF-estimated glomerular filtration rate; CI-onfidence interval, HR-hazard ration

Unfortunately, 30.43% of the patients who were treated with RRT (7 out of 23 patients) died during the hospitalization. Of those with stage 3 AKI who were not dialyzed, 36.4% (4 out of 11) died. Kidney function recovered sufficiently in 9 patients treated with RRT and no longer required dialysis upon discharge.

In the multivariable model, adapted to age, gender, and comorbidities, eGFR <60 ml/min, and AKI (stage 3) are associated with a higher risk of hospital mortality during the follow-up period (Table 4.)

Discussion

Acute kidney injury is common in critically ill patients with COVID-19, affecting approximately 20-40% of patients admitted to hospital and is considered as a marker of disease severity and an adverse prognostic factor for survival. AKI appears to result from the interaction of multiple variables via various basic pathophysiological mechanisms [5].

In this observational, retrospective study of COVID-19 patients, we found significant rates of patients who developed in-hospital AKI. Current evidence suggests that in COVID-19 patients, there is a higher prevalence of AKI in patients with more severe forms of COVID-19. AKI develops early during hospitalization and results from an interplay of virus-mediated injury and a dysregulated inflammatory response [6]. The need for dialysis is considered to be a negative survival prognostic factor. Knowledge of AKI can lead to better optimization and prognostication of patients with COVID-19.

Compared to studies of AKI in COVID-19 patients from other countries, we found our incidence to be is similar to that in an Italian study (27.8%) [7]. As compared with the above-cited study, the incidence of stage 3 AKI was highest in our cohort. It is not possible to determine with certainty the causes of this variation. However, we did remark a higher prevalence of comorbid conditions in our group.

We found that among the 269 patients included in this study, the incidence of AKI was substantially higher than the overall incidence of 0.5%-7% reported in previous studies [1] and was comparable to that in critically ill patients hospitalized with other illnesses [8]. The high incidence of AKI observed in this study was presumably attributed to several reasons. First, most of the COVID-19 patients included in this study had severe disease. Although many patients had low pulse oxygen saturation at admission, they appeared to have mild symptoms of dyspnea, possibly as a result of gradual deterioration of the condition to allow for adaption and compensation. The rapid deterioration after admission in many patients also suggests the severe condition of these patients. Second, the methods that we used to diagnose and stage AKI might cause overestimation of the incidence and severity. In the early stage of the COVID-19 outbreak, the medical resources were overwhelmed and many patients did not have a baseline serum creatinine test before admission or in the previous year so that we could only estimate the baseline serum creatinine according to the patients' sex, weight, medical history, and other related parameters. The incidence of AKI was determined based on baseline values and serum creatinine levels within seven days of admission. In order to reduce the bias of the estimation, we used the eGFR method for AKI diagnosis in these patients [9], by which the incidence of AKI was 28.6%, respectively. The estimated baseline serum creatinine levels by the eGFR method differed significantly from the test results of some of the patients whose baseline serum creatinine results were available. The inaccuracies in the estimated baseline serum creatinine level might have caused an overestimation of AKI incidence in our study.

However, even the overestimated incidence of AKI does not directly affect our investigation of the risk factors of AKI. We found that older age, multiple preexisting comorbidities, increased white blood cell count, and low lymphocyte count were all risk factors for AKI in patients with COVID-19. Markers of acute inflammation (ferritin and CRP), muscle injury (creatinine kinase), increased levels of PCT, and D-dimer levels were significantly higher in patients with a low eGFR at presentation and in those with AKI, suggesting causality by a dysregulated immune/inflammatory response, the so-called "cytokine" storm.

The prevalence of several preexisting comorbidities, including chronic lung diseases and dyslipidemia, did not differ significantly due to the relatively small number of cases of AKI in this study. Lymphopenia indicates that decreased immunity might occur in patients with COVID-19, and increased levels of PCT and CRP suggest that some patients may have secondary bacterial infections that caused excessive inflammatory responses. Previous studies [1,9] have shown that patients with COVID-19 have significantly increased D-dimer levels, multiple organ damage, and electrolyte disturbances. Our study showed that these abnormalities were more pronounced in patients with AKI. The occurrence and development of AKI often lead to the imbalance of blood volume and electrolytes, accumulation of metabolites, and aggravation of multiple organ dysfunction, thus creating a vicious cycle. The majority of patients with stage 1 AKI recovered and were discharged, but those who progressed into stage 2/3 AKI had a high mortality rate, possibly due to the untimely treatment. Early intervention of AKI is crucial in these patients, and continuous renal replacement should prevent AKI progression.

In our cohort, 23 of the 78 patients with AKI required RRT. Among those who received RRT, 7(20.58%) died versus 4(11.76%) in the stage 3 AKI group who did not undergo RRT ($p<0.001$). Thus, there was no significant improvement in survival, and the average mortality remained relatively high in both the RRT and non-RRT groups. These findings should prompt the early involvement of a palliative care team to define goals of care in patients with COVID-19 disease and stage 3 AKI. In our experience, ultrafiltration was not well tolerated. It often increased pressor requirements and did little to improve the ventilatory status. We observed a high incidence of hypercoagulability and frequent clotting of the dialysis filters, lines, and catheters. Thus, the patients required higher than the usual doses of heparin.

This study has several limitations. First, a small number of patients had a documented history of CKD, and we did not exclude them from this study. Data were collected retrospectively from medical records and often did not have information regarding prior renal function. Patients also may have had elevated creatinine on admission secondary to AKI suffered before hospitallization. If so, we may have underestimated the true overall incidence of COVID-19-associated AKI. It is not possible to rectify this problem, given the data at our disposal. This limits our study's general applicability but provides a unique insight into this population and broadens our understanding of COVID-19 disease. Data were missing on many patients at different stages of the hospitalization since they were collected retrospectively. Second, we did not explore the impact of treatment on AKI because our treatments were based on WHO's and (ADQI) standardized protocols [10,11], in which the antiviral drugs, antibacterial drugs, and hormones have little effect on renal function. Third, the urgency in data collection and the short follow-up

time of the patients (the shortest hospital stay of the patients was only 14 days) may affect the final prognostic evaluation of the patients to cause bias in survival time analysis. We especially emphasize that little data were available regarding urine output, a defining characteristic of AKI.
Nevertheless, even with the above limitations of our study, the high incidence of AKI and its negative impact upon survival is abundantly clear.

Conclusion

The kidney is a primary target organ of SARS-CoV-2 and the incidence of AKI is high in hospitalized patients with COVID-19. Deterioration of kidney function aggravates other organ damage. Preexisting cardiovascular and renal diseases are potential risk factors for AKI in patients with COVID-19.
Although the incidence of stage 1 AKI is high in critically ill patients, most of the patients can have favorable outcomes. However, progression into stage 2/3 AKI is associated with a very high mortality rate, and the prevention of AKI and monitoring of kidney function is thus vital in the clinical management of COVID-19. Our patients experienced a high incidence of AKI and high mortality, especially in AKI stage 3. Unfortunately, RRT provided little survival benefit. Larger, multicentered studies are needed to better understand AKI for its management in COVID-19 patients.

Conflict of interest statement: None declared

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BANTAO Journal 2020; 18(2): 60-63

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Original article

Ultrasound-Guided Percutaneous Sclerotherapy of Simple Renal Cysts – Five Years Report

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Abstract

Introduction. The sclerotherapy is considered a safe and effective treatment of simple renal cysts, usually performed by urologists. It was a five-year retrospective report on our tertiary clinical experience with simple renal cysts sclerotherapy performed by nephrologists.
Methods. We analyzed the medical histories of patients who underwent sclerotherapy from January 2015 until the end of December 2019 counting overall 23 sessions of sclerotherapy. The method (aspiration or drainage) was chosen according to cyst size and depth. Sclerotherapy with 96% alcohol was performed. The cyst size was recorded, and the curative effect was evaluated by the residual cyst volume; over 20% residua in the cyst size was considered as a failed treatment. Patients were reexamined by ultrasound at 12-month follow-up, or earlier if symptomatic.
Results. The mean age of patients was 58.68±11.08 years and majority of them were females. Most of the cysts [17] induced flank pain, dysregulated hypertension was present in 22% of patients and one have obstructted the urine flow. The mean cyst volume was 540±307.51 ml. All cysts were successfully treated. The mean cyst volume decreased significantly. Concerning the complications, sporadic cases of pain and vomitus occurred during only three treatment procedures. At the follow-up, all patients who suffered from unsatisfactory blood pressure control improved and the hydronephrosis resolved. In five cases there was reoccurrence of a symptomatic cyst, with a need of re-treatment in the follow-up period.
Conclusion. Ultrasound-guided aspiration and sclerotherapy of simple renal cysts is a safe and effective procedure that may be carried out by nephrologists.

Keywords: sclerotherapy, ultrasound, simple renal cysts, complications, cyst volume

Introduction

Renal cysts are spherical, thin-walled, variably sized distentions principally of the cortical or medullary renal tubules and are usually filled with clear, watery fluid. They are most commonly found in the adult population at increasing age that is highly associated with their incidence [1]. As per the current guidelines on renal cystic disease [2,3] and Bosniak cysts classification [4,5], asymptomatic class I and II cysts do not require future follow-up and imaging. In contrast, the other Bosniac cysts categories are at malignancy risk and should be treated. The intervention is also required in symptomatic cysts. The enlarged cyst might cause or worsen hypertension [6], hemorrhage [7], pain [8], urinary flow obstruction [9] and local or systematic infection [10]. The current treatments of simple symptomatic cysts consist of percutaneous aspiration and sclerotherapy techniques performed under ultrasound or CT guidance, up to surgical excision when necessary, done by urologists. After aspiration, sclerotherapy with different agents provides destroying cysts epithelium and cyst ablation. The most frequently used agents are sole alcohol [11-13] or in combination with fibrin glue [14], aethoxysclerol [15] or polidocanol [16]. The sclerotherapy is considered to be an efficient and safe method. Usually after a single episode over 80%-97% of cyst volume reduction is accomplished [11,13,15]. Minor complications include microhematuria, fever, nausea, pain [12,16], and rarely major complication is an aseptic abscess [16]. The effectiveness and long-term results are reported based on various follow-up periods. The recurrence of the cyst, and a high percentage of volume preservation after treatment are usual indices [17]. Although a routine practice intervention in urology departments, in our five-year retrospective study we report on the nephrological tertiary clinical experience with simple renal cysts sclerotherapy that may be quite satisfactory.

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Material and methods

We analyzed the medical histories of patients who underwent sclerotherapy from January 2015 until the end of December 2019. It was a single procedure performed in 14 patients, in three of them it was done twice and in one patient three times, counting for overall 23 sessions of sclerotherapy. Before admitting to the hospital, patients were examined by ultrasound and CT scan when necessary. Cyst volume was estimated according to the following formula: V = length×width×height ×π/6. Only symptomatic Bosniak 1 simple renal cysts were eligible for sclerozation. A strict protocol was followed: the procedure was explained to each patient and an informed consent was obtained. Antiplatelet or antithrombotic agents (e.g. aspirin, GPII/IIIa inhibitors, dipyridamole and non-steroidal inflammatory drugs) were discontinued at least 5 days before intervention and the prothrombin time had to be normalised. Pentoxifylline was not to be taken 1 day prior to admission. Also, one day before, platelet count, prothrombin time and activated partial thromboplastin time had to be normal. The procedure was not performed in patients with platelets count under 100 and an abnormal coagulation. A team of experienced interventional nephrologists performed the screening and interventions ultrasound-guided. The patients were placed in the prone position, and 2% lidocaine was administered for local infiltration of anesthesia at the puncture site. A 20-gauge coaxial needle (Monopty 2016B Bard, Tempe, AZ, USA) was used to puncture into SRCs, and a three-way drainage tube was used to connect to the coaxial needle. The method (aspiration or drainage) was chosen according to cyst size and depth: catheter drainage was done for larger (>6 cm) and shallow (<7.5 cm) cysts and needle aspiration was done for smaller or deeper (>7.5 cm) cysts. Sclerotherapy with 96% alcohol was performed. Control ultrasound was done and the reduction of the cyst volume was notified. Patients were discharged in a day or two monitoring complication occurrences. The cyst size was recorded, and the curative effect was evaluated by the residual cyst volume; over 20% residua in the cyst size was considered a failed treatment. Patients were reexamined by ultrasound at the 12-month follow-up, or earlier if symptomatic. Statistical analysis: all statistical methods were performed using the SPSS statistical software package, version 17.0. Parametric data were expressed as mean ± standard deviation, and nonparametric data were expressed as number and percentage of the total. Wilcoxon Signed Rank Test was used to compare cyst volumes pre- and post-procedure. A value of $p < 0.05$ was considered statistically significant.

Results

Demographics, clinical presentation of patients and cyst indices are given in Table 1. The mean age of patients was 58.68±11.08 years and majority of them were females (72%). Nearly one quarter of patients suffered from hypertension. Diabetes was present in 17 and CKD in 13% of patients. Having a simple renal cyst, fourteen patients were treated only once. In the follow-up period, the reoccurrence of the cyst was the reason for a second sclerotherapy in another three patients and also a third sclerotherapy in one patient has been performed. Overall, 23 cysts underwent sclerotherapy. Most of the cysts [17] induced flank pain, dysregulated hypertension was present in 22% and one have obstructed the urine flow. Cysts with larger diameter than 90 mm were present in 43% of patients while 35% of them exceeded volume of 500 ml. The mean cyst volume was 540±307.51 ml.

Table 1. Demographics, clinical presentation of patients and cyst indices

Nº patients =18		
Age (years)		58.68±11.08
Men (%)		5(28%)
Arterial hypertension		4(22%)
Diabetes mellitus		3(17%)
Chronic kidney disease		2(13%)
Nº of Cysts =23		
Clinical presentation		
Flank pain		15(65%)
Flank pain and vomiting		2(9%)
Dysregulated hypertension		5(22%)
Hydronephrosis		1(4%)
Cyst size	< 90 mm	13(56%)
	>90 mm	10(43%)
Cyst volume	≤ 500 ml	15(65%)
	>500 ml	8(35%)
Mean cyst volume (ml)		540.00±307.51

All cysts were successfully treated. The mean cyst volume decreased significantly to 23 ml as seen in Figure 1 and Table 2. In 78% of the treated cysts, there was a complete disappearance and in 4 cysts (17%)

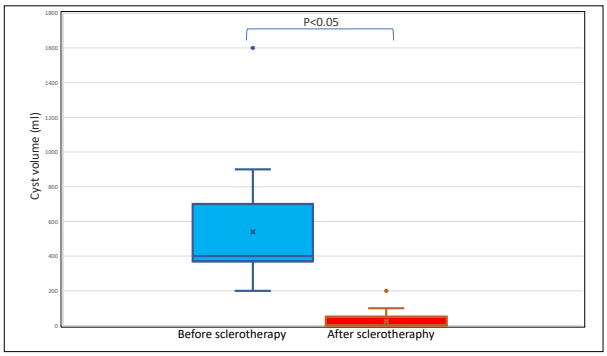

Fig. 1. Significant reduction of cyst volumes after sclerotherapy

only a small residual content up to 10% of the whole volume remained. Concerning the complications, sporadic cases of pain and vomitus occurred during only three treatment procedures. At the follow-up, all patients who suffered from unsatisfactory blood pressure

control improved. In three patients the blood pressure was well controlled with the same antihypertensive therapy and in two patients there was even reduction of doses. The hydronephrosis resolved. In four cases there was reoccurrence of a symptomatic cyst (flank pain), with a need of re-treatment in the follow-up period. The awareness of the re-enlarged cyst and fear of symptoms was the reason of re-intervention in one patient with previous flank pain.

Table 2. Complications and results of sclerotherapy

Nº of treated cysts = 23		
Mean cyst volume after procedure (ml)		23.9±47.68
Successful treatment		23(100%)
Residual cyst volume 0%		18(78%)
	1-10%	4(17%)
	10-20%	1(4%)
	>20%	0(0%)
Complications during/early post-procedure		
	Pain	2(8%)
	Vomitus	1(4%)
Recidive at 12 months		5(2%)

Discussion

The aspiration and sclerotherapy of simple renal cysts are routine practice interventions in urology departments [18,19]). In this study, we demonstrated the 5-year experience and results of these interventions in a tertiary nephrology department. Simple renal cysts are occasional findings that increases with age and may be present as a mass lesion [20]. These are more common in older people, and males are more prone to develop simple kidney cysts than females [21,22]. In our adult population, the average age was above 50 years and being predominantly females. It might be to a certain extent explained with the small number of symptomatic patients that needed treatment. Majority of our patients presented with flank pain as was also published in previous studies [8,23]. Cysts cause some degree of cllecting system obstruction in 2.5 to 16.0% of cases. Parapelvic cysts may obstruct the ureter or low pelvis, whereas peripheral cortical cysts can cause infundibular or calyceal obstruction [24]. One of our patients presented with a moderate pain, but the main reason for sclerotherapy was the hydronephrosis caused by the cyst. Fortunately, after cyst aspiration the patient was free of symptoms and obstruction. Dysregulated hypertension was correlated with the progressive enlargement of the cysts and was the reason for sclerosation intervention in five of our patients. In another study of 184 patients, an apparent association between the size of a simple renal cyst and hypertension was found and aspiration of cysts resulted in reduction of blood pressure [25] that was in agreement with our findings. After slerosation and during follow-up, all patients had satisfactory blood pressure control with either reduced or same therapy dosage. Cyst sclerotherapy is shown to be a safe procedure with rare complications [12,16,26]. Our overall results in 23 sclerosations were comparable with literature reports showing minor and rare complications [13,15]. Still, in five patients (2%) a second intervention was required due to the cyst recurrence and related symptoms. Other studies reported on similar results [18,23,26]. However, the shortcomings of our study were the small number of interventions and rather short duration of follow-up. Nevertheless, with this study we have shown the expanded variety of successful nephrological interventions at our Clinic.

Conclusion

Ultrasound-guided aspiration and sclerotherapy of simple renal cysts is a safe and effective procedure carried out by nephrologists.

Conflict of interest statement. None declared.

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BANTAO Journal 2020; 18(2): 64-67

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Case Report

Renal Lymphangiectasia: An Unusual Mimicker of Hydronephrosis – A Case Report

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Abstract

Renal lymphangiectasia is very rare benign lymphatic malformation of renal lymphatics, characterized by cystic dilatation of perirenal, peripelvic, or intrarenal lymphatic vessels. One of the rare mimickers of hydronephrosis and cystic renal lesions on the imaging findings. We report a case-patient with unilateral right renal lymphangiectasia with flank pain and arterial hypertension. The ultrasound examination revealed right kidney hydronephorosis. The renal lymphangiectasia was identified on contrast-enhanced computed tomography scan. The patient was managed conservatively with antihypertensive drugs. The report also contains a review of the literature on the pathophysiology of renal lymphangiectasia, clinical presentation, imaging findings, differentials, complications and treatment.

Keywords: renal, lymphatic system, lymphangiectasia, hydronephrosis, hypertension,

Introduction

Renal lymphangiectasia (RLM) is a rare, benign, and developmental disorder of the renal lymphatic system characterized by cystic dilatation of perirenal, peripelvic, or intrarenal lymphatic vessels [1]. It is mostly asymptomatic or with nonspecific symptoms, unilateral or bilateral, and unrelated to age or gender [2]. The incidence of RLM accounts for approximately 1% of all lymphangiomas [3]. The identified cases with renal lymphangiectasia were with familial, developmental, and acquired causes for malformation of the renal lymphatic tissue leading to obstruction and accumulation of lymph [4]. The diagnosis of renal lymphangiectasia is usually done by imaging techniques, either ultrasound (US), computed tomography (CT) or magnetic resonance (MRI) [4,5]. It is commonly misdiagnosed with hydronephrosis, cystic renal lesions, lymphoma, nephroblastoma, and perirenal liposarcoma [1]. The evolution of renal lymphangiectasia is ambiguous, and both, spontaneous regression or rapid worsening were described in the literature [5].

Case Report

A 30-year-old male presented with right flank pain, headache, and high blood pressure. The hiatal hernia, hydronephrosis of the right kidney, and well-controlled allergic asthma treated with an inhaled corticosteroid and oral antihistamines were conditions from his medical history. The hydronephrosis on the right kidney was diagnosed with an ultrasound examination before three years. Clinical examination of the patient showed increased blood pressure of 150/100 mmHg. All laboratory blood and urine analyzes were within normal limits. Ultrasound examination of the abdomen revealed increased right kidney with a dimension of 160 x 73.7 mm and parenchyma with granular appearance and thickness of 13.6 mm. Further US evaluation showed dilated anechoic pelvis and calyces of the right kidney, suspicious for a high grade of hydronephrosis. The left kidney was with normal size and parenchyma thickness of 19 mm. The patient underwent a contrast-enhanced CT scan of the abdomen. The CT scan demonstrated increased right kidney with multiple lobulated non-enhancing parenchymal and peripelvic fluid collections that were intimately associated with renal pelvis and calyces (Figure 1A). Fluid-filled lesions were also noted in the right perinephric space, surrounding the lower pole of the right kidney and adjacent to the abdominal aorta and inferior vena cava (Figure 1B). The delayed phase of the abdominal CT scan showed normal excretion of contrast with no evidence of leakage and dilatation of the pelvicalyceal system (Figure 2C and 2D). The CT angiography of renal vasculature was also performed because of suspicion for renovascular hypertension. CT angiography showed normal vascular anatomy of both kidneys, confirming the previous diagnosis of ectatic lymphatic vessels in peripelvic and retroperitoneal perivascular space. The unilateral right renal lymphangiectasia was diagnosed on a CT scan,

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and the other differential diagnoses were excluded. The patient was managed conservatively. The arterial hypertension was treated with a combination of an angiotensin-converting enzyme (ACE) inhibitor and a thiazide diuretic, with a good treatment response. No invasive interventions were considered necessary for further diagnosis or treatment of the patient. Regarding the reports for different clinical outcomes of RLM, the patient was advised for regular checkups to follow-up the course of the disease.

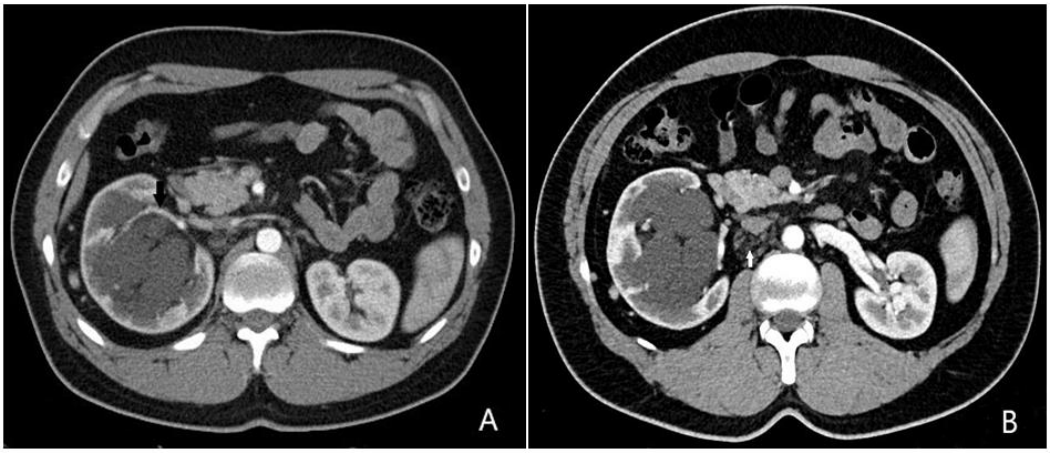

Fig. 1. (A) Axial contrast-enhanced CT scan at the level of right renal hilum showed thin renal parenchyma compressed by multiple lobulated non-enhancing intraparenchymal and peripelvic fluid collections with secondary displacement of hilar vessels (black arrow); (B) Retroperitoneal peri-aorto-caval cysts (white arrow).

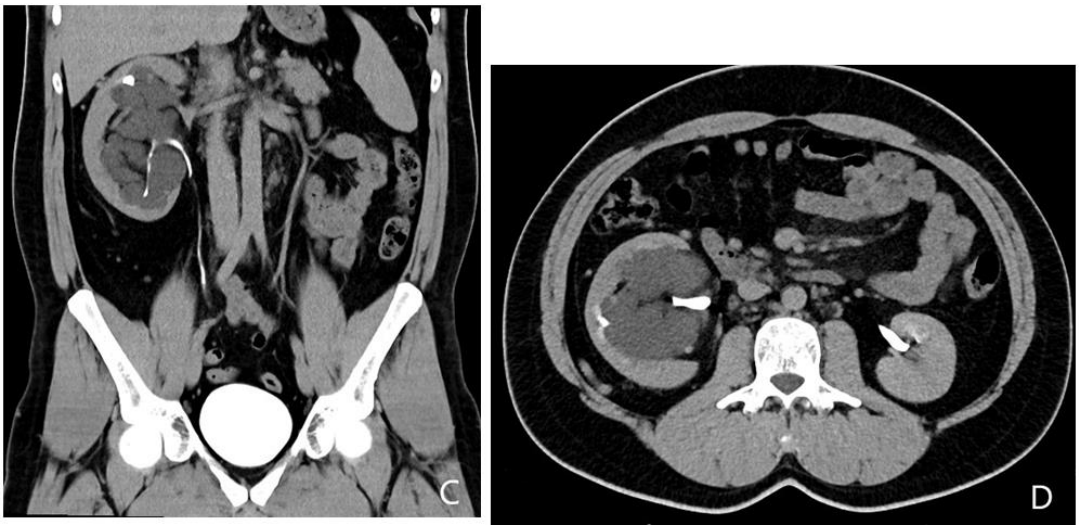

Fig. 2. Coronal (C) and axial (D) CT scan of the abdomen showed normal excretion of contrast and non-dilated excreting collecting system

Discussion

Pathophysiology: the lymphatic system of the kidneys begins in the cortex with a intralobular lymphatics which connect to the larger arcuate and interlobar lymphatic vessels that drain into a hilar lymphatics in renal sinus and hilum [6]. Via larger lymphatic trunks, lymph from both kidneys drains into the paraaortic, pericaval and interaortocaval lymph nodes [6,7]. In renal lymphangiectasia, there is impairment in the drainage of larger renal sinus lymphatic trunks with resultant dilatation of peripelvic, perinephric and intrarenal lymphatics [7,8]. The accumulation of lymph in renal lymphatic vessels causes subsequent dilatation and formation of localized or generalized cystic masses [7]. This condition can be either congenital or acquired. Familial predilection is seen in very few reported cases. Meredith *et al*. supported familial predilection of the disease, describing exacerbation of renal lymphangiectasia during pregnancy in two sisters [9]. No family association was found in any of the eight patients with RLM presented in the case study of Pandya VK *et al*. [4]. Blockage of lymphatic vessels due to inflammation or other obstruction like neoplasm, may cause acquired renal lymphangiectasia [1].

The lesions are usually asymmetric, bilateral, and may involve renal sinus, renal parenchyma or perirenal regions [7,10]. In case of unilateral disease, the left kidney is more frequently affected [4]. Our case patient had unilateral right kidney lymphangiectasia with

peripelvic and peri-aorto-caval fluid collections with no familial association. Out of eight patients in a case study of Pandya VK *et al*., six (75%) had peripelvic lymphangiectasia, and only two (25%) had peri-nephric lymphangiectasia. Four (50%) patients had bilateral lesions and rest four (50%) patients had unilateral lesions [4]. The retroperitoneal involvement with formation of peri-vascular cysts is the rarest form of the disease [7].

Clinical presentation: more often it is an asymptomatic condition and it is diagnosed incidentally. However, it may be presented with symptoms like flank pain, hematuria, proteinuria, abdominal mass, ascites, lower extremity edema, and hypertension. [11]. A few cases have also been reported with renal insufficiency and renal vein thrombosis [12,13]. Schwarz A et al. reported that hypertension was present in 59% of the cases with peripelvic or perirenal cysts and it was reversible or markedly improved after drainage or resection of the cysts [14]. The same authors also noted that hypertension was associated with elevated levels of circulating renin and aldosterone, and plasma levels of these factors dropped significantly postoperatively. These findings strongly support the assumption of renin-dependent hypertension secondary to renal ischemia caused by parenchyma compression from surrounding cysts. The flank pain was the most common complaint of the patients in the case study of Pandya VK *et al*. [4]. Five patients out of eight patients (62.5%) presented with flank pain and only one patient had associated hypertension. Rarely, formation of a junction between cyst and peritoneum or pelvi-calyceal system can result with ascites or chyluria, respectively [10]. Less commonly reported symptoms are rupture of the cyst with hemorrhage and hematuria [7,8,13,14]. Flank pain and hypertension were the main symptoms in our case patient with peripelvic lymphangiectasia.

Imaging techniques are essential in the diagnosis and further management of this condition. The dilated lymphatics appear as cystic lesions in the perirenal, peripelvic, and intrarenal locations. Ultrasound frequently reveals anechoic, multi-spectated, sharply defined cysts with thin walls located in peripelvic and/or perirenal regions [2,8,15]. Sometimes, cystic lesions are seen in the renal parenchyma, extending from there into the renal sinus and it can appear as a focal hyperechoic lesion in the renal cortex. US examination could misdiagnose this condition with cystic renal lesions, hydronephrosis, urinoma, or other renal cystic masses like Wilm's tumor or lymphoma [4,7]. Our case-patient was misdiagnosed with right kidney hydronephrosis with the US examination. Almost all case-patients (6 out of 8 patients) from the study of Pandya VK *et al.* were misdiagnosed with hydronephrosis with the US examination. One of the eight patients was misdiagnosed with polycystic kidney disease, and the other one was misdiagnosed with urinoma on ultrasound [4].

Far better assessment of this condition could be achieved by computed tomography (CT) scan and magnetic resonance imaging (MRI). On CT scan, renal lymphangiectasia is presented as well-delineated, multiseptated, non-enhancing fluid collections in perirenal or peripelvic regions, which could compress the kidney parenchyma and distort the calyceal system [2,8,15]. Less commonly, as in our case patient, there are dilated retroperitoneal lymphatics around the aorta and inferior vena cava with similar CT characteristics [2,4]. CT examination reveals cystic lesions showing fluid attenuation in the renal sinus (peripelvic or perirenal location) with or without septations. In contrast-enhanced CT, there is no opacification of cystic lesions on delayed scans in the excretory phase, which is an important feature that differentiates RLM from the dilated pelvicalyceal system [15,16]. Administration of iodinated contrast agents should be avoided in patients with impaired kidney function. In those cases, MRI with excretory urography could be used as an alternative imaging technique for the diagnosis of renal lymphangiectasia. The cystic lesion appears hypointense on T1-weighted images and hyperintense on T2-weighted images. In contrast-enhanced T1-weighted images, there is no enhancement in the early phases. There is no opacification of cystic lesions in the post-contrast T1-weighted MR excretory urography images [17]. Lymphoscintigraphy could be also used for the detection of renal lymphangiectasia [2]. In uncertain cases, percutaneous fluid aspiration with a subsequent cytological evaluation of the sample could confirm the diagnosis [4,15].

Differential: most common differential diagnoses are hydronephrosis and polycystic kidney disease [10,11, 17]. In polycystic kidneys, there are massively enlarged kidneys with multiple welldefined cysts of varying sizes in the cortex, replacing the normal renal parenchyma. There are no cysts in the renal cortex in renal lymphangiectasia, only enlarged kidney with raised renal cortical echoes and loss of corticomedullary differenttiation. The pelvicalyceal system appears normal in renal lymphangiectasia, in contrast to hydronephrosis.

Evolution and complications: lymphangiectasia may show sudden appearance and rapid growth or cessation of growth and spontaneous regression of symptoms [13]. Pickering SP *et al.* reported partial regression of this condition in neonatal patient, 13 months after initial diagnosis [18]. Battaglia M *et al*. observed no progression of the lesions in 10 patients with peripelvic multicystic lymphangiectasia during 8-years of follow-up [19]. In case described by Liorente JG *et al*., perirenal collections completely resolved after 6 years, but intrarenal lesions had progressive course and resulted with increasing nephromegaly [5]. The complications of RLM include renal vein thrombosis, renin-dependent arterial hypertension, obstructive uropathy features due to compression of the collecting system

by the larger cysts, intracystic hemorrhage, ascites, and superimposed infection [7,9,17,20].

Treatment: it is a benign entity. Asymptomatic cases usually receive conservative management, but due to potential complications, periodic follow-up is necessary [1,4,7]. Hypertension and secondary infections of the lesions are managed conservatively with antihypertensive drugs and antibiotics [4]. Ultrasound-guided percutaneous aspiration of the fluid is reserved for symptomatic patients, presenting with pain on the account of compression by the collection [12]. However, the success rate of percutaneous aspiration was very low in multi-septated larger lesions and led to a high rate of recurrences. Laparoscopic ablation and nephrectomy is reserved for complicated cases with severe renal disease, renal vein thrombosis, and cases with multiple recurrences. However, nephrectomy is not considered as a choice treatment in the case of bilateral renal involvement, because the cyst formations in the contralateral kidney may increase in size [7].

Conclusion

Renal lymphangiectasia is benign disorder that should be differentiated from other causes with intrarenal or perinephric cystic masses. Radiological modalities are important for early and proper diagnosis, determining extension, and further management of the disease. During the disease, the size of dilated lymphatics may remain unchanged or may increase causing renin-dependent hypertension, ascites, renal vein thrombosis, or nephromegaly. Therefore the patients with this condition need regular follow-up with guided treatment by the extensity and evolution of the disease.

Conflict of interest statement. None declared.

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BANTAO Journal 2020; 18(2): 68-70

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Case report

Can SGLT2 Inhibitors be a Good Option in the Management of Resistant Hypertension in Diabetic Hypertensive Patients?

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Abstract

67-year-old diabetic hypertensive female patient presented with severe headache and severe hypertension. Carvedilol and spironolactone were added, because her blood pressure could not be controlled with 3 antihypertensive drugs, one of which was diuretic. After the addition of SGLT-2 inhibitor, blood pressure values were found to be around 150-140/90 mmHg. Features of this case supports the possible role of SGLT2-inhibitors in resistant hypertensive and diabetic patients in appropriate clinical conditions.

Keywords: Resistant hypertension, SGLT2-inhibitors, Type 2 Diabetes Mellitus

Introduction

Resistant hypertension is defined as inability to control blood pressure despite optimum doses of 3 different antihypertensive drugs (one of which is a diuretic) or to provide adequate blood pressure control with 4 or more different antihypertensive drugs [1]. Despite advances in the diagnosis and treatment of resistant hypertension, there are still significant challenges and unmet needs for appropriate diagnosis and management [1]. The incomplete understanding of the precise pathophysiological mechanisms of resistant hypertension has hampered efforts to identify the optimal treatment approaches [2]. More research is needed on new treatment approaches, including different perspectives to treat resistant hypertension. Despite the widespread use of antihypertensive therapy, a significant portion of the hypertensive population remains uncontrolled, making it rational to test alternative approaches in patients with refractory hypertension [3]. On the other hand, considering the significant cardiovascular mortality burden of diabetic refractory hypertensive cases, there is a need for new treatment approaches that reduce blood pressure and improve cardiovascular outcomes [4]. In addition to other antihypertensives, SGLT2 inhibitors that reduce blood pressure as well as improve cardiovascular and renal morbidity and mortality may be promising in diabetic patients with resistant hypertension in favorable clinical conditions [5].

Case

A 67-year-old female patient with a diagnosis of diabetes and hypertension was admitted to the internal medicine clinic due to gradually increasing headaches and accompanying high blood pressure measured for the last two months. On physical examination, blood pressure was 220/110 mmHg, and pulse was 86/minute. Heart sounds were rhythmic, additional sounds and murmurs were not heard. Electrocardiography was in normal sinus rhythm and there were signs of left ventricular hypertrophy. Her body weight was 62 kilograms, her height was 165 cm, and her body mass index was 22.8 kg/m^2. There were no significant findings in the history of the patient, except for a history of hysterectomy due to menometrorrhagia 10 years ago. The patient, who described panic attacks from time to time, did not receive any treatment for this. During examination, the patient stated that she had sleep problems. Salt restriction and a diabetic diet were initiated. Intensive insulin therapy, which she was still using for diabetes, was continued. In laboratory tests, fasting blood glucose was 151 mg/dl, creatinine 0,8 mg/dl, urea: 57 mg/dL, LDL cholesterol value 129 mg/dl, HbA1c level 7.8%, and eGFR was calculated as 76 ml/min/1.73m^2. Left ventricular hypertrophy, left ventricular diastolic dysfunction were detected in echocardiography, and the ejection fraction was 60%. In the ambulatory blood pressure monitoring of the patient, the mean blood pressure at night was 160/100 and the mean blood pressure during daytime was 170/120 mmHg. Three antihypertensive drugs, one of which was a diuretic, were initiated for the patient. There were no significant differences between the blood pressures measured in four different extremities. Since blood pressure was not adequately controlled, 25 mg of carvedilol was added to her treatment. After psychiatric consultation antidepressant treatment with sertraline derivative was initiated. Spironolactone 50 mg was added to the treatment of the patient whose

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blood pressure did not return to the desired level during the follow-up. Meanwhile, to investigate the causes of secondary hypertension, abdominal ultrasonography, renal artery doppler ultrasonography, abdominal MRI, renal MR angiography were performed. Serum aldosterone and renin levels and catecholamine levels in 24-hour urine were measured in addition to the existing laboratory tests. No pathology was found to play a role in the etiology of secondary hypertension in the examinations. Dapagliflozin 10 mg, which is known to have a blood pressure lowering effect, was added to the treatment of the diabetic patient. It was observed that the blood pressure values of the patient, who was called to the outpatient clinic after 2 weeks, were around 150-140/90mmHg.

Disccussion

Resistant hypertension (RHT) is a multifactorial disease associated with several target organ damage such as microalbuminuria, left ventricular hypertrophy and arterial stiffness. Sodium glucose cotransporter 2 (SGLT-2) inhibitors have shown positive results in blood pressure levels, body weight and glycemic control in diabetic and hypertensive patients. Sodium glucose co-transporter 2 inhibitors lower blood pressure through osmotic diuresis and may be considered in diabetic patients with resistant hypertension. Given the significant cardiovascular mortality burden of resistant hypertension, there is a need for new treatment approaches that reduce blood pressure and at the same time improve cardiovascular outcomes [4]. Rather than inventing new classes of antihypertensive drugs, another strategy is to take advantage of existing classes of drugs that have proven efficacy in lowering blood pressure. As a "diabetes drug", Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been shown to improve renal and heart failure, in addition to reducing renal glucose reabsorption and increasing urinary glucose excretion. Possible mechanisms underlying clinical benefits are hypothesized to be through natriuresis, reduction in blood pressure, weight loss, improvement in arterial stiffness, and uric acid levels, in addition to the above. In a 12-week study, empagliflozin (10-25 mg per day) was shown to lower 24-hour SBP and diastolic BP (DBP) by approximately 3-4 and 1-2 mm Hg, respectively [4]. SGLT2 inhibitors have been shown to reduce 24-hour ambulatory systolic blood pressure by 3.7(95% CI 2.3-4.2) and diastolic blood pressure by 1.8(95% CI 1.3-2.4) mm Hg compared to placebo [6]. It is considered that patients with increased salt sensitivity could potentially benefit more from SGLT2 inhibitors to lower blood pressure due to their natriuretic and osmotic diuretic effects [4]. In a post hoc analysis of EMPA-REG OUTCOME, Ferreira *et al.* investigated the effects of empagliflozin in patients with presumed resistant hypertension [7]. In this study, 22.5% of patients meet the definition of resistant hypertension, the mean difference in SBP from baseline to week 12 relative to placebo was -4.5 (95% confidence interval, -5.9 to -3.1) mm Hg at RHT (P <0.001) and -3.7 (-4.5, -2.9) mm Hg in patients without RHT (P <0.001). SBP was controlled more frequently with empagliflozin than placebo (<130/80 mm Hg). Interestingly, patients with RHT had 1.5 to 2 times higher risk of hospitalization for heart failure, incident/worsening nephropathy and CV death [8]. Because of these dual effects, they reported that empagliflozin is a possible option to consider in patients with hypertension and T2DM [8]. It is thought that the blood pressure reduction achieved with SGLT2 inhibitors is less compared to spironolactone (8.7 mm Hg SBP reduction with spironolactone in the PATHWAY-2 study).

This case demonstrates several important points regarding the evaluation, management of RHT and also underlines the the complexity involved in determining the mechanisms of resistant hypertension in diabetic patients. RHT is difficult to manage due to the complex interaction between sodium and fluid retention, the renin-angiotensin-aldosterone system, and activation of the sympathetic nervous system, and those at high risk of cardiovascular disease [4]. For this reason, SGLT2 inhibitors, which reduce blood pressure as well as improve cardiovascular and renal morbidity and mortality, may be promising in appropriate clinical conditions in diabetic patients with resistant hypertension. In an 8-week study with type 1 diabetes, empagliflozin was shown to reduce arterial stiffness as assessed by measuring pulse wave velocity and augmentation index [8]. Due to their mechanism of action independent of insulin, SGLT2 inhibitors reduce blood pressure and improve glycemic control while avoiding the potential risks of increased insulin doses such as hypoglycemia, hypertension and weight gain. Although aortic pulse wave velocity is generally considered the "gold standard" in non-invasive assessments of arterial stiffness, pulse pressure (PP) determined by cardiac output and stiffness of elastic central arteries can be used as a surrogate marker in clinical practice. PP can be calculated as the difference between systolic BP (SBP) and diastolic BP (DBP) [9]. Chilton et al. in a post hoc analysis of data from a phase III study in T2DM and hypertensive patients receiving 12 weeks of empagliflozin and four phase III studies in T2DM patients receiving 24 weeks of empagliflozin, they reported that empagliflozin significantly (p<0.001) decreased PP, MAP, and DP (or RPP) compared to placebo in both cohorts [9]. They stated that in their methodology, MAP was calculated as 2/3 DBP+1/3 SBP (mmHg); and DP (or RPP) heart rate (bpm) × SBP (mmHg) [10]. The double product (DP), also known as the rate pressure product (RPP) is calculated as heart rate × SBP and provides an indirect measure of myocardial oxygen demand [10]. Decrease in blood pressure and arterial stiffness are the possible effects of SGLT2 inhibitors

that can improve CV risk and heart failure in patients with T2DM, and it has paramount important to confirm in larger studies. An additional possible mechanistic explanation for BP reduction by SGLT2 inhibitors is local inhibition of RAAS secondary to increased sodium delivery to the juxtaglomerular apparatus [11,12].

Conclusion

Although SGLT2 inhibitors do not have antihypertensive indications, mild blood pressure reductions observed during SGLT2 inhibitor therapy may provide an extra clinical advantage for patients with T2DM and resistant hypertension as well as improving glucose control. Finally, close follow-up of these patients is important and should include periodic laboratory testings.

Conflict of interest statement. None declared.

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BANTAO Journal 2020; 18(2): 71-74

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Case report

Fibrillary Nephropathy and Amyloidosis – Two Morphological Faces of the Myeloma Kidney

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Abstract

Myeloma-induced renal failure is associated with significant morbidity and mortality. Rapid intervention is critical to reverse kidney damage and improve renal function. We report two cases, one with fibrillary nephropathy and other one with kidney amyloidosis due to multiple myeloma, diagnosed by renal biopsy and treated in our department. Both patients had no other signs of multiple myeloma present, apart from acute renal failure and histological findings on renal biopsy. The renal biopsy was performed because of acute renal failure to exclude rapidly progressive glomerulonephritis. The histological analysis showed fibrillary glomerulopathy in one patient and kidney amyloidosis in the other, changes consistent with the diagnosis of multiple myeloma with kidney involvement. Further clinical investigation confirmed multiple myeloma and the patients treated accordingly.

Keywords: multiple myeloma, biopsy, chronic renal failure

Introduction

Multiple myeloma (MM), also known as plasma cell myeloma and simple myeloma, is a malignant disease of plasma cells, which are white blood cell that normally produce antibodies. Frequently, no symptoms are noticed initially [1]. However, bone pain, bleeding, infections, and anemia may occur during the clinical course of the disease. The cause of multiple myeloma is not known. Various complications of the disease can occur, and amyloidosis represents one of them [2]. In this study we report two cases of multiple myeloma and kidney involvement diagnosed by renal biopsy. One patient had fibrillary glomerulopathy and the other one renal amyloidosis. Both patients were treated at the Department of Nephrology, University Clinic of Nephrology, in Skopje.

Case 1

A 70-year-old woman was admitted to our department with a history of hypertension, actual presence of fatigue, inappetence, nausea, vomiting and weakness over a period of several weeks along with oedema in her legs. At the time of admission, she had impaired renal function (serum creatinine: 273μmol/l) and proteinuria (urinary protein: 2.14 g/24h). During her hospitalization, the renal function showed deterioration (serum createnine increased to 862 μmol/l) and the patient needed hemodialysis. The routine laboratory tests at admission and during hospitalization were as follows - Hb levels: 107 and 88 g/l; RBC: 3.74 and 3.11x10^9/l; Ht: 33% and 28%; WBC: 6.3, 3.8 and 6.3x10^3/l; total protein: 65 and 57g/l; albumin: 45 and 37 g/l; BUN: 16.5, 20.3 and 12.3 mmol/l; creatinine 408, 719 and 768 μmol/l; serum sodium: 143 and 136 mmol/l; serum potassium: 4.6 and 4.5 mmol/l; serum calcium: 2.13 mmol/l; uric acid: 389 and 285 μmol/l. Lipid levels were within normal range. Immunoglobulin IgA levels were 0.3 g/l; IgM: 0.2 g/l; IgG: 5.3 g/l and CRP levels 4.3 mg/L and 28.2 mg/L, respectively. Proteinuria increased to 3.8 g/24 hours. The ultrasound scan of the kidneys showed two normal kidneys with parenchyma of 20-22mm. A renal biopsy was performed to identify the cause of renal failure.

Renal biopsy findings: The histological examination showed enlarged glomeruli due to increased cellularity in the mesangial area and increased mesangial matrix deposition (Figure 1). There was also ischemic folding of the basement membrane. In tubulointerstitial area acute tubular lesions with dense eosinophilic protein casts, as well as focal lymphocytic infiltrates were identified. The immune-fluorescent analysis showed positive staining for IgG in deposits as well as in the intra-tubular protein casts. Ultrastructural analysis showed ischemic collapse of the glomerular basement membrane partially thickened with amorphic basal membrane deposits as well as irregularly thickened tubular membrane. On higher magnification fibrillary structures were recognized in the glomerular and tubular basement mem-

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brane, in subepithelial and subendothelial area (Figure 2). These fibrils were larger than amyloid fibrils, (from 12 to 24 nm) without any branching between them. These findings were compatible with fibrillary glomerulopathy, an entity usually associated with plasmocytic dyscrasias.

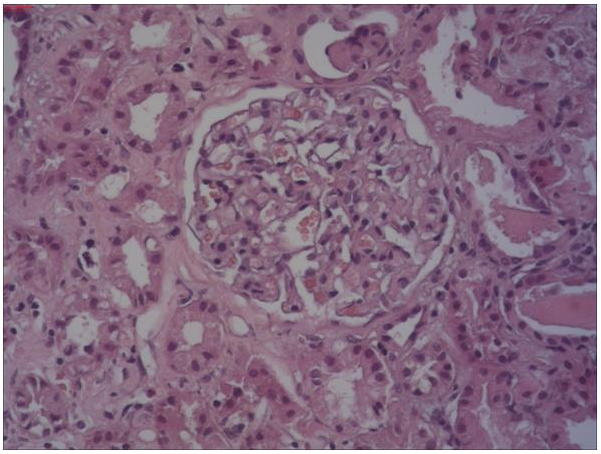

Fig. 1. Fibrillary glomerulonephritis HBE x400, Nikon Eclipse 80; Increased mesangial matrix deposition and slightly increased mesangial cellularity

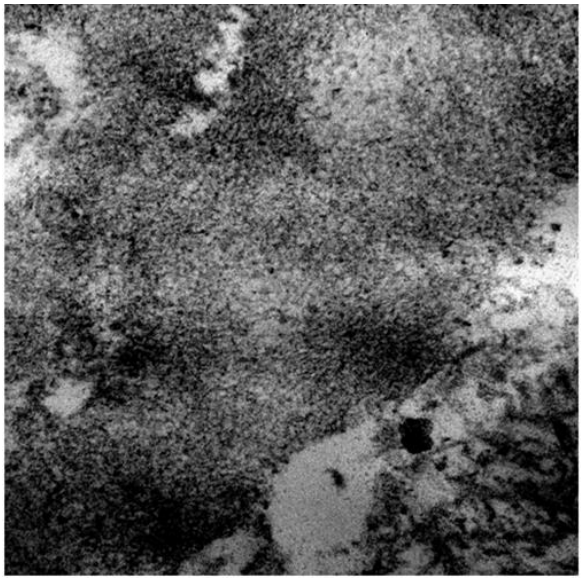

Fig. 2. Ultrastructural presentation of fibrillary glomerular deposits

A consultation from hematologists was requested and after the confirmation of neoplastic plasmocytic proliferation, chemotherapy using CTD protocol was applied to the patient who was also managed with intermittent hemodialysis. After 12 months of treatment the patient is in a good condition with a regular follow up from hematologist and nephrologist.

Case 2

A 57-year-old woman with fatigue, inappetence, nausea and vomiting was admitted in our Department as acute renal failure after dehydration. According to her history she has arterial hypertension properly regulated with antihypertensive drugs. She reported back pain but no treatment with medication known to be associated with renal dysfunction. The cardiac and pulmonary examination was normal.

Routine laboratory tests at admission and during the hospitalization were as follows: Hb: 99 and 86g/l; RBC: 3.54 and 3.0x10^9/l; WBC: 8.6, 7.7 and 9.5x10^3/l; Ht: 29%, 22% and 24%; serum protein: 77 and 76 g/l; albumin: 47 and 48 g/l; BUN: 22.1, 13.6 and 22.4mmol/l; serum creatinine: 886, 773 and 889μmol/l; uric acid: 607 and 324 μmol/l; serum sodium: 141 and 138 mmol/l; serum potassium: 6.7 and 4.4 mmol/l; serum calcium: 2.5 and 2.7mmol/l. Complement component C3: 0.73 g/l and C4: 1.2 g/l. Serum immunoglobulin levels were within the normal range. Proteinuria was progressively increased from 1.78 to 4.0 g/24hr but oedema was not present. The patient became anuric and treatment with hemodialysis was started.

The renal ultrasound scan showed enlarged kidneys with parenchyma 23mm, increased echogenicity and no evidence of obstruction.

A renal biopsy was performed to identify the cause of acute renal failure.

Renal biopsy findings: The histological examination showed slightly thickened glomerular basement membrane and amyloid resembling deposition in the paramesangial area (Figure 3). In the tubulointerstitial area the classical changes of myeloma kidney with dilated tubules and dense protein casts, giant cells and huge focal lymphoplasmacytic infiltration were recognized. Nodular hyaline thickening was also found in the blood vessels. The immune-fluorescent analysis was inconclusive due to non-specific staining. The ultrastructural analysis showed fine fibrillary branched and tangled fibrils

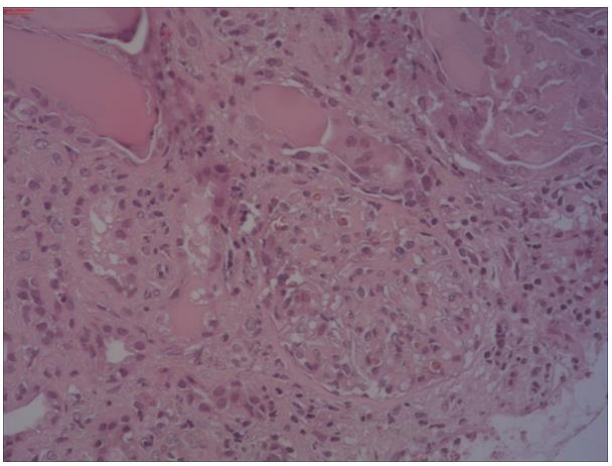

Fig. 3. Amyloid deposits in glomerular mesangium confirmed on TEM analysis

(7 to 13 nm-s), compatible with amyloid which widened the subendothelial spaces (Figure 4). A bone marrow biopsy was performed that revealed presence of neoplastic plasmocytic infiltrates. Although no radiological le-

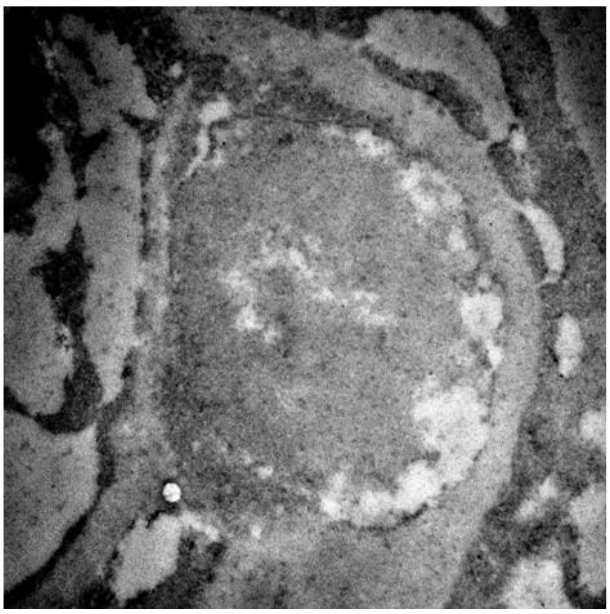

Fig. 4. Ultrastructural confirmation of the presence of amyloid deposits. There are dense protein casts in the tubule with giant cell

sions were found in the scull, the diagnosis of plasmacytoma-multiple myeloma was made.
A consultation from hematologists was requested and the patient was treated with chemotherapy, according to the proper protocol. The patient is in a good condition, but she remains in chronic intermittent hemodialysis.

Discussion

In this study we present the importance of meticulous exploration of the underlying cause of renal impairment in patients with acute kidney failure. In the first case the possible diagnosis of rapidly progressive glomerulonephritis had to be excluded whereas in the second case multiple myeloma was presented with acute renal failure.
The patients with multiple myeloma usually have lytic lesions, back pain or hypercalcemia. The lack of such typical clinical manifestations that occurs not very frequently makes the diagnosis of the disease difficult [3-5]. In patients with acute renal failure and anemia of unknown origin the possibility of an underlying multiple myeloma should always be investigated. In such cases three entities should be considered: fibrillary glomerulopathy (fibrillary glomerulonephritis, FGN), immunotactoid glomerulopathy (immune-tactoid glomerulonephritis, ITGN) and amyloidosis [4,6-8]. Fibrillary GN has been defined as an immune complex-mediated GN with amyloid-like but larger to amyloid fibrils which are IgG positive and usually Congo red negative. The specificity of the morphologic criteria is important for establishment of the diagnosis of fibrillary GN [6,7]. The fibrils are usually found in subepithelial, subendothelial and mesangial areas. Fibrillary glomerulonephritis is a rare idiopathic condition linked to malignancy, autoimmune disorders, monoclonal gammopathies and hepatitis C virus infection. No standardized treatment for the disease exists and the prognosis is usually poor resulting to end-stage renal disease within a few years [9-11]. The diagnosis of FGN can only be established by renal biopsy. FGN is defined by the ultrastructural finding of organized, randomly oriented, nonbranching fibrils with a mean diameter of 20 nm (range 12-24 nm). The incidence of FGN in native renal biopsies is less than 1% [2-5]. The deposition of fibrils that characterize FGN are predominantly restricted to the glomeruli and stained intensely in IF for IgG, C3, κ, and λ chains. These findings strongly suggest that the fibrils are composed of a complex of antibodies and antigens. Amyloid in renal amyloidosis is characteristically stained positive with Congo Red stain and has typical ultrastructural morphology with branching fibrils measuring from 7 to 12 nm-s. The differentiation between the two entities needs ultrastructural analysis. The diagnosis of FGN and its differentiation from amyloidosis and from immunnotactoid glomerulonephritis that is not described in this study, is not possible in the absence of electron microscopy.

Conclusion

Performance of renal biopsy is very crucial for the diagnosis in patients with renal failure of unknown origin. The examination of the kidney tissue with electronic microscopy sometimes is necessary for discrimination among various causes. FGN is a rare form of glomerular disease characterized by distinctive randomly oriented, nonbranching fibrils with a mean diameter of 20 nm (range 12-24 nm). The prognosis of FGN as well as of renal amyloidosis is poor, therapeutic options are limited, and optimal therapy remains to be defined. Although sometimes the typical clinical signs of multiple myeloma are absent, the early diagnosis is important for diagnosis of the disease.

Conflict of interest statement. None declared.

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BANTAO Journal 2020; 18(2): 75-78

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Case report

Plasma Cell Dyscrasia Presenting with Severe Hypertension and Acute Kidney Injury

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Abstract

Plasma cell dyscrasia may occur with different clinical pictures, in addition to being caused by neoplastic overgrowth of a single plasma cell clone. Although the kidneys are one of the target organs for plasma cell dyscrasias, acute kidney injury is rarely the first presentation sign of multiple myeloma. We wanted to share a patient who presented with severe hypertension and elevated serum creatinine and was eventually diagnosed with plasma cell neoplasia. In our case, severe hypertension, hematuria, proteinuria predominantly suggested nephritic syndrome, while the high erythrocyte sedimentation rate and the increase in kappa/lambda ratio led us to plasma cell dyscrasias. In the case of severe hypertension and increased serum creatinine, accompanying erythrocyte sedimentation rate above 100 mm/hour, it is of paramount importance to include plasma cell dyscrasias among the possible diagnoses.

Keywords: Plasma cell dyscrasia, severe hypertension, nephritic syndrome

Introduction

Plasma cell dyscrasia is caused by neoplastic overgrowth of a single plasma cell clone. In general, the diagnosis of plasma cell dyscrasia is based on demonstrating monoclonality by immunohistochemical examination of bone marrow biopsy and serum immunofixation electrophoresis (SIFE) and urine immunofixation electrophoresis [1]. Plasma cell dyscrasias can present with different faces and in different clinical ways. Multiple myeloma (MM) is a neoplastic plasma cell disease. MM is manifested by clonal proliferation of malignant plasma cells in the bone marrow, monoclonal proteins in blood or urine, and associated organ dysfunction [2,3]. In clinical practice, the diagnosis of multiple myeloma is based on bone marrow aspiration, biopsy and a series of clinical laboratory tests [4]. Kidneys are one of the target organs of plasma cell dyscrasias, and relatively rarely cases presenting with acute kidney injury may be the first sign of multiple myeloma [4]. We wanted to share a patient who presented with acute nephritic syndrome, severe hypertension, elevated erythrocyte sedimentation rate, increase in serum kappa light chain level and kappa/lambda ratio and was diagnosed with plasma cell neoplasia.

Case

A 48-year-old male patient with hypertension was admitted to the emergency room with weakness and vomiting. With the pre-diagnosis of acute kidney injury (AKI), he was hospitalized in the internal medicine service to investigate the etiology. The patient's blood pressure at the time of admission was 195/105 mm Hg, and Nitroglycerin IV+ amlodipine p.o was administered for blood pressure control. The laboratory values of the patient were as follows; urea: 109 mg/dl, creatinine: 4.1 mg/dl, potassium: 4.5 mmol/L, sodium: 140 mmol/L, calcium: 10.5 mg/dl, sedimentation: 104 mm/hour, hemoglobin:

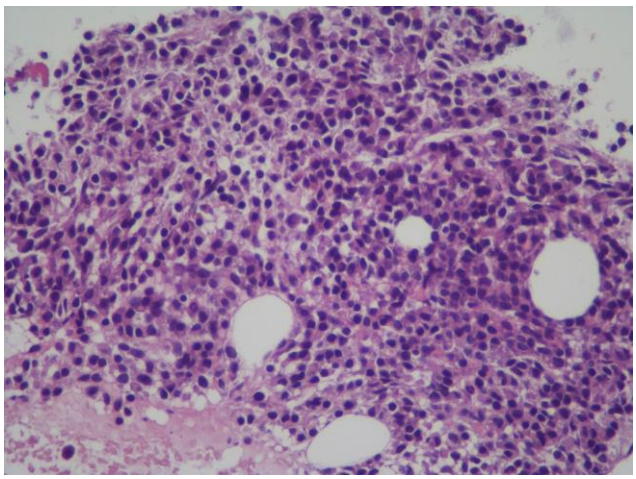

Fig. 1. Neoplastic plasma cells forming large groups, hematoxylin and eosin stain (400x)

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12 g/dl, MCV: 91.7fL, leukocyte: 8100x10∧3/uL, platelet: 159000x10∧3/uL, albumin: 3.6 g/dl, globulin: 3.6 g/dl, kappa light chain: 2930mg/l, lambda light chain: 10.3 mg/l, kappa lambda ratio: 284.4, immunoglubulin A: 16.2 g/L, immunoglubulin M: 0.19 g/L, immunoglubulin G: 3.18 g/In L, complete urinalysis, +3 erythrocyuria, 2+ proteinuria, 2.2 g/day proteinuria were detected. Echocardiographic findings were as follows: ejection fraction: 60%, left atrium dilated, left ventricular concentric hypertrophy and left ventricular diastolic dysfunction were noted. In the fundus examination, stage 2 hypertensive retinopathy was detected. Upon the suppression of two series in immunoglobulin tests and abnormality in kappa-lambda ratio was detected, bone marrow aspiration and biopsy were performed with the possible diagnosis of cast nephropathy.
Microscopic examination of the bone marrow aspiration showed an increase in plasma cells at a rate of 45%, some of them with atypical binuclear appearance. Over 10% increase in CD38 positive neoplastic plasma cells was observed in bone marrow biopsy (Figure 1), and almost all of these plasma cells were evaluated as kappa positive (Figure 2a and Figure 2b). Bone marrow Congo red stain was negative. The patient with monoclonal plasma cell increase in the bone marrow, acute kidney damage, anemia, and diffuse lytic bone lesions on PET-CT was evaluated as multiple myeloma. The patient was transferred to the hematology clinic and VCD (Cyclophosphamide, bortezomib, dexamethasone) chemotherapy protocol and zoledronic acid treatment for lytic bone lesions was initiated. At the end of the first course of chemotherapy treatment, improvement was noted in serum urea (51mg/dl) and creatinine (1.16 mg/dl) values, and the patient was discharged with a control recommendation to receive the second course of treatment.

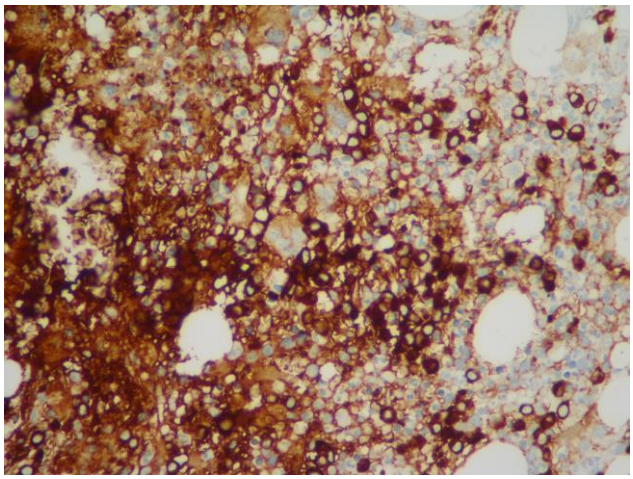

Fig. 2a. kappa positivity in plasma cells immunohistochemically (400x)

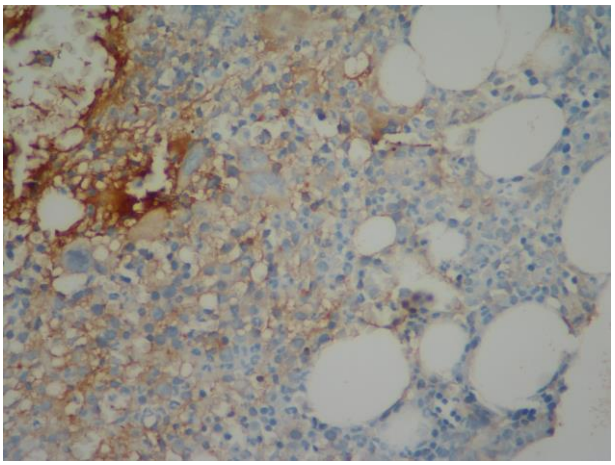

Fig. 2b. lambda negativity in plasma cells immunohistochemically (400x)

Disscussion

Multiple myeloma constitutes 1% of all malignancies and 10% of hematological malignancies [5,6]. MM often presents with severe weakness, bone pain, and recurrent infections [7,8]. Clinical findings in MM cases are classified under 4 main headings: anemia, hypercalcemia, bone lesions and acute kidney injury. Laboratory findings include anemia, high erythrocyte sedimentation rate, impaired renal function, inversion in the albumin/globulin ratio, and hypercalcemia [9]. In our case, severe hypertension, hematuria, proteinuria (2.2 g/day) predominantly suggest nephritic syndrome, while the high erythrocyte sedimentation rate (104 mm/hour) and the apparent increase in kappa/lambda ratio lead us to plasma cell dyscrasias in differential diagnosis. Severe hypertension, hematuria, nephritic proteinuria accompanying high erythrocyte sedimentation rate and marked increase in kappa/lambda ratio should prompt us to consider plasma cell dyscrasias in the differential diagnosis. MM may cause acute kidney damage with glomerular, tubular and interstitial involvement. One of the mechanisms underlying acute kidney injury (AKI) occurs when the toxic effects of light chains cause tubulointerstitial damage. Subtypes of tubulointerstitial kidney injury caused by plasma cell dyscrasias include isolated proximal tubular epithelial cell cytotoxicity, tubulointerstitial nephritis, and cast nephropathy, also known as myeloma kidney. Hypercalcemia, hyperuricemia, dehydration, intravenous radiocontrast agents themselves cause AKI primarily and/or by contributing to the toxic effects of light chains. Production of monoclonal free light chains (FLC) increases in plasma cell dyscrasias and increases hundreds of times above normal [10]. This increase exceeds the absorption capacity of the proximal tubules and abundant FLCs pass first into the tubular fluid and then into the urine, FLCs seen in urine are traditionally called Bence Jones proteins. FLCs may cause proximal tubule damage or the formation of intratubular cast by binding to Tamm Horsfall (THP) mucoprotein and then precipitation in the distal

nephron lumen [10]. Intraluminal casts also trigger inflammation and fibrosis by activating a series of chemokines. Here, the first line of treatment is to treat the underlying disease process, monoclonal plasma cell neoplastic overgrowth. Early initiation of chemotherapy with adequate hydration may prevent kidney damage that does not develop cast nephropathy. In our case, early diagnosis and treatment prevented the development of permanent kidney damage. Interestingly, the patient described in this case presented with severe hypertension, azotemia, hematuria, and nephritic level proteinuria. The most important thing in this context is the necessity to consider plasma cell dyscrasia as an etiology. In appropriate clinical situations, it is important to screen for the presence of potentially nephrotoxic monoclonal Free Light Chains (FLC) during etiology investigation in AKI. Quantitative measurement of serum FLCs by protein electrophoresis (with or without immunofixation) or nephelometric immunoassays can be used in the evaluation. With this last method, quantitative measurement of κ and λ FLCs is obtained; Overproduction of one of the monoclonal FLCs in the case of renal function impairment will cause the κ/λ FLC ratio to deviate outside the normal range (0.26-1.65), providing diagnostic benefit [10]. Multiple myeloma should be considered among our differential diagnoses in patients with kidney failure of unknown cause.

The three most common subtypes of monoclonal Ig-mediated kidney disease are cast nephropathy, monoclonal Ig deposition disease (MIDD), and AL amyloidosis [11]. Blood pressure can be a useful distinguishing feature because patients with amyloid often have hypotension with or without orthostasis as a result of coexisting myocardial amyloid, whereas patients with MIDD and kidney disease typically have hypertension [11]. Light chain deposition disease (LCDD) is the most common type of Monoclonal immunoglobulin deposition disease and renal involvement due to LCDD manifests itself with renal lesions, hypertension, microscopic hematuria, and proteinuria [12].

It is thought that the renin angiotensin system plays a role in hematopoietic stem cell plasticity [13]. It has been suggested that circulating ACE may be associated with clonal proliferation of malignant plasma cells in the bone marrow microenvironment [14]. It was hypothesized that the JAK-STAT pathway might serve as a crosstalk point between RAS components locally present in the bone marrow and hematopoiesis [15]. It has been noted that RAS components such as the ACE2 enzyme and ANG- (1-7) peptide may provide new targets for cancer therapy [16]. It is thought that RAS determines the processes of angiogenesis, cellular proliferation, inflammation and fibrosis and the cross-interaction between them, which will determine the tumor potential [16]. We need to know more about the complex role of RAS in dysproteinemias.

Chari *et al*. in their study investigating the incidence rates of hypertension and malignant hypertension in newly treated MM patients, they reported a 30% increase in hypertension risk for MM versus non-MM patients [17]. In this study, comorbid conditions that significantly increase the risk of malignant hypertension in MM patients with a history of hypertension; cardiomyopathy, kidney failure, and diabetes mellitus has been reported [17].

As a limitation of our study, we could not perform renal biopsy in our case, partially due to the effect of the Covid-19 pandemic process. After the diagnosis of plasma cell dyscrasia, the patient was transferred to the hematology clinic immediately and chemotherapy treatment was started energetically, and rapid improvement in renal functions was documented. In this Covid-19 Era, we thought the most prudent management of this case was to transfer the patient to the hematology clinic in order to be administer to apply specific treatment for plasma cell dyscrasia.

Conflict of interest statement. None declared.

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BANTAO Journal 2020; 18(2): 79-81

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Case report

Retractile Inguinal Herniation of Bladder - Case Report

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Abstract

The retractile organ is a term generally used for testis. It refers to the displacement of the organ over time in a specific route along the inguinal canal. The condition that we encounter in our case is similar. Hence, we define this event as a retractile bladder. The inguinal canal becomes a flabby pouch because of the weakening of its walls. The bladder moves within the inguinal canal without strangulation. The purpose of our paper draws attention to this situation. Herein, we present a case of an 84-year-old patient with a left inguinal retractile bladder hernia accompanied by computed tomography and ultrasonography findings.

Keywords: Inguinal hernia, Computed tomography, Bladder hernia, Retractile

Introduction

The urinary bladder is an extraperitoneal triangular-shaped organ located in the pelvis. Suspensor ligaments, ureters, and urethra provide to stand urinary bladder in its normal position. In other words, the bladder is a hanging organ. This mobility protects to bladder from traumatic stress. However, especially in elders, the bladder herniation becomes possible resulting from high bladder pressure and weakness of pelvic muscles [1]. The bladder can join 4 % of inguinal hernias. Inguinal bladder herniation is usually asymptomatic. The first case report belongs to Levine and published in 1951. In this subject, most of the information based on case reports [2,3].

The retractile organ is a term generally used for testis. It refers to the displacement of the organ over time in a specific route along the inguinal canal. The condition that we encounter in our case is a synonym for this. Hence, we define this event as a retractile bladder. The inguinal canal becomes a flabby pouch because of the weakening of its walls. The bladder moves within the inguinal canal without strangulation. The purpose of our paper draws attention to this situation. Herein, we present a case of an 84-year-old patient with a left inguinal retractile bladder hernia accompanied by computed tomography (CT) and ultrasonography (USG) findings.

Case report

84-year-old patient presented at the urology outpatient

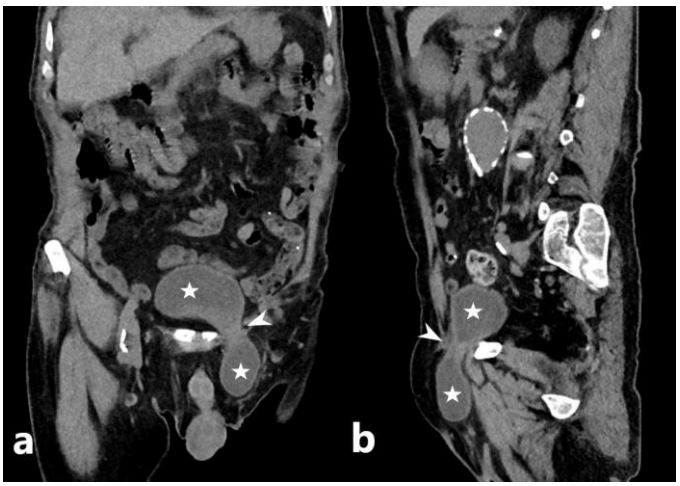

Fig. 1. Left inguinal bladder herniation and dumbbell sign in coronal (a) and sagittal (b) CT images. Bladder parts (stars) and trapped part in inguinal canal (arrowhead)

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clinic with complaints of difficulty in urination and swelling. The patient reported that his herniation is not stable and sometimes lost spontaneously. On the systemic physical exam, no remarkable feature. On the manual rectal examination, the anal tonus was normal. The prostate was large without palpable hard nodules. The patient was 1.74 cm in height and 86 kg in weight. Body mass index (BMI) was calculated in 28,4. He was in the overweighted group according to these values. Laboratory tests showed an elevated prostate-specific antigen (PSA) value of 15 ng/ml. USG was requested. Sonography showed a prostate of 117 gram. It was big in size. The urinary bladder was trabecular. The internal surface was irregular. Sonography after urination showed a high post-voiding residue of 132 cl. Bilaterally inguinal herniation was not observed in sonography. The patient was in control because of the history of old malignity. Also, CT was requested.
In CT except for previously known aorta aneurism, it was verified that the prostate is big. The bladder herniated into the left inguinal canal and extended to the inferior ring [Figure 1]. There was no evidence of strangulation. In coronal and the sagittal image showed dumbbell-shaped bladder [Figure 2]. It was diagnosed as inguinal urinary bladder herniation.

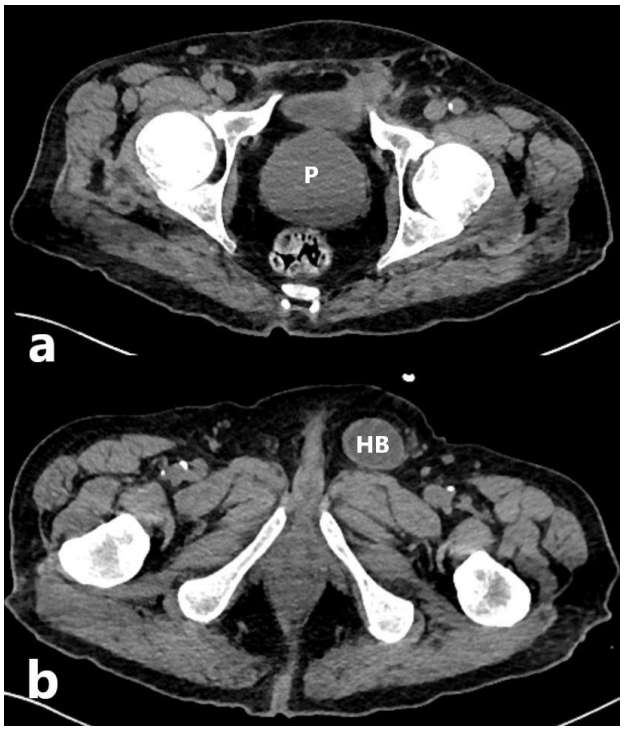

Fig. 2. As a triggered factor big prostate (a), and left inguinal herniation (b) in axial CT image. Abbreviations; P: Prostate HB: Herniated bladder

Surgery was recommended to the patient for the hernia. However, the patient refused the operation, saying that the hernia has been present for a long time. He discharged with medical treatment (α1-blockers) and was recommended control. He signed consent form on 20.01.2021 before preparing this case report.

Discussion

Bladder hernia is more common in males. Its frequentcy increases after the age of 50 [4]. It can be the inguinal, femoral, obturator, or scrotal type [5]. In the literature, incarcerated and complicated cases are usually reported. The self-reducted or retractile bladder is very uncommon. This condition indicated in this paper.
Many factors can trigger bladder herniation. Chronic bladder distension, loss of bladder tonus, large pelvic masses, and obesity are the main reasons. In other words, the reasons that increase the pressure of the intraabdominal region or bladder are predisposing factors. Our patient had a large prostate obstructing the bladder outflow tract. Also, He was elder [6]. Predisposing factors were present. Inguinal bladder hernia is usually asymptomatic. Expected clinical signs are dysuria, frequency of urination, urinary urgency, nocturia, and haematuria [7]. Our patient was asymptomatic. He presented to the hospital for his benign prostatic hyperplasia and routine control.
Any part of the bladder (diverticulum, part of the bladder, ureter, or the whole bladder) can be located in the hernia sac. If it descends into the scrotum, it is defined as a scrotal cystocele [8]. Only 7% of inguinal bladder hernias can be detected before surgery [4]. 16% of hernias cannot be noticed even during the operation. If postoperative urine leakage or bladder injury is detected, the presence of herniation can be understood [3].
The diagnosis can rarely be determined incidentally by USG, cystography or CT [6]. CT is accepted is the most useful method among radiological method. Most of the cases are noticed on CT. According to Branchu et al., CT can detect hernia at the rate of 47,9% [2]. Herniated and non-herniated part together with narrowed inguinal canal passage form a specific appearance. This appearance called dump-bell sign or dog ears sign seen in our case on CT is typical. If it is bilaterally, it called Micky-mouse in CT [9].
If the ureter is joined to the herniation, it can lead to hydronephrosis. CT is the best method to show hydronephrosis. CT should be requested before urinary disorders associated with inguinal hernia (Mery's Sign) [10]. Renal failure, urinary tract infections and bladder infarctions may occur as more serious complications resulting from obstructive uropathy and strangulation. In this case, open surgical repair is preferred [4].
A study in 2004 showed that 11.2% of inguinal bladder hernias were associated with urological malignancies and 23.5% with various complications [3].
Open surgical repair is the preferred treatment. Surgical approach technique varies according to the patient's condition and the presence of strangulation. Following

herniorrhaphy, either reduction or resection of the hernia is performed.

The defect can be repaired with or without mesh. Before the operation, every anatomical structure within the hernia sac should be clearly defined. In the past, resection of the herniated part of the bladder was preferred. Currently, bladder damage, neck necrosis, bladder tumours, diverticula and neck hernia smaller than 5 mm are indications for bladder resection. The bladder damaging is common during hernia surgery. It occurs in approximately 12% of operations [3,11].

Conclusion

Bladder hernia occurs resulting from the weakness of the bladder floor and increasing pressure of bladder. The detection rate before the operation is 7%. It is remarkable that this situation, which is anatomically and easily visualized, cannot be detected radiologically. Herein, we presented a bladder hernia in two different scans in 3 days. It was observed in CT but not in sonography. There was no evidence of strangulation. The bladder was retractile depend on the bladder fullness. Also, the patient's anamnesis was in this direction. This clinical picture was considered a retractile bladder.

Conflict of interest statement. None declared.

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BANTAO Journal 2020; 18(2): 82-85

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Case report

Rhabdomyolysis and Acute Kidney Injury in a Patient with Severe Form of Covid-19 Pneumonia - A Case Report

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Abstract

Introduction. The ongoing pandemic with the novel Corona virus poses unprecented challenges for the medical professionals worldwide. Acute kidney injury is frequently seen in patients infected with corona virus and often associated with a poor patient outcome. Rhabdomyolysis has been recognized as one of the possible contributing mechanisms.

Case. A 68-year-old man was referred to the emergency department complaining of a dry cough, myalgia, general weakness with devastated energy feeling, chest pain and difficulties in breathing, symptoms he experienced in the past five days. He also noticed that his urine was dark and in reduced amount. Quick antigen test for SARS CoV2 was performed, and the patient found Covid-19 positive. He was admitted at the hospital ward in a covid-designated unit. Laboratory findings revealed elevation of the inflammatory markers and electrolyte disbalance**.** Metabolic degradation products were markedly increased, serum urea was 44mmol/L (RF=2.7-7.8 mmol/L) and serum creatinine 689umol/L (RF=45-109umol/L), when deterioration of the kidney function was diagnosed. Urgent intermittent hemodialysis treatment was initiated. Patient suffered from a severe form of covid-19 pneumonia and was continuously on high flow oxygen mask. Duration of the patient hospitalization was 30 days, and thereafter, he was transferred to the rehabilitation center for 28 days. Complete restoration of the physical motion and activity was accomplished, oxygen support was no longer needed, since he maintained blood oxygen saturation above 95%. Renal function has also been recovered with degradation products maintained within normal ranges.

Conclusion. Rhabdomyolysis in covid-19 patients should be always kept in mind. Sometimes it can be an initial clinical manifestation in covid-19 patients [15], but on the other hand it can be presented as a late complication sometimes caused by the therapy itself. Multidisciplinary and comprehensive approach in the diagnosis, treatment and follow up of the patients can only guarantee timely detection and wide range of therapeutical modality, leading to a better prognosis and outcome.

Keywords: Covid-19 infection, acute kidney injury, rhabdomyolysis, renal replacement therapy

Introduction

The ongoing pandemic with the novel Corona virus poses unprecedented challenges for the medical professionals worldwide. According to World Health Organization statistics, so far more than 186 million cases, and more than 4 million deaths were registered as a result of infection with SARS CoV-2 [1]. Corona virus infection has a wide range of symptoms, and the clinical manifestation can vary from asymptomatic and mild cases to severe forms of disease with severe pneumonia, acute respiratory distress syndrome (ARDS), respiratory and multiorgan failure [2,3]. What was initially considered an isolated respiratory issue affecting the airways, lungs and its blood vessels, was shortly thereafter proven wrong. Numerous extrapulmonary manifestations had been seen, including neurological, gastrointestinal, endocrinologic, cardiovascular, dermatologic, renal and many others [2,3].

Acute kidney injury is frequently seen in patients infected with corona virus and often associated with a poor patient outcome. Studies were conducted to establish whether it was result of a direct effect of the virus (renal tropism and replication of the virus in kidney epithelial cells), or a consequence of numerous indirect factors such as the inflammatory process itself (cytokine mediated injury), nephrotoxin exposure, hemodynamic disorders and other factors [4,5]. Rhabdomyolysis has been recognized as one of the possible contributing mechanisms [6]. It is a condition characterized by muscle injury that leads to necrosis of the myocytes and release of intracellular contents into the circulation. Often seen

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causes are trauma/crush injury, infection (most common Influenza and other viral and bacterial), muscular strain, toxins/drugs, electrolyte disorders, inherited metabolic disorders and many others [8]. The classic presentation of this condition is a muscle pain, weakness, dark tea-colored urine (pigmenturia), and a marked elevation of serum creatine kinase (CK), five to ten times above the upper limit [7,8]. Myoglobin rises prior to CK levels and is removed through renal excretion in the first 24 hours, except when anuria occurs [8]. Electrolyte abnormalities usually include hyperkalemia, hypocalcemia, hyperuricemia, hyperphosphatemia and an anion gap acidosis [9]. In this report we present a case of a 68 year old man suffering from a severe form of covid-19 pneumonia, rhabdomyolysis and acute kidney injury, treated with renal replacement therapy until full recovery. A multidisciplinary approach in the treatment with well trained professionals from various specialties, (nephrology, pulmology, cardiology, endocrinology, transfusiology, infectology) warranted the best possible outcome for the patient's well-being.

Case presentation

A 68-year-old man was referred to the emergency department complaining of a dry cough, myalgia, general weakness with devastated energy feeling, chest pain and difficulties in breathing, symptoms he experienced in the past five days. He also noticed that his urine was dark and in reduced amount. No fever, high temperature or gastrointestinal symptoms were registered. His past medical history revealed Obesity, Diabetes type 2 on combined oral antidiabetics (Metformin) and insulin therapy; he also suffered from an acute myocardial infarction more than 3 years ago, for which a percutaneous coronary intervention, i.e. stent placement and a balloon angioplasty were performed. Beside antidiabetic drugs, his chronic therapy included antiplatelet therapy (Clopidogrel), diuretics (Furosemide and Spironolactone), ACE inhibitors (Lisinopril), nonselective B blocker (Carvedilol) and statin (Rosuvastatin) therapy. He has been taking this therapy for more than 3 years.

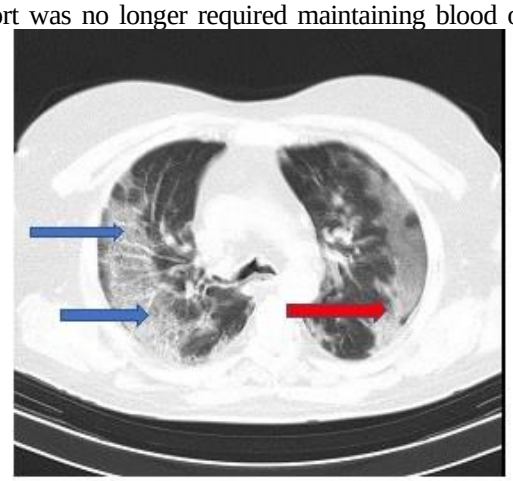
Quick antigen test for SARS CoV2 was performed, and the patient found Covid-19 positive. He was admitted at the hospital ward in a covid-designated unit. His nose swab PCR test was also positive for Sars CoV2.

The patient was dyspneic upon admission, with oxygen saturation 76% on ambient air, which raised up to 97% when he was put on oxygen support therapy with 12L/min flow face mask. Blood pressure was 80/40mmHg, heart pulse 95 beats per minute. Chest X-ray was performed and bilateral, diffuse zones of irregular consolidations with myopathic heart were revealed. Laboratory findings showed elevation of the inflammatory markers, C reactive protein 157mg/L (RF<6), white blood cells 12,6 per mcL of blood (RF=4,00-9,00) and ferritin >1500 ug/L (RF<500). Metabolic degradation products were markedly increased, serum urea was 44mmol/L (RF=2.7-7.8mmol/L) and serum creatinine 689umol/L (RF=45-109umol/L), when deterioration of the kidney function was diagnosed. Electrolyte disbalance showed hyperkalemia 6,73mmol/L (RF=3.8-5.5mmol/L), hyponatremia 129,63mmol/L (RF=137-145mmol/L) and hypocalcemia 1,76mmol/L (RF=2.1-2.6mmol/L). Creatinine kinase (CK) 1002U/L (RF=24-173) and lactate dehydrogenase (LDH) 559U/L (RF<248) were elevated, and a threefold increase of the hepatic enzymes was noted. Myoglobin tested dramatic increase of 1480.6 ng/ml (RF<75), normal range laboratory finding of cardiac troponin and electrocardiogram showed no sign of an acute cardiac event. Hemostatic investigation revealed increase of fibrin degradation products (D-dimer) up to 8000ngr/ml (RF=0-500).

Chest computer tomography (CT) scan was performed 5 days after the chest radiography was done, and small ground-glass opacites were seen in the perihilar and paracostal posterior parts of the left lung (Figure 1 and 2), but the right lung demonstrated huge ground-glass consolidation in the middle and inferior part (Figure 1 and 2).

Patient suffered from a severe form of covid-19 pneumonia and required oxygen delivery with high flow oxygen mask at the beginning of the treatment. In the following days, the oxygen requirements decreased, patient was switched to a regular face mask following a period of occasional supplemental oxygen of 2-5L/min on a nasal canule. He was treated with recommended doses of intra-venous corticosteroids, Azithromycin, Ceftriaxone, H2 blocker and hepatoprotective agents. Anticoagulant therapy with a low molecular weight heparin was administered, under the transfusion medicine specialist surveillance. The antiplatelet therapy was not interrupted. Urgent hemodialysis treatment was initiated at the first day of hospitalization. In total four hemodialysis treatments were performed. Diuresis was slowly restored after the third HD treatment. After an intensive fluid administration, the patient entered into the polyuric phase of acute kidney injury. Laboratory findings showed fast reduction in the urea, creatinine, myoglobin and CK values, while diuresis rose up to 5400ml per day. On day ten of hospitalization the femoral vascular catheter was removed and the patient was discontinued from hemodialysis treatment. Electrolytes were checked on a regular basis and substitutions were administered accordingly. Due to the treatment with corticosteroids, as well as the metformin effect prone to lactate acidosis, the glycemic control was disrupted and appropriate changes were made in the antidiabetic therapy. Namely, in consultation with the endocrinologist Metformin and mixed insulin were excluded from therapy, and rapid-acting and long-acting insulin combination was prescribed obtaining a better glycemic control. Duration of hospitalization was 30 days, and the patient was discharged and transferred to the rehabilitation center, where he stayed another 28 days. Complete restoration of

physical motion and activity was accomplished, oxygen support was no longer required maintaining blood oxygen saturation above 95%, and renal degradation pro-



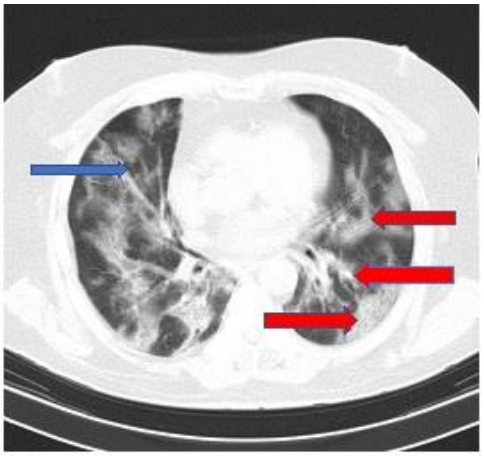


Fig. 1 and 2. Pulmonary CT scan: red arrows point at the small ground-glass opacities in the perihilar and para-costal posterior parts of the left lung and blue arrows at the huge ground-glass consolidation in the middle and inferior part of the right lung

ducts (urea and creatinine) balanced within normal ranges for a full recovery of renal function.

Discussion

The novel corona virus and acute kidney injury were associated since the early beginning of the pandemy when the first cases of disease in Wuhan were confirmed [10]. The initial reports from Wuhan suggested that acute kidney injury occurs in small percentage of the infected patients ranging from 3% to 9%. [10,11]. Subsequent analysis showed that the percentage of incidence is much higher, and overrates 15%. [11]. In studies made in USA among hospitalized patients, the incidence of acute kidney injury was between 37% and 40% [12]. This makes the acute kidney injury a common complication among hospitalized patients with severe covid infection. It is a poor prognostic factor which increases the risk of death, especially of those requiring dialysis treatment [12]. The exact mechanism of acute kidney injury is not well understood, it can be a result of the direct effect of the virus, or a consequence of the systemic inflammatory response, accompanied with the nephrotoxin exposure and hemodynamic disorders [13]. Rhabdomyolysis is recognized as one of the factors to blame for development of acute kidney injury. In our case report all possible etiological factors for rhabdomyolysis were excluded, as he denied intense physical activity, alcohol abuse, nephrotoxic medication (statines were taken more than 3 years), he did not report fever, convulsions, crush injures, so the viral myositis remained the most probable cause of it. Pathogenesis of the skeletal muscle injury remained completely unexplained. Different scientific approaches tried to explain the mechanism of the viral muscle damage, one blaming the direct invasion of the muscle tissue, other one the effect of the released myotoxic cytokines [14]. What remains important in the end is that rhabdomyolysis is a serios life-threating condition, requiring an early recognition and urgent treatment. According to the study made in Bronx, rhabdomyolysis increases the incidentce of a new- onset renal replacement therapy. In-hospital mortality was much higher in patients with severe covid infection, when rhabdomyolysis occurred [6]. Out of 140 patients that were included in the same study 74(52,9%) were discharged and 66 (47,1%) died in hospital. Rhabdomyolysis in covid patients should be always kept in mind. Sometimes it can be initial and sole manifestation in covid patients [15], but on the other hand it can be presented as a late complication, based on the particular therapeutical approach, as described in several cases after treatment with lopinavir and meropenem (used for the viral and pulmonary infection) [16]. Since the outbreak of the pandemic, it has been apparent that the disease prognosis has been depended from the multiorgan involvement. Comorbidities, especially cardiovascular and diabetes (as described in our case report) are the most common risk factors for severity and mortality [2].

Multidisciplinary and comprehensive approach in the diagnosis, treatment and follow up of the patients can only guarantee timely detection and wide range of therapeutical modality, leading to a better prognosis and outcome.

Conclusion

Novel corona virus was defined as a cause of various clinical manifestations, with wide spectrum of symptoms and severity forms. Acute kidney injury, as a result of rhabdomyolysis was described as bad prognostic factor for the patient outcome, very often underrated, and not recognized on time. Rhabdomyolysis in patients with covid-19 infection can occur at any time

of the patient illness, from the beginning till the recovery and thereafter. Prompt follow up of the patients by the multidisciplinary team is crucial for prevention, early recognition and urgent treatment of the multiorgan complication that can occur. Thus, the patient survival rate in this pandemic that took away many lives, could be markedly improved.

Conflict of interest statement. None declared.

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Letter to the editor

COVID-19 in Dialysis Patients: An Unexpected Silver Lining?

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Keywords: Covid-19, Infection, Catheter, Dialysis

Dear Editor,

In clinical practice, central venous catheter (CVC) use among hemodialysis patients is correlated with higher risk of infection compared to the use of an arteriovenous fistula. In fact, it is 3 times higher compared to prosthetic grafts, and 10 times higher than native fistulas [1,2]. For these reasons, international guidelines recommend the use of arteriovenous fistulas over central venous catheterization [3].

Dialysis facilities all over the world have been severely affected by the Covid-19 pandemic, registering several deaths among HD patients. Our country was no exception. As the nephrology department of a university hospital in the biggest city in Morocco, our unit used to admit numerous patients with bloodstream catheter-related infections. During this coronavirus pandemic, our department, as well as many others in the country, witnessed a substantial decrease in these infections, although we have no available data to support this affirmation.

Nevertheless, Heidempergher *et al*. [4] reported the same finding, with a 91% reduction in catheter-related bloodstream infections compared to the same period in 2019.This conclusion simply suggests that more rigorous hygiene precautions can decidedly ameliorate the issue of CVC-related infections in dialysis setting.

As the Covid-19 vaccination race continues worldwide, these striking results raise an important question: Will these strict hygienic precautions live on after the pandemic? In 2009, similar precautions were used in the flu pandemic, but were rapidly forgotten afterwards. Unfortunately, humanity has a short memory, and these measures will certainly fade away when the pandemic will be over.

Conflict of interest statement. None declared.

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