



BREAKING THE MOULD: A CASE SERIES HIGHLIGHTING UNUSUAL CLINICAL AND SEROLOGICAL MANIFESTATIONS IN LUPUS NEPHRITIS

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Abstract

Background: Lupus Nephritis (LN) is one of the most severe complications of Systemic Lupus Erythematosus (SLE) and usually presents with proteinuria, microscopic hematuria, low complement levels, and elevated anti-double-stranded DNA antibodies. However atypical clinical and serological presentations do occur and may delay diagnosis and mislead treating physician. Here we came across a series of patients with biopsy-proven lupus nephritis who presented with unusual manifestations including gross hematuria, normal complement levels in proliferative lupus nephritis, isolated low C3 with normal C4 levels, and lupus podocytopathy with familial clustering of lupus nephritis.

INTRODUCTION

Systemic Lupus Erythematosus is a chronic autoimmune disease characterised by immune complex formation and multisystem involvement. Nearly 40-60% of SLE patients tend to develop kidney involvement secondary to lupus which contributes to morbidity and mortality. Lupus nephritis is characterised by the formation of autoantibodies against a wide variety of autoantigens, particularly against chromatin material like double stranded DNA and nucleosomes, which happens as a result of defective clearance of apoptotic material and necrotic cells. Pathogenesis of LN is complex and it involves immune complexes deposition and complement activation which induces tissue inflammation and glomerular damage. Interferon alpha and other inflammatory mediators are released as a result of abnormal adaptive and innate immune responses, amplifying glomerular lesions. Typical presentation of lupus nephritis is proteinuria, microscopic hematuria, low serum complements, high double stranded DNA antibodies. Rarely LN can present with gross hematuria,

normal serum complement levels in proliferative lupus nephritis, lupus podocytopathy with familial clustering of lupus nephritis which are being highlighted in this case series.

CASE 1

A 31 years old female with no known comorbid illness presented to Nephrology op with history of episodes of gross hematuria for three months duration, multiple joint pain and pedal edema for one month duration. On examination patient found to have anemia, pitting pedal edema upto ankle and blood pressure 140/90mm Hg. Urine was red in colour. Her investigations revealed mild anemia with negative direct coombs test, urine albumin 3+ by dipstick method, dysmorphic RBCs in urine microscopy, urine spot protein creatinine ratio of 5.2, serum creatinine 1.89 mg/dl, urine culture was sterile, ultrasound showed normal size kidneys without any obstruction and urinary bladder wall was smooth. Coagulation profile was normal and patient was not on any antiplatelets or anticoagulant drugs. Syndromic diagnosis of Acute Nephritic syndrome was considered. Serum C3 was 118 mg/dl (90-120), C4 was 18 mg/dl (10-40), ANA(IF) was strong positive in nuclear compartment with granular pattern, Anti Sm, RNP, SSa Ab were strong positive; Anti Nucleosome, SSb, ds DNA Ab were positive. Hence SLE LN was considered as cause for acute nephritic syndrome. Renal biopsy revealed IgG(3+), IgM(1+), c3(3+), c1q(3+) on mesangium and focally on glomerular capillary loops without any light chain restriction in Immunofluorescence, 6 viable glomeruli in light microscopy with segmental endocapillary hypercellularity and neutrophilic infiltration were seen in 3 glomeruli, segmental sclerosis in other glomeruli, no spike formation or wireloop lesions, fibrocellular crescents in 2 glomeruli, fibrous crescent in 1 glomeruli, no hyaline thrombus or necrotising lesion without any IFTA. In view of paucity of number of glomeruli, activity and chronicity scores were not assigned. Final diagnosis of SLE – lupus nephritis class 4 with crescent was made. Patient was treated with intravenous methylprednisolone 250 mg for three consecutive days and given intravenous cyclophosphamide injection a week later. Gross hematuria and renal failure resolved within one week of starting methylprednisolone. Peculiarity of this case is gross hematuria as presenting complaint and normocomplementemia being class 4 lupus nephritis. Gross hematuria in lupus nephritis is rarely reported and normal complement levels in proliferative lupus nephritis is atypical.

CASE 2

A 38 years old female with no known comorbidities, presented with pedal edema and facial puffiness, multiple joint pain for 2 weeks duration found to have hypertension 150/100mm Hg, 2.5gram/day proteinuria and microscopic hematuria with dysmorphic RBCs and serum creatinine 1.7mg/dl. A Syndromic Diagnosis of Acute Nephritic Syndrome was made. ANA was strongly positive with high ds DNA titers, found to have low serum c3 level 76mg/dl (90-120) and normal serum c4 level 20mg/dl (10-40). Hence SLE LN was considered as cause for acute nephritic syndrome. In renal biopsy, immunofluorescence showed IgG(3+), IgM(2+), IgA(2+), C3(3+), C1q(2+) granular positivity on the capillary loops and mesangium, in light microscopy endocapillary and mesangial hypercellularity in all 19 glomeruli with NIH activity score of 5/24 and chronicity score of 0/12 was found, final biopsy diagnosis was class 4 lupus nephritis. Oral steroids and intravenous cyclophosphamide according to Eurolupus protocol was started and on follow up, patient had relapse in proteinuria after 4 months from onset of disease, during maintenance phase with oral mycophenolate. Peculiarity of this case is isolated low c3 and normal c4 levels being class 4 lupus nephritis. Isolated low c3 in proliferative lupus nephritis is rare, carries poor prognosis and higher rate of relapse with conventional treatment.

CASE 3

A 20 years old female with no known illness presented with pedal edema for 3 weeks duration, found to have normal blood pressure, proteinuria of 4 gram/day, no microscopic hematuria, dyslipidemia, normal serum creatinine level considered Syndromic Diagnosis of Nephrotic

Syndrome and Minimal Change Disease as cause for nephrotic syndrome underwent renal biopsy. Light microscopy and immunofluorescence was normal. Hence she was diagnosed to have minimal change disease. She was evaluated for SLE in view of sibling being affected with SLE, ANA was strongly positive with elevated ds DNA titers, low serum c3 and c4 levels, Hence a diagnosis of SLE - lupus podocytopathy (LP) was made considering the background. Patient was treated with oral prednisolone 1mg/kg/day, oral hydroxychloroquine and on follow up after one month, disease was under remission and steroids were tapered slowly. Patient's elder sister aged 21 years was diagnosed to have SLE with hepatitis, myositis, nephritis 6 months back and now disease was under remission with oral prednisolone, mycophenolate and hydroxychloroquine.

Peculiarity of this case is lupus podocytopathy, being a distinct variety of lupus nephritis, treatment involves oral steroids rather than cyclophosphamide/ mycophenolate, and also familial clustering of SLE (sibling also affected) though reported, occurrence is rare.

DISCUSSION

Atypical presentation in lupus nephritis challenge conventional diagnostic paradigms, often delaying recognition and treatment. This case series highlights three unusual ways by which lupus nephritis manifest.

1. Gross hematuria as the initial manifestation of LN is uncommon, contrasting with typical subnephrotic- nephrotic range proteinuria or microscopic hematuria. It occurs in fewer than 10% of cases at onset and it underscores hematuria underappreciation in proliferative forms where it signals severe glomerular injury like endocapillary proliferation, disruption of glomerular basement membrane in renal biopsy^{1,2,9}. Early biopsy confirmation is quintessential in order to rule out other causes of rapidly progressive glomerulonephritis and early immunosuppression rapidly resolves hematuria and underlying pathogenic mechanism.
2. Proliferative LN classically features hypocomplementemia due to classical pathway activation¹⁰. Low complements are seen in 75% of class 3 LN and 90% of class 4 LN. However, upto 20-30 percent of active proliferative cases show normal serum c3 and c4 levels, which can be attributed to genetic complement deficiencies or alternate pathway dominance³. These patients exhibit similar biopsy findings and renal outcomes, underscoring necessity of renal biopsy over serology alone.
3. Isolated low c3 with normal c4 deviates from the typical dual low c3, c4 level in LN flare. This pattern is seen in 15% of proliferative LN, reflecting activation of alternate complement pathway, consumption by c3 nephritic factors or properdin dysregulation^{4,5,11}. It correlates with active glomerular inflammation on histology, predicting poor response without intensified therapy.
4. Lupus podocytopathy (LP) is a distinct type of lupus nephritis which is not included in International Society of Nephrology/ Renal Pathology Society (ISN/RPS) classification of lupus nephritis, manifest as nephrotic syndrome. In renal biopsy, it mimicks Minimal Change Disease (MCD) or Focal Segmental Glomerulosclerosis (FSGS) without any significant immune deposits. In Electron microscopy, it is recognised as foot process effacement^{6,7}. Renal biopsy distinguishes LP from class 5 LN, guiding oral prednisolone therapy for remission.
5. Familial clustering of LN, including LP variants, implies shared HLA-DR2/3 alleles and monogenic defects like TREX1 mutations, with 5-10% of SLE kindreds showing renal involvement. Black SLE patients with nephritis showed familial ESRD clustering, independent of age or SLE duration, suggesting shared genetic risks for progressive renal failure⁸. Juvenile

onset and severe phenotypes amplified clustering in non- European cohorts. Studies have identified genetic associations involving genes of HLA, complement pathway, Fc receptor polymorphisms, interferon regulatory genes. Recognising familial clustering may allow early screening of relatives, prompt detection of renal involvement, improved understanding of disease pathogenesis.

CONCLUSION

Gross hematuria, normal complement levels and isolated c3 reduction represent important diagnostic pitfalls and deviate from classical descriptions. Similarly lupus podocytopathy challenges the traditional immune complex based classification of lupus nephritis. Greater awareness among clinicians is required to ensure timely biopsy to facilitate early diagnosis and appropriate treatment in order to allay long term renal damage.

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