Renal failure due to combined cast nephropathy, amyloidosis and light-chain deposition disease

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Abstract
Renal dysfunction commonly occurs in multiple myeloma (MM) and is caused by deposition of abnormal light chain within various compartments of the kidney. Renal pathologic findings are diverse and include cast nephropathy (CN), amyloidosis and light-chain deposition disease (LCDD). We report a case of renal failure in a patient with MM caused by concurrent CN, amyloidosis and LCDD which has not been previously described.

Keywords: amyloidosis; light chain; myeloma; nephropathy

Background
Kidney disease is a common sequela of multiple myeloma (MM). The aetiology of renal insufficiency in MM is heterogeneous and includes cast nephropathy (CN), amyloidosis and light-chain deposition disease (LCDD). Although most patients have only one pattern of renal pathology, up to two patterns occurring in the same patient has been described. CN and LCDD appear to be the most common combination [1], although amyloidosis with LCDD has been observed [2]. We report the case of a woman with MM and renal failure who had three concurrent pathologic findings on renal biopsy: CN, amyloidosis and LCDD.

Case Report
A 40-year-old woman with no previous medical history presented to an outside medical centre with hypertension and renal insufficiency. Serum protein electrophoresis showed an M-spike of 3.4 g/dL (34 g/L) and serum immunofixation demonstrated a monoclonal IgG kappa. Urine protein electrophoresis revealed a monoclonal kappa plus IgG kappa fragment. Initial renal biopsy was consistent with acute tubular necrosis, CN and focal arterial amyloidosis. She was transferred to our institution. On admission, serum kappa free light chain (FLC) level was elevated at 1050 mg/dL (0.33–1.94 mg/dL) with a creatinine of 4.3 mg/dL (380 µmol/L). Bone marrow biopsy showed approximately 9% monoclonal kappa plasma cells with negative Congo red staining. Bone survey was negative for any lytic lesions or pathologic fractures. cDNA sequencing was performed on the bone marrow plasma cells. A dominant clone expressing kappa 1 immunoglobulin light chain with mutations in the L12 locus was identified, consistent with the circulating monoclonal kappa light chain (Figure 1). The patient was diagnosed with MM and treated with plasma exchange followed by dexamethasone and thalidomide. Five months after presentation, she underwent autologous stem cell transplantation. At the time of transplantation, her creatinine was 3.5 mg/dL (309 µmol/L) with a serum FLC of 33 mg/dL. Bone marrow biopsy showed approximately 9% monoclonal kappa plasma cells with negative Congo red staining. Bone survey was negative for any lytic lesions or pathologic fractures. cDNA sequencing was performed on the bone marrow plasma cells. A dominant clone expressing kappa 1 immunoglobulin light chain with mutations in the L12 locus was identified, consistent with the circulating monoclonal kappa light chain (Figure 1). The patient was diagnosed with MM and treated with plasma exchange followed by dexamethasone and thalidomide. Five months after presentation, she underwent autologous stem cell transplantation. At the time of transplantation, her creatinine was 3.5 mg/dL (309 µmol/L) with a serum FLC of 33 mg/dL. She had 307 mg/24 h of proteinuria and a monoclonal kappa plus IgG kappa fragment on urine immunofixation. Six months after transplantation, the patient's serum FLC level increased and her creatinine climbed to 4.4 mg/dL (389 µmol/L). To further evaluate her decline in renal function, a renal biopsy was performed. Renal biopsy showed no significant glomerular mesangial matrix expansion or inflammatory features. Several tubules contained periodic acid Schiff (PAS) negative cast material that had a fractured appearance and was asso-
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Associated with a focal cellular reaction consistent with CN (Figure 2). In the interstitium and artery walls, pale deposits were noted (Figure 3A); these deposits stained with Congo red (Figure 3B) and exhibited apple-green birefringence with polarization (Figure 3C). Likewise, they stained for kappa light chain and serum amyloid P component. Stains for serum amyloid A component and lambda light chain were negative. Electron microscopy confirmed that these interstitial and vascular deposits were composed of numerous amyloid fibrils (Figure 3D). Another finding on immunofluorescence was tubular basement membrane staining for kappa light chain (3+) (Figure 4A) but not lambda light chain (Figure 4B). Electron microscopy confirmed the presence of granular tubular basement membrane electron-dense deposits consistent with LCDD (Figure 4C). No glomerular deposits were noted. Final pathology diagnoses included (i) CN, (ii) AL amyloidosis and (iii) LCDD. All of these features were primarily seen in the interstitium.

Fig. 1. Germline cDNA sequence from normal bone marrow plasma cells expressing kappa 1 immunoglobulin light chain (VK1); cDNA sequence from a dominant clone from bone marrow plasma cells in our patient expressing kappa 1 immunoglobulin light chain with mutations (highlighted in yellow) in the locus L12 consistent with the circulating monoclonal kappa light chain (KRO).

Fig. 2. Light microscopy PAS stain showing tubules containing fractured PAS-negative intraluminal cast material associated with a focal cellular reaction consistent with CN (arrow) (original magnification ×60).

Fig. 3. (A) Light microscopy PAS stain showing homogenous pale amyloid deposition within the interstitium (original magnification ×400); (B) Congo red stain showing deposition of congophilic amyloid material in an artery wall (original magnification ×40); (C) Congo red stain showing amyloid material exhibiting positive apple-green birefringence with polarization in an arterial wall (original magnification ×40); (D) electron microscopy showing numerous amyloid fibrils within the wall of an artery (original magnification ×46 000).
The patient was started on thalidomide and dexamethasone but had no significant response. Treatment was changed to bortezomib and dexamethasone and she experienced a partial response. At her most recent follow-up, approximately 2 years after stem cell transplantation, her creatinine was stable at 3.9 mg/dL (345 µmol/L) and her FLC level was improving.

Discussion

We present a unique case of renal failure caused by three different light chain diseases: CN, amyloidosis and LCDD. To our knowledge, ours is the first reported case of all three light chain-associated diseases occurring in the same kidney. MM is a haematologic malignancy characterized by proliferation of a plasma cell clone producing monoclonal immunoglobulin or fragments [3]. Deposition of the circulating monoclonal immunoglobulins results in tissue damage, including renal failure which occurs in 20–40% of patients with MM [4]. Renal pathology due to deposition of monoclonal FLCs in MM is variable and consists of three main patterns of injury: CN, amyloidosis and LCDD. CN is the most common pattern of renal injury and is seen on 30–50% of renal biopsies [3]. In CN, light chains deposit within tubular lumens causing obstruction and injury. Light microscopy features are fairly diagnostic and show fractured PAS negative casts with surrounding inflammatory cells. Casts may not show light-chain restriction on immunofluorescence due to nonspecific trapping of normal light chains [5] or under-sampling of the tissue. Amyloidosis is another pattern of renal injury in MM seen in 7–30% of patients [3]. In amyloidosis, light chains form fibrillary deposits which exhibit apple-green birefringence with Congo red staining [6]. Glomerular deposition is the most common, but vascular deposition predominates in 5–10% of patients [7]. A third pattern of renal damage in MM is LCDD which is seen in 19–26% of biopsies [3]. In contrast to amyloidosis, light chains in LCDD do not form fibrils or show birefringence with Congo red staining [8]. The abnormal light chains in LCDD form fine granular deposits in the mesangium and along the tubular basement membranes. Glomerular deposits are the most common, but cases affecting only tubules have been reported [9].

Physiologic properties of the abnormal light chains are thought to determine which pattern of renal injury occurs in MM [10]. In a seminal study, Solomon et al. showed that light chains from patients with CN produce CN when injected into mice and light chains from patients with amyloidosis produce amyloidosis when injected into mice [11]. Amyloidogenic light chains are thought to have different structural features than non-amyloidogenic light chains which predispose to fibril formation. For example, amyloidogenic light chains contain destabilizing mutations which decrease structural integrity and predispose to fibril formation [12]. Amyloidogenic light chains may also contain hydrophobic amino acid substitutions at exposed surfaces which predispose to aggregation and may contain domains more likely to be glycosylated leading to enhanced protein stability [12]. In addition, there appears to be a size difference between amyloidogenic light chains and non-amyloidogenic light chains. Deposits in amyloidosis generally consist of light chain fragments, whereas deposits in LCDD usually consist of intact light chains [13]. Recent work also suggests that light chains in amyloidosis have enhanced disulfide binding compared to light chains in LCDD which may interfere with their clearance and metabolism [13].

In addition to having different physiologic properties, light chains have different local effects within the kidney. Because they obstruct tubular cells and do not affect glomeruli, light chains involved in CN have been referred to as ‘tubulopathic’ light chains [14]. In contrast, light chains in amyloidosis and LCDD have been termed ‘glomerulopathic’ light chains because they interact with mesangial cells within glomeruli and alter mesangial homeostasis [14].
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Amyloidogenic and LCDD light chains do not have the same effect on mesangial cells. LCDD light chains appear to interact with mesangial surface receptors and stimulate mesangial cells to develop a myofibroblastic phenotype [15] without being endocytosed [16]. In contrast, amyloidogenic light chains are endocytosed and delivered to lysosomes where amyloid formation occurs [16]. They also stimulate mesangial cells to develop a macrophage-like phenotype [15].

Despite the rationality of the above theories, light chain pathophysiology appears to be more complex. Reported cases of CN combined with LCDD and cases of amyloidosis combined with LCDD exist [1,2]. CN occurring with amyloidosis has also been described [17]. Cases involving more than one pattern of light chain-related pathology have been explained with several different theories. First, a biclonal proliferative process may be involved in which more than one light chain causes damage [18]. Alternatively, the original light chain gene may mutate, giving rise to a second plasma cell clone [18]. This type of mutation has been seen with alkylating chemotherapy [19]. A third explanation for concurrent light chain pathologies is that non-fibrillar proteins may serve as precursors to fibrils [18].

To our knowledge, our case is the first to describe CN, amyloidosis and LCDD occurring in the same individual. The fact that only one abnormal kappa light chain was isolated from our patient suggests that a biclonal process was not present and implies that the same light chain was responsible for all three patterns of renal damage. Another interesting feature of our patient's biopsy was the absence of glomerular deposits. Lack of glomerular involvement may have reflected an early stage of disease [4] or a property of the circulating light chain itself. Recent research involving patients with combined CN and LCDD found that 69% of patients had normal glomeruli on biopsy [20]. Our patient's case illustrates the complexity of light chain pathophysiology and emphasizes that further studies examining the molecular characteristics and pathologic effects of light chains are needed.

Conflict of interest statement. None declared.

References


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