Case Report

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IgA nephropathy in a patient with IgG lambda light-chain plasmacytoma: a rare coincidence

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Introduction

Renal involvement in multiple myeloma (MM), which accounts for about 10% of all haematological malignancies, is not uncommon. Immunoglobulin A (IgA) nephropathy and IgA lambda myeloma with mesangial proliferative glomerulonephritis (GN) have been reported [1]. An interaction between mesangial cells and IgA as well as IgG immune complexes provides a possible mechanism for glomerular injury in IgA nephropathy [2]. IgA myelomatosis with nephritis and Henoch-Schoenlein purpura may coexist [3], and some have suggested a causal relationship between IgA nephropathy and IgA myeloma [4]. Unlike findings in patients with lupus-GN and other types of proliferative and membranous GN, patients with IgA nephropathy have positive staining for kappa- (κ) and lambda- (λ) immunoglobulin in their kidney biopsies [5], with more intense staining of the λ-light-chain than for the κ-light-chain.

Activation of the transcription factor nuclear factor κB (NF-κB) has been shown to be involved in the development of human GN, and the degree of glomerular expression of NF-κB correlated with the progression of glomerular injury in IgA nephropathy [6]. Inhibitors of NFκB may provide potential agents for treatment of immune GN [7], since inhibition of NFκB prevented inflammation in an experimental model of renal failure [8].

We report a patient with a plasmacytoma of the sacrum given local irradiation, various cytostatics and with thalidomide that showed acceptable responses during several years of treatment. Six years later the disease flared-up. Pneumonia and renal failure due to de novo IgA nephropathy developed and regular haemodialysis was started. Treatment with the NFκB inhibitor bortezomib resulted in temporary regression of the myeloma, recovery of kidney function and disappearance of IgA deposits in a repeat kidney biopsy.

Case

The subject was a 76-year-old man having a history of psoriasis, diplococcic meningitis and pneumonia from 15 years ago. At 3 months after a minor bicycle accident in 2001, he had right-sided loin pain and back-pain and was referred to our hospital. X-ray and magnetic resonance imaging (MRI) showed a tumour-mass in the sacrum-region involving the thoracolumbar column together with compression of the lower part of the thoracic spinal chord. A biopsy of the tumour disclosed atypical plasma cells in the infiltrate and clear λ-cell clonality consistent with plasmacytoma. In addition, pathologic lytic areas were discovered in several bone structures. Heart and lung examination results, blood pressure (BP), and kidney function were normal and serum creatinine concentration (s-creat) was 74 μmol/l. A monoclonal component consisting of IgG λ-light-chain was found in serum and bone marrow aspiration material that consisted of 10% of plasma cells verifying MM. Serum light-chain paraprotein concentration was 43.3 g/l and the urinary light-chain concentration was only 0.07 g/l.

Local irradiation (10 times á 3 GY) for relief of pain, and additional treatment with methylprednisolone, vincristine, lomustine (CCNU), cyclophosphamide, melphalan (MOCCA-regimen) was initiated. Supportive treatment with dinatrium chlорonate 1600 mg/day, followed by intravenous (i.v.) dinatrium pamidronate (90 mg/month), and then later i.v. zoledronic acid 4 mg/month with addition of calcium and vitamin-D was also given. This treatment
significantly reduced the paraprotein amount to 11.4 g/l. However, increases in paraproteins to 33.7 g/l and plasma cells to 50% in a repeat bone marrow examination led to new treatment with four courses consisting of vincristine, adriamycin and dexamethazone; the level of paraproteins then decreased to 17.8 g/l. However, a repeat increase in paraproteins to 35.4 g/l led to treatment with oral thalidomide 100 mg/day plus dexamethazone 40 mg during 4 consecutive days. In February 2006, the patient developed bilateral pneumonia and was given cefuroxime (Zinacef, GSK) 1.5 g 3 times daily i.v. and moxifloxacine (Avelox, Bayer) 400 mg daily orally for 2 weeks. At this time, C-reactive protein concentration (CRP) was 370 mg/l (ref. value <10 mg/l), haemoglobin (Hb) concentration 142 g/l and s-creat was 126 µmol/l. Other laboratory tests, including anti glomerular basement membrane antibodies (anti-GBM-ab), anti-neutrophil cytoplasmic antibodies (ANCA-ab) and anti-native DNA antibodies (DNA-ab) were negative, and complement C3 and C4 serum levels were within reference values. By this time, the amount of paraproteins had increased to 36.9 g/l, IgA concentration was 0.5 g/l (0.9–4.8 g/l) and IgM was 0.3 g/l (0.4–2.6 g/l). Selected laboratory results showing kidney function, protein concentrations, and serum light chain proteins are depicted in Table 1.

Despite recovery from the pneumonia, the patient continued to feel ill. S-creat concentration had increased to 205 µmol/l (GFR 29 ml/min; MDRD calculation), and increased further to 577 µmol/l (MDRD-GFR 10 ml/min) during the next 2–4 days. Serum urea-nitrogen (Urea) concentration was 16 mmol/l (ref. 2–7.4 mmol/l). Eight days later, s-urea and s-creat had increased to 36 mmol/l and 752 µmol/l (MDRD-GFR 7 ml/min), respectively, and regular haemodialysis (HD) treatment was initiated. A kidney biopsy was performed (Figure 1A and 2A). In April 2006, treatment with bortezomib (formerly known as PS-341) was started at an adjusted dose of 1 mg/m². Eight cycles consisting of four doses of bortezomib each, at days 1, 4, 8 and 11, and with an interval of 21 days were given. A 20 mg daily dose of dexamethazone was given at two consecutive days at the start of each bortezomib dosing. A repeat kidney biopsy was taken in January 2007 (Figures 1B and 2B).

Kidney biopsy

Light microscopic examination of the first kidney biopsy, taken in April 2006, disclosed GN with increased cellularity and increased amount of mesangial material within the glomeruli (Figure 1A). Malignant cells, myelomatotic or other casts were absent. Immunofluorescence and immunochemical staining of the biopsy material showed granular deposition of IgA in the mesangium (Figure 2A) together with mesangial positivity to κ- and λ-light-chain. Mesangial matrix material was slightly more prominent in the second biopsy taken in January 2007 (Figure 1B). IgA deposits were not found (Figure 2B). Staining for λ-light-chains was positive (data not shown) and staining for κ-light chains was negative (data not shown). Malignant cells, myelomatotic or other casts were again absent in the second biopsy.

Clinical development

Intensive bortezomib treatment for MM resulted in recovery of kidney function and HD was discontinued after 2 months; at this time, s-creat concentration had decreased to 192 µmol/l (MDRD-GFR 32 ml/min). Thereafter, s-creat fluctuated between 163 and 180, and was still 168 µmol/l at February (MDRD-GFR 38, 32 and 38 ml/min, respectively). Paraprotein was 36.91 g/l at start of bortezomib and it decreased to 15.98 g/l during treatment. A slight increase in the amount of paraprotein has occurred later, however. Thus far, our patient has experienced no adverse advents due to bortezomib treatment.

Table 1. Serum protein (S-Prot), serum immunoglobulin-G (IgG), serum immunoglobulin light chain lambda free chain (IgLcL-F) and plasma creatinine (P-Creat) concentration, and amount of urinary protein (dU-Prot) in 24 h urine collection in a patient with IgG lambda light chain plasmacytoma and simultaneous IgA glomerulonephritis

<table>
<thead>
<tr>
<th>Date</th>
<th>S-Prot (55–80 g/l)</th>
<th>dU-Prot (&lt;150 mg/24 h)</th>
<th>S-IgG (7–16 g/l)</th>
<th>S-IgLcL-F (8.6–26.5 mg/l)</th>
<th>P-Creat (60–100 µmol/l)</th>
</tr>
</thead>
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<tr>
<td>08/2001</td>
<td>101</td>
<td>260</td>
<td>43.3</td>
<td>86</td>
<td>73</td>
</tr>
<tr>
<td>11/2002</td>
<td>79</td>
<td>105</td>
<td>22.5</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>03/2003</td>
<td>83</td>
<td>150</td>
<td>28.3</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>05/2004</td>
<td>93</td>
<td>NA</td>
<td>33.7</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>06/2005</td>
<td>88</td>
<td>781</td>
<td>35.4</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>03/2006</td>
<td>85</td>
<td>205</td>
<td>NA</td>
<td>205</td>
<td>205</td>
</tr>
<tr>
<td>04/2006</td>
<td>64</td>
<td>751</td>
<td>NA</td>
<td>858</td>
<td>752</td>
</tr>
<tr>
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<td>3970</td>
<td>NA</td>
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<td>19.0</td>
<td>89.8</td>
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<td>NA</td>
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<td>188</td>
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<tr>
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<td>75</td>
<td>504</td>
<td>26.8</td>
<td>235</td>
<td>161</td>
</tr>
</tbody>
</table>

NA = Not analysed; normal reference values in parenthesis.
Discussion

To our knowledge, this is the first report of a patient having the rare combination of IgA nephropathy with λ-light-chain myeloma. The new and interesting observation in this case was the dramatic response to bortezomib treatment, not only with respect to correction of paraproteins, but also the improvement in IgA nephropathy, which included reversal of renal failure and disappearance of IgA deposits. This observation is in agreement with the previous suggestion that inhibitors of NFκB may represent a new class of compounds to treat IgA nephropathy as well as GN of other aetiologies [7]. However, this treatment remains to be tested in patients with IgA nephropathy. In addition, we acknowledge that the positive course and outcome in our patient may have been due to spontaneous remission of the IgA nephropathy.

It is likely that IgA nephropathy in our patient developed as an immunological response during the course of the respiratory infection. Infections such as upper respiratory infections may act as an initiating or superimposing factor to induce IgA nephropathy [9] and previous reports have shown associations between the presence of mesangial IgA deposition and broncho-pneumonia as well as other lung diseases [9]. In studies with mice, antigens from Staphylococcus aureus were able to induce IgA nephropathy [10]. In view of these reports [9,10], the IgA nephropathy in our patient may have been initiated by pneumonia. Because our patient had low serum IgA levels, measurement of serum IgA concentration was of little or no use. Patients with IgA secreting myelomas [11] or those with HIV [12] often have elevated serum IgA levels, and yet IgA nephropathy is rarely reported in these patient groups [11,12]. Nevertheless, high serum IgA levels were reported in a patient having rapidly progressive renal failure caused by gangrenous pyoderma and IgA λ-monoclonal gammapathy without λ-chains in the kidney biopsy material [13]. In the light of the low serum IgA concentration in our patient, it is unlikely that the IgA nephropathy was caused by increased production or secretion of IgA by plasma cells, and we believe that it was not caused by the myeloma. As was described in reports showing IgA nephropathy in conjunction with lymphoma or Hodgkin’s disease,
the present association appears to represent a rare coincidence.

Very little is known about the effect of bisphosphonates on the development of IgA nephropathy. Because glomerular pathology is associated with high doses of pamidronate, and since impaired renal function in patients with myeloma was due to focal segmental glomerulosclerosis and membranous GN, none of these pathologies corresponded to IgA nephropathy [14]. However, since our patient had been treated with three different compounds of this category, we cannot rule out the possibility that bisphosphonate use caused worsening of renal function.

Bortezomib is a synthetic, boronic acid dipeptide that has multiple effects on different MM cell lines, including the blocking of NF-κB activation [15]. There is evidence that activation of NF-κB is involved in the pathogenesis of experimental GN [16–18] and human nephropathy [19], and others have reported a correlation between NF-κB expression and progression of tissue injury in IgA GN [6]. Inhibition of NFκB activation by bortezomib or other proteasome inhibitors could therefore play a role in the repair of glomerular function during IgA nephropathy [6,7,17,18]. Mechanisms involving tubular NF-κB appeared to be active only in proteinuric patients with IgA nephropathy [19]. Endocytosis of light chains in the proximal tubules may cause activation of cytokines that contribute to the genesis of IgA nephritis, and this can be inhibited by blockade of NF-κB activation with bortezomib [20]. It is tempting to suggest that these mechanisms were responsible for the recovery from IgA nephropathy in our patient. The clearance of cytokines and other toxic molecules by HD treatment may have contributed to the restoration of kidney function in our subject.

Careful monitoring during bortezomib treatment in patients with renal failure has been recommended since this drug may cause deterioration of renal function in some cases [15]. In agreement with the present case, clinical trials in patients with impaired renal function suggest that bortezomib provides clinical benefits with manageable toxicities, and recovery of renal function in some patients.

If bortezomib was able to inhibit the transcription factor NFκB to then cause the regression of the IgA nephropathy and disappearance of IgA deposits, this finding may open new perspectives for treatment of this type of nephropathy. Thus, similar compounds should be tested in patients with IgA nephropathy and in patients with other types of GN having proteinuria.

Conflict of interest statement. None declared.

References


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