Anti–Glomerular Basement Membrane Disease

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KEYWORDS

• Goodpasture syndrome • Vasculitis • Rapidly progressive glomerulonephritis
• Pulmonary hemorrhage • Plasma exchange

KEY POINTS

- Anti–glomerular basement membrane (GBM) disease often presents with rapidly progressive glomerulonephritis with or without lung hemorrhage. It is rare to present with lung hemorrhage alone.
- Antibodies are generally directed at E_A or E_B epitopes found within the noncollagenous (NC1) domain of the $\alpha 3$ chain of type IV collagen.
- Renal and patient survival in untreated anti-GBM is poor, although intensive therapy provides improved outcomes in patients with alveolar hemorrhage or rapidly progressive glomerulonephritis not requiring dialysis at outset.
- Relapses are uncommon in patients with anti-GBM disease.
- Patients who are double positive for antineutrophil cytoplasm antibody and anti-GBM have more relapsing disease and often need maintenance immunosuppressive therapy.

Anti–glomerular basement membrane (anti-GBM) disease is a rare, life-threatening, small vessel vasculitis that can affect both the glomerular and pulmonary capillaries.[1] It usually presents as a rapidly progressive glomerulonephritis (RPGN), with or without pulmonary hemorrhage. Rare cases have been reported to present with pulmonary hemorrhage alone or with a more indolent course.

It is an immune complex–mediated disease, facilitated by antibodies directed against intrinsic antigens in the basement membranes of both pulmonary and renal vasculature. These autoantibodies are detectable by serum immunoassay or are

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seen as classic linear polyclonal immunoglobulin (Ig) G deposits on immunofluorescence staining of the GBM on analysis of kidney biopsy samples.

NOMENCLATURE

The term Goodpasture syndrome was the eponymous name given by Stanton and Tange[2] to a case series of 9 patients presenting with pulmonary hemorrhage associated with glomerulonephritis. This name was in acknowledgment of an earlier case report by Goodpasture[3] describing a fatal case of renopulmonary syndrome after influenza in 1919. However, the latter may not have referred to anti-GBM disease because there was also a description of a splenic vasculitic granuloma. Furthermore, at that time the culprit autoantibody had yet to be identified.

However, the term Goodpasture syndrome is still used widely in literature to describe the clinical constellation of both pulmonary hemorrhage and glomerulonephritis, regardless of the underlying cause. The term Goodpasture disease is used to describe renopulmonary syndrome in patients with detectable anti-GBM antibodies.

For the purpose of this article, the nomenclature is restricted to using anti-GBM disease as per the Chapel Hill Consensus.[1] Anti-GBM antibody is the term used to describe the circulating factor; however, it is clear that these antibodies target both glomerular and alveolar basement membranes (and potentially others in the retina, choroid plexus, and cochlea). These antibodies tend to be IgG autoantibodies against the noncollagenous (NC1) domain of the alpha 3 chain of type IV collagen in the basement membrane.

EPIDEMIOLOGY

Anti-GBM disease is a rare disorder, with an estimated frequency of 1 to 2 cases per million population per year in European populations. A recent study from Ireland was the first to report a national disease incidence (of 1.64 per million population per year).[4] It is rare to find cases of anti-GBM disease in African populations, but it has been well described in other white and Asian populations.

However, anti-GBM disease is a fairly common cause of RPGN.[5] Detectable antibodies or classic histologic findings are found in 10% to 15% of cases of RPGN, although this varies across different populations, with one Japanese study showing that only 6.6% of RPGN cases were attributable to anti-GBM disease.[6]

Anti-GBM disease seems to have a bimodal distribution, with younger patients (20–30 years old) being more frequently male and presenting with renopulmonary syndrome, whereas older patients (60–70 years old) have a female predominance with renal involvement only.[7]

PREDISPOSING FACTORS

Like many autoimmune diseases, there are strong positive and protective associations with human leukocyte antigen (HLA) polymorphisms in anti-GBM disease, and in particular with major histocompatibility complex class II genes. There is a hierarchy of associations with particular *DRB1* alleles: for example, *DRB1*1501* is a strong susceptibility allele, whereas the presence of *DRB1*01* confers a dominant-negative protective effect.[8] However, the susceptibility alleles are common in healthy populations, whereas disease is exceedingly rare, thus suggesting that additional factors, whether genetic or environmental, contribute to disease pathogenesis in humans.

Seasonal distribution and outbreaks of disease have been previously described,[7,9,10] as well as clusters linked anecdotally to influenza outbreaks.[11,12] In