

# Nephroquiz 5: a 51-Year-Old Man With Kidney Failure

Mohammad Tamaddondar,<sup>1</sup> Behdad Rahimi Kelarjani,<sup>2</sup>  
Peyman Torbati,<sup>3</sup> Pedram Ahmadpoor<sup>2</sup>

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<sup>1</sup>Department of Nephrology, Hormozgan University of Medical Sciences, Bandar-Abbas, Iran

<sup>2</sup>Department of Nephrology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

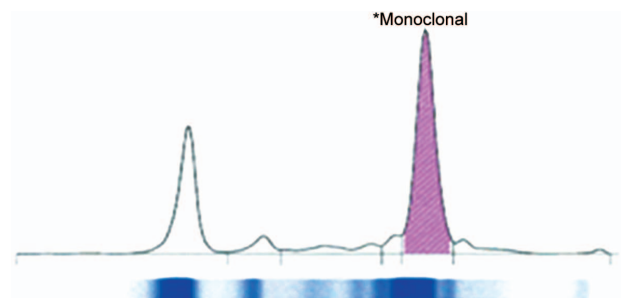
<sup>3</sup>Department of Pathology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

## CASE

A 51-year-old cigarette-smoker man was admitted because of progressive generalized weakness and early fatigability since 3 months earlier. He denoted that his symptoms developed after 2 days of fasting. He also complained of headache, lower extremities bone pain, and a recent episode of respiratory tract infection. The patient was not on any specific medications, and physical examination was unremarkable. Laboratory results are shown in the Table.

Results of hepatitis B and C viruses serology, serum complements 3 and 4, total hemolytic complement, antinuclear antibody, antineutrophilic cytoplasmic antibody, and anti-double-stranded DNA were all negative or in normal range. Urinalysis revealed proteinuria (2+) with 5 to 10 erythrocytes and 5 to 10 leukocytes per high-power field. Serum protein electrophoresis demonstrated hypoalbuminemia, hypogammaglobulinemia, and a monoclonal peak in the beta 2 region (Figure 1). With immunotyping, a high level of immunoglobulin A (IgA) was demonstrated (IgG, 196 mg/dL; IgA, 5965 mg/dL [reference range, 60 mg/dL to 490 mg/dL]; IgM, 6 mg/dL; and IgE, 14.2 mg/dL). Result of urine protein electrophoresis also revealed beta, 97.0%; alpha 2, 1.0%; and albumin, 2.0%. There was no evidence of lytic bone lesions in skull radiography. Chest radiography was negative for cardiomegaly, pulmonary infiltrates, effusions, or bony abnormalities in the ribs.

Because of increasing serum creatinine despite adequate hydration and



## Results of Primary Laboratory Data

| Parameter                             | Value |
|---------------------------------------|-------|
| Leukocyte count, × 10 <sup>9</sup> /L | 8.7   |
| Hemoglobin, g/dL                      | 7.5   |
| Mean corpuscular volume, fL           | 88    |
| Platelet count, × 10 <sup>9</sup> /L  | 120   |
| Blood urea nitrogen, mg/dL            | 21    |
| Serum creatinine, mg/dL               | 4.1   |
| Serum sodium, mEq/L                   | 137   |
| Serum potassium, mEq/L                | 3.9   |
| Serum calcium, mEq/L                  | 9.7   |
| Serum phosphorus, mEq/L               | 4     |
| Serum alkaline phosphatase, IU/L      | 115   |
| Carcinoembryonic antigen, ng/mL       | 0.95  |
| Alpha fetoprotein, ng/mL              | 2.2   |
| Erythrocyte sedimentation rate, mm/h  | 140   |

| Fractions     | %    | Reference %  | g/dL | Reference g/dL |
|---------------|------|--------------|------|----------------|
| Albumin       | 28.6 | 55.8 to 66.1 | 2.89 | 4.02 to 4.76   |
| Alpha 1       | 4.4  | 2.9 to 4.9   | 0.44 | 0.21 to 0.35   |
| Alpha 2       | 6.2  | 7.1 to 11.8  | 0.63 | 0.51 to 0.85   |
| Beta 1        | 3.1  | 4.7 to 7.2   | 0.31 | 0.34 to 0.52   |
| Beta 2        | 52.7 | 3.2 to 6.5   | 5.32 | 0.23 to 0.47   |
| Gamma         | 5.0  | 11.1 to 18.8 | 0.51 | 0.80 to 1.35   |
| *Monoclonal   | 52.2 |              | 5.27 |                |
| Total protein |      |              | 10.1 | 6.1 to 8.3     |
| A/G           |      |              | 0.40 | 1.5 to 2.5     |

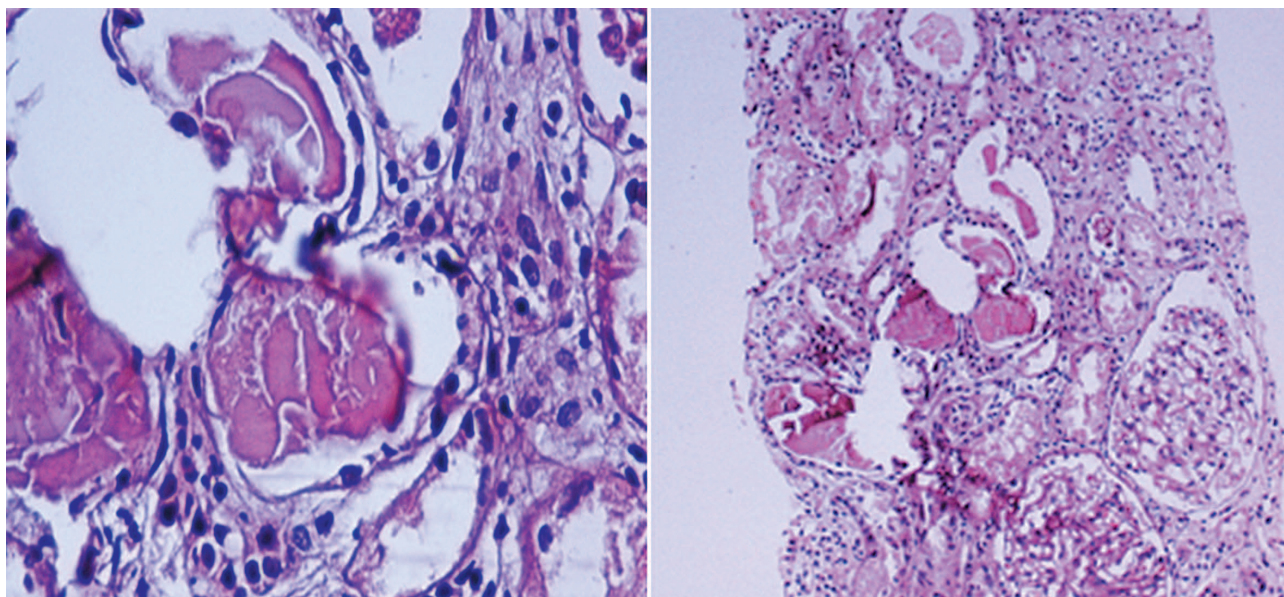
\*A monoclonal band (52.2%) in beta 2 region.

**Figure 1.** Serum protein capillary zone electrophoresis.

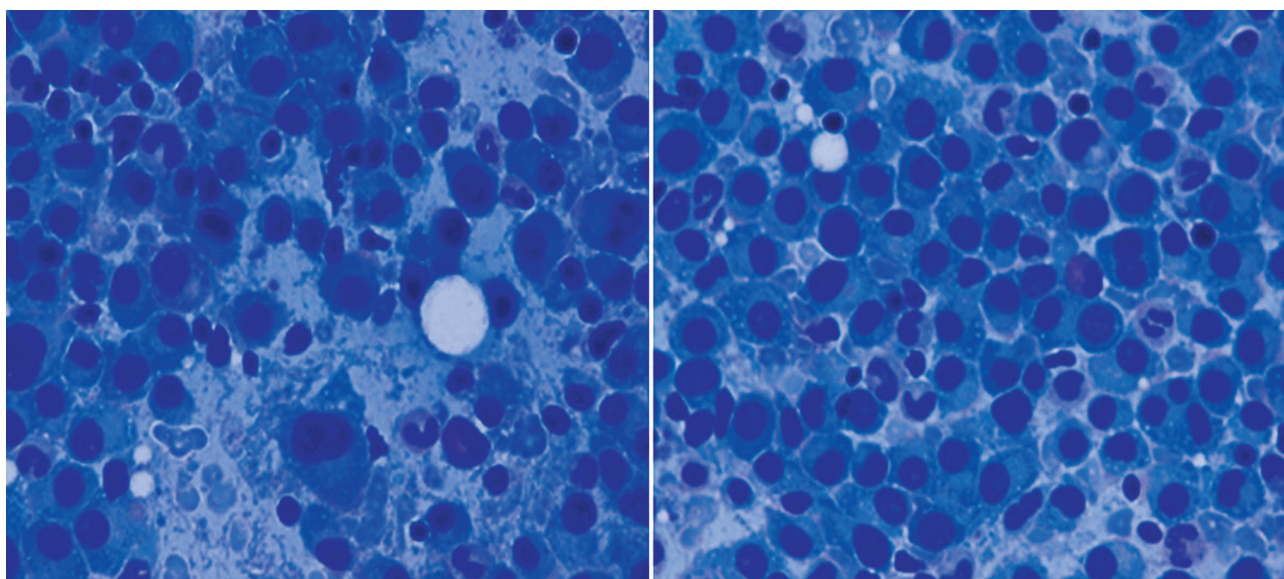
appearance of uremic symptoms hemodialysis via central vein catheter was initiated. Bone marrow and kidney biopsy was taken. On kidney biopsy, half of 18 glomeruli showed mild to moderate segmental mesangial hypercellularity and mesangial widening. Diffuse moderate lymphoplasmacytic infiltration in the interstitium was seen, and some of the tubules revealed degenerative changes (Figure 2, Left). Some tubules contained thick, fragmented, and cracked hyaline materials (Figure 2, Right). On bone marrow biopsy examination, bony trabeculae with intervening fibrotic spaces

could be demonstrated (Figure 3). Cellularity was markedly increased. Myeloid and erythroid series exhibited marked depletion. Megakaryocytes were decreased. The plasma cells population was increased up to 60% of the all nucleated cells and comprised both mature and immature plasma cells. Dysplastic and anaplastic plasma cells were identified.

Cast nephropathy due to IgA myeloma was diagnosed and treatment with dexamethasone and thalidomide, in addition to plasma exchange, was started. On follow-up, the patient became dialysis



**Figure 2.** Kidney needle biopsy specimens.



**Figure 3.** Bone marrow biopsy specimens.

free, and his last serum creatinine was 2.8 mg/dL, 6 weeks after discharge.

## QUIZ

### Do physicochemical characteristics of paraproteins determine the clinical picture?

Plasma cell disorders which include Waldenstrom macroglobulinemia, multiple myeloma (MM), primary amyloidosis, and heavy chain disease, all have common property of monoclonal proliferation of B-cell progenitors. In MM, a single clone of plasma cells proliferates and production of immunoglobulin out of antigenic stimuli is developed. Multiple myeloma accounts for 10% of hematologic and 1% of all malignancies.

The major criteria to diagnose this disease are (1) bone marrow plasmacytosis higher than 30%, (2) plasmacytoma, (3) presence of M component (IgG > 3.5 g/dL or IgA > 2 g/dL), and (4) Bence-Jones proteinuria higher than 1 g/d. Minor criteria are as follows: (1) bone marrow plasmacytosis between 10% and 30%, (2) lytic bone lesion, (3) presence of M component, and (4) immunoglobulin level less than 50% of normal value. With the presence of 1 major and 1 minor criteria or 3 minor criteria, one of which must be plasmacytosis or M component, the diagnosis is established.<sup>1</sup> The M component which denotes the presence of a sharp spike in protein electrophoresis could be seen in the  $\gamma$  globulin region or less commonly in the  $\beta$  or  $\alpha_2$  region and equals to about  $10^9$  antibody-producing cells or an antibody concentration more than 5 g/L.

Multiple myeloma is classified based on the types of secreted immunoglobulins as Ig G myeloma, Ig A myeloma, Ig M myeloma, IgD myeloma, IgE myeloma, and light-chain myeloma. In the most common type, IgG MM, which accounts for half of all MMs, about 50% of patients have kidney failure, and the prevalence of Bence-Jones proteinuria reaches up to 60%. In IgA MM, the second frequent type, hypercalcemia is an important clinical finding and the M component in immunoelectrophoresis study can be frequently detected in the  $\beta$  region as in our case. The IgE MM is the rarest form. The IgM MM differs from the others due to hyperviscosity, multiple organ infiltration, and less frequently, kidney failure. The IgM MM can be distinguished from Waldenstrom macroglobulinemia by the absence of organomegaly and lymphadenopathy. In the IgD MM, serum protein electrophoresis

is frequently normal. In this type of MM, like light-chain myeloma, prevalence of Bence-Jones proteinuria and kidney failure is highest, and in contrast to other types, their associated light-chain is more commonly  $\lambda$  than  $\kappa$ .<sup>2,3,4</sup>

Clinically, kidney involvement in MM presents as tubular dysfunction (Fanconi syndrome), kidney failure (cast nephropathy, hypercalcemia, recurrent infections, hyperuricemia, adverse drug reactions, or rarely, malignant cell infiltration of the kidney), and nephrotic syndrome. Light-chain proteinuria occurs in 47% to 70% of the patients during the course of MM. Asymptomatic light-chain proteinuria, albuminuria, acute kidney injury, chronic kidney disease, proximal and distal tubulopathy are consequences of light-chain proteinuria. The most common causes of kidney failure in MM are cast nephropathy and hypercalcemia.

Electrolyte abnormalities in this condition are pseudo hyponatremia, due to increment of nonaqueous component of plasma; hypercalcemia; hyperphosphatemia; hypophosphatemia (in Fanconi syndrome), and increase in plasma copper level. Anion gap decreases in MM because of accumulation of positive-charge immunoglobulin in plasma or hypoalbuminemia, but in IgA MM, negative-charge proteins increase the anion gap.

Pathologically, all parts of a nephron including glomeruli, tubulointerstitium, and vessels could be involved in plasma cell dyscrasia.<sup>5</sup> Glomerular damages occur due to interaction of immunoglobulins with mesangial cell and could be presented as AL amyloidosis or monoclonal immunoglobulin deposition disease. Tubulointerstitial damage could be proximal or distal. Complete immunoglobulins or monoclonal light chains are the offending molecules in kidney damage in plasma cell dyscrasia. Each immunoglobulin molecule contains 2 parts, a pair of longer chains of identical class or heavy chain (50 000 Da) and a shorter one, light chain (25 000 Da). Light chains in their aminoterminal end, namely variable region (VL part), contain 107 to 111 amino acids which are encoded by 2 genes, V gene for first 95 to 99 AA and J gene for next 12 AA. Their carboxyterminal end, namely constant region (CL part), also contains 107 to 111 amino acids. Heavy chain has also 2 regions, variable and constant. Light chains could be found freely in circulation, but heavy chains need to combine



with light chains before secretion from endoplasmic reticulum; therefore, no free heavy chain could be found in circulation, except in rare conditions known as heavy chain diseases.

In normal condition, circulating light-chain proteins are filtered through glomeruli, then reabsorption and catabolism by lysosomal enzymes of proximal tubular cells occur. Thus, minute amounts of light-chain proteins (< 50 mg/d) could be detected in urine. If this mechanism becomes overloaded due to increased production of light-chain proteins tubular damages will occur.

### Mechanisms of Damage

As noted before, damage could be in different parts of nephron. Apart from direct nephrotoxicity of light chains, their physicochemical characteristics determine their interactions with tissues and cellular components and local environmental conditions that may lead to the variety of renal presentations from cast nephropathy to glucosuria to nephritic syndrome and to deposition of these proteins just in proximal tubules with no evidence of intratubular cast formation.

### Direct Nephrotoxicity

Experimental studies showed that some light-chain proteins, not all of them, could be nephrotoxic and functional or morphologic changes could occur. Light chains have inhibitory effects on alanine and glucose uptake by brush border of proximal tubular cell in rat<sup>6</sup>; they can inhibit activity of sodium-potassium ATPase enzyme,<sup>7</sup> and impairs transport of paraaminohippurate and ammonium production.<sup>8</sup> Human kappa light chain in rat can decrease water and glucose reabsorption, but has no effect on chloride reabsorption or decreased chloride reabsorption, causing more chloride delivery to distal nephron.<sup>6</sup>

Morphologic changes include formation of kappa-containing droplet in proximal tubules, degenerative changes in tubular cells,<sup>9</sup> and loss of microvilli and desquamation.<sup>6,10</sup> In proximal tubules, cytoplasmic pale needle-shaped crystals with a localized distribution due to light chain has been reported.<sup>11</sup>

### Light Chain Characters

Isoelectric point is the particular pH of solution of an amphoteric electrolyte (aminoacid, protein)

in which the charged molecules do not migrate to polar electrode and proteins are least soluble at this pH. Isoelectric points (IP) of Bence-Jones protein determine the probability of kidney dysfunction; cationic Bence-Jones protein or those with IP less than urine pH cause more frequent cast formation and acute tubular necrosis.<sup>12</sup> In evaluation of relationship between light chains IP, polymerization, and sialylation with kidney function of patients from whom this light chain is extracted, higher IP was associated with more proximal tubulopathy, but there was no correlation between IP, sialylation and polymerization of light chain and kidney dysfunction or its recovery.<sup>13</sup> In this study, the patients' hydration, serum calcium level, medications, and urine chemical characteristics had not been reported.

### Tamm-Horsfall Mucoprotein

Koss and colleagues investigated the nephrotoxicity (cast formation in the distal renal tubules) of lambda chain in mice and showed presence of Tamm-Horsfall mucoprotein in renal tissue samples.<sup>14</sup> When urine sodium chloride concentration is greater than 80 mM, molecular size of Tamm-Horsfall mucoprotein will be increased, and more aggregation between Bence-Jones protein with Tamm-Horsfall mucoprotein will occur.<sup>10</sup> The reason of augmentory effect of furosemide for Bence-Jones protein obstructive tubulopathy may be due to more chloride delivery to distal nephron. In colchicines-treated rats, Tamm-Horsfall mucoprotein had no sialic acid and no co-aggregation with Bence-Jones protein.<sup>15</sup>

Multiple Myeloma is a monoclonal proliferation of plasma cell with different renal lesions in which all parts of nephron from glomeruli to distal tubules could be involved, and a variety of electrolyte abnormalities could be seen with each type of the disease. Nephrotic-range proteinuria in glomerular involvement secondary to AL amyloidosis or light-chain deposition disease, tubulointerstitial lesions such as Fanconi syndrome, acute tubular necrosis or cast nephropathy, and tubulointerstitial nephritis are main clinical manifestation of the disease. The site of lesion and clinical syndrome depends on the type of immunoglobulin (IgG, IgA, IgD, IgM, and IgE) or light chain ( $\kappa$  and  $\lambda$ ) secreted by neoplastic cells, the IP of sialylation, and their local catabolism. Moreover, Tamm-Horsfall mucoprotein

physicochemical characteristics and other urine chemical ingredients like chloride concentration may influence renal presentation. Some proteins cause proximal tubule damage, but cationic proteins or those with an IP less than urine pH or when they cause more distal delivery of chloride are more probably associated with cast nephropathy.

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Correspondence to:  
 Pedram Ahmadpoor, MD  
 Department of internal Medicine, Shahid Labbafinejad Medical Center, 9th Boustan St, Pasdaran Ave, Tehran, Iran  
 Tel: +98 21 2258 0333  
 Fax: +98 21 2258 0333  
 E-mail: pedram.ahmadpoor@gmail.com