Systemic lupus erythematosus : from diagnosis to prognosis

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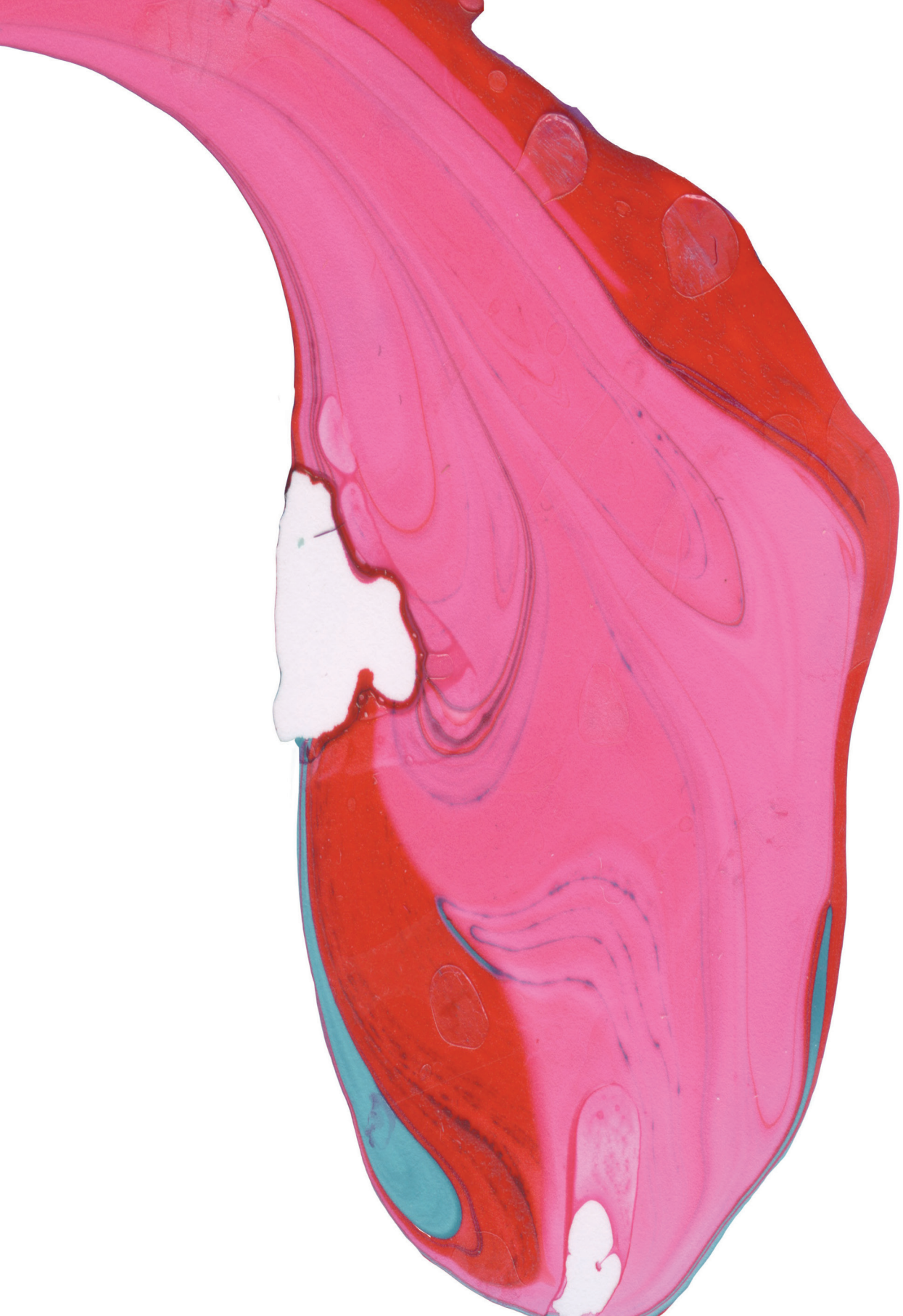

Chapter 3

Idiopathic Non-lupus Full House Nephropathy is Associated With Poor Renal Outcome

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ABSTRACT

Background

Full house immunofluorescence in combination with various histopathologic lesions in the renal biopsies of patients without overt systemic lupus erythematosus (SLE) poses a diagnostic challenge. In this setting, the biopsy findings are sometimes termed non-lupus "full house nephropathy" (FHN). It is presently unknown whether idiopathic non-lupus FHN is clinicopathologically and prognostically distinct from lupus FHN.

Methods

We included non-lupus FHN patients and lupus FHN controls (four or more ACR or SLICC criteria) who were biopsied between 1968–2014 at the Leiden University Medical Center. Non-lupus FHN patients were studied for progression to SLE and/or the presence of other conditions with FHN. The clinicopathologic characteristics and prognosis of idiopathic non-lupus FHN patients were compared to those of lupus FHN patients.

Results

Of 149 included patients, 32 had non-lupus FHN. During the median follow-up of 20 years, no non-lupus FHN patients developed SLE. Twenty non-lupus FHN patients had idiopathic non-lupus FHN, and in 12 patients secondary non-lupus FHN was considered due to membranous nephropathy (anti-PLA2R-positive, n=1; cancer-associated, n=3), IgA nephropathy (n=4), infection-related glomerulonephritis (n=2), or anti-neutrophil cytoplasmic antibody-associated glomerulonephritis (n=2). Idiopathic non-lupus FHN patients were more often male ($P<0.001$) than lupus FHN patients, and their renal biopsies more often showed a mesangial ($P=0.04$) or membranous pattern of injury ($P=0.02$), and less intense C1q staining ($P=0.002$). Clinically, they presented with lower-range erythrocyturia ($P=0.04$), more proteinuria ($P<0.01$), and less complement consumption in the classical pathway ($P<0.001$) than lupus FHN patients. By multivariable Cox regression analysis of patients with a lupus nephritis class III/IV pattern of injury, idiopathic non-lupus FHN compared to lupus FHN was an independent risk factor for end-stage renal disease (HR 5.31; 95% CI 1.47 to 19.24).

Conclusion

Our results show that the clinical recognition of idiopathic non-lupus FHN as a diagnostic category is critical.

INTRODUCTION

A typical finding in renal biopsies of patients with lupus nephritis (LN) is a full house pattern by immunofluorescence, which is defined as concurrent positive staining for IgA, IgG, IgM, C3, and C1q.[1] In a patient with extrarenal signs and symptoms of systemic lupus erythematosus (SLE), identification of nephritis with a full house immunofluorescence pattern on renal biopsy is consistent with LN. However, a diagnostic challenge ensues when patients present with various histopathologic lesions – either or not resembling LN – in combination with a full house pattern by immunofluorescence in the absence of autoantibodies and other classifying signs or symptoms of SLE. In this setting, the biopsy findings are sometimes termed non-lupus "full house nephropathy" (FHN).[2] Non-lupus FHN was first systematically described in a group of 24 patients by Wen and Chen, who defined the clinicopathologic spectrum of this entity and indicated that in future studies, the emergence of overt SLE remained to be elucidated.[2] Anecdotal reports have shown that only a minority of these patients eventually develop the autoantibodies characteristic of SLE and/or extrarenal symptoms of SLE during follow-up,[2-7] whereas other reports have shown that non-lupus FHN can be associated with atypical manifestations of other well-established pathologies.[2, 8-15] It remains unclear how to classify and treat non-lupus FHN patients for whom the origin of FHN is idiopathic.

In the present study, patients with idiopathic non-lupus FHN and non-lupus FHN due to other disease processes were identified from the largest cohort of patients with renal biopsies showing full house immunofluorescence to date. The clinicopathologic characteristics and prognosis of idiopathic non-lupus FHN patients were compared to those of lupus FHN patients according to four or more American College of Rheumatology (ACR)[16] or Systemic Lupus International Collaborating Clinics (SLICC)[17] criteria.

METHODS

The pathology archives of the Leiden University Medical Center were searched from 1968 to 2014 to identify all patients with native renal biopsies showing full house immunofluorescence, which was defined as concurrent positive staining for IgA, IgG, IgM, C3, and C1q with ≥1+ intensity on a 0–3+ scale. Only biopsies showing granular fluorescent staining along the capillary walls, in the mesangium, or both were included. Patients meeting these criteria and who were followed in our centre entered the study. In accordance with the ethics committee of the Leiden University Medical Center, all patient data were coded and kept anonymous throughout the study. Renal biopsies were re-evaluated by an experienced nephropathologist (IMB). In cases where renal biopsies were unavailable, the histopathologic diagnosis was deduced from the original biopsy report if possible; but they were excluded from analyses involving categorical pathology scoring. All biopsies were (re)

classified according to the ISN/RPS classification of LN,[18] regardless of the clinicopathologic diagnosis. Global glomerulosclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis were scored semi-quantitatively as (0) <5%; (1) 5–25%; (2) 26–50%; (3)>50% of glomeruli, tubules, or cortical area. The scores were summed to generate a total chronicity score. Finally, the pathologist made a differential diagnosis based on light microscopy findings knowing that the patients had a full house pattern by immunofluorescence.

All biopsies were processed for light and immunofluorescence microscopy according to the standard techniques at our centre. For immunofluorescence microscopy, sections were frozen in liquid nitrogen, and cryostat sections were stained with FITC-labelled antisera to human IgA, IgG, IgM, C3, and C1q. Immunofluorescence reports were originally prepared by four experienced nephropathologists who consistently scored the immunofluorescence intensity on a 0–3+ scale. Not all biopsies were sent in for analysis by electron microscopy; but if at hand, tissue was fixed in 1.5% glutaraldehyde and 1% paraformaldehyde and embedded in Epon.

The medical records of the patients were reviewed independently by investigators (ECR, YKOT, and TK) for the presence of four or more cumulative ACR[16] and/or SLICC[17] criteria for SLE at the time of renal biopsy. After independent review, a consensus was reached for fulfilment of the classification criteria. Cases that did not fulfil four or more ACR[16] or SLICC[17] criteria at the time of biopsy were considered representative of non-lupus FHN and were evaluated in a clinicopathologic conference by investigators (ECR, YKOT, TK, and IMB) reaching consensus on the clinicopathologic differential diagnosis at the time of biopsy. Additional serologic parameters were recorded for non-lupus FHN patients if available. Follow-up data of non-lupus FHN patients were meticulously studied to investigate whether they fulfilled ACR[16] or SLICC[17] classification criteria at any time after renal biopsy.

For lupus FHN and non-lupus FHN patients, serum creatinine, estimated glomerular filtration rate (eGFR),[19,20] 24h proteinuria, erythrocyturia, and grade of hypertension[21] were recorded at the time of renal biopsy. Induction immunosuppression was recorded for all patients, as was immunosuppression initiated after renal transplantation in non-lupus FHN. End-stage renal disease (ESRD) was defined as dialysis-dependence for >3 months or renal transplantation. Patients lost to follow-up were checked in the population register to see if they were alive at the end of this study (5 October 2015); if not, the date of death was recorded.

Statistical analyses

Normally distributed data were compared with *t*-tests, and non-normally distributed data with Mann-Whitney U tests. Categorical data were compared with Fisher's exact tests, chi-square tests, or linear-by-linear analysis.

The outcomes time to ESRD, death, and ESRD/death were analysed using Kaplan-Meier

curves and log-rank tests. The observation period considered for the outcome analyses started at the time of renal biopsy demonstrating FHN. Multivariable analyses included idiopathic non-lupus FHN and lupus FHN patients. The following subgroups classified according to the ISN/RPS classification were analysed separately: (i) class I/II; (ii) class III/IV (±V); and (iii) class V. The following candidate predictors of ESRD and/or death were entered in multivariable proportional hazards models: idiopathic non-lupus FHN; sex; age, eGFR, and proteinuria at the time of biopsy; and induction immunosuppression (model 1). A second model was designed including non-lupus FHN, induction immunosuppression and histologic chronicity score (model 2). All *P*-values are two-sided and were considered significant at $P<0.05$. Analyses were performed using SPSS 23.0 (IBM, Armonk, New York).

RESULTS

Of the 149 patients included, 117 patients had lupus FHN, while 32 patients had non-lupus FHN. A total of 26 non-lupus FHN and 99 lupus FHN patients had a renal biopsy available for re-evaluation. The median number of scorable glomeruli was 15 (range 6–65) in non-lupus FHN patients, and 14 (range 6–56) in lupus FHN patients.

Clinicopathologic diagnoses of non-lupus FHN patients

The clinicopathologic characteristics of individual non-lupus FHN patients are shown in **Table 1** (see **Appendix 3.1** for detailed descriptions). The 32 non-lupus FHN patients were neither originally diagnosed with SLE at the time of biopsy, nor after revision of the medical files and evaluation of SLE classification criteria. The following cumulative SLE criteria were registered at the time of biopsy in non-lupus FHN patients: oral/nasal ulcers (cases 5, 27, and 28), synovitis (case 6), serositis (case 6), hypocomplementaemia (cases 5 and 27), and anti-nuclear antibody (ANA) (cases 28, 31, and 32). During median follow-up of 20 years (interquartile range [IQR] 8.3–33.8), two cases developed additional ACR/SLICC criteria: case 12 developed arthritis 9 years after renal biopsy (likely attributable to rheumatoid arthritis), and case 19 developed serositis and arthritis 2 years after renal biopsy. However, none of the 32 patients were clinically diagnosed with SLE during follow-up or met four or more ACR or SLICC criteria.

In view of the presence of FHN in the absence of SLE in these 32 patients, we re-evaluated their clinical presentation including serologic and histopathologic findings, and long-term clinical follow-up (including follow-up biopsies) to investigate whether other differential diagnostic considerations than SLE would apply to some of them. In 12 patients, we considered atypical variants of the following entities (**Table 1** and **Appendix 3.1**): membranous nephropathy (anti-PLA2R-positive, n=1; cancer-associated, n=3), IgA nephropathy (n=4), infection-related glomerulonephritis (n=2), and anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (AAGN, n=2). We will henceforth refer to these 12 patients as "secondary non-lupus FHN". Importantly, 20 non-lupus FHN patients had idiopathic FHN.

Table 1 Clinical presentation and histopathologic findings in patients with non-lupus full house nephropathy (FHN).

Patient number	Sex	Age, y	Presentation	Clinicopathologic differential diagnosis
Idiopathic non-lupus FHN				
1	F	16	NS	Idiopathic
2	M	58	NS	Idiopathic
3	M	27	Hematuria, subnephrotic proteinuria	Idiopathic
4	F	16	Acute renal insufficiency	Idiopathic
5	M	58	RPGN	Idiopathic
6	M	56	NS	Idiopathic
7	M	31	NS	Idiopathic
8	M	29	Haematuria	Idiopathic
9	M	58	NS, haematuria	Idiopathic
10	M	45	NS	Idiopathic
11	F	28	NS, renal insufficiency, malignant hypertension	Idiopathic
12	M	52	RPGN	Idiopathic
13*	F	29	NS	Idiopathic
14	M	31	NS	Idiopathic
15	M	31	NS	Idiopathic
16*	M	67	Acute renal insufficiency	Idiopathic
17*	F	22	NS	Idiopathic
18	M	21	RPGN	Idiopathic
19	M	52	NS	Idiopathic
20	F	19	Hypertension	Idiopathic
Secondary non-lupus FHN				
21*	M	34	Macroscopic haematuria, subnephrotic proteinuria	IgA-like nephropathy
22	M	31	Haematuria, subnephrotic proteinuria	Crescentic IgA-like nephropathy
23	F	32	Malignant hypertension, acute renal insufficiency	Crescentic IgA-like nephropathy
24	F	18	Haematuria, subnephrotic proteinuria	Crescentic IgA-like nephropathy
25	M	55	Haematuria, microalbuminuria	Infection-related glomerulonephritis
26*	M	50	RPGN	Infection-related glomerulonephritis
27	F	21	RPGN	ANCA-associated glomerulonephritis
28	F	47	Haematuria, subnephrotic proteinuria	ANCA-associated glomerulonephritis
29	M	30	NS	MN (anti-PLA2R)
30	M	55	Haematuria, subnephrotic proteinuria	MN (cancer-associated) + FSGS
31	M	71	NS	MN (cancer-associated) + secondary glomerular sclerosis
32	F	50	NS	MN (cancer-associated) + minimal endocapillary proliferation

ANCA, anti-neutrophil cytoplasmic antibody; F, female; FSGS, focal segmental glomerulosclerosis; M, male; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome; RPGN, rapidly progressive glomerulonephritis; TMA, thrombotic microangiopathy. *The histopathologic diagnosis was deduced from the original biopsy report. †ISN/RPS 2003 classification of LN.[18]

Light microscopy pattern	Immunofluorescence					Classification as in SLE†
	IgA, +	IgG, +	IgM, +	C3, +	C1q, +	
Minimal lesions	1	1	2	2	2	I
Minimal lesions	2	2	2	2	2	I
Mesangioproliferative	2	2	1	2	1	II
Diffuse proliferative, crescents	2	2	3	3	3	IV-G (A/C)
Diffuse proliferative	2	3	3	2	2	IV-G (A/C)
Segmental chronic lesions, spikes	3	2	2	3	3	III (C) + V
Focal proliferative	2	3	2	2	2	III (A/C)
Focal proliferative	1	1	1	1	1	III (A/C)
Focal proliferative	1	3	2	1	1	III (A)
Focal proliferative	1	3	1	3	3	III (A/C)
Diffuse proliferative	2	2	1	1	1	IV-G (A)
Diffuse proliferative, crescents, fibrinoid necrosis	2	1	2	3	2	IV-G (A/C)
MPGN, spikes	2	2	2	2	2	IV-G (A/C) + V
Focal proliferative	1	3	2	2	2	III (A/C)
Membranous	2	2	1	2	1	V
Membranous	3	3	1	1	1	V
Membranous	1	3	2	2	3	V
Membranous, interstitial nephritis, minimal vasculopathy	3	3	1	3	1	V
Segmental chronic lesions, occasional spikes	1	3	2	2	2	III (C)
FSGS, segmental chronic lesions, TMA	1	1	1	2	1	III (A/C)
Segmental chronic lesions	2	1	1	2	2	III (C)
Focal proliferative, crescents	2	1	1	1	2	III (A/C)
Diffuse proliferative, crescents	3	2	2	3	2	IV-G (A/C)
Focal proliferative, crescents, fibrinoid necrosis	2	1	1	3	1	III (A/C)
Minimal lesions	2	2	1	2	2	I
Diffuse proliferative	2	3	2	3	3	IV-G (A)
Diffuse proliferative, crescents	1	1	1	1	1	IV-G (A/C)
Diffuse proliferative, crescents	2	2	2	2	2	IV-S (A)
Membranous	3	3	3	3	3	V
Focal proliferative, FSGS, spikes	3	3	1	3	1	III (A/C) + V
Membranous	1	3	1	1	3	V
Focal proliferative, occasional spikes	1	1	1	3	2	III (A)

Clinical presentation of idiopathic non-lupus FHN compared to lupus FHN patients

Of the 20 idiopathic non-lupus FHN patients, 12 (60%) presented with a nephrotic syndrome, 2 (10%) with abnormal urinary sediment, 2 (10%) with acute renal insufficiency, 3 (15%) with rapidly progressive glomerulonephritis, and 1 (5%) with hypertension and raised serum creatinine in the absence of erythrocyturia/proteinuria (**Table 1**).

The clinical characteristics of idiopathic non-lupus FHN compared to lupus FHN patients at the time of biopsy are shown in **Table 2**. Briefly, compared to lupus FHN patients, idiopathic non-lupus FHN patients were more often male ($P<0.001$); they had significantly more proteinuria ($P<0.01$), less erythrocyturia ($P=0.04$), and less complement consumption in the classical pathway ($P<0.001$ for C3, C4, and CH50). Up to and including the time of renal biopsy, oral/nasal ulcers (n=1), synovitis (n=1), serositis (n=1), and hypocomplementaemia (n=1) were observed in idiopathic non-lupus FHN patients.

Table 2 Clinical characteristics of patients with lupus full house nephropathy (FHN) compared to idiopathic non-lupus FHN at the time of renal biopsy.

Characteristic	Lupus FHN (n=117)	Idiopathic non-lupus FHN (n=20)	*P*
Sex, male/female	30/87	14/6	<0.001#
Age, y	32.6 ± 14.6	37.3 ± 16.6	0.195§
Hypertension stage, no hypertension/stage 1/ stage 2/stage 3	74/29/11/3	15/4/1/0	0.702†
Serum creatinine, µmol/L	97 (76–150)	114 (94–222)	0.074¶
eGFR, mL/min	75 ± 36	78 ± 51	0.760§
ESR, mm/h	68 ± 33	83 ± 47	0.296§
Leukocytes, $*10^9$/L	6.6 ± 3.3	6.2 ± 1.0	0.783§
Thrombocytes, $*10^3/mm^3$	250 ± 103	225 ± 40	0.629§
Proteinuria, g/24h	3.9 ± 4.1	6.9 ± 5.5	0.006§
Erythrocyturia, missing/-/+/++	28/16/28/45	13/4/2/1	0.037†
CH50, u/mL (ref. 207–467)	152 ± 118	433 ± 87	<0.001§
C3, mg% (ref. 47–80)	39 ± 20	81 ± 23	<0.001§
C4, mg% (ref. 13–39)	13 ± 11	40 ± 11	<0.001§
C1q, mg% (ref. 9–14)	11 ± 14	17 ± 2	0.463§
Acute cutaneous lupus, n/total (%)	66/117 (56)	0/20 (0)	<0.001‡
Malar rash, n/total (%)	48/112 (43)	0/20 (0)	<0.001‡
Photosensitivity, n/total (%)	25/112 (22)	0/20 (0)	0.014‡
Chronic cutaneous lupus, n/total (%)	14/117 (12)	0/20 (0)	0.222‡
Discoid rash, n/total (%)	11/106 (9)	0/20 (0)	0.367‡
Oral/nasal ulcers, n/total (%)	25/117 (21)	1/20 (5)	0.122‡
Non-scarring alopecia, n/total (%)	21/117 (18)	0/20 (0)	0.043‡
Synovitis, n/total (%)	86/117 (74)	1/20 (5)	<0.001‡

Table 2 Continued.

Characteristic	Lupus FHN (n=117)	Idiopathic non-lupus FHN (n=20)	*P*
Serositis, n/total (%)	44/117 (38)	1/20 (5)	0.004‡
Neurologic disorder, n/total (%)	18/117 (15)	0/20 (0)	0.074‡
Haemolytic anaemia, n/total (%)	20/117 (17)	0/20 (0)	0.044‡
Lympho-/leukopenia, n/total (%)	36/117 (31)	0/20 (0)	0.002‡
Thrombocytopenia, n/total (%)	28/117 (24)	0/20 (0)	0.013‡
Hypocomplementaemia, n/total (%)	94/109 (86)	1/13 (8)	<0.001‡
ANA, n/total (%)	116/117 (99)	0/16 (0)	<0.001‡
Anti-DNA, n/total (%)	80/109 (73)	0/19 (0)	<0.001‡
Anti-ENA, n/total (%)	50/66 (76)	0/3 (0)	1.000‡
Anti-SS-A, n/total (%)	26/57 (46)	0/3 (0)	1.000‡
Anti-SS-B, n/total (%)	14/57 (25)	0/3 (0)	1.000‡
Anti-RNP, n/total (%)	24/53 (45)	0/3 (0)	1.000‡
Anti-Sm, n/total (%)	18/56 (32)	0/3 (0)	0.546‡
Anti-Scl70, n/total (%)	8/53 (15)	0/3 (0)	1.000‡
Anti-Jo1, n/total (%)	12/53 (23)	0/3 (0)	1.000‡
Antiphospholipid antibody, n/total (%)	41/81 (51)	0/1 (0)	1.000‡
Direct Coombs', n/total (%)	25/75 (33)	0/7 (0)	0.095‡
PR3-ANCA, n/total (%)	2/39 (5)	0/4 (0)	1.000‡
MPO-ANCA, n/total (%)	30/39 (77)	0/4 (0)	0.006‡
Anti-C1q, n/total (%)	15/22 (68)	0/2 (0)	0.130‡

Normally distributed data are as expressed mean ± standard deviation. Non-normally distributed data are expressed as median (interquartile range). Cumulative SLE classification criteria were registered at the time of renal biopsy. Erythrocyturia was scored as: (−) 0–18 erythrocytes/μL; (+) 19–25 erythrocytes/μL; (++) >26 erythrocytes/μL. † Linear-by-linear analysis. ‡ Fisher's exact test. # Pearson chi-Square. § *t*-test. ¶ Mann-Whitney U test. ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; anti-ENA, anti-extractable nuclear antigen antibody; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate.

Histopathologic features of idiopathic non-lupus FHN compared to lupus FHN patients

The biopsies of idiopathic non-lupus FHN patients were histopathologically described as: no lesions (10%), focal segmental glomerulosclerosis (5%), mesangioproliferative (5%), focal proliferative (25%), segmental chronic lesions (10%), diffuse proliferative (10%), active crescentic (10%), membranoproliferative (5%), and membranous lesions (20%; see **Table 1**). By electron microscopy, immune deposits were consistent with findings in LN; showing the combination of mesangial, subendothelial and subepithelial deposits. Furthermore, in case 6 tubuloreticular inclusions were identified by electron microscopy (**Appendix 3.2**).

The histopathologic findings in lupus FHN compared to idiopathic non-lupus FHN patients are shown in **Table 3**. After classification of non-lupus FHN according to the ISN/RPS

classification, the distribution across LN classes was significantly different between lupus FHN and idiopathic non-lupus FHN ($P<0.001$). Absence of glomerular lesions or a purely mesangial pattern of injury by light microscopy (akin class I/II) was significantly more prevalent in idiopathic non-lupus FHN compared to lupus FHN ($P=0.04$), as was a membranous pattern (akin class V, $P=0.02$). Proliferative lesions (akin class III/IV) were significantly less prevalent in non-lupus FHN ($P<0.01$). Idiopathic non-lupus FHN patients had a different distribution across activity/chronicity subclasses (A, A/C, and C) associated with a class III/IV pattern of injury than lupus FHN patients – with chronic subclasses being present more frequently. However, individual chronic lesions were similar between lupus and idiopathic non-lupus FHN patients (global glomerulosclerosis, fibrous crescents, interstitial fibrosis and tubular atrophy, see **Table 3**). C1q immunofluorescence staining was significantly more intense in lupus FHN compared to idiopathic non-lupus FHN ($P<0.01$).

Table 3 Histopathologic findings in patients with lupus full house nephropathy (FHN) compared to idiopathic non-lupus FHN.

Histopathologic finding	Lupus FHN (n=117)	Idiopathic non-lupus FHN (n=20)	*P*
Light microscopy			
ISN/RPS 2003 class, n (%)			
I	1 (1)	2 (10)	
II	2 (2)	1 (5)	
III	24 (21)	7 (35)	
IV	79 (68)	4 (20)	
III/IV + V	2 (2)	2 (10)	
V	9 (8)	4 (20)	0.001#
III/IV (+V) A	45 (43)	2 (15)	
III/IV (+V) A/C	59 (56)	9 (69)	
III/IV (+V) C	1 (1)	2 (15)	0.001#
No lesions/ purely mesangial lesions, n (%)	3 (3)	3 (15)	0.040‡
Proliferative lesions, n (%)	105 (90)	13 (65)	0.008‡
Membranous lesions, n (%)	11 (9)	6 (30)	0.020‡
Glomeruli with global glomerulosclerosis, n (%)			
0%	70 (71)	9 (56)	
1–25%	22 (22)	5 (31)	
26 – 50%	4 (4)	1 (6)	
≥50%	3 (3)	1 (6)	0.245†
Glomeruli with fibrous crescents, n (%)			
0%	75 (76)	12 (75)	
1–25%	23 (23)	4 (25)	
26 – 50%	1 (1)	0	0.984†

Table 3 Continued.

Histopathologic finding		Lupus FHN (n=117)	Idiopathic non-lupus FHN (n=20)	*P*
Interstitial fibrosis, n (%)				
	Absent	57 (58)	6 (38)	
	Mild	33 (33)	7 (44)	
	Moderate	6 (6)	3 (19)	
	Severe	3 (3)	0 (0)	0.186†
Tubular atrophy, n (%)				
	Absent	60 (61)	6 (38)	
	Mild	29 (29)	8 (50)	
	Moderate	7 (7)	1 (6)	
	Severe	3 (3)	1 (6)	0.168†
Immunofluorescence microscopy				
IgA, n (%)				
	+	26 (22)	8 (40)	
	++	60 (51)	9 (45)	
	+++	31 (26)	3 (15)	0.087†
IgM, n (%)				
	+	27 (23)	8 (40)	
	++	64 (55)	10 (50)	
	+++	26 (22)	2 (10)	0.076†
IgG, n (%)				
	+	21 (18)	4 (20)	
	++	67 (57)	7 (35)	
	+++	29 (25)	9 (45)	0.265†
C3, n (%)				
	+	8 (7)	4 (20)	
	++	64 (55)	11 (55)	
	+++	45 (39)	5 (25)	0.074†
C1q, n (%)				
	+	9 (8)	8 (40)	
	++	67 (57)	8 (40)	
	+++	41 (35)	4 (20)	0.002†

All biopsies were rescored according to the ISN/RPS 2003 classification of LN regardless of clinicopathologic diagnosis.
† Linear-by-linear analysis. ‡ Fisher's exact test. # Pearson chi-Square.

Treatment and outcomes of non-lupus FHN patients

Half of the non-lupus FHN patients received immunosuppressive therapy after renal biopsy (**Table 4**). Four patients presented with acute renal insufficiency and required dialysis by the time of renal biopsy. Overall, ESRD developed in 8 of 15 non-lupus FHN patients who received immunosuppression (including corticosteroids), and in 9 of 16 who did not (*P*=0.39). In the idiopathic group, renal survival similarly was not different between

patients who did (n=9) and did not (n=11) receive immunosuppression (*P*=0.42). ESRD developed in 12 (60%) idiopathic and 6 (50%) secondary non-lupus FHN patients and death occurred in in 8 (40%) idiopathic and 5 (42%) secondary non-lupus FHN patients (see **Appendix 3.1**). By Kaplan-Meier analysis, progression to ESRD and/or death did not differ between idiopathic non-lupus FHN patients and non-lupus FHN patients with other differential diagnoses (*P*=0.55). Considering both patients with idiopathic and secondary non-lupus FHN, the overall group of non-lupus FHN patients progressed significantly more rapidly to ESRD and ESRD/death than lupus FHN patients (both *P*<0.01).

Table 4 Induction and maintenance immunosuppressive therapy for patients with lupus and idiopathic non-lupus full house nephropathy (FHN) after renal biopsy.

Treatment regimen	Lupus FHN (n=117)	Idiopathic non-lupus FHN (n=20)
Induction		
No immunosuppression, n (%)	2 (2)	11 (55)
Corticosteroids, n (%)	4 (3)	5 (25)
Cyclophosphamide ± corticosteroids, n (%)	44 (38)	0 (0)
Azathioprine ± corticosteroids, n (%)	45 (38)	3 (15)
Mycophenolate mofetil ± corticosteroids, n (%)	10 (9)	0 (0)
Other, n (%)	1 (1)	1 (5)
Unknown, n (%)	11 (9)	0 (0)
Maintenance		
No specific maintenance immunosuppression *, n (%)	11 (9)	17 (85)
Azathioprine ± corticosteroids, n (%)	48 (41)	3 (15)
Mycophenolate mofetil ± corticosteroids, n (%)	37 (32)	0 (0)
Other, n (%)	3 (3)	0 (0)
Unknown, n (%)	18 (15)	0 (0)

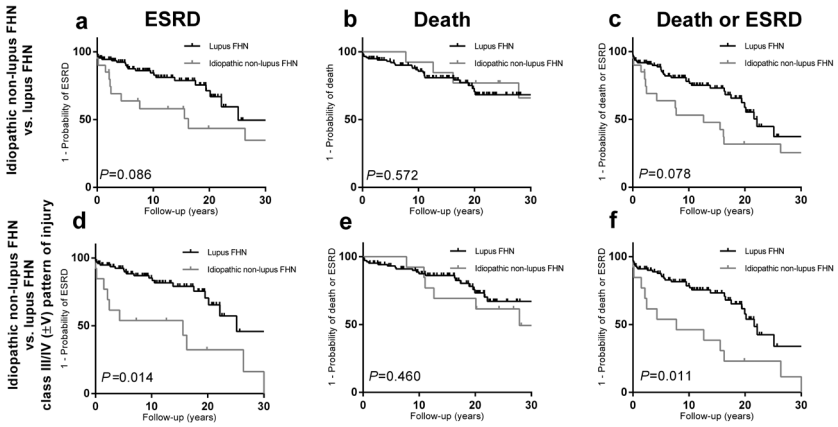
* "No specific maintenance immunosuppression" may include corticosteroids.

Outcomes of idiopathic non-lupus FHN compared to lupus FHN patients

Considering idiopathic non-lupus FHN patients only (excluding patients with secondary non-lupus FHN), outcomes were not significantly different between idiopathic non-lupus and lupus FHN patients (**Figure 1a-c**). No differences in outcome were noted between idiopathic non-lupus FHN and lupus FHN patients in the subgroups with classes I/II and class V (data not shown). In contrast, in the class III/IV (±V) subgroup, idiopathic non-lupus FHN patients (n=13) progressed significantly more rapidly to ESRD (*P*=0.01) and ESRD/death (*P*=0.01) than lupus FHN patients (n=105; **Figure 1d,f**).

In the class III/IV (±V) subgroup, idiopathic non-lupus FHN was an independent risk factor for ESRD adjusted for possible clinical confounders in models 1 (see overview of confounders in **Table 5**, HR 5.31; 95% CI 1.47 to 19.24) and 2 (HR 3.64; 95% CI 1.04 to 3.64).

Figure 1 Renal and overall survival of patient with lupus and idiopathic non-lupus full house nephropathy (FHN).



a-c: Kaplan-Meier analyses comparing lupus FHN (n=117) and idiopathic non-lupus FHN (n=20). a: Survival without end-stage renal disease (ESRD, median follow-up idiopathic non-lupus FHN: 10.2 years (interquartile range [IQR] 2.2–23.1); lupus FHN: 9.3 years [IQR 3.8–16.0]). b: Overall survival (median follow-up idiopathic non-lupus FHN: 24.4 years (IQR 11.8–35.1); lupus FHN: 14.1 years [IQR 7.2–20.8]). c: Survival without the combined outcome of death or ESRD (median follow-up idiopathic non-lupus FHN: 10.2 years (IQR 2.2–23.1); lupus FHN: 9.5 years [IQR 4.4–16.5]). d-f: Kaplan-Meier analyses of the subset of patients with a class III/IV (±V) pattern of injury comparing patients with lupus FHN (n=105) and idiopathic non-lupus FHN (n=13). d: Survival without ESRD. e: Overall survival. f: Survival without the combined outcome of death or ESRD. Vertical bars represent censored data.

Table 5 Predicting renal and/or patient survival in patients with a lupus (n=105) and idiopathic non-lupus (n=13) full house nephropathy (FHN) and a lupus nephritis class III/IV (±V) pattern of injury.

Model	Outcome: ESRD		Outcome: ESRD/death	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Model 1				
Idiopathic non-lupus FHN vs. lupus FHN	5.31	1.47; 19.24	3.23	1.01; 10.32
eGFR (mL/min)	0.99	0.98; 1.01	0.99	0.98; 1.00
Proteinuria (g/24h)	1.05	0.98; 1.12	1.02	0.96; 1.09
Female vs. male	1.05	0.40; 2.72	0.89	0.39; 2.02
Age (years)	1.00	0.97; 1.03	1.02	0.99; 1.04
Immunosuppressive therapy* vs. no immunosuppressive therapy	2.72	0.63; 11.84	1.93	0.51; 7.28
Model 2				
Idiopathic non-lupus FHN vs. lupus FHN	3.64	1.04; 3.64	1.32	0.76; 1.32
Immunosuppressive therapy* vs. no immunosuppressive therapy	1.96	0.43; 8.95	2.06	0.54; 7.79
Chronicity score	1.36	1.14; 1.63	1.41	1.22; 1.64

* Immunosuppressive therapy with at least corticosteroids. CI, confidence interval.

DISCUSSION

In this study, we investigated non-lupus FHN in the largest cohort of FHN patients to date. Of the 149 FHN patients, 32 (21%) patients had non-lupus FHN. None of these non-lupus FHN patients developed SLE during median follow-up of 20 years. Patients with non-lupus FHN represented a heterogeneous group with an overall poor outcome with some patients showing atypical presentations of other well-established renal diseases and 63% having idiopathic non-lupus FHN. Importantly, idiopathic non-lupus FHN was clinically and histopathologically distinct from lupus FHN, and idiopathic non-lupus FHN patients with a proliferative pattern of injury progressed significantly more rapidly to ESRD than lupus FHN patients with class III/IV (±V) LN. Our results indicate that FHN is pattern of renal injury most often encountered in SLE, but also rarely occurring in a number of other diseases, as well as being representative of an idiopathic variant urging careful consideration by the nephrologist.

To confine the group of patients with idiopathic non-lupus FHN, we considered a number of atypical presentations of other diagnoses in non-lupus FHN patients: membranous nephropathy, IgA nephropathy, infection-related glomerulonephritis, and anti-neutrophil cytoplasmic antibody-associated glomerulonephritis (AAGN). The combination of severe

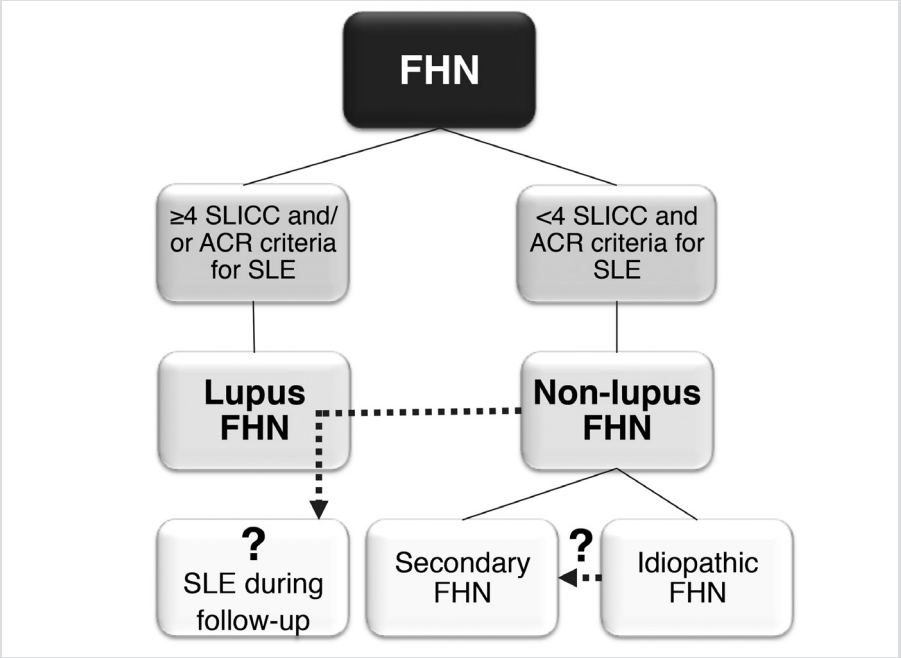
clinicopathologic features at presentation and poor renal survival of more than half of these patients raises the possibility that in some instances, non-lupus FHN may represent severe forms of other renal diseases that are accompanied by strong activation of the immune system, as has also been suggested in previous case series.[2, 8-15, 22, 23] Notably, three patients had recurrent IgA nephropathy with crescentic glomerulonephritis in their renal allograft, similar to patients reported by Kowalewska *et al.* showing an uncommon and aggressive form of IgA nephropathy.[24] Furthermore, we identified two patients with FHN and AAGN, one of whom required dialysis at the time of biopsy. Previous reports have demonstrated convincingly that glomerular immune complexes may be present in AAGN.[25] It has been suggested that immune complexes may act synergistically with ANCA to produce more severe glomerulonephritis than seen with either immune complexes or ANCA alone.[26] The possibility that secondary causes for which we could not test may underlie FHN in the remaining 20 idiopathic non-lupus FHN patients cannot be fully excluded, which is a limitation inherent to our retrospective study design. Nevertheless, it is crucial to realise that ESRD was associated with non-lupus FHN, irrespective of its cause. Importantly, although we did not observe such patients, patients have been reported in the literature with non-lupus FHN who developed SLE during follow-up,[2-5] adding the possibility that some non-lupus FHN patients may have latent SLE. Taken these considerations together, we compiled a diagnostic scheme for FHN (**Figure 2**).

Idiopathic non-lupus FHN patients show similarities with an entity previously described as "renal-limited lupus-like nephritis".[27] However, this entity was originally defined by a lupus-like constellation of immunofluorescence and electron microscopic evaluations, and not by a full house pattern *per se*.[27] In the study by Huerta and colleagues,[27] two of four "renal-limited lupus-like nephritis" patients had FHN, and both progressed to ESRD despite aggressive therapy. Importantly, our study indicates that idiopathic non-lupus FHN, as defined by the absence of sufficient SLE criteria and exclusion of other diagnoses, should be recognised as a category with poor outcome by itself, without the requirement of additional lupus-like pathologic features. Therefore, the term "lupus-like nephritis" should not be used for idiopathic non-lupus FHN – emphasising the clinical distinction from lupus.

The prevalence of non-lupus FHN in our cohort is in accordance with a previous study, in which non-lupus FHN was described in 28/94 (30%) cases with FHN identified over a 9-year period.[2] In our study, idiopathic non-lupus compared to lupus FHN patients were more often male. Moreover, laboratory results revealed lower-range erythrocyturia, predominantly nephrotic-range proteinuria, and less complement consumption in the classical pathway. We identified a number of immunohistochemical and histopathologic features that predominated in idiopathic non-lupus FHN compared to lupus FHN: weaker C1q staining by immunofluorescence; less frequent proliferative lesions and more frequent mesangial and membranous lesions by light microscopy; and an increased frequency of a chronic subclass associated with proliferative nephritis. Thus, in a patient with a renal biopsy showing FHN in the absence of sufficient SLE classification criteria, the features

above would support a diagnosis of idiopathic non-lupus FHN. Further study is warranted to identify additional indicators that could help to distinguish idiopathic non-lupus FHN from lupus FHN. Tubuloreticular inclusions would appear promising based on the study by Wen and Chen,[2] although we did find them in one patient with idiopathic non-lupus FHN. Other promising indicators, such as IgG subclass staining,[28] remain to be investigated.

Figure 2 Diagnostic scheme of full house nephropathy (FHN).



Dotted lines represent considerations that were not supported by our study, but remain to be investigated. ACR, American College of Rheumatology; SLICC, Systemic Lupus International Collaborating Clinics.

Since we performed the first study of idiopathic non-lupus FHN in which control cases with lupus FHN were included, we were able to compare outcomes between these groups to substantiate their clinical distinction. Given the heterogeneity of histopathologic lesions, we analysed renal and patient survival in subsets with relatively homogeneous injury patterns, and found that idiopathic non-lupus compared to lupus FHN was a strong independent risk factor for ESRD in the subset of patients with proliferative lesions (akin class III/IV [±V] LN). Possibly because the number of patients with others histopathologic patterns of injury was small, we could not demonstrate a survival difference in these subgroups. Our results are in agreement with previous reports that hinted that the clinical course and outcome of idiopathic non-lupus FHN patients are worse than those of patients with similar patterns of glomerulonephritis with SLE.[4, 6, 15, 27]

It is reasonable to speculate that a number of factors relating to idiopathic-non-lupus FHN patients contributed to their poor outcome. The higher levels of proteinuria and the tendency towards a higher chronicity score in idiopathic non-lupus FHN patients are remarkable in this aspect, although these factors did not explain the renal survival difference between idiopathic non-lupus and lupus FHN in our statistical models. A major conundrum of this study is that 11 of 20 idiopathic non-lupus FHN patients did not receive any type of immunosuppression; and of the 9 patients who did, 5 received corticosteroids alone and none received cyclophosphamide. This contrasts to the 38% of lupus FHN patients who did receive cyclophosphamide. Whereas we did not find that immunosuppression including corticosteroids affected renal survival within the group of idiopathic non-lupus FHN patients, the poor outcome of idiopathic non-lupus FHN patients may well be related to their lack of cytotoxic therapy. In a recent study of paediatric non-lupus patients with complement (C1q, C3) and immunoglobulin (IgG, IgM and/or IgA) glomerular staining, patients who received intensive cytotoxic immunosuppression had a favourable renal outcome.[7] Although FHN was defined differently, this study raises the possibility that idiopathic non-lupus FHN patients may also benefit from cytotoxic immunosuppression. On the other hand, the relative lack of immunosuppression in idiopathic non-lupus FHN patients in our study eliminates the possibility that treatment induced sustained remission and prevented latent lupus from becoming active systemically for the majority of these patients. This accentuates the clinical distinction from lupus, as none of the (idiopathic) non-lupus FHN patients developed SLE during long-term follow-up. It remains speculative as to whether the uncertainty of a definite diagnosis of SLE due to the lack of systemic signs and symptoms and/or the imminent progression to ESRD discouraged physicians from initiating intensive immunosuppression after risk-benefit assessment.

The aetiology and pathogenesis of idiopathic non-lupus FHN remain to be elucidated. Given its strong similarity to LN, it may be considered that the two entities share similar pathogenic mechanisms. In LN, it has been suggested that immune complexes may occur in the glomerulus both due to the deposition of preformed immune complexes and in situ formation. The formation of autoantibodies and the resulting immune complexes in LN may therefore originate from a combination of pathogenic mechanisms: (i) an increased antigenic load due to dysregulated apoptosis and defective clearance of apoptotic debris; (ii) a subsequent aberrant immune response directed to these endogenic antigens; and (iii) a defective clearance of immune complexes. Quantity, size, and type of the immune complexes determine the microscopic pattern of injury in LN related to the site of deposition.[29] The occurrence of full house glomerular deposits in LN may then be seen as the result of a pronounced immune response with polyclonal B cell activation in the setting of these mechanisms. The occurrence of full house glomerular deposits in the absence of a clinical diagnosis of SLE may similarly be seen as the expression of a more pronounced type of defective immune complex clearance following abnormal immune complex overload or immune complex handling.[30] The previously mentioned secondary forms of non-lupus FHN[2, 8-15, 22, 23] are likely associated with these mechanisms. Unidentified endogenous and/

or exogenous antigens involved in immune complex formation may underlie idiopathic non-lupus FHN. Moreover, genetic factors resulting in defective clearance of immune complexes that have been implicated in LN, such as Fcγ-receptor deficiency[31] and deficiency of the erythrocyte C3b-receptor,[32] may also be involved in idiopathic non-lupus FHN.

In conclusion, our study indicates that idiopathic non-lupus FHN is associated with poor renal survival and therefore, deserves careful consideration by the nephrologist. We pointed out what should prompt the recognition of idiopathic non-lupus FHN, and hopefully initiated efforts to determine possible underlying cause(s) and potential treatment.

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