Kidney Medicine

Heavy Chain/Light Chain Antibody Immunofluorescence to Identify Monoclonal Plasma Cells in a Case of Plasma Cell-Rich Acute Interstitial Nephritis

Niloufarsadat Yarandi, Mariam P. Alexander, Samih H. Nasr, and Nelson Leung

Heavy/light chain (HLC) antibodies can be used to quantify intact HLC pairs. In immunofluorescence studies, they allow differentiation of monoclonal versus polyclonal immunoglobulin deposits in kidney diseases that occur in the setting of monoclonal gammopathy. Here, we present a case of a patient with acute kidney injury with first kidney biopsy suggestive of acute interstitial nephritis with a polymorphous infiltrate of plasma cells. Routine immunofluorescence did not show a monotypic plasma cell infiltrate. Serum protein electrophoresis and immunofixation revealed monoclonal immunoglobulin A (IgA) lambda. She improved with steroid therapy, but kidney function worsened after steroids were stopped. She underwent a second kidney biopsy, which showed plasma cell-rich interstitial infiltrate with a population of IgA lambda-restricted plasma cells on routine immunofluorescence. In light of this finding, Hevylite HLC antibody was used to reassess the first biopsy, which confirmed the presence of a population of plasma cells with IgA lambda restriction. Because of the presence of monotypic plasma cells, anti-CD38 monoclonal antibody (daratumumab) was initiated.

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INTRODUCTION

It is critical to determine monoclonal versus polyclonal gammopathy involvement in kidney diseases because the management and outcomes are quite different.[1] Traditionally, correlation of clinical data with interpretation of light microscopy, immunofluorescence (IF), and electron microscopy in kidney biopsy, and sometimes supplementary methods including immunoglobulin (Ig) G subtype staining, paraffin IF, or mass spectrometry, are required to yield differentiation and diagnosis. Monoclonal Ig deposits are diagnosed on IF by Ig light chain isotype restriction. If the deposits are composed of entire Ig, both light chain and heavy chain restriction would be present.[1-3] These techniques may not be specific enough to diagnose monoclonal Ig-associated nephropathies when deposits are comprised of different classes of Igs.[1] Here we describe a case of plasma cell-rich interstitial nephritis with kidney biopsy showing polyclonal plasma cell infiltrates using traditional IF staining; however, anti-heavy/light chain (HLC) antibody revealed a population of monoclonal plasma cells staining for IgA lambda.

CASE REPORT

A woman in her 50s with past medical history significant for breast cancer 7 years prior and Hodgkin's lymphoma 40 years before presentation developed acute kidney injury. Her creatinine level was 3.72 mg/dL, increased from a baseline of 1.25 mg/dL 4 months earlier. Her serum protein electrophoresis and immunofixation revealed an IgA lambda monoclonal protein at a concentration of 2.1 g/dL, kappa free light chain of 12.8 mg/dL, lambda free light chain of 8.42 mg/dL, and a kappa to lambda ratio of 1.52. Her IgA level was 2,280 mg/dL.

Kidney biopsy showed acute interstitial nephritis polymorphous infiltrate with plasma cells (Fig 1A-C). Bone marrow biopsy did not show any monoclonal plasma cell population.

She was started on prednisone, resulting in an improvement in creatinine to 1.8 mg/dL. Prednisone was tapered and eventually discontinued. Three months after discontinuation of prednisone, creatinine level increased to 4.0 mg/dL, and IgA level was 2,360 mg/dL. The patient underwent a second kidney biopsy which revealed residual patchy acute interstitial nephritis with a population of IgA lambda-restricted plasma cells present in the interstitium (Fig 2).

The patient was restarted on prednisone. Her creatinine decreased to 2.02 mg/dL but plateaued. The presence of polyclonal plasma cell-rich infiltrates raised the suspicion of Sjögren syndrome. Further evaluation noted positive antinuclear antibody of 1:160 (negative < 1:80) in a speckled pattern, positive rheumatoid factor of 94 IU/mL (negative <15 IU/mL), positive Sjögren syndrome A IgG >8.0 U (positive ≥1.0 U), and negative Sjögren syndrome B IgG < 2.0 (negative < 1.0). The biopsy of the minor salivary gland showed lymphoplasmacytic sialadenitis consistent with Sjögren syndrome. Her repeat bone marrow biopsy revealed < 5% monotypic lambda light chain-restricted plasma cells. A positron emission tomographic scan did not show any evidence of lytic bone lesions or plasmacytoma.

To determine if the monoclonal plasma cells were in fact present in the first biopsy, IF with HLC antibodies (Hevylite) was performed. This showed the presence of

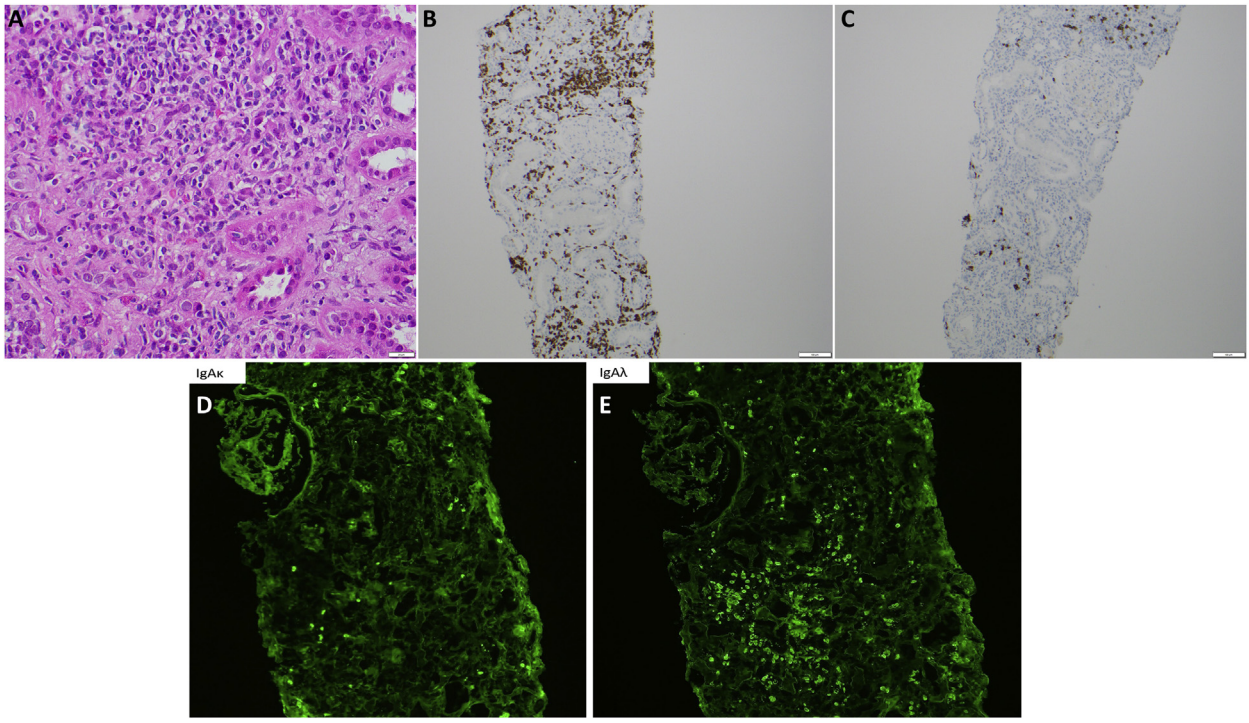

Figure 1. Pathologic findings in the first biopsy. (A) A polymorphous inflammatory infiltrate with a plasma cell population identified (hematoxylin and eosin; original magnification, ×40). (B-C) The dense lymphocytic infiltrates were predominantly composed of $CD3^+$ T cells (B, CD3 immunohistochemistry; original magnification, ×20) with a lesser number of $CD20^+$ B cells (C, CD20 immunohistochemistry; original magnification, ×20). Retrospective staining of this biopsy with HLC antibodies highlighted a population of monotypic plasma cells with IgA lambda restriction, which was admixed with polyclonal plasma cells. (D-E) The ratio of IgA lambda-positive plasma cells (E, Original magnification, ×20) to IgA kappa positive plasma cells (D, original magnification, ×20) was 9:1.

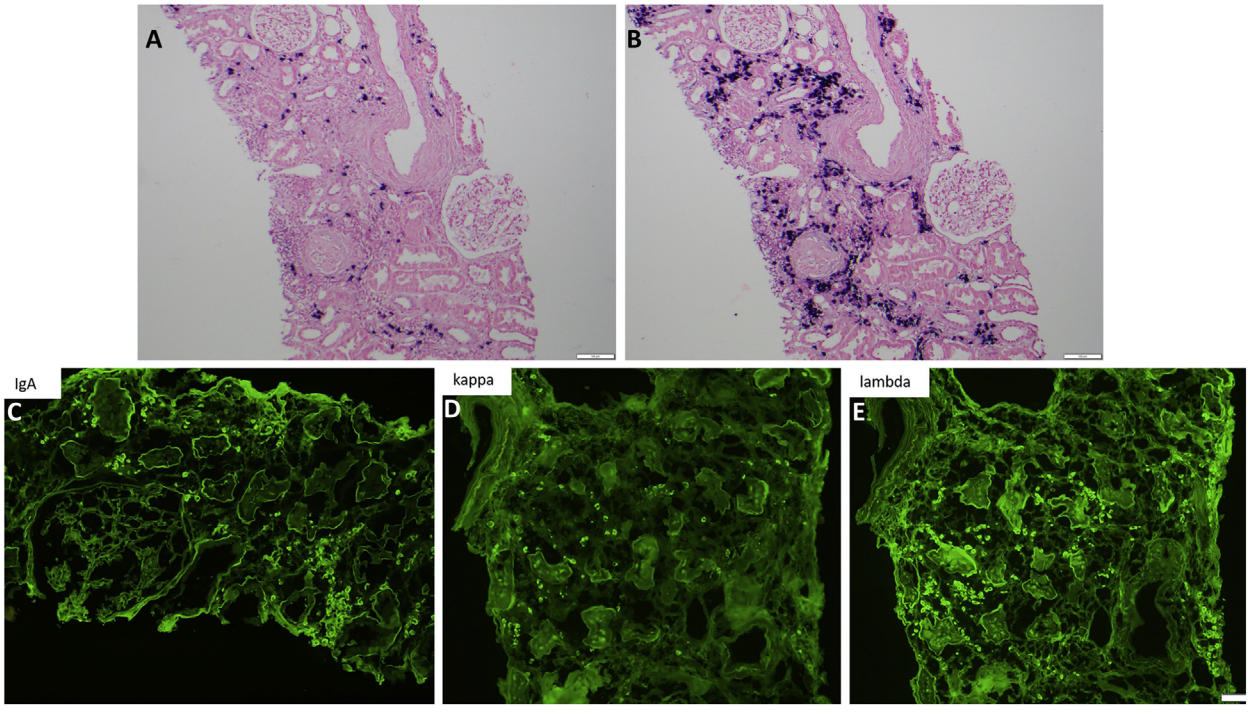

Figure 2. Pathologic findings in the second biopsy. (A-B) In situ hybridization (ISH) studies demonstrate the lambda-restricted plasma cell population (A, kappa ISH and B, lambda ISH; original magnification, ×20 for both). (C) Routine immunofluorescence highlighted a population of IgA lambda-restricted plasma cells present in the interstitium. IgA-positive plasma cells; original magnification, ×20. (D) Kappa light chain-positive plasma cells in the interstitial compartment are few (immunofluorescence; original magnification, ×20). (E) In contrast, there are numerous lambda light chain-positive plasma cells (immunofluorescence; original magnification ×20).

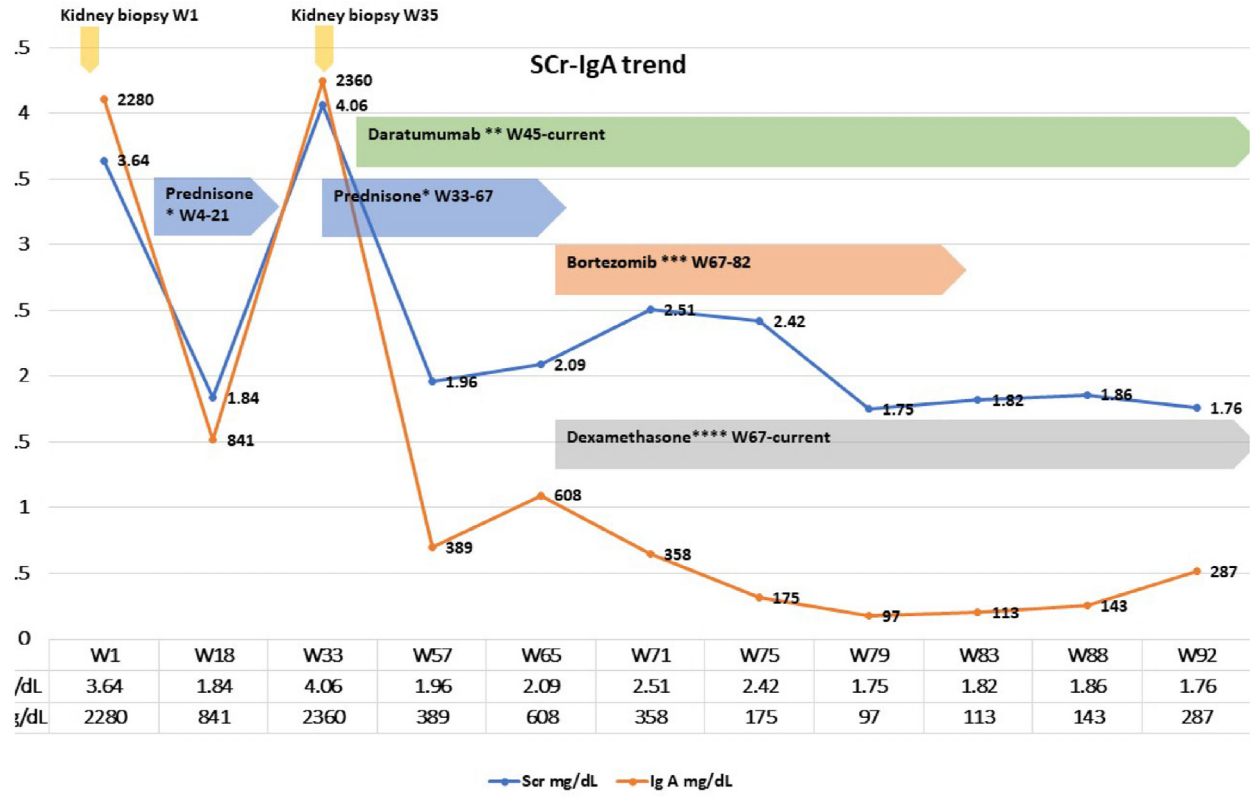

Figure 3. This figure demonstrates treatment course and medications with creatinine and IgA trends.*Prednisone 1: Week (W)4-21: Started at 50 mg/day and was tapered during this time period *Prednisone 2: W33-67: Started at 40 mg/day and was tapered during this time period **Daratumumab: W45-Current: W45-53: 16 mg/kg/dose intravenous (IV) every 2 weeks. W54-Current: 16 mg/kg/dose IV every 4 weeks. ***Bortezomib: W67-82: 1.5 mg/m^2/dose subcutaneous every 2 w. ****Dexamethasone: W67-Current: 40 mg IV day 1, 40 mg by mouth day 8, 15, 22 of each cycle Abbreviation: *IgA*, immunoglobulin A; *SCr*, serum creatinine. Values are reported in US conventional units. Conversion factors to SI units: SCr: mg/dL: ×88.4 μmol/L. IgA: mg/dL: ×0.01 g/L

interstitial monotypic plasma cells with IgA lambda restriction, which were admixed with polyclonal plasma cells (Fig 1D-E). Owing to the monoclonal nature of the plasma cells, anti-CD38 monoclonal antibody (daratumumab) was started.

Creatinine level trended down to 1.96 mg/dL after 3 cycles of daratumumab. Serum protein electrophoresis and immunofixation showed an IgA lambda monoclonal protein below the detectable level, kappa of 3.06 mg/dL, lambda of 2.68 mg/dL, and a kappa/lambda ratio of 1.14. Her IgA level trended down to 389 mg/dL (within normal limits). Following a sixth cycle of daratumumab therapy, IgA levels increased again to 608 mg/dL, with creatinine at 2.11 mg/dL. Bortezomib and dexamethasone were added to augment therapy. After 4 cycles of bortezomib, IgA level trended down to 118 mg/dL and creatinine to 1.82 mg/dL. However, she did not tolerate bortezomib because of orthostatic hypotension, musculoskeletal pains, and diarrhea. Bortezomib was discontinued and she remained on daratumumab/dexamethasone. Her creatinine continued to improve (1.76 mg/dL), IgA remained within normal limits (287 mg/dL), and M protein remained detectable but not quantifiable. (Fig 3).

DISCUSSION

The target epitopes of traditional fluorescein isothiocyanate-conjugated polyclonal Ig antibodies are in the crystallizable fragment portion of Ig.[1] However, HLC antibodies bind to their target epitopes at the CH1 and CL junction of an intact Ig, which allows them to show the differentiation between light chains of Igs (Fig 4).[1] The HLC IF method can be utilized in certain types of glomerulonephritis (GN) to detect monotypic deposits when there are suspected monoclonal deposits on conventional IF without any laboratory or clinical evidence of monoclonal gammopathy or lymphoma.[1,4] For example, it is known that a percentage of IgA nephropathies show a lambda light chain restriction on conventional IF.[5] HLC immunofluorescence is useful in this situation because it shows positive glomerular staining for both IgA kappa and IgA lambda in half of cases of GN with IgA deposits with apparent lambda restriction by frozen

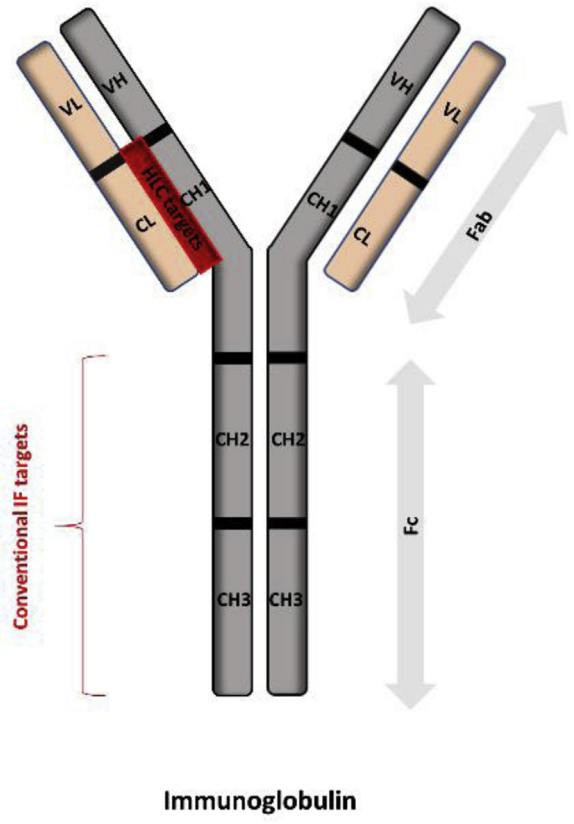

Figure 4. This figure compares targets of heavy chain/light chain (HLC) immunofluorescence (IF) antibodies versus conventional IF antibodies. F_c: Fragment crystallizable F_{ab}: Fragment antigen-binding CL, CH1, CH2, CH3: Constant domains VH: Variable region of Ig heavy chain VL: Variable region of Ig light chain

tissue IF, excluding monotypic IgA deposits. However, this distinction is not always possible.[1,6] IgA nephropathy with monoclonal deposits is differentiated from an IgA variant of proliferative GN with monoclonal IgG deposits (PGNMID) by the glomerular basement staining in PGNMID, whereas the deposits are mostly mesangial in IgA necropathy.[1,3,7-11] The presence of membranoproliferative or membranous patterns of injury on light microscopy or any paracrystalline organization of deposits on electron microscopy would also favor PGNMID-IgA over IgA nephropathy with lambda restriction.[1]

HLC antibody was instrumental in identifying polyclonal IgG deposits in a study with a series of DNAJ heat shock protein family (Hsp40) member B9-associated fibrillary GN, which were thought to be monotypic.[1,12] Using the HLC IF method resulted in excluding PGNMID-IgG in 20% of the cases that met the diagnostic criteria otherwise.[1,3,10,13] Moreover, HLC antibodies have been found to be helpful in diagnosis of certain types of mixed cryoglobulinemia and the pathologic distinction between type II and type III cryoglobulinemia GN and heavy chain deposition disease.[1,14,15] We recommend HLC IF in cases of GN with nonorganized IgG1 kappa-restricted deposits such as apparent "PGNMID-IgG or monotypic membranous nephropathy on conventional IF" in the absence of corresponding serum monoclonal protein; HLC IF may show staining for both IgG kappa and IgG lambda excluding monotypic deposits as evidenced in 38% of cases in one recent study. HLC IF is superior to paraffin IF in cases of GN with apparent nonorganized monotypic IgG or IgA deposits on conventional IF.[1,6] In our case, the HLC antibody identified monoclonal plasma cell infiltrates in the kidney biopsy of a patient with Sjögren syndrome and IgA lambda monoclonal gammopathy of undetermined significance, which was previously thought to have only polyclonal plasma cell infiltrates. Most common kidney involvement in primary Sjögren syndrome is tubulointerstitial nephritis, which usually has predominance in polytypic plasma cell infiltrates.[16-18] Tubulointerstitial nephritis with monotypic plasma cell infiltration of the kidney however has been described in case reports of patients with primary Sjögren syndrome and IgA monoclonal gammopathy of undetermined significance.[16,19,20] Our patient's initial kidney biopsy was significant for plasma cell-rich infiltrates. The plasma cells appeared to be polyclonal by conventional IF staining for IgA, IgG, IgM, C1q, kappa, and lambda. Her second kidney biopsy was obtained after the treatment with steroids, but this time, the plasma cell-rich infiltrate was monotypic for IgA lambda. While conventional IF could not identify the monoclonal IgA lambda plasma cells in the first biopsy, this was clearly shown by using HLC antibody IF.

We hypothesize that the original lesion in the first kidney biopsy was a plasma cell-rich infiltrate secondary to Sjögren syndrome. The steroid therapy was able to eradicate all the polyclonal plasma cells but left behind the monoclonal plasma cells resistant to steroids, which were then identified on the second biopsy. This corresponds to the monoclonal IgA lambda protein found in the serum during the initial evaluation. Anti-CD38 monoclonal antibody (daratumumab) was started because of the presence of monotypic plasma cells, which resulted in a good response. The HLC antibody confirmed the presence of monoclonal plasma cells in the first kidney biopsy. In conclusion, HLC antibody has the advantage of differentiating polyclonal versus monoclonal lesions more precisely as compared with the conventional methods

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