FACTORS ASSOCIATED WITH RAPID PROGRESSION TO END STAGE KIDNEY DISEASE IN LUPUS NEPHRITIS

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KEY INDEXING TERMS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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ABSTRACT

Background: Lupus nephritis (LN) may lead to end-stage kidney disease (ESKD) in 22% of patients over 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 LN patients.

Patients-Methods: Patients from the Toronto Lupus Clinic with biopsy-proven LN at presentation and eGFR≥60ml/min/1.73m^2 who developed ESKD within three 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 three 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±24.9ml/min/1.73m^2, proteinuria 2.7±1.04 grams/24h. The rate of kidney function decline was more than 43ml/min/1.73m^2/year (median). One patient had LN class III, five had LN class IV, two membranous LN (class V) and another two had mixed IV/V. Moreover, two patients had extensive thrombotic microangiopathy, one collapsing glomerulonephritis and one concomitant anti-glomerular basement membrane (anti-GBM) nephropathy. Four patients showed no unusual kidney pathology; all of them had severe non-compliance (discontinued all medications to follow alternative treatment).

Conclusions: 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.

INTRODUCTION

Lupus nephritis (LN) affects approximately 40% of patients with systemic lupus erythematosus (SLE) and may lead to end-stage kidney disease (ESKD) in 22% over 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-lupus 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 ≥20ml/min/1.73m^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 three years from diagnosis) progression to ESKD in patients with LN and initially normal or mildly impaired kidney function.

PATIENTS 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 (ACR) criteria for SLE classification or had three criteria and a supportive kidney biopsy [3]. Patients are followed regularly at 2-6 months' 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 (ISN/RPS) classification [4] along with all relevant laboratory (serum creatinine, 24-hour 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, glucocorticosteroids, angiotensin converting enzyme inhibitors and angiotensin receptor blockers etc.). Moreover, associated factors such as hypertension (including the level of blood pressure and relevant treatment) and diabetes are documented in each visit.

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

Patient Selection

For the purpose of the present study, UTLC patients with new-onset LN and normal or mildly impaired kidney function (eGFR≥60ml/min/1.73m^2) who developed ESKD (defined as the initiation of dialysis or eGFR<15ml/min/1.73m^2 for two consecutive clinic visits) within three 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, 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 three years; 7 of them were excluded since their baseline kidney function was severely impaired (eGFR 9-31ml/min/1.73m^2).

Ten patients with initially normal or mildly impaired kidney function (eGFR≥60ml/min/1.73m^2) (1.8% of the total LN population) developed ESKD within three 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 (>140/90mmHg) while none had diabetes.

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

Remission induction therapy included glucocorticosteroids (mean daily prednisone dose 53.3±10mg/day, six patients received intravenous pulses of methylprednisolone), immunosuppressives (cyclophosphamide in four, mycophenolate mofetil in six, azathioprine in 2/10), rituximab in two patients, and therapeutic plasma exchange in the patient with LN IV/anti-GBM nephritis. Nine were concomitantly treated with hydroxychloroquine and 5/10 with angiotensin converting enzyme inhibitors (ramipril 5-10mg/day). All four patients without unusual histopathologic features had severe non-compliance based on self-report (discontinued all their medications against medical advice to follow alternative treatment). The distinct histopathologic characteristics and therapeutic approach for each patient is shown in Table 2.

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 8/14 patients with CG progressed to dialysis in 15 months after diagnosis, while three had died of dialysis complications before that time point [7]. Due to its rarity, there is currently no evidenced-based treatment for CG and less than 10% of the patients respond to immunosuppressives [8]. Mycophenolate mofetil has been described to be efficacious in isolated cases [9].

Lupus nephritis with concomitant anti-GBM antibodies has been reported infrequently. Li et al. detected anti-GBM antibodies in 14/157 (8.9%) Chinese patients with SLE [10]. All of them developed LN and over a third were diagnosed with Goodpasture's 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 glucocorticosteroids, cyclophosphamide and plasma exchange therapy [11].

Histologic features of thrombotic microangiopathy 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 five years [12]. The use of anticoagulation in addition to conventional immunosuppressives seems promising. In a multicentre study of 97 patients with concomitant LN and TMA, anticoagulation achieved higher rates of complete renal response, especially in those with anti-phospholipid antibodies [13]. In selected cases, eculizumab may be of benefit. Park et al. reviewed 11 patients with concomitant LN/TMA (three with antiphospholipid antibodies) who were refractory to glucocorticosteroids, immunosuppressives and plasma exchange [14]. Eculizumab was successful in 8/10 patients; of seven patients who needed dialysis, four of them were off-dialysis by the time of discharge.

Interstitial inflammation as well as interstitial fibrosis and tubular atrophy 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 interstitial fibrosis and tubular atrophy (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 increases. The clinical significance of tubuloreticular inclusions (TRIs) is not known. In a recent report, 60% of the patients with TRIs 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, Henoch-Schönlein purpura and others [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 recent systematic review, the percentage of non-adherent SLE patients ranged from 43% to 75%,

with most studies consistently reporting rates >50% [18]. The key determinants of non-adherence 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 in SLE, including non-adherence 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 the lack of a control group. As such, definitive conclusions regarding the impact of certain histologic features and non-adherence on the progression to ESKD cannot be drawn. However, some of these features (e.g. collapsing glomerulopathy, thrombotic microangiopathy) are rare and further study would require a multicentre collaboration. Moreover, the chronicity index was already elevated at diagnosis implying the presence of kidney damage at the time of the biopsy. However, only two patients had a marginal eGFR (61ml/min/1.73m^2) at the same time indicating no significant chronic kidney disease. 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 three years from diagnosis is uncommon in LN. The major potentially associated factors are distinct histopathologic features such as collapsing glomerulopathy, anti-GBM antibodies, thrombotic microangiopathy 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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FIGURE LEGEND

Figure 1. A. Glomerulus displays endocapillary hyper-cellularity. Capillary loops are retracted. Retraction and periglomerular fibrosis are seen. Adhesions to the Bowman's capsule are identified. 40x PAS stain. **B.** Electron microscopy (same sample): capillary loop showing subendothelial widening (white star). There is endothelial swelling. Findings are suggestive of thrombotic microangiopathy. EM direct magnification 12000x. **C.** Two glomeruli displaying retraction of the glomerular tuft with hypertrophy and hyperplasia of the podocytes. PAS 20X. **D.** Electron microscopy (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 12000x

Table 1. DEMOGRAPHIC, HISTOPATHOLOGIC AND INITIAL RENAL FUNCTION CHARACTERISTICS OF THE PATIENTS	
Sex (females:males)	8:2
Age at LN diagnosis (years)	34.2±7.3
Disease duration (years)	2.2±2.5
Race/ethnicity	Blacks 5, Hispanics 2, Caucasians 2, Asian 1
LN histopathologic class	Class III: 1, Class IV: 5, Class IV/V:2, Class 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/1.73m^2)	90.2±24.9
Anemia* (n, %)	3 (30%)
Proteinuria (g/24h)	2.7±1.04
Nephrotic syndrome (n, %)	5 (50%)
Serum albumin (grams/L)	32.5±3.7
Hypertension** (n, %)	3 (30%)
Time to ESKD (months)	19.2±12.4
Rate of renal function decline (ml/min/1.73m^2/year)	43.3 (median)
*Defined as Hemoglobin<120g/l for females and <130g/l for males **Defined as BP>130/80mmHg	

Table 2. MAIN HISTOLOGIC AND TREATMENT CHARACTERISTICS IN PATIENTS WITH CATASTROPHIC PROGRESSION TO ESKD

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

F: female, M: male, C: Caucasian, B: Black, H: Hispanic, A: Asian, ISN/RPS: International Society of Nephrology/Renal Pathology Society, eGFR: estimated Glomerular Filtration Rate, GCS: glucocorticosteroids, AZA: azathioprine, MMF, mycophenolate mofetil, CYC: cyclophosphamide, AM: antimalarials, RTX: rituximab, TPE: therapeutic plasma exchange, GBM: glomerular basement membrane

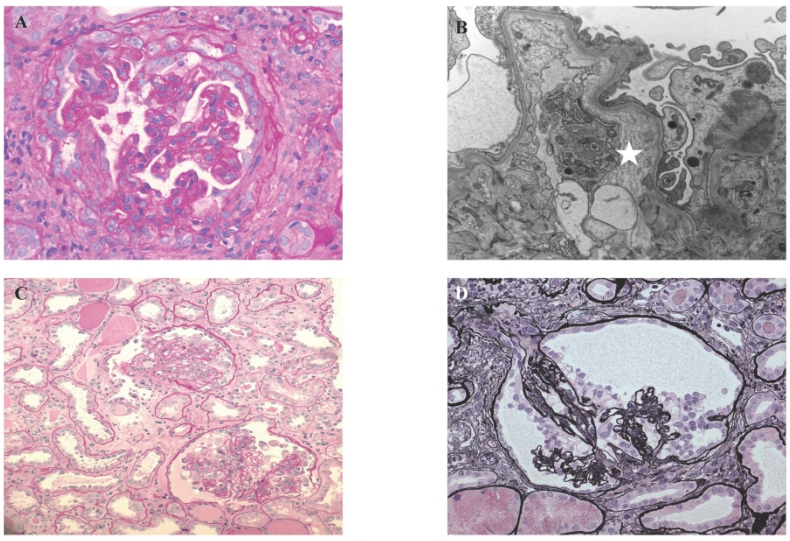

Figure 1 (A, B), one collapsing glomerulopathy, Figure 1 (C, D), and one concomitant anti-glomerular basement membrane (anti-GBM) antibodies

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