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Editorial

SGLT 2 inhibitors: Antidiabetic agents with promising effects beyond glucose control

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Type 2 diabetes mellitus is a growing public health problem worldwide. It has a close relation with metabolic problems like obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular diseases. There are different antidiabetic agents being used in the treatment of diabetes mellitus with different mechanisms of action and a patient centered approach is required when choosing the appropriate treatment option. Sodium-glucose cotransporter (SGLT) 2 inhibitors also called glucoretics or gliflozins are members of a relatively new group of antidiabetic agents with promising cardioprotective and renoprotective effects beyond their glucose lowering efficacies.[1-3]

Kidneys are involved in glucose homeostasis via gluconeogenesis and glucose reabsorption. Under normoglycemic conditions kidneys of healthy individuals filter about 140-160 grams of glucose daily. This amount corresponds to about 30% of daily energy intake. More than 99% of filtered glucose is reabsorbed in the proximal tubules of kidneys by SGLT 1 and 2. Reabsorption of approximately 90% of the filtered glucose load is from SGLT 2 and remaining from SGLT 1.[4,5] SGLT 2 inhibitors act by inhibiting the reabsorption of glucose in the proximal renal tubule, resulting an increase in urinary glucose excretion and reduction in serum glucose levels. The glucosuric effects of SGLT 2 inhibitors are regulated by the filtered glucose load. Inhibition of SGLT 2 reveals the masked potential of glucose carrying capacity of SGLT 1 by increasing glucose load in the late proximal tubule. SGLT 1 starts to reabsorb more glucose. This property limits the further risk of glycosuria and hypoglycemia when the filtered glucose load reaches ≤80 g/day.[4,5] In addition to loss of calories by glucosuria, SGLT 2 inhibition alters substrate utilization from carbohydrates to lipids. Enhanced lipolysis and reductions in visceral and subcutaneous fat mass are reported. They are shown to decrease body weight, body mass index and waist circumference in different studies.[4-8]

SGLT 2 inhibitors are thought to reduce cardiovascular risk by several different mechanisms. They possibly reduce vascular tone by affecting the renin angiotensin aldosterone system, lower blood pressure via natriuresis without increasing heart rate, improve diastolic function by reducing left ventricular mass index and probably control the level of certain biomarkers (NT-pro BNP and hsTn1) increased in case of cardiovascular disease. Decrease in blood pressure and plasma volume reduce both cardiac pre and afterloads leading to rapid benefits in heart, especially in patients with cardiac failure. In heart failure, SGLT inhibitor induced glucosuria is thought to lead modulation of cardiac metabolism with reduced glucose oxidation and increased use of ketone bodies by heart muscle which probably

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improve left ventricular function.[9-11] SGLT 2 inhibitors decrease serum uric acid levels. In vitro studies indicated that glucose entering proximal tubule lumen may facilitate intracellular urate exchange via GLUT 9 isoform 2 and increase urinary urate excretion.[12]

SGLT 2 inhibitors also decrease microalbuminuria. In some type 2 diabetic patients, glomerular hyperfiltration occurs at the onset of the disease which can increase the risk of diabetic nephropathy. SGLT 2 inhibitors have a glomerular filtration rate (GFR) lowering effect independent of blood glucose lowering property. Following this decrease, GFR increases over the following weeks that is preserved after a few years of treatment duration. Lowering glomerular hyperfiltration reduces kidney's demand for oxygen, lessens urinary albumin /creatinine ratio and albuminuria.[13-15] By controlling blood glucose, body weight, blood pressure, uric acid levels and microalbuminuria and by some specific additive effects on kidneys and heart, SGLT 2 inhibitors are shown to have positive effects on renal and cardiovascular outcomes in type 2 diabetic patients. Besides they are shown to improve liver function tests probably due to improvements in fatty liver disease as a result of glycemic control and weight reduction.[4,16,17] It's known that patients with type 2 diabetes lose their beta cell reserve and endogenous insulin within years. SGLT 2 inhibitors act independently of insulin secretion or action and can be an option for all type 2 diabetics within indication even those with reduced beta cell function and/or insulin resistance. SGLT2 inhibitors act synergistically with other antidiabetic agents. Although SGLT 2 inhibitors do not usually cause hypoglycemia in monotherapy, attention for hypoglycemia should be given in patients taking insulin or insulin secretagogues.[1,5,18]

Until today, four different types of SGLT 2 inhibitors have been introduced into clinical use. These are dapagliflozin, empagliflozin, canagliflozin and ertugliflozin. Among them the first three are available both in Europe and the United States and ertugliflozin only in the United States.[1,17,19] It is important to individualize the choice of therapy according to patient characteristics in type 2 diabetes. The approach to initial therapy in type 2 diabetic patients includes lifestyle interventions by programming medical nutrition treatment, body weight control and exercise. Besides metformin is given as the first line antidiabetic agent if not contraindicated. SGLT 2 inhibitors are not considered as the first line treatment option. According to the results of cardiovascular outcome trials with SGLT 2 inhibitors, in type 2 diabetic patients who cannot reach glycemic goals with metformin and lifestyle interventions with overt atherosclerotic cardiovascular disease empagliflozin or canagliflozin and with heart failure empagliflozin, canagliflozin or dapagliflozin can be used as an add on treatment option to metformin. SGLT 2 inhibitors can also be added to metformin and lifestyle modifications as a second drug in patients in whom weight gain, risk of hypoglycemia and injection therapy lead to significant problems. They can also be added as the third line treatment option in case of inadequate glycemic control with 2 different antidiabetics.[1,2]

SGLT 2 inhibitors are shown to reduce mean hemoglobin A1c levels approximately 0.5 to 1.0 % compared to placebo depending on baseline level of hyperglycemia in meta-analysis of different clinical trials.[5,9,19-22] SGLT 2 inhibitors are available in tablets with different milligrams (mg) given once daily. They are started with their lowest dose initially and then increased in case of higher requirement. They require dose adjustments in renal insufficient patients according to GFR (Table 1). It is not recommended to use empagliflozin and canagliflozin in type 2 diabetic patients with GFR <45 mL/min and dapagliflozin and ertugliflozin

Table 1. SGLT 2 inhibitors and their administration

SGLT 2 inhibitor	Tablet dosages (milligrams)	Recommended daily dose (milligrams)	Route of administration	Frequency of administration	Renal dose adjustment
Dapagliflozin	5 and 10	5 to 10	Oral	Once daily	Required
Empagliflozin	10 and 25	10 to 25	Oral	Once daily	Required
Canagliflozin	100 and 300	100 to 300	Oral	Once daily	Required
Ertugliflozin	5 and 15	5 to 15 mg	Oral	Once daily	Required

GFR <60 mL/min due to their mechanisms of action.[1,2,4,17]

Common side effects include symptoms of polyuria, fluid loss, thirst, hypovolemia, hypotension, dizziness, urinary tract infections and mycotic genital infections. Less common side effects are hypoglycemia, dehydration, serum cholesterol and transient serum creatinine elevations. Dehydration is more frequent in the elderly and in patients with extracellular volume depletion like the ones using loop diuretics. Urosepsis, pyelonephritis and Fournier's gangrene are rare but serious side effects reported. Canagliflozin and ertugliflozin may be associated with an increased risk of lower limb amputations. Fractures have been reported with canagliflozin. Euglycemic, mildly or moderately hyperglycemic diabetic ketoacidosis can develop due to fluid loss in type 2 diabetic patients treated with SGLT 2 inhibitors. SGLT 2 inhibitors should be discontinued in patients with major surgery, severe disease and infection. They should not be used in pregnancy and lactation.[1,17,22,23]

In conclusion, SGLT 2 inhibitors are a newer group of antidiabetic agents with promising renoprotective and cardioprotective effects with a very rare incidence of hypoglycemia and without weight gain. Long-term studies should be conducted to clearly define their therapeutic values in type 2 diabetic patients especially with vascular complications.

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Review

Might be Fabry Disease?

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Abstract

Fabry disease, also known as Anderson-Fabry disease, is a X-linked lysosomal storage disease. Alpha-galactosidase A (alpha-Gal A) enzyme deficiency leads globotriaosylceramide (Gb3) accumulation in several cells which causes clinical manifestations of the disease. The clinical heterogeneity and non-specific symptoms cause under-diagnosis and diagnosis delay. There are several clinical variants of FD which are associated with genetic and residual enzyme activity and listed as the classical, atypical (later-onset), renal and cardiac variants. Renal, cardiovascular and neurovascular involvement are the main causes of morbidity and mortality. Patients with acroparesthesias, episodic pain crises, proteinuria, chronic kidney disease, ventricular hypertrophy and cerebrovascular evets of unknown etiology should be screened for Fabry disease. Early initiation of enzyme replacement treatment improves the quality of life and prognosis. Therefore, it is essential to have awareness and knowledge about Fabry disease. Herein we aimed to summarize Fabry disease and point out that a Fabry patient might have visited you at your outpatient clinic.

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Keywords: Fabry disease, alpha-galactosidase A, chronic kidney disease

Introduction

Fabry disease (FD), also known as Anderson-Fabry disease, is a X-linked lysosomal storage disease. Alpha-galactosidase A (alpha-Gal A) enzyme deficiency leads globotriaosylceramide (Gb3) accumulation in several cells which causes clinical manifestations of the disease. Symptoms are linked to enzyme activity therefore clinical presentation is heterogeneous among sufferers. Furthermore, female heterozygotes have clinical differences due to X chromosome inactivation.

The consequence of clinical heterogeneity and non-specific symptoms are under-diagnosis and diagnosis delay. Renal, cardiovascular and neurovascular involvement are the main causes for morbidity and mortality. Early initiation of enzyme replacement treatment improves quality of life and prognosis. Therefore, it is essential to have awareness and knowledge about Fabry disease. Herein we aimed to summarize Fabry disease and point out that a Fabry patient might have visited you at your outpatient clinic.

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Definition

FD is a glycosphingolipid metabolism disorder due to the deficiency of lysosomal alpha-galactosidase A (alpha-Gal A) enzyme. Alpha-Gal A is a hydrolase in globoside metabolism which catalyzes the cleavage of the terminal galactose from globotriaosylceramide (Gb3).[1] Thereby, in the FD, Gb3 accumulates in several cells because of the low activity of the alpha-Gal A. Gb3 and derivatives have cytotoxic, pro-fibrotic and pro-inflammatory effects.[2] Exposure of vascular endothelium and smooth muscle cells are associated with vascular occlusion, ischemia and infarction which lead organ dysfunction and failure.

Epidemiology

FD is a X-linked genetic disorder which can be seen in all ethnicity. The prevalence is reported in a wide range as 1:1368 to 1:8882 in newborn studies.[3-6] The gene of the alpha- Gal A is encoded in the long arm of the X chromosome (Xq22.1 region).[7] Almost a 1000 mutations of alpha- Gal A gene have been identified. The effect of mutation on enzyme activity determines the phenotype. The hemizygous males are affected more seriously with undetectable enzyme levels. Besides, clinic manifestation differs among heterozygous females and is milder compared with hemizygous males. This diversity is a consequence of X chromosome inactivation. If the X chromosome with mutated gene is inactivated, the alpha- Gal A levels will be sufficient and she will be asymptomatic. Furthermore, in the same family phenotype can also be heterogenic among female members. This is explained by mosaicism pattern of X-inactivation. In this case Gb3 accumulation appears only in the tissues or organs in which defective X chromosome is inactivated.[8]

Clinic

The clinic manifestations (Table 1) are closely related with alpha- Gal A activity. A 30-35% activity of the enzyme is sufficient for adequate ceramide metabolism. An enzyme activity below 1-3% means no residual enzyme activity and is presented as classical FD. Between these ranges there is residual enzyme activity and is seen in female heterozygotes and other variants.[9]

Involvement of small nerve fibers of the peripheral somatic and autonomic nerve systems leads neuropathic pain and acroparesthesias, episodic pain crises, chronic pain and are early manifestations. Gastrointestinal symptoms, abdominal pain, diarrhea, nausea, and vomiting which may be related to the deposition of Gb3 in the autonomic ganglia of the bowel and mesenteric blood vessels manifest early too. The other early symptoms are anhidrosis, hypohidrosis, heat and exercise intolerance, chronic fatigue, tinnitus, hearing loss. Eye and skin involvement are quite specific findings compared with others. Corneal opacities- cornea verticillata, retinal vessel tortuosity, and cataracts can be seen in childhood. The most visible early clinical feature of FD is angiokeratoma which are mostly located on the buttocks, groin, umbilicus and upper thighs, also sometimes on mucosal areas.[1]

The Fabry patients have typical facial characteristics with periorbital fullness, prominent lobules of the ears, thickening of the lips, and bulbous nose. Besides, the dysmorphic facial features are not expected in cases with residual enzyme activity.

Renal, cardiac and cerebrovascular involvements are major ones that are associated with mortality and morbidity. Podocytes are the first affected part of the kidney and proteinuria is the initial presentation of the renal involvement. Renal manifestation begins at 2nd decade and progress to chronic kidney disease with glomerular, interstitial and tubular findings. Cases commonly reach end stage at 4th-5th decade and require renal replacement treatment.[1]

Cardiac involvement includes ventricular hypertrophy, myocardial fibrosis, heart failure, coronary artery disease, aortic and mitral valve abnormalities, and conduction abnormalities. Although severe cardiac symptoms are generally present at 4th decade, arrhythmias can manifest trough childhood.[1] Right ventricular hypertrophy is an important finding of Fabry disease.

Cerebrovascular manifestations are consequences of ischemia due to vascular involvement and Gb3 accumulation in nerve fibers. Neuropathic pain, ischemic cerebral events, headache, vertigo/dizziness, transient ischemic attacks, ischemic strokes and vascular dementia

Table 1. Clinical features of Fabry disease

	Early signs and symptoms (1st and 2nd decade)	Late signs and symptoms (3rd to 5th decade)
Skin	Angiokeratoma, hypohidrosis	
Eye	Corneal and lenticular opacities, vasculopathy (retina, conjunctiva)	
Nervous system	Acroparesthesias, Neuropathic pain, nerve deafness, heat and/or cold intolerance, tinnitus	TIA; ischemic stroke and (less frequently) hemorrhagic stroke; cerebral venous thrombosis; cervical carotid dissection
Gastrointestinal system	Nausea, vomiting, diarrhea, abdominal pain and bloating, early satiety, difficulty gaining weight	
Psychological		Common: depression; anxiety; panic attacks; social adaptive function difficulties. Rarely: cognitive decline and dementia
Renal	Albuminuria, proteinuria, impaired concentrating ability, increased urinary Gb3 excretion	Decreased glomerular filtration rate progressing to kidney failure
Cardiovascular	Impaired heart-rate variability, arrhythmias, ECG abnormalities (shortened PR interval), mild valvular insufficiency	Hypertrophic Cardiomyopathy, reduced exercise tolerance; syncope; cardiac fibrosis; heart failure (mostly with preserved ejection fraction). Bradycardia – chronotropic incompetence; atrial fibrillation, ventricular tachycardia; sudden cardiac death
Lung	Dyspnea, wheezing; dry cough; sleep-disordered breathing	
Other		Lymphedema in all or part of a limb (also below eyes), pitting edema; Osteopenia, osteoporosis

are common neurologic symptoms.[1]

Other clinical manifestations are lung involvement such as chronic bronchitis, wheezing, or dyspnea; lymphatic involvement, such as lymphedema, subconjunctival lymphangiectasia, varicosities, hemorrhoids, or priapism; subclinical hypothyroidism; azoospermia; and osteopenia or osteoporosis and aseptic osteonecrosis. Psychological manifestations, such as depression, anxiety, and chronic fatigue, are also common.[10]

Clinical variants

There are several clinical variants of FD which are associated with genetic and residual enzyme activity and listed as the classical, atypical (later-onset), renal and cardiac variants.

Classical variant

The patients who have the mutations causing no residual enzyme activity manifested and defined as the classical variant/ classical FD. These are almost hemizygous males with no enzyme activity. But also some heterozygous females present as classical variant. Clinical findings begin in childhood and spectrum of involvement progressively increases. Acroparastesia, gastrointestinal symptoms, skin abnormalities, heat intolerance were presented in childhood and adolescence. In adulthood, untreated patients were exposed to progressive renal, cardiac and cerebrovascular involvements which are associated with mortality usually after 5th decade.

Heterozygous females

Heterozygous females have phenotypic variability due to aforementioned reasons. They can be asymptomatic or present whole spectrum of involvement. In general compared with hemizygous males symptoms are milder and occurs on later ages.

Atypical (later onset) variant

They present later in life than those with the classical variant and have residual alpha-Gal A activity (between 3-30% of the normal mean). The clinic is typically dominated by a particular organ system, most commonly the heart.

Renal variant

Some patients may present with clinic limited to the kidney. At later ages other organ involvements like cardiac may occur.

Cardiac variant

It is the most common late-onset variant. They are generally asymptomatic for most of their lives and present at the 5th to 8th decade of life with ventricular hypertrophy, hypertrophic cardiomyopathy, conduction abnormalities, and arrhythmias. In the studies the rate of the cardiac variant of FD is up to 4% among patients with unexplained hypertrophic cardiomyopathy.[11-14]

Diagnosis

There are some specific points about diagnostic approach both for screening population and instruments. Because the clinic presentation of FD is usually with non-specific symptoms as aforementioned, there is a delay for almost 10 to 15 years from the earliest symptom until correct diagnosis.[15] If the clinician has knowledge about the disease and can keep in mind FD as a possible diagnosis, adequate diagnostic approach provides the diagnosis of approximately 5 more Fabry patients with the index case.[16]

An evaluation for FD should be performed in males or females with at least one of the clinical features of acroparesthesias, angiokeratomas, hypo- or anhidrosis, corneal and lenticular opacities; abdominal pain, nausea, and/or diarrhea of unknown etiology in young adulthood; left ventricular hypertrophy or hypertrophic cardiomyopathy, arrhythmias of unknown etiology; stroke of unknown etiology at any age; chronic kidney disease and/or proteinuria of unknown etiology, multiple renal sinus cysts discovered incidentally (Table 2). Family history of the features mentioned above is strong suggestive indicators.[1, 10, 17, 18]

The instruments for diagnosis differ among genders. The enzyme, alpha Gal-A, activity measurement is the initial method for males. The activity below 1-3% of the normal mean confirms the diagnosis for the males. Subsequently, genetic testing should be performed and genetic counseling in the patient's family is essential. If the enzyme activity is resulted between 3-35% of the normal mean, genetic testing should be done to define a disease-causing mutation.[1, 10, 18]

Genetic testing should be performed initially for the females, because there might be residual enzyme activity due to X inactivation.

All patients for both genders require mutation analysis to confirm the genetic variant. There are almost 1000 genetic mutations defined for GLA gene. However the phenotypic significance of the mutation is important. In these huge genetic findings there are reported mutations with unknown significance and the genetic disorder is significant to the extent that it affects the enzyme activity.[18]

Table 2. Recommendations for Screening Fabry disease

Acroparesthesia or neuropathic pain in hands or feet, anhidrosis, hypohidrosis, heat and exercise intolerance beginning in childhood or young adult
Corneal and lenticular opacities, vasculopathy of retina and conjunctiva
Persistent proteinuria of unknown etiology
Chronic kidney disease of unknown etiology
Hypertrophic cardiomyopathy, especially with prominent diastolic dysfunction
Stroke or transient ischemic attack of unknown etiology
Family history of ESRD, stroke, or hypertrophic cardiomyopathy
Persistent, or recurrent abdominal pain associated with nausea, diarrhea, and tenesmus of unknown etiology

Treatment

Management of FD is composed of Enzyme replacement treatment (ERT) and concomitant therapy for symptoms and organ involvements. ERT is the mainstay of FD management. It is essential to start the ERT as early as possible to prevent organ failure. There are 2 forms of ERTs, agalsidase alpha and agalsidase beta, which are both available in Turkey. Studies confirm that initiation of ERT at early ages has better outcomes. The patients in whom ERT was administered after 40 age and/or with moderate to severe organ damage do not have expected amelioration. Besides the oral small-molecule pharmacological chaperone migalastat, is available in Europe and Canada for the treatment of a subset of Fabry patients with particular mutations.[18]

Anticonvulsants for neuropathic pain, renin angiotensin aldosterone system blockers for proteinuria, stroke prophylaxis with anti-thrombotics and anti-coagulants, metoclopramide and H-2 blockers for gastrointestinal symptoms, bronchodilators for airway obstructions, renin angiotensin aldosterone system blockers and beta blockers for ventricular hypertrophy and arrhythmias, cardiac pacing if needed are adjunctive therapies for FD.

Hemodialysis, peritoneal dialysis and kidney transplantation can be performed when the patient requires renal replacement therapy. Fabry nephropathy does not recur in kidney graft. And transplanted Fabry patients have better outcomes compared with ones on dialysis.

Conclusions

In conclusion, FD is a genetic, multisystemic, progressive disease with generally non-specific symptoms. Furthermore, ERT is available which ameliorates symptoms and prevents organ failure in early cases. Although it has low prevalence, FD should be considered as an initial diagnosis in patients with acroparesthesias, angiokeratomas, hypo- or anhidrosis, ocular findings, ventricular hypertrophy, proteinuria, chronic kidney disease, stroke of unknown etiology. When the diagnosis is confirmed it is appropriate to transfer the patients for multidisciplinary management composed of geneticist, cardiologist, neurologist, nephrologist, and ophthalmologist experienced for FD.

Conflict of interest

The author declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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Granulocyte colony-stimulating factor usage in drug-induced neutropenia after kidney transplantation: a single-center experience

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Abstract

Introduction. Granulocyte colony-stimulating factor (G-CSF) therapy is commonly used in kidney and liver transplant recipients with severe neutropenia. However, rapid and high increases in neutrophil counts of some patients may occur during treatment. This retrospective study aimed to determine the efficacy and safety of G-CSF treatment in neutropenic kidney transplant recipients.
Methods. Eight kidney transplant recipients treated with G-CSF for drug-induced neutropenia (neutrophil count <1000 cells/μL) were included in the study. Daily renal function tests, leukocyte (WBC) and absolute neutrophil counts were measured.
Results. The median duration of G-CSF treatment was 4 days (2-5). The median WBC and neutrophil counts elevated from 1130 and 565 cells/μL to 4400 and 1950 cells/μL after treatment, respectively (p=0.012). The median peak WBC and neutrophil counts during treatment were 18,045 and 16,445 cells/μL, respectively. The WBC counts returned to normal limits after a median of 22 days from the maximum value. No acute rejection was observed within three months of discontinuation of treatment.
Conclusions. G-CSF may be a useful therapeutic alternative for kidney recipients with severe neutropenia. It seems reasonable to withdraw G-CSF treatment when WBC and neutrophil counts reach certain cut-off values during treatment.

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Keywords: Filgrastim, granulocyte colony-stimulating factor, kidney transplantation, leukopenia, neutropenia.

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Introduction

Post-transplant neutropenia is a common complication in kidney recipients. The incidence of neutropenia may range from 14.5% to 28% in the first year after transplantation.[1,2] It may be caused by immunosuppressive therapy (thymoglobulin, mycophenolate or sirolimus), antimicrobial therapy (trimethoprim/sulfamethoxazole, valacyclovir, valganciclovir or ganciclovir), bacterial and viral infections.[1,3-9] In drug-induced neutropenia, identification of the responsible drug is often difficult, and regression of neutropenia after drug discontinuation can be used as indirect evidence.[9]

Leukopenia or neutropenia in kidney transplant recipients is associated with a high risk of serious infections that may lead to septicemia. Although there is no widely accepted guideline on treatment strategies, most physicians often prefer to reduce the dose or discontinue the causative drug.[2] However, interventions to immunosuppressive drugs may cause graft loss.[10] Discontinuation of mycophenolic acid for more than 6 days may be associated with a high rate of allograft rejection.1 Another approach can be the usage of everolimus or azathioprine instead of mycophenolic acid rather than a reduction in the dosage of mycophenolic acid in patients with persistent neutropenia.[11,12] Tacrolimus-induced neutropenia is less recognized, and may be improved by discontinuing tacrolimus and switching to cyclosporine.[13] Recombinant human granulocyte colony stimulating factor (G-CSF) is a hematopoietic growth factor that selectively stimulates neutrophil colony formation and neutrophil cell differentiation.[14] G-CSF has been used successfully to reverse neutropenia in kidney and liver transplant recipients.[15-18] However, some patients may respond very quickly to the initial dose and the neutrophil counts may increase significantly.[19,20] This study aimed to determine the efficacy of G-CSF in persistent neutropenic recipients after kidney transplantation.

Methods

Neutropenic kidney transplant recipients were retrospectively identified among 170 adult patients who underwent kidney transplantation in our center between January 2012 and May 2014 in our center. Ten out of 170 patients treated with G-CSF for persistent neutropenia and/or leukopenia. Posttransplant leukopenia and neutropenia were defined as the count of white blood cells (leukocytes, WBC) below 3000 cells/μL and the absolute neutrophil count below 1000 cells/μL, respectively.[1,21-23] Two patients with sepsis were excluded from the study. Eight transplant recipients (5 males and 3 females) receiving G-CSF treatment for drug-induced neutropenia were included in this study. Primary diseases were Alport syndrome in 2 patients, focal segmental glomerulosclerosis in 2 patients, diabetes mellitus in 2 patients and unknown etiology in 2 patients. There was no history of hepatitis or acute rejection in all patients. Two patients had a history of ganciclovir treatment for CMV DNA positivity. The patients with persistent neutropenia were given a daily dose of 5 μg/kg filgrastim (recombinant human G-CSF, 30 or 48 MIU = 300 or 480 μg) subcutaneously. Demographic and clinical features of the patient, changes in WBC, neutrophil and creatinine values before and after treatment were obtained from the medical records.

All statistical analyses were performed using the IBM SPSS Software package of version 23.0 (IBM Corp, Armonk, NY, USA). The data was given as mean ± standard deviation (SD) or median (min:max). The numerical variables were compared with Wilcoxon signed-rank test within group. The relation between the variables was estimated with Pearson correlation test. Statistical significance was defined by $p < 0.05$.

Results

The dialysis types were hemodialysis in 3 patients and peritoneal dialysis in 4 patients. One patient underwent preemptive transplantation. The median duration of dialysis of seven patients was 38.6 months (6.5-196). Among the patients, 3 received a living donor and 5 deceased donor transplant. The transplant age of patients were 38.2±16.5 years. The mean body mass index at the time of transplantation was 20.9±4.7 kg/m^2. The median number of human leukocyte antigen (HLA) mismatch was 2.5 (1-4). The mean donor age was

51.3±13.4 years. Immunosuppressive regimens of eight patients consisted of cyclosporine (n=4) or tacrolimus (n=4) combined with mycophenolate mofetil and prednisolone. The induction therapy was performed with ATG in 2 patients and basiliximab in 6 patients.

The median duration of neutropenia after transplantation was 2.8 months (1.25-16.1). When leukopenia and/or neutropenia developed, the dose of mycophenolate was initially reduced in all patients. If WBC values continued to fall, it was discontinued. If there is any possible responsible drug, it is also discontinued. When leukopenia improved, mycophenolate treatment was restarted by reducing the dose. The cause of neutropenia was attributed to mycophenolate in 4 patients, teicoplanin in 2 patients, ganciclovir in 1 patient and valganciclovir in 1 patient. Six months after transplantation, one patient with CMV-DNA 282 copies/mL was treated with intravenous ganciclovir. CMV-DNA was negative (<20 copies/mL) after the treatment. On the 17th day of the treatment, the drug was discontinued when persistent neutropenia developed, and then the patient was given 4 doses of G-CSF after 5 days.

The median duration of G-CSF usage for post-transplant neutropenia was 4 days (5 days in 2 patients, 4 days in 4 patients, 3 days in 1 patient and 2 days in 1 patient). The mean dose of G-CSF was 1747±434 µg. The baseline WBC and absolute neutrophil values were 1271±856 (560-3170) and 565±333 (60-1080) cells/µL, respectively. The WBC and absolute neutrophil counts elevated to 5933±5187 (1780-17,300) and 4033±4247 (1340-12,700) cells/µL after G-CSF treatment, respectively (p=0.012). The mean peak WBC and absolute neutrophil counts were measured 20,158±12,556 (3080-44,600) cells/µL and 17,232±11,417 (2720-38,100) cells/µL after median 9.5 days (6-20), respectively. In 5 patients, WBC count increased above 4000 cells/µL after cessation of G-CSF treatment. WBC (8176±2426 cells/µL) and neutrophil (6201±2146 cells/µL) counts returned to normal ranges on average 17 days after discontinuation of G-CSF treatment. The changes in WBC and neutrophil counts are given in Figure 1.

All patients had a median serum creatinine level of 1.75 mg/dL (1.1-2.91) at 1 month after kidney transplantation. The baseline median creatinine levels of patients at the time of neutropenia were 1.5 mg/dL (1.1-2.4), and there was no significant difference between the mean serum creatinine levels at the time of neutropenia and 1 month after transplantation (p=0.441). Serum creatinine levels were measured as 1.53±0.52 mg/dL on the day after G-CSF discontinuation (p=0.115), 1.57±0.6 mg/dL on the day of peak WBC (p=0.262) and 1.75±0.66 mg/dL on the day that WBC returned to normal ranges (p=0.499) (Figure 2). These levels were comparable with the mean serum creatinine levels during neutropenia. No acute rejection episode was observed during the 3-month follow-up period after discontinuation of G-CSF. There was no a significant correlation between total G-CSF dose and treatment duration with

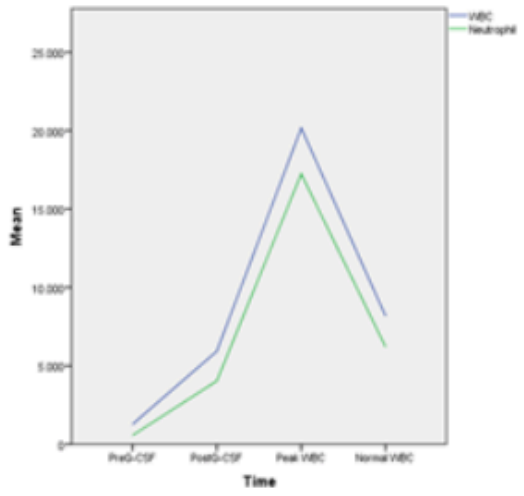

Figure 1. The changes in WBC and neutrophil counts after G-CSF treatment

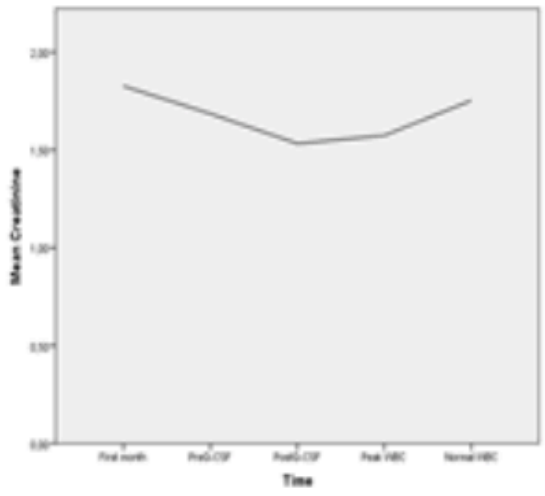

Figure 2. The changes in serum creatinine levels after G-CSF treatment

several variables including age, gender, presence of diabetes mellitus, history of CMV infection, calcineurin type, baseline serum creatinine level, baseline and peak WBC and neutrophil values ($p>0.05$). The neutropenia duration was positively correlated with pre-transplant body mass index value (r:0.836, p=0.010). None of the patients had bone pain associated with G-CSF usage.

Discussion

Incidence of combined leukopenia or neutropenia in kidney and/or pancreas transplant recipients can be as high as 58%.[21] The rate of neutropenia is reported to be 28% in the first year after transplantation.[1] In a study, the incidence of leukopenia was higher in patients receiving alemtuzumab (42% vs. 9% by antithymocyte globulin induction) and/or in patients had rapid steroid withdrawal in the early post-transplant period (44% vs. 16% in those without steroid withdrawal).[21] Neutropenia can be associated with many factors including thymoglobulin induction, tacrolimus, mycophenolate mofetil, female gender, Caucasian ethnicity, ischemic heart disease, donor cytomegalovirus positivity, and later year of transplant, deceased donor, expanded donor criteria, delayed graft function, higher panel reactive antibody and HLA mismatch.[2] In another study, the causes of 100 post-transplant neutropenia episodes in 50 recipients (14 kidney, 35 liver and 1 combined kidney and liver transplant) were ganciclovir (28%), CMV (21%), chemotherapy (12%), sepsis (11%), azathioprine (5%), interferon (3%) and others (20%).[24] The occurrence of neutropenia was found to be associated only with combined tacrolimus and mycophenolate treatment in a study.[1] Our study included drug-induced neutropenic patients, and neutropenia in half of the patients was associated with mycophenolate. The occurrence of neutropenia in our patients was similar to the previous reports.[1,2,25-27] The median duration of neutropenia after transplantation was 2.8 months.

Our findings and the results of other studies indicated that G-CSF treatment was safe and effective in reversing persistent leukopenia or neutropenia in solid organ transplant patients without no serious adverse effects.[8,14-18,20-22,24,27,28] The elevation of total WBC count in G-CSF-treated patients is mainly due to a specific increase of neutrophil granulocytes.[14] Our patients received G-CSF treatment for a median of 4 days. The median WBC and neutrophil counts elevated from 1130 and 565 cells/μL to 4400 and 1950 cells/μL after the treatment, respectively. In 62.5% of the patients, WBC count increased to over 3000 cells/μL when G-CSF treatment was discontinued. The rate of treatment failure was 12.5%. Because only one patient could not achieve the desired WBC response (peak value: 3080 cells/μL), however, the maximum neutrophil count of 2720 cells/μL was more reasonable and acceptable. The median peak WBC and neutrophil counts were 18,045 and 16,445 cells/μL in all patients, respectively. The WBC counts returned to normal ranges after a median of 22 days from the maximum value. In other retrospective study, 15 patients (13.3%) were treated with G-CSF for a median 2 days.[1] The mean duration of neutropenia did not differ between patients receiving G-CSF or not (16±14 vs. 26±23 days). In patients treated with G-CSF, the time to reach an absolute neutrophil count above 1000/μL was significantly shorter than in patients not receiving G-CSF (1.5±0.5 days). In another study including 25 patients who underwent either a kidney or a combined kidney and pancreas transplant, 35 neutropenia episodes were treated with a mean of 2.9 doses of G-CSF per episode without precipitate or aggravate allograft rejection.[20] The mean number of days to peak WBC after initiation of treatment was 4.6 days. In a retrospective cohort study in which 30 leukopenia episodes (2000 cells/μL) were evaluated in 19 kidney transplant recipients treated with G-CSF, the therapy was discontinued when the counts above 4000 cells/μL were reached,[14] and all patients responded to the therapy. The median duration of treatment per episode was 1 day (1-8). WBC counts increased from 1756±582 cells/μL to a peak of 8723±3038 cells/μL in 2.7±1.8 days (1-8) after the first G-CSF usage.14 When compared to historical control group, leukopenic episodes in treated patients were significantly shorter (1.29 days vs. 7 days), and bacterial infections occurred at a significantly lower rate.[14] In the largest retrospective study of 100 neutropenia episodes in 50 patients undergoing kidney or liver transplantation, WBC count increased to above

5000 cells/μL in 93% of patients within 3.7 days after G-CSF support for a mean of 10 days.[24] In 6 (7%) out of 7 cases that did not reach this count, G-CSF treatment lasted less than 4 days. In a retrospective study of 102 kidney and pancreas transplant recipients over 1 year, Hartmann et al.21 found 59 patients (58%) with total WBC <3000 cells/μL or absolute neutrophil count <2000 cells/μL, and 21 patients received G-CSF at some point during their management. Leukopenia was successfully treated with an average of 3.1 doses of G-CSF. Similar to our observations, a total G-CSF dose of four or less was sufficient in the majority of patients (85%). Hamel et al.[29] retrospectively evaluated 32 leukopenic (WBC <3000 cells/μL) kidney transplant recipients who started G-CSF treatment on mean 98±38 days after transplantation. The median time to WBC count recovery was 9 days (4-14) following a mean 2.1±1.9 doses of G-CSF. This time is longer than previously reported in the literature.[20,24,27,30] The mean interval from the onset of leukopenia to the initiation of G-CSF treatment was 15±16 days. In post-hoc analysis, WBC count recovery times were similar in patients with or without G-CSF therapy delays (median 10 vs. 5 days). The recovery time at 7 and 14 days was similar between patients receiving at least one dose of G-CSF and not receiving any dose (median 9 vs. 8.5 days).[29] Similar to the findings of Zafrani et al.1, there was no difference in time to WBC count recovery in patients with therapy delays in therapy or those who did not receive any G-CSF dose.[29] In the other study, 28 neutropenic patients were treated with a mean of 1.79 doses (1-5) of G-CSF (300 or 480 μg) without infection or acute rejection.[30] Overall, 87.5% of the cases reached a WBC count of at least 3000 cells/μL within 7 days of hospital discharge.

Although some studies did not find a difference between the rates of infection or acute rejection in patients with and without leukopenia,[21] neutropenia has long been recognized as a risk factor for the development of infection in solid organ transplant recipients.[15] Seven neutropenic patients in the era when G-CSF was not in use had more infectious episodes, more aggressive antibiotic therapy, longer hospital stay and higher mortality rates (57% vs. 14.3%) than those treated with G-CSF.[16] However, eight patients (16%) under G-CSF treatment in the cohort of Turgeon et al.[24] died from infection. They observed that patients with leukopenia secondary to drugs tolerated G-CSF well and received an appropriate WBC response. On the contrary, the outcome in patients receiving G-CSF treatment for sepsis associated leukopenia was particularly poor.[24] In one study, the frequency of infection requiring hospitalization or opportunistic infection was 14% in kidney recipients with leukopenia.[29] Our two patients were excluded in this study due to sepsis-induced leukopenia. Both patients who were given 1 and 5 doses of G-CSF died from infection. In sepsis models, G-CSF increases number of circulating granulocytes, decreases tumour necrosis factor (TNF) production and improves survival. A possible mechanism responsible for a lower rate of rejection in patients treated with G-CSF may be a significant reduction in serum TNF levels associated with G-CSF therapy.[31,32] In comparison to the 49 previous liver transplant recipients who did not receive G-CSF, 37 liver transplant recipients receiving G-CSF (5-10 mcg/kg/day) for the first 7-10 days after transplantation had a lower rates of acute rejection (22% vs. 51%), a decreased number of sepsis episodes per patient (0.92±1.5 vs. 2.18±2.8) and a lower percentage of sepsis-related mortality (8% vs. 22%).[31]

Many studies have reported an association between mycophenolate dose reductions and increased rates of acute rejection following kidney transplantation.[1,33,34] Discontinuation of mycophenolic acid due to neutropenia increases the risk of acute rejection, especially after a 6-day interruption, but this may not lead to reduced renal function at 1 year. The time from onset of neutropenia to discontinuation of the drug is associated with the duration of neutropenia.[1] Since steroid therapy affects mycophenolate mofetil bioavailability, tapering steroid dose may result in higher mycophenolate mofetil exposure.[35] In a retrospective cohort of 41,705 adult transplant patients, 6043 (14.5%) patients had neutropenia and leukopenia, and 740 (12.2%) of these patients received G-CSF. Post-transplant neutropenia was associated with a 1.59-fold loss of graft and 1.74-fold increased risk of death, but G-CSF did not increase the risk of graft loss.2 However, the use of G-CSF in transplant patients may increase the risk of rejection by overstimulating the immune system via leukocyte precursors.[30,36,37]

Colquhoun et al.[38] only reported 1 clinically and biopsy-documented rejection episode among 18 liver transplant recipients who received G-CSF for reversal of neutropenia. Similarly, G-CSF treatment has been reported to be associated with deterioration of graft function in a kidney recipient.[36] The results of several studies in mouse models of acute renal failure indicate contradictory effects of G-CSF on renal function, because G-CSF can attenuates or worsens renal injury in different settings.[39] Anupama et al.[37] described a kidney transplant patient with biopsy-proved acute tubular injury probably due to G-CSF therapy for profound leukopenia. The patient developed acute kidney injury with severe musculoskeletal pain four days after receiving G-CSF, and returned to near baseline creatinine in two weeks. The pathophysiology of this injury may be due to the cytokine nature of G-CSF.[40] In the cohort of Turgeon et al.[24], eight rejections (8%) were seen during G-CSF treatment or within 2 months of treatment. One kidney transplant patient (3.8%) had refractory rejection episodes previously and creatinine level was already high at the start of G-CSF treatment. Among liver and kidney–liver transplant recipients, 7 episodes of rejection (9.5%) within one year of transplant occurred during or following G-CSF, and 3 of them were biopsy proven. No correlation was found between the presence of rejection during or following G-CSF treatment and the peak WBC count, or the length or daily dose of G-CSF.[24] In the majority of studies, the use of G-CSF in solid organ transplant recipients did not increase the frequency of rejection episodes even in the early period with a higher risk of rejection.[14,15,20,26,29] In a relatively large population including a control group, the significant decrease of serum creatinine levels during the treatment period also reflected the concomitant improvement of graft function.[14]

Besides being expensive, G-CSF usage may be associated with several adverse events including bone pain and rare instances such as splenic rupture, allergic reactions, flares of underlying autoimmune disorders, acute myeloid leukemia, myelodysplastic syndrome, lung injury and vascular events in healthy bone marrow donors or persons with chronic neutropenia or cancer.[41] However, in transplant patients with lymphoma, G-CSF treatment may probably be less effective and cause suboptimal WBC increases.[42]

G-CSF is often used as a second-line treatment after discontinuation of potentially responsible drugs. In addition, the use of G-CSF in patients with severe neutropenia reduces the risk of serious infections such as CMV infections, and can provide better outcomes and cost savings. Kidney transplant recipients are also well tolerated for short-term therapy periods of up to 4 days. The decision to start or to continue G-CSF therapy should be based on the measurement of absolute neutrophil count rather than total WBC count.[14] Because leukopenia or neutropenia can be rapidly resolved in patients after G-CSF. In our study, the WBC count of 3 patients given G-CSF for 3, 4 and 5 days was 2280, 2780 and 1780 cells/μL at the end of treatment, respectively. Although the treatment was discontinued when the WBC count was below 4000 cells/μL, the peak leukocyte count reached 28,200 and 19,300 cells/μL in 2 patients. In the third patient, the WBC count increased from 1190 to 1780 cells/μL after 5 doses of G-CSF, but the peak leukocyte value was 3080 cells/μL. Approximately 2 months later, the WBC value was measured as 5490 cells/μL. In another patient, WBC count was after 2 doses of G-CSF elevated from 1280 to 4000 cells/μL. However, the peak leukocyte count was 24,100 cells/μL after 10 days. The peak WBC count increased to 44,600 cells/μL in one patient on the 6th day after 4 doses of G-CSF treatment. The WBC values of the patients returned to normal range median 9.5 days (1-58) after the maximum WBC value and median 22 days (8-65) after the first G-CSF dose.

Conclusions

The usage of short-term G-CSF in kidney transplant recipients appears to be safe and effective without acute rejection episode. It accelerates the recovery of neutropenia in severe neutropenic recipients and may be a good therapeutic alternative in addition to changes in immunosuppression and prophylaxis drugs. As yet, there are no published guidelines on management of neutropenia in kidney transplant recipients. When total WBC and absolute neutrophil counts rise to 2000-3000 cells/μL and 1000-1500 cells/μL, respectively, it seems reasonable to withdraw G-CSF treatment. However, it may be more appropriate for the

transplant physician to make individual decisions based on the severity of neutropenia, graft function, infection and acute rejection risk. Randomized controlled trials are still needed to determine minimum effective dose and therapeutic duration of G-CSF in this population.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Original Article

The Comparison of serum uric acid levels in patients on hemodialysis and peritoneal dialysis

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Abstract

Introduction. Uric acid levels increase in chronic renal failure especially due to protein metabolism. In this study, we aimed to compare uric acid clearance who are also nephrotoxic in patients with end-stage renal disease.
Methods. Sixty-one chronic peritoneal dialysis (PD) patients and fifty-one chronic hemodialysis (HD) patients were included in the study. Clinical and laboratory characteristics of PD and HD patients were compared. Duration of PD and HD, uric acid levels, age and gender of the patients evaluated. Uric acid levels in PD patients and HD patients compared.
Results. The mean ages of PD and HD patients were 56.7±13.5 and 57.2±16.4 years, respectively (p=0.864). The number of male patients was more in PD group and female in HD group (p=0.959). Duration of dialysis was 3.25 years in PD and 3.75 years in HD (p=0.925). The mean serum uric acid levels were 5.54±1.13 mg/dL in PD patients, and 5.76 ±1.52 mg/dL in HD patients (p=0.389).
Conclusions. Dialysis is used to remove toxins in end-stage renal disease. Uric acid levels may be elevated in patients with end-stage renal disease. However, there was no difference in serum uric acid levels in PD and HD patients in our study.

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Keywords: Hemodialysis, peritoneal dialysis, uric acid.

Introduction

Uric acid is the final product of the diet and endogenous purine metabolism synthesized mostly in the liver. Especially, uric acid levels are especially high in 10-15% of people over 40 years. In normal healthy individuals, the upper limit of uric acid is 7-8 mg/dL in men, and 6 mg/dL in women. The reason for being low in women is that the estrogen hormone shows uricosuric effect and low muscle mass. Consumption of meat, legumes, yeast and yeast-containing foods lead to increase in uric acid. It is also found high in diabetic patients, alcohol intake, medicines (thiazide diuretics etc.), heart failure, renal failure and disease with high turnover such as cancer (leukemia, solid tumors etc.). Plasma uric acid is present in the form of Na-urate. One third of them are excreted from the gastrointestinal system and the remaining two third are excreted in the urine. The level of serum

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uric acid increases in end stage renal disease (ESRD).[1] Uric acid is removed by dialysis. Which dialysis method is more effective is controversial?

In this study, we aimed to show which dialysis method is used to remove toxic uric acid more effectively.

Methods

Patients

The values of 51 hemodialysis and 61 peritoneal dialysis patients analyzed retrospectively. Age, gender, duration of dialysis, laboratory levels like uric acid evaluated. Only ESRD patients treated with hemodialysis or peritoneal dialysis analyzed. Patients who received renal replacement therapy for at least one year included in the study. The patients had been trained in nutrition. They did not receive a uric acid-lowering treatment. The average of the first and last uric acid values that recorded in the system evaluated, respectively.

Statistical analysis

Data analyzed using Statistical Package for the Social Sciences (SPSS) version 21 (IBM Acquires SPSS Inc., Somers, NY, USA). Descriptive statistical methods (mean, median, frequency, standard deviation, ratio) compared with Pearson Chi-square, paired t and Mann Whitney U test used to compare two groups of variables that did not show normal distribution. Differences considered significant if $p < 0.05$.

Results

In our study, 59 patients were male and 53 were female. The gender distribution of the patients did not differ (p=0.959). The mean age of patients was 57.2±16.4 and 56.7±12.5 years in HD and PD groups, respectively. Durations of dialysis were 3.25 (1-14) and 3.75 (1.25-16) years in HD and PD groups, respectively. There was no significant difference between ages (p=0.864) and dialysis durations (p=0.925) in the patients who underwent PD and HD. The mean serum uric acid levels were 5.76±1.52 mg/dL in HD patients, and 5.54±1.13 mg/dL in PD patients. There was no difference between the mean uric acid levels of the patients in both groups (p=0.389). Other laboratory parameters were given in Table 1.

Discussion

Uric acid is the final product of purine or nucleotides and about two out of three is excreted by the kidneys.[2,3] Chronic renal failure itself creates an inflammatory environment. In particular, the effect of toxins accumulated in the body plays a major role. Uric acid excretion decreases with increasing degree of renal failure.[4] Hyperuricemia in general population has been shown to be associated with metabolic syndrome, hypertension, peripheral and cardiovascular diseases, diabetes mellitus and chronic kidney disease.[5-10] High uric acid level increases mortality due to endothelial dysfunction, local renin angiotensin activation, oxidative stress and proinflammatory causes. Elevated serum uric acid concentration is an independent risk factor for mortality and CV risk, or it represents a surrogate marker for decreased kidney function, hypertension, and/or cardiovascular disease has been a matter of some debate. This controversy persists regarding those in the general population and patients with specific conditions such as diabetes and hypertension. Conflicting results also

Table 1. Laboratory parameters of the groups

	PD (n=61)	HD (n=51)	p
Age	56.77±12.58	57.25±16.45	0.864
Gender (Male/Female)	32/29	27/24	0.959
Duration of dialysis (Year)	3.25(1-14)	3.75(1.25-16)	0.925
Serum uric acid (mg/dL)	5.54±1.13	5.76±1.52	0.389
Ca (mg/dL)	8.45±1.39	8.34±1.27	0.653
P (mg/dL)	4.72±1.58	4.81±1.64	0.846
Parathormone(pg/mL)	304.8±112.4	289.4±105.7	0.885
Kt/V	1.83±0.458	1.58±0.25	0.226

PD: Peritoneal dialysis. HD: Hemodialysis. Ca: Calcium. P: Phosphorus.

exist regarding the role of serum uric acid level as a risk factor in patients with ESRD. Previous reports suggest that higher serum uric acid levels are related closely to other established risk factors, such as male sex, hypertension, and metabolic syndrome; thus, elevated serum uric acid concentration may contribute to increased mortality risk indirectly. Meanwhile, higher serum uric acid level may be considered a surrogate for better nutritional status, which is expected to decrease mortality in dialysis patients. There are studies describing positive and negative relationship between uric acid level and cardiovascular mortality in HD and PD patients as an independent risk factor.[11-17] Since the patients in our study were ESRD and dialysis patients, elevated uric acid levels expected in our study because our patients were end stage renal failure and underwent HD or PD. Elevated uric acid levels in these patients were due to renal dysfunction.[4] It is controversial which dialysis method is more effective. However, we have not found any studies on which dialysis form removes uric acid better.

Finally, in patients undergoing dialysis due to chronic kidney disease and ESRD, uric acid is high because it is not excreted sufficiently. It has been shown that elevated uric acid levels associated to hypertension, cardiovascular disease, diabetes mellitus and chronic kidney disease. Cardiovascular events are the most important cause of mortality in PD and HD patients. Our study described that uric acid, which shows its relationship with cardiovascular diseases, is cleaned in the same form in both dialysis types.

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CASE REPORT

Light Chain Cast Nephropathy Presenting with Asymptomatic Proteinuria

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Abstract

Kidney disease is a common complication of monoclonal gammopathies including multiple myeloma. Patients with multiple myeloma and other monoclonal gammopathies can present with a variety of kidney manifestations that depend upon the pathologic monoclonal proteins involved and the compartments of the kidney that are targeted. The most common clinical findings include acute or subacute kidney injury, chronic kidney disease, albuminuria or nephrotic syndrome and electrolyte abnormalities. The spectrum of kidney impairment ranges from mild to severe acute kidney injury (AKI) requiring hemodialysis. Most patients presenting with AKI have light chain cast nephropathy. 58-year-old female patient was referred to our clinic due to proteinuria. We aimed to represent a light chain cast nephropathy patient presenting with asymptomatic, non-nephrotic range proteinuria and whom were eventually treated with autologous stem cell transplantation. Light chain cast nephropathy should be kept in mind at the differential diagnosis of patients presenting with asymptomatic non-nephrotic range proteinuria especially whom were treated with anti-proteinuric medications. Kidney biopsy should not be deferred during the diagnostic process.

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Keywords: *Light Chain, Cast Nephropathy, Asymptomatic Proteinuria.*

Introduction

Kidney disease is a common complication of monoclonal gammopathies including multiple myeloma. Patients with multiple myeloma and other monoclonal gammopathies can present with a variety of kidney manifestations that depend upon the pathologic monoclonal proteins involved and the compartments of the kidney that are targeted. Approximately 20 to 50 percent of patients with multiple myeloma present with an elevated serum creatinine at the time of diagnosis.[1-5] The spectrum of kidney impairment ranges from mild to severe acute kidney injury (AKI) requiring hemodialysis. Most patients presenting with AKI have light chain cast nephropathy. Hypercalcemia is the most common electrolyte abnormality in patients with multiple myeloma (>%10, at the time

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of diagnosis).[2] Other electrolyte disorders include pseudohyponatremia and partial or complete Fanconi syndrome resulting in abnormalities such as renal tubular acidosis, hypouricemia, hypophosphatemia, aminoaciduria, renal phosphate wasting, and glycosuria. Laboratory tests used in the evaluation of monoclonal plasma cell disorders are serum free light chain (FLC) assay, serum protein electrophoresis and immunofixation, urine protein electrophoresis and immunofixation. The serum FLC assay is more sensitive than the urine protein electrophoresis for detecting FLCs.[6] We aimed to represent a light chain cast nephropathy patient presenting with asymptomatic, non-nephrotic range proteinuria and emphasize the importance of kidney biopsy for the patients even though indications are not certain.

Case Report

A 58-year-old female patient was referred to our clinic due to proteinuria. She was operated for breast cancer 7 years ago. She received radiotherapy and chemotherapy after the operation, and she was being followed in remission for the last 5 years. She was diagnosed with essential hypertension and she was receiving enalapril plus lercanidipine combination since then. The patient's blood pressure was 130/80 mmHg; pulse was 77 beats/min; temperature was 37^0C. No pathology was detected at her physical examination. In the laboratory tests, her renal function results and albumin levels were normal. Proteinuria was detected (++) in the dipstick urine test and 1.2 gr/day in the 24-hour urine sample. All laboratory tests which were performed in the patient's application are presented in Table 1. After detection of non-nephrotic range proteinuria, the levels of complement and autoimmune markers were found to be negative. All immunoglobulins were quantitatively diminished in plasma protein electrophoresis and immunofixation electrophoresis whereas monoclonal IgA protein was detected qualitatively. Kappa and lambda light chains detected in urine protein electrophoresis. Urine protein level was detected as 1.480 g/day quantitatively. Quantitative excretion of albumin fraction was detected as 1301.1 mg/L. Kappa light chain concentration was 2.89 mg/dL (0-0.9); lambda light chain concentration was 2.72 mg/dL (0-0.7) in urine immunofixation electrophoresis. Details of associated laboratory tests are presented at Table 2. We performed kidney biopsy because of the persistent proteinuria above 1g/day under angiotensin converting enzyme (ACE) inhibitor therapy. Histopathological examination of the biopsy material revealed that 3 of 32 glomeruli were global sclerotic, also mesangial expansion was detected at 6 glomeruli. Lymphoplasmacytic

Table 1. Laboratory Results

Lab Test	Results
Glucose (mg/dL)	93 (74-106)
Urea (mg/dL)	25 (17-43)
Creatinine (mg/dL)	0.66 (0.66-1.09)
Na (mmol/L)	138 (137-146)
K (mmol/L)	4 (3.5-5.2)
Cl (mmol/L)	101 (101-109)
Ca (mg/dL)	10.2 (8.8-10.6)
P (mg/dL)	3.7 (2.6-4.5)
Total Protein (g/L)	7.2 (6.6-8.3)
Albumin (g/dL)	4.1 (3.5-5.2)
Hb (g/dL)	10.7 (11.2-15.7)
Hct (%)	33.7 (34.1-44.9)
WBC ($x10^3/\mu l$)	7.27 (3.98-10.04)
Plt ($x10^3/\mu l$)	497 (180-370)
MCV (fL)	78.8 (79.4-94.8)
Blood Gas (venous)	PH:7.316 PCO_2:59.1 HCO_3:26
Dipstick Urine Test	Erythrocyte (-) protein (+)
Proteinuria (g/day)	1.2
AST (U/L)	12 (0-35)
ALT (U/L)	8 (0-35)

Na: Sodium; K: Potassium; Cl: Chlorine; Ca: Calcium; P: Phosphorus; WBC: white blood cells, Hb: Hemoglobin; Hct: Hematocrit; Plt: Platelet; MCV: Mean Corpuscular Volume; AST: Aspartate Transaminase; ALT: Alanine Aminotransferase

Table 2. Autoimmune Markers and other Laboratory Results

Lab Test	Results
ANA	NEGATIVE
p-ANCA	NEGATIVE
c-ANCA	NEGATIVE
C_3 (mg/dL)	167(90-180)
C_4 (mg/dL)	33.4(10-40)
IgG (g/L)	6.12 (7-16)
IgA (g/L)	0.65 (0,7-4)
IgM (g/L)	0.28 (0,4-2,3)
PEF	Albumin: 54.4% (40-65); alpha-1: 3.7% (1.5-4.2); alpha-2: 17.9 % (8.3-16.6); beta: 14% (8.5-17.9); gamma: 10% (9.5-20.7)
IEF_S	Whole immune globulins diminished quantitatively; monoclonal IgA protein detected qualitatively.
IEF_u	Urine kappa concentration 2.89 mg/dL; urine lambda concentration 2.72 mg/dL. Urine protein level is detected as 1.480 g/day quantitatively.
Kappa l.c (mg/L)	25.8(6.7-22.4)
Lambda l.c (mg/L)	>58.6(8.3-27)

ANA: Anti-Nuclear Antibody; ANCA: Anti Neutrophil Cytoplasmic Antibody; C_3: Complement 3; C_4: Complement 4; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IgA: Immunoglobulin A; PEF: Protein Electrophoresis; IEF_S: Immune fixation on electrophoresis; Kappa l.c: Kappa Light Chain; Lambda l.c: Lambda Light chain

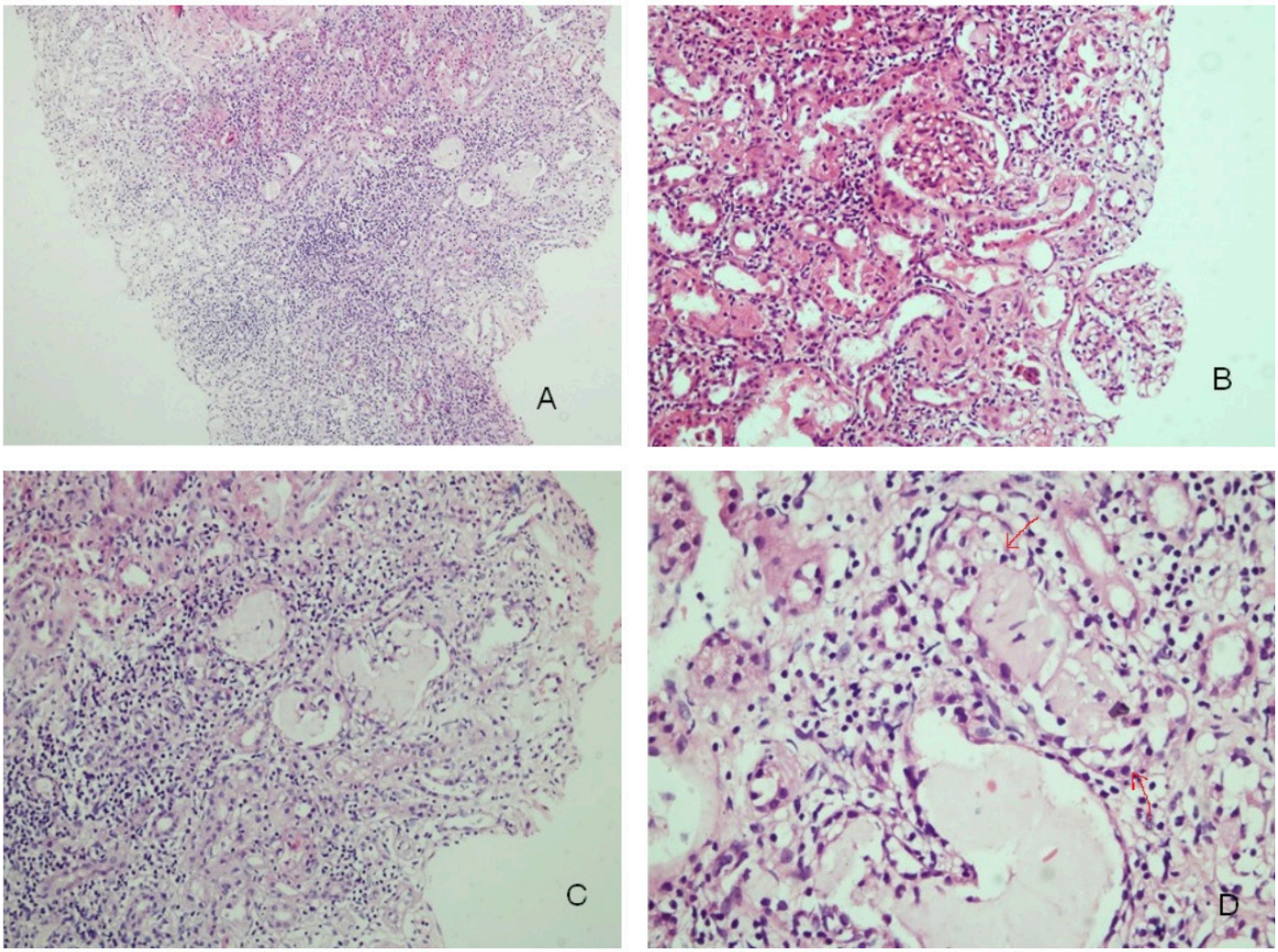

Figure 1. a) Massive tubulointerstitial nephritis at the medullar zone, **b)** Interstitial inflammation at the cortical zone, near normal glomerular structure, **c)** Cast material at the eosinophilic distal tubules in the medullar region, **d)** Cast material surrounded by histiocytic reaction at the distal tubules shown with arrows.

inflammatory infiltration including diffuse eosinophils were detected at tubulointerstitial area. Intertubular cast structures were detected predominantly at distal tubules but also at proximal tubules. Amyloid staining was positive with Kongo red at one of those cast structures. Interstitial fibrosis-tubular atrophy (IFTA) was presented at %10 of cortical area. C4d was determined granular positive by immunohistochemical method. Positive C4d staining supports the diagnosis of amyloid accumulation. The pathological images are presented at Figure 1 and Figure 2. After that result the patient referred to the hematology department for treatment and follow up arrangements.

Bone marrow biopsy was performed and reported as follows: cellularity is 55%, plasma cells at interstitium is increased. Histochemical examination revealed amyloid accumulation is negative with Kongo Red and reticular fiber degree I. Neoplastic plasma cells were positive with IgG and lambda at immunohistochemical examination. CD138 (+) plasma cells were about 30 % and distributed at interstitium. Neoplastic plasma cells were negative with CD3, cyclin D1, and c-myc. Interstitial lymphoid cells revealed partially T lymphocyte phenotype with CD3 and B lymphocyte phenotype with CD20 and CD19.

The bone marrow biopsy was reported as plasma cell disorder and patient were diagnosed as multiple myeloma. Patient treated with autologous stem cell transplantation after 4 cures chemotherapy and is still being followed up in nephrology, hematology clinics with normal kidney functions and proteinuria <1000 mg/day.

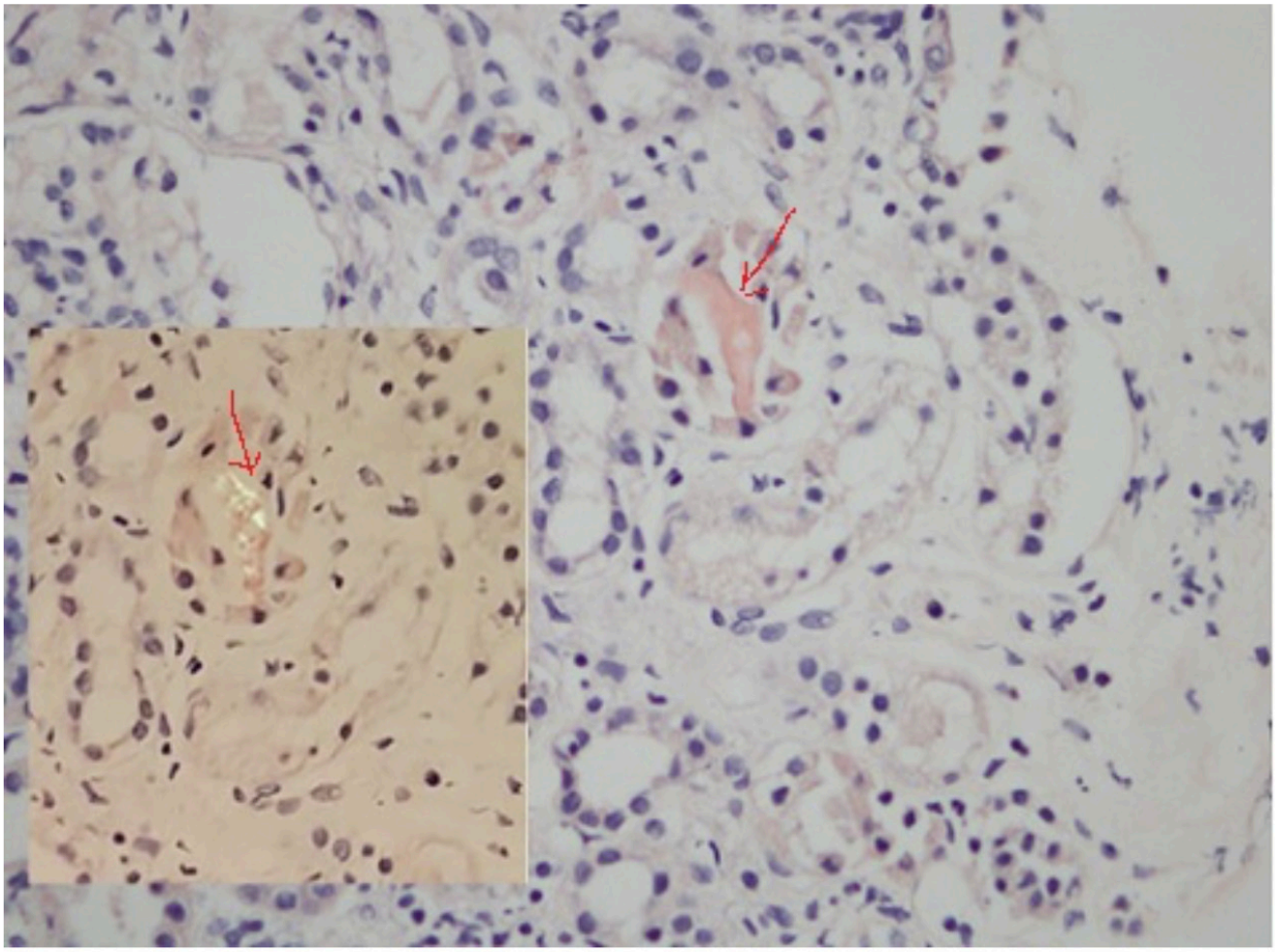

Figure 2. Kongo Red (+) cast material in the distal tubule, histiocytic accumulation shown with arrow and at the small figure bifragent view under polarized light microscope.

Discussion

Biopsy indications are not certain for patients with normal renal functions and proteinuria ranges between 1 g/day and nephrotic range (>3.5 g/day). Most clinicians prefer to follow up those patients especially if renal functions are normal. Our case differs from other similar cases by representation asymptomatically even though light chain cast nephropathy lies under. We performed kidney biopsy at our patient because of the persistent proteinuria greater than 1 g/day even after using more than a 6-month period (7 years) of ACE inhibitor. The whole basic laboratory workup was normal at the presentation of our case. The overall goal of evaluation of a patient with kidney disease and a monoclonal protein is to determine whether a monoclonal protein is involved in the pathogenesis of the kidney disease. Kidney biopsy is required to establish this association and to guide therapy in many cases unless contraindicated. Laboratory testing of monoclonal proteins can assist with narrowing the differential diagnosis and plays an important role in monitoring the response to treatment. We performed serum protein electrophoresis and immunofixation before the biopsy procedure. Hypogammaglobulinemia was detected at serum protein electrophoresis. After detecting cast nephropathy at the kidney biopsy sample, bone marrow aspiration and biopsy were performed. Serum FLC assay and urine protein electrophoresis and immunofixation were also performed.

Light chain cast nephropathy should be strongly suspected in any patient presenting with unexplained kidney impairment over a period of less than six months and an elevated FLC level of ≥1500 mg/L. By contrast, light chain cast nephropathy is uncommon in patients with low (<500 mg/L) serum FLC concentrations.[7-9] We detected low levels than expected in our case.

The extent to which the serum FLC ratio is abnormal may also distinguish light chain cast nephropathy from other lesions associated with myeloma. In one study, patients with light chain

cast nephropathy had much higher ratios compared with patients with either amyloidosis or light chain deposition disease (LCDD).[10]

After bone marrow biopsy, our case was diagnosed as multiple myeloma which referred with light chain cast nephropathy. Although most patients presenting with AKI have light chain cast nephropathy, we did not find any laboratory results compatible with kidney injury at the time of diagnosis. If we had had delayed the biopsy due to the normal laboratory results kidney failure might have ensued. It is known that, once kidney involvement occurs, the complication risk rises and the chance for cure diminishes.

The importance of our case is that, although whole laboratory results were not high enough as expected at those cases, we diagnosed by kidney biopsy which was not definitely indicated. After that, patient was treated appropriately with autologous stem cell transplantation owing to early detection of the disorder by kidney biopsy which is not often performed in most cases with asymptomatic proteinuria.

As a conclusion, we aimed to emphasize that light chain cast nephropathy should be kept in mind at the differential diagnosis of patients presenting with asymptomatic non-nephrotic range proteinuria especially whom were treated with ACE inhibitors longer than 6 months. Kidney biopsy should be performed at appropriate cases confidentially.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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CASE REPORT

Malignant Tumors with Low FDG-PET Uptake: A case Report and Review of the Literature

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Abstract

Fluorine 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a well-accepted examination for diagnosis, staging, and monitoring in clinical oncology. According to the higher glucose metabolism rate, malignant tumor cells have higher FDG uptake, besides higher FDG uptake is strictly correlated with poor prognosis in various types of cancer. However, FDG-PET has limitations associated with some of the cancer types that have low FDG uptake, even high metabolism. Low cellularity, low glucose metabolism, inadequate patient preparation, small-sized tumor, and cellular mucin might be cause to low FDG uptake. Low FDG uptake frequently presented in lepidic growth adenocarcinoma (formerly defined as bronchoalveolar adenocarcinoma), renal cell cancer, and mucinous neoplasms.

We report on a case of 57-year-old female biopsy proven Signet Ring Cell Carcinoma (SRCC) patient without FDG-PET uptake in the evaluation for staging. The patient admitted to hospital with massive ascites and dyspeptic complaints. Further evaluation revealed the existence of SRCC with no FDG-PET uptake.

FDG-PET reveals valuably findings in clinical oncology for diagnosis, staging, and monitoring. Although FDG-PET uptake is correlated with most of the malignant tumors' activity, some aggressive malignancies may have no/low FDG uptake and FDG uptake is not predictive of survival.

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Keywords: *FDG-PET, malignant tumors, signet cell.*

Introduction

Fluorine 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) has established the usefulness in clinical oncology for diagnosis, staging, and monitoring.[1] According to the higher glucose metabolism rate, malignant tumor cells have higher FDG uptake, besides higher FDG uptake is strictly correlated with poor prognosis in various types of cancer.[2] However, FDG-PET has limitations associated with some of the cancer types that have low FDG uptake, even high metabolism, and poor prognosis or high FDG uptake of benign tumors related to the high

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inflammatory process.[3] Likewise, studies revealed that low cellularity, low glucose metabolism, inadequate patient preparation, small-sized tumor, and cellular mucin might be cause to low FDG uptake.[4] As mentioned in the literature before, low FDG uptake frequently presented in lepidic growth adenocarcinoma (formerly defined as bronchoalveolar adenocarcinoma), renal cell cancer, and mucinous neoplasms.[4-5] Mucinous carcinoma defined as an epithelioid neoplasm that contains clear, gelatinous fluid called mucin and has low cellularity leading to low FDG uptake.[2] Clinical studies revealed that the presence of mucin is highly correlated with lower survival rates except for colorectal carcinomas.[6] Signet ring cell carcinoma (SRCC) is a rare mucinous adenocarcinoma, affects the stomach predominantly and occasionally ovary, colon, rectum, prostate, and bladder.[7] Although gastric cancer incidence is decreasing, recent studies showed the increasing incidence of gastric SRCC.[8] Approximately 15-28% of gastric carcinomas are SRCC, characteristically infiltrates the gastric wall diffusely, and associated with poor prognosis.[9] According to studies, SRCC patients have poor outcomes such as an inclination for metastasis and a reduced response to chemotherapy.[10,11]

In this case report, we are presenting a 57-year-old female biopsy proven SRCC patient without FDG-PET uptake in the evaluation for staging. The purpose of this report is to remind the limitations of FDG-PET usage in certain malignancies.

Case Report

A 57-year-old female patient admitted to internal medicine outpatient clinic with the complaints of severe abdominal distention and dyspepsia. The patient had history of admission to Ob/Gyn outpatient clinic with the same complaints three months ago. Gastric wall thickening was reported in abdominal computerized tomography (CT). Gastroscopic evaluation reveals no abnormal findings. Evaluation of gastric wall biopsy specimen shows chronic inactive gastritis. Proton pump inhibitor (PPI) therapy was prescribed.

In current admission patient admitted with massive ascites which aggravates dyspeptic complaints. Patient was hospitalized for further evaluation and paracentesis was performed. Macroscopically, the sample was hemorrhagic, and serum ascites albumin gradient was measured under 1.1 mg/dL (0.1 mg/dL). Tuberculosis or bacterial pathogens were not detected in ascitic fluid culture. CT scans showed diffuse gastric wall thickening, a decrease in gastric volume, and heterogeneous density areas on the mucosal faces of the stomach. Edematous, erythematous and fragile gastric corpus mucosa was observed in gastroscopic evaluation, and multiple site biopsy was performed. Pathological evaluation was reported as signet ring cell carcinoma (Figure 1). No significant metabolic activity was observed in any area, including the gastric region in FDG-PET evaluation (Figure 2).

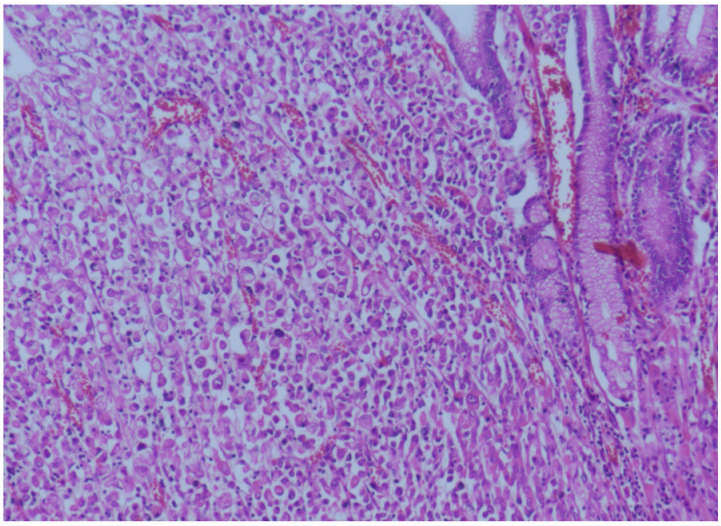

Figure 1. Gastric Signet Ring Cell Carcinoma at higher magnification (Hematoxylin & Eosin x100)

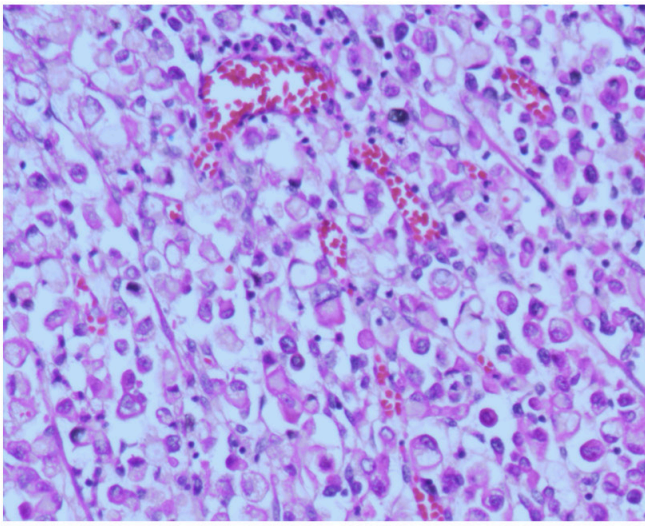

Figure 2. Gastric Signet Ring Cell Carcinoma at higher magnification (Hematoxylin & Eosin x200)

The patient had consulted to gastroenterological surgery and medical oncology. Chemotherapy has planned due to diffuse tumor spread. The patient assigned to the oncology service for chemotherapy. Docetaxel, Oxaliplatin, Leucovorin, and 5-fluorouracil (FLOT) chemotherapy were applied for eight cures. After the chemotherapy regimen, the patient underwent surgery six months after diagnosed with gastric SRCC.

Discussion

SRCC is a rare mucinous adenocarcinoma, mainly affects stomach.[7] Nearly 15-28 % of gastric carcinomas are SRCC, and recent studies revealed that the incidence of gastric SRCC is increasing.[8,9] Gastric SRCC is encountered frequently in the female and at a relatively younger age. SRCC has a worse prognosis compared to other advanced gastric cancers.[5,12] SRCC contains high levels of mucin and has a diffuse spreading pattern; therefore, has a low FDG uptake, notwithstanding high glucose metabolic activity.[9] Mucin is considered as an indicator for the aggressiveness of gastrointestinal tumors except colorectal tumors.[2,12,13] Baldus et al.[14] examined the correlation between mucin core peptide antigens (MUC) and TNM, as well as prognosis, in gastric carcinomas by immunohistochemistry studies. The study showed that the presence of MUC1 mucin is indicating increasing invasion and related to poor prognosis. Reversely, MUC2 mucin is indicating low metastasis potential.[2,14]

FDG-PET is a well-accepted examination for diagnosis, staging, and monitoring in clinical oncology. Even high FDG uptake is frequently correlated with malignancy and poor prognosis, studies have shown limitations of FDG-PET.[1,3] Particularly, mucin involving gastrointestinal tract carcinomas, lung carcinomas, and some of the malignant tumors have low FDG-PET uptake.[1,3] Also, studies claimed that FDG-PET may not guide to asses recurrent or metastatic disease in mucinous carcinoma.[2] Berger et al.[2] investigated FDG-PET detection of locally advanced gastric carcinoma in 40 patients and reported the sensitivity of FDG PET less than 60% (24/40). The rate of detection of tumors of the non-intestinal growth type was 41% (9/22). Furthermore, the study revealed that gastric carcinoma FDG uptake is not related to tumor aggressiveness.[2]

As mentioned in previous studies, low FDG-PET uptake is encountered in renal cell carcinomas (RCC) due to increased activity of healthy renal tissue, and FDG excretion to urine. Mutual findings of several studies claim that FDG- PET have a limited role in the evaluation of primary or metastatic RCC.[15]

In conclusion, we need to keep in mind that

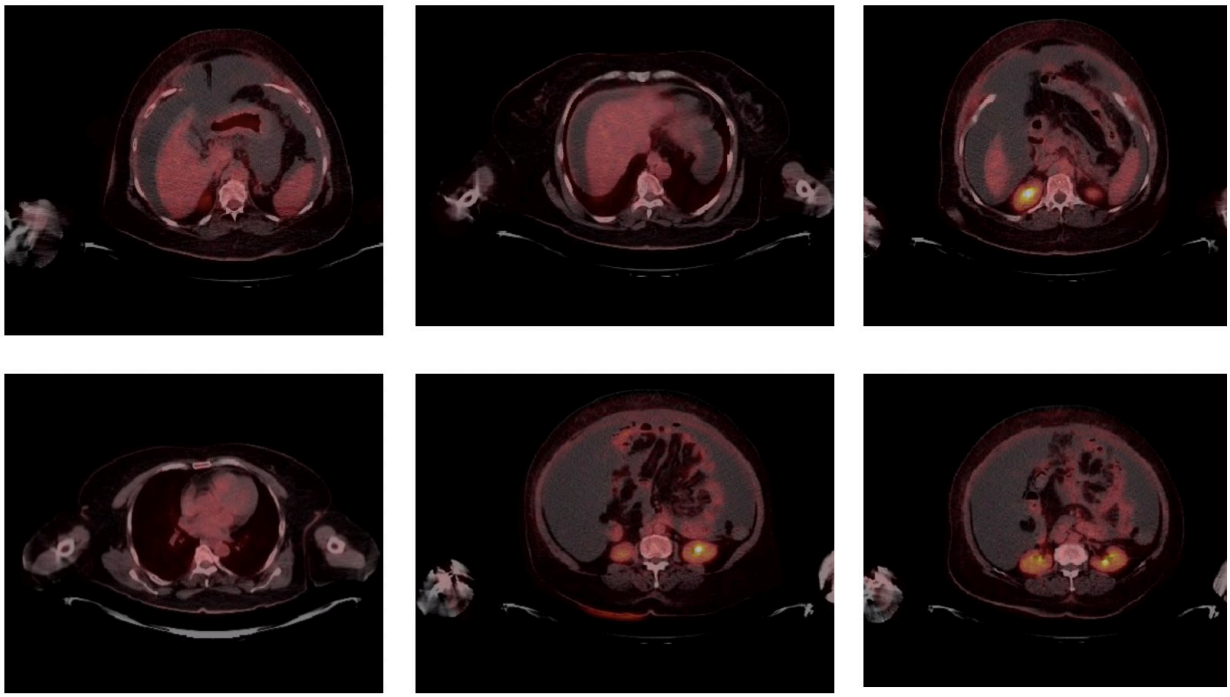

Figure 3. FDG-PET CT evaluation shows no significant uptake

although FDG-PET uptake is correlated with most of the malignant tumors' activity, some aggressive malignancies may have no/low FDG uptake. This report aimed to give rise to consider the limitations of FDG-PET in mucin involving tumors such as SRCC, lepidic growth adenocarcinoma, and renal cell cancer tumors. Additionally, to remind FDG uptake is not predictive of survival.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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