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Review

Low Molecular Weight Proteinuria - An Update

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Abstract

Low molecular weight proteins (LMWP) are those proteins with molecular weight below 67,000 Da, which can freely pass through the glomerular sieve. This passage is dependent on the size, configuration and charge of the protein molecule. In tubular disorders (e.g. Fanconi syndrome) there is defect in the tubular handling of LMWP and they appear in the urine in measurable concentrations. Determination of the LMWP in the urine is the basic diagnostic tool for tubular diseases. Urinary protein electrophoresis was the basic method for determination of LMWP but with the discovery of beta-2 microglobulin (molecular weight 11,600 Da) ensued a new era in urinary protein chemistry. There is a growing list of diseases with LMWP as a principal feature. Many of these diseases are genetic in origin. With huge advance in molecular genetic techniques (e.g. next generation sequencing) molecular basis of these diseases has already been elucidated as well as pathophysiological mechanisms which lead to occurrence of LMWP. Besides genetic diseases affecting the kidney tubules, there are also acquired diseases which can affect proximal tubules resulting in LMWP and additional tubular defects as in the case of drug induced Fanconi syndrome. LMWP is often unrecognized in the busy clinical practice. In this review we will focus on the pathophysiological events leading to LMWP, assays for its detection and various clinical disorders presenting with LMWP.

Keywords: proteinuria, molecular weight, proximal tubule, Fanconi syndrome, genetics

Introduction

Proteinuria was known as an associated feature of kidney disease many centuries ago, but the works of Butler and Flynn led to the discovery that tubular disorders were associated to particular pattern of proteinuria [1,2]. Electrophoresis of the urinary proteins enabled separation of the proteins according to the molecular weight (Figure 1). This pattern associated with tubular disorders was termed tubular or low molecular weight proteinuria (LMWP). There is a growing list of diseases with LMWP as a principal feature. Many of these diseases are genetic in origin. With huge advance in molecular genetic techniques (e.g. next generation sequencing) molecular basis of these diseases has already been elucidated as well as pathophysiological mechanisms which lead to occurrence of LMWP. Besides genetic diseases affecting kidney tubules, there are also acquired diseases which can affect proximal tubules resulting in LMWP and additional tubular defects as in the case of drug induced Fanconi syndrome. LMWP is often unrecognized in the busy clinical practice. The first step in evaluation of a patient with proteinuria is its quantifi-

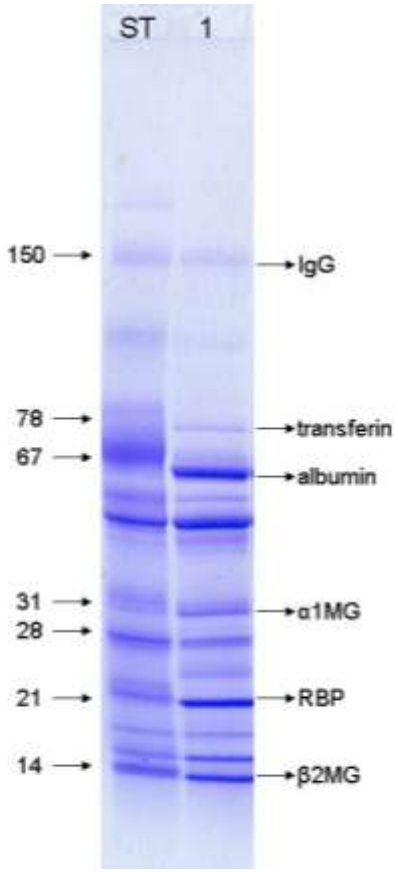

Fig. 1. SDS-PAG electrophoregram of a patient with mixed glomerulotubular proteinuria (lane 1). ST-standard

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cation and typization after exclusion functional causes (postural, exercise induced, febrile proteinuria) [3-9].
In this review we will focus on the pathophysiological events leading to LMPW, assays for its detection and various clinical disorders presenting with LMWP.

Physiologic basis

LMW proteins are those proteins with molecular weight below 67,000 Da, which can freely pass through the glomerular sieve. This passage is dependent on the size, configuration and charge of the protein molecule [10-12]. After filtration in the glomeruli LMW proteins are reabsorbed completely in the proximal tubule (99.9%) through the endocytosis and then catabolyzed to aminoacids in the lysosomes. In tubular disorders (e.g. Fanconi syndrome) there is a defect in the tubular handling of LMWP and they appear in the urine in measurable concentrations. Determination of the LMWP in the urine is the basic diagnostic tool for tubular diseases. As already mentioned urinary electrophoresis was the basic method for determination of LMWP [3]. With the discovery of beta-2 microglobulin (molecular weight 11,600 Da) ensued a new era in urinary protein chemistry [13]. The discovery of other urinary protein markers has led to improvement of classification (typization) of proteinuria. Retinol binding protein (RBP) was discovered in 1968. It is a carrier of vitamin A, molecular weight of 21,200 and is synthesized in the liver [13]. RBP is bound to the prealbumin and only the small free fraction (5%) is filtered through the glomeruli. The third LMWP alpha 1 microglobulin (A1M) was discovered in 1975 with molecular weight which varies from 24,800 to 31,000 Da [13]. Other LMW are ribonuclease, free kappa light chains of immunoglobulins and urine protein 1 (UP1), N-acetyl-[3-D-glucosaminidase], brush border enzymes (e.g. alanine aminopeptidase), the Tamm-Horsfall glycoprotein etc.

Assay methods

Urinary electrophoresis was the basic method for detection of LMWP. Sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) improved the detection of LMWP, but it lacked sufficient sensitivity. Modification of the techniques (silver staining) and western blotting resulted in better protein identification and quantification [14]. Nowadays there are many assays for the measurement of LMW proteins in urine. This measurement is based on enzyme-linked immunosorbent assay (ELISA) or turbidometry (nephelometry). Commercial kits are available for LMW proteins. Reference ranges for urine concentrations of LMW proteins in both adults and children have been published and should be expressed as ratio with urinary creatinine. One should have in mind that referent values for infants up to 6 months of age are much high due to the immaturity of the tubular function. Particular attention should be devoted to accurate collection and proceeding of samples for the analysis. B2M is unstable in the acidic urine which enhances its degradation at a pH less than 5.5 [13]. This degradation is both time and temperature dependent, especially during the overnight collections. Therefore, a second morning urinary sample is most suitable for analysis. Immediate alkalization of the urine after collection is also important to prevent degradation. RBP and AIM are stable in urine of physiological pH at room temperature, but RBP is unstable below pH 5.0 when stored frozen at -20^{o}C, in contrast to A1M.

Competition for reabsorption

Proteinuria can be divided into 3 basic patterns: glomerular, tubular or mixed types by quantitative assay of albumin and B2M in urine. However, this relationship is not applicable in disorders with heavy proteinuria as in the case of nephrotic syndrome. There is clear evidence from animal studies for competition between albumin and LMWP for reabsorption in the proximal tubule [15]. There is inverse relation between the LMW protein excretion in urine and GFR, occurring in both glomerular and tubular diseases. This may not be applied for advanced chronic kidney disease (GFR <30 ml/min per 1.73 m2) where the tubular reabsorptive capacities are insufficient for the elevated plasma levels of LMWP.

Clinical Disorders

Low molecular weight proteinuria is the hallmark of tubular and tubulointerstitial disorders, but it can also be seen in glomerular disease, kidney transplantation and diabetes mellitus.

Disease with isolated low molecular proteinuria

Imerslund-Grasbeck syndrome (IGS) is a rare genetic autosomal recessive disorder characterized by the triad: low molecular weight proteinuria, megaloblastic anemia and vitamin B_{12} deficiency [16]. The disease occurs after the fourth month of age and additional clinical features are failure to thrive, recurrent respiratory and intestinal infections, mild neurological signs and symptoms. Proteinuria is persistent and does not respond to treatment with vitamin B12. The renal prognosis is excellent. The disease is a result of mutation in two genes-cubilin (*CUBN)* and amnionless (*AMN*). Both proteins are expressed in the small intestine as well in the renal proximal tubular cells. In the kidneys they interact with the multi-specific endocytic receptor megalin allowing the reabsorption of a panel of filtered plasma proteins such as albumin, vitamin D-binding protein, apolipoprotein A-I, and transferrin.

Donnai-Barrow syndrome or facio-oculo-acoustico-renal syndrome (MIM 222448)) is characterized by typical craniofacial anomalies (hypertelorism, bulging eyes), corpus callosum agenesis, developmental delay, high grade myopia, sensorineural deafness and low molecular weight proteinuria [17]. This is a very rare autosomal recessive disorder due to mutations in the low density lipoprotein receptor-related protein 2 gene LRP2. LRP2 encodes megalin, a multi-ligand endocytic receptor important for receptor-mediated endocytosis (RME). Besides the kidney, megalin is expressed in many absorptive epithelia, including the neuro-epithelium. During the brain development megalin mediates neural tubule specification by acting as a clearance receptor of various ligands, such as bone morphogenic protein 4 from extra-embryonic fluids [18]. During optic nerve development, megalin modulates sonic hedgehog abundance and enables the recruitment of oligodendrocyte precursors [19]. Megalin is also expressed in the retinal pigment epithelium and nonpigmented ciliary body epithelium [20]. These observations explain the important role of the megalin in brain and eye development and also explain the disease phenotype.

Renal Fanconi syndrome is a heterogeneous entity due to different causes. It can be isolated or associated with affection of multiple organs and systems as in the case of cystinosis and mitochondrial cytopathies. It can be congenital (genetic) or acquired, transient or persistent, with preserved GFR or with progression to end-stage renal failure [21]. Some patients may have mild affection of the proximal tubular functions (Dent disease) or severe dysfunction (cystinosis). Genetic causes of Fanconi syndrome are given in Table 1.

Table 1. Genetic causes of Fanconi syndrome

Disease	Gene	Additional clinical features
Cystinosis	*CTNS*	Multiple organs affected, corneal cystine crystals
Oculocerebrorenal syndrome of Lowe	*OCRL*	Congenital cataracts, neurological deficit, kidney failure
Dent-1	*CLNC5*	Hypercalciuria, nephrocalcinosis, stones, kidney failure
Dent-2	*OCRL*	Hypercalciuria, nephrocalcinosis, stones, kidney failure, peripheral cataracts, mild intellectual disability
Tyrosinemia	*FAH*	Hepatic dysfunction, liver cancer, growth retardation
Wilson disease	*ATP7B*	Liver dysfunction, neurological abnormalities
Galactosemia	*GALT*	Jaundice, liver dysfunction, encephalopathy
Congenital Fructose Intolerance	*ALDOB*	Hypoglycemia, vomiting, hepatomegaly
Fanconi–Bickel syndrome	*GLUT2*	Hepatosplenomegaly, hypo-, hyperglycemia, poor growth, rickets
ARC syndrome	*VPS33B, VIPAR*	Arthrogryposis, cholestasis
Mitochondrial cytopathies	Multiple mitochondrial and nuclear DNA mutations	Multiorgan dysfunction
MODY1	*HNF4A*	Neonatal hyperinsulinism, Maturity-onset of diabetes in the young
FRTS1	Not known, linked to chromosome 15	Kidney failure
FRTS2	*SLC34A1*	Bone fractures due to hypophosphatemia
FRTS3	*EHHADH*	Preserved GFR

ARC syndrome- Arthrogryposis-renal dysfunction-cholestasis syndrome' FRTS-Fanconi Renotubular Syndrome

Aquired Fanconi syndrome in majority of cases is due to drug toxicity [22]. The modern medicine is characterized by the expansion of the pharmaceutical industry and creation of new modern drugs for treatment of diseases which were considered incurable such as cancer, epilepsy or HIV infection. However, many of these drugs have potential to damage the proximal tubules [23-25]. These drugs are extracted from the blood stream into the proximal tubular cells through a number of organic transporters expressed on the cell surface [26,27]. This leads to high intracellular concentration of these drugs, which explains their toxic effect. The precise prevalence of the drug-induced Fanconi syndrome is not known, because these drug-adverse effects may be mild and not always recognized and reported.

Platinum-containing compounds (cisplatin and carboplatin) are widely used anticancer drugs for treatment of adults as well children. Ifosfamide has similar chemical structure to cyclophosphamide, which is not nephrotoxic. The toxicity of ifosfamide is explained by its rapid uptake into tubular cells through the action of cationic organic transporters and its metabolism to toxic chloracetaldehyde [28]. In majority of cases toxicity from cisplatin and ifosfamide is reversible, but in some individuals can persist for years and lead to chronic tubulopathy.

Anti-viral drugs, nucleoside reverse transcriptase inhibitors (NRTIs) and nucleotide reverse transcriptase inhibitors (NtRTIs) designed a new revolutionary era in treatment of children and adults with HIV infection. Both groups of drugs expose tubular nephrotoxicity due to their high intracellular uptake by the organic transporters [29-34]. Tenofovor is a newer agent for treatment of HIV but also hepatitis B infection. Although initial safety studies did not show adverse effect on the glomerular filtration rate, further clinical reports described its tubulotoxic effect leading to Fanconi syndrome. It is estimated that serious toxicity ensues in less than 1% of patients [34].

Although aminoglycoside antibiotics (gentamycin, tobramycin and amikacin) are well known causes of drug-induced Fanconi syndrome, it seems that this adverse effect is nowadays rarely seen because of the increased awareness of the medical professionals and better monitoring during the administration of these drugs [35-39]. Tetracycline-induced Fanconi syndrome was described in classic textbooks, and has not been seen any more particularly in children because of the highly restrictive use of this drug [40-42].

Valproic acid is a widely used drug for treatment of epilepsy and mood disorders, particularly in children. Fanconi syndrome is described with the use of valproic acid, particularly in children with severe motor and intellectual disabilities [43-45]. Animal studies have revealed that pathomechanism of the tubular injury is related to the oxidative stress and mitochondrial dysfunction induced by valproic acid [46].

Other diseases

Many infectious agents can cause tubulointerstitial diseases resulting in tubular proteinuria and secondary Fanconi syndrome. Also vasculitides and autoimmune disorders can affect the proximnal tubules resulting in LMWP and other defects [47, 48, 49]. Here we should mention TINU syndrome (tubulointerstitial nephritis associated with uveitis) [50, 51]. Many papers reported about the presence of low molecular weight proteinuria in children with vesicoureteral reflux, idiopathic nephrotic syndrome, diabetic nephropathy and after kidney transplantation, but there is no clear evidence that LMWP is a predictor of the outcome and effect of the therapy in these diseases [52-59]. It seems that LMWP reflects the presence of the tubulointerstitial histology changes which can influence the disease course.

Transitory LMWP proteinuria may be seen in children with distal renal tubular acidosis [60-62]. The plausible explanation for this phenomenon is long-lasting hypokalemia and acidosis which can impair proximal tubular transporters resulting in LMWP and other defects. With metabolic compensation LMWP ceases in these patients.

Conclusion

Low molecular weight proteinuria may be found in many genetic and acquired kidney diseases. Often it is unrecognized in the busy clinical practice and may lead to unnecessary treatment with cytostatic agents and ACE inhibitors. Therefore, appropriate typization and classification should be an initial step in evaluation patients with proteinuria.

Conflict of interest statement. None declared.

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Original article

Characteristics and Outcome of Pediatric Hemolytic Uremic Syndrome

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Abstract

Introduction. Hemolytic uremic syndrome (HUS) is one of the most common causes of renal failure in pediatric population. It is characterized by renal failure in association with microangiopathic hemolytic anemia and thrombocytopenia.

Methods. This was a retrospective study. All children with the diagnosis of HUS in "Dr Sheikh Children Hospital" diagnosed from January 2006 to December 2016 were included in the study. They were divided into two groups: diarrhea positive HUS (D^+HUS) and diarrhea negative HUS (D^-HUS). We assessed demographic characteristics, laboratory data and outcome of patients.

Results. Thirty-six patients were identified; 70% were D^+HUS and 30% were D-HUS. Mean age of patients with D^-HUS was significantly higher than in D^+HUS patients. Oligo/anuria and unconsciousness were significantly more common in D^+HUS patients, while D-HUS patients more frequently had hematuria. Frequency of hypertension and duration of hospitalization were not significantly different between two groups.

Conclusion. Our cases of pediatric hemolytic uremic syndrome had a high rate of complications and we experienced many sequelae in these patients, including: renal, central nervous system, cardiac, respiratory, gastrointestinal complications and sepsis. It is a condition with significant mortality and morbidity. Prevention and early recognition is important.

Keywords: diarrhea, hemolytic uremic syndrome, renal failure, pediatrics

Introduction

One of the most common causes of pediatric renal failure is hemolytic uremic syndrome (HUS). It consists of the triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure [1]. HUS in its acute phase is a condition with significant mortality and morbidity. It has also chronic complications that can extend well beyond the acute phase of the condition [2]. Two main categories of this condition are:

- Typical HUS or classic HUS, also called diarrhea-associated HUS (D+HUS). This form is usually caused by Shiga toxin-producing Escherichia coli (STEC).
- Atypical HUS or D-Hus, which is usually due to genetic factors like complement system abnormalities.

Additionally, HUS may be associated with pneumococcal infection and is mediated by neuraminidase [3]. In cases of D+HUS, patients often present with diarrhea which is often bloody and/or watery. They may show other signs of gastrointestinal infection like abdominal tenderness and low-grade fever, followed by decreasing urine output and oligo/anuria. However, a temporary renal involvement and decreased glomerular filtration rate (GFR) might be seen due to dehydration in STEC gastroenteritis without HUS. Extrarenal involvement may occur in the acute phase of the condition including central nervous system (CNS), often accompanied by respiratory, cardiac and gastrointestinal complications. D-HUS may present with various atypical symptoms [4].

All clinical features of HUS results from the microangiopathic lesions and they are termed as thrombotic microangiopathy (TMA). TMA most often affects arterioles and capillaries of the kidneys and the CNS and the resultant decreased blood flow to the affected organ causes ischemic damage [4,5]. A large meta-analysis has estimated that renal complications without end-stage renal disease (ESRD) occurred in around 25% and ESRD in 3% of D+HUS cases [6].

HUS related mortality is 3-5% and is always due to severe extrarenal complications [2,3]. Long- term complication of HUS is usually related to kidneys and is manifested as hypertension and long-term proteinuria [7]. The mainstay of treatment in HUS is supportive therapy that includes: fluid therapy, dialysis and plasma exchange depending on the etiology of the condition [4,8]. Eculizumab is a C5 monoclonal antibody that has been used in the treatment of atypical HUS [4].

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In the present study we evaluate the epidemiologic and clinical features of childhood HUS in our population.

Materials and methods

We retrospectively reviewed chart and medical records of all children with a diagnosis of HUS admitted to "Dr. Sheikh Children Hospital" during the period from January 2006 to December 2016. This hospital is the pediatric kidney reference center in East of Iran and is affiliated with Mashhad University of Medical Sciences. Demographic data, symptoms, laboratory data, duration of dialysis, length of hospital stay, complications during hospitalization and outcome of patients were assessed. Statistical analysis was performed using SPSS16 statistical package. Data was expressed as mean± standard deviation. Chi square test and Student t-test were used for group comparisons. A P value <0.05 was considered as significant.

Results

A review of patient's records revealed 36 patients diagnosed with HUS during the study period. They were classified into two groups: D+HUS (25 patients, 14 male) and D-HUS (11 patients, 6 male). Mean age of patients in the D+HUS group was 40.3±27.6 months and 70.1±62.3 in D-HUS group (P=0.09). No significant difference was noted regarding patients gender.
Clinical characteristics of the patients are shown in Table 1.

Table 1. Clinical characteristics

Characteristic	D^+ HUS (n= 25)	D^- HUS (n= 11)	P value
Hypertension	6 (24%)	5 (45.5%)	0.198
Oligo/anuria	13 (52%)	2 (18%)	0.035
Hematuria	17(68%)	9 (81%)	0.0285
Seizure	9 (36%)	5 (45%)	0.592
Edema	17 (68%)	6 (54%)	0.439
Unconsciousness	11 (44%)	1 (9%)	0.041

The mean duration of hospitalization was 13.6 days in the first group and 14.9 days in the second group (P=0.6). Sixteen (64%) of patients in the D^+HUS group needed dialysis in the acute phase of the condition whereas dialysis was necessary in 8(73%) patients from the D^-HUS group (P=0.184). Majority of them underwent peritoneal dialysis. Plasma exchange and plasma infusion were used in 24% and 48% patients from the D^+HUS group and 27% for each one in the D^-HUS group. Hyperuricemia was detected in 12% and 36% of patients, respectively. It resolved in all patients after treatment of kidney failure or with administration of rasburicase. Mortality in the acute phase of the condition was 28% and 18% in the two groups, respectively.

Discussion

Hemolytic uremic syndrome is the leading cause of acute renal failure in children between 1-4 years and the second most common cause in children younger than one year and older than 4 years [1,9]. In this study we evaluated 36 patients with the diagnosis of hemolytic uremic syndrome. 69.5% had a history of diarrhea before presentation and were categorized as D^+HUS while 20.5% were categorized as D-HUS or atypical HUS. This proportion is similar to that presented in the study of Micheletti *et al*. [10]. Most studies have reported the prevalence of D^+ about 90% [1,2]. In the study by Jennsen *et al.* in Norway, the prevalence of D^+HUS was reported to be 80% [3]. The lower incidence of D^+HUS in our study could be due to the small sample size and more probability of genetic defects due to the prevalence of consanguine marriage in our population. Also, STEC infection may present without diarrhea in some cases [11,12]. The mean age of our patients in the D^- HUS group was similar to that of examined patients by Micheletti *et al.* [10], but in the D^+ group was similar to Jenssen's study [3]. Duration of hospitalization in our patients was similar to that reported in the Jenssen's study in Norway [3]. Duration of hospitalization in D+HUS was similar to previous studies [13], but for the D^-HUS it was different which could be due to different treatment modalities and complexity of the nature of disease.
Hypertension is one of the most common presentations of HUS and is present in 50% of cases. It could be due to elevated renin activity and other factors like volume overload [3,14]. In Micheletti' s study the prevalence of hypertension in the D+HUS and D^-HUS was reported to be 46% and 66%, respectively. Jenssen also reported the prevalence of hypertension in their study population: 24% for D^+HUS and 33% for D^-HUS at presentation and 83% and 100% during hospitalization period [3]. The lower incidence of hypertension in our study population may be due to the time of blood pressure measurement. Our patients' blood pressures were measured in the acute phase of the condition and could be affected by conditions like dehydration and sepsis. 52% of our patients in the D+ HUS group developed oligo/anuria and 64% needed dialysis. It was 18% and 73% in the D-group, respectively. Prevalence of oligo/anuria was 76% and 56% in Jenssen's study and 84%, and 100% in Michelet's study. Loos *et al*. reported an incidence of oligo/anuria in HUS patients following an outbreak of E-coli104: H4 infection producing shigatoxin to be 66% [15]. Similar to our study, a large number of other studies have reported the need for dialysis in HUS patients between 47-68% [16-20]. Central nervous system (CNS) involvement is common in HUS. CNS involvement in HUS has been reported between 0-50%

in different studies. The most common presentation is seizure, either generalized or focal; loss of consciousness, personality changes, transient hemiparesis and coma have also been reported. CNS involvement in HUS seems to be sometimes due to electrolyte abnormalities or hypertension, but these conditions sometimes cannot explain the severe neurologic manifestations in HUS [21,22]. Pathologic evaluation of the CNS in HUS patients who died due to HUS and neurologic dysfunction has showed nonspecific changes like hypoxic-ischemic changes or brain edema [21-24]. In our study 36% of D^+HUS and 45% of D^-HUS patients had seizures. There was no statistically significant difference between the two groups. In Micheletti's study, the prevalence of seizure was 15% and 22% respectively, and like in our study there was no difference between the two groups. In a study by Sheth *et al*., 27% of patients presented with seizures [24]. In our study 16% of patients in D^+ HUS group needed plasma exchange and 64% received plasma infusion. This percentage was 45% and 36% in D^-HUS group respectively, which is similar to a study by Loos *et al*. [5]. Of patients who had hyperuricemia, 7.4% received rasburicase which resulted in reduction in serum uric acid and improvement of renal function. In a study by Esmaeeli *et al*. including 15 patients with acute renal failure and concomitant hyperuricemia, they showed that treatment with rasburicase resulted in uric acid reduction and improvement of renal failure [25]. Acosta reported one-month-old infant with HUS and serum uric acid elevation who experienced complete renal function improvement and normalization of serum uric acid following therapy with one dose of rasburicase [26]. Mortality of D^+HUS has been reported between 3-50% and is slightly higher during the outbreaks [4]. In our study mortality was 28% and was due to complications of dehydration, renal failure complications, and neurologic involvement. In a study in North India, mortality was reported to be 60% and was due to renal failure and cortical necrosis [27]. Patients' mortality in D^-HUS in our study was 18% during the acute phase of the condition. It has been reported to range between 0- 25% in other studies [28,29].

Conclusions

Results of this study show that hemolytic uremic syndrome (HUS) is a condition with significant mortality and morbidity. Attempts should be made in prevention and early recognition of the condition.

Conflict of interest statement. None declared.

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Original article

Prevalence of Dermatologic Manifestations Among Patients on Chronic Hemodialysis: Single Center Study

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Abstract

Introduction. A large number of studies have revealed different cutaneous manifestations in patients with CKD, but few of them have compared the prevalence of these manifestations in CKD patients with general population. It was our aim to compare the prevalence of dermatologic manifestations among patients on maintenance HD in Tamin Ejtemaei Hospital in Takestan (located in Qazvin province) with the general population.

Methods. Forty-five patients undergoing regular hemodialysis and 45 individuals who were randomly selected from healthy hospital staff, were examined for dermatologic manifestations. The statistical analysis was performed with the statistical package SPSS Software (version 11.0, SPSS Inc., Chicago, Ill, USA). P value less than 0.05 was considered significant.

Results. Thirty-four (75.5%) hemodialysis patients and 11(24.4%) from the control group were found to have at least one dermatologic manifestation. Of all skin manifestations, most commonly observed in hemodialysis patients were pruritus and xerosis. Also, fungal, bacterial and viral infections were seen in hemodialysis patients. Seborrheic keratosis, skin Bowen's disease and skin basal cell carcinoma were seen in these patients.

Conclusion. These skin manifestations cause decreased patient function and poor quality of life. For better management of patients, awareness of involved medical team is necessary. These patients need periodical dermatologic evaluation.

Keywords: skin manifestations, hemodialysis

Introduction

Chronic kidney disease (CKD) is a progressive loss of renal function that is classified into 5 stages according to abnormally decreased and deteriorated glomerular filtration rate [1,2].

Patients with CKD on hemodialysis (HD) may experience a wide variety of dermatologic, mucosal membranes, hair and nail manifestations including hyperpigmentation, ichthyosis, pruritus, xerosis, onychomycosis, onycholysis, subungual hyperkeratosis, splinter hemorrhages, brittle hair, and sparse body scalp hair during treatment. Sometimes these symptoms are not seen during diagnosis of kidney failure and are only detected in advanced cases of the disease but are more often associated, directly or indirectly, with uremia in its broadest sense [3].

A large number of studies have revealed different cutaneous manifestations in patients with CKD, but few of them have compared the prevalence of these manifestations in CKD patients with healthy individuals in the general population [4-6]. It was our aim to compare the prevalence of dermatologic manifestations among patients on maintenance HD in Tamin Ejtemaei Hospital in Takestan (located in Qazvin province) with the general population.

Materials and methods

From June 2016 to March 2017, 45 patients undergoing regular hemodialysis (HD group), and 45 individuals who were randomly selected from hospital staff without any history of kidney function impairment confirmed by renal function tests (control group), were examined for dermatologic manifestations by a qualified dermatologist. The dialysis mode was high-flux membrane by using synthetic membranes including Polyethersulfone_membranes without hemodiafiltration line. Residual renal function (RRF) with average urea and creatinine clearance [(CCr+CU)/2] in 24-h urine (if >1 mL/min and diuresis >100 mL/day, RRF) was considered.

Data collection tool consisted of a check list including the following information: demographic data such as gender, age, smoking, cause of renal failure, primary and secondary diagnoses, medications, duration of renal failure and HD, and dermatologic manifestation.

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The study was approved by the Ethics Committee of the Takestan Tamin Ejtemaei Hospital before its initiation, and the protocols used conformed to the ethical guidelines of the 1975 Helsinki Declaration. All participants were informed about the study protocols and a written consent was obtained from each one.

The statistical evaluation was performed by computer analysis with SPSS Software (Statistical Package for the Social Sciences, version 11.0, SPSS Inc, Chicago, Ill, USA). Descriptive statistics such as mean and standard deviation were applied. One way ANOVA, Student's t-test, chi-square, or Fisher's exact test were used, where appropriate, for comparing clinical data between groups. P value less than 0.05 was considered significant.

Results

Among 45 patients in the HD group, 24 (53.3%) were men and 21(46.7%) were women. The mean age of these patients was 48.6±26.4 years (range 17 years-89 years) and the mean dialysis duration was 33.0±16.1 months. The causes of ESRD in the patients were as follows: diabetes mellitus (DM) in 35.5 %, hypertension (HTN) in 35%, chronic glomerulonephritis (CGN) in 11%, chronic interstitial nephritis (CIN) in 9% and other in 9% of subjects (Figure 1).

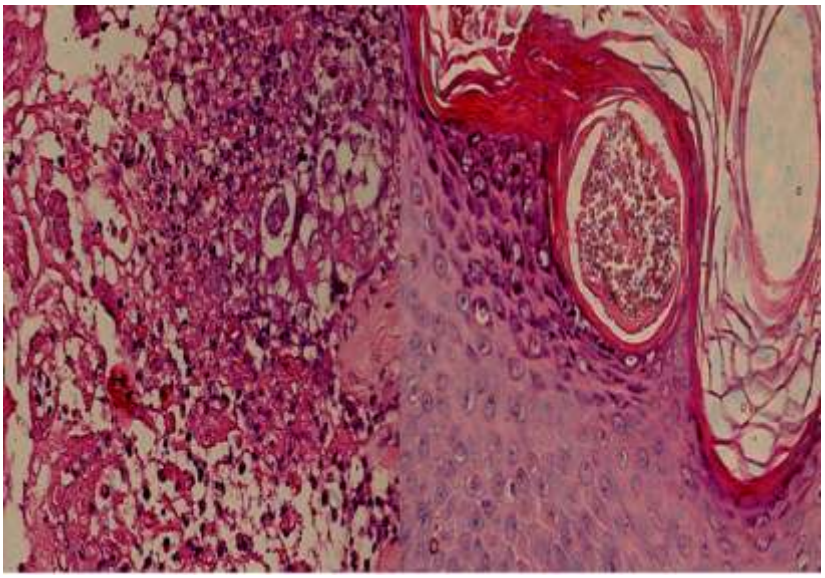

Fig. 1. The causes of ESRD in examined patients.
DM = diabetes mellitus, HTN= hypertension, CGN= chronic glomerulonephritis, CIN= chronic interstitial nephritis

Similar to the HD group, there were 24 males and 21 females in the control group. The mean age was 46.5± 16.5 years.

Overall, 34(75.5%) of HD patients and 11(24.4%) of control group were found to have at least one dermatological manifestation. Several patients had more than one dermatologic manifestation. Among skin manifestation, pruritus was found in 27 patients of the hemodialysis group, and in 8 individuals of the control group. Pruritus was found to be severe in diabetic patients. Xerosis was observed in 16 patients of hemodialysis group, and in 7 individuals of the control group. Skin infections such as fungal, bacterial and viral were seen in 13, 10, and 5 of HD patients, respectively (Figure 2, 3). Also seborrheic keratosis, skin Bowen's disease and skin basal cell carcinoma were seen in 6, 1 and 1 of HD patients, respectively (Figure 4, 5).

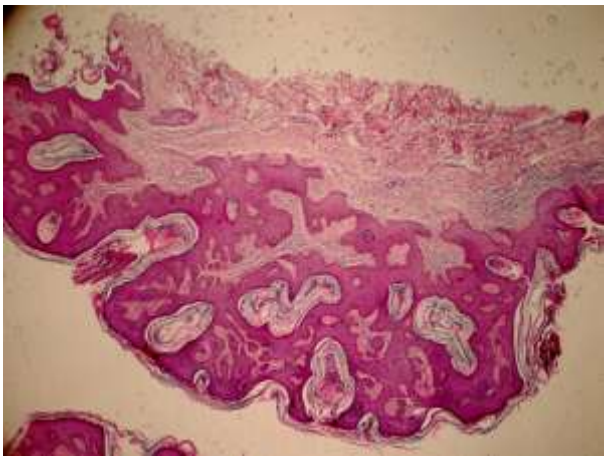

Fig. 2. a) Herpes simplex skin infections including epidermal necrosis, multinucleated keratinocytes with ground glass nuclei and moulding. **b)** Fungal skin infections, dermatophytes including pseudoepitheliomatous hyperplasia of epidermis, fungal spores and hyphae in horny cell layer (200, Hematoxylin & Eosin)

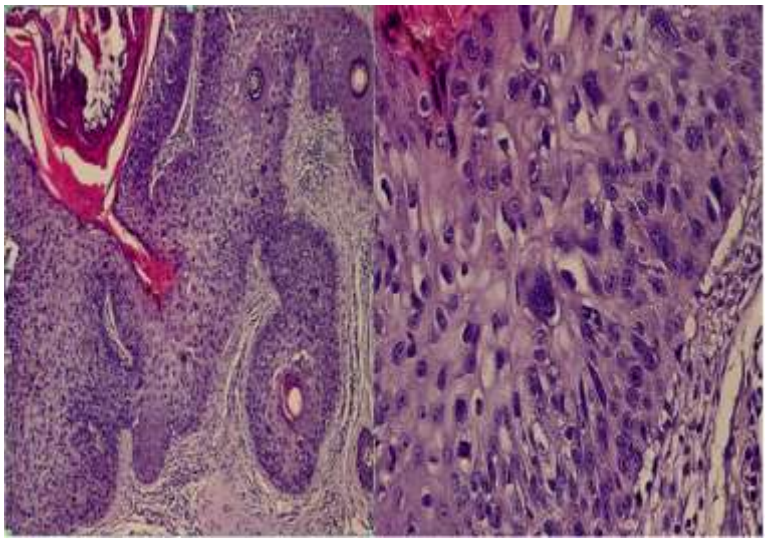

Fig. 3. Seborrheic keratosis including hyperkeratosis, acanthosis, papillomatosis of epidermis with true and pseudohorn cysts (40, Hematoxylin & Eosin)

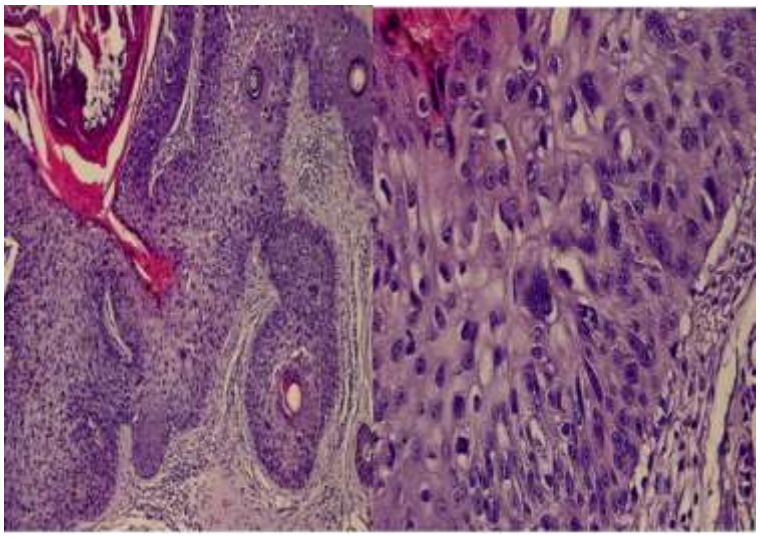

Fig. 4. a) Skin Bowen's disease including epidermal full thickness neoplastic proliferation with hyperkeratosis. B: necrosis, multinucleated keratinocytes with ground glass nuclei and molding (200, Hematoxylin & Eosin). **b)** Tumoral cells have hyperchromatic nuclei with multinucleation, and increased mitotic figures (400, Hematoxylin & Eosin).

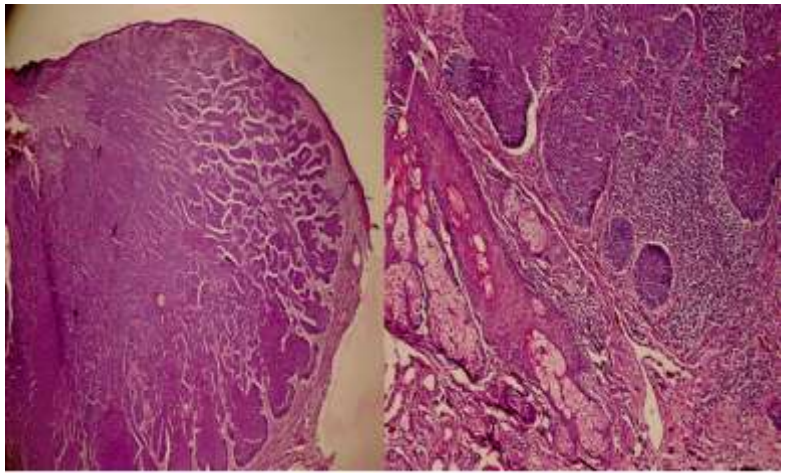

Fig. 5. a) Skin basal cell carcinoma including large tumor masses in the dermis. (100, Hematoxylin & Eosin). **b)** Basaloid tumor cells grow in syncytial pattern with peripheral palisading and cleft. (400, Hematoxylin & Eosin)

Onychomycosis was the most common fungal infections and herpes labialis and zoster were common viral infection in hemodialysis patients. Nail changes were observed in 33 patients of hemodialysis group and in 14 individuals of the control group. Hair changes were observed in 9 patients and mucosal changes were seen in 6 patients of hemodialysis group. The prevalence rates of the different types of manifestations detected in the patients on HD and in the controls are shown in Table 1.

Table 1. The prevalence rates of dermatologic manifestations in case and control groups

Dermatologic manifestations	HD group according to cause of ESRD						Control group	p-value
	HTN	DM	CGN	CIN	others	total		
Pruritus	7	10	3	3	4	27	8	< 0.05*
Xerosis	5	5	2	1	3	16	7	< 0.05*
Pigmentation	3	2	1	1	1	8	5	> 0.05
Fungal	4	6	1	1	1	13	4	< 0.05*
bacterial	3	4	1	1	1	10	3	< 0.05*
viral	1	2	1	0	1	5	3	> 0.05
Acne	1	1	0	1	1	4	4	> 0.05
Necrotic excoriation	1	3	1	0	0	5	3	> 0.05
Ichtus	1	1	0	1	1	4	3	> 0.05
Eczema	0	2	1	0	1	4	3	> 0.05
Aphthous stomatitis	2	0	1	0	1	4	4	> 0.05
Scrotal tongue	1	0	0	1	0	2	3	> 0.05
Furred tongue	0	1	1	0	0	2	2	> 0.05
Seborrheic dermatitis	1	1	2	1	1	6	5	> 0.05
Seborrheic keratoses	1	1	1	1	2	6	6	> 0.05
Skin Bowen's disease	0	1	0	0	0	1	0	> 0.05
Skin basal cell carcinoma	0	1	0	0	0	1	0	> 0.05
Drying and hair fragility	1	1	1	1	0	4	3	> 0.05
Scalp hair loss	1	1	1	0	0	3	2	> 0.05
Hair discoloration	0	0	1	1	0	2	1	> 0.05
Leukonychia	2	2	2	1	1	8	2	< 0.05*
Onychomycosis	1	3	0	0	1	5	2	< 0.05*
Half half nails(Lindsay's nails	2	2	1	1	1	7	2	< 0.05*
Onycholysis	2	2	1	0	1	6	4	> 0.05
Subungual hyperkeratosis	1	0	0	0	1	2	1	> 0.05
Pitting	0	1	0	0	0	1	1	> 0.05
Thin nail	0	0	1	0	0	1	1	> 0.05
Cyanosis	0	1	0	0	0	1	0	> 0.05
Clubbing	1	1	0	0	0	2	1	> 0.05

* *P* value < 0.05 as determined by *t* test

Of the 34 HD patients with at least 1 cutaneous or mucosal manifestation, 26(76.4%) patients were male, 16(47%) patients were ≥65 years of age, 23(67.6%) patients had diabetes mellitus, 23(67.6%) had hypertension, and 24 (70.5%) patients had long-term HD (> 8 years). These results were shown to be statistically related to gender, diabetes mellitus, hypertension and duration of HD (Table 2).

Table 2. Multivariate logistic regression analysis for overall dermatologic manifestation

Factor	HD patients with (n=57) & without (n=18) positive dermatologic manifestations OR(95% CI)	P-Value
Male gender	2.134 (1.056–5.487)	< 0.05*
Diabetes mellitus	1.184 (1.044–2.884)	< 0.05*
Hypertension	1.184 (1.044–2.884)	< 0.05*
Age ≥65	1.004 (0.658–1.586)	> 0.05
Long term hemodialysis	2.134 (1.056–5.487)	< 0.05*

* *P* value < 0.05 as determined by *t* test

Discussion

The occurrences of skin lesions in patients with CKD on hemodialysis are more common than in normal population. The pathogenesis of cutaneous lesions in patients on hemodialysis is multifactorial, including: main etiology of CKD, pro-inflammatory and inflammatory processes, biochemical and metabolic disturbances, uremia, electrolytes disorder, homeopathy and resulted multisystem dysfunction associated with therapeutic modulation effects [7]. Main of skin lesions are benign and their diagnosis is straightforward based on clinical pre-

sentation with good. Few of them including bullous lesions have unfavorable outcome with complication and their diagnosis is expensive since they are based on histopathology and immunofluorescence examinations [8]. The important causes of ESRD in our study subjects were compared with those in other studies [9]. Similar to other research results, in our study a significant number of subjects - 34(75.5%) complained on cutaneous presentations, which were more common in men [10,11]. In our patients, the most frequent dermatologic presentation was pruritus. These results are in agreement with those of De Marchi *et al.* [12] and Szepietowski *et al.* [13]. Among diabetic patients, pruritus was manifested in its severe form, which is similar to the findings of Kumar Kolla P *et al*. [14]. This might be due to multisystemic nature of DM and extensive inflammatory, immunologic interaction in disease course. The main underling etiology of pruritus in patients on hemodialysis is unclear but mutli factorial etiology and many predisposing effectors were described consists of cytokine associated pro inflammatory and inflammatory processes in hyperuremic status, hyper stimulation of inflammatory cellular elements including mast cells, basophils and platelets for degranulation of vasoactive amine including histamine, reactive proliferation and demargination of inflammatory cells including mast cells, hyperparathyroidism, hyperuremic induced polyneuropathy, xerosis, hypoalbominemia and raised of serum ferritin as an acute phase reactant in hyperuremic induced inflammatory status [15-19]. The second most common dermatologic presentation among our subjects was xerosis. This finding was supported by Kumar Kolla P *et al*. results [14]. In patients undergoing regular hemodialysis, sweat glands have diminished size and less than normal/impaired? function. Above changes present due to lower level of epidermal hydration and lipid content than normal epidermis. Also these patients received a large amount of diuretics and had high serum level of vitamin A [3]. Skin infections were seen in 28 of HD patients. This result is in agreement with the results obtained by Udaykumar *et al.*, but higher than those reported by Bakthavatchalu *et al*. [3,9]. Patients on hemodialysis are immunocompromised and immunodeficient subjects. They have decreased count and function of both B and T lymphocytes. Also, there is malfunction of reticuloendothelial system [20-22]. The poor hygiene status of patient also should be considered.

In our study, nail presentations in patients on HD were found in 33 subjects, which number is higher compared to the results of Bakthavatchalu P *et al*., but similar to those of Udayakumar *et al*. and Mookambika RV *et al*. [3,9,11]. The incidence of hair presentations in our HD patients was similar to that presented by Tawade YV *et al.* and Singh G *et al.*, but lower than that of Kumar Kolla P *et al*. findings [22,23,14]. Hair drying and fragility was associated with declined sebaceous discharge of sebaceous glands [3]. The mucosal manifestations were seen in 6 patients, which is similar to Kumar Kolla P *et al.* [14] findings compared to 90% incidence in Cohen GS study [25]. Few causes of oral mucosal changes in patients on HD were described and are as following: epithelial dehydration, breathing via mouth, high level of acid uric in saliva content, disturbances in metabolic pathway for converting acid uric to ammonia [14].

The non-melanocytic skin malignancies were seen in 2 of HD patients (basal cell carcinoma and Bowen's disease). This finding is consistent with the results published by Stewart JH *et al.* [26], results of Sułowicz J *et al.* [27] and Tercedor J *et al.* [28]. Patients undergoinge hemodialysis were at a higher risk of cancer including non-melanocytic skin malignancies. The few previously studies was performed for discovery of accurate underlying pathogenesis. For example, for a long period of time, these patients underwent multiple imaging interventions for optimal evaluation and management. Therefore, this notable cumulative exposure effect initiated and promoted oncogenic and carcinogenic effects. Therefore, these subjects identified as secondary immunodifficient group, due to underlying cause of ESRD, comorbid status, and use of many drugs. In these conditions, the patient is susceptible of developing malignancy [26,27].

One patient complained on indolent progressive painful pruritus skin papules over the trunk, which followed by vesicles formation. His medical history revealed diabetic nephropathy with hypertension, diabetic neuropathy; in addition he suffered from amputation of his left first and second toes due to diabetic foot. IgA-associated vesiculobullous disease of skin is unusual presentation in patients on HD. Today, accurate explanation of main underlying pathogenesis in these patients is impossible. However, genetic and environmental factors including many drugs and infectious causes /agents? were assumed for trigger etiology [29].

Conclusion

Many results of previous researches have revealed that patients on HD are susceptible to various benign or malignant or complex skin diseases. Skin manifestations can cause decreased patient function and poor quality of life. For better management of patients on HD, awareness of involved medical team about these presentations is necessary. These patients need periodical dermatologic evaluation.

Conflict of interest statement. None declared.

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Original article

Risk Factors in Early Arteriovenous Fistula Failure

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Abstract

Introduction. Nearly 20-60% of arteriovenous fistula (AVF) failure occurs at early stage. It was our aim to evaluate some risk factors in early AVF failure and postoperative complications of AVFs created for hemodialysis (HD) in two hospitals.

Methods. For this retrospective study data were evaluated from 210 patients who underwent AVF procedures for HD and selected by simple sampling method. All procedures were performed under local anesthesia and general anesthesia. Clinical, biochemical characteristics, AVF site and type, anesthetic techniques and postoperative complications of AVFs were collected from a check list. Both descriptive and statistical analysis methods were applied (P value <0.05).

Results. Overall 218 AVFs were created**.** Early AVF failure or thrombosis was seen in 25 cases (25/218 [11.46%]). Analyzing the risk factors of early failure or thrombosis of AVFs, multivariate logistic regression showed a significant correlation between female sex (OR=3.146, 95% CI 1.662-6.124), age >65 years (OR=3.410, 95% CI 1.541-5.523), diabetes (OR=1.125, 95% CI 0.873-2.576), hypertension (OR=1.411, 95% CI 0.831-3.351) and general anesthesia (OR=1.599, 95% CI 1.184-2.048) with early failure or thrombosis of AVFs**.**

Conclusion. Our rate of AVFs failure is comparable to published reports. Female sex, age >65 years, diabetes, hypertension and general anesthesia have negative effect on AVFs patency.

Keywords: arteriovenous fistulae, early failure

Introduction

Chronic renal failure (CRF) is unalterable decline of kidney work that usually develops to-end stage renal disease (ESRD). In this condition, renal replacement therapy (RRT) or hemodialysis (HD) is necessary for survival. Unfortunately, in recent years due to increasing rates of diabetes, hypertension, ageing population and etc. the incidence of ESRD is rising worldwide [1,2]. Just during the last 2 decades, the annual growth of patients was 6-12% in many developed countries [3].

Patients with ESRD need to receive HD through a durable access to the circulatory system to feed the extracorporeal circuit until RRT [4]. The ideal permanent vascular access should provide suitable supply blood flow rates to deliver the prescribed dialysis dose and minimal complication rates from infection and thrombosis. There are three main types of permanent vascular access used in HD patients: arteriovenous fistula (AVF), synthetic arteriovenous graft (AVG), and central venous catheter (CVC).

AVF is a surgically created communication between artery and vein that results in increased blood flow through an accessible conduit- it is created to meet this minimum flow requirement in patients. Today, it has been well established that autologous arteriovenous fistula (AVF) has higher patency rates and lower access complication rates as well as low risk of infection, hospitalization, and death than other forms of vascular access including grafts or catheters among ESRD patients and is a milestone of hemodialysis.

Similar to other performed procedures, AVFs are susceptible to access failure and associated complications. One of the usual complication is primary failure and presented as an AVF that never develops to support cannulation with 2 hemodialysis needles or unsuccessful within the first 3 months after its beginning cannulation [5]. Unfortunately, approximately 20-60% of AVF failure occurs at early stage [6]. This high failure rate depends on preoperative arterial and venous diameters, postoperative flow through the AVF, anesthetic and surgical techniques, AVF site, etc. [7].

If we could find the modifiable risk factors related to patency loss of AVF, it would be a substantial knowledge for improvement of AVF survival, life and health quality of the hemodialysis patients and decrease relevant costs. This work obviously decreased patients and their families' discomforts and distress and conspicuously

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increased their psychophysical health status. In this study, it was our aim to evaluate some risk factors in early AVF failure (patient clinical and paraclinical characteristics, AVF site and type, anesthetic techniques) and postoperative complications of AVFs created for HD in two hospitals.

Materials and methods

This observational retrospective analysis was performed in 210 patients who underwent upper limb vascular access (AVF procedures) for HD selected by a simple sampling method between March 2013 and April 2016 in two hospitals (Takestan Tamin Ejtemaei Hospital, Takestan, Iran and Velayat University Hospital, Qazvin, Iran). All patients had chronic renal failure and were appropriately referred by nephrologists for vascular access. All subjects accepted the information sheet and signed the consent form.

We categorized the subjects in two groups: a group with early AVF failure and a group with successful AVF creation.

Data collection tool consisted of a check list that contained the following information: demographic data such as gender, age, smoking, cause of renal failure, clinical and biochemical characteristics [waist circumference (WC) Body Mass Index (BMI), systolic and diastolic blood pressure (SBP,DBP), fasting blood sugar (FBS), lipid profile (Chol, LDL-C, Triglyceride, HDL cholesterol)], type of anesthesia (regional, general), type of AVF (Brescia-Cimino, Snuffbox, Brachiocephalic or Brachiobasilic), early complications (thrombosis, infection, psuedoaneurysm, hyperemia, hematoma, revisions due to hemorrhage). Subjects with medical history of myocardial infarction and associated interventional therapy, limb amputation due to peripheral artery occlusive disease, coagulopathy disorders, septicemia, Hb<7.5g%, veins<3 mm diameter, and arteries<2 mm diameter were excluded from the study [8].

Height and weight were assessed barefoot with tender underwear by using a wall-mounted stadiometer and calibrated digital scales, respectively. Height was rounded to the nearest 0.5 cm and weight to the nearest 0.1 kg. BMI was defined as weight in kilograms divided by height in meters squared (kg/m^2). On the basis of BMI, subjects were divided to normal weight (BMI= 18.5-24.9), overweight (BMI>25-29.9), and obese (BMI>30). WC was measured midway between the iliac crest and border of lower rib. Waist girth more than 102 cm for men and 88 cm for women indicated central obesity. Blood pressure was measured by trained and approved staff with a random zero sphygmomanometer, after the participant had been sitting for 5 minutes. The measurement of BP was done in the left mid arm by using a suitable gauge cuff. Systolic (the appearance of the first Korotkoff sound) and diastolic (the Korotkoff sounds were vanished) blood pressure were measured two times and mean of them was representative of BP.

Venous blood samples were obtained before the AVF surgery for measurements of fasting glucose levels as well as a lipid profile by certified staff after an overnight fast. After centrifugation, separated serum was immediately frozen at -20°C. Biochemical analyses were performed by using available calibrated auto-analyzer, Selectra 2, and kits of Pars Azmoon (Pars Azmoon Inc., Iran). Serum fasting blood glucose, total cholesterol, triglyceride and high density lipoprotein cholesterol, HDL-C were assayed using salt fractionation, glucose oxidase, enzymatic method, enzymatic method with glycerol phosphate oxidase and enzymatic method after precipitation with phosphotungstic acid, respectively. Low density lipoprotein cholesterol, LDL-C was calculated by using Friedwald,s formula (triglyceride≤400 mg/dl) [9].

The inclusion criteria were as follows: abdominal obesity (WC≥102 cm in men and ≥88 cm in women) or BMI>30, [2] elevated triglyceride level (≥150mg/dL); [3] low HDL cholesterol level (<40mg/dL for men and <50mg/dL for women); [4] elevated blood pressure (systolic≥130 mm Hg or diastolic≥85 mm Hg); and [5] elevated fasting plasma glucose concentration (>100 mg/dL) [10,11].

In the beginning of the study, careful examination of the arteries and superficial veins of the upper extremity (arterial pulse strength, presence of a recent access, formation of a prominent elastic structure upon application of pressure, and vein diameters) was performed in all study patients. For those patients who had more than one suitable site, the most distal one was generally selected in order to preserve the proximal site.

Thrombosis formation within the first month was supposed to be "early". Fistulae that were created two or more times were considered to be "repetition". All of the patients were followed up for the period starting from the creation of the AVF to the first HD.

Surgical and anesthetic techniques

Since our intention was to preserve the opportunity to move the AVF more proximally, the non-dominant upper extremity was primarily chosen for AVF. All surgical interventions were performed under local anesthesia, but if the local anesthesia was deemed inadequate, the patient was given general anesthesia. When creating the fistula, some factors including history of thrombophlebitis, prominence of superficial veins, segmental stenosis in the proximal vessel, atherosclerosis of the radial artery, and blood flow were considered.

Ethical approval

All subjects accepted the information sheet and signed the consent form. The patient-related information was

kept confidential. The study was approved by the Ethics committee of the Takestan Tamin Ejtemaei before its initiation, and the protocols used conformed to the ethical guidelines of the 1975 Helsinki Declaration.

Statistical analysis

The statistical evaluation was performed by the statistical SPSS Software (Statistical Package for Social Sciences, version 11.0, SPSS Inc., Chicago, Ill, USA). Descriptive statistics such as mean and standard deviation were applied. One-way ANOVA, Student's t-test, chi-square, or Fisher's exact test were used, where appropriate, for comparing clinical data between groups. P value less than 0.05 was considered significant.

Results

Although 210 patients participated in this study, overall 218 AVFs were performed (AVFs were created two times in 8 patients due to early failure). Of these patients 109(51.91%) were male and 101(48.09%) were female. The mean age was 50±3.5 years (range 29-72 years). Twenty-five (11.9%) subjects had smoking habit. Basic clinical and biochemical characteristics of participants are summarized in Table 1.

Table1. Basic clinical and biochemical characteristics of 210 participants

Variables	Mean± SD
Gender Male Female	N= 109 (51.9%) N= 101 (48.1%)
Age (Yrs)	50±3.5
WC (cm)	76±31
BMI (Kg/m2)	22.9±8.6
SBP (mmHg)	105±40
DBP (mmHg)	65± 25.5
TG (mg/dl)	135±100
Chol (mg/dl)	110±70
HDL (mg/dl)	25±14
LDL (mg/dl)	120±20
FBS(mg/dl)	178±42

WC: Waist Circumstances SBP: Systolic Blood Pressure, Diastolic Blood Pressure, FBS: Fasting Blood Serum, TG: Triglyceride, LDL: Low Density Lipoprotein, Chol: Cholesterol, BMI: Body Mass Index

Diabetes and hypertension were two major causes of ESRD in our patients; they are shown in Figure1.
Of the 218 AVFs, complete brachial plexus block was achieved in 141 (64.67%) cases. Thirty-eight (17.43%) cases were converted to general anesthesia and 39(17.88%) had AVF under general anesthesia from the start. Also, of all the AVFs, 145 (66.51%) cases were Brescia-Cimino AVF, 54(24.77%) cases were snuffbox AVF, and 19(8.71%) were antecubital brachiocephalic or brachiobasilic AVF (Table 2 summarizes types of AVF created based on the technique of anesthesia).

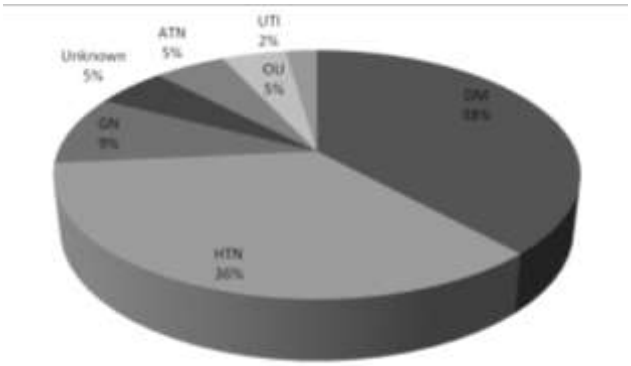

Fig. 1. Causes of ESRD in study patients
ATN=acute tubular necrosis; DM=diabetes mellitus; GN= glomerulonephritis; HTN=hypertension; OU=obstructive uropathy, UTI=urinary tract infections.

Table 2. Types of AVF created based on anesthesia type

Parameters	General anesthesia (n=77)	Regional anesthesia (n=141)
Brescia-Cimino	50	95
Snuffbox	21	33
Brachiocephalic	4	9
Brachiobasilic	1	5

The majority of patients (188/210 [89.52%]) in this study were undergoing their first AVF formation, whereas 22 patients (10.48%) had at least one previous fistula. Surgical intervention was performed on the left upper extremity in 139 (66.19%) patients and on the right upper extremity in 71 (33.81%) patients. Overall early AVF failure or thrombosis was seen in 25 cases (25/218 [11.46%]). Of these patients 16 cases was seen in Brescia-Cimino AVF group (16/145 [11.03%]), 7 cases in snuffbox AVF group (7/54 [12.96%]) and 2 cases were seen in antecubital brachiocephalic or brachiobasilic AVF group (2/19 [10.52%]). These results showed no significant difference between types of AVF on early failure or thrombosis (p=0.08) (Table 3).

Table 3. Effect of type of AVF on early failure or thrombosis

Type of AVF	No. of early failure or thrombosis of AVFs	Percentage
Brescia-Cimino (no=145)	16	11.03%
Snuffbox (no=54)	7	12.96%
Brachiocephalic or Brachiobasilic (no=19)	2	10.52%

p value between the three types of AVF=0.08; One-way ANOVA test

All cases with early AVF failure were subjected to repeated surgical intervention (AVFs were created two times in 8 patients). Also, thrombectomy was utilized successfully in 17 patients who presented with thrombosis. Therefore, early patency was found in 88% (185/210) of the AVFs created.

For analyzing the risk factors of early failure or thrombosis of AVFs, the multivariate logistic regression showed no significant correlation between male sex, smoking, body mass index >30 kg/m^2, hyperlipidemia, regional anesthesia and type of AVFs with early failure or thrombosis of AVFs. However, this analysis indicated that female sex (OR=3.146, 95% CI 1.662-6.124), age >65 year (OR=3.410, 95% CI 1.541-5.523), diabetes (OR=1.125, 95% CI 0.873-2.576), hypertension (OR=1.411, 95% CI 0.831-3.351) and general anesthesia (OR=1.599, 95% CI 1.184-2.048) were associated with early failure or thrombosis of AVFs (Table 4).

Overall complications were observed in 32/218 [14.67%] AVFs. Of these cases, 17 had early thrombosis and 15 cases had complications in the surgical area. Three patients had hyperemia at the incision site, 4 had infection at the incision site, 5 had hematoma at the incision site and 3 patients had revisions due to hemorrhage (Table 5). Regression of hyperemia and infection was achieved by standard antibiotic therapy, and re-exploration was performed for hematoma. There were no major complications from general or regional anesthesia in the present study. The patients commenced dialysis program approximately 4.6±2.4 weeks after AVFs were created.

Table 4. Multivariate logistic regression analysis for overall early failure or thrombosis of AVFs

Factors	Odd Ratio (95% Confidence Interval)	p-value
Male sex	2.430 (0.984-4.988)	0.078
Female sex	3.146 (1.662-6.124)	0.005*
Age > 65 years	3.410 (1.541-5.523)	0.012*
Smoking	1.635 (0.686-3.600)	0.118
Body mass index >30 kg/m^2	1.321 (0.574-2.792)	0.087
Diabetes	1.125 (0.873-2.576)	0.011*
Hypertension	1.411 (0.831-3.351)	0.014*
Hyperlipidemia	2.026 (1.110-2.836)	0.443
Regional anesthesia	2.754 (1.029-3.151)	0.104
General anesthesia	1.599 (1.184-2.048)	0.044*
Brescia-Cimino AVFs	2.445 (0.877-3.956)	0.062
Snuffbox AVFs	1.211 (0.548-1.011)	0.451
Brachiocephalic AVFs or Brachiobasilic AVFs	1.470 (0.954-1.689)	0.069

Table 5. Effect of type of AVF on complications

Parameters	Early thrombosis	Hyperemia	Infection	Hematoma	Revisions due to hemorrhage	Total number of complications
Brescia-Cimino (no=145)	12 (6.89%)	0	2 (1.37%)	4 (2.75%)	2 (1.37%)	20 (13.79%)
snuffbox (no=54)	3 (5.55%)	2 (3.70%)	2 (3.70%)	1 (1.85%)	1 (1.85%)	9 (16.66)
Brachiocephalic or Brachiobasilic (no=19)	2(10.52%)	1 (5.26%)	0	0	0	3 (15.78)
Total complication	17	3	4	5	3	32

p value between the three types of AVF= 0.06; One-way ANOVA test

Discussion

The early failure rates in previous literature reports are very diverse. Early failure rates in the range of 12%-29% have been observed in previous studies (12-17). Early failure is due to: severe dehydration, use of ill-suited veins, obstruction of the outlet, a vein kink near the anastomosis, a poor anastomosis, and compression of a hematoma [18,19].

In this study we evaluated 218 AVFs created in all patients. Early patency was found in 88% (185/210) of the AVFs created. So, early AVF failure or thrombosis was seen in 25 cases (25/218 [11.46%]). Of these 25 AVFs created, early thrombosis was seen in 17 cases (17/218[7.79%]).

In a similar study that evaluated 169 AVFs created in patients, early patency was found to be 73.6% and early failure was seen in 26.4% [20]. Also, Ekicei *et al.* [21] reported a 12% early thrombosis rate. This rate is higher than our results. We believe our lower early thrombosis rate is attributed to the use of topical papaverine and use of mechanical dilatation with a probe for spasm of both the veins and the arteries. Therefore, a proportion of early failure can be attributed to technical inadequacy, which can be avoided.

For analyzing the risk factors of early failure or thrombosis of AVFs, the multivariate logistic regression analysis indicated that female sex (OR=3.146, 95% CI 1.662-6.124), age >65 years (OR=3.410, 95% CI 1.541-5.523), diabetes (OR=1.125, 95% CI 0.873-2.576), hypertension (OR=1.411, 95% CI 0.831-3.351) and general anesthesia (OR=1.599, 95% CI 1.184-2.048) were associated with early failure or thrombosis of AVFs. Compared to our results, those of Miller *et al.* [22] showed a lower success

rate in women than in men. Gibbons [23] also reported lower patency rates in women. Previous data represented the fact about the hormonal responses that could in a direct manner help causing the access failure [24].
The influence of gender related to this concept has not been confirmed in some previous studies [21,25]. Also, in the group of patients with different known comorbidities, uremia, hypertension, dyslipidemia, diabetes mellitus etc., susceptibility to accelerated atherosclerosis and presence of a chronic low-grade inflammation, the creation and maintenance of vascular access has become more challenging concept [26,27].
Most often, neointimal hyperplasia and thrombus formation lead to narrowing juxta artery-vein anastomosing area and therefore early arteriovenous fistula failure [28].
The proliferation of smooth muscle cell of media layer in the venous intima is defined as neointimal hyperplasia and real underlying etiology of this process is controversial [29].
Several mediators including basic fibroblast and platelet-derived growth factors mediated proliferation of smooth muscle cell layer [30].
Although some literature reported that diabetes mellitus was one of the factors affecting the primary patency of AVF [31,32], Wolowczyk *et al.* [33] and Ekicei *et al.* [21] found that diabetes had no effect on AVF patency rates. We know that diabetes mellitus leads to impaired immunologic defense, especially cell mediated immunity [34]. Moreover, uremia may create immunosuppressive condition. So, this combination may lead to increased risk for bacteremia and AVF complication in HD patients. AVF patency also depends on the availability of a suitable vein and likewise on the ability of the artery to dilate, the dispensability of the arterial wall being an additional factor [35]. During the primary fistula creation, more vascular dystrophic calcifications of media layer were detected in diabetics and hypertensive patients in this study. More than half of all patients suffered from diabetes and arterial hypertension which were distinguished as independent risk factors associated with a decreased patency rate.
Advancing age in HD subjects cause malnutrition. This condition is a common problem in older dialyzed populations, causing immune defect and facilitating infection and AVF complications.
On the other hand, some other causes including peripheral arterial disease with thickened or even calcified arteries might have impaired fistula maturation [36].
In this study more patients underwent regional anesthesia instead of general anesthesia for vascular procedures. One of such procedures is vascular access for HD patients who usually have high prevalence of coronary artery disease, diabetes mellitus, and hypertension in addition to the ESRD. Similar to previous studies [37,38], we found early failure rate in general anesthesia higher than in regional technique. We believe these results are due to stress of induction and hypotension associated with general anesthesia technique [39].
In the early period following AVF formation, there may be a need for hospitalization or surgical revision due to local complications, including thrombosis, hyperemia, infection, hematoma or hemorrhage [40,41]. The most common complication, early and late, is thrombosis of the fistula [33]. In the present study, 32 complications including early thrombosis, hyperemia, infection, hematoma, and hemorrhage at the incision site, were occasionally observed. Early thrombosis found in 17 cases was a common complication in our study.
Our study was performed at two hospitals as an observational retrospective analysis, and study subjects may have not represented all risk factors in early AVF failure in hemodialysis patients. These limitations should be considered when interpreting the results of our study.

Conclusion

Our rate of AVFs failure is comparable to published reports. Female sex, age >65 years, diabetes, hypertension and general anesthesia have negative effect on AVFs patency.

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Original article

Comparison of Patients Treated with Hemodialysis and Peritoneal Dialysis in Terms of Arterial Stiffness

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Abstract

Introduction. It was our aim to compare volume status, arterial stiffness and anthropometric measurements of patients who were treated with hemodialysis (HD) and peritoneal dialysis (PD) in our study.

Methods. We included a total number of 60 patients, 44 of whom were treated with HD and 16 with PD in both in inpatient and outpatient settings during the period between January 2014 and January 2015. The following parameters were analyzed: age, gender, height, weight, body mass index, triceps skinfold thickness, smoking habit, waist circumference, left atrium diameter, pulse wave velocity (PWV); blood hemoglobin, parathyroid hormone, calcium, phosphorus, albumin levels; comorbidities such as hypertension, diabetes mellitus, coronary heart disease. All data were statistically analyzed by using SPSS, ver. 22. Appropriate statistical tests were used for each analysis.

Results. PWV was higher among smokers ($p<0.01$) and overweight population who has a body mass index higher than 25 ($p=0.027$). Triceps skinfold thickness, serum calcium level, systolic blood pressure values were statistically different among PD and HD groups. PWV, hemoglobin level, left atrium diameter, serum phosphorus, albumin, parathyroid hormone levels, ejection fraction, diastolic blood pressure values were not statistically different among PD and HD groups. When all patients together were evaluated, there were positive correlations between hemoglobin and albumin level, LDL and waist circumference, LDL and triceps skinfold thickness, parathyroid hormone and phosphorus level (p values of :<0,001; 0,004; 0,039; <0,001, respectively).

Conclusions. In our study we found out that PD and HD as renal replacement therapy models did not affect patients volume status and arterial stiffness. In the end-stage renal disease population, patients volume status and arterial stiffness were affected by age and smoking. Further studies including a larger number of patients are needed for clarification of the issue.

Keywords: hemodialysis, peritoneal dialysis, arterial stiffness

Introduction

Chronic kidney disease (CKD) is characterized by progressive decrease in glomerular filtration rate (GFR) which goes parallel with kidney dysfunction for over a period of 3 months because of different pathological mechanisms. According to Chronic Kidney Disease Evaluation and Classification Guideline 2002 prepared by National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI), the definition of CKD is: 1) Occurrence of functional or structural abnormalities in kidney which lasts more than 3 months with or without decline in GFR, 2) Having a GFR<60 ml/ min/1.73 m^2 for more than 3 months with or without kidney damage [1]. Prevalence of CKD is 11% in USA, 10% in Australia, 12% in Taiwan, 13% in China, and 15.7% in adult population in Turkey [2,3]. A number of traditional, novel, and uremia-specific risk factors coexist in CKD and contribute to the increased cardiovascular risk in CKD population [4]. There is no single gold standard test for evaluation of malnutrition in CKD population. NKF/DOQI (National Kidney Foundation/ DOQI) guideline suggests co-evaluation of clinical assessment and biochemical tests [5]. Chronic kidney disease (CKD) is a chronic inflammatory state leading to a postulated 'malnutrition, inflammation, atherosclerosis' (MIA) syndrome in which malnutrition, inflammation and atherosclerosis contribute to an elevated cardiovascular mortality rate [6]. Malnutrition prevalence in CKD population is approximately 18-75 % in hemodialysis patients and 10-50 % in peritoneal dialysis patients [6]. In the majority of patients in the HEMO Study there were protein and energy intake levels below the National Kidney Foundation Kidney Dialysis Outcome Quality Improvement (NKF-KDOQI) guidelines [7]. Various methods are applied to detect malnutrition including anthropometric measurements, serum albumin levels,

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SGA and nPCR [8]. To evaluate body fat composition, triceps and subscapular skinfold measurement can be used [9]. Traditional risk factors of atherosclerosis such as diabetes mellitus (DM), hypertension (HT), dyslipidemia, additionally novel risk factors specific to CKD such as volume overload, oxidative stress, inflammation, malnutrition, uremic toxins contribute to progression of atherosclerosis [10]. Vascular calcification, arterial stiffness, and accelerated atherosclerosis often occur in early stages of renal failure [11]. The augmentation index (Alx) and Pulse Wave Velocity (PWV) are the most important indicators of arterial stiffness [11]. In CKD, arterial stiffness is an indicator of the onset and progression of the atherosclerotic process [12-14]. It was our aim to compare volume status, arterial stiffness and anthropometric measurements of patients undergoing hemodialysis and peritoneal dialysis treatment in our study.

Material and methods

After obtaining approval from the local Ethics Committee of the Izmir Tepecik Health Research and Application Center, 60 patients (on dialysis treatment for at least 6 months) of whom 44 hemodialysis and 16 peritoneal dialysis patients were included in the study. They were registered in the dialysis center of the same hospital between January 2014 and January 2015. Demographic and socioeconomic data, height, weight, body mass index, waist circumference, triceps skinfold thickness (Holtain Skinfold Caliper-98210ND®), comorbidities, smoking habit, hemoglobin (in women 12.2-16.2 gr/dL, in men 14.1-18.1 gr/dL) (Beckmen Coulter® LH 780), parathyroid hormone (15-65 pg/mL), phosphorus (2.7-4.5 mg/dL), LDL cholesterol levels (62-129 mg/dL), calcium levels (8.5-10.5 mg/dL), albumin (3.5-5.5g/dL) (Olympus AO5800), echocardiographic left atrium diameter and ejection fraction percentage were registered in the case data sheet. Pulse wave velocity (PWV), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), mean blood pressure (mmHg), heart rate (/min) values were measured by "Mobil-O-Graph® ARC solver algorithm" device with HMS CS (Hypertension Management System Client Server) software. After all data were collected, they were statistically analyzed using the SPSS, v.22 software (version 22.0, SPSS Inc., Chicago, IL). Nonparametric tests were used for statistical analysis. Statistical differences among the groups were tested with the Kruskal-Wallis test. Data are presented as means, minimum and maximum. If differences were significant, Mann-Whitney U-test was used. P-values <0.05 were considered statistically significant.

Results

In hemodialysis group, there were 20 male and 24 female patients and in peritoneal dialysis group there were 8 male and 8 female patients, which meant a total of 60 examined patients. Twenty-seven patients (45%) were male and 33 patients (55%) were female. Their mean age was 60.8 years. In peritoneal dialysis group

Table 1. Recorded data of all patients

Variable	N	Mean	SEM	Minimum	Maximum
Age (years)	60	60.8	13.7	24	80
Height (cm)	60	161	9.1	143	180
Weight (kg)	60	69	14.5	35	120
Body mass index (kg/m2)	60	26.3	5.3	15.5	46.8
Waist circumference (cm)	60	99.80	17.529	70	174
Triceps skinfold thickness (mm)	60	16.1	7.2	2.6	40
Hemoglobin (g/dL)	60	10.552	1.6219	7.4	13.6
Calcium (mg/dL)	60	8.183	.9944	5.3	10.0
Phosphorus (mg/dL)	60	4.633	1.4998	1.7	7.3
Parathyroid hormone (pg/mL)	60	153.40	59.842	66	310
Albumin (g/dL)	60	3.720	.3424	2.8	4.3
LDL cholesterol (mg/dL)	60	101.00	30.475	26	192
Ejection fraction (%)	60	53.55	8.985	20	65
Left atrium diameter (mm)	60	39.07	3.354	31	48
Systolic blood pressure (mmHg)	60	133.83	26.418	88	199
Diastolic blood pressure (mmHg)	60	78.45	16.309	55	129
Pulse wave velocity (m/s)	60	9.052	2.0378	5.0	14.7

Table 2. Recorded data of patients with classification according to dialysis method

Variable	Peritoneal dialysis group (mean)	Hemodialysis group (mean)
Ejection fraction (%)	56.8	52.3
Left atrium diameter (mm)	39.1	39.05
Systolic blood pressure (mmHg)	151	127
Diastolic blood pressure (mmHg)	86	75
Smoking habit	6 people	13 people
Diabetes Mellitus as comorbidity	8 people	13 people
Coronary Heart Disease as comorbidity	4 people	13 people
Hypertension as comorbidity	14 people	34 people

the mean age of patients was 48.3 years and in hemodialysis group 65.4 years. The mean height of patients was 161 cm; the mean weight was 69 kg and the mean body mass index was 26.3 kg/ m^2 (Table 1) and the rest of the data is shown in Table 2.

Table 3. Variables positively correlated with pulse wave velocity

PWV	Variable	p value
	Age	<0.001
	Calcium level	0.04
	Left atrium diameter	0.04
	Ejection fraction	0.03
	Body mass index	0.05

A positive correlation between pulse wave velocity and age, calcium level, left atrium diameter, ejection fraction, body mass index was detected (Table 3).

There were no correlations between pulse wave velocity and waist circumference, gender, dialysis method, diabetes and hypertension, comorbidities, hemoglobin, phosphorus and albumin level. Pulse wave velocity was significantly higher in smoking group than in non-smokers (p<0.01). Pulse wave velocity was lower in patients with BMI<25 compared to patients with BMI>25. Triceps skinfold thickness, calcium level, systolic blood pressure variables were significantly different in hemodialysis group compared to peritoneal dialysis group Table 4.

Table 4. Variables statistically associated with the dialysis method

Variables	Peritoneal dialysis group mean	Hemodialysis group mean	p value
Triceps skinfold thickness (mm)	20.6	14.5	0.01
Calcium level (mg/dl)	7.7	8.3	0.03
Systolic blood pressure (mmHg)	151	127	0.02

There was no statistically meaningful correlation between peritoneal dialysis group and hemodialysis group in terms of hemoglobin level, pulse wave velocity, left atrium diameter, phosphorus level, parathyroid hormone level, albumin level, ejection fraction, diastolic blood pressure. When all patients together were evaluated, there were positive correlations between hemoglobin and albumin level, LDL and waist circumference, LDL and triceps skinfold thickness, parathyroid hormone and phosphorus level (p values of :<0.001; 0.004; 0.039; <0.001, respectively).

Discussion

Arterial stiffness predicts cardiovascular events in hypertensive, diabetic and healthy population. Aortic pulse wave velocity measurement is the gold standard method to predict arterial stiffness. Arterial stiffness can also be measured based on techniques using brachial, radial, carotid, and femoral arteries. The measurement of arterial stiffness in office is much more beneficial for predicting cardiovascular outcomes beyond risk factors such as age, gender, BMI. Hansen *et al.* showed a strong relationship between aortic PWV and cardiovascular outcomes [15]. In this study it was shown that cardiovascular event risk increased by 16-20 % with 1 standard deviation increase in PWV. In light of previous studies we aimed to compare pulse wave velocity recorded from brachial artery and nutrition parameters, volume status, anemia parameters and social structures of patients from 2 different groups-hemodialysis and peritoneal dialysis patients. London *et al.* showed that age-related increases in PWV were higher in the ESRD group when they were studying 156 hemodialysis patients and 73 healthy controls to prove early arterial aging in ESRD [16]. Akdam *et al.* compared 3 groups of patients: patients diagnosed with stage 3B-5 CKD without dialysis treatment, patients on peritoneal dialysis and healthy individuals. In this study mean PWV was 7.5 m/s, in stage 3B-5 CKD patients, 6.3 m/s in patients on peritoneal dialysis and 5.9 m/s in healthy individuals (10). Detection of lower PWV values in PD and HD patients than predialysis stage 5 CKD patients indicates that dialysis may improve arterial stiffness.

In our study systolic blood pressure was higher in PD group than in HD group. There was no difference of PWV among the 2 groups. Although there was no control

group in our study, there was a strong association between PWV increase and age in both groups (p<0.001). We detected positive correlations between PWV and ejection fraction, serum calcium level and left atrium diameter (p values: 0.05, 0.04, 0.03, respectively).

Tsai *et al.* showed that PWV recorded from brachial artery was inversely related to estimated GFR. PWV is much higher if CKD and metabolic syndrome are combined. Without CKD diagnosis, PWV recorded from brachial artery was positively associated with age, BMI, systolic blood pressure, diastolic blood pressure, fasting plasma glucose level, triglyceride level, HDL cholesterol and hs-CRP level [17]. Metabolic syndrome (MS) is common in peritoneal dialysis patients [18]. There is an increase in arterial stiffness parameters in PD patients with MS. Increase in proinflammatory cytokine levels, decrease in nitric oxide and adiponectin levels may contribute to increased arterial stiffness by accelerating the process of atherosclerosis in PD patients with MS [18]. It has been well-defined that obesity is associated with increased vascular stiffness in previous studies. Individuals with obesity can reverse this increase in vascular stiffness by losing weight. Thus, weight control can improve insulin sensitivity and help prevent CVD. However, some studies suggest that overweight and obese people have a better prognosis in heart failure, hypertension, end-stage renal disease and mortality than normal weight individuals [19]. This phenomenon has been described as the obesity paradox. BMI may not be the most accurate index for obesity, since visceral adipose tissue and ectopic fat accumulation play an important role in the development of insulin resistance independently of total body fat mass. It has been suggested that triceps skinfold thickness may be indicative of arterial stiffness in hypertensive patients [19]. In our study, although the mean skin fold thickness value of the peritoneal dialysis group was higher, there was no higher PWV value compared to the hemodialysis group. Overall, there was a positive correlation between PWV and BMI when all patients were included.

Mikolasevic *et al*. followed 129 hemodialysis patients for 6 months. During the study, nutritional status was evaluated at three and six months by using values such as dry weight, BMI, triceps skinfold thickness, serum albumin and cholesterol levels. As a result, triceps skinfold thickness was statistically positively correlated with BMI, dry weight, mid-arm circumference, serum albumin and cholesterol levels [20]. The authors suggest that measuring triceps skinfold thickness by caliper is a relatively quick and inexpensive method that can be used to assess the nutritional status in hemodialysis patients. In our study, triceps skinfold thickness was higher in peritoneal dialysis group (p=0.01). Albumin level was not correlated with triceps skinfold thickness. However, the triceps skinfold thickness measurement and mean BMI values of the PD group were higher than in the HD group.

Raggi *et al*. found that abdominal aorta X-ray calcium scores were associated with PWV after multivariate adjustments in a study with 131 hemodialysis patients [21]. The presence of aortic calcification on plain radiographs may indicate increased arterial stiffness. In our study we discovered a positive relationship between serum calcium level and PWV in both groups (p=0.01). The main purpose of our study was to determine and compare arterial stiffness and volume status in both hemodialysis and peritoneal dialysis patients. When we compared the two groups in terms of these variables, we could not find any relation between dialysis method and PWV and volume status. Systolic blood pressure was significantly higher in peritoneal dialysis group than in hemodialysis group. It may be an indirect sign of inadequate ultrafiltration rate in the peritoneal dialysis group. As a possible indicator of nutritional status, triceps skinfold thickness was higher in the peritoneal dialysis group. However, as a limitation of our study, the mean age of the peritoneal dialysis group was 48.3 years whereas the mean age of the hemodialysis group was 60.8 years. The relative low PD patient count is another limitation of our study. In general, patients with a BMI less than 25 and non-smokers clearly have less PWV. Weight and smoking were considered to be risk factors for having a higher PWV.

Arterial calcification (AC) is a paramount complication of CKD-mineral bone disorder, which may increase arterial stiffness and CV risk [22]. MIA has been suggested as a new risk factor for AC [22]. When MIA, AC, and arterial stiffness (AS) are evaluated together, it can be assumed that AS parameters may be potential and possible markers of MIA and AC.

Conclusion

In our study we discovered that peritoneal dialysis or hemodialysis itself alone did not affect volume status and arterial stiffness of patients. Arterial stiffness was affected by multiple variables such as age, smoking habit, metabolic syndrome, presence of comorbidities in patients diagnosed with ESRD. New studies are needed to clarify this issue.

Conflict of interest statement. None declared.

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Short communication

Vancomycin Dosing in Low Flux Hemodialysis: Is Adjustment of Drug Dosage Necessary?

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Abstract

Introduction. Vancomycin is a widely useable antibiotic against Gram-positive bacterial species in different clinical settings, particularly in hemodialysis patients; however, maintaining its optimal therapeutic serum level is necessary in such patients with the purpose of maximizing its efficacy and minimizing its toxicity. The present study aimed to assess the serum level of vancomycin before and after hemodialysis.

Methods. This cross-sectional study was performed in patients who were hospitalized and medicated by vancomycin with the loading dose of 1000 mg followed by the maintenance dose of 500 mg after each dialysis session every other day. All patients were dialyzed with a low-flux dialyzer membrane. Half an hour before and immediately after dialysis, 2 ml blood sample was taken and stored at -20°C until assaying the level of vancomycin.

Results. The average reduction in the serum level of vancomycin was totally 17.65±1.69% (ranged from 12.43% to 21.56%). The mean reduction in the serum level of vancomycin was significantly higher in patients aged higher than 60 years as compared to older ones (17.95% versus 16.90%, p=0.035). But, the level of drug was independent to gender or body mass index.

Conclusion. By using low-flux dialyzer membranes, the average reduction in the serum level of vancomycin is expected to be in the range of 12.43% to 21.56%. This reduction may significantly change by increasing age and thus adjusting and monitoring the serum level of drug in old ages even in the cases of using low-flux dialyzer membranes is recommended.

Keywords: vancomycin, hemodialysis. renal failure, drug toxicity

Introduction

Vancomycin is a wide useable antibiotic against Gram-positive bacterial species in different clinical settings, particularly in hemodialysis patients [1]. In fact, because of high incidence of stenting-related bacterial infections, following vascular accessing, vancomycin is widely used in hemodialysis patients. This antibiotic is excreted by kidneys and thus its renal clearance as well as its therapeutic plasma level should be monitored accurately, in patients who are candidates for hemodialysis, especially in those who receive high-flux hemodialysis [2-6]. According to the common clinical approaches, this drug should be administered with a loading dose of one gram following dialysis or within the last hour of each session of dialysis followed by administrating maintenance dose of the drug in the range of 0.5 g to 1.0 g after dialysis [5]. By this approach, the level of vancomycin is maintained between 5 -20 μg/ml in most of the patients; however, it may be leveled lower than 10 μg/ml in about 30 to 40% leading to antibiotic treatment failure [8,9]. It can especially occur on highly permeable dialysis membranes that results in high clearance value of this drug by the kidneys in these patients. In such situations, therapeutic and non-toxic vancomycin levels were recommended to be obtained by giving 1000 mg of vancomycin, intravenously, as a loading dosage and 500 mg during every subsequent dialysis to achieve optimal drug efficacy as well as appropriate drug clearance [10]. Moreover, increasing cumulative dosages of drug in those patients with renal failure due to the failure of renal clearing process in nephrotoxicity may be predictable, leading to high drug toxicity rate [11]. The present study aimed to assess the serum level of vancomycin before and after hemodialysis. In other words, we determined the therapeutic dose of drug and its main determinants in patients undergoing hemodialysis.

Materials and methods

This cross-sectional study was conducted at Dialysis wards in Rasoul-e-Akram Hospital, between April and December 2015, in patients who were hospitalized and medicated by vancomycin with the loading dose of 1000 mg followed by the maintenance dose of 500 mg after each dialysis session every other day. This study was approved by the Ethics Committee of the Iran University of Medical Sciences. Informed consent was obtained

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from all patients or their families. Human rights were respected in accordance with the Helsinki Declaration.
All patients in our study aged over 18 years who suffered from end-stage renal disease required hemodialysis three times a week (every session from 3.5 to 4.0 hours). The subjects received vancomycin therapy due to prophylaxis protocol or to definitive diagnosis of bacterial infection; dialysis were performed with a filter of a 1.3 m2 surface area by low-flux dialyzer membrane (PS13 LF, editechsys Co, Tehran, Iran). The baseline characteristics including demographics, body mass index (BMI), underlying disorders that led to end-stage renal disease (diabetes mellitus, hypertension, or other diseases), the type of renal disease requiring dialysis (acute or chronic kidney injury), drug history (categorized as nephrotoxic or non-nephrotoxic medications), the time of receiving vancomycin, and blood access of dialysis (catheter or fistula) were extracted from hospital files and entered into the study checklists. Half an hour before and immediately after dialysis, 2 ml blood sample was taken and stored at -20°C until assaying the level of vancomycin. According to the protocols, the therapeutic range of vancomycin was considered to be 10-20 mg/L.
Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was analyzed using the Kolmogorov-Smirnov test. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5 were observed. Quantitative variables were also compared with t-test or Mann-Whitney U test. For the statistical analysis, the statistical software SPSS, version 16.0 for Windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results

In total, 55 patients (33 men and 22 women) were assessed. Of those, 70.9% were older than 60 years and 7.2% were obese (BMI>30 kg/m^2). Regarding underlying disorders leading to end-stage renal disease, 20% suffered from diabetes mellitus type II, 38.0% were hypertensive, and 42.0% suffered from other diseases. Overall, 78.2% suffered from chronic kidney disease undergoing chronic hemodialysis, while 21.8% were affected by acute kidney disease and 10.9% had received nephrotoxic drugs simultaneously with vancomycin. Regarding the dose of vancomycin, 9.1% received the first dose, 12.7% received the second dose, 65.4% received the third dose, and 12.7% received the fourth dose of vancomycin. Of 55 patients assessed in the present survey, 16.4% had fistula and 83.6% had catheter as vascular access (Table 1).
The average reduction in the serum level of vancomycin was 17.65±1.69% (ranged from 12.43% to 21.56%) (Table 2). There was no difference in the average reduction in the level of vancomycin between men and women (17.86% versus 17.33%, p=0.256), but it was significantly higher in patients aged over 60 years as compared to older ones (17.95% versus 16.90%, p=0.035). Also, no difference was revealed in the mean reduction of the level of drug between obese and non-obese patients (17.76% versus 17.64%, p=0.891) (Table 3). Of 55 patients assessed in the study, the post-dialysis serum level of vancomycin maintained at the therapeutic range (10-20 mg/L) in 53 patients (96.4%) and thus

Table 1. Baseline characteristics of study population

Gender	
Male	33 (60.0)
Female	22 (40.0)
Age	
More than 60 years	39 (70.9)
Less than 60 years	16 (29.1)
Body mass index	
Higher than 30 kg/m^2	4 (7.27)
Lower than 30 kg/m^2	51 (92.72)
Underlying disease	
Diabetes mellitus	11 (20.0)
Hypertension	20 (38.0)
Other	24 (42.0)
Type of kidney injury	
Chronic	43 (78.2)
Acute	12 (21.8)
Receiving nephrotoxic drugs	6 (10.9)
Dose of vancomycin	
First	5 (9.10)
Second	7 (12.72)
Third	36 (65.45)
Fourth	7 (12.72)
Vascular access	
Fistula	9 (16.36)
Catheter	46 (83.64)

Table 2. Average percent reduction in serum level of vancomycin before and after dialysis in patients, using low-flux polysulfone membranes 13

Average	17.6515
Mean	17.79
Standard deviation	1.69
Minimum	12.43
Maximum	21.56

Table 3. Average reduction in the serum level of vancomycin

	Average reduction	**P-value**
Gender		
Male	17.86	0.256
Female	17.33	
Age		
More than 60 years	17.95	0.035
Less than 60 years	16.90	
Body mass index		
Higher than 30 kg/m^2	17.76	0.891
Lower than 30 kg/m^2	17.64	

adjusting the dose of drug was required for only 3.6% of patients.

Discussion

According to the literature, the most important factor affecting the reduction of the level of vancomycin in hemodialysis patients was the type of dialysis membrane. The use of high-flux membranes might lead to an average reduction of 35% to 50% in the level of vancomycin [12]; thus, adjustment of drug dosage is essential to avoid antimicrobial treatment failure. In contrast, the average reduction of the level of vancomycin in low-flux membranes was shown to be about 17% without need to following an especial protocol for adjusting drug dosage [13]. According to our survey in which we used low flux, the average reduction in the serum level of vancomycin was revealed to be 17.6%. It was comparable with previous reports, indicating no need to adjust the dose of vancomycin during dialysis with low-flux membrane. Of baseline variables, only age was directly associated with average reduction of vancomycin level. Hence, lowering level of drug could be predictable in older patients, while the reduction of the level of drug was completely independent to gender or BMI. In other words, the likelihood for reducing drug level in the serum can increase in older ages and consequently need for controlling titration of drug dosages may be required in old ages, even after using low-flux dialysis membranes. Overall, it seems that using a vancomycin dosing nomogram in conditions when high-flux membranes are used or in older adults that are planned for low-flux membranes can significantly improve and accelerate the achievement of target trough concentrations [14]. As a rule, vancomycin is not significantly dialyzable when hemodialysis is performed using a low flux membrane, while vancomycin is dialyzable when hemodialysis is performed using a high flux membranes [15]. However, except for the potential effects of the type of the membrane, other probable confounding factors should be considered. Based on the results obtained in our study, older age is a main factor that affects the clearance of vancomycin. As indicated in previous studies, preexisting renal impairment and concomitant therapy with other nephrotoxic agents should also be considered as potential confounders that may affect the efficacy of the drug in dialysis patients. For instance, as presented in the literature, the accepted incidence of nephrotoxicity secondary to vancomycin monotherapy is <5%, but it increases to 43% in patients receiving concomitant nephrotoxic medications [16]. In other words, considering concurrent use of nephrotoxic agents is vital because it may lead to increased vancomycin toxicity synergistically; thus, adjusting the dose of vancomycin in these conditions is potentially required. As a total rule, for vancomycin therapy to be optimal, adequate trough concentrations of vancomycin should be maintained and elevated peak concentrations especially in older ages, as well as concomitant use of nephrotoxic drugs should be avoided. Therefore, routine monitoring of vancomycin in all conditions, in which high-flux membranes are applied or other nephrotoxic agents are used, should be planned. As an important point, in cases when low-flux membranes are used, drug dosage monitoring should also be considered in older adults.

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This study was approved by the Ethics Committee of the Iran University of Medical Sciences. Informed consent was obtained from all patients or their families. Human rights were respected in accordance with the Helsinki Declaration.

Conflict of interest statement. None declared.

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Short communication

Theoretical Model of Back Filtration for Acute Tubular Obstruction in Oliguric/Anuric Acute Kidney Injury

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Abstract

Introduction. It is a very common clinical observation that cardiogenic and septic shocks as well as acute tubular damages result in anuria and acute kidney injury. This condition is associated with high mortality. The model was developed to protect the kidneys from acute damages and recover to its partial functional potential.
Methods. The governing equations by the renal modelers across the world for renal function, which include glomerular and tubular functions, were studied. A theoretical model for a single kidney was developed based on the governing equations.
Results. The single nefron glomerular filtration rate (SNGFR) can be modified by transient occlusion. The backpressure transiently reduces filtration, however, the permeability (k) and surface area (S) of the filtration and nephron recruitment (n) increases. By altering the chloride levels (Σ) in the macula densa the tubuloglomerular feedback (g) and the afferent arteriolar diameter can be modified or dilated. By increasing the back diffusion, the hydrostatic pressure and the diameters of the ascending as well the descending tubular sizes can be increased. By altering the pH of the back diffusion fluid, the obstructed tubules can be opened. By addition of proteolytic enzymes the inflammasomes and inflammatory proteins could be modified or degraded and the tubular recovery may be achieved. By increasing the back diffusion pressure to hydro-nephrotic range the glomerular filtration pores could be cleansed and opened. Hence, the final model is transient pulsatile occlusion of the pelvicalyceal ureter and back diffusion by fluids of low chloride and pH near 5.5, and pressure of about 30 mm Hg with proteolytic enzymes in the fluids. The proposed time for occlusion of the ureter could be about 5 to 6 min.
Conclusions. There is potential for a novel back-diffusion method for the recovery of anuric or oliguric kidneys. Further experiments need to be performed in animal models to prove the concept.

Key words: back diffusion, acute renal failure, mathematical models

Introduction

Acute renal shut down due to shock syndromes is often seen in clinical practice [1]. The etiology leading to this condition resulting in anuria is varied. It could be pre-renal causes, renal glomerular or tubular obstructive pathologies. Septic shock syndromes [2] and cardiogenic shock disorders [3], though the pathogenesis is different, frequently lead to oliguria/anuria, which could result in fatal outcomes. Snakebite with hemolytic disorders leads to tubular obstruction and anuria or oliguria. Drug/contrast-induced renal failure leads to renal tubular obstruction. A recovery of this oliguria renal failure is difficult with supportive therapy with optimal fluids, diuretics, and dialysis if required. Inotropes are frequently required to correct associated hypotension. High mortality is observed in these scenarios irrespective of the etiology leading to oliguric renal failure. Hence, in this study a novel treatment is proposed by following the existing governing equations in renal function.

The model of back filtration in acute kidney injury

Acute renal failure due to various etiologies results in tubular obstruction and restriction in the glomerular filtration process. The various etiologies often lead to activation of inflammatory cascade through inflammasomes, and a variety of proteins are synthesized in the tubules, and also the ultrafiltrated inflammatory proteins tend to occlude the glomerulus and the tubules [4-6]. Heat shock proteins also play an essential role in acute kidney diseases [7]. A search was made for mathematical modeling of renal physiology and transport, and the governing equations were studied [8-13].
A model is proposed for this condition, which could eventually reduce the renal failure or relieve the oliguria. The normal pelvic pressure is about 7 to 13 cm of water, and in hydronephrosis, it reaches about 20 to 30 cm of water or more. Hence, raising the pressure to about 23 mm Hg or 30 cm of water would result in hydronephrosis and functionally it induces back diffusion in the nephrons [14-16].

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The concept is a transient occlusion for about 5 to 6 min. of the ureter of the unilateral kidney, which could result in back diffusion, which is similar to the hydro-nephrotic range of changes. Also, a device design has been proposed which could have mechanisms of perfusion in the distal end of the catheter. Figure 1 shows the proposed device method and the possible variations that can be done with this simple balloon catheter system. The proximal end of the catheter is located near renal pelvis with perforations in the distal end of the catheter. The proximal end of the catheter can be connected to a pressure controlled by the system. The pressures and the pulses of applied pressures can be altered.

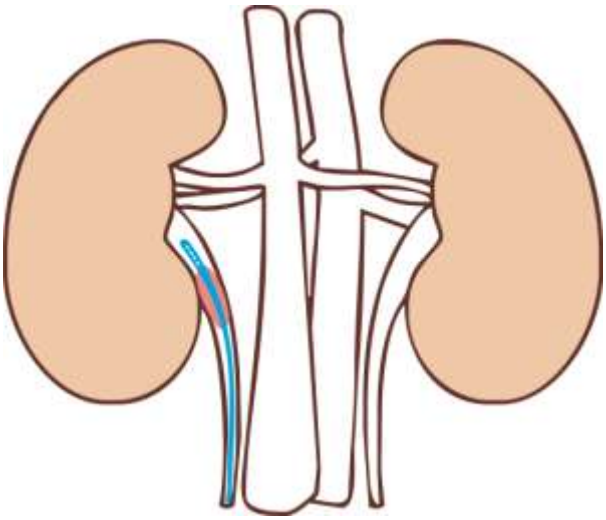

Fig. 1. Proposed model of balloon catheter with perforations at the tip for fluid infusion and pressure transmission

A balloon, located in the distal tip which could be inflated, and the pressure in the renal pelvis could be increased to the hydro-nephrotic range which is usually about 20 mm Hg. When the renal pelvic pressure increases to 23 mmHg (30 cm of water) hydro-nephrotic changes in the glomerulus and the tubules can be introduced, which is dilatation of the tubules and the globular apparatus. By pulsatile application of the pressures, the effects in the renal tubules and the glomerulus can be more exaggerated than the constant non-pulsatile application of pressures through the proposed catheter model. A pulsatile model has advantages over a continuous flow model [17]. This has been consistently observed in the left ventricular assist devices, which perform better with pulsatile characteristics. This is due to reduced wall shear stress ($\delta p/\delta y$) and the pressure in the center of the lumen ($\delta p/\delta x$) is higher compared to the continuous flow methods, in which the pressure dynamics is vice versa. However, the pulsatile design is not mandatory as the fluid is applied in lower pressure, unlike left ventricular assist devices, which function at higher pressures.

The single nefron glomerular filtration rate (SNGFR) would be modified by this transient occlusion. The back-pressure transiently reduces filtration due to higher glomerular pressures, however, the permeability (k) and surface area (S) of the filtration and nephron recruitment (n) increase. The chloride levels highly control the tubule-glomerular feedback, which has a major role in renal auto-regulation. By altering the chloride levels in the macula densa the tubuloglomerular feedback (γ) and the afferent arteriolar diameter can be modified or dilated. When the chloride levels are reduced in the back diffusion, fluid afferent arteriolar vasodilatation could be achieved.

When the back diffusion is increased further, it could result in tubular injuries. The time frame of 5 to 6 min. is suggested as prolonged pressures can result in damage to the ureters or the pelvicalyceal junction. It has to be emphasized that this model is proposed to be used in one kidney.

Acidification is a known technique to denature proteins. Acidification of the fluid used to perfuse the nephrons with back diffusion can result in denaturation of the obstructive proteins in the tubules [18,19]. Normal pH of the urine is in the range of 5 to 8 [20,21]. A pH of about 5.5 is physiologic, and it would result in acidification of obstructive proteins in a milieu of tubular obstruction induced by the inflammasomes and ultrafiltrated proteins.

Increasing the temperature of the back diffusion fluids to the upper limit of physiological milieu, for example, 39 to 40C, could further accelerate the lytic changes in these proteins [22-24]. This is a usual technique observed for denaturation of proteins. However, a very high increase in temperature could lead to release of heat shock proteins in the tubular podocytes. Hence, a safe temperature limit has to be determined by experimental studies.

Adding specific proteolytic enzymes in appropriate/diluted doses can disrupt the tubular obstruction, and it can even disrupt or dissolve the deposits beneath the glomerular membranes. Pepsin and trypsin are powerful proteolytic enzymes, which are well known for their proteolytic activity [25-28].

This proposed model could be used for a wide range of etiologies causing this condition. Hence, it is necessary to investigate this concept for further analysis. Conversion of this oliguria to non-oliguric renal failure has a significant therapeutic advantage in a critically ill patient, and if the modeling works in real-time patients, it will have a significant therapeutic benefit and lifesaving. This will have mortality benefits and reduction in the hemodialysis or development of chronic renal failure in the future. The catheter model is simple and practical, and it is easy to design this balloon-catheter device. At this moment, it is a theoretical proposal, which needs to be validated with animal models after creating an oliguria renal failure. Also, as a therapeutic measure it is proposed in only one kidney in the initial stages, and if successful results are obtained in the experiments, bilateral interventions could be tried to recruit more functional nephrons.

Conclusion

This novel method has a potential to induce transient back diffusion in the anuric kidney for recovery of renal function as a theoretical method. Further experiments need to be performed in animal models to evaluate the clinical benefits of the proposed technique.

Conflict of interest statement. None declared.

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Case report

Renal Artery Thrombosis Due to Paroxysmal Atrial Fibrillation in a Patient with Multiple Thrombosis History

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Abstract

Atrial fibrillation (AF) is the most common persistent cardiac arrhythmia. When left untreated, atrial fibrillation often causes systemic embolization. We present a case of multiple thrombosis possibly associated with paroxysmal atrial fibrillation presenting with abdominal pain and renal artery thrombosis.

Keywords: renal artery thrombosis, atrial fibrillation, embolization

Introduction

Atrial fibrillation is the most common persistent cardiac arrhythmia and the lifetime prevalence is approximately 25% [1]. Atrial fibrillation is associated with a 3 to 4-fold increased risk of ischemic stroke and a 2-fold increased risk of death [2]. Known risk factors for atrial fibrillation include advanced age and age-related diseases such as hypertension, myocardial infarction and heart valve disease [3]. It is expected that the prevalence of atrial fibrillation will increase about 2 times in the 2010-2060 period, following the ongoing demographic change and improvement in survival in western societies, as well as the predisposition to heart diseases such as myocardial infarction [4]. Atrial fibrillation is an important public health problem and it is increasingly important to determine the risk of cardiovascular complications targeting preventive strategies [5]. Atrial fibrillation or flutter (AFF) creates an intra-atrial stasis with the potential to cause thrombus formation and embolization [6].

AFF has been associated with increased risk of other arterial and venous events beyond increasing ischemic stroke risk [7]. The patient was an 81-year-old woman with a past medical history remarkable for myocardial infarction, cerebrovascular disease and mesenteric ischemia who was referred to the Internal Medicine Clinic with a chief complaint of worsening abdominal pain.

Case Report

An 81-year-old female patient was admitted to the emergency room due to abdominal pain which started 3-4 days before, was not associated with food, and became increasingly severe. The patient was transferred to the Internal Medicine Clinic for workup of severe abdominal pain. The patient's past medical history was significant for an operation history associated with mesenteric ischemia, myocardial infarction, cerebrovascular disease. She was also treated with clopidogrel. On physical examination, the general condition of the patient was moderate, conscious open, cooperative. The patient was oriented to time and place. Vital signs revealed a blood pressure of 110/70 mmHg, a regular pulse of 76 bpm and a temperature of 36.2°C. The abdomen was non-tender. ECG (electrocardiography) showed normal sinus rhythm. The patient's admission labs were significant for creatinine of 1.1 mg/dl, hemoglobin of 13 gr/dl, white blood cell count of 18,000 mm3 and LDH of 1051 ul. The rest of the lab tests were as follows: PLT: 264.000/ul, urea: 26 mg/dl, creatinine: 1.1 mg/dl, glucose: 122 mg/dl, Na: 140 mmol/l, K: 3.86 mmol/l, Ca:9.3 mg/dl, AST:30 U/l, ALT:17 U/l, lipase: 16 U/l. Routine urine analysis was normal. An echocardiogram was performed that reveale normal chamber sizes. Defense and rebound findings were not detected. Right costovertebral region was slightly sensitive on palpation. Abdominal ultrasonography scan was normal. Abdominal angio-CT (computed tomography angiography) was performed for abdominal pain etiology. In angio-CT, hypoperfusion was found in more than 50% of the right kidney, and the distal end was found to be thrombosed when the right main renal artery was open (Figure 1).

SMA (superior mesenteric artery) was detected in a thrombosed appearance after 3 cm from the initial segment. The splenic artery was open but the spleen had

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an infarct area secondary to distal microthrombosis. Celiac truncus, IMA (inferior mesenteric artery) and left renal artery were patent and no stenosis was detected. The patient with renal artery thrombosis was admitted

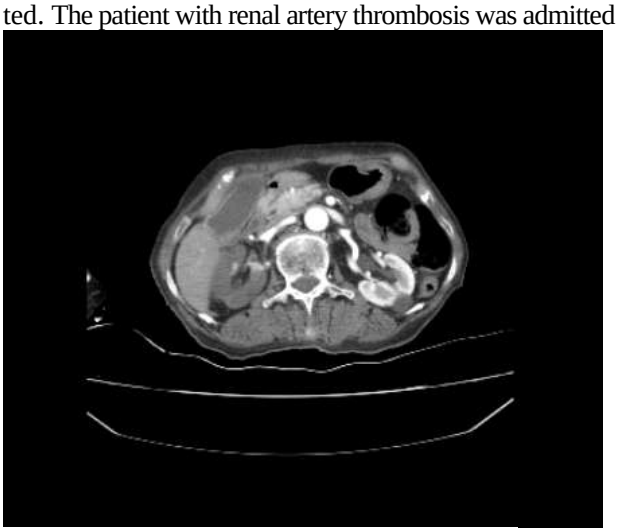

Fig. 1. Distal end thrombosis of right renal artery and hypoperfusion of right kidney

to the Internal Medicine Clinic for examination and treatment of the etiology of multiple thrombosis. A consultation was requested from the Interventional Radiology Clinic for thrombi formed in the renal arteries and branches. As the first 24-hour time limit for intra-arterial thrombolytic therapy was exceeded, no intervention was considered for the patient. Low-molecular-weight heparin therapy was initiated with clopidogrel therapy discontinued. PNH (paroxysmal nocturnal hemoglobinuria) panel, autoimmune markers and lupus anticoagulants, tumor markers for malignancy and imaging studies were requested for pathologies that may produce thrombosis susceptibility. No pathology was found in the requested examinations. Medical Genetics Department was consulted for clopidogrel insensitivity. Blood sample was sent for *CYP2C19* genotyping, which is responsible for clopidogrel metabolism. No evidence of clopidogrel resistance was detected in the gene analysis. A 24-hour ECG monitor (Holter ECG) was performed in the patient without documented cardiac arrhythmia, in terms of paroxysmal atrial fibrillation (PAF). Frequent atrial and ventricular premature beats and atrial fibrillation was detected in 2 times in Holter ECG. The patient was discharged after direct-acting oral anticoagulant (Dabigatran 110 mg 2x1) was initiated for PAF.

Discussion

The patient's past medical history did not include any cardiac rhythm disturbances. Although there were no known arrhythmia and documented AF in our case, 2 times AF was detected in the Holter ECG. AFF is associated with increased myocardial infarction, peripheral embolism, hemorrhagic stroke, and venous thromboembolism within 1 year, especially during the first 30 days after AFF, as well as being a risk factor for ischemic stroke [8]. The incidence of peripheral thromboembolic events associated with AFF is lower than the incidence of cerebrovascular thromboembolic events [8]. This is thought to be due to the fact that the majority of cerebral arteries are functional end-arteries, whereas many other arterial occlusions are protected by collateral circulation [9]. In our patient with renal artery thrombosis who had multiple thrombosis, no pathology was detected in terms of hypercoagulability, hematologic, oncologic and rheumatologic parameters and examinations which may cause thrombosis tendency. Cardiac causes were investigated in terms of thrombosis etiology, and echocardiography and ECG showed no pathological findings. In 1 of 20 acute stroke patients, AF was defined with systemic ECG monitoring [10]. This rate is much greater than that established by standard 12-lead electrocardiography (ECG) recordings. AF may remain undiagnosed for a long period of time (silent AF) and many patients with AF are not admitted to the hospital [10]. For this reason, the true prevalence of AF is likely to be close to 2% of the population [10]. Despite the absence of known arrhythmia and documented AF in our patient, two episodes of AF in the Holter ECG were detected. AFF is associated with an increased risk of developing cerebrovascular and peripheral thrombosis. As in our case, patients with multiple and recurrent thromboses should be evaluated with a Holter ECG and PAF should be kept in mind even if AFF is not detected with standard ECG. The differential diagnosis is expansive; however the presentation contains several clues to help focus the clinician's further evaluation. This case illustrates the importance and the value of Holter ECG in the evaluation of a patient with multiple and recurrent thrombosis. The patient manifests as a collection of findings highly suggestive of renal artery thrombosis due to paroxysmal atrial fibrillation.

Conflict of interest statement. None declared.

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Case report

Rare Coagulase Negative Staphylococci May Cause Peritoneal Catheter Loss

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Abstract

Introduction. Members of *coagulase negative staphylococci* family (CNS) may cause peritonitis frequently in CAPD patients. *Staphylococcus lugdunensis* and *Staphylococcus warnerii* are members of this family. They are generally believed to be easily treated based upon having lower virulence. However, they may cause severe peritonitis resulting in technique failure.
Case presentation. We present 3 CAPD patients suffering from peritonitis. The first patient presented with two peritonitis episodes. The organism was isolated as *Staphylococcus Lugdunensis*. The second patient presented with *Staphylococcus Warnerii* peritonitis but could be treated successfully. The third patient presented with three peritonitis episodes arising from *Staphylococcus Warnerii.* The infection could be controlled by antibiotherapy only in one of our patients. The other patients lost their peritoneal catheter.
Conclusions. *S. Warneri* and *S.Lugdunensis* are known to have the ability to form biofilm over peritoneal catheters. Two of our patients infected with these bacteria were transferred to hemodialysis. Hence, these bacteria should be accepted as having the potential to cause technique failure if they are ignored.

Keywords: peritoneal dialysis, peritonitis, technique failure

Introduction

Peritonitis is a common complication of peritoneal dialysis. It may cause peritoneal fibrosis, ineffective dialysis and catheter loss. It may also cause death if arising from antibiotic resistant organisms. Diagnosing the offender agent rapidly and starting proper antibiotics is crucial. We had 2 uncommon organisms isolated from peritoneal cultures of 3 peritonitis patients recently.
Dialysis fluid samples were aspirated by our specialist continuous ambulatory peritoneal dialysis (CAPD) nurse by an aseptic technique and delivered to our microbiological laboratory in 30 minutes. Leukocyte count was performed by Nageotte Brightline hemacytometer. Giemsa and Gram staining were performed to the dialysate specimencs. Approximately 5 cc dialysate was inoculated in a BACTEC BacT/ALERT (BIOMERIEUX, INC. Durham) and %5 sheep blood and Eosin-Methylene blue agar. After 24 hours of inoculation cultures were controlled. Identifications were determined using the Vitek2 system (bioMeriux SA, France).

Case report 1

A 56-year-old female had end-stage renal disease (ESRD) due to chronic tubulo-interstititial nephritis. She was on CAPD for twelve months. She was admitted to our clinic with decreased ultrafiltration of 3 days. There were 19200/mm^3 leukocytes, %90 as polymorphonuclear leukocytes (PNL) in the peritoneal fluid sample. Her leukocyte count was 5850/mm^3, 64% as PNL on hemogram. Serum CRP was 54 mg/L. Cefazolin and ceftazidime antibiotherapy was started empirically. *S. Lugdunensis* was isolated from the peritoneal culture on the 3th day. Ceftazidime was stopped as it was sensitive to methicllin. The peritoneal leukocyte number was 40/mm^3 and CRP value was 22 mg/L on the 3th day. The following peritoneal fluid cultures were negative. The antibiotherapy was stopped on the 14th day.
She was admitted again with abdominal pain and fatique after trouble-free 4 months. No rebound tenderness was present. She had recognized that her peritoneal effluent was cloudy for 2 days. 1320 leukocytes were detected on peritoneal fluid leukocyte count. 90% of the leukocytes was PNL. Her leukocyte count was 5850/mm^3, 64% as PNL on hemogram. Serum CRP was 77 mg/L. Emprical cefazolin and ceftazidime was introduced. Once again *S. Lugdunensis* was isolated from the peritoneal culture. It was methicillin-sensitive. Ceftazidime was stopped. Catheter wipe sample culture was obtained on

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the 2nd day. *S.lugdunensis* was identified also on this specimen. There were no concomitant dermal infections as an additional risk factor. In addition, any exit-site or tunnel infection was not detected with serial and detailed examinations. Her peritoneal fluid leukocyte count was 160/mm^3 and CRP was 4 mg/L on the 3th day. Cefazolin monotherapy ensured healing succesfully with 12/mm^3 peritoneal fluid PNL on the 14th day. The following cultures were negative. Peritoneal catheter was removed because of obstruction with fibrinous material leading to ultrafiltration failure 2 months later.

Case report 2

A 57-year-old man was on CAPD due to ESRD for 3 years. He was admitted with abdominal pain, nausea and vomiting of 2 days. His peritoneal dialysis fluid was cloudy. Microscopic examination of the fluid showed 2240/mm^3 leukocytes, 90% as PNL. His leukocyte count was 11460/mm^3, 79% as PNL on hemogram. Serum CRP was 72 mg/L. Cefazolin and ceftazidime was introduced emprically. *S. Warnerii* was isolated from the peritoneal fluid culture on the 2nd day. The fluid culture that was inseminated into the blood culture bottle was also positive for *S.Lugdunensis*. As a result this organism was accepted as the offender agent. Ceftazidime was stopped because the detected organism was methicillin-sensitive. No concomitant dermal infection, exit-site or tunnel infection were detected as additional risk factors. The following cultures were negative. CRP fell to 8 mg/L and peritoneal leukocyte count fell to 24/mm^3 on the 6th day. He was cured completely on the 10th day.

Case report 3

A 43-year-old male was on CAPD for 6 years. He had ESRD secondary to hypertension. He was admitted to our clinic with cloudy peritoneal fluid of 1 week. There were 2400/mm^3 leukocytes, %90 as PNL in the peritoneal fluid. Serum CRP was 64 g/L. His leukocyte count was 7200/mm^3, 62% as PNL on hemogram. Cefazolin and ceftazidime was introduced empirically. Peritoneal culture was negative. The peritoneal leukocyte count fell to 48/mm3 on the 3rd day. The last peritoneal leukocyte count was 4/mm^3 and CRP value was 3.3 g/L on the 10th day. As a result, the antibiotherapy was stopped.
He was admitted with intermittent cloudy peritoneal fluid after trouble-free 2 months. He described intermittent cloudy peritoneal fluid after his last discharge from the hospital. On microscopic examination, there were 560/mm^3 leukocytes, %90 as PNL. Serum CRP was 11 mg/L. Emprical piperacillin-tazobactam was started for its anti-pseudomonal efficiency, as he had recent hospitalization history. Culture results were negative the first days. Then liquid nutrient broth was used and we were able to detect the organism. The organism that grew on peritoneal fluid culture was methicillin-sensitive *S. Warnerii*. It was accepted as the culprit organism. Peritonitis was treated succesfully with piperacillin-tazobactam monotherapy. Peritoneal leukocyte count was 16/mm^3 and CRP value was 9 mg/L on the 6th day. The following peritoneal fluid cultures were negative. Antibiotherapy was stopped on the 14th day.
He was called for cadaveric renal transplanatation as the first patient of the waiting list 5 months later. He had no complaints. Nevertheless, he declared intermittent cloudy peritoneal fluid occasionally after his 2nd peritonitis treatment. Microscopic examination of the fluid revealed 680/mm^3 leukocytes, 80% as PNL. Serum CRP was 20 mg/L. Leukocyte count was 6800/mm^3, 63% as PNL on hemogram. He was started to empirical cefazolin and ceftazidim antibiotherapy. Dermal infection, exit-site or tunnel infection were not detected. The catheter was removed because of biofilm formation doubt. Leukocyte count fell to 12/mm^3 on the 5th day. No organisms were isolated from the peritoneal fluid and the catheter culture.

Discussion

Peritonitis episodes are destructive for peritoneal membranes of CAPD patients. Prompt isolation of the offending organism is crucial for proper antibiotic selection. Empiric therapy must be changed with compatible antibiotics according to the antibiogram. Clinicians must regard rare organisms even if some of them are accepted to have lower virulence for peritonitis. As patient inadaptibility and unawareness may still be responsible factors, the patients must be educated about peritonitis and asepsis techniques periodically. Our patients are educated regularly at their monthly visits.
The most common peritonitis agents in CAPD patients are CNS. *S. epidermidis* is predominant among members of this family. Peritonitis of CNS usually has a milder course when compared to *Staphylococcus Aureus*. Treatment is generally easier and catheter loss is rare [1,2]. In addition to frequent organisms, peritoneal dialysis patients are also under threat of rare organisms like skin commensals that are commonly presumed as non-pathogenic. However, data comparing the outcome of peritonitis caused by different CNS species are inadequate. *S. Lugdunensis* is a member of CNS. It is generally accepted as a skin commensal with low virulence. But it can occasionally be isolated from skin and soft tissue infections. Despite the belief that it is less infective, *S. lugdunensis* has been reported to have a more severe course than other CNS species when isolated. It resembles *S. Aureus* from this point on [3,4]. Seong-Ho *et al*. also showed that *S. Lugdunensis* may cause serious infections like sepsis. Importantly, catheters were the most common entrance sites for hospital-acquired bacteremia in their trial [5].
S. Lugdunensis have been reported very infrequently as a peritonitis agent in the literature. We could find a

peritonitis case series of Ludlam *et al*., with 3 *S. lugdunensis* isolates from 106 episodes [6]. Unfortunately, there were no pieces of information about clinical findings, antibiotherapy and outcome of those patients with *S. Lugdunensis*. They also did not mention about catheher survival. One rare available informative S. Lugdunensis peritonitis case was reported by Schnitzler *et al*. Catheter exit and tunnel infection with a deep abscess was accompanied with peritonitis, in which intraperitoneal vancomycin had no effect. That episode resulted in catheter loss [7]. In our first patient, we isolated *S. Lugdunensis* from the peritoneal fluid during her first episode. It was not accepted as the culprit agent initially because of being a skin member with low virulence. Culture result was thought as contamination. On the second episode, *S. Lugdunenesis* was identified again. The antibiogram result was the same with the first episode. Catheter was saved owing to successful antibiotherapy. Unfortunately, the catheter was removed as a result of dysfunction 2 months later. Catheter culture was negative in our patient. This may be a result of the removal during antibiotherapy.

S. Warnerii is another CNS and a commensal of the epithelial flora and mucosal membranes. It represents nearly 1% of the skin *staphylococci* [10]. It has occasionally been reported to cause severe infections like endocarditis, hematogenous vertebral osteomyelitis and ventriculoperitoneal shunt-related meningitis [8-10]. Besides, Kamath *et al*. described *S.warnerii* as an important nosocomial pathogen, particularly in catheter-related infections. Most of their patients with catheter-related bacteremia suffered from underlying immunosuppressive illnesses [11]. Biofilm formation may be the cause of the catheter-related infections in those patients. Unfortunately, no data could be obtained on this issue.

S. Warnerii was rarely reported to cause peritonitis. Camargo *et al.* isolated *S. Warnerii* in only 7% of peritonitis episodes in the CAPD patients [12]. In another review, CAPD patients were followed for 15 years. Only 1 of 93 peritonitis agents was *S.Warneri* in this trial [13]. The worst part was the absence of any data about the outcomes including catheter survival. Our first *S. Warneri* peritonitis patient was managed successfully with standard antibiotherapy and peritoneal catheter was saved. But the second patient had a poor response to treatment leading to catheter loss.

In our patients, accompanying dermal infections were examined carefully before catheter placement. Additionally, proper surgical techniques were performed during catheter placement in order to prevent infectious complications. No exit-site or tunnel infections were detected by serial and detailed examinations. There were no accompanying dermal infections as additional risk factors in our patients unlike patients in the study of Schnitzler *et al*. [7]. Our patients were re-educated after their first peritonitis episodes against these skin commensals. Even so, the infections with the same organisms recurred. We think that as chronic renal failure itself is an immunsuppressive condition and as peritoneal dialysis requires an indwelling catheter that breaks the skin barrier protecting the underlying structures, the pathogenicity of these skin commensals may increase. Furthermore, the ability of *S. Warneri* and *S.Lugdunensis* to form biofilm over peritoneal catheters may behave as an additional risk factor.

Conclusion

In conclusion, this case report shows that *S. Lugdunensis* and *S. Warneri* may result in recurrent peritonitis episodes and resultant catheter loss. In addition, clinicians must be more eager to accept them as potential peritonitis agents in order to improve the outcomes.

Conflict of interest statement. None declared.

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Case report

Mycobacterium Tuberculosis Associated Immune Reconstitution Inflammatory Syndrome in a Renal Transplant Patient

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Abstract

Introduction. Solid organ transplant (SOT) recipients are at an increased risk of developing reactivation of a latent Myobacterium Tuberculosis (MTB) infection or primary infection. MTB infections in this patient group follow a more aggressive extrapulmonary course and can present with atypical symptoms. Immune reconstitution inflammatory syndrome (IRIS) is a pathological inflammatory response to a pathogen that paradoxically occurs after initiating treatment for an underlying infection. Classically, MTB associated IRIS is a known complication of highly active antiretroviral therapy (HAART) treatment in HIV patients. However, current reports indicate an increased risk for IRIS in solid organ transplantations.

Case Report. Here we describe a case of a deceased donor renal transplant recipient who developed extrapulmonary MTB and subsequently IRIS from antimycobacterium treatment.

Conclusion. IRIS is becoming more prevalent in the setting of SOT with MTB. Physicians should keep a high level of clinical suspicion if a patient begins to paradoxically deteriorate after initiating therapy.

Keywords: tuberculosis, IRIS, kidney transplant, extrapulmonary tuberculosis, immunosuppression

Introduction

Immune reconstitution inflammatory syndrome (IRIS) is a dysregulated inflammatory response that causes a paradoxical worsening of symptoms, signs and radiologic findings after treating an infection in an immunocompromised patient [1]. It is most commonly elicited by MBT with an estimated prevalence ranging from 8 to 43% [2]. Numerous literature studies describe this process occurring in advanced HIV patients with MTB after receiving HAART, causing significant morbidity and mortality [1,3,4]. However, there have been limited reports detailing IRIS related MTB in other immunocompromised states such as SOT [5]. Still, IRIS is a poorly understood condition with ambiguous diagnostic criteria in SOT, leading to delays in diagnosis with unnecessary diagnostic tests and treatment modifications.

Case Report

Our patient, a 71-year-old Croatian female with end-stage renal disease of unknown etiology was treated with hemodialysis in 2004 before receiving a kidney transplant from a deceased donor in 2007. She was discharged on an immunosuppressive therapy consisting of cyclosporine (Sandimun Neoral®), mycophenolate mofetil (Cellcept®), and prednisone (Decortin®), with a serum creatinine of 108 µmol/L. Until present symptoms, the patient had been treated for urinary tract infections.

The patient was transferred to our hospital in Zagreb after spending 3 weeks at her local hospital for suspected E.coli. urosepsis and prescribed meropenem. The presenting signs and symptoms were lumbar pain with radiation to the right groin area, subfebrility to febrility up to 39°C and a loss of appetite. Physical exam revealed bibasilar crepitations in her lungs. Labs showed an elevation in inflammatory markers with a CRP of 91.2 mg/L. The white count remained in normal range, but there was an increase in the neutrophil percentage to 79.9% and a decrease in the lymphocyte percentage to 7.7%. Cyclosporine levels were in the therapeutic range. Repeat of urine culture was negative for E.coli. The dose of mycophenolate mofetil was decreased due to the febrility; meropenem was changed to cefepine, and the patient was given IV crystalloid hydration with diuretics. A Quantiferon test performed at her local hospital was negative. CT imaging at our institution revealed centrally necrotic para-aortic and interaortocaval lymph nodes caudally from the level of the left renal vein to the bifurcation of the inferior vena cava (IVC); the mass compressed the lower portion of the IVC and had noticeably grown in size from a CT performed 3 weeks earlier at her local regional hospital (Figure 1).

CT showed diffuse reticulonodular changes with deformation of the bronchi at all levels, a lamellar pleural

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effusion with 1cm widening, and disturbed ventilation of the lower left lung lobe. There was also widening of

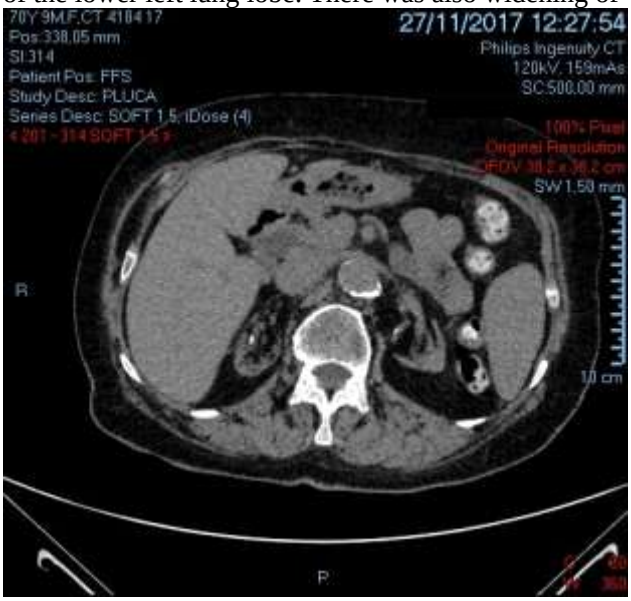

Fig. 1. Central necrotic mass with inhomogeneous infiltrate and vascularized edges. While there is compression of the IVC, it cannot be definitively concluded that there is invasion into the vasculature.

the fat tissue surrounding the ascending to the transverse colon suggesting inflammatory changes but without a definite cause. The patient had positive IgM and IgG to Toxoplasma gondii and was empirically started on pyrimethamine, sulfadiazine and leuocovorin. Subsequent testing revealed that the patient had negative PCR testing for EBV DNA and MTB DNA, but a mildly detectable level of polyomavirus BK DNA. Serology showed negative HSV2 immunoglobulins, but a borderline result for HSV1 IgM. Aspergillus galactomannan antigen also tested negative.

A few days later, an exploratory laparotomy aspirated and drained 23 ml of purulent fluid from the enlarged interaortocaval lymph node. The lymph node contents tested positive for acid fast bacteria and MTB was isolated on culture media. Pyrazinamide, rifampicin and isoniazid were subsequently started. A repeat Quantiferon ELISA was positive for MTB. Review of records showed that the patient's father died because of MTB in 1952.

Six weeks later, the patient's symptoms were still persistent and showed a lack of clinical improvement. Ethambutol, ciprofloxacin, metronidazole and fluconazole were added to the therapy.

Two weeks after adjusting the therapy, the patient began to deteriorate with increasing fatigue, weakness, nausea and vomiting, inspiratory crepitations, abdominal tenderness, tachycardia, fevers up to 39.6^{o}C and a 10 kg weight loss. Labs showed an abrupt increase in leukocytes to 26.7x10^{9}/L, with an elevated neutrophil percentage of 91.1% and a decreased lymphocyte percentage of 1.8%, mild normocytic anemia, CRP of 151.9 mg/L, and a subtherapeutic level of cyclosporine. Creatinine levels rose to 149 µmol/L.

The patient had been consuming an enteral formulation, Ensure® Plus Advance, since the onset of her symptoms 3 months ago. She complained of dysphagia to solid foods, but did tolerate fluids. In an effort to address the rapid weight loss, hypoproteinemia and hypoalbuminemia, we added the enteral formulation, Diben Drink®. Pending the oral intake of this trial, we were considering switching the patient to total parenteral nutrition.

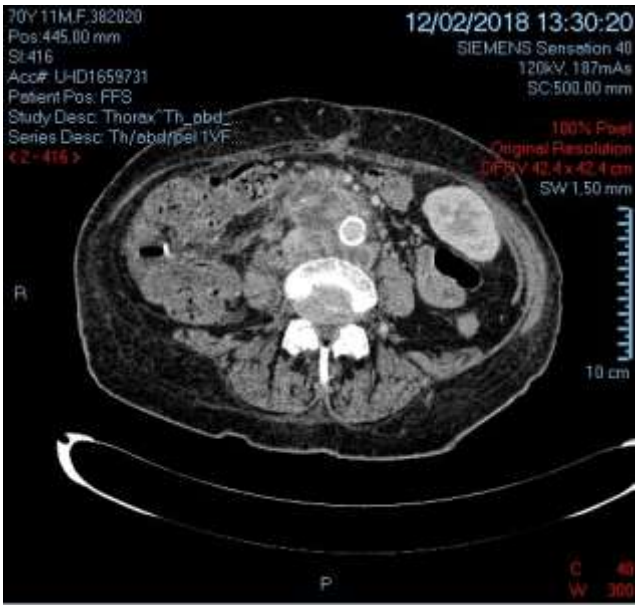

Fig. 2. Conglomerate of lymph nodes with vascularized edges and necrotic center that is extending from the great vessels to the right psoas major. The largest dimension is 7.6x5.7cm. The iliac lymph nodes remain unaffected

Control CT showed an increase in mass of the previously noted interaortocaval lymph nodes. The lymph nodes encircled around the aorta and most of the IVC extending into the right psoas major (Figure 2). There was some involvement of the lymph nodes in-between the portal vein and IVC, which increased in size from the previous CT scans. The pleural effusion had disappeared from previous CT; however the lungs showed more diffuse reticular peripheral changes, especially on the lung borders (Figure 3). There was also a poorly demarcated hypovascular area in the spleen, which was not seen on previous films. In an effort to explain this deterioration, MTB cultures were sent for multidrug-resistance testing.

It was postulated that her lack of response to therapy could be due to polymorphisms of her metabolic enzymes. Although gene analysis showed that she did have the fast metabolic variant of CYP3A4 and a high activity of N-acetyltransferase 2, the analysis recommended a normal dosing regimen.

Multiple cultures of her blood and urine proved to be negative despite rising inflammatory markers. We switched from fluconazole to caspofungin, piperacillin

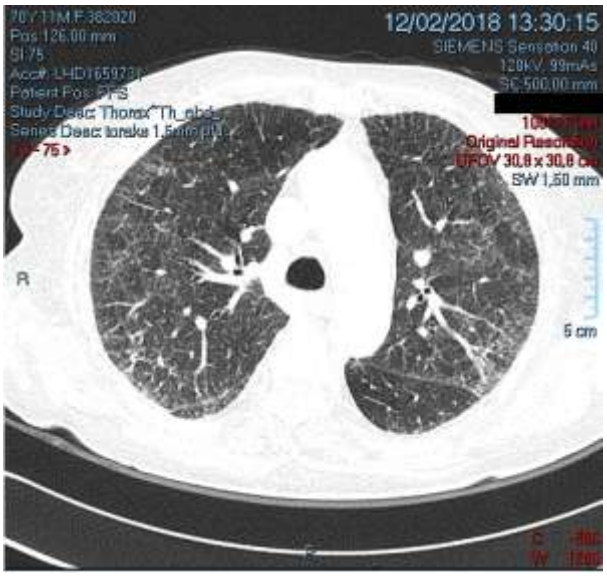

Fig. 3. Disseminated reticulonodular pattern of the lungs

and tazobactam instead of ciprofloxacin and metronidazole. Yet inflammatory markers remained constant and the lymph nodes continued to grow. The clinical picture represented IRIS secondary to MTB. We decided to stop immunosuppressive therapy except for prednisone as recommended by literature for treatment of IRIS [6], and started to prepare the patient for an eventual graftectomy upon stabilization. However, 1 week later the patient died during the sleep. Autopsy finding revealed large abscess collections in abdominal cavity with MTB content.

Discussion

The onset of MTB-IRIS usually occurs within 3 months from the start of treating the infection and is more frequently seen when there is diffuse MBT lymph node and pleural involvement [4]. The archetypal disease presentation consists of fever, weight loss, night sweats, enlarging lymphadenitis with suppuration, and worsening respiratory symptoms secondary to new or worsening pleural effusions that present with cough, dyspnea and shortness of breath [1]. Nonetheless, cases have reported less common lesions involving the central nervous system, subcutaneous tissues, abdomen (retroperitoneal lymphadenopathy and peritonitis), musculoskeletal system and obstructive endobronchial lesions [1]. Our patient's presentation was similar to findings listed in literature with abdominal tenderness, back pain, loss of appetite, weight loss, weakness, febrility and respiratory envelopment. Her MBT involvement of the retroperitoneal lymph nodes and psoas major, along with lymphopenia, anemia and rapid immune reconstitution were all risk factors for the onset of IRIS [1,3,4]. Still, this presentation in a kidney transplant recipient has rarely been reported [5]. It is possible that decreasing the mycophenolate mofetil dose and a subtherapeutic level of cyclosporine relieved the immunosuppression and triggered this severe form of IRIS. Moreover, rifampin is known to cause subtherapeutic doses of cyclosporine through drug-drug interactions [7].

Conclusion

In conclusion, physicians dealing with an idiopathic collection of inflammatory symptoms in an immunosuppressed SOT recipient should consider IRIS as a potential differential diagnosis. Additional research is needed to understand the convoluted pathogenesis of IRIS so that diagnostic and treatment guidelines can be made to prevent adverse outcomes.

Conflict of interest statement. None declared.

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