Successful Steroid Therapy for Cefdinir-induced Acute Tubulointerstitial Nephritis with Progressive Renal Failure
Yasukazu Kimura, Minoru Kawamura, Masahiko Owada, Takuya Fujiwara, Chihaya Maesawa* and Katsuhiko Hiramori

Abstract
A 58-year-old woman was admitted to our hospital because of renal dysfunction that continued to progress even after withdrawal of cefdinir, the presumed cause of acute renal failure. Renal histologic findings included interstitial fibrosis accompanied by moderate lymphocytic infiltration, and tubular atrophy with reduced numbers of epithelial cells. Mesangial cells and glomerular basement membranes were nearly normal. Scintigraphy with 67gallium disclosed diffuse abnormal accumulation in both kidneys. A lymphocyte stimulation test with cefdinir was positive. The patient was diagnosed with acute tubulointerstitial nephritis caused by cefdinir. Serum creatinine concentrations continued to rise after withdrawal of the drug, but steroid therapy was effective in normalizing renal function. (Internal Medicine 40: 114–117, 2001)

Key words: lymphocyte stimulation test, 67gallium scintigraphy

Introduction
Drug-induced acute tubulointerstitial nephritis is a rare cause of potentially reversible acute renal failure. Certain cephalosporins have been associated with this complication, as have other antibiotics and various drugs including nonsteroidal anti-inflammatory agents, diuretics, H2-blockers, and anticonvulsants (1–3). However, we found no report of the cephalosporin cefdinir causing this renal disorder. As this form of acute tubulointerstitial nephritis is an allergic drug reaction, steroid therapy is often administered. However, since randomized controlled studies have not been performed, whether the therapy hastens recovery or improves prognosis is uncertain (2, 4). Under these circumstances well studied cases treated with steroid therapy are informative. We report a case in which steroids were dramatically effective in reversing progressive renal failure from cefdinir-induced acute tubulointerstitial nephritis.

Case Report
A 58-year-old woman presented to a clinic on November 30, 1998 with complaints of pyrexia and a slight cough. In 1996 she had been found to have essential hypertension, which was treated with amloidipine. At the time of periodic routine examination in July 1998, the serum creatinine concentration was 0.7 mg/dl and urinalysis was normal. The patient was diagnosed with acute bronchitis, and was given cefdinir (300 mg/day). After 6 days, symptoms had not improved, and the patient complained of nausea. The serum creatinine concentration was elevated to 2.1 mg/dl. The antibiotic was changed to ofloxacin, a new-quinolone antimicrobial agent, and famotidine, an H2-blocker, was added. After ofloxacin had been administered for 5 days, the creatinine concentration continued to rise, and the second antibiotic was discontinued. The patient was referred for admission to Iwate Medical University Hospital on December 22, 1998.

Her history was negative for renal disease and other illnesses except for hypertension. On physical examination, her temperature was 37.3°C, blood pressure was 134/82 mmHg, and no rash was present. No other physical abnormalities were noted on examination of the skin, chest, abdomen, or extremities. Table 1 presents the laboratory data obtained from the patient on admission. Serum urea nitrogen, creatinine, and C-reactive protein concentrations were elevated, while eosinophilia was not observed. Urinalysis showed microscopic hematuria, proteinuria, and an abnormally high excretion of β2-microglobulin, while the urine culture was negative and eosinophils were not seen in the urinary sediment. No antibodies indicating autoimmune disorders were detected. A drug lymphocyte stimulation test was performed (SRL Laboratories, Tokyo); an index value of >180% was considered positive for suspected drugs (5). Cefdinir showed an index value of 200%, while ofloxacin and famotidine showed the values of 126% and 114%, respectively.

The renal biopsy was performed after 4 weeks after admini-
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Table 1. Laboratory Data at the Time of Admission

<table>
<thead>
<tr>
<th>Blood counts</th>
<th>Renal function</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells</td>
<td>10,520/mm³</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>79.4%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>9.8%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1.5%</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.4%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>7.1%</td>
</tr>
<tr>
<td>Red blood cells</td>
<td>384×10⁶/mm³</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.7 g/dl</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>37.4%</td>
</tr>
<tr>
<td>Platelets</td>
<td>41.1×10⁹/mm³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood biochemistry</th>
<th>Immunologic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein</td>
<td>7.2 g/dl</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.0 g/dl</td>
</tr>
<tr>
<td>AST</td>
<td>18 IU/l</td>
</tr>
<tr>
<td>ALT</td>
<td>14 IU/l</td>
</tr>
<tr>
<td>LDH</td>
<td>166 IU/l</td>
</tr>
<tr>
<td>ALP</td>
<td>239 IU/l</td>
</tr>
<tr>
<td>γ-GTP</td>
<td>21 IU/l</td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>43.9 mg/dl</td>
</tr>
<tr>
<td>Creatinine</td>
<td>3.9 mg/dl</td>
</tr>
<tr>
<td>Uric acid</td>
<td>5.7 mg/dl</td>
</tr>
<tr>
<td>Sodium</td>
<td>139 mEq/l</td>
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<tr>
<td>Potassium</td>
<td>4.2 mEq/l</td>
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<tr>
<td>Chloride</td>
<td>107 mEq/l</td>
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<tr>
<td>Calcium</td>
<td>8.1 mg/dl</td>
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<tr>
<td>Phosphorus</td>
<td>3.8 mg/dl</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>150 mg/dl</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>5.2 mg/dl</td>
</tr>
</tbody>
</table>

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istration of cefdinir. Figure 1 shows microscopic findings in the specimen. Three glomeruli were observed. One of them showed slight expansion of mesangial matrix and collapse of capillaries but not a significant increase in the number of mesangial cells, and the glomerular basement membranes were nearly normal. The remaining two glomeruli showed only minor abnormalities. The interstitium showed fibrosis, and moderate infiltration by lymphocytes, and tubular cells showed atrophy and reduced numbers. Immunofluorescence was not performed in the present case. By renal ultrasonography, both kidneys had a normal size in terms of the long axis (right, 10.0 cm; left, 10.8 cm); no pyeloectasis or abnormal masses were present. Diffuse abnormal tracer accumulation was evident in both kidneys with ⁶⁷gallium scintigraphy (Fig. 2).

From the various findings, the patient was diagnosed with acute tubulointerstitial nephritis caused by administration of cefdinir. As the serum creatinine concentration had raised to 4.8 mg/dl on December 28, intravenous treatment with 500 mg of methylprednisolone was initiated on the following day, and continued for 3 days. This was followed by daily oral administration of prednisolone 40 mg (Fig. 3). After institution of steroid therapy, the creatinine and C-reactive protein concentrations rapidly fell to 1.8 mg/dl and <0.3 mg/dl, respectively, at the time of discharge from hospital. After discharge, the dose of prednisolone was tapered, with discontinuation in March 2000. At this time, the serum creatinine concentration was 1.1 mg/dl, and urinalysis showed no proteinuria or microscopic hematuria.

Discussion

To our knowledge this case presents the first case report of cefdinir-induced acute tubulointerstitial nephritis. Among the 41 kinds of cephalosporins available in Japan, this complication has been reported in 12 according to a Medline of in English language reports from 1972 to 1999. As this drug reaction occurs in only small numbers of patients, associations depend on reports of single cases. The pattern suggests that any cephalosporin potentially could cause acute interstitial nephritis if given to sufficient numbers of patients. Therefore, vigilance for this complication is important when any cephalosporin is administered.

The frequently mentioned triad of fever, skin rash, and eosinophilia is seen in less than one-third of cases of acute tubulointerstitial nephritis (4, 6); the only definitive diagnostic test is renal biopsy. The pathologic findings in the present case were compatible for this disorder (7). Scintigraphy with ⁶⁷gallium is also a useful diagnostic test for this disease, Linton et al found the sensitivity to be 100% and specificity, 83% (8). Abnormal gallium accumulation in our patient’s kidneys sup-
Figure 1. Microscopic findings in the renal biopsy specimen. Panel A shows no increase in mesangial cells and no change in the glomerular basement membrane. Interstitial fibrosis with atrophy and a reduction in the number of tubular cells are shown, Periodic acid-Schiff, ×300. Panel B shows fibrosis and moderate infiltration of lymphocytes in the interstitial region. Periodic acid-Schiff, ×400.

Figure 2. Scintigraphy with $^{67}$gallium scintigraphy showed abnormally increased accumulation in both kidneys.

ported the diagnosis. Autoimmune or infectious diseases were unlikely to have caused acute tubulointerstitial nephritis in our case because immunologic findings were negative and urine cultures were negative. Furthermore, the normal size of both kidneys by ultrasonography helped to rule out other possible causes of acute renal failure, such as urinary tract obstruction.

The etiology of nephritis in this case appears to be cefdinir by both clinical history and the positive finding of a drug lymphocyte stimulation test. As the serum creatinine concentration and urinalysis were normal 4 months prior to the onset of acute tubulointerstitial nephritis, and cefdinir was the only drug prescribed during the pre-onset period, cefdinir is the likely cause. Shibasaki et al have concluded that the drug lymphocyte stimulation test is applicable to the etiologic diagnosis of drug-induced acute tubulointerstitial nephritis, finding a sensitivity in identifying the suspected agent of 75% (9/12), while all drugs administered except for the suspected agents tested negative (9). Therefore, we concluded that cefdinir caused the acute tubulointerstitial nephritis in this case.

In this case, the increased serum creatinine concentration appeared within a week after the administration of cefdinir, however the renal dysfunction in acute tubulointerstitial nephritis generally appears a few weeks later (2). Although cefdinir had never been administered before the present administration, it is likely that antibiotics, which possess a structure similar to cefdinir, had been administered and her immune system had been sensitized by the drug in advance. The existence of interstitial fibrosis in renal biopsy, which generally appears in the chronic phase, may support this presumption.

We treated our patient with steroid therapy for two reasons. First, marked tracer accumulation in both kidneys was seen in $^{67}$gallium scintigrams, and the C-reactive protein concentration remained high, suggesting active inflammation in the renal interstitium. Second, the likelihood of complete recovery may be considered to be inversely proportional to the duration of renal failure (10). Renal function continued to deteriorate after admission, and intervention appeared to be necessary as it took 4 weeks following the onset of renal dysfunction in this case. Steroid therapy was clearly effective in improving renal function, serum creatinine concentration rapidly decreased, and no complications of steroid therapy occurred. Therefore, we would strongly recommend steroid therapy in such a case. However, we cannot completely rule out the possibility that this amelioration merely result from the discontinuation of the administration of cefdinir.

In summary, this is the first reported case of cefdinir-induced acute tubulointerstitial nephritis. Steroid therapy proved highly effective after withdrawal of cefdinir failed to improve renal function and active inflammation in the renal interstitium was
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Admission Renal biopsy Discharge
m-PSL 500 mg/day

Figure 3. Clinical course of the patient in response to treatment with steroids. PSL: prednisolone, m-PSL: methylprednisolone.

demonstrated to persist.

References