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Exceptional Case

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Anti-GBM disease with a mild relapsing course and low levels of anti-GBM autoantibodies

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Abstract
Anti-glomerular basement membrane disease (anti-GBM) is usually characterized by rapidly progressive glomerulonephritis, and when autoantibody production has ceased, relapses are rare. Here, we report a 71-year-old women diagnosed at a stage of mild renal insufficiency. Over a period of 10 years, she experienced three mild relapses with return of anti-GBM antibodies, haematuria and slight elevations in serum creatinine level. All three relapses responded to immunosuppressive therapy, and all were preceded by peaks of myeloperoxidase-antineutrophil cytoplasm antibodies (MPO-ANCA). This case shows that long-term follow-up is warranted in patients treated for anti-GBM-mediated disease, but urinary dipsticks may be sufficient for early detection of relapses.

Keywords: anti-GBM; glomerulonephritis; Goodpasture's disease; relapses

Background

The disease caused by autoantibodies with specificity for the NC1 domain of the α3-chain of Type IV collagen, often referred to as anti-glomerular basement membrane disease (anti-GBM disease) or Goodpasture's disease, is characterized by rapidly progressive glomerulonephritis (GN) often accompanied by lung haemorrhage [1]. Disease progression is usually dramatic, and a substantial proportion of patients in recently published series present with oliguric or anuric acute renal failure [2–4].

Detectable amounts of anti-GBM antibodies usually do not remain in the circulation for >6–12 months, even without the use of cytotoxic drugs. After that time, the recurrence of anti-GBM antibodies as well as relapse of glomerulonephritis (GN) is rare [3–5]. Here, we report a case of a clinically and histologically mild form of GN, associated with low levels of anti-GBM antibodies but complicated by a protracted relapsing course.

Case report

A 71-year-old woman with a medical history that included a peripheral facial paresis and an irritable colon sought medical attention in August 2000 after a 6-month period of general malaise, intermittent subfebrility and myalgia. The weeks preceding the appointment her condition had worsened. Dipstick tests revealed haematuria and proteinuria. Blood tests indicated a mild renal failure with a serum creatinine of 100 µmol/L and an erythrocyte sedimentation rate of 80 mm/h. A week later her creatinine had risen to 130 µmol/L and serology was positive for anti-GBM with 61 and myeloperoxidase-antineutrophil cytoplasmic anitbody (MPO-ANCA) >320 ELISA units (above 10 is considered as positive in both the assays).

She was transferred to the Lund University Hospital, where she received apheresis with Protein A adsorption columns. A renal biopsy showed focal necrotizing glomerulonephritis with crescents in 6 of 16 glomeruli and a typical linear immunofluorescence pattern for IgG, kappa and lambda. After three Protein A sessions, her anti-GBM antibodies were undetectable. She was discharged with oral cyclophosphamide 75 mg per day and prednisolone. After 5 months, the medication was switched to azathioprine 50 mg daily, which was continued for 12 months. Serum creatinine remained stable at a level of 90 µmol/L and anti-GBM antibodies were below the detection limit (Figure 1).

Two years later in the fall of 2004, she experienced a relapse with re-emergence of anti-GBM antibodies, return of microscopic haematuria and a slight elevation of serum creatinine (maximum 108 µmol/L). Treatment with azathioprine was restarted. During 2005, anti-GBM remained positive at low level, but turned negative in April 2006. Haematuria was noted until November 2005. Azatioprine therapy was continued for 25 months.

In October 2007, she experienced her second minor relapse with return of anti-GBM antibodies, microscopic haematuria and a slight elevation of creatinine (maximum 131 µmol/L). Treatment with pulse cyclophosphamide therapy was initiated, resulting in disappearance of anti-GBM antibodies and haematuria. After six cyclophosphamide pulses, azathioprine was restarted.

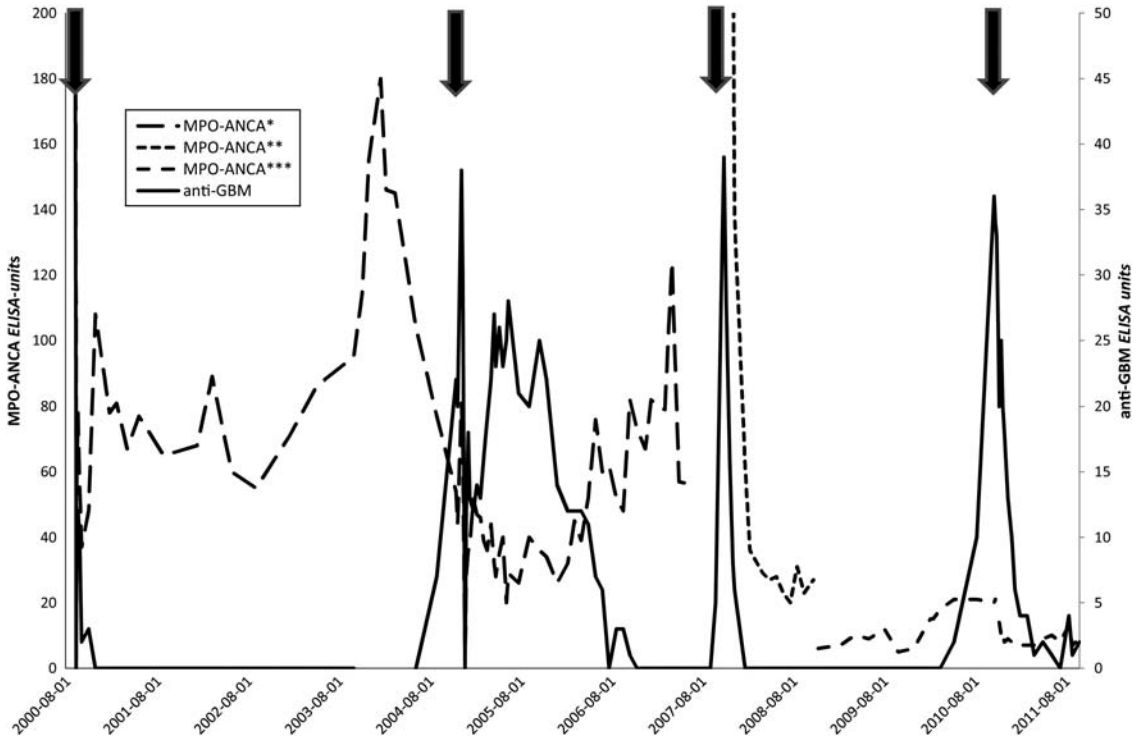

Fig. 1. The solid line represents levels of anti-GBM antibodies measured by the enzyme-linked immunosorbent assay (ELISA) and expressed in arbitrary ELISA units as indicated by the right vertical axis. The patient exhibited four distinct serological exacerbations separated by intervals with negative tests. The serological relapses coincided with clinical relapses; start (and restart) of immunosuppressive treatment is indicated by arrows. Dotted lines represent MPO-ANCA levels measured by three different ELISA methods. Method* was used until June 2007, then method** was used until November the same year when method***, using international units, was introduced. ELISA units for MPO-ANCA are indicated on the left vertical axis, levels differ between the three assays.

In November 2010, both haematuria and anti-GBM antibodies returned, like at previous relapses there was no malaise or other symptoms of general inflammation. This third relapse was curbed with an increase in azathioprine doses to 150 mg and reinstitution of a moderate prednisolone dose. Once again, there was a response with vanishing haematuria and autoantibodies. At the most recent follow-up in October 2011, anti-GBM was negative, there was no haematuria, and creatinine was 106 µmol/L.

Discussion

The clinical course in this case was benign, with preserved renal function for more than a decade. Most cases of anti-GBM disease are diagnosed at a more advanced stage. In our series of 75 cases, only two had a serum creatinine <140 at the time of diagnosis [3]. It is impossible to discern whether the benign clinical course was due to the inherent nature of the case or a direct result of the swift initiation of aggressive autoantibody lowering therapy. A finding in favour of a mild inherent nature in this case is the relatively low levels of anti-GBM antibodies, 61 ELISA units, compared with a median level of anti-GBM antibodies in positive cases at the laboratory of 112 units (interquartile range 39–197). Previous studies have indicated that levels of anti-GBM antibodies at diagnosis are predicative of long-term outcome [2, 3]. However, it is probable that without treatment, levels of anti-GBM would have increased along with an accelerated intensity of the glomerulonephritis.

The most remarkable feature of this case is the three mild relapses. In all instances, the return of anti-GBM antibodies was associated with the return of microscopic haematuria, strongly indicating a pathogenic capacity of the autoantibodies. However, formal proof of relapsing anti-GBM disease with repeat biopsy was never obtained. There are only a few reports of late relapses of anti-GBM disease [5–7]. Levy *et al*. reported two cases with relapses among 71 patients in his long-term follow-up study [4] and we found one among 75 [3].

In the present case, the anti-GBM antibodies were accompanied by MPO-ANCA. This combination is common and was found in 30% of the patients in our Swedish cohort [3], and other studies have found similar frequencies [8]. The MPO-ANCA levels fluctuated, and even though four peaks can be identified, the MPO-ANCA and anti-GBM curves were not parallel. A temporal separation of anti-GBM and MPO-ANCA in the form a sequential appearance of the autoantibodies has previously been reported [9, 10]. The combination of ANCA and anti-GBM could indicate some sort of overlap syndrome between Goodpasture's disease and ANCA-associated vasculitis, but while there was a strict correlation between anti-GBM and microscopic haematuria, there was no obvious correlation between the MPO-ANCA levels and clinical findings. Also in the case described by Serratrice *et al*., the flare of anti-GBM disease was preceded by a rise in MPO-ANCA levels that had peaked several months earlier [10].

In summary, this case shows that anti-GBM antibodies might be present in cases with relatively mild renal failure, and that high vigilance is necessary as mild disease might be at hand only during a relatively short window of opportunity. Even though this case might represent an overlap syndrome with ANCA-associated vasculitis, the return of the anti-GBM antibodies several years after successful treatment demonstrates that long-term surveillance is warranted. How the follow-up should be organized with respect to frequency of visits and anti-GBM test is difficult to discern. However, the present case suggests that negative dipstick tests for haematuria might be sufficient to rule out recurrence of anti-GBM nephritis.

Conflict of interest statement. J.W. works for Eurodiagnostica AB. The authors have no other conflicts of interest.

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