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Renal Involvement in Idiopathic Inflammatory Myopathies

David Cucchiari[1] · **Claudio Angelini**[1]

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Abstract Renal involvement in idiopathic inflammatory myopathies is not as uncommon as was previously thought, as it develops in about one fifth of patients. Clinical presentation includes either acute kidney injury or chronic glomerulonephritis. The former usually develops abruptly during acute phases of rhabdomyolysis: in this case, kidney injury is caused by the toxic effects that myoglobinuria has on the kidney tubules, including cast formation and iron-induced oxidative stress and the development of a third space into the injured muscles. The latter instead has an autoimmune nature, a pleomorphic histological picture, and a more indolent course, with the exception of crescentic glomerulonephritis. Accurate diagnosis and management is crucial for these patients, as timely evaluation and treatment can prevent most of the complications. In the setting of rhabdomyolysis-induced acute kidney injury, the necessity of dialysis can be avoided through aggressive hydration and alkalinization, in order to force diuresis and avoid acidosis and hyperkalemia. In immune-mediated glomerulonephritis, renal biopsy is of undoubtedly value in the diagnostic process and can add prognostic and therapeutic information. In these forms, the development of chronic kidney disease can be prevented or at least delayed by the institution or modification of immunosuppressive treatment. Moreover, the use of drugs that inhibit the renin-angiotensin-aldosterone system and some lifestyle modifications, such as smoking cessation, weight loss, and salt restriction have also value in reducing proteinuria and the progression of kidney damage. In this review, we have summarized the currently available evidence and the different case series in an attempt to provide the readers with the most complete and practical notions that are needed to handle these delicate patients.

Keywords Acute kidney injury · Glomerulonephritis · Dermatomyositis · Polymyositis

Introduction

Inflammatory idiopathic myopathies (IIMs) constitute a heterogeneous group of autoimmune illnesses, whose main feature is muscle inflammation. They include dermatomyositis (DM), polymyositis (PM), inclusion-body myositis, and necrotizing autoimmune myositis. Apart from the hallmark of muscle inflammation, these diseases can involve other organs, including the lungs and the heart [1]. Renal involvement in IIMs was believed to be quite a rare event, described only in anecdotic case reports, and represents the focus of this review. However, some retrospective series have shown that its prevalence may be as high as 21–23 % of all these patients, a percentage that has not to be undervalued [2, 3]. Since renal involvement has been described only in association with DM and PM, only these IIMs will be mentioned in this review. Although some dermatologic findings are specific for DM (i.e., Gottron papules, heliotropic rash, shawl sign), the clinical presentation of these entities is similar and is characterized by progressive weakness of proximal muscle groups of the extremities, along with characteristic biochemical, pathological, and EMG findings. First-line treatment for these diseases is the same, with most patients being responsive to steroids [4]. However, this does not reflect similar pathogenic mechanisms: while in DM complement-mediated destruction of microvasculature leads to perivascular inflammatory infiltrates

✉ David Cucchiari
david.cucchiari@gmail.com

Claudio Angelini
claudio.angelini@humanitas.it

[1] Nephrology and Dialysis Unit, Humanitas Clinical and Research Center, via Manzoni 56, 20089 Rozzano (Mi), Italy

and perifascicular atrophy, in PM CD8+ cytotoxic T cells directly attack striated muscle cells with the appearance of patchy inflammatory infiltrates at muscle biopsy [1]. Two different kinds of renal involvement in PM and DM actually exist: an autoimmune mechanism that causes a glomerulonephritis (GN) and rhabdomyolysis-induced acute kidney injury (AKI), the latter often accompanied by acid–base and electrolytes disorders. In the first case, renal disease is in most cases indolent, with only mild degrees of proteinuria and/or hematuria in the setting of slowly progressing glomerulonephritis. In the second case, the disease can even be fulminant when massive rhabdomyolysis occurs in severe phases of muscle inflammation. Prompt recognition and adequate treatment are essential in order to prevent the development of life-threatening electrolyte imbalances and chronic kidney disease (CKD) eventually leading to dialysis-dependent end-stage renal disease (ESRD). For the purpose of this review, these two major forms of renal involvement in IIMs will be discussed separately. Sometimes, when PM is accompanied by Raynaud phenomenon, interstitial lung disease, anti-synthetase antibodies (such as anti-JO1), arthritis and cutaneous manifestation (mechanics' hands), patients are classified into the so-called "anti-synthetase syndrome" [5]. For clarity purposes, when discussing previously reported cases of patients with anti-synthetase syndrome who have undergone renal biopsy, we will refer to them as having PM.

Rhabdomyolysis-Induced Acute Kidney Injury and Electrolyte and Acid–Base Disturbances

The most feared kind of renal involvement in IIMs is rhabdomyolysis-induced AKI. Apart from the acute development of renal failure, rhabdomyolysis itself induces several electrolytes and acid–base imbalances, which can sometimes be life-threatening.

The pathophysiologic effects of rhabdomyolysis have been better studied and elucidated in the setting of the so-called "crush syndrome", which is always a hyper-acute post-traumatic event. Inflammatory myositis instead may have an acute, subacute or chronic course; thus, the clinical picture may be blunted. However, it has to be highlighted that patients with IIMs who have the highest risk of developing AKI are those who have a fulminant course of their disease, so the clinical picture often resembles crush-syndrome.

Pathophysiology of Rhabdomyolysis-Induced Electrolyte and Acid–Base Disturbances

Breakdown of muscle cells during acute phases of inflammatory myositis leads to the release of several intracellular components including potassium, phosphate, myoglobin, and organic acids into the bloodstream [6]. Suffering muscle cells can no longer maintain osmotic and electrolyte equilibrium across membrane compartments; disruption of this equilibrium leads to the composite clinical picture of these patients. Release of organic acids into the bloodstream causes metabolic acidosis, even before AKI develops. Along with the release of acids, potassium is massively released from muscle cells, causing hyperkalemia. The more severe the muscle inflammation is, the worse the severity of hyperkalemia will be, since potassium is the major cation of the intracellular compartment. Moreover, extracellular acidosis and decreased renal function often contribute to further increase blood potassium levels.

Another electrolyte whose levels are characteristically deranged during rhabdomyolysis is calcium, which is one of the most important cations of striped muscles cells, since it is essential for the mechanism of contraction. Of note, the calcium gradient between cytoplasm and extra-cellular compartment has one of the most intense magnitudes of the whole human body. This is due to the intense work of calcium channels, which actively pump calcium out of the cytoplasm in order to increase the gradient. Upon arrival of a nerve stimulus, acetylcholine-mediated activation of nicotinic receptors leads to the opening of calcium channels, with a massive entry of calcium into the muscle cells cytoplasm along the previously created gradient. The calcium-troponin interaction is indeed the mechanism at the base of muscle contraction. When muscle cells are damaged by ischemia, hypoxia, and inflammation, calcium channels activity is deranged and can no longer maintain the above-mentioned gradient. In the long term, this can cause ectopic calcifications of the affected muscles. In cases of massive rhabdomyolysis, a biphasic behavior of serum calcium may occur: in the first phase, during the inflammatory/necrotic process, calcium massively precipitates into muscle cells causing hypocalcemia. High plasma phosphate levels due to phosphate release from muscles can contribute to hypocalcemia, since phosphate is able to bind ionized calcium, thus reducing the amount of plasmatic free calcium.

Thereafter, when reparative processes ensue, the massive amount of calcium sequestered into the damaged muscles is progressively released. In up to 25 % of patients with massive rhabdomyolysis, this leads to the occurrence of severe hypercalcemia some weeks after the initial insult that can occasionally be life-threatening [7].

Pathophysiology of Rhabdomyolysis-Induced Acute Kidney Injury (AKI)

AKI develops along with these electrolyte disturbances essentially through three mechanisms: cast formation, renal vasoconstriction, and direct heme toxicity. Myoglobin is freely filtered by glomeruli and precipitates into the tubular lumen in aggregation with the Tamm-Horsfall protein, causing the formation of granular reddish-brown casts (the reddish hue is

due to the presence of the heme component). Cast formation is favored by low urinary pH and slow urinary flow and causes intratubular obstruction. Even uric acid, which is markedly increased in patients with rhabdomyolysis, can contribute to casts formation when filtered. Renal vasoconstriction follows the development of a third space into the edematous affected muscles. This activates all the systems designated to raise blood pressure, such as the sympathetic nervous system, the renin-angiotensin-aldosterone system, and vasopressin release, that all together favor oliguria [6]. Finally, the heme component of myoglobin causes oxidative damage at the tubular level thanks to the iron-induced production of active oxygen radicals [8].

Clinical Issues

The hallmark of rhabdomyolysis-induced AKI is gross pigmenturia due to myoglobinuria. Reddish to brown urine should not be confused with hematuria, which is defined by the presence of red blood cells at the urinary sediment. Some doubts may arise in differential diagnosis between hematuria and myoglobinuria, since urinary dipstick tests cannot distinguish between hemoglobin and myoglobin. In fact, the urinary dipstick reacts with the heme component, which is present in both of these proteins. Thus, examination of urinary sediment is necessary to assess the presence of either red blood cells or pigmented granular casts (Table 1 and Fig. 1). Reddish to brown urine can occur in other conditions, including porphyria, hemoglobinuria, some drugs and foods. Moreover, other causes of AKI should be taken into consideration before making a wrong diagnosis of rhabdomyolysis-induced AKI. IIMs are often associated to other systemic diseases that require potential nephrotoxic treatments. For instance, cases of AKI have been described in association with the use of some immunosuppressive drugs, such as intravenous immunoglobulins [9]. Patients with cancer-related IIMs may also experience chemotherapy-induced renal damage, such as in the case of cisplatine used to treat lung neoplasms. It has been reported that, at least in 40 % of these cases, AKI was not a direct manifestation of IM but rather was due to drug toxicity [3]. This issue has to be taken into consideration when evaluating a patient with inflammatory myopathy who develops AKI and suggests the importance of a good history taking, a careful physical examination, and a thorough drugs review.

Moreover, AKI development also depends on the associated conditions and not only on the degree of rhabdomyolysis. In fact, there is a weak correlation between creatine kinase peak value and the incidence of renal failure [10]. Some coincident conditions, such as sepsis and dehydration, may contribute to kidney damage. In addition, some comorbidities, especially CKD, can predispose some patients to develop AKI more easily than other patients who were previously healthy. Couvrat-Desvergnes et al. have noted that male sex, cardiovascular risk factors, cardiac involvement and proteinuria >0.3 g/daily were associated with the development of AKI in one of the largest cohort of IIMs patients studied [3].

Therapeutic Issues

Therapeutic choices can be borrowed from those used for crush syndrome, which mainly include aggressive hydration and alkalinization. In this setting, especially hyperkalemia has to be treated aggressively: in four of the five patients reported by Yen et al. with AKI due to IIMs-related rhabdomyolysis, hyperkalemia precipitated ventricular arrhythmias and caused death [2]. Some tools to temporarily reduce serum potassium levels include repolarizing solutions (glucose and insulin), sodium bicarbonate infusion, and beta-adrenergic agonists inhalation. However, in order to remove the high amount of potassium and myoglobin released by damaged muscles, other means of increasing their clearance must be taken into consideration. Forcing diuresis is the best way to remove both potassium and myoglobin from the body. Saline infusion should be promptly started, at a rate ranging from 400 to 1000 ml/h, depending on the clinical setting, targeting a urine output of at least 3 ml/kg/h [6]. Alkalinization through the infusion of sodium bicarbonate solution is recommended for both acidosis and hyperkalemia. Moreover, raising urinary pH decreases the risk of myoglobin precipitation into casts. This has to be balanced with the risk of further lowering free plasmatic calcium levels. Calcium infusion is not recommended, unless hypocalcemia is symptomatic or hyperkalemia leads to

Table 1 Main differences in urinary examination (dipstick and urinary sediment analysis) between rhabdomyolysis-induced AKI and GN

	Rhabdoyolysis-induced AKI	GN
Proteins (dipstick)	+ to ++	+ to ++++
Hemoglobin (dipstick)	+ to ++++[a]	+ to ++++
Supernatant	Red	Yellow
Sediment	Normal	Red
Casts	Pigmented granular casts	Erythrocyte, granular, leucocyte and RTECs casts[b]

RTECs renal tubular epithelial cells

[a] The false positivity for hemoglobin is given by the heme moiety of myoglobin

[b] The particular type of cast is related to the specific kind of renal involvement

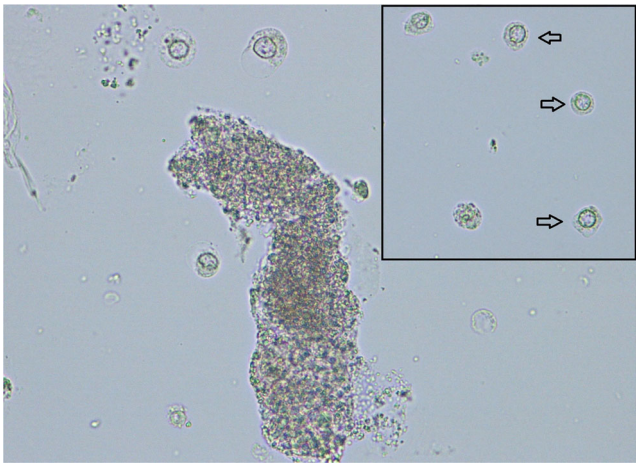

Fig. 1 Urinary sediment analysis showing the typical pigmented cast that is found in rhabdomyolysis-induced AKI. The acute tubular necrosis caused by myoglobinuria detaches renal tubular epithelial cells from the tubular basement membrane, so they can be easily found at the urinary sediment (*upper right, arrows*). Light microscopy, 400×

malignant arrhythmias. Calcium, in fact, can precipitate in muscles, causing in the long-term soft tissue calcifications, and can favor the occurrence of rebound hypercalcemia in the recovery phase [7]. Loop and osmotic diuretics may also be added to increase diuresis when necessary. When oliguria, acidosis, hyperkalemia, and volume overload are resistant to these interventions, the use of renal replacement therapy has to be considered. In this setting, the use of some high cut-off hemofilters (with a molecular cut-off up to 45 Kd) has been proven to be efficient in clearing myoglobin, whose molecular weight is 17 Kd and is not efficiently cleared by the usual hemodialysis membranes [11].

All these therapeutic interventions are based on clinical experience acquired in the caring of crush-syndrome patients, even though solid evidences currently miss and most data have been obtained by retrospective series. However, the most important step in the management of these patients seems to be the prompt start of aggressive hydration [12]. This underlines the risk of neglecting the complications of rhabdomyolysis and to delay the start of an adequate treatment. Moreover, it warrants the necessity to conduct well-designed studies in the field of rhabdomyolysis-induced AKI, in order to provide the most stringent recommendations for health-care providers.

Glomerulonephritis and Other Renal Diseases Associated to Inflammatory Idiopathic Myopathies

Another group of PM/DM patients may develop a glomerulonephritis (GN) that leads to the appearance of proteinuria and/or hematuria. Moreover, in a minority of cases, either Tubulo-Interstitial Nephritis (TIN) or vascular lesions resembling accelerated hypertension have also been described [3].

To our knowledge, there are 50 cases in which renal biopsy has been performed in patients with PM or DM who did not have neoplasms or any other systemic diseases that could involve both the muscles and kidneys, such as systemic lupus erythematosus (SLE), systemic sclerosis, pauci-immune vasculitis, and mixed connective tissue disease. Thirty-one patients have PM (Table 2), while 19 have DM (Table 3). Of all of these, 23 patients developed the renal disease simultaneously with the myopathy. In the other cases, renal involvement developed either after the onset of myopathy, from some months to up to 18 years, or before it in three cases. GN was diagnosed in 43 cases, TIN in two cases, while in other five cases vascular involvement was the chief finding. Outcome was good in the majority of cases: improvement of renal involvement has been reported in 72 % of cases (36/50), while progression to CKD or ESRD in 20 % (10/50). Death occurred in four patients (8 %). Age at IIMs onset, male sex, history of a cardiovascular event, and a previous AKI episode seem to be associated to CKD development [3].

Pathogenesis

In some cases, the inflammatory myopathy develops concurrently with GN and both diseases improve together after therapy has begun. Therefore, it is reasonable to speculate that the underlying autoimmune mechanism causing DM/PM can cause the GN as well. One can expect that DM and PM patients have different and specific pictures at renal biopsy, reflecting the activation of either humoral or cell-mediated immunity, as it happens in muscle biopsies. In this regard, it has been proposed that PM patients usually present with a picture of mesangial proliferative GN, while DM patients more often have membranous nephropathy [13, 14].

However, this is not always the rule. There are reports of PM patients who developed membranous nephropathy [3, 15, 16] and, on the other side, DM patients who had mesangial proliferative IgA nephropathy [2, 17]. Moreover, several other forms of GN have been described for both diseases (Table 4) and it is not clear why a humoral (DM) or a T cell-mediated (PM) disease should respectively cause membranous nephropathy or mesangial proliferative GN, since both of them are considered to be immune complex diseases.

Another issue that speaks in favor of different pathogenic mechanisms of renal involvement is that the reported immunofluorescences are really different. There are some cases of membranous nephropathy in which IF is positive for IgG and C3 [18], as it happens in the well-known idiopathic form, and other cases in which full-blown positivity for IgA, IgG, IgM, C1q, and C3 is present [19] and some others where complement deposition has not been reported [20].

The same has been noted in mesangial proliferative GN that, in some cases, has been classified as Berger's disease (IgA Nephropathy) due to the dominance or codominance of

Table 2 Histology, treatment, and outcomes of the previously reported cases of renal biopsy performed in patients with PM who did not have neoplastic diseases and/or systemic autoimmune diseases that could involve both the muscles and kidneys (such as systemic lupus erythematosus)

Reference	Sex/Age	Histologic diagnosis	Immunofluorescence	Time between IIM onset and renal disease onset	Treatment	Final outcome
[32]	39/M	Acute TIN	Negative	7 m	Cs	Improved
[34]	n/a	Amyloidosis	n/a	n/a	Cs	Improved
[3]	63/F	Chronic TIN	n/a	1y[a]	Cs	CKD
[27]	21/F	Crescentic	IgM, IgG, C3	0	Cs	ESRD
[25]	56/M	Crescentic	n/a	6y	Cs, PE	Improved
[33]	51/F	Cryoglobulinemic DPGN	n/a	4y	Cs, CYC, PE	Improved
[40]	54/F	mesPGN	IgM	0	Cs	Death
[3]	60/F	FSGS	n/a	2y	CSA, AZA, Cs	Improved
[34]	n/a	Endocapillary GN	n/a	n/a	Cs	CKD
[35]	55/M	MCD	Negative	0	Cs	Improved
[34]	n/a	MCD	n/a	n/a	Cs	Improved
[22]	41/M	mesPGN	n/a	0	Cs, MTX	Improved
[22]	24/M	mesPGN	IgG, IgM, IgA, C3	0	Cs	Improved
[22]	21/F	mesPGN	Negative	0	Cs	Improved
[22]	31/M	mesPGN	IgG, IgM	0	Cs, MTX	Death
[41]	37/M	mesPGN	n/a	0	Cs, CYC	Improved
[23]	56/M	mesPGN	IgM, C1q	0	Cs+CYC	Improved
[24]	28/M	mesPGN	IgM	0	Cs	Improved
[13]	58/M	mesPGN	IgA, IgG, IgM, C1q, C3	0	Cs, IVIg, CSA	Improved
[16]	65/F	mesPGN	n/a	10 m	Cs	Death
[42]	33/F	mesPGN with FSGS	n/a	0	Cs	Improved
[3]	38/F	IgAN	n/a	0	Cs, MTX, IVIg, TNF-i	Improved
[3]	43/M	IgAN	n/a	18y	Cs, MTX	Improved
[21]	35/M	IgAN	IgA	6 m	Cs, CYC, AZA	Improved
[15]	68/F	MN	IgG, IgA, IgM, C3	0	Cs, CYC	Improved
[16]	54/M	MN	n/a	10 m	Cs, CYC	Death
[3]	58/M	MN	n/a	1 m	Cs, MTX	Improved
[3]	45/F	Crescentic	n/a	4y[a]	CLM, Cs, MMF, CSA	CKD
[3]	55/M	VL	n/a	0	Cs	ESRD
[3]	67/F	VL	n/a	3 m	Cs	ESRD
[3]	70/M	VL	n/a	4 m	Cs	ESRD

DPGN diffuse proliferative GN, *mesPGN* mesangial proliferative GN, *MCD* minimal change disease, *FSGS* focal segmental glomerulosclerosis, *MN* membranous nephropathy, *VL* vascular lesions, *TIN* tubulo-interstitial nephritis, *Cs* corticosteroids, *PE* plasma exchange, *CYC* cyclophosphamide, *CSA* ciclosporin, *AZA* azathioprine, *MTX* methotrexate, *TNF-i* TNF-alpha inhibitors, *IVIg* intravenous immunoglobulins, *MMF* mycophenolate salts, *CLM* cloraminophen, *IgAN* IgA nephropathy, *n/a* not available, *CKD* chronic kidney disease, *ESRD* end-stage renal disease

[a] In these cases, renal involvement preceded IIMs onset

IgA at immunofluorescence [2, 3, 17, 21], while other patients had a deposition of a wide repertoire of different immunoglobulins and complements [13, 22–24].

Couvrat-Desvregnes et al. also reported a peculiar pattern of vascular lesions in patients who presented with AKI and uncontrolled hypertension. In these cases, renal biopsy showed edematous thickening of the intima of the interlobular and arcuate arteries and extensive atherosclerosis phenomena, resembling those features that are usually seen in malignant hypertension or scleroderma renal crisis [3].

Therefore, the pathogenic link between muscle and kidney involvement is much more complicated and troublesome to be understood, as it seems that different pathogenic pathways can cause an immune-mediated renal injury in the course of IIMs. Nevertheless, some considerations can be done. In most cases, glomerular diseases are characterized by immunoglobulin deposition and complement activation. When immunoglobulins bind directly some epitopes of the normal glomerulus, immunofluorescence displays a linear deposition of them. This picture is usually seen in Goodpasture syndrome, in which an

Table 3 Histology, treatment, and outcomes of the previously reported cases of renal biopsy performed in patients with DM who did not have neoplastic diseases and/or systemic autoimmune diseases that could involve both muscles and kidneys (such as systemic lupus erythematosus)

Reference	Sex/Age	Histologic diagnosis	Immunofluorescence	Time between IIM onset and renal disease onset	Treatment	Final Outcome
[28]	51/M	Crescentic	IgG	10y	Cs, CYC	Improved[c]
[29]	47/F	Crescentic	IgG, C3	5 m	Cs, CYC, MMF	Improved
[43]	44/F	DPGN	IgG, C1q, C3	0	Cs, RTX	Improved
[44]	7/M	FSGS	IgG	1 m[a]	Cs, IVIg, CYC, PE	Improved[b]
[3]	70/F	FSGS+VL	n/a	14y	Cs	Improved
[34]	n/a	endocapillary GN	n/a	n/a	Cs	Improved
[3]	39/F	MCD	n/a	0	Cs, AZA	CKD
[3]	42/M	MCD	n/a	0	Cs, MTX, IVIg	Improved
[34]	n/a	MCD	n/a	n/a	Cs	Improved
[17]	14/F	IgAN	IgA	0	PDN+MTX	Improved
[2]	26/F	IgAN	IgA, C3	1,5y	Cs+AZA	Improved
[18]	43/F	MN	IgG, C3	9y	Cs, CSA	Improved
[45]	37/M	MN	IgG, IgA	0	Cs	Improved
[19]	35/M	MN	IgG, IgA, C3, C1q	2y	Cs	Improved
[20]	46/F	MN	IgG	0	Cs	Improved
[46]	10/M	MN	IgA, IgG, C1q	0	Cs	Improved
[47]	52/F	MPGN	IgG, C3	6y	Cs, CYC, MMF	Improved
[3]	68/M	VL	n/a	2y	Cs, AZA, MMF	ESRD
[3]	34/M	VL	n/a	0	AZA, RTX	CKD

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[a] In this case, renal involvement preceded IIMs onset

[b] Renal function improved, but nephrotic syndrome persisted

[c] In this case, anti-glomerular basement membrane disease due to the presence of linear IgG deposits along the capillary walls was diagnosed

antibody directed against an epitope of collagen IV is produced. However, this mechanism of disease is rare, and only one case of PM displayed these features [21]. Actually, the most common form of renal involvement usually consists of immune complexes against non-renal self or foreign antigens (such as DNA nucleosomes or HCV-related proteins) that appear as granules at immunofluorescence. Immune complexes can develop in situ or can directly precipitate from circulation. The site in which immune complexes develop or precipitate usually determines the subsequent clinical and pathological picture, and this depends on both hemodynamic and physicochemical factors, i.e., size and charge of the immune complex itself. When visceral epithelial cells (podocytes) are involved, a non-inflammatory injury develops, since they are separated from the bloodstream by the glomerular basement membrane, and this physical barrier prevents the engagement of infiltrating leukocytes. The result is a functional change in glomerular permeability that leads to the development of massive proteinuria and nephrotic syndrome, as it happens in membranous nephropathy. On the other side, when endothelial or mesangial cells are involved, circulating leukocytes can infiltrate the glomerulus. Resident cells proliferate under their stimulus and glomeruli appear hypercellular at light microscopy, as seen in proliferative lupus nephritis, IgA nephropathy, and membranoproliferative GN. When the noxious stimulus is severe enough, thrombosis of capillary lumen, segmental or global necrosis of the glomerular tuft, and crescent formation can occur. Clinically, this inflammatory involvement of the kidney causes hematuria and various degrees of proteinuria. Depending upon disease severity, a normal to reduced filtration occurs and the patient can become oliguric.

Keeping in mind these basic pathogenic notions, some reports seem to suggest that most often GN in IIMs patients is a consequence of immune complexes deposition in glomeruli. Tsunemi et al. noted in a PM patient with crescentic glomerulonephritis the presence of serum immune complexes measured by the C1q binding assay. After plasma exchange, the concentration of immune complexes markedly dropped, and renal function improved as well [25]. Dyck et al. in 1979 suggested the possibility that immune complexes consisting

Table 4 Relative incidence of renal histologic involvement described in association with either PM or DM

PM (n=31)	DM (n=19)
32 % mesPGN (10/31)	26 % MN (5/19)
10 % MN (3/31)	16 % MCD (3/19)
10 % VL (3/31)	11 % Crescentic (2/19)
10 % Crescentic (3/31)	11 % IgAN (2/19)
10 % IgAN (3/31)	11 % FSGS (2/19)
7 % MCD (2/31)	11 % VL (2/19)
3 % Endocapillary GN (1/31)	5 % Endocapillary GN (1/19)
3 % Acute TIN (1/31)	5 % DPGN (1/19)
3 % Amyloidosis (1/31)	5 % MPGN (1/19)
3 % Chronic TIN (1/31)	
3 % Cryoglobulinemic DPGN (1/31)	
3 % FSGS (1/31)	

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of myoglobin-antimyoglobin antibodies trigger glomerular injury [22] and, in the same years, Nishikai documented the presence of anti-myoglobin antibodies in the sera of 22 of 31 patients with PM [26]. Therefore, the deposition of immune complexes may represent the first step of glomerular damage in most IIMs patients, after which complement deposition and leukocytes infiltration produce the observed pathological and clinical consequences.

Clinical Issues

Patients' presentation is heterogeneous, ranging from minor urinary abnormalities to rapidly progressive glomerulonephritis. Sometimes renal involvement can be neglected, when it presents with only small degrees of proteinuria and/or hematuria. Instead, in cases of accelerated renal failure, oliguria can be the first concern and some problems may arise in differential diagnosis between rhabdomyolysis-induced AKI and rapidly progressive GN. This difference is of paramount importance, since volume expansion is vital in the former case, while it can precipitate acute pulmonary edema in the latter. However, the occurrence of a rapidly progressive glomerulonephritis in IIMs patients is a rare event, as it has been reported in only four cases [25, 27–29]. Some clinical hints have to be looked for when vasculitis is suspected: high blood pressure with peripheral edema, urinary sediment with dysmorphic hematuria, and positive ANCA titer [28, 29] strongly suggest the presence of an active glomerular inflammation. On the other side, important elevation of muscle enzymes, hypotension, and pigmented casts usually suggest AKI due to rhabdomyolysis (Table 1).

Therapeutic Issues

Regarding therapy, some initial steps should be considered before starting an immunosuppressive treatment specifically directed at the kidney. Recommendations can be inferred from the actual guidelines about the general management of patients with GN [30]. Lifestyle modifications, including weight loss, smoking cessation, and regular exercise constitute an essential part of the therapy for blood pressure control, which is one of the most important factors that leads to progressive loss of glomerular filtration. Salt restriction is even more important, especially in nephrotic patients. Reduction of proteinuria, which, independently from the nature of GN, has toxic effects on podocytes and tubular cells, can be achieved by means of an ACE-inhibitor or an angiotensin-receptor blocker. Hyperlipemia should be treated according to the guidelines aimed at the reduction of cardiovascular risk; however, the use of statins in IIMs patients is controversial due to reports of statin-induced immune-mediated myositis, which persisted even after drug cessation [31]. In severely nephrotic patients, hypercoagulability should be treated with prophylactic low-dose anticoagulation.

In DM/PM patients with only small degrees of proteinuria and/or hematuria and a normal renal function the usual steroid schedule for IIMs, which includes prednisone 1 mg/Kg for 4–6 weeks [4], can be effective for both the kidneys and muscles [22, 32].

In patients who are otherwise symptomatic for GN (i.e., nephrotic patients) or who develop a progressive worsening of their renal function, the addition of another immunosuppressive drug should be considered, depending on the single case.

In previously reported cases of IIMs-related GN, several drugs have been added to steroids, including cyclophosphamide, methotrexate, azathioprine, rituximab, intravenous immunoglobulins, cyclosporine, and mycophenolate salts (Tables 2 and 3). Moreover, plasma exchange has been performed with good results in some cases of rapidly progressive glomerulonephritis [25, 33].

Given the paucity of data and the systemic nature of disease in these patients, which makes their GN somehow different from the better-known idiopathic forms, no guidelines actually exist and no formal recommendation can be done. A wise approach can be to choose therapy on the basis of patients' symptoms, renal function decline, renal histology, and single-center experience although, whenever possible, patients should be referred to more experienced centers in the treatment of IIMs and related complications.

Renal biopsy is of undoubtedly value in evaluating prognosis and deciding therapy: active proliferative lesions and the presence of crescents can deserve a more aggressive approach, while the evidence of chronic lesions, such as the presence of severe interstitial fibrosis, tubular atrophy, and glomerular

obsolescence may suggest to be more cautious. Some therapeutic hints can be taken from the actual guidelines for management of idiopathic glomerulonephritis [30]. For instance, in adults with nephrotic syndrome due to minimal change disease (MCD), the usual treatment consists of oral prednisone, and this regimen appeared to be effective in some MCD patients with PM [34, 35] and DM [34]. The recommended schedule consists of 1 mg/Kg dose, from a minimum of 4 weeks to a maximum period of 16 weeks [30]. When remission is reached, tapering should be slow, over a total period of 6 months. Thus, the occurrence of MCD in IIMs patients could require a period of steroid treatment much longer than that usually needed for achieving remission in PM or DM alone. Even IgA Nephropathy is usually treated with a 6-month long course of steroids as well, if proteinuria persists >1 g/24 h after 3–6 months of ACE-inhibitors or angiotensin-receptor blockers therapy. One of the most commonly used regimens is based on boluses for the first 3 days at months 1, 3, and 5, followed by oral steroid 0.5 mg/Kg, for a total period of 6 months [36]. The eventual addition of another immunosuppressive agent should be considered in case of worsening of renal function and the presence of crescents at renal histology [30].

Membranous nephropathy is usually treated with a 6-month course of alternating monthly cycles of corticosteroids and alkylating agents, such as cyclophosphamide and chlorambucil. To our knowledge, steroids and cyclophosphamide have already been used in two patients with PM, with conflicting results [15, 16]. Moreover, other patients with membranous nephropathy improved just after a steroid course that is known to be ineffective in achieving remission in the idiopathic form [37]. This may reflect the different pathogenesis between IIMs-related membranous nephropathy and the classical idiopathic form. In crescentic pauci-immune vasculitis, the addition of cyclophosphamide to steroids is recommended to achieve remission. Rituximab can also be considered in patients without severe disease or in whom cyclophosphamide is contraindicated. For maintenance therapy, azathioprine is the drug of choice while micophenolate mofetil (MMF) and methotrexate can be considered in patients allergic to, or intolerant of, azathioprine. In patients resistant to the induction therapy, the addition of rituximab, intravenous immunoglobulins, and plasmapheresis should be taken into consideration [30]. In previously reported cases of IIMs patients with pauci-immune vasculitis, outcome was fair when either cyclophosphamide [29] or plasma exchange [25] were added to steroid therapy. In a 1978 case report of a 7-year-old girl, steroid treatment alone was ineffective, and the patient eventually developed ESRD [27].

It is worthy to emphasize that, before deciding any treatment, the physician must evaluate if the severity of renal involvement parallels or exceeds the muscle disease and must rule out secondary causes of GNs. As mentioned previously, GNs can also develop in patients with inflammatory myopathies who also have systemic autoimmune disease, especially SLE [2, 38] or neoplasms, such as lung cancer [39]. In the latter case, the eventual successful treatment of the underlying neoplasm can lead to the disappearance of both myopathy and GN [14]. Therefore, even if a GN appears months or years after myopathy, this warrants a diagnostic work-up to rule out the presence of either a systemic autoimmune disease or an occult neoplasm.

Conclusions

Renal involvement in IIMs is not as uncommon as previously thought. When muscle inflammation precipitates myoglobinuria-induced AKI, prompt recognition and treatment are vital. In some other cases, renal involvement can be subtle and manifests with a pauci-symptomatic GN. This underlines the importance of careful monitoring of kidney function, proteinuria, and urinary sediment in all IIMs patients. Among these, patients who deserve a much more accurate screening are those with a previously impaired renal function, those who have to be treated with potential nephrotoxic drugs, and those who are going to start immunosuppressive treatment.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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