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Contents

I. Editorial

II. Short communication

III. Case reports

IV. Letter to the editor

V. In memoriam

BANTAO Journal 2021; 19(2): 65-66

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Editorial

SGLT-2 Inhibitors and GLP-1 Receptor Agonists May Prevent Cardiovascular and Chronic Kidney Disease Progression in Patients Regardless the Diabetic Status

Goce Spasovski[1], Merita Rroji[2], Goce Hristov[3], Natasha Nedevska[4], and Irena Rambabova Bushletikj[1]

[1]Department for Nephrology, Medical Faculty, University Sts. Cyril and Methodius, Skopje, N. Macedonia, [2]Department for Nephrology, University of Tirana, Tirana, Albania [3]Department for Internal medicine and Diabetes – General Public Hospital Strumica, Strumica, N. Macedonia, [4]Department for Endocrinology and Diabetes – General Public Hospital "8th September" Skopje, N. Macedonia

The most frequently developed complication of long-term diabetes is cardiovascular (CVD) and chronic kidey disease (CKD). The CVD prevalence in diabetic patients is around 32.2% [1], with a two-fold increased mortality risk compared to those without diabetes [2]. The question remains about the proportion of patients with type 2 diabetes (T2D) at high risk of mortality that could probably achieve the most significant benefit from an aggressive control of the modifiable risk factors and expectedly newer glucose-lowering agents.

Nowadays, two classes of anti-hyperglycemic drugs may reduce CV risk in patients with T2D [sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA)]. Empaliflozin treatment (10 mg) for around two years reduced the risk of a composite of CV death or hospitalization for heart failure (HF) by 21% [3]. FDA approved dapagliflozin and empagliflozin as drugs reducing the risk of CV death or hospitalization for HF in patients regardless of their diabetic status [4,5]. In addition, despite the similar benefit (RR 12 to 14%) of the two drugs on major cardiovascular events (MACE) in T2D patients, only GLP-1RA reduces the risk of stroke. Conversely, the hospitalization rate for HF in SGLT-2i treated patients is around threefold as compared to GLP-1RA treatment. However, in cases where SGLT-2i are contraindicated or not tolerated, GLP-1RA may exert the same effect on HF hospitalization. As for kidney outcomes, both drugs have shown similar protective cardiorenal effects. In a recent retrospective study, both drugs reduced the 10-year risk for CVD in T2D patients in primary cardiovascular prevention [6], while SGLT-2i had a more significant cardioprotective benefit for secondary prevention [7]. Nevertheless, the optimal clinical management of T2D seems not clear yet mainly because of the panoply of anti-glycemic targets and variety of existing drugs for the first and consequent drug choice, risk factors graduation for prevention of vascular complications, and achieved treatment outcomes (surrogate vs. clinical).

Additionally, the existing and new treatment guidelines releases generate more confusion than help in improving the guidance among clinicians [8]. Given that all available combinations in treatment could not be feasible and treatment algorithms could not be evidence-based lacking in comparative studies, the confusion among physicians leads towards clinical inertia for these drugs [8,9]. Hence, there is a need for coordinated action for the appropriate treatment of T2D patients with CVD and CKD with an SGLT-2 inhibitor or GLP-1RA. This is especially important in view of the recent survey about the declining glycemic control and increased number of vascular diabetic complications in the last decade [10,11].

In conclusion, SGLT-2i and GLP-1RA reduce CVD and CKD risks while controlling glycemia in patients with T2D. On top of it, SGLT-2i may be beneficial even in nondiabetic patients with HF with or without presserved ejection fraction introducing these therapies in patients at risk or with established CV or CKD. Finally, the medicare system should incorporate these treatment possibilities as regular support through the health insurance system for both (with or without T2D) patient groups at risk or with established CVD and CKD.

In light of the new evidence, we may say a new perspective might be opened for treatment of CKD that postpone disease progression and development of end-stage kidney disease and the need for renal replacement therapy. This effect certainly goes along with cardiovascular disease prevention and prolonged survival of CKD patients. In the last two decades, mainstream therapy for preventing CKD progression in patients with and without T2D was either angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin receptor blo-

Correspondence to: Goce Spasovski, University Clinic for Nephrology, Vodnjanska 17, 1000 Skopje, R. N. Macedonia; E-mail: spasovski.goce@gmail.com

ckers (ARB). However, the holistic treatment approach would also include a decreased risk of all-cause mortality in these CKD patients regardless of the presence of diabetes as a major risk factor.

Hence, in a couple of randomized, placebo-controlled studies in patients with T2D, in addition to the signifycant reduction of the cardiovascular risk, SGLT2 inhibitors improved the renal outcomes (reduction of the kidney function, worsening of albuminuria, stage kidney disease (ESKD) or death from renal cause) in comparison with placebo [12-14]. Regardless of the improvements achieved in these studies, they were not designed to evaluate treatment benefits in CKD patients consisting of a minor proportion of patients with eGFR of ≤60 mL/min/1.73 m2.

So, expectedly, the recent evidence showed a positive effect of SGLT2i in the designated kidney outcome trials in CKD patients with T2D (CREDENCE) [15], regardless of T2D status (DAPA-CKD) [16]. Here, canagliflozin has achieved significantly reduced risk of CKD progression in T2D patients, the same as reported for Dapagliflozin (in patients with or without T2D) with additional effect on the reduced all-cause mortality risk. Recently, among a wide range of patients with CKD at risk for the disease progression, EMPA-KIDNEY trial showed that empagliflozin treatment led to a lower risk of CKD progression or death from cardiovascular causes compared to placebo [17]. Hence, a new hope on the horizon appeared in view of the SGLT2i treatment of early CKD patients with or without diabetes. Based on the findings of the studies mentioned above, the Food and Drug Administration (FDA) has expanded the approval of canagliflozin for T2D patients with diabetic nephropathy (albuminuria ≥300 mg/day and an eGFR ≥30 mL/min/1.73 m2 [18], and for dapagliflozin in patients with CKD with an eGFR ≥25 mL/min/1.73 m2 at risk of CKD progression [19].

In conclusion, and considering the presented evidence, our Balkan nephrological community should be aware of this new added value in the retardation of CKD progression in patients with or without diabetes. We should also make sensible our authorities and health providers for the cost-efficacy of the SGLT2i in the management of CKD patients. Finally, this new class of renoprotection should be gradually implemented into our clinical practice for the benefit of our patients and the healthcare system.

Conflict of interest statement. None declared.

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Short communication

Focal Segmental Glomerulosclerosis and Collapsing Glomerulopathy after Covid 19 Infection

Vesna Ristovska[1], Pavlina Dzekova Vidimliski[1], Vlatko Karanfilovski[1], Zaklina Sterjova-Markovska[1], Aleksandra Canevska-Taneska[1], Igor Nikolov[1], Galina Severova[1], Lada Trajcevska[1], Panche Zdravkovski[2] and Gordana Petrusevska[2]

[1]University Clinic for Nephrology, [2]Institute of Pathology, Medical Faculty, University Sts. Cyril and Methodius, Skopje, N. Macedonia

Abstract

Introduction. Focal segmental glomerulosclerosis (FSGS) is defined as an increase in the mesangial matrix in some glomeruli with obliteration of capillary lumens, sclerosis, hyalinosis, foam cells, and adhesions to the Bowman's capsule. Collapsing glomerulopathy is a morphologic variant of focal segmental glomerulosclerosis (FSGS) characterized by segmental and global collapse of the glomerular capillaries, marked hypertrophy and hyperplasia of podocytes, and severe tubulointerstitial disease. Actually secondary collapsing glomerulopathy is a heterogeneous group including numerous causes: viruses, toxins and drugs such as heroin and pamidronate.

Case reports. We report on two cases with glomerular disease after COVID-19 infection. The first patient, 53 years old male, with nephrotic syndrome and histopathologic features of glomerular capillary collapse. He was admitted in our department with nephrotic syndrome and renal failure. Several months ago, he had COVID-19 infection and was treated for COVID-19 pneumonia, but he had not symptoms for any renal disease. In following months, the patients manifested symptoms such as nausea, dysuria and light malleolar edema. Laboratory findings presented increased values of BUN 27mmol/l, creatinine 453 μmol/l, with proteinuria 4,6 g/24h. In order to identify the cause for these results, renal biopsy was performed with diagnose of collapsing glomerulopathy. The patient was followed up for a period of 6 months and treated with corticosteroid therapy. The values for creatinine were decreased to 195 μmol/l, with proteinuria 1 g/24h. After that the patient was stable, but with slowly increasing values for creatinine up to 242μmol/l and proteinuria 0,61 g/24h, for a period of the next several months.

Second case was a patient 58 years old, male with pulmo-renal syndrome, with bilateral pneumonia and acute kidney injury. COVID 19 infection was established with BUN 36 mmol/l and serum creatinine up to 586 μmol/l. Several weeks the patient was treated with hemodialysis. After that the patient was stable, the values for BUN and serum creatinine were still higher but without necessity for dialysis treatment. Proteinuria of 1,98 g/24hours still remained and renal biopsy was performed. Focal segmental glomerulosclerosis was diagnosed. The follow up in next several months included therapy with corticosteroids, after that with cyclosporin, with effect on improved kidney function with BUN 14 mmol/l, creatinine 156 μmol/l and values for proteinuria of 0,96 g/24hours.

Conclusion. SARS-CoV-2 associated renal disease seems to have different outcome and follow up despite the treatment. Renal biopsy may be crucial along with the molecular testing for COVID 19.

Keywords: focal segmental glomerulosclerosis, collapsing glomerulopathy, COVID 19 infection, kidney injury

Introduction

Cases of even mild symptomatically COVID 19, are accompanied by acute kidney injury or heavy proteinuria and glomerulopathy. Although acute kidney injury was seen among most of them, uncommon pathology such as collapsing glomerulopathy were detected and most of these patients progressed to irreversible kidney injury and dialysis [1-3].

Collapsing glomerulopathy is a morphologic variant of focal segmental glomerulosclerosis (FSGS) characterized by segmental and global collapse of the glomerular capillaries, marked hypertrophy and hyperplasia of podocytes, and severe tubulointerstitial disease [3-5]. Actually secondary collapsing glomerulopathy is a heterogeneous group including numerous causes: viruses, toxins and drugs such as heroin and pamidronate.

The data suggest that collapsing glomerulopathy is clinically, pathologically, and epidemiologically different from noncollapsing FSGS. Although collapsing glomeru-

Correspondence to: Vesna Ristovska, University Clinic for Nephrology, Vodnjanska 17, 1000 Skopje, N. Macedonia; E-mail: v.ristovska@yahoo.com

lopathy resembles HIV-nephropathy both pathologically and clinically, it differs clinically by having no evidence for associated HIV infection and other viruses such as COVID 19, and differs pathologically by lacking endothelial tubuloreticular inclusions. Patients with repeated renal biopsy showed transition from minimal change disease to collapsing focal segmental glomerulosclerosis [6].
COVID-19 has been associated with acute kidney injury and published reports of native kidney biopsies have reported diverse pathologies [4,7-9].

Case report 1

We report on patient, 53 years old, male with nephrotic syndrome and histopathologic features of glomerular capillary collapse. He was admitted in our department with nephrotic syndrome and renal failure. Several months ago, he had COVID 19 infection and was treated for COVID pneumonia, but he had not symptoms for any renal disease. In following months, the patient manifested symptoms such as nausea, dysuria and light malleolar edema. Laboratory findings presented increased values of BUN 27mmol/l, creatinine 453μmol/l, CRP 1,7, total protein 62g/l, albumin 33 g/l, with proteinuria of 4,6 g/24h. In order to identify the cause for these results, renal biopsy was performed. The histopathologic findings presented 3 completely ischemic collapsing glomeruli and segmental sclerosing changes in 3 of the glomeruli, with fibrous thickened Bowman membrane. The tubulointerstitial compartment exhibits acute tubular injury with areas of tubular atrophy (Figure 1). TEM analysis showed one completely collapsed glomerulus, and another one with segmental sclerosis. Ultra-structurally, we revealed ischemic collapsed basal membrane with huge subendothelial deposition of collagenous fibrils, some associated with glomerular basement membrane spikes like (Figure 2). Tubular epithelium revealed ischemic lesions. In one segment the basal membrane showed relatively preserved contour with edema of the endothelial cells. Tubular basement membrane revealed ischemic collapsing changes with ischemic lesion of the tubular epithelial changes. There are neutrophils, lymphocytes and histiocytes in the interstitium. Some structures suspicious for virus inclusions were seen on high magnifications, such was x200.000, with location in the endothelial cells. Some of these structures showed spikes typical for COVID 19 viral morphology (Figure 3).
The patient was followed up for a period of 6 months and treated with corticosteroid therapy. The values for creatinine were decreased to 195 μmol/l, with proteinuria of 1 g/24h. After that the patient was stable, but with slowly increasing values for creatinine up to 242 μmol/l and proteinuria 0,61 g/24h, for a period of the next several months.

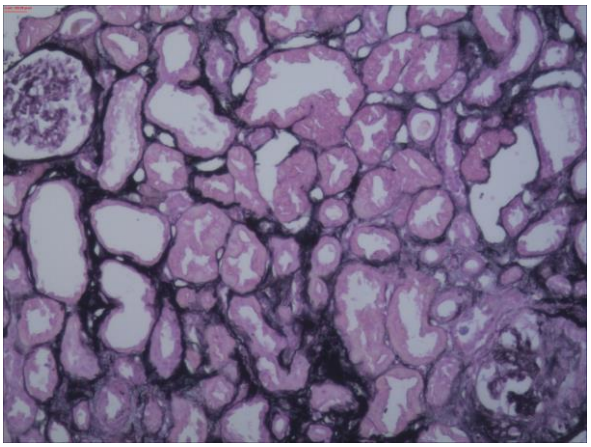

Fig. 1. Collapsing glomerulopathy after COVID 19 infection. Tubulointerstitium exibit acute tubular injury with areas with tubular atrophy

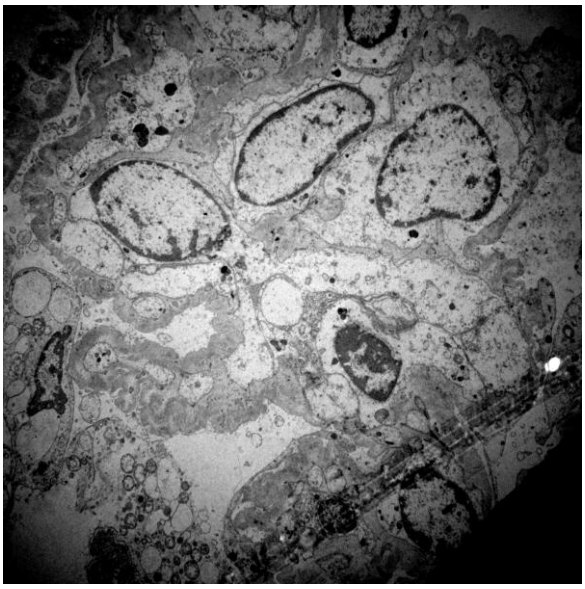

Fig. 2. Collapsed basal membrane with subepithelial deposition of collagenous fibrils

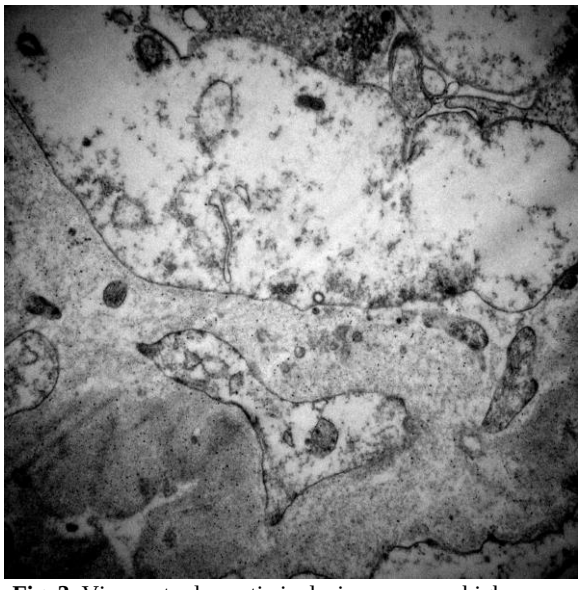

Fig. 3. Virus cytoplasmatic inclusions seen on high magnification

Case report 2

Second case was a patient, 58 years old, male with pulmo-renal syndrome, with bilateral pneumonia and acute kidney injury. COVID 19 infection was established with BUN 36 mmol/l and serum creatinine up to 586 μmol/l. Several weeks the patient was treated with hemodialysis. After that the patients was stable, although the values for BUN and serum creatinine were still higher, but without necessity for dialysis treatment. Proteinuria of 1,98 g/24hours still remained and renal biopsy was performed and focal segmental glomerulosclerosis was diagnosed. The histopathological findings revealed 3 glomeruli with relatively preserved structure, with slightly enlargement of the mesangial matrix. The other 6 glomeruli showed different grades of focal and segmental glomerulosclerotic lesion (Figure 4). In tubules there were erythrocyte cylinders with focal tubular atrophy and interstitial fibrosis. On semithin section analysis there was increased number of mesangial cells and mesangial matrix with opened capillary lumina.

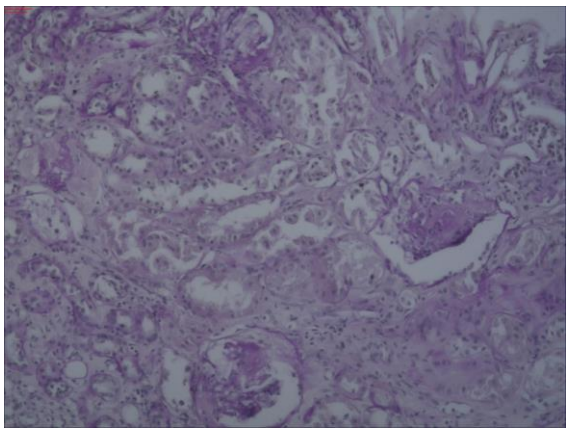

Fig. 4. Different grades of focal and segmental glomerulosclerotic lesions after COVID 19 infection

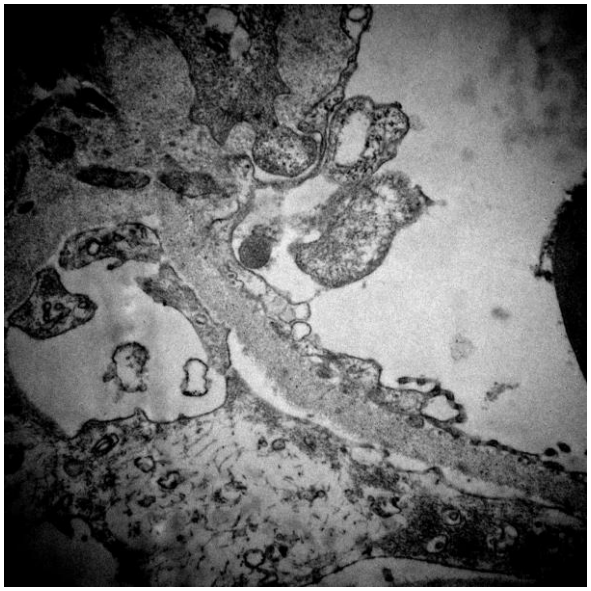

Fig. 5. Detachment of podocytes from GBM.

There were synechiae between visceral and parietal cells. Ultra-structurally the glomerular basement membrane had regular thickness with obvious segmental fusion of podocytes. There were found osmiophylic lipid inclusions in the visceral epithelial cells. In one segment detachment of the visceral epithelium from the GBM was seen (Figure 5). In some areas there were found GBM ischemic lesions with capillary intraluminal lymphocytes and histiocytes. There were some structures which were with morphologic characteristics of viral particles with present spikes like structures in the endothelial cell's cytoplasm and in lymphocytes. Some of them were included in membrane structures as cytoplasmatic inclusions (Figure 6).

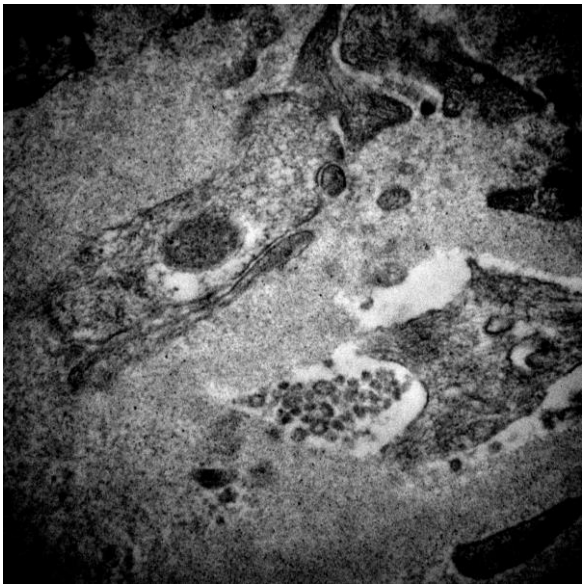

Fig. 6. Viral inclusions in endothelial cells of the glomeruli

The follow up in the next several months included therapy with corticosteroids, after that with ciclosporin, with effect on better kidney function with BUN 14 mmol/l, creatinine 156μmol/l and values for proteinuria 0,96g/24hours.

Discussion

The incidence of acute kidney injury associated with COVID-19 is variable depending on the geographic regions, and occurs in approximately 25-30% of patients admitted to hospitals [8,10]. The most common injury observed in autopsy and biopsy findings is acute tubular injury [8]. In a recently published studies, authors reported SARS-CoV-2 causing specific manifestations of proximal tubule dysfunction [11,12]. Histopathology showed proximal tubular injury, acute tubular necrosis, intraluminal debris, marked decrease in megalin expression in the brush border and electron microscopy evidence of particles resembling coronaviruses in cisternae of the endoplasmic reticulum in proximal tubule cells

[11]. Reports also indicate that rhabdomyolysis occurs in 7-20% of patients with COVID-19 acute kidney injury.
Infection with SARS-CoV-2 has been associated with cytokine release syndrome, a cytokine storm which contributes to hypoperfusion related injury of renal tubules [8]. Viral infection in alveolar cells, leads to massive recruitment of immune cells causing cytokine-mediated acute kidney injury [8-10].
Over the past several decades various pandemics have highlighted the different mechanisms by which viruses cause kidney disease [7,11-13]. With the novel coronavirus pandemic which has so far affected 96 million people as of January 2021 a new cohort of patients with kidney injury has been reported. The high infectivity causing rapid spread of this virus among the global population can have a significant long-term kidney complication than prior pandemics. Although there have been several publications over the past few months with attempts to identify the exact mechanism of kidney injury in these patients, the exact pathophysiology of COVID-19, the kidney injury remains unclear. The absence of viral particles demonstrated an alternate mechanism for renal injury explained in part by a dysfunctional immune response leading to a cytokine storm causing a cascade of renal injury including acute tubular injury, interstitial inflammation, microangiopathy, proteinuria, and possible glomerulopathy. As in the case of the hepatitis viruses and HIV-associated kidney disease, we may be seeing the start of a new disease entity as recently described of COVID-19-associated nephropathy (COVAN) along with increased chronic kidney disease in patients with COVID-associated kidney injury in the future [9,14]. Patients with COVID-19 develop a wide spectrum of glomerular and tubular diseases. Indications for kidney biopsy were recorded as any combination of acute kidney injury, even superimposed on chronic kidney disease, nephrotic-range proteinuria, or nephrotic syndrome, as previously described. The biopsy series reveal diverse kidney pathology in SARS-CoV-2-infected patients [9, 12]. The findings highlight the potential for viral infection to influence on immune responses that trigger new glomerular disease. Acute tubular injury is common and likely multifactorial and develops in up to 37% of hospitalized patients with COVID-19 and its pathophysiology has not been fully elucidated [15]. The lack of definitive virus in kidney cells argues against direct viral infection as the major pathomechanism [14].
Our findings provide two cases of focal segmental glomerulosclerosis, and its rare variant manifested as collapsing glomerulopathy, with evidence for the presence of at least some viral particles of COVID 19, mostly in the endothelial cells of the glomerular structures. In our cases we found different findings, but with clinical feature for chronic kidney injury. Renal biopsies were processed by standard techniques for light microscopy, immunofluorescence, and electron microscopy. The findings presented 2 variants of glomerular disease, but with similar clinical feature, manifested with proteinuria and edema, followed by the decrease of the renal function. The follow-up for several months presented well response on the therapy with corticosteroids and cyclosporine. After that period the patient with focal segmental glomerulosclerosis was stable with improvement of the renal function, but the patient with collapsing glomerulopathy as a variant of focal segmental glomerulosclerosis, had poor prognosis with progression of the disease to chronic renal failure.

Conclusion

We can say that SARS-CoV-2 associated renal disease has different outcome and follow up despite the treatment. The necessity for renal biopsy with extensive ultrastructural analysis as well molecular testing for COVID 19 positivity is obvious for diagnosis of the renal injury. That fact is important for the further follow up and treatment of these patients, after COVID 19 infection.

Conflict of interest statement. None declared.

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BANTAO Journal 2021; 19(2): 72-74

BJ

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Short communication

Tacrolimus Induced Acute Exacerbation of Chronic Calcifying Calculous Pancreatitis in a Kidney Transplant Patient - Case Report and Literature Review

Zoran Sabljic, Vesna Furic-Cunko, Lea Katalinic, Ivana Juric, Nikolina Basic-Jukic

Department of nephrology, arterial hypertension, dialysis and transplantation, Clinical hospital centre Zagreb, Zagreb, Croatia

Abstract

Introduction. The purpose of this case report is to describe our experience in the treatment of potential tacrolimus-induced pancreatitis in a renal transplant patient.

Case report. We present a case of a 35-year Caucasian female kidney transplant patient who developed an acute exacerbation of chronic calcifying calculous pancreatitis twice in the early posttransplant period. Before undergoing a kidney transplant, she had been hospitalized on three occasions due to episodes of acute pancreatitis, which was successfully treated with conservative therapy. The second episode of acute exacerbation of chronic pancreatitis, which occurred two months after kidney transplantation, was much more severe than the first, which occurred on the sixth day after transplantation, and was complicated by the formation of multiple pseudocysts in the head and body of the pancreas, with a further tendency to grow. The resulting compression on the surrounding structures required surgical drainage of the cysts. Furthermore, tacrolimus was switched to parenteral cyclosporine due to intolerance of oral food and fluid intake, and oral cyclosporine therapy was continued after recovery. The patient was discharged without recurrent clinical and laboratory signs of acute exacerbation of chronic pancreatitis during the further follow-up of 6 months.

Conclusion. Tacrolimus is the most likely cause of acute exacerbation of chronic pancreatitis in our patient. Switching from tacrolimus to cyclosporine should be considered.

Keywords: acute exacerbation of calcifying calculous chronic pancreatitis, kidney transplant, tacrolimus, pancreatic pseudocysts

Introduction

Tacrolimus (or FK506), a calcineurin inhibitor (CNI) introduced in the field of transplantation in the 1990s, is the cornerstone of most immunosuppressive regimens in solid organ transplantation, and its use has revolutionized the future of kidney transplantation. It has been associated with better graft survival, a lower incidence of rejection, and improved drug tolerance with fewer side effects than cyclosporine [1]. According to a review article by Jones MR *et al*. acute pancreatitis due to medications generally is rare (incidence of 0.1% to 2%), with common drugs being tetracyclines, isoniazid, macrolides, metronidazole, and angiotensin-converting enzyme inhibitors [2].

Drug-induced pancreatitis is classified (class I - IV) based on the number of cases reported, demonstration of a consistent latency period (time from initiation of the drug to development of pancreatitis), and reaction with rechallenge [3]. A population-based case-control study by Floyd A *et al*. pancreatitis, reported in solid organ transplantation and allogeneic stem cell transplantation cases, was related to immunosuppressive agents. However, only azathioprine has been confirmed to be the cause of pancreatitis with solid evidence so far [4]. We report a rare but clinically important case of tacrolimus-induced acute exacerbation of chronic calcifying calculous pancreatitis in a renal transplant patient.

Case report

35-year-old Caucasian female kidney transplant patient developed an acute exacerbation of chronic calcifying calculous pancreatitis during tacrolimus therapy. She was diagnosed with autosomal dominant polycystic kidney disease (ADPKD) with liver and ovarian cysts in 2009. Nine relatives also have ADPKD, and all have had kidney transplants. From December 2018, due to end-stage renal disease, she was started to replace renal function with peritoneal dialysis, initially with continuous ambulatory peritoneal dialysis (CAPD) and from June 2019 with automated peritoneal dialysis (APD) as the treatment modality. In August 2019, she was

Correspondence to: Nikolina Basic-Jukic, Department of nephrology, arterial hypertension, dialysis and transplantation Clinical hospital centre Zagreb, Kispaticeva 12, 10000 Zagreb, Croatia; E-mail: nbasic@kbc-zagreb.hr

hospitalized for persistent upper abdominal pain with nausea. Laboratory tests showed elevated serum amylase of 462 U/L (normal range 23-91) and lipase of 1130 U/L (normal range 13-60), suggesting acute pancreatitis without a clearly defined etiology.

Further radiological diagnosis in terms of multi slice computed tomography (MSCT scan) corroborated the suspicion of chronic calcifying calculous pancreatitis (numerous mineral stones of the pancreas were descrybed, with a dilated central pancreatic duct (Wirsung) up to 7 mm and also a dilated accessory pancreatic duct (Santorini) and also dilated choledochal duct up to 10 mm, without visible signs of obstruction in terms of lithiasis or tumor. The applied symptomatic and supportive therapy was accompanied by clinical improvement but serum amylase and lipase remained elevated. In September 2019, on the advice of the gastroenterologist, she underwent magnetic resonance cholangiopancreatography (MRCP) which revealed a dilated choledochal duct up to 6 mm with suspected choledocholithiasis and a possible diagnosis of pancreatic divisum (noting that the ducts were not fully visible). In November 2019, she was readmitted to the hospital for clinical and laboratory signs of acute exacerbation of chronic pancreatitis (abdominal pain and elevated serum amylase 3774 U/L and lipase 7400 U/L). Endoscopic ultrasound (EUS) revealed calcifications in the head of the pancreas, with a tortuous main pancreatic duct and with possible protein plugs, without lithiasis. Although laboratory and microbiological analysis showed no signs of acute peritonitis, acute exacerbation of chronic pancreatitis was understood as a possible complication of peritoneal dialysis. She was switched to hemodialysis. During the aforementioned hospitalization, clinical improvement occurred with symptomatic and supportive therapy.

In July 2020, she was hospitalized again due to clinical (abdominal pain and vomiting) and laboratory (elevated serum amylase 3630 U/L and lipase 8829 U/L) signs of acute exacerbation of chronic pancreatitis which again improved on symptomatic and supportive therapy. A fecal elastase test was performed, and the finding was within normal range, indicating normal pancreatic exocrine function.

After completion of appropriate pretransplant diagnostics, the patient underwent the deceased donor kidney transplantation in June 2021, with a standard immunosuppression protocol that included induction of basiliximab 20 mg (day 0 and +4) with tacrolimus, mycophenolate mofetil (MMF), and steroids as maintenance therapy. On the sixth posttransplant day, the patient complained of abdominal pain. Laboratory tests revealed an increase in serum amylase (2089 U/L) and lipase (2951 U/L), indicating an acute exacerbation of chronic pancreatitis, which was gradually improved with supportive and symptomatic therapy applied. In August 2021, she was hospitalized again for an acute exacerbation of chronic pancreatitis, with a more complicated clinical picture of severe abdominal pain accompanied by vomiting and diarrhea. Laboratory tests showed an increase in C-reactive protein (CRP) up to 197 mg/L, in addition to elevated amylase (731 U/L) and lipase (264 U/L. In addition, an abdominal MSCT examination was performed on two occasions. On the first occasion, multiple pseudocysts were seen in front of the head and body of the pancreas in addition to acute pancreatitis, the largest of which was approximately 13 cm in diameter, and five days later, progression of the cysts to a size of 17 cm, with an indentation between the large curvature of the stomach, spleen, trunk, and tail of the pancreas was described. Since endoscopic drainage of the cysts was no longer possible, the surgeon performed medial laparotomy and cystogastrostomy and drainage of the pseudocysts according to Jurasz [5], and the procedure passed without complications. Further, the patient was transferred to the intensive care unit (ICU), and after improvement of clinical condition, she was transferred to the ward for transplant patients to continue the previously started treatment. In the meantime, due to intolerance of oral food and fluid intake, oral immunosuppressive therapy with tacrolimus was switched to parenteral therapy with cyclosporine, and the dose of intravenous steroids was increased, while MMF was also gradually excluded from therapy. Switching from tacrolimus to cyclosporine, in addition to empiric and targeted antibiotics (ciprofloxacin and linezolid) and other supportive therapies, resulted in an improvement in clinical condition and a gradual decrease in laboratory parameters of pancreatic inflammation. The use of oral cyclosporine was continued with dose adjustment depending on the drug concentration in the blood. MMF was also gradually returned to therapy with oral steroid therapy dose reduction and the patient was discharged from the hospital without any discomfort. Oral supplementation of pancreatic enzymes was introduced.

At the outpatient nephrological controls, the patient was subjectively well, with stable graft function and no objective clinical deterioration and laboratory indicators of acute pancreatitis. On the control ultrasound of the pancreas, pseudocysts regression size was described.

Review of the literature

In a case report by Liu X *et al*. they presented a 24-year-old male patient who had undergone kidney transplantation and who, among others, had immunosuppressive therapy with tacrolimus, and on the tenth after transplantation, he developed clinical, laboratory, and radiological signs of acute pancreatitis. After excluding other possible causes, they concluded that tacrolimus was the definite inducer of pancreatitis because his symptoms decreased and laboratory tests improved after exclusion of tacrolimus, which was

temporarily switched by cyclosporin. Furthermore, tacrolimus was on day 61 again returned to therapy with consequent laboratory and radiological relapse of acute pancreatitis. The patient has switched from tacrolimus to cyclosporine again, followed by normalization of laboratory tests and after all, he was discharged home with no relapse of acute pancreatitis [6].

Xu J *et al*. presented a case of a 45-year-old male who underwent kidney transplantation and received immunosuppressive therapy of tacrolimus, and on day 67 after transplantation, he developed acute pancreatitis with an extremely high blood tacrolimus concentration. They also excluded other possible causes and speculated tacrolimus was the probable inducer of pancreatitis. After tacrolimus was discontinued and alternated with cyclosporine, the patient gradually recovered and was discharged home with no relapse [7].

Mallory and Kern have established a criterion for a definite association of any drug with pancreatitis. This includes (a) appearance of this complication during treatment with the drug, (b) disappearance upon with drawal of the drug, (c) exclusion of other causes, and (d) relapse upon reintroduction [8].

In our patient, 3 of 4 criteria are fulfilled, so we can assume with a high degree of probability that the last two acute exacerbations of chronic pancreatitis were triggered by tacrolimus.

Conclusion

The goal of this article is to emphasize that clinicians should be aware of the possibility of tacrolimus-induced pancreatitis during tacrolimus treatment in renal and other transplant patients.

Conflict of interest statement. None declared.

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Short communication

Lindsay's Nails and Terry's Nails in End Stage Renal Disease - Case Series

Ivana Dohcheva Karajovanov[1], Suzana Nikolovska[1], Irena Rambabova Bushljetich[2], Julija Mitrova Telenta[1], Maja Dimova[1], Dejan Filipovich[1], Sasho Dohchev[3] and Goce Spasovski[2]

[1]University Clinic for Dermatology, [2]University Clinic for Nephrology, [3]University Clinic for Urology, Faculty of Medicine, Ss. Cyril and Methodius University, Skopje, N. Macedonia

Abstract

Introduction. Nail changes occur as part of a single organ disease, multisystemic diseases or because of the intake of some medications. Chronic kidney disease (CKD) is associated with various nail abnormalities. To identify Lindsay's nails and Terry's nails in patients with end stage renal disease (ESRD) on maintenance hemodialysis (HD) and to determine the common anamnestic, clinical and/or laboratory parameters that would help elucidate the etiopathogenesis of these nail pathology.
Methods. Twenty patients with ESRD on hemodialysis were included into the study. Dermatological examination took place during the dialysis session. Lindsay's nails were identified when the distal part of the nail bed is red/rose-brown, clearly separated from the proximal part of the nail bed, occupying 20-60% of the entire length of the nail bed. The proximal part of the nail bed is whitish, resembling grounded glass. When pressing the nail, the discoloration of the distal part of the nail bad does not fade completely. Terry's nails were identified by a 0.5-3.0 mm wide distal band, pink-brown in color, with a proximal part of the nail bed that is white and occupies 80% of the entire nail bed. Data on demographic characteristics, history of the disease and the laboratory values were noted for each patient.
Results. Out of 20 patients, all males, we diagnosed Half-and-Half nails, also called Lindsay's nails, and Terry's nails in 6(30%) patients [5 Half-and-Half nails (25%), and 1 with Terry's nails (5%)]. All patients had sideropenic-free anemia, elevated urea and creatinine values and elevated parathyroid hormone (PTH) values (>190 pg/L, range 190.3-387.5 pg/L).
Conclusion. After searching the relevant literature (MEDLINE, PubMed), we found this is the first study to link elevated PTH values and Half-and-Half nails (also called Lindsay's nails), and Terry's nails in patients with ESRD on HD.

Keywords: Lindsay's nails, Terry's nails, end stage renal disease, hemodialysis, etiopathogenesis

Introduction

Nail changes can be associated with or may be due to systemic disorders. These disorders occur as part of some single organ disease, multisystemic diseases or because of the intake of some medication. Chronic kidney disease is associated with various nail abnormalities such as Half-and-Half nails, absence of lunula, onychomycosis, leukonychia, onycholysis, splinter hemorrhage, Terry nails, subungual hyperkeratosis, Mees' lines or acropachy. The representation of these changes in CKD patients ranks from 52% to 71% [1-3].
One of the most common nail pathologies in patients with ESRD on chronic HD is Half-and-Half nails or Lindsay's nails. For the first time, Half-and-Half nails were described by Bean, 1963 [4] in two patients with renal insufficiency and azotemia. In published literature, Lindsay's work [5] is more cited, defining Half-and-Half nails as clearly limited discoloration with red/rose-brown color of the distal part and affection of 20–60% of the length of the nail bearing. The discolorration of the distal part does not fade completely after pressing the nail. The proximal part of the nail bearing is white, resembling coiled glass. One or all of the fingernails and toenails may be affected. The prevalence of Half-and-Half nails in HD patients in various studies ranged from 7.7% to 50.6% [2, 6-10]. Lindsay nails are not a specific phenomenon in CKD patients, but also occur in other diseases such as Morbus Crohn (with or without associated zinc deficiency), Morbus Behcet, in patients receiving isoniazide, cytostatic therapy or may be idiopathic [11-15]. Half-and-Half nails have been observed in a patient with a severe clinical picture of COVID-19 infection [16].
Similarly, Terry's nails have been also found in HD patients. The essential difference in the clinical picture is that in Terry's nails, the distal band is less than 20% of the total length of the nail bed presented as 0.5-3.0 mm wide distal band, pink-brownish painted, and a proximal part of the nail bed that is whitened and covers 80% of the entire surface of the nail bed. Although promoted as one of the signs of hepatic cirrhosis [17] and an

Correspondence to: Ivana Dohcheva Karajovanov, University Clinic for Dermatology, 1000 Skopje, N. Macedonia; E-mail idohcheva@gmail.com

early sign of autoimmune hepatitis [18], Terry's nails are often associated with chronic congestive heart failure, chronic renal insufficiency, hematological diseases and adult diabetes mellitus, but may also occur in healthy individuals as part of the physiological aging process [19].
Pathophysiology responsible for nail transverse discoloration in HD patients is not fully clarified. Proximal white band is thought to be a consequence of chronic anemia, and distal rosemary or brown band is the result of melanin deposition, probably stimulated by uremic toxins.
The aim of our paper was to determine common history, clinical and/or laboratory parameters that would help disclosing the etiopathogenesis of Half-and-Half nails and Terry's nails in patients with ESRD on HD.

Materials and methods

This is an observational descriptive study conducted at the University Clinic for Nephrology, Skopje, N. Macedonia. We have examined a series of six patients with ESRD on chronic HD program with a clinical picture of Half-and-Half nails or Lindsay's nails and Terry's nails. The inclusion criteria were: patients with glomerular filtration rate (GFR) <15 ml/min/1.73m^2 being on chronic HD > 3 months, age ≥18, with a written informed consent for participation in the study.
The exclusion criteria were: patients with Morbus Crohn and Behcet, those receiving isoniazid or cytostatic therapy, or those with congenital, systemic or primary skin disorders that contribute to nail change, the use of any colors/paints, nail injuries or infection, Carpal Tunnel Syndrome, ischemic syndrome secondary to arterial-venous fistula.
A clinical examination was performed of the fingernails and toenails in 20 patients with ESRD on a chronic hemodialysis program in the University Clinic for Nephrology. The dermatological examination to evaluate nail changes of the type of Half-and-Half nails and Terry's nails took place in the dialysis centre during the dialysis session. The room was illuminated by natural daylight, ceiling electric lighting, and a hand-held additional lamp was used for the examination of the nails when needed. Half-and-Half nails or Lindsay's nails and Terry's nails were diagnosed clinically based on diagnostic definitions for both nail changes.
Data on demographic characteristics (age and gender) were provided for each patient, the history of the disease (primary cause for ESRD, standard therapy, HD duration) and for laboratory values of medical histories [hemoglobin, ferritin, calcium, phosphorus, albumins, creatinine, urea and parathormone (PTH)], (Table 1).

Table 1. Demographic data, disease history data and laboratory parameters

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	67	47	53	66	58	74
Sex	Male	Male	Male	Male	Male	Male
HD duration	8	6	6	8	25	9
Primary cause for ESRD	MesPGN	HTN	APKD	Bilat. Nx due to kidney cancer	UND	Bilat. RPD
Hemoglobin (g/L)	113	103	88	113	131	110
Ferritin (µg/L)	697.2	605.7	296.4	679.1	73.9	469.2
Urea (mmol/L)	20.3	20.2	29	16.5	24.1	16.8
Creatinine (µmol/L)	731	713	1019	709	868	88
Albumin (g/L)	45	45	35	47	41	41.8
Parathormone (pg/ml)	387.5	265.9	268.2	190.3	264.9	277.6
Medications	Fe, ESA, CaCO3, vit. D3, CCB, ACT, statin, BB, DIU	Fe, ESA, CaCO3, vit. D3, ACT, CCB	Fe, ESA, CaCO3, vit. D3, ACT, CCB	Fe, ESA, CaCO3, vit. D3, ACT, CCB	Fe, ESA, CaCO3, vit. D3, ACT, vit. C, BB, statin, PDN, ASA	Fe, ESA, CaCO3, vit. D3, statin, PPI, NSAID
Nail changes	Terry's nails	Half-and-Half nails	Half-and-Half nails	Half-and-Half nails	Half-and-Half nails	Half-and-Half nails

Abbreviations: MesPGN= Mesangial proliferative glomerulonephritis; HTN=Hypertensive nephropathy; APKD=Adult polycystic kidney disease; Bilat Nx= Bilateral Nephrectomy; UND= Undifferentiated; RPD=Renal parenchymal disease; ESA=Erythropoietin-stimulating agent; $CaCO_3$=calcium carbonate; Fe= Iron; vit=vitamin; CCB= calcium channel blocker; ACT= Anticoagulant Therapy; Statin= HMG-CoA reductase inhibitors; BB= Beta blocker; DIU= Diuretic; PDN= Prednisone; ASA= Aminosalicylate;PPI= Proton pump inhibitor

Results

In 6 out of 20 patients with ESRD on hemodialysis, n=20 (14 men, 6 women) who underwent a dermatological examination, nail changes of type Half-and-Half nails and Terry's nails were diagnosed (30%). Half-and-Half nails were diagnosed in 5 patients (25%), and only 1 patient was diagnosed with Terry's nails (5%). The images with nails changes of fingernails and toenails are presented in Figure1.

All six patients were men. The mean age of patients was 60.83±9.99 years (ranging from 47 to 74 years). The mean hemodialysis duration was 10.33±7.28 years (in the rank of 6 to 25 years). Half-and-Half nails were equally present on both hands and feet in patients of our series. None of the patients knew how to indicate a time or an event related to the nail changes. All 6 had the same comment that they had noticed nail changes over the years, but before the dermatological examination they were not even aware that it could be of any importance related to CKD and/or dialysis. The cause of CKD was different in each individual patient. All patients had anemias without sideropenia, low-hemoglobin and elevated ferritin levels, expectedly elevated urea and creatinine levels, and no patient had hypoalbuminemia. Chronic medication therapy was identical in all 6 patients. PTH levels were elevated (>190 pg/L, range 190.3-387.5 pg/L) in all 6 patients, as well.

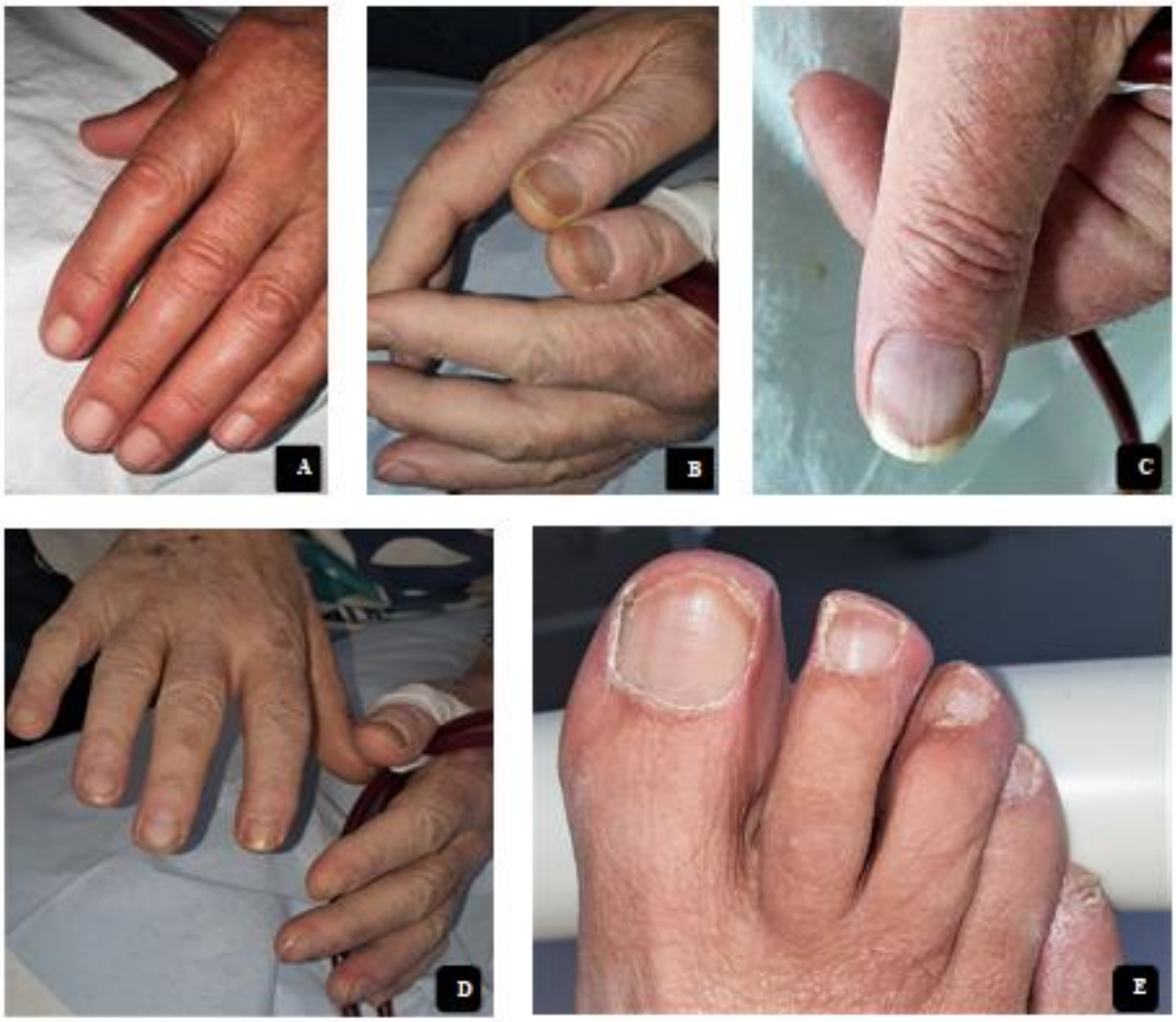

Fig. 1A. Terry's nails - a 1 mm wide distal band with brown color and a distal whitish part that covers 90% of the entire surface of the nail bed. **B.** Half-and-Half nails - red/brown color of the distal part of the nail bed, covering 60% of the entire length of the nail bed and a proximal part of the nail with grounded glass color. **C.** Half-and-Half nails - a clearly expressed demarcation zone between distal and proximal discoloration. **D., E**. Half-and-Half nails - more fingernails and toenails are affected

Discussion

Our case series of patients with Half-and-Half nails and Terry's nails represented 30% of total ESRD patients on HD that underwent examination This proportion fits with numbers in the reports from other studies where the prevalence of this type of nail changes in HD patient stages from 7.7% to 50.6% [2]. There is also evidence that in certain cases these nail abnormalities withdraw after several months of successful kidney transplantation, while in others the prevalence is higher in transplanted patients compared to patients on hemodialysis [20]. Half-and-Half nails can occur on one or all fingernails and toenails. However, this condition is more common on the fingernails. In our study, Half-and-Half nails were observed equally on both fingernails and toenails, all 6 patients being males. In the literature, the ratio males/females is reported as 2:1, while another case control study did not observed any gender difference [2]. There were various causes for renal insufficiency: mesangial proliferative glomerulonephritis (MesPGN), hypertensive nephropathy or nephroangiosclerosis (NAS), adult polycystic kidney disease (APKD), bilateral nephrectomy due to urothelial cell carcinoma (TCC) on the left and hydronephrosis on the right kidney, undifferentiated chronic kidney disease, and unknown bilateral renal parenchymal disease. All patients received identical therapy, although the duration of HD and age varied widely. Anemia, elevated urea and creatinine levels, and secondary hyperparathyroidism (sHPTH) with PTH values >190 pg/L were present in all patients. These findings are similar to the findings of the Study of Dyachenko et al. from 2007, which indicates the prevalence of nail changes in patients with CKD is not significantly dependent on age, gender, duration of CKD, medication or underlying disease that caused ESRD. This study of Dyachenko *et al*. established a significant correlation between these particular nail changes and PTH > 220 μlEq/mL or 2.06 (1.34-4.52).

Lindsay's nails and Terry's nails pathogenesis is not fully clarified so far. There is an opinion that the red-brown distal tape is due to melanin deposition in the nail plate and/or increased capillary density [21,22]. In the study Fernandez-Somoa *et al*. from 2021, capillaroscopy has not determined an increased amount of melanin. Instead, a dilation of the venous plexus from the nail bed has been found [23]. It is considered that proximal white band is caused by chronic anemia, increased thickness of capillary walls and excessive growth of the connective tissue between the nail and bone.

After searching the relevant literature (MEDLINE, PubMed), we found no study describing the connection of sHPTH to Half-and-Half nails and Terry's nails. sHPTH is a common disorder in patients with HBB and is characterized by increased levels of PTH in serum, parathyroid hyperplasia and calcium and phosphorus metabolism disorder. sHPTH develops in the early stages of CKD and worsens by the reduction of renal function. PTH is the major uremic toxin responsible for long-term consequences such as renal osteodystrophy, vascular calcification, alterations in cardiovascular structure and function, immune system dysfunction and anemia. These adverse effects contribute to increased mortality and morbidity from cardiovascular disease in patients with ESRD patients [24]. PTH has a vasorelaxant effect on smooth muscle cells of the blood vessels and is a potent activator of endothelial nitrogen oxide synthesis [25]. Thus leading to vasodilation of small blood vessels. The elevated PTH levels in all patients in our case series leads to the hypothesis that sHPTH in ESRD patients on HD might be responsible for red/brown color of the distal part of the nail plate due to the vasorelaxation of the blood vessels and the increased synthesis of endothelial nitrogen oxide resulting in an enlarged venous plexus of the nail bed. Anemia and deposits of calcium in blood vessels caused by the elevated levels of PTH create a microenvironment of hypoxia responsible for the proximal white coloration of the nail plate.

Conclusion

This study was designed to determine common history, clinical and/or laboratory parameters that would help disclosing the etiopathogenesis of the Half-and-Half nails and Terry's nails in patients with ESRD on HD. All patients from this case series had low hemoglobin and elevated PTH levels. sHPTH originates the hypothesis that PTH with its vasorelaxant and vasodilatation effect is responsible for the presence of dilated venous plexus in the nail bed and red-brown discoloration of the distal part of the nail. Conversely, the white color of the proximal part of the nails may be due to the anemia and calcium deposits of calcium in the blood vessels wall caused by the increased PTH, which create hypoxia and the growth of connective tissue between the bone and the nail plate. To prove this hypothesis, studies with a larger number of ESRD patients on HD are needed to determine PTH levels, capillaroscopic evaluation of blood vessels and high-frequency ultrasonography to evaluate calcium deposits of blood vessels.

Conflict of interest statement. None declared.

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Case report

Laparoscopic Cholecystectomy In A Patient With End Stage Renal Disease Undergoing Continuous Peritoneal Dialysis – A Case Report

Ana Stojanoska Severova[1], Svetozar Antovic[2], Elma Kandic[3], Nikola Gjorgjievski[1], Igor Nikolov[1], Galina Severova[1], Lada Trajceska[1], Pavlina Dzekova-Vidimliski[1], Irena Rambabova-Busljetic[1], Vesna Ristovska[1] and Goce Spasovski[1]

[1]University Clinic of Nephrology, [2]University Clinic of Digestive Surgery, [3]University Clinic of Cardiology, Faculty of Medicine, Ss. Cyril and Methodius University Skopje, N. Macedonia

Abstract

Introduction. Peritoneal dialysis (PD) is a treatment of choice in end stage renal disease (ESRD) patients, especially those with vascular access problems. However, occasionally, these patients' condition may be complicated by cholecystopathy, including either cholelithiasis and/ or cholecystitis. Importantly, surgical interventions for a disease that disturb the integrity of abdominal cavity boundaries can disrupt the regular PD schedule.

Case report. 19-year-old white female, presented at University Clinic of Nephrology with dyspepsia, vomiting, and intermittent right upper quadrant abdominal pain, present for couple of weeks. She was with ESRD on maintenance peritoneal dialysis program since 2017. The history of a recurrent right upper quadrant abdominal pain with the laboratory data at the hospital admission, suggested that a gastroenterohepatologist should be contacted for ultrasonography examination of the abdomen. The evidence of a gall-bladder mass, indicated the need for cholecystectomy. Abdominal surgeon was contacted, and cholecystectomy was scheduled. The patient underwent laparoscopic cholecystectomy (LC). The peritoneal catheter was still placed in the peritoneal cavity regardless of the surgical procedure. No complications during surgery were reported. Post - operative course was also uneventful.

Conclusions. Recent reports suggest that it is possible to successfully and safely perform laparoscopic procedures in patients on PD without removing the PD catheter and with a relatively short period of HD in the interim period before resuming PD.

Keywords: laparoscopic cholecystectomy, peritoneal dialysis, PD catheter

Introduction

Peritoneal dialysis is a treatment of choice in ESRD patients, especially those with vascular access problems. PD offers a therapeutic approach that is rational for managing end-stage renal disease in the broader context of overall health care. It is associated with reduced stress on the cardiovascular system, better preservation of the residual renal function and minimal variation in the intravascular volume status [1-3]. However, occasionally, these patients' condition may be complicated by cholecystopathy, including either cholelithiasis and/or cholecystitis [4,5] Importantly, surgical interventions for a disease that disturb the integrity of abdominal cavity boundaries can disrupt the regular PD schedule, and in certain instances, interim hemodialysis (HD) or even permanent transfer to HD might be indicated [6-11]. Since 1987, laparoscopic cholecystectomy has become an established procedure for treatment of cholelithiasis [12-14]. However, there is no consensus on the use of LC in patients receiving chronic ambulatory PD (CAPD) [7]. In addition, there are no clear recommendations in the literature regarding the continuation or interruption of CAPD in the perioperative period among this patient population for laparoscopic procedures [7]. Before the introduction of laparoscopic techniques, surgical interventions often required interruption of CAPD with temporary hemodialysis allowing surgical repair and return of the peritoneal integrity before CAPD could be resumed [7]. The traditional practice after laparoscopic surgery has been to delay reinitiating of CAPD for a minimum of 6 weeks because of the belief that increased intra-abdominal pressure might stress the peritoneum and abdominal wall at the surgical sites, that may result in peritoneal rupture and fluid leakage during CAPD [15]. Additionally, there is a potential for wound dehiscence, abdominal hernia, inferior ultrafiltration due

Correspondence to: Ana Stojanoska Severova, University Clinic of Nephrology, 1000 Skopje, N. Macedonia; E-mail: stojanoska.ana@hotmail.com

to the peritoneal edema or dialysate leakage, postoperative sepsis, peritonitis, hemoperitoneum due to impaired host defenses, uremic coagulopathy, and protein depletion.

Case report

19-year-old white female, presented at University Clinic of Nephrology in December 2019, with dyspepsia, vomiting, and intermittent right upper quadrant abdominal pain, present for couple of weeks. As for her previous conditions, she has had multiple comorbidities as an atrial septal defect that has been repaired surgically in the childhood, hormonally inactive tumor on the left adrenal gland (detected and diagnosed in 2018), and a chronic kidney disease since 2017 (etiology not confirmed). She has been on maintenance PD since September 2019 with one episode of peritonitis, two months before the actual admission at our Clinic. The patient was on bagless CAPD with a y-set drainage system, four 2-L exchanges/day. The physical examination on admission revealed a blood pressure of 140/ 89 mmHg, a temperature of 37 C, and a heart rate of 92/min. The lungs were clear. Abdominal examination revealed a Tenckhof catheter in place with a healthy-looking exit site, free from abdominal tenderness. Neurologic examination was not remarkable.

At admission, laboratory data revealed normal electrolyte levels, with serum creatinine and blood urea nitrogen (BUN) values of 1051 μmol/l and 12.5 mmol/l, respectively. Other laboratory test results, showed in Table 1, were gamma-glutamyl transferase 182 U/L (normal range 9-64 U/L), alkaline phosphatase 273 U/L (normal range 36-126 U/L), aspartate aminotransferase 271 U/L (normal range 10-34 U/L), alanine transaminase 208 U/L (normal range 10-45), white blood cells 9.7, hemoglobin 120 g/l. The peritoneal lavate, showed no signs of infection and inflammation.

Table 1. Laboratory data of the patient from admission till discharge

10 Dec 2019		**16 Dec 2019**		**23 Dec 2019**	
Hemoglobin	120 g/l	Hemoglobin	123 g/l	Hemoglobin	96 g/l
WBC	9.7 x 10^9 L	WBC	6.8 x 10^9 L	WBC	4.9 x 10^9 L
sCreatinine	1051 μmol/l	sCreatinine	1054 μmol/l	sCreatinine	959 μmol/l
sUrea	12.5 mmol	sUrea	15.5 mmol/l	sUrea	9.1 mmol/l
GGT	182 U/L	GGT	106 U/L	GGT	92 U/L
ALP	273 U/L	ALP	162 U/L	ALP	113 U/L
AST	271 U/L	AST	26 U/L	AST	29 U/L
ALT	208 U/L	ALT	80 U/L	ALT	39 U/L

Abbreviations: WBC: white blood cells; GGT: gamma glutamyl transferase, ALP: alkaline phosphatese, AST: aspartate aminotransferase, ALT: alanine transaminase

The history of recurrent right upper quadrant abdominal pain and the laboratory data from the admission, required gastroenterohepatology department consultation for an ultrasonography examination of the abdomen. The evidence of a gall-bladder mass, indicated the need for cholecystectomy. Abdominal surgeon has confirmed the need of a cholecystectomy that was scheduled in the following days. Two days before surgery, CAPD was done with four 1-L exchanges of dialysate. At the day before cholecystectomy, considering that the patient is also listed for a living donor kidney transplantation in a month, she was transferred from PD to hemodialysis. Femoral central venous catheter was inserted and hemodialysis performed prior to the surgery. The peritoneal catheter remained inserted in the peritoneal cavity during the surgical procedure.

The patient underwent laparoscopic cholecystectomy. A 10mm trocar was placed in the right side of the epigastrium, a 5mm trocar in the right side in the midaxillary line, a 5mm trocar in the anterior axillary line, and a 10mm trocar was introduced through an infraumbilical incision. The infraumbulical port was used to introduce the laparoscope. The PD catheter was clearly seen lying in the pelvis. Minimal intraabdominal adhesions and a few adhesions near the gall bladder have been observed. No complications during surgery were reported. Post - operative course was also uneventful. She was treated with usual antibiotics and other supportive therapy.

Discussion

Acute cholecystitis is commonly associated with inflammation caused by prolonged obstruction of the cystic duct with gallstones [16]. Even though gallstones are the most important factor in the pathogenesis of acute cholecystitis, on the other hand, many other investigated factors for developing gallstones have been considered [17,18]. Despite many studies have investigated the relationship between gallstones and ESRD, it remains to be clarified whether gallstones are more common in patients with ESRD [15-17]. Some studies report that the gallstones incidence in patients on hemodialysis was not different from that in controls [19-24], while others have reported a higher incidence

of gallstones in patients on hemodialysis compared to the control group [25-30].

Hypoperfusion in organs happen in patients on hemodialysis because of the fluctuations in the hemodynamics. The result of that is frequent mesenteric ischemia. Furthermore, the mesenteric ischemia can make disruption of the gut mucosal structure, leading to chronic malnutrition with, of course, a higher incidence of peptic ulcer disease. Hence, a higher incidence of peptic ulcer disease is seen in dialysis patients with poor nutrition [31]. The same situation might occur in the gallbladder. Additionally, system inflammation can happen to these patients due to increased circulating levels of uremic toxin. Moreover, increased leukocyte margination and focal lymphatic dilation with interstitial edema are associated with local microvascular occlusion [32-34]. In peritoneal dialysis patients, acute cholecystitis is stimulated to happen by chronic active inflammation of the peritoneum. Endotoxemia as well. [35,36]. The hypothesis remains that chronic inflammation of the gallbladder and decreased gallbladder motility due to uremia, are main causes of the increased incidence of cholecystitis.

When it comes to managing acute cholecystitis, laparoscopic cholecystectomy is recommended as a first-line treatment in the general population [37]. However, following the outcomes of patients with ERDS undergoing cholecystectomy by looking at previous studies on that matter, the conclusion was that ESRD is an independent risk factor for postoperative morbiddity [38,39]. Although patients on dialysis are at risk of postoperative complications, laparoscopic cholecystectomy is recommended as a first-line treatment for acute cholecystitis even in patients undergoing peritoneal dialysis [7,40-42].

Ekici *et al*. [43] conducted a study where laparoscopic cholecystectomy was performed in patients with end-stage renal disease treated with continuous ambulatory peritoneal dialysis. The comparison was between 11 patients receiving peritoneal dialysis treatment, and 33 patients without end-stage renal disease who had undergone an elective laparoscopic cholecystectomy. All their medical records and laboratory values were reviewed, as well as the outcomes and results. Their peritoneal dialysis group showed a higher frequency of associated disease and previous abdominal surgery, a lower platelet and hemoglobin count and elevated alkaline phosphatase, creatinine values and blood urea nitrogen. One procedure in each group was converted to an open cholecystectomy. No other catheter-related complications were noted that occurred. Laparoscopic cholecystectomy may be performed with low complication rates in patients undergoing continuous ambulatory peritoneal dialysis with an experienced team, was the conclusion from the authors.

When it comes to the management of asymptomatic gallstone disease among the ESRD patients, there is no consensus and no evidence was found for increased morbidity or mortality related to gallbladder disease. Cholecystectomy is indicated only in symptomatic cholelithiasis patients with ESRD, as in the general population.

Homogeneous to the case report we are presenting, Attard *et al*. [44] conducted a study about laparoscopic procedures in patient undergoing peritoneal dialysis without removal of the PD catheter. The thing that was different from our case, was that a 61-year-old male had undergone elective right hemicolectomy. For 4 years he had been doing well on ambulatory peritoneal dialysis. When routine hemoglobin assay was done, initially normal, the suggestion was development of iron deficiency anemia. Therefore, he was referred for colonoscopy. This showed the presence of a caecal carcinoma. When Staging CT was done, it did not reveal any spread. The next step was that he was established on hemodialysis via a temporary venous line, and furthermore, he underwent laparoscopic right hemicolectomy through 4 ports. Pneumoperitoneum was established via the PD catheter which was left in situ.

Conclusion

The suggestion from recent reports is that it is possible to successfully and safely perform laparoscopic procedures in patients on PD without removing the PD catheter, and with a relatively short period of HD in the interim period before resuming PD. Laparoscopic cholecystectomy [45], laparoscopic radical nephrectomy [46], and laparoscopic appendicectomy for perforated appendicitis [47] have been reported using this approach. In our case, laparoscopic cholecystectomy was done without removing the PD catheter without any complications for the patient. Furthermore, renal transplantation was successfully performed in February 2020.

Conflict of interest statement. None declared.

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Case report

Plasma Cell Dyscrasia Presented with Hypercalcemia, Intracranial Mass and Lytic Bone Lesions in a Geriatric Patient

Ezgi Bastopcu[1], Turker Sarikaya[1], Gulen Gul[2] and Harun Akar[1]

[1]Department of Internal Medicine, [2]Department of Pathology. University of Health Sciences, Tepecik Education and Research Hospital, Izmir, Turkey

Abstract

The presence of an intracranial mass, hypercalcemia, lytic bone lesions, and height loss suggesting a pathological fracture in the vertebra led to the diagnosis of plasma cell dyscrasia at the diagnosis stage of our case. The purpose of this case report is to raise awareness about intracranial plasmacytomas and multiple myeloma with intracranial growth.

Keywords: intracranial plasmacytoma, intracranial involvement in plasmacytomas, intracranial mass, Intracranial plasma cell tumors

Introduction

Intracranial involvement in plasmacytomas and multiple myeloma is rarely reported in the literature [1]. While the presence of an intracranial mass at the diagnosis stage of our case caused diagnostic difficulties at the beginning, the presence of hypercalcemia, lytic bone lesions and loss of height in the vertebra led us to consider the diagnosis of plasma cell dyscrasia. Diffuse lytic bone lesions, intracranial mass and hypercalcemia in our case were thought to be due to multiple plasmocytic infiltration of the skeleton.

Case report

When the 72-year-old female patient was admitted to the emergency department with the complaints of weakness, intermittent consciousness, general condition disorder, serum calcium value was 12.7 mg/dl, and cranial computerized tomography examination revealed intracranial mass and lytic bone lesions. The patient was hospitalized in the outer center intensive care unit to investigate the etiology of malignancy and a PET-CT examination was performed. Laboratory examinations of the patient revealed glucose 174 mg/dL, urea 44 mg/dL, creatinine 0.8 mg/dL, uric acid 9.8 mg/dL, calcium 12.7 mg/dL, albumin 3.5 g/dL. The patient was referred to our internal medicine clinic to investigate the etiology of hypercalcemia and disseminated lytic bone lesions. The patient had diagnoses of hypertension and diabetes mellitus. In the physical examination of the patient, her neurological examination was normal; the patient was conscious, orientated and cooperative. Respiratory sounds were normal. On cardiac examination S1, S2 and rhythm were normal, there was no additional sound, there was no murmur. Abdominal examination was normal, hepatosplenomegaly was not detected. In laboratory examinations; hemoglobin 11.3 g/dL, hematocrit 31.4%, MCV 92 Fl, platelet 423.000, leukocyte 14.900, neutrophil 7800, albumin 4g/dL, globulin 2.7 g/dL, glucose 169 mg/dL, urea 43 mg/dL, creatinine 0.9 mg/dL, AST 14 U/L, ALT 18 U/L, LDH 184 U/L, total bilurubin 0.48 mg/dL, direct bilurubin 0.1 mg/dL, Na 141 mmol/L, K 3.7 mmol/L, Cl 101 mmol/L, calcium 12.3 mg/dL, phosphorus 3.6 mg/dL, Mg 1.2 mg/dL, CRP 2.8 mg/dL were detected. Parathormone (PTH) was 13.6 pg/L and 25 OH D vitamin level was 42.74 pg/L. Hyperparathyroidism was excluded in the patient with low PTH levels. Intracranial mass and lytic bone lesions were detected in the outer center, diffuse lytic lesions were observed in direct cranial radiographs. Hydration and diuretic treatment were started for the patient to treat hypercalcemia. The missing electrolytes were replaced. The patient underwent a malignancy scan, a contrast computed tomography examination was performed. The computerized tomography examination revealed a 44x33 mm mass lesion with a heterogeneous enhancement showing growth towards the petrous apex in the left lateral of the clivus, hypodense lesions in the clavicle and vertebrae, right occipital and right temporal bone squamous mucosa. Heterogeneity and multiple hypodense appearances were detected in thoracic bone structures. It was thought that the height losses observed in the T8, T11, L1 and L4 vertebrae were secondary to the pathological fracture. Intense hypodensities were observed in the pelvic bones, the largest in the pelvic region, which are considered to be the left wing. It was learned from the patient's history that he had a total abdominal hysterectomy and bilateral

Correspondence to: Ezgi Bastopcu, Health Sciences University, Tepecik Education and Research Hospital, Department of Internal Medicine, Izmir, Turkey; E-mail: ezgibastopcu@gmail.com

salpingo-oophorectomy operation. Breast examination of the patient was considered normal. Breast ultrasonography and mammography were requested for screening, BIRADS 2 benign findings were detected. Serum immunoglobulin levels were low, albumin/globulin reversal was not detected. (IgA: 0.26 g/L, IgM: 0.17 g/L, IgG: 4.94 g/L, total IgE: 10.8 IU/ml). Multiple diffuse bone lytic lesions and a slightly increased 18 FDG uptake in the right lung hilar millimetric lymph node were reported in the patient's PET-CT scan at the outer center (SUV MAX: 4.1). In the thorax computed tomography examination of the patient, active parenchymal pathology was not observed, while a millimetric lymphadenopathy-compatible appearance was observed in the right hilar region. In order to investigate hypercalcemia etiology, the patient was consulted with chest diseases clinic, sarcoidosis was not considered. Osteoporosis was not detected in bone densitometry. Bone marrow showed 75% cellularity in aspiration. Bone marrow biopsy was hyper cellular and shows 50 percent involvement by abnormal appearing CD38 positive plasma cells (Figure 1-3).

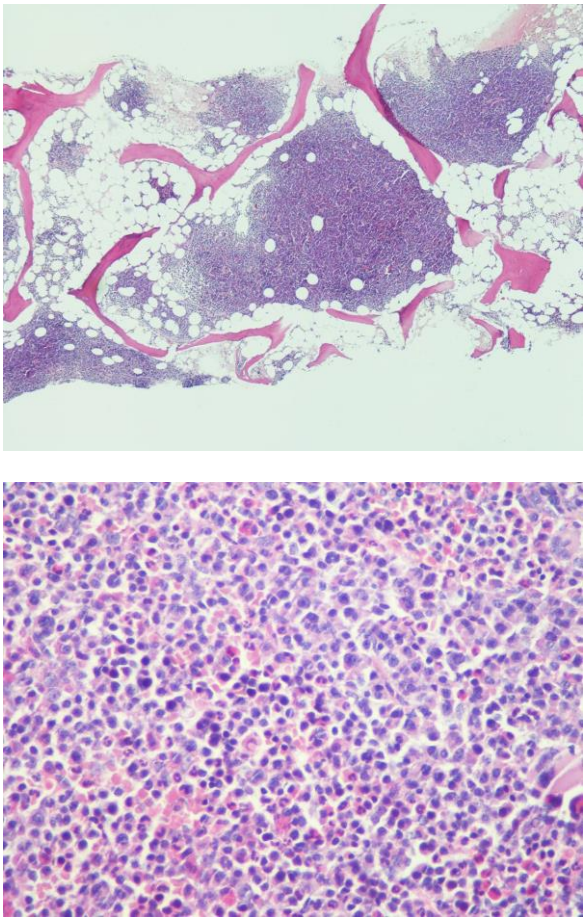

Fig. 1, 2. Sheets of plasma cells, hematoxylin and eosin (40x and 400x)

Almost all plasma cells are kappa positive (Figure 4). With Lambda, there are positivity in a few cells (Figure 5). Based on the morphological and immunohistochemical findings bone marrow biopsy reported as plasma cell neoplasia and recommended to evaluate the case in terms of myeloma with its clinical, laboratory and radiological findings. As a result, pathological

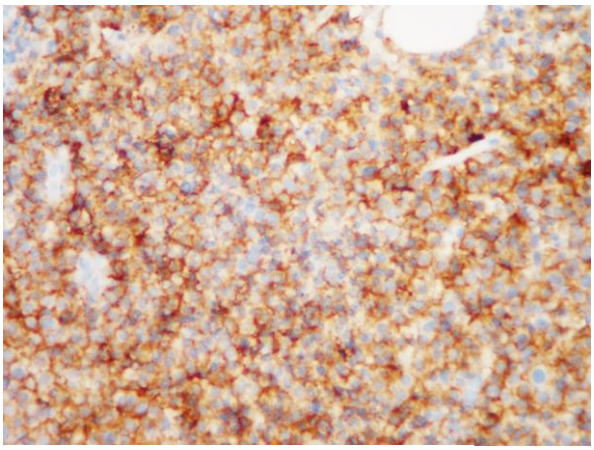

Fig. 3. CD38 immunohistochemical stain (400x)

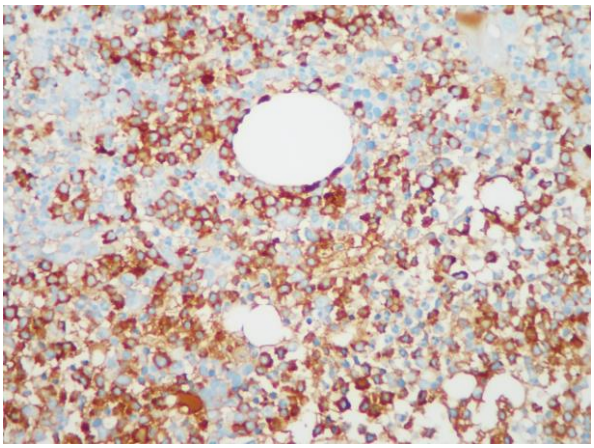

Fig. 4. Kappa immunohistochemical stain (400x)

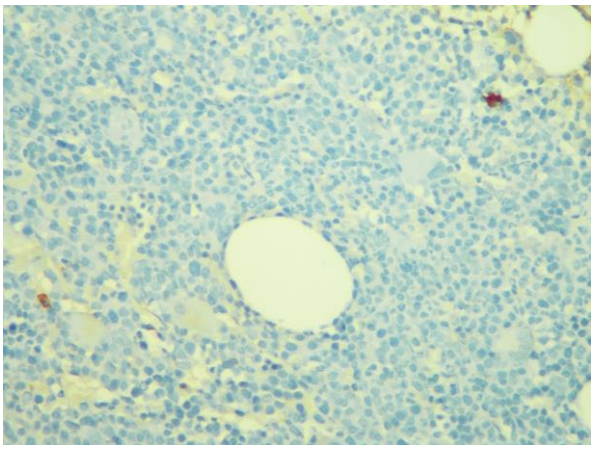

Fig. 5. Lambda immunohistochemical stain (400x)

diagnosis was reported as plasma cell neoplasia. The patient was transferred to the Hematology Clinic with the diagnosis of multiple myeloma and treatment was started with the VCD protocol.

Discussion

Plasma cell neoplasia, metastatic tumors, sarcoidosis and parathyroid diseases were considered among the possible differential diagnoses due to the clinical picture of the patient and presenting with hypercalcemia. The presence of an intracranial mass at the diagnosis stage of our case caused diagnostic difficulties at the beginning, while the presence of hypercalcemia, lytic bone lesions, loss of height suggesting pathological fracture in the vertebrae led to the diagnosis of plasma cell dyscrasia. The patient described here is rare because it was associated with diffuse lytic bone lesions, intracranial mass and hypercalcemia, all thought to be due to multiple plasmocytic infiltration of the skeleton. In our case, myelomatous disease was clinically apparent on initial presentation. For systemic evaluation, in addition to PET-CT imaging, contrasted computed tomography images and bone marrow aspiration and biopsy were performed in our patient.

Intracranial plasma cell tumors have been reported to be extremely rare and may be alone or part of a systemic multiple myeloma [1]. A plasmacytoma involving the pituitary gland has been reported as an extremely rare condition with approximately 22 cases [2]. It is thought that the occurrence of plasma cell neoplasm as a cranial or intracranial mass is a rare condition [3]. It is thought that it is even rarer that myelomatous first appears as a sellar mass and mimics a pituitary adenoma [3]. While there are few reports of plasma cell tumors involving clivus [4-7], cases of plasma cell dyscrasia occurring as a mass in the posterior fossa have been reported less frequently in the literature [8, 9,10]. Tumor cells are believed to originate from the surrounding bone in the sellar region or the mucosa within the petrous or sphenoid bone [11]. In other words, intracranial involvement is usually thought to result from direct spread from adjacent bone lesions in the head dome, skull base, nose, or paranasal sinuses [12].

Intracranial plasmacytoma can be differentiated from the usual meningioma cases, since the skull will often have lytic lesions [10]. Although it is generally known that intracranial plasmacytomas are very sensitive to radiation; definitive treatment for intracranial plasmacytoma complete surgical resection plus radiation therapy have been reported.

The purpose of this case report is to increase the awareness of the intracranial plasmacytomas and multiple myeloma with intracranial growth [12].

In patients presenting with headache, diplopia, intermittent loss of consciousness and accompanying signs and symptoms suggestive of multiple myeloma, plasma cell dyscrasias should also be considered in the differential diagnosis [5]. From a broader perspective, intracranial plasmacytoma and multiple myeloma with intracranial enlargement may be appropriate to be among the neurological aspects of multiple myeloma [13].

In rare cases, intracranial plasmacytoma should be considered in the differential diagnosis in combination with hypercalcemia, diffuse lytic bone lesions and intracranial mass lesion. This report, although rare, reminds us of the value of including a plasma cell tumor in the differential diagnosis of intracranial masses with bone involvement. This case illustrates a rare and interesting presentation of multiple myeloma and highlights that MM can come to the clinic with different faces, as in this case.

Conflict of interest statement. None declared.

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Case report

First Case of Atypic Hemolytic Uremic Syndrome after Pfizer-Biontech Vaccine

Demet Kotekoglu[1], Omer Burcak Binicier[2], Hilal Sahin[3] and Emel Ebru Pala[4]

[1]Department of Internal Medicine, [2]Department of Gastroenterology, [3]Department of Radiology, [4]Department of Pathology, University of Health Sciences, Tepecik Education and Research Hospital, İzmir, Turkey

Abstract

The SARS-COV-2 virus, which has become a part of our lives since December 2019, has caused severe viral pneumonia as well as severe disease in many cases due to organ damage secondary to endothelial damage. Due to the pandemic of the disease, vaccine studies have gained momentum and many different vaccines have been started to be applied. Although the common side effects of vaccines are mild, cases of thrombotic thrombocytopenia, thrombosis with thrombocytopenia syndrome, vaccine-induced prothrombotic immune thrombocytopenia syndrome, endothelial damage, which is a common feature of both vaccine and virus, and secondary organ damage to the resulting thrombotic process have begun to appear. Here, we present the first case of complement mediated hemolytic uremic syndrome (HUS) in a young woman without any known comorbid disease who presented to the emergency department with abdominal pain and hematochezia two days after the first dose of Pfizer-BioNTech BNT16B22 vaccination. Since the patient did not respond to intravenous immunoglobulin and steroid treatments, her disease was controlled with Eculizumab treatment.

Keywords: COVID-19, hematochezia, hemolytic uremic syndrome

Introduction

Coronavirus 2019 (Covid-19) is a global epidemic that causes high mortality and morbidity, affecting the whole world, especially China. In order to prevent this epidemic, vaccine studies were emphasized, and the mRNA vaccine, Pfizer-BioNTech BNT16B2b2 (Biontech), was included in the vaccination program in more than one country.

Microthrombus formations seen after Covid-19 infection were thought to be secondary to the interaction between inflammation and coagulation cascade. This is clinically seen as thrombosis formation in various organs [1]. There have been case reports of post-vaccine thrombocytopenia and organ damage secondary to thrombosis similar to the complement-mediated platelet activation caused by Covid-19 [2]. Venous and arterial thrombosis that is observed after Covid-19 vaccine is explained by different mechanisms. Arterial thrombosis develops as a result of platelet activation and venous thrombosis occurs as a result of excessive activation of the procoagulant system or insufficient anticoagulation [3].

Thrombocytopenia and thrombosis caused by Covid-19 vaccines are explained by different mechanisms. It is thought that vaccines acting through adenovirus vector cause vaccine-associated immune thrombocytopenia by acting on CD46 antibodies and platelet factor-4 antibodies. On the other hand, although it is thought to be more effective and safer in mRNA-based vaccines, it causes temporary expression of the SARS-CoV-2 spike protein and activates the alternative complement pathway on the cell surface and causes competitive inhibition with complement factor H binding to heparan sulfate. Thus, the SARS-CoV-2 spike protein in cells can convert the inactivator surface to the activetor surface and cause complement-mediated endothelial damage. The response to these two vaccines is generally mild, but increased complement amplification may theoretically cause an increase in the incidence of diseases such as paroxysmal nocturnal hemoglobinuria (PNH), thrombotic microangiopathies (TMAs) or present patients in remission with attacks [2-7].

Complement Factor H deficiency is seen as homozygous or heterozygous and causes complement-mediated HUS or membranoproliferative glomerulonephritis secondary to C3 convertase dysregulation. Here, we present a 24-year-old female patient who applied to the emergency service of our institution with severe segmental colitis findings after Biontech vaccination. She was diagnosed with complement-mediated HUS and was successfully treated.

Correspondence to: Omer Burcak Binicier, Department of Gastroenterology, University of Health Sciences, Tepecik Education and Research Hospital, İzmir, Turkey; E-mail: binicieromer@yahoo.com

Case report

A 24-year-old female patient with no history of chronic disease was admitted to the emergency department with abdominal pain and hematochezia that started 48 hours after the first dose of Biontech vaccine. The patient, who had no history of additional disease or drug use, had a healthy normal birth history one year ago. The patient had no history of abortion or cesarean section, had no history of oral contraceptive use or gastrointestinal symptoms, and adverse reactions to childhood vaccines. There was no history of bleeding disorder, autoimmune disease, or inflammatory bowel disease in her family history.

The patient's body temperature was 37.5°C, blood pressure was 100/60 mm/Hg, pulse rate was 72 per minute and respiration rate was 12 breaths per minute. In the physical examination of the patient, no findings were observed except diffuse, mild tenderness in all quadrants of the abdomen on palpation and fresh blood smear on the rectal touche. Normal stomach contents came from the nasogastric tube. Blood tests showed that white blood cell count was 10.600/L (reference, <10.800), hemoglobin level was 12.7 gr/dL (reference, 14.0-18.0 gr/dL), platelet count was 203.000/L (reference, 180.000-400.000/L). Erythrocyte sedimentation rate was 12 mm/h (reference, <20 mm/h), high sensitivity C-reactive protein was 36.6 mg/L (reference, <5 mg/L). SARS-COV-2 PCR test was negative, other blood tests were normal, hepatitis and torch panel were negative.

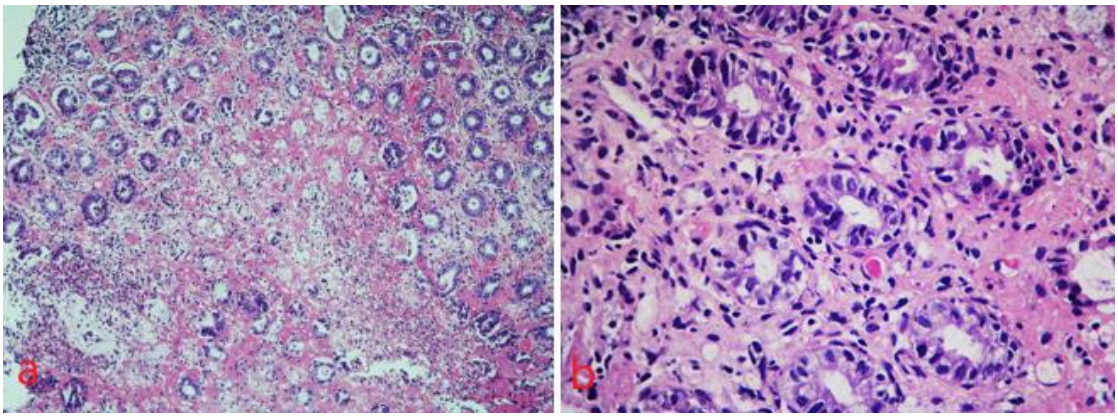

Fig. 1a, b. (a) Acute inflammatory exudate, mucosal necrosis and lamina propria hyalinization. (b) Fibrin thrombi in capillaries and reactive, degenerative atypia in crypt epithelium.

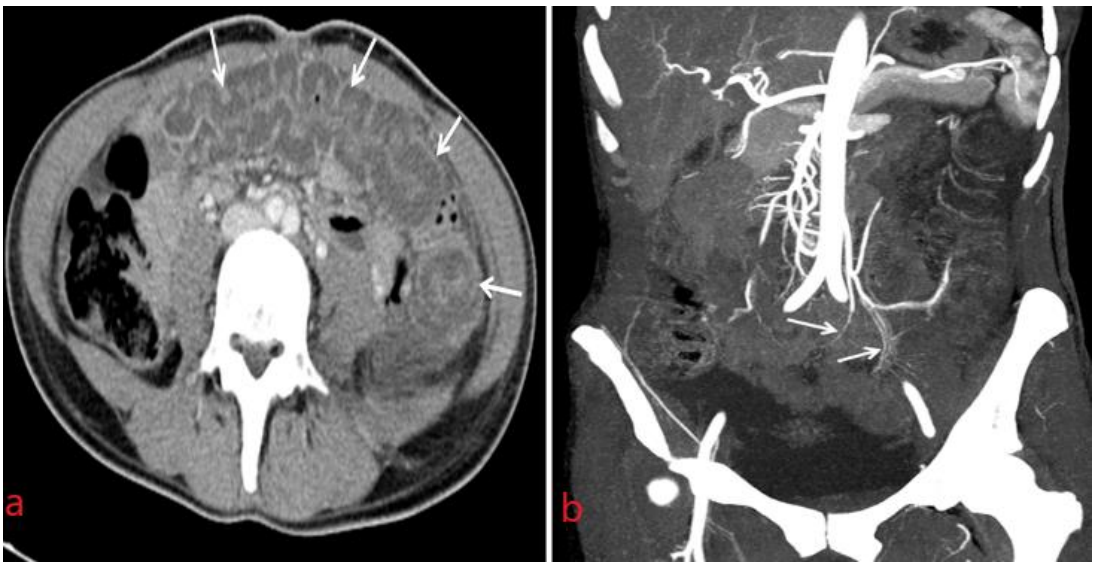

Fig. 2a, b. (a) Axial plane computed tomography image shows diffuse wall thickening of transverse colon and descending colon with low density which is consistent with ischemic colitis. (b) Coronal reformatted MIP image shows subtle enhancement of thinned and irregular distal branches of inferior mesenteric artery.

Severe segmental colitis findings were observed from the proximal to the transverse colon to the distal of the sigmoid colon has been observed during the colonoscopy of the patient. In the histopathology of biopsy samples taken from this area; acute inflammatory exudative changes, mucosal necrosis and hyalinization in the lamina propria, as well as fibrin thrombi in the capillaries were observed (Figure 1a, b). Inclusion bodies for infectious causes were found to be negative. The patient was presented with acute onset abdominal pain and

hematochezia had segmental colitis findings on colonoscopy she had been performed arterial and venous phase contrast-enhanced abdominal CT imaging for possible ischemic colitis. In addition to diffuse wall thickness increase from the proximal transverse colon to the distal sigmoid colon, irregularities that may be compatible with microthrombus were observed in the thinned and distal branches of the inferior mesenteric artery (Figure 2a, b). No pathology was observed in the stool culture and direct examinations of the patient for an infectious cause, including clostridium difficile. Tissue transglutaminase IGA and IGG, Anti-gliadin IGA and IGG, CMV-DNA, ANA, anti-dsDNA, anti-phospholipid antibody, MPO-ANCA, C-ANCA were negative. Echocardiography was normal. On the 3rd day of the patient's hospitalization, hemoglobin was 9.6 g/dL, platelet was 21 x 10^3/UL, total bilirubin was 3.55 mg/dL (reference, 0.3-1.2 mg/dL), direct bilirubin was 0.47 mg/dL (reference, <0.2 mg/dL).

In the peripheral smear of the patient who developed hyperbilirubinemia, anemia, and thrombocytopenia under indirect dominance, large platelets and 3-4% schistocytes were detected. ADAMTS-13 for non-immune hemolytic anemia in terms of TMAs and PNH in a patient with haptoglobulin 0.08 g/L (reference, 0.3-2 g/L), LDH level of 1119 U/L (reference, 0-247 U/L) and Coombs negative and the PNH panel was sent. ADAMTS13 level was 0.88 IU/mL (reference, 0.4-0.13). PNH was excluded in the patient without CD59 AND FLAER/ CD24 deficiency. No Factor V Leiden mutation was observed in the patient whose protein C, S and anti-thrombin III levels were normal.

Acute renal failure and massive proteinuria developed on the second day of 1 mg/kg/day steroid and 1 g/kg/day IVIG (Intravenous immunoglobulin) treatment for immune -thrombocytopenia (BUN 43.5 mg/dL, creatinine 2.07 mg/dL, protein in spot urine. 615.41 mg/dL, creatinine 48 mg/dL, 24-hour urine protein 12900.62 mg/day, creatinine 532 mg/day, kappa light chain 54.6 mg/L, lambda light chain 45.3 mg/L). Renal biopsy could not be performed in the patient because of severe thrombocytopenia. Hemodialysis treatment was started due to the progression in creatinine values (4.0 mg/dL) and metabolic acidosis on the eighth day of the follow-up of the patient, who did not have pathology in the Doppler USG of the renal artery and vein. Plasmapheresis treatment was started after hemodialysis due to continued decrease in hemoglobin values (5.3 g/dL), progression in LDH values (1293 U/L) and thrombocytopenia (15x10^3/UL) despite steroid and IVIG treatments. BUN (30 mg/dL), creatinine (1.9 mg/dL) and bilirubin values improved after plasmapheresis and hemodialysis treatments.

Eculizumab treatment was initiated as complement levels were found to be low. Before eculizumab treatment, prophylactic meningococcal vaccination was performed. Nine hundred mg was administered for the first 4 weeks, followed by 1200 mg at the 5th week. The patient achieved significant remission after eculizumab treatment. She was followed up via nephrology and hematology departments, and response to treatment was monitored. At the end of two months, significant improvement was observed in hemoglobin (13.9 g/dl), platelet (246 x10^3/UL), and creatinine (0.82 mg/dL) levels.

Discussion

Hemolytic uremic syndrome is one of the subgroups of microangiopathic hemolytic anemias and presents as Shiga-toxin-related or complement-mediated (atypical-HUS). In atypical HUS, complement system activation or complement regulatory proteins (factor I, H, thrombomodulin, membrane cofactor proteins) is explained by endothelial damage that develops as a result of impaired functions.

Although the importance of detecting complement proteins or complement gene mutations is still unclear, if the atypical hemolytic syndrome is evaluated as complement-mediated, plasma exchange or eculizumab therapy should be initiated as soon as possible to prevent irreversible renal damage. As a result, normal complement levels do not exclude the diagnosis of complement-mediated HUS.

SARS-COV-2 mRNA vaccine, which creates an immune response with a different mechanism than childhood vaccines, aims to give an adequate immune response in case of encountering the virus again, with the proliferation of the proteins of the virus and the development of the response to it. RNA vaccine not only creates an immune response, but also causes thrombotic events, similar to the endothelial damage caused by the disease, as a result of expressing the proteins of the virus. The development of a post-vaccine attack in young patients with immune thrombocytopenia or paroxysmal nocturnal hemoglobinuria in follow-up patients was evaluated as secondary to the thrombotic events caused by messenger RNA (mRNA) based vaccines that cause temporary expression of the SARS-CoV-2 spike protein [2]. High levels of sC5b-9 occur as a result of activation or dysregulation of the complement pathway in two-thirds of patients infected with SARS-COV-2 [10]. mRNA vaccines developed with a similar mechanism of action also produce the protein produced by the virus and provide an immune response. The adverse effects seen after the production of the SARS-COV-2 spike protein are explained in this way. It is thought that mRNA-based vaccines developed to prevent SARS-COV-2 and SARS-COV-2 transmission cause complement-mediated hemolytic uremic syndrome by causing complement-mediated endothelial damage.

It has been reported that TTP or ITP developed in individuals infected or vaccinated with the SARS-COV-2 virus during the pandemic [11-12]. A case of atypical HUS developed after ChAdOx1 nCoV-19 vaccine

was also observed in an individual with CFHR3/CFHR1 homozygous gene mutation [13].

Conclusion

In this case we have reported first atypical HUS caused by complement activation following the administration of Biontech vaccine. Considering the case as atypical HUS, starting plasma exchange therapy primarily ensured the clearance of factor H antibodies, then initiating C5 monoclonal antibody eculizumab treatment, which is recommended to be administered in the first 24-48 hours in atypical HUS, prevented the endothelial damage secondary to inflammation.

Conflict of interest statement. None declared.

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Letter to the editor

Acute COVID-19 in Kidney Transplant Recipients - Another Obesity Paradox?

Dubravka Mihaljevic and Nikolina Basic-Jukic

Department of nephrology, Clinical hospital centre Osijek, Department of nephrology, arterial hypertension, dialysis and transplantation, Clinical hospital centre Zagreb, Croatia

Dear Editor,

In the general population, diabetes, hypertension, smoking, and obesity increase the risk of mortality from COVID-19. Solid-organ transplant recipients have an increased risk of developing severe COVID-19 disease and death.

Obesity, compared to a healthy weight, increases the risk for many severe diseases and health conditions. However, the obesity paradox exists and is based on the fact that obesity in elderly patients and patients with different chronic diseases has a protective effect associated with reduced mortality. Likewise, increased body mass index is associated with reduced all-cause and cardiovascular mortality in hemodialysis patients (reverse epidemiology). The explanation of this phenomenon is complex. Obesity is characterized by alterations in nutritional status and hormonal and metabolic changes, and the impairment of different organs and tissues. it significantly impacts functionality and quality of life by interfering with psychological and social factors. In acute COVID-19, obesity negatively impacts the cardiorespiratory reserve and immune response, contributing to developing more severe forms of the disease. Adipose tissue has a proinflammatory effect leading to increased expression of cytokines.

The influence of obesity on mortality in KTR with acute COVID-19 is controversial. In the meta-analysis, older age, transplantation from a deceased donor, and comorbidities were associated with increased mortality risk. However, obesity was not a significant predictor of mortality in KTR. According to our results, obesity was not a predictor of complications after acute COVID-19. Diabetes, hospitalization for acute SARS-CoV-2 infection, and increased fibrinogen were associated with clinical complications after acute COVID-19, while better allograft function had a protective role [1]. In a multicentre cohort study investigating hospitalizations and death after acute COVID-19, obesity was not associated with an increased risk for hospitalization [2].

What is the reason for the lack of association of obesity with increased mortality risk in KTR with acute COVID-19? Immunosuppression or previous exposure to uremic status might override or interfere with the effect of ectopic fat deposition, leading to higher mortality of COVID-19 in KTR compared to the general population. However, further studies are needed to evaluate this hypothesis.

Conflict of interest statement. None declared.

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Correspondence to: Nikolina Basic-Jukic, Department of nephrology, arterial hypertension, dialysis and transplantation, Clinical hospital centre Zagreb, Croatia; 10000 Zagreb, Croatia; E-mail: nbasic@kbc-zagreb.hr; nina_basic@net.hr

BANTAO Journal 2021; 19(2): 93-94

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In memoriam

Prof. Dr. Spira Strahinjić

(1925-2022)

With great sadness we received the news that Prof. Dr. Spira Strahinjic, our teacher, retired full professor of the Medical Faculty in Nis, founder and longtime director of the Institute of Nephrology and Dialysis, passed away on January 25th, 2022 in Niš.

He had a very challenging but not very easy life. He was born in a poor family on January 25th, 1925 in the village of Orane near Bojnik, Leskovac. He received his primary education in the village and finished high school in Leskovac in 1946. Being graduated from the Faculty of Medicine in Belgrade in 1953, he specialized in internal medicine at the same faculty in 1960. During his specialization in 1961/62, he studied in Strasbourg and then in Bern.

He has been working at the Medical Faculty in Nis since 1960, and until 1972 he was the head of the Cardiology department at the Internal Clinic of the General Hospital. During that time, he launched an initiative to establish an Institute of Nephrology. By the decision of the Faculty of Medicine, the Institute of Nephrology was established on January 13, 1972 and he was appointed the first director. He remained in that position until his retirement in 1990. The organization of the Institute was unique in Yugoslavia and beyond, because under "one roof" clinical and basic medicine worked together. As the director of the Institute of Nephrology, he had a clear vision of its development, and he carried it out with great love for the benefit of thousands and thousands of patients, as well as the doctors at the Institute. He used to say ‘even one day of life is life’ which indicates his dedication to most difficult patients.

As a legate, Professor Stahinjic left numerous dialysis institutions that he established in the region of Serbia, Kosovo and Montenegro. He was among the first doctors to describe a new, hitherto unknown disease, endemic nephropathy, which occurred not only in Serbia but also in the surrounding Balkan countries. His scientific work, which includes over 400 publications in national and international journals, was widely recognized and quoted thus spreading the reputation of Serbian nephrology and nephrologists not only in the Balkans region but also in Europe and around the world.

His perhaps most precious legacy are his students, doctors and followers. Numerous doctoral students have made significant scientific contributions under his mentorship. He selflessly cared about the training of his associates and always emphasized knowledge as the most important part of medicine.

Today, when we remember him with reverence, it is difficult to list all his professional, scientific and teaching contributions. Under his leadership, the Institute of Nephrology became one of the most prestigious institutions in former Yugoslavia. He started training his staff for the transplant program in Lyon and Paris, and in 1979 he successfully led the first living kidney transplantation performed by surgeons from Nis under the leadership of professor Di Bernard and his team from Lyon. He organized regular annual seminars, symposia and workshops in various fields of nephrology: endemic nephropathy, dialysis, transplantation, which were very well attended by participants allover former Yugoslavia. The most of the Meetings were organized in association with leading nephrologists of the Balkans and the world.

Professor Strahinjic was a favorite figure among nephrologists in Yugoslavia and the Balkans. Everyone respected his great work aimed at the development of, at that time, young branch of medicine-nephrology. He is one of the pioneers and founders of both Serbian Society

Correspondence to: Vidojko Gjorgjevic, University of Nish, Nish, Serbia; E-mail: drvidza@gmail.com

of Nephrology and the Faculty of Medicine in Nis, where he was the head of the Department of Internal Medicine for many years. He is also one of the founders of the Medical Academy of Serbian Medical Society and president of its branch for southeastern Serbia. Together with leading nephrologists from the region, he was the founder and supporter of BANTAO. He was a member of EDTA, ISN, and many other medical associations.

As his associates and followers, we are proud to have learned from him, and we are grateful that he provided us with support during our work and enabled us to improve in prestigious institutions around the world. It taught us how to fight for 'every second of human life'.

Professor Strahinjic received many recognitions for his work: the SLS Lifetime Achievement Award, the City of Niš Award, the 7th July Award of Serbia, and the Order of Labor with a Red Star.

His life and work should be an example to young people of how to love and practice medicine, and how to invest in future generations. As very loyal as a husband to his wife Lenka, his daughter Cica and granddaughter Tijana, he served as an example of how to get inspiration in a family full of love, from which he drew support and understanding for successful work in medicine and a personal life.

We will remember him as a creator, an extraordinary organizer, a scientist, a teacher, the founder of nephrology, and above all as a wonderful man with a big heart.

Prof. Dr. Vidojko Gjorgjevic
Medical Faculty Nish, Nish, Serbia

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2. Roberts NK. *The cardiac conducting system and the His bundle electrogram.* Appleton-Century-Crofts, New York, NY: 1981; 49-56
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University Department of Nephrology
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Email: spasovski.goce@gmail.com

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