Chapter 9
Renal Disease Associated with Monoclonal Gammopathy

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Nearly 60 years after the description of the Bence-Jones protein, Alfred von Decastello described the plugging of renal tubules by an amorphous substance in a patient who died of multiple myeloma [1]. This was one of the first descriptions of a kidney disease resulting from a monoclonal protein which later became known as "cast nephropathy." Since cast nephropathy almost always occur with multiple myeloma, the term myeloma kidney became synonymously used. Indeed, one study noted that only 3 % of myeloma patients with renal impairment had low tumor burden [2]. However, this association between a malignant condition and a kidney disease is not entirely accurate. First, cast nephropathy can be seen in patients with chronic lymphocytic leukemia (CLL) or lymphoplasmacytic lymphoma with Waldenström's macroglobulinemia (WM) [3, 4]. In addition, the human kidney diseases: cast

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nephropathy, immunoglobulin light-chain (AL) amyloidosis, monoclonal immunoglobulin deposition disease (MIDD) and light-chain Fanconi syndrome (LCFS) can be replicated by injecting just the monoclonal protein into animals [5]. Finally, except for cast nephropathy, multiple myeloma or lymphoma is not required for the development of the above kidney diseases. The evidence overwhelmingly supports the monoclonal proteins and not the tumor as the agent directly responsible for the kidney disease. This chapter will review the clinicopathologic characteristics of these renal diseases and their association with monoclonal gammopathy of renal significance.

Monoclonal Gammopathy of Renal Significance

Kidney diseases, once linked to multiple myeloma or lymphoma, are now recognized to be capable of developing independently of the malignancy. Only about 15 % of AL amyloidosis and 20–65 % of MIDD patients meet criteria for multiple myeloma or lymphoma [6–8]. Many of these patients never progress to multiple myeloma [9]. In fact, their biology is more similar to monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma than multiple myeloma. However, the use of the term MGUS in these patients is problematic and confusing. First, the term MGUS denotes undetermined significance and requires the absence of end-organ damage. In these patients, the significance of kidney damage has been established. Furthermore, the current guidelines regarding the treatment of plasma cell disorders clearly recommend against treating patients with MGUS [10]. This makes sense in true MGUS patients where there is no end-organ damage and the transformation rate to multiple myeloma or other more serious conditions is low. This is not applicable to patients who have pathologic lesions attributable to their monoclonal gammopathy. The conflicts created by the term MGUS make it inappropriate for these patients. As a result, a new term monoclonal gammopathy of renal significance (MGRS) has been created to better classify these patients and avoid confusion.

The main difference between MGRS and MGUS is the presence of a kidney disease that is attributable to the monoclonal protein [11]. Both conditions are characterized by less than 10 % clonal plasma cells in the bone marrow, <3 g/dl of monoclonal (M) protein and the absence of other defining features of multiple myeloma such as hypercalcemia, anemia, and bone lesions. However, where there is no end-organ damage in MGUS, the kidney is injured by the monoclonal protein in MGRS. This is most often as a result of deposition of monoclonal immunoglobins, but monoclonal protein can also injure the kidney by other means such as activation of the complement system. Regardless of the pathophysiology, this direct link between the kidney and the monoclonal protein is what defines MGRS. By definition, cast nephropathy is not a MGRS-related kidney disease because it is almost always associated with multiple myeloma [2, 12].

MGRS-Related Kidney Diseases with Organized Monoclonal Immunoglobulin Deposits

AL Amyloidosis

AL amyloidosis is a fatal systemic disease characterized by the extracellular deposition of congophilic fibrils in soft tissues [13]. The amyloid in AL is composed of monoclonal immunoglobin light chains (LC) while monoclonal immunoglobulin heavy-chain amyloid is called AH and those containing the intact components of immunoglobulin light and heavy chain are ALH [14, 15]. AL is by far the most common subtype representing over 95 % of the cases of immunoglobulin amyloidosis and for the purpose of this chapter will represent all of the subtypes of immunoglobulin amyloidosis. The pathogenesis is the result of the misfolding of immunoglobulin LCs into a lower energy state. The misfolded LC self-aggregates to form fibrils, which are more resistant to degradation. These are deposited in various organs. There is increasing evidence to suggest that cellular toxicity cannot be entirely explained by deposition. In a zebra fish model, impaired cardiac function, pericardial edema, and

increased cell death can be induced by the introduction of amyloidogenic LC but not control LC from myeloma patients [16]. These changes are observed prior to any fibril formation. In addition, divergent phenotypic changes are observed in mesangial cells incubated with LC from patients with AL amyloidosis versus LC from MIDD patients [17]. This data strongly suggest the toxicity is determined by the primary sequence of the LC. Finally, repeat renal biopsy of patients treated with autologous stem cell transplantation shows no regression of the amyloid deposits despite achievement of a complete hematologic response (CR) and significant improvement in proteinuria [18].

AL amyloidosis is the most common glomerular lesion in patients with MM [19, 20]. It is found in 5–15 % of patients with MM at autopsy [19, 21, 22]. However, only a small percentage of patients actually have multiple myeloma. In a study of 474 patients, 22 % of patients have 10–19 % plasma cells while 18 % of patients have >20 % plasma cells in the bone marrow [6]. Seven percent of patients have >3 g/dl of M protein in the serum. Only 9.5 % met criteria for MM, and they all had lytic bone lesions. Median age of patients with AL amyloidosis is 64 years, and 69 % are male. The light chains are not equally represented as 70 % of the M-proteins are lambda restricted. AL amyloidosis has also been reported to occur in B-cell lymphoproliferative disorders and CLL [23, 24].

In systemic AL amyloidosis, kidney is the most commonly involved organ. An abnormal creatinine is seen in nearly half of the patients. Proteinuria and nephrotic syndrome are noted in 73 and 28 %, respectively [6]. Median proteinuria is 5.8 g/d. The proteinuria is mainly albuminuria, which makes up on average 70 % of the urinary proteins [25]. In a small percentage of patients, a vascular-limited AL amyloidosis has been described, which presents with progressive renal insufficiency but little (<1 g/d) or no proteinuria [26]. Rare patients may present with nephrogenic diabetes insipidus [6]. End-stage renal disease (ESRD) mainly developed in those who presented with renal manifestations. In a study of 145 patients, ESRD developed in 41.6 % of patients who presented with renal manifestations versus 4.9 % without [27]. ESRD appeared to negative impact survival as the median survival was 10.4 months after the start of dialysis.

The diagnosis of AL amyloidosis requires a biopsy. In the kidney, amyloid appears as an amorphous periodic acid–Schiff (PAS)-negative and silver-negative deposits (Fig. 9.1). By definition, amyloid deposits regardless of type are Congo red positive and exhibit an apple green birefringence when viewed under polarized light. Amyloid deposits are seen in glomeruli and vessels in the vast majority of cases and in the interstitium in more than half of cases. Glomerular involvement leads to mesangial expansion, which may show nodular appearance at times. When amyloid affects the glomerular basement membrane, it usually forms spicules, a characteristic feature of this disease, which can be readily identified on silver stain. For AL, the deposits should stain for a single LC by immunofluorescence (IF) (Fig. 9.1). A single heavy chain would also stain positive in ALH while only the heavy chain will stain in AH. Amyloid fibrils have a diameter of 7–12 nm and are randomly arranged when viewed by electron microscopy (EM) (Fig. 9.1). Since only amyloidosis of immunoglobulin subtypes are treated with chemotherapy, typing of the amyloid is essential prior to initiation of treatment [28]. While IF can be quite informative for AL and its subtypes, laser microdissection followed by proteomics by mass spectrometry (LM-MS) has become the gold standard and should be performed in equivocal or uncertain cases [14].

Tremendous advances have been made in the treatment of AL amyloidosis in the past decades. During this time, overall survival has increased from 18 months to over 5 years [29–32]. Details regarding treatment are covered in other chapters. What is important to note is that response in the kidney is associated with patient survival. Using a 50 % reduction in proteinuria as a marker of response, renal response was strongly associated with patient survival [33]. In subgroup analysis, patients who achieved 75 % or more proteinuria reduction were the ones who benefitted in overall survival and those who achieved 95 % reduction had the best outcomes [34]. Patients who had between 50 and 74 % reduction in proteinuria did not show an improvement in OS as compared to those who had <50 % reduction in proteinuria. Of note, the reduction in proteinuria can take 10–12 months to occur [35]. More rapid method of assessment of renal response is currently being investigated.

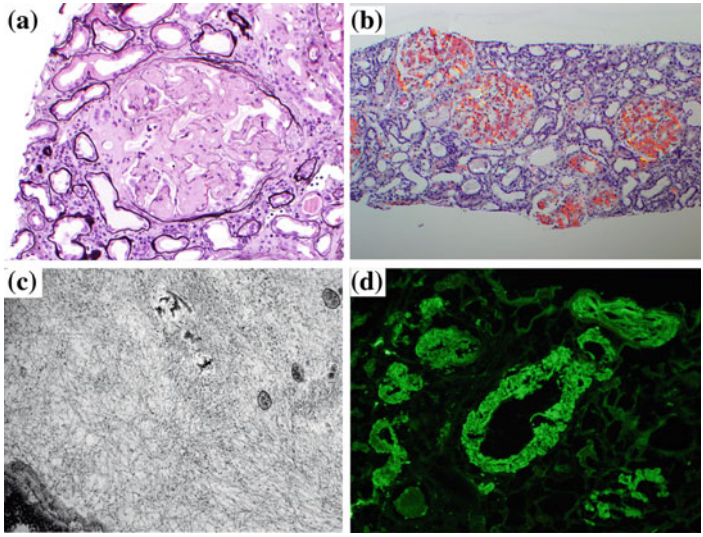

Fig. 9.1 Pathology of renal AL amyloidosis. **a** There is extensive, global mesangial, and segmental glomerular capillary wall deposition of acellular, silver-negative amyloid deposits (jones methenamine silver, ×400). **b** The figure shows global glomerular Congo red-positive amyloid, which exhibits *red/yellow/green* colors when viewed under polarized light (×100). **c** On electron microscopy, amyloid fibrils appear haphazardly oriented and measure between 7 and 12 nm in diameter (×46,000). **d** On immunofluorescence, amyloid deposits appear smudgy and stain for one of the light chains only. The figure shows smudgy transmural, arterial, and arteriolar staining for lambda (×200). Staining for kappa was negative (not shown)

Immunotactoid Glomerulonephritis

Immunotactoid glomerulonephritis (ITG) is a rare kidney disease characterized by the deposition of microtubules in the glomerulus [36]. Unlike amyloid, these fibrils are much larger and do not stain with Congo red. The average diameter of immunotactoid fibrils is 38.2 nm with a range of 20–55 nm (Fig. 9.2). The most distinguishing feature, however, is the hollow center, which is similar to microtubules. Other fibrils with similar features are cryoglobulins, thus by definition, cryoglobulinemia must be ruled out. Historically, fibrillary glomerulonephritis has been described together with ITG and was once thought to the same disease.

Histologically, they do share common features such as membranoproliferative pattern (Fig. 9.2) with endocapillary proliferation, mesangial expansion and hypercellularity, membranous-like pattern (Fig. 9.2), even hyaline pseudothrombi in the glomeruli and crescents [20, 37, 38]. Major differences include smaller fibril size in fibrillary glomerulonephritis. The fibrils are solid and randomly arranged in fibrillary glomerulonephritis whereas the microtubules in ITG are hollow and usually arranged in parallel arrays (Fig. 9.2) [37]. More importantly, ITG microtubules are commonly composed of entire monoclonal immunoglobulins while fibrillary glomerulonephritis is rarely monoclonal [39].

Clinically, patients with ITG present with heavy proteinuria. Median proteinuria is 11.1 g/d with a range of 1.4–36 g/d [20, 37, 38]. Microscopic hematuria is often present. Renal impairment is often mild with a median serum creatinine (SCr) at presentation of 1.5 mg/dl (0.7–3.8 mg/dl). The percentage of male patients ranges from 71.4 to 83.0 %, and the median age is from 59 to 66 years. Monoclonal gammopathy is present in 63–86 % of cases. One unique characteristic of ITG is the high rate of CLL reported in these patients. It can be up to 50 % in some series. Multiple myeloma was found in 12.5 % of cases in another series [40]. There are currently no clinical trials on ITG. Cytotoxic agents capable of reducing the clone have been found to be successful at preserving renal function [37].

Light-Chain Fanconi Syndrome

Light-chain Fanconi syndrome (LCFS) is a rare condition characterized by electrolyte abnormalities as a result of proximal tubular injury. The tubular injury is due to intracellular crystalline deposition of monoclonal light chains. Fanconi syndrome and proximal tubular cytoplasmic crystals may also be present in crystal-storing histiocytosis (CSH). The latter, however, is different from LCFS in that the crystals are mainly seen within the cytoplasm of histiocytes in the renal interstitium, bone marrow, and other organs. Like CSH, nearly 90 % of the cases of LCFS are kappa restricted with V_{kI} being the most common subtype [41, 42]. Multiple myeloma is

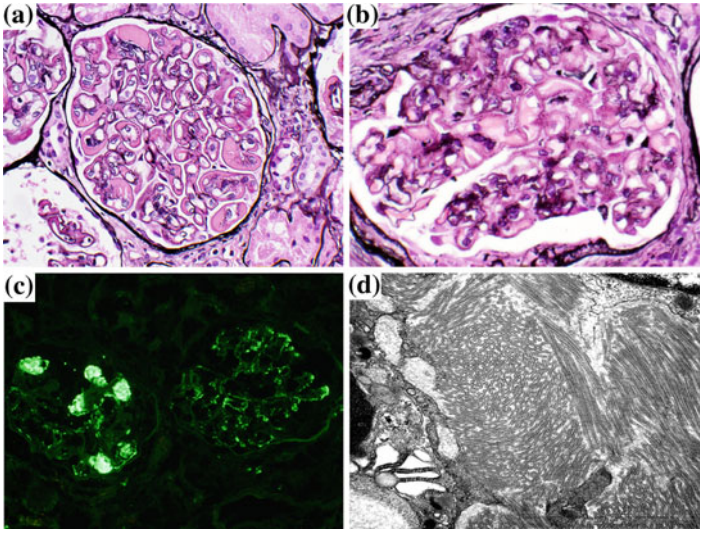

Fig. 9.2 Pathology of immunotactoid glomerulonephritis. **a** In this case of immunotactoid glomerulonephritis and a membranoproliferative pattern of injury, there is global mesangial and glomerular capillary wall deposition of silver-negative immune material together with widespread duplication of the glomerular basement membrane (jones methenamine silver, ×400). **b** In this case of immunotactoid glomerulonephritis with a membranous pattern of injury, the glomerular basement membrane appears thickened and shows global silver-positive spikes (jones methenamine silver, ×400). **c** In this case of immunotactoid glomerulonephritis, there is bright glomerular capillary wall, mesangial, and intraluminal staining for IgG (immunofluorescence, ×200). Similar glomerular staining for lambda is seen, with negative staining for kappa (not shown). **d** Electron microscopy from a case of immunotactoid glomerulopathy shows mesangial deposits composed of large microtubules with hollow centers, which are organized in parallel arrays. The microtubules measured 52 nm in mean thickness (×24,500)

diagnosed in about half of the patients with smaller percentage of patients diagnosed with WM, CLL, smoldering MM, and MGRS.

LCFS patients often present in their sixth decade with a median age of 57 years. It is slightly more common in men with 58 % male. Typical presentation includes tubular proteinuria (usually not high grade), glycosuria, and renal insufficiency. Extrarenal manifestations include bone pain, osteomalacia, and fatigue. Insufficiency fractures are not uncommon. Many patients will also have electrolyte abnormalities such as hypouricemia (66 %),

hypophosphatemia (50 %), and hypokalemia (44 %), but these tend to disappear as the renal function declines [41]. One clue may be normal levels of uric acid, potassium, and phosphorus despite advanced degree of chronic kidney disease. Diagnostically, aminoaciduria (100 %) is the most common urinary abnormality followed by glycosuria (~100 %) and phosphaturia (43 %). Patients who have aminoaciduria but no glycosuria or phosphaturia are considered to have an incomplete Fanconi syndrome.

On kidney biopsy, elongated hypereosinophilic and PAS-negative crystals can be identified within proximal tubular cells (Fig. 9.3), usually accompanied by patchy tubular injury and varying degrees of tubular atrophy and interstitial fibrosis. Occasionally, proximal tubular cells appear swollen by the crystals [42]. Toluidine blue is the best stain for the identification of crystals. Only a single immunoglobulin LC should be present on IF (Fig. 9.3). On EM, rhomboid or rod-shaped crystals are seen in the cytoplasm (Fig. 9.3). Cast nephropathy is not uncommonly seen coexisting within the same biopsy.

The renal outcome in LCFS is variable. The percentage of patients reaching ESRD ranged from 15.6 to 72.7 % [41, 42]. It was interesting that one study found the presence of multiple myeloma was not a risk factor for ESRD [41]. Unfortunately, interpretation of the data regarding treatment had been difficult. Since most of the data came from the melphalan and prednisone era, patients who underwent treatment often did worse due to infection and other complications. Furthermore, treatment did not seem to improve renal function. The results may be quite different with the use of novel agents. There are reports of 2 patients improving after treatment with bortezomib-based therapy [43]. Both had a significant reduction in their serum kappa FLC levels.

The term light-chain proximal tubulopathy should be discussed, and it is often associated with LCFS in the literature but the precise definition has yet to be unified. Sometimes, it refer to LCFS without crystals while in others, it is used to describe light-chain crystal deposition but the absence or presence of just a partial Fanconi syndrome [44, 45]. Some feel LCFS and light-chain proximal tubulopathy are the same entity while others feel they are separate [46, 47]. One series found that light-chain proximal tubulopathy without crystals represented 3.2 % of cases of light-chain-related renal diseases, compared to 0.9 % for

light-chain proximal tubulopathy with crystals [45]. In this series, 9 of the 10 cases with light-chain proximal tubulopathy without crystals were composed of lambda light chain that is opposite of what one would expect for LCFS. Patients exhibited lysosomal abnormalities (some of which had a mottled appearance) along with signs of acute tubular injury such as cytoplasmic swelling, blebbing or flattening with dilatation of tubular lumen and loss of brush border. Multiple myeloma was diagnosed in 8 of 13 patients who were diagnosed with light chain proximal tubulopathy. In another series of 190 biopsies of patients with multiple myeloma, only 1 was diagnosed as light-chain proximal tubulopathy with crystals [20]. Clearly, more research is needed in order to better define the entity of light-chain proximal tubulopathy.

Cryoglobulinemia

Cryoglobulins have the characteristic of reversibly precipitating in cold temperatures. They are composed of immunoglobulins. Three types of cryoglobulins have been identified. In type I, the immunoglobulin is monoclonal, often IgM but it can also be IgG or IgA [48]. Type II involves a monoclonal immunoglobulin most commonly IgM with affinity toward polyclonal immunoglobulins. This is often referred to as rheumatoid factor activity. Type III is composed of polyclonal immunoglobulin. Only types I and II can be considered to be MGRS and only if they are not the result of a lymphoma or multiple myeloma. Type I is the result of a B-cell lymphoproliferative disorders. Most commonly, it occurs in lymphoplasmacytic lymphoma with WM, but can be seen in multiple myeloma and CLL [48]. The most common causes of type II cryoglobulinemia are infections and autoimmune diseases but a lymphoproliferative disorder producing a monoclonal IgM will also result in type II cryoglobulinemia. The number one infectious cause of type II cryoglobulinemia in the world is hepatitis C infection, accounting for as many as 73 % of cases in some series [49].

Clinical manifestations are the result of precipitation, hyperviscosity, and leukoclastic vasculitis due to the cryoglobulins [48]. Manifestations can range from cutaneous rash and ulcers, to

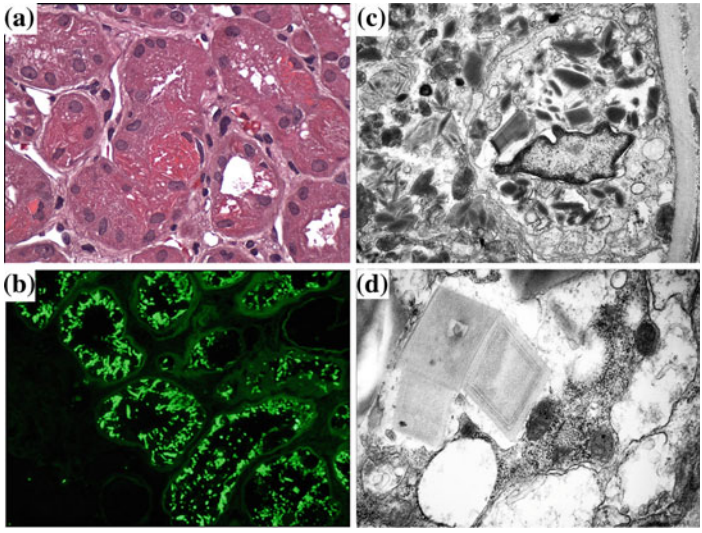

Fig. 9.3 Pathology of light-chain proximal tubulopathy. **a** Large rhomboid and rod-shaped hypereosinophilic crystals are seen within proximal tubular cells. (H&E, ×600). **b** Proximal tubular cell crystals stain strongly for kappa by immunofluorescence performed on pronase-digested, paraffin-embedded tissue (×400). The crystals were negative for lambda. C&D are from a different case of light-chain proximal tubulopathy. The proximal tubular cells are loaded with electron-dense non-membrane-bound light-chain crystals with rhomboid, rod or rectangular shapes (electron microscopy, ×13,500 for **c** and 33,000 for **d**)

neuropathy, arthritis, acrocyanosis, and Raynaud's to acral ischemia. In the kidney, cryoglobulinemia presents as glomerulonephritis with or without endovasculitis. The most common histologic pattern is membranoproliferative glomerulonephritis, but mesangioproliferative and endocapillary proliferative glomerulonephritis are also frequently observed (Fig. 9.4). Even membranous pattern has been reported. Florid monocytic infiltration of glomeruli is typical of cryoglobulinemic glomerulonephritis. Cryoglobulins can be seen forming pseudothrombi in the lumen of glomerular capillaries (Fig. 9.4) and may also be seen in the intima and lumina of arterioles and interlobular arteries, occasionally causing endovasculitis. On IF, the deposits should stain for the monoclonal immunoglobulin involved in the cryoglobulin (Fig. 9.4). C3 can also be detected. Most patients present with

proteinuria and moderate renal insufficiency [49]. Only 20 % of patients have nephrotic syndrome at presentation. Another 20–30 % may present with a nephritic picture with macro- or microhematuria. A small percentage will present like a rapidly progressive glomerulonephritis (RPGN) with quick loss of renal function. One striking feature of cryoglobulinemia is severe hypertension. Hypertension associated with cryoglobulinemia is often difficult control. In fact, studies have found only 15 % of patients with cryoglobulinemia died of renal failure, but they are much more likely to die of cardiovascular complications or infection [49].

Treatment of cryoglobulinemia depends on the type and etiology. Anti-viral therapy has been effective for type II cryoglobulinemia secondary to hepatis C [49]. This can be combined with rituximab in severe cases [50]. Rituximab can also be used in type II secondary to autoimmune diseases and type I secondary to a lymphoproliferative disorder [49]. Plasmapheresis can be an effective adjuvant therapy to reduce hyperviscosity and ischemia. A known complication of rituximab is cryoglobulin flare. While most cases are benign and it does not denote treatment failure, the flare can result in typical complications of cryoglobulinemia [51]. Plasmapheresis and additional immunosuppressive therapy may be needed to treat the flare.

MGRS-Related Kidney Diseases with Non-organized Monoclonal Immunoglobulin Deposits

Monoclonal Immunoglobulin Deposition Disease

MIDD represents a group of kidney diseases characterized by deposits of monoclonal immunoglobulin and its components. They include light-chain deposition disease (LCDD), light- and heavy-chain deposition disease (LHCDD), and heavy-chain deposition disease (HCDD) [7]. LCDD is the most common subtype of MIDD. MIDD is seen in 5 % of MM patients in autopsy series at

approximately half the incidence of AL amyloidosis [19]. The kidney is almost universally affected while systemic involvement in the lungs, heart, liver, and other soft tissue is less common and often asymptomatic [52]. The most common malignant condition associated with MIDD is multiple myeloma occurring in 59–65 % of cases while CLL is found in 3 % [7, 8]. In the past, the remainder of patients was described as idiopathic [8]. However, a recent study found 100 % of the patients with MIDD had an abnormal serum FLC ratio suggesting that these patients would be more accurately classified as MGRS [7, 11].

The most characteristic histological lesion in MIDD is nodular mesangial sclerosis [7, 53–55]. On light microscopy, these nodules are PAS and silver positive similar to Kimmelstiel–Wilson nodules of diabetic nephropathy (Fig. 9.5). Other features include mesangial sclerosis without nodules, membranoproliferative pattern, and crescents. The deposits in MIDD are Congo red negative. The most distinguishing features are seen on IF where monoclonal light chains, heavy chains or entire immunoglobulin can be seen in a linear pattern along the GBM and even more consistently along the tubular basement membranes (TBM) (Fig. 9.5). Staining of the immunoglobulin components can be seen in the mesangium, but it is less consistent than the TBM or GBM. C3 may also be detected in cases of LCHDD and HCDD. The deposits should not have any organized structure on EM and should appear as powdery or amorphous electron-dense deposits in the same compartment as seen on IF (Fig. 9.5). Occasionally, small fibers have been described.

Kappa is more commonly represented in LCDD. In opposite proportion to AL amyloidosis, 75 % of MIDD cases are due to a kappa clones [7, 8, 55, 56]. Even within the kappa light-chain family, the V_{kI} subtype seems to be most common [57]. A potential explanation may be found in its tertiary and quaternary structure. Analyses show a β-edge that is formed in the CDR2 loop of kappa light chains as a result of a conserved cis-proline at position 8 [58]. In lambda light chains, this proline is in the trans-position and it is often followed by another trans-proline at position 9 making formation the β-edge extremely unlikely. As a result of exposure of the β-edge, spontaneous aggregation of kappa light chains into oligomers has been demonstrated. These oligomers can then elongate into a fibril. These fibrils do not bind serum amyloid P

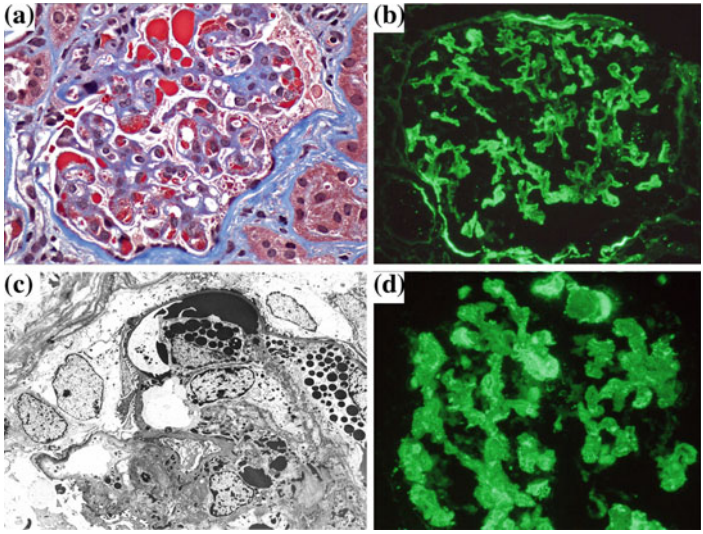

Fig. 9.4 Pathology of cryoglobulinemic glomerulonephritis. **a–d** are images from a 57-year-old female who was referred for new onset hypertension, proteinuria, and hematuria. Serum, urine, and cryoprecipitate immunofixation showed an IgG kappa monoclonal protein. Bone marrow biopsy showed 5 % plasmacytosis. **a** On light microscopy, glomeruli show mesangial hypercellularity and large glassy intracapillary hyaline thrombi "pseudothrombi," which stain bright red on trichrome stain (×400). **b** Ultrastructural examination shows large highly electron-dense subendothelial and mesangial deposits. Adjacent macrophages contain numerous phagolysosomes with the same electron density as the subendothelial deposits, consistent with phagocytosed immune material (×2000). The glomerular deposits stain brightly for IgG (**c**, ×400) and kappa (**d**, ×600) with negative lambda, trace IgM, and negative IgA (not shown) consistent with type 1 cryoglobulinemic glomerulonephritis

(SAP) or Congo red and possess no amyloid properties. It is postulated that these oligomers form the deposits that are seen in MIDD.

Median age of presentation ranged from 51 to 57 years, and roughly two-thirds of the patients were male [7, 8, 59, 60]. Proteinuria was nearly universally present with a median proteinuria of 2.7–4.1 g/d [7, 8]. Approximately 40 % of patients had nephrotic range proteinuria. Patients with HCDD present with have higher degree of proteinuria [7]. Microscopic hematuria was common (62 %), but gross hematuria was rare (3 %). Renal

insufficiency was also nearly universal with an average serum creatinine of 3.8 mg/dl [7, 8]. End-stage renal disease (ESRD) was reached by 39–57 % of patients.

The prognosis of these patients is variable. One study noted a 13-month overall survival in patients with LHCDD while another showed a 90-month overall survival [7, 60]. Independent factors that influenced overall survival were age, serum creatinine at diagnosis, the presence of multiple myeloma, and the presence of lytic bone lesions [7, 8, 60]. In patients who have multiple myeloma or CLL, treatment should be specified by the disease type. Patients with MGRS should also be treated to prevent the development of ESRD. In one study, although the patient survival was 71 % at 5 years, the renal survival was only 40 %. Inadequate treatment was one of the factors leading to the high rate of ESRD. It is important to recognize that these patients do not have a malignant condition so minimizing chemotherapy-related toxicity is as important as efficacy since these patients may live for a long time with their adverse effects. Bortezomib has been shown to be effective in these patients especially with its ability to inhibit NFκB [61, 62]. The least toxic schedule and route should be employed as toxicities have been reported [63]. Autologous stem cell transplantation either alone or after induction has also produced good results [62, 64–67]. In the past, kidney transplantation in MIDD was avoided due to the high rates of recurrence (~80 %) [68]. However, patients who had achieved a hematologic complete response (CR) prior to kidney transplantation may have lower risk of recurrence and better kidney allograft outcome [65].

Membranoproliferative Glomerulonephritis with Monoclonal Deposits

Membranoproliferative glomerulonephritis (MPGN) is a group of kidney diseases that share a common histopathologic pattern of injury. MPGN traditionally had been classified by the location of the deposits. Of the three types, type II MPGN, also known as dense deposit disease (DDD), had a unique pathophysiology [69, 70]. DDD is the result of abnormal complement activation resulting in the deposition of C3 [71]. MPGN secondary to infection,

autoimmune diseases, malignancy and other complement dysregulation can present as either type I or III. The contribution of monoclonal gammopathy in the pathogenesis of MPGN was not recognized until recently. In a single-center study that excluded patients with hepatitis (B & C) and DDD found 41 % of the MPGN cases had a circulating monoclonal protein [72]. Monoclonal protein deposits were found in the kidney in most of these patients. While majority of the cases were MGRS, 21 % met criteria for multiple myeloma and another 17.8 % had WM, CLL, and other lymphomas.

Histologically, MPGN is characterized by mesangial hypercellularity, endocapillary proliferation, and capillary wall remodeling [70]. The glomeruli often appear lobular, and double contours can be seen along the basement membranes on light microscopy. Electron-dense immune deposits can be seen in the mesangium and subendothelial space with or without subepithelial deposits. Granular deposits can be seen on IF that should stain for single heavy chain and a single light chain [72]. C3 deposits are usually found along the capillary walls.

Renal impairment and proteinuria were the most common presentation. Median SCr was 2.5 mg/dl, and proteinuria was 3.8 g/d [72]. Many of the patients also had microscopic hematuria. Hypertension, which was usually mild, was common among these patients. Complement levels were normal. Median age at presentation was 59 years with 57 % males. Limited follow-up did not allow for long-term prognosis assessment. However, patients with concomitant multiple myeloma appear to have the worse renal outcomes.

Proliferative Glomerulonephritis with Monoclonal IgG Deposits

A relatively new kidney disease associated with MGRS is the proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) [15, 73]. A unique feature of these patients is their preference for monoclonal IgG3. IgG3-κ accounts for more than 50 % of cases, and IgG3-λ contributes to another ∼13 % of cases. Hematologically, they tend to have a low clonal disease burden.

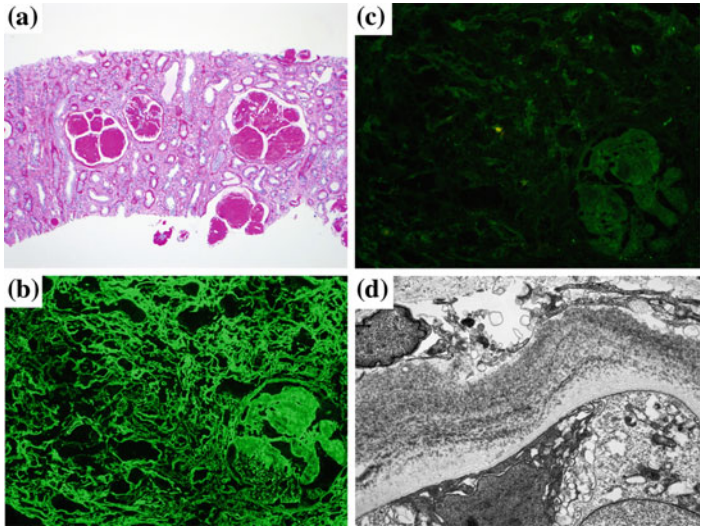

Fig. 9.5 Pathology of renal monoclonal immunoglobulin deposition disease. **a** Glomeruli have a nodular appearance due to mesangial sclerosis and massive deposition of lambda light chain. The nodules are paucicellular, glassy, and stain PAS positive, mimicking diabetic glomerulosclerosis (PAS, ×100). **b** and **c** are from the same biopsy as **a**. Immunofluorescence shows diffuse linear glomerular and tubular basement membranes and smudgy mesangial staining for lambda (**b**, ×200) with negative staining for kappa (**c**, ×200). The diagnostic ultrastructural finding in MIDD is punctate, powdery electron-dense deposits involving the inner aspect of the glomerular basement membranes (not shown) and the outer aspect of the tubular basement membranes (**d**, electron microscopy, ×9700)

Less than 10 % of patients qualify for multiple myeloma and over half do not even have detectable circulating monoclonal protein. Despite that, they have a high rate of recurrence after kidney transplantation, which has been detected as early as 3 months post-transplant [74].

On biopsy, the dominate feature is mixture of proliferative and membranoproliferative glomerulonephritis (Fig. 9.6). This is often diffuse endocapillary proliferation and leukocyte infiltration. PGNMID may show membranous features and crescents [15]. Interstitial fibrosis can be seen in more advanced cases. Glomerular capillary walls and the mesangial deposits are granular in

appearance on IF and should be positive for only a single IgG subtype and light chain (Fig. 9.6). C3 and C1q are detected in glomeruli in most cases. By EM, the deposits are predominantly granular (i.e., without substructure) and are predominately subendothelial and mesangial in location (Fig. 9.6). A minority of deposits may show lattice-like array with a periodicity of 15 nm. An IgA variant has been described [75].

These patients commonly present with nephrotic syndrome (>50 %) [73]. Mean proteinuria is 5.7 g/d. Most will also have renal impairment with the median SCr of 2.8 mg/dl. Microscopic hematuria may be detected in majority of the patients. Mean age of presentation was 54 years with 62 % females. During a mean follow-up of 30 months in one study, 21.9 % of the patients developed ESRD and 15.6 % had died [73]. Response has been reported with alkylator and steroids, rituximab, and steroids alone. Experience with anti-myeloma therapy especially with novel agents is small, and effectiveness remains to be determined.

MGRS-Related Kidney Disease Without Monoclonal Immunoglobulin Deposits

C3 Glomerulonephritis

C3 glomerulonephritis (C3GN) is a subset of C3 glomerulopathy that includes DDD and CFHR3 nephropathy [76]. It is characterized by deposits that are predominate C3 and without C1q, C4 or immunoglobulins (Fig. 9.7) [77]. By light microscopy, it may show features of MPGN, mesangial proliferative glomerulonephritis or endocapillary proliferative glomerulonephritis (Fig. 9.7) It may also exhibit prominent glomerular neutrophil infiltration mimicking postinfectious glomerulonephritis. Deposits can be both subendothelial, subepithelial, and/or mesangial on EM (Fig. 9.7). The appearance is, however, less electron dense than those of immunoglobulin deposits (Fig. 9.7).

Majority of the cases of C3GN is due to dysfunctional regulation of the alternative complement pathway. This is similar to the pathophysiology of DDD [77]. However, some patients with C3GN also have circulating monoclonal protein [78, 79]. In one

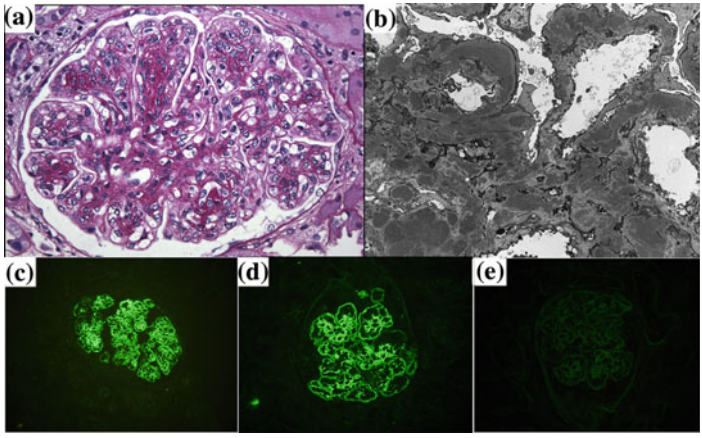

Fig. 9.6 Pathology of proliferative glomerulonephritis with monoclonal IgG deposits. **a** The glomerulus exhibits a membranoproliferative glomerulonephritis pattern of injury with moderate global mesangial hypercellularity and sclerosis, together with segmental duplication of the glomerular basement membrane and endocapillary hypercellularity (PAS, ×400). **b** On electron microscopy, there are large mesangial, intramembranous, and subendothelial deposits, together with segmental duplication of the glomerular basement membrane. The electron-dense deposits appear granular (without substructure) (×3000). **c–e** Glomeruli in this patient with PGNMID exhibit bright global mesangial and glomerular capillary wall staining for IgG3 (**c**) and kappa (**d**). Glomeruli are negative for lambda (**e**), IgA, IgM, IgG1, IgG2, and IgG4 (not shown). No extraglomerular staining for IgG or kappa is seen (×400 for **c–e**)

series, the incidence was up to 31 %. It has been shown that autoantibodies known as C3 nephritis factor (C3nef) can bind C3 convertase to stabilize it against the degradation effects of factor H [76]. These autoantibodies were typically thought to be polyclonal [80]. However, a study of 17 serum samples of patients with C3nef activity showed differential C3nef activity in samples treated with either anti-κ or anti-λ Sepharose, suggesting the possibility of monoclonal proteins acting as C3nef [81]. Indeed, monoclonal IgG and IgM C3nef have been isolated from patients with MPGN [82]. These evidences support the possibility that a monoclonal gammopathy could have C3nef activity resulting in C3GN or DDD [83].

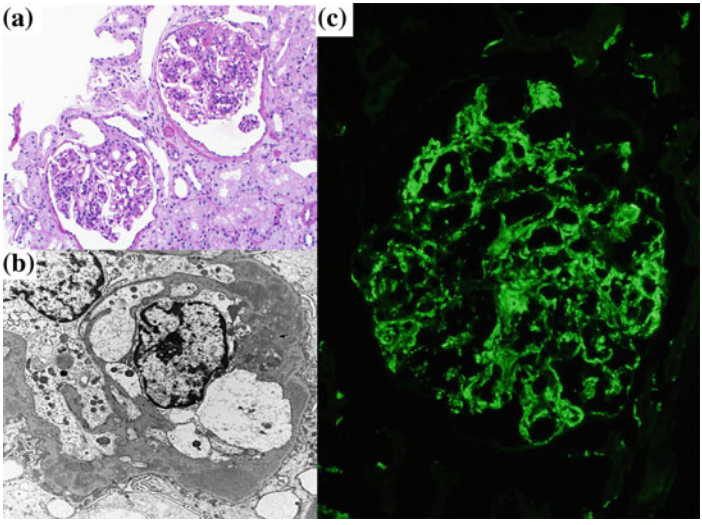

Fig. 9.7 Pathology of C3 glomerulonephritis. **a** On light microscopy, glomeruli show marked global mesangial hypercellularity (PAS, ×200). **b** On electron microscopy, there are large moderately electron-dense, ill-defined mesangial, intramembranous, and subendothelial deposits (×10,000). **c** On immunofluorescence, there is global granular mesangial and glomerular capillary wall staining for C3 (×400). Glomeruli are negative for IgG, IgA, IgM, kappa, and lambda in this case (not shown)

Thrombotic Microangiopathy in POEMS Syndrome

POEMS syndrome also known as Crow–Fukase syndrome is multisystemic disease most commonly due to a lambda-restricted monoclonal gammopathy [84]. The name POEMS is taken from 5 of the more common presentations, which include polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin manifestations, and sclerotic bone lesions [85]. Other features include extravascular volume overload, thrombocytosis, elevated levels of vascular endothelial growth factor (VEGF), and interleukin (IL)-6. The monoclonal protein is almost always lambda. This disease mimics MGUS as the median percentage of plasma cells in the bone marrow is 5 %. POEMS syndrome can also arise

from smoldering multiple myeloma, plasmacytoma, lymphoplasmacytic lymphoma, and Castleman disease.

Renal manifestations are not prominent features in POEMS. Often, patients may have renal insufficiency due to issues with volume. One unique feature is asymmetric size of the kidneys, which is thought to be due to unilateral renomegaly while other feels it is due to unilateral atrophy [86]. Rare patients can develop ESRD. Renal pathology in these patients often shows an MPGN-like lesion [87]. Immunoglobulin deposits are often not found [88]. In addition to the typical mesangial and endocapillary proliferation, mesangiolysis, microaneurysm, and swelling of the endothelial cells resembling thrombotic microangiopathy are common found, but thrombi associated with microangiopathic hemolytic anemia have not been reported [87–90]. Alterations in VEGF, platelet-derived growth factor (PDGF) and IL-6 levels have been suggested as the pathogenesis but elevated levels are not consistently found in patients with renal involvement [91]. Renal response to treatment has been reported but relapses are common although no data on renal response with novel agents had been reported [87].

Recurrent Diseases After Kidney Transplantation

One common feature shared by all MGRS-related kidney disease is the high frequency of recurrence after kidney transplantation. All glomerular diseases can recur after kidney transplantation. Diseases such as membranous nephropathy and focal segmental glomerulosclerosis have recurrence rates between 7 and 50 % [92]. Recurrence of IgA nephropathy can be as high as 61 % but loss of kidney allograft is uncommon. Recurrence of ANCA-associated vasculitis is less than 10 % likely the result of immunosuppression [93]. On the other hand, MGRS-related kidney diseases can recur at >80 %. Often, this is associated with allograft loss and death of the patient, making kidney transplantation difficult.

The best example of the high recurrence rate in MGRS-related kidney diseases is MIDD. In a single-center study, 5 of 7 patients with LCDD developed recurrent disease in their renal allograft

[68]. Median time to recurrence is 33 months with a range of 3–45. Recurrence disease was associated with loss of kidney allograft and/or death. Similar experience was noted in a review of 7 patients where 6 eventually developed recurrent disease [94]. Similar results are found in patients with fibrillary glomerulonephritis. In a study of 12 patients with fibrillary glomerulonephritis, 4 of 7 patients with a monoclonal gammopathy had recurrent disease after kidney transplantation [95]. One patient had recurrence in the second allograft after losing the first allograft to recurrent disease. In comparison, patients with fibrillary glomerulonephritis but without monoclonal proteins had no recurrence. In a study of recurrent MPGN, the only factor that was predictive of recurrence was abnormal complement levels at the time of kidney transplantation [96]. However, the presence of a monoclonal gammopathy showed a trend toward significance with nearly 3 times as many recurrences in those with a monoclonal protein. No large studies have been reported for PGNMID but recurrences have been reported. Recurrence tends to be rapid in these patients with a median time to recurrence at 3.8 months [74]. Graft lost is not uncommon.

Diagnosis of MGRS-Related Kidney Diseases

The definition of MGRS requires that the monoclonal gammopathy has a direct role in the pathogenesis of the kidney disease [11]. This can only be demonstrated by a kidney biopsy. This is especially important in patients over the age of 60 where the rate of MGUS far exceeds the rate of kidney disease [97, 98]. In separate studies from the same county, the prevalence of glomerular disease was found to be 9.0/100,000 person-year while the incidence of finding a monoclonal gammopathy in persons between the ages of 60–70 was 3 and 4.6 % for those 70–80 years of age. The presence of a monoclonal gammopathy and renal insufficiency is not sufficient to make the diagnosis. The most direct way to establishing the association between the kidney disease and the monoclonal protein is to demonstrate deposition of the monoclonal protein in the kidney. This can be assessed by immunofluorescence [14]. Restriction to a single light chain and/or heavy chain is required for

demonstration of monoclonality. In some cases, immunohistochemistry may be inconclusive. In such circumstances, proteomics by mass spectrometry has been extremely useful. In fact, mass spectrometry has become the gold standard for protein identification and typing for amyloid deposits [99]. Proving the connection between C3 deposits and a monoclonal gammopathy is more difficult. Ideally, a C3 (or C4) nephritic factor should be detected and should be identified as the monoclonal protein. This would insure that the monoclonal protein is activating complement. However, a C3 (C4) nephritic factor is not always found. In one series, only 2 of 10 patients with C3 glomerulonephritis and monoclonal gammopathy had a C3nef [79]. In another series, none of the 6 patients with MPGN and monoclonal gammopathy demonstrated a C3nef activity but two patients had anti-factor H IgG antibodies [78].

Once the monoclonal protein deposits have been identified in the kidney, the monoclonal protein should be measured in the circulation and the clone responsible should be identified. The monoclonal protein in blood or urine confirms the deposits are monoclonal. It also serves as a marker for treatment response. It is particularly important when there is a biclonal gammopathy to identify the pathologic one for targeting and monitoring. Identification of the clone will allow better and more direct treatment. Many of these clones may be very small, and higher sensitivity techniques such as flow cytometry may be needed. For lymphocytic clones, lymph node biopsy may provide additional information.

Treatment of MGRS

In the past, the risk of therapy-related myelodysplastic syndrome was often considered too high to use cytotoxic therapy for MGRS-related kidney diseases [100]. The one notable exception was AL amyloidosis. Since it is capable of being rapidly fatal, cytotoxic therapy including high-dose chemotherapy was accepted even for patients without multiple myeloma [32, 101, 102]. The same approach, however, was not practiced with the other MGRS-related kidney diseases. In a study of Italian patients with MIDD, patients with multiple myeloma were more likely to receive

vincristine–doxorubicin–dexamethasone (VAD) or vincristine–doxorubicin–methylprednisolone (VAMP) than patients without multiple myeloma ($p = 0.007$) [8]. Whether this practice affected the life expectancy of MIDD patients without multiple myeloma was unclear, but the poor renal recovery rate and high recurrence rate after kidney transplant were attributable to inadequate treatment [59, 68]. In diseases with low rate of multiple myeloma such as PGNMID, myeloma therapy was rarely used [74]. Fortunately, the introduction of novel agents in the treatment of multiple myeloma had changed the perspectives. First, concern of myelodysplastic syndrome is much less with novel agents than with alkylators [103]. More importantly, the higher and deeper responses afforded by novel agents have changed the renal outcome of these patients.

Treatment for some of these diseases is covered in greater details in other chapters (Please refer to the respective chapters for details). Instead, this section will cover the principles of treatment. First, as much as possible, treatment should be tailored to each specific clone rather than the kidney disease. In patients without an identifiable clone, one practical approach is to start with cyclophosphamide, bortezomib, and steroids [104]. The use of bortezomib as a frontline agent is preferred over other novel agents due to its rapid response, lack of nephrotoxicity or need for dosage adjustment in renal impairment [105]. Since many of the MGRS-related diseases have low malignant potential, the primary purpose of treatment for most cases (except AL amyloidosis) is preservation of kidney function rather than life [11]. Thus, for patients with advance degree of renal damage with little prospect of renal recovery and no other systemic involvement, and who are not candidates for kidney transplantation, treatment may not be necessary [104]. On the other hand, patients with rapidly declining renal function should be treated aggressively to avoid development of ESRD. Similarly, patients with advance chronic kidney disease or ESRD who are eligible for kidney transplantation should be treated in order to minimize their chances of recurrence after kidney transplantation. One important aspect to keep in mind when treating these patients is the separation between hematologic response and renal response. While renal response is dependent on hematologic response, it is also depended on the severity of the

renal damage [35]. Kidneys with advanced damage may not recover despite achievement of complete hematologic response.

Kidney transplantation in the past has been difficult due to the high rate of recurrence and graft loss and ineffective and risky therapies [68]. Adding alkylator therapy to immunosuppression often resulted in overimmunosuppression leading to infection and sepsis. The use of high-dose therapy followed by autologous stem cell transplantation (SCT) has made it possible to perform kidney transplantation in these patients. The achievement of hematologic complete response (CR) either prior to or after kidney transplant has produced satisfactory results in both allograft and patient survival in patients with AL amyloidosis [106]. Similar strategy has been successfully employed in patients with MIDD to prevent recurrence in the kidney allograft [65, 66]. Whether CR is required prior to kidney transplantation remains a question and is dependent on the disease. One consideration is damage to the renal allograft during treatment. Changes in immunosuppression during SCT have resulted in acute rejection of the kidney allograft [107]. Another important aspect is how quickly the disease can recur. In LCDD and PGNMID, recurrence can occur within 3 months of kidney transplantation whereas it is much slower in AL amyloidosis [68, 74, 108]. In diseases with rapid recurrence, achievement of CR should be done prior to kidney transplantation to avoid unnecessary damage to the kidney allograft. With the deep responses novel agents are capable of producing, the question whether SCT is required is valid and pertinent [61, 109–111]. More data are needed for salvage therapy after kidney transplantation before further recommendations can be made.

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