# Tubulointerstitial Nephritis Accompanying Gamma-Heavy Chain Deposition and Gamma-Heavy Chain Restricted Plasma Cells in the Kidney

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Monoclonal immunoglobulin heavy chain (HC) diseases are rare proliferative disorders of B lymphocytes or plasma cells characterized by the presence of monoclonal α-, μ-, or γ-HC without associated light chains in the blood, urine, or both. We report a 59-year-old woman with a history of Hodgkin disease who developed hypercalcemia, proteinuria, and impaired kidney function. Protein electrophoresis and immunofixation displayed γ-HC without associated light chains in the serum and urine. Pathologic examination demonstrated severe tubulointerstitial nephritis associated with diffuse and strong linear staining of the glomerular and tubular basement membranes as well as Bowman capsules for γ-HC, but not for κ- or λ-light chains. Immunohistochemical examination of the kidney and bone marrow demonstrated numerous CD138+ plasma cells immunoreactive for γ-HC, but not for κ- or λ-light chains. This is the first report of tubulointerstitial nephritis associated with γ-HC deposition and γ-HC restricted plasma cells in the kidney. This report heightens awareness about tubulointerstitial nephritis as a possible manifestation of γ-HC deposition in the kidney.

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Case Report

## INTRODUCTION

Monoclonal immunoglobulin heavy chain diseases (HCD) are rare proliferative disorders of B lymphocytes or plasma cells characterized by the presence of monoclonal α, μ, or γ heavy chains (HCs) in the blood, urine, or both.[1,2] The monoclonal protein consists of a truncated HC without associated light chain (LC). In γ-HCD, the monoclonal protein is a truncated γ-HC that often forms dimers. The etiology of γ-HCD is unknown. The median age at the time of diagnosis of γ-HCD is 60 years. The clinical manifestations of γ-HCD range from a subclinical state (monoclonal gammopathy of undetermined significance) to an aggressive variant of non-Hodgkin lymphoma. Gamma-HCD involving the kidney is exceedingly rare. Histologically, it is characterized by nodular glomerulosclerosis, occasionally with crescents.

Although tubulointerstitial nephritis is a recognized pattern of kidney injury in plasma cell dyscrasias,[3-6] association between γ-HC deposition in the kidney and tubulointerstitial nephritis has not been reported. We report a 59-year-old woman with a remote history of Hodgkin disease who developed proteinuria and impaired kidney function. Protein electrophoresis and immunofixation displayed γ-HC in the serum and urine. Renal biopsy demonstrated severe tubulointerstitial nephritis, γ-HC restricted plasma cells, and γ-HC deposition in the kidney.

## CASE REPORT

A 59-year-old woman presented with altered mental status and was found to have hypercalcemia and impaired kidney function. The patient was

diagnosed with Hodgkin lymphoma and treated with splenectomy and radiation in 1992. Five years later, she was treated with adriamycin, bleomycin, vinblastine, and dacarbazine for recurrent disease. Past medical history was also notable for long-standing hypertension, dyslipidemia, hypothyroidism, and premature menopause. Past surgical history was remarkable for splenectomy, tonsillectomy, and breast surgery for microcalcifications. Medications included amlodipine, metoprolol, folate, levothyroxine, estradiol, and progesterone. The patient denied use of over-the-counter medications, tobacco products, and recreational drugs. She would occasionally drink alcoholic beverages. Family history was notable for ovarian cancer and hypertension.

Review of the systems was remarkable for nocturia, leg edema, and unexplained weight loss. She denied cough, hemoptysis, shortness of breath, vomiting, abdominal pain, diarrhea, dysuria, arthralgia, bone pain, skin rash, and focal neurologic deficits. On physical examination, the patient was a thin woman in no acute distress. The body temperature was 37°C, blood pressure was 134/76 mm Hg, pulse was 80 beats per minute, respiratory rate was 12 breaths per minute, oxygen saturation was 98% while breathing ambient air, and body weight was 46.8 kg. Jugular venous pressure was normal. Cardiovascular and pulmonary examination was unremarkable. There was no lymphadenopathy or organomegaly. There was pitting edema over shins. There was no skin rash. There were no focal neurologic deficits.

Laboratory data are summarized in Tables 1 and 2. There was mild hypercalcemia, hyponatremia, and hyperkalemia. Parathyroid hormone level was reduced, while parathyroid hormone-related peptide was elevated. Total 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were normal. Serum creatinine and urea nitrogen concentrations were elevated at 1.7 mg/dL and 26 mg/dL, respectively. There was mild monocytosis and eosinophilia. Examination of a peripheral blood smear demonstrated normocytic normochronic erythrocytes and mature leukocytes. There were no plasma cells or atypical lymphocytes. Urinalysis revealed proteinuria. Daily urinary protein excretion was 2.3 g, estimated using random urine protein-creatinine ratio. Serum immunoglobulin G level was markedly elevated, while serum immunoglobulin

**Table 1.** Blood Studies

| Parameter | Value | Reference Range |
|---|---|---|
| Sodium, mmol/L | 130 | 135 to 145 |
| Potassium, mmol/L | 5.0 | 3.4 to 4.8 |
| Chloride, mmol/L | 92 | 99 to 109 |
| Carbon dioxide, mmol/L | 26 | 21 to 30 |
| Urea nitrogen, mg/dL | 26 | 7 to 22 |
| Creatinine, mg/dL | 1.7 | 0.8 to 1.4 |
| Glucose, mg/dL | 83 | 65 to 99 |
| Calcium, mg/dL | 10.4 | 8.6 to 10.3 |
| Phosphorus, mg/dL | 3.8 | 2.5 to 4.5 |
| PTH, pg/mL | 8 | 10 to 65 |
| PTH-RP, pg/mL | 36 | 14 to 27 |
| AP, IU/L | 58 | 30 to 130 |
| Protein, g/dL | 7.1 | 6.2 to 8.3 |
| Albumin, g/dL | 4.2 | 3.5 to 5.2 |
| AST, IU/L | 28 | 5 to 45 |
| ALT, IU/L | 16 | 5 to 60 |
| Bilirubin, total, mg/dL | 0.5 | 0.1 to 1.2 |
| Hemoglobin, g/dL | 11.9 | 13.6 to 16.7 |
| Hematocrit, % | 34.8 | 40.0 to 49.0 |
| MCV, $\mu m^3$ | 97.2 | 80 to 100 |
| Leukocyte count, x $10^9$/L | 10.3 | 4.8 to 10.8 |
| Neutrophils, x $10^9$/L | 5.7 | 1.5 to 7.0 |
| Lymphocytes, x $10^9$/L | 2.4 | 1.0 to 3.7 |
| Monocytes, x $10^9$/L | 1.6 | 0.0 to 0.7 |
| Eosinophils, x $10^9$/L | 0.6 | 0.0 to 0.4 |
| Basophils, x $10^9$/L | 0.05 | 0.0 to 0.1 |
| Platelet count, x $10^9$/L | 374 | 130 to 400 |
| C-reactive protein, mg/dL | 0.1 | <0.8 |
| ESR, mm/h | 1 | 0 to 20 |
| ANA | Negative | Negative |
| Rheumatoid factor, IU/mL | < 14 | < 14 |
| Hepatitis C antibody | Negative | Negative |
| HIV 1 antibody | Negative | Negative |
| Serum protein electrophoresis | Abnormal | Normal |
| Alpha-1 globulins, g/dL | 0.1 | 0.1 to 0.3 |
| Aalpha-2 globulins, g/dL | 0.7 | 0.5 to 1.0 |
| Beta globulins, g/dL | 2.5 | 0.8 to 1.4 |
| Gamma globulins, g/dL | 0.2 | 0.6 to 1.6 |
| Serum IgG, mg/dL | 4607 | 694 to 1618 |
| Serum IgA, mg/dL | 108 | 81 to 463 |
| Serum IgM, mg/dL | 31 | 48 to 271 |
| Serum light chains | | |
| Total kappa light chain, mg/dL | 92 | 74 to 295 |
| Total lambda light chain, mg/dL | 46 | 32 to 156 |
| Total Kappa-lambda ratio | 2.0 | 1.3 to 2.7 |
| Free Kappa light chain, mg/dL | 1.2 | 0.3 to 1.9 |
| Free Lambda light chain, mg/dL | 0.7 | 0.6 to 2.6 |
| Free Kappa-lambda ratio | 1.7 | 0.3 to 1.7 |

*PTH indicates parathyroid hormone; PTH-RP, parathyroid hormone-related peptide; AP, alkaline phosphatase; AST, Aspartate transaminase; ALT, Alanine transaminase; MCV, mean corpuscular volume; ESR, erythrocyte sedimentation rate; and ANA, antinuclear antibodies.

**Table 2.** Urine Examination

| Parameter | Value | Reference Range |
|---|---|---|
| Urinalysis | | |
| Color | Yellow | Yellow |
| Turbidity | Clear | Clear |
| Specific gravity | 1.011 | 1.001 to 1.030 |
| pH | 6.0 | 4.6 to 7.8 |
| Glucose | Negative | Negative |
| Ketones | Negative | Negative |
| Bilirubin | Negative | Negative |
| Blood | Trace | Negative |
| Protein | 2+ | Negative |
| Nitrites | Negative | Negative |
| Leukocyte esterase | Negative | Negative |
| Leukocyte, count per HPF | 0-2 | 0 to 2 |
| Erythrocyte, count per HPF | 0-2 | 0 to 2 |
| Urine protein, mg/dL | 187 | 5 to 24 |
| Urine creatinine, mg/dL | 80 | 20 to 370 |
| Urine protein to creatinine | 2.3 | 0.02 to 0.13 |
| Urine protein electrophoresis | Abnormal* | Normal |

*Abnormal peak in the beta region

M level was mildly reduced. Serum protein electrophoresis displayed hypogammaglobulinemia and an abnormal band in the β region. Serum immunofixation revealed γ-HC, but there were no monoclonal proteins in the κ or λ lane. Serum concentrations of total and free κ- and λ-LC were normal. Urine protein electrophoresis displayed an abnormal band in the β region and virtually no proteins in the γ region. These findings were consistent with circulating monoclonal γ-HC in the serum and urine.

Renal ultrasonography demonstrated a right kidney measuring 11.7 cm and a left kidney measuring 11.0 cm in length. There was no hydronephrosis or calculi. There were 3 simple renal cysts measuring up to 1.8 m in diameter. Doppler ultrasonography demonstrated no evidence of renal artery stenosis. Despite intravenous fluids, kidney function remained impaired. Considering the presence of a monoclonal protein in the blood and urine, renal biopsy was undertaken. Histologic examination demonstrated 15 glomeruli, 5 of which (33%) were globally obsolescent. The remaining glomeruli showed mild segmental expansion of mesangial matrix. The interstitium was edematous and demonstrated diffuse intense polymorphonuclear and mononuclear inflammatory cell infiltration, including plasma cells and eosinophils (Figure 1A). Nodular aggregates of mononuclear inflammatory cells resembling lymphoid follicles were scattered in the interstitium. Special stain for amyloid (Congo red) was nonreactive. Immunofluorescence examination demonstrated diffuse and strong (3+) linear γ-HC staining of the glomerular and tubular basement membranes as well as Bowman capsules (Figure 1B). However, there was no significant immunostaining for κ- and λ-LC (Figures 1C and 1D). Immunohistochemical examination showed numerous CD138+ plasma cells that stained strongly for γ-HC, but not for κ- and λ-LC (Figures 1E to 1L). The interstitium also contained numerous CD68+ macrophages and monocytes, CD3+ T and CD20+ B lymphocytes. In the sample submitted for electron microscopy, no intact glomerulus was present for ultrastructural evaluation. A pathological diagnosis of diffuse severe acute and chronic (active) tubulointerstitial nephritis associated with γ-HD deposition was rendered.

Bone marrow aspiration and biopsy were performed. Examination of bone marrow smear demonstrated normal erythropoiesis, myelopoiesis, and megakaryopoiesis. There were no dysplastic changes. Examination of bone marrow revealed normal cellularity for age (50%) and maturing trilineage hematopoiesis (Figure 2A). Immunohistochemical examination of the bone marrow revealed increased numbers of CD138+ plasma cells (10%; normal, < 1%; Figure 2B). Most CD138+ plasma cells showed increased immunostaining for γ-HC, but not for κ- and λ-LC (Figure 2C to 2E). Rare scattered cells immunostained for α- and μ-HC (Figure 2F and 2G). The percentages of CD20+ B and CD3+ T lymphocytes were 3% and 10% of all nucleated cells, respectively (Figures 2H and 2I). An increase in eosinophils (8%; normal, about 1%) was also noted. Flow cytometry of the bone marrow aspirate failed to detect a monoclonal cell population. Cytogenetic analysis of the bone marrow aspirate detected no chromosomal abnormalities in the cells analyzed.

Extensive imaging studies including computed tomography, magnetic resonance tomography, positron emission tomography, bone survey, and bone scan did not show localizable neoplastic disease. The patient was started on high-dose glucocorticoids, which led to a decline in serum creatinine concentration from 1.7 mg/dL to 1.2 mg/

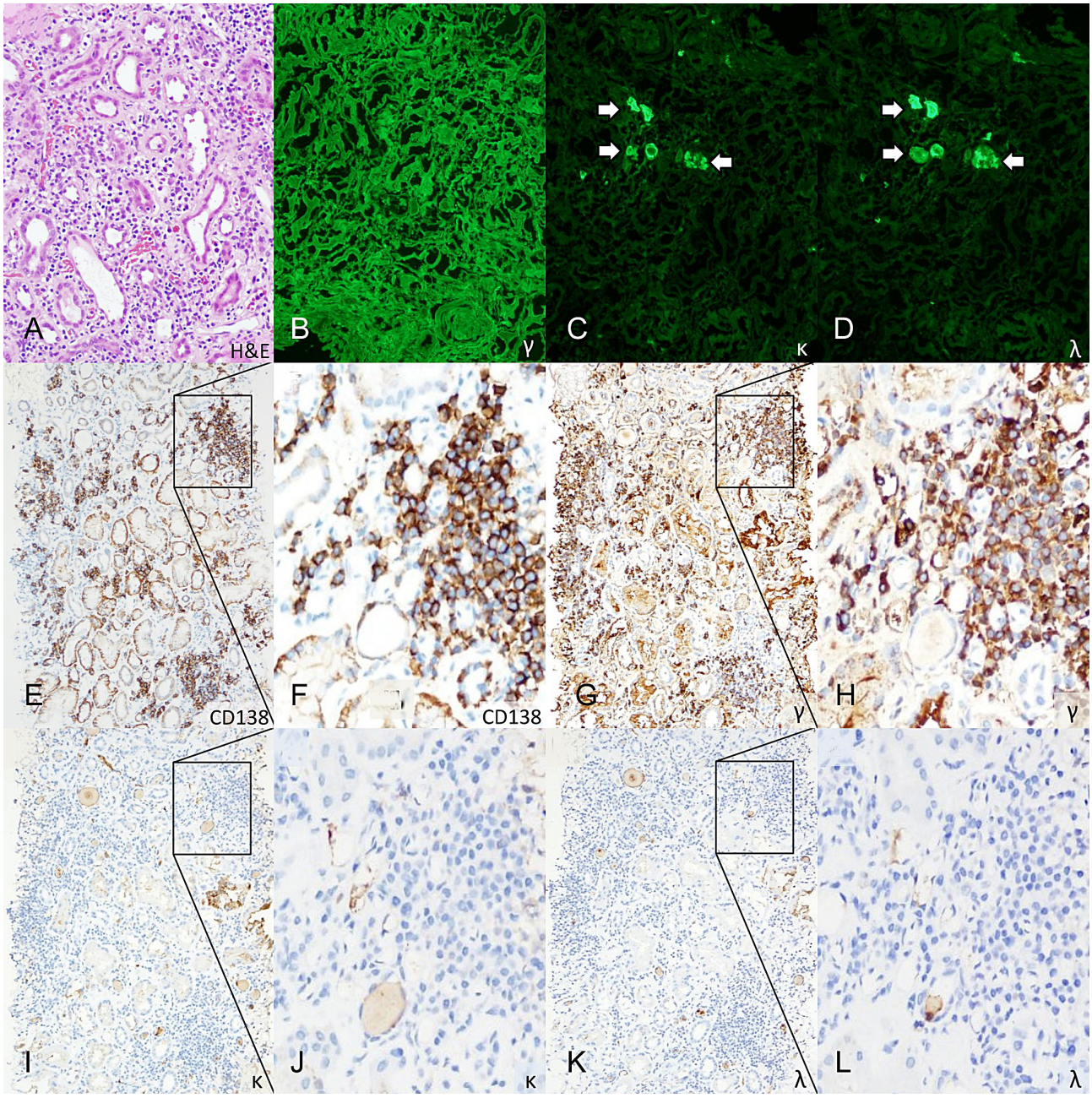


**Figure 1.** Tubulointerstitial nephritis accompanying γ-heavy chain deposition and γ-heavy chain restricted plasma cells in the kidney. **A**, Photomicrograph demonstrating separation of tubules due to edema and inflammatory cell infiltration in the interstitium (hematoxylin-eosin). **B to D**, Immunofluorescence examination revealing diffuse strong immunoreactivity for γ-heavy chain, but not for κ- and λ-light chains. A few hyaline casts in the tubules (arrows in C and D) demonstrating nonspecific immunoreactivity for κ- and λ-light chains (immunofluorescence staining). **E to L**, Immunohistochemical examination revealing strong immunoreactivity of CD138+ plasma cells for γ-heavy chain (E to H), but not for κ- and λ-light chains (I to L; immunoperoxidase staining). Photomicrographs in F, H, J, and L are higher magnifications of those in E, G, I, and K, respectively.

dL over the subsequent 3 weeks. Later, she was treated with oral cyclophosphamide, intravenous bortezomib, and oral dexamethasone for γ-HCD.

## DISCUSSION

With a remote history of Hodgkin disease treated with splenectomy, radiation, and chemotherapy, a 59-year-old woman developed hypercalcemia, proteinuria, and impaired kidney function. Protein electrophoresis and immunofixation displayed monoclonal γ-HC in the serum and urine. Serum concentrations of total and free κ- and

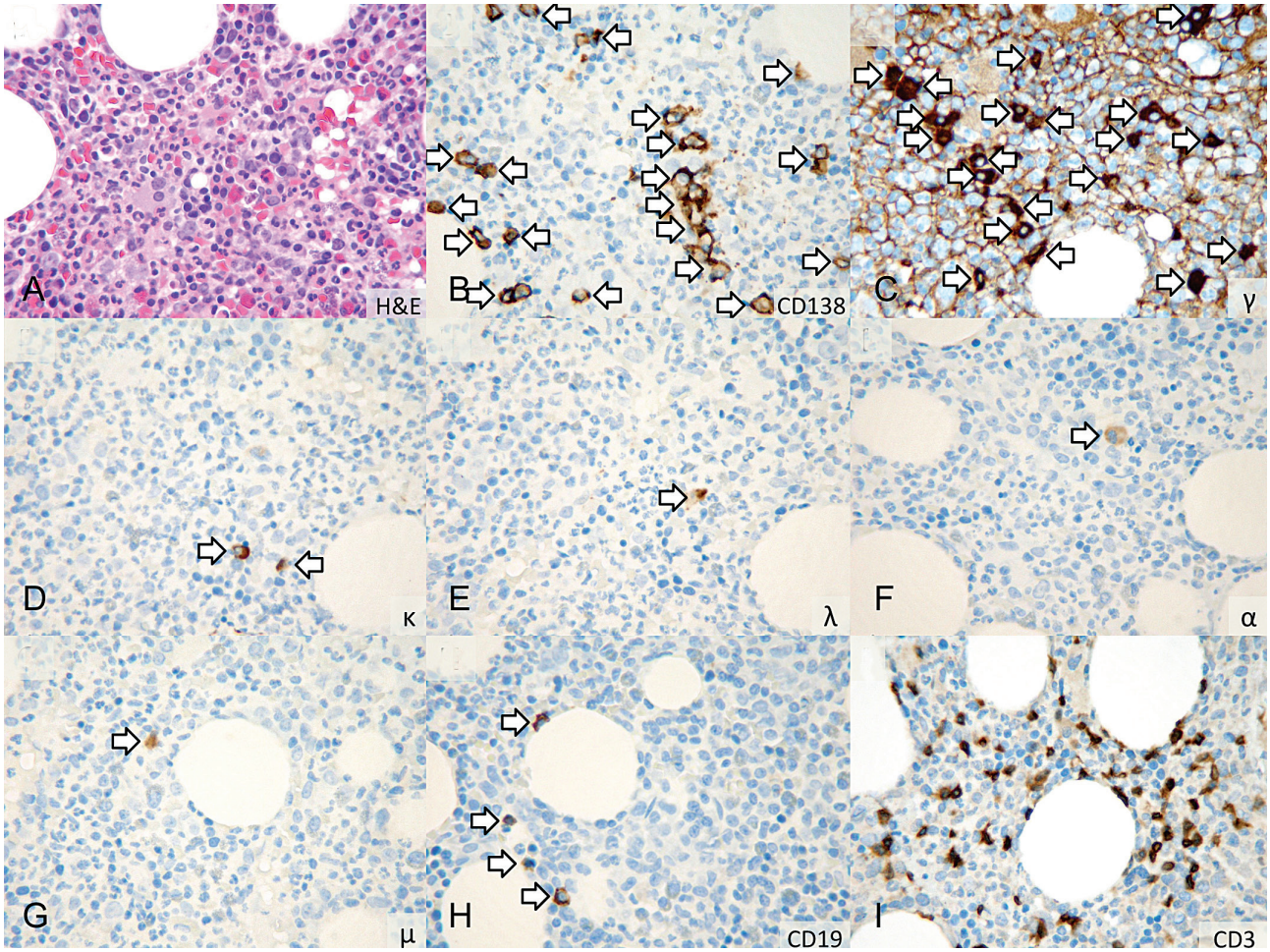


**Figure 2.** Gamma-heavy chain restricted plasma cells in the bone marrow. **A**, Bone marrow biopsy revealing normal cellularity for age and maturing trilineage hematopoiesis (hematoxylin-eosin). **B to G**, Immunohistochemical examination revealing the majority of CD138+ plasma cells (arrows in B) expressing γ-heavy chain (arrows in C), but not κ- or λ-light chains (D and E). Rare scattered cells showing weak immunoreactivity for κ- and λ-light chains (arrows in D and E) as well as for α- and μ-heavy chains (arrows in F and G; immunoperoxidase staining). **H and I**, Immunostaining for CD20 and CD3 revealing scattered B and T lymphocytes, respectively (immunoperoxidase staining).

λ-LC were normal. Renal biopsy demonstrated tubulointerstitial nephritis associated with γ-HC deposition. Plasma cells in the kidney and bone marrow expressed γ-HC without associated LCs. The patient was diagnosed with severe interstitial nephritis and γ-HC deposition in the kidney.

The clinical manifestations of γ-HCD are distinct from multiple myeloma and range from a subclinical state (monoclonal gammopathy of undetermined significance) to an aggressive lymphoproliferative disorder. In approximately 25% of cases, γ-HCD is associated with an autoimmune disorder such as rheumatoid arthritis. While constitutional symptoms, lymphadenopathy, and splenomegaly are the usual features of γ-HCD, bone lesions are rarely encountered. Serum protein electrophoresis may or may not demonstrate a monoclonal gammopathy. Immunofixation or immunoelectrophoresis is required for the detection of monoclonal γ-HC in the serum or urine. The bone marrow or lymph nodes usually demonstrate an increase in plasma cells, lymphocytes, or plasmacytoid lymphocytes. At times, an increase in eosinophil count is noted. Neoplastic cells in γ-HCD may be blended with large immunoblasts with atypical nuclei resembling Reed-Sternberg cells suggesting Hodgkin disease. The choice of therapy depends on the biological behavior of γ-HC and ranges from observation to an aggressive antineoplastic regimen.

The monoclonal immunoglobulin deposition in the kidney is characterized by accumulation of monoclonal light, heavy, or combined light

and heavy chains in the kidney.[7-9] Monoclonal HC deposition in the kidney is exceedingly rare. Proteinuria, frequently in the nephrotic range, edema, hematuria, and renal insufficiency are the usual manifestations of HC deposition in the kidney. Hypocomplementemia is occasionally present and appears to be related to the complement binding ability of the particular subclass of the monoclonal HC. Histologically, nodular glomerulosclerosis is the usual pattern of renal injury. Crescents are occasionally present. Immunofluorescence examination reveals strong staining of the mesangium and the glomerular, tubular, and vascular basement membranes for HC, but not for κ- or λ-LC. At times, there is immunoreactivity for complements C1q and C3. Ultrastructural examination reveals electron-dense deposits generally in the same distribution pattern as demonstrated by immunofluorescence examination. In the series of monoclonal heavy chain deposition in the kidney reported by Nasr and colleagues,[9] the monoclonal protein was γ-HC in 6 of 7 cases (86%).

An important histopathologic feature of the kidney disease in our case was severe acute and chronic active tubulointerstitial nephritis. Macrophages/monocytes (CD68+), T lymphocytes (CD3+), B lymphocytes (CD20+), and eosinophils were diffusely distributed in the edematous interstitium and focally invaded the tubules. Nodular aggregates of mononuclear inflammatory cells resembling tertiary lymphoid follicles were scattered in the interstitium. It is conceivable that tubulointerstitial nephritis could have been superimposed on γ-HCD in the kidney. However, no precipitating factor such as a new medication could be elicited. Tubulointerstitial nephritis is a recognized but often overlooked pattern of renal injury in plasma cell dyscrasias.[3-6] Cast nephropathy, LC nephropathy, and LC deposition disease can be associated with tubulointerstitial nephritis.[3,6] Using ultrastructural immunogold labeling, Gu and Herrera reported an association between acute tubulointerstitial nephritis and an unusual pattern of LC deposition along tubular basement membranes.[5] However, an association between γ-HC deposition in the kidney and tubulointerstitial nephritis has not been reported. Castelino and colleagues described a patient with Sjögren syndrome who had γ-HCD and tubulointerstitialnephritis.[10] However, tubulointerstitial nephritis is a common renal complication in Sjögren's syndrome.[3]

Another important aspect of our case was the demonstration of neoplastic plasma cells in the bone marrow and kidney. Flow cytometry of the bone marrow aspirate failed to detect a monoclonal cell population likely due to the low numbers of neoplastic cells in the sample analyzed. We demonstrated the clonality of plasma cells by their selective immunoreactivity for γ-HC, but not for α-HC, μ-HC, κ-LC, or λ-LC. As noted earlier, the clinical course of γ-HCD is extremely variable and the choice of therapy depends in part on the extent of the disease.[1,2] Therefore, special attention to the clonality of plasma cells present in tissues sampled is prudent.

In conclusion, we present the first report of tubulointerstitial nephritis associated with γ-HC deposition and γ-HC restricted plasma cells in the kidney. This case heightens awareness about tubulointerstitial nephritis as a possible manifestation of HCD in a proper context.

## CONFLICT OF INTEREST

None declared.

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