Goodpasture's Syndrome with normal renal function

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*Goodpasture's Syndrome with normal renal function. Ph. Carre, J.J. Lloveras,
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ABSTRACT: Two cases of Goodpasture's syndrome with severe pulmo-
nary 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.
Eur Respir J., 1989, 2, 9911–915

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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 con-
sidered 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 pul-
monary 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 anti-
rust products on his whole car.

On admission, his blood pressure was 140/80 mmHg,
pulse 115·min⁻¹, rectal temperature 38°C, and respir-
ations 25·min⁻¹. He had bilateral crepitations of his lung
bases. A chest X-ray showed basal and peri-hilar alveo-
lar densities bilaterally. The heart was not enlarged,
with a normal electrocardiogram. Arterial blood gases
showed a Pao_2 of 6 kPa and a $Paco_2$ of 4 kPa. Hae-
moglobin level was 74 $g \cdot l^{-1}$, and haematocrit value was
23%. The white blood cell count was 10,800·mm⁻³, with
normal differencial count, with 468,000 platelets·mm⁻³
and erythrocyte sedimentation rate 35 mm·h⁻¹. Blood
glucose was 4.9 $mmol \cdot l^{-1}$, blood urea nitrogen 7.8
$mmol \cdot l^{-1}$ and serum creatinine 90 μmol·l⁻¹. Serum electro-
lytes 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 abnormali-
ties, proteinuria was absent.

Fibreoptic bronchoscopy revealed diffuse haemorragic
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% haemosiderin-laden macrophages.

Viral, bacterial, parasitic and mycologic studies
(fibrescopy 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 $ml \cdot min^{-1} \cdot mmHg^{-1}$ (predicted 29).

Two days after discharge, he was readmitted with acute respiratory distress. His blood pressure was 90/60 mmHg, pulse $120 \cdot min^{-1}$, rectal temperature 39°C and respirations $30 \cdot min^{-1}$. Arterial blood gases showed a Pao_2 of 4.9 kPa, a $Paco_2$ of 5.2 kPa, with mottled alveolar opacities over both lung fields on the chest X-ray. Renal function remained normal; labstix-urine was protein trace positive but negative for haematuria; blood haemoglobin level was 75 $g \cdot l^{-1}$. 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 antiserums; 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 $120 \cdot min^{-1}$, 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; Pao_2 5.5 kPa, $Paco_2$ 4 kPa. Electrocardiogram was normal. Haemoglobin level was 57 $g \cdot l^{-1}$, haematocrit 17%, white cell count $14,600 \cdot mm^{-3}$ with a normal differential count, with 550,000 platelets per mm^{-3}. The serum iron was 4 $\mu mol \cdot l^{-1}$, total iron binding capacity 59 $\mu mol \cdot l^{-1}$ and serum creatinine 133 $\mu mol \cdot l^{-1}$. Urinalysis revealed 2+ protein and 3+ blood, urinary sediment 300 red blood $cells \cdot mm^{-3}$ and 5 white blood $cells \cdot mm^{-3}$. 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 $l \cdot min^{-1}$, 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 $mg \cdot kg^{-1}$ daily for one month, which was gradually reduced to 0.25 $mg \cdot kg^{-1}$ 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 $mg \cdot kg^{-1}$ daily for fifteen days, then reduced to 1 $mg \cdot kg^{-1}$ 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.

Source	Year	Age & sex	Initial symptoms	Serum anti-GBM antibodies		Abnormal urinalysis	Renal biopsy findings	Linear deposition along		Steroid therapy	Follow-up
				I.F.	R.I.A.			G.B.M.	A.B.M.		
Present report	1986	M, 23	haemoptysis dyspnoea	-	-	no	N	IgG	-	yes	died pulm. haem.
Present report	1986	M, 21	haemoptysis	N.A.	+	yes	crescents in 3/25 glomeruli	IgG	N.A.	no	improved 1 yr
ABBOUD [13]	1978	M, 28	haemoptysis	-	+	yes	N	IgG+C3	IgG	yes	improved 9 mth.
ASAMER [12]	1975	M, 32	haemoptysis	N.A.	N.A.	yes	mesangioprol glomerulon	IgG+C3	N.A.	yes	improved 11 mth.
BAILEY [14]	1981	M, 18	haemoptysis	N.A.	+	yes	crescents in 2/20 glomeruli	IgG+C3	N.A.	no	improved 4.5 yr
BAILEY [14]	1981	M, 20	haemoptysis	N.A.	+	yes	minim mesangial increase	IgG	N.A.	no	improved 4 yr
BERNIS [4]	1985	F, 19	anaemia dyspnoea	N.A.	-	yes	mild focal glomerulon	IgG+C3	N.A.	no	improved 2.5 yr.
BERGREM [17]	1980	F, 19	anaemia	+	N.A.	?	focal glomerular changes	IgG+ C3	N.A.	yes	died pulm. haem.
C.P.C. [11]	1976	F, 19	haemoptysis A.R.D.	N.A.	N.A.	yes	fibrinoid necrosis 10% of glomeruli	IgG+C3	IgM+C3	yes	died pulm. haem
DONALD [16]	1975	F, 18	A.R.D.	N.A.	N.A.	yes	N	IgG	-	yes	improved 8 mth.
MATHEW [9]	1975	M, 18	anaemia	N.A.	N.A.	no	minim mesangial increase	IgG+C3+ IgA+IgM	N.A.	yes	improved 15 mth.
WILSON [15]	1972	F, 43	anaemia	-	N.A.	yes	mild glomerulon	IgG+C3	N.A.	no	improved 5 yr.
WILSON [10]	1974	M, ?	haemoptysis	+	N.A.	no	N	IgG	IgG	?	improved 6 mth.
ZIMMERMAN [8]	1978	M, 18	A.R.D.	-	-	yes	minim mesangial increase	IgG+IgM	N.A.	yes	improved 1 yr.
ZIMMERMAN [8]	1978	M, 29	haemoptysis	-	+	yes	minim mesangial increase	IgG+C3 +C4	N.A.	yes	improved 5 mth.

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.

with fresh frozen plasma and albumin replacement) were 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.

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 haemosiderosis; renal immunofluorescence findings were

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 evocated 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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Syndrome de Goodpasture avec fonction rénale normale. Ph. Carré, J.J. Lloveras, A. Didier, B. Gorguet, C. Orfila, D. Durand, P. Léophonte.

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 glomérulonéphrite 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 glomérulaires. 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-stéroides, même si l'hémorragie pulmonaire est initialement contrôlée et la fonction rénale normale.

Eur Respir J., 1989, 2, 911–915