

Crescentic glomerulonephritis

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Introduction

Crescentic glomerulonephritis is not a specific disease but rather is a morphologic expression of severe glomerular injury that can be caused by many different aetiologies and pathogenic mechanisms [1,2]. The major pathogenic event that causes crescent formation is rupture of glomerular capillaries, which allows cellular and humoral inflammatory mediators to spill into Bowman's space. Because this structural phenotype indicates severe glomerular injury, it is not surprising that it usually correlates with clinical manifestations of severe active glomerulonephritis and rapid loss of renal function, i.e. rapidly progressive glomerulonephritis. Rapid and accurate diagnosis of crescentic glomerulonephritis, which must include precise subclassification, is essential for optimum renal and patient outcome. This is reflected in the strong correlation between outcome and the serum creatinine at the time of initiation of treatment.

On the basis of immunopathologic findings, crescentic glomerulonephritis can be classified into three major categories: immune complex glomerulonephritis, anti-glomerular basement membrane antibody (anti-GBM) glomerulonephritis, and pauci-immune glomerulonephritis, which often is associated with antineutrophil cytoplasmic autoantibodies (ANCA) [1,2]. Each of these categories can be further divided based on clinical, pathologic and serologic findings (Figure 1). This categorization is useful for clinical management of crescentic glomerulonephritis.

Immune complex crescentic glomerulonephritis

As demonstrated in Figure 1, immune complex glomerulonephritis has less often crescent formation

than anti-GBM glomerulonephritis or ANCA glomerulonephritis [2]. Because crescents are a marker of severe glomerulonephritis, this indicates that, in general, immune complex glomerulonephritis is a less aggressive category of glomerulonephritis than anti-GBM glomerulonephritis or ANCA glomerulonephritis. Within a given category of immune complex glomerulonephritis, for example IgA nephropathy or lupus glomerulonephritis, the prognosis correlates directly with the percentage of crescents. However, the prognostic significance of a given percentage crescents is not the same in different categories. For example, a patient with diffuse proliferative lupus glomerulonephritis who has 25% crescents has a much worse prognosis than a patient with post-streptococcal acute diffuse proliferative glomerulonephritis and 25% crescents.

Anti-GBM disease

Anti-GBM glomerulonephritis is caused by autoantibodies directed against the alpha 3 chain of type IV collagen [3,4]. Anti-GBM glomerulonephritis has the most severe glomerular injury at the time of biopsy (Table 1), which correlates with, and is the basis for, its aggressive clinical manifestations. Approximately half of patients with anti-GBM glomerulonephritis have pulmonary haemorrhage, and thus manifest pulmonary–renal vasculitic syndrome. However, ANCA-glomerulonephritis with ANCA-pulmonary capillaritis more often is the cause for pulmonary–renal vasculitic syndrome than anti-GBM disease [5]. The term Goodpasture's syndrome should be reserved for patients with pulmonary–renal vasculitic syndrome caused by anti-GBM antibodies. Approximately a third to a quarter of patients with anti-GBM disease also are ANCA-positive [6]. This is an important determination to make, because anti-GBM patients with ANCA are at risk for developing small vessel vasculitis in organs other than kidneys and lungs, and may have recurrences of ANCA-disease after the anti-GBM disease has resolved.

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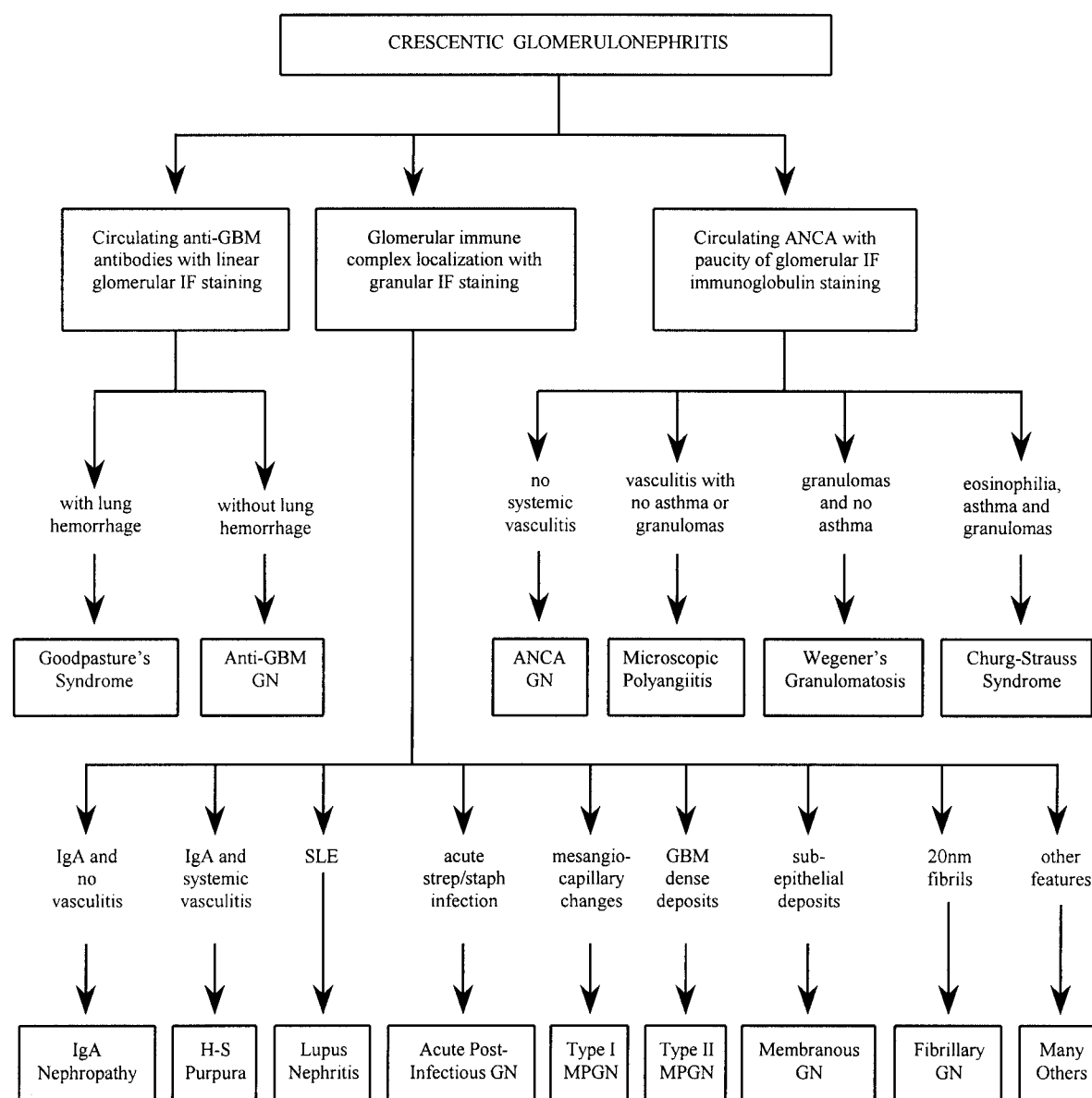


Fig. 1. Algorithm for resolving the differential diagnosis of crescentic glomerulonephritis. The approach requires integration of clinical, pathologic and serologic data to identify specific categories of crescentic glomerulonephritis that have distinctive natural histories (prognoses) and different optimum treatment regimens.

ANCA-Small vessel vasculitis and glomerulonephritis

When glomeruli in patients with crescentic glomerulonephritis are evaluated for the presence of immunoglobulins, most patients do not have evidence for either immune complex or anti-GBM localization [7,2]. Approximately 80–90% of these patients with a paucity of glomerular immunoglobulin staining have ANCA in their circulation [8,9]. These autoantibodies react with proteins in the primary granules of neutrophils and the lysosomes of monocytes, and may be pathogenic [8]. The antigen specificity of ANCA in patients with glomerulonephritis is usually for proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA) [8,9]. PR3-ANCA usually cause cytoplasmic

staining of neutrophils in indirect immunofluorescence assays (C-ANCA), whereas MPO-ANCA usually cause perinuclear staining (P-ANCA).

ANCA-glomerulonephritis may occur as a renal-limited disease; however, over three-quarters of patients with ANCA-glomerulonephritis have evidence for small vessel vasculitis. ANCA-small vessel vasculitis includes microscopic polyangiitis, Wegener's granulomatosis, and Churg–Strauss syndrome [9]. Microscopic polyangiitis is characterized by systemic necrotizing small vessel vasculitis that can affect arteries, arterioles, capillaries, venules, and veins [10]. Wegener's granulomatosis and Churg–Strauss syndrome have this same background of small vessel vasculitis. Patients with Wegener's granulomatosis have the additional finding of necrotizing granulomatous inflammation,

Table 1. Correlation of crescent formation with category of glomerulonephritis based on an analysis of over 6000 native kidney biopsies evaluated in the UNC Nephropathology Laboratory

Disease	Percent of patients with any crescents	Percent of patients with 50% or more crescents	Percent of glomeruli with crescents (when present)
Anti-GBM glomerulonephritis	95	81	77
ANCA glomerulonephritis	90	48	48
Immune complex glomerulonephritis			
Lupus glomerulonephritis (class III and IV)*	40	11	31
Henoch-Schönlein purpura glomerulonephritis*	53	5	24
IgA nephropathy*	27	5	24
Acute post-infectious glomerulonephritis*	25	4	17
Fibrillary glomerulonephritis	20	7	29
Type I membranoproliferative glomerulonephritis	20	3	21
Membranous lupus glomerulonephritis (class V)	12	1	17
Membranous glomerulonephritis (non-lupus)	5	0	17

*Extent of crescent formation in the biopsied patients shown in this table is higher than in all patients with these diseases because more severe examples of glomerulonephritis are more often evaluated by renal biopsy. Reprinted with permission [2].

usually in the respiratory tract, and Churg–Strauss syndrome patients have blood eosinophilia and a history of asthma (Figure 1). All patients with major organ damage, such as severe glomerulonephritis, caused by ANCA-disease require aggressive immunosuppressive therapy [9], thus, once a patient has a diagnosis of ANCA-crescentic glomerulonephritis, there is no need to delay treatment until the patient can be categorized as renal-limited disease, microscopic polyangiitis, Wegener's granulomatosis, or Churg–Strauss syndrome.

Summary

Crescentic glomerulonephritis is caused by many different aetiologies and pathogenic mechanisms, which determine the natural history and appropriate treatment. Therefore, diagnostic evaluation of patients with rapidly progressive glomerulonephritis should include precise and expeditious categorization based on current knowledge of aetiology and pathogenesis. This knowledge is very incomplete. Thus our current diagnostic system unquestionably will evolve as our knowledge grows.

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