

Multiple Myeloma

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J Am Soc Nephrol 17: 2533–2545, 2006. doi: 10.1681/ASN.2006020139

Multiple myeloma is a plasma cell dyscrasia that accounts for almost 10% of all hematologic malignancies (1,2). The annual incidence of multiple myeloma is 4.3 per 100,000 people (3,4), but the incidence ranges from 1 per 100,000 for people who are 40 to 49 yr of age to 49 per 100,000 population for those who are ≥ 80 yr of age (5). To distinguish multiple myeloma from other plasma cell dyscrasias, the diagnosis is based on histologic, serologic, and radiographic features and includes bone marrow with clonal plasma cells or histologic confirmation of a plasmacytoma; a monoclonal protein in the serum or urine (unless the patient has a nonsecretory myeloma [3% of patients]); and end-organ damage evidenced by renal insufficiency, hypercalcemia, anemia, or lytic bone lesions (2,6). The diagnosis of myeloma often results from the workup of unexplained renal disease, and in a study of renal biopsies in elderly patients with unexplained renal failure, 40% of patients with cast nephropathy had previously undiagnosed myeloma (7).

Renal Disease in Multiple Myeloma

Renal disease in myeloma most often presents as renal insufficiency and proteinuria. Occasionally, patients with myeloma present with renal tubular dysfunction, including defects in acidification and concentration and, rarely, the Fanconi syndrome (8–14).

Renal insufficiency (serum creatinine of >1.3 mg/dl) is found at presentation in almost 50% of patients with myeloma (11,15–18), and severe renal insufficiency (serum creatinine >2.0 to 2.5 mg/dl) is seen in >15 to 20% of cases (15–17,19). Because patients with myeloma are elderly and have reduced muscle mass, the use of serum creatinine may underestimate the proportion with renal insufficiency. Therefore, renal function is determined best by calculation of the creatinine clearance using either the Cockcroft-Gault equation or the Modification of Diet in Renal Disease (MDRD) formula (15,16).

Although proteinuria is observed in $>80\%$ of cases, it most often consists of light chains, and light-chain proteinuria can be massive (>10 g/d). Fewer than 15 to 25% of patients with myeloma actually develop the nephrotic syndrome (17,20).

The spectrum of renal lesions that is seen in patients with myeloma include “myeloma kidney,” or cast nephropathy;

light chain (AL) amyloidosis; monoclonal Ig deposition disease (MIDD); and, less frequently, cryoglobulinemic glomerulonephritis and proliferative glomerulonephritis (21). Autopsy studies in patients with myeloma found cast nephropathy in 30 to 50%, light-chain deposition disease in 2 to 3%, and amyloidosis in 4 to 5% of cases (22,23). In one study (22), acute tubular necrosis was seen in 34% of cases. Because these autopsy studies include $<10\%$ of patients who die of a plasma cell dyscrasia, the results may underestimate the extent of renal involvement. In native renal biopsy studies of patients with myeloma and renal disease, 40 to 63% had cast nephropathy, 19 to 26% had light-chain deposition disease, 7 to 30% had amyloidosis, and $<1\%$ had cryoglobulinemic renal disease (10,20). A biopsy-based diagnosis is important in the evaluation of patients with myeloma because each of the renal lesions has its own therapeutic and prognostic implications.

Pathogenesis of Renal Disease in Multiple Myeloma

The renal pathology of cast nephropathy, MIDD, and amyloidosis is diverse, but in each instance, the initial pathogenetic step is the production in the bone marrow of an abnormal Ig fragment (usually an Ig light chain) by a clone of neoplastic plasma cells. During normal and neoplastic Ig synthesis, plasma cells produce an excess of light chains that are released into the circulation. However, normal light chains are filtered by the glomeruli and are endocytosed and metabolized by the tubules, and they neither deposit in renal structures nor cause pathology (24). The dichotomous behavior of light chains that is produced by normal and neoplastic plasma cells suggests that mutations in the Ig molecule are the basis for the discrete pathologic lesions that are seen in multiple myeloma. Furthermore, light chains from patients with multiple myeloma and kidney disease cause disease-specific pathology when injected into mice (25–27). Biochemical studies have identified specific Ig structural abnormalities that are associated with multiple myeloma, MIDD, and amyloidosis, but the mechanisms that transmit the biochemical abnormalities into the specific pathologic entities remain largely speculative.

Cast Nephropathy

Patients with cast nephropathy present with renal insufficiency that can be severe (*i.e.*, serum creatinine >7 mg/dl; Table 1) (20). In up to 50% of patients, the renal failure is acute in nature and often is attributed to a precipitating factor such as dehydration, infection, hypercalcemia, or the use of contrast

Published online ahead of print. Publication date available at www.jasn.org.

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Table 1. Presentation and outcome in myeloma-associated renal disease^a

	Cast Nephropathy	LCDD	Amyloidosis	P
<i>n</i>	48	22	35	
Presenting features				
hemoglobin (g/dl)	8.9	10.3	12.0	0.04
calcium (mmol/L)	2.5	2.17	2.11	<0.001
serum creatinine (mg/dl)	7.1	4.7	2.7	<0.001
acute renal failure (%)	48	23	3	<0.001
nephrotic syndrome (%)	10	18	54	<0.01
Durie-Salmon stage 3 (%)	56	36	0	
Outcome				
follow-up (mo)	15 ± 21	37 ± 62	24 ± 25	NS
chronic dialysis (%)	46	32	40	NS
time to dialysis (mo)	3 ± 5	18 ± 19	15 ± 20	0.001
median survival on dialysis (mo)	6	48	22	<0.01
total deaths (%)	69	41	54	NS

^aData from reference (20). LCDD, light-chain deposition disease.

medium or nonsteroidal anti-inflammatory drugs (NSAID) (8,10,11,18,20,28). Despite that proteinuria (primarily light-chain proteinuria) is a presenting feature in all patients with cast nephropathy, only 10% have the nephrotic syndrome. Patients with cast nephropathy are more likely to have hypercalcemia, severe anemia, advanced myeloma (Durie-Salmon stage 3), and light-chain myeloma compared with patients who have myeloma without renal failure (11,15,16,20,29). The risk for renal failure is associated with the level of light-chain excretion (15). Renal insufficiency was found in 16% of patients with <1 g/d light-chain proteinuria, 47% of patients with 1 to 10 g/d, and 63% with >10 g/d ($P = 0.001$) (15). Although it once was thought that renal failure more likely was associated with the excretion of λ light chains (9,30), more recent studies find no light-chain predominance (15,16,29).

Pathology of Myeloma Cast Nephropathy. The kidneys of patients with multiple myeloma and renal insufficiency show a variety of pathologic lesions, but the most common is cast nephropathy. The diagnosis of cast nephropathy is based on the demonstration of tubular casts in the distal nephron that are composed of Ig light chains, and the light chain in the cast is the same as that in the serum and urine (31); immunofluorescence microscopy demonstrates staining restricted to one or the other light chain (Figure 1). The casts contain either Ig light chain, Ig, and other serum proteins (31–36), including Tamm-Horsfall glycoprotein. In hematoxylin- and eosin-stained sections, the casts are intensely eosinophilic, and they seem “brittle” because they are lamellated and fractured frequently (Figure 2). The casts often are surrounded by macrophages and giant cells (31,33,37,38). Casts are associated with tubular rupture (37), and when they rupture, they cause interstitial nephritis (37). The extent of cast formation does not parallel the degree of interstitial fibrosis and tubular atrophy, and despite the role of casts in the pathogenesis of the tubulointerstitial lesion, renal function correlates with interstitial fibrosis and tubular atrophy (31,37,39), not with cast formation (31).

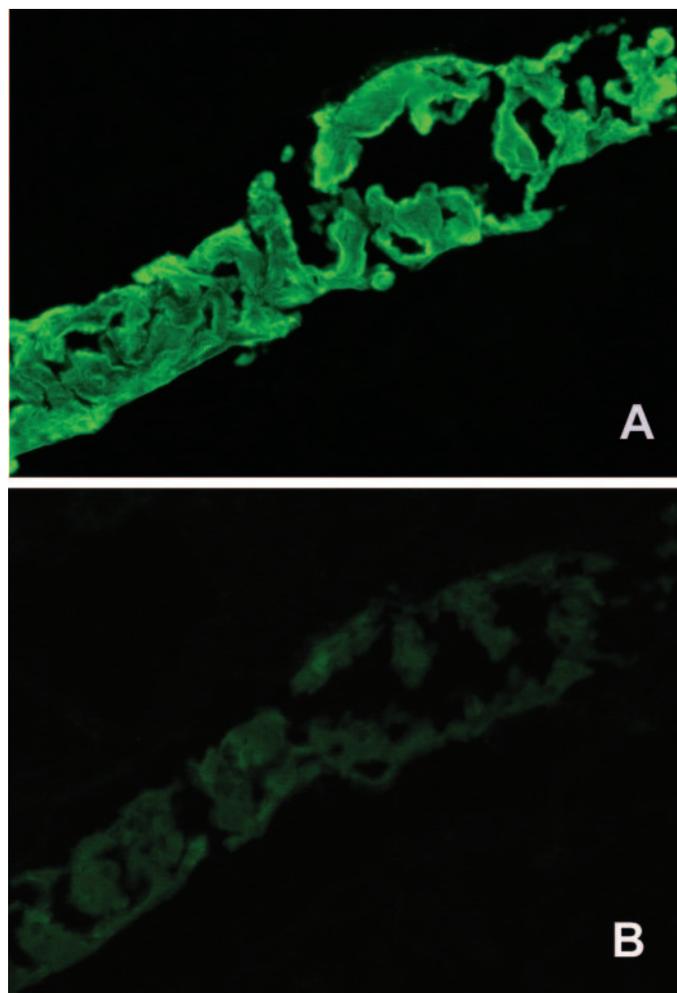


Figure 1. Myeloma cast nephropathy demonstrating light-chain restriction in the casts. The cast stained with κ Ig light chain (A) shows bright (3+) staining. The same cast stained in a serial section for λ light chain (B) is negative.

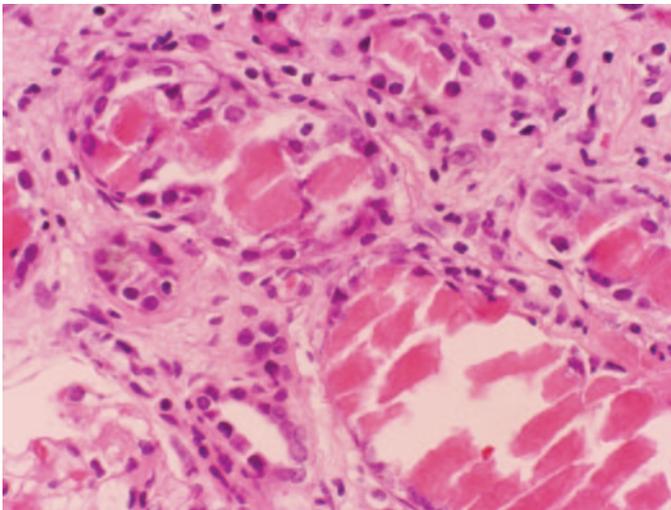


Figure 2. Myeloma cast nephropathy. The eosinophilic casts are “fractured” into plate-like fragments that suggest that they are “brittle.” The tubules are atrophic with flattened epithelium, and the interstitium is fibrotic with a sparse lymphocytic infiltrate. Hematoxylin and eosin stain.

The filtered light chains may cause intrarenal obstruction in the distal nephron (40) by co-aggregating with the carbohydrate moiety of Tamm-Horsfall glycoprotein, which is produced in the thick ascending limb of the loop of Henle (41). Factors that lead to cast formation are implicated in the pathogenesis of cast nephropathy, and they include the type and concentration of Bence Jones glycoprotein, calcium concentration, pH, sodium chloride concentration, tubular flow rate, dehydration, hypercalcemia (30,40,41), furosemide, NSAID, and intravenous contrast material (30,40).

Tubular injury also occurs as a result of light-chain dose-dependent toxicity to the proximal tubule epithelial cells, resulting in tubular necrosis, and the casts and the tubular epithelial cells may contain rhomboid or needle-shaped crystals in cases that are associated with the Fanconi syndrome (42,43). The crystals usually consist of κ Ig light-chain fragments, resulting from cathepsin B digestion, that do not bind Tamm-Horsfall glycoprotein, and this explains why cast nephropathy and Fanconi syndrome rarely coexist (44,45). Rarely, patients with multiple myeloma present with acute interstitial nephritis without cast nephropathy or glomerular or vascular light-chain deposition. All but one of these patients has had linear tubular basement membrane deposition of κ light chains associated with the most severe inflammation, and they may be considered as a type of MIDD (see below) with pathology limited to the tubular-interstitial compartment (22).

Prognosis of Myeloma and Cast Nephropathy. The presence of renal disease—renal insufficiency, in particular—in patients with myeloma is of prognostic importance because it is associated with a significant increase in morbidity and mortality (18,46). The median survival in patients with myeloma is approximately 36 mo, with a 5-yr survival of 18 to 27% (5,17,47,48), and renal failure is one of the most common causes of death, second only to infection. In fact, early deaths (within

60 d of diagnosis), seen in 10% of patients, most often are attributed to infection (45% of cases) and renal failure (28% of cases) (46), and the presenting serum creatinine is prognostic (20,28,47,48). In patients who present with a serum creatinine of <1.4 mg/dl, the median survival is 44 mo, compared with 18 mo for patients with a creatinine of 1.4 to 2.0 mg/dl, and ≤ 4 mo in patients with a creatinine of >2.0 mg/dl (48). As a result of the poor prognosis and increased morbidity associated with renal disease, early and aggressive management of renal insufficiency and myeloma is critical.

Treatment of Myeloma and Cast Nephropathy. Initial treatment is directed at correcting the reversible factors that contribute to reduced GFR and cast precipitation (11,20). This includes aggressive hydration (2 to 3 L/d), alkalinization of the urine, discontinuation of NSAID, and avoidance of intravenous iodinated contrast media (49). Although bisphosphonates are useful in the management of hypercalcemia, they, too, may be associated with acute renal failure (ARF) and must be used with caution (50,51). This initial therapy (along with chemotherapy described below) leads to recovery of renal function in up to 50% of cases, often within 1 mo, and is associated with patient survival that is similar to those in patients who have myeloma without renal failure (8,10,11,28,29,52). Factors that are predictive of a recovery of renal function after therapy include previous normal renal function or mild renal insufficiency, the presence of precipitating factors (*e.g.*, dehydration, NSAID, hypercalcemia), and early, aggressive treatment (29).

The main goal of therapy in myeloma is to reduce the level of light-chain production by inducing a remission in the underlying malignancy with chemotherapeutic regimens alone or followed by autologous stem cell transplant (ASCT) (1). The use of melphalan and prednisone is reserved for patients who are not eligible for ASCT because of advanced age (>70 to 75 yr) and/or significant comorbidity (1,2). The preferred approach to newly diagnosed myeloma is induction therapy that consists of dexamethasone alone or in combination with thalidomide or with vincristine, cyclophosphamide, and doxorubicin (melphalan is avoided because it can interfere with stem cell mobilization) followed by ASCT. With the use of ASCT, response rates are as high as 85% (1,2,53), and the overall median survival is increased by 12 mo, compared with standard chemotherapy. The transplant-associated mortality rate is $<4\%$ (1,53). In ASCT patients who attain remission, the median overall survival ranges from 40 mo (in patients with a partial remission) to 89 mo (in patients with a complete remission), compared with 26 mo in nonresponders (53). The use of ASCT in patients with myeloma and renal insufficiency (serum creatinine >2 mg/dl) and ESRD has resulted in similar response rates and outcomes; however, the transplant-related mortality rate was higher, up to 13% (54–57). In patients who have myeloma and are new to dialysis, successful ASCT has led to recovery of renal function and discontinuation of dialysis in up to 24% of cases (57). As a result, ASCT is the preferred therapy even in patients with myeloma, including those with advanced renal failure (56).

Plasmapheresis has been used to reduce the plasma concentration of light-chains rapidly in patients with renal insufficiency (58). Two small, prospective studies demonstrated im-

provement in renal function (59,60) and patient survival (60) after plasmapheresis, and it has been recommended in the management of ARF in multiple myeloma (49,58). However, findings from a recent large, prospective, randomized trial of plasmapheresis in the treatment of ARF in 97 patients with newly diagnosed myeloma, 30% of whom required dialysis at the onset, failed to show any benefit (61). During the course of 6 mo, dialysis was discontinued in 50% of control and 66% of plasma exchange patients who were on dialysis at the start of the study, and dialysis was initiated in 20% of patients in each group. There were no significant differences in composite outcome of death, dialysis dependence, or severely reduced renal function between the plasma exchange and control patients (58 *versus* 69%). These findings show that plasma exchange is of no additional benefit to the current chemotherapeutic approach in the management of ARF in multiple myeloma, and it is no longer recommended (62).

Dialysis and Renal Transplantation in Cast Nephropathy. Even with aggressive treatment, progression to ESRD occurs in up to 65% of patients with cast nephropathy within 3 mo of diagnosis (Table 1) (10,20). Patients who present with severe or advanced renal failure are most likely to have irreversible disease, with >80% requiring dialysis at presentation and only 15% regaining renal function (18).

The median survival on chronic dialysis has ranged from 4 to 28 mo, with 1- and 2-yr survival rates of 29 to 84% and 19 to 50%, respectively (8). On the basis of data from the US Renal Data System, patients with myeloma have an adjusted relative risk (RR) for death that is 2.5 times that of other dialysis patients and a significantly greater 2-yr mortality rate (58 *versus* 31%) (63). The more advanced the myeloma, the poorer the survival on dialysis. The median survival on dialysis for patients with myeloma and Durie-Salmon stages 1, 2, and 3 is 18, 6, and 2 mo, respectively (20). The prognosis on dialysis depends on response to chemotherapy, with responders surviving 37 mo compared with 12 mo for nonresponders (64). Therefore, in myeloma, features that are prognostic of patient survival are the extent of tubulointerstitial disease that is seen on biopsy, tumor mass, and response to therapy (20,65).

Patients with myeloma and ESRD have been treated with hemodialysis and peritoneal dialysis, and they seem to be equally effective (8,66,67). However, sepsis is a major cause of morbidity, with one episode per 6 patient-months, and sepsis may significantly affect the success of therapy (64). In addition, cardiovascular disease and severe anemia can be significant problems. Fortunately, recombinant erythropoietin successfully corrects anemia (68,69).

Renal transplantation has not been considered a viable option in most patients with multiple myeloma because of their poor prognosis. However, patients with stable disease have received cadaveric renal transplants that survived >12 mo (range 14 to 144 mo) without recurrence of myeloma kidney (8,70–72). Therefore for patients without extrarenal manifestations of myeloma for >1 yr, transplantation has been successful and may prove to be an alternative to dialysis. The successful use of ASCT in dialysis-dependent patients with myeloma may increase the potential for renal transplantation in these patients.

MIDD

MIDD occurs in one quarter of patients who have myeloma and present with renal insufficiency, and the renal biopsy diagnosis of MIDD precedes the diagnosis of dysproteinemia in up to 70% of cases (73). The most frequent form of MIDD is light-chain deposition disease (LCDD), which accounts for >70% of cases (73–75), and in >70% of LCDD cases, κ light chains are identified. MIDD also is caused by monotypic heavy chains (heavy-chain deposition disease) in 20% of cases, and monoclonal light- and heavy-chain deposition is seen in almost 10% of cases. Multiple lesions that are associated with dysproteinemias may coexist in the same biopsy and are of prognostic significance. Cast nephropathy occurs in up to 21% of MIDD cases; less frequently, patients with MIDD have amyloid in the renal biopsy (73–75).

MIDD, like myeloma with cast nephropathy, is a disease that primarily affects older adults, and renal involvement is a presenting feature in essentially all patients (Table 1). In a large multicenter experience reported by Pozzi *et al.* (76) in 63 patients with LCDD, the average age at presentation was 58 yr (range 28 to 94 yr). The serum creatinine was >1.5 mg/dl (median 3.8 mg/dl) at presentation in 96%, and this was deemed to be acute in 52% and chronic in 44%. Proteinuria >1 g/d (median 2.7 g/d) was observed in 84%, and 40% of patients had nephrotic-range proteinuria. A monoclonal protein was identified in the serum or urine by immunofixation in 94%, and 65% had multiple myeloma at presentation. Patients who presented with myeloma were more likely to have ARF (67 *versus* 18%; $P < 0.0001$), and they had a significantly higher serum creatinine (median 4.7 *versus* 2.6 mg/dl) than patients who had LCDD without myeloma.

Extrarenal manifestations of MIDD, as with amyloidosis, are frequent. Cardiac disease (*e.g.*, congestive heart failure, cardiomegaly, arrhythmias) or liver involvement (*e.g.*, hepatomegaly, portal hypertension, hepatic insufficiency) have been reported in up to 80% of patients (77). Gastrointestinal or neurologic features are less frequent (<30%). In the large series reported by Pozzi *et al.* (76), 35% of patients with LCDD had symptoms of extrarenal disease. Cardiac (21%) and liver (19%) involvement were the most frequent.

Pathology of MIDD. MIDD is diagnosed by the demonstration of monoclonal Ig light, heavy, or light and heavy chains in the basement membranes of kidneys and other viscera that do not take up Congo red and do not form fibrils when examined by electron microscopy (78). First recognized as isolated deposits of κ light chains, examples of λ light-chain, light- and heavy-chain, and isolated heavy-chain deposits now define the immunopathologic spectrum (73,79). MIDD may coexist with typical myeloma cast nephropathy in one third of the cases, and this confers a poorer prognosis because these patients are more likely to have myeloma and renal failure at presentation (73). In addition, there are cases of MIDD that affect only the tubules without glomerular deposits, nodular glomerulosclerosis, or cast nephropathy.

The histologic and ultrastructural pathology of the various monoclonal Ig deposits are similar. Nodular glomerulosclerosis, resembling diabetic glomerular disease, is present in 60% of

cases (73,78). The glomeruli have multiple, acellular, periodic acid-Schiff–positive, nonargyrophilic, Congo red–negative nodules that compress the capillaries, which may be thickened (Figure 3). There are inconstant electron-dense, subendothelial, granular, punctuate deposits that may diffusely infiltrate the basal lamina. Although the glomeruli usually contain linear deposits of monotypic Ig, the finding is inconsistent.

Although glomerular proteinuria is common and many patients have the nephrotic syndrome (see above), the defining immunochemical features and associated histologic findings are seen in the renal tubules (78,80–82). The tubules show bright, retractile, periodic acid-Schiff–positive, Congo red–negative, ribbon-like thickening of their basement membranes, and this finding is most prominent in the medulla. Similar deposits may be seen surrounding the vasa recta and lying free in the medullary interstitium. The tubular basement membrane deposits are smooth and linear by fluorescence microscopy (Figure 4). Complement is rarely present, and amyloid P component is absent (19). Punctate electron-dense deposits are seen on the external (interstitial) side of the tubular basement membranes by electron microscopy (Figure 5), with no evidence of fibril formation (81,83).

The pathogenesis of nodular glomerular sclerosis in MIDD depends on the interaction of fibrogenic monoclonal Ig with mesangial cells (84), and specific Ig light chain sequences are associated with MIDD with either κ or λ classes (85,86). Under the influence of fibrogenic cytokines, the mesangial cells syn-

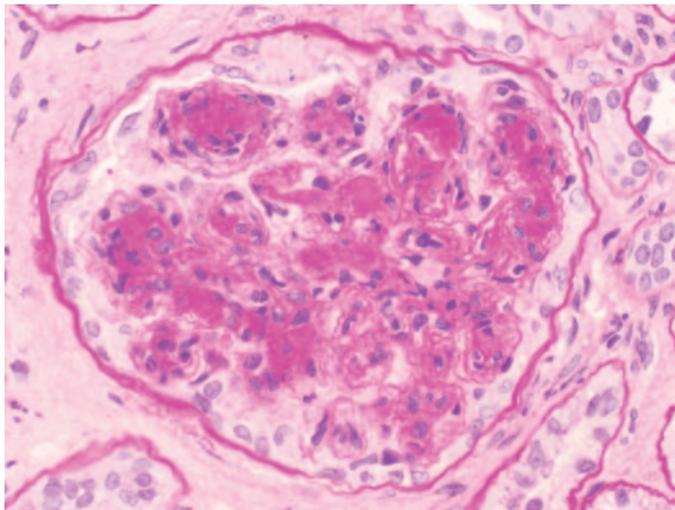


Figure 3. Monoclonal Ig deposition disease (MIDD) with diffuse and nodular glomerulosclerosis. There is prominent diffuse mesangial expansion by periodic acid-Schiff–positive matrix that focally forms nodules. Although the glomerulus shows atrophy with some capillary collapse, the resemblance to diabetic glomerulosclerosis is obvious. There were monoclonal deposits of κ Ig light chains in the glomerular and tubular basement membranes, and there were typical punctuate deposits in the basement membranes seen by electron microscopy. Periodic acid-Schiff stain. Courtesy of Jean L. Olson, University of California San Francisco, School of Medicine, San Francisco, California.

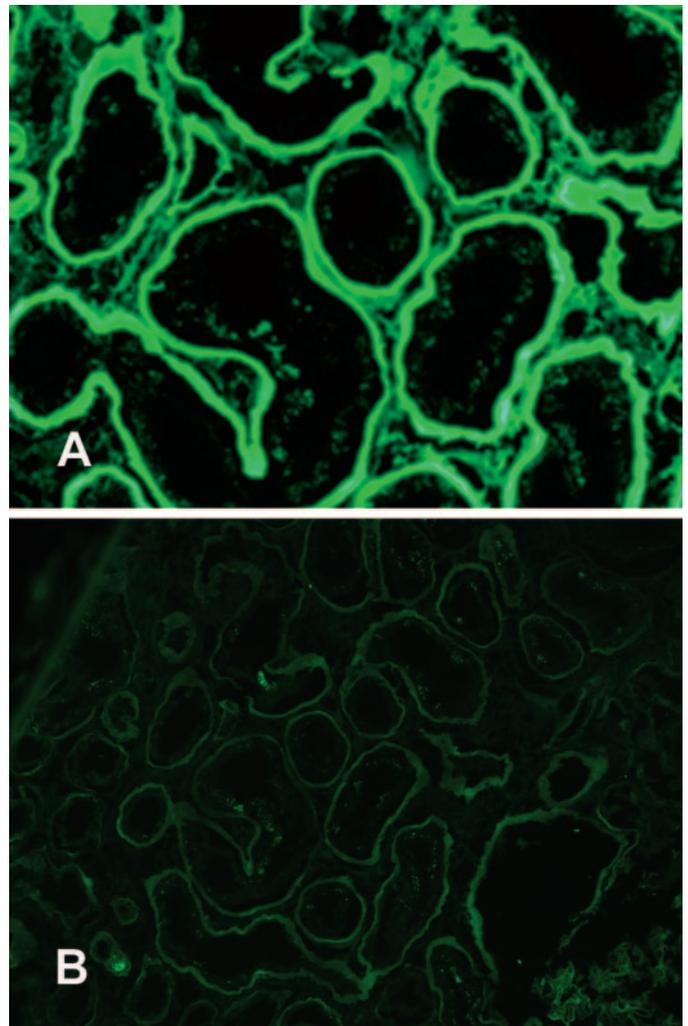


Figure 4. MIDD showing light chain restriction by immunofluorescence microscopy. The tubular basement membranes stained with κ Ig light chain (A) show bright (3+) staining. The tubular basement membranes stained for λ light chain (B) are negative.

thesize matrix proteins that comprise the nodules (87,88). The factors that are responsible for and the pathogenetic significance of monoclonal Ig deposition in glomerular and tubular basement membranes have not been identified.

Prognosis and Treatment of MIDD. The median patient survival is 4 yr, with survival at 6 mo, 1 yr, and 4 yr of 86, 66, and 52%, respectively (76). Significant predictors of death are age (RR 1.06 per year), presence of myeloma (RR 2.75), and extrarenal manifestations (RR 2.24). Progression to ESRD occurs in the majority of patients with MIDD (20,73,76,89). The median renal survival is almost 3 yr, with survival at 6 mo, 1 yr, and 4 yr of 67, 62, and 40%, respectively (76). The variables that are predictive of ESRD are age and serum creatinine at presentation (73,76). Patient and renal survival are significantly worse in patients with coexisting cast nephropathy (73). Lin *et al.* (73) found that whereas the proportion of patients who died was similar among patients with cast nephropathy and MIDD and patients with MIDD alone (55 versus 43%; NS), the average time

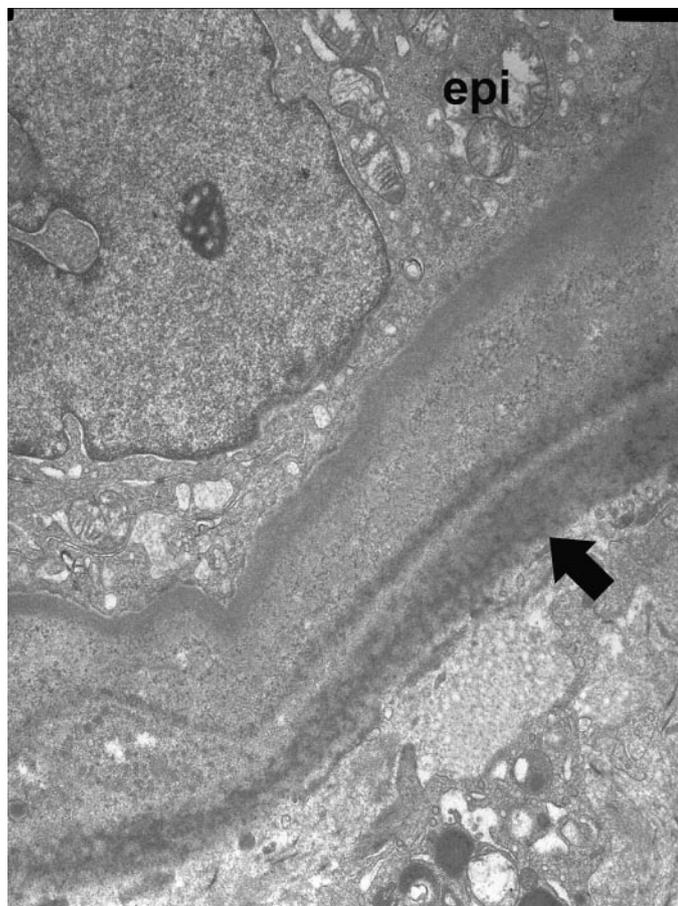


Figure 5. MIDD, ultrastructural appearance of the deposits. The tubular epithelium (epi) is separated from the interstitium by a grossly thickened basement membrane, and the punctuate, electron-dense deposits (arrow) are concentrated on the interstitial side of the basement membrane.

to death was significantly shorter in those with cast nephropathy (22 versus 54 mo; $P = 0.05$). The renal survival also was worse in patients with MIDD and cast nephropathy (91 versus 48% required dialysis), and the median time to ESRD was significantly shorter (4 versus 22 mo; $P = 0.01$) than in patients with MIDD alone. Therefore, in patients with MIDD and cast nephropathy, the prognosis is worse than in MIDD alone and similar to that seen in cast nephropathy (Table 1).

Therapy of MIDD is similar to that for multiple myeloma and consists of chemotherapy alone, often with melphalan and prednisone, or in combination with ASCT. Melphalan and prednisone therapy has an overall 5-yr patient and renal survival of 70 and 37%, respectively (89). An elevated serum creatinine at presentation adversely affects response to treatment. In patients with a serum creatinine <4 mg/dl at presentation, $>60\%$ will have improvement or stabilization of their renal function with chemotherapy, whereas 80% of patients with a serum creatinine ≥ 4 mg/dl progress to ESRD (89). Clinical remission of LCDD with long-term chemotherapy has resulted in resolution of nodular glomerulopathy and κ chain deposits (90). Therefore, early identification and treatment of patients with MIDD may improve the course of renal disease.

The use of high-dosage chemotherapy followed by ASCT has been evaluated in two small studies of patients with MIDD. Pozzi *et al.* (76) treated five patients with LCDD, four of whom had myeloma: There were no deaths, and only one patient progressed to ESRD after a follow-up of 44 mo. Royer *et al.* (91) treated 11 patients with MIDD. All were younger than 65 yr, and 10 of 11 had myeloma. Six patients had a complete remission; after 51 mo, four of 11 patients had improvement in renal manifestations, and all four patients with cardiac involvement had improved. One patient died, and one patient progressed to ESRD. One patient in remission successfully underwent renal transplantation. Therefore, small, uncontrolled studies support high-dosage chemotherapy with ASCT as an option for patients with MIDD.

Dialysis and Renal Transplantation in MIDD. Survival on dialysis for patients with MIDD ranges from 7 mo (primarily in patients with myeloma) to 48 mo (20,76,92). Therefore, the poor prognosis of MIDD generally precludes renal transplantation for ESRD. However, renal transplantation has been performed in 14 patients with MIDD (93,94). Eleven (70%) of 14 had recurrence of renal disease, leading to graft failure in eight (72%). The median times to recurrence and graft loss after recurrence were 33 and 11 mo, respectively. The median graft survival was 37 mo. At last follow-up only two (14%) of 14 patients were alive with a functioning graft, three (21%) of 14 were alive on dialysis, and nine (64%) of 14 had died. The median time to death was 72 mo. Because of poor graft and patient survival, renal transplantation should not be performed in patients who have LCDD and do not achieve hematologic remission (93). However, successful ASCT in patients with ESRD and LCDD may allow for subsequent renal transplantation.

AL-Amyloidosis

AL-amyloidosis is found in up to 30% of patients who present with multiple myeloma; conversely, multiple myeloma is present in up to 20% of patients who present with AL-amyloidosis (95,96). Proteinuria is the most common renal manifestation at presentation, occurring in up to 80% of patients, with the nephrotic syndrome seen in 30 to 50% of these patients (95–97). Renal insufficiency, which more often is chronic than acute, is observed in almost 50% of patients, and in 20%, the creatinine level is >2 mg/dl (96,98). Using immunofixation or immunoelectrophoresis, a monoclonal protein is identified in the urine or serum in 90% of patients with AL-amyloidosis at the time of diagnosis (96,99–101). Monoclonal light chains are found in the urine in 70% of patients, and in contrast to patients with MIDD, they are λ light chains in 80%. The diagnosis of AL-amyloidosis requires histologic demonstration of amyloid. Because a combination of fat aspirate and bone marrow biopsy is diagnostic in 90% of patients, fat aspiration is recommended as the initial diagnostic procedure, followed by bone marrow biopsy (100,102,103). If these studies are negative, then a renal biopsy is diagnostic in $>95\%$ of patients with clinical evidence of renal disease (97,100).

Renal Pathology of Amyloidosis. Renal amyloidosis is diagnosed by the histochemical and ultrastructural demonstra-

tion of amyloid in kidney tissue. Amyloid deposits are eosinophilic, acellular, and weakly periodic acid-Schiff positive. They are distinguished from other hyaline deposits such as collagen, fibrin, and insudative glomerular and vascular lesions by their affinity for Congo red dye and birefringence of Congo red-stained material under polarized light (Figure 6). By electron microscopy, amyloid deposits are randomly arranged, nonbranching fibrils with an average diameter of 90 to 110 Å (Figure 7) (104,105). It is almost always present in the glomeruli and blood vessels (106,107), and the initial glomerular deposits are in the mesangium (106–109). As the deposits extend into the subendothelium (109) and infiltrate and replace the basal lamina, focal fraying, loss of argyrophilia (106,109), and breaks (108) in the basement membrane occur. Subepithelial deposits may form silver-positive spikes (108,109) that may be confused with membranous glomerulonephritis (98). Tubular involvement and interstitial involvement are less frequent in biopsy material, but when they occur, the medullary interstitium and vasa recta are more frequently involved than the cortex (106,108,110).

Amyloid fibrils in multiple myeloma (AL amyloid) are derived from circulating, homogeneous Ig light chains or light-chain fragments that contain the N-terminal, variable (V_L) portion (usually λ light chain). The fibrils are composed of polypeptide chains that are oriented perpendicular to the axis of the fibril in a twisted β -pleated sheet, and the tertiary structure of the amyloid fibril is reflected in its ultrastructural and histochemical specificity (111). Rarely, AL amyloid is composed of Ig heavy-chain fragments (IgG or IgM heavy chains) (112,113). Amyloid fibrils are associated with other proteins,

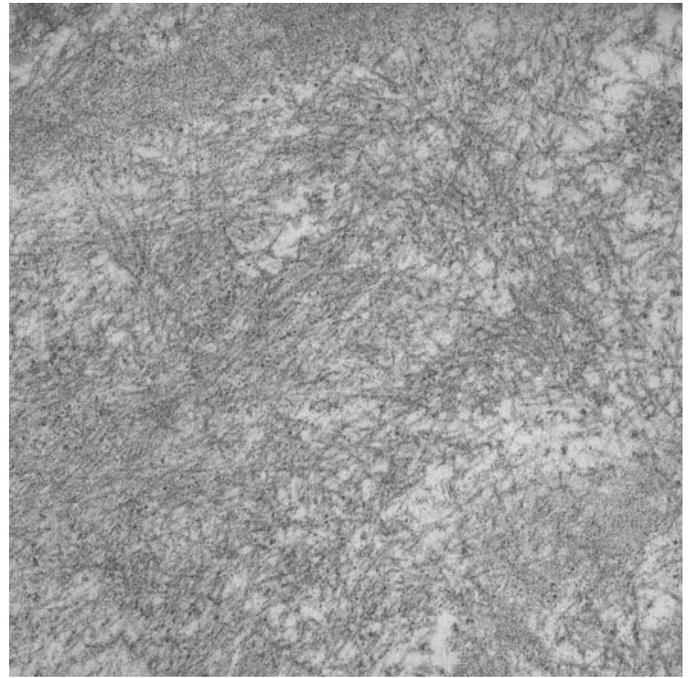


Figure 7. Renal amyloidosis, ultrastructural appearance. Amyloid deposits are seen as randomly arranged, 10-nM fibrils of indefinite length when viewed at high magnification by electron microscopy. Magnification, $\times 30,000$.

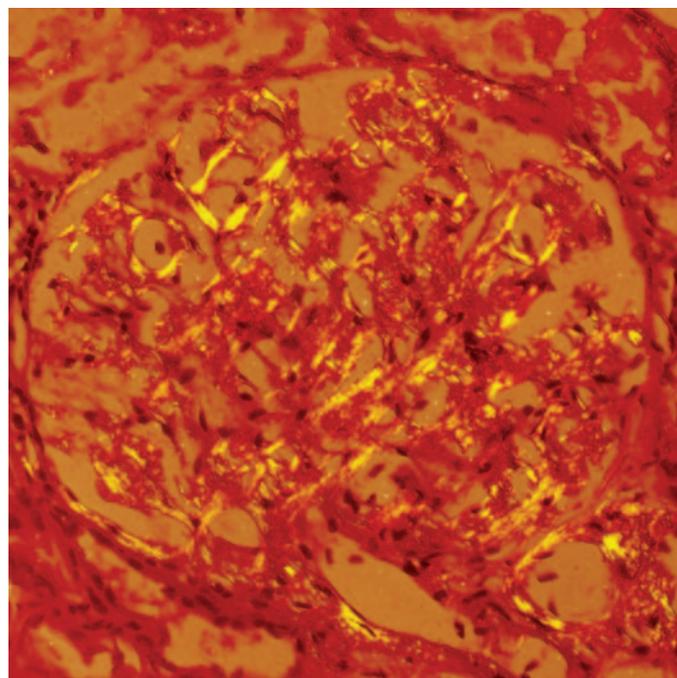


Figure 6. Renal amyloidosis, Congo red birefringence. Glomerulus stained with Congo red demonstrates green birefringence when viewed through crossed Polaroid filters.

including amyloid P, glycosaminoglycans, proteoglycans, fibronectin, and apolipoprotein E (114–116). In the kidney, the mesangial cells or mesangial macrophages play a central role in amyloidogenesis by endocytosing the precursor proteins into lysosomes, where amyloid fibril formation takes place (84,117). However, not all light chains are amyloidogenic (111,118–120), and the association between multiple myeloma and amyloid suggests that specific abnormal light-chain sequences underlie fibrillogenesis. Therefore, amyloidogenic proteins contain sequences that form β -pleated sheets when they are altered by proteolysis; mutational changes that predispose the molecule to proteolysis; or point mutations, deletions, or structural modifications that render the molecule amyloidogenic without proteolysis (121).

The Congo red staining and ultrastructural appearance of AL amyloid is identical to the other forms of amyloid that affect the kidney, including amyloid secondary to chronic inflammation (secondary amyloidosis [AA amyloid]) and hereditary amyloidoses. Because the prognostic and therapeutic implications for each biochemical class of amyloid are different, typing the amyloid by identifying the precursor protein in the deposits is the standard of care. Fluorescence microscopy on frozen sections using antisera against κ and λ Ig light chains is the most readily available technique for identifying AL amyloid, and light-chain restriction with reduced staining of one of the Ig light chains is diagnostic. Unfortunately, as many as 35% of patients with proven AL-amyloidosis have negative immunofluorescence for κ and λ Ig light chains (122), because the immunogenic portion of the light chain is deleted or destroyed during fibrillogenesis. Because of the high rate of false negative

results, negative or equivocal staining for Ig light chains does not exclude AL amyloid, and when the clinical diagnosis of multiple myeloma also is in doubt, the material should be referred to an amyloid center for diagnosis.

Prognosis in AL-Amyloidosis. The median survival in patients with AL-amyloidosis and the nephrotic syndrome is 16 mo (101). The 24-h urine protein level does not correlate with survival, but patients with λ light chains have a poorer prognosis than patients with κ light chains (12 versus 30 mo median survival; $P = 0.01$) (123). Renal insufficiency also is associated with a poor prognosis. Patients who present with a serum creatinine >1.3 mg/dl had a median survival of 15 mo, compared with 26 mo ($P = 0.007$) for patients with normal renal function (123). Finally, the prognosis for AL-amyloidosis is poorest for patients who present with congestive heart failure, with a median survival of <6 mo (101).

Treatment in AL-Amyloidosis. The treatment of AL-amyloidosis has focused on inhibiting the production of the monoclonal paraprotein by cytotoxic regimens that often include prednisone and melphalan (standard chemotherapy) and, more recently, the use of high-dosage chemotherapy and ASCT. Recent studies using the more sensitive and quantitative free light chain assay have demonstrated significant improvement in survival (5-yr survival of 88 versus 39%; $P < 0.0001$) and stabilization or even regression of AL-amyloidosis when a hematologic remission ($>50\%$ reduction in serum free light chain) is induced by treatment (124,125).

Melphalan and prednisone alone has led to a hematologic remission in 28% of patients, with a median survival of up to 50 mo (101). In nephrotic patients, a response to therapy with melphalan and prednisone produced a reduction or complete resolution of proteinuria and improvement in renal function (126–128). The addition of other chemotherapeutic agents to melphalan and prednisone did not significantly improve the response rate (129,130).

Currently, high-dosage melphalan followed by ASCT has been used in select patients (those without evidence of cardiac involvement and <70 yr of age) with AL-amyloidosis. In a retrospective, case-control study, the overall patient survival after 4 yr was significantly better in patients who received ASCT compared with standard chemotherapy (71 versus 41%; $P < 0.001$) (131). The use of ASCT in patients with AL-amyloidosis and renal disease has resulted in a hematologic response in 42% of patients, and a renal response was observed in 71% of patients with an hematologic response compared with 11% in patients without a hematologic response (132). Only 8% of patients progressed to ESRD. Patient survival is significantly improved in renal responders (133). Transplant-related mortality can be as high as 23%, and mortality is associated with older age and evidence of three or more organs involved (132–134). Serum creatinine at baseline also has been associated with increased mortality in patients who undergo ASCT (133). However, in a recent report of ASCT in dialysis-dependent patients with amyloidosis, transplant-related mortality was only 13% (similar to that of patients without ESRD), and a hematologic response was obtained in eight of 15 patients (135). The median survival after treatment for all patients who had ESRD and

received a transplant was 25 mo (not significantly different from that for patients who did not have ESRD and underwent ASCT), which not only is greater than the 8 mo (136) previously reported for patients with AL-amyloidosis and ESRD but is even greater than that reported for nondialysis patients who were treated with melphalan and prednisone alone (16 mo [101]).

The use of ASCT seems to be the treatment of choice in select patients with AL-amyloidosis, even in those with ESRD. Unfortunately, $<20\%$ of patients with AL-amyloidosis qualify (137). Because ASCT is available only to patients with limited-stage disease, early diagnosis and initiation of therapy are critical.

Dialysis and Renal Transplantation in AL-Amyloidosis. Renal disease is common in AL-amyloidosis, and progression to ESRD is a major complication that occurs in approximately one third of patients (136). The median time from diagnosis of amyloidosis to the initiation of dialysis is approximately 15 mo (Table 1), and the median survival on dialysis ranges from 8 to 22 mo (20,136,138). Although amyloidosis accounts for $<0.5\%$ of patients who are treated for ESRD in the United States, the 1-yr mortality rate on dialysis of 44% for patients with AL-amyloidosis, compared with 22% of all ESRD patients, is surpassed only by myeloma cast nephropathy and AIDS nephropathy (49 and 45%, respectively) (139). The primary cause of death on dialysis is a result of extrarenal progression of amyloidosis, primarily from cardiac amyloidosis (136,138).

Because of the poor prognosis for patients who have ESRD and systemic amyloidosis and a high likelihood for graft loss as a result of recurrence of amyloidosis, patients with amyloidosis rarely have been considered for renal transplantation (140–143). However, with the improved prognosis in patients with ESRD and AL-amyloidosis related to ASCT, renal transplantation has become a viable option. The outcome of renal transplantation in eight patients (seven living related and one cadaveric) with successful ASCT has been encouraging (135,144). Graft survival ranged from 18 to 72 mo without clinical or histologic evidence of recurrence. Therefore, successful ASCT may allow more patients with AL-amyloidosis the opportunity for renal transplantation.

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