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Factors Associated With Rapid Progression to Endstage Kidney Disease in Lupus Nephritis

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ABSTRACT. ***Objective.*** Lupus nephritis (LN) may lead to endstage kidney disease (ESKD) in 22% of patients over a period of 15 years, with the risk being particularly higher in diffuse proliferative forms. The rate of kidney function decline varies. However, a catastrophic course leading to ESKD within a few years from onset is uncommon. The aim of the present study was to assess the factors associated with rapid progression to ESKD in patients with LN.

Methods. Patients from the Toronto Lupus Clinic with biopsy-proven LN at presentation and estimated glomerular filtration rate (eGFR) 60 mL/min/1.73 m^2, who developed ESKD within 3 years were retrieved. Pathology reports were reviewed with particular emphasis on distinct histopathologic features. Demographic, clinical, laboratory, and therapeutic variables were also analyzed.

Results. Ten patients (1.8% of the total LN population) developed ESKD within 3 years of diagnosis. Their mean age was 34.2 ± 7.3 years, mean time to ESKD 19.2 ± 12.4 months, initial eGFR 90.2 ± 24.9 mL/min/1.73 m^2, proteinuria 2.7 ± 1.04 g/24 h. The median rate of kidney function decline was > 43 mL/min/1.73 m^2/year. One patient had LN class III, 5 had LN class IV, 2 had membranous LN (class V), and another 2 had mixed IV/V. Moreover, 2 patients had extensive thrombotic microangiopathy, 1 collapsing glomerulonephritis, and 1 concomitant antiglomerular basement membrane (anti-GBM) nephropathy. Four patients showed no unusual kidney pathology; all of them had severe noncompliance (discontinued all medications to follow alternative treatment).

Conclusion. Catastrophic progression to ESKD is uncommon in LN. The major associated factors are poor compliance and distinct histopathologic features such as thrombotic microangiopathy, collapsing glomerulopathy, and concomitant anti-GBM nephropathy.

Key Indexing Terms: endstage kidney disease, lupus nephritis, rapid progression

Lupus nephritis (LN) affects approximately 40% of patients with systemic lupus erythematosus (SLE) and may lead to endstage kidney disease (ESKD) in 22% over a period of 15 years[1]. The risk was particularly high (up to 44%) in those with diffuse proliferative forms (class IV). Kidney injury is also the most important predictor of mortality in this population. Compared to non-SLE patients with ESKD, patients with LN on dialysis have a greater than 4-fold increased risk of death (95% CI 1.2–15.2)[2].

Although the rate of kidney function decline varies among patients, a "catastrophic" course defined as ≥ 20 mL/min/1.73 m^2/year of the estimated glomerular filtration rate (eGFR) is rather uncommon. The aim of the present study was to assess the factors associated with rapid (within 3 years of diagnosis) progression to ESKD in patients with LN and with initially normal or mildly impaired kidney function.

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MATERIALS AND METHODS

Setting. The University of Toronto Lupus Clinic (UTLC) has currently enrolled 2008 patients since its establishment in 1970. All patients fulfilled the revised American College of Rheumatology criteria for SLE classification, or had 3 criteria and a supportive kidney biopsy[3]. Patients are followed regularly at 2- to 6-month intervals according to a standardized research protocol, which is regularly updated. Regarding LN, the protocol captures the histopathologic class according to the International Society of Nephrology/Renal Pathology Society classification[4] along with all relevant laboratory (serum creatinine, 24-h proteinuria, urinary sediment including hematuria and casts, titers of anti-dsDNA antibodies, and levels of complements C3 and C4, etc.) and therapeutic data [dose and type of immunosuppressives, glucocorticoids (GC), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers, etc.]. Moreover, associated factors such as hypertension (including blood pressure level and relevant treatment) and diabetes are documented in each visit.

All individuals have provided written informed consent for studies being conducted at the UTLC. This study was approved by the University Health Network Research Ethics Board (UHN/REB 11-0397).

Patient selection. For the purpose of the present study, the data of the UTLC patients with new-onset LN and normal or mildly impaired kidney function (eGFR 60 mL/min/1.73 m^2) who developed ESKD (defined as the initiation

of dialysis or eGFR < 15 mL/min/1.73 m^2 for 2 consecutive clinic visits) within 3 years since LN diagnosis were retrieved. Time to ESKD was defined as the period from the kidney biopsy (index date) to the incident ESKD date.

Study design. The medical records of the eligible patients were reviewed with particular emphasis on the distinct histopathologic features, including moderate-to-severe glomerular sclerosis, interstitial fibrosis, tubuloreticular inclusions (TRI), thrombotic microangiopathy, collapsing glomerulonephritis, and podocyte effacement. The medical records were also reviewed for reports of poor compliance in the clinic visits preceding ESKD.

RESULTS

Five hundred and sixty patients with biopsy-proven LN were retrieved from the database, 43 of whom developed ESKD. Seventeen patients developed ESKD within 3 years; 7 of them were excluded because their baseline kidney function was severely impaired (eGFR 9–31 mL/min/1.73 m^2). Ten patients with initially normal or mildly impaired kidney function (eGFR 60 mL/min/1.73m^2; 1.8% of the total LN population) developed ESKD within 3 years of LN diagnosis. The demographic, histopathologic, and kidney function characteristics are given in Table 1. Five patients had elevated blood pressure at the time of diagnosis (> 130/80 mmHg), whereas none had diabetes.

In addition, 2 patients had extensive thrombotic microangiopathy (TMA), 1 in the context of catastrophic antiphospholipid syndrome (Figures 1A,B), 1 collapsing glomerulopathy (Figures 1C,D), and 1 concomitant antiglomerular basement membrane (anti-GBM) antibodies. Severe interstitial inflammation was detected in 2 patients (1 class IV, 1 class IV/V). Moderate-to-severe interstitial fibrosis and tubular atrophy (IFTA) was reported in 4 patients, while severe podocyte effacement was reported in 3, and severe TRI in another 2. Four patients showed no unusual kidney pathology.

Remission induction therapy included GC (mean daily prednisone dose 53.3 ± 10 mg/day, 6 patients received intravenous pulses of methylprednisolone), immunosuppressives [cyclophosphamide (CYC) in 4, mycophenolate mofetil (MMF) in 7, azathioprine in 2], rituximab in 2 patients, and therapeutic plasma exchange in the patient with LN IV/anti-GBM nephritis. Of the 10 patients, 9 were concomitantly treated with hydroxychloroquine and 5 with ACEI (ramipril 5–10 mg/day). All 4 patients without unusual histopathologic features had severe noncompliance based on self-report (discontinued all medications against medical advice in order to follow alternative treatment). The distinct histopathologic characteristics and therapeutic approach for each patient are shown in Table 2.

Table 1. Demographic, histopathologic, and initial renal function characteristics of the patients.

	Values
Sex, female:male	8:2
Age at LN diagnosis, yrs	34.2 ± 7.3
Disease duration, yrs	2.2 ± 2.5
Race/ethnicity, n	
Black	5
Hispanic	2
White	2
Asian	1
LN histopathologic class	
III	1
IV	5
IV/V	2
V	2
Activity index	5.7 ± 4.9
Chronicity index	3.3 ± 3.0
Serum creatinine, μmol/L	82.1 ± 15.5
eGFR, mL/min/1.73 m^2	90.2 ± 24.9
Anemia, n (%)[a]	3 (30%)
Proteinuria, g/24 h	2.7 ± 1.04
Nephrotic syndrome, n (%)	5 (50%)
Serum albumin, g/L	32.5 ± 3.7
Hypertension, n (%)[b]	5 (50%)
Time to ESKD, months	19.2 ± 12.4
Rate of renal function decline, mL/min/1.73 m^2/yr, median	43.3

[a] Defined as hemoglobin < 120 g/L for females and < 130 g/L for males. [b] Defined as blood pressure > 130/80 mmHg. eGFR: estimated glomerular filtration rate; ESKD: endstage kidney disease; LN: lupus nephritis.

DISCUSSION

The progression of LN to ESKD has been associated with several factors including ethnicity, younger age, male sex, diffuse proliferative LN, impaired kidney function at diagnosis, nephrotic range proteinuria, poor response to immunosuppressive therapy, hypertension, diabetes, and obesity[5]. A catastrophic course to ESKD, however, is rather uncommon. This study demonstrates that certain histopathological features and poor compliance are the main associated factors.

Collapsing glomerulopathy (CG) affects the podocytes with notable pathological features including tuft collapse and visceral epithelial hypertrophy. Its prognosis is typically poor, with 50–100% of patients progressing to ESKD despite immunosuppressive treatment[6]. Detwiler, *et al* reported that 8 of 14 patients with CG progressed to dialysis in 15 months after diagnosis, while 3 had died of dialysis complications before that timepoint[7]. Due to its rarity, there is currently no evidence-based treatment for CG, and fewer than 10% of the patients respond to immunosuppressives[8]. MMF has been described to be efficacious in isolated cases[9].

LN with concomitant anti-GBM antibodies has been reported infrequently. Li, *et al* detected anti-GBM antibodies in 14 of 157 (8.9%) Chinese patients with SLE[10]. All of them developed LN, and over a third were diagnosed with Goodpasture syndrome. The prognosis is not known, although the presence of such antibodies may contribute to further glomerular injury. The therapeutic approach is empiric and consists of GC, CYC, and plasma exchange therapy[11].

Histologic features of TMA may be detected in up to 20% of patients with LN and have been associated with poor prognosis[12]. Patients with concomitant LN and TMA have a 6-fold greater risk of progression to ESKD compared to patients with LN alone (30% vs 5%) within 5 years[12]. The use of anticoagulation in addition to conventional immunosuppressives seems promising. In a multicenter study of 97 patients with concomitant LN and TMA, anticoagulation achieved higher rates of complete renal response, especially in those with antiphospholipid antibodies[13]. In selected cases, eculizumab may be of benefit.

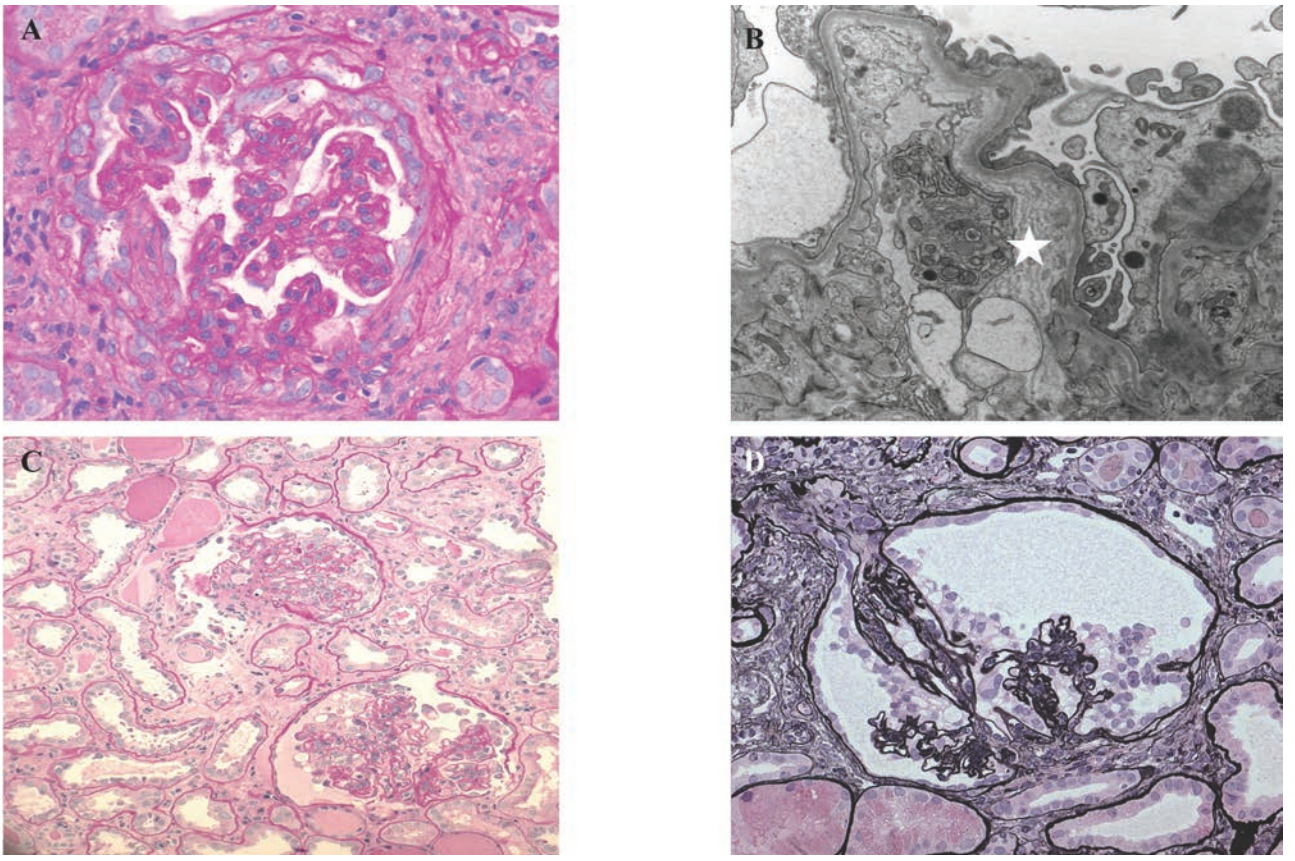

Figure 1. (A) Glomerulus displays endocapillary hypercellularity: Capillary loops are retracted; retraction and periglomerular fibrosis are seen; adhesions to the Bowman's capsule are identified; 40× PAS stain. (B) EM (same sample): Capillary loops show subendothelial widening (white star); there is endothelial swelling; findings are suggestive of thrombotic microangiopathy; EM direct magnification 12000×. (C) Two glomeruli displaying retraction of the glomerular tuft with hypertrophy and hyperplasia of the podocytes; PAS 20×. (D) EM (same sample): Marked retraction of the glomerular tuft with podocyte hypertrophy and hyperplasia; there is segmental scarring at the tip area (opposite to the vascular pole); findings are suggestive of collapsing glomerulopathy; EM direct magnification 12000×. EM: electron microscopy; PAS: Periodic acid–Schiff.

Park, *et al* reviewed 11 patients with concomitant LN and TMA (3 with antiphospholipid antibodies) who were refractory to GC, immunosuppressives, and plasma exchange[14]. Eculizumab was successful in 8 of 10 patients; of 7 patients who needed dialysis, 4 of them were off dialysis by the time of discharge.

Interstitial inflammation as well as IFTA are also associated with worse outcomes in LN. Severe interstitial inflammation (> 50%) significantly increased the risk for ESKD as compared to mild disease (< 5%) in any LN class (HR 7.7, 95% CI 3.8–15.7)[15]. That was particularly evident in LN IV (HR 14.1, 95% CI 4.5–44.1). Moreover, a combination of IFTA > 50% had a similar impact on the risk for ESKD compared to IFTA < 5% (HR 14, 95% CI 4.9–39.8). Overall, there was a gradual decrease in kidney survival as interstitial inflammation or IFTA increased. The clinical significance of TRI is not known. In a recent report, 60% of the patients with TRI at kidney biopsy had LN, 20% had chronic viral infections (hepatitis B, hepatitis C, and human immunodeficiency viruses), and another 20% had other diseases such as IgA nephropathy and Henoch-Schönlein purpura[16]. In a small series of 49 LN patients, TRIs were detected in 12 and associated with class IV and increased activity index[17].

Poor compliance was another factor to complicate patients with rapid progression to ESKD. In a previous systematic review, the percentage of nonadherent SLE patients ranged from 43% to 75%, with most studies consistently reporting rates > 50%[18]. The key determinants of nonadherence included depression, rural residence, lower education level, and polypharmacy. Bruce, *et al* also identified several patient-related factors contributing to the development of advanced chronic kidney disease (CKD) in SLE, including nonadherence due to potential adverse events, financial difficulties, or preference for alterative medications[19].

Limitations of the present study are the small number of patients included and lack of a control group. As such, definitive conclusions regarding the effect of certain histologic features and nonadherence on the progression to ESKD cannot be drawn. However, some of these features (e.g., CG, TMA) are rare, and further study would require a multicenter collaboration. Moreover, the chronicity index was already elevated at diagnosis, implying the presence of kidney damage at the time of the biopsy. However, only 2 patients had a marginal eGFR (61 mL/min/1.73 m^2) at the same time, indicating no significant CKD. The therapeutic approach was not standardized; as such, conclusions on the efficacy of any treatment should be cautiously interpreted. Moreover, genetic risk factors (such as the APOL1 allele)[20] were not assessed in our patients.

In conclusion, catastrophic progression to ESKD within 3

Table 2. Main histologic and treatment characteristics in patients with catastrophic progression to ESKD.

Sex/Race/ Age, yrs	ISN/RPS Class	eGFR	Time to ESKD, months	Treatment	Factors Associated With ESKD
F/H/42	V	110	36	GC, AZA, AM, ACEI	Patient achieved complete remission for 24 months and then discontinued all medications to follow a naturopathic approach
M/W/26	III	137	23	GC, MMF, AM, ACEI	Patient achieved complete remission at 12 months and then discontinued all medications to follow alternative treatments
F/B/41	IV/V	82	31	GC, CYC, AM, MMF, ACEI	Severe interstitial inflammation and tubuloreticular inclusions
F/A/44	IV/V	61	11	GC, AZA, AM, ACEI	Patient discontinued all medications after 3 months
F/B/26	V	88	25	GC, MMF, AM, ACEI	Collapsing glomerulopathy
F/B/33	IV	111	12	GC, CYC, AM, MMF	Patient did not achieve remission and discontinued all medications after 6 months
F/B/38	IV	81	6	GC, MMF, AM, RTX	Extensive thrombotic microangiopathy
F/B/31	IV	61	36	GC, CYC, MMF	Severe interstitial inflammation and tubuloreticular inclusions
M/W/24	IV	93	6	GC, CYC, AM, TPE	Anti-GBM nephropathy (anti-GBM antibodies detected at disease onset)
F/H/37	IV	81	6	GC, MMF, AM, RTX	Thrombotic microangiopathy (catastrophic APS)

A: Asian patients; ACEI: angiotensin-converting enzyme inhibitor; AM: antimalarials; APS: antiphospholipid syndrome; AZA: azathioprine; B: Black patients; CYC: cyclophosphamide; eGFR: estimated glomerular filtration rate; ESKD: endstage kidney disease; F: female; GBM: glomerular basement membrane; GC: glucocorticoids; H: Hispanic patients; ISN/RPS: International Society of Nephrology/Renal Pathology Society; M: male; MMF, mycophenolate mofetil; RTX: rituximab; TPE: therapeutic plasma exchange; W: White patients.

years of diagnosis is uncommon in LN. The major potentially associated factors are distinct histopathologic features such as CG, anti-GBM antibodies, TMA, and severe interstitial inflammation. Poor compliance was also an aggravating factor in certain cases. Recognition of these features may stratify prognosis in the clinical setting and guide decisions for early intervention.

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