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Review

Renal involvement in anti-neutrophil cytoplasmic autoantibody associated vasculitis

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ABSTRACT

Renal involvement is a common and often severe complication of anti-neutrophil cytoplasmic autoantibody (ANCA) associated vasculitides (AAV).
With the exception of Churg–Strauss syndrome (CSS), where kidney involvement is not a prominent feature, renal disease is present in about 70% of patients with Wegener's granulomatosis, now called granulomatosis with polyangiitis (GPA) and in almost 100% of patients with microscopic polyangiitis (MPA).
Kidney involvement is generally characterized by a pauci-immune necrotizing and crescentic glomerulonephritis with a very rapid decline of renal function (rapidly progressive glomerulonephritis).
Even though there are not qualitative differences in glomerular lesions in patients with GPA or with MPA, chronic damage is significantly higher in MPA (and/or P-ANCA positive patients) than in GPA (and/or C-ANCA positive patients).
If untreated necrotizing and crescentic glomerulonephritis has an unfavorable course leading in a few weeks or months to end stage renal disease.
Serum creatinine at diagnosis, sclerotic lesions and the number of normal glomeruli at kidney biopsy are the best predictors of renal outcome.
Corticosteroids and cyclophosphamide (with the addition of plasma exchange in the most severe cases) are the cornerstone of induction treatment of ANCA-associated renal vasculitis, followed by azathioprine for maintenance.
Rituximab is as effective as cyclophosphamide in inducing remission in AAV and probably superior to cyclophosphamide in patients with severe flare, and could be preferred in younger patients in order to preserve fertility and in patients with serious relapses.

Contents

1. Introduction

The term vasculitides encompasses a group of inflammatory disorders that may affect the kidney by damaging its blood supply. Virtually any size or type of vessel may be involved; involvement of glomerular

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capillaries leads to necrotizing glomerulitis, while involvement of larger arteries can cause renal infarction and ischemia. Although the kidney may be affected by many types of systemic vasculitis, renal involvement is particularly frequent in some forms of small vessel systemic necrotizing vasculitis that are considered primary, such as Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and Churg–Strauss syndrome (CSS), collectively called anti-neutrophil cytoplasmic autoantibody (ANCA) associated vasculitis (AAV) [1–3].

Renal involvement is of particular importance in AAV because of its frequency and because of its impact on prognosis. With the exception of CSS, where kidney involvement is not a prominent feature [4–6], renal involvement is present in about 70% of patients with Wegener's granulomatosis [7,8], now called granulomatosis with polyangiitis (GPA) [9], and in almost 100% of patients with microscopic polyangiitis [10,11] (Fig. 1). Data from the Italian registry of kidney biopsies have shown that necrotizing vasculitis is the major form of nephropathy in patients presenting with acute renal failure undergoing kidney biopsy [12]. Moreover, the presence and severity of kidney involvement are associated with poorer prognosis (both patient and renal survival). Indeed, renal involvement at diagnosis is correlated in GPA with a worse patient survival (hazard ratio of 4.45; 1.48 to 13.65); when an impaired renal function is present the risk of death rises to a hazard ratio of 5.1 (1.59 to 10.16) and, in the case of dialysis dependence, to 8.2 (2.03 to 33.11). In MPA too, the presence of a significant renal insufficiency at diagnosis is an adverse survival marker (hazard ratio 3.69, 95% Confidence Interval 1.006 to 13.4) [13,14].

2. Clinical presentation

The main clinical presentation of renal involvement in AAV is represented by rapidly progressive glomerulonephritis (RPGN) (Fig. 1). RPGN is characterized clinically by a rapid decrease in the glomerular filtration rate (GFR) of at least 50% over a short period, from a few days to 3 months and, histologically, by extensive glomerular crescent formation. Other features include microscopic hematuria with, often, erythrocyte casts, and usually non nephrotic proteinuria [15].

Quite often RPGN is so severe to cause dialysis dependence at diagnosis in almost 60% of patients [16]. With improvement in early diagnosis a minor but significant number of patients may have just urinary abnormalities, microscopic hematuria and proteinuria, with serum creatinine within the normal range. A small but significant percentage of patients, especially those with MPA (14% in our series), may have a more indolent course and present, at diagnosis, with chronic renal insufficiency [16–18].

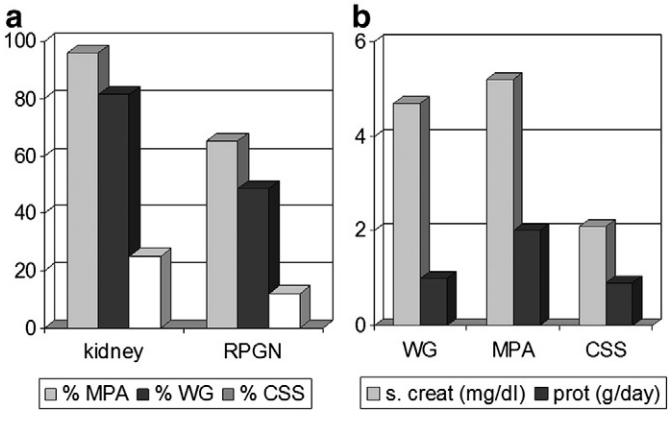

Fig. 1. a. Prevalence of renal involvement and rapidly progressive glomerulonephritis in patients with Wegener's granulomatosis, microscopic polyangiitis and Churg–Strauss syndrome. b. Serum creatinine and proteinuria at diagnosis in patients with Wegener's granulomatosis, microscopic polyangiitis and Churg–Strauss syndrome. Abbreviations: RPGN, rapidly progressive glomerulonephritis; MPA, microscopic polyangiitis; WG, Wegener's granulomatosis; CSS, Churg–Strauss syndrome; s. creat, serum creatinine; prot, proteinuria.

RPGN is one of the clinical presentations of glomerular diseases. It is one of the most dramatic, and must be considered as a medical emergency. As said before, it is characterized by:

- Renal insufficiency which develops in a few days or weeks
- Hematuria with cellular and erythrocyte casts
- Proteinuria which is usually non nephrotic (less than 3 g)
- Normal or slightly elevated blood pressure.

RPGNs are classified according to their pathogenesis and immunofluorescence patterns (Fig. 2) [15]. Type 1 is caused by the deposition of autoantibodies to glomerular basement membrane (GBM) and is characterized by linear deposits of immunoglobulin G. When lung involvement is present, the association of RPGN (due to anti-glomerular basement membrane antibody) and pulmonary hemorrhage is named Goodpasture syndrome. Type 2 RPGNs are due to the deposition of immune-complexes and are characterized by granular deposits of immunoglobulin and/or complement in the glomerulus. Rapidly progressive GN that we see in AAV is classified as type 3 or pauci-immune because immune deposits are absent or scanty and its pathogenesis is probably ANCA related. Type 3 RPGN accounts for more than 50% of all RPGNs, especially in older ages [12,13]. RPGNs are characterized by extracapillary proliferation (the so-called crescents) which is very similar in all the 3 types and can be distinguished from each other on the basis of the immunofluorescence pattern (Fig. 2) [15–18].

Renal vasculitis can occur at any age, but is seen particularly frequently in middle-aged and elderly subjects [17]. The median age at presentation is between 55 and 65 years in the majority of studies, being significantly greater for MPA (60.2 ± 16.4 vs. 52.6 ± 17.2 yrs in GPA in our series of 180 patients; $p = 0.0090$).

Because of the high prevalence of renal involvement in AAV, urinary sediment as well as renal function tests (serum creatinine, glomerular filtration rate and proteinuria) should be performed at diagnosis and at follow-up in all patients. Kidney biopsy has a fundamental role in AAV not only for diagnosis but also for prognosis and can be used to guide treatment.

3. Pathology

Renal involvement in AAV is characterized clinically by rapidly progressive renal failure and, histologically, by a pauci-immune necrotizing crescentic GN. The basic lesions are represented by necrosis of capillary loops, extracapillary proliferation with crescent formation, periglomerular and interstitial infiltrates, necrotizing arteritis and absence or paucity of immune deposits (Table 1). Capillaritis appears as fibrinoid necrosis of capillary loop and is usually (but not invariably) accompanied by extracapillary proliferation with crescent formation. Crescents can involve only a part of the glomerular tuft or can be circumferential with collapse of the glomerular tuft. They can be florid or fibrous according to the stage of the disease. Usually, there are important interstitial and periglomerular infiltrates which can be massive. Necrotizing arteritis is present in less than 20% of biopsy specimens. These lesions, although characteristics, are not pathognomonic. However, when such lesions are present in the contest of a paucity of immune deposits they become diagnostic [15–18]. Crescents (and necrosis) can involve less than 50% of glomeruli (focal forms) or more (diffuse), and the lesions can be restricted to a part of the glomerular tuft (segmental) or involve all the glomerulus (global). Interstitium and tubuli can also be involved to a various degree. The extension and the stage of the lesions determine the severity of the clinical manifestations [19].

On the basis of the extension of the lesions and their characteristics (active or sclerotic), the European Vasculitis Study Group (EUVAS) has proposed a histopathological classification for ANCA-associated glomerulonephritis [19]. The classification scheme has four general categories of lesions named focal, crescentic, sclerotic,

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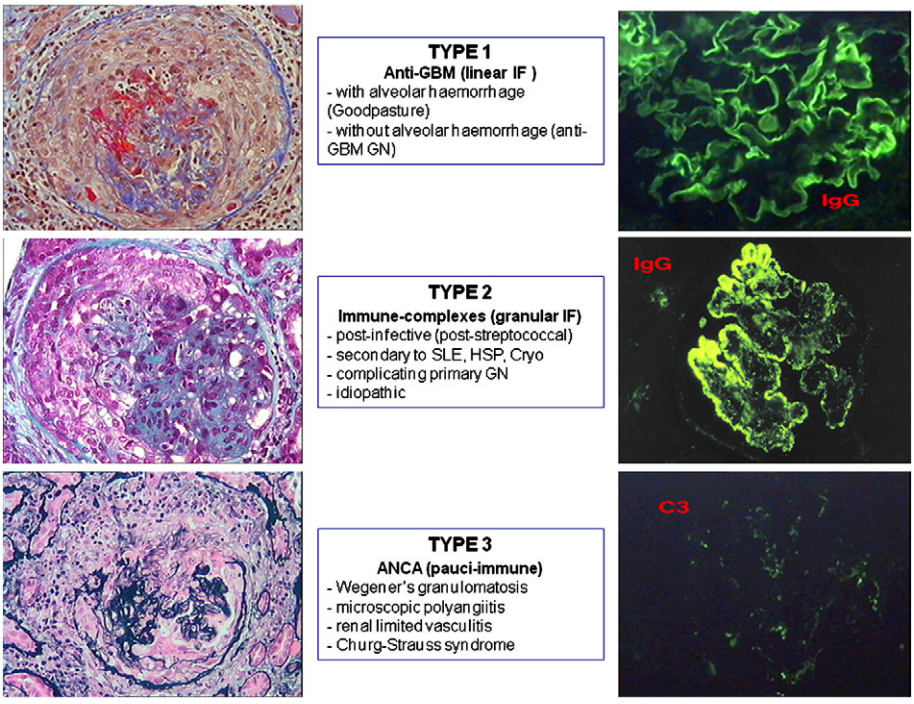

Fig. 2. Optical microscopy pictures (left) and immunofluorescence patterns (right) in the three types of rapidly progressive glomerulonephritis classified on the basis of pathogenesis and immunofluorescence pattern. Abbreviations: IF, immunofluorescence; ANCA, anti-neutrophil cytoplasmic autoantibody; GBM, glomerular membrane basement; GN, glomerulonephritis; SLE, systemic lupus erythematosus; HSP, Henoch–Schonlein purpura; cryo, cryoglobulinemia.

and mixed (Table 1). The first 3 categories are based on the predominance of normal glomeruli, glomeruli with cellular crescents, and globally sclerotic glomeruli, respectively. The mixed category represents a heterogeneous phenotype, and comprises those biopsies in which none of the aforementioned features is dominant [19,20]. Preliminary results have shown that the proposed classification system is of prognostic value for 1- and 5-year renal outcomes [19].

Even though there are not qualitative differences in glomerular lesions in patients with GPA or with MPA, chronic damage is significantly higher in MPA (and/or P-ANCA positive patients) than in GPA (and/or C-ANCA positive patients) [18,20–22]. Moreover, P-ANCA positive patients have significantly higher percentage of globally sclerosed glomeruli whereas C-ANCA positive patients show more glomeruli with active lesions and arteritis [21,22]. This difference has been explained by a delayed establishment of diagnosis in MPA compared to patients with GPA and/or by a different pathogenesis of renal lesions [21].

Necrotizing crescentic glomerulonephritis in AAV is defined as pauci-immune because of the absence or paucity of significant immunoglobulin deposits. However, a subgroup of patients (18%) has substantial deposition of immunoglobulin in the mesangium and/or along the glomerular basement membrane [23]. Such deposits are found even in a higher percentage (54%) of cases by electron microscopy [24]. The presence of immune deposits is associated with a significantly greater degree of proteinuria [23,24].

Table 1
Renal histology (elementary lesions) and histopathological classification of ANCA-associated vasculitis.

Necrosis of capillary loops (capillaritis)	
Extracapillary proliferation (crescents)	
Periglomerular infiltrates (sometime granuloma-like)	
Interstitial infiltrates	
Necrotizing arteritis	
Immunoglobulin deposits absent or scanty (pauci-immune)	
Class	**Features**
Focal	≥ 50% normal glomeruli
Crescentic	≥ 50% cellular crescents
Sclerotic	≥ 50% globally sclerotic glomeruli
Mixed	None of the above

4. Clinical and pathological correlations

Several studies have examined the correlations between renal clinical presentation, in particular renal function, and histological features [21,22,25]. Generally, the percentage of normal glomeruli is the strongest predictor of glomerular filtration rate (GFR) at diagnosis, with higher GFR in those patients whose biopsy had shown the highest percentages of normal glomeruli [21,22]. Other parameters which are correlated with serum creatinine are: percentage of glomeruli with cellular crescents, percentage of globally sclerosed glomeruli, extent of interstitial infiltrates, interstitial fibrosis and tubular lesions [21,22]. No correlation is usually found between renal function and fibrinoid necrosis or with the presence of arteritis [21].

5. Prognosis and prognostic factors

Untreated necrotizing and crescentic glomerulonephritis has an unfavorable course leading in a few weeks or months to end stage renal disease (ESRD). Even if the prognosis has improved in the last years with the introduction of corticosteroids and cyclophosphamide as treatment of choice, a significant percentage of patients still require renal replacement therapy because of progressive disease. In a recently published large series, 14 and 18% of patients required permanent dialysis and 23 and 40% had died by 1 and 5 years, respectively [22].

The presence and severity of renal involvement at diagnosis have an important impact on both renal and patient survival [25,26].

Among predictors of renal outcome a number of clinical and histological determinants have been identified. They can be summarized,

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pooling data from different large cohorts of patients, as follows: older age, female gender, serum creatinine for clinical predictors and chronic lesions (glomerulosclerosis, interstitial fibrosis and tubular atrophy) for histological parameters [21,22,25,26]. Other predictors are treatment resistance and relapses (Table 2) [23]. Considering diagnosis, MPA and renal limited vasculitis tend to have a worse prognosis because of older age and because of more chronic lesions at kidney biopsy [21–27].

The new proposed EUVAS classification has also been shown to be of prognostic value [19,20].

6. Renal involvement in Churg–Strauss syndrome

CSS is considered to be one of the so-called ANCA-associated systemic vasculitis because of its clinical and pathologic features that overlap with those of the other AAV, Wegener's granulomatosis and microscopic polyangiitis [1]. However, these two diseases differ from CSS clinically, by the absence of asthma, and pathologically, by the absence of eosinophilia and eosinophil-rich tissue infiltrates [5,6]. Moreover, whereas ANCA are consistently found in 75–95% of patients with active GPA and MPA [28–30], the prevalence of ANCA in CSS is much lower [31–34].

Two recent independent studies on large cohorts of patients, one from the French Vasculitis Study Group, the other from Italy, have found that ANCA, usually P-ANCA/MPO-ANCA, are present in only about 40% of patients [32,33].

In both studies, patients with CSS who were ANCA positive were significantly more likely to have disease manifestations associated with small-vessel vasculitis, including renal involvement, mononeuritis, and purpura. Patients who were ANCA negative were significantly more likely to have cardiac involvement. In the French study, ANCA negative patients had a higher frequency of pleural effusion whereas, in the Italian study, ANCA negative patients had more frequently all kinds of pulmonary involvement (pleurisy was not considered by its own), other than alveolar hemorrhage, which was found more often in ANCA positive cases. Furthermore, in both studies vasculitis was documented less frequently in histological specimens from ANCA negative patients in comparison with ANCA positive ones [32,33].

Table 2
Clinical and histological (shaded area) predictors of renal outcome.

Reference	de Lind van Wijngaarden (25)	Hauer (21)	Hogan (26)	Day (22)
Number of patients	100	96	350	390
Age	Yes	Yes	Yes	No
Sex	Yes	No	Yes	No
Ethnicity	ND	ND	Yes	ND
Diagnosis	No	No	No	No
Serum creatinine	Yes	Yes	Yes	Yes
Dialysis dependance	Yes	ND	ND	ND
Treatment (plasma exchange)	Yes	ND	ND	Yes
ANCA type	No	No	Yes	No
Proteinuria	ND	No	ND	ND
Normal glomeruli	Yes	Yes	ND	Yes
Fibrinoid necrosis	No	Yes	ND	No
Crescents	No	No	Yes	ND
Glomerulosclerosis	Yes	Yes	Yes	Yes
Interstitial infiltrates	Yes	Yes	ND	ND
Interstitial fibrosis	Yes	Yes	Yes	Yes
Tubular atrophy	Yes	Yes	Yes	Yes
Arteritis	No	No	ND	ND
Arteriolosclerosis	No	No	Yes	Yes

Abbreviations. ND, not determined; ANCA, anti-neutrophil cytoplasmic autoantibody.

Renal disease is often an overlooked feature of CSS. Although less frequent and severe than in the other ANCA-associated vasculitides, renal manifestations occur in 25% of CSS patients and range from isolated urinary abnormalities to rapidly progressive glomerulonephritis; some patients have chronic renal failure at diagnosis [4,31]. The most typical picture is pauci-immune focal and segmental necrotizing glomerulonephritis, with or without crescents, which usually involve less than 50% of the glomeruli. Tubulo-interstitial nephritis with eosinophilic predominance is found only occasionally; a few patients have mesangial glomerulonephritis or focal segmental sclerosis [4,35,36].

Patients with necrotizing crescentic glomerulonephritis and, in general, patients with clinical signs of glomerular involvement, have a higher prevalence of ANCA positivity [4,32,33]. In our series patients with renal disease had a greater frequency of constitutional symptoms (90 vs. 57%, $p=0.001$), and ANCA positivity (75 vs. 27.5%, $p<0.001$); moreover, Birmingham Vasculitis Activity Score (BVAS) was significantly higher in patients with kidney involvement as well as the prognostic Five Factor Score [4].

Renal flares are rare, and long term prognosis and outcome are generally good [4]. Nonetheless, kidney disease is an adverse prognostic factor for CSS patients; the largest study accurately assessing renal involvement in CSS demonstrated a (albeit not statistically significant) higher 5-year mortality rate in patients with than in those without renal involvement [4]; previous studies also showed that particularly proteinuria >1 g/24 h was a strong predictor of mortality in CSS [34].

7. Renal involvement not only glomerulonephritis

Renal involvement in AAV is not caused only by glomerulonephritis; rare cases of obstructive uropathy due to ureteral granulomatous vasculitis have been described in patients with CSS or GPA [4,37] and isolated interstitial nephritis can be found too [38]. Cases of ruptured arterial aneurysm of the kidney caused by involvement of larger vessels have been reported [39,40].

8. Treatment of renal involvement

Therapy of AAV will be covered in another article of this issue of the journal. However, some guidelines on the specific aspects of treatment of necrotizing crescentic glomerulonephritis will be given.

EUVAS has categorized renal AAV patients in 2 subgroups according to the presence and severity of kidney involvement [40–42]. Randomized controlled trials have been conducted in order to obtain evidence based recommendations [43–45].

Patients with serum creatinine lower than 500 μmol/l (5.7 mg/dl) should be treated with prednisone and cyclophosphamide for 3–6 months until remission is reached [43]. Oral and pulse cyclophosphamide have been shown to be equivalent in terms of clinical response [45]. Cyclophosphamide pulses are, however, associated with less episodes of leukopenia and the cumulative dose of the drug is inferior to that found in the oral cyclophosphamide treated patients [45]. A tendency towards more frequent relapses has been shown in cyclophosphamide pulse treated patients [44–46].

Once that disease is into remission (usually within 3–6 months), azathioprine is as effective as cyclophosphamide and more effective than mycophenolate/mofetil to maintain remission [43,47]. Methotrexate has also been shown to be equivalent to azathioprine but it should not be used in patients with renal impairment [48].

How long to continue maintenance therapy is not known, but at least one year since remission is recommendable.

Patients with generalized vasculitis and renal involvement with a serum creatinine higher than 500 μmol per liter (5.7 mg/dl) should be treated with a course of plasma exchange (7 sessions in 2 weeks) in addition to prednisone and oral cyclophosphamide. In a randomized controlled trial, plasma exchange was shown to be more effective

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than methylprednisolone pulses in terms of renal function recovery [44,49].

Rituximab, a chimeric monoclonal antibody to CD20, is as effective as cyclophosphamide in inducing remission in AAV and should be preferred to cyclophosphamide, at least in younger patients, in order to preserve fertility [50–52]. Rituximab was superior to cyclophosphamide in patients enrolled in the RAVE (Rituximab in ANCA-Associated Vasculitis) randomized controlled trial because of a severe flare and, therefore, this kind of patients should be treated accordingly [51].

Rituximab has some efficacy in refractory cases and could be used in patients who do not respond to standard treatment [50,53,54].

Rituximab has been used also to maintain remission in non controlled trials with promising results and a randomized controlled trial is ongoing [50,53].

Preliminary results from small pilot studies indicate that mycophenolate mofetil is effective for induction and maintenance of remission in microscopic polyangiitis with mild to moderate renal involvement [55–57].

Prophylaxis and monitoring for many conditions, including *Pneumocystis jiroveci* infection, fungal and other opportunistic infections, osteoporosis should be considered in all patients [41,42].

A significant percentage of patients will remain with some degree of chronic renal impairment in terms of either reduced GFR or proteinuria or both. In this setting, anti-proteinuric treatment with angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs) is warranted in order to prevent or delay ESRD [58,59].

All the patients should be monitored closely in order to identify renal flares. Urinary sediment is fundamental for an early diagnosis and for differential diagnosis between proteinuria due to chronic damage from proteinuria due to active disease [57,58].

Proteinuria due to renal scarring should not be treated as an active disease with corticosteroids and immunosuppressants.

In doubtful cases a repeat kidney biopsy should be performed if not contraindicated.

9. Take-home messages

- Renal involvement is a frequent and often severe complication of ANCA-associated vasculitis.
- It is characterized clinically by rapidly progressive renal failure and histologically by pauci-immune necrotizing and crescentic glomerulonephritis.
- Among the numerous predictors of renal outcome, older age, serum creatinine at diagnosis, treatment resistance, relapses and chronic lesions at kidney biopsy are the most important.
- In patients with severe renal insufficiency due to necrotizing and crescentic glomerulonephritis (serum creatinine higher than 500 μmol/l) plasma exchange should be added to prednisone and cyclophosphamide to improve renal function.

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