Autoimmunity Reviews 13 (2014) 723–729

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Rapidly progressive crescentic glomerulonephritis: Early treatment is a must

Gabriella Moroni [a,*], Claudio Ponticelli [b]

[a] Division of Nephrology, Fondazione Ca' Granda Ospedale Maggiore IRCCS, Milano, Italy
[b] Division of Nephrology, Humanitas Scientific Institute, Rozzano, Milano, Italy

ARTICLE INFO

Article history:
Received 4 February 2014
Accepted 14 February 2014
Available online 19 March 2014

Keywords:
Rapidly progressive glomerulonephritis
End stage renal disease
Goodpasture syndrome
ANCA-associated vasculitis (AAV)

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.

Published by Elsevier B.V.

Contents

1. Introduction

Crescentic glomerulonephritis, also called rapidly progressive GN, is not a specific disease, but a histological manifestation of severe glomerular damage, characterized by accumulation in the Bowman's space of cells derived by proliferating and de-differentiated visceral and parietal cells. These cells surround and compress the glomerular tuft. Clinically, crescentic GN is usually associated with macroscopic or microscopic hematuria, erythrocyte casts, variable degrees of proteinuria and leads to a loss of renal function within 3 months from clinical onset. The etiology of crescentic GN can be different but whatever the cause is, the final result consists in damage of the GBM, passage of fibrin and fibronectin in the urinary space where they activate parietal

* Corresponding author at: Divisione di Nefrologia e Dialisi, Padiglione Croff, Fondazione Ospedale Maggiore, Mangiagalli, Regina Elena, Via della Commenda 15, 20122 Milano, Italy. Tel.: +39 02 55 03 45 52; fax: +39 02 55 03 45 50.
E-mail address: gmoroni@policlinico.mi.it (G. Moroni).

http://dx.doi.org/10.1016/j.autrev.2014.02.007
1568-9972/Published by Elsevier B.V.

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 isoform). 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 5(IV)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 "conformeropathy" [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 autoantibody 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 alpha5NCI, 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–Schonlein 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–Schonlein 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

Table 1
Pathogenetic mechanism of crescent formation.