Case Report

Antiglomerular basement membrane glomerulonephritis following D-penicillamine-associated nephrotic syndrome

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Introduction

Antiglomerular basement membrane (anti-GBM) glomerulonephritis (GN) is rare and is characterized by rapidly progressive GN with IgG linear deposits along the GBM in immunofluorescence study and circulating anti-GBM antibodies.

This form of GN usually occurs without previous renal disease, but some cases of membranous GN have been reported with secondary development of anti-GBM disease [1,2]. Administration of drugs such as D-penicillamine, which are useful for the treatment of rheumatoid arthritis, can be complicated by glomerular disease, more precisely membranous GN, but also minimal-change GN, and crescentic GN [3–5]. Mechanisms for the ability of penicillamine to induce autoimmunity have been reviewed recently [5].

We report a patient with rheumatoid arthritis who, after long treatment with D-penicillamine, developed

Fig. 1. Massive tuft necrosis and disruption of the glomerular basement membrane (Masson’s trichrome, ×400).

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Fig. 4. Western blot analysis. The NC1 domain of type IV collagen was first separated by SDS–PAGE and then transferred to a nitrocellulose paper and incubated with different antibodies to the alpha chains and the serum of the patient.
nephrotic syndrome which disappeared after stopping the drug. A few months later typical anti-GBM disease occurred. Circulating anti-GBM antibodies were detected, but their unusual target led us to consider that pre-existing glomerular lesions played a role in this particular complication.

Case report

In February 1992, a 65-year-old man was referred to the Nephrology Unit because of nephrotic syndrome. From 1958 he had been treated by non-steroid anti-inflammatory drugs, corticosteroids, and gold salts for destructive seropositive rheumatoid arthritis. In 1982, D-penicillamine was started and was well tolerated without proteinuria. In 1992 the patient was receiving D-penicillamine 600 mg/day, prednisone 7.5 mg/day, and sporadically indomethacin. Suddenly, typical nephrotic syndrome appeared with rapid weight gain, oedema, proteinuria 7–10 g/24 h, albuminuria 23 g/l without haematuria. The patient had normal blood pressure and renal function. His arthritis remained stable. Renal biopsy was refused and rectal biopsy was negative for amyloidosis. D-penicillamine was stopped and 18 months later, proteinuria had disappeared.

In October 1994, the patient was referred to the Pneumology Unit for dyspnoea. Chest X-ray and arterial blood gas were unchanged but serum creatinine level was 146 μmol/l, associated with proteinuria 1.81 g/24 h, haematuria and haemoglobinemia 12.7 mg/dl. Oxygen therapy and ventollin were delivered associated with i.v. methylprednisolone (60 mg/day), with rapid improvement of respiratory signs. Two days later, gross haematuria appeared, followed by total anuria. Haemodialysis was started. Renal biopsy was performed and showed severe glomerular necrosis with ruptured Bowman’s capsule surrounded by a strong inflammatory reaction (Figure 1). By immunofluorescence study, the residual fragments of the GBM showed IgG linear fixation (Figure 2). No alveolar haemorrhage was detected by bronchoalveolar lavage. Circulating anti-GBM antibodies were detected by indirect immunofluorescence. ELISA and Western blotting detecting different fractions of collagen IV were positive against the non-collagenic domain of α1, α3 and α4 chains (Figures 3, 4). Other immunological studies (ANCA, PR3-ANCA, MPO-ANCA, serum complement, and rheumatoid factors) were normal or negative. HLA haplotype was A1, A3, B7, B8, DR15 and DR3. Despite treatment by high-dose pulse methylprednisolone and subsequent oral prednisone therapy, no recovery was observed. After 1 year, circulating anti-GBM antibodies are still present.

Discussion

Antirheumatic drugs (gold salts and D-penicillamine) can be responsible for renal complications with development of heavy proteinuria. Proteinuria can appear very late after the beginning of treatment [3], as illustrated by the patient described in this Case Report. Our patient developed nephrotic syndrome during 10-year treatment with D-penicillamine. Unfortunately, no renal histology is available, but membranous GN was suspected because of the known association between D-penicillamine and membranous GN. In the absence of nephrotoxic drug intake, rapidly progressive GN with IgG linear deposits appeared. It is of note that the patient’s HLA haplotype was DR15 (susceptibility for Goodpasture syndrome) and B8 DR3 (susceptibility for drug-induced GN).

Membranous GN complicated by anti-GBM GN has been described [1,2]. In one report, the presence of circulating anti-GBM antibodies preceded the appearance of acute renal failure, which suggests the role of these antibodies in the development of this complication [2]. In another report, sera from patients with membranous GN contained antibodies directed against the 7S domain of type IV collagen [6]. On the basis of our observations, we hypothesize that pre-existing and presumably membranous GN modified the antigenicity of the GBM and induced susceptibility to develop secondary anti-GBM antibodies. Usually anti-GBM antibodies are directed against the NC1 domain of the α3 chain forming collagen IV [7]. In our observation, circulating anti-GBM antibodies were directed against the NC1 domain of the α3 chain forming collagen IV, but also against the NC1 domain of the α1 and α4 chain forming collagen IV. This unusual target for anti-GBM would be explained by previous modification of the GBM.

Thus, this case shows that patients treated by D-penicillamine must be watched carefully, particularly if they have a predictive haplotype for GBM disease or drug-induced GN. Serial determination and characterization of anti-GBM antibodies should be performed if glomerular abnormalities appear.

References


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