Review

Rapidly progressive crescentic glomerulonephritis: Early treatment is a must

Gabriella Moroni,⁎ Claudio Ponticelli

Division of Nephrology, Fondazione Ca’ Granda Ospedale Maggiore IRCCS, Milano, Italy
Division of Nephrology, Humanitas Scientific Institute, Rozzano, Milano, Italy

Abstract

The term crescentic glomerulonephritis (GN) refers to a pathologic condition characterized by extracapillary proliferation in ~50% of glomeruli. Clinically crescentic GN is characterized by a nephritic syndrome rapidly progressing to end stage renal disease (ESRD). Three types of crescentic GN have been identified. Type 1 includes cases of Goodpasture syndrome characterized by linear deposits of antibodies along the glomerular basement membrane (GBM) at immunofluorescence. Type 2 is a heterogeneous group of primary or secondary glomerular diseases complicated by crescentic GN. In this category there are granular deposits of immunoglobulins and complement fractions on the glomerular tuft. Type 3 includes cases of ANCA-associated small-vessel vasculitis. Immunofluorescence is negative or may show only faint deposits of immunoglobulins. The etiology and the initial pathogenetic factors are different in the three types, but the final mechanisms leading to crescent formation and the renal symptoms and signs are similar. The prognosis depends on the timeline of diagnosis and treatment. Although some patients requiring dialysis may recover a good renal function, usually the higher the serum creatinine at presentation the worse the outcome. When treatment is initiated early, most patients obtain a complete or partial remission. High-dose corticosteroids and cyclophosphamide represent the standard therapy for crescentic GN. The addition of plasma exchange may also be helpful, particularly in patients with massive alveolar hemorrhage. Anti-B monoclonal antibodies have also been used in some patients with crescentic GN, but their role in this particular area is still poorly established.

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epithelial cells to proliferate, causing breaks in the Bowman capsule which leads to a large influx of macrophages and fibrin [1]. These changes eventually lead to obstruction of the tubular outlet, glomerular scarring and loss of the affected nephron (Table 1).

2. Classification of crescentic GN

There are three categories of crescentic GN based on the presence and the distribution of immune deposits at immunofluorescence [2,3] (Fig. 1).

Type 1 accounts for only 10% of crescentic GN. Goodpasture syndrome is the typical example of this category. In normal GBM, alpha 3, alpha 4, and alpha 5 type IV collagen have a hexamer structure and are cross-linked to adjacent NC1 domains to form dimers (D isofrom). In patients with Goodpasture syndrome, there are linear deposits of immunoglobulins G (IgG) directed against the non-collagenous 1 (NC1) domain of the alpha-3 chain of type IV collagen in the GBM and in the membrane of pulmonary alveoli. More recently, antibodies against alpha 5IV NC1 have also been identified in anti GBM disease [4]. The etiology of Goodpasture syndrome is still unknown. Genetic and environmental factors may predispose patients to the development of the Goodpasture syndrome. It has been shown that autoimmunity to the NC1 domain of the alpha3-chain of type IV collagen is strongly associated with HLA-DR15. However, alpha3 (IV)NC1 presentation to T cells seems to be determined more by “processing factors” than by the preferences of relatively indiscriminate DR15 molecules [5]. Smoking, viral respiratory infection or exposure to hydrocarbon solvents may be frequently associated with Goodpasture syndrome and may contribute to its development [6]. Today the Goodpasture syndrome is defined as an autoimmune “conformopathy” [4]. Accordingly, the disease is triggered by a perturbation of the quaternary structure of the alpha345NC1 hexamer, inducing a pathogenic conformational change in the alpha3NC1 and alpha5NC1 subunits, which in turn elicits autoimmune antibody formation. The injury caused by antibodies can produce gaps in the glomerular capillary wall that allow the entrance of coagulation factors and inflammatory cells in the Bowman space, where they promote crescent formation [1,3]. Although direct injury involving local production of complement and polymorphonuclear activation is probably the main cause for activating parietal epithelial cells, it is likely that T cell response and regulation may also play a pathogenetic role [7].

Almost all cases of Goodpasture syndrome present with rapidly progressive GN. The nephritic syndrome is often associated with anemia, pulmonary hemorrhage and dyspnea. The diagnosis can be confirmed by detecting anti-GBM antibodies in the blood and by immunofluorescence analysis of kidney tissue showing linear deposits of IgG along the GBM. In 10 to 38% of patients, anti-myeloperoxidase cytoplasmic antibodies (p-ANCA) or, more rarely, anti-proteinase-3 neutrophil cytoplasmic antibodies (c-ANCA) may also be detected [8,9].

Rare cases of membranous nephropathy preceding or following recovery from Goodpasture syndrome have been reported, suggesting the possibility of increased antigen synthesis, exposure of cryptic epitopes, and/or capping and shedding of antigen–antibody complexes [10]. Detection of antibodies to phospholipase A2 is crucial to discriminate between patients with primary MN and those with a secondary form of the disease, as both forms require different diagnostic approaches and treatment strategies [11].

Rarely, type 1 crescentic GN may develop in patients with Alport’s syndrome who receive a kidney transplant. The presence in the transplanted kidney of antigenic epitopes that are lacking in the native kidneys can trigger the production of antibodies. In most cases there is a transient IgG linear deposition along the GBM without circulating anti-GBM antibodies, but in 3% to 12% of patients anti-GBM antibodies can produce severe crescentic glomerulonephritis [12]. The epitopes recognized by the anti-GBM antibodies in X-linked Alport syndrome are non-cryptic intact hexamer of the alpha5NC1, unlike those of the classic Goodpasture syndrome in the native kidneys [4,13,14].

Type 2 accounts for 15–20% of crescentic GN. It is a heterogeneous group of rapidly progressive GN characterized by granular deposits of immunoglobulins. Different immune-complex diseases may contribute to develop type II crescentic GN, including post-infectious acute GN [15,16], lupus nephritis [17–19], Henoch–Schönlein purpura [20,21], mixed cryoglobulinemia [22,23], IgA nephritis [24,25], immune-complex mediated membranoproliferative glomerulonephritis [26], diabetic glomerulosclerosis [27] and primitive or secondary amyloidosis [28]. The occurrence of crescentic GN has been estimated to range around 16% for postinfectious GN [15], 8% for lupus nephritis [18], 2.7% for adults with Henoch–Schönlein purpura [21], and 11% for cryoglobulinemic nephritis [22]. In these diseases the deposition of circulating immune complexes in the GBM or in situ formation of immune complexes within the glomerular capillaries activates inflammatory cells and complement causing damage to the GBM [1,3,29]. Moreover, the glomerular injury may trigger inflammation and activate the innate immune response with recruitment of macrophages, natural killer cells, granulocytes and maturation of dendritic cells which stimulate the adaptive immune response with production of TH1 and TH17 cells [30]. This chain of events contributes to crescent formation.

Type 3 is the most common form of crescentic GN accounting for around 60–80% of all cases. It was the most frequent cause of acute renal kidney injury reported in the Italian registry of kidney biopsies [31]. This type of crescentic GN is characterized by the absence of immune glomerular deposits and is now considered to be a small-vessel renal vasculitis. Actually, although in a few patients who present the typical clinical and pathological features of crescentic GN without immune deposits the signs of vasculitis are absent, most of the afflicted patients have circulating antineutrophil cytoplasmic antibodies and signs of systemic vasculitis. A recent consensus conference proposed to reclassify type 3 crescentic GN as ANCA-associated vasculitis (AAV) [32]. This term includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA). In our cohort of 89 patients with AAV and renal involvement crescentic GN developed in 70% of patients with GPA and in 65% of patients with MPA. Crescentic GN was more rare in EGPA with renal involvement accounting for only 13.8% of cases in the experience of Sinico et al. [33]. All these conditions, although with difference in prevalence, share renal lesions characterized by diffuse extracapillary proliferation and necrotizing inflammation of capillaries, venules, arterioles and small arteries [34]. However, the accompanying signs and symptoms are different. In all the three diseases lesions of skin, gastrointestinal system and neurologic system may be present. In GPA the renal lesions are usually associated with granulomatous involvement of the
Fig. 1. Main features of crescentic GN at optic microscopy and immunofluorescence.
was 2.0 times higher for subjects of European ancestry than for non-Europeans [59]. A Swedish study reported a higher prevalence of vasculitis, 160 per million inhabitants for GPA, 94 for MPA, 31 for polyarteritis nodosa and 14 for EGPA [60]. In a British study, the overall annual incidence for AAV was 18/million, 7.9/million for GPA, 7.5/million for MPA, 7.0/million for polyarteritis nodosa and 1.3/million for EGPA [61]. With the exception of EGPA, where kidney involvement is not a prominent feature, renal disease is present in about 70% of patients with GPA, and in almost 100% of patients with MPA [62].

4. Clinical presentation and diagnosis

Nephritic syndrome and rapidly progressive GN are common features in all types of crescentic GN. With the exception of pauci-immune GN, extra-renal signs and symptoms may also be present. Pulmonary hemorrhage and severe anemia are frequent in Goodpasture syndrome. Arthralgias, skin rash, pleurisy, pericarditis, and more rarely cerebritis may be associated with lupus nephritis [63]. Purpura, arthralgias and abdola column characterize Henoch–Schonlein purpura. Purpura, fatigue, joint pain, hepato-splenomegaly, and peripheral neuropathy are frequent manifestations of cryoglobulinemic nephritis. The clinical picture of small-vessel vasculitides is extremely variable. In GPA pulmonary cavitating and noduli are frequent. Multiplex mononeuritis, rhinitis, sinusitis, otitis media, and episcleritis are also frequent. In MPA pulmonary infiltrates, skin ulcers and nodules, and arthralgias are often present. EGPA is characterized by asthma, sinusitis, skin and lung involvement, and peripheral neuropathy.

Blood tests make it possible to differentiate between the different diseases. Circulating anti-GBM antibodies are typical of Goodpasture syndrome. In around 30% of cases pANCA may also be present or precede the clinical onset [64]. Low C3 levels are frequent in post-infectious GN. Anti-nuclear antibodies, anti-DNA antibodies, and low C3 and C4 levels characterize lupus nephritis. Circulating cryoglobulins and hypocomplementemia are markers of cryoglobulinemic nephritis. High levels of IgA are present in many patients with Berger disease or Henoch–Schonlein purpura. ANCA test is the immunologic marker of AAV, present in 90% of cases. However, it should be borne in mind that circulating ANCA may be detected in 10–38% of the cases in Goodpasture syndrome, in around 20% of lupus patients and in rare cases of post-infective GN, Henoch–Schonlein purpura, and cryoglobulinemia.

Renal biopsy is very helpful (Table 2). Although the histologic picture at light microscopy may be similar in all the three types of crescentic GN, intracapillary proliferation is usually absent in types 1 and 3 while it is almost constant in type 2 crescentic GN. Fibrinoid necrosis can be seen in lupus nephritis and is frequent in AAV. Granuloma may be seen in GPA, and eosinophil infiltration can occur in EGPA. Of great importance are the findings of immunofluorescence. Linear deposits of immunoglobulins G along the GBM are typical of Goodpasture syndrome. Granular deposits of immunoglobulins and complement characterize type 2 crescentic GN. Instead, in AAV immunoglobulin deposits are absent or faint.

5. Prognosis

Independently of the original disease, the prognosis of crescentic GN was ominous until a few years ago. Modern treatment has improved the outcome. Yet, even today, the prognosis largely depends on serum creatinine at presentation. In a series of 71 patients with anti-GBM crescentic GN treated with plasma exchange and aggressive immunosuppression, those who presented with a creatinine concentration less than 5.7 mg/dL had 100% patient survival and 95% renal survival at 1 year. In patients who presented with a creatinine concentration ≥ 5.7 mg/dL but did not require immediate dialysis, patient and renal survival were respectively 83% and 82% at 1 year. In patients who presented with dialysis-dependent renal failure, patient and renal survival were 65% and 8% at 1 year. All patients who required immediate dialysis and had 100% crescents on renal biopsy remained dialysis dependent [65].

Even in type 2 crescentic GN high levels of serum creatinine at presentation are predictors of poor prognosis [66], although cases of oligo-anuric patients who recovered partial renal function have been reported [67,68].

At multivariate analyses serum creatinine at presentation was an independent factor associated with renal survival also in small-vessel vasculitis, while age and pulmonary hemorrhage were associated with an increased risk of death [69,70]. In a European survey, an estimated glomerular filtration rate (GFR) < 15 mL/min, advancing age, higher Birmingham Vasculitis Activity Score, lower hemoglobin and higher white cell count were significant negative prognostic factors for patient survival in the long-term [71]. On the other hand, it has been pointed out that there is no absolute level of serum creatinine above which treatment is always ineffective [72].

Apart from serum creatinine, renal biopsy can also indicate the prognosis. Crescents extended to > 80% of glomeruli are usually associated with a poor prognosis in type 2 crescentic GN [67]. A validation study on 100 renal biopsies from AAV patients reported that at 5 year patients with ≥50% of normal glomeruli (focal group) had 93% renal survival in comparison to 50% survival in those with ≥50 global sclerotic glomeruli (sclerotic group), and 76% in patients with cellular crescents in ≥50 glomeruli (crescentic group) [73].

Patients with “double positive” ANCA and anti-GBM antibodies share extrarenal manifestations similar to patients with vasculitis while the renal manifestations resemble those seen in anti-GBM patients clinically and histologically. The renal prognosis of these patients is poor despite treatment [74,75].

6. Treatment

Early treatment is of paramount importance for patients with crescentic GN. The current approach is based on a combination of corticosteroids and cytotoxic drugs with the aims of quenching the active inflammation and abating the cellular response and the antibody production [76]. Usually treatment is initiated with intravenous methylprednisolone pulses followed by oral prednisone 1 mg/kg/24 h progressively reduced over time and cyclophosphamide, either intravenously at a dosage of 0.5–1 g/m² or orally at a dose of 2–3 mg/kg/24 h. These doses should be reduced in old or frail patients. Plasmapheresis can be added to remove circulating antibodies or immune-complexes. Patients with Goodpasture syndrome respond well to corticosteroids and cyclophosphamide if treatment is initiated early. Plasma exchange is indicated in patients with massive alveolar hemorrhage [77]. Plasmapheresis may also offer some other advantages over immunosuppression alone, including an earlier disappearance of circulating anti-GBM antibodies.

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Table 2

Main characteristics of the different types of crescentic glomerulonephritis at kidney biopsy examination.

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<th>Light microscopy</th>
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<tr>
<td>Type 1. Extracapillary proliferation. Intracapillary proliferation absent.</td>
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<tr>
<td>Type 2. Extracapillary and intracapillary proliferation.</td>
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<tr>
<td>Type 3. Extracapillary proliferation. Intracapillary proliferation usually absent (some mesangial proliferation in eosinophilic granulomatosis with polyangiitis).</td>
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<tr>
<td>Granuloma may be seen in granulomatosis with polyangiitis. Infiltration of eosinophils may occur in eosinophilic granulomatosis with polyangiitis.</td>
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<th>Immunofluorescence</th>
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<td>Type 1. Linear deposits of immunoglobulins IgG along the glomerular basement membrane</td>
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<tr>
<td>Type 2. Granular deposits of immunoglobulins and C3 in post-infectious glomerulonephritis (GN), membranoproliferative GN and cryoglobulinemic GN. “Full house” pattern in crescentic lupus nephritis. Mesangial deposits of IgA in IgA nephritis and in Henoch-Schonlein purpura.</td>
</tr>
<tr>
<td>Type 3. Absent or faint deposits of immunoglobulins and/or C3.</td>
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and better serum creatinine levels at recovery. However, the prognosis depends more on the number of crescents and serum creatinine than on the type of therapy [78]. Usually the treatment of Goodpasture syndrome is discontinued at 3 months, when circulating antibodies are undetectable. Late recurrence is very rare and usually responds to treatment.

The treatment of crescentic GN type 2 also rests on high-dose corticosteroids and cyclophosphamide [79,80]. In resistant cases plasma exchange improves the response in some cases of IgA nephritis [81], and corticosteroids and cyclophosphamide [79,80]. In resistant cases plasma exchange is discontinued at 3 months, when circulating antibodies are undetectable. Late recurrence is very rare and usually responds to treatment.

In patients with ANCA-associated vasculitis and rapidly progressive crescentic GN an early aggressive treatment with high-dose corticosteroids and cyclophosphamide is mandatory. Plasma exchange is recommended in patients with lung hemorrhage [85] and in those with severe ANCA-related renal vasculitis. With a schedule based on the combination of high-dose corticosteroids, intravenous cyclophosphamide and plasma exchange, 65% of 41 dialysis-dependent patients with ANCA-associated vasculitis were alive with independent renal function one year after clinical onset of crescentic GN [86]. The role of rituximab in type 3 crescentic GN is unclear, but it is likely that this monoclonal antibody may be of benefit, since rituximab associated with corticosteroids can induce and maintain remission in the majority of patients with severe forms of ANCA-associated vasculitis [87–92], including those with concomitant infection [93].

7. Conclusions

Crescentic GN may develop in a number of immune-mediated renal and systemic diseases. While the natural course of crescentic GN usually leads to ESRD, an appropriate treatment may halt the progression and even lead to complete remission. Prompt diagnosis and treatment are essential to reverse progression. We recommend that, even before a precise diagnosis is made, any patient presenting with a nephritic syndrome and a rapidly progressive course should start immediate treatment with high-dose corticosteroids and cyclophosphamide unless there are very clear contraindications. In the meantime immunological investigations should be performed to establish the etiology, which can be confirmed by renal biopsy. Once a complete diagnosis has been ascertained a rational treatment should be planned, taking into account the age, the general conditions and the comorbidity of the patient. Frequent monitoring of the clinical and biological parameters is a good guide for modulating the doses of immunosuppressive drugs or replacing the agents responsible for adverse events.

Take-home messages

• In a patient with a rapid increase of serum creatinine, associated with nephritic signs such as dysmorphic erythrocytura, erythrocyte casts and proteinuria a clinical diagnosis of crescentic glomerulonephritis should be made.

• While awaiting for the results of immunological and pathological investigations, an immediate treatment with methylprednisolone pulses and cyclophosphamide is essential.

• To assess the etiology of crescentic glomerulonephritis the following blood tests should be made: anti-GBM antibodies, ANCA, anti-dsDNA antibodies, search for cryoglobulins, C3 and C4 levels, IgA levels, anti-streptolysin titer, blood culture.

• Kidney biopsy with immunofluorescence analysis is necessary unless very clear contraindications exist.

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References

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Autoimmune diseases and vitiligo

Vitiligo is known to be associated with various autoimmune disorders; however the rates of this association differed between various geographical locations suggesting that genetics and environmental factors may play a role. Recently Nejad SB, et al. (Pak J Biol Sci. 2013 Jun 15;16(12):570-4), in a control study of 86 patients with vitiligo, studied the association between autoimmune disorders. All patients were screened for autoimmune disorders and were compared to an age-and gender-matched normal population. They have demonstrated that the prevalence of thyroid disorders in vitiligo patients was statistically more significant than the control group (p = 0.008) and that the most common autoimmune disorder associated with vitiligo was hypothyroidism.

Yaron Zafrir