Reversal of Dialysis-Dependent Anti-Glomerular Basement Membrane Disease Using Plasma Exchange, Glucocorticosteroids, and Rituximab

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CASE PRESENTATION

A 29-year-old man presented to the emergency department of the Imelda Institution with a 4-day history of increasing general malaise, nausea, anorexia, and oliguria evolving to anuria on admission. Further systems review was negative (including smoking history or use of illicit drugs). His medical history was also unremarkable with the exception that 4 years before presentation a dens serotinus was extirpated. Clinical examination showed an acutely ill patient with a regular tachycardia of 100 beats per minute and a blood pressure of 146/74 mm Hg. He was afebrile, and oxygen saturation while breathing room air was 98%. Auscultation of heart and lungs was normal. The abdomen was not tender. Inspection of skin, ear, nose, and throat was nonrevealing, with a notable absence of purpura. There were also no signs of arthritis or serositis. His biochemistry (Table 1) was severely disturbed, with a serum creatinine of 20 mg/dl (a value of 1.20 mg/dl, which was appropriate for his muscle mass, had been measured 4 years ago), uric acid of 17.8 mg/dl, blood urea nitrogen of 137 mg/dl, and the presence of hyponatremia and hyperkalemia with acidosis. His liver and muscle enzyme values were normal except for an isolated and moderate rise in lactate dehydrogenase, which was not accompanied by decreased haptoglobin or increased bilirubin levels. A complete blood count showed a severe anemia without the presence of schistocytes, slightly elevated platelets, and leukocytosis with a leftward shift. International normalized ratio was elevated to 1.8. C-reactive protein was 320 mg/l with a concomitant raise in fibrinogen and D-dimer levels. Ultrasound showed enlarged kidney volumes with hype echogenic cortex. A chest X-ray was normal. After administration of fresh frozen plasma, a kidney biopsy sample was obtained. Urgent interpretation of a frozen section showed a 100% (8/8 glomeruli) cellular crescentic glomerulonephritis without evidence of chronic or irreversible interstitial damage. A subsequent urgent enzyme-linked immunosorbent assay for antimielyoperoxidase and proteinase 3 antibodies was negative.

MANAGEMENT

After discussion of the dismal prognosis concerning renal recovery and the potentially severe treatment-related side effects, a decision was made to administer an i.v. bolus of methylprednisolone (1 g) and to start with 4 L plasma exchange (PE), using fresh frozen plasma. This was followed by a 3-hour hemodialysis session, using citrate as an anticoagulant. The second and third days of admission, this treatment was repeated (except for the use of albumin as replacement fluid), and a discrete diuresis of 100 and 200 ml/24 h was noted, as well as subjective improvement. Meanwhile, classical light microscopy results of the fixed biopsy tissue showed 3 of 31 obsolete glomeruli and 28 of 31 crescents (of which 27 were cellular and 1 indecisive between cellular and fibrocellular) with breach Bowman capsule in some glomeruli. The interstitial tissue was edematous with lymphoplasmocytic infiltration, with no notable fibrosis or tubular atrophy. Immunohistochemistry on the frozen biopsy sections showed linear deposits of C3d and IgG along the glomerular basal membrane. Staining for IgA and IgM was negative (Figure 1a, b). A new discussion on further treatment was held, and it was agreed to continue treatment with daily PE and oral steroids (1 mg of methylprednisolone/kg body weight).
plus rituximab (RTX), with cessation of PE during 48 hours after first dose of RTX (1 g on day 5). Hemodialysis was also continued 3 times weekly. After a total of 10 PE sessions, diuresis had fully recovered, and a second dose of RTX (1 g) was administered.

FOLLOW-UP

Over the course of the next 4 weeks, the dialysis dose was diminished until a complete stop 6 weeks after admission. As summarized in Figure 2, this was paralleled by a drop in anti-glomerular basement membrane (GBM) antibodies from over the upper limit of enzyme-linked immunoassay (ThermoScientific, Uppsala, Sweden) detection limits (>680) to 44, 25, 5, and 1.9 AU at respectively 1, 2, 4, and 6 months after initial presentation. Serum creatinine leveled out to 2.40 mg/dl. A repeat biopsy, performed 3 months after admission, showed evolution to 40% to 45% interstitial fibrosis and tubular atrophy with 13 of 39 obsolete and 11 or 12 of 39 crescentic glomeruli (2 cellular, 4 or 5 fibrocellular, and 5 fibrous crescents), and immunohistochemistry remained positive for IgG (Figure 1c, d). A slow steroid taper was started with a maintenance dose of 6 mg of methylprednisolone daily at 6 months. Apart from impressive steroid acne, side effects were negligible so far. The rationale for the steroid taper was based on the fact that anti-GBM disease is typically a “1-hit” disease. In addition, the patient remained B-cell depleted. The results of the repeat biopsy were considered in the context of evolution toward chronic and irreversible tissue damage resulting from the original anti-GBM “hit.”

DISCUSSION

Anti-GBM disease is a very rare autoimmune disorder caused by autoantibodies directed to the non-collagenous domain 1 of the α3 chain of collagen IV, which is abundantly present in both alveolar and glomerular basement membrane. The clinical course can range from mild to severe, with either predominantly alveolar or glomerular manifestations. Outcome depends on early diagnosis and treatment, which consists of both removing circulating antibody and inhibiting further antibody formation. Currently this encompasses PE, high-dose i.v. glucocorticoid pulses (typically 1 g of methylprednisolone daily during 3 days), followed by high doses of oral steroids and cyclophosphamide. Such therapy is not without potentially major side effects, and retrospective analyses have shown that chances of renal recovery are virtually zero in patients presenting with dialysis dependency and 100% crescentic glomeruli on biopsy. Guidelines agree that the full treatment (including PE) should be attempted only in patients who either present with predominantly renal disease but are not yet dependent on dialysis, or have life-threatening pulmonary disease. However, a scenario with absence of pulmonary disease, but acute renal failure necessitating dialysis in a young and

| Table 1. Summary of most relevant laboratory results |
| --- | --- | --- | --- | --- | --- |
| | Day 1 | Day 7 | Day 28 | Day 60 | Day 120 | Day 179 |
| Hb (g/dl) | 7.4 | 7.4 | 9.8 | 10.2 | 11.9 | 11.9 |
| Hct (%) | 24 | 24 | 34 | 35 | 39 | 39 |
| WBC/neutrophil (10^3/µl) | 13.3/9.9 | 15.2/13.7 | 10.6/9.1 | 12.9/10 | 11.2/7.3 | 9.9/8.8 |
| Platelets (10^3/µl) | 449 | 213 | 227 | 233 | 300 | 377 |
| Serum creatinine (mg/dl) | 20 | 6.5 | 3.8 | 3.2 | 2.3 | 2.4 |
| BUN (mg/dl) | 137 | 70 | 50 | 70 | 36 | 30 |
| Na (mmol/l) | 130 | 141 | 141 | 144 |
| K (mmol/l) | 6.1 | 4.9 | 4 | 4.4 |
| Cl (mmol/l) | 86 | 105 | 104 | 106 |
| HCO3 (mmol/l) | 16 | 20 | 24 | 25 |
| C0 (mmol/l) | 2.23 | 2.27 | 2.34 | 2.28 |
| P (mmol/l) | 3.11 | 2.11 | 1.34 | 1.36 |
| INR | 1.8 | 1 |
| CRP (mg/dl) | 320 | 5.9 | <0.6 | <0.6 | <0.6 |
| Anti-GBM (AU) | >680 | 44 | 25 | 5 | 1.9 |
| ANCA, ANF | Negative |
| C3, C3d, C4 | Normal |
| Serum immunophoresis | no M-peak |
| Ig A (g/l) | 3.54 |
| PTH (ng/l) | 50 |
| LC immunophenotyping | <0.01% B cells |

ANCA, antineutrophil cytoplasmic antibody; ANF, atrial natriuretic factor; Anti-GBM, anti–glomerular basement membrane; AU, arbitrary unit; BUN, blood urea nitrogen; CRP, C-reactive protein; INR, international normalized ratio; LC, lymphocyte; PTH, parathyroid hormone; WBC, white blood cell.

*To convert creatinine to mmol, divide by 88.

*Anti-GBM: <7 AU is considered normal; titration is done up to an upper limit of 680.

*PTH was assayed using a second-generation bioassay; normal values: 15 to 65 ng/l.
functionally fit individual, can pose a vexing dilemma in which the clinician can be inclined to attempt treatment despite potentially major risks.

In our opinion, 2 salient features emerge from this case report. First, the course of this case confirms the suggestion by the American National Kidney Foundation that Kidney Disease: Improving Global Outcomes (KDIGO) guidelines might be too overtly pessimistic concerning the treatment and outcome of patients with anti-GBM disease requiring renal replacement therapy without major pulmonary involvement upon presentation.4 In selected cases, that is, in young and functionally fit persons, a constellation of very acute and severe renal disease, preserved kidney size on ultrasound, and absence of chronicity on renal biopsy, the disease can be successfully reversed. However, it should be emphasized that chances of renal recovery in such cases remain extremely poor, and the potential treatment related side-effects are not negligible. Hence, a thorough shared decision-making process should precede the start of therapy. Second, to our knowledge, this is the first report in which RTX is used to completely replace cyclophosphamide successfully in the treatment of such a severe degree of disease. Because anti-GBM disease is caused by circulating autoantibodies, treatment with RTX is reasonable from a pathophysiological point of view. Indeed, cases of successful use of RTX have been reported in the literature. However, this was always on top of treatment with other immunosuppressants, such as cyclophosphamide.5 In addition, there is a steady increase of

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**Figure 1.** Renal biopsy sample (a,b) on admission and (c,d) 3 months after admission. (a) Renal biopsy sample at time of admission, showing a diffuse extracapillary proliferative glomerulonephritis. All crescents were cellular (arrowhead) (periodic acid–Schiff stain, original magnification ×100). (b) Renal biopsy sample at time of admission: glomerulus with a cellular crescent and linear IgG positivity in the remaining parts of the glomerular tuft (anti-IgG stain, original magnification ×400). (c) In the second biopsy sample, crescents were still present, although the majority of them showed signs of healing (fibrosis) (arrow). A few cellular crescents were also present (arrowhead) (periodic acid–Schiff stain, original magnification ×100). (d) The anti-IgG stain remained positive in the second biopsy sample (anti-IgG stain, original magnification ×200).

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**Figure 2.** Evolution of anti–glomerular basement membrane (GBM) antibodies and serum creatinine (creatinine). To convert creatinine to mmol/l, divide by 88. Anti-GBM antibodies: <7 arbitrary units (AU) is considered normal; titration is done up to an upper limit of 680 AU/l. PE, plasma exchange; RTX, rituximab.
reported data suggesting not only a similar efficacy but also a favorable safety profile of rituximab over cyclophosphamide in the treatment of other renal autoimmune diseases such as membranous glomerulonephritis. Nevertheless, the majority of the available evidence regarding anti-GBM disease to date consists of cyclophosphamide-based therapy. We fully acknowledge that it is not possible to draw firm conclusions from only 1 case report. However, prognosis and treatment strategies regarding a particular subgroup of patients with an already very rare disease are unlikely ever to be tested in a randomized trial.

In conclusion, the presented case might ease the decision to attempt kidney salvage in young patients struck by extremely aggressive renal anti-GBM disease, who are otherwise not affected by pulmonary disease.

**DISCLOSURE**

All the authors declared no competing interests.

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