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REVIEW

Renal disorders in rheumatologic diseases: the spectrum is changing (Part 1: connective tissue diseases)

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Abstract

The kidney is frequently involved by autoimmune rheumatic diseases. The renal manifestations may be variable, ranging from asymptomatic proteinuria and microscopic haematuria to nephrotic syndrome and rapidly progressive glomerulonephritis or vasculitis. In a number of cases the kidney involvement is related to the treatment of the original disease and may represent a major cause of morbidity and mortality. Thus, it is important for nephrologists and rheumatologists to remember that dysfunction of the kidney may be part of the primary systemic disorder or consequence of its pharmacotherapy. In the first part of this review we will analyse the kidney involvement in four autoimmune connective tissue diseases: systemic lupus erythematosus, Sjögren syndrome, polymyositis/dermatomyositis, and systemic sclerosis. Renal disease is common in lupus and is a main cause of morbidity and mortality. About 10% of patients with Sjögren syndrome may present interstitial nephritis or, more rarely, glomerulonephritis. Myoglobinuria and acute kidney injury is a frequent complication of polymyositis. Renal disease is one of the most serious complications of systemic sclerosis and may present with a dramatic renal crisis, characterized by malignant hypertension, oligo-anuria, and microangiopathic thrombocytopenic anaemia.

Keywords Lupus nephritis · Sjögren syndrome · Polymyositis · Scleroderma · Myoglobinuria · Malignant hypertension

Many rheumatologic diseases may have important renal manifestations that may present with microscopic haematuria, proteinuria, hypertension, acute kidney injury (AKI), or chronic kidney disease (CKD). In a number of cases the kidney involvement may be extremely severe and life-threatening. The pathogenesis is extremely variable and may depend on the rheumatic disease or on the drugs used in these instances. In the last few years, the clinical presentation, the prognosis and the treatment of renal disorders in rheumatologic diseases is changed and the physiopathology of kidney involvement and original disease have been better elucidated.

In this review we report an updated review of renal involvement in systemic autoimmune connective diseases including systemic lupus erythematosus (SLE), Sjögren syndrome, polymyositis and dermatomyositis (PM,DM), and systemic sclerosis (SS).

Lupus nephritis (LN)

Kidney involvement is common in patients with SLE and is usually called lupus nephritis. LN is initiated by the glomerular deposition of immune complexes including circulating anti-nuclear, anti-C1q, and cross-reactive anti-glomerular autoantibodies. Recent studies employing laser microdissection of glomeruli and/or of single cells from tubulointerstitial areas followed by elution and characterization of renal antibodies by proteomics allowed a significant progress in definition of renal autoimmune components in human lupus biopsies and sera. The innovative approach highlighted different panels of autoantibodies deposited in glomeruli and in tubulo-interstitial areas [1]. IgG2 was the major isotype; new podocyte proteins (α-enolase, annexin AI) and already known implanted molecules (DNA, histone 3, C1q) were their target antigens in glomeruli [2]. Vimentin, is an intermediate filament protein expressed in mesangial

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matrix. Epitopes of native vimentin are antigenic and may be involved in several autoimmune disease. Anti-vimentin antibodies are often associated with therapy-resistant LN [3]. Matching renal autoantibodies with serum allowed the definition of a typical autoantibody serum map of LN that included the same anti-α-enolase, anti-annexin AI, anti-DNA, and anti-histone 3 IgG2 already detected in renal tissue. Anti-histone 3 and anti-α-enolase IgG2 levels had the most remarkable increase in LN serum and represented a discriminating feature of LN versus SLE without renal involvement and rheumatoid arthritis. Serum levels of these specific autoantibodies were tenfold increased in patients with lupus nephritis allowing a clear differentiation from both rheumatoid arthritis and other glomerulonephritis [4].

These immune complexes can access the whole glomerulus and can deposit in subendothelium or subepithelium. Immune deposits may trigger the complement cascade, or may activate intrinsic glomerular cells inducing the release of inflammatory chemokines and cytokines [5]. Subendothelial lesions cause endothelial injury and through a direct contact between endothelial and mesangial cells [6] can cause proliferative lesions that can be amplified by several mechanisms, including toll-like receptors 7 and 9 activation, dendritic cells maturation and endothelin-1 secretion. Instead, subepithelial deposits cause podocyte and glomerular basement membrane injury but both mesangial cells and podocytes have limited regenerative capacity and their loss is associated with glomerulosclerosis. On the other hand, tubulointerstitial inflammatory cells include mature myeloid and plasmacytoid dendritic cells. These may recognize cell debris as danger associated molecular pattern and may present them as autoantigens to the quiescent cells of the adaptive immunity. Activated T cells proliferate and differentiate in Th1 and Th17. The cooperation between T cells and B cells can promote B cells to differentiate into plasmacells with production of autoantibodies to renal antigens [7]. Plasmacytoid dendritic cells can also stimulate the production of interferon-α which has a critical role in inflammation and contributes to many of the immune system alterations that characterize SLE to the tissue manifestations of disease [8].

An emerging aspect in the development of LN is the role of protective autoantibodies including the recently identified anti-PTX3 antibodies [9]. PTX3 is an acute phase protein involved in opsonization of invading pathogens and/or apoptotic cells with an overall anti-inflammatory activity under physiological conditions. However, in case of extensive tissue damage, e.g., ischaemia–reperfusion injury, or in presence of an exaggerated burden of exposed antigens, PTX3 may be shifted towards a pro-inflammatory phenotype resulting in an uncontrolled complement activation and inflammation [10]. Accordingly, PTX3 deposition was observed in kidneys of patients with LN where it correlated with the extent of fibrosis and proteinuria [11], while anti-PTX3 antibodies were inversely associated with LN occurrence in both patients and lupus models. Indeed, immunization with PTX3 dampens production of nephritogenic antibodies and ameliorates disease in lupus nephritis models. Notably, it has been shown that PTX3 is preferentially deposited in glomerular electron dense deposits [12].

The clinical manifestations of LN varied from asymptomatic urinary abnormalities to nephrotic syndrome, nephritic syndrome and rapidly progressive renal insufficiency. The histological lesions are extremely variable too. According to the revisited classification of LN [13], LN histology is classified as minimal or mesangial proliferative LN (class I or II), focal or diffuse proliferative LN (class III and IV), membranous LN (class V) and advanced sclerosis LN (class VI). In a number of cases a combination of class III or IV with class V can occur. Other histological pictures triggered by SLE or its treatment may include lupus podocytopathy, thrombotic microangiopathy, acute tubulo-interstitial nephritis. The positivity for antiphospholipid antibodies (aPL Abs) may aggravate the outcome of LN. It is often associated with thrombotic microangiopathy or vascular complications. In this setting, aβ2GPI-D1 antibody detection might provide a second-line assay to be performed in aβ2GPI positive patients with LN, allowing more accurate stratification of the renal vascular involvement risk [14]. Anti-aPL Abs may also play a role in the damage caused by proliferative LN. In a study LN patients positive for aPL Abs had lower serum complement C3 and C4 levels and higher intensity of C1q deposition in kidney tissue than aPL antibody negative proliferative LN patients [15].

The prognosis of Class I and II is good unless there is a transformation into more severe class; class III and IV had a course punctuated by renal or extra-renal flares alternating with periods of quiescence. When untreated or undertreated, particularly when associated with class V, most patients with proliferative LN progress to ESRD or die within few years from clinical onset. The natural course of Class V may be slowly progressive with about 50% of patients developing end stage renal disease (ESRD) if not treated appropriately. Although class I and II in the great majority of cases present with only asymptomatic proteinuria and microhaematuria and proliferative forms (Class III and IV) tend to present with the most severe clinical presentation (nephritic syndrome or rapidly progressive renal disease), renal biopsy is very useful in patient with signs of renal involvement [16] since in most cases, clinical, serological or laboratory tests cannot accurately predict renal biopsy findings [17]. Although any decision should always be taken by considering the clinical conditions of the patient, there are no doubts that repeat renal biopsy may represent an useful tool to evaluate the response to therapy, to modulate the intensity of treatment, and to predict the long-term renal outcome both in quiescent lupus and in flares of activity (Fig. 1). The value of

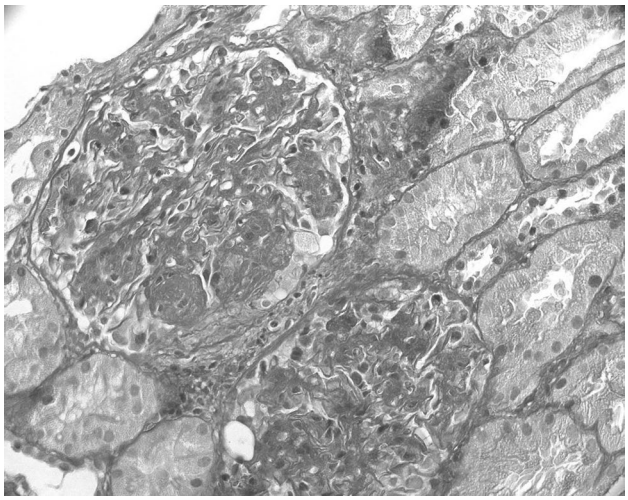

Fig. 1 Class IV lupus nephritis: glomeruli with segmental extracapillary proliferation, global endocapillary proliferation and subendothelial deposits

renal biopsy in patients without clinical renal manifestations is debated. Except for few reported cases of class III and IV diagnosed without clinical renal manifestations who had a worse outcome, in all the other biopsies of patients with the so-called silent LN, class I and II are diagnosed.

In the last few years, several changes occurred in the clinical presentation of LN. More cases with mild clinical involvement are diagnosed in comparison to the past. This is probably due to a more diffuse use of LN markers, such as proteinuria, urine sediment, serum creatinine [18–20]. By reviewing our own experience, in 71 patients with LN diagnosed 1969 and 1989, the clinical presentation was characterized by urinary abnormalities in 28% of cases, by nephrotic syndrome in 30%, nephritic syndrome in 27% and rapidly progressive glomerulonephritis in 15%. Instead, in 131 patients with LN diagnosed between 2000 and 2015, the number of cases presenting with urinary abnormalities increased to 54% of cases, nephrotic syndrome reduced to 23%, nephritic syndrome to 18% and rapidly progressive glomerulonephritis to 5% [21]. Despite changes in clinical presentation, the distribution of the histological classes did not change between the two periods, the proportion of patients with class III and IV was similar [22].

Compared to the past a number of complications or new treatments may cause renal disease in SLE patients. A substantial and increasing proportion of kidney pathology might not directly relate to LN but instead might be explained by non-immune mediated factors such as diabetes, hypertension, and obesity [23]. The presence of anti-phospholipid antibodies can cause thrombosis at any level of kidney vasculature [24]. Drugs currently in use such as quinolones, antiviral agents, proton pump inhibitors (PPI), and especially non-steroidal anti-inflammatory agents(NSAIDs) can cause kidney injury nowadays [25–27], while in the past the most frequent nephrotoxic drugs were captopril, aminoglycosides, radiocontrast agents or amphotericin B which are now used with more caution.

The prognosis of LN is progressively improved over the time [21, 28]. This was recently confirmed in a large multicentre study [29]. The analysis of the outcome of 499 LN patients diagnosed from 1970 to 2016 demonstrated a progressive and significant increase in patient age at LN diagnosis, and a longer time between SLE onset and LN development. The frequency of renal insufficiency at the time of LN presenation progressively decreased and that of urinary abnormalities increased. No changes in histological class and activity index were observed, while chronicity index significantly decreased from 1970 to 2016. The 10-year survival without end-stage renal disease (ESRD) improved from 87% between 1970 and 1985 to 94% between 1986 and 2001 and to 99% between 2002 and 2016. At multivariate analysis, male gender, arterial hypertension, absence of maintenance immunosuppressive therapy, increased serum creatinine, and high activity and chronicity index were independent predictors of ESRD.

Treatment of LN is also changed in the last years (Table 1). The complications of immunosuppressive therapy- including infections, osteoporosis, cardiovascular disease and reproductive effects -impaired the life expectancy and the quality of life of many patients with LN. In the induction therapy, the high- dose intravenous (iv) pulses of cyclophosphamide have been replaced by low-dose pulses

Table 1 The present landscape of lupus nephritis

The clinical presentation of lupus nephritis is changed at least in Caucasians patients. Compared with the past, more patients have now asymptomatic urinary abnormalities and less patients present with renal insufficiency or rapid progression
The renal prognosis is considerably improved and the causes of ESRD have changed in the last years. In many cases renal function deterioration is not caused by lupus nephritis per se but by comorbid diseases, such as hypertension, diabetes, infections. related to SLE or its treatment
In induction treatment the doses of intravenous methylprednisolone pulses (MPP) and intravenous cyclophosphamide have been lowered. In many cases cyclophosphamide is replaced by mycophenolate salts and/or MPP are substituted with Rituximab. Cyclophosphamide may be given by mouth instead of intravenously. Maintenance treatment is based on low-dose prednisone associated with either azathioprine (less expensive) or mycophenolate (more effective). Cyclosporine or tacrolimus are useful in patients with persistent proteinuria. Ancillary treatment with belimumab or hydroxychloroquine may spare the use of corticosteroids. The immunosuppressive treatment may be progressively tapered until complete withdrawal

[30] or by oral administration [31]. A meta-analysis showed that in comparison with iv cyclophosphamide, tacrolimus could significantly increase complete remission, serum albumin level and decrease urine protein [32]. Rituximab has been frequently used to reduce the use of corticosteroids both in induction therapy and in frequently flaring or persistent active LN [33]. Although the randomized phase III trial in patients with class III and IV LN, failed to demonstrate the superiority of Rituximab over standard therapy in improving the clinical outcome at 1 year [34], targeting B cell and reducing autoantibody production represents a promising therapeutic approach in LN, particularly in difficult cases [35].

In the maintenance phase, mycophenolate mofetil (MMF) allowed to avoid the long-term use of cyclophosphamide and proved to be superior than azathioprine in maintaining renal response [36]. Low-dose cyclosporine proved to be safe and effective in reducing proteinuria [37, 38], but there is no data about the long-term effects of cyclosporine [39]. Voclosporin is a novel calcineurin inhibitor, a trans isomer of cyclosporine,which possesses most of the beneficial effect of the drug. In a recent randomized trial in lupus the addition of low-dose voclosporin to mycophenolate mofetil and corticosteroids for induction therapy of active LN resulted in a superior renal response compared to mycophenolate mofetil and corticosteroids alone, but higher rates of adverse events including death were observed [40]. Although not seen on trials, in real life the addition of belimumab to the conventional therapy in lupus nephritis obtained steroid-sparing effects [41]. In a randomized controlled trial of maintenance treatment, a multitarget therapy based on tacrolimus, MMF and low-dose prednisone in lupus nephritis resulted in lower renal relapse rate and fewer adverse events in comparison with azathioprine and low-dose prednisone [42]. Ancillary treatment with hydroxychloroquine [43] may reduce the doses of glucocorticoids and the risk of lupus flares. It has also been reported the possibility of progressive tapering of immunosuppressive therapy until its complete withdrawal in patients with clinically stable LN. This allowed to significantly improve renal survival and treatment-related side effect in the long term [44]. Others suggested a more careful approach based on the absence of renal activity at kidney biopsy, in order to reduce the risk of flares [45]. In summary, earlier diagnosis and treatment, refinement in monitoring and managing LN and availability of new drugs led to progressive improvement of LN over the time.

Sjögren syndrome

Sjögren syndrome is an autoimmune disease characterized by inflammation and destruction of exocrine glands, principally lachrymal, parotid, and salivary glands as well as by involvement of multiple organ systems. The syndrome may be classified as primary Sjögren when it is isolated or secondary when associated with other autoimmune rheumatic disease, especially rheumatoid arthritis, delineating a condition named overlap connective tissue disease. In Sjögren syndrome infiltration of lymphocytes and plasma cells can be observed in glands and in other organs, including kidney. Indeed, renal involvement has been reported in less than 10% of patients and is characterized by interstitial nephritis or, more rarely, glomerulonephritis [46].

Interstitial nephritis is the prevalent kidney disease. In a large multicentre French study; 98% of 95 patients showed tubulointerstitial nephritis at renal biopsy [47]. The interstitial nephritis may remain asymptomatic for a long period and may eventually present with fatigue, muscular weakness, or polyuria [48]. Skeletal manifestation is also a common finding in patients with Sjögren syndrome [49]. Initial biochemical analysis shows hypokalaemia, hyperchloremia and reduced kidney function. Further investigations demonstrate the presence of an underlying tubular acidosis. Type I distal tubular acidosis is the most frequent disorder. It is characterized by a reduced hydrogen ions secretion by the alpha intercalated cells in the distal convoluted tubules leading to hyperchloremic acidosis and hypokalaemia. Metabolic acidosis may also affect bone by exchanging hydrogen ions for sodium, potassium, calcium, carbonate and phosphate [50]. The continuous sequestration of protons in bone stimulates both osteoclast differentiation and osteoclast activity. Eventually, this mechanism leads to net bone loss and hypercalciuria, that coupled with alkaline urine may lead to stunted growth and bone abnormalities in children or in nephrocalcinosis and nephrolithiasis in adults [51].

Type II tubular acidosis is less frequent. It involves proximal tubules and is caused by poor reabsorption of bicarbonate [52]. Tubular acidosis may occur without involvement of other solutes [53] or may be associated with urinary loss of phosphate, uric acid, glucose, amino acids and low-molecular-weight proteins as part of the Fanconi syndrome [54, 55]. Renal biopsy shows tubulointerstitial nephritis with infiltrate of lymphocytes, macrophages and plasma cells around the tubules with complete sparing of the glomeruli [56, 57]. In advanced cases severe pathological changes with extensive interstitial fibrosis and tubular atrophy are present.

Glomerulonephritis is a rare kidney complication in Sjögren syndrome. It may present with proteinuria associated with microscopic haematuria or, rarely, with a nephrotic syndrome. Deterioration of kidney function is frequent [58, 59]. Membranous nephropathy [60] and IgA nephritis [61] are frequent forms of glomerulonephritis in Sjögren syndrome; however, endocapillary and extracapillary proliferative glomerulonephritis [62, 63] have also been described. In a number of cases

membranoproliferative glomerular lesions are related to an associated disease such as vasculitis, SLE, mixed cryoglobulinaemia or occult hepatitis C infection [64–66].

The long-term renal prognosis varies in patients with primary Sjögren syndrome who have clinically significant kidney involvement. Patients with interstitial nephritis display a favourable prognosis, although occasional cases of renal failure may occur as a consequence of diffuse tubule-interstitial lesions or nephrocalcinosis. Appropriate screening must be performed at least once a year in patients with Sjögren syndrome in order to facilitate the early detection of renal complications. More severe is the prognosis of patients with glomerulonephritis, which may progress to ESRD [67, 68].

Treatment depends on the nature of the underlying kidney disease. In case of chronic interstitial nephritis, some studies reported that treatment with glucocorticoids alone or associated with mycophenolate improved the renal function in few patients [69], others found only marginal or no benefit of glucocorticoids and other immunosuppressive agents [70]. If hypokalaemic distal tubular acidosis is present, alkali administration equivalent to the sum of endogenous acid production and bicarbonate wastage is needed. In general, the total replacement is 1–2 mEq/kg per day of sodium bicarbonate or citrate, which is its metabolic equivalent. Greater amount may be needed in children who have larger wastage of bicarbonate than adults. Correction of acidosis may improve hypokalaemia and hypercalciuria and can increase the citrate excretion, with decreased incidence of nephrocalcinosis and nephrolithiasis. In children with proximal tubular acidosis, sodium bicarbonate 5–15 mEq/kg per day is enough to compensate for the urinary bicarbonate loss and the endogenous acid production (Table 2). The management of glomerular diseases secondary to SLE, vasculitis, or cryoglobulinemia is that of the associated systemic disease.

The recent EULAR guidelines recommended that the use of glucocorticoids, synthetic immunosuppressive agents (cyclophosphamide, azathioprine, methotrexate, leflunomide, mycophenolate), intravenous immunoglobulins and biologics should be restricted to patients with active systemic disease but only after a careful evaluation of both severity and organ damage. Recommendations on the need for/duration of induction and maintenance therapies should be decided on case-by-case [71].

Polymyositis and dermatomyositis

The idiopathic inflammatory myopathies (IIMs) are a group of rare and heterogeneous acquired diseases affecting striated skeletal muscles, which include polymyositis (PM), dermatomyositis (DM), necrotizing autoimmune myopathy (NAM), and inclusion body myopathy (IBM). They are all characterized by elevation of muscle enzymes levels in serum and distinctive findings on electromyography and muscle biopsy. The pathogenesis is still unknown, but immune-mediated and non-immune mediated mechanisms can contribute to tissue damage. In the last few years, a number of myositis- specific and myositis-associated antibodies have been found. It has been hypothesized that endogenous antigens, i.e., aminoacyl-tRNA synthetase enzyme, may trigger activation of signalling pathways inducing the expression of multiple genes involved in the inflammatory response [72].

Predominant symptoms are proximal muscle weakness and typical skin finding in DM (heliotrope rash and Gottron's papules). The disease may also afflict oesophagus, lung, and rarely myocardium. Pulmonary manifestations are major life-threatening events in IIMs and are frequent in patients with positive anti-synthetase antibodies. Overlap with systemic sclerosis is frequent accounting for approximately 40% of all cases of myositis overlap. IIMs have a high morbidity, and not infrequently are the first sign of an associated malignancy [73]. The first line therapy consist of glucocorticoids that proved to be effective in many patients. Immunosuppressants, IVIg and plasma-exchange are used as rescue therapy in patients with refractory manifestations, but no randomized controlled trials are available to guide efficacy and safety.

Data regarding the kidney involvement in patients with IIMs are scarce. Two large retrospective series of patients with IIMs reported a prevalence of renal disease between 21

Table 2 The clinical spectrum of Sjogren syndrome

Primary Sjogren syndrome is a multisystemic autoimmune disease that mainly affects exocrine glands; secondary Sjogren syndrome affects other autoimmune diseases, especially rheumatoid arthritis. Renal disease is rare affecting only 10% of patients with Sjogren syndrome. Interstitial nephritis with tubular acidosis is the most common renal disorder. Glomerulonephritis is less frequent
Patients with interstitial nephritis display a favourable prognosis, although occasional cases of renal failure may occur as a consequence of interstitial nephritis or nephrocalcinosis. More severe is the outcome for patients with glomerulonephritis that may progress to renal failure
Treatment depends on the nature of the underlying kidney injuries. Glucocorticoids alone or associated with mycophenolate may sometimes improve renal function. In case of hypokalaemic distal tubular acidosis sodium bicarbonate or citrate is recommended. The management of secondary glomerulonephritis is that of the original systemic disease. The recent EULAR guidelines recommend that glucocorticoids, immunosuppressive drugs or biologic agents should be restricted to patients with active systemic disease but only after a careful evaluation of both severity and organ damage

and 23% [74, 75]. The most frequent type of kidney lesions in IIMs is acute renal failure that may be caused by rhabdomyolysis, drug toxicity or infection. Less frequent is an association with chronic glomerulonephritis.

Myoglobinuria may occur in as many as 20% of patients with IIMs [76]. When great amounts of myoglobin are released, an acute kidney injury may occur. It can be caused by casts formation and obstruction of the tubular lumen, and by the toxic effects of myoglobinuria on kidney tubules, including iron-induced oxidative stress and the development of a third space into the injured muscles [77–81]. The latter event causes vasoconstriction that in turn activates renin–angiotensin–aldosterone system, sympathetic nervous system and vasopressin release. All of them converge in causing profound vasoconstriction, ischaemia and oliguria [82]. The output of reddish to brown urine is the main clinical manifestations of rhabdomyolysis-induced acute renal failure. The microscopic examination of urinary sediment is necessary for the differential diagnosis with macroscopic haematuria, in which red blood cells are found, while only pigmented granular cells can be observed in rhabdomyolysis. However, in the cohort of Couvrat-Desvergnes et al. [75] only few cases of rhabdomyolysis were observed, the main cause of acute kidney injury was drug toxicity (40% of all the cases), mainly due to IV immunoglobulins, but also related to the use of tacrolimus or cisplatin for associated cancer. Other clinical situations such as intercurrent sepsis and dehydration can contribute to kidney injury [83].

A wide range of immune-complex glomerulonephritis has been reported in patients with IIMs submitted to renal biopsy. The results of around 50 renal biopsies performed in IIMs have been reported in the literature [revised in 76, 78, 84]. IgA nephropathy was the most frequent glomerular disease, followed by membranous nephropathy, minimal change disease and focal segmental glomerulosclerosis. Few cases of membranoproliferative glomerulonephritis, pauci-immune crescentic glomerulonephritis and tubulointerstitial nephritis have been reported. A peculiar pattern of severe acute renal vascular damage consisting mainly of oedematous thickening of the intima of arterioles has been described in five patients [75]. The occurrence of such a variegate phenotypes of glomerular diseases may be related to a dysregulated generation of different autoantibodies in inflammatory myopathies. The mechanisms underlying this dysregulated generation of autoantibodies remain unclear. The clinical presentation of IIMs-associated glomerulonephritis varies from mild urinary abnormalities to nephrotic syndrome or rapidly progressive renal insufficiency. Probably, glomerular diseases in IIMs are underestimated because not all cases of mild proteinuria or microscopic haematuria are submitted to renal biopsy. In some cases, the development of glomerular disease is concomitant to the myopathy diagnosis.

The renal prognosis depends on the type of kidney injury and comorbidity. The outcome of acute kidney injury was poor in a series: of 16 patients 13 (81%) progressed to CKD and 2 (12.5%) reached ESRD. Age at IIMs onset, male gender, a history of cardiovascular events, and a previous episode of kidney injury were associated with the risk of CKD. The prognosis of glomerular diseases depends on the histological and clinical features at presentation. It is usually good for patients with normal renal function and mild proteinuria. It may be severe for patients with deteriorated kidney function, nephrotic syndrome and a picture of extracapillary glomerulonephritis at renal biopsy.

The choice of treatment is based on the type of kidney disease (Table 3). In case of rhabdomyolysis-associated acute renal failure, treatment consists of aggressive alkalinisation and hydration and rapid reduction of hyperkalaemia to prevent cardiac arrhythmias [77]. Patients with mild proteinuria and normal renal function may benefit from ACE-inhibitors or angiotensin-receptor blockers. The steroids schedule in use for IIMs includes prednisone 1 mg/kg/day for 4–6 weeks [72], which can be effective for kidney and muscles. In cases of nephrotic syndrome, the addition of another immunosuppressive drug-cyclophosphamide, azathioprine, cyclosporine, tacrolimus, mycophenolate or rituximab- may be considered. However, no randomized controlled trial could

Table 3 Clinical characteristics of polymyositis-dermatomyositis

Polymyositis (PM) and dermatomyositis (DM) are autoimmune diseases that affect skeletal muscles and skin respectively. Overlap with systemic sclerosis and other rheumatic diseases is frequent
The pathogenesis is still unknown but endogenous antigens may trigger activation of signal pathways and induce expression of multiple genes involved in the inflammatory response
Data regarding the kidney involvement are scarce. Retrospective series reported a prevalence of renal disease between 21 and 23%. Two main types of kidney injury have been described. The most frequent is rhabdomyolysis-related acute kidney injury. Drug toxicity is another frequent cause of acute kidney injury. The outcome of these events may be poor in patients with other comorbidities. Chronic glomerulonephritis is less frequent. The prognosis depends on the type of glomerular lesions
Treatment of rhabdomyolysis-related acute kidney injury rests on alkalinization, hydration, and rapid reduction of hyperkalaemia. Patients with normal renal function and mild proteinuria may benefit from inhibitors of renin-angiotensin system. In case of nephrotic syndrome or progressive deterioration of kidney function glucocorticoids or other immunosuppressive agents may be considered

confirm the validity of these treatments. Regular renal follow-up of these patients is recommended.

Systemic sclerosis

Systemic sclerosis (SS), also called scleroderma, is an immune-mediated rheumatic disease of unknown aetiology that is characterized by fibrosis of the skin, blood vessels and visceral organs including the gastrointestinal tract, lungs, heart, and kidneys. It primarily affects women and there are two clinical subsets according to the extent of skin involvement: diffuse cutaneous SS and limited cutaneous SS. The pathogenesis of SS is extremely complex, but there is now evidence that immunogenetics, immune dysfunction, inflammatory mediators, fibroblasts, extracellular matrix and the endothelial damage can interact and affect each other eventually leading to the pathological and clinical manifestations of SS [84]. Several studies reported that both non-HLA genes, *KIAA0319L*, *PXK*, and *JAZF1* [85] and HLA genes, especially B35 [86, 87], are associated with SS susceptibility. Of note, B35 influences the production of endothelin-1, a potent vasoconstrictor and profibrotic factor, while decreases nitric oxide synthase which catalyses the production of the vasodilator nitric oxide. In this permissive genetic background, abnormalities of the innate and adaptive immune systems lead to production of autoantibodies and cell-mediated autoimmunity that coupled with increased expression of endothelin-1 [88] and reduced production of nitric oxide synthase [89] cause hypoxia, vasoconstriction, intimal proliferation and endothelial injury. In the meantime, endothelin-1 activates and re-programs the functional phenotypes of vascular smooth muscle cells, microvascular pericytes and tissue fibroblasts into pro-fibrogenic cell populations with myofibroblasts-like properties [90]. Platelets are also activated in SS and can release chemokines, cytokines and growth factors, including TGF-β1 that increases the production of collagen and extracellular matrix [91]. Thus, the disease targets the vasculature, connective tissue-producing fibroblasts/myofibroblasts components, microvascular endothelial cell/small vessel fibroproliferative vasculopathy, and fibroblast dysfunction eventually generating excessive accumulation of collagen and other matrix components in skin and internal organs.

Renal disease is one of the most serious complications of SS. It is more often observed in the context of extensive diffuse skin disease. Some individuals are initially asymptomatic or show only mild proteinuria, microscopic haematuria and occasional casts. These patients may follow an indolent course until hypertension and progressive deterioration of kidney function develop. Histologically, renal vessels show intimal proliferation, medial thinning and increased collagen deposition in the adventitial layer. Both post- and antemortem studies suggest that endothelial lesions occur before the clinical diagnosis of renal disease and precede the histological evidence of fibrosis [92].

In almost 10% of diffuse cutaneous SS patients and in rare cases of limited cutaneous SS a scleroderma renal crisis (SRC) may develop, sometimes preceding the clinical diagnosis of SS [93]. The clinical presentation is dramatic, SRC being one of the few emergencies in clinical rheumatology. It is characterized by a malignant hypertension, oliguric acute renal failure, pulmonary oedema, microangiopathic haemolytic anaemia in about 40% of cases, and central nervous system involvement with encephalopathy and seizures. In around 15% of cases, SRC may present with normal blood pressure and is termed normotensive SRC. In these cases, the clinical picture is very severe with haemolytic anaemia in 90% of patients, thrombocytopenia in 83%, and frequent lung haemorrhage. Almost 2/3 of patients received glucocorticoids before the development of normotensive SRC [94]. This clinical presentation is similar to that of thrombotic microangiopathy and the differential diagnosis may be difficult. Typical SRC exhibits prominently elevated blood pressure and worsening of renal function initially, followed by mild thrombocytopenia. Conversely, normotensive SRC and thrombotic microangiopathy presents first with severe thrombocytopenia, followed by elevated blood pressure and renal function deterioration [95]. Microscopically arterial lesions predominate. Small interlobular and arcuate arteries as well as small arteries and arterioles are affected (Fig. 2). The early changes consist in marked proliferation of intimal cells and accumulation of mucoid ground substance composed by glycoproteins and mucopolysaccharides. This proliferation may damage the internal elastic lamina allowing muscle-like cells to migrate into the intima. There is also a fibrous thickening of adventitia. Gross narrowing of the blood levels leads to ischaemia which may be aggravated by

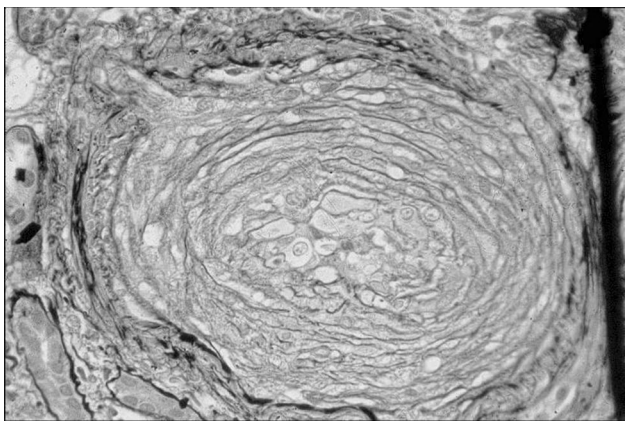

Fig.2 Scleroderma renal crisis.Interlobular artery showing intimal mucoid oedema and endothelial swelling resulting in "onion skin" concentric appearance

vascular thrombosis with consequent atrophy of the nourished tissues. Fibrinoid changes in the walls or arterioles and microinfarct are also frequent.[96, 97]. Glomeruli may be normal but may be necrotic or ischaemic in the area with infarct. In cases of thrombotic microangiopathy, there are mesangiolysis, thickening of capillary walls, intracapillary thrombosis and areas of fibrinoid necrosis. Juxtaglomerular apparatus is hypertrophic. Tubular atrophy and interstitial fibrosis are frequent [98]. The aetiopathogenesis of SRC is presumed to be a series of insults to the kidneys resulting in the narrowing of renal arterioles. An important role is played by the renin-angiotensin system which is overactivated as shown by the markedly increased levels of plasma renin [99] leading to decreased blood flow, hyperplasia of the juxtaglomerular apparatus, hyperreninemia, and accelerated hypertension. Risk factors include rapid skin thickening, use of certain medications such glucocorticoids or cyclosporine, new-onset microangiopathic haemolytic anaemia and/or thrombocytopenia, cardiac complications (pericardial effusion, congestive heart failure, and/or arrhythmias), large joint contractures, and presence of anti-RNA polymerase III antibody [100].The clinical impression is that the prevalence of SRC seems reduced over the time: however, a meta-analysis of studies reported from 1983 to 2011 found no statistical reduction in the temporal prevalence of SRC patients with diffuse cutaneous SS (7–9%), or patients with limited cutaneous SS (0.5–0.6%) based on either the start date of the cohort or publication date [101].

The prognosis of renal SS largely depends on the rapid control of malignant hypertension and improvement of the ongoing renal ischaemia. The advent of angiotensin-converting enzyme inhibitors (ACEI) allowed to reverse the dreadful outcome of SRC (Table 4). In a pivotal prospective study carried out in a cohort of 108 SRC patients, the 1-year survival rate was 76% in those treated with ACEI and 15% in those who were ACEI free [102]. Despite the improvement, SRC remains a life-threatening manifestation characterized by a high rate of mortality and progression into permanent dialysis [103–105]. In a retrospective study, the clinical charts of 606 patients, affected with SS were reviewed. Twenty (3.3%) patients developed SRC. One year after SRC onset, 55% of patients developed ESRD. The survival rate was 70% at 1 year and 50% at 5 years, the mortality rate related to SRC was 35% [106]. In summary, short-term prognosis of SRC has improved, but long-term prognosis remains disappointing particularly in patients in renal replacement therapy [107]. Mortality is reduced but a substantial number of patients with SRC still die of cardiac or lung complications. Some patients may progress to ESRD and need dialysis. Scleroderma recurrence after renal transplantation is possible [108] but the risk is low [109].

Immunosuppression may improve many aspects of SS, but it is not curative [109]. Treatment of SRC is mainly based on anti-hypertensive drugs. Early treatment is mandatory to prevent irreversible organ damage. However, blood pressure should not be reduced below the limit of cerebral autoregulation to prevent the risk of iatrogenic ischemia. It is also recommended not to lower blood pressure too fast in order to prevent relative or actual hypovolemia associated with vasodilatation of constricted vessels which can further decrease kidney perfusion. Thus intravenous antihypertensives such as nitroprusside and labetalol or powerful drugs such as minoxidil should be avoided. For the majority of hypertensive emergencies, mean arterial pressure should be reduced by approximately 10–20% within the first hour and by another 5–15% over the next 24 h. This often results in a target blood pressure of less than 180/120 mm Hg for the first hour and less than 160/110 mm Hg for the next 24 h, but rarely less than 130/80 mm Hg during that time frame [110–112]. The decision of which drug to use depends on numerous factors including the clinical indications, pharmacokinetics, toxicity and drug interactions. Furthermore, more than one of the recommended drugs is often required for the successful lowering of the patient's blood pressure. ACE-inhibitors remain the mainstay in the therapy of SRC due to the critical role of renin-angiotensin system in the pathogenesis of SRC [113]. Dihydropyridine calcium-channel blockers, such as nifedipine, can also reverse SRC and even prevent its development [114]. In refractory cases a combination of ACE inhibitors with endothelin receptor blockers [115] and agents targeting the complement component five has been proposed [88]. Plasma-exchange seems

Table 4 The clinical spectrum of scleroderma renal crisis

Some patients with systemic sclerosis may develop renal disease. This may be asymptomatic and associated with mild proteinuria or microscopic haematuria. However, the typical presentation is the scleroderma renal crisis (SRC), a combination of acute oliguric renal failure associated with severe hypertension. Microangiopathic haemolytic anaemia can also occur
The prognosis depends on the rapid control of malignant hypertension and prevention of renal ischemia. The short-term outcome is improved in the last years, but patients with thrombotic microangiopathy or those who received a late treatment have a poor prognosis. In the long-term, a sustained number of patients who survived the SRC may eventually enter end-stage renal disease or die because of cardiac or lung complications
An early anti-hypertensive treatment is mandatory to prevent irreversible organ damage. The use of ACE inhibitors or calcium channel blockers may avoid severe organ damage in the acute phase of SRC but cannot inhibit a late progression of vascular lesions eventually leading to renal failure

to give some benefits in patients with SRC and microangiopathy or in subjects intolerant to ACE-inhibitors [106, 116, 117]. SRC may lead to complement system activation through the classical pathway. Early administration of Eculizumab, a monoclonal antibody blocking C5, has been used with success in patients with SRC complicated by thombotic microngiopathy [118–120].

Compliance with ethical standards

Conflict of interest The authors do not have any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within 3 years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent This type of study formal consent is not required.

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