

# Renal involvement in rheumatoid arthritis: analysis of 53 renal biopsies

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## ABSTRACT

**Background:** Rheumatoid arthritis (RA) is a systemic inflammatory disorder characterized by joint inflammation, associated with autoantibody production. Renal involvement arises as a complication of treatment or can be related to the disease itself.

**Methods:** 53 biopsies from patients with RA from 1989 to 2015 were reviewed. Histologic diagnosis, age, gender, duration of RA, drug therapy, renal function, proteinuria and haematuria were analyzed.

**Results:** Amyloidosis was the most common renal histologic pattern (21 patients). Membranous Nephropathy (MN) was found in 12 patients, followed by Mesangial Proliferative Glomerulonephritis (n=4) and Focal and Segmental Glomerulosclerosis (n=4), IgA Nephropathy (n=3), Necrotizing Glomerulonephritis (n=3), Chronic Interstitial Nephritis (n=3), Endocapillary Proliferative Glomerulonephritis (n=2) and Minimal Change Disease (n=1). Amyloidosis correlated with long duration RA ( $14.9 \pm 6.66$  years vs  $8.84 \pm 6.37$  years;  $p < 0.001$ ), presenting with nephrotic proteinuria in the majority of the cases ( $5.11 \pm 2.94$  g/24h vs  $3.52 \pm 2.71$  g/24h  $p = 0.03$ ), which correlates with dominant glomerular amyloid deposition ( $7.0 \pm 2.28$  g/24h vs  $3.04 \pm 2.08$  g/24h;  $p < 0.001$ ). In patients with MN, renal function was preserved (serum creatinine  $0.83 \pm 0.21$  mg/dl vs  $2.03 \pm 0.21$  mg/dl;  $p < 0.001$ ) and one third of the cases presented with haematoproteinuria. Disease modifying antirheumatic drugs (DMARDs) could be related with MN in six cases. Patients with Necrotizing Glomerulonephritis had a severe renal involvement, as did patients with Chronic Interstitial Nephritis.

**Conclusion:** We found a wide spectrum of histological lesions that cannot be predicted with only clinical and laboratory findings. Thus, renal biopsy is essential to ensure correct diagnosis in RA patients who present with urinary abnormalities or deteriorated renal function.

**Key-words:** Glomerulonephritis, renal biopsy, rheumatoid arthritis.

## INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disorder that affects primarily the joints. Extra-articular involvement may also occur, with appearance of rheumatoid nodules, pulmonary interstitial fibrosis, pulmonary nodules, pericarditis, mononeuritis multiplex, episcleritis and systemic vasculitis<sup>1</sup>. Renal findings in RA can be divided into three categories: secondary amyloidosis related to serum amyloid A protein (SAA); complications

of treatment with disease modifying antirheumatic drugs (DMARDs), analgesics or non-steroidal anti-inflammatory agents (NSAIDs); renal disease related to RA itself or with an autoimmune predisposition<sup>2</sup>. The incidence of renal disease in RA is relatively low, but it causes significant morbidity and mortality, especially if renal amyloidosis is present<sup>3,4</sup>.

Renal histopathologic lesions are heterogeneous and cannot be predicted with clinical and laboratory

findings only. Thus, renal biopsy plays a key role in ensuring correct diagnosis. In this study we analyzed renal involvement in 53 patients with RA.

## PATIENTS AND METHODS

We studied renal biopsies of 57 patients, received by our laboratory from January 1989 to December 2015. The diagnosis of RA was made in line with the 2010 RA classification criteria of the American College of Rheumatology/European League Against Rheumatism. We excluded four patients because their renal pathology was probably not related with RA or DMARDs – one patient with normal kidney, one patient with hypertensive nephroangiosclerosis, one patient with cast nephropathy and one patient with sclerotic lesions that could not be included in any histological diagnosis. Thus, we had a representative sample of 53 patients (34 female and 19 male). The mean age of the patients was  $53.81 \pm 15.91$  years (range 16-87 years) and the mean RA duration was  $11.2 \pm 57.06$  years (range 2-30 years).

Proteinuria was defined as protein urinary excretion of more than 300mg/24h and haematuria was defined as urine sedimentary red blood cell counts of more than five in the visual field of a x400 microscope.

Renal biopsy specimens were examined by light microscopy (LM) and immunofluorescence (IF). Electron microscopy was performed only in a patient who had a diagnosis of minimal change disease (MCD). The LM analysis was performed after staining with haematoxylin and eosin (HE), periodic acid Schiff (PAS), periodic acid methenamine silver (PAM), Masson's trichrome and Congo-red. The IF evaluation was performed in frozen sections using fluorescein isothiocyanate conjugated antisera to human immunoglobulins (IgG, IgA, IgM), light chains ( $\lambda$  and  $\kappa$ ), complement (C1q, C3), and fibrinogen. Amyloid substance was characterized using immunofluorescence or immunohistochemistry staining for SAA or  $\kappa$  and  $\lambda$  light chains.

We searched for a relationship between renal histologic findings and clinical data, such as gender, age, serum creatinine (Scr) and glomerular filtration rate estimated (eGFR) by Modification of Diet in Renal Disease (MDRD) study equation, haematuria, proteinuria, duration of RA and predominant location amyloid deposits (glomerular vs vascular).

Statistical analysis was performed using SPSS, version 22. We used mean and standard deviation to

characterize quantitative variables, and qualitative variables were analyzed using absolute and relative frequencies. The relationship between qualitative variables was accessed with the chi-square test. Quantitative variables were analyzed using the Mann-Whitney and Kruskal-Wallis tests. Non-parametric methods were used because of sample size and distribution type of quantitative variables. A p value of  $<0.05$  was considered significant.

## RESULTS

### Renal histology

The most frequent diagnosis was renal amyloidosis (n=21). Twelve patients had membranous nephropathy (MN) and the remaining patients had heterogeneous renal findings, with similar frequency (Table I).

All patients had proteinuria, however only 14 (26.4%) had microhaematuria (haematoproteinuria group). The relation between urinalysis and renal histopathologic findings are shown in Graphic I.

Mean Scr, eGFR and duration of RA varied according to the underlying histologic pattern, while age and degree of proteinuria were similar between groups. (Table II).

Proteinuria was equal or more than 3.5g/24h in 49% patients (n=26) and, in this group, 19 patients had also nephrotic syndrome (Table III).

**Table I**

Renal histopathologic findings

	Female	Male	Total
Amyloidosis	17 (50.0%)*	4 (21.1%)	21 (39.6%)
MN	6 (17.6%)	6 (31.6%)	12 (22.6%)
MesGN	2 (5.9%)	2 (10.5%)	4 (7.5%)
FSGS	2 (5.9%)	2 (10.5%)	4 (7.5%)
Necrotizing GN	2 (5.9%)	1 (5.3%)	3 (5.6%)
IgA nephropathy	1 (2.9%)	2 (10.5%)	3 (5.7%)
CIN	2 (5.9%)	1 (5.3%)	3 (5.7%)
EPGN	1 (2.9%)	1 (5.3%)	2 (3.8%)
MCD	1 (2.9%)	0 (0%)	1 (1.9%)
Total	34 (100%)	19 (100%)	53 (100%)

MN – Membranous nephropathy; GN – Glomerulonephritis; MesGN – mesangial proliferative glomerulonephritis; FSGS – focal and segmental glomerulosclerosis; CIN – chronic interstitial nephritis; EPGN – endocapillary proliferative glomerulonephritis; MCD – minimal change disease; \*p<0.05 ( $\chi^2$ -test).

**Table II**

Renal histopathologic findings and association with age, creatinine, eGFR and proteinuria.

	Age (years)	Duration (years)	Creatinine (mg/dl)	eGFR (ml/min/1.73m <sup>2</sup> )	Proteinuria (g/24h)
Amyloidosis	56.48±17.69	14.90±6.66	1.67±1.16	57.29±39.58	5.11±2.94
MN	47.00±14.96	6.92±3.02	0.83±0.21	99.00±8.31	4.62±3.78
MesGN	57.25±7.89	8±5.03	2.15±0.90	44.25±21.36	3.55±2.00
FSGS	55.50±15.35	8±7.41	1.25±0.24	57.5±11.27	3.38±1.69
Necrotizing GN	66.00±10.54	20±8.72	3.90±1.01	13.33±4.73	2.40±1.15
IgA nephropathy	46.67±24.01	9.79±10.73	2.43±1.86	46.67±34.02	2.07±0.90
CIN	58±7.00	9.72±4.61	3.90±2.00	21.67±18.58	1.60±1.22
EPGN	39.00±12.73	8±7.07	3.15±2.76	41.00±42.43	4.10±1.27
MCD	61.00	2	0.80	77.50	12
Kruskal-Wallis (p-value)	p=0.351	p=0.003	p=0.002	p<0.001	p=0.270

MN – Membranous nephropathy; GN – glomerulonephritis; MesGN – mesangial proliferative glomerulonephritis; FSGS – focal and segmental glomerulosclerosis; CIN – chronic interstitial nephritis; EPGN – endocapillary proliferative glomerulonephritis; MCD – minimal change disease; eGFR – estimated glomerular filtration rate by Modification of Diet in Renal Disease (MDRD) study equation.

**Table III**

Relation between renal histology and proteinuria

	Proteinuria <3.5g/24h	Proteinuria ≥3.5g/24h
Amyloidosis	8 (29.6%)	13 (50.0%)
MN	6 (22.2%)	6 (23.1%)
MesGN	2 (7.4%)	2 (7.7%)
FSGS	1 (3.7%)	3 (11.6%)
Necrotizing GN	2 (7.4%)	1 (3.8%)
IgA nephropathy	3 (11.1%)	0 (0%)
CIN	3 (11.1%)	0 (0%)
EPGN	1 (3.7%)	1 (3.8%)
MCD	1 (3.7%)	0 (0%)
Total	27 (100%)	26 (100%)

MN – Membranous nephropathy; GN – glomerulonephritis; MesGN – mesangial proliferative glomerulonephritis; FSGS – focal and segmental glomerulosclerosis; CIN – chronic interstitial nephritis; EPGN – endocapillary proliferative glomerulonephritis; MCD – minimal change disease.

**Table IV**

Relation between renal histology and serum creatinine

	Creatinine <1.5mg/dl	Creatinine ≥1.5 mg/dl
Amyloidosis	11 (34.4%)	10 (47.6%)
MN	12 (37.5%)	0 (0%)
MesGN	3 (9.4%)	1 (4.8%)
FSGS	3 (9.4%)	1 (4.8%)
Necrotizing GN	0 (0%)	3 (14.3%)
IgA nephropathy	1 (3.1%)	2 (9.5%)
CIN	0 (0%)	3 (14.3%)
EPGN	1 (3.1%)	1 (4.8%)
MCD	1 (3.1%)	0 (0%)
Total	32 (100%)	21 (100%)

MN – Membranous nephropathy; GN – glomerulonephritis; MesGN – mesangial proliferative glomerulonephritis; FSGS – focal and segmental glomerulosclerosis; CIN – chronic interstitial nephritis; EPGN – endocapillary proliferative glomerulonephritis; MCD – minimal change disease.

**Graphic I**

Distribution of histologic diagnosis according with urinalysis. MN – Membranous nephropathy; GN – glomerulonephritis; MesGN – mesangial proliferative glomerulonephritis; FSGS – focal and segmental glomerulosclerosis; CIN – chronic interstitial nephritis; EPGN – endocapillary proliferative glomerulonephritis; MCD – minimal change disease.

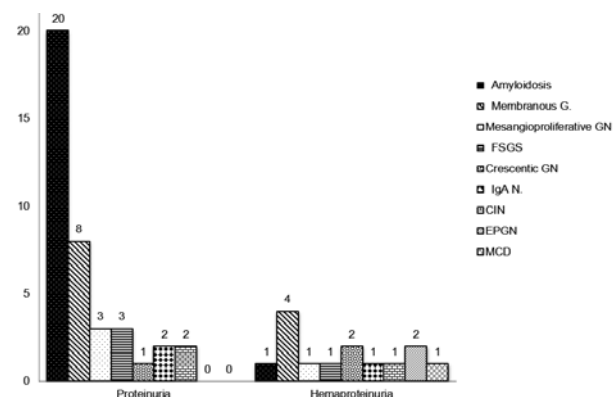


Table IV represents the relationship between renal function and renal histology. Twenty-one patients had Scr ≥1.5mg/dl, and the majority of them had renal amyloidosis (n=10). All patients with MN had Scr <1.5mg/dl. In contrast, patients with Chronic Interstitial Nephritis and Pauci-immune Necrotizing GN had Scr ≥1.5mg/dl.

## ■ Clinical and pathologic features of each histologic pattern

### 1. Amyloidosis

Amyloidosis was the most frequent renal finding (39.6%). Only amyloid A deposits were detected (AA amyloidosis). The majority of these patients were

female ( $n=17$ ;  $p=0.03$ ), and presented mostly with nephrotic proteinuria ( $5.11\pm 2.94$  g/24h vs  $3.52\pm 2.71$  g/24h;  $p=0.03$ ), including 12 with nephrotic syndrome. Only one patient presented with haematuria. This diagnosis mainly occurred in patients with long duration RA ( $14.9\pm 6.66$  years vs  $8.84\pm 6.37$  years;  $p<0.001$ ) and in older patients ( $56.48\pm 17.69$  years), but renal function was only slightly deteriorated: Scr  $1.67\pm 1.16$  mg/dl and eGFR  $57.29\pm 39.58$  ml/min/1.73m<sup>2</sup>. Amyloid deposits were located in glomeruli, arteries and interstitium (two cases). The patients with dominant glomerular amyloid deposition ( $n=11$ ) had significantly higher levels of proteinuria ( $7.0\pm 2.28$  g/24h vs  $3.04\pm 2.08$  g/24h;  $p<0.001$ ) and more severe deterioration of renal function ( $2.03\pm 1.41$  mg/dl vs  $1.28\pm 0.68$  mg/dl;  $p=0.173$ ), than those with predominantly vascular deposits.

## 2. Membranous Nephropathy

MN was diagnosed in 12 patients. All patients had proteinuria (six in nephrotic range, but only four patients had nephrotic syndrome) and four also had microhaematuria. Renal function was mostly preserved and all patients were biopsied with Scr  $<1.5$  mg/dl ( $0.83\pm 0.21$  mg/dl vs  $2.03\pm 0.21$  mg/dl;  $p<0.001$ ). MN occurs in younger patients ( $47\pm 14.96$  years) with short duration RA ( $6.91\pm 3.03$  years). MN appeared to be related with penicillamine in two cases and with gold sodium thiomalate in four cases. According to Ehrenreich and Churg's classification, two patients had MN in stage I, and ten patients in stage II. All six patients with MN associated with DMARDs were lost to follow-up. Circulating anti-phospholipase A2 receptor autoantibodies were found in the remaining six patients. With regard to the treatment, all these patients achieved complete remission (proteinuria  $<300$  mg/24h): two patients with a 1-year treatment with cyclosporine; four patients with 6-month treatment with cyclophosphamide. No relapses were detected.

## DISCUSSION

The renal histologic findings found in this study were similar to that reported in previous studies<sup>5-9</sup>. AA Amyloidosis was the most common diagnosis, followed by MN. Reported as the most frequent diagnosis in several studies, we found MesGN only in 7.5% of cases, presenting with proteinuria in three cases and haematoproteinuria in one case. Both patients with nephrotic proteinuria were treated with gold sodium thiomalate. Korpela *et al.* reported 23 patients with MesGN that presented with haematuria (ten patients), isolated

proteinuria (six patients) and haematoproteinuria (seven patients) with normal renal function in most of the cases. They determined that mesangial lesion presenting with proteinuria was associated to DMARD (mainly gold and penicillamine) and was reversible on drug withdrawal. However, the mesangial proliferation presenting with isolated haematuria was not linked to any therapy and was persistent, even with discontinuation of DMARD<sup>10</sup>. By IF evaluation, our cases of MesGN had mainly IgM with few mesangial deposits of C3 and it was similar to other previous reports. In 40 cases of MesGN reported by Helin *et al.*<sup>8,10</sup>, mesangial deposits were mainly IgM (12 specimens), associated with lesser amounts of IgA, IgG and C3. In RA, the high levels of IL-6<sup>11</sup> promote proliferation of mesangial cells and it has been proposed as a pathogenic pathway to explain mesangial proliferation in kidneys of RA patients<sup>12</sup>. Pollet *et al.* found association between IgM rheumatoid factor (IgM-RF) and MesGN, and suggested that mesangial lesions are a consequence of a functional response by renal mesangium to remove immunocomplexes formed by IgM-RF and IgG<sup>13</sup>. We detected elevated titers of serum rheumatoid factor, but its immunoglobulin class was not evaluated.

We described three patients with IgA Nephropathy who had elevated serum IgA levels and elevated rheumatoid factor (not characterized). IgA nephropathy has been associated with RA due to: (1) common pathogenic pathways, including HLA-DR4<sup>14</sup>; (2) increased IgA levels in both diseases<sup>15</sup>; (3) IgA-rheumatoid factor<sup>16</sup>.

AA amyloidosis was the most frequent diagnosis in our case series. These patients had higher levels of proteinuria and, rarely, haematuria, and occurred mainly with long-duration RA. As expected, in cases of glomerular dominant amyloidosis, proteinuria was higher than in patients with dominant vascular deposits. Compared to previous studies, we report a higher frequency of amyloidosis. This is explained by many reasons: (1) the main indication for renal biopsy was proteinuria; (3) patients were older; (2) patients had a long duration RA. However, analyzing the last 10 years, we found only 1 patient with AA amyloidosis. The incidence of amyloidosis in RA patients seems to be decreasing, possibly as consequence of more effective inflammation control with new therapeutic agents<sup>17</sup>. There is no specific treatment for AA amyloidosis, but control of inflammation can lead to better outcomes. If the level of SAA is maintained at less than 10mg/L, the 10-year survival rate increases to 90%, but when SAAL levels are more than 10mg/L, this rate decreases to less than 40%<sup>18</sup>. Recently, anti-TNF- $\alpha$

agents etanercept<sup>19</sup>, infliximab<sup>20</sup>, and tocilizumab (a humanized anti-IL-6 receptor antibody)<sup>21</sup> have shown efficacy in the treatment of RA-associated AA amyloidosis. A promising drug is eprodisate, a sulfonated molecule with structure similar to heparin sulfate, which competitively binds to glycosaminoglycan-binding sites on SAA and inhibits fibril polymerization and amyloid deposition. A recent randomized clinical trial showed that eprodisate may reduce progression in AA amyloidosis<sup>22</sup>.

The second most frequent diagnosis was MN (22.6%). In half of patients, MN seems to be associated with DMARD (4 with gold sodium thiomalate and 2 with penicillamine). In our experience, the patients with MN had normal renal function in accordance with other studies. *Makino et al.* described 100 patients with RA and renal disease. Thirty-one patients had MN and presented with preserved renal function. Twenty-four cases of MN were presumptively related with DMARD<sup>23</sup>. Gold therapy (oral or parental administration) is complicated with proteinuria in 10% of patients and about 85% of patients develop proteinuria (range 0.7g – 30g) within the first 24 months of treatment, including nephrotic syndrome in one third of cases (in our study 4 of 12 patients had nephrotic syndrome)<sup>24,25</sup>. In most of the cases, the proteinuria remits when DMARDs are stopped, but in some cases the proteinuria persists<sup>26</sup>. Proteinuria can be detected in about 30% of patients treated with penicillamine and resolves after drug withdrawal<sup>27</sup>. MN associated with penicillamine and gold has the same histologic pattern as idiopathic MN. The pathogenesis in both cases is unknown, but it was proposed an association with HLA-DRw3 and HLA-B8<sup>28</sup>. Gold is a tubular toxin and, in one study, it was suggested that damaged tubules could release antigens that induce an autoantibody response to related podocyte proteins<sup>29</sup>.

Necrotizing GN was found in three patients and all had positive MPO-ANCA. It has been described the association between necrotizing GN and RA, and the majority of these patients had positive MPO-ANCA and extra-renal manifestations<sup>30</sup>. This type of renal limited vasculitis has also been described in association with penicillamine<sup>31</sup> and anti-TNF- $\alpha$  agents<sup>32</sup>. In our experience, all patients responded well to the treatment (two cases treated with cyclophosphamide and one case successfully treated with rituximab).

Chronic Interstitial Nephritis is historically correlated with NSAIDs and analgesic consumption. Our three cases presented with low-grade proteinuria, reflecting

slight glomerular damage, probably secondary to severe tubular lesions. Lack of alterations in urinalysis delay the diagnosis, which could explain why this group of patients had higher Scr. Although only three patients were diagnosed with Chronic Interstitial Nephritis, tubule-interstitial lesions were detected in 35 patients, characterized by tubular atrophy (52%), mononuclear cell infiltration (32%) and interstitial fibrosis (78%), explained not only by nephrotoxicity of NSAIDs and analgesic drugs, but also by cyclosporine and, at least, by massive proteinuria secondary to glomerular lesions.

Our work has several limitations. This is a retrospective study and the analysis is based on biopsies performed on the basis of clinical criteria and does not represent the entire renal pathology in RA patients. Another important limitation concerns the absence of analysis by electron microscopy.

This study shows that kidney disease in RA patients has a wide spectrum. Renal biopsy is essential to diagnosis and prognosis for the reason that isn't possible predict with good accuracy histologic findings only with clinical and laboratory data. Over the last decade, the understanding of RA pathogenesis has led to the development of new biologic agents, which have dramatically changed the treatment, with improvements in RA symptoms, slowed disease progression and improved physical function and quality of life for patients<sup>33</sup>. It's expected that the effective control of disease can lead to the avoidance of renal complications of chronic systemic inflammation, such as secondary amyloidosis, and change the incidence of renal disease in RA.

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