

CORE CURRICULUM IN NEPHROLOGY

Renal Manifestations of Plasma Cell Disorders

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INTRODUCTION

Plasma cell dyscrasias represent a group of diseases characterized by the clonal expansion of abnormal plasma cells. The result of this clonal expansion is the overproduction of a monoclonal (M) protein which could be either the whole immunoglobulin or a fragment (heavy or light chain alone). Thus, these disorders are also collectively referred to as monoclonal gammopathies.

The most common monoclonal plasma cell disorders are monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), multiple myeloma, light-chain (AL) amyloidosis, and Waldenström macroglobulinemia (Table 1). MGUS and SMM are asymptomatic disorders that by definition lack end-organ damage. On the other hand, multiple myeloma is characterized by the presence of end-organ damage, most commonly anemia, hypercalcemia, renal failure, and osteolytic bone lesions. AL amyloidosis is a less common disorder that can affect any organ, the most common being heart (restrictive cardiomyopathy), kidney (nephrotic syndrome or renal failure), liver, gastrointestinal tract, and peripheral nerves. Waldenström macroglobulinemia is associated with an immunoglobulin M (IgM) monoclonal protein, and can cause hyperviscosity syndrome, anemia, lymphadenopathy, and hepatosplenomegaly.

Renal disease is particularly common in patients with monoclonal plasma cell disorders. Manifestations of renal disease vary depending on the mechanism of injury. This review will concentrate on light-chain cast nephropathy, immunoglobulin light-chain amyloidosis (AL), and monoclonal immunoglobulin deposition disease.

RENAL DISEASE OF PLASMA CELL DYSCRASIA

I. Common

- A. Light-chain cast nephropathy (myeloma kidney)
- B. Immunoglobulin light-chain (AL) amyloidosis (also referred to as primary amyloidosis)
- C. Light chain deposition disease (LCDD)

D. Light heavy chain deposition disease (LHCDD)

E. Acute tubular necrosis

1. Drugs (nonsteroidal antiinflammatory drugs (NSAIDs), bisphosphonates)
 - i. Bisphosphonates have been associated with acute renal failure in patients with and without multiple myeloma; both zoledronic acid and pamidronate have been associated with acute tubular necrosis in these patients; focal segmental glomerulosclerosis and minimal change disease, however, have only been reported with pamidronate
2. Intravenous iodinated contrast
3. Hypercalcemia

F. Cryoglobulinemic glomerulonephritis (GN)

II. Uncommon

A. Acquired Fanconi syndrome

1. Proximal tubulopathy characterized by wasting of amino acids, glucose, uric acid, calcium, phosphate and other organic acids
2. Crystals made up of light chain fragments are often seen in the proximal tubular cells

B. Crystalline nephropathy

1. Crystals can be heterogeneous in size and randomly arranged or homogeneous and arranged in a lattice-like pattern
2. Usually associated with a monoclonal immunoglobulin G (IgG), but monoclonal IgAs have been reported

C. Heavy chain deposition disease (HCDD)

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Table 1. Diagnostic Criteria and Clinical Course of Selected Monoclonal Plasma Cell Disorders

Disorder	Disease Definition*	Clinical Manifestations and Course
Monoclonal gammopathy of undetermined significance (MGUS)	<ul style="list-style-type: none"> ● Serum monoclonal protein < 3g/dL ● Bone marrow plasma cells <10% ● Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to a plasma cell proliferative disorder 	<ul style="list-style-type: none"> ● Asymptomatic ● 1% per year progress to myeloma or related malignancy
Smoldering multiple myeloma (also referred to as asymptomatic multiple myeloma)	<ul style="list-style-type: none"> ● Serum monoclonal protein (IgG or IgA) ≥3g/dL and/or bone marrow plasma cells ≥10% ● Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to a plasma cell proliferative disorder 	<ul style="list-style-type: none"> ● Asymptomatic ● 10% per year progress to myeloma
Multiple Myeloma	<ul style="list-style-type: none"> ● Bone marrow plasma cells ≥10% ● Presence of serum and/or urinary monoclonal protein (except in patients with true non-secretory multiple myeloma) ● Evidence of lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to the underlying plasma cell proliferative disorder. 	<ul style="list-style-type: none"> ● Presence of end-organ damage is needed for diagnosis ● Median survival is approximately 4 years
Waldenström macroglobulinemia	<ul style="list-style-type: none"> ● IgM monoclonal gammopathy ● ≥10% bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype 	<ul style="list-style-type: none"> ● Clinical features include hyperviscosity, anemia, lymphadenopathy, and hepatosplenomegaly ● Median survival is approximately 5-6 years
Systemic Light-chain (AL) Amyloidosis	<ul style="list-style-type: none"> ● Amyloid-related systemic syndrome (such as renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement) ● Positive amyloid staining by Congo red in any tissue ● Evidence that amyloid is light-chain related established by direct examination of the amyloid tissue ● Evidence of a monoclonal plasma cell proliferative disorder 	<ul style="list-style-type: none"> ● Any organ can be involved. Most common are heart, kidney, peripheral nerves, gastrointestinal tract, and liver ● Median survival is approximately 2 years

Adapted from Rajkumar SV, Dispenzieri A, Kyle RA: Monoclonal Gammopathy of Undetermined Significance, Waldenström Macroglobulinemia, AL Amyloidosis, and Related Plasma Cell Disorders: Diagnosis and Treatment. Mayo Clinic Proceedings 81:693-703, 2006; used with permission.

*For each disease entity, all of the listed criteria need to be fulfilled for the diagnosis.

D. Immunoglobulin heavy chain (AH) amyloidosis

E. Fibrillary glomerulonephritis

1. Randomly arranged extracellular Congo red negative fibrils with diameter ranging from 13 to 29 nm

2. Common renal histology include membranoproliferative GN, diffuse proliferative GN, and crescents

3. Clinical presentation includes hematuria, proteinuria, and renal insufficiency

4. Extrarenal manifestations have been reported
 5. Deposits often contain IgG1 and IgG4, but not IgG2 or IgG3
- F. Immunotactoid glomerulonephritis
1. May be a subgroup of fibrillary GN
 2. Fibrils are typically larger (20-55 nm) with a hollow center; they are arranged in an organized pattern resembling microtubules
 3. The deposits often stain positive for monoclonal immunoglobulins
- G. Acute tubulo-interstitial nephritis
- H. Hyperviscosity syndrome
1. Waldenström macroglobulinemia
 2. IgM, IgA, and rarely IgG myeloma
- I. Membranoproliferative glomerulonephritis
1. Myeloma
 2. MGUS (monoclonal gammopathy of unknown significance)
 3. POEMS syndrome (Crow Fukase syndrome) characterized by Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein and Skin lesions
- J. Focal segmental glomerulosclerosis
1. Pamidronate
 2. Also reported in a few myeloma patients who did not receive pamidronate
- K. Plasma cell infiltration
- L. Pyelonephritis
- M. Uric acid nephropathy

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INCIDENCE OF MONOCLONAL GAMMOPATHY-RELATED KIDNEY DISEASE

- I. Varies depending on definitions
- II. In myeloma patients, renal insufficiency is noted in 18% to 56%
- III. At autopsy, renal involvement is seen in approximately 50% of patients with multiple myeloma
 - A. Light chain cast nephropathy (29%-32%)
 - B. AL amyloidosis (5%-11%)
 - C. LCDD (3%-5%)
 - D. Acute tubular necrosis
 1. Common finding
 2. Can occur alone or in conjunction with other pathologies
- IV. Less is known about the incidence of monoclonal gammopathy related kidney disease in patients without myeloma
- V. In patients who have significant proteinuria or renal insufficiency warranting a renal biopsy, more than half have a monoclonal gammopathy-related kidney disease
 - A. Cryoglobulinemic glomerulonephritis – 16.5%
 - B. LCDD – 11.6%
 - C. Light chain cast nephropathy – 10.7%
 - D. AL amyloidosis – 10.7%
 - E. Light heavy chain deposition disease – 4.1%

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MECHANISMS OF RENAL INJURY

- I. Tubular precipitation
 - A. Light chain cast nephropathy
- II. Deposition
 - A. Amyloidosis
 - B. Monoclonal immunoglobulin deposition disease (MIDD)
 1. Light chain deposition disease
 2. Light heavy chain deposition disease
 3. Heavy chain deposition disease
 - C. Crystalline nephropathy
 - D. Fanconi syndrome
- III. Hyperviscosity
 - A. Waldenström macroglobulinemia
 - B. Myeloma with elevated serum concentration
 1. IgM > 30 g/L
 2. IgA > 60 g/L
 3. IgG > 40 g/L
- IV. Glomerular reactions
 - A. AL amyloidosis
 - B. MIDD
 - C. Membranoproliferative glomerulonephritis
 - D. Immune complex mediate glomerulonephritis
 - E. Pamidronate induced focal segmental glomerulosclerosis
 - F. Pamidronate induced minimal change disease
- V. Tubular toxicity
 - A. Acute tubular necrosis
 1. NSAIDs

2. Iodinated contrast

B. Fanconi syndrome

VI. Tubulointerstitial nephritis

A. Associated with the giant cell reaction around light chain cast

B. Likely the result of cytokines released by the presence of light chains

VII. Characteristics of the light chains

A. The nature of the renal disease appears to be predetermined by the primary amino acid sequence of the light chain

1. Cast nephropathy—increased affinity toward Tamm-Horsfall protein

2. Amyloidosis—a higher propensity to misfold due to presence of hydrophobic amino acids in key positions

VIII. Factors that increase susceptibility of the kidney to monoclonal proteins

A. Concentration effect

1. Light chains and heavy chain fragments are freely filtered and are concentrated in the urine

2. Nonfilterable proteins can still be trapped on the glomerular basement membrane

B. Unique environment within the kidney

1. Low pH, high osmolarity, and high urea concentration can increase the pathogenic potential of light chains by promoting abnormal protein confirmation or folding

C. Tamm-Horsfall protein (only found in the distal tubule) is a substrate for binding and aggregation leading to light chain cast formation

D. Molecular receptors exist for light chains in the mesangial cells and proximal tubular cells; the cubilin/megalin complex is the receptor for light chains on the proximal tubular cells; the receptor on mesangial cells has yet to be identified

E. Nephrotoxicity secondary to NSAIDs and intravenous contrast is increased in the presence of the monoclonal light chains

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LIGHT-CHAIN CAST NEPHROPATHY

- I. Clinical features
 - A. More likely in patients with high tumor burden (Durie-Salmon stage III)
 - B. Acute onset of renal failure
 - C. 10% to 15% present with end stage renal disease
 - D. Greater than 75% have sub-nephrotic range proteinuria
 1. Mainly Bence-Jones proteinuria
 2. Often dipstick negative
 - E. Precipitating factors
 1. Volume depletion
 2. Hypercalcemia
 3. NSAIDs
 4. Intravenous contrast
 5. Infections
- II. Pathogenesis
 - A. Increased tubular concentration of light chains
 1. Decreased uptake in proximal tubule
 2. Increased serum concentration
 - B. Binding and co-aggregation with Tamm-Horsfall protein
 1. Obstructive cast forms initially in the distal tubule but can extend into the proximal tubule
 2. Inflammatory response
 3. Reaction enhanced by decreased urine flow and furosemide
- III. Histologic findings
 - A. Intratubular light chain casts
 1. Light chain restriction by immunofluorescence
 2. Crystalline or fractured appearance
 - B. Inflammatory reaction
 1. Giant cell (macrophage) reaction around the casts
 2. Rupture of tubule causes interstitial nephritis
 - C. Acute tubular necrosis is often present
- IV. Prognosis
 - A. Recovery of renal function can be achieved in 26% to 58%
 - B. Factors that favor recovery of renal function
 1. Hypercalcemia
 2. Milder degree of renal impairment
 - C. Renal recovery impacts patient survival
 1. Renal impairment significantly shortens overall survival
 2. Recovery of renal function improves survival to that of patients without renal failure
 3. Response to chemotherapy also determines survival
- V. Treatment
 - A. Restore intravascular volume
 - B. Remove offending agents and nephrotoxic drugs
 1. Hypercalcemia
 - i. Volume repletion and, if necessary, loop diuretics
 - ii. Bisphosphonates should be given in refractory cases, but caution is required given the risk of osteonecrosis and renal toxicity
 - C. Reduce light chain levels
 1. Chemotherapy to decrease light chain production as rapidly as possible
 - i. Thalidomide plus dexamethasone, or
 - ii. Bortezomib plus dexamethasone
 2. Plasma exchange (controversial)
 - i. Efficacy was demonstrated in 2 older studies
 - ii. A more recent study using a combined outcome (dialysis dependence, death, GFR < 30 mL/min/1.73 m²) failed to show any benefits with plasma exchange; however, the new study did not use renal histology as an inclusion criteria; the addition of death into the combined outcome complicated the results since patients who recovered renal function but died would be counted as a failure
 - iii. At this point, plasma exchange may still have a role in patients with cast nephropathy

3. Plasma exchange is still the standard treatment of hyperviscosity in patients with Waldenström macroglobulinemia
- D. Stem cell transplantation is an option in selected patients following initial chemotherapy, primarily to treat underlying myeloma
 1. End-stage renal disease (ESRD) patients are eligible with dose adjustments
 2. Autologous stem cell transplantation
 3. Tandem autologous stem cell transplantations
 4. Allogeneic
 - i. Only potentially curative therapy, but use is limited due to high treatment related mortality rates
 - ii. Option of receiving a kidney transplant from the same donor
 - iii. The kidney transplant can often be accomplished without long term immunosuppression

VI. Management of ESRD

- A. Survival on dialysis is significantly decreased in patients with dysproteinemia who reached ESRD
 1. Median survival was 4 years for LCDD, 2 years for AL amyloidosis and 1 year for multiple myeloma
 2. Infection rate does not appear different than patients without dysproteinemia

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MONOCLONAL IMMUNOGLOBULIN DEPOSITION DISEASE

- I. Subtypes
 - A. Light chain deposition disease (most common)
 - B. Light heavy chain deposition disease
 - C. Heavy chain deposition disease
 - D. MIDD with cast nephropathy
 - E. MIDD with amyloidosis
- II. Clinical features
 - A. Renal involvement is nearly universal
 1. Renal insufficiency
 2. Proteinuria
 - i. Nephrotic range in 40%
 - ii. Usually dipstick positive
 3. Hypertension
 - B. Extrarenal manifestations present in 35%
 1. Most common
 - i. Cardiac – congestive heart failure
 - ii. Liver – elevated liver enzymes
 2. Less common
 - i. Peripheral neuropathy, muscle wasting, carpal tunnel syndrome
 - ii. Deposits have also been found in the lung, gut, nervous system, salivary glands
 - iii. Deposits were found in the brain of one patient with psychosis

- C. Myeloma
 1. 37% to 65% meet criteria for multiple myeloma
 2. More likely to have coexisting cast nephropathy
- D. Light chain restriction
 1. Predominately kappa light chains (3:1)
 2. Over-represented by V_{κ_1} and $V_{\kappa_{1V}}$
- III. Histologic findings
 - A. Light microscopy
 1. Mesangial matrix expansion
 2. Nodular sclerosis glomerulopathy
 3. Glomerular basement membrane thickening
 4. Membranoproliferative and even crescentic glomerulonephritis have been rarely reported
 5. Tubulointerstitial nephritis and atrophy
 6. Vascular sclerosis
 7. Congo red negative
 - B. Immunofluorescence
 1. Linear staining of the tubular basement membrane by antiserum to either kappa or lambda
 - i. This is the most sensitive histologic finding
 2. Glomerular capillary loops are also often positive
 3. Staining of nodules can be weak or absent since nodules are composed of mostly matrix proteins
 - C. Electron microscopy
 1. Granular electron dense deposits are commonly found:
 - i. Subendothelial
 - ii. Subepithelial
 - iii. Focally in the mesangium
 - iv. Occasionally in the vascular wall
- IV. Prognosis
 - A. Kidney
 1. Median time to ESRD is 2.7 years
 2. Predictors of ESRD
 - i. Multiple myeloma
 - ii. Coexistence of cast nephropathy
 - iii. High presenting serum creatinine
 - B. Patient
 1. Median survival varies between 18 months to over 5 years

2. May be related to presence of multiple myeloma
3. Histology may also determine survival

V. Treatment

- A. Renal-limited disease without myeloma
 1. ESRD
 - i. No cytotoxic therapy is necessary
 - ii. Kidney transplant is not advisable unless there is hematologic remission due to the high recurrence rate (>80%)
 2. Not in ESRD
 - i. No consensus
 - ii. Anti-myeloma chemotherapy is reasonable with a goal of stopping renal damage and preserving renal function
 - iii. High dose therapy followed by stem cell transplantation
- B. Extrarenal disease or myeloma
 1. Chemotherapy
 2. High dose therapy followed by stem cell transplant
 - i. Kidney transplant may be considered if complete hematologic response is achieved

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IMMUNOGLOBULIN LIGHT-CHAIN AMYLOIDOSIS

- I. Background
 - A. Historically known as primary systemic amyloidosis
 - B. Usually caused by a monoclonal light chain (light-chain amyloidosis; AL)
 - C. Rare cases of monoclonal heavy chain amyloidosis (AH) have been reported
- II. Clinical features
 - A. Proteinuria
 1. 75% present with proteinuria
 2. Can be massive > 20 g/d, nephrotic range in ~ 30%
 3. High concentration of albumin (dipstick positive)
 - B. Renal insufficiency
 1. Half present with reduced renal function
 2. 20% have serum creatinine > 2 mg/dL
 - C. Hypotension
 1. Often despite a previous history of hypertension
 2. Intolerance to antihypertensives
 - i. Especially with ACE inhibitors or angiotensin receptor antagonists which can precipitate acute renal failure
 3. Orthostatic
 - i. Autonomic dysfunction
 - ii. Low intravascular volume
 - D. Extravascular volume overload
 1. Peripheral edema
 2. Ascites, pleural effusion, pericardial effusion
 - E. Vascular instability
 1. Purpura
 - F. Myeloma
 1. ~18% meet criteria for multiple myeloma
 2. Prognosis is determined by amyloidosis and therefore the distinction is not necessary
 - G. Light chain
 1. Lambda > kappa (2:1)
 2. $V_{\lambda V I}$
 - H. Extrarenal manifestations
 1. Cardiac
 - i. Congestive heart failure
 - ii. Conduction defects
 2. Gut
 - i. Diarrhea (malabsorption)
 - ii. Gastrointestinal hemorrhage
 3. Nervous system
 - i. Peripheral neuropathy
 - ii. Autonomic dysfunction
 4. Soft tissue
 - i. Carpel tunnel syndrome
 - ii. Tongue enlargement
 5. Liver
 - i. Hepatomegaly
 - ii. Elevated liver enzymes
 6. Amyloidoma
- III. Diagnostic criteria for AL amyloidosis
 - A. Demonstration of amyloid fibrils in tissues
 1. 8 to 12 nm fibrils
 2. Congo red positive
 3. Heart, kidney, and liver are most commonly involved sites (>90%)
 4. Fat aspirate and gut biopsy are less sensitive (~80%)
 - B. Fibrils must be composed of monoclonal light chains
 - C. Helpful but not sufficient:
 1. Demonstration of a clonal plasma cell population
 2. Circulating monoclonal protein
- IV. Histologic findings
 - A. Pale amorphous eosinophilic deposits that replace normal mesangial structures
 1. Deposits
 - i. Weakly stain with periodic acid-Schiff
 - ii. Deposits are nonargyrophilic
 - iii. Spikes can be seen on silver stain
 2. Location
 - i. Mesangium
 - ii. Glomerular basement membrane
 - iii. Interstitium
 - iv. Vascular wall
 3. Immunofluorescence
 - i. Demonstrates restriction to either kappa or lambda light chain
 4. Electron microscopy
 - i. Randomly arranged 8 to 12 nm fibrils
 - ii. Extracellular
 5. Amyloid stains
 - i. Apple green birefringence with Congo red

- ii. Yellow-green birefringence with Thioflavin T
 - iii. Persistent staining after potassium permanganate treatment
- B. Amyloid deposits may be difficult to detect
 - 1. Mistaken for minimal change disease
 - 2. The amount of amyloid does not correlate with degree of proteinuria
- V. Prognosis
 - A. 18% progress to ESRD
 - B. Median time from diagnosis to ESRD is 14 months
 - C. Median survival after dialysis is 8 months with conventional chemotherapy
- VI. Treatment
 - A. Conventional chemotherapy
 - 1. Melphalan plus high dose dexamethasone
 - i. 33% complete hematologic response
 - ii. No treatment related mortalities
 - iii. A good option for non-transplant candidates
 - iv. Some studies show equivalence with autologous stem cell transplantation
 - B. High dose chemotherapy followed by autologous stem cell transplantation in selected patients with limited number of organs affected by amyloidosis
 - 1. 40% complete hematologic response rate
 - 2. Organ response follows hematologic response
 - 3. Long-term survival in organ responders
 - C. In patients with ESRD
 - 1. Autologous stem cell transplantation can be performed
 - i. Response rate is similar to non-ESRD patients
 - ii. Higher morbidity rate
 - iii. Responders have successfully undergone kidney transplantation
 - 2. Kidney transplant prior to stem cell transplantation
 - i. Morbidity similar to patients without ESRD
 - ii. Not an option for patients with significant heart involvement as

kidney transplant will cause a delay of stem cell transplantation

- D. Newer agents
 - 1. Thalidomide and dexamethasone
 - i. 19% complete hematologic response
 - ii. 26% organ response
 - iii. High percentage of treatment toxicity (65%)
 - iv. Not suitable for some patients
 - 2. Lenalidomide and dexamethasone

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DIAGNOSTIC APPROACH TO RENAL DYSFUNCTION IN PLASMA CELL DYSCRASIAS

- I. Serum protein electrophoresis
 - A. Monoclonal proteins will appear as a spike in the pattern (Fig 1)
 - B. Sensitivity (500-2000 mg/L)

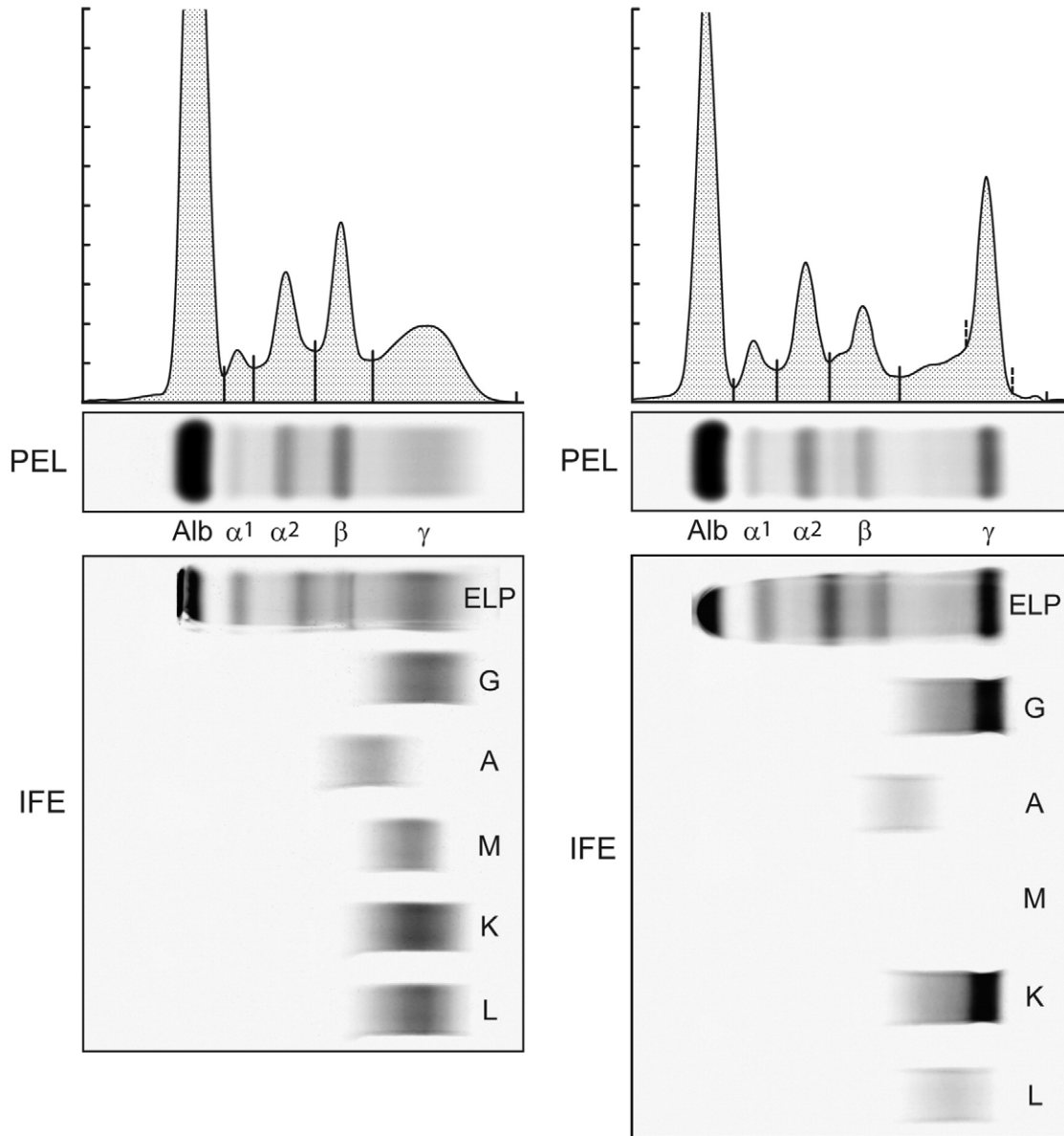


Figure 1. Serum protein electrophoresis showing a normal pattern with a broad-based gamma globulin region (A) and an abnormal pattern with a tall church-spire type monoclonal (M) protein (B).

- C. May not pick up small bands or bands outside of the gamma region
- II. Urine protein electrophoresis
 - A. Useful to determine the make up of the urinary protein
 - 1. A high albumin content suggests a glomerular process
 - B. Both serum and urine should be tested in increase detection to ~95%
- III. Immunofixation
 - A. Anti-serums to light and heavy chains are used to aid in the detection of monoclonal protein after the proteins are separated by electrophoresis
 - B. More sensitive than electrophoresis (detection limits 150-500 mg/L)
- IV. Serum free light chains (FLC) assay
 - A. Most sensitive (detection limit of 0.5 mg/L)

- B. Assay does not detect monoclonality of the light chain but rather an abnormal ratio of kappa versus lambda (for AL amyloidosis FLC is 91% sensitive vs 69% with serum immunofixation and 83% for urine immunofixation)
- C. Sensitivity is 99% when FLC is combined with serum and urine immunofixation
- V. Bone survey
- VI. Bone marrow biopsy
 - A. Test for light chain restriction in the plasma cells
 - 1. Normal percentage of plasma cells does not equal normal
 - B. Congo red stain to test for amyloid
- VII. Fat aspirate
 - A. 80% sensitive for AL amyloidosis
- VIII. Renal biopsy
 - A. Should be performed on all cases if risk permits
 - B. Only way to distinguish between various kidney diseases
 - C. Kidney provides tissue for amyloid typing
 - 1. Always confirm AL type before administering cytotoxic agents
 - D. Based on above test results, with rare exceptions, the diagnosis of AL requires all 4 of following criteria:

- 1. Presence of an amyloid-related systemic syndrome
- 2. Positive amyloid staining by Congo red (eg, fat aspirate, bone marrow, or organ biopsy)
- 3. Evidence on direct examination (immunoperoxidase staining, direct sequencing, etc) reveals amyloid is light-chain related
- 4. Evidence of a monoclonal plasma cell proliferative disorder (serum or urine M protein, abnormal free light chain ratio, or clonal plasma cells in the bone marrow)

ADDITIONAL READING

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