Clinicopathological Pattern of Non-lupus Full House Nephropathy

Abstract

Background and Aims: Full-house immunofluorescence in a kidney biopsy is a common observation in lupus nephritis (LN) and was previously used synonymously with the diagnosis of LN. Though a minority of the patients will develop features suggestive of SLE during follow-up, a majority of the patients will continue without any clinical or serological evidence of systemic lupus erythematosus (SLE) over time. Our aim to conduct this study was to work up the clinicopathological spectrum of these “full-house” nephropathies (FHN) which were not due to lupus nephritis. Methods: A total of 6244 renal biopsies were evaluated at SGPGIMS Lucknow from January 2007 to December 2017 for full-house immunofluorescence. All those patients who had no clinical or serological evidence of SLE at the time of renal biopsy or at any time during follow up were included. Results: Among 498 patients with full house immunofluorescence, 81 patients had no clinical or serological evidence of SLE at the time of renal biopsy or at any time during follow up. The prevalence of non-lupus FHN in this study was 19.4%, and the major diagnoses were membranous nephropathy (25.9%), IgAN (22.2%), MPGN (14.8%), DPGN (12.3%), Crescentic GN (12.3%), Amyloidosis (8.6%), C1q nephropathy (3.7%). Conclusions: Full-house nephropathy (FHN), not otherwise suggestive of lupus nephritis, can also be found in a number of other conditions. Non-lupus full house nephropathy is an umbrella term for such cases which do not satisfy the standard criteria of SLE. This will prevent misclassifying these patients into SLE and further prevent them from unnecessary immunosuppression protocols.

Keywords: C1q Nephropathy, full house nephropathy, immunofluorescence, lupus nephritis, membranous nephropathy.

Introduction

Systemic Lupus Erythematosus (SLE) is known to affect kidneys with a variety of renal lesions. Nonetheless certain features are characteristic of Lupus Nephritis (LN) and include: a “full-house” immunofluorescence, cytoplasmic tubuloreticular inclusions (TRI) on electron microscopy (EM), and membranous nephropathy (MN) with mesangial deposits.[1] Full-house immunofluorescence in a kidney biopsy means that all 5 major immunofluorescent stains on a renal biopsy (IgG, IgA, IgM, C3, and C1Q) are positive. In lupus nephritis, it is a common observation and there is immunostaining for IgG in more than 90% of cases; IgA and IgM staining in 60-70% of cases; and C3 and C1Q in around 80% of cases.[2]

In the SLICC (The Systemic Lupus International Collaborating Clinics) classification, isolated finding of a kidney biopsy consistent with Lupus Nephritis (LN) in the presence of Anti-nuclear antibodies (ANA) and/or Anti-double-stranded DNA (anti-dsDNA) antibodies is a criterion enough to make diagnosis of SLE and does not require >4 criteria employed in the American College of Rheumatology (ACR) classifications.[3] So it becomes imperative to diagnose a renal lesion carefully to avoid misclassification into systemic lupus erythematosus, seeing the prognosis and treatment of SLE differs from many other diseases. Earlier, full-house pattern was used synonymously with the diagnosis of lupus nephritis. These cases were known as ‘Sero-negative LN’ when the serology was negative for autoantibodies. Further, seroconversion from negative to positive lupus serology over years of follow-up has been reported.[1] These reports suggest that full-house nephropathy may be the first symptom of SLE.[4] Nevertheless, majority of these patients do not behave like lupus nephritis and continue without any clinical or serological evidence of SLE over time.[5]
In the setting of full-house nephropathy (FHN), patients usually are treated with immunosuppressive drugs in a variety of combinations and permutations based on the severity of histological features. In a recent study, Emilie C. Rinink, et al. found that idiopathic non-lupus Full House Nephropathy (FHN) is associated with poor renal survival. This underscores the importance of prompt recognition of idiopathic non-lupus FHN along with determination of possible etiology so as to institute appropriate treatment. In literature many conditions are reported to have full house immunostaining pattern on immunofluorescence including membranous nephropathy (MN), IgA nephropathy, membranoproliferative GN (MPGN), post-infectious GN (PIGN), C1Q nephropathy, and unclassified mesangial GN.

Our aim to conduct this study was to work up the clinicopathological spectrum of these full-house nephropathies which did not qualify the diagnosis of lupus nephritis at the time of biopsy or any time during follow up. Present Literature is deficient in characterizing such cases and this study is largest series of such patients till date.

Methods

The computerised database of Pathology Department of the Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS), Lucknow, India was searched from 2007 to 2017 to identify all patients with native renal biopsies showing full-house immunofluorescence, which was defined as concurrent positive staining for IgG, IgM, IgA, C3 and C1Q. Only those biopsies showing fluorescent staining along the capillary walls, in the mesangium or both were included. All biopsies were processed for light and immunofluorescence microscopy according to the standard techniques at our centre. For immunofluorescence microscopy, sections were stained with fluorescein isothiocyanate–labelled antisera to human IgG, IgM, IgA, C3 and C1Q. These biopsies were validated by renal pathologists. The medical records of the patients were reviewed independently for the presence of 4 or more cumulative ACR or SLICC criteria for SLE at the time of renal biopsy. Cases that did not fulfil ACR or SLICC criteria at the time of biopsy were included as non-lupus full house nephropathies. These patients were followed up to look for their fulfilment of ACR or SLICC classification criteria any time during their follow-up. Further, these cases were classified into various groups based on their clinicopathological similarities and each group was studied to know its composition and homogeneity.

Results

This study is an 11-year long retrospective observational study. A total of 6244 biopsies, not including repeat biopsies, were evaluated at our centre from January 2007 to Dec 2017, of which full-house nephropathy was observed in 498 patients. Among them, 417 cases satisfied ACR or SLICC classification criteria at any time after renal biopsy. The remaining 81 patients with no clinical or serological evidence of SLE at the time of renal biopsy or at follow-up were enrolled in this study.

The prevalence of non-lupus FHN in this study was 19.4%. In our study, there were 54 males and 27 females with a male: female ratio of 2:1. The mean age was 37 years (age range 8-84 years). The most common age of presentation was around 40 years. Renal biopsy showed various types of glomerulonephritis (GN). The morphological diagnoses were decided on the basis of the most prevalent and diffuse glomerular lesions and included 21 (25.9%) cases of membranous GN, 18 (22.2%) of IgAN, 12 (14.8%) of MPGN, 10 (12.3%) of DPGN, 10 (12.3%) Crescentic GN, 7 (8.6%) of Amyloidosis, 3 (3.7%) of C1Q nephropathy; as shown in Figure 1.

Full House Membranous Nephropathy

This was the largest subgroup in which 21 out of 81 patients (25.9%) had Membranous Nephropathy (MN). Mean age at presentation was 43 years with youngest patient being 16 years and oldest 82 years of age. Nineteen patients (90.5%) had nephrotic syndrome with sub-nephrotic proteinuria and mild renal insufficiency as the major clinical features. All patients had primary membranous nephropathy as their etiological diagnosis, except for one patient who had concomitant hepatitis B infection.

Full house immunoglobulin A nephropathy

Among the 81 patients, 18 (22.2%) cases had Mesangial Proliferative GN (MesPGN), in which all had IgA as dominance/codominance on immunofluorescence. This was the second most common group of FHN patients in our study. The mean age of patients in this group was 29.8 years, youngest patient was 8 years and oldest
was 53 years of age. Most of these patients (16/18) had primary IgA nephropathy, while the remaining 2 patients had features consistent with infection-associated glomerulonephritis.

**Full house membranoproliferative glomerulonephritis**

Membranoproliferative glomerulonephritis (MPGN) was the 3rd most common group of non-lupus full house nephropathy patients with 12 out of 81 patients (14.8%) with this diagnosis. Mean age at presentation was 41.5 years with minimum age of 9 years and maximum of 64 years. Five patients presented as rapidly progressive glomerulonephritis (RPGN), four with nephritic-nephrotic syndrome and three had pure nephrotic syndrome with normal eGFR.

**Full house diffuse proliferative glomerulonephritis**

Among the 81 patients, 10 patients were found to have diffuse proliferative glomerulonephritis (DPGN) on light microscopy. Mean age was 32 years with youngest patient being 9 years and oldest 62 years of age. Males were 6 in number and females were 4. 5 patients presented as nephrotic syndrome, 2 patients presented as acute nephritic syndrome, one patient had a mixed nephritic-nephrotic picture and 2 patients presented as chronic glomerulonephritis.

**Full house crescentic glomerulonephritis**

All patients with full-house nephropathy (FHN) with >50% crescents were taken in this group. A total of 10 patients out of 81 FHN patients were identified with youngest being 23 years, the oldest being 73 years old. There were 6 males (60%) and 4 females (40%). These full-house crescentic glomerulonephritis (CrGN) were 50% type 1 (Anti-GBM CrGN) and 50% type 2 (immune-complex CrGN).

**Amyloidosis with full house on immunofluorescence**

A total of 7 patients with amyloidosis and full-house immunofluorescence were seen with youngest patient being 32 years old and oldest patient being 65 years old, and a mean age of 48 years. 5 were males and 2 were females. AL amyloidosis was present in only 2 patients, while secondary amyloidosis was present in 5 patients.

**Full house C1Q nephropathy**

C1Q nephropathy diagnosis requires ≥2+ (on a scale of 0 to 4+) immunostaining for C1Q with a predominantly mesangial distribution, frequently accompanied by IgG and IgM, which may be less intense, equally intense, or more intense, in patients without evidence of SLE. Only 3 patients (male, n = 1 and female, n = 2) satisfied the diagnostic criteria of C1Q nephropathy. One male patient (age; 40 years) had proliferative glomerulonephritis and two female patients (age; 11 and 24 years each) had minimal change glomeruli in light microscopy.

**Discussion**

The prevalence of non-lupus FHN in our study was 19.4% which was in accordance with another study conducted by Emilie C. Rijnink, et al. (2017) in which 32 of 149 (21%) patients had non-lupus FHN.[9] Earlier, another study had described non lupus FHN in 28 out of 94 (30%) patients with FHN.[7] Most common light microscopy diagnosis was Membranous nephropathy (25.9%), followed by IgAN (22.2%), MPGN (14.8%), DPGN (12.3%), Crescentic GN (12.3%), Amyloidosis (8.6%) and C1Q nephropathy (3.7%).

For many decades now, it is being recognized that there is a group of patients with membranous nephropathy (MN) who have pathological features suggestive of Lupus membranous Nephropathy but don’t satisfy diagnostic criteria of systemic lupus erythematosus (SLE). In 1964, Simenhoff and Merrill even called these patients as having renal-limited SLE.[10] This non-lupus full house MN was observed by Wen YK, et al. (2010) as the most common cause of full-house nephropathy not due to lupus nephritis.[7]

Non-lupus full-house membranous nephropathy was the largest subgroup in our study also, in which 21 out of 81 patients (25.9%) had Membranous Nephropathy (MN) with full house pattern without the diagnosis of SLE. All patients in this group had primary membranous nephropathy as their etiological diagnosis, except for one patient who had concomitant hepatitis B infection which was incriminated as a secondary cause for his membranous nephropathy. Secondary cause was presumed in view of increased mesangial matrix and cellularity besides thickened capillary walls in glomeruli. Except for this case where IgM was dominant in immunofluorescence, rest all other cases had IgG predominance. Renal biopsy findings in HBV associated MN are marked by the presence of multiple findings more typical of a secondary form of disease, including features that overlap with membranous Lupus Nephritis. Lai et al.[11] reviewed the renal biopsy finding in 22 patients with HBV MN and found that immunofluorescence positivity for IgG and C3 was present in all cases, similar to primary MN. In contrast to primary MN, however, staining for IgM, IgA, and C1Q were each present in 16 of 22 cases (73%).

**Fullhouse immunoglobulin A nephropathy**

These patients with Mesangial Proliferative light microscopy glomerular lesions and dominance/codominance of IgA on immunofluorescence comprised the second most common group of FHN patients in our study. This was in concordance with other studies,[6,7] where IgA was also the second most common cause of FHN and that conducted by Jones E, et al. (1982).[12] where full house immunostaining was seen in patients with idiopathic ‘focal’ (mesangio) proliferative glomerulonephritis. Among 18 patients,
2 patients were suspected to have Infection related GN (IRGN) in view of synfebrile nephrotic syndrome and IgA dominant mesangial and endocapillary proliferation. One patient was a 10-year-old boy who presented with nephrotic syndrome and had history of fever at the onset. Another patient with similar febrile history had nephritic-nephrotic presentation and DPGN pattern renal lesions on light microscopy. Both of these glomerular illnesses started with fever and recovered on their own without use of steroids or immunosuppression.

In the remaining 16 patients, idiopathic IgA nephropathy was presumed in view no secondary cause could be found. Only 2 out of the 16 patients had asymptomatic sub nephrotic proteinuria with active urinary sediment and normal GFR. Among the rest 14 symptomatic patients, one patient presented with nephrotic-nephritic picture associated with skin rash in both lower limbs, polyarthralgia’s and pain abdomen consistent with Henoch-Schoenlein Purpura. This male patient recovered after receiving steroids which were tapered over 6 months. Three patients had rapidly progressive GN (RPGN) presentation and crescentic transformation of glomeruli in light microscopy (percentage of crescents being 50%, 50% and 28% respectively). 6 patients presented with nephrotic syndrome and five patients had moderate to advanced renal failure with sub nephrotic proteinuria and active urinary sediment. Of the latter, two patients had to be started on renal replacement therapy. The higher incidence of nephrotic/nephritic syndrome in our group of full house IgAN can be postulated because of higher IgA immune complex deposition in mesangium. Same can be postulated for higher percentage of crescentic IgAN (3/16 = 18.7%).

**Full house membranoproliferative glomerulonephritis**

Membranoproliferative glomerulonephritis (MPGN) as the third most common group of non-lupus full house nephropathy patients was consistent with a study done by Wen YK et al. (2010). Among 12 patients, 5 patients presented as rapidly progressive glomerulonephritis (RPGN), 4 with nephritic-nephrotic syndrome and 3 had pure nephrotic syndrome with normal eGFR. Patients with RPGN had all shades of crescentic transformation from no crescents to 9%, 14%, 15% and 25%, respectively. Among these RPGN patients one patient who had full house MPGN in histology also had high anti-PR3 ANCA and 15% crescentic transformation in biopsy. There were no features suggestive of ANCA associated vasculitis. Even the biopsy didn’t have features of focal necrotizing glomerulonephritis. This high percentage of RPGN in full house MPGN further supports the hypothesis that full house nephropathies including MPGN can be aggressive in nature even in the absence of crescentic transformation of much significance (that is <50%). However, it needs to be validated in further studies.

2 patients, a 30-year-old male and a 15-year-old female, had presented with nephritic-nephrotic syndrome onset preceded by skin rash in both lower limbs and fever around 10-15 days of onset of edema. These 2 cases were presumed to be post-infectious GN.

One patient, a 36-year-old male, had syndromic presentation with nephrotic syndrome along with chylous ascites, coloboma both eyes and marfanoid features. To our knowledge, no such case has ever been described in literature.

**Full house diffuse proliferative glomerulonephritis**

Among 10 patients with diffuse proliferative glomerulonephritis (DPGN), 7 were idiopathic and 3 patients had features suggestive of post-infectious glomerulonephritis (PIGN) like fever, sore-throat/skin rash, latency period and positive ASO titres or blood cultures. Whereas idiopathic DPGN presented predominantly as nephrotic syndrome, PIGN had acute nephritic presentation predominantly and all three cases had history of fever preceding the onset of nephritic syndrome at intervals varying between 13 to 20 days.

**Full house crescentic glomerulonephritis**

All patients with full house nephropathy (FHN) with >50% crescents were taken. Out of 10 patients, 5 patients (50%) had high titres of Anti-GBM antibody in blood along with linear staining of IgG along the capillary wall. Ours is the first study to find cases of Anti-GBM CrGN with full house immune deposition. None of these patients, except one patient, were ANCA positive. Besides testing positive for anti-MPO ANCA antibody, this patient also tested positive for Anti-GBM in blood. Since immunofluorescence showed linear deposition of IgG, this double positive CrGN was more of an Anti-GBM disease than ANCA associated GN. Nevertheless, previous reports have demonstrated convincingly that glomerular immune complexes may be present in ANCA-associated GN, and they may act synergistically with ANCA to produce more severe GN than seen with either immune complexes or ANCA alone. The remaining 5 patients (50%) had type 2 (immune-complex) CrGN. Among these patients, 2 patients had fever followed by onset of RPGN after a latency period of around 10 days and these 2 cases were classified as PIGN with crescentic transformation. Rest of the three patients were classified as idiopathic full house CrGN in view no etiology could be discerned.

**Amyloidosis with full house on immunofluorescence**

Ours is the first study to see full house immune deposition in cases of renal amyloidosis. we couldn’t find any case report/series with concomitant amyloid deposits and full house immunofluorescence. Among 7 patients with amyloidosis and full house immunofluorescence, AL amyloidosis was present in only 2 patients and Secondary
amyloidosis was present in 5 patients. This finding is inconsistent with the epidemiology of systemic amyloidosis where AL amyloidosis outnumbers all other types of amyloidosis including AA amyloidosis. Mean age of patients with primary amyloidosis was 51 years, whereas secondary amyloidosis patients were younger with mean age around 46 years.

In primary amyloidosis, both patients had lambda light chain monoclonal gammopathy. One patient had IgG Lambda monoclonal gammopathy and another patient had IgA Lambda biclonal gammopathy. Both of these patients had around 8-10% plasma cells in bone marrow.

Among secondary amyloidosis, 2 patients had sputum smear positive pulmonary tuberculosis with one patient having onset of tuberculosis symptoms only 6 months back whereas other one had sputum smear positive tuberculosis for 5 years with history of noncompliance initially and later on treatment failure likely due to multi drug resistant tuberculosis. One patient of ankylosing spondylitis for 20 years had history of Non-Steroidal Anti-inflammatory Drug abuse and infliximab therapy. In another patient secondary nature of renal amyloidosis was suggested by deposits showing KMN04 sensitive apple green birefringence under polarised light. One patient, 65-year-old female, had amyloidosis coexisting with membranous nephropathy (argyrophilic epitubular spikes of glomerular basement membrane on silver stain) with no specific etiology. To our knowledge, no such case with concomitant amyloidosis and membranous nephropathy is on record in literature.

Full house C1q nephropathy

C1Q nephropathy was diagnosed in only 3 patients. One patient of 40 years age had C1Q nephropathy with proliferative glomerulonephritis who had presented as RPGN and advanced renal insufficiency for which haemodialysis was given. Pulse methylprednisolone was given and oral steroids were continued after 3 pulses of methylprednisolone. Patient showed recovery and was discharged on steroids. Meanwhile his steroid doses were tapered in view of steroid toxicity and mycophenolate mofetil (MMF) was added. Patient developed a nephritic flare after one year when his MMF dose was tapered and after increasing his MMF dose from 1000 mg/d to 2000 mg/d he again achieved complete remission.

Another two patients both of who were females of 11 and 24 years each had C1Q nephropathy with unremarkable glomeruli (minimal change phenotype) on light microscopy. The elder one, a 24-year-old, had presented with nephrotic syndrome and was put on steroids after biopsiy. She was steroid resistant and continued with severe nephrosis and later on died of spontaneous bacterial peritonitis causing severe sepsis. Another patient of 11 years age was biopsied for primary steroid resistant nephrotic syndrome. Both of these patients had primary steroid resistant nephrotic syndrome.[15,16]

Conclusion

In the absence of SLE, full-house nephropathy otherwise suggestive of lupus nephritis can also be found in a number of other conditions. Non-lupus full-house nephropathy is an umbrella term for such cases which do not satisfy the standard criteria of SLE. This will prevent misclassifying these patients into SLE and further prevent them from unnecessary immunosuppression protocols. However, these patients should be followed up closely because a minority of them would turn to be SLE after a variable time. The heterogeneity of non-lupus full-house nephropathy can further be homogenized by classifying these patients as per the groups suggested above. Further treatment protocols can be tested in these individual groups for comparison.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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