Case Report

Conversion of Goodpasture’s syndrome into membranous glomerulonephritis

Jan Thomas Kielstein¹, Udo Helmchen², Kai-Olaf Netzer³, Manfred Weber³, Hermann Haller and Jürgen Floege⁴

¹Division of Nephrology, Medical School Hannover, Hannover, ²Department of Pathology, University of Hamburg, Hamburg, ³Medizinische Klinik I, Krankenhaus Köln-Merheim, Köln and ⁴Medizinische Klinik II, Rheinisch-Westfälische Technische Hochschule, Aachen, Germany

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Introduction

An autoimmune response to the non-collagenous NC-1 domain of the α3-chain of type IV collagen is the pathogenetic basis for the development of anti-glomerular basement membrane (GBM) disease. In Goodpasture’s syndrome clinical involvement of both kidneys and lungs is present. In rare cases an association of Goodpasture’s syndrome/anti-GBM disease with membranous glomerulonephritis has been reported [1,2]. In all of these cases an initially membranous glomerulonephritis evolved into Goodpasture’s syndrome. Based on these clinical observations, it has been hypothesized that damage to the GBM in the course of membranous glomerulonephritis may have resulted in the release of normal or altered basement membrane material, leading to the formation of anti-GBM antibodies [2]. Here we describe a patient in whom the sequence of events was reversed, i.e. he presented with Goodpasture’s syndrome and subsequently developed membranous glomerulonephritis.

Case

Development of Goodpasture’s syndrome

A 17-year-old Caucasian male with an unremarkable medical history presented in November 1996 with his first episode of haemoptysis. The patient had smoked 15 cigarettes per day for the last 3 years, had no exposure to solvents or heavy metals, including mercury, and no preceding infections. A chest X-ray taken by his family doctor in November 1996 showed patchy infiltrates in both lungs (Figure 1a). Due to persistent haemoptyses and the development of exertional dyspnoea, the patient was admitted to a regional hospital on 11 December 1996. Upon admission the physical examination was significant for shortness of breath at rest and tachycardia (100/min) but was otherwise unremarkable. Laboratory evaluation revealed marked anaemia (haemoglobin 9.5 mg/dl) and an increased sedimentation rate (30/58) but no leukocytosis. Blood gas analysis showed hypoxia (arterial pO2 44 Torr, O2 saturation 80%). Urine dipstick testing was positive for blood and leukocytes, but not for protein. An Addis count showed massive erythrocyturia. Under the assumption of a pulmonary infection, the patient received gentamicin (160 mg), cefoxitin (3×2 g), and roxithromycin (2×300 mg) from 11–17 December. This was followed by rapid clinical improvement and resolution of the pulmonary infiltrates (Figure 1b). At this time a test for anti-GBM-antibodies registered positive. The presence of anti-GBM antibodies was evaluated by ELISA using human α3(IV) NC1 as an antigen (Laboratory Dr Limbach, Heidelberg, Germany). Specificity of the test for anti-GBM antibodies was evaluated by ELISA using human α3(IV) NC1 as an antigen (Laboratory Dr Limbach, Heidelberg, Germany). Specificity of the test for anti-GBM antibodies was confirmed by prior incubation of the serum with soluble α3(IV) NC1 for 30 min. On 20 December 1996 the patient was transferred to our hospital for further nephrological evaluation and treatment. Upon admission to the Hannover Medical School, the patient was in no apparent distress and the physical examination was unremarkable. Laboratory findings showed microcytic, hypochromic anaemia (haemoglobin 9.5 mg/dl, mean cellular volume (MCV) 75.7 fl, mean corpuscular haemoglobin (MCH) 25.3 pg, reticulocytes 132/nl). Arterial blood gases and serum creatinine and urea concentrations were within normal
limits. No significant proteinuria was noted (0.14 g/24 h). Glomerular haematuria was present (220 red cells/mm², of which 74% were dysmorphic, and a few red-cell casts). Circulating anti-GBM antibodies were present (63%; normal <15%) with a positive anti-GBM inhibition test. Antinuclear antibodies, ANCA, complement C3 and C4 concentrations and CH₅₀ as well as hepatitis B and C were absent or within normal limits. Pulmonary function tests and chest X-ray findings were unremarkable. Abdominal ultrasound showed kidneys of normal size but with bilateral mild enhancement of renal echogenicity.

In view of the resolution of pulmonary haemorrhage, the normal renal function, relatively mild renal findings, and the young age of the patient, immunosuppressive therapy was withheld, no renal biopsy was performed, and the patient was discharged in January 1997. He subsequently remained in good health and maintained normal renal function, but microhaematuria persisted. Until May 1997 the patient’s proteinuria progressed slowly to 4.2 g/24 h in the continuing presence of circulating anti-GBM antibodies (53%); a renal biopsy was performed. The biopsy contained five glomeruli with normal capillary loops. Immunohistology showed scattered linear IgG and C3 deposits (Figure 2a). Upon electron microscopy, GBM ruptures or mesangial or subendothelial electron-dense deposits were absent but very rare and small subepithelial dense deposits were noted (Figure 2b). The latter can sometimes be observed in necrotizing anti-GBM nephritis, but the finding had raised the question of an evolving membranous glomerulonephritis. The patient had neither the HLA-DR2 nor the HLA-DR3 antigen, the former of which is associated with Goodpasture’s syndrome and the latter with membranous glomerulonephritis.

Progression of Goodpasture’s syndrome to membranous glomerulonephritis

Between May and July 1997 the patient continued to receive no therapy, and proteinuria further increased to 6.9 g/24 h with consecutive hypoproteinaemia (60 g/l) and hypercholesterolaemia (6.7 mmol/l). Neither leg oedema nor microhaematuria was present, and renal function remained normal. At this point immunosuppressive therapy was initiated (methylprednisolone 0.5 g/day for 3 days plus an i.v. bolus infusion of cyclophosphamide 500 mg/m²). A repeat determination of anti-GBM antibody concentration, obtained on the day of cyclophosphamide infusion, showed spontaneous remission of anti-GBM antibodies to the normal range. In view of this result, immunosuppressive therapy was stopped. Subsequently proteinuria increased to 9.9 g/day and a second renal biopsy was performed. Eight glomeruli were obtained, all with normal capillary loops. Immunohistology showed granular IgG deposits and faint linear IgG deposits along the capillary wall (Figure 2c) as well as rare deposits of C1q, complement, and IgM. No IgA, fibrin/fibrinogen, or glomerular C3 deposits were present. On electron microscopy, diffuse podocytic foot process fusion and subepithelial dense deposits, which were partially included within the peripheral basement membrane, were detected (Figure 2d). No glomerulosclerosis, glomerular crescent formation, or tubulointerstitial damage was noted. A diagnosis of membranous glomerulonephritis stage I-III was made. Without further specific treatment, proteinuria decreased to 1.3 g/day in August 1998, and hypoproteinaemia and hypercholesterolaemia resolved.

Discussion

The patient described initially presented with classical signs of Goodpasture’s syndrome, i.e. pulmonary...
haemorrhage, anaemia, and renal involvement yet normal renal function (the latter being compatible with reports in the recent literature) [3]. The diagnosis was confirmed by the demonstration of high circulating anti-GBM antibody concentrations and linear IgG and C3 deposits in the kidney. Our case is notable for a spontaneous remission of lung and renal involvement as well as a spontaneous remission of the high circulating anti-GBM antibody concentrations. Albeit rare, similar courses of the disease have been described previously [4,5].

In parallel with the remission of Goodpasture’s syndrome, our patient developed all classical signs of membranous nephropathy, i.e. nephrotic syndrome accompanied by the demonstration of granular IgG deposits along the capillary walls (absence of glomerular C3 deposits as noted in our patient in the second biopsy is observed in 20–30% of all cases of membranous nephropathy; U. Helmchen, unpublished data). Again, a spontaneous partial remission of the nephrotic syndrome occurred during 1 year of follow up. Based on current data on the therapy of
membranous nephropathy, it appears unlikely that the single, low-dose cyclophosphamide bolus administered in 1997 accounted for the remission. Rather, we presume that a spontaneous partial remission of the nephrotic syndrome had occurred, which again is well recognized in patients with membranous nephropathy, in particular during the first 6–12 months after diagnosis.

As noted above, a few cases have been described, in which a membranous glomerulonephritis evolved into Goodpasture’s syndrome [1,2,6]. We are aware of only a single Australian patient who exhibited the reverse order and in whom the diagnoses were established by light, immuno- and electron microscopy. This patient followed a very similar course to ours, i.e. he presented with classical signs of Goodpasture’s syndrome and normal renal function, went into remission after immunosuppressive therapy, and then developed membranous glomerulonephritis with nephrotic syndrome 9 months later [2]. Apart from the immunosuppressive therapy, the only other notable difference between our case and the Australian patient is in the HLA antigens. While the Australian patient had both the Goodpasture’s syndrome-associated HLA DR-2 and the membranous glomerulonephritis-associated HLA-DR-3, our patient had neither.

Since there is no definite proof that the two diseases were directly related to each other a mere coincidence cannot be excluded and the pathogenetic relationship between the two diseases remains speculative. However, it is conceivable that a common autoimmune pathogenesis may have accounted for the combined development of membranous glomerulonephritis and Goodpasture’s syndrome in our patient.

While the autoimmune pathogenesis of Goodpasture’s syndrome has been clarified to a large extent, the role of autoimmunity in the pathogenesis of membranous nephropathy is still speculative [7]. Based on insights from an animal model of membranous nephropathy, i.e. passive Heymann nephritis, in which, amongst others, antibodies to podocyte antigens are injected, it is currently assumed that an (auto-) immune response to podocytes may also contribute to the pathogenesis of human membranous nephropathy. Alternatively to a common autoimmune pathogenesis, anti-GBM antibodies may alter the permeability of the glomerular basement membrane, allowing circulating immune complexes to access otherwise inaccessible parts of the GBM. Thus, it has been demonstrated that anti-GBM antibodies facilitate the access of anti-gp330 antibodies to antigens on glomerular epithelial cells [8].

In line with the above discussion, in some animal models anti-GBM antibodies can be detected prior to the development of subepithelial deposits. In rabbits receiving soluble basement membrane antigens isolated from normal urine, an anti-GBM glomerulonephritis followed by ultrastructural changes of an immune complex disease have been described [9]. Secondly, Druet et al. described initially linear IgG patterns followed by a membranous pattern of granular capillary wall IgG deposition in the Brown–Norway rat mercuric chloride model [10]. These observations appear compatible with our interpretation that a changed permeability of the GBM to circulating immune complexes (already existing or newly generated) after anti-GBM antibody damage might be a possible mechanism causing a sequence of the two diseases as described in our case.

References


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