Lupus: Open Access

OPEN ACCESS Freely available online

Commentary

Detecting Lupus Nephritis

De Rosa Marcelo[1*], Brad H. Rovin[2], Salem Almaani[2]

[1]*Department of Nephrology, University of Buenos Aires, Argentina*

[2]*Department of Nephrology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA*

ABSTRACT

Cutaneous Lupus Erythematosus (CLE) is an autoimmune disease that encompasses a wide range of dermatologic manifestations with varying degrees of association with systemic disease. Treatment options for CLE are limited, and no medication has been approved specifically for CLE. However, increased emphasis on the role of biological therapies for CLE has emerged in recent years due to an improved understanding of the pathogenesis of CLE. This review summarizes the recent insights into the pathogenesis of CLE and current advances in the development of CLE treatments.

Keywords: Cutaneous lupus erythematosus; Lupus; Systemic lupus erythematosus; Discoid lupus; Autoimmune; Discoid lupus erythmatosus

DESCRIPTION

Lupus Nephritis (LN) is a common and serious manifestation of Systemic Lupus Erythematosus (SLE) and is a major contributor to morbidity and mortality [1]. Most SLE patients who develop LN do so in the first 3-5 years after the diagnosis of SLE [2,3]. The kidney biopsy is the gold standard for establishing a diagnosis of LN. Clinical practice guidelines recommend obtaining a kidney biopsy when SLE patients demonstrate clinical signs of nephritis such as glomerular hematuria, proteinuria, or abnormal kidney function that cannot otherwise be explained [4]. However, this approach assumes that those clinical signs represent immune-complex-mediated kidney injury with high fidelity. This assumption is not entirely accurate as there is discordance between clinical signs of LN and histological evidence of LN. For example, some patients with LN do not manifest any urine abnormalities, an entity termed "silent nephritis", and frequently develop proliferative forms of LN. In a cohort of 86 SLE patients without overt signs of kidney disease (proteinuria <400 mg/d, absence of glomerular hematuria or pyuria) who underwent a kidney biopsy, 15% had a proliferative form of LN, and 10% had membranous lupus nephritis [5]. A smaller cohort of 30 SLE patients without overt proteinuria (<300 mg/d) and a normal urine sediment demonstrated similar results, with 23% having a proliferative form of LN, and 7% having membranous LN [6].

Additionally, patients with glomerular hematuria and modest amounts of proteinuria can also have a significant degree of LN. In our cohort of 222 patients with LN that underwent a kidney biopsy for suspected nephritis, 46 patients had glomerular hematuria with proteinuria levels <500 g/d [7]. Of those, 85% were found to have a proliferative form of LN (Table 1). Moreover, in the 25 patients who had proteinuria <0.25 g/d, 76% had proliferative forms of LN (Table 1). Taken together, those findings demonstrate that aggressive forms of LN can exist despite the absence of overt signs of kidney disease, and that the sensitivity of the kidney biopsy for identifying proliferative forms of LN increases when hematuria and/or proteinuria are present.

Table 1: Clinical and histological characteristics of a cohort of lupus nephritis patients from Argentina.

Cohort characteristics	Proteinuria <0.5 g/d	Proteinuria ≥ 0.5 g/d	P-value2
	(n 46)	(n 176)	
Female	36 (78.3)	155 (88)	0.097
Duration of lupus, months	12 (2–60)	11 (1–168)	NS
Glomerular hematuria present	46 (100)	169 (96)	NS
Proteinuria g/d	0.23 (0.0–0.42)	3.60 (0.5–20)	<0.0001
Serum creatinine, mg/dl	0.70 (0.4–1.3)	0.9 (0.46–7.8)	<0.0001

Correspondence to: Dr. De Rosa Marcelo, Department of Nephrology, University of Buenos Aires, Argentina, E-mail: drmarceloderosa@gmail.com

Received: April 30, 2021; **Accepted:** May 14, 2021; **Published:** May 21, 2021

Citation: Marcelo DR, Rovin BH, Almaani S (2021) Recent Advances in Cutaneous Lupus Erythematosus. Lupus: Open Access. 6:168.

Anti-dsDNA–positive	31 (67.4)	114 (64.8)	NS
C3, mg/dl	66 (15–174)	69 (14–180)	NS
C4, mg/dl	12 (1–43)	9 (1–46)	NS
ISN/RPS class			
II	5 (10.9)	0	NS
III	14 (30.4)	18 (10.2)	0.002
IV	21 (45.7)	135 (76.7)	0.0001
V	2 (4.3)	3 (1.7)	NS
III or IV + V	4 (8.7)	19 (10.8)	NS
IV	0	1 (0.6)	NS
Activity index	6 (0-14)	9 (1-21)	<0.0001
Chronicity index	2 (0-4)	3 (0-8)	<0.0001

[1]Data are expressed as number of patients (% of group) or as median (range)

[2]Comparing patients with proteinuria <0.5 g/d to patients with proteinuria ≥ 0.5 g/d

Abbreviations: Anti-dsDNA: Anti-Double-Stranded DNA Antibody; C3: Complement C3; C4: Complement C4; ISN/RPS: International Society of Neurology/Renal Pathology Society; NS: Non-Significant.

Although proteinuria has long been viewed to be one of the cardinal signs of active nephritis in SLE patients, patients with no histological signs of LN activity can have a significant amount of proteinuria. In a study of patients with LN who received protocol biopsies after completion of induction therapy, 8 of the 13 patients who achieved histological remission (defined as a NIH activity index score of 0) still had proteinuria that was more than 500mg/d (median 1720 mg/day, range: 750–3000 mg/day) [8]. Thus one can conclude that the currently utilized clinical markers of nephritis, especially proteinuria, are not robust markers of disease activity. Additionally, those clinical markers are not optimal for early detection of kidney damage. In the cohort of silent LN patients described by Zabaleta-Lanz [6-10], the mean NIH chronicity index (CI) score was 1.9. Moreover, 30% of patients with silent LN who had proliferative forms of LN in Wakasugi's cohort had some degree of global glomerular sclerosis [5]. Similarly, we found that the median CI in our patients with glomerular hematuria and minimal proteinuria (<0.25 g/d) was 2 [7]. Thus a significant amount of kidney damage may occur before overt clinical signs of LN are detected.

Earlier identification of kidney involvement may result in earlier initiation of therapy potentially decreasing the rate of progression of kidney damage. Non-invasive biomarkers of kidney involvement can help reach that goal. Urine soluble CD163 (usCD163) is a potential biomarker that reflects LN activity. In a study by Mejia-Vilet usCD163 levels increased prior to development of a nephritis flare, and decreased after treatment in patients who achieved remission [9]. The decrease in usCD163 levels occurred prior to the resolution of proteinuria suggesting it could be an early marker of response. In addition, usCD163 had an excellent correlation with histological markers of injury which was superior to that of proteinuria. Urine epidermal growth factor (uEGF) is another potential biomarker that demonstrated utility in LN [10]. Unlike usCD163 which is a marker of disease activity, uEGF levels demonstrated excellent correlation with the NIH CI and thus is representative of chronic kidney damage. If validated, usCD163 and uEGF have the potential to serve as more sensitive and hence earlier markers of active LN and kidney damage respectively.

To conclude, histological evidence of LN often predates the development of clinically recognized urinary abnormalities. Proteinuria and hematuria are not optimal markers of LN and may lead to a delay in identifying patients with active disease. Biomarkers that are more sensitive for detection of LN and highly representative of kidney histology have the potential to revolutionize the care of patients with LN.

REFERENCES

1. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clinical Journal of the American Society of Nephrology. 2017;12(5):825-835.

2. Hiraki LT, Feldman CH, Liu J, Alarcon GS, Fischer MA, Winkelmayer WC, et al. Prevalence, incidence, and demographics of systemic lupus erythematosus and lupus nephritis from 2000 to 2004 among children in the US Medicaid beneficiary population. Arthritis and rheumatism. 2012;64(8):2669-26676.

3. Feldman CH, Hiraki LT, Liu J, Fischer MA, Solomon DH, Alarcon GS, et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000-2004. Arthritis and rheumatism. 2013;65(3):753-763.

4. Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Annals of the rheumatic diseases. 2019;78:736-745.

5. Wakasugi D, Gono T, Kawaguchi Y, Hara M, Koseki Y, Katsumata Y, et al. Frequency of class III and IV nephritis in systemic lupus erythematosus without clinical renal involvement: an analysis of predictive measures. J Rheumatol. 2012;39(1):79-85.

6. Zabaleta-Lanz ME, Munoz LE, Tapanes FJ, Vargas-Arenas RE, Daboin I, Barrios Y, et al. Further description of early clinically silent lupus nephritis. Lupus. 2006;15(12):845-851.

7. De Rosa M, Rocha AS, De Rosa G, Dubinsky D, Almaani SJ, Rovin BH. Low-Grade Proteinuria Does Not Exclude Significant Kidney Injury in Lupus Nephritis. Kidney Int Rep. 2020;5(7):1066-1068.

8. Malvar A, Pirruccio P, Alberton V, Lococo B, Recalde C, Fazini B, et al. Histologic versus clinical remission in proliferative lupus nephritis. Nephrology, dialysis, transplantation. 2017;32(8):1338-1344.

9. Mejia-Vilet JM, Zhang XL, Cruz C, Cano-Verduzco ML, Shapiro JP, Nagaraja HN, et al. Urinary Soluble CD163: a Novel Noninvasive Biomarker of Activity for Lupus Nephritis. Journal of the American Society of Nephrology. J Am Soc Nephrol. 2020;31(6):1335-1347.

10. Mejia-Vilet JM, Shapiro JP, Zhang XL, Cruz C, Zimmerman G, Méndez-Pérez RA, et al. Association Between Urinary Epidermal Growth Factor and Renal Prognosis in Lupus Nephritis. Arthritis & rheumatology (Hoboken, NJ). 2021;73(2):244-254.