Membranous Nephropathy Associated with the Relatively Selective Cyclooxygenase-2 Inhibitor, Etodolac, in a Patient with Early Rheumatoid Arthritis

Toshiro Sugimoto¹, Masahiro Aoyama¹, Katsuhisa Kikuchi², Masayoshi Sakaguchi¹, Naoko Deji¹, Takashi Uzu¹, Yoshihiko Nishio¹ and Atsunori Kashiwagi¹

Abstract

Renal dysfunction and urinary abnormalities, which are usually related to drug toxicity, secondary amyloidosis, or those which overlap with other autoimmune conditions, are frequently observed in patients with rheumatoid arthritis. This is the first case report of membranous nephropathy in a patient with early-stage rheumatoid arthritis treated with the relatively selective cyclooxygenase-2 inhibitor, etodolac. The present case suggests that any kind of non-steroidal anti-inflammatory drug can cause membranous nephropathy; thus, physicians should be aware of this renal toxicity when prescribing these drugs.

Key words: membranous nephropathy, rheumatoid arthritis, selective cyclooxygenase-2 inhibitor

(DOI: 10.2169/internalmedicine.46.0094)

Introduction

Renal dysfunction and urinary abnormalities, which are usually related to drug toxicity, secondary amyloidosis, or those which overlap with other autoimmune conditions, are frequently observed in patients with rheumatoid arthritis (1). Membranous nephropathy is well-known to occur in rheumatoid arthritis patients treated with gold salt, D-penicillamine or bucillamine (1-3). Here, we describe a patient with short-duration rheumatoid arthritis who presented with membranous nephropathy associated with the relatively selective cyclooxygenase-2 inhibitor, etodolac (4).

Case Report

A 56-year-old Japanese woman was admitted because of proteinuria and persistent leg edema. She did not have any remarkable past history, i.e., urinary abnormalities, edema, or hypertension. One year prior to admission she had noted bilateral wrist pain and morning stiffness and 6 months prior to admission she was started on the non-steroidal anti-inflammatory drug, etodolac, at the dose of 400 mg per day at a local clinic. One month before admission she had reported the development of edema of her lower extremities. Two weeks prior to admission proteinuria (urinary protein, 2+; urinary occult blood, negative) and hypoalbuminemia (3.0 g/dl) was noticed at another local clinic, etodolac was stopped, and one week prior to admission she visited the outpatient clinic of our hospital. Marked proteinuria (protein 3+, 10.0 g/g creatinine) was also noted at the outpatient clinic; thus, she was admitted to our hospital. On admission, her height was 153.0 cm and her weight was 58.5 kg. Her blood pressure was 108/78 mmHg, and pulse was 72 beats/min and regular. Physical examination was unremarkable except for pitting edema of the lower extremities and bilateral wrist swelling with tenderness. She denied having dry eyes, dry mouth, and dysphagia. Further, no ophthalmological abnormalities, e.g., corneal erosion, were identified. Her complete blood cell count including eosinophil and coagulation test were normal, as were the serum electrolyte levels. Total protein was 5.7 g/dl; albumin, 3.0 g/dl; total cholesterol, 397 mg/dl; blood urea nitrogen, 8 mg/dl; and serum creatinine, 0.40 mg/dl. The urinalysis revealed 3+ protein with 4-5 erythrocytes/high-power field and no remarkable casts. A 24-hour urine collection disclosed a creatinine clearance of

¹Department of Internal Medicine, Shiga University of Medical Science, Otsu and ²Department of Orthopedic Surgery, Shiga University of Medical Science, Otsu
Received for publication February 10, 2007; Accepted for publication March 19, 2007
Correspondence to Dr. Toshiro Sugimoto, toshiro@belle.shiga-med.ac.jp
112 ml/min and a total daily protein excretion of 2.7 g. The serological test showed mild elevation of C-reactive protein (4.10 mg/dl) and normal gamma-globulin and complement concentrations. Rheumatoid factor, anti-nuclear antibodies, anti-double-stranded-DNA antibodies, anti-SS-A (Ro)/B (La) antibodies, cryoglobulin, hepatitis B antigens (HBs and HBe), anti-hepatitis B antibodies (HBc and HBs), and anti-hepatitis C antibodies were negative.

Percutaneous renal biopsy was performed on day 2. The pathological findings included normocellular glomeruli without capillary wall thickening and patchy tubular atrophy with a few small foci of mononuclear cell infiltrates (Fig. 1A-C). Immunohistochemistry revealed faintly granular deposits of IgG on the capillary wall, but no deposits of IgA, IgM, C3, C4, or C1q. Electron microscopy showed small and discrete electron-dense subepithelial deposits without surrounding glomerular basement membrane reactions (Fig. 2), indicating stage 1 membranous nephropathy.

Although plain radiography of the hands did not show any remarkable changes, magnetic resonance imaging of the wrists and finger joints revealed several erosions in carpal bones (Fig. 3). Furthermore, strongly positive anti-cyclic citrullinated peptide antibody (>100 U/ml, reference range: <5 U/ml) indicated that she had early-stage rheumatoid arthritis (5), and oral prednisolone at 15 mg per day was started on day 10. Her symptoms, i.e., wrist pain, morning stiffness and leg edema, were immediately improved, and she was discharged on day 18. Four weeks after discharge, when she was seen at a follow-up visit, she did not complain of any symptoms and daily protein excretion was

Figure 1. The renal biopsy specimen includes normocellular glomeruli without marked thickening of basement membrane and patchy tubular atrophy with a few small foci of mononuclear cell infiltrates (A, PAS staining, magnification, ×100; B, PAS staining, ×400; C, PAM staining, ×400).

Figure 2. Electron-microscopic examination shows small, discrete electron-dense subepithelial deposits (arrows) without surrounding glomerular basement membrane reactions (original magnification; ×4,000).
markedly decreased, to 0.4 g (Table 1). Methotrexate was started for rheumatoid arthritis, together with tapering of the dose of prednisolone. At eight months after discharge, she remained well and her urinary protein excretion was below 0.2 g per day (Table 1).

**Discussion**

Early-stage membranous nephropathy occurred in this patient with rheumatoid arthritis of short duration. The present patient’s condition fulfilled only two diagnostic criteria of the American College of Rheumatology for rheumatoid arthritis, but carpal bone erosions were detected with magnetic resonance imaging and anti-cyclic citrullinated peptide antibody was also detected; thus, we diagnosed her as having early-stage rheumatoid arthritis and started the low-dose corticosteroid therapy to relieve her symptoms (5). Laboratory and clinical data did not reveal any apparent causes of membranous nephropathy, i.e., systemic lupus erythematosus, viral hepatitis, solid tumors, or Sjögren’s syndrome (6). An association of membranous nephropathy with rheumatoid arthritis has been reported, but it is thought usually to occur in rheumatoid arthritis patients treated with gold salt, D-penicillamine, or bucillamine (1-3). The present patient had never been treated with these disease-modifying antirheumatic drugs (DMARDs). There are several reports of membranous nephropathy in rheumatoid arthritis patients not treated with these DMARDs (7, 8). However, it remains controversial whether membranous nephropathy should be considered an inherent renal lesion in rheumatoid arthritis, because the influence of other factors, i.e., non-steroidal anti-inflammatory drugs (9, 10) or complication by other collagen diseases (1, 6), can not be entirely ruled out.

The present patient had a history of treatment with the non-steroidal anti-inflammatory drug, etodolac. She showed the relatively rapid onset of leg edema, and her renal biopsy showed early stage membranous nephropathy, perhaps reflecting this early presentation as a result of the rapidity of proteinuria onset. Further, in spite of low-dose corticosteroid, her marked proteinuria was rapidly decreased, within 10 weeks (Table 1), after etodolac withdrawal. Therefore, we believe she might have non-steroidal anti-inflammatory drug-related membranous nephropathy; Radford et al noted as clinical features that may help to distinguish non-steroidal anti-inflammatory-drug-related from idiopathic membranous nephropathy: the relatively rapid onset of symptoms, early-stage of membranous nephropathy (stage 1 or 2), the rapid remission after the drug withdrawal, and the absence of recurrent disease (9). The present patient did not show any clear evidence of the association with rheumatoid arthritis and other collagen diseases, which are known to cause secondary forms of membranous nephropathy (e.g., systemic

---

**Figure 3.** T1-weighted magnetic resonance imaging of the hands shows bone erosions (arrowheads) in the carpal bones.

---

**Table 1. Laboratory Findings in the Present Case**

<table>
<thead>
<tr>
<th>Variable</th>
<th>day 0</th>
<th>day 5</th>
<th>day 15</th>
<th>day 45</th>
<th>day 105</th>
<th>day 170</th>
<th>day 200</th>
<th>reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein (g/dl)</td>
<td>5.7</td>
<td>5.2</td>
<td>5.4</td>
<td>6.0</td>
<td>6.3</td>
<td>6.5</td>
<td>6.3</td>
<td>6.3-8.3</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.0</td>
<td>2.8</td>
<td>3.0</td>
<td>3.5</td>
<td>3.7</td>
<td>3.9</td>
<td>3.8</td>
<td>4-5.2</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.40</td>
<td>0.42</td>
<td>0.36</td>
<td>0.4</td>
<td>0.42</td>
<td>0.43</td>
<td>0.44</td>
<td>0.4-0.8</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>8</td>
<td>9</td>
<td>8</td>
<td>8-20</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>397</td>
<td>308</td>
<td>326</td>
<td>321</td>
<td>266</td>
<td>271</td>
<td>251</td>
<td>125-220</td>
</tr>
<tr>
<td>C-reactive protein (mg/dl)</td>
<td>4.10</td>
<td>4.21</td>
<td>0.13</td>
<td>0.13</td>
<td>0.19</td>
<td>0.15</td>
<td>0.18</td>
<td>0-0.29</td>
</tr>
<tr>
<td>Urinary total protein (g/day)</td>
<td>2.7</td>
<td>1.4</td>
<td>1.6</td>
<td>0.4</td>
<td>0.1</td>
<td>0.07</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

**Notes**

- PSL: prednisolone
- MTX: methotrexate
- PSL, 10 mg/day
- PSL, 7.5 mg/day
- MTX, 4 mg/day
- MTX, 6 mg/day
lupus erythematosus, or Sjögren’s syndrome) (1, 6), but this association could not be completely ignored; thus, further clinical follow-up is necessary.

Non-steroidal anti-inflammatory drugs can induce two different forms of renal diseases: hemodynamically-mediated renal dysfunction, and glomerular or interstitial renal diseases, e.g., minimal change nephropathy, membranous nephropathy, or tubular/interstitial nephritis (10, 11). The former is thought to be directly related to the reduction in prostaglandin synthesis caused by these drugs. The latter is caused by relatively small doses of non-steroidal anti-inflammatory drugs and is thought to be an idiosyncratic reaction to the offending drugs, and this reaction is not drug class specific because it can be induced by any kind of non-selective non-steroidal anti-inflammatory drugs (9, 10, 12). Etodolac is one of the older non-steroidal anti-inflammatory drugs, but this drug has been found to inhibit cyclooxygenase-2 more than cyclooxygenase-1; thus, it is now classified as a relatively selective cyclooxygenase-2 inhibitor (2, 13). To our knowledge, this is the first reported case of membranous nephropathy associated with this relatively selective cyclooxygenase-2 inhibitor. Further, there are a few reported cases of the occurrence of similar types of glomerular diseases in patients treated with the selective cyclooxygenase-2 inhibitor celecoxib, which is structurally unrelated to nonselective non-steroidal anti-inflammatory drugs (14-16). These glomerular diseases have been thought to be caused by non-steroidal anti-inflammatory drugs-induced hypersensitivity (10); however, these cases including ours suggest that immunological dysregulation evoked by their cyclooxygenase inhibition might also contribute to the development of these glomerular injuries.

As selective cyclooxygenase-2 inhibitors, e.g., celecoxib, are not available in Japan, relatively selective cyclooxygenase-2 inhibitors, e.g., etodolac and meloxicam, have been commonly prescribed for patients with rheumatic diseases to prevent non-steroidal anti-inflammatory drug-related gastrointestinal complications (2). The present study suggests that any kind of non-steroidal anti-inflammatory drugs can cause membranous nephropathy; thus, physicians should be aware of this renal toxicity when prescribing this class of drugs.

References


© 2007 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html

DOI: 10.2169/internalmedicine.46.0094