Utility of Kappa and Lambda Immunofluorescence to Evaluate Plasma Cell Dyscrasias on Renal Biopsies

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ABSTRACT

Background

Routine assessment of renal biopsies requires staining with Congo Red staining for amyloidosis as well as immunofluorescence staining for kappa and lambda to detect monoclonal gammopathies. Correlating with histopathology, we can diagnose the nature of renal involvement of plasma cell dyscrasias, which may be in the form of myeloma cast nephropathy, light chain deposition disease, interstitial nephritis, and toxic tubulopathy. If there is nodular glomerulosclerosis which may resemble diabetic kidney, combination of Congo Red and kappa/lambda can be helpful in diagnosis of AA vs AL amyloidosis.

Method

On retrospective analysis of all renal biopsies received over 2017-2024, a total of 12 cases were finalized out of 824 total renal biopsies. The biopsies had undergone the usual processing with routine stains and immunofluorescence studies. Cases were diagnosed with the help of clinical features, biochemical findings, histopathological analysis and immunofluorescence studies.

Result

Patients with either amyloidosis or kappa/lambda monoclonality were more commonly males with median age of 62.5 years and increased creatinine level. Nephrotic syndrome was the most common clinical presentation. Myeloma cast nephropathy, light chain deposition disease and nodular amyloidosis were the most common histopathological diagnoses and lambda was more commonly predominant on immunofluorescence.

Conclusion

Immunofluorescence with kappa/lambda is essential in the diagnosis of renal involvement by myeloma which may precede, occur simultaneously, or follow bone marrow involvement.

Keywords: Myeloma, Renal, Amyloidosis, Kappa, Lambda, Immunofluorescence, Congo Red

Introduction

Routine immunofluorescence staining in evaluation of renal biopsies includes the addition of kappa and lambda to check for monoclonality. Various diseases may show presence of kappa or lambda predominance in addition to positive respective immunoglobulins on immunofluorescence. Examples include IgA nephropathy, lupus nephritis, and membranous glomerulonephritis.[1] In IgA nephropathy, cases with lambda predominance were associated with findings such as endocapillary hypercellularity on biopsy; however, the long term outcome was not affected. [2]

Renal involvement can be seen in up to half of the patients with multiple myeloma. Causes of immunoglobulin dependent renal failure include cast nephropathy, light chain deposition disease, AL amyloidosis, glomerulonephritis, and tubulointerstitial nephritis.[3]

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Differential diagnosis of nodular glomerulosclerosis include diabetic nephropathy, amyloidosis, membranoproliferative glomerulonephritis, fibrillary glomerulonephritis and idiopathic nodular glomerulosclerosis.[4]

Our study focuses on those diseases showing isolated kappa or lambda predominance without positivity of other immunoglobulins. We evaluate the role of including these immunofluorescence stains for diagnosis of renal involvement of myeloma.

Materials and Methods

In this retrospective study, all renal biopsies received in the Department of Pathology, Grande International Hospital during the period of 2017-2024 were reviewed. Among these, cases of renal amyloidosis and cases with isolated predominant kappa or lambda without presence of any other immunoglobulins were selected. Routine and special staining with hematoxylin and eosin, PAS, Trichrome and Congo Red were performed on all biopsies. In addition, the immunofluorescence panel consisting of IgG, IgA, IgM, c3, c1q, kappa and lambda (DAKO reagents with appropriate dilutions) were done in all these cases (scores 0 to 4+) and scores of 3+ and 4+ were considered positive. Biopsies were interpreted using light microscopy and correlated with immunofluorescence findings using our Leica immunofluorescence microscope (model no DM-500). Other clinical parameters and investigations were also reviewed.

Results

A total of 824 renal biopsies were included for analysis. Among these, 13 cases were identified which showed features of renal amyloidosis or isolated kappa/lambda predominance. One such case with lambda predominance showed diabetic nodular glomerulosclerosis on electron microscopy and was excluded from this study. Hence, a total number of 12 cases were included in this study.

Of the twelve included cases with either amyloidosis or isolated kappa/lambda predominance, most of them were male (M:F = 5:1). The age of the patients ranged from 46 years to 83 years, with an average age of 63 years and median age of 62.5 years. Nephrotic syndrome (6 cases) and acute kidney injury(5 cases) were the most common clinical presentations. Creatinine levels ranged from 0.6 to 6.4mg/dl at presentation with mean of 2.8mg/dl and median of 2.75mg/dl. The underlying table shows the clinical findings and investigations (Table 1).

Table 1: Clinical presentation and diagnostic parameters

Age	Sex	Clinical Presentation	Creat mg/dl	Diagnosis	Special stains/ immunofluorescence	Other significant findings
62	M	AKI	4.8	Toxic tubulopathy	Kappa 3+ in tubular droplets	M band, IFE shows M-spike as kappa
67	M	Chronic kidney disease III	2.6	Interstitial nephritis	Kappa 3+ linear in tubular basement membranes	FLC assay kappa increased, M band
46	F	Nephrotic syndrome	0.7	LCDD	Kappa 3+ linear in tubular basement membranes	Diagnosed case of myeloma
83	M	Nephrotic syndrome	0.6	LCDD	Lambda 3+ in nodules	M band at beta1 and gamma
75	M	Nephrotic syndrome	1.1	LCDD / nodular glomerulosclerosis	Lambda 3+ in nodules, Congo -ve	Ig Lambda on electrophoresis,, FLC increased
68	M	AKI	6.4	Myeloma cast nephropathy	Lambda 4+ in casts	M band at beta2
62	M	AKI	3.6	Myeloma cast nephropathy	Lambda 3+ in casts	Bence Jones Protein+, M band, marrow plasmacytosis
55	M	AKI	3.8	Myeloma cast nephropathy	Kappa 3+ in casts	
70	M	Nephrotic syndrome	0.8	Nodular amyloidosis	Congo +ve, DIF negative	
53	M	Nephrotic syndrome	1.4	Nodular amyloidosis	Congo +ve, DIF negative	Known case of carcinoma colon
53	F	Nephrotic syndrome	2.9	Nodular amyloidosis, AL amyloid	Congo +ve, lambda 4+ in nodules	
63	M	AKI	4.9	Tubulo-interstitial nephritis	Lambda 4+ in casts	Sudden deterioration in past 3 wks, M band at gamma

*LCDD=light chain deposition disease, AKI=Acute kidney injury, DIF=direct immunofluorescence

The most common histopathological diagnoses were myeloma cast nephropathy, light chain deposition disease and nodular amyloidosis accounting for 3 cases each. Less common histopathological diagnoses were toxic tubulopathy, interstitial nephritis and tubulo-interstitial nephritis accounting for one case each. Calculation of the p-value was done using SPSSv16, and p value was 0.01 indicating statistical significance between diagnosis of disease and monoclonality of kappa/lambda.

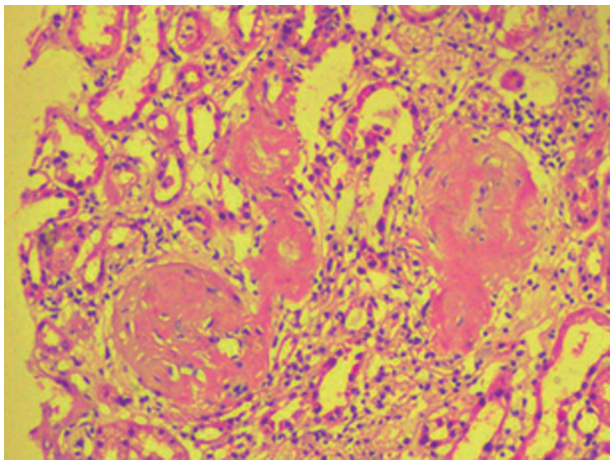

Figure 1: Case of renal amyloidosis with deposition of pink amorphous amyloid in glomeruli forming vague nodules and in the blood vessel walls. (H&E stain, x400)

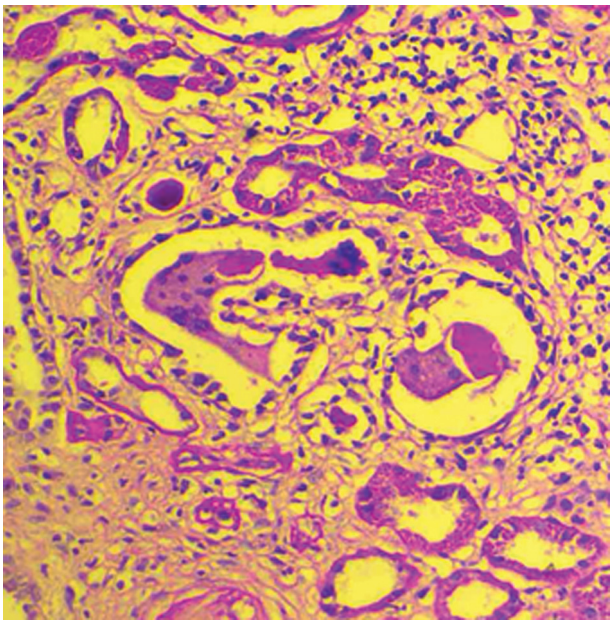

Figure 2: Dilated tubules with pink casts surrounded by multi-nucleate giant cells and inflammatory cells from a case of myeloma cast nephropathy (PAS stain, x 400)

On histopathology, the pertinent findings were nodular deposits of amyloid in cases of renal amyloidosis (Figure 1), typical casts with inflammatory and histiocytic reaction in cast nephropathies (Figure 2) and tubular basement membrane thickening, nodular glomerulosclerosis, interstitial nephritis, and toxic tubulopathy/ tubular injury in light chain deposition disease. Sites of positive immunofluorescence included predominant kappa or lambda staining in casts, nodules of glomerulosclerosis, mesangial, and linear staining in tubular basement membranes (Figure 3). Lambda was predominant in 6 of the cases and kappa was predominant in 4 cases.

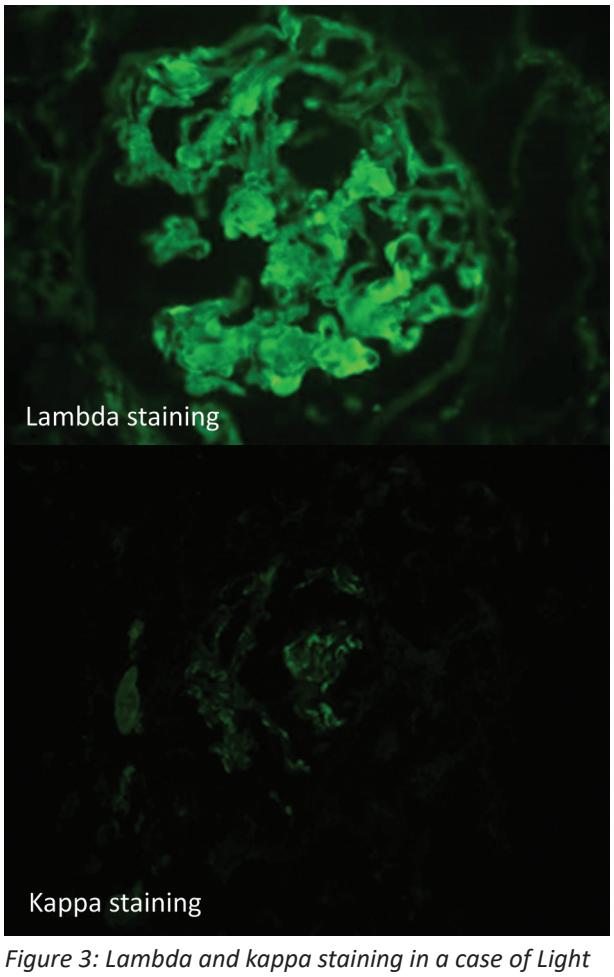

Figure 3: Lambda and kappa staining in a case of Light Chain Deposition Disease in which only lambda is strongly positive (3+) in mesangial nodules and kappa is barely visible/trace positive (Immunofluorescence microscopy, x400)

Discussion

The importance of renal biopsy in the evaluation of patients with suspected plasma cell dyscrasia cannot be understated, as these various renal lesions may have different therapeutic implications and prognoses.[5]

If renal biopsy is inconclusive, other investigations including bone marrow aspiration, electrophoresis and immunotyping should be done in cases of renal dysfunction with suspected plasma cell dyscrasia.[6]

Our patients presented most commonly with nephrotic syndrome and acute kidney injury. They were mostly males with a M:F ratio of 5:1. Similarly, in a study performed in India, most patients presented with renal dysfunction followed by nephrotic syndrome with males being more commonly affected (M:F = 4.3:1).[7] Renal failure can be one of the presenting manifestations of myeloma patients. Causes of renal failure include hypercalcemia, dehydration, NSAIDs, infections or past renal disease.[8]

In this study, the most common diagnoses were myeloma cast nephropathy and light chain deposition disease. Similarly, the most common histopathological diagnoses were myeloma cast nephropathy, light chain deposition disease, and AL amyloidosis in a study by Shankar et al in India.[9]

Light chain deposition disease presents with Congo Red negative deposits and in the study by Ardalan, immunofluorescence revealed mostly kappa light chains.[10] The most common finding is nodular glomerulosclerosis which shows PAS positivity and Congo Red negative nodules. In addition, there may be thickening of glomerular capillary loops. Tubules may be atrophic and also show ribbon-like thickening of the basement membrane. Renal transplantation may show good results but eventually light chains will deposit in the graft.[11]

All forms of amyloidosis may show positivity for Congo Red. Differentiation between AA and AL types requires immunofluorescence for kappa and lambda in renal biopsy.[12] Cases of AA type amyloidosis, which are secondary to other diseases do not show monoclonal immunofluorescence deposits whereas cases with AL type amyloidosis will show either kappa or lambda predominance.

One of our cases of nodular amyloidosis which showed Congo Red positive deposits was a known case of carcinoma of colon under treatment. There have been reports of biopsy proven amyloidosis in patients being treated with checkpoint inhibitors for carcinoma of colon, metastatic lung carcinoma and melanoma.[13]

On immunofluorescence, most of the cases with monoclonal gammopathy showed predominance of lambda light chains (60% lambda, 40% kappa). These findings are in accordance with the study done by Khosla et al.[7]

Conclusion

Kappa and lambda immunofluorescence evaluation was instrumental in diagnosis of plasma cell dyscrasias. Most of the patients were males, who presented with renal dysfunction and were diagnosed as forms of renal involvement of myeloma. In some of our cases, isolated kappa or lambda predominance led to further investigations and eventually the diagnosis. In addition, Congo Red staining was also useful to rule out the possibility of renal amyloidosis.

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