Exceptional Case

IgA-mediated anti-glomerular basement membrane disease: an uncommon mechanism of Goodpasture’s syndrome

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Abstract

Goodpasture’s (GP) disease is usually mediated by IgG autoantibodies. We describe a case of IgA-mediated GP, in a patient presenting with isolated rapidly progressive glomerulonephritis. The diagnosis was established on kidney biopsy, since routine enzyme-linked immunosorbent assay (ELISA) targeted at IgG circulating autoantibodies failed to detect the nephritogenic antibodies. Immunofluorescence microscopy showed intense linear deposition of IgA along the glomerular capillary walls. An elevated titre (1:80) of circulating IgA anti-glomerular basement membrane (GBM) antibodies was retrospectively demonstrated by indirect fluorescence. Despite immunosuppressive regimen, the disease progressed to end-stage renal failure (ESRF). Transplantation was not associated with recurrence in the kidney graft. We reviewed the 11 previously reported cases of IgA-mediated GP.

Keywords: anti-glomerular basement membrane disease; Goodpasture’s disease; IgA

Background

Goodpasture’s (GP) disease is an autoimmune condition responsible for rapidly progressive glomerulonephritis often accompanied by alveolar haemorrhage. It is mediated by autoantibodies directed against specific antigens of the glomerular basement membrane (GBM), the noncollagenous-1 (NC1) domain of collagen IV chains α3 or α5 [1–2]. In most cases, the causative body is IgG. Early recognition relies on enzyme-linked immunosorbent assay (ELISA) detecting circulating anti-GBM IgG antibodies in serum sample [3]. We describe a case of IgA-mediated GP, in which routine ELISA failed to detect the nephritogenic antibodies, and provide a review of prior cases.

Case report

A 49-year-old man was admitted to the renal unit for rapidly progressive glomerulonephritis. His past medical history included chronic kidney disease (CKD) stage 3 due to left kidney agenesis (serum creatinine, 124 µmol/L; estimated glomerular filtration rate (eGFR) by modification of diet in renal diseases 56 mL/min/1.73 m²) and smoking habit.

On admission, physical examination including blood pressure (120/70 mmHg) was normal. Serum creatinine had risen from 264 µmol/L to 539 µmol/L over the past 6 weeks. Urinary examination disclosed nephrotic range proteinuria (3.5 g/day) and microscopic haematuria, without anaemia. The routine ELISAs were negative for anti-GBM (Luminex, Bio-Rad, Marnes-la-Coquette, France), anti-nuclear antibodies and ANCA. Screening for a paraprotein was negative in serum and urine. There was no quantitative defect of IgG, IgA and IgM subclasses. Computed tomography (CT) scan ruled out significant alveolar haemorrhage.

A kidney biopsy was performed (Figure 1). Pathological examination showed crescentic glomerulonephritis with both cellular and fibrocellular crescents and Bowman capsule’s rupture. Immunofluorescence microscopy showed an intense linear deposition along the GBM with anti-alpha, anti-kappa and anti-lambda sera. Staining with anti-gamma revealed a similar but weak pattern. These results prompted us to check for circulating IgA anti-GBM; indirect fluorescence on macaque kidney slices using anti-IgA as secondary antibodies demonstrated circulating IgA anti-GBM antibodies. The titre was elevated at 1:80.

In addition to daily plasma exchanges (PE), the patient was started on steroids (methylprednisolone, 1 mg/kg/day) and oral cyclophosphamide (CYC, 2 mg/kg/day). Despite this treatment and negative testing for circulating IgA anti-GBM after 14 PE, his renal function worsened rapidly and regular haemodialysis (HD) was started. The patient received a cadaveric kidney graft 18 months later.
A transplant biopsy at month 5 revealed no recurrence of linear IgA deposits along the GBM in the immunofluorescence study. At last follow-up, his serum creatinine was 124 µmol/L.

Discussion

GP is a rare disease, with an incidence of one case/million inhabitants/year. It is characterized by a pulmonary-renal syndrome, which includes rapidly progressive glomerulonephritis and alveolar haemorrhage. In approximately one-third of cases, there is no pulmonary involvement [1]. In a former study with an indirect immunofluorescence procedure, detection of antibodies in the serum proved negative in up to 40% of the cases. The development of sensitive and specific ELISA relying on the NC1 domain of the collagen IV α3 chain is much more reliable, with high specificity, and high titres of antibodies are detected in almost every patient with anti-GBM glomerulonephritis at the time of active disease, or even several months before the onset [4]. However, rare circulating anti-GBM antibodies may escape detection by ELISA or western blotting techniques, in renal patients and in isolated mild pulmonary disease. A highly sensitive device called highly sensitive biosensor could detect the culprit antibodies in two such cases [3]. In addition, since all these methods targeted IgG antibodies, rarely did the patients with IgA- or IgM-mediated GP disease remain unrecognized by serological testing.

IgA-mediated GP disease is very uncommon: in our renal unit, 33 patients with GP were diagnosed in the last decade (2000–2010). None except this case exhibited IgA-mediated disease. So far, only 11 cases have been reported in the literature [5–16]. Clinical and pathological findings are summarized in Table 1. In all but three cases, renal presentation was consistent with rapidly progressive glomerulonephritis. Pulmonary involvement was found in only 4/10 cases. On kidney biopsy (10/11 patients), the percentage of crescentic glomeruli ranged from 6 to 75%. An immunofluorescence study demonstrated linear staining for IgA in all cases. Concomitant linear staining for IgG and C3 were reported, respectively, in one and two cases, while monotypic linear deposits of kappa or lambda light chains were found in one case each. Circulating IgA anti-GBM antibodies were detected in the nine patients in whom they were looked for. In our patient and a prior case [16], the kidney biopsy showed mild linear IgG deposits along the GBM, in addition to the intense IgA pattern. Mild linear IgG deposits along the GBM can be observed under various conditions (old age, diabetes mellitus, etc.), and should be interpreted in view of the clinical setting, as well as with regards to other immunological findings [3].

Kidney biopsy is the primary test used to recognize IgA-mediated GP. Its usefulness was reinforced by
IgA-mediated Goodpasture syndrome

Table 1. Clinical and pathological features in 12 reported cases of IgA-mediated GP disease

| Reference | Age/gender | Serum creatinine (mg/dL) | Initial treatment | Renal pathology | Alveolar haemorrhage | Follow-up | Serum IgA | Serum IgA anti-GBM | % of crescents | Immuno-fluorescence (linear GBM deposits) | Overall survival | Nephropathy |
|-----------|------------|--------------------------|-------------------|-----------------|---------------------|-----------|----------|------------------|--------------|------------------------------------------|-----------------|-----------|
| Borza et al. [5, 6] | 67/M | 3.0 | Positive | ? | IgA, κ | CS, CYC | Death (M1, acute dissection) | CS, CYC | Yes | CS, CYC | Censored at 8 years | ESRD at 5 years; KT → ESRD | Moderate CKD |
| Fervenza et al. [6] | 69/M | 3.8 | Positive | ? | IgA; κ and λ | CS, CYC | Death (M20, acute alveolar haemorrhage) | CS, CYC | Yes | CS, CYC | Death (M100, alveolar haemorrhage) | Censored at M60 | Normal |
| Maes et al. [7] | 67/M | 3.5 | Positive | ? | IgA; κ | CS, CYC | Death (M2, alveolar haemorrhage) | CS, CYC | Yes | CS, CYC | Death (M2, alveolar haemorrhage) | Censored at M60 | HD |
| Carreras et al. [8] | 69/M | 20.0 | ? | ? | IgA, κ and λ | No | PE | No | ? | ? | Censored at M36 | Normal |
| Maes et al. [7] | 67/M | 9.0 | Positive, IgA | ? | ? | CS, CYC | Death (M23, stroke) | CS, CYC | Yes | CS, CYC | Death (M23, stroke) | Moderate CKD |
| Savage et al. [9] | ?/M | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? |
| Shaer et al. [10] | 35/M | 20.0 | ? | ? | IgA, κ and λ | No | CS | Death (M20) | HD | IgA, κ and λ not specified | No | CS, AZA |
| Gris et al. [11] | 62/M | 9.0 | Positive, IgA | ? | ? | CS, CYC | Death (M20, alveolar haemorrhage) | CS, CYC | Yes | CS, CYC | Death (M20, alveolar haemorrhage) | Censored at M60 | HD |
| Nakano et al. [12] | 43/M | ? | 75% IgA, C3 not specified | Yes | CS | Death (M13, sepsis) | CS | No | ? | ? | ESRF | Moderate CKD |
| de Caestecker et al. [14] | 55/M | Normal | Positive 10% | Anti-GBM | ? | ? | ? | ? | ? | ? | ? | ? |
| Border et al. [15] | 49/M | 6.1 | ? | ? | IgA, κ | ? | Censored at M30 | HD, then KT | ? | ? | ? | ? |
| Ho et al. [16] | 74/F | 1.2 | Positive >40% | IgA, λ | ? | CS, CYC | Death (M100, alveolar haemorrhage) | CS, CYC | Yes | CS, CYC | Death (M100, alveolar haemorrhage) | Censored at M60 | HD |

In summary, IgA-mediated GP is extremely rare. Pathogenic autoantibodies cannot be detected by routine ELISA profiling to detect IgG circulating autoantibodies. Recognition relies on immunofluorescence microscopy of the kidney biopsy. Despite intensive therapy modeled on IgG-mediated GP, the renal prognosis is poor. Kidney transplantation is an option for ESRF.

Conflict of interest statement. None declared.

(See related Editorial comment by A.S. Bomback. Antiglomerular basement membrane nephritis: why we still ‘need’ the kidney biopsy. Clin Kidney J 2012; 5: 496–497)

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Received for publication: 20.6.12; Accepted in revised form: 22.6.12