

Diagnostic and prognostic role of renal histopathology in rheumatic diseases

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SUMMARY

The objective was to evaluate renal involvement in several rheumatic diseases (*i.e.* rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, systemic sclerosis, systemic vasculitides).

The method chosen was to define histopathological profiles reported in renal biopsies performed on patients with renal involvement due to different rheumatic diseases.

Renal involvement observed in patients with rheumatic disease can be the direct result of the disease *per se* and/or a complication of drugs used in the disease treatment. The clinical-pathological correlations derived from the study of renal tissues can be useful for differential diagnosis, prognosis assessment and therapeutic decisions.

Renal biopsy should be considered as an important tool for the management of nephropathies in patients with systemic rheumatic diseases.

Key words: Renal involvement; Renal histopathology; Renal biopsy; Lupus glomerulonephritis; Autoimmune Rheumatic diseases.

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■ INTRODUCTION

Renal insufficiency, regardless of the etiology, is a well-known predictor of mortality. Several rheumatic diseases are associated with unequivocal and often severe renal involvement. However, especially for mild renal damage, it is not clear whether it results from the disease itself or whether it arises from the drug treatment of the disease, or both (1). In addition, renal co-morbidity (*i.e.* hypertension, diabetes mellitus, malignancy) is common in patients with rheumatic diseases (2).

■ RHEUMATOID ARTHRITIS

Urinary abnormalities and impaired renal function are reported in up to 30% of patients with rheumatoid arthritis (RA) (3, 4). In renal biopsies from RA patients, the most common histological findings are mesangial glomerulonephritis (GN), membranous nephropathy and secondary amyloidosis. These lesions have been related

to chronic inflammation and drug toxicity, but no specific renal disease is considered a specific manifestation of RA.

Mesangial GN is found in 20-40% of renal biopsies from RA patients and it is characterized by proliferation of mesangial cells (5-11). Immunofluorescence (IF) shows mesangial deposits of immunoglobulins and complement: IgM (33-78%), IgA (8-57%) and C3 (8-40%) (10-12). According to some Japanese studies, IgA-positive mesangial GN has peculiar associations, such as young age and severe haematuria; however, these observations were attributed to a population bias (8, 10). Mesangial GN is the most common histological pattern in biopsies from patients with haematuria but with normal renal function (10-13).

Membranous nephropathy is reported in one third of renal biopsies (5-11, 14, 15). Histology shows diffuse subepithelial deposits of IgG, with marked podocytic lesions and mesangial expansion (10, 11). The prevalence of membranous nephropathy increased between 1980 and 2010 due

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to the large use of disease-modifying anti-rheumatic drugs (DMARDs) (8, 14). The association with DMARDs is confirmed in more than half of the cases, particularly with gold salts, penicillamine and bucillamine (6-11, 15, 16). Membranous nephropathy is mostly observed in patients with normal renal function undergoing biopsy because of proteinuria (10, 11).

Frequency of renal amyloidosis decreased after the introduction of new effective treatments in RA (16-18). In recent studies, its frequency is 19-37% but amyloid deposits are found in almost all renal biopsies from RA patients with long disease duration (5, 7, 8, 11, 12, 14, 15). Decrease in mesangial cells and atrophy of vessels, tubules and interstitium are often associated with amyloid deposits in the glomerulus (10, 16). Thus, amyloidosis is the main cause of reduced renal function and of renal failure in RA patients (4, 8, 10, 11, 19).

Extracapillary GN is reported in 0-15% of RA renal biopsies (10, 11, 14, 20-23). Histology shows an extracapillary proliferation, necrotizing GN and, occasionally, crescents (11, 20, 21). The clinical manifestation is severe, with rapidly progressing renal impairment and it is often associated with systemic vasculitic manifestations, positive RF (in 60-90% of patients) and anti-neutrophil cytoplasmic antibody (ANCA) antibodies (in 20%) (11, 20, 21). A number of cases were related to treatment, specifically gold salts, penicillamine and *tumor necrosis factor- α* (TNF- α) inhibitors (24-28).

A minor percentage of renal biopsies from RA patients show only minimal morphological changes, mainly in the glomerulus (3, 5, 7, 10, 11, 14, 17). Other occasional findings are papillary necrosis, usually associated with non-steroidal anti-inflammatory drugs (NSAIDs) use, and nephrosclerosis which is frequent in autopsies of RA patients and is often the cause of renal failure (4, 24, 25). Rheumatoid nodules in the kidney cortex are an exceptional histopathological finding (29).

Tubulointerstitial changes, both acute and chronic, are reported as the main lesions in less than 10% of biopsies, but they can be

found in almost two thirds of RA patients (9-11, 14). Methotrexate precipitation in the renal tubules can cause acute kidney injury (2%) (27). The clinical presentation of chronic alterations, such as interstitial fibrosis and tubular atrophy, is impairment of renal function with no urinary abnormalities. These alterations are common in elderly patients with long disease duration but in some cases they are related to NSAIDs use (10, 28, 30).

Cyclosporine and

NSAIDs renal toxicity is not related to a specific histological pattern (31). Nevertheless, some severe renal alterations have been described with biological drugs, such as TNF- α inhibitors, tocilizumab and abatacept (24). TNF- α inhibitors might induce a variety of renal diseases, including GN, which is undistinguishable from lupus-like syndrome and usually recovers when the treatment is discontinued (24).

■ SYSTEMIC LUPUS ERYTHEMATOSUS

Lupus nephritis (LN) is among the most severe manifestations of systemic lupus erythematosus (SLE), occurring in up to 50-80% of patients, and can lead to end organ damage if not properly treated (32). Clinical manifestations are heterogeneous and often do not mirror the underlying histological abnormalities.

Histological lesions: glomeruli

Immune complexes (IC) are visible by IF and electronic microscopy (EM) and they are usually formed locally, triggering renal lesions according to the site of deposition (33, 34). Indeed, IC precipitation in the mesangium leads to activation of scavenging mesangial cells and secretion of extracellular matrix and cellular proliferation (35). IC localizing in the subendothelial space may directly harm endothelial cells and access the vascular space where they can activate the complement pathway and trigger recruitment of inflammatory cells (36-38). Conversely, IC deposition in the subepithelium is associated with less inflammation and podocyte damage, which can lead to

nephron loss and glomerulosclerosis due to the poor renewal capability of podocytes (33, 36, 39). *Wire loops* are defined as capillary wall thickening due to abundant subendothelial IC deposition (33). *Hyaline thrombi* are not real thrombi but IC gathering in the capillary lumen, usually associated with subendothelial IC (33).

Cellular proliferation indicates hyperplasia of glomerular cells, depending both on increase in native cell number and infiltrating inflammatory cells, seen by light microscopy (LM) (33). Hyperplasia is due to the pro-inflammatory activity of IC and can affect either the mesangial, endocapillary or extracapillary compartment. Mesangial proliferation does not involve glomerular capillaries, which remain patent and normocellular; conversely, endocapillary proliferation leads to obliteration of capillary lumen and is frequently associated with proliferative LN (33, 39). Extracapillary proliferation of resident and inflammatory cells takes place in the urinary space and may trigger formation of cellular crescents, which indicate persistent inflammation, and can themselves progress to fibrosis. Proliferative lesions are frequently associated with active glomerular lesions including fibrinoid necrosis and lesions of the glomerular basement membrane (GBM), which in severe cases may cause rupture of the capillary wall and haemorrhage in the Bowman space.

Histological lesions: tubule and interstitium

The tubule-interstitial compartment is extensively involved in LN: increased inflammation and especially fibrosis at this level correlate with reduced renal function (33, 39, 40). Initial lesions include the interstitial edema followed by interstitial fibrosis and tubular atrophy which indicate chronic damage; IC (IgG) deposition along the tubular basement membrane may be seen by IF or EM and correlate with glomerular IC deposition.

Renal arteries and arterioles are often affected by non-complicated IC deposition. However, more severe lesions are possible and include necrotizing lupus vasculopathy

caused by IC-mediated arteriolar obstruction as well as non-specific lesions such as glomerular vasculitis or thrombotic microangiopathy, or sclerotic lesions following uncontrolled hypertension (33).

Classification and prognostic utility of histology

Since 1974, several classification systems have been developed for LN, all converging on characterization of glomerular lesions; currently the chosen set is the ISN/RPS 2003 classification (Table I) (33-42). Despite several investigations into the role of a specific histological feature on patient outcome in the long term, data remain conflicting (42-44). Proliferative classes are considered the heralds of a more hazardous disease but they usually respond to initial therapy, while membranous class V may underlie a peculiar pathogenesis with a smoldering yet not harmless phenotype (45, 46). Moreover, according to more recent observations, it looks as if the point is not only the histological class the patient belongs to, but rather what is the ratio of chronic over active lesions and how extensive renal damage is, thereby considering not only glomerular but also tubular and vascular lesions (47, 48). Cellular and fibrous crescents, fibrinoid necrosis and interstitial fibrosis/tubular atrophy are indeed emerging as harmful markers of LN, which can lead to a worse prognosis including end-stage renal disease (43, 47, 49). Hence, a search for specific histological hallmarks as well as assessment of clinical parameters, especially baseline serum creatinine and urinary sediment, should always be added to histological classification in order to have a comprehensive picture of the patient's likely outcome (47, 50).

So far, renal biopsy still represents the gold standard for LN investigation and histology is a sufficient clinical criterion to classify patients as having SLE (51). Validated recommendations indicate as threshold for renal biopsy a persistently increased proteinuria >0.5 g/day especially in the presence of active urinary sediment (52). This notwithstanding, the value of renal biopsy was challenged in the past and it still is,

Table I - Classes of lupus glomerulonephritis and histological features according to ISN/RPS 2003 classification.

<i>Class I LN (minimal GN)</i>	Glomerular histology is normal at light microscopy, while some mesangial IC deposits are visible by IF or EM. There are no deposits along capillary walls (41).													
<i>Class II LN (mesangial GN)</i>	Mesangial proliferation can be seen by light microscopy, while IC mesangial deposits are seen by IF. Minimal IC deposits may also be found at a subendothelial level, although this is not a typical feature and has a controversial prognostic value (33, 41).													
<i>Class III LN (focal GN)</i>	<table border="1"> <thead> <tr> <th colspan="2">Lesions occurring in class III and IV are distinguished between Active (A) or Chronic (C)</th> </tr> </thead> <tbody> <tr> <td>Endocapillary hypercellularity with reduction in capillary lumen +/- leukocyte infiltrate</td> <td>Glomerulosclerosis</td> </tr> <tr> <td>Karyorrhexis</td> <td rowspan="2">Adhesions</td> </tr> <tr> <td>Fibrinoid necrosis</td> </tr> <tr> <td>GBM rupture</td> <td rowspan="3">Fibrous crescents</td> </tr> <tr> <td>Cellular or fibrocellular crescents</td> </tr> <tr> <td>Subendothelial deposits visible by light microscopy (<i>wire loops</i>)</td> </tr> <tr> <td>Endoluminal IC aggregates (<i>hyaline thrombi</i>)</td> <td></td> </tr> </tbody> </table>	Lesions occurring in class III and IV are distinguished between Active (A) or Chronic (C)		Endocapillary hypercellularity with reduction in capillary lumen +/- leukocyte infiltrate	Glomerulosclerosis	Karyorrhexis	Adhesions	Fibrinoid necrosis	GBM rupture	Fibrous crescents	Cellular or fibrocellular crescents	Subendothelial deposits visible by light microscopy (<i>wire loops</i>)	Endoluminal IC aggregates (<i>hyaline thrombi</i>)	
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<i>Class IV LN (diffuse GN)</i>	Glomerular lesions involve >50% of total glomeruli (diffuse) and are often global (i.e., they affect more than 50% of glomerular tuft). According to whether lesions are segmental or global, class IV can be divided into class IV-(S) and IV-(G), the clinical relevance of which is currently debated (42). In class IV, subendothelial deposits are widespread and more abundant than in class III, with a variable mesangial proliferation (41). Cellular crescents reflect a severe, long-lasting disease and are more commonly found in class IV. Cellular crescents may then progress to a fibrous grade (fibrous crescents) forming true synechiae in glomerulosclerosis (33).													
<i>Class V LN (membranous GN)</i>	This class is characterized by widespread subepithelial IC deposition, which triggers diffuse alterations of the GBM, consisting of a wide uniform thickening of capillary walls leading to the formation of a neomembrane. Mesangial proliferation is variable. Class V may be associated with class III or IV if subendothelial deposits and/or endocapillary proliferation are present at a high rate (39, 41).													
<i>Class VI LN (sclerohyaline GN)</i>	Glomerulosclerosis involves >90% of all glomeruli and is accompanied by marked interstitial fibrosis, tubular atrophy and chronic vascular damage. No active lesions are present (41).													

GN, glomerulonephritis; LN, lupus nephritis; IF, immunofluorescence; EM, electronic microscopy; GBM, glomerular basement membrane; IC, immune complexes.

especially when facing an acute clinical picture with active urinary sediment, sustained proteinuria, hypertension and/or swelling or clinical signs of renal insufficiency, where renal biopsy is endowed with procedural risks (53, 54). Conversely, when alterations are less prominent but persist despite treatment it is mandatory to know how active renal lesions are and thus how aggressive the therapy should be, so histological examination is frequently not yet dispensable.

■ SJÖGREN SYNDROME

Primary Sjögren syndrome (pSS) can involve the kidney with a prevalence ranging from 18.4% to 67% (55). Nevertheless, re-

nal involvement is frequently misdiagnosed due to different factors, such as the various classification criteria used by authors or the fact that tubular dysfunction, which is the most common alteration in pSS patients, is quite difficult to be recognized. The spectrum of pSS renal manifestations varies from isolated electrolyte disturbances to tubular interstitial nephritis (TIN) and acute or chronic GN. Since prognosis is reported to be good and favourable in most cases, kidney biopsy is not always encouraged, but it is strongly suggested for GN secondary to cryoglobulinemia and for differential diagnosis with other disorders (i.e. IgG4-related disease and sarcoidosis) (56). TIN is the most common kidney presentation in pSS (56-58). Clinically, it often

results in renal tubular acidosis with moderate, acute or more frequently chronic renal disease and/or tubular proteinuria (56, 58, 59). Histology shows an inflammatory infiltrate of B and T cells in the tubular-*interstitium*. When B cells are predominant (10% of cases), an anti-B cell therapy (*i.e.* Rituximab) can be suggested for pSS with renal involvement (56). However, literature findings are contrasting: in a recent study on 95 patients, Jasek et al. showed that plasma cells can be the predominant cellular lines (up to 25%), since they are detected in 75% of subjects with TIN (60). By contrast, another study observed that TIN mostly includes T cells, particularly T CD4+ (61). Apart from these findings, diagnosis is tricky, due to tubular loss of proteins, which is not usually assessed by urinary exams; moreover, TIN with tubular atrophy often leads to chronic renal disease, which is a very aspecific condition (55, 56, 60). Thus, a kidney biopsy is not mandatory to confirm a suspected renal tubular acidosis; however, when TIN is suspected, it should be performed to better define treatment and outcome (56, 59).

Another manifestation of renal involvement, though rarer than TIN, is acute or chronic GN, which occurs with haematuria, proteinuria, or even nephrotic syndrome (55, 59). Its incidence varies from 5% to 13.9% and it may often be associated with other rheumatic diseases (*i.e.* SLE or combined cryoglobulinemia); indeed, the majority of subjects with GN and pSS display IgM-containing cryoglobulins, along with low C4 levels (55, 62). Furthermore, the presence of C3 and IgM deposits in biopsy specimens further supports the idea that cryoglobulinemia might play a pathogenetic role for the development of GN in pSS (63). GN encompasses different entities: cryoglobulinemic membrane-proliferative GN, focal segmental glomerulosclerosis, mesangial proliferative GN, membranous nephropathy and minimal change disease; a single case of amyloidosis has also been recently reported (64, 65).

Membranoproliferative GN (type 1), secondary to cryoglobulinemia, occurs in up to 30% of patients with pSS and is the most

common GN in pSS (56, 60, 63). Unlike TIN, it can be easily suspected and diagnosed: it occurs with hypertension, proteinuria, haematuria, nephritic syndrome and rapidly progressive GN leading to acute renal failure (56). However, renal biopsy is essential to confirm cryoglobulinemia and for differential diagnosis with other glomerular lesions such as proliferative/membranoproliferative GN without cryoglobulinemia, where endoluminal thrombi, vasculitis and IgM sub-deposit are absent (66).

■ SYSTEMIC SCLEROSIS

Renal involvement is a rare but severe manifestation in patients affected with systemic sclerosis (SSc): it is more frequent in the cutaneous diffuse (4%) than in the cutaneous limited form (2%) of the disease (67).

The scleroderma renal crisis (SRC) is the principal renal manifestation observed in SSc, affecting 2-15% of patients in different cohorts (68-70). It is a life-threatening complication of SSc and has a 1-year mortality rate of 20-35% (71, 72). The frequency of SRC appears to be decreasing: in a recent analysis on 637 patients with diffuse cutaneous SSc with a disease duration <4 years from the *European League Against Rheumatism Scleroderma Trials and Research* (EUSTAR) cohort, it has been shown that the prevalence of SRC was only 2.4% (73, 74). SRC is defined by a severe or worsening arterial hypertension (>150/85 mmHg) and a rapidly progressive, acute deterioration of renal function, evolving in kidney failure (75, 76). Concomitant abnormalities supporting the diagnosis of SRC include oligoanuria, non-nephrotic proteinuria, haematuria, mechanic haemolytic anaemia, moderate thrombocytopenia, renal sodium overload or pulmonary edema (77).

The cause of SRC is still unknown: the characteristic vascular injury and fibrosis of SSc might represent the risk factors for SRC. The decreased renal perfusion due to vasculopathy is thought to contribute to SRC, but the exact trigger factors of SRC remain to be clarified. The absence of inflammatory infiltrates in renal biopsy

specimens and the presence of thickening/cell proliferation in the arteriolar intima suggest that ischemia is the major cause of tissue damage (78). Nevertheless, autoimmunity with immune-system activation might be a trigger of endothelial activation: pathognomonic of SRC is the *onion bulb* aspect related to endothelial injury, mucinous vascular intimal thickening, proliferation of endothelial cells and vascular smooth muscle cells, and hyperplasia. Vascular remodelling leads to the obstruction of the vascular lumen that is promoted by the presence of glycoprotein/mucopolysaccharides and fibrinoid necrosis in the thickened intima as well as by the accumulation of glomerular intracapillary eosinophilic material corresponding to fibrin thrombi of arterial walls, without signs of inflammation (79). Platelet activation leads to the formation of thrombosis and thrombotic microangiopathy can be found in up to 43% of cases (80). The lesions are usually localized in small and medium arteries, especially in the interlobular arteries and arterioles and arcuate arteries, with adventitial fibrosis and intra-glomerular thrombosis (78). On renal biopsy specimens, vascular, glomerular, tubular and interstitial lesions can be seen, but the hallmark of SCR is a proliferative and obliterative arteriolar vasculopathy with hypertensive vascular damage, thrombotic vascular occlusion and onion skinning with intimal myoid ac-

cumulation and adventitial fibrosis leading to glomerular ischemic collapse (81, 82). Glomerular changes, usually focal, are often observed: Ig and complement deposits may be detected but are not specific (*i.e.* IgM, IgG and IgA, C3, or C1q deposits in glomeruli or mesangium as well as in small arteries can be found). Notably, these changes can be observed also in renal biopsies from SSc patients without SRC and in cases of malignant hypertension in patients without SSc (83). Mesangiolytic may also be present. The ischemic process can affect also the tubular epithelium, with acute multifocal tubular necrosis and/or diffuse tubular atrophy (83).

Renal biopsy is not necessary to confirm the diagnosis of classic SRC but it plays a key role in cases with atypical presentation (*i.e.* normotensive patients) or in case of doubt with other causes of kidney damage (Table II) (84, 85). The mainstay of management of SCR is immediate initiation of angiotensin-converting enzyme (ACE)-inhibitors following a definite diagnosis (86).

■ SYSTEMIC VASCULITIDES

Vasculitides are an inflammatory process, histologically characterized by vessel wall destruction and vascular lumen occlusion leading to usually similar and overlapping clinical manifestations, so the final diagnosis sometimes may be uncertain. The kidneys could be affected directly by small vessel vasculitis (GN) or indirectly by medium to large vessel vasculitis (ischemic damage).

ANCA-associated vasculitides

Renal disease is a frequent and clinically unfavourable feature of ANCA-associated vasculitides (AAV), characterized by a wide spectrum of manifestations ranging from hypertension and sediment changes, to a rapidly progressive deterioration of renal function (87).

AAV are characterized by necrotizing vasculitis of small vessels and lack or paucity of immune deposits within the vessel wall (88). Granulomatosis with polyangiitis (GPA) differs from micro-

Table II - The most common differential diagnosis of scleroderma renal crisis in systemic sclerosis (in order of frequency).

ANCA-associated glomerulonephritis
Thrombotic thrombocytopenic purpura and haemolytic uremic syndrome
Other vasculitides (<i>i.e.</i> polyarteritis nodosa, mixed cryoglobulinemia and Goodpasture syndrome)
Membranous nephropathies
Drug-induced nephropathies (<i>i.e.</i> D-penicillamine or cyclosporin A)
Oxalate nephropathy
Renal artery stenosis
Membranoproliferative nephropathies
Pre-renal causes (<i>i.e.</i> sepsis, dehydration)

scopic polyangiitis (MPA) due to the presence of a granulomatous inflammation, whereas eosinophilic GPA is usually associated with interstitial eosinophilic infiltrates (89, 90).

In all AAV, the typical histopathological lesion is a pauci-immune crescentic focal and segmental necrotizing GN with negative IF staining, even if a weak granular staining pattern of IgG, IgM, or complement could be observed (91). LM shows focal thrombosis of glomerular capillaries with fibrinoid necrosis in early stages, and later on rupture of the GBM, karyorrhexis and poor definition of cellular membranes. In addition, the extracapillary proliferation, which consists in cell proliferation in the urinary space between the Bowman capsule and the capillary tuft, compresses the glomerular tuft and decreases the filtration surface, leading to a rapid loss of renal function (92). This results in crescent formation, initially predominantly cellular, leading later to more fibrous crescents. This GN is often associated with periglomerular accumulation of mononuclear cells while, periglomerular granulomatous reactions, synechiae and mesangial hypercellularity are less frequently observed (93).

The presence of a purely cellular extracapillary proliferation, interstitial edema, tubular necrosis and tubular intraepithelial infiltrates are associated with active disease. Conversely, long lasting kidney inflammation leads to glomerulosclerosis, interstitial fibrosis, arteriosclerosis and tubular atrophy (92). Notably, these irreversible scars together with tubular cast formation are more often reported in MPA as well as in renal limited vasculitis (AAV without extrarenal symptoms) compared to GPA. None of the above-mentioned lesions is specific for vasculitis; thus, renal histopathology, even if it is not useful for differential diagnosis, remains crucial for AAV prognosis (94).

Other vasculitides associated with renal damage

The pathognomonic elements for Goodpasture Syndrome are a typical linear staining for IgG in GBM on IF study and anti-GBM

positivity at blood serology (95). However, this GN is indistinguishable from AAV pauci-immune crescentic GN at the LM because both, typically, have prominent fibrinoid necrosis and crescent formation without significant endocapillary proliferation. Moreover, there is a group of small vessel vasculitides that, as opposed to AAV, is characterized by IC deposits detectable by IF: cryoglobulinemic vasculitis, Henoch-Schoenlein purpura (HSP) and hypocomplementemic urticarial vasculitis (96).

Cryoglobulinemic GN is characterized by cryoglobulin deposits, which could lead to a membranoproliferative injury (97). Renal biopsy usually shows diffuse and global endocapillary cellular infiltrate rich in monocyte, even if neutrophils could be frequently seen in the acute phase. The typical lesion is a mesangial proliferation with eosinophilic and strongly periodic acid-Schiff (PAS) positive intra-luminal *cryo-plugs* while the GBM acquires double contours. One third of the patients have signs of leukocytoclastic vasculitis in renal small arteries, while crescents are rarely observed (97). IF reveals irregular subendothelial, mesangial and intra capillary deposits of IgM, IgG and complement (97). EM easily identifies the cryoglobulin deposits that usually present short fibrillary substructure and a tactoid organization, even if monoclonal cryoglobulins tend to acquire a more regular and more organized substructure (97-100).

HSP is a systemic vasculitis, typical of childhood, associated with IgA deposits. HSP nephritis and IgA nephropathy are considered related diseases with similar histological features and their differential diagnosis is mainly clinical because their histological findings are similar (101, 102). In both cases, on IF study, renal biopsy shows diffuse, granular and mesangial IgA deposits (more frequently formed by subclass IgA1), that are usually detectable also in the late and more fibrotic stages. The association of IgG and C3 deposition is also frequent while IgM deposits are more rarely reported. EM also detects the IgA deposits typically in the mesangium and capillary wall (sub endothe-

lium) (101, 102). By LM, HSP nephritis is characterized by a broad spectrum of glomerular lesions depending on the timing of renal biopsy. In fact, it shows cellular infiltrate of mesangium and capillary lumen with fibrinoid sclerosis and small cellular crescent in early stages, leading to fibrous crescents in the late stages (101). However, the most important diagnostic and prognostic histological features are the presence and the extension of crescents that represent the prominent criteria of the International Study for Kidney Diseases in Children (ISKDC) histological classification for HSP nephropathy (Table III) (102). Crescents associated with endocapillary proliferation and glomerular sclerosis, currently head the most widely applied adult-HSP nephropathy classification (Table IV) (101-103). Extra-glomerular lesions include tubulointerstitial lesions, which are often associated with renal impairment and vascular lesions (e.g. intimal-media thickening of small arteries, interlobular artery arteriosclerosis and, very rarely, necrotizing vasculitis of a small arterial vessel) (101).

■ ANTIPHOSPHOLIPID SYNDROME

Renal involvement in antiphospholipid syndrome (APS) has been reported in about 9-25% of cases with different clinical manifestations depending on the size and type of vessels where the thrombosis occurs (104). One of the most common clinical features is hypertension (>90%), which can occur with or without renal artery stenosis (e.g. the typical smooth and potentially reversible narrowing in the mid-portion of the renal artery) (27, 105). At the renal biopsy, APS nephropathy is characterized by acute and/or chronic lesions due to the arterial lesions but, besides renal infarction and ischemic changes, several types of glomerular lesions have been reported (e.g. proliferative or pauci-immune GN, minimal change disease, membranous nephropathy, glomerulosclerosis) (104, 106). Thus, APS histology can often resemble the haemolytic-uremic syndrome or thrombotic thrombocytopenic purpura.

The elective treatment is the anticoagulation; the addition of immunosuppression

Table III - Histological classification of Henoch-Schoenlein purpura nephritis according to the International Study for Kidney Diseases in Children (ISKDC).

Class	Histological features
I	Minimal histological alteration
II	Pure mesangial proliferation
III	Focal (IIIa) or diffuse (IIIb) mesangial proliferation with <50% crescentic glomeruli
IV	Focal (IVa) or diffuse (IVb) mesangial proliferation with 50-75% crescentic glomeruli
V	Membranoproliferative-like glomerulonephritis

Table IV - Classification of glomerular lesions in adult Henoch-Schoenlein purpura.

Class	Histological definition	Histological features
I	Mesangiopathic glomerulonephritis	Normal or subnormal glomeruli with mesangial thickening and hypercellularity
II	Segmental and focal proliferative glomerulonephritis	Focal and segmental proliferative lesions
III	Diffuse endocapillary proliferative glomerulonephritis	Diffuse exclusively endocapillary proliferative lesions that may be segmental (IIIa) or global (IIIb) Class III b can be associated with extracapillary focal proliferation
IV	Endo and extra capillary proliferative glomerulonephritis	Extracapillary diffuse proliferation with focal or diffuse crescents and the presence of endocapillary diffuse proliferative lesions.
V	Kidney fibrosis	Terminal glomerular fibrosis

and plasmapheresis can be useful in selected patients with acute kidney injury related to APS in order to reduce the risk of chronic damage (27). In fact, it has been demonstrated that APS nephropathy increases the risk of end-stage renal disease as well as transplant failure and pregnancy complications in general population and especially in lupus patients (104, 107, 108). Notably, isolated microangiopathic thrombosis is reported in 10% of lupus patients with antiphospholipid antibodies; however, it is important to document the absence of glomerular or arterial immune deposits by IF/EM since the mainstay of therapy differs from the immunosuppression to anticoagulation therapy, as for primary APS (109). In addition, it has been reported that lupus patients with APS nephropathy more easily develop arterial thromboses while those without APS nephropathy usually develop venous thromboses (109). Thus, the presence of renal small-artery vasculopathy at the renal biopsy can be useful also for initiating a specific prophylaxis for APS, which is a well-known independent predictor of damage in SLE (110).

■ OTHER RHEUMATIC DISEASES

Nephropathy in mixed connective tissue disorder is uncommon, despite having been reported in up to 50% of patients, especially in children, with predominant but not severe glomerulopathy or interstitial/vascular disease depending on the predominant autoimmune features (111).

Renal involvement in idiopathic inflammatory myopathies (polymyositis, dermatomyositis and inclusion body myositis) occurs in 20-25% of patients (27). In dermatomyositis, histological findings vary widely, including a peculiar pattern of acute vascular damage and IC GN (mainly mesangial-proliferative and membranous GN) (112). In particular, rhabdomyolysis or drug induced acute kidney injury (10-11%) can lead to several complications in the short term (*i.e.* sudden cardiac event) as well as in the long term (*e.g.* chronic renal disease in more than 80% of cases) (113).

■ CONCLUSIONS

Clinical-pathologic correlations derived from the study of renal tissue can be useful for differential diagnosis, prognosis assessment and therapeutic decisions in patients affected with rheumatic diseases. Thus, renal biopsy should be considered an important tool in the management of nephropathies in such patients.

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