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CLINICAL VIGNETTE

Monoclonal Immunoglobulin Deposition Disease due to Chronic Lymphocytic Leukemia causing Nephrotic Syndrome

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Case

A 79-year-old female with essential hypertension, hyperlipidemia, asthma and pre-diabetes was referred to Nephrology for proteinuria. Patient initially presented to her primary care physician with bilateral lower extremity edema. At the time she was on amlodipine which was discontinued and replaced with chlorthalidone for her hypertension. Duplex ultrasound of bilateral lower extremities did not reveal venous thrombosis. After switching to chlorthalidone her edema had marginally improved. She denied any fever, chills, shortness of breath, dyspnea on exertion, abdominal distention, and change in bowel habits or weight loss. She did report foamy urine, without dysuria, urgency, frequency or gross hematuria. Her age-appropriate cancer screening was up to date, including recent negative mammogram and prior negative colonoscopy.

On examination vital signs included BP 158/74, HR 50. She had bilateral trace pitting pre-tibial lower extremity edema and otherwise normal cardio-pulmonary exam.

Initial laboratory evaluation included CBC significant for leukocytosis of 18.8, absolute lymphocyte count 11.22, hemoglobin 11.2, hematocrit 34.7, and platelet count 322. Serum creatinine 0.55 g/dL, sodium 142, potassium 4.1, BUN 17, serum albumin 3.4. Urinalysis had 9 WBC, 8 RBC-within limits for reporting lab. Specific gravity 1.014, 3+ protein. Spot urine total protein creatinine ratio 8 g.

Further evaluation with serum and urine immunofixation showed monoclonal free kappa light chain consistent with monoclonal gammopathy. Serum IgG- 324, Serum IgA- 169, Serum IgM- 32. Kappa/lambda free light chain ratio 40.7. Other testing was negative including ANA, dsDNA, ANCA serologies.

She was referred to Hematology and was further evaluated with Flow Cytometry. Findings revealed kappa-light chain restricted monotypic B-cells (38% of the total) expressing CD5, CD23 (dim, partial) and negative for CD10. No discrete population of blasts, no pan T-cell aberrancy. She was diagnosis of Chronic Lymphocytic Leukemia (CLL) and possible Myelodysplatic Syndrome (MDS). Initial recommendation was to monitor with serial labs every 6 months.

Due to persistent nephrotic syndrome after appropriate blood pressure control, the patient underwent a kidney biopsy. This revealed a monoclonal immune deposition disease most consistent with light and heavy chain deposition with acute tubular necrosis, atypical lymphoid infiltrate and features of glomerular limited thrombotic microangiopathy, focal and segmental glomerulosclerosis likely due to secondary etiology. There was minimal tubulointerstitial scarring. Strong immunofluorescence staining for IgG kappa light chain was consistent with light and heavy chain deposition disease with associated nodular glomerulosclerosis. Tissue showed multiple small foci of atypical lymphoid infiltrates consistent with patient's previous diagnosis of CLL. There was no other paraprotein mediated disease including amyloidosis, light chain crystalline nephropathy or light chain cast nephropathy.

Based on biopsy results patient was started on treatment with Ibrutinib 420 mg daily. Prior to initiation of therapy patient's proteinuria with a spot urine protein creatinine ratio was 8 g. One month after starting therapy her proteinuria dropped to 5.2 g. It further decreased to 2.7 g 3 months after therapy initiation. After 1 year of therapy, she was considered to be in remission with urine protein creatinine ratio 0.4 g.

Initial recommendation by hematologist after diagnosis of CLL and possible MDS was to monitor labs every 6 months. However, after the kidney biopsy showed light chain nephropathy Ibrutinib was started. Patient was in remission on Ibrutinib, however, this was changed to Venetoclax due to cardiology concerns about worsening cardiomyopathy. She was treated for about a year but developed diarrhea and fatigue. Treatment was discontinued with very close monitoring of patient's CBC and urine studies. She continues to be in remission with urine protein creatinine ratio of 0.2 g and serum creatinine ranging 0.8-0.9 g/dL.

Discussion

Chronic Lymphocytic Leukemia (CLL) is a progressive, lymphocytic proliferative disorder characterized by a monoclonal population of functionally incompetent lymphocytes. Renal involvement is uncommon but this potential complication can occur at any stage of CLL.[1] The spectrum of kidney involvement includes immune-mediated glomerulonephritis (GN),

interstitial infiltration, tubular obstruction, and drug toxicity.[2] The most frequently reported glomerular lesions are Membranoproliferative glomerulonephritis (MPGN), thrombotic microangiopathy (TMA) and minimal change disease. It is rare to see monoclonal immunoglobulin deposition disease associated with CLL. The incidence of nephrotic syndrome in patients with CLL is 1 to 2%.

MIDD are a group of disorders characterized by the deposition of light chains, heavy chains or both light and heavy chains along both the glomerular basement membrane and tubular basement membrane. The abnormal immunoglobulin components are secreted by an abnormal plasma cell or, rarely, a lymphoplasmacytic neoplasm.[3] Based on the type of monoclonal immunoglobulin deposits, MIDD are classified into three types- Light chain deposition disease (LCDD) representing 80 percent of cases, in which deposits are composed of light chains only. In approximately 80 to 90 percent of LCDD, the light chains are kappa light chains. Heavy chain deposition disease (HCDD) is seen in 10 percent of cases where deposits are composed of heavy chains only. Light and heavy chain deposition disease (LHCDD is seen in approximately 10 percent of cases where deposits are composed of both light and heavy chains.[4,5]

Diagnosis of MIDD requires a kidney biopsy which typically shows increased mesangial matrix, deposition of light chains, heavy chains or both light and heavy chains. Mesangial areas can show diffuse and prominent nodular expansion and associated hypercellularity. Congo red staining is typically negative. Therapeutic approach is aimed at controlling the proliferative B cell disorder in order to preserve kidney function and improve survival.

Our patient presented with Nephrotic syndrome, which led to a diagnosis of CLL. She did not develop any acute kidney injury and due to prompt diagnosis of MIDD after kidney biopsy, she was started on timely treatment leading to a complete remission of Nephrotic Syndrome. It is important to appropriately evaluate patients who present with Nephrotic Syndrome for all possible etiologies and consider a kidney biopsy for prompt diagnosis and treatment.

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