Goodpasture's Syndrome with normal renal function


ABSTRACT: Two cases of Goodpasture's syndrome with severe pulmonary haemorrhage and normal renal function are described. In spite of minor (patient 2) or even no (patient 1) biological or light microscopic signs of glomerulonephritis, immunofluorescence of Immunoglobulin G (IgG) was strongly positive in a linear fashion along the glomerular basement membranes in both patients. We suggest that renal biopsy in patients with apparently idiopathic pulmonary haemorrhage may lead to an early diagnosis of Goodpasture's syndrome. It is not possible in this disease to recognize on presentation those patients who will remit spontaneously and those who will undergo severe disease. The deadly evolution for patient 1 and some cases in the literature lend support to the notion that cytostatics and plasma exchanges must be added to corticosteroids, even if pulmonary haemorrhage is not active and renal function is normal at the time.

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A usual feature of Goodpasture's syndrome is the association of pulmonary haemorrhage and rapidly progressive glomerulonephritis [1]. Here we report two cases with normal renal function, which is more rarely described in the literature [2]. Therapeutic choice and follow up in our cases are compared to the literature data. Although these isolated pulmonary forms are considered to have a good response to corticosteroids, we believe that a definitive way of therapy should remain imprecise since only few cases have been seen.

Case Report

Patient 1

A 23 yr old man was admitted to the hospital on December 26th, 1985, for evaluation of increasing shortness of breath. He had no past history of pulmonary or cardiovascular disease. Thyroidectomy had been performed in 1980 for Basedow's disease. He was a 2 pack-years cigarette smoker. Three weeks before the onset of dyspnoea he was massively exposed to hydrocarbon solvents, since he sprayed paints and rust products on his whole car.

On admission, his blood pressure was 140/80 mmHg, pulse 115-min⁻¹, rectal temperature 38°C, and respiration 25-min⁻¹. He had bilateral crepitations of his lung bases. A chest X-ray showed basal and peri-hilar alveolar densities bilaterally. The heart was not enlarged, with a normal electrocardiogram. Arterial blood gases showed a Pao₂ of 6 kPa and a Paco₂ of 4 kPa. Haemoglobin level was 74 g·l⁻¹, and hematocrit value was 23%. The white blood cell count was 10,800·mm⁻³, with normal differential count, with 468,000 platelets·mm⁻³ and erythrocyte sedimentation rate 35 mm·h⁻¹. Blood glucose was 4.9 mmol·l⁻¹, blood urea nitrogen 7.8 mmol·l⁻¹ and serum creatinine 90 μmol·l⁻¹. Serum electrolytes and bilirubin, coagulation studies, direct and indirect Coomb's test and cold agglutinin titre were normal. Serum iron was 5 μmol·l⁻¹ and iron-binding capacity 62 μmol·l⁻¹ Urinalysis disclosed no abnormalities, proteinuria was absent.

Fibreoptic bronchoscopy revealed diffuse haemorrhagic secretions filling smaller bronchioles; no endobronchial lesions were noted. Broncho-alveolar lavage showed red blood cells: 856,000·mm⁻³, white blood cells: 28,000·mm⁻³ with 48% neutrophils, 1% eosinophils, 6% lymphocytes and 45% haemoglobin-laden macrophages.

Viral, bacterial, parasitic and myologic studies (fibroscopy aspiration, blood cultures, serologies) were all negative, acid-fast bacilli, influenza viruses, legionella and opportunistic micro-organisms included. Tests researching antinuclear antibodies, rheumatoid factor, cryoglobulins or circulating immune complexes were all negative. Serum C3 was 1.38 mg·ml⁻¹ (normal range values 0.8 to 1.5 mg·ml⁻¹) and C4 was 0.3 mg·ml⁻¹ (normal range 0.16 to 0.47 mg·ml⁻¹). Ponderal dosage of immunoglobulins and serum electrophoresis were normal, Hbs antigen negative. Serum anti-glomerular basement membrane (GBM) antibodies were negative by indirect immunofluorescence.
The patient was transfused with 4×200 cc packed red cells and treatment was started by methylprednisolone, 120 mg daily, one day after admission. Radioimmunoassay (R.I.A.) for circulating anti GBM antibodies was carried out by Bowman and Lockwood [3] on a serum sample taken after two days of treatment; the result was negative, and inhibition test non-conclusive. Dramatic improvement occurred and the patient was discharged on the 10th day with methylprednisolone 100 mg daily. At this time he was clinically asymptomatic; chest X-ray, spirometry and haemoglobin level were normal. His diffusing capacity for carbon monoxide was a little lowered, at 23 ml-min⁻¹·mmHg⁻¹ (predicted 29).

Two days after discharge, he was readmitted with acute respiratory distress. His blood pressure was 90/60 mmHg, pulse 120-min⁻¹, rectal temperature 39°C and respirations 30-min⁻¹. Arterial blood gases showed a Pao₂ of 4.9 kPa, a Paco₂ of 5.2 kPa, with mottled alveolar opacities over both lung fields on the chest X-ray. Renal function remained normal; labutix-urine was protein trace positive but negative for haematuria; blood haemoglobin level was 75 g·l⁻¹. The patient denied renewed exposure to hydrocarbon solvents or cigarette smoking. A small amount of haemoptysis had occurred one day before admission. A high percentage of nasal oxygen failed to improve the clinical status, and a few hours after admission he was placed on a volume-controlled respirator with positive end-expiratory pressure. However, deadly refractory hypoxaemia, caused by extensive haemorrhagic intra-alveolar infiltration, rapidly occurred.

At autopsy, the myocardium and pericardium were normal. The lungs were found to be extremely heavy, weighing about 1000 g each. They appeared diffusely haemorrhagic. The microscopic section showed that most of the alveoli were filled with red cells among which were macrophages containing haemosiderin. The kidney appeared normal macroscopically and on light microscopic examination. For immunofluorescence stainings, lung or kidney biopsy specimens were frozen with liquid nitrogen and stored at -70 °C. Preparations included fixation of 4-6 μm thick specimens in acetone followed by reactions during 30 min in a moist chamber with commercially prepared fluorescein-isothiocyanate labelled antisera; anti-human IgG, C₃ complement, fibrinogen and albumin (Highland Division Travenol Labs Inc, Deerfield, Illinois). Lung immunofluorescence studies were all negative. Conversely, a strong (3+) linear staining for IgG was seen along the glomerular basement membranes in all the glomeruli. There was also a faint glomerular staining for C₃, in an interrupted linear pattern. Stains for fibrinogen and albumin were negative. No vascular or tubular fluorescence was detected.

**Patient 2**

A 21 yr old man, 4 pack-years cigarette smoker, was in good health until mid-March 1986, when he developed progressive dyspnoea, mild recurrent haemoptysis and a low grade fever. He initially improved under amoxicillin and prednisone 40 mg daily given by his personal physician for fifteen days. But one week after the end of this treatment severe dyspnoea relapsed, and he was referred to the hospital on April 8, 1986. On admission he was extremely pale, tachypneic, and his blood pressure was 140/80 mmHg, pulse 120-min⁻¹, and rectal temperature 37°C. Physical examination disclosed bilateral basal crepitations.

Chest roentgenogram revealed bilateral diffuse interstitial and alveolar infiltrates, with minimal cardiomegaly. Arterial blood gases were as follows; Pao₂ 5.5 kPa, Paco₂ 4 kPa. Electrocardiogram was normal. Haemoglobin level was 57 g·l⁻¹, haematocrit 17%, white cell count 14,600·mm⁻³ with a normal differential count, with 550,000 platelets per mm³. The serum iron was 4 μmol·l⁻¹, total iron binding capacity 59 μmol·l⁻¹ and serum creatinine 133 μmol·l⁻¹. Urinalysis revealed 2+ protein and 3+ blood, urinary sediment 300 red blood cells·mm⁻³ and 5 white blood cells·mm⁻³. The twenty four hours urine protein was 40 mg. All urine specimens were sterile. Routine infectious inquiries of diffuse pneumonitis were all negative. Sputum did not contain siderophages. Antinuclear antibodies, circulating immune complexes and rheumatoid factor were not detected. Serum anti-GBM antibody testing by ELISA was strongly positive with a titre of 1/500. Anti GBM antibodies were also detected by R.I.A. at a level of 25% (expressed as % binding of radio-labelled antigen; normal range less than 10%).

The patient was treated initially with nasal oxygen, at 4 l·min⁻¹, erythromycin, ethacrynic acid, and transfused with 4×200 cc of packed red cells. This treatment led to much improved dyspnoea; on April 15, 1986, lung crepitations were not audible, chest X-ray abnormalities had strongly decreased and arterial blood gases had returned to normal.

A percutaneous renal biopsy was performed on April 16, 1986. Light microscopy revealed a mild focal proliferative glomerulonephritis with crescent formation in 3 out of 25 glomeruli, and some mesangial hypercellularity. In contrast, immunofluorescent staining showed a linear diffuse fixation of IgG along the basement membranes in all the glomeruli with a few granular deposits of C₃ and fibrinogen. Although initial evolution was good with supportive treatment alone, we added immunosuppressive treatment and plasma exchanges, because we had been frightened by the sudden relapse of patient 1.

Dating from April 18, 1986, the patient received oral prednisone, 1 mg·kg⁻¹ daily for one month, which was gradually reduced to 0.25 mg·kg⁻¹ daily over the next three months, then tapered to alternate day dosage for the next three months. Together with prednisone, cyclophosphamide was given orally at 25 mg·kg⁻¹ daily for fifteen days, then reduced to 1 mg·kg⁻¹ daily for the next month and stopped after a total duration of two months. Nine plasma exchanges (4 litres every two days
Table 1. Clinical presentation, treatment and evolution in 15 cases of Goodpasture’s Syndrome with normal renal function.

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Age &amp; sex</th>
<th>Initial symptoms</th>
<th>Serum anti-GBM</th>
<th>Abnormal renal biopsy</th>
<th>Steroid therapy</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present report</td>
<td>1986</td>
<td>M, 23</td>
<td>haemoptysis</td>
<td>-</td>
<td>no</td>
<td>N</td>
<td>yes died</td>
</tr>
<tr>
<td>Present report</td>
<td>1986</td>
<td>M, 21</td>
<td>haemoptysis</td>
<td>N.A. +</td>
<td>yes</td>
<td>IgG</td>
<td>no improved</td>
</tr>
<tr>
<td>ASAMER [12]</td>
<td>1975</td>
<td>M, 32</td>
<td>haemoptysis</td>
<td>N.A. N.A.</td>
<td>yes</td>
<td>IgG-C3</td>
<td>yes improved</td>
</tr>
<tr>
<td>ZIMMERMAN [8]</td>
<td>1978</td>
<td>M, 29</td>
<td>haemoptysis</td>
<td>-</td>
<td>yes</td>
<td>IgG-C3</td>
<td>yes improved</td>
</tr>
</tbody>
</table>

I.F: immunofluorescence; A.R.D: acute respiratory distress; N.A: not available; +: positive; -: negative; ABM: alveolar basement membrane; N: normal; Mesangioprol: mesangioproliferative; Glomerulon: glomerulonephritis; Minim: minimal; yr: year; mth: months; pulm. haem: pulmonary haemorrhage.

Discussion

The Goodpasture’s syndrome, as currently defined, usually affects young persons 14–30 yrs of age with a strong predilection for males. Renal failure secondary to crescentic glomerulonephritis is common and usually rapid. The two patients described here were atypical cases of Goodpasture’s syndrome, since major involvement was pulmonary rather than renal. Nevertheless, with the routine use of immunopathological studies, it has become evident that a wide spectrum of clinical involvement is likely to occur, and that there is a subset of Goodpasture’s syndrome with mild glomerular lesions throughout the course of the disease: about one third of the cases reported during the last decade, as pointed out by Bernis et al. [4].

Patient 1 had apparently idiopathic pulmonary haemorrhage; renal immunofluorescence findings were with fresh frozen plasma and albumin replacement performed, over a period from April 21 to May 8, 1986. Anti-G.B.M antibody titre rapidly decreased: 1/200 on April 21, 1/100 on April 23th, negative on April 25th. On May 6th, 1986, chest X-ray had returned to normal and spirometry disclosed no abnormalities. Today the patient is totally symptom-free, and serum anti GBM antibodies can no longer be detected.
the single argument for diagnosis of Goodpasture’s syndrome. Since non-specific linear staining of IgG on GBM has been reported in 25% of autopsy kidneys without renal disease [5], it is possible that the linear deposition in this case is non-specific. Nevertheless, the brightness of linear glomerular deposits strongly evoked an anti-GBM antibody-mediated disease. Furthermore, albumin was not present, and C3 was noted in the glomeruli, a finding not found with non-specific staining [5]. The clinical presentation with pulmonary haemorrhage and initial diminution with prednisone therapy was consistent with a Goodpasture’s syndrome, as well as the exposure to hydrocarbon solvents which has been shown to frequently trigger or exacerbate the disease [6]. Furthermore, absence of circulating anti-GBM antibodies does not contradict the diagnosis since they are not always detectable, even by radioimmunoassay [7, 8] and are of no prognostic value for either the clinical outcome or immunofluorescence findings [4]. Alveolar immune deposits may also be absent, contrary to glomerular immunofluorescence which is constantly positive [2].

In reviewing the literature, 13 other cases of Goodpasture’s syndrome with normal renal function were found [8-17]. Data on these cases and our two cases are presented in Table 1. Light microscopy of the kidney biopsy was normal or showed focal and segmental changes. In two cases of the literature [9, 10], there were no urine abnormalities at the moment of immunological renal diagnosis; the presence of linear renal staining and the clinical pulmonary presentation were sufficient for a diagnosis of Goodpasture’s syndrome, even in the absence of clinical or light microscopy manifestations of renal disease. With Mathew et al [9], we suggest that there may be an indication for carrying out renal biopsies in patients with apparently idiopathic pulmonary haemosiderosis and that this may lead to an early diagnosis of Goodpasture’s syndrome.

Goodpasture’s syndrome with normal renal function is considered to have a relatively good prognosis with steroid therapy [8, 12, 13], and even spontaneous remissions may occur [4, 14, 15]. Nevertheless, mild renal biopsy findings do not necessarily mean a good prognosis, as demonstrated by some renal fulminant histological progressions [18, 19]. Furthermore, in the subset with normal renal function throughout the course of the disease, death from pulmonary haemorrhage has been reported inspite of cortisone [11, 16]. It remains difficult to recognize, on presentation, those patients who will undergo severe disease. We suggest that in the absence of any possibility to foresee evolution, full treatment, as advised by Savage et al [20], with addition of cyclophosphamide and plasma exchanges to cortisone, is indicated in those cases of Goodpasture’s syndrome with normal renal function. Further experience is necessary to determine predictors of evolution and to modulate the treatment choice.

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References


RÉSUMÉ: Description de deux cas de syndrome de Goodpasture accompagné d’hémorragie pulmonaire sévère et d’une fonction rénale normale. Dans les deux cas, malgré l’absence (patient 1) ou la présence de signes mineurs (patient 2) de gloméronéphrite à l’examen biologique ou en microscopie optique, l’immuno-fluorescence des immunoglobulines G (IgG) s’avère fortement positive, et de forme linéaire autour des membranes basales gloméruilaires. Nous suggérons que la biopsie rénale chez des patients atteints d’hémorragie pulmonaire apparemment idiopathique pourrait conduire à un diagnostic précoce de syndrome de Goodpasture. Il n’est pas possible dans cette affection de différencier au début les patients qui auront une rémission spontanée de ceux qui évolueront vers une maladie sévère. L’évolution mortelle du patient 1 et quelques cas de la littérature suggèrent la notion que les cytostatiques et les plasmaphérèses doivent être ajoutés aux cortico-stéroïdes, même si l’hémorragie pulmonaire est initialement contrôlée et la fonction rénale normale.