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REVIEW

Light Chain Cast Nephropathy in Multiple Myeloma: Prevalence, Impact and Management Challenges

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Abstract: "Cast nephropathy" (CN) is a pathological feature of myeloma kidney, also seen to a lesser extent in the context of severe nephrotic syndrome from non-haematological diseases. The name relates to obstruction of distal tubules by "casts" of luminal proteins concentrated by intensive water reabsorption resulting from dehydration or high-dose diuretics. Filtered proteins form complexes with endogenous tubular Tamm-Horsfall glycoprotein. The resulting gel further slows or stops luminal flow upon complete obstruction of distal convoluted tubules and collecting ducts. Thus, a tubular obstructive form of acute kidney injury (AKI) is a common consequence of CN. The pathogenesis of CN will be reviewed in light of recent advances in the understanding of monoclonal disorders of B lymphocytes, leading to the release of immunoglobulin components (free light chains, FLC) into the bloodstream and their filtration across the glomerular basement membrane. Treatment aiming at reduction of the circulating burden of FLC may help recovery of renal function in a fraction of these patients, besides filling the void between the onset of AKI, histopathological diagnosis, and full response to pharmacologic treatment.

Keywords: light chain cast nephropathy, monoclonal gammopathies, multiple myeloma, immunoglobulins, hemodialysis, HFR-SUPRA

The term "Cast nephropathy" (CN) relates to a pathological feature mostly seen in myeloma kidney, but also present to a lesser degree in the context of severe nephrotic syndrome (NS) by whatever cause. In many renal biopsies from patients with a monoclonal (MC) serum component, heavy proteinuria or the NS, distal convoluted tubules and/or collecting ducts appear obstructed by luminal proteinaceous material, ie, Ig free light chains (FLC).[1–4] Such finding reflects protein concentration following intensive water reabsorption due to dehydration or aggressive diuretic therapy. Filtered proteins form complexes with endogenous tubular Tamm-Horsfall glycoprotein (THGP, also labelled uromodulin).[5–8] The resulting "gel" fills the tubules with LC casts in the context of CN (LCCN), further slowing luminal flow, which may eventually come to a stop upon complete obstruction. Thus, luminal "obstructive" acute kidney injury (AKI) may be a final common consequence of CN. Many Clinicians and Pathologists believe that AKI during the course of NS may be at least in part related to CN, along with the pre-renal effects of hypovolemia, oedema of the kidney ("nephrosarca"), or renal vein thrombosis.[9,10] Beyond this purely physical mechanism, the issue of direct tubular toxicity of LC (historically labelled as Bence-Jones protein) and filtered plasma proteins at large has also been raised by several Investigators. Under normal circumstances, in the healthy kidney only trace amounts of proteins filter across the glomerulus, mostly albumin, to be rapidly reabsorbed and disposed of by proximal tubules. Reabsorption involves carrier proteins such as megalin and cubilin heterodimers, which bind enzymatically filtered proteins and deliver them into cytoplasmic acidic microvescicles, derived from lysosomes, where further hydrolysis is carried out, resulting in the release of small polypeptides or single aminoacids.[11,12] These are then reabsorbed and recycled via the brush-border and basolateral surface of tubular epithelial cells. Any overload of this delicate mechanism, as in the case of microalbuminuria in diabetes/hypertension, heavy

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proteinuria in the NS, or FLC in MC gammopathies, results in some degree of tubular epithelial injury.[11–13] This is clearly shown by tubular cell injury and necrosis, an obvious histologic feature of CN.[3,4,11–13] Indeed, proteinuria itself is believed to represent one of the key factors leading to progression of renal failure and eventual fibrosis in a variety of kidney diseases.[14,15] Current pharmacologic strategies to slow down progression of renal failure aim at reducing proteinuria by preventive treatment with angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, or sodium glucose cotransporter-2 inhibitors.[14,15]

The present review will thus focus on the clinical implications of FLC-induced tubular obstruction and injury as a model of a broader phenomenon underlying acute and chronic, progressive renal diseases. Potential therapeutic strategies aiming at preserving or restoring renal function along with treatment of the underlying haematologic disorder will be reviewed, in view of the growing interest in an interdisciplinary approach to plasma cell dyscrasias.

Toxicity of Light Chains as a Trigger of Progressive Tubulo-Interstitial Disease

As stated earlier, LCCN is a quite typical feature of plasma cell dyscrasias, encompassing many clinical presentations, ranging from MC gammopathies of unknown significance (MGUS), of renal significance (MGRS), multiple or solitary myeloma, plasma cell leukemias, to renal amyloidosis.[1–4,16,17] Clearly, a prerequisite for an obstructive tubulopathy to promote acute kidney injury (AKI) is a large burden of filtered FLC/Bence Jones protein, as seen in the LC deposition disease (LCDD) pattern; on the other hand, renal biopsies or autopsy series show features of CN in about 50% of patients with MC gammopathies, even when the leading type of injury is amyloidosis or proliferative glomerulonephritis/crystalline podocytopathy.[16,18] Thus, LCCN should be considered as a histopathologic diagnosis by itself only when AKI or a rapidly progressive renal failure is occurring in response to a monoclonal disorder with a heavy burden of serum FLC.[19] In the absence of AKI and in the NS related to glomerulonephritis or diabetic nephropathy, CN should be regarded as a frequent collateral finding, but not a distinctive feature typifying renal histopathology.[20]

Accumulation of MC proteins/FLC has long been recognized as a harmful, toxic event for the renal microvasculature and the tubular compartment as well, a mechanism additional or alternative to tubular occlusion.[13,20–24] Early experiments in animals injected with myelomatous plasma cells, purified Bence-Jones protein or FLC clearly showed renal signs of LCCN, with protein accumulation/luminal obstruction occurring at proximal tubules or more distal segments.[3,25] The loop of Henle is the main site of production of THGP, which binds FLC at a complementary-determination region known as CDR3.[5–8] THGP/FLC complexes have the highest potential for luminal precipitation in the distal tubules, whereas proximal tubular accumulation of FLC is mostly responsible of a Fanconi-type syndrome (tubular acidosis, normoglycemic glycosuria, aminoaciduria, phosphaturia, uricosuria).[13] Luminal chloride is also a cofactor in the precipitation of THGP/FLC, as its concentration is known to occur in the distal convoluted tubule as well in the collecting duct, particularly upon intense water reabsorption.[26] THGP/FLC aggregates are known to trigger inflammation with leukocyte recruitment, reactive oxygen species and cytokine release, and multiple kinase activation.[21,26] Interstitial peritubular inflammatory infiltrates are common in areas of LCCN, and tubular cell apoptosis/necrosis initiate a process of rapid scarring of the renal parenchyma.[20]

Cofactors Precipitating Cast Nephropathy

While the burden of filtered FLC is certainly a key factor in the onset of LCCN, it should be noted that MM and related MGRS implicate collateral disorders and pharmacologic adverse events that amplify the phenomenon of LCCN (Box 1). First and foremost, dehydration. Patients with LCDD or amyloidosis with heavy proteinuria tend to accumulate fluids in the context of the NS, a process counteracted by high-dose diuretic therapy. LCCN complicates the NS due to intense diuretic-induced Cl delivery and water diuresis with subsequent concentration of THP/FLC luminal proteins.[3,13,17,19] The issue is similar to decompensated liver cirrhosis with ascites, which is often precipitated into an oliguric "hepato-renal syndrome" type of AKI by high-dose diuretics.[27]

Hypercalcemia is also often found in MM with extensive bone involvement. As a result of a direct inhibitory effect of Ca^{2+} on aquaporin-2 translocation to the luminal surface of collecting duct cells, distal water reabsorption is impaired, leading to polyuria and dehydration.[19,28] Compensatory water recovery at the level of the loop of Henle and the proximal convoluted tubule further

Box 1 Factors Precipitating Light Chain Cast Nephropathy (LCCN)

- Heavy FLC filtered load (high concentration of paraproteins in tubular luminal fluids)
- Dehydration, high-dose diuretics (low tubular flow following initial diuresis)
- Hypercalcemia (through polyuria and dehydration)
- Hyperviscosity syndrome
- Nephrotoxic drugs
  - Nonsteroidal anti-inflammatory drugs
  - Aminoglycoside antibiotics
  - Bisphosphonates (zoledronate, alendronate)
- Radiologic contrast media

Abbreviation: FLC, free light chains.

concentrates THP/FLC, precipitating CN in distal tubules. Bisphosphonates and denosumab are often employed to control hypercalcemia and alleviate bone symptoms related to osteolytic events.[29–32] However, zoledronate and pamidronate have been reported to be toxic for renal tubules in dehydrated patients, resulting in AKI, and/or to trigger focal segmental glomerulosclerosis, adding a further proteinuric burden to filtered FLC.[29,30,33]

Of course, the use of NSAIDs to alleviate bone/articular pain and the direct renal toxicity of contrast media in patients with an urinary paraprotein are additional causes of renal damage, often enhancing LCCN development (Box 1).[3,34] Indeed, contrast media employed for CT imaging have often been implicated in AKI in patients with pre-existing renal failure, particularly those with a MC component.[35–38] Actually, it is often current practice to screen patients with a serum protein electrophoresis for a MC beta- or gamma peak prior to a contrast-enhanced CT scan to assess the risk to precipitate a LCCN or any form of nephrotoxicity. The issue of contrast-induced nephropathy (CIN) has largely been downsized following the introduction of low-osmolarity contrast media and the current practice of pre-treating patients at risk with large amounts of crystalloids prior to and in the 6 hours after the CT or other contrast-enhanced procedure.[35–38]

Diagnosis of Cast Nephropathy

CN is not a histopathologic entity by itself, since most proteinuric disorders are responsible of tubular flooding with filtered proteins, including the NS induced by glomerulonephritides or diabetic nephropathy.[20] The clinical behaviour of a rapidly progressive renal failure in any proteinuric disorder should always prompt the clinical suspicion of CN-induced tubulo-interstitial damage. In the context of MM, earlier autopsy series have clearly shown that 30 to 52% of subjects deceased with kidney involvement had histopathologic features of LCCN.[3,39] Like in most forms of MGRS, the diagnosis of LCCN can be safely made by renal biopsy, which are unfortunately not routinely performed in MM or MGRS, despite the clear advantages in terms of diagnosis and prognosis of the renal abnormalities.[20,40] While not contraindicated by a higher incidence of bleeding or complications when compared to glomerulonephritis,[41] several Centers still rely mostly on bone marrow histology and detection of circulating or urinary FLC.

The typical renal histology of LCCN includes dilated distal tubules/collecting ducts, filled with amorphous material resembling the colloid substance of thyroid follicles ("simil-thyroid" appearance of the renal medullary compartment).[20,40,42,43] LC casts are eosinophilic, mildly PAS-positive, fractured, with irregular and angulated shapes (Figure 1). LC-derived crystalline inclusions are often seen in glomerular podocytes and basement membranes, as well as within the cast matrix and tubular walls.[44,45] Signs of tubulitis, with an interstitial leukocyte infiltration of peritubular surrounding spaces are suggestive of toxic damage and reactive inflammation, as typically seen in LCCN. Tubular necrosis is common, particularly around tubules filled with fractured casts.[20] If cast material leaks across the tubular wall, a reactive "granulomatous" inflammation is often seen, with mononuclear cells, macrophages, and occasionally eosinophils (Figure 1). Multinucleated cells surrounding broken tubular membranes are thought to originate from macrophages.[20,40–43] On immunofluorescence, intense positivity for κ LC (more rarely λ, as in Figure 1) is quite suggestive of a plasma cell dyscrasia as the main cause of renal damage. Interestingly, selectivity of the LC fluorescence tends to be lost with time, so that bright fluorescence for κ or λ LC has been suggested to reflect ongoing damage, that is, recent influx of paraprotein.[20] Crystals of LC are often seen within the casts, and by electron microscopy (EM) amidst amorphous deposits on the inner side of the glomerular and tubular basement membranes.[44] Rarely, fibrils or microtubular

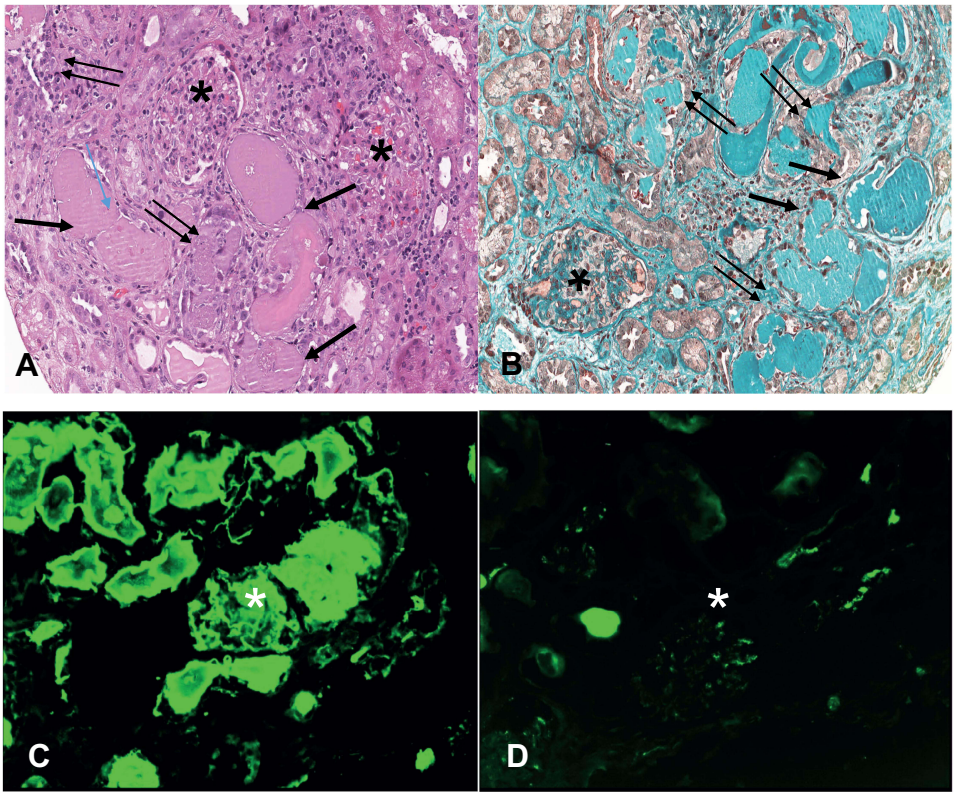

Figure 1 Pathologic findings in kidney biopsy tissue from a case of λ light chain myeloma. Hematoxylin-Eosin (**A**) and Masson's trichrome (**B**) stains showing tubules filled with "fractured" casts surrounded by a typical granulomatous cell reaction. Direct immunofluorescence for λ light chain (**C**) vs κ (**D**) demonstrate restriction of the light chains involved in cast formation. (**A** and **B**) "fractured" cast (arrow); (**A**–**D**) granuloma-like cell reaction (double arrows); glomeruli (*, asterisks). Original magnification, 200X.

immunotactoid deposits can be detected, whereas amyloid substance can be easily distinguished on EM as thin (2–5 nm), random-oriented fibrils.[20]

In a large collaborative effort of the International Kidney and Monoclonal Gammopathy Research Group[4] the following findings were reported on the basis of a thorough review of 178 patients with a LCCN histopathologic and clinical diagnosis, 82% of which with AKI (stage 3 by AKIN criteria): acute tubular necrosis was present in 94% of cases, tubulitis in 82%, giant cell reaction around casts in 60%, THP extravasation in 32%. Casts were as an average 3.2/mm^2 (1.4–6.4) in the cortex and 2.2/mm^2 (0.8–4.5) in the medulla, whereas only 6.2% of the biopsies showed features of LCDD, either glomerular or tubular. This confirms that LCCN associated with AKI is far more frequent than nodular accumulation along the basement membranes of proximal tubules, often presenting as the Fanconi syndrome.[4] Fibrosis and tubular atrophy seemed to correlate with the extent of cast deposition and ensuing inflammation, in turn related to higher levels of serum FLC and the abundance of THP extravasation around areas of tubulitis. Concerning response to treatment, 26% of 154 patients who remained on follow-up after the initial diagnosis and the renal biopsy eventually needed regular hemodialysis (HD) treatment; 56% of 71 patients who had AKI and needed HD at presentation or later during the course of treatment remained HD-dependent.[4]

Another recent multicenter study on 94 renal biopsies with a diagnosis of LCCN in 52% employed logistic regression analysis with multiple clinical indicators to develop a model for the non-invasive diagnosis of AKI in patients with MM.[45]

Taken together with several other series that have been published over the past 12 years, the advantages of obtaining a renal biopsy in a MGRS largely exceed the risks and hospital costs related to the procedure.[1–4,16–19,42–45] Nevertheless, the onset of AKI in patients with an established diagnosis of MM, a large MC component, or elevated serum FLC levels strongly suggests the presence of a LCCN, prompting treatment in the shortest possible time, in order to avoid the need for acute HD and/or the onset of irreversible fibrosclerotic lesions in the kidney (Figure 2).

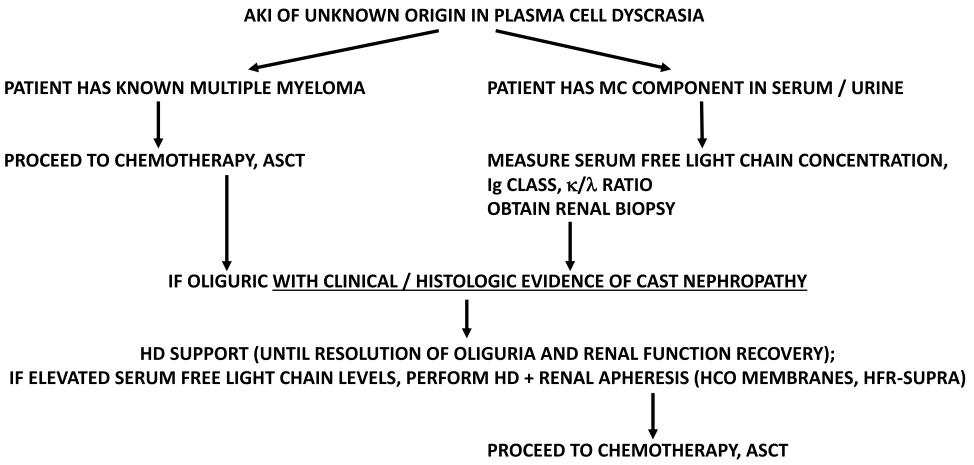

Figure 2 Light Chain Cast Nephropathy: a diagnostic/therapeutic Flow Chart.
Abbreviations: AKI, acute kidney injury; MC, monoclonal; ASCT, autologous stem cell transplantation; Ig, immunoglobulin; HD, hemodialysis; HCO, high cut-off; HFR-SUPRA, hemodialysis with ultrafiltrate reinfusion (Medtronic Italia, Milan, Italy).

Management of Cast Nephropathy

The first issue that arises when the Nephrologist is confronted with AKI in the context of a MM or MGRS is whether acutely impaired renal function results from MC protein precipitation in the kidney.[19,46–48] Differential diagnosis should include other causes of AKI, such as dehydration (pre-renal acute renal failure), hypercalcemia, nephrotoxic drugs, co-existing renal disease (eg, diabetic nephropathy, glomerulonephritis, renal vascular disorders, etc.) (Figure 2). Once again, the renal biopsy is always a key tool when other diagnoses are suspected. If however a renal biopsy is not readily available and there is a strong suspicion of a LCCN due to a large burden of filtered MC proteins/FLC, careful hydration should be attempted, with the goal of bringing urine output to 3 litres or more/per day.[3,47,48] Diuretics should be avoided or used at the lowest possible doses, as they are associated with increased distal reabsorption of water and electrolytes due to activation of the renin/ANG II/aldosterone axis. Water reabsorption almost invariably results in distal tubular luminal protein concentration, a key event in cast precipitation.[13]

When providing parenteral fluid support in patients that are unable to drink large amounts of water, care should be taken not to overload the renal tubules with filtered NaCl, as in the case of 0.9% normal saline infusions. The reason is that increased distal delivery of Na^+ and Cl^- promotes water reabsorption, thus increasing protein concentration in the cortical convoluted tubules and collecting ducts. At the same time, Cl^- favours the formation of complexes between filtered FLC and THGP. A half-saline, 0.45% NaCl solution or 5% glucose solutions are preferable, again with a goal of urine output exceeding 3 liters per day.[3,47] Obviously, anuric patients or individuals with congestive heart failure should not receive large volumes of fluids, choosing instead one of the apheretic techniques discussed later. While some studies advocated urine alkalinization with $NaHCO_3$ infusions as an effective method to solubilize and dislodge tubular casts, it turns out that precipitation of Na or Ca phosphate may instead occur, aggravating tubular and interstitial injury initiated by LCCN.[47–49]

All potential offending drugs should be withdrawn as soon as AKI sets in; a long list of medications that may have harmful effects and potentiate LCCN includes nonsteroidal anti-inflammatory drugs (NSAIDs), high-dose loop diuretics, bisphosphonates, ACE inhibitors, ANG II-receptor antagonists.[28–30,34–38,49] On the other hand, glucocorticoids decrease local inflammation, leukocyte chemoattraction, reduce FLC formation and deposition, and antagonize tubulo-interstitial fluid accumulation (renal oedema).[50] Moreover, glucocorticoids are first-line agents in most chemotherapy protocols currently applied to the treatment of MM and MGRS, thus resulting a convenient early approach while choices are made concerning the best suited pharmacologic combinations.[50] These include to this date at least 3 groups of agents, with variable effectiveness, alone or in combination, based on the clinical features of the MC disorder: the proteasome inhibitors (bortezomib), immunomodulatory imide drugs (thalidomide, lenalidomide, pomalidomide), monoclonal Abs (anti-CD38,

daratumumab).[51] Such compounds along with autologous stem cell transplantation (ASCT) are presently the mainstay of treatment for MM or MGRS. Many other molecules belonging to these or novel classes (immune checkpoint inhibitors, elotuzumab, pembrolizumab, nivolumab) are under scrutiny in clinical trials, but so far none appears specific for the kidney involvement related to LCCN.[51] Hence, the interest in a different, non-pharmacologic approach that could target more directly the circulating levels of FLC, in order to lessen the obstructive burden to renal tubules in LCCN (Figure 2).

Renal Apheretic Techniques

About half of all patients with MM experience some degree of kidney damage, ranging from mild to moderate, whereas acute kidney injury (AKI) occurs in approximately 9% of cases.[19,51–54] Reversal of renal failure predicts improved survival as a result of effective treatment. On the other hand, AKI requiring hemodialysis (HD) is often irreversible.[54,55] Tubular obstruction and the known direct toxicity of FLC, resulting in LCCN, make reducing exposure of the kidney to FLC the goal of both preventive and rescue therapeutic strategies.[55–59] The likelihood of renal recovery is a function of both the degree and speed of FLC reduction.[59] The half-life of circulating FLCs is 3–6 h in subjects with normal renal function, but since the kidney is the main site of clearance of FLC, any reduction of GFR increases FLC half-life, up to 10-fold in patients with CKD stage 5.[59] A rapid and substantial reduction of serum FLC concentration by at least 50% is thus needed to achieve renal rescue.[59] The ability of chemotherapy to decrease FLC levels in a short time is frustrated by the vast volume of distribution of these paraproteins, well beyond the intravascular compartment. Actually, refilling of serum levels continuously occurs from FLC previously accumulated in soft tissues and extravascular spaces.[60,61] The kidney might therefore handle elevated levels of FLC for weeks, even after a timely initiation of chemotherapy.[60] Considerable interest has therefore arisen around removal of circulating FLC as a strategy to alleviate ongoing kidney damage and to enhance recovery from AKI.[61–64] Over the past decade, extracorporeal techniques for therapeutic apheresis provided an interesting approach to rapidly clearing circulating FLC while awaiting for chemotherapy to reduce or possibly halt their production from monoclonal plasma cells.[61]

Extracorporeal blood purification offers various approaches to accomplish therapeutic apheresis (TA). This treatment has been employed for decades to treat renal and systemic disorders involving immune complexes, allo- or autoantibodies, cryoglobulins etc. Removal of these macromolecules has proven succesful in achieving a total remission, usually as a support to immunosuppressants.[65] Plasmapheresis in the course of MM was first employed in 1952 in patients with a hyperviscosity syndrome.[66] Actually, plasmapheresis was the only extracorporeal technique available to remove circulating FLC until 2005. Its efficacy in terms of treating renal dysfunction related to MM has been questioned, since at least three published randomized and controlled clinical trials failed to demonstrate a therapeutic effect of plasmapheresis on FLC deposition disease/LCCN.[65–67] The major issue related to removal of FLC by plasmapheresis is the relatively limited volume of plasma exchanged as compared to the much higher volume of distribution of FLC across extravascular body fluids.[67,68] A retrospective study on plasmapheresis based on renal histology and actual FLC reduction clearly illustrates the importance of the renal biopsy and the relationship between FLC reduction and clinical outcomes in MM cast nephropathy.[59]

In 2005, a new generation of HD "protein leaking membranes" was developed with the goal of providing greater clearances of high MW substances involved in uraemia, which are not removed by conventional high-flux membranes.[69] These so-called "high cut-off membranes" owe their name to larger pore sizes, which increase the MW cut-off to 50–60 KDa.[70] High cut-off dialyzers (HCO-HD) have been shown to achieve a far greater drop in post-dialysis serum FLC levels. Indeed, the use of a HCO-1100 dialyzer, with a membrane surface area of 1.1 m^2, was quite effective in reducing both κ and λ FLC levels.[64] Two HCO-1100 dialyzers in series achieved a greater increase in FLC clearance and reduction ratios by doubling the membrane surface area.[70–72] Patients with a substantial response to chemotherapy regimens plus adjunctive HCO-HD had a greater renal recovery compared to historical controls.[64–70] Key studies on FLC removal by using HCO dialyzers were published in 2007 and 2009 by the same group showing that HCO-HD could potentiate the decrease of serum FLCs obtained by effective chemotherapy.[62,64] Consistent with earlier experience with plasmapheresis in autoimmune disorders, it was confirmed that extracorporeal depuration alone was capable of inducing only a transient decrease of FLC, followed by a "rebound" thereafter.[63,64] Far greater results were instead obtained with concurrent chemotherapy decreasing at the same time the FLC production rate. Two other studies[59,61] examined whether an early

reduction of serum FLC levels was associated with better outcomes, and a specific FLC reduction threshold could be identified that granted renal improvement. These results indicate that a FLC reduction at day 21 was associated in up to 60% of patients with a renal recovery, while 80% remained HD-independent. Other randomized clinical trials were designed to prove the efficacy of HCO-HD as an adjuvant tool for HD-dependent AKI in MM patients receiving concomitant chemotherapy.[72–77] Among them, the "MYRE Study" on hemodialysis independence in LCCN[73] did show an interesting advantage of the HCO-HD treatment vs conventional HD patients, albeit not achieving statistically significance on a total population of 98 patients. The "European Trial of Free Light chain removal by extended HD in cast nephropathy" (EuLITE, 90 patients)[74] similarly failed to demonstrate better clinical outcomes when patients with recent MM diagnosis and LCCN-AKI were treated with bortezomib plus HCO-HD vs bortezomib plus standard high-flux HD (HF-HD).[74] Therefore, the rationale seemed rather frail for a phase-3 study of HCO-HD in these patients.[72–74] Moreover, price considerations, elevated protein loss with the need for albumin replacement, and calcium/magnesium wasting are major limitations to diffusion of this technique.[65,75,76] It is noteworthy that the International Myeloma Working Group (IMWG) on MM-related renal impairment stated as early as 2011 that current data support the use of HCO-HD in LCCN with a grade B evidence.[53]

More recently, in order to improve the clearance of "middle molecules" with MW between 15 and 60 KDa without losing serum albumin, the pores within the dialysis membranes were re-designed to a tighter distribution. The medium-cutoff membranes (MCO) dialyzers use this new pore density. In clinical practice, these membranes should improve the clearance of large molecules without inducing a massive albumin loss.[76,77] The REMOVAL-HD study so far demonstrated safety and efficacy of MCO in comparison with high-flux dialysis sessions.[77]

Renal Apheresis in the Treatment of AKI/CN: Beyond HD

Haemodiafiltration (HDF) has been shown to be more efficient than conventional HD to reduce the levels of middle-size molecules by enhancing convective clearances.[78] Haemofiltrate reinfusion (HFR) is a further development of haemodiafiltration (HDF), in which reinfusion employs a "regenerated" ultrafiltrate from the patient itself, resulting from a separate cartridge containing a hydrophobic styrene resin. The HFR-SUPRA system thus utilizes separated convection, diffusion and adsorption.[79–82] In the initial convective phase, pure ultrafiltrate (basically plasma water) passes through a sorbent cartridge containing 40 mL of hydrophobic styrene resin with numerous pores and channels extending its surface area (~700 m^2 /g). Treatment is performed on a Flexya monitor (Medtronic Italia, Milan, Italy) equipped with a software that automatically determines the optimal ultrafiltration flow rate.[79,82] The sorbent cartridge selectively binds a variety of uraemic toxins and middle molecules, including β2-microglobulin, homocysteine, angiogenin, leptin, parathyroid hormone (PTH), several chemokines, cytokines and immunoglobulin. Urea, creatinine, uric acid, Na^+, K^+, Ca^{2+}, phosphate and bicarbonate are not adsorbed, and remain unchanged after passage through the cartridge. They can be managed by diffusion across the second, conventional HD filter. Thus, the "regenerated" ultrafiltrate becomes an endogenous ultrapure replacement fluid with a normal concentration of bicarbonate.[79–81]

The depurative superiority of convective over diffusive strategies in MM patients has been confirmed by a retrospective analysis.[68] This approach is particularly suited to FLC apheresis due to the high protein-bound toxin adsorption capacity without removal of albumin.[68,81–84] HFR-SUPRA indeed provides efficient clearance of FLC in view of its molecular size cut-off, which selectively enables FLC passage, coupled with high affinity of the adsorptive cartridge.[82]

We have used HFR-SUPRA in a pilot experience on 6 patients with MM and AKI initially treated with i.v. dexamethasone, followed within one week by a Bortezomib-based chemotherapy (Table 1).[85] In each session, the average decrease of FLC ranged between 37.7 ± 21.3% and 60.6 ± 15% for κ chains and from 48.8 ± 8.7% to 71.6 ± 5% for λ. Five sessions of HFR-SUPRA on alternate days (instead of conventional bicarbonate HD) thus resulted in a fast and stable reduction of serum FLC levels, notwithstanding the serum rebound due to refilling from tissue deposits (2 representative cases of κ and λ-chain MM are shown in Table 1). Furthermore, albumin wasting was negligible throughout the entire cycle of treatment (average loss ranging from 3 to 7%). In terms of recovery of renal function, 2 of our patients achieved a complete remission, while 4 older subjects who had a longer history of misdiagnosed or untreated MM symptoms remained HD-dependent.[85]

Table 1 HFR-SUPRA Therapeutic Apheresis with Endogenous Reinfusion of Ultrafiltrate: Representative Comparison of Free Light Chain (FLC) Levels Before and After Each Single Session (Post-Treatment Levels are Corrected for Ultrafiltration) in 2 Patients with κ and λ Chains Multiple Myeloma, Respectively

Pre/Post HFR	FLC (mg/dl) κ chains	% Removal	FLC (mg/dl) λ Chains	% Removal
Pre 1st	5300	45.4	3140	44.1
Post	2895		1756	
Pre 2nd	5080	46.7	3180	40.9
Post	2709		1940	
Pre 3rd	6620	60.1	4780	63.5
Post	2640		1742	
Pre 4th	4750	74.4	5210	48.4
Post	1214		2689	
Pre 5th	3960	76.4	2880	47.2
Post	935		1520	
Mean ± SD		60.6 ± 15.0		48.8 ± 8.7
p		0.001		<0.0001

Abbreviations: HFR-SUPRA, hemodiafiltration with endogenous reinfusion; FLC, free light chains.

Conclusions

CN is a common phenomenon in the kidney challenged by heavy proteinuria, particularly when FLC are the molecular species involved, as seen in MGRS and MM with LCNN. The phenomenon is often overlooked in the absence of AKI and if a renal biopsy is not performed, but may actually occur in a large number of cases. The renal biopsy is strongly recommended whenever a MGUS (that is, a MC gammopathy not matching the haematologic criteria for MM) associates with renal symptoms or abnormal laboratory parameters, thus upgrading the diagnosis to MGRS. Even though AKI in the absence of drug effects or dehydration/hypercalcemia is almost always the consequence of a LCCN, a long time may elapse between the onset of a MC disorder and clinically apparent LCCN (that is, AKI). A renal biopsy may highlight initial LCCN (while renal function is still normal or minimally decreased), and actually recommend treatment well before to the onset of AKI. A proliferative glomerulonephritis with MC deposits may be an alternative diagnosis that should not be treated with apheretic techniques. Nevertheless, both disorders require prompt haematologic treatment, without any delay as often happens when waiting for bone marrow histopathologic or molecular diagnosis,[86] particularly if a diagnosis of MM could not be confirmed. A renal biopsy may also help avoiding false steps in cases of AKI unrelated to the existing MC disorder.

Concurrent adverse events, such as dehydration, toxic effects of therapies, electrolyte disorders, along with renal damage to other, non-tubular compartments (amyloidosis, glomerulonephritis with MC immune deposits, LCDD, crystal nephropathies) may enhance tubular protein precipitation as LCCN and eventually lead to AKI or rapidly progressive renal failure.

Early intervention is the only chance to reverse the renal situation, as LCCN is not easily reversible; moreover, it should not only be considered a purely obstructive event, but rather a tubular toxic and inflammatory injury. Apheretic techniques coupled with pharmacologic treatment seem an ideal combination capable of bridging the gap between diagnosis and effective pharmacologic inhibition of the offending clone, so that a prompt decrease of serum levels of MC LC may facilitate recovery of distal tubular flow and function. The introduction of novel immunotherapeutic agents will once more offer a chance to assess whether the rates of renal function recovery after a LCNN are actually increased by an early renal apheretic approach, and there is in fact an advantage over conventional HD.

Ethics and Consent

All patients gave informed consent to the use of their anonymized clinical data under the standards set by our institutional Ethics Committee.

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