Changes in the Urinary Excretion of β2-Microglobulin (β2MG) and N-acety-β-D-glucosaminidase (NAG) during Treatment for Lupus Nephritis

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Abstract

Tubulointerstitial involvement in the kidneys is frequently found but it is a less emphasized feature of lupus nephritis (LN). Recent studies have shown increases in the urinary excretion of β2-microglobulin (β2MG) and N-acetyl-beta-D-glucosaminidase (NAG), which are considered to indicate the presence of tubulointerstitial damage, particularly in cases of LN. However, the changes in these urinary parameters during the clinical course of LN have not yet been fully clarified. In this report, we describe the changes in the urinary excretion of β2MG and NAG during immunosuppressive treatment combined with double filtration plasmapheresis in a case of LN.

Key words: β2-microglobulin, N-acetyl-beta-D-glucosaminidase, lupus nephritis, tubulointerstitial nephritis, double filtration plasmapheresis

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multiple organ involvement. Renal manifestation, i.e., lupus nephritis (LN), is one of the most important organ deficiencies in SLE (1). The formation of immune complexes within the glomeruli seems to be a central event in the pathophysiology of LN. Tubulointerstitial involvement is another well recognized but less frequently emphasized abnormality in LN (2, 3). Several proteins other than albumin excreted in the urine such as β2-microglobulin (β2MG) and N-acetyl-beta-D-glucosaminidase (NAG) are considered useful parameters for the evaluation of renal tubulointerstitial lesions (2, 4, 5).

We herein describe a case of LN associated with the elevation of β2MG and NAG. A renal biopsy revealed the presence of tubulointerstitial damage, and the urinary excretion of these molecules decreased along with an improvement of proteinuria. To our knowledge, this is the first report demonstrating the changes of these molecules during treatment for LN.

Case Report

A 47-year-old man was admitted to our hospital in March 2003 with the chief complaint of progressive swelling of his legs. One year before admission, he developed a skin rash in a sun-exposed area and had been suffering from intermittent polyarthritis. He had no apparent past history of kidney disease. On admission, he looked well and also appeared alert and oriented. Laboratory findings on admission are listed in Table 1. Based on the revised American Rheumatic Association criteria for SLE (6), he was diagnosed to have SLE with serum antinuclear antibodies (ANA), anti-Smith antibody (αSmab), and clinical pictures, including photosensitivity, intermittent polyarthritis, and nephrotic syndrome. The renal biopsy revealed segmental endocapillary proliferation associated with mesangial alterations (Fig. 1 Panel A) and interstitial infiltration of inflammatory cells (Fig. 1 Panel B). In addition to mesangial proliferation, subepithelial and subendothelial deposits were also confirmed by

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electron microscopy (Fig. 1 Panel C). As a result, we made a final diagnosis of diffuse proliferative LN Class IV-S (A/C) + V based on the classification criteria of the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 (7).

From the 21st hospital day, intravenous methylprednisolone (mPSL), 1,000 mg, was given daily for three days, followed by 40 mg prednisolone (PSL) per day orally. As shown in Fig. 2, the initial decrease in the daily urine protein was temporal and hypoalbuminemia persisted. Then, we decided to give him an intravenous pulse dose of cyclophosphamide (0.5 g/m² body surface area). Since his nephrotic state persisted, we applied therapeutic apheresis. Double filtration plasmapheresis (DFPP), which filtered 3 L of plasma with 25 g of supplemental albumin, was performed on the 67th, 70th, 76th, and 83rd hospital days. In each DFPP session, an ethylene-vinylalcohol membrane plasma fractionator with an average pore size of 0.025 μm and effective surface area of 1.7 m² (EC-40W; Asahi Medical Co., Tokyo, Japan) was used together with a hollow fiber polyethylene membrane plasma separator with an average pore size of 0.3 μm and an effective surface area of 0.8 m² (OP-08; Asahi Medical Co., Tokyo, Japan). After the initiation of DFPP, the urinary protein excretion gradually decreased and an improvement in hypoproteinemia was also seen. The urinary excretion of β2MG, NAG decreased along with an improvement in the serological abnormalities (Fig. 2). Along with the remission of nephrotic syndrome, PSL was gradually tapered to 5 mg per day.

**Discussion**

Tubulointerstitial changes in renal tissue have been found in conjunction with glomerular disease in from 38% to 66% of renal biopsy specimens from patients with LN (2, 3). The extraglomerular deposits of immune complexes are thought to mediate the development of various degrees of damage within the tubulointerstitium (8). The pathological and clinical scenario of tubulointerstitial damage can also occur in combination with disease of diverse etiology, including infectious, drug-related, metabolic, obstructive, habitual, toxic mechanisms and other collagen diseases such as Sjögren syndrome (9). However, there is no available information suggesting such a possibility in this case. On the other hand, the nephrotic range of proteinuria observed in the present case might play a role in the observed interstitial damage since it is considered that high urinary protein content may elicit proinflammatory and profibrotic effects that could contribute to tubulointerstitial damage and loss of renal function (10).

An increased amount of urinary β2MG, which is synthesized by most nucleated cells and is filtered freely in the glomerular basement membrane, has also been considered to reflect the renal inflammatory activity in patients with LN (2). In addition, an increased activity of NAG has been considered to be an early indicator of tubular epithelial damage and therefore determination of the urinary NAG activity may be a useful supplement to a routine biochemical analysis of urine in cases of LN (5). However, the longitudinal changes in the urinary excretion of these molecules during the treatment of LN still remain to be elucidated.

**Table 1. Laboratory Data on Admission**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>4300/μl</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>9.6g/dl</td>
</tr>
<tr>
<td>Platelet</td>
<td>10.8×10⁴/μl</td>
</tr>
<tr>
<td>Total protein</td>
<td>5.7g/dl</td>
</tr>
<tr>
<td>Albumin</td>
<td>1.7g/dl</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>19mg/dl</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.96mg/dl</td>
</tr>
<tr>
<td>C3</td>
<td>74mg/dl</td>
</tr>
<tr>
<td>C4</td>
<td>19mg/dl</td>
</tr>
<tr>
<td>CH50</td>
<td>31.6U/ml</td>
</tr>
<tr>
<td>ANA</td>
<td>10240 times</td>
</tr>
<tr>
<td>Anti-ds-DNA/Ab</td>
<td>&lt;5.0IU/ml</td>
</tr>
<tr>
<td>Anti-Sm antibody</td>
<td>256IU/ml</td>
</tr>
<tr>
<td>Urinary protein</td>
<td>12.6g/day</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>92.4ml/min</td>
</tr>
</tbody>
</table>

**Figure 1.** A: The renal biopsy specimen in this case showing endocapillary hypercellularity, capillary double contours, wire loop lesion. B: Infiltration of numerous inflammatory cells was seen in the interstitium (arrow). Atrophic changes of tubules were also demonstrated. Periodic-acid Schiff (PAS) stain. C: Mesangial proliferation, subepithelial (arrowhead) and subendothelial deposits (arrow) were seen by electron microscopy of renal biopsy specimen (×18,000). The scale bar is indicated in each panel (A, B).
The present report clearly demonstrated for the first time that the urinary excretion of β2MG and NAG decreased along with an improvement of proteinuria during the treatment. These observations suggest the prompt recovery of the tubulointerstitial damage probably induced by the high urinary protein. Therefore, the monitoring of these urinary proteins seems to be useful for evaluating the effect of treatment of LN as well as the disease activity within the interstitium. Alternatively, the latent relationship between the changes in the urinary excretion of β2MG and NAG and the subsequent outcome of LN needs to be elucidated, since recent studies suggest that not only glomerulopathy but also tubulointerstitial lesions play a role in making an accurate prognosis of many forms of glomerular disease, including LN (2, 3, 11, 12).

Non-specific immnosuppression by corticosteroids and cytotoxic agents remains the gold standard treatment for LN (13), and no clear advantage has been demonstrated by performing therapeutic apheresis as a routine treatment for LN. However, there are still several anecdotal reports suggesting a beneficial effect of apheresis as an adjunct to conventional immunosuppressive treatment for removing immune complexes, autoantibodies, inflammatory cytokines, and other unrecognized mediators in cases of LN (1, 14). In the present case, we initially treated with corticosteroid, however, the elevation of ANA and αSma persisted, and the decrease in the urinary protein was temporary even after the administration of cyclophosphamide. We therefore decided to apply therapeutic apheresis as an adjunct treatment with expectation of removal of several putative humoral factors that might play a major role in LN.

The choice of the mode of apheresis could be an important determinant of the beneficial and adverse effects of apheresis. Indeed, there is a potential risk for transmission of disease especially when fresh frozen plasma is used as replacement fluid (15). Conversely, it is reported that the treatments in which albumin is administered as volume replacement fluid are associated with fewer adverse reactions when compared to those using fresh frozen plasma (1). We therefore chose DFPP as an adjunct treatment for lupus nephritis in our case. It may be difficult to evaluate the impact of DFPP exclusively in our present cases since it was used in combination with immunosuppressive treatments. However, the rapid improvement in the clinical parameters after DFPP, i.e., a further decrease in the urinary protein levels along with an improvement in the symptoms of hypoproteinemia, suggests that DFPP may have facilitated the recovery of above described renal injuries.

References
