A Case Report on Renal Amyloidosis

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Abstract
Amyloidosis involves the deposition of abnormal proteins in various tissue and result in progressive organ dysfunction, commonly affecting multiple organs. Two types of systemic amyloidosis are AA and AL, the former is associated with acute phase reaction and the later is composed of light chain immunoglobulin. This disease commonly affects the kidneys and is evidenced by massive proteinuria. A biopsy is the gold standard of diagnosis, with Congo Red staining revealing an apple green birefringence under polarized light microscope. We are presenting a 45 years old male who presented with rapid rising serum creatinine with history of multiple myeloma (non secretory). There was also history of spine tuberculosis.

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Introduction

Amyloidosis is defined as an in vivo deposited material that can be distinguished from nonamyloid deposits by characteristic fibrillary electron microscopic appearance, typical X-ray diffraction pattern and specific staining reactions, particularly affinity for the dye Congo red with resulting green birefringence.[1] The term 'amyloid' was coined in 1853 by Rudolf Virchow when he discovered that the depositions , when stained with iodine, looked similar to starch.[2] There is a growing list of more than thirty two different proteins thought to be involved in the pathogenesis of amyloidosis; among them, the most common is immunoglobulin light chain (AL) amyloidosis.[3] Light chain amyloidosis and light chain deposition disease, most often secondary to lymphoproliferative disorders, are systemic diseases caused by an abnormal production of monoclonal immunoglobulin light chain and their abnormal deposition in systemic tissue.[4] Indeed, about 18% of multiple myeloma patients have light chain disease.[5] Myeloma kidney is predominantly contributed by the cast nephropathy and patients with this kind of involvement suffer from renal insufficiency.[6] However, 75% of patients with amyloidosis are detected to have proteinuria. The extent of proteinuria can vary from mild to massive (>20 g/day).[7] The median age of diagnosis is 60 years; it is uncommon under age of 40.[8]

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A biopsy is the gold standard for diagnosis and it should be performed when amyloidosis is on the differential. It should be confirmed with immunofluorescent staining to evaluate the type of protein that is being deposited.9 It can be also confirmed by Electron microscopy where amyloid fibrils are observed. A study showed kappa light chain deposition in renal tubular and basement membranes which demonstrated continuous punctate deposits in the inner layer of glomerular basement membrane.[4]The disordered and non-branched amyloid fibrils deposited in the GBM, the diameter of which was from 7.7 nm to 13.6 nm.[4] Here, we are discussing about a 45 years male who presented with rapid rising serum creatinine with history of multiple myeloma (non secretory). There was also history of spine tuberculosis.

Case report

A 45 years male presented with rapid rising serum creatinine (Serum Creatinine: 6.3 mg/dl) with history of multiple myeloma (non secretory) and also history of spine tuberculosis. He was also detected to have 1.42 grams of protein in a 24-hours urine sample, urine albumin 3(+) and urine RBC 3-5/HPF. Renal biopsy (core biopsy) was done and tissue was sent for histopathology and Direct Immunofluorescence. Routine H&E along with PAS, Masson trichrome and Congo red were done.

Light microscopy showed renal cortex and medulla comprising 32 glomeruli, of which none showed global or segmental sclerosis. The glomeruli showed eosinophilic deposits with in the mesangial spaces as well as at periglomerular areas, which were negative for PAS. Congo red staining showed apple green birefringence on polarization. No mesangial or endocapillary proliferation was seen. Glomerular basement membrane thickness was increased. No crescent formation or tuft necrosis was seen.

Interstitial fibrosis and tubular atrophy occupied 30% of cortical area. Also mild acute tubular injury was seen. Most of the tubules were containing eosinophilic Congo red positive casts which were forming crystals. Focal interstitial lymphocytic infiltration was also seen.

Arterial walls were thickened with deposition of PAS negative eosinophilic deposits which also showed apple green birefringence on Congo red staining.

Direct immunofluorescence study reveals 36 glomeruli. Mesangial deposits as well as tubular casts are IgG (2+), Kappa (2+). No IgA, IgM, C3 or C1q deposit was seen.

Based on the clinical indicators and pathological findings, the patient was finally diagnosed as renal amyloidosis (kappa restricted) with tubular amyloid casts with IFTA 30%. IHC for SAA is recommended to know the type of amyloid.

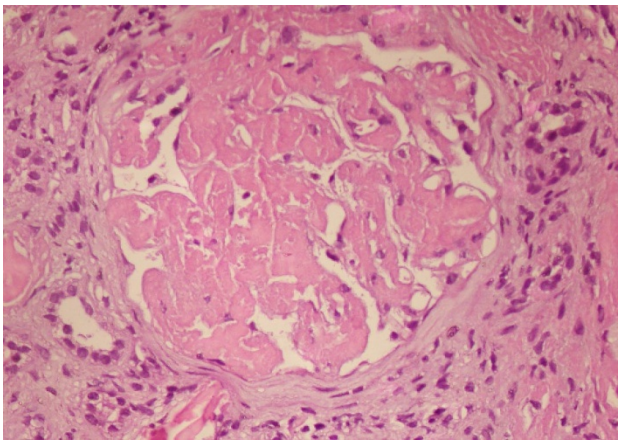

Figure 1. Glomeruli show eosinophilic deposits within mesangium

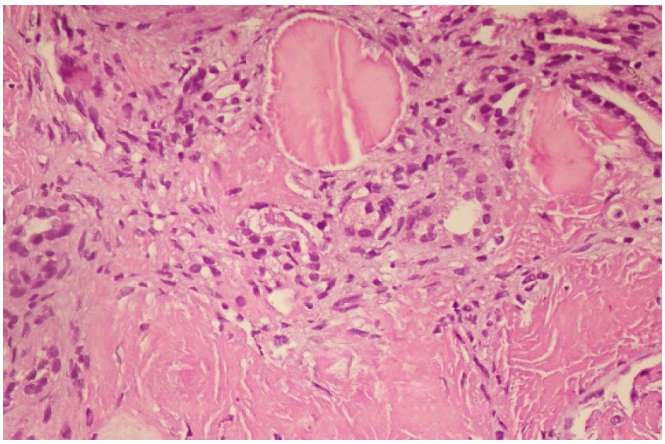

Figure 2. Eosinophilic deposits in renal tubules

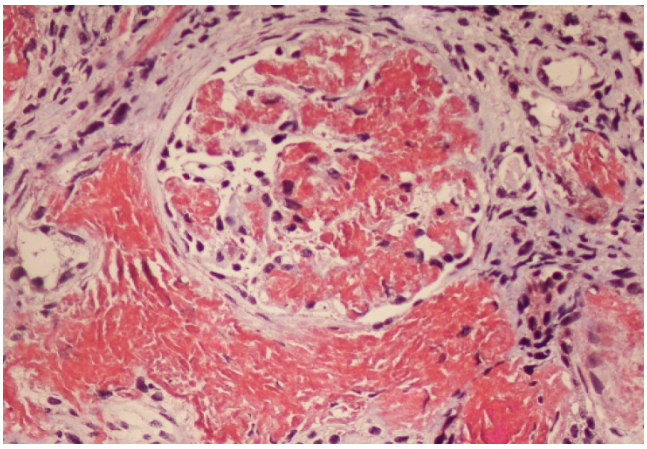

Figure 3. Congo red positive deposition in renal tubule mesangium

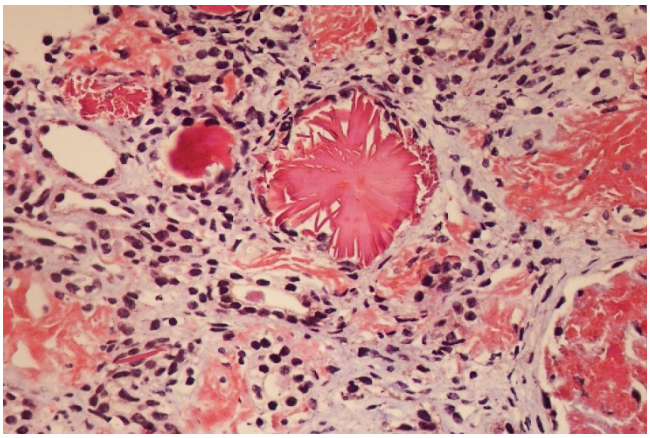

Figure 4. Congo red positive deposition in renal tubules

Discussion

Amyloidosis is an extremely rare entity that is difficult to diagnose. Amyloidosis may be systemic or localized. The kidneys are most frequently involved in systemic amyloidosis.[10] The incidence of amyloidosis in patient with nephrotic syndrome and proteinuria was found in 2% to 12% of renal biopsies.[11] Kidney involvement in amyloidosis is associated with an increase in morbidity and mortality.[12,13]AL type amyloidosis is the most common type of systemic amyloidosis and has been associated with the abnormal proliferation of monoclonal plasma cells as well as with lymphoproliferativedisease.[14]The presence of renal amyloidosis may be suspected clinically; but the diagnosis is confirmed by renal biopsy. Diagnosis of renal amyloidosis can be made on one glomerulus or even if there are no glomeruli is found or inperirenal soft tissue in the renal needle biopsy specimen.[15] Amyloid deposition is found in different degrees in mesangium, capillary walls, interstitium and blood vessels. The most common and often the earliest site of amyloid deposition in the kidney is the glomeruli.[15]

On light microscopy, the amyloid material deposited in the glomerulus appears as amorphous material in the mesangium and

capillary loops. Mesangial deposition can be intense and produce an amorphous hyaline appearance with a nodular configuration on hematoxylin& eosin staining.While the nodular aspect can raise the differential diagnosis of diabetic kidney disease and light chain deposition disease, the amyloid protein predominates in tissues affected by amyloidosis, with reduced collagen deposition in the extracellular matrix evidenced by weak staining with periodic acid-Schiff (PAS). Tubulointerstitial deposits of amyloid, in contrast, produce tubular atrophy and interstitial fibrosis.[16]

Congo red staining continues to be the gold standard in the routine diagnosis of amyloidosis. This takes on a salmon color when stained with Congo red.Amyloid deposits stain with congo red show apple green birefringence under polarized light.[16]

In addition, detection of monoclonal free light chains is also an important diagnostic aid for a variety of monoclonal gammopathies and is especially important in light chain diseases, such as primary systemic amyloidosis, light-chain myeloma etc.[17]Serum free light chain (FLC) is a breakthrough biomarker of multiple myeloma with a sensitivity close to 100% for non-secretory myeloma, as its FLC ratio is always abnormal, even in the absence of M-protein, thus rendering this marker an optimal tool for monitoring oligo- or non-secretory plasma cell disorders.[17] The normal serum range of kappa free light chains is 3.3 to 19.4 mg/dL. For lambda, it is between 5.7 to 26.3 mg/dL with a kappa-to-lambda ratio of 0.26 to 1.65.In AL amyloidosis, free lambda or (less commonly) free kappa levels are elevated.[17]

DIF is commonly used to document the deposition of immunoglobulin proteins in the kidney and is typically performed on biopsy sample. It show the type of light chain restricted in renal tissue with deposition of other immunoglobulin protein. A DIF study on a patient with acute kidney injury with hematuria and proteinuria show lamda light chain restriction in the cast. IgG, IgA, IgM, C3 and C1q were negative.[18]In our case kappa chain restriction is found.

AL amyloid includes the variable domain of immunoglobulin κ or λ light chains. Because of sequence variability of this domain and alterations in the structure of the light chains in the amyloid, antibodies raised against intact light chains may not react to an amyloid fibril. Conformational or fragmentational changes can mask or eliminate specific epitopes and obscure the diagnosis.[19]Additionally, since antibodies are typically developed against the constant region, limited or no reactivity would be expected. In a small percentage of cases with AL-amyloidosis (about 10-15%), commercially available antibodies do not detect the mutated light chains.[19]

Combine IHC and electron microscopy to identify amyloid has greater sensitivity and specificity.A study analyzed 423 cases of amyloidosis with IHC and electron microscopy and appropriately identified the specific amyloid protein type (Alλ, Alκ, AA, Mutated ATR, Senile ATTR and others) in more than 99% of cases.[20]In our case, kappa chain restriction is found in glomeruli as well as in renal tubules by DIF microscopy. Now IHC for SAA is recommended to know the type of amyloid but we were not able to do it because it is not available in Bangladesh.

Conclusion

Renal amyloidosis is a disease with serious diagnostic difficulties because it commonly has nonspecific forms of presentation. Most of the time diagnosis is only considered when the patient presents with organ failure. Moreover, among renal amyloidosis our case is distinct because here crystal formation is

found with cast nephropathy, which is very rare. However, the frequency, clinical and pathological significance of this intratubular amyloid is poorly understood. Generally, the unusual morphology of amyloid cast nephropathy in renal biopsy resulting poor prognosis

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