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Monoclonal Gammopathies: Multiple Myeloma, Amyloidosis, and Related Disorders

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Monoclonal proliferations of the B cell lineage, often referred to as plasma cell dyscrasias, are characterized by abnormal and uncontrolled expansion of a single clone of B cells at different maturation stages, with a variable degree of differentiation to immunoglobulin (Ig)-secreting plasma cells. Therefore, they are usually associated with the production and secretion in blood of a monoclonal Ig and/or a fragment thereof. An ominous consequence of secretion of monoclonal Ig products is their deposition in tissues. These proteinaceous deposits can take the form of casts (in myeloma cast nephropathy [CN]), crystals (in myeloma-associated Fanconi syndrome [FS]), fibrils (in light-chain [LC] and exceptional heavy-chain [HC] amyloidosis), or granular precipitates (in monoclonal Ig deposition disease [MIDD]) (Table 60.1). They may disrupt organ structure and function, inducing life-threatening complications. In a large proportion of patients with crystals, fibrils, or granular deposits of Ig products, major clinical manifestations and mortality are related to visceral Ig deposition rather than to expansion of the B cell clone. Indeed, except for myeloma CN, which is generally associated with a large tumor mass malignancy, Ig precipitation or deposition diseases often occur in the course of a benign B cell proliferation or of a smoldering or low-mass myeloma.[1]

The presence of abnormal urine components in a patient with severe bone pain and edema was first recognized in the 1840s by Henry Bence Jones and William MacIntyre, who described unusual thermal solubility properties of urinary proteins, far later attributed to Ig LCs. To perpetuate this discovery, monoclonal LC proteinuria is often referred to as Bence Jones proteinuria. This term is not appropriate because less than 50% of LCs do show thermal solubility. Renal damage characterized by large protein casts surrounded by multinucleated giant cells within distal tubules was identified in the early 1900s and termed myeloma kidney. This term must, however, be abandoned because CN with acute renal failure may occasionally occur in conditions other than myeloma and because other patterns of renal injury were subsequently found in patients with myeloma. The first of these was amyloidosis, wherein tissue deposits are

characterized by Congo red binding and fibrillar ultrastructure. In 1971, Glenner et al.[2] showed that the amino acid sequence of amyloid fibrils extracted from tissue was identical to the variable region of a circulating Ig LC, thereby providing the first demonstration that an Ig component could be responsible for tissue deposition. The spectrum of renal diseases due to monoclonal Ig deposition has expanded dramatically with the advent of routine staining of renal biopsy specimens with specific anti-κ and anti-λ LC antibodies, and of electron and immunoelectron microscopy (Table 60.1). These morphologic techniques associated with more sensitive and sophisticated analyses of blood and urine monoclonal components have led to the description of new entities, including nonamyloid monoclonal LC deposition disease (LCDD),[3] HC (or AH) amyloidosis,[4] nonamyloid HC deposition disease (HCDD),[5,6] glomerulopathies with organized microtubular monoclonal Ig deposits,[7,8] and proliferative glomerulonephritis with non-organized monoclonal IgG deposits.[9] All of these pathologic entities principally involve the kidney, which appears as the main target for deposition of monoclonal Ig components. This is not only explained by the high levels of renal plasma flow and glomerular filtration rate (GFR), but also by the sieving properties of the glomerular capillary wall and by the prominent role of the renal tubule in LC handling and catabolism.[10,11]

Polymorphism of renal lesions may be due to specific properties of Ig components influencing their precipitation, their interaction with renal tissue, or their processing after deposition. Alternatively, the type of renal lesions may be driven by the local response to Ig deposits, which may vary from one patient to another. That intrinsic properties of Ig components are responsible for the observed renal alterations was first suggested by in vitro biosynthesis of abnormal Ig by bone marrow cells from patients with lymphoplasmacytic disorders and visceral LC deposition[12] and by recurrence of nephropathy in renal grafts.[13] A further demonstration of the specificity of Ig component pathogenicity was provided by Solomon et al.[14] They showed that the pattern of human renal lesions associated with the production of monoclonal LC, that is, myeloma CN, LCDD, and LC (or AL) amyloidosis,

60.1	Pathologic Classification of Diseases Featuring Tissue Deposition or Precipitation of Monoclonal Immunoglobulin-Related Material				
	Organized			**Nonorganized**	
Crystals	**Fibrillar**	**Microtubular**	**MIDD ("Randall type")**	**Other**
Myeloma cast nephropathy[a]	Amyloidosis (AL, AH)	Cryoglobulinemia kidney	LCDD	GN with monoclonal IgG
Fanconi's syndrome	Nonamyloid	Immunotactoid	LHCDD	Crescentic GN (IgA or IgM)
Other (extrarenal)			HCDD	

[a]Crystals are predominantly localized within casts in the lumen of distal tubules and collecting ducts, but may also occasionally be found in the cytoplasm of proximal tubule epithelial cells.
AH, heavy-chain amyloidosis; AL, light-chain amyloidosis; GN, glomerulonephritis; HCDD, LCDD, LHCDD, MIDD, heavy-chain, light-chain, light- and heavy-chain, monoclonal immunoglobulin deposition disease.
Adapted from Preud'homme JL, Aucouturier P, Touchard G, et al. Monoclonal immunoglobulin deposition disease (Randall type): relationship with structural abnormalities of immunoglobulin chains. Kidney Int. 1994;46:965, with permission.

could be reproduced in mice injected intraperitoneally with large amounts of LCs from patients. The good correlation between experimental findings and human lesions led to the conclusion that physicochemical or structural properties of LCs might be responsible for the specificity of renal lesions.

A normal Ig is composed of two LCs and two HCs, which are themselves made up of so-called constant (C) and variable (V) globular domains. Whereas a limited number of genes encode the constant region, multiple gene segments are rearranged to produce a variable domain unique to each chain. Diversity is further amplified by junctional molecular events that affect the third hypervariable zone (CDR3), and then by the hypermutation process that occurs in the germinal centers of lymphoid follicles. Consequently, although LCs (and HCs) have many structural similarities, they also possess a unique sequence that may be responsible for physicochemical peculiarities, hence their deposition in tissue or interaction with tissue constituents. A number of structural and physicochemical abnormalities of Ig have already been described. They include deletions of C_H domains in HCDD[5,6] and HC amyloidosis,[4] shortened or lengthened LCs and abnormal LC glycosylation in LCDD,[12,15] and resistance to proteolysis of the V_L fragment in FS.[16] Moreover, overrepresentation of certain V_L gene subgroups was also reported in amyloidosis[17,18] and LCDD.[19] The mechanisms generating Ig diversity may randomly create HCs or LCs with peculiar properties such as proneness to deposition, whereas mistakes in the rearrangement or hypermutation processes may result in altered genes encoding truncated Ig. It must be stressed, however, that some abnormal Ig chains produced in immunoproliferative disorders are not associated with any special clinical features. Conversely, structural abnormalities of LCs are not a constant feature of diseases associated with LC

deposition. These observations suggest the need to increase the number of nephritogenic Ig components to be analyzed at the complementary DNA (cDNA) and protein levels.

Myeloma- and AL amyloidosis-induced renal failure accounts for less than 2% of the patients admitted to a chronic dialysis program each year.[20] This is due in part to the relative rarity of these immunoproliferative diseases, but also to a deteriorated clinical condition of patients at the time of end-stage renal disease. A substantial effort of prevention must therefore be carried out, relying in part on a better understanding of the structural and physicochemical properties of Ig components leading to deposition or precipitation in tissues. Any progress in this field may also enlighten the pathogenesis of immunologically mediated renal diseases, especially glomerulonephritides, because properties of monoclonal Ig components favoring their deposition may apply as well to polyclonal Ig involved in the formation of immune complexes.

We have classified the various forms of renal involvement in monoclonal gammopathies according to the lesions observed in renal biopsy specimens. The majority of patients (63% in a series of 87) with serum and/or urine monoclonal gammopathy who undergo renal biopsy have disease unrelated to monoclonal gammopathy deposition.[21] Therefore, the diagnosis of virtually all of the entities to be discussed is critically dependent on the inclusion of κ and λ in the standard of immunofluorescence stains. In some of the rarer entities, a more refined and precise diagnosis can be made with immunofluorescence staining for the subclasses of IgG. Collectively these stains may demonstrate light chain isotype restriction and γ-heavy chain subclass restriction, which strongly favors, but does not definitely prove, the presence of a monoclonal Ig. Demonstration of monoclonality requires serum and urine studies by immunoelectrophoresis or immunofixation.

MYELOMA-ASSOCIATED TUBULOPATHIES

The prevalence of tubular lesions in patients with myeloma is difficult to assess because most patients do not undergo a renal biopsy, but it is most likely high. In Ivanyi's necropsy study including immunofluorescence, 18 of 57 patients (32%) had CN, whereas 6 (11%) had renal amyloidosis and 3 (5%) had κ-LCDD.[22] The higher prevalence of CN (30%) was confirmed in the more recent autopsy series of Herrera.[23] Tubular alterations are also demonstrated by increased urinary concentrations of the low molecular weight proteins normally reabsorbed by the proximal tubule, increased urinary elimination of the tubular lysosomal enzyme β-acetyl-D-glucosaminidase, and frequent abnormalities in renal tubular acidifying and concentrating ability[24] in patients with LC proteinuria. However, myeloma-associated FS remains an exception.

CN is not only the most frequent lesion in myeloma patients, it is also the major cause of renal failure, which is observed in about 25% of patients with multiple myeloma. In nephrology departments that usually receive only myeloma patients with severe renal abnormalities, the prevalence of CN assessed histologically varies from 63% to 87%[25–28] among the myeloma patients with renal failure. This prevalence is most likely underestimated because patients with presumed CN do not systematically undergo a renal biopsy, whereas those exhibiting significant albuminuria or a fortiori the nephrotic syndrome do. In myeloma patients with an albumin urinary output of less than 1 g per day, there is a good correlation between the diagnosis of CN and renal failure. Of note, CN may occur in other immunoproliferative disorders featuring urinary LC excretion including Waldenström macroglobulinemia[29] and μ-HC disease.[30] In a case of μ-HC disease, the urinary secretion of large amounts of free κ-chain was responsible for acute renal failure with a typical histologic presentation of "myeloma kidney."[30]

Myeloma Cast Nephropathy

Pathophysiology of Myeloma Cast Nephropathy

CN occurs mainly in patients with myeloma with a high LC secretion rate. That LCs are the main culprits is supported also by the following clinical, pathologic, and experimental data:

1. Renal lesions may recur on grafted kidneys.
2. Similar crystals may occasionally be seen within casts, proximal tubule cells, and plasma cells. Their usual lack of staining with anti-LC antibody is most likely due to degradation or masking of the relevant epitopes.
3. Mice injected with LC purified from patients with CN developed extensive cast formation in the distal renal tubules.[14]

However, a number of patients produce large amounts of LCs and yet fail to present significant signs of renal involvement throughout the course of the disease. This may be related to the absence of enhancing factors (see later text), but this also suggests that some LCs may be particularly prone to induce renal lesions, especially cast formation.

LCs are directly toxic to epithelial cells, resulting in decreased proximal reabsorption of the LCs and increased delivery to the distal tubule in which they coprecipitate with Tamm-Horsfall protein (THP). Tubular obstruction by large and numerous casts may also contribute to the development of tubular lesions. For clarity, we will analyze separately the pathogenesis of proximal tubule lesions that result from renal metabolism of LCs, the mechanisms of cast formation, and the respective role of tubular obstruction and tubular lesions in the genesis of renal failure (Fig. 60.1).
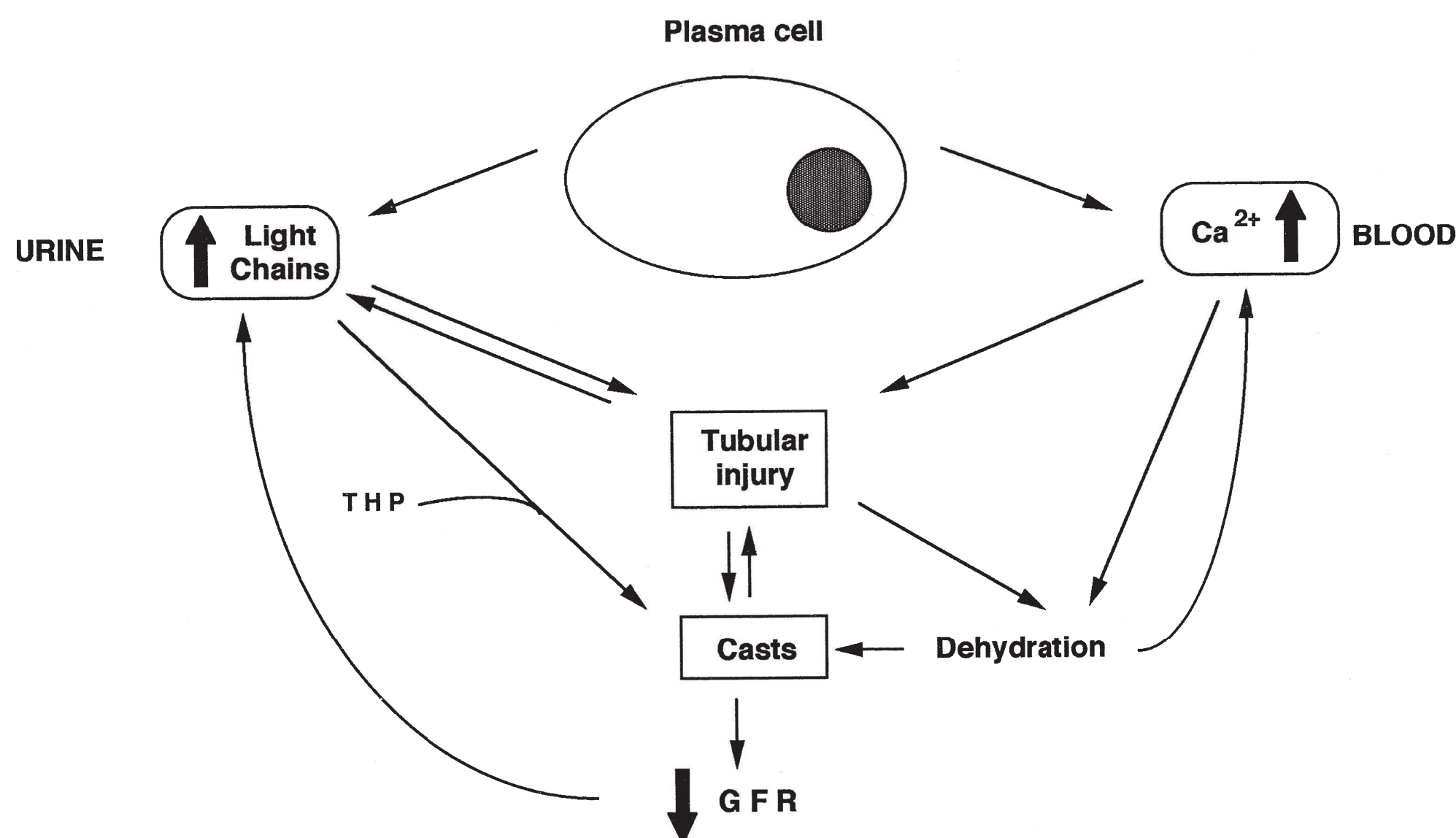

FIGURE 60.1 Schematic representation of the pathogenesis of myeloma cast nephropathy. *GFR*, glomerular filtration rate; *THP*, Tamm-Horsfall protein. (Adapted from Winearls CG. Nephrology forum: acute myeloma kidney. *Kidney Int.* 1995;48:1347.)

Renal Metabolism of Light Chains and Pathogenesis of Proximal Tubule Lesions. Normal as well as malignant plasma cells can secrete free LC, in addition to complete Ig molecules; the amount of free LC secretion is highly variable, depending on the variable (V_L) domain structure. The LCs are normally filtered by the glomerulus and then reabsorbed by the proximal tubule. Lambda and, to a lesser extent, κ-LCs circulate mainly as covalently linked dimers that have a mass-restricted glomerular filtration. In normal individuals, several hundred milligrams per day of circulating free polyclonal LCs are filtered by glomeruli and more than 90% of these are reabsorbed and catabolized by proximal tubular cells. LCs bind to a single class of low affinity, high capacity noncooperative binding sites on both rat and human kidney brush-border membranes. These sites exhibit relative selectivity for LCs compared with albumin and β-lactoglobulin. It has been shown that LCs could bind to the tandem receptor cubilin[10] and megalin,[11] a multiligand receptor belonging to the large family of low density lipoprotein receptors, located in the intermicrovillar areas of the brush border. After binding to the luminal domain of proximal tubular epithelial cells, LCs are incorporated in endosomes that fuse with primary lysosomes where proteases, mainly cathepsin B, degrade the proteins into amino acids, which are returned to the circulation by the basolateral route.

When the concentration of filtered LCs is increased as in myeloma patients, profound functional and morphologic alterations of proximal tubule epithelial cells may occur. The functional disturbances include low molecular weight proteinuria and inhibition of sodium-dependent uptake of amino acids and glucose by brush-border preparations. Furthermore, in human proximal tubule cells, endocytosis of LCs was shown to induce activation of redox pathways,[31,32] NF-κB,[33] and mitogen activated protein kinases (MAPK),[34] resulting in cytokine production including interleukin (IL)-6, IL-8, transforming growth factor (TGF)-β, and monocyte chemoattractant protein-1 (MCP-1). Part of these effects may be mediated by megalin itself because megalin possesses intrinsic signaling properties. Moreover, excessive LC endocytosis may promote apoptosis[35] and induce epithelial-mesenchymal transition of tubular cells.[36,37] Increased cytokine production may be a major mechanism mediating tubulointerstitial injury and progressive kidney disease in some patients with myeloma. Suppression of proinflammatory cytokine production using inhibition of p38 MAPK and translocation of NF-κB by pituitary adenylate cyclase-activating polypeptide with 38 residues (PACAP38) was shown to dramatically prevent injury of cultured renal proximal tubule cells caused by myeloma LCs.[38]

Morphologically, some of the LCs infused in mice or rats or perfused in rat nephrons in vivo accumulated in enlarged, distorted endosomes and lysosomes of the proximal convoluted tubule with frequent crystalloid formations. This was associated with mitochondrial alterations, focal loss of the microvillus border, and epithelial cell exfoliation.

Pathogenesis of Cast Formation. Because myeloma casts are composed principally of the monoclonal LC and THP/uromodulin, it has long been hypothesized that interaction of these two proteins was a key event in cast formation. THP is a highly glycosylated and acidic protein (isoelectric point [pI] = 3.2) synthesized exclusively by the cells of the ascending limb of the loop of Henle. It is the major protein constituent of normal urine, and an almost universal component of casts. This 80-kDa protein is also remarkable for its ability to form reversibly high-molecular-size aggregates of about 7×10^6 daltons at high but physiologic concentrations of sodium and calcium, and at low urinary pH. The role of THP in cast formation has prompted a wealth of studies on its interactions with LCs. These studies were performed with the aim of defining a population of myeloma patients at risk of developing renal damage. The role of LC pI has long been suggested. It was proposed that LC with a high pI (greater than 5.6) and THP could bear opposite charges in the normal urine pH range, and undergo polar interaction and precipitation. However, this hypothesis was not confirmed in further experimental and clinical studies.[25,39]

In a rat model, development of casts and injury to proximal tubule cells in renal tubules microperfused with human nephritogenic LC were not correlated with LC pI, molecular form, or isotype.[40] Intranephronal obstruction was aggravated by decreasing extracellular fluid volume or adding furosemide. In perfused loop segments, cast-forming LCs reduced chloride absorption directly, thereby increasing tubule fluid [Cl$^-$] and promoting their own aggregation with THP.[41] Pretreatment of rats with colchicine, which prevents addition of sialic acid to the protein, completely prevented obstruction and cast formation in perfused nephrons, and THP from those rats did not aggregate with LCs in vitro, contrary to THP purified from control rats. In vitro studies suggest that THP can undergo both self (homotypic) aggregation and heterotypic aggregation with LCs. Homotypic aggregation is enhanced by calcium, furosemide, and low pH, and is dependent on THP sialic-acid content. Heterotypic aggregation requires previous binding of LC to the THP protein backbone. A 9-residue sequence of the THP was identified as a binding site of LCs, including a histidine at position 226, which explains, at least partially, the pH dependence of molecular interactions.[42] LCs bind to THP through their third complementary determining region (CDR3).[43] The sugar moiety is also essential for coaggregation of LC and THP. THP from normal volunteers treated with colchicine had a lower sialic acid content and a decreased aggregation potential in the presence of pathogenic LCs. These findings suggest that colchicine may be useful in the treatment of cast nephropathy and that it is conceivable to design peptides or analogs that would inhibit interactions of LCs with THP and theoretically prevent myeloma CN.

Cast formation may not rely only on interactions between LC and THP. First, 5 of 12 LCs purified from the urine of patients with CN failed to react with THP.[16] Second, myeloma casts occasionally do not stain for THP in human

biopsies, and casts induced in mice by LC injection do not seem to contain THP during the first 24 hours, indicating that some LCs may undergo aggregation or precipitation in the absence of THP. This hypothesis is supported by studies showing that the deposition of certain LCs in vivo may be related to their capability to aggregate in vitro.[44] Resistance of LCs to renal and macrophage-released proteases may also contribute to cast formation and persistence.[16]

Role of Tubular Obstruction by Casts in the Genesis of Renal Failure. The role of casts as plugs obstructing the tubules has been clearly shown in micropuncture studies. In myeloma patients, the correlation between severity of renal insufficiency and the number of casts remains controversial.[24,25,45] This may be explained partly by the prominent medullary localization of casts, the count of which is underestimated in superficial kidney cortex biopsy specimens. The first indication that antibodies to THP could serve as probes of tubular obstruction was provided by Cohen and Border,[46] who identified the protein in glomerular urinary spaces of two myeloma patients. This finding is indicative of intratubular urinary backflow. We detected THP in glomerular urinary spaces in 16 of 18 biopsies of patients with myeloma CN (Ronco and Mougenot, personal data) (Fig. 60.2). The proportion of obstructed tubules is too small to account by itself for renal failure. Renal failure induced by CN is multifactorial, implicating also tubular epithelial cell and interstitial lesions. Tubule obstruction by casts may explain the slow recovery of renal function noted in many patients.[25]

Interstitial deposits of THP were also found in 8 (44%) of the 18 biopsies (Ronco and Mougenot, personal data). They probably result from a leakage of the protein through

FIGURE 60.2 Myeloma cast nephropathy. Immunofluorescence stain with anti–Tamm-Horsfall protein (THP) monoclonal antibody. Glomerular deposits in Bowman's space delineate the inner aspect of Bowman's capsule and penetrate between lobules of the capillary tuft. Identification of THP in the urinary spaces of glomeruli supports the obstructive role of casts with reflux of tubular urine. (Magnification, ×312.)

gaps in the tubular basement membrane favored by tubular obstruction. Clinical and experimental models have implicated the protein in the pathogenesis of tubulointerstitial nephritis. Thomas et al.[47] identified a single class of sialic acid–specific cell surface receptors for THP on polymorphonuclear leukocytes, and further showed that in vitro activation of human mononuclear phagocytes by particulate THP led to the release of gelatinase and reactive oxygen metabolites, both probably contributing to tissue damage.

Clinical Presentation

Changing Presentation of Patients with Myeloma-Induced Renal Failure. When DeFronzo et al. reported the first series of 14 myeloma patients with acute renal failure in 1960,[48] it was established that renal failure occurred at some time during the illness in approximately half of the patients, but that the mode of presentation was usually chronic with a slow progression over a period of several months to years.

The mode of presentation of renal failure in myeloma has changed dramatically over the years. In their review of 141 patients treated in Nottingham between 1960 and 1988, Rayner et al.[49] showed that the absence of severe renal impairment at presentation predicted a low probability of developing renal failure subsequently. In only 5 of 34 patients of our own renal series[25] did the diagnosis of myeloma antedate the discovery of renal failure by more than 1 month. In three patients, the presence of a monoclonal Ig was known for 10 to 18 years, but it only showed criteria of malignancy for less than 9 months. Two-thirds of the 107 patients referred to the Oxford Kidney Unit from 1987 to 2006[50] had myeloma diagnosed after their admission with acute kidney injury (AKI). More aggressive treatment of myeloma and higher awareness of the conditions that induce CN in the last two decades may have prevented LC precipitation within the tubule lumen in the patients with an established diagnosis of myeloma.

Demographic and Hematologic Characteristics of Patients with Cast Nephropathy-Related Renal Failure. Table 60.2 summarizes the clinical and pathologic data in four large series of myeloma patients with acute renal failure in which a renal biopsy was performed in at least 40% of the patients. A diagnosis of myeloma CN was established histologically in 81 of 99 (82%) renal biopsies, and lesions compatible with this diagnosis were found in 10 further biopsy specimens (10%). In comparison with the Mayo Clinic series of 869 unselected myeloma cases[52] in which the mean age was 62 years and the male–female ratio was 1.55, patients with acute renal failure did not show any demographic particularity. Myeloma patients with renal failure are characterized by high tumor mass and virtually constant urinary LC loss, often of high output.

More than 70% of patients in the renal series have a high tumor burden (Table 60.2). This is confirmed by the

TABLE 60.2 Clinical and Pathologic Characteristics of Patients with Myeloma-Induced Renal Failure of Presumed or Established Tubulointerstitial Origin

Series	No. of Patients	Age (yr)	Male–Female Ratio	Tumor Mass		Serum Creatinine (μmol/L)	Urinary Light Chain >2 g/day	Renal Lesions in Biopsy Specimen
				IIB	IIIB			
Rota et al.[25]	34	66 (33–90)	0.88	15%	73%	960 (164–2000)	53%	26 MCN 2 ATN 2 CIN
Pozzi et al.[26]	50	63 (47–60)	1.38	12%	82%	798 (273–1518)	41%[a]	16 "Myeloma kidney"[b] 8 other
Pasquali et al.[27]	25	60 (48–74)	2.12	24%	72%	891 (455–1391)	72%	25 MCN
Irish et al.[51]	56	67 (42–82)	1.33	22%	78%	811 (302–2600)	NA	16 MCN, 5 AIN[c]

[a]Total proteinuria, including light chains.
[b]Presumably myeloma cast nephropathy.
[c]"Compatible with myeloma."
AIN, acute interstitial nephritis; ATN, acute tubular necrosis; CIN, chronic interstitial nephritis; MCN, myeloma cast nephropathy; NA, not available; IIB, intermediate tumor mass; IIIB, high tumor mass.

Alexanian series, which included 494 consecutive patients referred to an oncology center (Table 60.3).[53] Only 3% of patients with myeloma of low tumor mass had renal failure, whereas 40% of those with high tumor burden had a serum creatinine greater than 180 μmol/L. These data contrast with the hematologic characteristics of patients with other renal complications of dysproteinemia including FS, amyloidosis, and MIDD, in whom the monoclonal B lymphocyte or plasma cell proliferation is either malignant but usually of low magnitude, or often benign from a hematologic point of view.

Another salient feature of myeloma associated with renal failure is the high prevalence of pure LC myelomas. Although they represent only about 20% of all myelomas, they are found in between 37% and 64% of patients with renal failure of presumed or established tubulointerstitial origin. Development of CN in two studies in which this diagnosis was established histologically[25,27] was associated with urinary excretion of LCs exceeding 2 g per day in 53% and 72% of the patients (Table 60.2). LC protein excretion emerges as a highly significant independent factor of renal failure on multivariate analysis (Table 60.4). The risk of developing renal failure is twice as high in patients with pure LC myeloma, and five to six times greater in patients with LC proteinuria greater than 2.0 g per day compared to those with proteinuria less than 0.05 g per day. This indicates that in patients producing complete Ig molecules, CN essentially occurs in those synthetizing an excess of LCs. The frequency of renal failure is identical in patients excreting κ or λ LCs. IgD myeloma has the greatest potential for causing renal disease.[50] Hypercalcemia also is a prominent independent pathogenetic factor on multivariate analysis, with a risk of renal failure five times greater in those patients with corrected calcium greater than 2.87 mmol/L.[53]

TABLE 60.3 Relation Between Tumor Mass and Renal Function

Tumor Mass	No. of Patients[a]	% of Patients with Serum Creatinine (μmol/L)		
		<180	180–270	>270
Low	151	97	1	2
Intermediate	183	89	5	6
High	160	60	17	23

[a]This series included 494 consecutive, previously untreated patients with multiple myeloma.
From Alexanian R, Barlogie B, Dixon D. Renal failure in multiple myeloma: pathogenesis and prognostic implications. Arch Intern Med. 1990;150:1693, with permission.

| 60.4 | Features Associated with Renal Failure in Myeloma | | |

	No. of Patients[a]	%with Renal Failure	P
All patients	494	18	
Urinary LC (g/day)			
>2.0	123	39	0.00001
0.05–2.00	149	17	
<0.05	222	7	
Myeloma protein type			
Only LC protein	93	31	0.0003
Other	401	15	
Serum calcium (mmol/L)[b]			
>2.87	104	49	0.00001
≤2.87	390	10	

[a]Same series of patients as in Table 60.3.
[b]Corrected calcium (mmol/L).
LC, light chain.
From Alexanian R, Barlogie B, Dixon D. Renal failure in multiple myeloma: pathogenesis and prognostic implications. Arch Intern Med. 1990;150:1693, with permission.

The Clinical and Urinary Syndrome of Myeloma Cast Nephropathy. CN-induced renal failure is remarkably silent. Clinical signs are due to myeloma (or to hypercalcemia), including weakness, weight loss, bone pain, and infection. Because of their nonspecificity and their frequency in older patients, they often do not lead patients to take medical advice or physicians to prescribe serum and urinary electrophoreses, which are the key laboratory investigations for the diagnosis of myeloma. Peaks visible on serum or urine electrophoresis are then identified by immunoelectrophoresis or immunofixation. A preserved corrected calcium at presentation in patients with unexplained renal failure should alert clinicians to the possibility of myeloma.

The main urinary feature is the excretion of a monoclonal LC, which accounts for 70% or more of total proteinuria in 80% of patients.[25] LC proteinuria is usually not detected by urinary dipsticks, but only by techniques measuring total proteinuria. Certain LCs fail to react or react weakly in some widely used precipitation assays, such as the sulfosalicylic acid method, leading to falsely negative or underestimated results. The remaining proteins are composed of albumin and low molecular weight globulins that have failed to be reabsorbed by proximal tubule cells. In the rare patients with albuminuria greater than 1 g per day, CN is usually associated with glomerular lesions due to amyloidosis or MIDD. There is no hematuria in pure CN.

Precipitants of Cast Nephropathy. These are of paramount importance because of measures to prevent precipitation (Table 60.5). It is often difficult to identify a particular event responsible for precipitating renal failure, as these patients experience many of the complications of the disease at once, a common thread of which seems to be an effect on renal perfusion.

Hypercalcemia is an important precipitant found in 16% to 44% of the renal series (Table 60.5), and in 57% of the patients with renal failure in Alexanian nonrenal series.[53] Presumably, hypercalcemia acts by inducing dehydration as a result of emesis and a nephrogenic diabetes insipidus. It may also enhance LC toxicity and cause nephrocalcinosis.

| 60.5 | Precipitants of Acute Renal Failure in Myeloma | | | | | | |

Series	No. of Patients	Dehydration	Sepsis	Hypercalcemia	Contrast Medium	NSAIDs	None
Rota et al.[25]	34[a]	65%	44%	44% (>2.60 mmol/L)	0%	24%	—
Pozzi et al.[26]	50[a]	24%	10%	34% (≥2.60 mmol/L)	4%	0%	44%
Ganeval et al.[28]	80[b]	10%	9%	30%	11%	—	35%
Irish et al.[51]	56[a]	4%	4%	23%	0%	11%	57%
Haynes et al.[50]	107	6%	5%	16% (> 2.90 mmol/L)	—	18%	65%

[a]Renal lesions are described in Table 60.2.
[b]Includes 19 patients with myeloma cast nephropathy, two with amyloidosis, and eight with LCDD (light- and heavy-chain deposition disease).
NSAIDs, nonsteroidal anti-inflammatory drugs.

Dehydration, with or without hypercalcemia, and infection are other major risk factors for acute renal failure. Rota et al.[25] found a high rate of urinary infections (10/34, 29%), which were associated in three cases with an increased proportion of polymorphonuclear leukocytes in the renal biopsy, suggesting an etiologic link between infection and deterioration of renal function. Infection also operates by causing dehydration and prompting the use of nephrotoxic antibiotics.

Contrast media have hitherto been considered an important precipitant of acute renal failure. It was hypothesized that the contrast medium bound to intratubular proteins, especially the LC and THP, causing them to precipitate and obstruct tubular flow. Contrast media also have vasoconstrictive effects, decreasing GFR and urinary output. McCarthy and Becker[54] reviewed seven retrospective studies of myeloma patients receiving contrast media, involving 476 patients who had undergone a total of 568 examinations. The prevalence of acute renal failure (which was not defined) was 0.6% to 1.25%, compared to 0.15% in the general population. This is a low risk and contradicts the dogma that contrast media should not be used in myeloma patients. This change may reflect awareness of the risk and care taken to hydrate patients actively with alkaline solutes before and during the administration of contrast media. No clinical data currently support the preferential use of non-ionic agents in myeloma patients to decrease the risk of acute renal failure.

A number of drugs are noxious in myeloma patients. They include antibiotics, particularly aminoglycosides, and nonsteroidal anti-inflammatory drugs (NSAIDs).[25,50] NSAIDs reduce the production of vasodilatory prostaglandins that help to maintain an appropriate GFR in patients with renal hemodynamics compromised by dehydration. Angiotensin-converting enzyme (ACE) inhibitors can also precipitate renal failure because they reduce GFR dramatically in dehydrated patients. Their use as that of angiotensin type-1 receptor antagonists should be avoided as long as a risk of decreased renal perfusion persists.

Recently introduced therapies including bisphosphonates may also induce toxic tubular injury. Renal failure secondary to acute tubular necrosis was reported with zoledronate, a potent bisphosphonate that is in widespread use for the treatment of hypercalcemia of malignancy,[55] and with short-term, high-dose pamidronate.[56] Doses should be adapted to GFR to avoid toxicity.

Renal Pathology and the Value of Kidney Biopsy

A kidney biopsy should not be routinely performed in patients with a presumed diagnosis of myeloma CN. However, it is useful in three circumstances:

1. To establish the cause of renal failure in anuric patients with clinically silent myeloma without evidence of serum monoclonal component on electrophoresis;

2. To analyze tubulointerstitial lesions and predict the reversibility of renal failure in patients with presumed CN but multiple precipitating factors;

3. To identify glomerular lesions in patients with urinary albumin greater than 1 g per day and no evidence of amyloid deposits in "peripheral" biopsies (accessory salivary glands, rectum, abdominal fat).

A kidney biopsy should be systematically performed in patients enrolled in therapeutic protocols because renal lesions should be precisely identified.[57]

Myeloma Casts. Myeloma CN is characterized by the presence of specific casts associated with severe alterations of the tubule epithelium. Myeloma casts are large and usually numerous. Their prevailing localization is the distal tubule and the collecting duct, but they may also be found in the proximal tubule and even in the glomerular urinary space. They often have a "hard" and "fractured" appearance, and show polychromatism upon staining with Masson's trichrome (Fig. 60.3). Casts may also have a stratified or laminated appearance. They may stain with Congo red, but only exceptionally do they show the typical yellow-green dichroism of amyloid under polarized light.

An important diagnostic feature of myeloma casts is the presence of crystals, which may be suspected by light microscopy.[58] Such casts are often angular or heterogeneous because they contain multiple rhomboid or needle-shaped crystals surrounded by amorphous material and cell debris.

Casts are frequently surrounded by mononuclear cells, exfoliated tubular cells, and, more characteristically, by multinucleated giant cells whose macrophagic origin has been established by specific antibodies. These cells are often seen engulfing the casts and at times actually phagocytizing fragments. In some cases, the cellular reaction is made
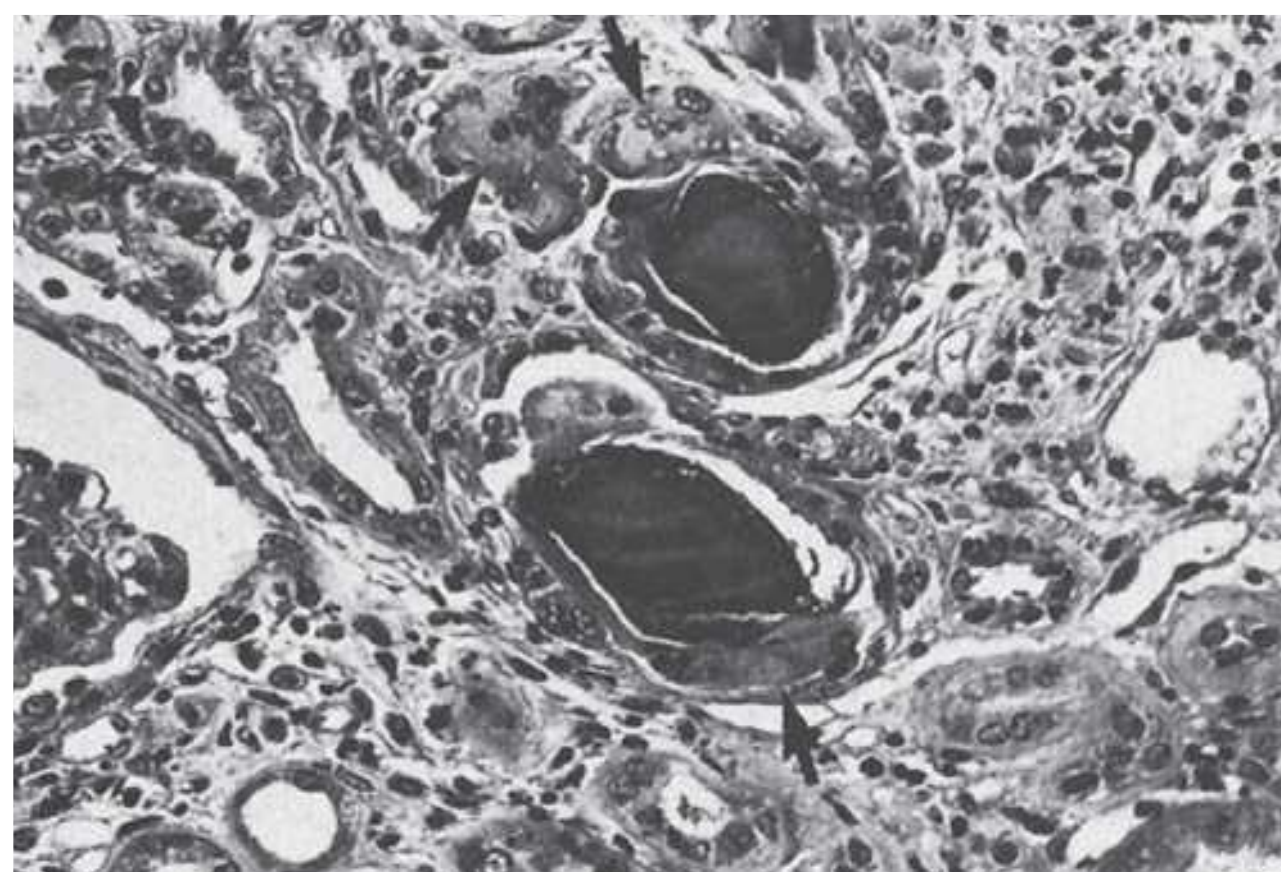

FIGURE 60.3 Myeloma cast nephropathy. Typical myeloma casts with fractured appearance are surrounded by multinucleated macrophagic cells (*arrows*) in a patient with λ–light-chain myeloma. (Masson's trichrome, ×312.)

of polymorphonuclear leukocytes in the absence of urinary tract infection. Typical myeloma casts with a giant, multinucleated cell reaction (Fig. 60.3) can be very occasionally detected in other hemopathies including μ-HC disease[30] and Waldenstöm's macroglobulinemia.[29] In myeloma CN, there is a great variability in the respective percentage of typical myeloma casts and of nonspecific hyaline casts. In some instances, most casts have nonspecific characteristics by light microscopy, even if by immunofluorescence the vast majority consists predominantly of one of the two LC types. The search for typical casts has to be conducted on all available sections if necessary.

By immunofluorescence, myeloma casts are essentially composed of the monoclonal LC excreted by the patient, together with THP. In most cases, casts are stained exclusively or predominantly with either the anti-κ or the anti-λ antibody. However, in about 25% of myeloma biopsies, casts stain for both antibodies because they contain polyclonal LCs, together with albumin and fibrinogen.[58] Staining of "angular" casts is often irregular, and more intense at the periphery (Fig. 60.4). In heterogeneous casts, the crystals themselves fail to stain, whereas the matrix of the cast and the surrounding cellular debris and amorphous material often stain positively for one of the LC isotypes.

Cast ultrastructure was studied by electron microscopy in 24 biopsies of myeloma CN by Pirani et al.[58] Crystals were detected in 14 biopsy specimens and suspected in another 4. The authors have identified four major categories of casts, according to their content and ultrastructural appearance. One category characterized by large rectangular crystals, or fragments thereof, with a pentagonal or hexagonal cross-section, is found only in myeloma CN. It seems to be closely linked to the development of a giant cell reaction around the cast. A second category also frequently contains crystals, but they are small, electron-dense, and
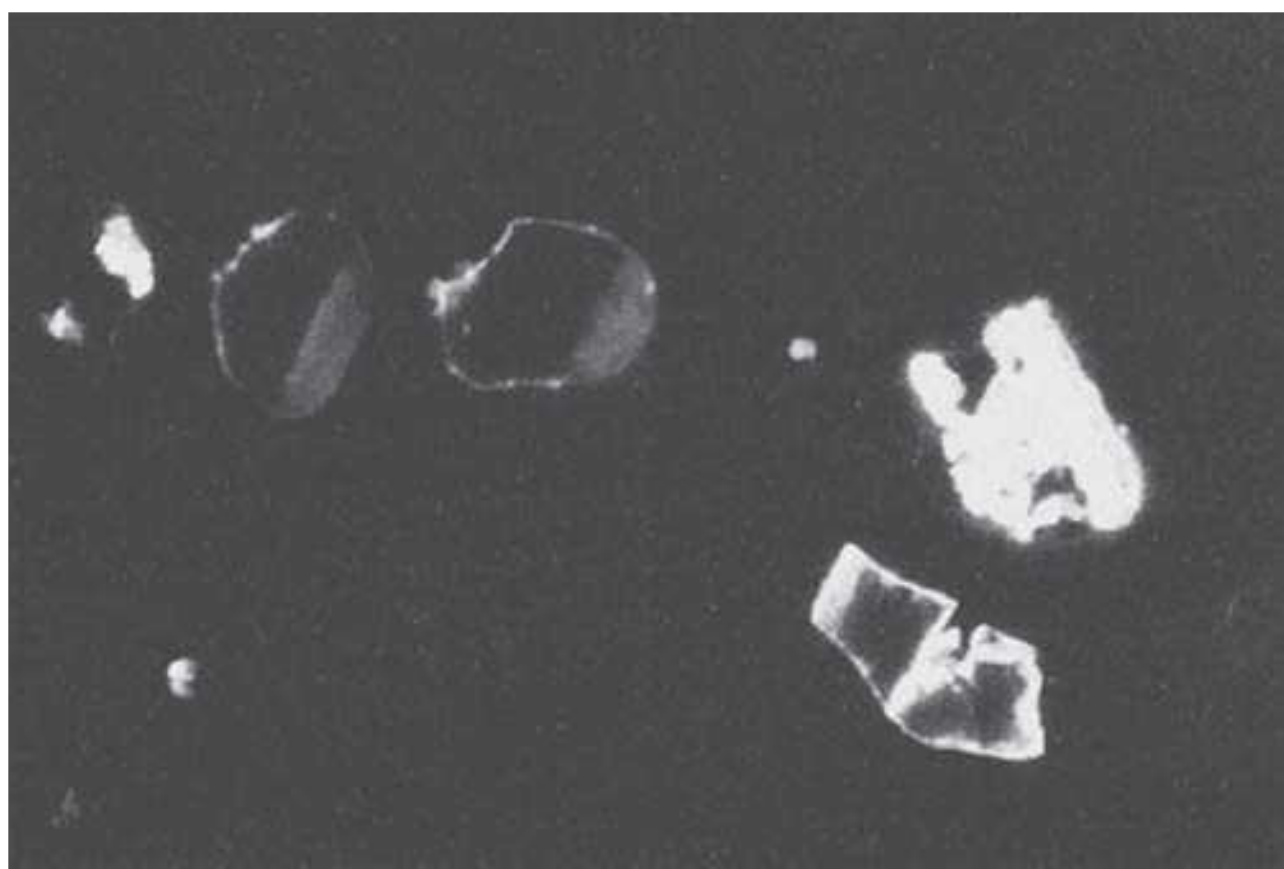

FIGURE 60.5 Myeloma cast nephropathy. Rectangular crystals presumably composed of λ-light chains in tubular cells. (Electron micrograph, uranyl acetate, and lead citrate, $\times$7,000.)

needle-shaped, and seemingly not associated with a cellular reaction. Similar large rectangular and small, needle-shaped crystals can be found within plasma cells. They are also seen occasionally within the cytoplasm of either proximal or distal tubular cells (Fig. 60.5), surrounded by a single smooth membrane, which suggests that they are located within lysosomes.

Tubules and Interstitium. Considerable tubular damage is almost always present in myeloma CN. Epithelial tubular lesions are not only seen in the distal tubules where casts are principally located, but also in proximal convoluted tubules, where the epithelium undergoes atrophy and degenerative changes. Frank tubular necrosis may also be seen, with or without typical myeloma CN.[25] By immunofluorescence, a variable number of tubule sections contain numerous "protein reabsorption droplets" staining for the monoclonal LC.[46]

Interstitial lesions are often associated with the tubular damage. They may be mild and consist of inflammatory infiltrates and fibroedema, but fibrosis and its correlate, tubular atrophy, may also be fairly extensive. In severe cases with epithelial denudation and gaps in the continuity of the tubular basement membrane, often in close contact with myeloma casts, granulomatouslike formations containing macrophages and histiocytes develop around the ruptured tubules (Fig. 60.6).[46]

Glomeruli and Vessels. The glomeruli are usually normal, except for small clusters of globally sclerotic glomeruli and a mild thickening of the mesangial matrix. When mesangial thickening is more prominent, the possibility of an associated

FIGURE 60.4 Myeloma cast nephropathy. Several tubules contain large casts, one of which has an angular and fractured aspect. The stain with anti-κ antibody is more intense at the periphery of most casts. (Immunofluorescence, $\times$312.)
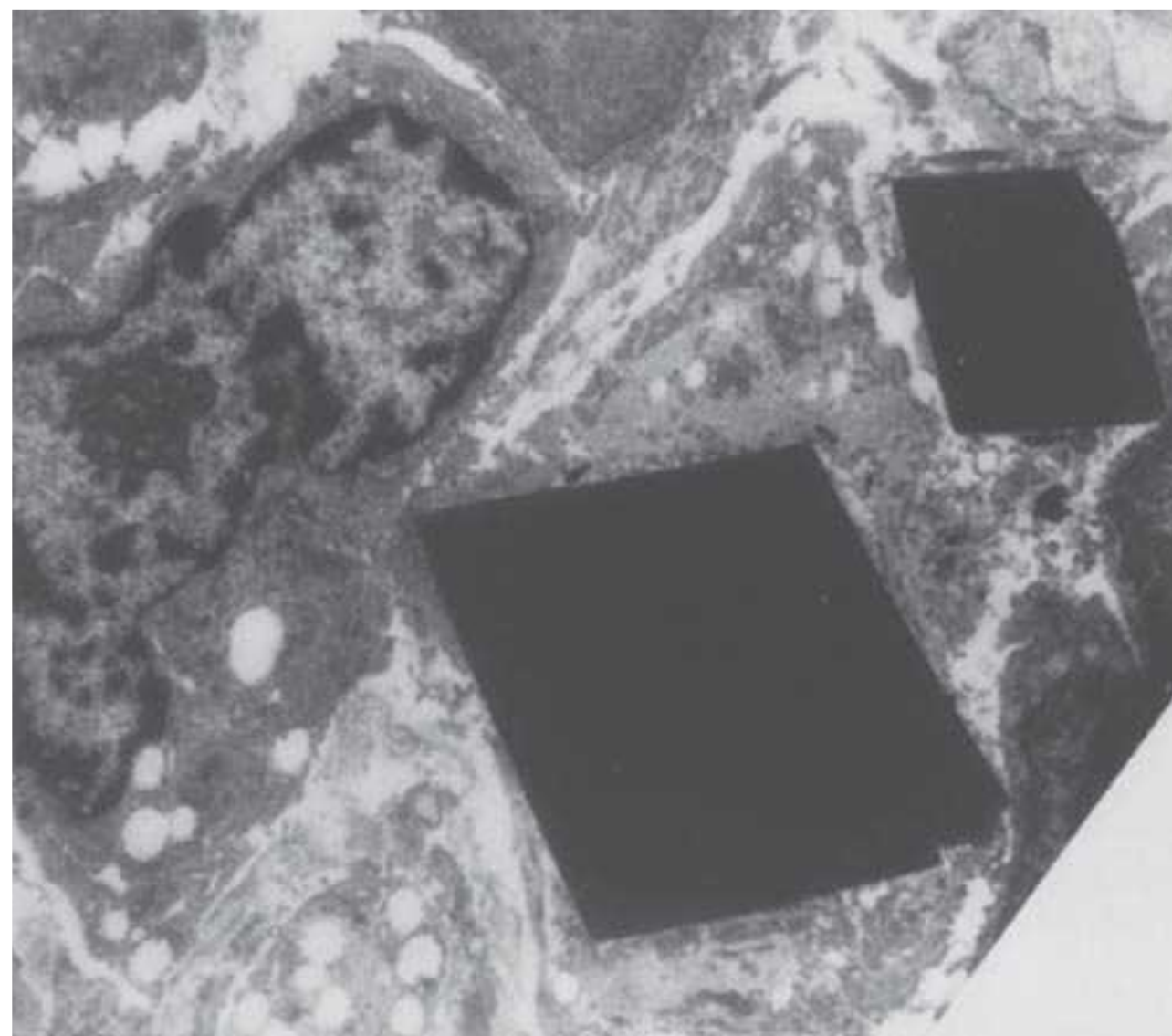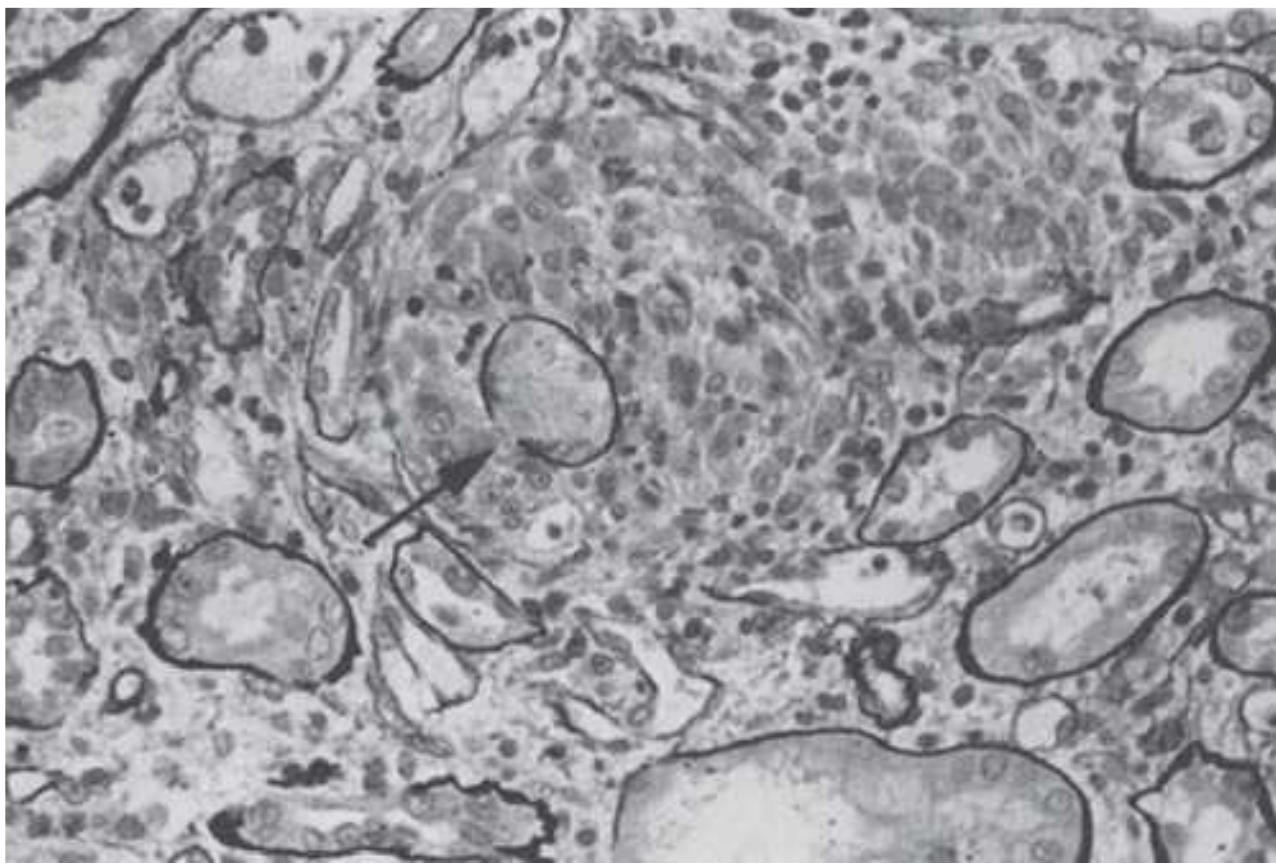
FIGURE 60.6 Myeloma cast nephropathy. Interstitial granulomatous-like formations with macrophages surrounding disrupted tubular basement membrane (*arrow*) were numerous in this λ-chain cast nephropathy. (Silver stain, ×312.)

MIDD should be considered. Rarely, amorphous deposits reminiscent of myeloma casts can be seen in capillary loops or in the glomerular urinary space. In younger patients, severe chronic vascular lesions are sometimes observed, which may contribute to progression of sclerosis.

Outcome and Prognosis of Myeloma Cast Nephropathy

Until the 1980s, myeloma-induced renal failure was associated with a very poor prognosis, with a median survival of less than 1 year.[48] In recent years, the outcome of patients with myeloma, including those with renal impairment, has improved with the introduction of novel therapies, including high dose therapy followed by autologous stem cell support, and development of new drugs with a strong anti-myeloma effect (bortezomib, thalidomide, lenalidomide).[59] However, because patients with elevated serum creatinine levels were excluded from most randomized controlled studies, optimal treatment of multiple myeloma with renal failure remains to be defined. The establishment of consensus criteria for the assessment of renal function and renal response in multiple myeloma, and the use of modern sensitive tests to evaluate hematologic response, such as as nephelometric assays for serum free LC,[60] should help to improve renal and patient outcomes in the future.[61]

Renal Outcome and Prognostic Factors. Renal prognosis in patients with myeloma who present with renal failure remains poor, as complete or partial renal recovery occurs in half of patients after weeks to months,[62] and in only 20% to 40% of those with dialysis-dependent renal failure.[63–66] Elevated plasma creatinine concentration or decreased estimated GFR (calculated using the MDRD equation) have been quoted as markers of poor renal prognosis in most studies,[26,28,62,65,67] implying that renal functional impairment

of any degree should be treated as a medical emergency. In the study by Rota et al.,[25] main prognostic indicators were provided by renal histology. Renal response was seen in patients with typical cast nephropathy and/or tubular necrosis without interstitial damage. Global tubular atrophy and interstitial fibrosis were associated with partially or totally irreversible renal failure, whereas the number of casts has a controversial predictive value.[25,26,68]

The rapid achievement of sustained hematologic response appears as a key factor for renal prognosis.[57,65,69,70] In three recent studies a minimum of 50% reduction in serum free LC concentration was required for recovery of renal function in patients with biopsy proven CN.[57,70,71] Recent data indicate that outcome of severe renal failure may be substantially improved by bortezomib plus dexamethasone-based chemotherapy[61,65,66,72] and, in patients requiring dialysis, by extended hemodialysis using a high-cut off dialyzer that allows effective removal of LCs.[70,73]

Survival and Predictors. Myeloma patients with renal failure have a shorter survival than those with normal renal function. In the presence of renal failure, mortality in the first 3 months is about 30%,[26,28,67] and median survival ranges from 9 to 22 months. However, several studies have indicated that recovery of renal function is associated with improved survival, close to that of patients who do not develop renal failure.[25–28,50,67,62,69] A response to chemotherapy is a key predictor of renal outcome and patient survival.

Treatment

Myeloma patients with renal failure should be treated with chemotherapy just as those without renal failure, and any measures that may contribute to improved renal function should be undertaken from the day of diagnosis.

Decreasing Precipitability of the Urinary LC by Immediate Symptomatic Measures. Because co-precipitation in renal tubules of free LC and THP is the main nephritogenic event, measures to reduce concentration and precipitability of both partners are essential and urgent. These include rehydration, correction of hypercalcemia, stopping administration of NSAIDs and ACE inhibitors, and treatment of infections with nonnephrotoxic antibiotics. Despite controversy about the role of LC pI in cast formation, alkalinization of urine remains recommended because solubility of THP is reduced at low pH. Therefore, a daily urine output greater than 3 L and a urine pH greater than 7.0 should be reached in all patients whose cardiac and renal function can tolerate a deliberate expansion of the extracellular fluid volume. These measures alone are sufficient to improve renal function in the majority of patients with renal impairment at presentation, especially in those with hypercalcemia.[53] However, they must be completed by therapeutic means aimed at decreasing the amount of urinary LCs filtered by glomeruli.

Reducing the Production Rate (and Concentration) of the Monoclonal Light Chains

Conventional Chemotherapy. The goal of chemotherapy is to obtain a rapid and profound reduction in the rate of production of monoclonal LC in order to induce a renal response, which is a main prognostic factor for patient survival. Therefore, chemotherapy should be initiated without delay, as soon as the diagnosis of myeloma is confirmed. The choice of first-line chemotherapy in patients with multiple myeloma and inaugural renal failure is still under investigation. Because of their anti-inflammatory properties, high-dose steroids are considered as mandatory. A retrospective review from a single institution demonstrated reversal of renal insufficiency in 73% of patients treated with high-dose dexamethasone, either alone or combined with other agents.[69] Renal elimination of some agents may limit their use in patients with reduced GFR. Melphalan containing regimens in general should be avoided, as they have slow antimyeloma effect, and because clearance of melphalan is partly dependent on renal function. As the risk of severe hematologic side effects increases with reduced creatinine clearance, melphalan dose should be adapted in patients with impaired renal function.[74] The vincristine, doxorubicin, dexamethasone (VAD) regimen, which induces earlier responses compared to the melphalan plus prednisone combination and has the advantage of being used without dose adaptation in renal failure, has been widely employed, despite cardiac toxicity of doxorubicin and peripheral nerve complications of vincristine.

New Agents. The recent introduction of novel agents, such as the immunomodulatory drugs thalidomide and lenalidomide, and, above all, the proteasome-inhibitor bortezomib, has transformed the strategy of initial chemotherapy in multiple myeloma with renal failure. Pharmacokinetics of thalidomide are not modified in patients with impaired renal function. However, due to the risk of central nervous system side effects, including seizures, thalidomide dose in patients with impaired renal function should not exceed 200 mg per day. Moreover, serum potassium levels should be closely monitored, as severe hyperkalemia has been described in thalidomide-treated patients on dialysis.[60] Little information is available on the efficacy of thalidomide in myeloma patients with renal failure. In a recent series of 31 patients with newly diagnosed myeloma and a creatinine clearance ≤50 mL per min (seven of whom required chronic hemodialysis), thalidomide plus dexamethasone therapy induced hematologic response in 74% of patients, of whom 82% showed improvement in renal function.[76] In a previous retrospective study, the median time for renal response was significantly lower (0.8 versus 2 months) in patients treated with thalidomide plus dexamethasone compared to those who received dexamethasone alone or combined with other agents.[69]

Lenalidomide, which is mainly eliminated through the kidney, should be used with reduced dose depending on the value of creatinine clearance. A subgroup analysis of two phase 3 trials (MM-009 and MM010) using lenalidomide and dexamethasone found that 68% of the patients with renal failure had at least one level of improvement in renal function according to chronic kidney disease stages. The incidence of severe thrombocytopenia was higher in patients with severe renal failure, who required more frequent reductions of lenalidomide dose and had a shorter overall survival.[77]

Because of its potent inhibitory effect on the NF-κB mediated production of pro-inflammatory cytokines, which is likely to play a central role in the pathogenesis of CN, bortezomib appears as a molecule of choice in association with high-dose dexamethasone, in first-line therapy of myeloma with renal failure. Moreover, bortezomib is devoid of nephrotoxicity and may be used without dose adaptation, whatever the degree of renal impairment, including in patients requiring dialysis, with a safety and efficacy similar to those observed in myeloma patients with preserved renal function.[64,78,79] Side effects related to bortezomib therapy mainly involve the gastrointestinal tract, bone marrow (thrombocytopenia), and peripheral nerves.

In several retrospective studies, bortezomib plus dexamethasone-based regimens (combined or not with other agents) appeared to be safe and effective in myeloma patients with renal failure. They induced rapid hematologic responses (usually in less than 2 months) in more than two thirds of patients, with a complete reponse rate of around 30%, close to that of patients with preserved renal function,[65,66,72] and an overall survival of 50% to 60% at 2 years.[66,72] Renal response occurred in 40% to 60% of patients in a median time of 2 months in most series, with a complete renal response (as defined by improvement of creatinine clearance from lower than 50 mL per min at baseline to ≥60 mL per min) rate around 40%.[65,66,72] In a recent prospective phase III trial, hematologic response rates, overall survival, and time to progression were higher in patients with renal failure who received a combination of bortezomib, melphan, and prednisone (VMP), compared to those treated with melphalan plus prednisone (MP). Complete renal responses were 44% in the VMP group and 34% in the MP group.[80] In the VMP group, the incidence of severe hematologic side effects was increased in patients with renal failure, as in patients treated with bortezomib, dexamethasone, and doxorubicin in another study.[81] The impact on renal function and survival of bortezomib-based regimens, and their tolerance in patients with severe renal failure, remain to be investigated in prospective controlled studies. In patients requiring dialysis, bortezomib-based regimens have also shown similar rates of hematologic responses, with an incidence of severe side effects comparable to that observed in patients with preserved renal function. However, the rate of discontinuation of renal replacement therapy was low, ranging from 17% to 33% suggesting that, in this situation, other measures should be undertaken in combination with chemotherapy to rapidly decrease the burden of circulating free LCs.

High-Dose Therapy with Autologous Blood Stem Cell Transplantation. High-dose therapy with autologous blood stem cell transplantation (ASCT) is currently considered as standard therapy in patients aged less than 65 years, with good performance status. In 1996, a randomized controlled trial first demonstrated the benefits of high-dose therapy over conventional chemotherapy in terms of complete remission rate, event-free survival, and overall survival in patients with normal renal function.[82] High-dose therapy with ASCT can lead to a median overall survival exceeding 5 years.[83] In patients with preserved renal function, it is usually based on a single dose of melphalan 200 mg per m^2, given after hematologic response has been obtained with few cycles of chemotherapy (generally based on bortezomib-containing regimens), and peripheral stem cell collection. Several studies have demonstrated that the procedure is feasible in patients with renal failure, but with increased melphalan-related toxicity.[84–86] Despite a 5-year event-free and overall survival of 24% and 36%, respectively, treatment-related mortality (TRM; i.e., in the first 3 months) was high, reaching up to 19% in a series of 59 patients, mainly related to mucosal, infectious, and cerebral complications.[85] However, renal function improved in 24% of patients with dialysis-dependent renal failure, after a median of 4 months following high-dose therapy. Reduction of melphalan dose reduced TRM and did not affect the efficacy of the procedure. In patients less than 65 years old with creatinine clearance lower than 60 mL per min, high-dose therapy may thus be considered; however it is recommended to reduce melphalan dose to 140 mg per m^2,[61,84,85] although the place of high-dose therapy with ASCT in patients with myeloma and renal failure has not been established in prospective controlled studies.

Removal of Circulating Free LCs. Rapid sustained reduction in circulating free LC is the goal of therapy in multiple myeloma. Beside rapid introduction of effective chemotherapy, free LC removal from the serum should be considered. Ig LCs can be directly removed from the circulation by either plasma exchange or intensive haemodialysis using high cut-off membranes. Plasmapheresis has been used in this indication for 30 years and is very effective at reducing LC concentration rapidly. However, its efficacy has not been established, except in patients with hyperviscosity syndrome. Three randomized controlled trials have been published to date[63] and did not support evidence for a beneficial effect of plasmapheresis in improving the rate of renal recovery in patients with myeloma-associated renal failure. As the distribution of Ig LCs is predominately extravascular, a short duration treatment as plasmapheresis might be inappropriate to significantly reduce the burden of LCs.[87]

Recently an extended hemodialysis technique, using a new generation dialyser with very high permeability to proteins that allows reduction of 35% to 70% in serum free LC levels after 2 hours of dialysis, has shown encouraging results.[73] Hutchison et al. reported a series of 19 patients with biopsy-proven myeloma CN and dialysis-dependent renal failure, who received extended high cut-off hemodialysis (using two dialyzers in series, with a dialysis schedule of daily 8 hour sessions for 5 days, then progressively tapered), combined with conventional chemotherapy (mostly based on high-dose dexamethasone plus thalidomide). Treatment resulted in a median reduction of 85% in serum free LC concentration in 13 patients, in whom hemodialysis was withdrawn after a median time of 27 days. Survival of patients free of dialysis was significantly improved.[70] Clinical tolerance of extended high cut-off dialysis appears to be good, although due to the high membrane permeability to large molecules, an infusion of albumin is required after each dialysis session.[73] Preliminary reports indicate that online high-efficiency hemodiafitration is another interesting option to rapidly remove circulating free LCs.[88] Wether these novel strategies may improve prognosis in myeloma cast nephropathy remains to be evaluated in randomized prospective studies.

Supportive Therapy. Blood transfusion, analgesia, erythropoietin, and bisphosphonates are important adjuncts to therapy. Beyond delaying the onset of skeletal events, the new generation of bisphosphonates, pamidronate and zoledronate, also exert antimyeloma effects indirectly by inducing osteoclast apoptosis, thereby reducing a major source of the antiapoptotic IL-6 molecule, or directly by inducing myeloma cell apoptosis. Bisphosphonates were shown to reduce skeletal events in myeloma patients with bone disease, but their use in the absence of bone disease needs to be further evaluated in the context of potential nephrotoxicity. Cases of acute renal failure[55,56] and nephrotic proteinuria with focal segmental glomerulosclerosis and its collapsing variant were indeed reported in patients receiving zoledronate and pamidronate.[89] Therefore, pamidronate (90 mg intravenously over at least 2 hours monthly) and zoledronate (4 mg intravenously over at least 15 minutes monthly) should be given at the appropriate doses, with careful monitoring of renal function and albuminuria.

Dialysis and Renal Transplantation. Dialysis is clearly indicated for the treatment of acute renal failure and end-stage renal disease, except in patients with refractory myeloma.[90] It should be started early to avoid the complications of uremia and to compensate for the hypercatabolic state induced by the use of high doses of corticosteroids. If peritoneal dialysis is chosen, the early placement of a permanent indwelling dialysis catheter is recommended to avoid infectious peritonitis, the risk of which is increased by chemotherapy-induced leukopenia.[50] Residual renal function must be carefully monitored because of possible improvement after several months of dialysis. Two early reports from Great Britain[91] and the United States[92] suggested that chronic dialysis could be a worthwhile treatment in patients with myeloma and renal failure. Survival at 1 year was 45% in the British study (23 patients) and 54% in the American study (731 patients). At 30 months, survival declined to 25% compared with 66%

in nondiabetic ESRD patients without myeloma.[92] In the United States Renal Data System registry, the 2-year all-cause mortality of patients with myeloma during the period 1992 to 1997 was 58% versus 31% in all other patients.[93] In the ERA-EDTA Registry study which gathered patients with CN and LCDD,[20] the median patient survival was 0.91 years, compared to 4.46 years for nonmyeloma patients. Myeloma patients requiring long-term dialysis live as long as those with less severe renal failure,[90] with little difference between hemodialysis and peritoneal dialysis,[51,91,94] although most authors insist on the serious risk of infection in continuous ambulatory peritoneal dialysis (CAPD) patients.[91] However, median survival was less in patients on hemodialysis with myeloma CN (12 months) than in those with AL amyloidosis (24 months) or with LCDD (48 months), most likely because of higher tumor burden.[95] Nevertheless, recent data from the ERA-EDTA Registry[50] showed that the incidence of renal replacement therapy for end-stage renal disease due to myeloma (including cast nephropathy and LCDD) has progressively increased over the past 20 years in Europe, probably because of increased acceptance and improved treatment of myeloma as shown by a 5-year event-free survival in 25% of 59 myeloma patients on dialysis treated with high-dose melphalan and ASCT.[85]

The experience with renal transplantation in myeloma is extremely limited, as the risk of infectious complications and exacerbation of the disease with immunosuppression is usually regarded as prohibitive and myeloma-related lesions may occur.[96,97] Recent data suggest that combined HLA-matched donor bone marrow and renal allotransplantation result in sustained renal allograft tolerance and prolonged antimyeloma response, with acceptable toxicity.[98] However, very few patients are eligible for the procedure. The place of renal transplantation in myeloma, which should be limited to carefully selected patients with an inactive hematologic disease, remains to be defined.

Finally, if most cases of severe renal failure cannot be prevented because they occur simultaneously with the finding of myeloma, it is necessary to avoid or correct all precipitating factors of renal failure in patients with established myeloma. It is particularly important to reduce the use of NSAIDs as analgesic drugs, to detect and control hypercalcemia as soon as possible, and to correct dehydration.

Fanconi Syndrome

Fanconi syndrome (FS) is characterized by renal glycosuria, generalized aminoaciduria, hypophosphatemia, and, frequently, by chronic acidosis, hypouricemia, and hypokalemia. It often includes osteomalacia, with pseudofractures. These manifestations result from functional impairment of the renal proximal tubule. The first association of FS with myeloma was reported by Sirota and Hamerman,[99] although these authors considered FS and myeloma as two separate diseases. Engle and Wallis[100] identified crystal-like inclusions in both tumor cells and renal tubule epithelial

cells, and suggested that FS and myeloma could be related. Costanza and Smoller[101] described the cytoplasmic inclusions as round or rodlike electron–opaque structures with longitudinally oriented fibrils. Lee et al.[102] established clearly that myeloma was a cause of adult FS. Maldonado et al.[103] reported 17 cases of FS associated with plasma cell dyscrasia, and two more recent studies described the clinicopathologic features of the disease in two series of 11 and 32 patients.[104,105] The disease is most likely underdiagnosed. The rarity of FS in patients with myeloma contrasts, however, with the high prevalence of tubule alterations in myeloma autopsy series. This suggests that unusual specific properties of LCs, mostly κ, are involved in the pathophysiology of FS.
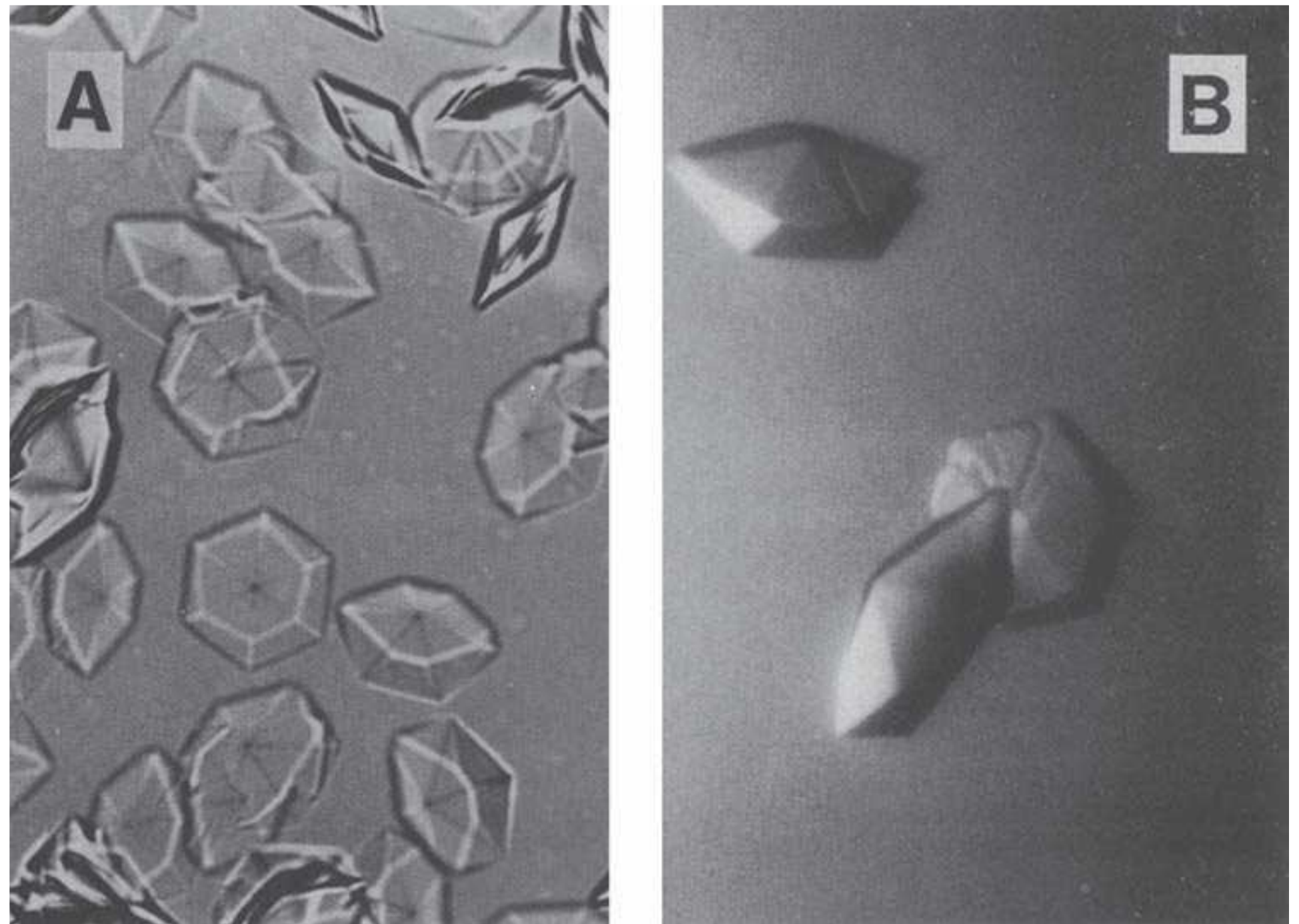
Pathophysiology of Plasma Cell Dyscrasia-Associated Fanconi Syndrome

The peculiar propensity of certain LCs to form crystals in vivo is attested by experimental studies in mice[14] and rats.[40] It is remarkable that the κ LCs that induced crystallization in vivo, also significantly reduced the glucose, chloride, and volume fluxes.

Crystal composition was analyzed in a patient with myeloma-associated FS and hexagonal crystals in kidney proximal tubular cells, bone marrow plasma cells, and phagocytes.[106] N-terminal sequencing and mass spectrometry studies showed that a 107-amino acid fragment corresponding to the variable domain of the κ-LC (Vκ) was the essential component of crystals forming spontaneously from the patient's urine (Fig. 60.7A). Vκ was also crystallized alone using the hanging drop technique (Fig. 60.7B). Crystals were hexagonal bipyramids and had the same 6.0-nm periodicity on electron micrographs as those found in the cells. The V domain (12-kDa) resisted proteolysis by trypsin, pepsin, and cathepsin B, self-reacted, and formed crystals in vitro, which may explain its accumulation in plasma cells and proximal tubular cells. The resistance of LC V domains to proteolytic enzymes including cathepsin B was confirmed in further studies,[16,104] except in a few patients with a high-mass myeloma or Waldenström's macroglobulinaemia[107] and FS. At variance with the observations made in patients with CN,[16] LCs from patients with FS did not bind THP, except in one case where both syndromes were associated.

The unusual physicochemical behavior of FS κ-chains was tentatively correlated with their structure in a number of cases.[108] Sequence analyses showed that 90% of LCs belonged to the VκI variability subgroup, whereas this subgroup only accounts for 56% of all monoclonal κ-LCs.[104,109] The VκI appeared to originate from only two germline genes, IGKV1-39 in five cases and IGK1-33 in four. Analyses of the DNA sequence suggested that all structure peculiarities arose from somatic mutations in the proliferating clone.[110] In the 10 available sequences, residues had never or rarely been reported among VκI subgroup LCs. The unusual presence of nonpolar or hydrophobic amino acids in the complementary determining region (CDR)-L1

FIGURE 60.7 Plasma cell dyscrasia-associated Fanconi syndrome. Crystals spontaneously obtained in vitro from a Sephadex G100 fraction of the patient's urinary proteins (A) and by the hanging drop technique from purified Vκ fragment (B). (A, magnification, ×400; B, size of these crystals, 0.25 mm.) (From Aucouturier P, Bauwens M, Khamlichi AA, et al. Monoclonal Ig L chain and L chain V domain fragment crystallization in myeloma-associated Fanconi's syndrome. *J Immunol.* 1993;150:3561, with permission.)

loop at position 30, together with a nonpolar amino acid at position 50, seems to be specific for FS LCs derived from gene IGKV1-39. These hydrophobic residues are exposed to the LC surface[108] and may be involved in the pathophysiology of FS, as is suggested by site-directed mutagenesis in an experimental model for FS.[111] Recently, a transgenic mouse model with overexpression of human FS κ LC (CHEB) was generated through insertion of the V domain from CHEB LC in the Igκ locus of the mouse. This resulted in the expression of a hybrid κ LC made up of the human V domain and the mouse constant (C) region. Despite the replacement of the human C region, animals exhibited characteristic LC crystals within proximal tubular cells. This model confirmed that LC aggregation in FS is promoted by the V domain structure. The extent of tubular inclusions was proportional to the production rate and serum levels of CHEB LC. Using an inducible CRE mediated deletion of the CHEB V domain, tubular lesions were shown to recover after a few weeks when the LC production was stopped.[112]

After endocytosis, LCs are processed in the endosomal and lysosomal compartment where "normal" LCs are degraded. In FS, accumulation of the protease-resistant V domain fragment generated by lysosomal enzymes may induce crystal formation. Clogging of the endolysosomal system may subsequently alter apical membrane recycling and/or adenosine triphosphate (ATP) production (hence, Na^+-K^+-ATPase functioning) as suggested by mitochondrial injury,[102] and lead to progressive impairment of sodium-dependent apical transporters. However, in a few cases of FS, crystalline inclusions were not observed within proximal tubular cells.[104,107,108] In two patients, LCs, which belonged to the VκIII subgroup, showed no common substitution with

previously described FS VκI LC and did not display resistance to proteolysis, suggesting that other mechanisms of toxicity may be involved in the pathogenesis of the disease.[107,108] Furthermore, why FS does not occur in patients with apparently the same degree of distortion of the lysosomal compartment as can be seen in certain myeloma patients with or without CN is unclear. The molecular mechanisms responsible for glycosuria, phosphaturia, generalized aminoaciduria, and uric acid loss remain poorly understood. An impairment of the megalin-cubilin system might be involved.

Clinical Presentation

The clinical features are summarized in Table 60.6.[104] The median age at diagnosis is 57 years. Most common initial manifestations are bone pain and weakness, principally due to osteomalacia. The major cause of this osteomalacia is hypophosphatemia, which results from increased urinary clearance of phosphate. Chronic acidosis and abnormal renal vitamin D metabolism further contribute to the development of bone lesions. Bone pain may also be the consequence of lytic lesions in patients with a high-mass myeloma. Other revealing signs are essentially due to the proximal tubule impairment, including hypokalemia. Renal failure occurs more frequently than one would expect in a disease of the proximal tubule.

Criteria for the diagnosis of FS may not all be present together, especially in patients with renal failure.[109] The diagnosis of FS is often unrecognized for several years in patients presenting with proteinuria, bone pain, or renal failure. The mean time from onset to diagnosis of FS is about 3 years.[104] Typically, the diagnosis of FS precedes that of the plasma cell dyscrasia, most often a κ-LC-excreting multiple

60.6	Clinical Characteristics of Patients with Plasma Cell Dyscrasia-Associated Fanconi Syndrome[a]						
Total No. of Patients	Age Mean/ Extremes	Gender	Initial Manifestations	Bone Lesions	Renal Failure[c]	Plasma Cell Dyscrasia	Light-Chain Isotype
68	57 22–81	30 males 38 females	Bone pain (25)[b] Weakness, fatigue (16) Weight loss (7) Polyuria– polydipsia(7) Hypokalemia- related signs (4) Proteinuria (18) Renal failure (16) Renal glycosuria (13)	Osteomalacia (25) High-mass myeloma (12) Plasmacytoma (1)	54	Myeloma (36)[d] MGUS (21)[e] MGUS/ myeloma (4)[f] Lymphoma/ CLL (4)[g] "Atypical" plasma cell dyscrasia (1)	49κ 7λ

[a]Figures in parentheses indicate number of patients.
[b]Related to osteomalacia.
[c]Serum creatinine >130 μmol/L, or creatinine clearance
[d]Including 12 patients with a high-mass myeloma.
[e]Monoclonal gammopathy of undetermined significance (MGUS).
[f]Undetermined diagnosis, mostly due to cytoplasmic inclusions in plasma cells making interpretation of cytology difficult.
[g]Chronic lymphocytic leukemia (CLL).
From Messiaen T, Deret S, Mougenot B, et al. Adult Fanconi's syndrome secondary to light-chain gammopathy: clinicopathologic heterogeneity and unusual features in 11 patients. Medicine (Baltimore). 2000;79:135, with permission.

myeloma, because the hematologic disease has a low tumor burden and a slow progression. In 35 of 98 (36%) published cases,[104,105] even criteria for the diagnosis of myeloma were lacking, and patients were classified initially as having a benign monoclonal gammopathy of undetermined significance (MGUS). In some patients, the diagnosis of the plasma cell dyscrasia remained undetermined between myeloma and MGUS because it may be difficult to recognize the cytologic characteristics of myeloma cells when their cytoplasm is stuffed with crystals. Three patients of 99 had Waldenström's macroglobulinemia.[104,105,107]

Conversely, the metabolic disorders of FS may be overseen in the context of myeloma, and FS-related bone lesions should not be interpreted as the consequence of high-mass myeloma.

Pathologic Data

Typically there are prominent crystals in enlarged proximal tubular cells and degenerative changes of proximal tubules.[104] Proximal tubular cells are stuffed with microcrystals that stain red or green with Masson's trichrome and are periodic acid-Schiff negative. In the most severely affected tubules, crystal-containing exfoliated cells are seen in the tubular lumen, whereas intracytoplasmic crystals are still present in atrophic tubules. In other cases, crystals

can only be suspected by the presence of a finely granular material of glassy appearance in an enlarged proximal tubular epithelium (Fig. 60.8A). Their presence is more easily demonstrated by toluidine-blue staining of semi-thin sections and by hematoxylin and eosin staining of cryostat sections. In the same tubule sections, all the cells are not equally affected; cells with a normal aspect coexist with those stuffed with crystals.

A universal feature is the additional presence of severe lesions of the proximal tubule epithelium apparently devoid of crystals. These lesions include vacuolization, loss of the luminal brush border, and focal cell sloughing, with cell fragments in the lumen of the tubules. Interstitial cellular infiltrate, including plasma cells, may contain crystalline inclusion bodies. Patchy tubular atrophy and focal interstitial fibrosis, together with a variable number of obsolescent glomeruli, are often observed.

In several cases, attempts to characterize the crystal proteins with anti-Ig conjugates, including anti-LC antibodies, have failed. When immunohistochemical studies are positive, crystals stain only (or predominantly) for the monoclonal LC, most often κ (Fig. 60.8B).

By electron microscopy, crystals of various size and shape (rectangular, rhomboid, round, or needle-shaped) are detected within the cytoplasm of proximal tubule cells
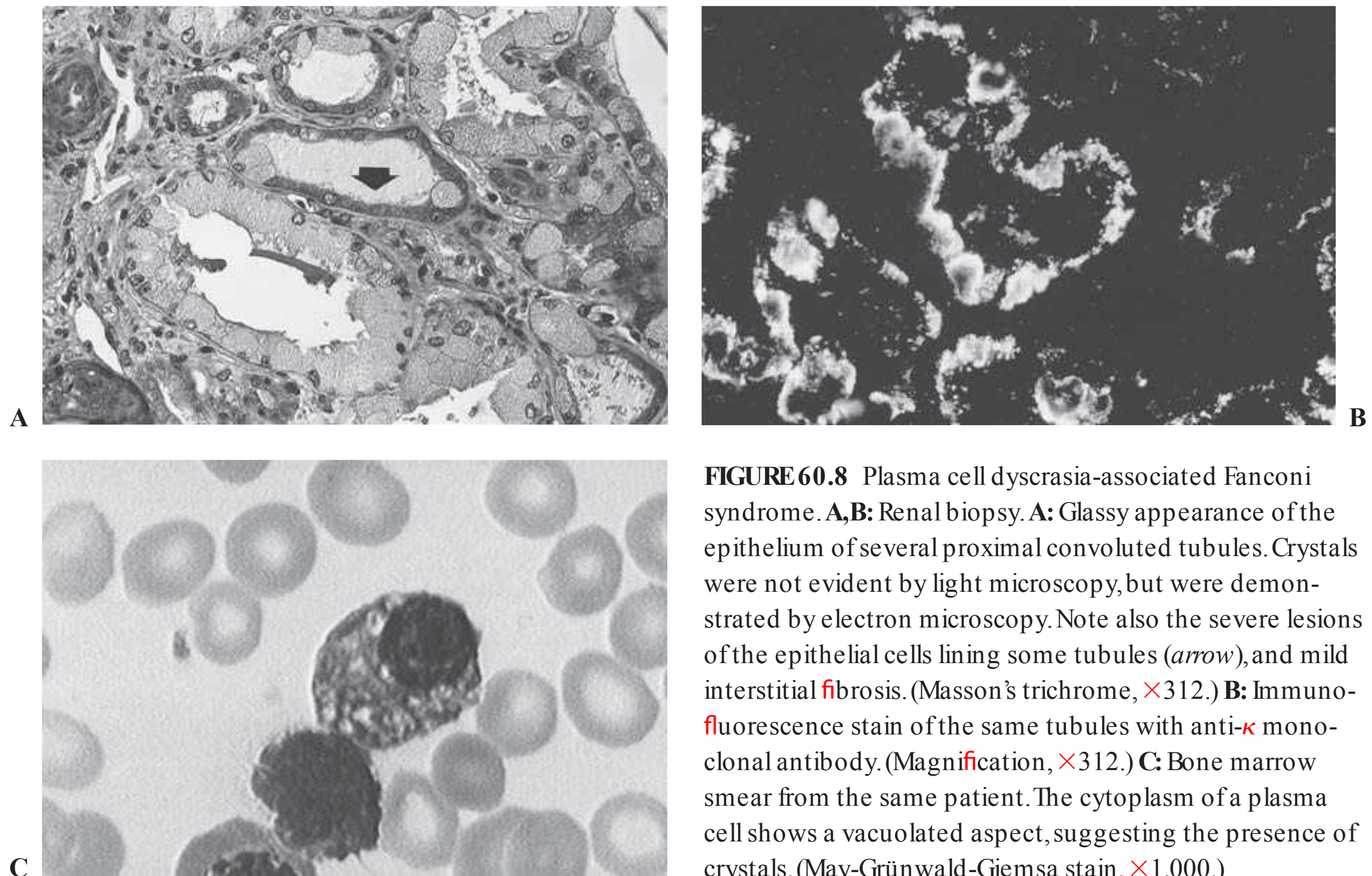
FIGURE 60.8 Plasma cell dyscrasia-associated Fanconi syndrome. **A,B:** Renal biopsy. **A:** Glassy appearance of the epithelium of several proximal convoluted tubules. Crystals were not evident by light microscopy, but were demonstrated by electron microscopy. Note also the severe lesions of the epithelial cells lining some tubules (*arrow*), and mild interstitial fibrosis. (Masson's trichrome, ×312.) **B:** Immunofluorescence stain of the same tubules with anti-κ monoclonal antibody. (Magnification, ×312.) **C:** Bone marrow smear from the same patient. The cytoplasm of a plasma cell shows a vacuolated aspect, suggesting the presence of crystals. (May-Grünwald-Giemsa stain, ×1,000.)

(Fig. 60.8C). Intracytoplasmic crystals are surrounded by a single smooth membrane, likely of lysosomal origin.[58,106] In rare cases, crystals are also seen in distal tubule cells. In other cases, crystals are not found by light microscopy, but electron microscopy shows enlarged vesicular bodies containing dense tubular and rod-like structures[101–103] or fibrils and needle-shaped deposits very close to crystalline structures.

Crystal formation in plasma cell dyscrasia–associated FS is not limited to renal tubule epithelium but also occurs in bone marrow and tissue-infiltrating plasma cells, and in macrophages (Figs. 60.8C and 60.9).[103,106] In plasma cells, crystals are localized not only in lysosomes, but they are also frequently found inside the granular endoplasmic reticulum. Crystal formation in these organelles therefore suggests incomplete proteolysis of LCs. The slow progression of myeloma disease in typical FS associated with crystal formation may be explained by the deleterious effects on cell growth of the accumulation of crystalline inclusions in the tumor plasma cells. A peculiar accumulation of LC crystals may be observed within lysosomes of macrophages in the bone marrow and other organs, defining "crystal-storing histiocytosis" (CSH). In CSH, invariably associated with κ LC monoclonal gammopathy, crystals appear to be mostly made up of monoclonal κ LC, and more rarely of entire IgG. Renal manifestations in CSH are mostly represented by chronic tubulointerstitial nephritis and FS with accumulation of monoclonal κ LC crystals within proximal tubular cells. Perirenal and interstitial infiltration by histiocytes containing eosinophilic crystalline inclusions (pseudo-pseudo Gaucher

cells) is suggestive of the disease. Specific molecular peculiarities in the V domains of CSH monoclonal κ LCs may account for crystal accumulation within histiocytes and multiple organ involvement.[113]

Although crystals are a salient feature of the plasma cell dyscrasia–associated FS, they are neither specific nor absolutely constant. Crystals were found in 16 of 28 (57%) patients in the two largest series published so far.[104,105] They may also be found, albeit in low amounts, in proximal tubule epithelial cells of patients with CN,[16,58] and occasionally in myeloma patients with isolated tubular lesions, that is, in the absence of myeloma casts.

Outcome and Treatment

As expected, patients with multiple myeloma have shorter survival time than those with MGUS. In the Mayo Clinic's series, only one of the 14 patients with MGUS developed multiple myeloma, and at the end of follow-up, only 5 of 32 patients had evolved to end-stage renal disease.[105]

In patients with osteomalacia, considerable improvement can be obtained with 1α-hydroxyvitamin D, calcium, and phosphorus supplementation. The effect of chemotherapy on the proximal tubule impairment is much more debated. It was reported that the treatment of underlying myeloma improved urinary signs and tubular transport abnormalities. However, no significant change in renal function was observed in the two largest series.[104,105] It has been suggested that the presence of crystals within plasma cells should be added to the list of criteria against chemotherapy in
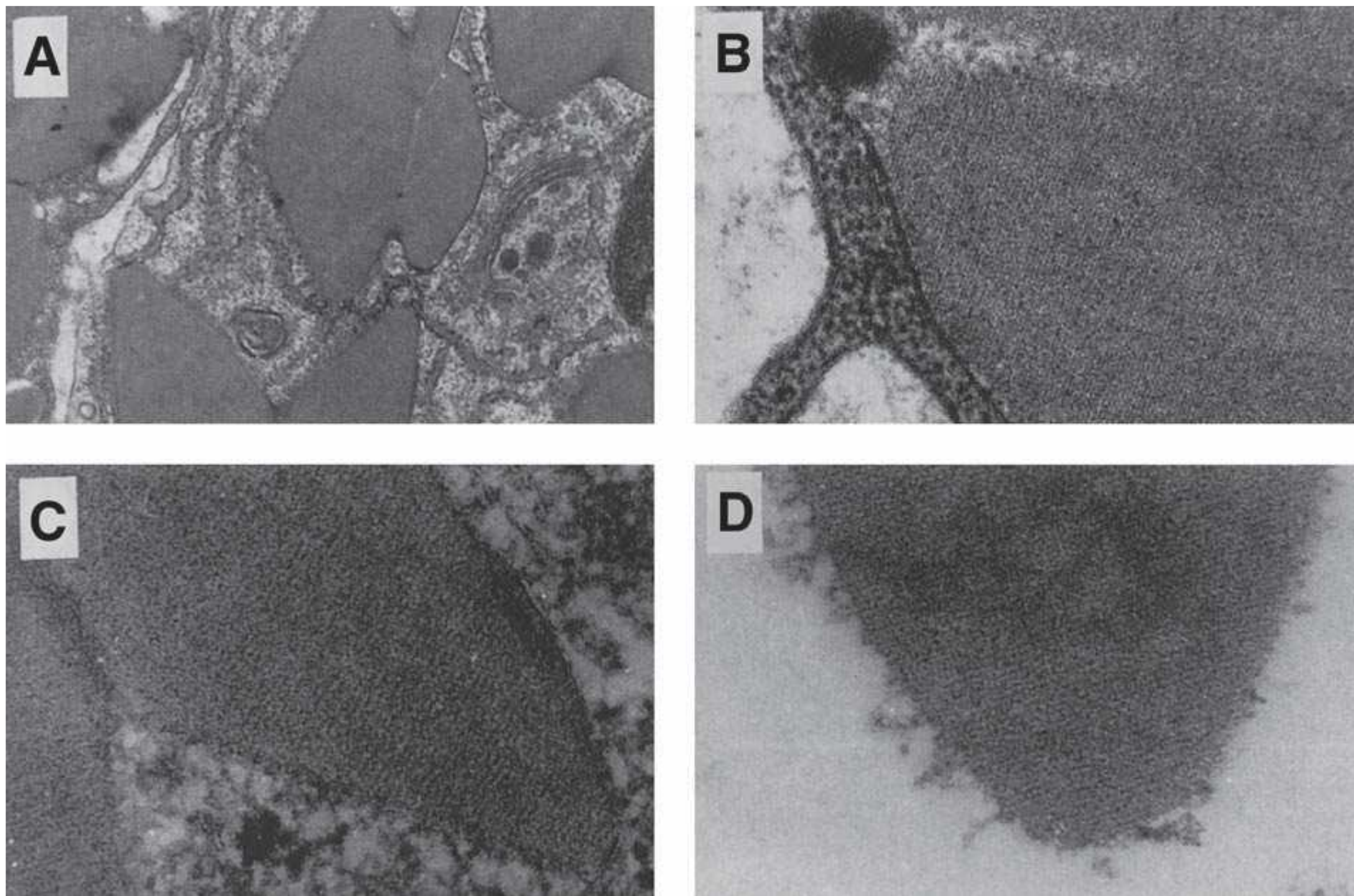
FIGURE 60.9 Plasma cell dyscrasia-associated Fanconi syndrome in same patient as in Figure 60.7. Electron microscopic study of intracellular (*A, B,* and *C*) and in vitro-formed crystals in the same patient. **A:** Bone marrow plasma cell (and a macrophage on the left). (Magnification, ×8,000.) **B:** Bone marrow macrophage. (Magnification, ×50,000.) **C:** Proximal convoluted tubular epithelial cell. (Magnification, ×50,000.) **D:** Crystal obtained in vitro from Sephadex G100 fraction C from the patient's urine. (From Aucouturier P, Bauwens M, Khamlichi AA, et al. Monoclonal Ig L chain and L chain V domain fragment crystallization in myeloma-associated Fanconi's syndrome. *J Immunol.* 1993;150:3561, with permission.)

myeloma. Because chemotherapy, especially with alkylating agents, carries a significant risk of complications but without much benefit for kidney function, and because patients who do not have an overt malignancy show a relatively benign course, the risks and benefits of chemotherapy should be weighed carefully. Whether novel antimyeloma agents might improve renal prognosis in FS remains to be established.

AMYLOIDOSIS

Amyloidosis has been known to be associated with or to cause renal disease for more than 100 years. Amyloid was originally identified as a waxy substance by Rokitansky in 1842, but the term amyloid was coined by Virchow in 1854 because the substance stained with iodine in a way that was similar to starch and cellulose. Although the protein content of amyloid was recognized subsequently, the term amyloid persisted. The diversity of amyloidotic disease was rapidly suspected on clinical grounds, but chemical studies in the late 1960s actually provided the basis of the present classification of amyloid (Table 60.7). In 1968, Pras et al.[114] isolated and purified amyloid fibrils, which opened the

way to further chemical analyses. In 1971, Glenner et al.[2] found that the amyloid fibril proteins from two patients had an N-terminal sequence identical to Ig LCs, which was the first demonstration of a relation between amyloidosis and Ig. They also generated "amyloidlike" fibrils by proteolytic digestion of some human LCs, thereby demonstrating their propensity for forming amyloid.[115]

AL amyloidosis is certainly among the most severe complications of plasma cell proliferative disorders. The only efficient therapeutic tools to date are chemotherapeutic drugs against B cell proliferations. However, pathophysiologic considerations and advances in the treatment of other types of amyloidosis may open new therapeutic avenues (Table 60.7).

General Characteristics of Amyloidosis

A Common Ultrastructural Molecular Organization Defining a Morphologic Entity

Amyloidosis is the general term for a morphologic entity, defined by visceral, extracellular deposition of protein material with unique tinctorial properties and ultrastructural characteristics. After Congo red staining, amyloid deposits exhibit

60.7 Classification of Amyloidoses

Amyloid Protein	Precursor	Distribution	Type	Syndrome or Main Involved Tissues
AA	**Serum amyloid A**	**Systemic**	**Acquired**	**Secondary amyloidosis, reactive to chronic infection or inflammation including hereditary periodic fever (FMF, TRAPS, HIDS, FCU, and MWS)**
AApoAI	**Apolipoprotein A-I**	**Systemic**	**Hereditary**	**Liver, kidney, heart, skin, larynx**
AApoAII	**Apolipoprotein A-II**	**Systemic**	**Hereditary**	**Kidney, liver, adrenal glands, spleen, skin**
Aβ	Aβ protein precursor	Localized Localized	Acquired Hereditary	Sporadic Alzheimer disease, aging Prototypical hereditary cerebral amyloid angiopathy, Dutch type
Aβ2M	β_2-microglobulin	Systemic	Acquired	Chronic hemodialysis
ABri	Abri protein precursor	Localized or systemic?	Hereditary	British familial dementia
ACys	Cystatin C	Systemic	Hereditary	Icelandic hereditary cerebral amyloid angiopathy
AFib	**Fibrinogen Aα chain**	**Systemic**	**Hereditary**	**Kidney**
AGel	**Gelsolin**	**Systemic**	**Hereditary**	**Finnish hereditary amyloidosis**
AH	**Immunoglobulin heavy chain**	**Systemic or localized**	**Acquired**	**Primary amyloidosis, myeloma-associated**
AL	**Immunoglobulin light chain**	**Systemic or localized**	**Acquired**	**Primary amyloidosis, myeloma-associated**
ALys	**Lysozyme**	**Systemic**	**Hereditary**	**Kidney, liver, spleen, adrenal glands**
APrP	Prion protein	Localized Localized	Acquired Hereditary	Sporadic (iatrogenic CJD, new variant CJD) (alimentary?) Familial CJD, GSSD, FFI
ATTR	**Transthyretin**	**Systemic**	**Hereditary** **Acquired**	**Prototypical FAP** **Senile heart, vessels**
ALECT2	**Leukocyte chemotactic factor 2**	Systemic	**Acquired?**	Kidneys, liver, adrenal glands

Lines in bold characters indicate amyloid types with kidney involvement.

The following proteins may also cause amyloidosis: calcitonin, islet-amyloid polypeptides, atrial natriuretic factor, prolactin, insulin, lactadherin, keratoepithelin, and Danish amyloid protein (which comes from the same gene as ABri and has an identical N-terminal sequence).

CJD, denotes Creutzfeldt-Jakob disease; FAP, familial amyloidotic polyneuropathy; FCU, familial cold urticaria; FFI, fatal familial insomnia; FMF, familial Mediterranean fever; GSSD, Gerstmann-Strüassler-Scheinker disease; HIDS, hyper-IgD syndrome; MWS, Muckle-Wells syndrome; TRAPS, tumor necrosis factor receptor-associated periodic syndrome.

Adapted from Westermark G, Benson MD, Buxbaum JN, et al. Amyloid fibril protein nomenclature—2002. Amyloid 2002;9:97; Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med. 2003;349:583.

birefringence under polarized light, which indicates the presence of highly ordered structures. These deposits have been extensively studied at the ultrastructural level by electron microscopy, infrared spectroscopy, and X-ray diffraction. Glenner[116] clustered all amyloidoses under the denomination of β-fibrilloses on the basis of the highly similar organization of the amyloid deposits. These are "typically composed of a felt-like array of 7.5- to 10-nm wide rigid, linear, nonbranching, aggregated fibrils of indefinite length." One amyloid fibril is made of two twisted 3-nm–wide filaments, each having a regular antiparallel β-pleated sheet configuration; the β-sheets are perpendicular to the filament axis. A regular packing of peptides or proteins with a β-sheet conformation results in the elongation of amyloid fibrils. The numerous hydrogen bonds between virtually all amide functions of the peptide backbones make such a structure highly stable. Other components, described in subsequent text, are supposed to stabilize the fibrils.

Amyloid Protein Precursors and Classification of Amyloidoses

Amyloid protein precursors share the property of either a native β-pleated conformation or a high propensity to form β-sheets. All are globular structures, clearly distinct from fibrillar proteins such as collagen, which are proline-rich polymers with a longitudinal arrangement.

The International Committee for Amyloidosis recommended a nomenclature essentially based on the nature of amyloid proteins[117]; the abbreviated name of each amyloid protein is preceded by the letter A. The list provided in Table 60.7 is not exhaustive. Twenty-seven different amyloid protein precursors have been identified to date. It is worth noting that hereditary and secondary forms of the same disease exist and should be distinguished; for instance, normal transthyretin is responsible for senile systemic amyloidosis, whereas certain mutations are the cause of familial amyloidotic polyneuropathy (Fig. 60.10A). Multiple different factors, either intrinsic (structural) or external (concentration of the precursor proteins, tissue factors, etc.), may influence the pathogenicity of a variety of potentially amyloidogenic proteins.

Other Constituents of Amyloid

In addition to the unique "pseudocrystalline" stacking of β-sheets, a few structural features are shared by all types of amyloid, and might help the understanding of some aspects
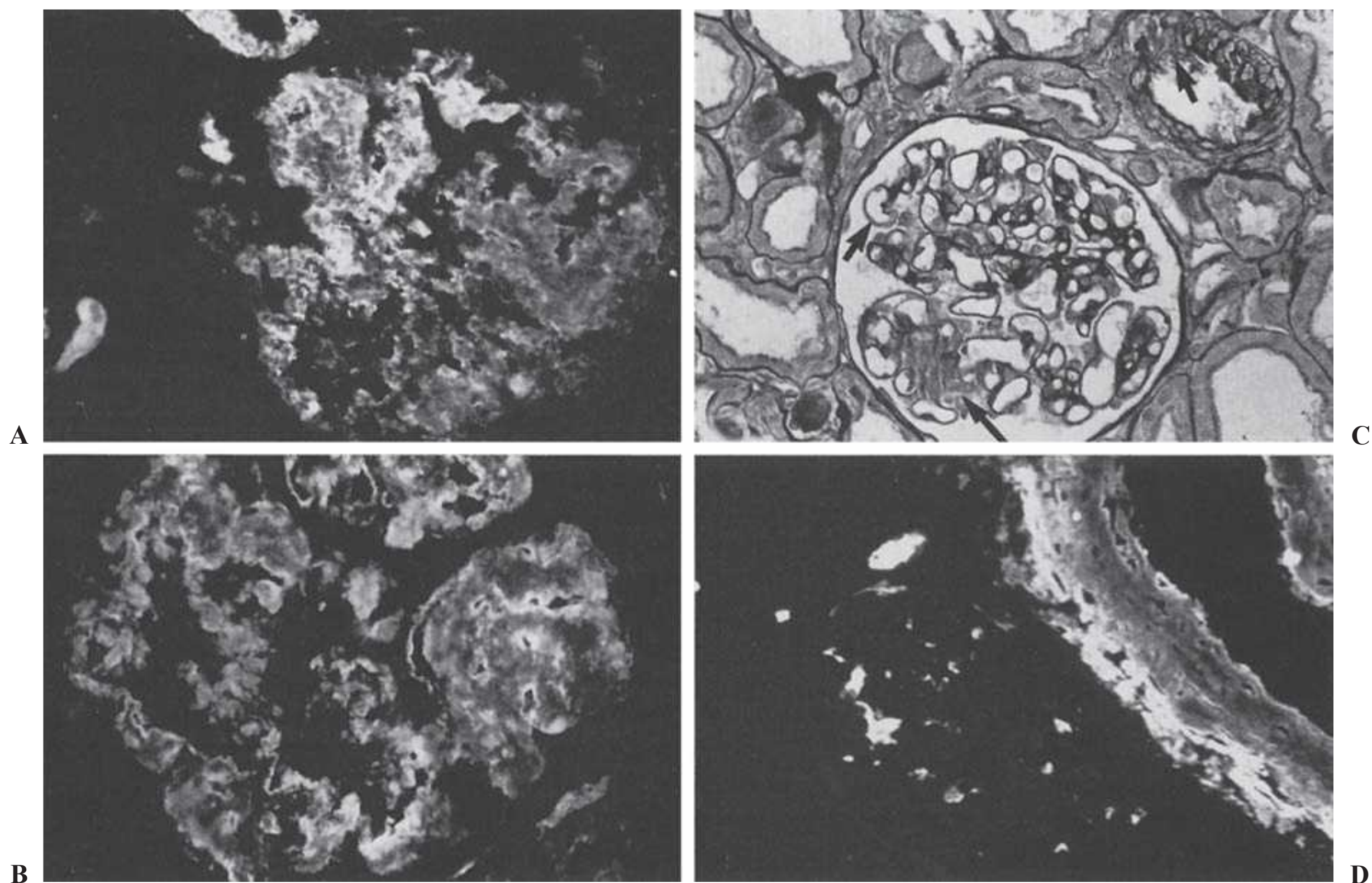

FIGURE 60.10 Amyloidosis. **A:** Glomerular and vascular heavy amyloid deposits stained with antitransthyretin antibody in a patient with Portuguese-type hereditary amyloidosis. (Immunofluorescence, ×312.) **B:** Co-deposition of amyloid P (AP) component in a glomerulus from the same patient as in (**A**). (Immunofluorescence stain with anti-AP component antibody, ×312.) **C:** Glomerulus with early amyloid deposits in mesangium, capillary walls, and arteriolar wall (*arrows*) from a patient with AA amyloidosis. (Light microscopy, periodic acid-Schiff, ×312.) **D:** Glomerulus from a patient with AL amyloidosis. Scanty glomerular deposits contrast with almost complete replacement of arterial walls by amyloid. (Immunofluorescence stain with anti-κ antibody, ×312.)

of the pathophysiology. Glycosaminoglycans (GAGs) have been found tightly associated with all isolated amyloid fibrils. GAGs are polysaccharide chains made of repeating uronic acid–hexosamine units of several types and normally linked to a protein core, thus constituting proteoglycans, which are important constituents of extracellular matrices. The invariable presence of GAGs in amyloid fibrils raises two suggestions:

1. Proteoglycans might interact with amyloidogenic precursors during the nucleation steps of amyloidogenesis; indeed, most GAGs associated with fibrils are of the heparan sulfate type, and heparan sulfate proteoglycans are essential components of the basement membranes, which are preferential sites of amyloid deposition. Recent data indicate that specific interactions occur between motifs within heparan sulfate and properly modified AL LCs.[118]

2. Sulfated GAGs might be important for inducing and stabilizing the β-pleated structure of the amyloid fibrils.[119]

Another constituent of all amyloid deposits is a protein of the pentraxin family, the serum amyloid P component (SAP) (Fig. 60.10B). SAP is a plasma glycoprotein made up of two noncovalently linked pentamers of identical subunits. The β-pleated structure of SAP[120] is strongly homologous to that of legume lectins such as concanavalin A. It shows no allelic polymorphism and displays striking interspecies homology. Furthermore, no occurrence of SAP deficiency has yet been described, which suggests that it has essential physiologic functions. SAP is a calcium-dependent lectin, with binding affinities toward DNA, C4-binding protein, and the collagenlike region of C1q, and several constituents of extracellular matrices such as fibronectin and proteoglycans. SAP was shown to bind apoptotic cells and nuclear debris, and mice with targeted deletion of the SAP genes spontaneously develop anti-DNA antibody and a syndrome resembling human systemic lupus erythematosus.[121] Two calcium sites are involved in carbohydrate binding. In the presence of calcium, SAP is remarkably resistant to proteolytic digestion, suggesting a physiologic role in maintaining extracellular matrix structures. Coating of amyloid fibrils with unaltered SAP is a constant feature that could result in their protection from catabolism. It is probable that SAP binding to amyloid deposits is mediated by GAGs through the formation of multicomponent complexes. The high affinity of SAP toward all types of amyloid is used for diagnosing and monitoring the extent of systemic amyloidosis using scintigraphy with ^{123}I-labeled SAP.[122] SAP binding to all ligands is inhibited by specific sugars such as β-D-galactose cyclic pyruvate acetal. Moreover, the knowledge of SAP structure offers the opportunity of designing competitive inhibitors as potential drugs for the treatment of amyloidoses. Recently, CPHPC, a compound that specifically binds to SAP allowing a rapid decrease in serum SAP levels, has been developed.[123] The combination of CPHPC with an antibody specific for SAP, which targets amyloid deposits and enables their elimination by recruiting phagocytic cells, has shown impressive results in an experimental mouse model of systemic AA amyloidosis.[124]

General Mechanisms of Fibrillogenesis

The amyloidoses are diseases of protein conformation in which a particular soluble innocuous protein transforms and aggregates into an insoluble fibrillar structure that deposits in extracellular spaces of certain tissues. Fibrillogenesis may be the consequence of several mechanisms of processing the amyloid precursor, including partial proteolysis and conformational modifications. In systemic AA amyloidosis, removing of the C-terminal part of an apolipoprotein acute-phase reactant, SAA, yields a 5- to 10-kDa fibril-forming fragment. Phagocytic cells, in particular macrophages, supposedly play a central role in this disease by providing the intralysosomal processing of the precursor. In other forms of amyloidosis, such as those involving transthyretin and Ig LCs, partial proteolysis has been demonstrated but may as well occur after fibrillogenesis, as shown in AA amyloidosis. The demonstration of small fragments from the LC constant domain in deposited fibrils also argues in favor of a postfibrillogenic proteolysis in AL amyloidosis.

In certain types of hereditary amyloidoses due to mutations in the genes coding for the precursor protein,[125] amyloid formation seems to occur via a conformational change leading to a soluble partially folded intermediate. The property shared by these amyloidogenic variants is a native conformation that is thermodynamically less stable than that of the normal counterpart. A reduction in the stability of the variant was shown to favor the formation of partially folded conformers (alternative spatial arrangements of the same polypeptide) that have a strong propensity to self-aggregate and assemble into fibrils. Whether conclusions from structural studies of transthyretin or lysozyme mutants may be extended to other amyloidoses, including AL and AA amyloidoses, remains questionable.

Amyloidogenesis seems to be a nucleation-dependent polymerization process. Unlike other protein deposition diseases, in which amorphous aggregates are the consequence of insolubility of the pathogenic protein in the tissues, amyloid may result from a "one-dimensional crystallization." Formation of an ordered nucleus is the initial and limiting step, followed by a thermodynamically favorable addition of monomers leading to elongation of the fibrils. As shown in Alzheimer and prion diseases, the nucleation step can be overrun by adding a preformed nucleus to a supersaturated solution of the amyloidogenic protein. A similar "seeding" phenomenon may explain the "amyloid-enhancing factor" activity of extracts from amyloid-containing tissues in AA amyloidosis animal models. Recent data indicate that this activity can reside in macrophages.[126]

Distribution of Amyloid: Localized Versus Systemic Amyloidosis

Tissue localization of the deposits is characteristic of many amyloidoses (Table 60.7). Single-organ involvement may reflect either local secretion or particular tropism of the amyloid precursor. Systemic amyloidoses are derived from

circulating precursors, which either display unusual structural features or are present at abnormally high plasma levels, or both. Although most cases of LC amyloidosis are due to systemic organ deposition of LCs, localized forms of LC amyloidosis have also been reported mostly in the orbit, larynx, nasopharynx, lung, skin, and the genitourinary tract. A local infiltration of plasma cells is then usually found in proximity to the amyloid deposits, and may be responsible for the secretion of an amyloidogenic LC.

Pathologic Data with Special Emphasis on Renal Involvement

Despite the diversity of amyloidogenic proteins, they all deposit in tissue as fibrils constituted by the stacking of β-pleated sheets as identified by X-ray crystallography and diffraction studies. This unique protein conformation is responsible for the tinctorial and optical properties revealed by Congo red staining of tissue sections, and for the relative resistance of the fibrils to solution in physiologic solvents and to normal proteolytic digestion, which leads to their implacable accumulation in tissues.[116]

By light microscopy, the deposits are extracellular, eosinophilic, and metachromatic. After Congo red staining, they appear faintly red and show the characteristic apple-green birefringence under polarized light. This light microscopic method is the most reliable to detect amyloid because it yields virtually no false-positive findings. Sections thicker than those usually recommended for renal pathologic examination (i.e., $>5\mu$m in thickness) may be necessary to produce sufficient color density. Metachromasia is also observed with crystal violet, which stains the deposits in red. The use of other stains such as thioflavine T has been proposed, but the results lack specificity. The permanganate method may help to discriminate AA from AL fibrils if the sections are treated with permanganate before the Congo red procedure. AL amyloid is resistant, whereas AA amyloid is sensitive to permanganate oxidation. However, this method has been supplanted by immunohistochemical analysis of the deposits.

In the kidney, the earliest lesions are located in the mesangium, along the glomerular basement membrane, and in the blood vessels (Fig. 60.10C). Within the mesangium, deposits are associated primarily with the mesangial matrix, and subsequently irregularly increase by spreading from lobule to lobule and then invading the whole mesangial area. Amyloid deposits may also infiltrate the capillary basement membrane or be localized on both sides of it. When subepithelial deposits predominate, spikes recalling those seen in membranous glomerulopathy may be observed. It was shown that the severity of proteinuria correlated with the presence of spicules and podocyte destruction rather than with the amount of amyloid in the glomerulus. Glomerular cell proliferation is infrequent. Advanced amyloid typically produces a nonproliferative, noninflammatory glomerulopathy, responsible for a marked enlargement of the

kidney. The amyloid deposits replace normal glomerular architecture with loss of cellularity. When glomeruli become massively sclerotic, the deposits may be difficult to demonstrate by Congo red staining, and electron microscopy may then be helpful. The latter may also be required at very early stages, which may not be detected by light microscopy examination in patients presenting with the nephrotic syndrome. Except in fibrinogen A α-chain amyloidosis, which characteristically does not affect renal vessels, the media of the blood vessels is prominently involved at early stages. Vascular involvement may predominate, and occasionally occur alone, particularly in AL amyloidosis (Fig. 60.10D). Deposits may also affect the tubules and the interstitium, leading to atrophy and disappearance of the tubular structures and to interstitial fibrosis. In apolipoprotein AI amyloidosis related to the Leu160Pro variant, deposits markedly predominate in the interstitium, whereas glomeruli are not or are occasionally involved.[127]

Because of the heterogeneity of amyloidotic diseases, which results in specific diagnostic and therapeutic strategies adapted to the type of protein deposited within tissues, immunofluorescence examination of snap-frozen biopsy specimens with specific antisera should be routinely performed.[128–130] In the first series published by Gallo et al.,[129] immunohistochemical classification of amyloid type was possible for 44 (88%) of 50 patients using anti-LC and anti-AA antisera. However, Noel et al.[128] pointed out that immunofluorescence with sera directed against HCs and LCs of Ig might be more difficult to interpret than with anti-AA antiserum. This is likely due to the frequent loss of LC constant domains in fibrils, accounting for the absence of epitopes normally recognized by antibodies. It is also possible that the pseudocrystalline structure of the fibrils makes these epitopes poorly accessible to antibodies. In a more recent series, 12 of 34 patients (35.3%) with proven AL-amyloidosis had negative immunofluorescence staining for κ and λ light chains, which confirms the relatively low sensitivity of immunofluorescence microscopy in the detection of AL amyloidosis in the kidney and underscores the need to pursue additional diagnostic studies to identify the plasma cell dyscrasia.[131] A genetic cause should be sought in all patients with amyloidosis that is not the reactive systemic amyloid AA type and in whom confirmation of the AL type cannot be obtained. Indeed in 350 patients with systemic amyloidosis, in whom a diagnosis of the AL type of the disorder had been suggested by clinical and laboratory findings and by the absence of a family history, amyloid mutations were present in 34 cases, most often in the genes encoding fibrinogen A α-chain (18 patients) and transthyretin (13 patients).[130] A low-grade monoclonal gammopathy was detected in 8 of the 34 patients (24%), but none of these patients had free LC identified in the urine. When the nature of the amyloid deposits remains undetermined using conventional immunohistochemical methods, novel sensitive and specific techniques, such as laser microdissection of deposits followed by mass spectrometric-based proteomic analysis, should be used, as it allows accurate typing of amyloid in most cases.[132,133]
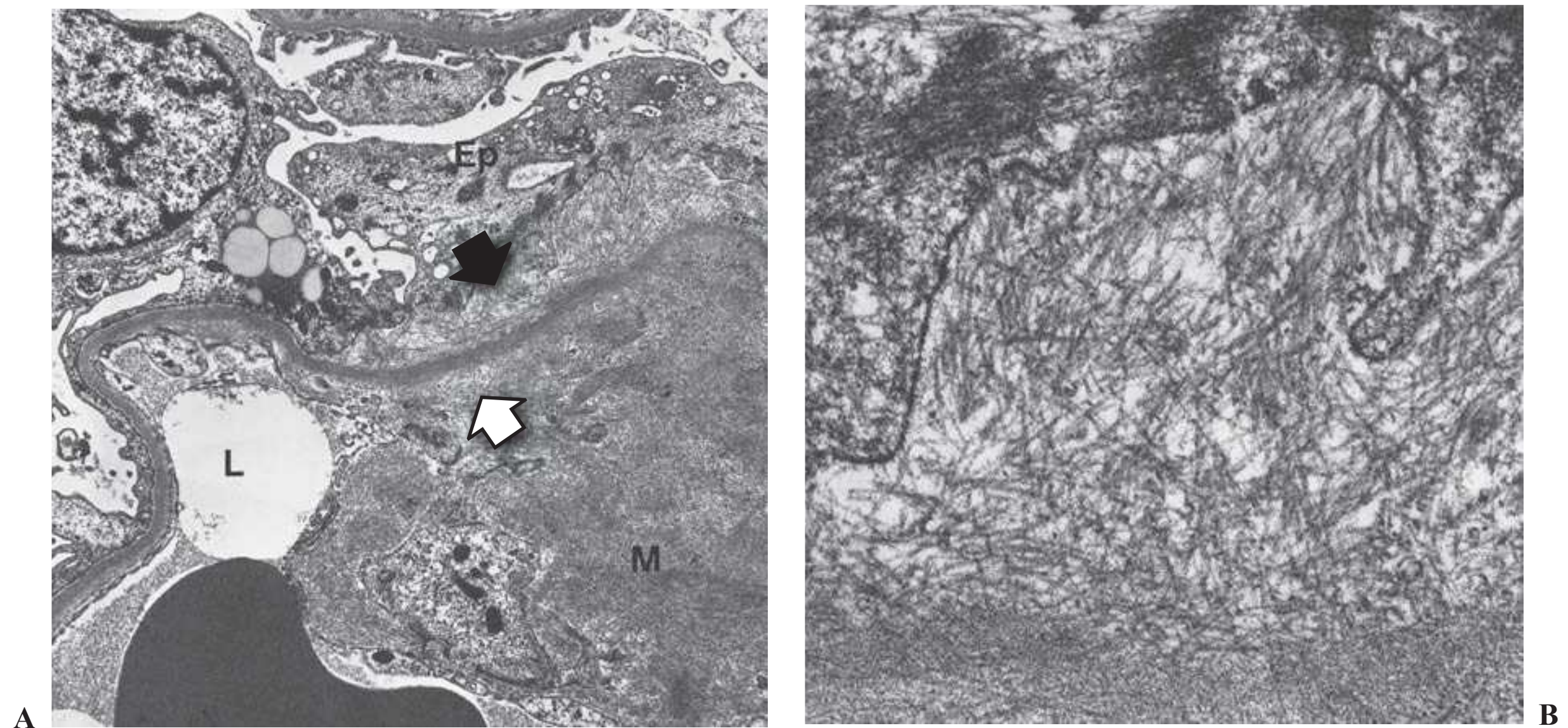
FIGURE 60.11 Amyloidosis. **A:** Electron micrograph of glomerular deposits of amyloid. Fibrils are seen in the basement membrane on both sides of the lamina densa (*arrows*). The lamina densa is attenuated. *Ep*, epithelium; *L*, capillary lumen; *M*, mesangium. (Magnification, ×5,000.) **B:** High magnification view of the randomly oriented fibrils on the epithelial aspect of the basement membrane. (Magnification, ×30,000.)

By electron microscopy, amyloid deposits are characterized by randomly oriented, nonbranching fibrils with an 8- to 10-nm diameter (Fig. 60.11). Early deposits can be found in close connection with mesangial cells that undergo important changes, and in the capillary walls distant from the mesangium on both sides of the basement membrane SAP has been found in all chemical types of amyloid thus far examined. In studies using double-label immunogold staining of AL and AA amyloid deposits, Yang and Gallo[134] showed that SAP represented 1.5% and 6.5% of the total gold label in AL and AA, respectively. SAP occurred as widely separated single units while the major fibril protein was labeled in single rows, similar to beads on a string. Immuno-electron microscopy can also be useful for the correct identification of amyloid fibril type in the fat tissue.[135]

Pathophysiologic Considerations of AL Amyloidosis

Studies on the mechanisms of AL amyloidogenesis are made particularly difficult by the unique degree of structural heterogeneity of the precursor. Each monoclonal LC is different from all others. An Ig LC typically includes two globular domains of 105 to 110 amino acids, strongly homologous to each other, that exhibit the classic conformation of all domains belonging to the "Ig superfamily" of proteins. The COOH-terminal domain (constant domain, C) is encoded by a single gene segment with very little allelic polymorphism in κ-chains and by no more than four different gene segments in λ-chains. Conversely, the NH2-terminal domain structure (variable domain, V) results from complex somatic rearrangement and mutation events

occurring in the course of B-cell differentiation, and leads to a high degree of diversity. The antiparallel β-pleated ("β-barrel") structure of Ig domains seems particularly adapted to amyloid formation. It is worth noting that another protein of the Ig superfamily, β_2-microglobulin, may form amyloid fibrils.

The implication of Ig HC in amyloidosis is exceptional. In the first case of AH amyloidosis almost entirely documented at the molecular level, the pathogenic IgG HC had an internal deletion of half the molecule, so that the V domain was directly joined to the COOH-terminal C domain C_H3, thus strikingly resembling an LC.[7] Other AH-amyloidosis cases related to deposition of IgA-related α-heavy chain,[136] or of V domains only,[137,138] or of γ3 heavy chain.[133] A case of γ-HC amyloidosis was also reported in a patient whose nephrotic syndrome recurred 6 years after autologous peripheral blood stem cell transplantation for a λ-LCDD.[139]

Not All Light Chains are Amyloidogenic

Despite predisposing conformation, a majority of Ig chains are not amyloidogenic, even at long-lasting high secretion rates. Several LC characteristics are considered amyloidogenic, particularly the LC isotype. First, the $\lambda-\kappa$ ratio is between 2:1 and 4:1, depending on the series. Second, a homology family of LC V region, the $V_{\lambda VI}$ variability subgroup, was shown to be overrepresented in AL amyloidosis.[17] This rare subgroup is expressed exclusively in amyloid-associated monoclonal Ig and represents 41% (17/41) of amyloidogenic λ-chains.[18] A study of 55 consecutive unselected cases of primary amyloidosis showed a very skewed repertoire, as only two germline genes belonging to the λIII and λVI

families, namely 3r (22% of cases, λIII) and 6a (20%, λVI), contributed equally to encode 42% of amyloid V_λ regions.[140] Furthermore, there was a significant correlation between the use of the $V_{\lambda VI}$ germline donor, IGLV6-57, and renal involvement[141,142] and that of the $V_{\lambda III}$ gene, IGLV3-1, with soft-tissue AL.[142] The use of a biased V_L gene repertoire also correlated with clinical outcome; the use of $V_{\lambda II}$ germline genes was associated with cardiac amyloidosis and affected survival adversely.[142] In contrast, no significant imbalance of the variability subgroups of κ-chains was found, but patients with κLCs were more likely to have dominant hepatic involvement.[141]

Empirical studies also show that amyloidogenicity is often associated with some physicochemical features such as the presence of low molecular mass LC fragments in the urine, and low pI; together with LC isotypy, these parameters allow the prediction of the amyloidogenic/nonamyloidogenic character of a monoclonal LC, with a correct allocation in 81% of tested cases.[143]

Comparison of Structures of Amyloid Light-Chain Precursors and Deposited Light Chains: A Role for Proteolysis?

After the demonstration by Glenner et al. that an LC was the predominant constituent of amyloid fibrils,[2] the possibility that a mutant form or a molecular variant of the soluble LC could be the amyloid precursor still remained, and only 20 years later the complete sequence identity between a circulating and a deposited LC was established.[144] Analyses of LC precursor primary structures were performed either at the protein or at the cDNA levels. All cases had an overall normal structure, including a normal C domain sequence.

The essential role of the V domain in fibrillogenesis is supported by analyses of fibrils extracted using adaptations of the method of Pras et al.,[114] which showed it to always be the main amyloid constituent. The C domain is often partially or totally absent from the fibrils after extraction. In a few cases, intact LC was present together with fragments; such heterogeneity might have been present but unrecognized in other cases. These results raise the hypothesis of a possible role of proteolysis, as already demonstrated in other forms of amyloidosis. Bellotti et al.[145] showed the disappearance of a conformational LC idiotope in the course of fibril formation, and suggested that polymerization results from the loss of the dimer conformation, possibly due to proteolysis of the C domain.

The question of a role of LC proteolysis in the amyloidogenic process has been addressed in different ways, but has not yet received a fully satisfactory answer. Abnormally low molecular mass LCs were secreted in in vitro biosynthesis experiments on bone marrow cells from AL amyloidosis subjects, but they might result from either abnormal synthesis or proteolytic processing, or both.[146,147] In vitro digestion experiments using pepsin, trypsin, and kidney lysosomes yielded fibrils resembling amyloid by electron microscopy and displaying typical Congo red binding and green polarization birefringence.[148] However, most tested LCs were from patients without amyloidosis, and the in vitro fibrils generally contained smaller fragments than those found in vivo. Another intriguing matter of all in vitro fibrillogenesis experiments is the absence of GAGs and SAP, which are invariable constituents in vivo. Although these studies contribute to the general understanding of the molecular mechanisms of fibril formation, their validity as models is questionable. In bone marrow cell culture from an AL amyloidosis patient, Durie et al.[149] found amyloidlike material immediately adjacent to macrophages, and concluded that a processing of the LCs by these cells, similar to that observed in AA amyloidosis, might lead to amyloid formation. Conversely, several observations point to the amyloidogenic potential of intact LCs; specifically, experimental mouse amyloid fibrils are made essentially of the entire injected human LC[150]; in vitro fibrils with characteristic properties of amyloid can be generated after simple reduction of the interchain disulfide bond of an intact LC dimer. Considering the sensitivity of C domains to proteases, it is conceivable that they are digested after constitution of the fibrils and tissue deposition, or during the purification process. Several recent studies have also highlighted a previously underestimated role for the LC constant domains in amyloid fibril formation, by initiating aggregation and providing a template for the V domain deposition.[151,152]

Amyloidogenic Light Chains: Light Chains with Peculiar Sequence or with Affinity for Extracellular (Matrix) Constituents?

The search for primary sequence peculiarities of the LC V domains first led to disappointing conclusions. Several unusual features such as N-glycosylations, insertion of acidic residues, and changes charged to hydrophobic residues have been noted. Infrequent amino acids at certain positions have been considered to affect the secondary structure of the framework regions or the LC dimerization. This led Stevens et al.[153] to determine amyloid-associated LC residues from the comparison of 52 pathogenic sequences with a bank of 128 other LCs. In a further report that collected 100 LCs of the $V\kappa I$ variability subgroup, including 37 amyloidosis cases, Stevens defined a limited number of structural risk factors, based on three sites of amino acid substitution and the occurrence of N-glycosylation.[154] A study with LC mutants bearing certain amino acids found in amyloidogenic precursors suggested that an unfolding step facilitated by these substitutions could be required for fibril formation[155]; however, the in vitro conditions were clearly nonphysiologic, and such models with single replacements have an essentially theoretical interest. Mutations in specific structural regions of LCs seem to be associated with free LC levels and amyloidogenic propensity.[156]

Environmental factors may also play some role. For example, the kidney contains high concentrations of urea that were shown to enhance fibril formation by reducing the

nucleation lag time.[157] The same LC can assemble into fibrils or form granular aggregates upon exposure to various environmental conditions.[158]

One AL amyloidosis-associated LC, protein Mcg, has been extensively studied at the three-dimensional level by X-ray crystallography.[159] The dimer Mcg is strikingly "normal" and similar to other known mouse and human LCs and antigen-binding (Fab) fragments. The combination of hypervariable regions (CDRs) from both monomers mimics a normal antigen-binding site with affinities toward haptenlike compounds such as dinitrophenyl (DNP)-lysine and opioid peptides.[160] The number of contact residues and consequent binding affinity are decreased after reduction of the disulfide bond between COOH-terminal cysteinyls of the C domains.[161] Because DNP-lysine can bind specifically amyloidogenic dimers, it is possible that covalent binding between LCs influences their pathogenicity. The hypothesis that specific recognition by amyloidogenic LCs plays a pathogenic role is enforced by the demonstration of their higher dimerization constants,[162] and by the finding of high rates of somatic mutations clustered in the CDRs, suggesting antigen-driven selection.[163,164] Specific affinity of an LC toward an extracellular structure might create a nucleus that could lead to elongation of a fibril, in accordance with proposed mechanisms of other forms of amyloidogenesis.

Mechanisms of Tissue Injury

Tissue injury is mostly the consequence of extensive deposition of amyloid. However, at least in some tissues such as the heart, the infiltration alone did not correlate well with the degree of heart failure or survival. Infusion of LCs from patients with cardiac amyloidosis caused diastolic dysfunction in isolated mouse hearts.[165] Amyloid LC proteins isolated from patients with amyloid cardiomyopathy specifically provoke oxidative stress, cellular dysfunction, and apoptosis in isolated adult cardiomyocytes through activation of p38 mitogen-activated protein kinase (MAPK).[166,167] Amyloid LCs may thus contribute directly to the pathogenesis of amyloid cardiomyopathy, independent of extracellular fibril deposition. This is illustrated by the dramatic improvement in cardiac symptoms, with pararallel decrease in serum levels of sensitive markers of amyloid heart disease (NT-proBNP and troponin) whereas cardiac deposits are unchanged, that is sometimes observed after clonal response to chemotherapy. Along the same line, LCs from AL amyloid patients incubated with cultured human mesangial cells induced a macrophage-like phenotype, whereas those from LCDD patients induced a myofibroblastic phenotypic transformation.[168]

Epidemiology and Clinical Features of AL Amyloidosis

Epidemiology

The incidence of primary AL amyloidosis in the United States is 9 per million per year and has remained stable during the last four decades.[169] The male-to-female ratio varies from 1 to 2 according to series.[170–172] The median age at diagnosis is between 60 and 65 years. About two thirds of patients are between 50 and 70 years of age at diagnosis, and only 1% to 4% are younger than age 40 years.[171,173]

Amyloid deposits are found in approximately 10% of myeloma cases,[22] and this incidence reaches 20% in patients with pure LC myeloma. The high frequency of amyloidosis associated with myeloma (56%) in Alexanian's series[174] was attributed to the referral of more myeloma patients for chemotherapy to the authors' institution. Conversely, a minority (probably less than one of four) of patients with AL amyloidosis are considered to bear a patent immunoproliferative disease, which usually is a multiple myeloma, although other forms such as Waldenström macroglobulinemia and non-Hodgkin lymphoma[160] may occur. AL amyloidosis without overt immunoproliferative disease is usually referred to as primary amyloidosis. If multiple myeloma is not present at the diagnosis of AL amyloidosis, it is unlikely to develop.

Clinical and Laboratory Features of AL Amyloidosis

In a series of 474 patients with biopsy-proved amyloidosis, 99% of the patients were 40 years of age or older; 69% were men and 31% were women. Seventy-one patients (15%) had a myeloma. Two hundred and nineteen (56%) of 391 patients had an increased number ($\geq$6%) of plasma cells in the bone marrow.[173]

The clinical and laboratory features at presentation and at diagnosis are summarized in Tables 60.8 and 60.9.[173,176] The main clinical symptoms at presentation are weakness and weight loss. Except for bone pain, there is no difference in the incidence of initial symptoms in patients with and without myeloma. Nephrotic syndrome, orthostatic hypotension, and peripheral neuropathy are, however, more common at diagnosis in patients with AL amyloidosis without myeloma than in those with associated myeloma (Table 60.9).

Proteinuria mainly composed of albumin is noted in 55% of the patients, indicating that glomerular involvement is a common feature of AL amyloidosis. There is a poor correlation between the extent of amyloid deposits seen on a kidney biopsy specimen and the extent of proteinuria. Even small amyloid deposits have been associated with severe nephrotic syndrome.[177] Microscopic hematuria is an exception, and, therefore, should prompt the search of a bleeding lesion of the urinary tract. Renal manifestations may also include renal tubular acidosis (mostly as a part of Fanconi syndrome) and polyuria-polydipsia (resulting from urinary concentration defect), when amyloid deposits occur around proximal tubules and Henle's loops or collecting ducts, respectively. High urinary protein excretion and high serum creatinine at diagnosis are pejorative renal predictors.[178,179] Renal insufficiency occurs usually in the presence of marked kidney enlargement and is usually not associated with hypertension.

Restrictive cardiomyopathy is found at presentation in up to one third of patients and causes death in about half.

60.8	**Clinical and Laboratory Features at Presentation in 474 Patients with Proven AL Amyloidosis**

Initial Symptoms	
Fatigue	62%
Weight loss	52%
Pain	5%
Purpura	15%
Gross bleeding	3%
Physical Findings[a]	
Palpable liver	24%
Palpable spleen	5%
Lymphadenopathy	3%
Macroglossia	9%
Laboratory Findings	
Increased plasma cells (bone marrow $\geq$6%)	56%
Anemia (hemoglobin <10 g/dL)	11%
Elevated serum creatinine ($\geq$1.3 mg/dL)	45%
Elevated alkaline phosphatase	26%
Hypercalcemia (>11 mg/dL)	2%
Proteinuria ($\geq$1.0 g/24 hours)	55%
Urine light chain	73%[b]
κ chain	23%
λ chain	50%

[a]A comparison of the prevalence of clinical syndromes according to the presence or the absence of myeloma is given in Table 60.10.
[b]Of 429 patients. All other figures refer to all 474 cases.
Data from Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol. 1995;32:45.

Characteristic features of amyloid on ECG include low voltages and a pattern suggestive of myocardial infarction without evidence of ischemic damage on echocardiography. Infiltration of the ventricular walls and the septum may be recognized by echocardiography. The ejection fraction is frequently normal or even increased. Doppler flow studies are required to identify diastolic dysfunction frequently missed in routine studies. Amyloid may also induce dysrhythmias and the sick sinus syndrome. Amyloid deposits in the coronary arteries may result in angina pectoris and myocardial infarction. Blood levels of cardiac troponins (including high-sensitivity cardiac troponin T) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are sensitive markers of myocardial dysfunction and powerful predictors of overall survival in patients with AL amyloidosis.[180–184]

Involvement of the gastrointestinal tract is also common and can cause motility disturbances, malabsorption, hemorrhage, or obstruction. Macroglossia occurs in about one fifth of these patients. It may interfere with eating and obstruct airways. Hepatomegaly occurs initially in one third of the patients, but abnormalities of hepatic function remain generally mild. Hyposplenism, usually associated with splenomegaly, is occasionally found. Peripheral neuropathy occurs in one fifth of cases and is usually responsible for a painful sensory polyneuropathy followed later by motor deficits. Autonomic neuropathy causing orthostatic hypotension, lack of sweating, gastrointestinal disturbances, bladder dysfunction, and impotence may occur alone or together with peripheral neuropathy. Orthostatic hypotension is one of the major hampering complications of AL amyloidosis, causing some patients to be bedridden. Skin involvement may take the form of purpura, characteristically around the eyes, as well as ecchymoses, papules, nodules, and plaques, usually on the face and upper trunk. AL amyloidosis may also infiltrate articular structures and mimic rheumatoid or an asymmetric seronegative synovitis. Infiltration of the shoulders may produce severe pain and swelling ("shoulder-pad" sign). A rare but potentially serious manifestation of AL amyloidosis is an acquired bleeding diathesis that may be associated with deficiency of factor X and sometimes also factor IX, or with increased fibrinolysis.[185] It should be systematically sought before any biopsy of a deep organ. Actually, AL amyloidosis may infiltrate almost any organ other than the brain and thus be responsible for a wide variety of clinical manifestations.

On average, monoclonal LCs can be detected by immunoelectrophoresis in 73% of the urine samples, and the λ-isotype is twice as common as the κ-isotype, contrasting with the 1:2 λ-to-κ ratio observed in patients with multiple

60.9	**Syndromes at Diagnosis in 229 Patients with Proven AL Amyloidosis**	
Syndromes	**Without Myeloma (182 patients)**	**With Myeloma (47 patients)**
Nephrotic syndrome	37%	13%
Carpal tunnel syndrome	21%	38%
Congestive heart failure	23%	23%
Peripheral neuropathy	20%	6%
Orthostatic hypotension	16%	4%

Data from Kyle RA, Greipp PR. Amyloidosis (AL): clinical and laboratory features in 229 cases. Mayo Clin Proc. 1983;58:665.

myeloma alone. With the use of more sensitive immuno-chemical techniques, a serum and/or urine monoclonal Ig and/or a dysbalanced concentration of serum free LCs is found in more than 90% of patients.[186,187] It is, however, worth noting that, even under such conditions, there is no detectable monoclonal Ig in the serum and urine of some patients.

"Primary" Amyloidosis: A True Plasma Cell Dyscrasia

It is now well established that "primary" amyloidosis (i.e., AL amyloidosis without myeloma) is a true plasma cell dyscrasia. This concept, introduced by Osserman et al.,[188] was elegantly confirmed by immunofluorescence and biosynthetic studies of bone marrow cells. Preud'homme et al.[146] identified, by immunofluorescence, monoclonal plasma cell populations in 12 of 14 patients with "primary" amyloidosis, even in those without detectable serum and urine monoclonal Ig and with a normal percentage of bone marrow plasma cells. Moreover, the synthesis and excretion of large amounts of free monoclonal LCs by plasma cells were demonstrated in every patient studied by Buxbaum[147] and Preud'homme et al.,[146] together with the presence of LC fragments in almost all patients. This contrasted with nonmyelomatous secondary amyloidosis, which was characterized by normal distribution of bone marrow plasma cells by immunofluorescence and by synthesis of normal-sized Ig, without free LC secretion and fragments.[146]

From a pathophysiologic point of view, myeloma-associated and "primary" AL amyloidoses represent two ends of a single entity. The intrinsic pathogenicity of the precursor free LC is probably highly variable from one patient to another, so that expression of the disease occurs in the context of very different tumor masses and LC secretion rate. AL amyloidosis is typical of these forms of plasma cell dyscrasias in which malignancy is conferred by the pathogenic LC rather than the underlying hematologic disease.

Diagnostic Procedures in AL Amyloidosis

AL amyloidosis should be considered in any patient who presents with nephrotic range proteinuria with or without renal insufficiency, nondilated cardiomyopathy, peripheral neuropathy, hepatomegaly, or autonomic neuropathy, whether or not a paraprotein can be detected in the serum or urine. Particular vigilance should be maintained in patients with multiple myeloma or MGUS, especially of the λ isotype. Initial investigation should confirm the diagnosis of amyloidosis on tissue biopsy and this should be followed by investigations to establish the type of amyloid present and the extent of organ involvement.

All patients require immunofixation of serum and urine in an attempt to demonstrate the presence of a monoclonal LC. A bone marrow specimen is necessary because 10% of patients will not have a demonstrable monoclonal LC by immunofixation, and a clone of plasma cells detected in the bone marrow by immunofluorescence or immunohistochemistry

is strong supportive evidence of AL. Immunonephelometric quantitation of free LCs is a useful complement to immunofixation, because it shows remarkable specificity and sensitivity. The assay gives a positive result (raised level of either κ or λ together with an altered ratio of free κ to free λ LC) in >90% of patients with systemic AL amyloidosis.[187,189]

Histologic diagnosis may be achieved by biopsies of various tissues. Biopsy of an affected organ is usually diagnostic, but less invasive alternatives should be preferred first. As indicated in Table 60.10, the less invasive procedures yield positive results in up to 90% of cases.[173,190] Rectal biopsy is diagnostic in greater than 80% of cases, provided that the biopsy specimen contains submucosal vessels in which early deposits are located. Bone marrow biopsy should also be stained with Congo red for the presence of amyloid, and involvement of the bone marrow is strongly suggestive of the AL type. Evaluation of adequate specimens in experienced laboratories is necessary to maintain high diagnostic sensitivity and specificity. Both false-positive and false-negative interpretations are not uncommon.

60.10	Diagnostic Yield of Biopsies in 100 Patients with AL Amyloidosis According to the Site of Biopsy	
Site of Biopsy	**No. Tested**	**Sensitivity of the Diagnostic Procedure**
Bone marrow	44	52.3
Gingiva	6	83.3
Rectal mucosa	21	85.7
Small bowel	8	87.5
Subcutaneous abdominal fat	97	88.7
Kidney[a]	21	100
Heart[a]	14	100
Liver[a]	11	100
Skin[a]	3	100
Nerve[a]	2	100
All other	22	

[a]Organ biopsy was performed because of clinical manifestations.
Data from Skinner M, Anderson J, Simms R, et al. Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. Am J Med. 1996;100:290.

It is not always easy to be certain that amyloidosis is of the AL type because immunohistochemical staining for Ig LCs is not fully reliable, and the presence of a monoclonal component is strong but not conclusive evidence of AL. Caution is required when patients have an intact monoclonal Ig in the serum without evidence of circulating free LCs in the serum or in the urine. In those cases, hereditary forms of amyloidosis should be considered because they may produce clinical syndromes indistinguishable from AL and coexist with MGUS.[130] In cases of doubt, DNA analysis and/or amyloid fibril typing by mass spectrometric-based analysis may be necessary. Imaging using SAP scanning may be helpful in demonstrating bone marrow involvement.

A consensus panel has established criteria that define organ involvement, organ response, and organ disease progression (Table 60.11).[191] Particularly, elevation of NT-proBNP,[181] and cardiac troponins[180] are markers of myocardial dysfunction in AL amyloidosis that strongly correlate

		60.11	Criteria for Organ Involvement, Organ Response, and Organ Disease Progression in Patients with AL Amyloidosis	

	Organ Involvement	Organ Response	Organ Disease Progression
Kidney	24-hour urine protein >0.5 g, predominantly albumin	50% decrease (at least 0.5 g/day) of 24-hour urine protein (urine protein must be >0.5 g/day pretreatment); in the absence of a reduction in eGFR ≥25% and an increase in serum creatinine ≥0.5 mg/dL (2010 consensus opinion)	50% increase (at least 1 g/day) of urine protein to greater than 1 g/day
Heart	Echo: mean wall thickness >12 mm, no other cardiac cause; or an elevated (> 332 ng/L) concentration of NT-proBNP in the absence of renal failure or atrial fibrillation (2010 consensus opinion)	Mean interventricular septal thickness decreased by 2 mm, 20% improvement in ejection fraction, improvement by two NYHA[a] classes without an increase in diuretic use, or improvement by one NYHA class associated with a 50% reduction in diuretic requirements and no increase in wall thickness; reduction (≥30% and ≥300 ng/L) of NT-proBNP concentration (2010 consensus opinion)	Interventricular septal thickness increased by 2 mm, increase in NYHA class by 1 grade with a decreasing ejection fraction of ≥10%
Liver	Total liver span >15 cm in the absence of heart failure or alkaline phosphatase >1.5 times upper limit of normal	50% decrease in abnormal alkaline phosphatase, decrease in liver size radiographically of at least 2 cm	50% increase of alkaline phosphatase above the lowest value
Nerve	P[b] (clinical): symmetric lower extremity sensorimotor neuropathy	Improvement in electromyogram nerve conduction velocity (rare)	Progressive neuropathy by electromyography or nerve conduction velocity
	A[c]: gastric-emptying disorder, pseudo-obstruction, voiding dysfunction		

[a]NYHA: New York Heart Association.
[b]P: peripheral.
[c]A: autonomic.
[d]Not related to direct organ infiltration.
Data from Gertz M, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in primary systemic amyloidosis AL. Am J Hematol. 2005;79:319.

with prognosis and should be used for risk assessment staging.[182] A new consensus panel has recently updated these criteria: an elevated concentration of NT-proBNP in the absence of renal failure or atrial fibrillation, or a mean left ventricular wall thickness >12 mm by echocardiography provide criteria for cardiac involvement.[192]

Outcome and Treatment of AL Amyloidosis

"Natural" History and Markers of Prognosis

AL amyloidosis is among the most severe complications of plasma cell proliferative disorders, with a median survival of only 12 months in patients not treated or with refractory disease.[173] The natural history varies with the extent and nature of organ involvement (Table 60.12). Heart involvement is a main predictive factor of prognosis that represents more than 30% of all causes of death and is associated with a median survival of less than 6 months in patients with symptomatic heart failure.[193,194] Cardiac troponins, B natriuretic peptide (BNP), or its N-terminal fraction (NT-proBNP) have all been recognized as reliable prognostic markers in AL amyloidosis. A prognostic score based on the serum levels of troponin T and NT-proBNP has been proposed, with three stages defined by normal serum levels of troponin T and NT-proBNP (stage 1), increased level in one marker level (stage 2), or in

60.12	Prognostic Factors in Patients with AL Amyloidosis

Pejorative Prognostic Indicators
   Symptomatic or substantial echocardiographic
      evidence of cardiac amyloid (median survival of
      about 6 months)
   Autonomic neuropathy
   Liver involvement with hyperbilirubinemia
   Associated multiple myeloma
   A large whole-body amyloid load on SAP
      scintigraphy and evidence of accumulation of
      amyloid on serial SAP scans when available

Better Prognostic Indicators
   Proteinuria or peripheral neuropathy (without
      autonomic neuropathy) as the dominant clinical
      feature
   Substantial suppression of underlying clonal disease
      by chemotherapy
   Decrease in serum troponin and NT-proBNP levels
   Regression of amyloid deposits on serial SAP
      scintigraphy when available

Adapted from guidelines Working Group of UK Myeloma Forum; British Committee for Standards in Haematology, British Society for Haematology. Guidelines on the diagnosis and management of AL amyloidosis. Br J Haematol. 2004;125:681.

both (stage 3).[182] The rapid achievement of hematologic response (i.e., a 50% or more reduction in serum free LC levels) is a key determinant of prognosis in AL amyloidosis,[130] particularly when serum NT-proBNP levels decrease simultaneously.[196] Recent studies suggest that treatment should aim at obtaining normal serum free LC levels and kappa/lambda ratio to improve overall and renal survival.[172,197]

Monitoring AL Amyloidosis and Assessing Response

As tissue catabolism of amyloid fibrils is a slow process, results of chemotherapy in amyloidosis may be difficult to document clinically, because organ response is often delayed after the achievement of hematologic response. Scintigraphy after the injection of ^{123}I-labeled SAP component is helpful for monitoring the extent of systemic amyloidosis,[122,189] but this technique is not readily available. Therefore, the goal of treatment in AL amyloidosis is to rapidly and efficiently suppress the underlying plasma cell, lymphoplasmacytic, or lymphoproliferative disorder that is responsible for the secretion of the amyloid precursor. As the assessment of treatment efficacy is primarily based on the evaluation of hematologic response,[191] routine measurements of serum free LC levels and markers of cardiac disease are mandatory to evaluate the effects of treatment and to rapidly modify chemotherapy if required. New criteria for hematologic response have been proposed in 2010, based on the evaluation of the difference between involved and uninvolved FLC (dFLC), the measurable absolute concentration of the involved FLC being defined by a dFLC >50 mg per L. A complete hematologic response is defined by negativity of serum and urine for a monoclonal protein by immunofixation, with normal serum free LC ratio, and less than 5% plasma cells in the bone marrow. Partial and very good partial responses are defined by a ≥50% decrease in dFLC, and by a dFLC <40 mg per L, respectively.[192] Criteria for organ response and organ disease progression are depicted in Table 60.11.

Principles of Treatment

As therapy is aimed at annihilating the plasma cell clone, all treatment strategies which have shown efficiency in multiple myeloma or in lymphoproliferative disorders can be used in AL amyloidosis, providing that they are adapted to the type of the causal hematologic disease, to the nature and number of affected organs, and bearing in mind their potential toxicity. Supportive measures to preserve organ function are essential adjuncts to therapy.

Chemotherapy and High-Dose Therapy with Stem Cell Support

MP (melphalan and prednisone) has been used for years as first-line therapy in AL amyloidosis (Table 60.13). In the 1990s two randomized controlled clinical trials showed that MP was superior to colchicine alone in terms of response and survival. However, the beneficial effect was limited, with a

60.13	Outcome in Previously Untreated AL Amyloidosis					
Regimen	Series	No. of Patients	Response (% all patients)[a]	TRM[b]	Overall Survival (Median)	Comments
MP	Kyle et al.[193]	77	28	Not reported	18 months	Risk of MDS
	Gertz et al.[198]	52	27	Not reported	29 months	
VAD	Lachmann et al.[199]	98	54 (63% of evaluable)	7%	50 months (projected)	Selected patients
IDM	Lachmann et al.[199]	33	46	18%	Not reached	Poor risk group
M-Dex	Palladini et al.[200]	46	67	None	Not reached	Patients ineligible for PBSCT
	Jaccard et al.[201]	50	68 (ITT: 52%)	2%	56.9 months	Selected patients
PBSCT	Comenzo and Gertz[202]	148	39 (62% of evaluable)	21%–39%	60%–70% at 1 year	Selected patients
	Skinner et al.[203]	312	40	13%	54 months	Selected patients
	Jaccard et al.[201]	50	67 (ITT: 36%)	19%	22.2 months	Selected patients

[a]Response criteria have varied but generally include response of either plasma cell dyscrasia and/or organ dysfunction.
[b]Treatment-related mortality (TRM) is defined as death during treatment or within 100 days from completing treatment. Note that the reported TRM in PBSCT studies did not include deaths during mobilization and reinfusion of peripheral blood progenitor cells.
[c]21% average of four single center studies; 39% average of two multicenter studies.
IDM, intermediate dose melphalan; ITT, intent to treat; MDS, myelodysplastic syndrome; M-HDD, melphalan and high-dose pulsed dexamethasone; MP, melphalan and prednisone; PBSCT, peripheral blood stem cell transplantation; VAD, vincristine, Adriamycin, dexamethasone.
Adapted from guidelines Working Group of UK Myeloma Forum; British Committee for Standards in Haematology, British Society for Haematology. Guidelines on the diagnosis and management of AL amyloidosis. Br J Haematol. 2004;125:681.

median overall survival of 18 months, compared to 12 months in patients who received no treatment or colchicine therapy alone. The poor efficacy of MP is related to a hematologic response rate of less than 30%, with a median time to response of about 12 months, far too long in patients with severe disease, particularly in those with heart involvement.

In the past 10 years, tremendous advances have been made in the treatment of AL amyloidosis. They have consisted of three major steps.

High-Dose Chemotherapy with Stem Cell Support. Ray Comenzo and colleagues first demonstrated the feasibility and efficacy of high-dose mephalan followed by ASCT (Table 60.13).[204,205] The protocol includes a step of stem cell collection after mobilization through injections of G-CSF-type growth factor, followed by high-dose melphalan of 100 to 200 mg per m^2, depending on the patient's age and disease extension. In highly experienced centers, this strategy results in a hematologic response (defined by a ≥50%

reduction in sFLCs) rate of more than 60%, including 40% complete responses (CR) (defined by the absence of detectable monoclonal Ig with normal sFLCs and kappa/lambda ratio) and a median survival around 4.5 years.[203] However, the toxicity of ASCT is such that only certain patients benefit. The 100-day TRM is substantially higher among patients with AL amyloid than among those with multiple myeloma: it initially comprised between 13% and 39% mortality[202,203,206–208] and now approaches 10% even in the largest centers after careful patient selection.[209] ASCT is not recommended in patients with any of the following: age older than 70 years; symptomatic cardiac amyloid; symptomatic autonomic neuropathy; history of gastrointestinal bleeding due to amyloid; dialysis-dependent renal failure; and more than two organ systems involved.[171] In highly selected patients, the benefits of high-dose therapy with ASCT over conventional treatment are questionable. Dispenzieri et al.[210] examined data from patients with AL amyloid treated at the Mayo Clinic from 1983 to 1997, and identified 229 patients

who would now have been eligible for ASCT based on age younger than 70 years and well-preserved cardiac, renal, and hepatic function. At a median follow-up of 52 months, their median survival was 42 months and 5- and 10-year survival rates were 36% and 15%, respectively. Although more than 50 studies have confirmed its efficacy over the last 10 years, ASCT in AL amyloidosis remains restricted to selected patients as previously defined.

High-Dose Dexamethasone-Based Chemotherapy. In parallel, several investigators have shown the efficacy of high-dose dexamethasone-based regimens at inducing hematologic responses and prolonging survival. Unexpected efficacy, close to that of ASCT, was obtained with the vincristine-Adriamycin-dexamethasone (VAD) and melphalan dexamethasone (MDex) regimens (Table 60.13).[189,200] MDex consists of melphalan 10 mg/m^2/day and dexamethasone 40 mg per day, 4 days per month for 6 to 12 months. MDex, which needs to be dose-adapted according to GFR and age, is more rapidly effective than the MP regimen, allowing a 60% hematologic response rate, including 25% CR and clinical responses among 50% of patients.[200] In 2007, a French multicenter randomized prospective trial showed that, compared to ASCT, MDex had similar efficacy with less toxicity, resulting in better survival (56.9 vs. 22.2 months).[201] The place of ASCT is currently debated, and to date, there is no evidence that ASCT is superior to conventional chemotherapy in improving overall survival in AL amyloidosis. Due to a low toxicity profile, with a TRM between 2% and 7%, dexamethasone-based regimens may be used even in patients with advanced disease. However, among patients with advanced amyloid cardiomyopathy, mortality remains substantial and alternative strategies are required.

Novel Antimyeloma Agents. Recently, several preliminary studies have shown encouraging results with newer antimyeloma drugs such as thalidomide, lenalidomide, and the proteasome inhibitor bortezomib. Combined with dexamethasone, these agents induce rapid hematologic responses in most patients, even in those with refractory or relapsing disease. The cyclophosphamide, thalidomide, and dexamethasone regimen appears to produce similar results as MDex alone,[211] whereas the combination of MDex with lenalidomide slightly increases hematologic response rates.[212] A striking difference has been observed with the introduction of bortezomib, which results in clonal response rates of 70% tp 90%, including around 40% of CR. Furthermore, the bortezomib plus dexamethasone regimen has shown remarkable efficacy in previously treated patients with refractory disease. These high hematologic response rates are achieved with manageable toxicity and within a relatively short time span.[213–216] In a recent phase II study, MDex plus bortezomib induced a 94% hematologic response rate, with 60% CR.[217] This combination will soon be compared to MDex in an international randomized trial. Bortezomib has to be used with caution in patients with advanced amyloid heart disease, who may occasionally develop abrupt reduction in left ventricular ejection fraction. Nevertheless, due to their superior tolerability and efficacy compared to ASCT and MDex, bortezomib-based regimens will probably become first-line therapy in systemic AL amyloidosis in the near future.

Treatment of AL Amyloidosis with Underlying Lymphoplasmacytic Proliferation

In patients with underlying lymphoplasmacytic proliferation (usually associated with an IgM monoclonal gammopathy), treatment regimens should be similar to those used in Waldenström disease (i.e., based on rituximab combined with fludarabine-cyclophosphamide) or dexamethasone plus cyclophosphamide or bortezomib.[218] Intensive therapy with high dose of melphalan followed by autologous stem cell transplantation also appears to be effective.[219]

Renal Supportive Care and Kidney Transplantation

Organ function in amyloid is precarious, and renal or cardiac failure is easily precipitated, even in individuals with apparently normal organ function by factors such as intravascular fluid depletion or intercurrent infection.

End-stage renal disease occurs in 13% to 40% of patients with AL amyloidosis,[172,219,220] after a median time that has progressed from 14 months[95,221] to about 30 months over the past 20 years,[172,220] with improved treatment strategies. Impaired renal function, and, in some series, proteinuria above 2 g per day at diagnosis, are predictive of poor renal outcome.[220–222] Above all, the achievement of hematologic response is the main factor that influences renal prognosis. In a cohort of 36 patients requiring dialysis, median time to end-stage renal disease was 6.9 months in those who did not achieve a clonal response, versus 92 months in responders.[220] The depth of clonal response also influences renal outcome: in a series of 923 patients with renal AL amyloidosis, achieving more than 90% FLC response at 6 months was associated with a fourfold increase in the chance of renal response (P < 0.001) and a 68% reduction in the risk of renal progression (P < 0.001).[172]

Median survival in patients on chronic dialysis has also progressed from 8 to 10 months to 26 to 39 months in recent series.[172,222] The survival rate of patients treated with chronic ambulatory peritoneal dialysis (CAPD) is similar to that of patients on hemodialysis.

Cardiac amyloid is the most important predictor of poor survival in patients with AL amyloidosis undergoing dialysis, and cardiac deaths represent the main cause of mortality in such patients.[220–222] Congestive heart failure, atrioventricular or intraventricular conduction defects, and dysrhythmias due to amyloid myocardial involvement often occur. The management of patients with AL amyloid on hemodialysis is also often complicated by permanent hypotension, gastrointestinal hemorrhage, chronic diarrhea, and difficulties in the creation and maintenance of vascular accesses. It has, therefore, been suggested that CAPD could have several advantages over hemodialysis in the management of end-stage renal amyloidosis, including avoiding vascular access and deleterious ef-

fect on blood pressure; however, CAPD may induce protein loss in the dialysate fluid and thereby enhance malnutrition.

AL amyloidosis is usually considered a relative contraindication to renal transplantation, even among patients with isolated renal involvement, due to organ shortage and the lack of effective therapy to prevent disease recurrence in the allograft and/or progressive extrarenal amyloidosis. The same limitations were also applied to cardiac transplantation in patients with dominant cardiac disease. Furthermore, risk of death from infectious complications of kidney transplantation was reportedly high.[223] As survival of patients on chronic dialysis has progressively improved in recent years, an increasing number of patients are candidates for kidney transplantation. Recent studies suggest that renal transplantation may be a valid option in patients with limited extrarenal manifestations, and whose underlying clonal plasma cell disease has remitted following chemotherapy. In a series of 22 renal transplant recipients with AL amyloidosis, 1- and 5-year patient survival was 95% and 67%, respectively. Nineteen patients had received chemotherapy or ASCT before renal transplantation, which induced clonal response in 14 of 15 evaluable patients. No transplant failed due to amyloid recurrence, despite evidence of amyloid within the allografts of five patients.[224] In another recent study of 19 patients, 11 underwent renal transplantation after a hematologic response had been achieved either with ASCT (six patients) or conventional chemotherapy (mostly MDex-based, five cases). In the remaining patients kidney transplantation was performed prior to ASCT. Twelve patients had limited extrarenal disease, including heart involvement in nine. Hematologic treatment resulted in clonal CR in all but one patient. After a median follow-up time of 41.4 months, 15 patients (79%) were alive. Recurrence of LC amyloid deposits on the renal allograft occurred in two cases. All allograft losses were the result of patient death, mainly related to infectious or cardiovascular events.[225] New drugs, particularly bortezomib, which are effective and well tolerated in patients with ESRD, will probably enable more patients with AL amyloidosis to be eligible for solid organ transplantation by inducing deep and sustained hematologic responses.

Epidemiology and Specific Features of AA Amyloidosis

Although AA amyloidosis does not involve deposition of Ig fragments and thus should not be classified within the group of monoclonal gammopathies, it shares with AL amyloidosis pathogenetic pathways, high prevalence of renal involvement, and some therapeutic aspects that deserve further consideration.

AA amyloidosis develops in 5% of patients with sustained elevation of serum amyloid A protein (SAA). Patients at risk are those with long duration of chronic inflammatory disease (median, about 10 years), high magnitude of acute phase SAA response, homozygosity for SAA1 isotype, familial Mediterranean fever (FMF) trait (heterozygosity for variant pyrin), and family history of AA amyloidosis (50% risk).

An important epidemiologic aspect of AA amyloidosis is the changing spectrum of underlying diseases (Table 60.14).

TABLE 60.14	Changing Spectrum of Underlying Diseases in Secondary AA Amyloidosis[a]						
	Dahlin[226] (n = 30)	Brownstein et al.[227] (n = 100)	Browning et al.[228] (n = 60)	Gertz and Kyle[229] (n = 64)	Joss et al.[230] (n = 43)	Gillmore et al.[231] (n = 80)	Lachmann et al.[232] (n = 374)
Rheumatic disease	2 (7)	15 (15)	55 (73)	42 (66)	30 (70)	60 (60)	224 (60)
Granulomatous infection (tuberculosis, fungus, leprosy)	9 (30)	28 (28)	8 (11)	0	6 (14)	0	3 (1)
Pyogenic infection	10 (33)	35 (35)	5 (7)	11 (17)	0	7 (9)	53 (14)
Inflammatory bowel disease	2 (7)	4 (4)	3 (4)	6 (9)	1 (2)	2 (3)	17 (4)
Malignancy/Castleman	7 (23)	18 (18)	3 (4)	2 (3)	1 (2)	2 (3)	11 (3)
Other[b]	—	—	2 (3)	3 (5)	5 (12)	9 (11)	34 (9)

[a]Data are number of patients (percentage).
[b]Including hereditary recurrent fevers and unknown.

Pyogenic and granulomatous infections, especially tuberculosis, account for far fewer cases than in the older series. This is because of the efficacy of antibiotic treatments for bacteria, which shows that amyloidosis can be efficiently prevented when its cause is suppressed. In contrast, the prevalence of amyloid linked to autoimmune inflammatory diseases, such as rheumatoid arthritis and juvenile chronic arthritis, has increased dramatically, reaching 60% in the largest series published to date.[232] AA amyloidosis in patients with Hodgkin disease has virtually disappeared with more efficient treatment of the hematologic disease. In contrast, hereditary AA amyloidoses associated with familial recurrent fever syndromes are claiming an increasing portion of about 10% of cases in recent series.

There are a number of clinical manifestations of AA amyloidosis (Table 60.15).[228,229] The main target organ by far is the kidney, affected in almost all patients with AA amyloidosis. Renal dysfunction may be acute with nephrotic syndrome, or very insidious. Proteinuria is absent in about 5% of cases. Gastrointestinal disturbances (including diarrhea, constipation, and malabsorption) and hepatosplenomegaly are the most common after kidney manifestations. In contrast with AL amyloidosis, congestive heart failure, peripheral neuropathy, macroglossia, and carpal tunnel syndrome occur in less than 10% of patients. Peripheral or autonomic neuropathy is rare, as well as involvement of adrenal glands and thyroid. The reason for the differential distribution of AA and AL tissue deposits is not understood.

The optimal method for diagnosing AA amyloidosis remains controversial. Although kidney biopsy is positive in about 100% of symptomatic patients, less invasive biopsy procedures should be preferred first (Table 60.15). Biopsies of accessory salivary glands, abdominal fat, and rectal mucosa yield positive results in 50% to 80% of patients. Immunohistochemical staining using antibodies to SAA is required to confirm that Congo red positive amyloid deposits are of AA type. SAP scintigraphy, when available, shows early accumulation of amyloid in spleen, kidneys, and adrenal glands whereas bones are not affected (contrary to AL amyloid).

Survival time of patients with AA amyloidosis is usually longer than in AL amyloidosis (Table 60.15). Elevated serum creatinine or end-stage renal disease at baseline, older age, and a low serum albumin are strong adverse prognostic indicators. Main causes of death are infections and dialysis complications, but not cardiac complications. Estimated survival was about 40% at 3 years, and median survival time was approximately 2 years, in older series.[228,229] In a recent series, estimated median survival from diagnosis was 133 months, indicating that prognosis of systemic AA has improved over the years.[232]

Amyloid load and clinical outcome in AA amyloidosis are dependent on circulating concentrations of SAA.[231] In a cohort of 374 patients who were followed for a median of 86 months, Lachmann et al. showed that amyloid burden increased in 12%, was unchanged in 48%, and decreased in 39%; SAA values were significantly lower (median, 7 mg per L) in patients in whom amyloid regressed, than in those in whom the amyloid burden increased (median, 54 mg per L) (P <0.001). The median SAA concentration during each year of follow-up was strongly associated with survival: the relative risk of death among patients with a SAA level <4 mg per L was 18 times lower than among patients in whom SAA level was ≥155 mg per L. Similarly, median SAA values were 6 mg per L in patients in whom renal function improved, and 28 mg per L in those who showed progression of chronic kidney disease (CKD).[232] These data emphasize the fact that underlying inflammatory diseases responsible for amyloid must be treated as vigorously as possible and SAA (preferentially to C reactive protein [CRP]) levels must be monitored monthly and maintained at a target value of less than 5 to 10 mg per L. In patients with inflammatory arthritis, antitumor necrosis factor-α therapy may help to achieve this goal.[233]

Other factors promote progression of CKD in systemic AA amyloidosis, including the amount of proteinuria, and associated cardiac or hepatic disease.[220,230] Kidney biopsy may also provide indicators of pejorative renal outcome, such as predominant glomerular pattern of deposits, glomerular inflammation,[234] quantity of amyloid deposition, extent of tubulointerstitial and vascular damage.[235] End-stage renal disease, that occurs in 23% to 47% of patients within variable median time (18 to 245 months) after diagnosis is a factor of poor patient survival.[220,230,232] Median survival of patients with SAA amyloidosis on renal replacement therapy is 37 months, whatever the method used, hemodialysis or peritoneal dialysis, with amyloid heart involvement being the major cause of death.[220] A few studies have shown encouraging results with renal transplantation in patients with AA amyloidosis, close to that of the general population of transplant recipients.[223,236–238] In a series of 62 renal transplantations including 29 grafts from related living donors,[223] the 1-year actuarial patient survival rate was 79%, decreasing to 65% after 5 years. Recently, in 59 renal recipients with AA amyloidosis, 5- and 10-year patient survival rates were 82.5% and 61.7%, respectively, significantly lower when compared with a control group of 177 renal transplant recipients. However, no statistical difference was observed in the 5- and 10-year graft survival censored for death between the two groups.[239] Amyloid deposits recur in about 10% of the grafts.[223,236,239] There is a high risk of infection that is the main cause of early deaths. As with dialysis, cardiac involvement is a major threat for patients receiving renal transplants. Efforts should be made to control SAA levels in these patients to improve both graft and patient outcomes.

Familial Mediterranean Fever and Other Hereditary Recurrent Fever Syndromes

Familial Mediterranean fever (FMF) is both a particular type of AA amyloidosis and the most common cause of familial amyloidosis. Colchicine has proved to be efficient both in the prevention and treatment of this type of

amyloidosis.[240] FMF is usually transmitted as an autosomal recessive disorder and occurs most commonly in Sephardic Jews and Armenians.[241] Mutations of the gene for proteins called pyrin or marenostrin have been demonstrated.[242,243] Clinically, there are two independent phenotypes. In the first, brief episodic febrile attacks of peritonitis, pleuritis, or synovitis occur in childhood or adolescence and precede the renal manifestations. In the second, renal symptoms precede and may be the only manifestation of the disease for a long time. The attacks are accompanied by dramatic elevations of acute phase reactants, including SAA. Amyloid deposits of the AA type are responsible for severe renal lesions with prominent glomerular involvement leading to end-stage renal disease at a young age, and early death. Zemer et al.[240] showed that in a cohort of 1,070 patients with FMF, colchicine, an agent effective in preventing attacks,[244] could prevent the appearance of proteinuria and deterioration of renal function (in patients with amyloidosis who had proteinuria but not the nephrotic syndrome or renal insufficiency). Life-table analysis showed that the cumulative rate of proteinuria was 1.7% after 11 years in the compliant patients and 48.9% after 9 years in the noncompliant patients (P <.0001). In 1992, the authors further showed that colchicine reversed the nephrotic syndrome in three patients.[245] They insisted on the importance of a dosage adapted to the clinical situation. The minimum daily dose of colchicine for prevention of amyloidosis is 1 mg even if attacks are suppressed by a smaller dose. Patients with clinical evidence of amyloidotic kidney disease and kidney transplant recipients should receive daily doses of between 1.5 and 2.0 mg. The recombinant IL-1 receptor antagonist anakinra and potentially other IL-1 targeting drugs may represent an effective treatment in the 10% of patients who are resistant to colchicine therapy,[246] or develop severe side effects with colchicine.

Next to FMF, there is a growing family of hereditary autoinflammatory disorders that bear the significant risk of developing AA amyloidosis (Table 60.16). Recent advances into their pathogenesis with the identification of susceptibility genes and characterization of pathways involved in raised acute phase response have resulted in new therapeutic approaches. Among these, Il-1 blockade with anakinra and anti-TNF agents have shown variable results in the treatment of TNF receptor-associated periodic syndrome (TRAPS) and hyper IgD syndrome. Remarkably, Il-1 blockade with either anakinra,[247] rinolacept,[248] or canakinumab (a human anti-IL1β monoclonal antibody)[249] was shown to produce rapid and complete clinical and inflammatory responses in most patients with cryopirin-asociated periodic syndrome (CRAPS), an entity that comprises three different diseases: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic, cutaneous, and articular (CINCA) syndrome. Anakinra is also effective in the treatment of the newly described auto-inflammatory disease due to deficiency of the IL-1 receptor antagonist.[250]

Therapeutic Prospects

New therapeutic strategies should be directed at the three steps of the amyloidogenic process: synthesis of the precursor, deposition of amyloid fibrils, and removal or dissolution of amyloid fibrils.

Prevention of Amyloid Precursor Synthesis

Curing the underlying disease has proved to be extremely effective, as shown in inflammation-related AA amyloidosis. This objective must be envisioned in all forms of amyloidosis. The possibility of immunotargeting against precursor synthesis is also worth exploring.

Prevention of Amyloid Fibril Deposition

A potential therapeutic strategy is blockade of RAGE (receptor for advanced glycation end-products), a multiligand receptor of the immunoglobulin superfamily that also is a receptor for the amyloidogenic form of serum amyloid A. Antagonizing RAGE with a soluble form of the receptor or with blocking antibodies inhibits amyloid deposition in the spleen of mice injected with amyloid-enhancing factor and silver nitrate.[251]

Rapidly growing data on the nucleation process might lead to the synthesis of nucleation inhibitors for all types of amyloid. Low-molecular-weight (135 to 1,000) anionic sulfate or sulfate compounds were shown to interfere with heparan sulfate-stimulated β-peptide fibril aggregation in vitro.[252] When administered orally, these compounds by inhibiting polymerization and tissue deposition of amyloid fibrils substantially reduced murine splenic AA amyloid progression. In a prospective randomized trial in patients with AA amyloidosis and kidney involvement, one of these compounds, eprodisate, reduced by 30% the mean rate of decline in creatinine clearance, compared to placebo.[253] Further studies are needed to evaluate whether such agents (that may theoretically apply to other types of amyloid), will have a major impact on patients with AA amyloidosis who do not respond to therapy for the underlying disorder.

Removal or Dissolution of Amyloid Fibrils and Immunotherapeutic Perspectives

The regression of amyloid deposits under effective treatment of the underlying disease as well as the finding that amyloid deposits may undergo redistribution strongly suggest that amyloid fibrils can be catabolized and removed from tissues. This process is most likely restrained by proteinase inhibitors that have been detected in amyloid deposits of various types, and by fibril coating with the calcium-dependent lectin SAP.[120] A potential approach, therefore, would be to block these inhibitors to target proteolytic enzymes at the amyloid deposition site or to dissociate SAP with competitive ligands.

At present, most attempts to use dimethylsulfoxide (DMSO) as an amyloid solvent have been disappointing because of lack of efficacy and bad odor from the patient's breath. Similarly the clinical efficacy of the iodinated anthracycline, (4'-iodo-4'-deoxydoxorubicin) that binds
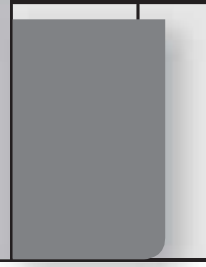
specifically and with high affinity to all the natural amyloid fibrils and promotes the disaggregation of fibrils both in vitro and in vivo,[254] is not established.[123,255]

A competitive inhibitor of SAP binding to amyloid fibrils has been developed by Pepys et al.[123] This palindromic compound, referred to as R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid (CPHPC), also crosslinks and dimerizes SAP molecules, leading to their very rapid clearance by the liver, and thus produces a marked depletion of circulating human SAP. Preliminary studies of the therapeutic effect of CPHPC in mice and humans were unsuccessful, because despite efficient depletion in circulating SAP, significant amounts of SAP remained in the amyloid deposits. Recently, the same group elegantly demonstrated the validity of this approach. In an experimental model of AA amyloidosis in mice transgenic for human SAP, depletion of circulating SAP with oral CPHPC, followed by a single injection of polyclonal antihuman SAP antibodies, efficiently removed massive visceral amyloid deposits, without adverse effects. Elimination of tissue deposits was related to a potent complement-dependent macrophage-derived giant cell reaction, triggered by human anti-SAP antibodies.[124] Clinical evaluation based on a fully humanized anti-SAP antibody is planned.

The immune system might be manipulated in order to recognize amyloid fibrils as harmful foreign entities. In AL amyloidosis, Hrncic et al. demonstrated that a monoclonal antibody specific for a conformational determinant could accelerate the clearing of amyloid.[256] This antibody recognizes an epitope contained within the first N-terminal amino acids of misfolded LCs.[257] Although we are still far from applicable human immunotherapy, such experimental approaches might lead to future developments.

MONOCLONAL IMMUNOGLOBULIN DEPOSITION DISEASE

History and Nomenclature

It has been known since the late 1950s that nonamyloidotic forms of glomerular disease can occur in multiple myeloma. Kobernick and Whiteside[258] and Sanchez and Domz[259] first described glomerular nodules "resembling the lesion of diabetic glomerulosclerosis," lacking the staining features and fibrillar organization of amyloid. The monoclonal LC content of these lesions was confirmed by Randall et al.,[3] who published the first description of LCDD in 1976.

Monoclonal HCs were found together with LCs in the tissue deposits from certain patients, and the term light and heavy chain deposition disease (LHCDD) was proposed.[260] Deposits containing monoclonal HCs only, that is, in the absence of detectable LCs, were first observed in 1993 in patients affected with otherwise typical Randall disease (HC deposition disease [HCDD]),[5] and three series of similar patients were published later.[6,261,262] More than 30 cases of HCDD have been reported so far, but this disease is most likely underdiagnosed. In two further cases, termed "pseudo-γ HCDD," predominant γ4 chain deposits were demonstrated with similar pathologic aspects; the authors suggested that misfolding or denaturation of the LC was responsible for its nonreactivity with specific antibodies.[263]

In clinical and pathologic terms, LCDD, LHCDD, and HCDD are essentially similar and are now gathered under the generic term of monoclonal Ig deposition disease (MIDD). They differ from amyloidosis by the lack of affinity for Congo red and lack of fibrillar organization. The distinction also relates to different pathophysiology of amyloid, which implicates one-dimensional elongation of a pseudocrystalline structure, and of MIDD, which would rather involve a one-step precipitation of Ig chains.

Pathophysiology

The pathogenetic mechanisms leading to MIDD remain entirely hypothetical because circulating or urinary monoclonal immunoglobulin chain precursors are frequently not detected, or present at very low levels, making their purification and analysis particularly difficult, and data on the precise nature of the visceral deposits remains speculative. In LCDD, there is a modest but significant overrepresentation of κ chains occurring in approximately 80% of cases (versus approximately two-thirds among polyclonal Ig), which contrasts with the increased λ to κ ratio observed in AL-amyloidosis. The rare Vκ_{IV} variability subgroup is frequent,[19] which is worth noting because this subgroup features a strikingly long complementarity-determining region 1 (CDR1) loop that contains several hydrophobic residues; however, contrary to the Vλ_{VI} subgroup, which was found exclusively on monoclonal LCs from AL amyloidosis patients,[18] Vκ_{IV} LCs may be encountered in myeloma without renal involvement.

That immunoglobulin chain deposition involves unusual immunoglobulin chain properties is supported by the absence of detectable monoclonal component in the serum and urine in 10% to 20% of patients with MIDD, the recurrence of the disease in the transplanted kidney, and the biosynthesis of abnormal LCs by bone marrow plasma cells.[12,260]

Abnormal Glycosylation and Structure of MIDD LCs

Structural abnormalities of immunoglobulins in MIDD have long been suggested by empirical studies of in vitro bone marrow cell biosynthesis products.[12,260] In a study of immunoglobulin biosynthesis by bone marrow plasma cells in eight consecutive patients, LCs were of normal size in two cases, and short or apparently large in the other six patients. These short or large LCs showed a striking ability to polymerize when secreted in vitro. Abnormal glycosylation may be responsible for an increase in apparent molecular weight of the corresponding LC.

When pathogenic LCs could not be detected in the serum and urine, they were N-glycosylated in all tested cases.[19,263] In vitro biosynthetic labeling experiments on short-term plasma cell cultures showed that LCs which

were absent in the urine actually were secreted by the bone marrow plasma cells.[12,15,260] Together with the presence of exposed hydrophobic residues, LC glycosylation might increase the propensity of LCs to precipitate in tissues and displace the equilibrium from soluble toward deposited forms so that they are no more detectable in the body fluids.

Sequence Analysis

The first complete primary structure of an LC in LCDD was determined by Cogné et al. in 1991.[15] The 30-kDa κ chain found in the kidney was presumably identical to that secreted by the malignant plasma cells, since they shared the same apparent molecular mass and 13-amino acid N-terminal sequence. It was encoded by a normal-sized κ mRNA and was N-glycosylated. The C region was entirely normal and the V region belonged to the $V\kappa_{IV}$ subgroup. Eight mutations were observed, including replacement of Pro95 (considered as essential for the conformation of the third hypervariable region). Replacement of Asp70 by Asn determined a N-glycosylation site.

The primary structures of a few further LCDD precursors were analysed at the complementary DNA and protein levels. Most peculiarities are clustered in peptide loops corresponding to CDRs, that is, parts of the molecules normally implicated in antigen binding, suggesting that a first step of the pathogenesis could be an LC tropism for extracellular components behaving as antigenlike structures. The most remarkable observations were unusual hydrophobic residues at positions where they could either be exposed to the solvent or strongly modify the conformation, potentially leading to LC aggregation or interaction with other hydrophobic molecules.[265] A role for V domain in renal tissue deposition was demonstrated in a mouse experimental model, in which the injection of hybridoma cells transfected with the human LCCD Vκ4 FRA LC resulted in diffuse granular glomerular deposits, identical to those observed in the patient's kidney biopsy. Injection of cells that secreted a control Vκ4 LC, with the same C domain, but which differed from FRA by few residues in the hypervariable region, did not induce LC glomerular deposition.[266]

In a recent study, it was shown that LCDD LCs are characterized by cationic isoelectric points (pIs), whereas pI profile of AL amyloid LCs is heterogeneous, suggesting that fibrillar amyloid deposits form by electrostatic interaction between oppositely charged polypeptides, whereas granular deposits in LCDD result from binding of cationic polypeptides to anionic basement membranes.[267]

However, as in AL amyloidosis, extrinsic conditions may also contribute to aggregation of the LC. The same LC can form granular aggregates or amyloid fibrils depending on the environment, and different partially folded intermediates of this protein may be responsible for amorphous or fibrillar aggregation pathways.[268]

Heavy-Chain Deposition Disease: A Disease Featuring Heavy-Chain Deletions

A deletion of the first constant domain C_H1 was found in the deposited or circulating HC in all patients with γ-HC deposition disease where this deletion was searched for (Table 60.17).[5,6,262,269–272] It also was suggested in a patient

60.17	Immunologic Characteristics of Patients with Heavy-Chain Deposition Disease (HCDD) According to IG Subtype[a]			
	No. of Patients	C_H1 Deletion	Complement Deposition	Complement Activation
$\gamma1$	10	7/7[b]	7/10	9/10
$\gamma2$	1	NS	1 (weak)	0/1
$\gamma3$	6	4/4	4/4	4/4
$\gamma4$	3	2/2	1 (weak)	NS
γ (isotype not specified)	4	NS	1/1	0/1
α	2	NS	1/2	0/2
μ	1	NS	1/1	0/1

[a]Cases are from references 8, 9, 352, 359, and 360.
[b]In one patient, C_H1 and C_H2 were deleted.[8]
NS, not specified.

with α HCDD.[273] A larger deletion also including the C_H1 domain, the hinge, and the C_H2 domain was found in one case.[5] In the blood, the deleted HC was associated with LCs, mostly of the λ isotype, or circulated in small amounts as a free unassembled subunit.[6] It is likely that the C_H1 deletion facilitates the secretion of free HCs that are rapidly cleared from the circulation by organ deposition.[274] Deletion of the C_H1 is also found in HC disease, a lymphoproliferative disorder with free HC secretion without corresponding renal tissue deposition, and in AH amyloidosis in which deposits have a fibrillar organization. In heavy chain disease, however, the variable domain also is partially or completely deleted, which suggests that the V_H domain is required for tissue precipitation. Sequence analysis of two HCDD proteins did show unusual amino acid substitutions in the V_H, which might change their physicochemical properties, including charge and hydrophobicity.[375]

Deposition Does Not Mean Pathogenicity

The finding by Solomon et al.[14] of unexpectedly frequent (14 of 40) deposition of human monoclonal LCs along basement membranes in a mouse experimental model raises the question of the relationship between tissue precipitation and pathogenic effects. Although approximately 80% of MIDDs are caused by κ chains, human LCs that deposited along basement membranes in mice were predominantly of the λ type (9 of 14). In addition, LC deposition similar in aspect to LCDD by immunofluorescence but with only scanty granular electron-dense deposits in the tubular basement membrane may occur in the absence of glomerular lesions and tubular basement membrane thickening.[262] Whether the diagnosis of MIDD should be restricted to the patients with extracellular matrix accumulation, remains debated. However, follow-up data indicate that the subgroup of patients with evidence of LC deposition by immunofluorescence and negative electron microscopy is not characterized by a milder course.[261]

Pathophysiology of Extracellular Matrix Accumulation

A striking feature of MIDD is the dramatic associated accumulation of extracellular matrix.[277] Nodules are made of normal constituents and of tenascin-C. They stain weakly for the small proteoglycans, decorin and biglycan. A role for transforming growth factor-β (TGF-β) is supported by its strong expression in glomeruli of MIDD patients, and by in vitro experiments using cultured mesangial cells.[278] In a series of 36 patients with LC-related renal diseases including AL amyloidosis, CN, fibrillary glomerulopathy, and LCDD, transforming growth factor-β (TGF-β) was detected only in glomeruli of the three patients with LCDD and nodular glomerular lesions.[279] In the control series, TGF-β was essentially found in nodular diabetic glomerulosclerosis, which may suggest that distinct initial insults to the glomerular mesangium may trigger similar fibrogenetic

pathways. Because of the similarities between MIDD- and diabetes-induced nodular glomerulosclerosis, including the strong reactivity of lesions with the periodic acid-Schiff (PAS) reagent, it has been suggested that immunoglobulin chains might stimulate mesangial cells in a similar manner to advanced glycation end-products (AGEs). Recent experiments[280] showed that monoclonal LCs responsible for LCDD or AL amyloidosis are endocytosed by cultured mesangial cells through a yet unidentified caveolae-associated receptor, and that different pathologic actions probably result from distinct cellular trafficking. Indeed, mesangial cells incubated with LCs from patients with MIDD or AL amyloidosis undergo either a myofibroblastic or a macrophagelike phenotypic transformation after incubation with LCDD or AL LCs, respectively. LCCD LCs, when incubated with mesangial cells, induce cell changes, production of PDGF-β, TGF-β, and MCP-1, as well as increased expression of Ki-67, a proliferation marker. This results in increased synthesis of extra-cellular matrix proteins (particularly tenascin-C), that, combined with decreased production and activity of metalloproteases, is likely to be involved in the development of glomerulosclerosis.[168,281,282]

Pathologic Features

Light Microscopy

MIDD should not be considered a pure glomerular disease. In fact, tubular lesions may be more conspicuous than the glomerular damage. Tubular lesions are characterized by the deposition of a refractile, eosinophilic, PAS-positive, ribbon-like material along the outer part of the tubular basement membrane in virtually all patients with MIDD. The deposits predominate around the distal tubules, Henle's loops, and in some instances the collecting ducts, the epithelium of which is flattened and atrophied. Typical myeloma casts are only occasionally seen. In advanced stages, a marked interstitial fibrosis including refractile deposits is frequently associated with tubular lesions. In rare cases, inflammatory infiltrates composed predominantly of lymphocytes and plasma cells and associated with tubulitis, are observed in the absence of glomerular lesions.[283]

Glomerular lesions are much more heterogeneous.[274] Nodular glomerulosclerosis is the most characteristic (Fig. 60.12A), being found in 30% to 100% of patients with LCDD.[262,274] Kappa-LC deposition is more likely than λ-LC deposition to be associated with nodular glomerulosclerosis and granular electron-dense deposits (see subsequent text).[261] Expansion of the mesangial matrix was observed in all cases of HCDD, with nodular glomerulosclerosis in almost all of them.[6,262] Mesangial nodules are composed of PAS-positive membranelike material and are often accompanied by mild mesangial hypercellularity. The capillary loops stretch at the periphery of florid nodules and may undergo aneurysmal dilation. The Bowman's capsule may contain a material identical to that present in the center of the nodules. These lesions resemble nodular diabetic glomerulosclerosis,
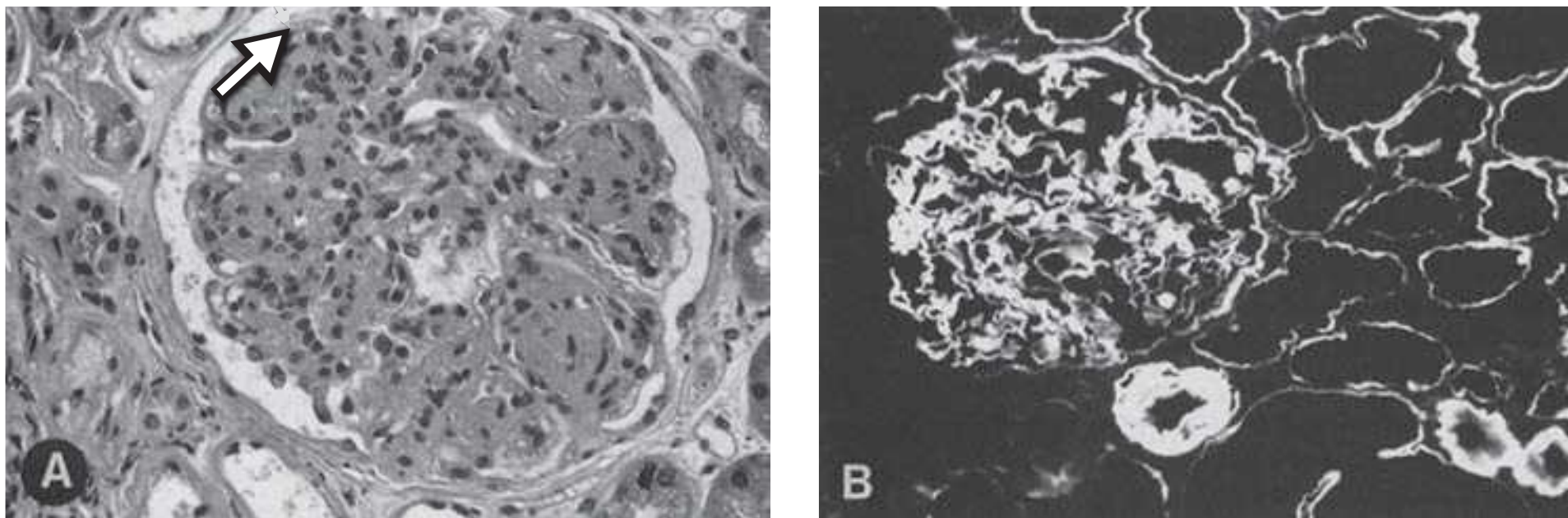
FIGURE 60.12 Monoclonal immunoglobulin deposition disease. **A:** Typical nodular glomerulosclerosis. Note membranelike material in the center of the nodules and nuclei at the periphery. Some glomerular capillaries show double contours (*arrow*). Note also thickening of the basement membrane of atrophic tubules. (Light microscopy, Masson's trichrome, ×312.) **B:** Bright staining of tubular and glomerular basement membranes, and of mesangium and arteriolar wall with anti-κ antibody in a patient with κ–light-chain deposition disease without nodular glomerular lesions. (Immunofluorescence, ×312.)

but some characteristics are distinctive: The distribution of the nodules is fairly regular in a given glomerulus, the nodules are often poorly argyrophilic, and exudative lesions as "fibrin caps" and extensive hyalinosis of the efferent arterioles are not observed. In occasional cases with prominent endocapillary cellularity and mesangial interposition, the glomerular features mimic a lobular glomerulonephritis.

Milder forms simply show an increase in mesangial matrix and sometimes in mesangial cells, and a modest thickening of the basement membranes appearing abnormally bright and rigid. Glomerular lesions may not be detected by light microscopy but require ultrastructural examination. These lesions may represent early stages of glomerular disease or be induced by LCs with a weak pathogenic potential. Their diagnosis would be unrecognized without the immunostaining results.

Arteries, arterioles, and peritubular capillaries all may contain LC deposits in close contact with their basement membranes.

Immunofluorescence

A key step in the diagnosis of the various forms of MIDD is immunofluorescence examination of the kidney. All biopsy specimens show evidence of monotypic LC and/or HC fixation along tubular basement membranes (Fig. 60.12B). This criterion is requested for the diagnosis of MIDD. In contrast with AL amyloidosis, the κ-isotype is markedly predominant.

The tubular deposits stain strongly and predominate along the loops of Henle and the distal tubules, but they are also often detected along the proximal tubules. In contrast, the pattern of glomerular immunofluorescence displays marked heterogeneity. In patients with nodular glomerulosclerosis, deposits of monotypic Ig chains are usually found along the peripheral glomerular basement membranes and, to a lesser extent, in the nodules themselves. The staining in glomeruli is typically weaker than that observed along the tubular basement membranes. This may not be a function of the actual amount of deposited material,

since several cases have been reported in which glomerular immunofluorescence was negative despite the presence of large amounts of granular glomerular deposits by electron microscopy.[58] Local modifications of deposited LCs might thus change their antigenicity.[264] In patients without nodular lesions, glomerular staining occurs along the basement membrane, but it may involve the mesangium in some cases (Fig. 60.12B). Linear Ig-chain staining is usually present along Bowman's capsule basement membrane. Deposits of Ig chains are constantly found in vascular walls (Fig. 60.12B). Focal staining of tubular basement membranes was seen in interstitial forms.[283]

In patients with HCDD, immunofluorescence with anti-LC antibodies is negative, despite typical nodular glomerulosclerosis. Monotypic deposits of γ-, α-, or μ-HC may be identified. Any γ-subclass may be observed. Analysis of the kidney biopsies with monoclonal antibodies directed to the various constant domains of the γ-HC showed that C_H1 domain determinants were undetectable in all tested cases (Table 60.17 and Fig. 60.13). In addition, monoclonal antibodies to the $\gamma1$ C_H2 domain also failed to react with the renal deposits of one patient, due to a combined deletion of C_H1 and C_H2 domains (5). In most cases of HCDD (Table 60.17) and in LHCDD,[284] especially when a $\gamma1$ or $\gamma3$ chain was involved, complement components could be demonstrated in a granular or pseudolinear pattern. Complement deposits were often associated with signs of complement activation in serum.

Electron Microscopy

The most characteristic ultrastructural feature is the presence of finely or coarsely granular electron-dense deposits that delineate the outer aspect of the tubular basement membranes (Fig. 60.14). They appear to be in contact with a well-preserved basal lamina. The deposits are usually quite large and may protrude into the adjacent part of the interstitium.

Ultrastructural glomerular lesions are characterized by the deposition of a nonfibrillar, electron-dense material
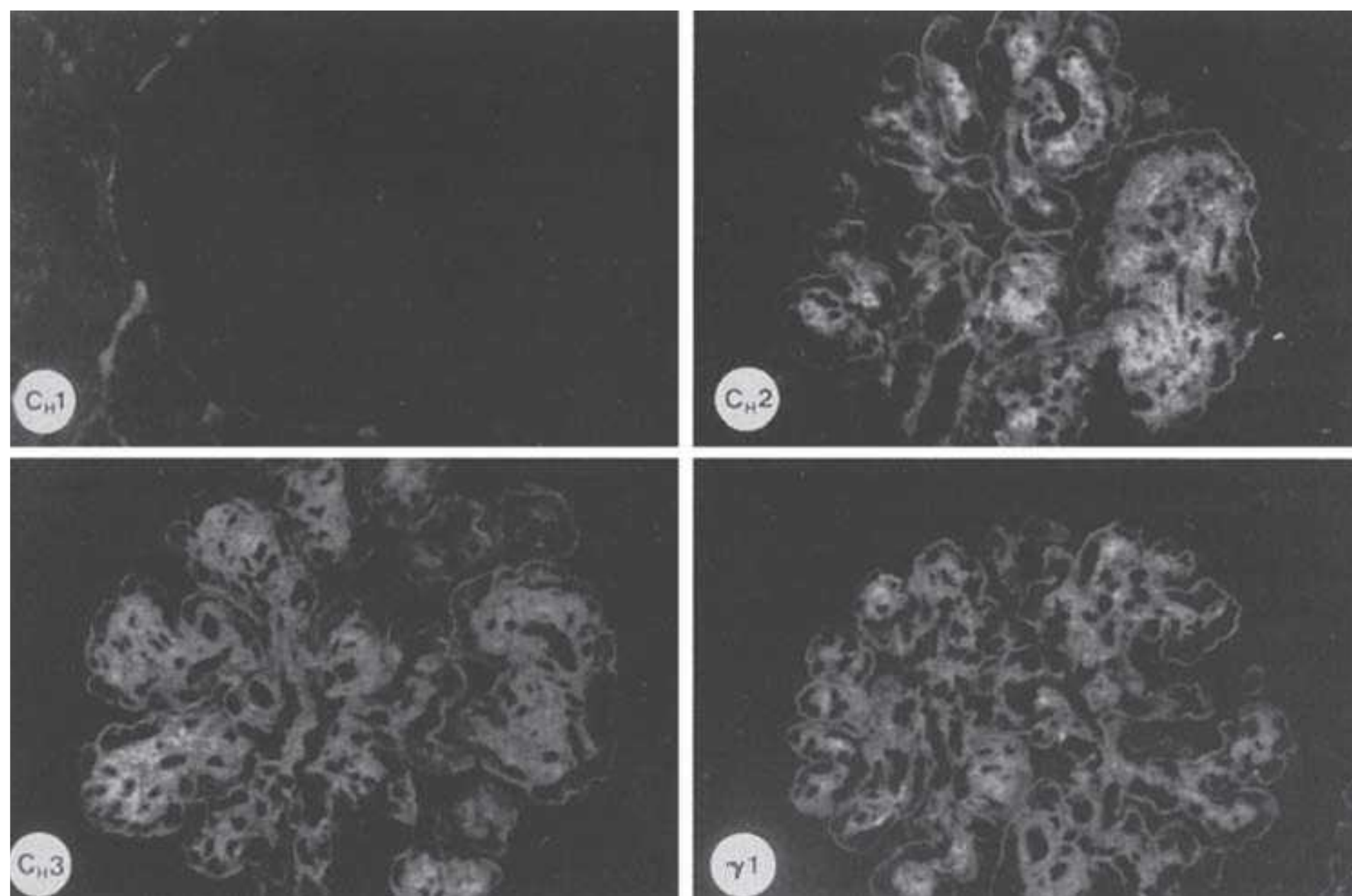
FIGURE 60.13 Heavy-chain deposition disease in a patient presenting with nodular glomerulosclerosis. Mesangial and parietal deposits stain with a monoclonal antibody specific for the γ1-isotype in the absence of detectable light chain (*bottom right*). Immunofluorescence with a panel of monoclonal antibodies directed to the various constant domains of the γ-heavy chain shows that the glomerular deposits are stained with anti-C_H2 and -C_H3, but not with anti-C_H1 antibodies. (Magnification, $\times$312.) (From Moulin B, Deret S, Mariette X, et al. Nodular glomerulosclerosis with deposition of monoclonal immunoglobulin heavy chains lacking C_H1. *J Am Soc Nephrol.* 1999;10:519, with permission.)
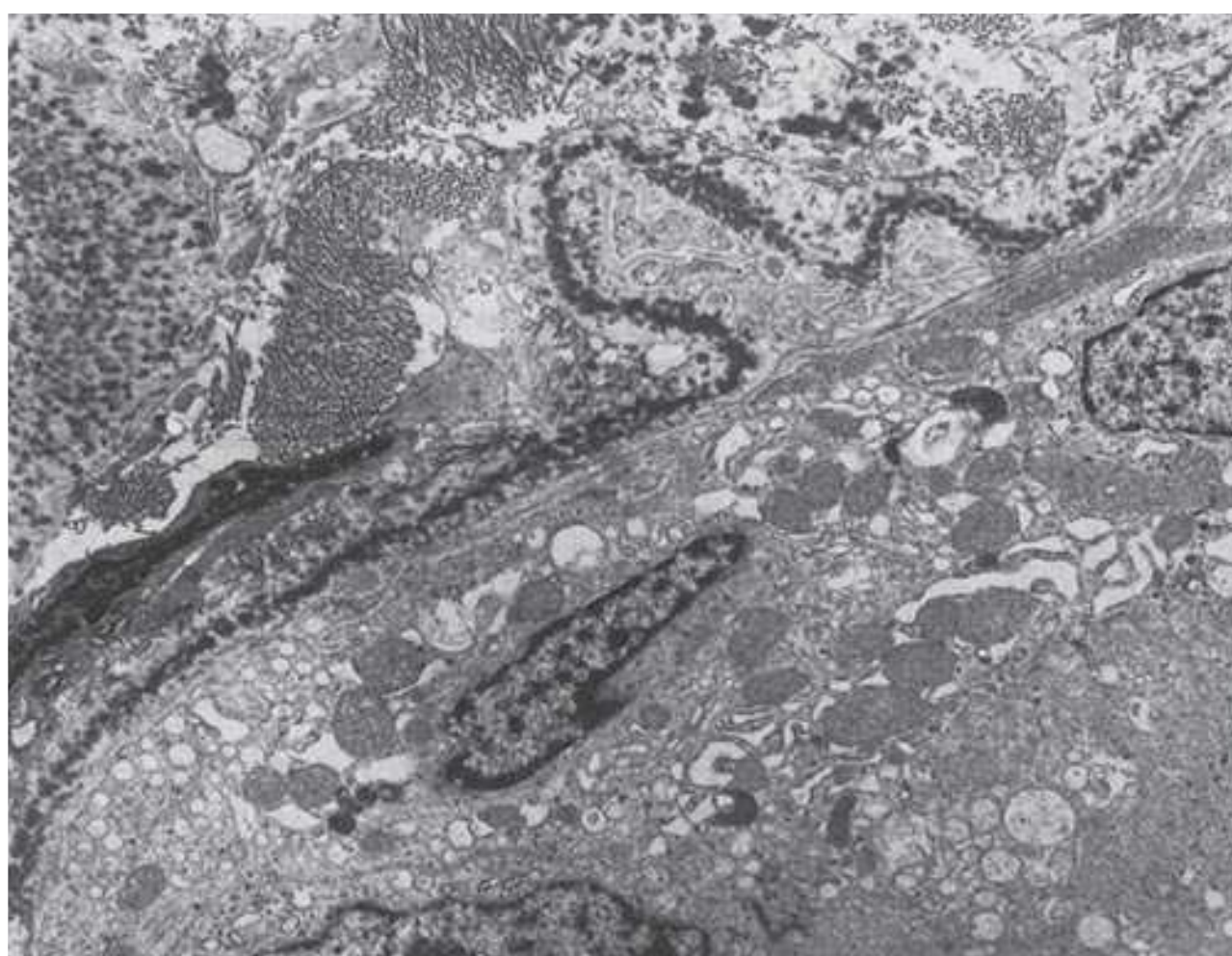

FIGURE 60.14 Light-chain deposition disease. Coarsely granular dense deposits lining the outer aspect of the tubular basement membrane. (Electron microscopy, uranyl acetate and lead citrate, $\times$6,000.) (From Ganeval D, Mignon F, Preud'homme JL, et al. Visceral deposition of monoclonal light chains and immunoglobulins: a study of renal and immunopathologic abnormalities. *Adv Nephrol Necker Hosp.* 1982;11:25, with permission.)

in the mesangial nodules and along the glomerular basement membrane. The mesangial material is usually finely granular with a membranoid appearance (Fig. 60.15), but in some cases, it may contain strongly electron-dense granules identical to the peritubular deposits. The deposits along the glomerular basement membrane appear as a prominent, but thin, continuous band delineating the endothelial aspect of the basement membrane. The limits between the deposits and the basement membrane may be difficult to distinguish. In rare cases the deposits invade the lamina densa. Glomerular endothelial cells are separated from this material by areas of electron-lucent fluffy material. Deposits can also be found in Bowman's capsules and in the wall of small arteries between the myocytes.[274]

Ultrastructural immunogold labeling may aid the demonstration of monotypical LCs along basement membranes in some cases.[285]

Clinical Presentation

In Tables 60.18 and 60.19 are summarized the main data from five large series.[260,261,262,286,287] They show an unexpectedly wide range of affected ages (28 to 94 years), with a male preponderance. MIDD is a systemic disease with Ig-chain deposition in a variety of organs leading to various clinical manifestations,[274] but visceral Ig-chain deposits may be totally asymptomatic and found only at autopsy.
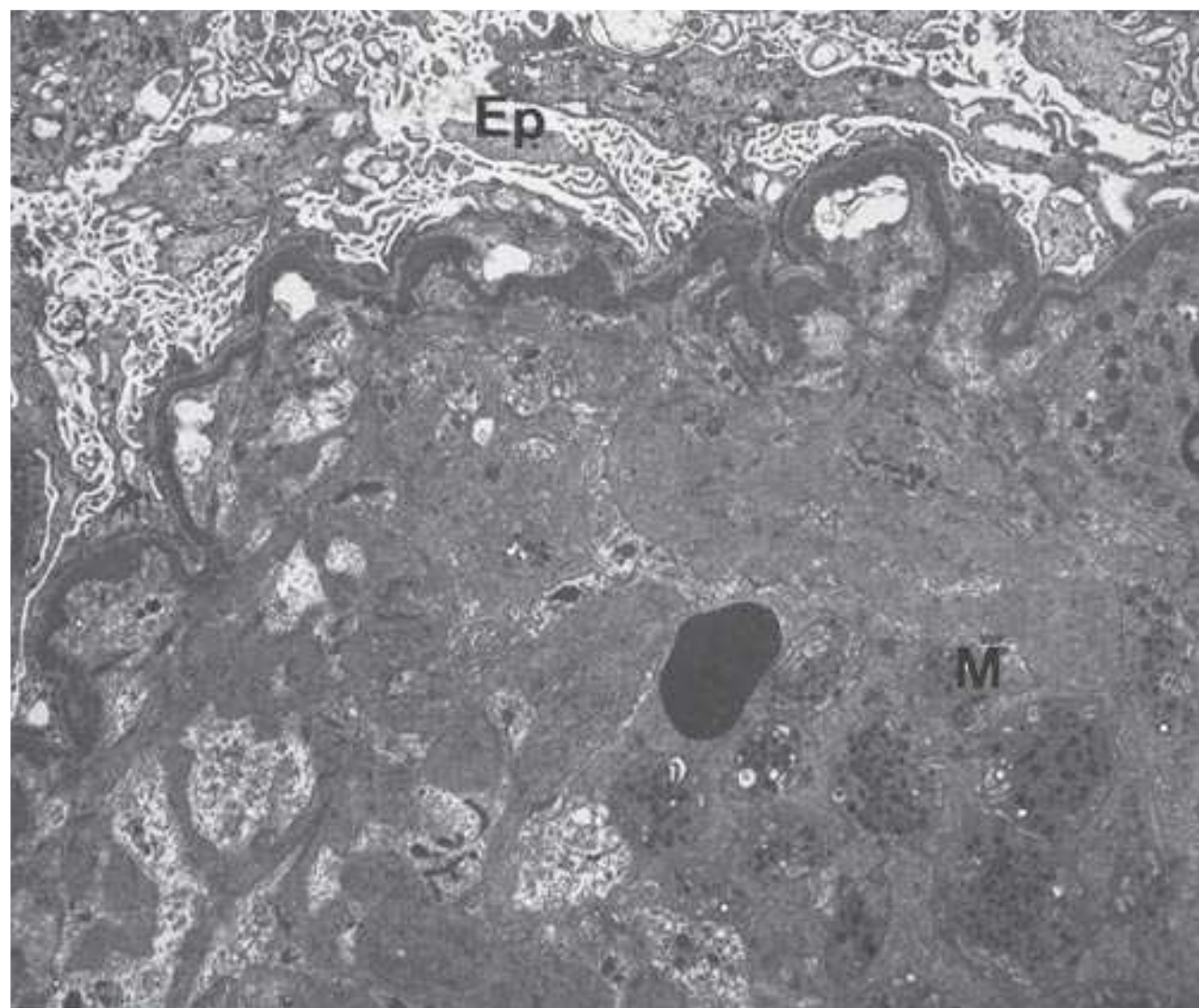
FIGURE 60.15 Light-chain deposition disease. A heavy layer of dense granular deposit lies along the inner part of the basement membrane lining a large mesangial nodule. *Ep*, epithelium; *M*, mesangium. (Electron microscopy, uranyl acetate and lead citrate, ×2,500.)

Renal Features

Renal involvement is a constant feature of MIDD, and renal symptoms, mostly proteinuria and renal failure, often dominate the clinical presentation (Table 60.18). In 23% to 53% of the patients, albuminuria is associated with the nephrotic syndrome. However, in about 20% of the cases, it is less than 1 g per day, and these patients exhibit mainly a tubulointerstitial syndrome.[283] Albuminuria is not correlated with the existence of nodular glomerulosclerosis, at least initially, and may occur in the absence of significant glomerular lesions by light microscopy. Hematuria is more frequent than one would expect for a nephropathy in which cell proliferation is usually modest, with a few exceptions.

The high prevalence, early appearance, and severity of renal failure are other salient features of MIDD.[3,261,262,274,288] In most cases, renal function declines rapidly, which is a main reason for referral. It occurs with comparable frequency in patients with either low or heavy proteinuria,[264] and thus presents in the form of a subacute tubulointerstitial nephritis or a rapidly progressive glomerulonephritis, respectively. The prevalence of hypertension is variable, but must be interpreted according to associated medical history.

60.18	**Renal Manifestations at Presentation in Patients with Light-Chain Deposition Disease (LCDD) and Light-and Heavy-Chain Deposition Disease (LHCDD)**						

Series (ref. no.)	Age (yrs)	Male–Female Ratio	Proteinuria >1 g/d	Nephrotic Syndrome	Hematuria	Renal Failure	Hypertension
Ganeval et al.[286] (n = 17)	57 (38–73)	11/6	13 (76%)	5 (29%)	5 (29%)	15 (88%)	3 (23%)[d]
Buxbaum et al.[260] (n = 13)	NS (35–71)	9/4	10 (77%)	3 (23%)	NS	12 (92%)	8 (61%)
Heilman et al.[287] (n = 19)	51 (37–77)	12/7	NS	10 (53%)	11 (58%)	17 (89%)	12 (63%)
Lin et al.[262,a] (n = 17)	57 (NS)	9/8	NS	3 (18%)	8 (47%)	16 (94%)	12 (71%)
Pozzi et al.[261,b] (n = 63)	58 (28–94)	40/23	53 (84%)	25 (40%)	NS	60 (96%)	NS
Masai et al.[284] (n = 12)	57 (39–60)	9/12	9/10 (90%)	3 (25%)	NS	8 (67%)[c]	NS
Total (n = 129)	57	1.5/1	83%	35%	45%	93%	53%

[a]Cases of LCDD with MCN (n = 11) are not included.
[b]Including 10 cases with MCN that could not be distinguished from those without MCN.
[c]Defined by serum creatinine >1.2 mg/dL.
[d]Plus three patients with past history of hypertension.
NS, not specified.

60.19	Hematologic Features, Extrarenal Manifestations, and Outcomes of Patients with Light-Chain Deposition Disease (LCDD) and Light- and Heavy-Chain Deposition Disease (LHCDD)			
Series (ref. no)	**Plasma Cell Dyscrasia**	**Monoclonal Component in Blood or Urine**	**Extrarenal Manifestations**	**Survival**
Ganeval et al.[286] (n = 17)	Myeloma—9 Waldenström—1	12/17 (71%)(8κ)	Liver—10 Heart—4 Lung —2 Spleen—3 Nervous system—4	1–46 mos 8/16 deceased
Buxbaum et al.[260] (n = 13)	Myeloma—4	10/12 (83%) (6κ)	Heart—6 Liver—3	1 mo to 10 yrs 9/13 deceased
Heilman et al.[287] (n = 19)	Myeloma—6 Malignant LPD—1	16/19 (84%) (15κ)	Heart—4 Nervous system—2	89% : 1 yr 70% : 5 yrs
Lin et al.[262] (n = 17)	Myeloma—8	15/17 (88%)[a]	NS	LCDD, 69 mos[b] LHCDD, 13 mos[b] 9/17 deceased
Pozzi et al.[261] (n = 63)	Myeloma—41 LPD—2	59/63 (94%) (43κ)	Heart—13 Liver—12 Spleen—5 Nervous system—5	66%: 1 yr 31%: 8 yrs 37/63 deceased
Masai et al.[284] (n = 12)	Myeloma—5	6/12 (50%) (5κ)	Heart—4 Liver—2	8/12 deceased (time to death: 81 mos) 7/12 hemodialysis
Total (n = 129)	Myeloma—52%	84% (κ65%)	Heart—25% Liver—22%	71/121 (59%) deceased

[a]14 κ chains in 17 kidney biopsies.
[b]Mean patient survival time.
LPD, lymphoproliferative disease.

Renal features of patients with HCDD are basically similar to those seen in LCDD and LHCDD although hypertension, nephrotic syndrome, and hematuria may be more common (Table 60.20).

Extrarenal Manifestations

Liver and cardiac manifestations occur in about one-fourth of patients (Table 60.19).[286] Liver deposits were constant in patients whose liver was examined. They were either discrete, confined to sinusoids and basement membranes of biliary ductules without associated parenchymal lesions, or massive with marked dilation and multiple ruptures of sinusoids resembling peliosis. Hepatomegaly with mild alterations of liver function tests was the most usual symptom, but several patients developed hepatic insufficiency and portal hypertension, and some of them died because of hepatic failure.[264]

Cardiac involvement is also frequent and may be responsible for cardiomegaly and severe renal failure. Dysrhythmias, conduction disturbances, and congestive heart failure are seen. Echocardiography and catheterization may reveal diastolic dysfunction and reduction in myocardial compliance similar to that seen in cardiac amyloid. As in the kidney and liver, immunofluorescence showed monotypic LC deposits in the vascular walls and perivascular areas of the heart, in all autopsy cases.[264]

Deposits may also occur along the nerve fibers and in the choroid plexus, as well as in the lymph nodes, bone marrow, spleen, pancreas, thyroid gland, submandibular glands, adrenal glands, gastrointestinal tract, abdominal vessels, lungs, and skin.[274] They may be responsible for peripheral neuropathy (20% of the reported cases), gastrointestinal disturbances, pulmonary nodules, amyloidlike

60.20 Comparison of Clinical Manifestations, Renal Lesions, and Hematologic Features in Patients with Monoclonal Immunoglobulin Deposition Disease (MIDD)		
Characteristics	**LCDD/ HCDD[a] (n = 129)**	**HCDD[b] (n = 27)**
Male–female ratio	1.5	0.7
Age (y)	57 (28–94)	56 (26–79)
Hypertension (%)	53	90
Renal failure (serum creatinine ≥130 μmol/L) (%)	93	85
Nephrotic syndrome[c] (%)	35	50
Hematuria (%)	45	88
Nodular glomerulo-sclerosis (%)	31–100	96
Multiple myeloma (%)	52	22
M component (blood or urine) (%)	84	56[d]

[a]Patients are from the series of Tables 60.19 and 60.20.
[b]Cases are from references 5, 6, 261, 268–272, 283, 288–295.
[c]Proteinuria ≥3 g/day.
[d]Including two cases with only free κ chain.

arthropathy, and sicca syndrome. In some patients, non-amyloidotic, localized nodules, termed "aggregomas," developed in the lung or as a cervical mass without systemic LCDD.[297,298] It is not certain whether they are truly localized or they represent an initial expression of a silent, systemic LCDD. In some cases, LCDD present as isolated bilateral cystic lung disease with emphysematous-like changes, dilatations, and rapidly progressive chronic obstructive respiratory insufficiency. In all patients, a lung monoclonal B cell population was found that shared an unmutated antigen receptor variable region sequence, suggestive of an antigen-driven process. Bilateral lung transplantation is the only effective therapy.[299,300]

Extrarenal deposits are less common in patients with HCDD. They have been reported in the heart,[269] synovial tissue,[269,301] skin,[293] striated muscles,[293] pancreas,[5] around the thyroid follicles,[5] and in Disse's spaces in the liver.

Hematologic Findings

The most common underlying disease in MIDD is myeloma, which accounts for about 50% of pure MIDD (Table 60.19) and greater than 90% of LC deposits associated with myeloma CN. MIDD was found at postmortem examination in 5% of myeloma cases.[22] MIDD, like AL amyloidosis, often is the presenting disease that leads to the discovery of myeloma at an early stage. In some patients who first presented with common myeloma and with normal-sized monoclonal Ig without kidney disease, LCDD occurred when the disease relapsed after chemotherapy, together with Ig structural abnormalities.[264,302] Because melphalan was shown to induce Ig gene mutations, the disease in these patients might result from the emergence of a variant clone induced by the alkylating agent. Apart from myeloma, MIDD may complicate Waldenström macroglobulinemia, chronic lymphocytic leukemia, and nodal marginal-zone lymphoma.[302,303] It often occurs in the absence of detectable malignant process, even after prolonged (more than 10 years) follow-up (Tables 60.19 and 60.20). In such "primary" forms, a monoclonal bone marrow plasma cell population can be documented easily by immunofluorescence examination.

Diagnostic Procedures in MIDD

The diagnosis of MIDD must be suspected in any patient with the nephrotic syndrome or rapidly progressive tubulointerstitial nephritis, or with echocardiographic findings indicating diastolic dysfunction, and the presence of a monoclonal Ig component in the serum and/or the urine. The same combination is also seen in AL amyloidosis, but the latter is more often associated with the λ LC isotype. Sensitive techniques including immunofixation and free light chain assay fail to identify a monoclonal Ig component in up to 20% of patients with LCDD/HCDD[304] and about 40% of patients with HCDD (Table 60.20). Renal biopsy plays an essential role in the diagnosis of MIDD and of the associated dysproteinemia.

The definitive diagnosis is made according to the immunohistologic analysis of tissue from an affected organ, in most cases the kidney, using a panel of Ig chain-specific antibodies, including anti-κ and anti-λ LC antibodies to stain the non-Congophilic deposits. When the biopsy stains for a single heavy chain isotype and does not stain for light chain isotypes, the diagnosis of HCDD should be suspected, and antibodies specific for the three constant HC domains (CH) should be applied to detect deletion of the CH1.

The diagnosis of the plasma cell dyscrasia relies on bone marrow aspiration and bone marrow biopsy with cell morphologic evaluation and, if necessary, immunophenotyping with anti-κ and anti-λ antisera to demonstrate monoclonality. Diagnostic criteria for a multiple myeloma are present in about half of the patients with LCDD, and in one-fourth of those with HCDD.

Outcome and Treatment

The outcome of MIDD remains uncertain, mainly because extrarenal deposits of LCs can be totally asymptomatic or cause severe organ damage leading to death. Survival from onset of symptoms varies from 1 month to 10 years (Table 60.19). In the largest series as yet reported of patients with LCDD,[276] 36 of the 63 (57%) patients reached uremia, 37 of those patients (59%) died during follow-up (mean, 27.5 months), and patient survival was only 66% at 1 year and 31% at 8 years, although 54 patients (86%) were treated by chemotherapy. Multivariate analysis showed that the only variables independently associated with renal survival were age and degree of renal insufficiency at presentation[276] or at the time of renal biopsy.[262] Those independently associated with a worse patient survival were age, associated multiple myeloma, and extrarenal LC deposition,[276] or initial serum creatinine.[262] The survival of the uremic patients treated with dialysis was not different from that of the patients not reaching uremia.[276] Renal and patient survivals were significantly better in patients with "pure" MIDD (mean, 22 and 54 months, respectively), compared with those who presented with myeloma CN (mean, 4 and 22 months).[262]

As in AL amyloidosis, treatment should be aimed at reducing Ig production. Whether appropriate treatment can result in sustained remission has long remained unclear. Clearance of the LC deposits has been unequivocally demonstrated in some patients after intensive chemotherapy with syngeneic bone marrow transplantation or blood stem cell autografting.[305–307] Disappearance of nodular mesangial lesions and LC or γ3 HC deposits was also reported after conventional long-term chemotherapy.[271,308] These observations demonstrate that fibrotic nodular glomerular lesions are reversible, and they argue for intensive chemotherapy in patients with severe visceral involvement.

In a retrospective study of 11 young (<65 years) patients with LHCDD treated by high-dose therapy (HDT) with the support of autologous blood stem cell transplantation (ASCT), no treatment-related death occurred.[309] A decrease in the monoclonal Ig level was observed in eight patients, with complete disappearance from serum and urine in six cases. Improvement in manifestations related to deposits was observed in six patients, and histologic regression was documented in cardiac, hepatic, and skin biopsies. No manifestation related to deposits occurred or recurred in any patient. Other groups have recently confirmed that HDT with ASCT is a valid option in young patients (aged less than 65 years) with LCDD, in whom it provides prolonged hematologic reponse and survival.[310–313] Reversal of dialysis dependency and sustained improvement in renal function was also noted in one patient with LCDD by Firkin et al.[314] Novel antimyeloma agents might further improve renal and patient outomes, but their efficacy remains to be established. In four patients with LCDD and renal failure, renal and hematologic response

(including complete clonal response in two patients) was obtained after six cycles of bortezomib plus dexamethasone in all cases. Two patients developed peripheral neuropathy that regressed with bortezomib dose adaptation. Three patients relapsed and were later succesfully treated with HDT and ASCT.[315]

As in AL amyloidosis, monitoring of LC production should rely on free LC assay, particularly in the patients without a blood and urine monoclonal component.

Kidney transplantation has been performed in a few patients with MIDD. Recurrence of the disease is usually observed, with an overall median allograft survival of only 33.3 months. Therefore, kidney transplantation should not be an option for LCDD patients unless measures have been taken to reduce LC production.[13] A prerequisite to kidney transplantation is hematologic complete remission as defined by normalization of $\kappa : \lambda$ free LC ratio.

COMBINED GLOMERULAR AND TUBULAR LESIONS

Tubular Lesions Associated with Glomerular and Tubular Light-Chain Deposits

The association of monoclonal LC deposits, mostly along renal tubular basement membranes, with typical myeloma CN is more frequent than reported initially. Myeloma casts were found in 11 of 34 (32%) patients with MIDD.[262] Nodular glomerulosclerosis is, however, infrequent (<10%), and some ribbonlike tubular basement membranes are seen in less than one half of the patients. One third of the patients do not have granular-dense deposits by electron microscopy. The lack of matrix accumulation in most of these patients who present with acute renal failure in the setting of a true myeloma may relate to insufficient time for the development of fibrosis or to a weaker sclerogenic effect of the LC, if any.[274] As discussed in the preceding text, the presence of LC deposits along the tubular basement membrane is not sufficient to make a diagnosis of MIDD. The pattern of renal lesions may change with time under chemotherapy. In three patients with typical myeloma cast nephropathy on initial biopsy, casts were replaced by massive tissue deposits of LCs (κ chains in two, amyloid in one),[45] suggesting chemotherapy-induced mutation of the LCs.[302]

More exceptional is the association of AL amyloidosis with a Fanconi syndrome unrelated to massive amyloid infiltration of the kidney.[103,316,317] Finkel et al.[318] noticed that nodular amyloid deposits were surrounded by atypical lymphoid cells containing numerous needle-shaped crystals, and suggested that "a product" from these cells "may have been involved with both crystal formation and amyloid production." Since the nucleation processes initiating amyloid and crystal formation may share similarities, it is tempting to speculate that the responsible LC bore unusual physicochemical properties, inducing both pathologic conditions.

Combined AL or AH Amyloidosis and Monoclonal Immunoglobulin Deposition Disease

Since the description of MIDD, it was expected that the two types of deposits might coexist at different sites in a single patient. A review by Gallo et al.[319] indicated that in approximately 7% of 135 cases of light-chain deposition disease, amyloid was found in one or more organs. Because amyloid deposits were focal, the true incidence of the association may be markedly underestimated. In patients with both types of deposits, amyloid P component was found in the fibrillar, but not the nonfibrillar, LC deposits by immunohistochemical methods. The pathophysiologic significance of this association remains controversial. Some light chains may possess intrinsic properties, which make them prone to form both fibrillar and nonfibrillar deposits, depending on the tissue microenvironment,[268] although in the absence of structural analysis of the deposited LCs, one cannot exclude that they are generated by different variant clones. In a patient with IgD myeloma, MIDD and amyloidosis were associated with cast nephropathy.[320]

Late development of systemic λ-LC amyloidosis was reported in a patient with γ-HCDD during long-term follow-up.[321] Copeland et al.[139] reported the metachronous development of nonamyloidogenic λ-LCDD and γ-HC amyloidosis in the same patient. Given the length of time between the development of the two diseases (6 years) and the apparent success of stem cell transplantation in treating the first, it is most likely that the patient produced two different plasma cell clones.

OTHER DYSPROTEINEMIA-ASSOCIATED GLOMERULAR LESIONS

Glomerulopathies Associated with IgM-Secreting Monoclonal Proliferations

Glomerulonephritis with intracapillary thrombi of IgM is almost specific of Waldenström's macroglobulinemia (WM).[322] In the series of 16 autopsy and biopsy cases published by Morel-Maroger et al.,[322] this lesion was found in six cases and was associated with a variable degree of proteinuria and normal or slightly altered renal function. It was characterized by PAS-positive, non-Congophilic endomembranous deposits in a variable number of capillary loops. Deposits were sometimes so voluminous as to occlude the capillary lumens partially or completely, thereby forming thrombi. By immunofluorescence, thrombi and deposits were stained with anti-IgM (three cases studied) and with anti-κ (one case studied) antibodies. Two of the six patients had cryoglobulinemia and slight glomerular cell proliferation. In the remaining four, the amount of circulating IgM was higher than in the other patients of the series with amyloidosis or no detectable renal lesion, which suggested that hyperviscosity could favor IgM deposition in glomerular capillaries where ultrafiltration further increases the protein concentration.

However, recent data indicate that the spectrum of renal lesions associated with IgM monoclonal gammopathies has changed over the years, due to early management and development of effective chemotherapy in WM and other IgM secreting lymphoproliferative disorders. In 2008, Audard et al. showed that out of 14 patients with a circulating monoclonal IgM (including seven patients with WM) and renal disease, only five patients had typical granular intracapillary IgM thrombi occluding capillary lumens. In the remaining patients, renal disease was related to atypical membranoproliferative glomerulonephritis with IgMκ deposits (three cases), lambda LC amyloidosis (two cases), or CD20+ lymphomatous infiltration.[323] These findings strongly suggest that kidney biopsy should be performed to ascertain the nature of renal lesions in patients with WM and evidence of renal disease. Because renal biopsy may be hazardous in patients with Waldenström macroglobulinemia with frequently increased bleeding time, it is wise to search for amyloid deposits first by a less invasive tissue biopsy.

Recent studies have focused on AL amyloidosis associated with IgM monoclonal gammopathy, which appears as a distinct entity with frequent lymph node involvement. Variable outcomes have been reported, related to variable hematologic response rates to alkylating agents. Therefore, appropriately tailored chemotherapeutic regimens that specifically target the underlying clonal disorder (mostly lymphoid), based on purine analogs, HDT with ASCT, or new antimyeloma agents, should be considered to improve prognosis (see chapter Treatment of AL amyloidosis).[325,326]

Glomerulonephritis with Nonamyloid Organized Monotypic Deposits

These entities are characterized by fibrillar or microtubular deposits in mesangium and glomerular capillary loops that are readily distinguishable from amyloid because fibrils are thicker and are not stained by Congo red. They were termed "fibrillary glomerulonephritis" (FGN) by Alpers et al.[327] and immunotactoid glomerulopathy (IT) by Korbet et al.[328] There has been considerable debate about the relationship of FGN to IT, and most authors suggested that the two denominations might cover partly different morphologic entities as defined by the size and aspect of organized structures. For Alpers,[329] the distinguishing morphologic features of IT are the presence of organized deposits of large, thick-walled microtubules, usually greater than 30 nm in diameter, which are often hollow and arranged in parallel or stacked arrays, whereas FGN is characterized by more amyloidlike deposits with smaller fibrils (12 to 22 nm).

Although these criteria remain controversial,[330–333] distinguishing IT from FGN may be of great clinical and pathophysiologic interest because the former seemed to be more often associated with monotypic Ig deposits. However, until 2002, it was difficult to assess precisely from the literature, the respective prevalence in each entity of monotypic deposits and of circulating monoclonal Ig because studies of

biopsies with anti-LC antibodies were often incomplete, urine and blood data uncertain, and, even more, patients with dysproteinemias were excluded a priori from several series.[328–330] This issue has been settled in three studies,[333–335] which confirmed that IT has a significant association with underlying dysproteinemia whereas FGN has a wide spectrum of etiologies. Therefore, differentiation of IT from FGN appears justified on immunopathologic and clinical grounds, and this has important therapeutic consequences.

Epidemiology and Clinical Manifestations

The incidence of glomerulopathies with nonamyloid deposition of fibrillary or microtubular material in a nontransplant adult biopsy population is estimated to be about 1% (equivalent to that of antiglomerular basement membrane [anti-GBM] disease). Despite a growing number of case reports, this is most likely underestimated because of the insufficient attention given to atypical reactions with histochemical stains for amyloid and the lack of immuno-histochemical and ultrastructure studies of most biopsy specimens.

The characteristics of fibrillary and immunotactoid glomerulopathies are described in Table 60.21 by comparison with AL amyloid. Patients with IT and FGN have a mean age of 53 to 60 years (extreme: 19 to 86 years) with a male-to-female ratio that varies from one series to another.[8,333–335] They usually present with the nephrotic syndrome, microscopic hematuria, and mild-to-severe renal failure. In most recent series,[333–335] there was no significant difference between IT and FGN patients in serum creatinine level, incidence of nephrotic syndrome, microscopic hematuria, hypertension, and renal failure.

TABLE 60.21 Immunologic and Clinical Characteristics of Fibrillary and Immunotactoid Glomerulopathies

Characteristics	Amyloidosis (AL-type)	Fibrillary Glomerulonephritis (FGN)	Immunotactoid Glomerulopathy (IT)
Congo red staining	Yes	No	No
Composition	Fibrils	Fibrils	Microtubules
Fibril or microtubule size	8–15 nm	12–22 nm	>30 nm[a]
Organization in tissues	Random (β-pleated sheet)	Random	Parallel arrays
Immunoglobulin deposition	Monoclonal LC (mostly λ)	Usually polyclonal (mostly IgG4), occasionally monoclonal (IgG1, IgG4)	Usually monoclonal (IgGκ or IgGλ)
Glomerular lesions	Deposits spreading from the mesangium	MPGN, CGN, MP	Atypical MN, MPGN
Renal presentation	Severe NS, absence of hypertension and hematuria	NS with hematuria, hypertension; RPGN	NS with microhematuria and hypertension
Extrarenal manifestations (fibrillar deposits)	Systemic deposition disease	Pulmonary hemorrhage	Microtubular inclusions in leukemic lymphocytes
Association with LPD	Yes (myeloma)	Uncommon	Common (CLL, NHL, MGUS)
Treatment	Melphalan + prednisone; intensive therapy with blood stem cell autograft	Corticosteroids ± cyclophosphamide (crescentic GN)	Treatment of the associated LPD

[a]Mean diameter of the substructures did not differ between fibrillary glomerulonephritis (15.8 ± 3.5 nm) and immunotactoid glomerulopathy (15.2 ± 7.3 nm) in Bridoux's series.[333]

CGN, crescentic glomerulonephritis; CLL, chronic lymphocytic leukemia; GN, glomerulonephritis; LC, light chain; LPD, lymphoproliferative disorder; MN, membranous nephropathy; MP, mesangial proliferation; MPGN, membranoproliferative glomerulonephritis; NHL, non-Hodgkin lymphoma; NS, nephrotic syndrome; RPGN, rapidly progressive glomerulonephritis.

Pathologic Features

Immunotactoid Glomerulopathy. In IT, renal biopsy shows either membranous glomerulonephritis (often associated with segmental mesangial proliferation) or lobular membranoproliferative glomerulonephritis.[333] By immunofluorescence, coarse granular deposits of IgG and C3 are observed along capillary basement membranes and in mesangial areas. In a series of 23 patients based on ultrastructural appearance of the deposits, IgG deposits were monotypic in 13 of 14 patients with IT (κ, seven cases; λ, six cases), and in only one of nine patients with FGN.[333] However, a circulating monoclonal Ig was detected by immunoelectrophoresis or immunoblotting in only 6 of the 14 patients with IT.[333] Among the five cases of IT available for IgG subtype analysis reported by Rosenstock and associates,[334] four cases featured monotypic deposits of IgG1 subclass, whereas deposits composed of a single gamma subtype (two IgG1 and two IgG4) but with equivalent staining for the κ and λ LCs were found in four of 19 FGN cases.

By electron microscopy, the distinguishing morphologic features of IT are the presence of organized deposits of large, thick-walled microtubules, usually greater than 30 nm in diameter, at times arranged in parallel arrays (Fig. 60.16). However, the mean diameter of the substructures did not differ with their ultrastructural fibrillar or microtubular appearance in Bridoux's series,[333] with the mean external diameter of the microtubules ranging from 9 to 45 nm in patients with IT.

Of the 14 patients with IT reported by Bridoux et al.,[333] six had a chronic lymphocytic leukemia, one a small lymphocytic B cell lymphoma, and three a MGUS. Intracytoplasmic crystal-like Ig inclusions were found in four patients with chronic lymphocytic leukemia and in the lymphoma patient.[333] They showed the same microtubular organization and contained the same IgG subclass and LC isotype as renal deposits. Whether crystallization in lymphocytes and the glomerulus results from unusual intrinsic physicochemical properties of the monoclonal Ig, or from reactivity with a shared epitope, remains to be established. These properties may also account for rapid disappearance of the Ig from the blood and its recurrence on renal graft noted in several patients.[336–339]

Fibrillary Glomerulonephritis. Mesangial proliferation and aspects of membranoproliferative glomerulonephritis are predominantly reported in series of FGN. Glomerular crescents are present in 17% to 30% of the biopsies.[334,335] Immunofluorescence studies mainly show IgG deposits of the γ4-isotype[333,341] with a predominant mesangial localization and along the GBM. Monotypic deposits containing mostly IgGκ are detected in no more than 15% of patients. In a recent series of 66 patients with FGN,[335] seven of 61 biopsies (11%) showed monotypic deposits including five IgGλ and two IgGκ. By electron microscopy, fibrils are randomly arranged and their diameter varies between 9 and 26 nm. Of note, the fibril size alone is not sufficient to distinguish nonamyloidotic fibrillary glomerulonephritis from amyloid.

Although fibril deposition is almost always confined to the kidney, similar fibrillary deposits have been reported in the alveolar capillary membrane in patients presenting with a pulmonary–renal syndrome and in the skin of a patient with a leukocytoclastic vasculitis. In a patient with IT who suffered from severe mononeuritis multiplex of the lower limbs, peripheral nerve biopsy showed a similar ultrastructural microtubular organization to the glomerular deposits.[333]
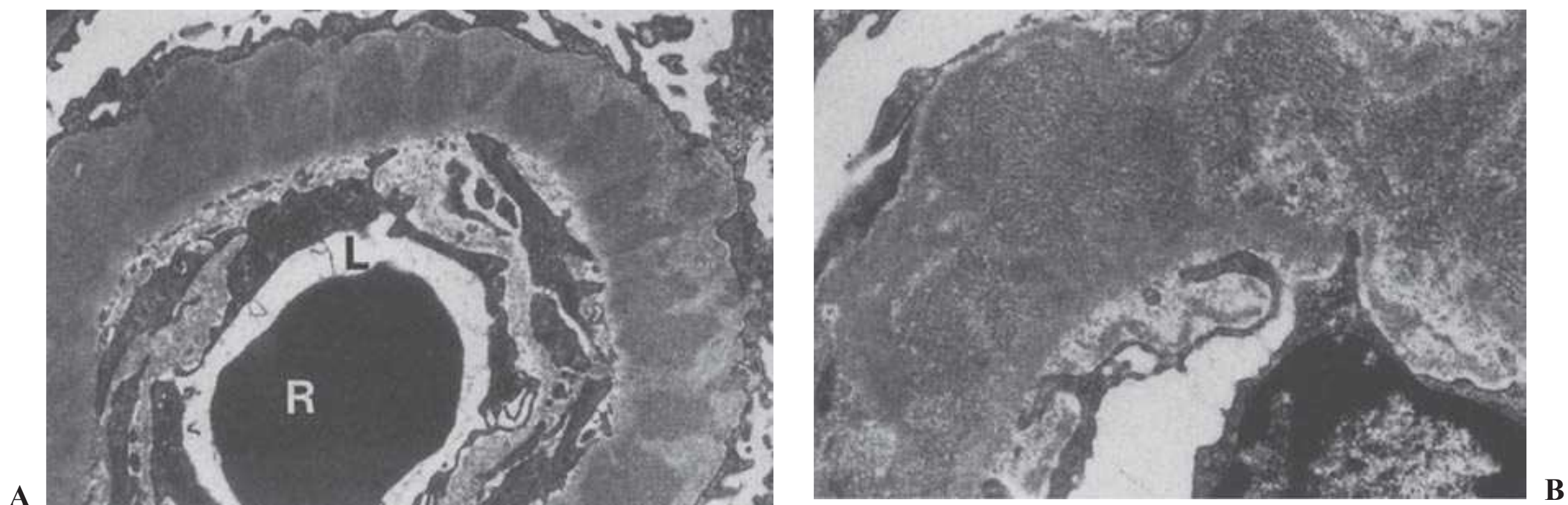

FIGURE 60.16 Immunotactoid glomerulopathy. Atypical membranous glomerulonephritis showing exclusive staining of the deposits with anti-immunoglobulin G and anti-κ–light-chain antibodies, in a patient with chronic lymphocytic leukemia. **A:** Electron microscopy of a glomerular capillary showing subepithelial deposits with effacement of the foot processes and mesangial interposition. *L*, capillary lumen; *R*, red blood cell. (Uranyl acetate and lead citrate, ×4,400.) **B:** Higher magnification of the capillary wall showing microtubular structure of the deposits. (Magnification, ×12,000.) (From Moulin B, Ronco PM, Mougenot B, et al. Glomerulonephritis in chronic lymphocytic leukemia and related B-cell lymphomas. *Kidney Int.* 1992;42:127, with permission.)

Pathogenesis

The cause of FGN is not known. The exclusive or prevailing presence of IgG4 in the immune deposits of patients with FGN is of great interest. Although not monoclonal, this isotype-restricted homogeneous material made of highly anionic Ig may facilitate fibril formation. Amyloid P component has also been found in the fibrils. The description of fibrillar cryoprecipitates consisting of Ig-fibronectin complexes in the serum of patients with FGN without evidence of systemic disease indicates that serum precursors can lead to the formation of fibrillary deposits.[341]

The mechanisms of Ig deposition in lymphocytes and kidney of patients with IT are also poorly understood. Analysis of monoclonal Ig both at the protein and mRNA levels has not disclosed size abnormalities in two patients.[342]

Treatment and Outcome

Patients with FGN usually respond poorly to corticosteroids and cytotoxic drugs, with an incidence of end-stage renal disease of 40% to 50%.[328,331,335,340,343] By contrast, in those with IT, corticosteroid and/or chemotherapy were associated with partial or complete remission of the nephrotic syndrome in most cases, with a parallel improvement of the hematologic parameters.[331,333]

After a mean follow-up period of 54 months for the IT group and 56 months for the FGN group, patient survival (71.4% vs. 88.8%, respectively) was found to be similar for the two groups.[333] The incidence of chronic renal failure (IT: 8/14, 57.1%; FGN: 8/9, 88.8%) and end-stage renal failure (IT: 2/14, 14.3%; FGN: 4/9, 55.8%) tended to be lower in the IT group, but the difference was not statistically significant. In the largest series of FGN published so far,[335] persistent renal dysfunction and end-stage renal failure occurred in 43% and 44% of patients, respectively. Renal transplantation has been performed in only a few patients, and recurrent disease occurred in several.[336–339]

IT (microtubular) glomerulopathies must now be added to the list of glomerulopathies caused by B cell chronic lymphocytic leukemia and related lymphomas, including AL amyloidosis and the larger cohort of cryoglobulinemia-associated membranoproliferative glomerulonephritis (Table 60.22).

60.22 Renal Lesions Observed in B-Cell Proliferations

Renal Lesions	Multiple Myeloma	Waldenström Macroglobulinemia	Chronic Lymphocytic Leukemia and Related Lymphomas
Tubular lesions			
Cast nephropathy	+++	−	−
(Proximal) tubule lesions[a]	+	−	−
Fanconi syndrome	+ (smoldering)	−	−
Glomerular lesions[b]			
AL amyloidosis	++	+	+
MIDD (nodular, membranoproliferative, minimal change)	++	+	−
Nonamyloid organized deposits[c]	−	−	+
Type I and type II cryoglobulinemia	+ −	++ +	++ −
IgM capillary thrombi	+	+	+
Other (crescentic, minimal change, etc.)			
Interstitial lesions			
B cell infiltrate	+[d]	++	++
Nephrocalcinosis	+	−	−
Pyelonephritis (infections)	+	−	−

[a]Without detectable myeloma casts, sometimes acute tubular necrosis.
[b]Glomerular involvement is usually but not always preponderant.
[c]Usually atypical membranous (or membranoproliferative) glomerulonephritis.
[d]Exceptionally, plasmacytoma.
−, not or exceptionally observed; + to +++, semiquantitative rating of the prevalence of renal lesions; MIDD, monoclonal immunoglobulin deposition disease

Proliferative Glomerulonephritis with Nonorganized Monoclonal Ig Deposits

Recently, it has been shown that in the absence of detectable cryoglobulin, glomerular deposition of monoclonal IgG could produce a proliferative glomerulonephritis that mimics immune complex glomerulonephritis by light and electron microscopy.[9] Proper recognition of this entity requires confirmation of monoclonality by staining for the γ-heavy chain subclasses and the LC isotypes. In the largest series to date,[344] that included 37 patients, clinical presentation included renal insufficiency in 68%, proteinuria in 100%, nephrotic syndrome in 49%, and microhematuria in 77%. None of the patients had significant extrarenal symptoms. A monoclonal serum protein with the same heavy and light chain isotype as that of the glomerular deposits (mostly IgG1 or IgG2) was identified in 30% of cases. Most patients displayed membranoproliferative or endocapillary proliferative patterns with membranous features. Glomerular monotypic deposits were made up of IgG3 (mostly κ) in two thirds of the cases. By electron microscopy, granular nonorganized deposits were mostly subendothelial and mesangial, and, by contrast with MIDD, were confined to the glomerular compartment. Tissue fixation of complement was observed in virtually all cases, wherears around 30% of patients had hypocomplementemia.

Treatment with steroids alone or combined with immunosuppressive drugs with or without renin-angiotensin sytem blockade was given in 56% of patients, half of whom achieved complete or partial renal recovery. During an average 30 months of follow-up, 38% of patients had at least partial renal recovery, whereas 38% had persistent renal dysfunction and 22% progressed to end-stage renal disease. Only one patient had myeloma at presentation, and none developed hematologic malignancy over the course of follow-up.[344]

Since the first description of the disease,[345] an increasing number of endocapillary proliferative or membranoproliferative glomerulonephritis cases characterized by monoclonal nonorganized granular IgG or IgM deposits (mostly associated with κ LC) have been reported.[346,354] Similarly with Nasr's series, the disease appears as a renal-limited condition mostly associated with monoclonal IgG3, without C_H1 deletion and systemic monoclonal Ig deposition. MGUS is the most commonly associated clonal disorder, but some patients have evidence of myeloma, chronic lymphocytic laukemia, or other non-Hodgkin B cell lymphomas. As with other renal diseases associated with monoclonal gammopathy, it is likely to recur after kidney transplantation.[347] Whether or not specific treatment aimed at suppressing the underlying clonal disease may reverse or halt progression of chronic kidney disease remains to be confirmed in further studies. Recent studies indicate that treatment with anti-CD20 antibody alone may be very efficient in patients with no overt hematologic malignancy.[348]

Other Types of Glomerulonephritis

Additional histologic forms of glomerulonephritis have been described in monoclonal gammopathies. In type I cryoglobulinemia, a membranoproliferative glomerulonephritis (MPGN) with macrophage infiltration is the most characteristic histologic pattern and the deposits are typically, but not invariably, organized into fibrillary or microtubular structures at the ultrastructural level.[349] Type II cryoglobulinemias are much more common.

Few cases of nonorganized monoclonal Ig deposition disease with a membranous pattern have been reported.[9,346,350,351] Guiard et al. recently reviewed the cases of 26 patients with non-cryoglobulinemic glomerulonephritis and monoclonal Ig deposits. Patients were almost equally divided in two distinct histologic patterns with 14 patients having a membranous nephropathy and the 12 remaining ones having a membranoproliferative glomerulonephritis.[348]

There was a striking relationship between the type of glomerulopathy and the subclass of deposited IgG. As previously reported,[348] IgG3 was the predominant deposited subclass in patients with membranoproliferative glomerulonephritis (80% of cases) whereas IgG1 was identified in 64% of those with a membranous pattern. The κ LC isotype was largely predominant (21/26 cases). A circulating monoclonal Ig could be detected in only 8 of 26 patients. Ultrastructural studies showed that immune deposits were not organized in the majority of patients (78%). In a similar case with a membranous pattern and nonorganized IgG1λ deposits, the circulating monoclonal IgG1λ deposits showed unusual in vitro aggregation properties, including dependence on low ionic strength and neutral pH, which suggest that electrostatic interactions had a role in the precipitation process.[352]

Renal manifestations may also occur in POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes), although they are not related to deposition of the monoclonal immunoglobulin.[353] Finally, rare observations of dense deposit disease[354] and glomerulonephritis with isolated C3 deposits[355] have been recently reported in patients with monoclonal gammopathy or smoldering myeloma. Patients usually present with hematuria, proteinuria, nephrotic syndrome, and severe renal failure. Systemic activation of the complement alternative pathway (CAP) is found in most cases, with autoantibodies against complement factor H in some patients. Kidney biopsy shows glomerular electron-dense C3 deposits without concomitant monoclonal immunoglobulin deposition. Isolated glomerular C3 deposits probably represent an unusual complication of plasma cell dyscrasia related to systemic or local complement activation, through an autoantibody activity of the monoclonal immunoglobulin against a CAP regulatory protein.[356]

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