# Chapter 6
# Immunoglobulin Deposition Diseases

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## Introduction

Monoclonal immunoglobulins may be associated with a variety of renal diseases as a result of direct deposition of the monoclonal immunoglobulin and also from an indirect mechanism via dysregulation of the alternative pathway of complement. A thorough and complete clinical evaluation of the patient is required prior to categorizing their renal disease as related to the monoclonal protein. Tissue biopsy is essential for the diagnosis, and the initial workup should also include quantification and identification of monoclonal proteins with serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), immunofixation (IFE), and quantitative serum light-chain assay. However, some may also present without evidence of a circulating paraprotein. Furthermore,

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T.M. Zimmerman and S.K. Kumar (eds.),
*Biology and Management of Unusual Plasma Cell Dyscrasias*,
DOI 10.1007/978-1-4419-6848-7_6

in a significant proportion of patients, with a detected circulating monoclonal paraprotein, the end-organ pathology may not be directly attributable to monoclonal gammopathy making a directed biopsy of the kidney essential in establishing the diagnosis [33].

This chapter will review the clinical presentation and management of a spectrum of rare monoclonal gammopathy-associated renal lesions such as: monoclonal immunoglobulin deposition disease (MIDD), Type I cryoglobulinemia, proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID), C3 monoclonal-associated glomerulonephritis, immunotactoid glomerulonephropathy (ITG), light-chain proximal tubulopathy (LCPT) or Fanconi's syndrome and light-chain crystallopathy. Myeloma-related cast nephropathy and renal disease secondary to systemic light-chain amyloidosis will not be discussed in this chapter.

## Monoclonal Immunoglobulin Deposition Disease (MIDD)

MIDD is a systemic disorder characterized by tissue deposition of monoclonal immunoglobulin protein. An underlying plasma cell proliferative disorder is responsible for production and secretion of these immunoglobulin chain fragments, leading to their deposition into vital organs such as kidneys, heart, and liver, resulting in organ dysfunction. Depending on the component or fragment of the immunoglobulin that is deposited, MIDD is divided into light-chain deposition disease (LCDD), heavy-chain deposition disease (HCDD), or mixed light- and heavy-chain deposition disease (LHCDD). Although, MIDD remains a rare disease with an estimated annual incidence of 8 cases per million [22], large retrospective case series and database analyses have attempted to improve our understanding of the disease. In the largest case series of 64 patients with pathologically verified renal MIDD [31], a majority of patients carried a diagnosis of LCDD (80 %; 51 of 64), followed by 7 patients with HCDD and 6 patients with LHCDD.

## *Clinical Presentation and Course*

Most of the clinical data on MIDD are based on reports of patients with LCDD. The median age of patients is around 50–60 years which is significantly lower than other plasma cell dyscrasias. The incidence is higher in men as compared to women. They tend to present in an insidious fashion; however, cases of rapid progression manifested by rapid organ dysfunction have been described. The most common site of immunoglobulin deposition is the kidneys, presenting with progressive decline in glomerular function leading to renal insufficiency, albuminuria which often reaches nephrotic range, hypertension, and hematuria. In the absence of timely initiation of therapy, renal dysfunction progresses to ESRD [17], and in a small but significant number of patients, ESRD requiring renal replacement therapy is the presenting feature. Cardiac involvement is relatively less frequent and may be symptomatic with findings consistent with congestive heart failure and life-threatening arrhythmias [38]. The plasma cell burden is low in MIDD and does not meet criteria for diagnosis of MM [11]. Additionally, cytogenetic abnormalities associated with MM are rare in MIDD [11]. Other organ systems that may be involved include the liver, lungs, and nervous system. The degree of hepatic involvement ranges from mild transaminitis to portal hypertension and liver failure [38].

In LCDD, light microscopy demonstrates monoclonal protein deposits along glomerular and tubular basement membrane resembling nodular glomerulosclerosis (Fig. 6.1). Immunofluorescence (IF) reveals clonality of deposited immunoglobulin light chains (Fig. 6.2). On electron microscopy (EM), the deposits appear granular and unorganized in nature. The light chains are predominantly κ in nature in up to 85 % cases [22]. In contrast to amyloidosis, LCDD does not show a β-pleated folding configuration or fibrillar pattern and does not stain positive with Congo red or show apple green birefringence under polarized light [22]. In HCDD, either complete heavy-chain or truncated heavy-chain immunoglobulins are deposited into tissues, often along with light-chain fragments. The heavy chains are composed of γ isotype [31]. As in LCDD, HCDD is distinguished from AH

amyloidosis by non-fibrillar deposits and negative Congo red staining.

The prognosis of MIDD is dependent upon various factors, such as degree of renal and cardiac involvement, age, clinical comorbidity, and timeliness of initiation of therapy. Length of survival, therefore, ranges widely across various case series, with a median of 4 years [27]. In a case series of 63 patients, factors independently associated with poor prognosis and inferior survival in LCDD included increased age at presentation, coexisting plasma cell proliferative disorder, and extrarenal light-chain deposition [35].

## *Treatment*

Given rarity of disease, no randomized trial data are available to establish standard of care. The primary goal of therapy is to abrogate production of immunoglobulin light chains and prevent further renal damage. Essentially, this translates into administration of therapy directed at elimination of the underlying clonal plasma cells, which are typically associated with a low proliferative index.

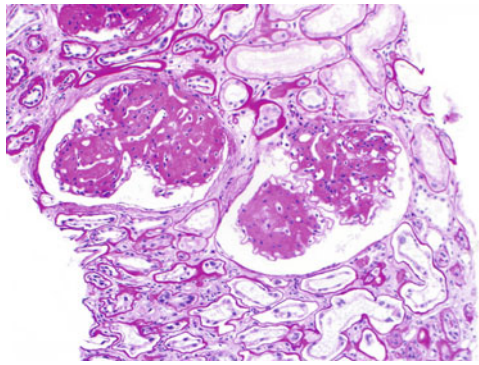

**Fig. 6.1** A case of LCDD shows nodular mesangial sclerosis and thickening of tubular basement membranes. The monoclonal protein deposits in the mesangium and tubular basement membranes are positive for periodic acid–Schiff stain (X 400)

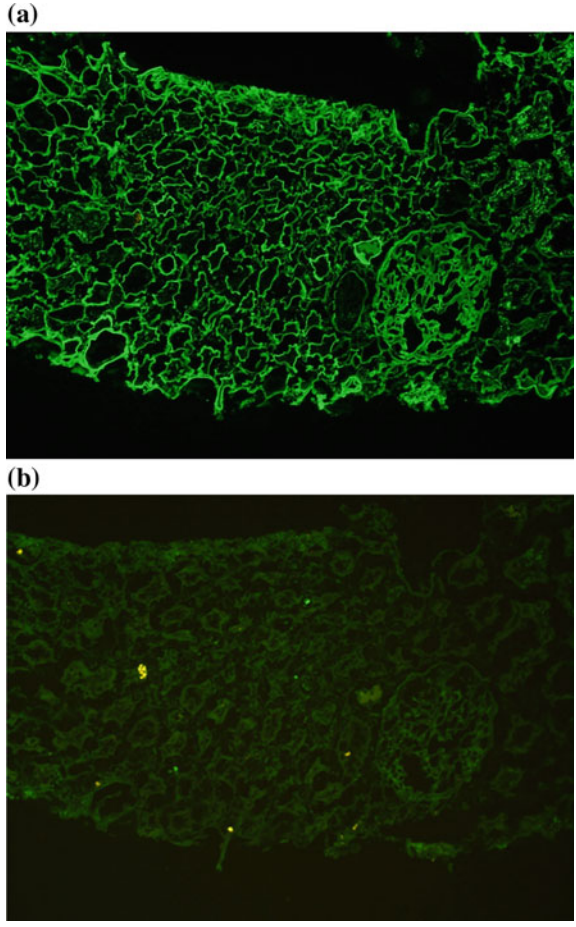


**Fig. 6.2** Immunofluorescence on a case of lambda type LCDD shows diffuse linear glomerular and tubular basement membranes positivity for lambda (**a**) with negative kappa (**b**) (X200)

Currently, the use of induction-based chemotherapy followed by consolidation with an autologous stem cell transplant if appropriate is the favored approach of managing such patients.

The combination of melphalan and prednisone remained a frontline agent in the management of LCDD for years. In appropriate candidates, consolidation therapy with stem cell transplantation is

associated with acceptable toxicity and improved long-term outcomes as opposed to chemotherapy alone [40, 50]. Improvements in renal function after ASCT have been reported, with reversal of dialysis dependence in one report [10, 50]. Weichman et al. [50] reported a case series of six patients with LCDD, who underwent ASCT with melphalan-based conditioning. Five of total six patients achieved a complete hematological remission (CHR), which was maintained at a median follow-up of 12 months. Encouragingly, improvement in renal function was also noted [50]. In another single-center retrospective analysis of six patients, high-dose chemotherapy followed by ASCT achieved both hematological and renal response [23]. Similarly, another report from Telio et al. [46] retrospectively reviewed eight patients with LCDD or LHCDD who underwent ASCT with melphalan-based conditioning regimen resulting in high rates of hematological and renal response.

Novel agents such as proteasome inhibitors may also be especially useful in this disease, as they are effective in patients with plasma cell dyscrasias presenting with renal insufficiency. Kastritis et al. reported the use of combination of bortezomib and dexamethasone as induction regimen in four patients with LCDD resulting in partial response in two and complete response in the other two patients. Of these, three patients proceeded to ASCT with melphalan-based conditioning and achieved a CHR at last follow-up [20]. Recently, Tovar et al. have reported the use of combination of bortezomib and dexamethasone as induction therapy followed by ASCT in three patients, of which two achieved a complete response (CR) with last follow-up at 34 and 40 months [48].

End-organ dysfunction and damage necessitates appropriate supportive care. Given near universal renal involvement, renal replacement therapy in the form of dialysis may be needed. The role of renal transplantation is unclear [22]. Median allograft survival in patients with LCDD is low secondary to recurrence of primary disease in the transplanted kidney. In a retrospective analysis, 71 % of patients were noted to have recurrence LCCD leading to a median graft survival of only 37.5 months, which is significantly lower than the decade or longer survival seen in non-LCDD patients [22]. Given poor allograft survival, selection of appropriate patients for renal transplantation is necessary.

Patients who achieve a complete hematological response with residual renal dysfunction may be appropriate candidates in this regard. Close surveillance and institution of further therapy as needed to prevent production and deposition of monoclonal immunoglobulins is needed to justify allocation of donor organs.

## Type I Cryoglobulinemia

Cryoglobulinemia is characterized by the presence of cryoglobulins which are serum proteins that tend to precipitate under conditions of cold exposure. The broquet classification, based on the clonality of involved immunoglobulins, classifies cryoglobulinemia into Type I (monoclonal; commonly IgG or IgM), Type II (both monoclonal and polyclonal), and Type III (polyclonal) [4].

Type I cryoglobulinemia is associated with clonal plasma cell or B-cell disorder, commonly MM or Waldenstrom's macroglobulinemia.

### *Clinical Presentation and Course*

The majority of patients with Type I CG remain asymptomatic. Depending on the degree of cryoglobulinemia and offending factors, patients may present with sequelae of thrombosis characteristically manifesting as Raynaud phenomenon, acral cyanosis, and ischemia or with symptoms of hyperviscosity such as blurred vision, headache, diplopia, and confusion. Cryoglobulinemia, however, has protean manifestations, and the involvement of other organ systems such as cutaneous, pulmonary, renal, and musculoskeletal structures is common. Of these, renal involvement presents as membranoproliferative glomerulonephritis with microtubular deposits composed of monoclonal cryoglobulin [19].

## *Treatment*

The management of cryoglobulinemia relies heavily on patient education and close monitoring for complications. Limiting cold exposure is encouraged. The treatment of underlying plasma cell or lymphoproliferative disorder may be required if preventive measures are inadequate. The general paradigm of managing cryoglobulinemia is to direct treatment against the underlying cause leading to the formation of cryoglobulins. It is also important to gauge the severity of the cryoglobulinemia symptoms when choosing an appropriate therapeutic regimen. For mild symptoms such as purpura, arthralgias, or mild neuropathy, observation, avoidance of cold temperatures, or wearing warm clothing should suffice.

Type I cryoglobulinemia should be managed with therapies directed against eradicating the underlying clonal cells responsible for producing the offending immunoglobulin. In cases secondary to overt neoplastic disorders such as MM, non-Hodgkin's lymphoma, or Waldenstrom's macroglobulinemia, established chemotherapeutic regimens for each of those respective malignant conditions should be utilized to halt the production of cryoglobulins [13, 34, 41]. In one series, high-dose melphalan chemotherapy was utilized in four patients with Type I cryoglobulinemia due to MM, all of whom derived disease control for at least 18 months or more [34]. However, more indolent clonal processes such as MGUS can be treated with agents ranging from corticosteroids or alkylating agents [9, 47]. Novel biological agents such as bortezomib, thalidomide, and lenalidomide may be used in severe and/or refractory patients [2, 5, 9, 32, 47].

Patients with life-threatening vasculitis including cryoglobulinemic nephropathy, skin ulcers, or symptoms related to hyperviscosity may require the use of plasmapheresis to help reduce the levels of circulating cryoglobulin complexes [37, 43, 45]. However, this does not treat the underlying disease and is unable to achieve long-term disease control. Furthermore, there can be rebound elevation in cryoglobulin production after the cessation of plasmapheresis [7]. Thus, cytotoxic therapy must be instituted concurrently to help maintain disease control.

## Proliferative Glomerulonephritis with Monoclonal IgG Deposits (PGNMID)

PGNMID is a distinct entity that resembles immune complex-mediated glomerulonephritis except that immunoglobulin deposits are comprised of intact monoclonal immunoglobulins [29].

### *Clinical Presentation and Course*

The most common clinical features include varying degrees of hematuria, renal insufficiency, hypertension, and nephrotic syndrome. A low serum C3 level can also be present. The kidney biopsy typically shows a membranoproliferative pattern of injury in most cases. On immunofluorescence, monoclonal immunoglobulins deposits are seen in the mesangial and capillary wall. If the heavy chain consists of IgG, subtyping the IgG commonly finds the IgG3 subclass [30]. In the Nasr study, a monoclonal serum protein was detected at presentation in 30 % of patients, only one patient had multiple myeloma; however, none of rest of the patients went on to develop an overt hematological malignancy. In 32 patients for which extended follow-up was available, complete response (CR) as defined by remission of proteinuria to <500 mg/d with normal renal function was noted in 4 and partial response (PR) as defined by reduction in proteinuria by at least 50 % with stable renal function in 8 patients, while progression to ESRD was noted in 7 patients.

### *Treatment*

There is no standard treatment for PGNMID. In one case series, 18 patients received immunomodulatory drugs, 9 received angiotensin-converting enzyme inhibitors (ACE) or angiotensin II receptor blockers (ARB), 3 received alkylating agents, 1 each received bortezomib or combination of bortezomib and thalidomide, while 5 patients were not treated. Patients demonstrating at least a PR or better were seen in 8 of 18 patients who received

immunomodulatory agents and 4 of 9 patients who received an ACEi or an ARB [30]. If the offending monoclonal immunoglobulin detected on a renal biopsy is also detected in serum or urine or both, we prefer to combine bortezomib, cyclophosphamide, and dexamethasone for IgG and IgA monoclonal proteins and rituximab alone or in combination with cyclophosphamide and dexamethasone for IgM monoclonal proteins.

## C3 Monoclonal-Associated Glomerulonephritis

C3 monoclonal-associated glomerulonephritis (C3 GN) is characterized by proliferative glomerulonephritis in response to aberrant glomerular deposition of complement factors secondary to functional inhibition of complement regulatory pathways by monoclonal paraproteins [51]. The hallmark pathological finding is intense C3 staining without evidence of concomitant immunoglobulin deposition.

### *Clinical Presentation*

In a retrospective review of 32 patients by Zand et al., the clinical course was variable reflecting the heterogeneous nature of the disease. Despite aggressive workup, only 10 (31 %) had a serum monoclonal protein, of these 1 patient was identified to have chronic lymphocytic leukemia, while the rest were classified as MGUS. One patient, who underwent a kidney transplant, developed pathological evidence of recurrent C3 GN on follow-up biopsy of the graft, suggesting the importance of controlling the underlying clonal cell disorder.

### *Treatment*

In many cases, the condition remains indolent and requires no therapy. However, in the setting of progressive renal dysfunction,

steroids or steroids in combination with cyclophosphamide can be used in patients with no detectable monoclonal protein. There is no clear evidence of the benefit of immunomodulatory agents, proteasome inhibitors, or alkylator-based regimens in the management of C3 GN. However, in patients who have an IgG or IgA monoclonal protein with rapidly progressive disease not responsive to steroids alone or steroid in combination with cyclophosphamide, bortezomib in combination with cytoxan and dexamethasone has been used. Furthermore, for IgM monoclonal protein, rituximab alone or in combination with cyclophosphamide and dexamethasone can be used. Within this context, interventions are dictated by the clinical picture and close follow-up remains important. Targeting the complement system remains an active area of research.

## Immunotactoid Glomerulonephropathy (ITG)

ITG is an extremely rare disorder associated with a monoclonal gammopathy, as exemplified by an incidence rate of ~0.06 % based on 10,108 native kidney biopsies [39]. It is characterized by proliferative glomerulonephritis on light microscopy, IgG deposits on immunofluorescence microscopy, and focal intraglomerular deposition of non-amyloid microfibrils or microtubules, usually >30 nm in diameter and arranged in parallel or stacked arrays as seen on electron microscopy. It is important to distinguish ITG from the more common fibrillary glomerulonephritis (FGN), which is associated with polyclonal immunoglobulin deposits and lack of association with underlying plasma cell and lymphoproliferative disorder.

### *Clinical Presentation*

Clinically, hematuria, renal insufficiency, hypertension, and nephrotic syndrome are commonly seen in patients with ITG [36]. Extrarenal involvement is rarely seen in these patients. The common hematological malignancies associated with ITG are chronic

lymphocytic leukemia, myeloma, and lymphoplasmacytic lymphoma.

### *Treatment*

The management strategy is aimed at treating the underlying hematological process. Given rarity of disease, no clear outcome with specific agents is identified. Reports have demonstrated that one patient with underlying chronic lymphocytic leukemia did have a response to treatment with fludarabine-based regimen with decreased proteinuria and improvement in renal function. Cadaveric renal transplantation has been performed in these patients with maintenance of the allograft function for significant duration despite ITG recurrence in the transplanted kidney.

## Light-Chain Proximal Tubulopathy (LCPT) or Fanconi Syndrome

LCPT is the most common subtype of crystal-storing histiocytosis disorders which are a group of monoclonal gammopathy disorders characterized by lysosomal processing and intracellular deposition of crystallized immunoglobulin free light chains in the kidneys, and other organ systems, such as the spleen, liver, and bone marrow, may also be involved [25].

### *Clinical Presentation*

In LCPT, the disease is localized to the proximal renal tubular epithelium and extrarenal manifestations are rare [42]. The underlying plasma cell dyscrasia is commonly low-grade MM or MGUS [24] secreting immunoglobulin light chains [26]. It is rarely associated with LPL [3, 49]. The clinical presentation is consistent with defects in sodium-coupled cellular co-transport mechanisms.

This is then seen clinically as Type II renal tubular acidosis, aminoaciduria, glycosuria, and phosphaturia [42]. Urinary loss of phosphorus leads to increase in parathyroid hormone and resultant vitamin D-resistant osteomalacia, often presenting as microscopic bone fractures and bone pain [11, 16, 26].

### *Treatment*

The optimal therapy is unknown; however, institution of therapy directed at the underlying hematological disorder may be required in a small number of patients. Recently, stem cell transplantation has been utilized with good success in stabilization or improvement of the renal function in LCPT patients. Fortunately, the rate of progression to ESRD or symptomatic multiple myeloma remains low. Furthermore, measures to ameliorate further bone loss include calcium, phosphate, and vitamin D supplementation [6].

## Light-Chain Crystallopathy

The crystallization and subsequent deposition of monoclonal paraproteins into systemic vasculature is exceedingly rare, with less than fifty reported cases in literature [1, 8, 14, 15, 18, 21, 28, 44]. Among these, an underlying plasma cell dyscrasia, most commonly MM, is often identified. However, there are no clearly identified risk factors in myeloma patients who are predisposed to crystallopathy.

### *Clinical Symptoms*

Crystalglobulin deposition injures and activates the vascular endothelium, thus triggering procoagulant mechanisms, ultimately leading to thrombosis and consequent vascular compromise leading to end-organ damage. The renal vasculature is most commonly involved and often presents as sudden decline in renal function, which is often irreversible. Less appreciated are the cutaneous,

ocular, neurological, and musculoskeletal complications. Biopsy of the involved organ, commonly kidneys and skin, is required to establish the diagnosis.

### *Treatment*

Despite rarity of the condition, crystal-induced glomerulopathy should be included in the differential diagnosis, as directed and timely therapy to reduce monoclonal paraproteinemia in the form of plasmapheresis and high-dose steroids may prevent or reverse renal dysfunction and also serve as bridging therapy for definitive therapy. The mainstay of therapy remains treatment of the underlying plasma cell disorder. There is no clear evidence for efficacy of alkylator-based therapy. Hashimoto et al. reported resolution of cutaneous ulcers and partial correction of renal dysfunction in a patient treated with thalidomide- and dexamethasone-based therapy [15]. We have recently employed a bortezomib-based approach with encouraging results in one patient, with stabilization of renal dysfunction and complete resolution of cutaneous ulceration [12].

## Conclusion

Renal diseases associated with monoclonal gammopathy are the result of a toxic monoclonal protein produced by lymphoid-derived hematopoietic cells such as B cells or plasma cells. These disorders rarely require treatment to prevent their progression to overt malignancy, but urgent therapy is sometime required to prevent deterioration of renal complications. A thorough and complete clinical evaluation that may involve a renal biopsy must be performed in every patient suspected of having their renal disease related to a monoclonal gammopathy.

**Acknowledgments** We thank Dr. Samih H. Nasr for providing the images used in this manuscript.

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