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Review

Goodpasture's syndrome: A clinical update

Antonio Greco [a], Maria Ida Rizzo [b], Armando De Virgilio [a,b,*], Andrea Gallo [c], Massimo Fusconi [a], Giulio Pagliuca [c], Salvatore Martellucci [c], Rosaria Turchetta [d], Lucia Longo [a], Marco De Vincentiis [a]

[a] Department Organs of Sense, ENT Section, 'Sapienza' University of Rome, Viale del Policlinico 155, 00100 Roma, Italy
[b] Department of Surgical Science, 'Sapienza' University of Rome, Viale del Policlinico 155, 00100 Roma, Italy
[c] Department of Medico-Surgical Sciences and Biotechnologies, Otorhinolaryngology Section, 'Sapienza' University of Rome, Corso della Repubblica, 79, 04100 Latina, LT, Italy
[d] Department Organs of Sense, Audiology Section, 'Sapienza' University of Rome, Viale del Policlinico 155, 00100 Roma, Italy

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ABSTRACT

Goodpasture's syndrome (GS) is a rare and organ-specific autoimmune disease that is mediated by anti-glomerular basement membrane (anti-GBM) antibodies and has pathology characterized by crescentic glomerulonephritis with linear immunofluorescent staining for IgG on the GBM. It typically presents as acute renal failure caused by a rapidly progressive glomerulonephritis, accompanied by pulmonary hemorrhage that may be life-threatening. It was first described as a distinctive syndrome by Pasture in 1919. Autoimmune Inner Ear Disease (AIED) may be associated. The etiology of GS is unknown. Researchers hypothesized a genetic predisposition HLA-associated. Complex immunological mechanisms are in the pathogenesis. The disease is caused by autoantibodies against the NC1 domain of the alpha 3 chain of type IV collagen. The limited presence of this molecule in the body explains the interest confined to specific target organs, such as the lung and kidney. It occurs when the immune system attacks the walls of the lungs and the tiny filtering units in the kidneys. Without prompt diagnosis and treatment, the disease can lead to bleeding in the lungs, kidney failure, and even death.

Contents

* Corresponding author at: Department Organs of Sense, ENT Section, 'Sapienza' University of Rome, Viale del Policlinico 155, 00100 Roma, Italy. Tel.: +39 380 3408909; fax: +39 06 49976803.
E-mail address: armando.devirgilio@gmail.com (A. De Virgilio).

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1. Introduction

Goodpasture's syndrome (GS) is a rare disease, identified by Dr. Ernest Goodpasture in 1919 [1,2]. It is an organ-specific autoimmune disease that is mediated by anti-glomerular basement membrane (anti-GBM) antibodies and has pathology characterized by crescentic glomerulonephritis with linear immunofluorescent staining for IgG on the GBM. It typically presents as acute renal failure caused by a rapidly progressive glomerulonephritis, accompanied by pulmonary hemorrhage, that may be life-threatening [3–6].

Other acronyms and names include Goodpasture's disease, anti-GBM disease and crescentic glomerulonephritis type 1 [7–11].

Numerous reports of single patients with this disorder, as well as small case series, have been published [12–20]. There is the lack of systematic data on GS.

2. Epidemiology

The incidence of GS is estimated to be 1 case per million per year, but it is a cause of acute renal failure in approximately 20% of all cases of rapidly progressive or crescentic glomerulonephritis [21]. This disorder occurs more commonly in white people than in black people. The age distribution is bimodal, 20–30 years and 60–70 years. The prevalence of the disease is higher in men in the younger age group and women in the older age subgroup [22].

3. Etiopathogenesis

In the 1950s, Krakower and Greenspon [23] identified GBM as the antigen. In 1967, Lerner, Glassock, and Dixon [24] confirmed that the antibodies taken from the diseased kidneys produced nephritis in experimental animals. The discovery of anti-GBM antibodies led to the understanding of the pathogenesis of GS.

GS or Anti-GBM disease is an autoimmune disorder characterized by autoantibodies directed against the glomerular/alveolar basement membrane. The autoantibodies bind to their reactive epitopes in the basement membranes and activate the complement cascade, resulting in tissue injury. This is a classic type II reaction in the Gell and Coombs classification of antigen–antibody reactions. This binding of antibodies can be visualized as the linear deposition of immunoglobulin along the glomerular basement membrane and, less commonly, the alveolar basement membranes, by direct immunofluorescent techniques.

In most patients, the autoantibody in GS is directed against a 28-kd monomeric subunit present within the noncollagenous domain of the alpha 3 chain of type IV collagen (alpha3[IV]NC1) [22–25]. Two conformational epitopes of anti-GBM antibodies have been defined at residues 17–31 and 127–141 of alpha3(IV)NC1, which were named as EA and EB, respectively [Fig. 1].

Although basement membranes are ubiquitous, only the alveolar and glomerular basement membranes are affected clinically. The preferential binding to the alveolar and glomerular basement membranes appears to be caused by greater accessibility of epitopes and greater expansion of alpha 3 collagen units. Furthermore, the alpha 3 collagen chains of glomerular and basement membranes are structurally integrated in such a way that they are more accessible to the circulating antibodies [26,27].

Strong evidence exists that genetics play an important role. Patients with specific human leukocyte antigen (HLA) types are more susceptible to disease and may have a worse prognosis.

There is an increased prevalence of HLA-DR15 (previously known as HLA-DR2) and DRB1*03, DRB1*04 and a decreased frequency of DRB1*01 and DRB1*07 [28,29]. Goodpasture disease is strongly associated with the DRB1*1501 and to a lesser extent the DRB1*1502 allele. Although a strong association exists between anti-GBM disease and HLA DRB1*1501, this allele is present in as many as one third of individuals in white populations. It is therefore clear that additional factors, either genetic or environmental, are required for disease expression [30–33].

While the exact cause of GS is unknown, certain behaviors and environmental factors are believed to put people at higher risk. Certain respiratory infections may trigger the disease. Exposure to hydrocarbon fumes, metallic dust, tobacco smoke, or substances such as cocaine may also increase risk.

The recent literature shows that an initial insult to the pulmonary vasculature is required for exposure of the alveolar capillaries to the anti-GBM antibodies, and predisposing factors for such exposure include the following: association with HLA-DR15; exposure to organic solvents or hydrocarbons; smoking; infection (e.g., influenza A2); cocaine inhalation; exposure to metal dusts; and lymphocyte-depletion therapy, such as alemtuzumab [34–39].

4. Symptomatology

Symptoms may start out slowly, gradually affecting the lungs and the kidneys. Other times they may progress rapidly, becoming severe in a matter of days. Constitutional symptoms like malaise, chills and fever, and/or arthralgias may precede or be concurrent with pulmonary or renal manifestations. Initial symptoms may include fatigue, weakness, or lethargy nausea and/or vomiting, loss of appetite, unhealthy, pale appearance. Substantial variation exists in the clinical manifestations of patients with anti-GBM disease. 60 to 80% of the patients have clinically apparent manifestations of pulmonary and renal disease, 20–40% have renal disease alone, and less than 10% have disease that is limited to the lungs [40–43].

If the disease moves to affect the lungs, hemoptysis is usually the presenting symptom and the following symptoms like dry cough or coughing up blood, shortness of breath or dyspnea may occur. Sometimes symptoms affecting the lungs can become life-threatening, if there is a massive pulmonary hemorrhage leading to respiratory failure. Chest pain is present in less than half of the patients. Significant anemia may result from persistent intrapulmonary bleeding.

If the disease affects the kidneys, it may cause burning sensation during urination, hematuria or foamy urine, swelling of the hands and feet, high blood pressure, and back pain below the ribs. Other renal manifestations include edema and eventually uremia.

Autoimmune Inner Ear Disease (AIED) is present in the same cases [44,45]. The symptoms of AIED are sudden hearing loss in one ear [46] progressing rapidly to the second ear. The hearing loss can progress over weeks or months. Patients may feel fullness in the ear and experience vertigo [47]. In addition, a ringing, hissing, or roaring sound in the ear may be experienced [44,45].

5. Diagnosis

Diagnosis of GS is made by detection of circulating anti-GBM antibodies, and more specifically, the anti-α3(IV) NC1 antibodies on solid-phase immunoassays. Kidney biopsy provides definitive diagnosis. On light microscopy, the early changes are of a focal proliferative GN. This proliferative response usually progresses to necrosis and extensive crescent formation with interstitial inflammation. The pathognomonic finding on direct immunofluorescence is the linear deposition of immunoglobulin G (IgG) along the GBM and sometimes along the distal tubular basement [48].

Diagnosis of AIED-Goodpasture-associated is difficult and AIED is often mistaken for otitis media until the patient develops a loss in the second ear [44,45].

5.1. Physical examination

Physical examination findings in patients with anti-GBM disease include the following: tachypnea; inspiratory crackles over lung bases;