Rituximab-induced long-term remission of membranous lupus nephritis

Sir,

Rituximab is a chimeric anti-CD20 monoclonal antibody that has proved to be effective in depleting B-lymphocytes in vivo [1]. We report here a case of a woman with severe membranous lupus nephritis who was treated with rituximab with significant and persistent improvement during a 3 year follow-up. She had previously failed to respond to therapy with cyclophosphamide, prednisolone, cyclosporine and mycophenolate mofetil (MMF).

A 16-year-old female with SLE and nephrotic syndrome had a renal biopsy performed showing membranous lupus nephritis (WHO class V). The patient was treated with prednisolone continuously and a sustained remission of the nephrotic syndrome was achieved. At the age of 22, the patient had a relapse and a new renal biopsy showed WHO class V. The prednisolone dose was increased and i.v. cyclophosphamide was administered monthly for 6 months. A re-biopsy showed persistent WHO class V. Cyclophosphamide i.v. pulse therapy was continued but due to incomplete effect and side effects, therapy was stopped after two infusions. The patient was started on oral cyclosporine, 24-h urine albumin was 5.2 g and glomerular filtration rate (GFR) was 59 ml/min. During treatment, proteinuria decreased to approximately 1 g/24 h.

At ~27 months (before start of rituximab) the then 25-year-old woman was treated with cyclosporine 75 mg and prednisolone 5 mg/day (Table 1). At ~12 months, the nephrotic syndrome relapsed and the dose of cyclosporine was increased to 150 mg. Prednisolone to 30 mg and MMF 1 g/day was added, subsequently increased to 2 g/day. A year later (~1 month), the patient developed pneumonia with septicaemia and a severe nephrotic syndrome with extensive oedema, pericardial effusion and hypertension developed. GFR was 5 ml/min. Cyclosporine and MMF were withdrawn and the patient was given high doses of i.v. methylprednisolone. Kidney biopsy showed lupus nephritis WHO class Vb and vasculopathy with thrombotic microangiopathy and signs of malignant hypertension. At that time (month 0), i.v. rituximab (Mabthera) 375 mg/m² body surface area was given once weekly for 4 weeks in combination with i.v. cyclophosphamide 0.5 g/m² twice. After treatment, the CD19 positive B-lymphocytes were totally depleted, starting to recover after approximately 1 year. By then, the ongoing low-dose prednisolone treatment was combined with MMF in a dose of 0.5 g/day. 24 months after treatment with rituximab, GFR had increased to 40 ml/min. At 36 months, treatment consisted of prednisolone 5 mg in combination with MMF 1 g/day and antihypertensive drugs. Serum creatinine was 118 μmol/l, serum albumin 36 g/l and 24-h urine albumin 7 mg (Table 1).

In membranous lupus nephritis the optimal treatment is controversial although remission of the nephrotic syndrome can occur following the treatment with steroids in combination with cyclophosphamide, cyclosporine or MMF. Despite extensive immunosuppressive treatment during the disease course, the nephrotic syndrome persisted in our patient and was further complicated by infectious complications and renal failure. At that time rituximab was given in combination with two infusions of cyclophosphamide with long-standing beneficial results. Rituximab-induced remission of refractory nephrotic syndrome has previously been reported in patients with idiopathic membranous nephropathy and membranous lupus nephritis [2,3] and promising effects of rituximab in short-term follow-ups in lupus nephritis patients have been described [4,5]. This strengthens the view that depletion of B-cells with rituximab may be a new therapeutic option in patients with severe therapy-resistant membranous lupus nephritis.

Conflict of interest statement. None declared.

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1. Maloney DG. Preclinical and phase I and II trials of rituximab. Semin Oncol 1999; 26 [Suppl 14]: 74–78

Table 1. Laboratory examinations prior and after treatment with rituximab

<table>
<thead>
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<th>Reference range</th>
<th>Months</th>
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<tr>
<td></td>
<td>–27</td>
<td>–12</td>
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<tr>
<td>Creatinine (μmol/l)</td>
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<td>Albumin (g/l)</td>
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<td>GFR (ml/m²×1.73 m²)</td>
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<td>IgG-dsDNA (FEIA) (IU/ml)</td>
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**Rapidly progressive glomerulonephritis in a patient with brucellosis**

Sir,

Subclinical renal involvement in the course of brucellosis is a common scenario in the area of brucella endemicity [1,2]. However, few reports of brucellosis with overt renal failure exist in the literature. Brucella nephropathy may be secondary to glomerulonephritis (GN), interstitial nephritis, renal vasculitis and granuloma or abscess formation [1–4]. Membranous glomerulopathy, mesangial proliferative GN, IgA nephropathy and mesangiocapillary GN have been reported [1,3,5]. Due to the paucity of reports, the nature of brucella nephropathy has remained largely unidentified. We describe a case of brucellosis associated with rapidly progressive renal failure.

A 28-year-old man was admitted to hospital due to rapidly progressive renal failure. He had vomiting, anorexia and weakness and also reported frequency and nocturia for 5 months. A history of surgical correction of ventricular septal defect was present. He had also had serologically proven brucellosis 4 months previously, for which he had received specific antibiotics and apparently was not compliant with them. Examination revealed an ill man with BP of 90/60 mmHg and BT of 37.5°C. A grade V/VI holosystolic murmur was prominent over the pulmonary area. Otherwise, the examination was unremarkable.

Remarkable laboratory findings were: haemoglobin 8.8 g/dl, haematocrit 25.6%, CRP 2+; first-hour ESR 55 mm, serum creatinine 4 mg/dl, urea 101 mg/dl, uric acid 8.3 mg/dl, calcium 8.2 mg%, phosphorus 6 mg/dl. C3 complement level was low at 57 mg/dl (normal 70–170 mg/dl). Hepatitis and HIV serology, P-ANCA, C-ANCA, ANA and antibodies to dsDNA and glomerular basement membrane were all negative. Brucella serum agglutination test was positive at a titer of 1/2560. Urine sediment examination showed many red blood cells casts. There was a proteinuria of 1 g/day. Renal ultrasonography revealed increased parenchymal echogenicity. Echocardiography demonstrated moderate pulmonary stenosis. No valvular vegetations were detected.

Light microscopy of the renal biopsy specimens revealed mesangial cell proliferation, matrix expansion, glomerular basement membrane thickening (double-contour appearance) and accentuation of lobular architecture in some glomeruli (Figure 1). Immunofluorescence study showed intense mesangial staining for C3 and C1q in a granular pattern that was negative for any immunoglobulins and Kappa and Lambda light chains. The diagnosis of mesangiocapillary GN was made.

The patient was placed on rifampin (200 mg/day) and doxycycline (900 mg/day) as well as intravenous methylprednisolone pulses (500 mg/day for three consecutive days) followed by oral prednisolone. One week later, his general condition dramatically improved. At day 12, serum creatinine level and urinalysis returned to normal. Rapid response to steroid and specific antibiotic therapies led us to consider the diagnosis of brucella GN for this patient.

Brucella may involve renal glomeruli, interstitium and/or renal vasculature [1,4,5]. Brucella nephropathy seems to be an underdiagnosed entity. Hence, a high index of suspicion for it is particularly necessary in the area where the brucella is endemic.

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