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Nephrotic syndrome with rapidly progressive renal failure(RPRF) in light chain myeloma

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Introduction

Nephrotic syndrome, defined by proteinuria with bland sediments, hypoalbuminaemia and oedema is not a known cause of RPRF as opposed to crescentic glomerulonephritides. Light chain deposition disease on the other hand, could instill a dual hit to the nephron, at both glomerular and tubular levels resulting in a nephrotic syndrome with rapidly progressive renal impairment. Therefore it is of value in the diagnostic approach to a patient with RPRF.[1]

We present a 44-year-old previously healthy woman with arapidly progressive non-oliguric renal failure and nephrotic range proteinuria with bland sediments.There was no bleeding tendency, evidence of recurrent infections, chronic back or joint pain, acrocyanosis, skin rashes, oral ulcers, history ofnephrotoxic drug use, recurrent pyelonephritis or urolithiasis. She was found to have a normochromic normocytic anaemia with moderate rouleaux formation, arapid erythrocytic sedimentation rate and a pseudohyponatremia suggestive of an underlying para-proteinemia. Her serum calcium waslow with high phosphate on account of the degree of renal impairment. On further evaluation rheumatoid factor, anti nuclear, anti neutrophil cytoplasmic antibody, hepatitis B, C and HIV serology and cryoglobulin levels were all in the normal ranges. The kidneys were of normal size ultrasonicallywithout evidence of obstructive uropathy. Serum protein electrophoresis revealed an abnormal monoclonal band in the gamma region with mild immunoparesis. Estimated gamma globulin levels were modestly elevated(0.1g/dL). Serum and urine Immunofixation confirmed the abnormal monoclonal band to consist predominantly of lambda free light chains suggestive of light chain disease. Serum free light chain assay revealed significantly elevated serum free lambda chains (148.00 mg/L (4.23 – 27.69) and a Kappa / Lambda ratio of 0.26 (0.22 – 1.74)). Subsequent bone marrow biopsy showed a markedly hypercellular marrow with 50% plasma cells and mildly suppressed erythropoiesis and granulopoiesis with intact megakaryopoiesis. Cast nephropathy was suspected as the cause for the rapid decline in renal function. Further urinalysis did not show a significant urinary loss of sodium, potassium, albumin or glucose suggestive of a proximal tubulopathy. Crystal nephropathy was less likely with normal calcium and uric acid levels. The significant monoclonal plasma cell proliferation in the bone marrow and the presence of anaemia and renal impairment was sufficient for thediagnosis of an oligosecretorymultiple myeloma.

Her renal biopsy showed mild mesangial expansionwithout a mildhypercellularity and focal thickening of glomerular capillary membrane. There was no evidence of fibrinoid necrosis or crescents. Tubules were packed with eosinophilic fractured casts confirming our suspicion of cast nephropathy. These casts were negative for PAS and Congo red stains thus making amyloidosis unlikely. Immunofluorescence was staining strongly for lambda in glomerular capillary walls, tubular walls, blood vessel walls and interstitium and negative for Ig G,M and A and Kappa. This confirmed coexistent light chain deposition disease with cast nephropathy.

The patient was offered haemodialysisfor metabolic acidosis that was resistant to medical treatment. She was started on dexamethasone, thalidomide and bortezomib regimen.

Discussion

Monoclonal gammopathies are characterized by a proliferation of a single clone of plasma cells which produce immunologically similar (monoclonal) gamma globulin called M proteins. A circulating M protein can be a light chain, heavy chain or a combination of both.These monoclonal proteins deposit in various tissues including the kidneys . Monoclonal immunoglobulin deposition disease (MIDD) encompasses three clinical entities: Light-Chain only, Light- and Heavy-Chain, and Heavy-Chain only deposition disease. But 70% of MIDD is light chain deposition disease (LCDD). [2].LCDD typically presents with hy-

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pertension, microscopic hematuria, and proteinuria. Light chains have a predilection to deposit in the tubular and glomerular basement membranes and Bowman's capsule. The location of the deposits defines the clinical presentation.[3,4] Renal insufficiency and mild proteinuria in those with tubular deposits and nephrotic syndrome when deposition is predominantly glomerular as in the index case.

The light chains which are filtered from the glomerular basement membrane combine with tamm horsfall proteins of the tubules forming complexes that cannot be reabsorbed giving rise to casts formed commonly in the distal tubules of the nephron. Light chains cause cast nephropathy when they form obstructing tubular casts. Cast nephropathy also called myeloma kidney is always associated with MM. It manifests as acute kidney injury. Our patient had raised creatinine on presentation suggesting the presence of cast nephropathy. Renal biopsy revealed tubules packed with eosinophilic fractured casts suggesting presence of cast nephropathy. However, that could not explain the massive proteinuria she had on presentation. PAS and Congo red negative deposits excluded the AL amyloidosis as a cause for this nephrotic range proteinuria. In addition, the focal glomerular capillary basement membrane thickening present in this patient's biopsy suggested the monoclonal immunoglobulin deposition. Immunofluorescence showed Lambda chain deposition in tubular and glomerular basement membranes. This confirmed coexistent Lambda light chain deposition disease with light chain cast nephropathy in this patient.

Serum free light chain assay showed a Kappa chain restriction and excess Lambda chains. Usually, Lambda chain deposition is associated with AL amyloidosis and Kappa is the type of light chain that is associated with LCDD.[5] In this patient unusually Lambda chain deposition has resulted in LCDD instead of AL amyloidosis.

Light chain deposition disease is characterized by the nonimmune deposition of a monoclonal light chain in the renal basement membrane as well as the glomerular mesangium. Multiple Myeloma is found in about 50% of LCDD. On the other hand, 15-20% of MM secretes monoclonal light chains.[2] This subtype, Light Chain MM is associated with a poorer outcome.

The characteristic light microscopic appearance of glomeruli in LCDD is of a nodular lesion, virtually indistinguishable from the nodular diabetic glomerulosclerosis (Kimmelstiel Wilson nodules). The differential diagnosis of nodular glomerulosclerosis includes diabetes mellitus, amyloidosis, cryoglobulinemia and LCDD.[6] Diabetes was excluded by normal HbA1C in our patient. Renal biopsy was negative for Congo red staining of amyloid fibrils. Lack of cryoglobulin excluded cryoglobulinemia. Early diagnosis of LCDD is challenging because mostof the patients with LCDD do not have a serum monoclonal band of whole immunoglobulin. However, serum free light chain (FLC) assay is always abnormal in patients with LCDD.[7] Serum FLC measurement should be performed in the diagnostic workup of adults presenting with renal disease, independent of the presence of a serum or urine monoclonal protein.

Without treatment LCDD progresses to chronic kidney disease subsequently leading to renal replacement therapy. However reported outcomes with renal transplantation have generally been poor, with most allografts failing due to recurrence of LCDD in the graft within a few years.[8]

Conclusion

LCDD should be considered in the diagnostic workup in a patient with nephrotic syndrome and raised creatinine whose biopsy shows nodular sclerosis. Serum FLC is an essential investigation in adults suspected of renal disease and monoclonal gammopathy. Concurrent presence of two different renal pathologies should be considered when clinical picture is ambiguous.

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