Lupus or not? Idiopathic full house glomerulonephritis: a rare nephropathy with unexpectedly severe outcome

S. Sciascia[1], M. Cozzi[1], A. Fadaeibahreini[1], M. Radin[1], I. Cecchi[1], A. Barreca[2], G. Amore[1], E. De Simone[1], R. Fenoglio[1], D. Roccatello[1]

[1]University Center of Excellence on Nephrologic, Rheumatologic and Rare Diseases (ERK-Net, ERN-Reconnect and RITA-ERN Member) with Nephrology and Dialysis Unit and Center of Immuno-Rheumatology and Rare Diseases (CMID), Coordinating Center of the Interregional Network for Rare Diseases of Piedmont and Aosta Valley, ASL Città di Torino and Department of Clinical and Biological Sciences, University of Turin, Italy; [2]Division of Pathology, Città Della Salute e Della Scienza Hospital, University of Turin, Italy.

Abstract

Objective

A full-house pattern at immunofluorescence in kidney biopsies is usually associated with lupus nephritis. The cases that do not meet criteria for diagnosis of systemic lupus erythematosus (SLE) and have no secondary causes are classified as idiopathic full house (non-Lupus) nephropathy (iFH-N), which is a poorly defined entity. We aimed to evaluate the clinical presentation, renal outcome and development of SLE in the long term.

Methods

We carried out a retrospective observational study from 2012 to 2022 on patients with iFH-N, i.e. having a full-house pattern at immunofluorescence, but not meeting the criteria for the diagnosis of SLE and without a secondary cause.

Results

Of 2210 patients, 91 presented with full-house pattern at immunofluorescence: 84 had the criteria for SLE diagnosis, 2 had secondary causes, 5 were idiopathic. iFH-N cases were all young females with histological pattern of membranous nephropathy and impaired kidney function, at presentation two had a nephrotic syndrome, three a nephrotic range proteinuria. Mean serum creatinine was 2.1 mg/dl (SD± 0.47), mean eGFR 35.2 ml/min/1.73m^2 (SD±11), mean proteinuria 7.1 gr/24h (SD±3.2). Four had negative antinuclear antibodies; none had anti-dsDNA, anti-extractable nuclear antigens, antiphospholipid antibodies; three had low C3 levels. All received aggressive immunosuppression (IS), including steroids, cyclophosphamide, mycophenolate mofetil or Intensified B Cell Depletion Protocol. Mean follow-up was 7.4 year (SD ± 2.4). Four patients (80%) developed end stage renal disease, three within 24 months, one patient chronic kidney disease stage 4. One subject developed SLE after two years.

Conclusion

All patients with iFH-N had similar clinical presentation, appeared to be refractory to aggressive IS, and had poor renal outcome.

Key words

idiopathic full house glomerulonephritis, lupus nephritis, lupus, antibodies

*Savino Sciascia, MD, PhD**
*Martina Cozzi, MD**
Amin Fadaeibahreini, MD
Massimo Radin, MD, PhD
Irene Cecchi, MD, PhD
Antonella Barreca, MD
Giorgio Amore, MD
Emanuele De Simone, MD, PhD
Roberta Fenoglio, MD
Dario Roccatello, MD

**Contributed equally.*

Please address correspondence to:
Savino Sciascia
Dipartimento di Scienze Cliniche e Biologiche,
Università di Torino,
Ospedale S. Giovanni Bosco,
Piazza del Donatore di Sangue 3,
10154 Torino, Italy.
E-mail: savino.sciascia@unito.it

Received on December 5, 2024; accepted in revised form on March 5, 2025

Competing interests: none declared.

Introduction

A full house pattern is a usual finding in kidney biopsies of patients affected by systemic lupus erythematosus (SLE) with lupus nephritis (LN). This pattern is defined by simultaneous positivity for IgG, IgM, IgA, C3 and C1q staining at Immunofluorescence (IF) and, when encountered, is highly suggestive of SLE (1-2). It can also be secondary to other conditions, including infections (for example HBV, HCV, syphilis, endocarditis), lymphoid neoplasms, other autoimmune diseases or drugs (4-7).

In a minority of cases, however, patients with this finding at kidney biopsy do not meet enough clinical and/or serological criteria to be diagnosed with SLE, nor they have an identifiable secondary cause of full house pattern. Consequently, they are classified as having an idiopathic full house non-lupus nephropathy (iFH-N). They usually have negative anti-nuclear (ANA) and anti-double stranded DNA (anti-dsDNA) antibodies, and they often have a renal-limited disease, with few or absent systemic signs and symptoms. IFH-N represents a rare entity described in small cohorts of patients, with variable clinical presentation and renal outcomes (8-13). Correlation between SLE and iFH-N still remains controversial. In fact, it is currently not known if iFH-N represents a distinct nosological entity from LN and SLE or it precedes the development of SLE. Being such a rare condition, iFH-N still needs to be further defined in its clinicopathological features, specific therapies, and outcomes.

In this study, we performed a retrospective observational analysis to evaluate cases of iFH-N diagnosed at our University Center, specifically aiming at defining nephropathological features, clinical presentation, renal outcome and SLE development during follow-up.

Materials and methods

We retrospectively reviewed all native kidney biopsies performed from January 2012 to December 2022 at the University Center of Excellence on Nephrological, Rheumatological and Rare Diseases at San Giovanni Bosco Hub in Torino, Italy.

Patients' clinical data at the time of kidney biopsy and during follow-up (every 6-months) were obtained from hospital electronic medical records.

Inclusion criteria for our study were: age ≥18, a kidney biopsy showing a full-house pattern at immunofluorescence, not meeting criteria for a diagnosis of SLE according to American College of Rheumatology (ACR) 1997 classification (14) or Systemic Lupus International Collaborating Clinics (SLICC) 2012 criteria (15) at the time of kidney biopsy.

Exclusion criteria were: absence of full-house pattern at kidney biopsy, having a definitive diagnosis of SLE, having a secondary cause of full-house pattern (such as infections, including HBV, HCV, HIV, syphilis, endocarditis, drugs, cryoglobulins, monoclonal gammopathies, or other hematologic disorders), insufficient follow-up (at least 2 years).

For included patients, the following clinical and laboratory data were collected (at kidney biopsy and during the regular follow-up): serum creatinine (mg/dl), estimated glomerular filtration rate (eGFR) (ml/min/1.73m^2) calculated with 2021 CKD-EPI equation, 24h proteinuria (gr/die), C3 and C4 serum levels (mg/dl), albuminaemia (gr/l), ANA, anti-dsDNA antibodies, extractable nuclear antigens (ENAs), antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, anti-beta2glycoprotein antibodies), data on performed therapies and renal outcome, clinical and laboratory parameters for SLE diagnosis during follow-up.

Kidney biopsies were reviewed by two expert nephropathologists. Full-house pattern was defined as the presence of a simultaneous positive staining for IgG, IgM, IgA, C3, and C1q with an intensity of at least 1+ on a scale ranging from 0 to 3+ at IF (16). Data on pattern of glomerular injury, presence or absence of extracapillary proliferation (cellular / fibrocellular / fibrous crescents), percentage of global glomerulosclerosis, tubular atrophy, and interstitial fibrosis at light microscopy were recorded. Global glomerulosclerosis, interstitial fibrosis and tubular atrophy (IF/TA), and the presence of fibrous crescents

were scored according to the modified NIH chronicity index for LN, with <25% classified as 1+, 25-50% as 2+, >50% as 3+, according to the 2018 revision of ISN/RPS classification for LN (16).

Genetic testing performed as previously described failed to identify significant alterations (17).

Biopsies with membranous nephropathy (MN) at light microscopy were additionally evaluated with PLA2R staining (rabbit polyclonal, Sigma-Aldrich, St. Louis, MO), THSD7A staining (rabbit polyclonal, Sigma-Aldrich) and Exostosin staining (rabbit polyclonal, Invitrogen) at IF.

Patients' clinical and laboratory data were analysed using means and standard deviations for continuous variables and frequencies and percentages for categorical variables.

The study was performed according to regulations established by the Regional Health Department on the off-label therapy in rare diseases in Piedmont (northwest Italy). The study was conducted according to the Piedmont and Aosta Valley (Northwest Italy) legislation for Rare Diseases (no. 1577/UC/SAN of 11.10.2005 based on Regional Government Act 23 April 2007 dealing with Rare Diseases; article. 1: 796 paragraph Z, law no. 296 of 2006, no. 5-5740).

Results

Clinical and histological data

From January 2012 to December 2022, 2210 patients underwent a kidney biopsy at our University Center. Of these patients, 91 (4.2%) had a histological finding classified as full-house pattern and were initially included for further evaluation. Of these 91 individuals, 84 received a diagnosis of SLE and were subsequently excluded. Seven patients did not meet criteria for a diagnosis of SLE according to ACR or SLICC classification at the time of presentation and were further evaluated. In this subgroup, two patients were excluded, having another clinical condition that could have justified a full house finding at IF, specifically, a monoclonal gammopathy of renal significance and a cryoglobulinaemia in an HCV-positive patient. Finally, five patients were labelled as having an idiopathic full house (non-lupus) nephropathy (iFH-N) and were included in our study.

All five included patients were females, four Caucasians (80%) and one Black (20%), with mean age 28.2 years (range 21–40). At presentation, they all had impairment of kidney function, two had a full-blown nephrotic syndrome, and three had a nephrotic range proteinuria. Mean serum creatinine was 2.1 mg/dl (SD± 0.47), mean eGFR was 35.2 ml/min/1.73m^2 (SD±11), mean proteinuria 7.1 gr/24h (SD±3.3). Antinuclear antibodies (ANA) were negative in four of five patients; the fifth patient had ANA positivity at mid-low titre (1:160, speckled pattern). Anti-dsDNA, ENAs, and antiphospholipid antibodies were negative in all subjects. Low C3 levels were detected in three of five subjects.

Considering kidney biopsies, mean number of glomeruli was 32.8 (range 18–50). At light microscopy, all five patients had a membranous nephropathy (MN) pattern, resembling a class V lupus nephritis. Notably, mean percentage of global glomerulosclerosis was 42.6% (SD ±11.5%). Moreover, two of 5 (40%) of patients has 2+ (moderate to severe) IF/TA and other two (40%) had 3+ (severe) IF/TA, with overall 80% of individuals having a significant chronic tubulointerstitial damage. Calculated mean chronicity index (CI) was 6.4 (range 3–9 out of 12 points). Two cases had evidence of extracapillary proliferation with florid cellular crescents. No fibrous crescents were detected in any of the biopsies at presentation. IF staining for PLA2R, THSD7A and EXT was negative in all individuals. Complete data on clinical, laboratory, and histological data per each patient are listed in Table I.

Mean follow-up from time of biopsy was 7.4 year (SD±2.4) (range 3–10 years). During follow-up, three patients underwent a second kidney biopsy for histological re-evaluation due to lack of response to therapy or disease flare. Repeated kidney biopsies all demonstrated disease progression, with increased global glomerulosclerosis and interstitial fibrosis / tubular atrophy.

Management, renal outcome and SLE development

All patients underwent aggressive schemes of immunosuppressive therapies. The schemes used included high-dose intravenous (iv) glucocorticoids (GC) in association with cyclophosphamide (CYC) or mycophenolate mofetil (MMF), or Intensified B Cell Depletion Protocol (*i.e.* iv methylprednisolone pulses + CYC and rituximab) (18). The applied therapies are summarised in Table II.

Considering renal outcome, during follow-up, four patients (80%) developed end-stage renal disease (ESRD), three of them within 24 months after presentation. In detail, the two patients with extracapillary proliferation had a severe prognosis, starting dialysis 4 and 10 months after presentation, respectively. The fourth patient developing ESRD started dialysis after 6 years of follow-up. The fifth patient, at last follow-up, had chronic kidney disease (CKD) stage 4, 7 years after initial presentation.

Considering long-term onset of SLE, only one patient developed serological criteria to be classified as SLE 2 years after initial presentation. At the time of disease onset, this patient had nephrotic syndrome, proteinuria 8.1 gr/24h, renal impairment (SCr 1.8 mg/dl) and low C3 levels (37 mg/dl), with negative autoantibody serology. Aggressive IS with GC pulses and CYC was used due to rapid deterioration of kidney function and temporary need for dialysis. Initial response was observed, with significant improvement of kidney function, weaning from dialysis and reduction of proteinuria to 1.2 gr/24h. Two years after presentation, the patient had a disease flare with rapidly progressive glomerulonephritis, low C3 and new positivity for ANA at high titre (1:640, homogeneous patter) and anti-dsDNA (1:20) antibodies, without other systemic signs or symptoms of the disease. Repeated kidney biopsy confirmed MN with FH and progression of chronic lesions. Renal involvement, low C3 and positive serology were diagnostic for SLE according to SLICC criteria, but not ACR criteria. Finally, patients were further re-evaluated with the new European League

Table I. Clinical and histological data at presentation.

Pt	Age/Sex	Ethnicity	SCr (mg/dl) / eGFR (ml/min/1.73m^2)	Proteinuria (gr /24h)	Nephrotic syndrome	ANA / Anti-ds DNA	Low C3	Comorbidities	Pattern	LN Class	Extra-capillary proliferation	n. of glomeruli	Glom with global glomerulo-sclerosis	IF/TA	CI
1	32 / F	Caucasian	2.2 / 30	3.7	x	neg / neg	√	Hypothyroidism	MN	V	No	25	12 (48%)	>50% (3+/3+)	8
2	23 / F	Caucasian	2.8 / 24	4.5	x	neg / neg	x	Thalassaemia trait	MN	V	**Yes** 3 cellular crescents	40	17 (42%)	25-50% (2+/2+)	6
3	25 / F	Caucasian	1.4 / 54	12	x	neg / ng	x	None	MN	V	No	18	8 (44%)	25-50% (2+/2+)	6
4	21 / F	Caucasian	1.8 / 41	8.2	√	neg / neg	√	None	MN	V	No	31	17 (55%)	>50% (3+/3+)	9
5	40 / F	Black	2.3 / 27	7.5	√	1:160 / neg	√	None	MN	V	**Yes** 28 cellular crescents	50	12 (24%)	<25% (1+/1+)	3

CI: Chronicity Index according to the modified NIH indexes for lupus nephritis; IF/TA: interstitial fibrosis/tubular atrophy; LN: lupus nephritis; MN: membranous nephropathy; SCr: serum creatinine; eGFR: estimated glomerula filtration rate.

Table II. Therapies, renal outcome and SLE development.

Pt	Therapies	no. of kidney biopsies	SCr at presentation (mg/dl)	SCr at 12 months (mg/dl)	SCr at 24 months (mg/dl)	SCr at last FU (mg/dl)	FU (years)	Time from biopsy to ESRD (months)	ACR criteria	SLICC criteria
1	IBCDT	1	2.2	2.8	2.9	3.2	7	-	x	x
2	IBCDT (1st line) MMF + GC (2nd line)	2 (lack of response)	2.8	ESRD	ESRD	ESRD	8	10	x	x
3	CYC + GC (1st line) IBCDT (2nd line)	2 (flare)	1.4	1.3	3.5	ESRD	10	72	x	x
4	CYC + GC (1st line) MMF + GC (2nd line)	2 (flare)	1.8	1.9	ESRD	ESRD	9	24	x	√
5	IBCDT	1	2.3	ESRD	ESRD	ESRD	3	4	x	x

ACR: American College of Rheumatology 1997 classification for SLE; CYC: cyclophosphamide; ESRD: end stage renal disease; FU: follow up; GC: glucocorticoids; IBCDP: Intensified B Cell Depletion Protocol (*i.e.* iv methylprednisolone pulses + cyclophosphamide and rituximab); MMF: mycophenolate mofetil; SCr: serum creatinine; SLE: systemic lupus erythematosus; SLICC: Systemic Lupus International Collaborating Clinics 2012 classification.

Against Rheumatism / American College of Rheumatology (EULAR/ACR) classification for SLE defined in 2019 (17). According to the new classification, four of five individuals with negative ANA titre at presentation could not have been classified as SLE at the onset of their clinical manifestations. The fifth patient, with mid-low positive ANA at presentation (1:160) could have been re-classified as having SLE at the time of presentation, considering renal involvement and low C3. The patient developing new positivity for ANA and anti-dsDNA two years after disease onset would have met EULAR/ACR 2019 criteria for SLE as well at the time of disease flare. Follow-up data are summarised in Table II.

Discussion

Idiopathic full house non-lupus nephropathy remains a rare and poorly defined condition. In this study, we reported a case series of patients with a diagnosis of iFH-N with one of the longest times of follow-up available in current literature. All patients with iFH-N (all young females) had a similar histological pattern of membranous nephropathy, and clinical presentation, with nephrotic range proteinuria and impaired kidney function. They all had an aggressive form of kidney disease, refractory to different regimens of immunosuppression, and with poor long-term renal outcome.

In the present literature, clinical presentation, histologic features and renal outcome of iFH-N varied across different studies. In the largest reported cohorts, subjects more often were males, they often presented with nephrotic syndrome or nephrotic range proteinuria, mild impairment of kidney function, they had lower consumption of complement levels, if compared to patients with LN, and in 20–46% of cases had a MN at light microscopy in kidney biopsy, they received different therapies and had variable renal outcome (8, 10, 13). Rijnink *et al*. (10) described 20 cases of iFH-N and compared them with cases of LN. As in our study, iFH-N often presented with nephrotic range proteinuria and impairment of kidney function. Specifically, 12 (60%) presented with nephrotic syndrome, 5 (25%) with acute kidney injury, or rapidly progressive glomerulonephritis. MN was one of the most frequent histological findings, accounting for 20% of cases, along with focal (25%) and diffuse (10%) proliferative lesions. Immunosuppressive therapy was used in 15 of 20 iFH-N. Notably, 60% of patients with iFH-N progressed to ESRD, including 8 of the 15 individuals who received immunosuppression.

It should be noted, however, that used immunosuppressive therapies included corticosteroids and azathioprine, but no patient received CYC or MMF.

In another large cohort from India, Mahanta *et al*. (13) described 21 cases of iFH-N, comparing them to patients with LN. Similarly to Rijnink *et al*., patients were more often males, they mainly presented with nephrotic syndrome and impairment of kidney function. At kidney biopsy, the most frequent findings were focal and proliferative lesions (23% and 19% of cases, respectively), or MN (19%). The majority of patients (18 of 21 cases) received some form of immunosuppression. In contrast to the abovementioned experience, there was no difference in renal outcome between iFH-N and LN, with 16 of 21 iFH-N having complete or partial remission and only two cases progressing to ESRD. It should be noted that, in this study, patients were treated with more aggressive regimens of immunosuppression, including induction therapy with steroids + CYC or + MMF, as in LN.

A recently published meta-analysis analysed 47 studies with overall 148 individuals having a non-lupus full house finding at kidney biopsy (7). Fifty-one cases had an identifiable secondary cause of full house pattern, while 57 were labelled as having iFH-N, six of them being paediatric cases. Looking at iFH-N cases, there was no difference in male/female ratio, patients mostly presented with nephrotic range proteinuria, normal or mildly impaired kidney function, and 25% had MN at kidney biopsy. In most cases (73%) immunosuppression was used, with a complete response or partial response to therapy in 46% and 42% of cases, respectively, overall with a good renal prognosis, as in the Mahanta *et al*. experience.

As mentioned, iFH-N can present with variable pattern of injury at light microscopy. Across available reports, some studies focused on individuals with iFH-N and MN, as were patients in our case-series. The largest experience came from China, with 153 patients labelled as having "atypical" membranous nephropathy (aMN) with a full house pattern, and compared to idiopathic MN (19). Most of these patients had nephrotic range proteinuria and preserved kidney function. More than 90% of them received some form of immunosuppression, including steroids + CYC or + CNI. At follow-up, there was no difference in proteinuria remission rate and renal outcome between the two groups, with 20% of aMN cases experiencing worsening of kidney function and only 3.8% progressing to ESRD. Despite huge numbers, results from this study might not be compared to our and other smaller cohorts of iFH-N MN. In fact, among aMN cases, 82 cases (53%) tested positive for PLA2R antibodies, which could have been causative of the observed disease. Moreover, patients who developed SLE during follow-up were completely excluded from study analysis at the time of enrollment.

In another experience on iFH-N MN, Sam *et al*. described 23 cases of "lupus-like" MN and compared them to idiopathic MN and lupus MN (20). Nephrotic range proteinuria and preserved kidney function were the most frequent clinical presentation of lupus-like MN. Notably, despite no signs of systemic disease, 52% of patients included in the lupus-like group had ANA positivity, while in all other series, including our study, patients were in most cases ANA negative. Moreover, in Sam *et al*. study, only one third of patients received immunosuppression. After 3.5 years of follow-up, 17% of subjects with lupus-like MN and only 6% of lupus MN had developed ESRD, with a good long-term renal prognosis.

Our case series differs from previously discussed studies for several reasons. Firstly, patients were carefully selected before inclusion in the study, excluding all individuals with possible secondary causes underlying their condition. Considering clinical presentation and outcome, they were all females, while male predominance was highlighted in some of the abovementioned reports (10, 13), and, most of all, they all had a rapid decline in kidney function. Despite aggressive immunosuppression, including CYC and rituximab, they all had a severe renal prognosis, while an overall good renal outcome was highlighted in previous experiences, including results from the meta-analysis on iFH-N (7). It is worth noting that, despite abrupt onset of the disease with acute clinical presentation, in our study all patients had relevant signs of chronic damage at kidney biopsy. Mean global glomerulosclerosis was 42.6%, and in 80% of patients there was a moderate to severe or severe chronic tubulointerstitial injury, with a surprisingly high mean chronicity index (6.4). A rapid evolution of tissue damage to chronic sclerosis of glomerular and interstitial compartment plausibly affected likelihood of response to therapy of our patients and favored rapid progression to ESRD. In fact, over the last decade, it has become well-established that IF/TA represents an independent risk factor for progression to ESRD in patients with LN (21-23). In 2018, a revision of ISN/RPS classification was released (16) with the adoption of activity and chronicity indexes, endorsing the need for a scoring system for LN that considers also acute and chronic tubulointerstitial injury, in addition to glomerular injury. Chronic index (CI), which assesses four parameters – glomerulosclerosis, fibrous crescents, tubular atrophy and interstitial fibrosis – on a scale from 0 to 12 points, has been strongly associated with progression to CKD and ESRD (24).

IF/TA not only predicts ESRD, but also serves a marker of likely unresponsiveness to therapy (21, 25). In our cohort, two patients failed to respond to therapy, other two experienced a disease flare withing the first 24 months of follow up, and all ultimately progressed to ESRD. Thus, histological findings in our study help explain why our patients overall experienced a poor renal outcome compared to other abovementioned studies. On the other hand, these findings underline the severity of iFH-N, with a rapid progression from acute to chronic injury and the need for a prompt diagnosis, therapy and monitoring during follow up.

The risk of developing SLE in patients with iFH-N and relationship between the two conditions represent another key element of debate. Some authors suggested that iFH-N may represent

a form of latent SLE, which becomes fully expressed over several months to years after the initial presentation (20). Others believe that, even if iFH-N results from a dysregulation of the immune system, it represents a separate condition from LN and SLE (10, 13, 26). In the current literature, the development of SLE during long-term follow-up varied between 0 and 25% across different studies. For example, in the abovementioned report by Rijnink *et al*. (10) during a long-term follow-up of 20 years, no patient had developed SLE. In another study on 24 cases of iFH-N, Wen & Chen reported development of SLE in two of 24 patients after a follow-up of 2 years (8). Development of SLE seems to be more frequent in paediatric experiences, where patients who presented with a full-house nephropathy during paediatric age more likely develop an overt systemic disease during follow up especially younger, female patients (22).

In our experience, one of five patients developed SLE two years after presentation, with new positivity for ANA and anti-dsDNA antibodies at high titre concurrently with a renal flare, without other systemic manifestations. In this case, patient's condition satisfied SLICC criteria, but not ACR criteria to receive a diagnosis of SLE.

With the EULAR/ACR 2019 classification of SLE (27), which requires ANA positivity as an entry criterion, four of our five patients with negative ANA titre at presentation could not have been classified as having SLE at the onset of their disease. However, the fifth patient, who at presentation had ANA positivity, low C3 levels, and renal involvement, would have met the minimum score criteria for SLE diagnosis, despite no other clinical sign or symptom, nor anti ds-DNA positivity.

Beyond a technical classification, it should be underlined that all our patients received aggressive immunosuppressive therapy due to the severe renal involvement of the disease at presentation, as if they had a definite diagnosis of LN, but, unfortunately, none of them had a satisfactory response.

Our study presents some main limitations, first of all its retrospective nature and the small sample size. Newly available antigens to specifically characterised MN, including NELL1 (28) were not tested. Nevertheless, IF staining for PLA2R, THSD7A and Exostosin (29) were all tested and resulted negative in our cases. Another histological feature not addressed in our patients, given the retrospective nature of the study, was the identification of IgG subclasses at IF staining. IgG characterisation may indeed be helpful in further classify iFH-N. It t is well-know that different IgG subtypes can be identified in secondary forms of membranous nephropathy, including lupus MN, and primary forms of MN (30-32). Specifically, IgG4 are usually distinctive feature of primary MN, while IgG2 and IgG3 are more often encountered in secondary forms of MN, including Lupus MN. This distinction, although not univocal, may help proper classification of kidney injury with MN pattern at light microscopy and deserves further investigation also in iFH-N affected patients. Finally, the strengths of our observation were the meticulous selection of patients for inclusion in the study and long duration of follow-up, at least two years, as inclusion criterion.

In conclusion, iFH-N is a rare entity that still needs to be fully characterised in its pathogenesis, prognosis and correlation with SLE. As clinical features, response to therapy and outcomes varied across studies, it is plausible that different entities are incorrectly classified under the same label of iFH-N. Unfortunately, specific biomarkers to better define distinct entities are currently missing and the rarity of such condition constitutes a further challenge to its definite characterisation. Being able to better classify these patients would be of utmost importance in order to offer appropriate therapies, aggressively treating severe forms, like our cases, while sparing from strong immunosuppression more benign conditions.

Rheumatologists should be aware of this rare and severe entity for two key reasons. First, certain forms of IFH-N, such as those in our cohort, carry a high risk of flare or poor response to therapy and can progress rapidly to ESRD. Second, although the disease may initially be limited to the kidneys, the possibility of developing overt SLE during follow-up cannot be excluded. Therefore, careful patient monitoring is essential.

Further studies on larger cohorts of highly selected patients are needed to define iFH-N in its pathogenesis, presentation and outcome, and exploring its relationship with SLE, which still remains controversial.

References

1. CAMERON JS: Lupus nephritis. *J Am Soc Nephrol* 1999; 10(2): 413-24. https://doi.org/10.1681/asn.v102413
2. MORETTI M, TREPPO E, MONTI S *et al*.: Systemic lupus erythematosus: one year in review 2023. *Clin Exp Rheumatol* 2023; 41(4): 765-73. https://doi.org/10.55563/clinexprheumatol/4uc7e8
3. SCHILIRÒ D, SILVAGNI E, CIRIBÈ B *et al*.: Systemic lupus erythematosus: one year in review 2024. *Clin Exp Rheumatol* 2024; 44(3): 583-92. https://doi.org/10.55563/clinexprheumatol/mnvmvo
4. LAI FM, TO KF, WANG AY *et al*.: Hepatitis B virus-related nephropathy and lupus nephritis: morphologic similarities of two clinical entities. *Mod Pathol* 2000; 13(2): 166-72. https://doi.org/10.1038/modpathol.3880031
5. HAAS M, KAUL S, EUSTACE JA: HIV-associated immune complex glomerulonephritis with "lupus-like" features: a clinicopathologic study of 14 cases. *Kidney Int* 2005; 67(4): 1381-90. https://doi.org/10.1111/j.1523-1755.2005.00215.x
6. LEE L-C, LAM K-K, LEE C-T, CHEN J-B, TSAI T-H, HUANG S-C: "Full house" proliferative glomerulonephritis: an unreported presentation of subacute infective endocarditis. *J Nephrol* 2007; 20(6): 745-49.
7. UZZO M, KRONBICHLER A, ALBERICI F, BAJEMA I: Non-lupus full house nephropathy. *Clin J Am Soc Nephrol* 2024; 19(6). 743-54. https://doi.org/10.2215/cjn.0000000000000438
8. WEN YK, CHEN ML: Clinicopathological study of originally non-lupus "full-house" nephropathy. *Ren Fail* 2010; 32(9): 1025-30. https://doi.org/10.3109/0886022x.2010.510614
9. HUERTA A, BOMBACK AS, LIAKOPOULOS V *et al*.: Renal-limited "lupus-like" nephritis. *Nephrol Dial Transplant* 2012; 27(6): 2337-42. https://doi.org/10.1093/ndt/gfr663
10. RIJNINK EC, TENG YKO, KRAAIJ T, WOLTERBEEK R, BRUIJN JA, BAJEMA IM: Idiopathic non-lupus full-house nephropathy is associated with poor renal outcome. *Nephrol Dial Transplant* 2017; 32(4): 654-62. https://doi.org/10.1093/ndt/gfx020
11. RAMÍREZ-GÓMEZ LM, RUIZ-LEIJA I, MARTÍNEZ-GALLA D *et al*.: Lupus-like membranous nephropathy. Is it lupus? Report of 5 cases in a reference hospital in Mexico. *Lupus* 2021; 30(8): 1347-57. https://doi.org/10.1177/09612033211013584
12. AHMED M, LOVE T, MOORE C *et al*.: The spectrum of renal diseases with lupus-like

features: a single-center study. *Ren Fail* 2022; 44(1): 581-93. https://doi.org/10.1080/0886022x.2022.2057862
13. MAHANTA P, ALAM S, PARRY M *et al*.: Idiopathic nonlupus full-house nephropathy: clinicopathological presentation and comparison with lupus full-house nephropathy. *Saudi J Kidney Dis Transplant* 2022; 33(1): 37-45. https://doi.org/10.4103/1319-2442.367824
14. HOCHBERG MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40(9): 1725. https://doi.org/10.1002/art.1780400928
15. PETRI M, ORBAI A-M, ALARCÓN GS *et al*.: Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012; 64(8): 2677-86. https://doi.org/10.1002/art.34473
16. BAJEMA IM, WILHELMUS S, ALPERS CE *et al*.: Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int* 2018; 93(4): 789-96. https://doi.org/10.1016/j.kint.2017.11.023
17. VAISITTI T, SORBINI M, CALLEGARI M *et al*.: Clinical exome sequencing is a powerful tool in the diagnostic flow of monogenic kidney diseases: an Italian experience. *J Nephrol* 2021; 34(5): 1767-81. https://doi.org/10.1007/s40620-020-00898-8
18. ROCCATELLO D, SCIASCIA S, NARETTO C *et al*.: A prospective study on long-term clinical outcomes of patients with lupus nephritis treated with an intensified B-cell depletion protocol without maintenance therapy. *Kidney Int Rep* 2021; 6(4): 1081-87. https://doi.org/10.1016/j.ekir.2021.01.027
19. JIANG Z, CAI M, DONG B *et al*.: Renal outcomes of idiopathic and atypical membranous nephropathy in adult Chinese patients: a single center retrospective cohort study. *BMC Nephrol* 2021; 22(1): 1-10. https://doi.org/10.1186/s12882-021-02348-4
20. SAM R, JOSHI A, JAMES S *et al*.: Lupus-like membranous nephropathy: Is it lupus or not? *Clin Exp Nephrol* 2015; 19(3): 395-402. https://doi.org/10.1007/s10157-014-1002-1
21. SCIASCIA S, COZZI M, BARINOTTI A *et al*.: Renal fibrosis in lupus nephritis. *Int J Mol Sci* 2022; 23(22). https://doi.org/10.3390/ijms232214317
22. WILSON PC, KASHGARIAN M, MOECKEL G: Interstitial inflammation and interstitial fibrosis and tubular atrophy predict renal survival in lupus nephritis. *Clin Kidney J* 2018; 11(2): 207-18. https://doi.org/10.1093/ckj/sfx093
23. LEATHERWOOD C, SPEYER CB, FELDMAN CH *et al*.: Clinical characteristics and renal prognosis associated with interstitial fibrosis and tubular atrophy (IFTA) and vascular injury in lupus nephritis biopsies. *Semin Arthritis Rheum* 2019; 49(3): 396-404. https://doi.org/10.1016/j.semarthrit.2019.06.002
24. MORONI G, PORATA G, RAFFIOTTA F *et al*.: Beyond ISN/RPS Lupus Nephritis Classification: Adding Chronicity Index to clinical variables predicts kidney survival. *Kidney360* 2022; 3(1): 122-32. https://doi.org/10.34067/kid.0005512021
25. MANNON RB, MATAS AJ, GRANDE J *et al*.: Inflammation in areas of tubular atrophy in kidney allograft biopsies: a potent predictor of allograft failure. *Am J Transplant* 2010; 10(9): 2066-73. https://doi.org/10.1111/j.1600-6143.2010.03240.x
26. L'ERARIO I, FREZZOLINI A, RUGGIERO B, DE PITÀ O, EMMA F, GIANVITI A: Usefulness of skin immunofluorescence for distinguishing SLE from SLE-like renal lesions: a pilot study. *Pediatr Nephrol* 2011; 26(1): 77-83. https://doi.org/10.1007/s00467-010-1655-2
27. ARINGER M, COSTENBADER K, DAIKH D *et al*.: 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheumatol* 2019; 71(9): 1400-12. https://doi.org/10.1002/art.40930
28. SETHI S, DEBIEC H, MADDEN B *et al*.: Neural epidermal growth factor-like 1 protein (NELL-1) associated membranous nephropathy. *Kidney Int* 2020;9 7(1): 163-74. https://doi.org/10.1016/j.kint.2019.09.014
29. SETHI S, MADDEN BJ, DEBIEC H *et al*.: Exostosin 1/Exostosin 2-associated membranous nephropathy. *J Am Soc Nephrol* 2019; 30(6): 1123-36. doi:10.1681/asn.2018080852
30. SONG YS, MIN KW, KIM JH, KIM GH, PARK MH: Differential diagnosis of lupus and primary membranous nephropathies by IgG subclass analysis. *Clin J Am Soc Nephrol* 2012; 7(12): 1947-55. https://doi.org/10.2215/cjn.04800511
31. MURTAS C, GHIGGERI GM: Membranous glomerulonephritis: histological and serological features to differentiate cancer-related and non-related forms. *J Nephrol* 2016 ;29(4) :469-78. https://doi.org/10.1007/s40620-016-0268-7
32. NA W, YI K, SONG YS, PARK MH: Dissecting the relationships of IgG subclasses and complements in membranous lupus nephritis and idiopathic membranous nephropathy. *PLoS One* 2017; 12(3): 1-14. https://doi.org/10.1371/journal.pone.0174501