Renal Limited Lupus-Like Nephritis – A Case Report and Review of Literature

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Abstract

Biopsy diagnosis of lupus nephritis with no extra-renal features of systemic lupus erythematosus, normal complement levels, negative or weekly positive anti-nuclear antibody and negative other serology is a rare entity known as “Renal Limited Lupus Like Nephritis” (RLLLN). So far, only 39 cases of RLLLN in adults have been reported in literature. The prognosis of these patients varied depending on their clinical presentation. Herein, we report a case of an elderly Arab female with RLLLN who presented with massive proteinuria and acute kidney injury with crescents, however had a good outcome contrary to reported cases with similar presentations. We also reviewed all reported cases thus far.

Resume

Le diagnostic par biopsie de la néphropathie lupique dépourvue de caractéristiques extra-rénales du lupus érythémateux disséminé, de niveaux de complément normal, d'anticorps anti-nucléaire négatifs ou hebdomadaires positifs et d'une autre sérologie est une entité rare appelée « Néphrite Rénale Limitée semblable au Lupus » (RLLLN). Jusqu'à présent, seuls 39 cas de RLLLN chez les adultes ont été rapportés dans la littérature. Le pronostic de ces patients variait en fonction de leur présentation clinique. Ici, nous rapportons le cas d'une femme arabe âgée souffrant de RLLLN qui présentait une protéinurie massive et une lésion rénale aiguë accompagnée de croissants, mais dont le résultat était satisfaisant contrairement aux cas rapportés avec des présentations similaires. Nous avons également examiné tous les cas signalés jusqu'à présent.

Keywords: Renal-Limited Lupus-Like Nephritis, Lupus Nephritis, Full-House pattern

Lupus nephritis is a common feature of systemic lupus erythematosus (SLE) usually occurring in young females and diagnosed by renal biopsy.¹ Only 10 cases have been reported in adults where patients with lupus nephritis have negative serology and no extra-renal SLE manifestations. This rare entity is known as Renal Limited-Lupus-Like Nephritis (RLLLN). Reported outcomes varied from good to poor. We herein report a case of an elderly female with Renal-Limited Lupus-Like Nephritis who presented with massive proteinuria, gross hematuria and acute kidney injury with crescents. However, she had a good outcome unlike previous cases with similar presentation.

Case Report

A 63-year-old Arab female with no previous history of renal or autoimmune disease presented in November 2014 to an outside facility with 1-day history of gross hematuria and decreased urine output. On arrival, she was found to have proteinuria. 2 days after presentation, she became anuric with signs of volume overload, severe hyponatremia, and had worsening renal function requiring urgent hemodialysis. She was referred to our facility 1 week after initial presentation for further care and management. The patient had no history of joint pain/swelling, rash, oral ulcers,

recent infections, fever, or other constitutional symptoms. No history of medication use.

On examination, she had stable vital signs, no rash, or evidence of active synovitis. She had minimal bilateral pitting edema and remainder of the examination was unremarkable.

Laboratory investigations showed creatinine 6.1 mg/dL, serum sodium 128 mEq/L, Hemoglobin 11.4 g/dL, platelets 310,000, and leukocytes 12.8 k with no left shift. Urine analysis showed gross hematuria with dysmorphic RBCs. Serum albumin 2.9 g and total urinary protein excretion 23 g. No abnormal “M” spike or monoclonal protein on serum protein electrophoresis. She had a borderline ANA (titer 1:80); speckled pattern. Negative Anti double stranded DNA, Anti-Smith, and Anti-neutrophil cytoplasmic antibodies. Anti SS-A/Ro, Anti SS-B/La, Anti-Jo1, Glomerular base antibodies were negative. C4 level was normal and C3 was borderline suppressed 8 mg/dL (normal 9–180). HIV, hepatitis B and C were negative.

Computed tomography-guided percutaneous renal biopsy revealed endocapillary proliferative, crescentic and membranous glomerulonephritis consistent with class IV and V lupus nephritis. Most glomeruli showed marked global mesangial and endocapillary hypercellularity with abundant intracapillary infiltrating lymphocytes, monocytes, and neutrophils. The basement membranes were thickened and 43% of glomeruli showed active crescents (Figure 1). Immunofluorescence showed a “full-house” pattern with positive mesangial and capillary wall staining for IgG, IgA, IgM, C1q, kappa, and lambda. On electron

microscopy, there was segmental duplication of basement membrane with cellular interposition, and abundant global mesangial, intramembranous, subendothelial, and segmental subepithelial electron dense granular deposits (Figure 2). Few endothelial tubuloreticular inclusions were present. These findings are consistent with RLLN.

The patient continued dialysis and was started on methylprednisolone and cyclophosphamide (CYC). As per the National Institutes of Health (NIH) protocol, the patient was given intravenous (IV) cyclophosphamide (500 mg/m²) during this hospital stay. She received a total of 6 doses of cyclophosphamide over 1 month (500 mg/m²) as induction, IV pulse cyclophosphamide as maintenance once every 3 months (quarterly) for 2 years, for a total of 14 cycles. The cyclophosphamide dose was adjusted based on the patient’s renal function and hemodialysis; as recommended by Aronoff in 2007.¹³ The patient completed her therapy and tolerated it well. She had no cyclophosphamide-related side effects during and after receiving treatment. The patient was also weaned off dialysis. Over 3 years after initial presentation, she continues to be in remission with normal creatinine level and only moderate proteinuria (30 mg/dL) (Figure 3). She follows up regularly with the nephrology service, has no change in serology status and no signs or symptoms of SLE.

Discussion

Lupus nephritis is a known major cause of morbidity in SLE. Up to 60% of adult lupus patients eventually develop renal

Figure 1. Glomeruli exhibiting mesangial and endocapillary hypercellularity (arrow), infiltrating neutrophils (arrow head) and lymphocytes, thickened basement membranes, and segmental cellular crescents (*).

Figure 2. Electron microscopy showing abundant intramembranous (*) and mesangial deposits (arrow head) with diffuse foot-process effacement of podocytes (arrow).

Figure 3. Patient's protein/creatinine trend.

impairment.³ It usually happens early in the SLE disease course, and in 15–20% of patients, nephritis may be the first clinical presentation of SLE.¹ The incidence of lupus nephritis varies depending on the population. It occurs more in those of Asian descent, followed by Africans, Hispanics, and finally Caucasians.² SLE in general, has a clear female predominance, and renal disease in SLE specifically tends to be more common in the younger age group.⁴ The presence of lupus nephritis in SLE is an indicator of poor prognosis.²

The most common clinical feature of lupus nephritis is proteinuria. In 1999, Cameron found that proteinuria occurred in 100% of patients with lupus nephritis.³ Other features include microscopic hematuria, granular or red cell casts, hypertension, and decreased renal function. Biopsy remains the best modality of diagnosis. In 2003, the International Society of Nephrology/Renal Pathology Society (ISN/RPS) developed a lupus nephritis classification system based on biopsy findings. Positive staining for IgG, IgM, IgA, C3, and C1q, known as the “full-house pattern,” on immunofluorescence is strongly suggestive of lupus nephritis. It is seen in one-quarter of patients with nephritis due to lupus and is very rarely seen in other causes of nephritis.³ Other strongly suggestive pathology findings include immune-complex deposits present diffusely in the mesangium, subendothelium, and subepithelium, extraglomerular immune-complex deposits in the tubular basement membranes, interstitium, and blood vessels, and the presence of endothelial cells tubuloreticular inclusions.⁵ These tubuloreticular inclusions are mostly associated with lupus nephritis and may be seen less commonly with other renal disease causes such as hepatitis B, hepatitis C, or HIV.⁶ Patients with lupus nephritis also have low complement levels and positive serology for ANA, Anti-Double stranded DNA and Anti-Smith antibodies seen in SLE.

There have been cases with biopsy diagnosis of lupus nephritis but have no extra-renal manifestations of SLE, have normal complement levels, negative or weakly positive ANA and negative reminder serology. This rare entity is known as RLLLN. The majority of cases reported are in children with

some subsequently developing SLE features or positive serology. Very few cases have been reported in adults. Based on literature review using PubMed, Cochrane Library, and Google Scholar, using the terms “Renal-Limited Lupus-Like Nephritis,” “Renal Limited Lupus,” and “Full-House Nephritis,” we found only 39 reported cases of RLLLN in adults.^{5,7,8–11} We looked for cases of patients age 18 or above to target the adult age-group literature in our review. Edward Jones first reported this disease in 5 adults in 1982.⁸ Andrew Sharman then reported 5 similar cases in adults in 2004.⁹ In 2005, Ozdemir reported an additional case.¹⁰ In 2010, Y.K. Wen published a study which included 21 patients with Renal Limited Lupus.¹¹ Ana Huerta later reported 4 similar cases in 2011, and in 2013, Chi Young reported an additional case.^{5,7} The cases varied in their presenting features and subsequently their outcome (Table 1).

We present the first case of RLLLN in an elderly female with excellent outcome despite her initial presentation of acute kidney injury, creatine of 6.1, and crescentic nephritis. We included her initial presentation, disease course, diagnostic findings, management plan, and finally her outcome and follow up. We emphasized some unique findings in our case by comparing them to all similar cases reported so far and information obtained from our review of literature.

A study done in 2016 including 924 SLE patients, found that renal disease is more common in the young, specifically in those under 55 years of age.^{1,4} The majority of reported cases (2/3) were in younger adults (< 55 yrs) and a majority presented with proteinuria or microscopic hematuria; the 2 most common findings in lupus nephritis.³ Our patient, presented at an older age (66 years), had proteinuria, in addition to gross hematuria and acute kidney injury which occur in 1–2% of patients.³ Our patient's lack of extra-renal manifestations, negative serology, and renal biopsy findings are all consistent with RLLLN.

Treatment of patients with RLLLN is of utmost importance, and the regimen includes 2 phases; induction and maintenance. IV cyclophosphamide is the usual induction drug. Oral mycophenolate mofetil has also been used as another option for induction.¹ Oral azathioprine, oral mycophenolate mofetil, or IV cyclophosphamide are used for maintenance. Different protocols have been established for the management of lupus nephritis. We followed the standard protocol published by the NIH in 1992. Despite the possible risk of cumulative cyclophosphamide effect, the NIH protocol was selected for this patient as it is the protocol preferred by the treating teams at our institute. This protocol includes the use of monthly intravenous cyclophosphamide (500–1000 mg/m²) for 6 months as induction therapy, followed by the use of intravenous pulse cyclophosphamide every 3 months (quarterly) for 2 years as maintenance.¹² We also adjusted the cyclophosphamide dose based on renal function

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Table 1. Literature Review on Reported Cases of Renal-Limited Lupus-Like Nephritis in Adults*

Year	Author	Number of Cases	Patient's Age (Years)	Initial Presentation	Initial Creatinine (mg/dL)	Crescents	Management	Outcome
2013	Chi Young	1	40	Proteinuria	Normal	None	1. CYC & Methylprednisolone 2. MMF & Prednisone	<ul style="list-style-type: none"> • Good; Normal renal function • Proteinuria <43000 mg/24 hrs
2012	Ana Huerta	4	36	Proteinuria & Microscopic hematuria	Normal	Present (46%)	1. Prednisone & MMF 2. CYC 3. CYC with MMF & Prednisone 4. Hemodialysis	• Poor; ESRD then Renal Tx
			19	Proteinuria & Microscopic hematuria	Elevated (1.7)	Present (55%)	1. Prednisone 2. MMF 3. Methylprednisolone 4. MMF & Prednisone	• Poor; ESRD then Renal Tx
			50	Lower limb edema & worsening HTN	Elevated (2)	Present (43%)	1. Prednisone 2. Temporary Hemodialysis	• Poor; CKD stage 3
			46	Fever, Vomiting & Nephrotic Syndrome	Elevated (3.5)	Present (75%)	1. Prednisone & CYC 2. Switched to MMF (due to CYC side effects) 3. Hemodialysis	• Poor; ESRD on Hemodialysis
2010	YK Wen	21	57	Acute renal failure	†	Present in 4 patients (†)	Methylprednisolone, CYC, & Prednisone	†
			79	Acute renal failure	†		Methylprednisolone, CYC, & Prednisone	†
			28	Chronic renal failure	†		ACEI	†
			30	Proteinuria	†		Prednisone	†
			77	Chronic renal failure	†		ACEI	†
			61	Nephrotic syndrome	†		Prednisone	†
			35	Rapid progressive renal failure	†		Methylprednisolone & Prednisone	†
			30	Nephritic syndrome	†		Antibiotic	†
			59	Nephritic syndrome	†		None	†
			23	Nephrotic syndrome	†		ACEI	†
			23	Nephrotic syndrome	†		Prednisone & AZA	†
			51	Nephrotic syndrome	†		Prednisone, CYC & ARB	†
			76	Nephrotic syndrome	†		ACEI	†
			58	Nephrotic syndrome	†		Prednisone & ARB	†
			20	Nephrotic syndrome	†		Interferon	†
			40	Nephrotic syndrome	†		Prednisone, CYC, ACEI	†
			72	Nephrotic syndrome	†		ACEI	†
			59	Nephrotic syndrome	†		Prednisone & CYC	†
			64	Proteinuria	†		Prednisone, CYC, ACEI	†
			61	Nephrotic syndrome	†		Prednisone, AZA	†
			69	Nephrotic syndrome	†		Prednisone & CYC	†

Table 1. Literature Review on Reported Cases of Renal-Limited Lupus-Like Nephritis in Adults* (Continued)

Year	Author	Number of Cases	Patient's Age (Years)	Initial Presentation	Initial Creatinine (mg/dL)	Crescents	Management	Outcome
2005	FN Ozdemir	1	28	Proteinuria, HTN, Lower limb edema	Elevated (2.3)	Present (46%)	Methylprednisolone & CYC	• Improvement of renal function & proteinuria (values not specified in case report)
2004	Andrew Sharman	7	65	Proteinuria & Microscopic hematuria	Elevated (8.4)	Present (t)	Prednisone & CYC	• Poor; Death
			39	Nephrotic syndrome	Elevated (3.0)	None	Prednisone	• Poor; CKD Stage 2 • Proteinuria 400 mg/24 hrs
			26	Proteinuria & Microscopic hematuria	Normal (0.8)	None	None	• Good; Normal renal function • Proteinuria > 200 mg/24 hrs
			63	Proteinuria & Microscopic hematuria	Normal (1.1)	None	None	• Poor; CKD Stage 2 • Proteinuria < 300 mg/24 hrs
			30	Proteinuria	Normal (0.6)	None	None	• Good; Normal renal function • Proteinuria 500 mg/24 hrs
			19	Proteinuria	Normal (0.6)	None	None	• Good; Normal renal function • Proteinuria 400 mg/24 hrs
			31	Proteinuria & Microscopic hematuria	Normal (0.8)	None	None	• Good; Normal renal function • Proteinuria 1000 mg/24 hrs
1982	Edward Jones	5	19	Nephrotic Syndrome	Normal (0.7)	None	Prednisone & AZA	• Good; Normal renal function • Moderate proteinuria 2900 mg/24 hrs
			31	Proteinuria & Microscopic hematuria	Normal (0.8)	None	None	• Good; Normal renal function • Moderate proteinuria 2829 mg/24hrs
			18	Nephrotic Syndrome & Microscopic hematuria	Normal (0.8)	Present (< 20%)	Prednisone & AZA	• Good; Normal renal function • Moderate proteinuria 2000 mg/24 hrs

Table 1. Literature Review on Reported Cases of Renal-Limited Lupus-Like Nephritis in Adults* (Continued)

Year	Author	Number of Cases	Patient's Age (Years)	Initial Presentation	Initial Creatinine (mg/dL)	Crescents	Management	Outcome
1982	Edward Jones	5	38	Proteinuria & Microscopic hematuria	Normal (1.2)	None	AZA	<ul style="list-style-type: none"> • Poor; Moderate decrease in renal function (Cr 1.8) • Moderate proteinuria 2600 mg/24 hrs
			30	Microscopic hematuria	Normal (1.3)	None	None	<ul style="list-style-type: none"> • Good; Normal renal function • Microscopic hematuria • Moderate proteinuria 75 mg/dL

*Adult: age ≥ 18.

CYC = cyclophosphamide, MMF = mycophenolate mofetil, AZA = azathioprine, ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, HTN = hypertension, ESRD = end stage renal disease, CKD = chronic kidney disease, Tx = transplant, Cr = Creatinine. † = data not reported in literature.

and hemodialysis status as Aronoff recommended in 2007.¹³ We found this protocol to be effective in managing our patient. Achieving disease remission is reported to be associated with evidentially better renal and patient survival.¹⁴ This remission may be complete; where proteinuria is less than 0.5 g/day, or partial; where there is a decrease in proteinuria to less than or equal to 50% from baseline.¹⁵

Due to the limited data, no definite prediction of the prognosis of RLLN has been made so far. The outcomes reported in literature were variable. In our review, 17 of the 39 cases had reported outcomes with regards to creatinine and proteinuria values. 52.9% had a good outcome with no renal impairment, and 47% had a poor outcome with permanent decrease of renal function. We noticed that all cases with good outcome had normal creatinine levels upon initial presentation but found no predicting association between those of poor outcome and their initial creatinine. Also, 62 % of patients with poor outcome had glomerular crescents involving 43–75% of the glomeruli. Only one patient with a good prognosis had crescents but seen in less than 20% of glomeruli. Gupta and Sachdeva noted in 2012 that the presence of crescentic lupus nephritis indicated a poor prognosis with derangements of renal function, and the percentage of crescentic glomeruli was related to the severity of renal failure.¹⁶

In contrast to literature, our patient went into remission with no residual effect on renal function despite her severe disease, elevated creatinine level on initial presentation and presence of crescents involving 43% of glomeruli. We thus, propose a possible good prognosis for this disease with early treatment, and emphasize the importance of early diagnosis and early initiation of aggressive treatment during management of similar cases.

References

- Saxena R, Mahajan T, and Mohan C. Lupus nephritis: Current update. *Arthritis Res Ther* 2011;13(5):240.
- Salgado AD and Herrera-Diaz C. Lupus Nephritis: An overview of recent findings. *Autoimmune Dis* 2012;1–21.
- Cameron JS. Lupus Nephritis. *JASN* 1999;10(2):413–24.
- Ambrose N, Morgan TA, Galloway J, et al. Differences in disease phenotype and severity in SLE across age groups. *Lupus* 2016;doi:10.1177/0961203316644333
- Huerta A, Bomback AS, Liakopoulos V, et al. Renal-limited 'lupus-like' nephritis. *Nephrol Dialysis Transplant* 2011;27(6):2337–42.
- Lee C, Suh K, Kim K, et al. The clinicopathologic significance of endothelial tubuloreticular inclusions in glomerular diseases. *Ultrastruct Pathol* 2013;37(6):386–94.
- Park CY, Kim J, Shin SP, et al. A case of renal-limited lupus-like nephritis. *Soonchunhyang Med Sci* 2013;19(2):104–107.
- Jones E and Magil A. Nonsystemic mesangiopathic glomerulonephritis with "full house" immunofluorescence: pathological and clinical observations in five patients. *Am J Clin Pathol* 1982;78(1):29–34.
- Sharman A, Furness P, and Feehally J. Distinguishing C1q nephropathy from lupus nephritis. *Nephrol Dialysis Transplant* 2004;19(6), 1420–26.
- Ozdemir FN, Elsurur R, Akcay A, et al. Seronegative systemic lupus erythematosus: Etiology of nephrotic syndrome and acute renal failure in early postpartum period. *Lupus* 2005;14(8):629–31.
- Wen Y and Chen M. Clinicopathological study of originally non-lupus "full-house" nephropathy. *Renal Failure* 2010;32(9):1025–30.
- Boumpas D, Austin H, Balow J, et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *The Lancet* 1992;340(8822):741–45.
- Aronoff GR. Drug prescribing in renal failure (5th ed.). Philadelphia: American College of Physicians; 2007.
- Chen YE, Korbet SM, Katz RS, et al. Value of a complete or partial remission in severe lupus nephritis. *Clin J Am Soc Nephrol* 2008;3(1):46–53.
- Ruggiero B, Vivarelli M, Gianviti A, et al. Outcome of childhood-onset full-house nephropathy. *Nephrol Dial Transplant* 2016;1–10.
- Gupta V, Sachdeva S, Khan AS, and Haque SF. Diffuse Proliferative Crescentic Lupus Nephritis with Normal Renal Function. *Saudi J Kidney Dis Transpl* 2012;23(2):343–45.