Renal involvement in multiple myeloma: new insight into mechanisms

Şule ŞENGÜL[1], Vecihi BATUMAN[2]

[1] Department of Nephrology, Ankara University Medical Faculty, Ibn-i Sina Hospital, Ankara, Turkey
[2] Nephrology Section, VA Medical Center, and Tulane University Medical Faculty, New Orleans, LA, USA

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RENAL INVOLVEMENT in MYELOMA: RECENT INSIGHT into MECHANISMS

Multiple myeloma is characterized by neoplastic proliferation of a single clone of plasma cells producing an M-protein. The clone of plasma cells proliferates in the bone marrow and frequently invades the adjacent bone causing skeletal destruction that results in bone pain and fractures. Anemia, hypercalcemia and renal involvement are among main features of multiple myeloma. Renal involvement is present in approximately 20-50% of the cases at diagnosis and includes a variety of renal disorders[1-5]. Renal insufficiency portends a worse prognosis and complicates the management of this already difficult-to-treat cancer. A recent review from the United States Renal Data System (USRDS) shows that renal morbidity from multiple myeloma is a considerable burden[6]. Of the 375.152 patients in the registry initiated on ESRD therapy in the United States between January 1, 1992 and June 30, 1997, 3298 (0.88%) had myeloma associated kidney disease. These patients were disproportionately male (59.5% vs. 53.2%) and Caucasian (76.2% vs. 64.1%) and older (68.00 ± 11.78 vs. 60.69 ± 16.55 years). Patients with myeloma associated kidney disease had lower serum hemoglobin, higher creatinine, and were more likely to have been started on hemodialysis than peritoneal dialysis. The two-years all-cause mortality of patients with myeloma kidney involvement during the study period was significantly greater, 58% vs. 31% in all other patients. Furthermore, myeloma kidney disease was independently associated with 2.5-fold increase in all-cause mortality[6].

There is now considerable body of work that has improved our understanding of the mechanisms of kidney involvement in multiple myeloma. In this review we will summarize the type of kidney involvement and highlight the current understanding of the pat-

Multipl miyelomada renal tutulum: Mekanizmalara yeni bir bakış

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hophysiologic mechanisms of kidney disorders with multiple myeloma and include a brief discussion of therapy.

The monoclonal light chains produced by a neoplastic clone of B cells cause almost all of the renal disorders with the exception of hypercalcemic nephropathy, rarely, heavy chain or intact immunoglobulin deposition and even more rarely, plasma cell infiltration. Thus it can be argued that perhaps the renal disorders that accompany myeloma are unique to myeloma or to light chain overproduction states and that these lesions are not encountered in other diseases, although there is emerging evidence that renal involvement in myeloma may involve common pathophysiologic pathways with other proteinuric diseases. In this review, we will also briefly examine this brief notion that studies on the mechanisms of kidney disease in multiple myeloma may provide surprising clues to the mechanisms of kidney disease in other proteinuric diseases.

Kidney disorders in myeloma can be viewed in three broad categories: alterations in renal tubular functions, structural abnormalities associated with acute or chronic kidney failure and other disorders not directly linked to monoclonal gammopathy (Table 1).

Renal Handling of Light Chains

For a more complete understanding of renal disorders associated with light chain proteinuria a brief overview of the renal handling and metabolism of light chains would be helpful. Free immunoglobulin light chain fragments, MW approximately 22 to 25 kDa in monomeric form, are present in plasma. In normal humans aged 21 to 90 using a new method Katzmann et al estimated the diagnostic interval for free κ light chains at 3.3-19.4 mg/L, and for free λ light chains at 5.7-26.3 mg/L. Although the precise filterability of free light chains in the glomerulus is unknown, because of their size and relative to albumin cationic net charge, light chains have been assumed to be relatively freely filtered in the glomerulus[7,8]. In one review the glomerular sieving coefficient for free κ light chains is given as 0.09[8]. Using this value for the total free light chain (κ + λ), an average filtered load of 100 to 600 mg/24 h light chain can be estimated to be presented to the kidney tubule. That the urine is virtually free of light chains-normal humans excrete less than 3-5 mg/24 h light chain, clearly implies a huge capacity by the renal tubule to absorb filtered light chains[8-10]. Recent studies have shown that filtered light chains are endocytosed by the proximal tubule cells via the tandem scavenger receptor system cubilin/megalin and targeted to catabolic sites through the classical endosomal/lysosomal pathway, catabolized to its amino acid constituents, and are returned to circulation[11-15].

Overproduction of light chains in myeloma and excessive endocytosis may lead to "protein overloading" and can interfere with the physiologic transport functions of proximal tubule cells probably because of impaired cell trafficking of cell surface transporters, such as amino acid, phosphate transporters. Prolonged protein overloading can trigger cell stress responses and result in apoptosis/necrosis as well as induction of inflammatory and proinflammatory cytokines[12,16-23].

Furthermore, when overproduction exceeds the endocytic capacity of the proximal tubule, increased concentrations of light chains in the renal tubule may be available for interaction with Tamm-Horsfall proteins and formation of the typical myeloma casts[24].

There is considerable variability among the light chains that are associated with kidney disorders in myeloma[25-29]. In some patients small amounts of light chain proteinuria may be associated with severe nephropathy while in others light chain proteinuria up to 8-9 g/day or greater maybe associated with minimal if any renal dysfunction. This has been taken as evidence of variability among light chains' nephrotoxicity. In gene-

Table 1. Kidney involvement in multiple myeloma

Tubular functional abnormalities
Fanconi syndrome
Concentrating defect
Distal renal tubular acidosis
Hypercalcemic nephropathy
Low-molecular weight proteinuria
Structural abnormalities
"Myeloma kidney" (chronic tubulointerstitial nephropathy)
Acute cast nephropathy
Glomerulopathy
Light chain deposition disease
Amyloidosis, type AL
Fibrillary (monotypical membranous) glomerulonephritis
Vascular lesions
Neoplastic cell infiltration
Others (miscellaneous)
Dehydration and contrast media-induced renal failure
Acute uric acid nephropathy
Obstructive nephropathy
Hyperviscosity syndrome
Asymptomatic light chain proteinuria

ral, the variability in light chain nephrotoxicity has been found determined by the variable region, V_L, of light chain molecule [25-27,30-32]. For example, among the light chain subtypes, λVI light chains have been found most frequently but not exclusively in AL amyloidosis[33]. In an in vitro model λVI light chains formed amyloid rapidly while others did not. The precise determinants of variable toxicity however have not been fully identified. It is now widely accepted that both κ and λ light chains can be equally nephrotoxic, although λ light chains are more frequently associated with amyloidosis while κ chains are more frequent than λ in Fanconi syndrome[27,34-37]. The earlier reports that the net electrical charge, pI, of the light chain molecule correlated with toxicity has not been confirmed in later studies[38-41].

Tubular Functional Abnormalities

These changes are often subtle and frequently missed in early stages. Tubular functional alterations, like other myeloma associated renal disorders, are associated by light chain proteinuria. Proximal tubular events prevail and full Fanconi syndrome, characterized by aminoaciduria, renal-proximal tubular acidosis, glycosuria, kaliuresis, phosphaturia, hyperuricosuria may occur[27,31,42-44]. Increased urinary excretion of potassium, uric acid and phosphate often is associated with hypokalemia, hypouricemia and hypophosphatemia and may be clues to a proximal tubular dysfunction that may initiate clinical investigations identifying the underlying myeloma[34,45]. Multiple myeloma is the most common cause of proximal renal tubule acidosis in the adult.

The pathophysiology of Fanconi syndrome appears to be mediated through direct toxic effects of myeloma light chains on proximal tubule cells[16,17,23]. Although κ light chains are more frequently associated with Fanconi syndrome both subtypes have been implicated[26,27,31,36,37,46-48]. This is consistent with studies that have demonstrated that both κ and λ light chains can inhibit transport of glucose, amino acids and phosphate, in vitro, at concentrations that can be found in tubule fluid of patients with multiple myeloma and light chain proteinuria. Furthermore, a direct inhibitory effect by light chains on the renal isoform of Na-K-ATPase on proximal tubule cells at both protein and gene level may interfere with cells' energy metabolism and may be a contributing mechanism for the proximal tubular functional abnormalities[16].

Clinical studies have shown that many multiple myeloma patients with light chain proteinuria also suffer from concentrating defect that may result in polyuria and polydypsia[49]. The precise cellular mechanisms for this disorder in myeloma have not been identified, but are attributed the tubulointerstitial changes and tubule unresponsiveness to vasopressin, i.e., a nephrogenic diabetes insipidus.

Distal renal tubular acidosis can also occur in multiple myeloma patients who have light chain proteinuria. This, however, is rare and there are no studies that address the pathophysiologic mechanisms[45].

Myeloma Kidney

The most common type of renal involvement in multiple myeloma is a chronic tubulointerstitial nephropathy characterized by tubular atrophy and tubulointerstitial fibrosis often associated with casts, and also referred to as "cast nephropathy" (Figure 1)[2,41,42,50-57]. There is much research on pathophysiologic mechanisms and considerable new insight on the role of light chains in the genesis of chronic kidney injury. Sanders et al have demonstrated that certain types of light chains, which may be characterized as "castogenic" behave as ligands binding to defined sites on Tamm-Horsfall proteins and that these light chains are responsible for "cast nephropathy"[42,55,58-62]. Animal models with hybridomas prepared from myeloma patients have confirmed that cast-forming myelomas produce similar kidney lesions in mice[28]. However, these casts are seldom extensive and how occasional casts would lead to a pervasive sequence events that result in tubulointerstitial inflammation, scarring and fibrosis has not been fully addressed.

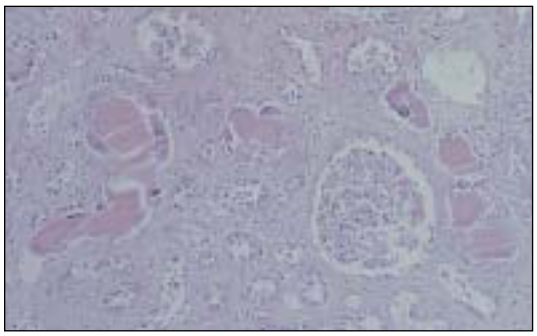

Figure 1. Myeloma kidney. Section from the kidney of a patient with multiple myeloma illustrating findings typical for "myeloma kidney". The field shows extensive interstitial fibrosis and tubular atrophy with casts in tubule lumens. The fractured lamellated appearance of the casts is said to be typical for myeloma casts. By immunocytochemistry, these casts are demonstrated to contain monoclonal light chains. PAS stain 400x.

Recent studies from our laboratory provide intriguing clues to a novel pathophysiology of the chronic tubulointerstitial nephropathy that accompanies myeloma[16,22,63,64]. These studies probed the role of the most abundant cell type in the kidney, the proximal tubule epithelium, which also is the cell type responsible for endocytosis and catabolism of filtered light chains. A series of myeloma light chains collected and purified from the urine of multiple myeloma patients with mild to moderate renal insufficiency and without albuminuria, i.e., without evidence of glome-

rulopathy, were shown in these studies to induce apoptosis and increased DNA degradation in cultured proximal tubule cells[64]. Prolonged exposures were also shown to lead to necrosis. More interestingly, these tubulopathic light chains at concentration either at or considerably below levels expected in the glomerular ultrafiltrate of a typical myeloma patient with modest amount of light chain proteinuria were also shown to induce inflammatory/proinflammatory cytokine production[22,63]. Detailed investigations suggest that these cytokine responses are due to activation of cell stress responses due to increased endocytosis and overloading by myeloma light chains. In these studies light chains are shown to induce production of interleukin 6 (IL-6), IL-8, MCP-1 but no TGF or IL-1. These cytokine responses were mediated by activation of nuclear factor-κB and AP-1 and dependent on light chain endocytosis. Maneuvers that either inhibit the activation of these transcription factors or block light chain endocytosis, both abrogated cytokine responses. Light chain activation of nuclear transcription factors appears to be signaled through the MAPKs ERK 1/2, JNK and p38. Pharmacologic inhibitors of these MAPKs blocked these cytokine responses in vitro in proximal tubule cells exposed to light chains. The totality of these findings strongly argue for a major role for proximal tubule cells and cytokines produced by these cells in the pathogenesis of chronic tubulointerstitial inflammation that is the hall-mark of myeloma kidney. Furthermore, the relatively nontoxic pharmacologic inhibitors of both NF-κB and MAPKs may provide potential therapeutic options for patients with myeloma kidney[22,63].

These cytokine responses are similar to those observed in albumin exposed proximal tubule cells in a series of experiments concluding that the propensity to inexorable progression to end-stage in proteinuric diseases may be mediated by albumin overloading[19-21]. In contrast, in head-to-head comparisons with light chains, we found human serum albumin at equimolar or greater concentrations much less potent than light chains in inducing cytokine responses in cultured human proximal tubule cells[22,63]. In previous experiments, we had also observed that the affinity of albumin binding to proximal tubule cell endocytic receptors was much lower than that of light chains[12,15,65]. These observations cast doubt on the pathogenic potential of albumin. Indeed, progressive kidney injury is almost never seen in glomerular diseases associated with selective albuminuria, such as minimal change nephrotic syndrome in children. Most proteinuric diseases in adults are, in contrast, non-selective and large quantities of other proteins including light chains are present in the urine of such patients. For example in a study on early diabetics Groop et al found increased κ-light chain excretion in the urine even though the blood concentrations of light chains were not elevated in these patients[66]. These observations suggest that the pathophysiologic events that occur in myeloma kidney may be common to other proteinuric diseases, pointing out to myeloma kidney disease as a useful model for the study of progressive kidney disease. Our findings that light chains at low concentrations can induce inflammatory cytokines raises the possibility that light chains as well as other low molecular weight proteins that inevitably accompany albumin in disease states where glomerular permselectivity is impaired may be the true perpetrators of progression.

Acute Cast Nephropathy

There are cases documented to present with severe acute oliguric renal failure often associated with significant dehydration and with massive cast deposition both in distal but more prominently in proximal tubules[4,67-69]. Occasionally this presentation is seen concomitantly with contrast administration and additive nephrotoxicity of contrast dye as well as the accompanying dehydration have been implicated as contributing factors[4,70,71]. Acid pH in tubular fluid, reduced renal plasma flow and hypercalcemia are

among other factors implicated in cast formation. Precipitates of Tamm-Horsfall glycoprotein in the presence of contrast media have also been demonstrated[72-74]. Hypercalcemia and Bence-Jones proteinuria and hypovolemia have been present in most patients who developed this syndrome. Contrary to the widely held contention that contrast dye use is contraindicated in patients with myeloma, it has now been shown that contrast procedures can safely be performed provided that the patients are adequately hydrated using normal saline prior to, during and after the procedure[75].

Acute cast nephropathy perhaps is associated with the worst outcome among all types of kidney involvement in myeloma and warrants aggressive treatment, which some investigators believe should include plasmapheresis. There are no good large controlled trials demonstrating convincingly the effectiveness of plasmapheresis[76]. However, in one small controlled trial in a total of 29 patients, Zucchelli et al found plasmapheresis was associated with superior renal outcomes and better overall survival[77].

Light Chain Deposition Disease and Amyloidosis

Glomerular involvement in myeloma may manifest as either light chain deposition disease (LCDD) or as amyloid light chain (AL) amyloidosis[2,78-80]. Both disorders are associated with monoclonal light chains often in the setting of multiple myeloma or occasionally with monoclonal gammopathy of unknown significance (MGUS), a condition in which there may be overproduction of modest quantities of a monoclonal immunoglobulin but without overt myeloma. Rarely, LCDD presents without any detectable gammopathy and in kidney biopsy the nodular glomerular deposits can be mistaken for diabetic nephropathy if immunohistochemical studies are not carried out (Figure 2a and b)[81].

Amyloid deposits stain for Congo red on light microscopy and have characteristic fibrillary appearance on electron microscopy. On the other hand deposits in LCDD are detected by immunocytochemical techniques using specific antibodies against light chains and display a granular appearance on electron microscopy. Combined kidney and liver involvement can occur both in primary amyloidosis (AL amyloidosis) and LCDD, often detected histologically and rarely clinically[78,82,83]. Renal manifestations include proteinuria, nephrotic syndrome, and progressive renal failure. End-stage renal disease requiring dialysis is observed in about 20% of patients with AL amyloidosis and in 70% of patients with LCDD. The mean survival time is about 12 to 18 months in AL amyloidosis and 34 months in LCDD. The most important prognostic factor is severe cardiac involvement, which reduces the mean survival to only six months. Hepatic manifestati-

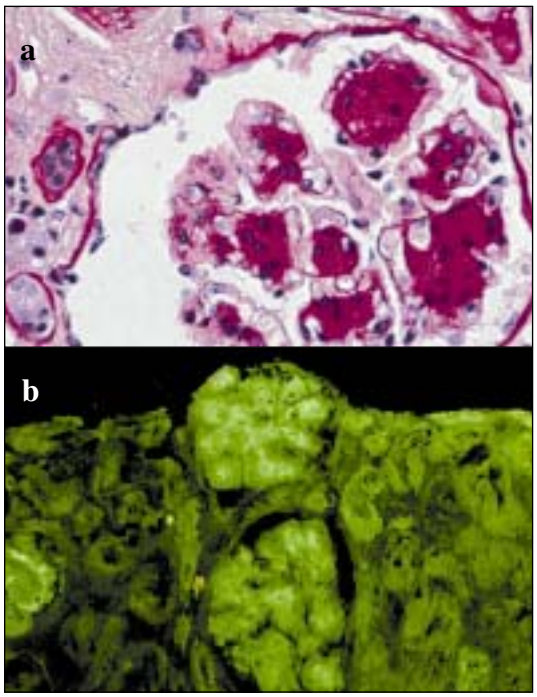

Figure 2 a. Section shows homogenous nodular deposits within the glomeruli. **b.** Immunofluorescent staining confirms that the deposits consist of kappa light chains. (Figure courtesy of Professor Dr. Suzanne Meleg-Smith, Nephropathology Program, Tulane University Medical School).

ons include hepatomegaly, portal hypertension, ascites, intrahepatic cholestatic jaundice, and liver failure. The mean survival of patients with liver involvement is 14 months, and is as low as 5 months in patients with cholestatic jaundice[82].

There is no specific treatment for either AL amyloidosis or LCDD, and the prognosis remains poor. Treatment aimed to suppress proliferation of the abnormal clone of plasma cells is often attempted. The regimens, including melphalan-prednisone (MP) or vincristine-doxorubicin-dexamethasone (VAD), are used both in AL amyloidosis and in LCDD with some effectiveness[82,84]. Dialysis apparently does not influence the outcome in either disease because survival of patients on dialysis is not different from that of patients not reaching uremia. Kidney and liver transplantation is found effective, though amyloidosis or LCDD may occur in transplanted organs[82,85]. The most interesting therapeutic approach is autologous-blood stem-cell transplantation, which may produce a complete remission of the plasma-cell dyscrasia and a substantial improvement of clinical manifestations related to LC deposits[82].

The pathophysiology of glomerulopathy appears to be mediated through the interaction of glomerulopathic monoclonal light chains with mesangial cells. Early signaling events control mitogenic activities and cytokine production, which participate in the subsequent pathologic events. Mesangial homeostasis is affected in two very different ways, depending on whether the glomerulopathic light chain is from a patient with LCDD or light chain-related amyloidosis (AL-Am). In contrast, tubulopathic light chains from patients with myeloma cast nephropathy do not interact significantly with mesangial cells and result in no alterations in mesangial homeostasis. Therefore, understanding early events in the monoclonal light chain-mesangial cell interactions is fundamental. In a study by Russell et al mesangial cells in culture were exposed to light chains obtained and purified from the urine of patients with plasma cell dyscrasias and biopsy-proven renal disease, including LCDD, AL-Am, and myeloma cast nephropathy. Incubation of mesangial cells with glomerulopathic, but not tubulopathic light chains, resulted in cytoskeletal and cell morhopology changes, activation of platelet-derived growth factor-beta (PDGF-ß) and its corresponding receptor, cytoplasmic to nuclear migration of c-fos and NF-κB signals, and production of MCP-1, as well as increased expression of Ki-67, a proliferation marker. Although NF-κB activation was directly related to MCP-1 production, c-fos activation regulated proliferative signals and cytoskeletal changes in MC. Interestingly, amyloidogenic light chains were avidly internalized by the mesangial cells, whereas LCDD-light chain effector targets were located at the MC surface. These cellular events are likely initiated as a result of interactions of the glomerulopathic light chains with yet-uncharacterized mesangial surface receptors. Conceivably, these receptors may involve the tandem cubilin/megalin system, as they are known to be expressed in mesangial cells also[86].

Nonlight chain mediated kidney disorders: Kidney involvement may occur through nonlight chain mediated mechanisms in various other circumstances. Among these disorders to be briefly discussed are vascular lesions, plasmacytic infiltration, hypercalcemia, acute uric acid nephropathy, urinary tract obstruction from plasmacytoma and hyperviscosity syndrome.

Vascular lesions: Although isolated involvement of the renal vasculature is unusual, glomeruli and other vessels are concomitantly affected by light chain deposition. Amyloid or granular light chain deposition can be found. Light chain deposits are generally localized to the walls of arterioles and small and medium arteries. Both proliferative and nonproliferative vasculopathies can occur and contribute to progressive loss of renal function in some patients[2].

Neoplastic cell infiltration: Actual renal parenchymal infiltration by neoplastic plasma cells is a very rare entity as either a solitary plasmacytoma or a manifestation of multiple myeloma[87-89]. On some occasions, especially when associated with amyloidosis, the kidneys may attain a huge size and become palpable by abdominal examination. Plasmacytoid cells have been recovered from urine sediment in some patients with massive cell infiltration.

Hypercalcemia

Mild hypercalcemia (11-13 mg/dL) occurs in more than 25% of patients; marked hypercalcemia (more than 13 mg/dL) may also be encountered. The hypercalcemia is secondary to enhanced bone resorption mediated by osteoclast activating factors, a family of cytokines including lymphotoxins, interleukin-1ß, a parathyroid related protein, and IL-6 produced by the neoplastic cells or by marrow stromal cells[90-93]. Hypercalcemia can interfere with renal concentrating ability and simultaneously may have vasoconstructive actions on renal vasculature causing decreased glomerular filtration rate, hypovolemia and prerenal azotemia. Decreased urine formation and tubule flow rate enhance cast formation and sometimes may precipitate acute cast nephropathy. Saline administration usually reverses hypercalcemia, provided that renal function is not severely impaired. Loop diuretics also increase calcium excretion, but furosemide should not be given until the patient is clinically euvolemic, because it may facilitate nephrotoxicity from light chains. Generally most patients respond to volume repletion and chemotherapy. Rarely more aggressive management is necessary. Both gallium nitrate and bisphosphonates are nephrotoxic and should be administered only to euvolemic patients. Response to biphosphonates occurs within the first several days of treatment; interrupting therapy is indicated as the calcium level normalizes. The effect of these agents is transient but often allows time for chemotherapy and hydration to prevent recurrence of hypercalcemia[94,95]. In some patients with markedly elevated serum levels of abnormal immunoglobulins, the total concentration of serum calcium is elevated because of binding to globulins, but the ionized fraction remains normal[96]. This spurious hypercalcemia does not require treatment. Similarly, spurious hyperphosphatemia due to binding of inorganic phosphorus to the elevated immunoglobulins has also been observed[97,98].

Acute Uric Acid Nephropathy

In patients with multiple myeloma hyperuricemia can occur from the increased nucleic acid turnover, either spontaneously or as a result of chemotherapy. Although patients with other lymphoproliferative disorders may have marked hyperuricemia (uric acid > 20-25 mg/dL) and acute uric acid nephropathy, this is rare in patients with multiple myeloma. Judicious use of hydration with normal saline together with alkalinization of the urine and pretreatment with allopurinol has nearly eliminated this complication[99].

Obstructive Nephropathy

Obstructive nephropathy directly related to myelomatosis can occur secondary to ureteral amyloidosis, nephrolithiasis, papillary necrosis, huge proteinaceous renal pelvic cast formation, and neurogenic bladder due to spinal cord or nerve injury resulting from vertebral collapse[100,101].

Hyperviscosity Syndrome

Although hyperviscosity occurs frequently in Waldenstrom's macroglobulinemia, rarely it can also be seen in multiple myeloma when the serum concentration of the monoclonal gamma globulin reaches very high levels[96,102,103]. It is usually manifested by impaired urine concentration, azotemia, and occasionally hematuria. Very rarely, it can cause acute renal failure or permanent renal damage. Under emergency situations, plasmapheresis with the removal of large amounts of macroglobulins can be accomplished. Exchange transfusions may also be done.

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Address for Correspondence:

Vecihi BATUMAN, MD

Nephrology Section-SL45
Tulane Medical School
1430 Tulane Avenue
New Orleans, LA, USA

e-mail: *vbatuma@tulane.edu*