

Goodpasture's disease

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Abstract

Goodpasture's disease is characterized by the association of pulmonary hemorrhage, extracapillary glomerulonephritis, and anti-glomerular basement membrane antibodies. It is due to autoantibodies against the NC1 domain of the alpha3 chain of type IV collagen. Goodpasture's disease is a very rare disease, and in Europe its annual incidence has been estimated to be about 0.5 to 1 cases per million inhabitants. This incidence is not constant all year long, and it increases in spring and early summer. Treatment is based on the association of corticosteroids, cyclophosphamide, and plasma exchange. With this treatment, patients' survival is about 75% at one year. Renal survival at one year is higher than 90% for patients who are treated early, but is lower than 10% when patients are dialysis-dependent at the start of treatment.

Keywords

Goodpasture's disease , Anti-GBM antibodies , Crescentic glomerulonephritis , Pulmonary hemorrhage

Disease name and synonyms

- Goodpasture's disease (eponym used since 1958);
- Antiglomerular basement membrane antibody-mediated nephritis with pulmonary hemorrhage;
- Antiglomerular basement membrane antibody disease with pulmonary hemorrhage.

The name Goodpasture syndrome should be abandoned, since it has been ambiguously applied to both pulmonary-renal syndromes and Goodpasture's disease.

Excluded diseases

- All associations of pulmonary hemorrhage and glomerulonephritis that are not due to anti-

glomerular basement membrane (GBM) antibodies.

- Anti-GBM antibody-mediated nephritis without pulmonary hemorrhage.

Diagnosis criteria

- The diagnosis is based on the association of:
- extracapillary (i.e. crescentic) glomerulonephritis;
- pulmonary hemorrhage;
- anti-GBM antibodies, that are characteristically deposited along the renal and pulmonary GBM.

Differential diagnoses

Goodpasture's disease should be differentiated from the other pulmonary-renal syndromes, and it is important to remember that only about 10% of cases of pulmonary hemorrhage with acute nephritis are due to Goodpasture's disease. In particular, it should be distinguished from:

- vasculitides that are responsible for pulmonary hemorrhage and extracapillary glomerulonephritis, not associated with glomerular deposition of anti-GBM antibodies, but usually with blood antineutrophil cytoplasmic autoantibodies (ANCA), such as microscopic polyangiitis or [Wegener's granulomatosis](#);
- other causes of acute renal failure with pulmonary hemorrhage, such as cryoglobulinemia, systemic lupus erythematosus, Schönlein-Henoch purpura, or hemolytic and uremic syndrome;
- acute renal failure associated with pulmonary edema;
- pulmonary infections associated with acute renal failure.

Frequency

Goodpasture's disease is a very rare disease, and in Europe its annual incidence has been estimated to be about 0.5 to 1 cases per million inhabitants. This incidence is not constant all year long, and it increases in spring and early summer.

Goodpasture's disease occurs most often in Caucasian populations, and is slightly more frequent in male than in female. It can affect people of any age, but it is more common in the third and sixth decades. In more than 80% of cases, it affects people carrying HLA-DR15 or -DR5.

Clinical description

Usually, the first manifestations of Goodpasture's disease are non-specific, consisting of flu-like syndrome, asthenia, mild breathlessness, or dry cough. This explains that the diagnosis is often delayed.

Lung disease

Pulmonary hemorrhage is responsible for cough, typically (but not always) associated with hemoptysis, and dyspnea. Physical examination may reveal chest crackles. Chest X-ray films typically show bilateral alveolar infiltrates, which may be confused with hemodynamic pulmonary edema. However, there is no pleural effusion and no cardiomegaly. Alveolar infiltrates can also disclose segmental infiltrates not seen on chest X-ray, or they can be completely normal. In that latter case, tomodensitometry can detect

alveolar infiltrates not seen on chest X-ray. This alveolar hemorrhage is almost always responsible for iron deprivation and anemia.

Lung hemorrhage is favored by cigarette smoking, lung infections, and possibly also by inhalation of noxious substances such as hydrocarbon fumes.

Renal disease

Extracapillary glomerulonephritis is responsible for rapidly progressive renal failure, associated with hematuria (which can be macroscopic, and is associated with red-cell casts), and with moderate proteinuria (typically 1 to 3 g/day). Blood pressure is usually normal, in the absence of end-stage renal failure.

In very rare cases, renal disease is mild, only responsible for microscopic hematuria, associated or not with a slight elevation of serum creatinine.

Management including treatment

With the current therapeutic strategies, over 90% of patients survive the acute phase of the disease. Death usually is due to lung hemorrhage or to treatment-related infections. Nevertheless, Goodpasture's disease is a therapeutic emergency, since renal outcome is tightly linked to renal function at the start of treatment, and since sudden occurrence of dramatic lung hemorrhage is always a threat.

Immunosuppressive therapy

The immunosuppressive therapy of Goodpasture's disease is based on the association of:

- corticosteroids, started at a dose of 1 mg/kg/day and then progressively tapered over 6 to 9 months;
- oral cyclophosphamide, given at a daily dose of 2 to 3 mg/kg (this dose being reduced in patients over 60 years) for about 3 months;
- plasma exchanges. The standard protocol consists of daily plasma exchanges (50 ml/kg, maximum 4L) for 14 days, or until circulating anti-GBM antibodies can no longer be detected. Human serum albumin is the standard replacement fluid, but it may be necessary to use fresh frozen plasma to prevent bleeding.

With this treatment, patients' survival is about 75% at one year. Renal survival at one year is higher than 90% for patients who are treated early, but is lower than 10% when patients are dialysis-dependent at the start of treatment.

Other therapies

Depending on the severity of renal failure and pulmonary hemorrhage, patients may require dialysis and/or respiratory support.

It is essential to carefully avoid fluid overload and to rapidly treat infections (and in particular pulmonary infections), in order to decrease pulmonary hemorrhage.

Smoking should be prohibited, since it might trigger further pulmonary hemorrhage.

Dialysis-dependent patients

Recovery of renal function is very unlikely in patients who are dialysis-dependent at the time of diagnosis, and especially when all glomeruli contain crescents on renal biopsy. Thus, a less aggressive management of these patients has been advocated. In particular, it has been suggested to use pulses of methylprednisolone instead of plasma exchanges (as a first-line therapy), since pulmonary hemorrhage is usually well responsive to this treatment.

In case of end-stage renal disease, renal transplantation carries no extra-risk if circulating anti-GBM antibodies has been undetectable (by ELISA or RIA) for at least 6 months.

Etiology

Goodpasture's disease results from an immune reaction against the NC1 domain of the alpha3 chain of type IV collagen. The restricted distribution of this molecule explains that the disease affects only specific organs, such as lung and kidney.

The pathogenic role of anti-GBM antibodies has been clearly illustrated by transfer experiments in animals, and by recurrence of Goodpasture's disease in renal transplant patients who had circulating antibodies at the time of transplantation. Nevertheless, Goodpasture's disease should not be viewed as solely due to anti-GBM antibodies, and autoreactive T cells also appear to play a role in the pathogenesis

Diagnostic procedures

Crescentic glomerulonephritis with anti-GBM antibodies

Renal biopsy plays a key role in the diagnosis. On light microscopy, it shows the presence of crescents, usually of similar age and affecting most glomeruli. Furthermore, immunohistochemistry analyses show linear deposits of IgG along the GBM, which are of paramount importance for the diagnosis. Anti-GBM antibodies correspond much less often to IgA or IgM.

Pulmonary hemorrhage

Bronchoalveolar lavage (BAL) is the most reliable procedure to confirm alveolar hemorrhage. It usually shows a uniformly bloody BAL fluid. Fluid may not be macroscopically bloody in patients with chronic alveolar hemorrhage but contain an elevated percentage of Perls-positive macrophages in the absence of lung infection or pulmonary edema.

Some physicians used to rely on a raised corrected carbon monoxide gas transfer factor to confirm the diagnosis of pulmonary hemorrhage. However, this test has a low sensitivity and is difficult to perform in patients with severe dyspnea.

Circulating anti-GBM antibodies

Circulating anti-GBM antibodies can be detected by ELISA or RIA in more than 98% of patients with Goodpasture's disease, and this test is highly specific with less than 1% false-positive results. It may occasionally be useful to confirm the specificity of the antibodies by Western blotting. The titer of anti-GBM antibodies has no prognostic value, but it is useful to follow efficacy of plasma exchanges.

Detection of anti-GBM antibodies by indirect fluorescence assays using normal kidney samples is much less sensitive, with about 25% false negative results, and it is also less specific.

Unresolved questions

The major unsolved questions are probably:

- the mechanisms by which an immune reaction develops against a normal component of basement membranes;
- the respective roles of cell-mediated and antibody-mediated immune responses;
- the development of therapies that are more selective and thus have fewer side effects.

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