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Peer Reviewer of *World Journal of Clinical Cases*, Maria Koukoulaki, MD, MPhil, PhD, Consultant Physician-Scientist, Department of Nephrology "G. Papadakis", General Hospital of Nikaia - Peiraias "Agios Panteleimon", Nikaia 18454, Greece. mkoukoulaki@gmail.com

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CASE REPORT

Congophilic fibrils in the glomeruli with polyclonal immunoglobulin gamma staining - another cause for diagnostic overlap: A case report

Maria Bernadette Che-Ying Chow, Lucas Bushrow, Irmeen Siddiqui, April Chiu, Mirza Hamirani, Anjali A Satoskar

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Maria Bernadette Che-Ying Chow, Lucas Bushrow, Irmeen Siddiqui, Anjali A Satoskar, Department of Pathology, The Ohio State University Medical Center, Columbus, OH 43210, United States

Maria Bernadette Che-Ying Chow, Department of Pathology, North District Hospital, Sheung Shui, Hong Kong, China

April Chiu, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55905, United States

Mirza Hamirani, Department of Internal Medicine, S. Joseph's Hospital, Parkersburg, WV 26101, United States

Corresponding author: Anjali A Satoskar, MD, Professor, Department of Pathology, The Ohio State University Medical Center, B073 Graves Hall 333 W 10th Ave, Columbus, OH 43210, United States. anjali.satoskar@osumc.edu

Abstract

BACKGROUND

Glomerulopathy with fibrillary deposits is not uncommon in routine nephropathology practice, with amyloidosis and fibrillary glomerulonephritis being the two most frequently encountered entities. Renal amyloid heavy and light chain (AHL) is relatively uncommon and its biopsy diagnosis is usually limited to cases that show strong equivalent staining for a single immunoglobulin (Ig) heavy chain and a single light chain, further supported by mass spectrometry (MS) and serum studies for monoclonal protein. But polyclonal light chain staining can pose a challenge.

CASE SUMMARY

Herein we present a challenging case of renal AHL with polyclonal and polytypic Ig gamma (IgG) staining pattern by immunofluorescence. The patient is a 62-year-old Caucasian male who presented to an outside institution with a serum creatinine of up to 8.1 mg/dL and nephrotic range proteinuria. Despite the finding of a polyclonal and polytypic staining pattern on immunofluorescence, ultrastructural study of the renal biopsy demonstrated the presence of fibrils with a mean diameter of 10 nm. Congo red was positive while DNAJB9 was negative. MS suggested a diagnosis of amyloid AHL type with IgG and lambda, but kappa

light chains were also present supporting the immunofluorescence staining results. Serum immunofixation studies demonstrated IgG lambda monoclonal spike. The patient was started on chemotherapy. The chronic renal injury however was quite advanced and he ended up needing dialysis shortly after.

CONCLUSION
Tissue diagnosis of AHL amyloid can be tricky. Thorough confirmation using other available diagnostic techniques is recommended in such cases.

Key Words: Heavy and light chain amyloid; Fibrillary glomerulonephritis; DNAJB9; Serum immunofixation; Protein electrophoresis; Mass spectrometry; Congo red; Case report

Core Tip: Amyloidosis and fibrillary glomerulonephritis are the two most commonly encountered glomerulopathies with fibrillary deposits. Accurate diagnosis and differentiation between these two entities are important for patient management. Furthermore, accurate subtyping is also required for amyloidosis cases to further guide treatment. This case report highlights an uncommon diagnostic pitfall that a nephropathologist may encounter while distinguishing light and heavy chain amyloid from fibrillary glomerulopathy. The possible underlying mechanisms are discussed, and we reiterate the importance of a clinical-pathological correlation and the use of multiple available diagnostic modalities if needed, particularly for these overlapping diagnostic entities.

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INTRODUCTION

Deposition of electron dense randomly arranged fibrils (without periodicity) in the kidney is seen in two major disease processes-amyloidosis and non-amyloidotic fibrillary glomerulonephritis (FGN). Both consist of abnormally folded proteins.

Proteins forming amyloid are heterogeneous. Up to 36 different protein types and many more variants have been identified in human amyloidosis. A diagnosis of renal amyloidosis mainly relies on the demonstration of congophilic amorphous eosinophilic deposition within the glomeruli (and/or in other compartments in the kidney) with apple green birefringence under polarized light. This is further substantiated by the presence of fibrils, with an average 8 to 10 nm in diameter, on ultrastructural examination. Subtyping of amyloid is critical to inform disease management. The methods widely used are: (1) Immunostaining for the major constituent protein (amyloid-forming protein); and (2) Laser capture with mass spectrometry (MS). Immunostaining is available for a limited number of proteins only, including immunoglobulin (Ig) light chains, Ig heavy chains, serum amyloid A, fibrinogen and transthyretin A (mainly cardiac amyloid, uncommon in the kidney). For the rest, MS is required.

FGN is more uniform in its composition, staining for Ig gamma (IgG) heavy chain along with polyclonal light chains but with slight kappa predominance and typically Congo red negative. The fibril diameter is in the range of 10 to 20 nm, thus differs from that of amyloid fibrils. The Congo red negativity is the most important distinguishing feature from amyloidosis. Recently, MS has demonstrated the heat shock protein DNAJB9 to be consistently present in the deposits of FGN. Immunostaining for DNAJB9 has therefore become a highly sensitive and specific marker for FGN and is particularly useful in the absence of EM[1]. Although rare, cases of "congophilic FGN" have been reported necessitating the use of DNAJB9 immunostaining and EM for correct diagnosis in such cases. Another reported pitfall in the differentiation between FGN and amyloidosis is presented by amyloid heavy and light chain (AHL) due to the presence of concomitant Ig heavy and light chain as seen in FGN (albeit monoclonal).

Light chain amyloidosis is the most common form of renal amyloidosis in North America, associated with underlying monoclonal gammopathy. AHL which is also associated with monoclonal gammopathy occurs much rarely. For majority of the reported cases of AHL, the amyloid fibrils are derived from fragments of one IgG heavy chain, and one light chain, giving rise to a monoclonal and monotypic Ig staining pattern. Other heavy chains (such as IgA) are reported.

Here we present an intriguing case of AHL-type with both kappa and lambda light chain staining as well as multiple IgG subclass staining on direct immunofluorescence (DIF).

CASE PRESENTATION

Chief complaints

A 62-year-old Caucasian male presented to an outside institution with persistently rising serum creatinine and heavy proteinuria.

History of present illness

Acute on chronic kidney disease with nephrotic range proteinuria.

History of past illness

He had medical history of hypertension for the past 5 years and chronic renal insufficiency presumed to be due to hypertensive nephrosclerosis.

Physical examination

Blood pressure was up to 160/90 mmHg but there were no neurologic deficits or other specific findings such as rash or edema.

Laboratory examinations

Baseline serum creatinine was stable at 1.7 mg/dL for 6 years until recent lab work revealed an elevation to 5.1 mg/dL and further increasing to 8.1 mg/dL within a span of a few months along with nephrotic-range proteinuria. Urinalysis showed greater than 300 mg/dL albumin, numerous red blood cells, and 5-10 white blood cells/high power field. Hepatitis B and hepatitis C serologies were negative. Other relevant laboratory data is shown in Tables 1 and 2.

Histopathological examination

A renal biopsy was performed to elucidate the cause of his rapidly worsening renal function, proteinuria and hematuria. The biopsy showed a total of 30 glomeruli and 17 of them were sclerotic/solidified. Three glomeruli showed features of fibrocellular crescents. The remaining glomeruli showed focal mesangial expansion, non-argyrophilic on Jones methenamine silver stain. Interstitial fibrosis and tubular atrophy were moderately advanced involving 50%-60% of the renal cortex. DIF showed strong smudgy IgG, kappa and lambda staining in the glomeruli and vascular walls (Figure 1A-C). EM showed randomly arranged fibrils with a mean diameter of 10 nm (Figure 1D). Congo red stain was positive. IgG subclass staining showed strong IgG1, but also moderate IgG2 and IgG4 staining (polytypic pattern). IgG3 was negative (Figure 1E-H).

Further investigations

Immunostain for DNAJB9, performed at the Mayo Clinic, was negative. Serum protein electrophoresis (SPE) and serum immunofixation (SIfix), performed at the referring hospital, revealed a monoclonal IgG lambda spike. Flow cytometry on bone marrow showed 0.2% lambda-restricted plasma cells. MS was subsequently performed and the result was stated to be "possible AHL amyloid with IgG and lambda".

FINAL DIAGNOSIS

AHL-type with IgG lambda

TREATMENT

The patient was started on chemotherapy after the kidney biopsy diagnosis consisting of Cyclophosphamide, Bortezomib and dexamethasone, at the outside hospital and then referred to our institution for second opinion. The diagnosis of AHL amyloidosis was confirmed based on the existing biopsy and laboratory results. Subsequently a decision was made to add Daratumumab to the regimen.

OUTCOME AND FOLLOW-UP

The patient required dialysis shortly after the renal biopsy. He remains on dialysis upon 2-month follow-up.

DISCUSSION

Renal AHL is rare comprising 7.3% of renal Ig-related amyloidosis cases[2]. To date, fewer than twenty cases of AHL have been reported. They demonstrate monoclonal staining pattern with one Ig heavy chain and one light chain on

Table 1 Laboratory results

Test	Result	Reference ranges
Hemoglobin, g/dL	8.4	13.8-17.2
White blood cell count, /μL	10000	4500-11000
Platelet count, K/μL	227000	150000-450000
Serum creatinine, mg/dL	8.1	0.72-1.25
eGFR, mL/min/1.73 m^2	7	> 90
Calcium (total), mg/dL	8.0	8.4-10.2
Phosphorus, mg/dL	7.4	3.4-4.5
Serum C3, mg/dL	95	90-180
Serum C4, mg/dL	34	15-45

eGFR: Estimated glomerular filtration rate (calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation).

Table 2 Hematologic work-up for monoclonal gammopathy

	Serum assays performed at outside hospital	Reference range and units (in our institution)
Immunofixation, serum	Single spike-IgG lambda	Negative
Monoclonal protein 1 (mg/dL)	900	≤ 0.0
Monoclonal protein 2 (mg/dL)	Absent	≤ 0.0
Serum kappa free light chains (mg/L)	37.7	3.9-26.0
Serum lambda free light chains (mg/L)	366.3	6.4-22.1
Serum kappa:lambda ratio	0.10	0.51-1.72

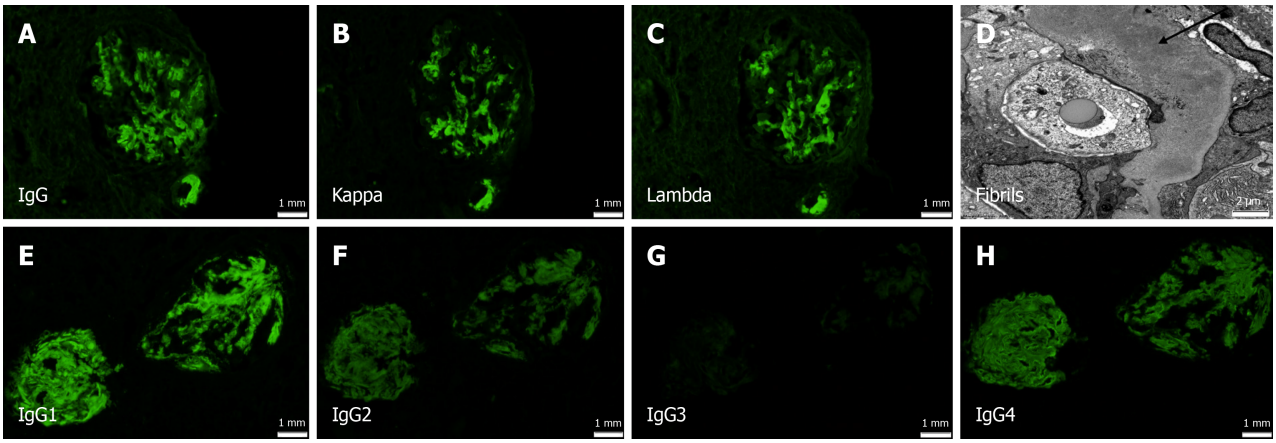

Figure 1 Direct immunofluorescence on frozen tissue along with electron microscopy. A-C: Immunoglobulin gamma (IgG), kappa and lambda, smudgy predominantly mesangial staining; D: Ultrastructural examination shows randomly arranged fibrils in the glomeruli, measuring 10 nm in mean diameter (uranyl acetate lead citrate fixation); E-H: Direct immunofluorescence (DIF) for IgG subclasses demonstrated predominantly IgG1 but also mild to moderate IgG2 and IgG4, appears polytypic. IgG3 is negative (DIF images 40 ×).

immunofluorescence. Although a few cases of IgA- and one case of IgM-containing AHL amyloid are described, the majority is made up of IgG heavy chain[2-4]. Conventionally, the diagnosis of renal AHL should be limited to cases that show strong equivalent staining for a single Ig heavy chain and a single light chain[2]. This stringent diagnostic criterion is essential to avoid over-diagnosing this rare entity. However, our exceptional case nicely demonstrates that even with a polyclonal IgG pattern on DIF, it could still be a monoclonal gammopathy-associated AHL amyloid. A more detailed review of the MS protein identification report ("scaffold") was performed. Along with the common amyloid components (such as serum amyloid P component, apolipoprotein A4 and apolipoprotein E) and specific AHL amyloid components (high peptide counts for IgG heavy chain, lambda light chain), it also showed peptide counts for kappa light chains

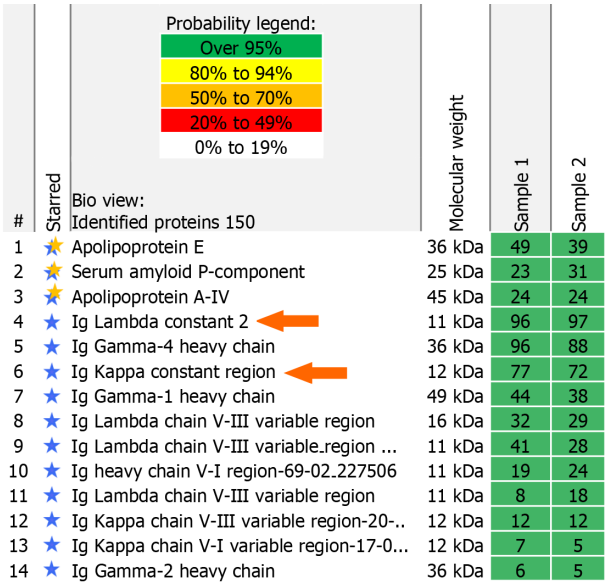

Figure 2 Mass spectrometry protein identification report ("scaffold") shows presence of proteins deposited with amyloid of all types including serum amyloid P component, apolipoprotein A4 and apolipoprotein E; thereby confirming the diagnosis of amyloidosis. In addition, it also shows high peptide counts for IgG heavy chain and lambda light chain, but kappa light chains are seen as well.

(Figure 2). This supported our tissue staining results on the kidney biopsy (which remained consistent on repetition). We want to highlight this diagnostic pitfall and review potential causes.

Fallacies in tissue staining can occur[5,6]. Eculizumab (composed of human and murine IgG and kappa chains) binds to tissue at the site of action and therefore can be seen on DIF stained tissue as positive staining for IgG and kappa[5]. However, this patient had not been receiving any targeted recombinant antibodies before the time of the biopsy, excluding this possibility. The reason in this case could be "non-specific trapping" of immunoreactants by the amyloid fibrils, or "contamination" of the amyloid deposit by abnormally high levels of other serum proteins (kappa light chains in this case)[7-9]. The trapped immunoreactants usually show lower intensity of staining compared to the true amyloid-forming protein (IgG and lambda light chain in this case). However, in this exceptional case, the trapped kappa light chains show equally strong staining intensity as the lambda, giving the deposits a polyclonal appearance. Accumulation of kappa light chains in serum due to limited glomerular filtration and increase in serum half-life of kappa light chains has been described in advanced chronic kidney disease[10]. Normally, kappa free light chain (FLC), which is a monomeric molecule (molecular weight 22.5 kDa), is cleared at a faster rate than the dimeric lambda FLC (molecular weight 45 kDa)[11]. Under circumstances with impaired renal function, the clearance of kappa light chains tends to be slower than usual. The alternative route of removal of FLC is through pinocytosis by the reticuloendothelial system[11]. This alternative route is not influenced by the molecular weight of FLC. Therefore, the serum half-lives as well as the clearance rate of kappa and lambda FLCs become comparable as renal function worsens[12]. This could be a reason for kappa light chain trapping and the non-specific staining for kappa in the amyloid deposits in this case. Such non-specific staining patterns can produce inconclusive and confusing results. This could be one of the reasons that immunostaining-based amyloid typing is fraught with difficulties, necessitating the use of MS which is considered the gold standard[4,7,8].

The other less likely possibility is the co-existence of two amyloid fibril proteins in the same patient[9], but this is unlikely. The first SPE and SIfix performed at the outside hospital prior to the kidney biopsy showed only a monoclonal IgG lambda spike in the serum.

CONCLUSION

Our case illustrates that the possibility of amyloidosis (particularly AHL) cannot be completely ruled out even if the immunofluorescence pattern is polyclonal with polytypic IgG staining. The importance of utilizing multiple diagnostic modalities, including special stains, immunohistochemistry, immunofluorescence, electron microscopy and even MS, in the interpretation of renal biopsies is re-emphasized. Finally, correlation with serum electrophoresis and immunofixation studies is critical, along with the knowledge of therapeutic targeted antibodies used in the management of these patients as these can potentially interfere with serum assays.

FOOTNOTES

Author contributions: Chow MBCY drafted and revised the manuscript; Bushrow L helped draft the manuscript; Siddiqui I helped with serum immunofixation results; Chiu A provided mass spectrometry result and Figure 2; Hamirani H provided clinical follow-up and obtained patient consent; Satoskar AA conceptualized and the idea and implemented the collaborative effort, drafted and revised the manuscript, and provided immunofluorescence images.

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ORCID number: Anjali A Satoskar 0000-0002-3332-0161.

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