A Case of Granulomatous Renal Sarcoidosis with a Dramatic Response to Corticosteroid and Urokinase Therapy

Yasuhiko TOMINO, Yutaka SHIINA, Kazuaki NISHIZAWA, Takao SUGA, Masahiko MIURA, Masayuki ENDOH, Katsuto WATANABE, Yasuo NOMOTO, Hideto SAKAI

Ikuo MIKUNI* and Yoshiyuki OSAMURA**

Department of Internal Medicine,
*Department of Ophthalmology, **Department of Pathology,
School of Medicine, Tokai University
(Received March 18, 1983)

A case of renal granulomatous sarcoidosis that presented with chronic renal failure (CRF) is described. Renal biopsy specimens revealed typical features of sarcoidosis in light microscopy and immunofluorescence microscopy examinations. The absence of bilateral hilar lymphadenopathy (BHL) was a distinctly unusual feature of sarcoidosis although uveitis and rectal granuloma were observed during the clinical course. A dramatic response occurred on corticosteroid and urokinase therapy, characterized by a fall of serum creatinine levels.

(Key Words: CRF, no BHL, Light Microscopy, Immunofluorescence, Granuloma)

INTRODUCTION

Sarcoidosis is a systemic, granulomatous disease of undetermined etiology and pathogenesis (3). Mediastinal and peripheral lymph nodes, lungs, liver, eyes and other organs are most often involved in this disease (3). It is considered that the impaired renal function may occur secondary to hypercalcemia and/or hyperuricemia, and less commonly, because of direct granulomatous involvement (1-3).

In this report, a case of renal granulomatous sarcoidosis that presented with chronic renal failure (CRF) without bilateral hilar lymphadenopathy (BHL) was described. Corticosteroid and urokinase therapy were started after diagnosis, and a dramatic response to these treatments was observed. It is suggested that a combined therapy with corticosteroid and urokinase might be effective in improving proteinuria and impaired renal function in patients with renal granulomatous sarcoidosis.

CASE REPORT

A 44-year-old male was admitted to the Tokai University Hospital, Kanagawa-ken, Japan on December 1, 1982, because of impaired renal function and anemia. He was well until 30 years of age, when he suffered...
a thunderbolt accidently. At the same time, his necrotic intestine was resected by a local medical doctor (diagnosis was unknown). After that he had noted increasing general fatigue. On October 18, 1977, he suffered from visual impairment, and visited the Department of Ophthalmology of Tokai University Hospital. At that time, an ophthalmologist made a diagnosis of “uveitis” and prescribed corticosteroid (30mg/day, per os) for about three years although BHL was not observed in the chest X-rays. There was no family history of kidney and/or lung diseases. He did not have a history of tuberculosis, diabetes mellitus, hepatitis, drug allergy, skin rash, parasitic diseases or other infections. On physical examination his blood pressure was 102/58mmHg and pulse rates 96/min. The chest and abdomen were normal except post-operative scars in the abdomen. There were no peripheral edema, ascites and/or pleural effusions. There was no costovertebral angle tenderness. The neuromuscular examinations were normal. Laboratory tests showed a hematocrit of 29.4%, red blood cell count of 3.58 x 10⁴/cumm, white blood cell count 11.4 x 10³/cumm and platelet count of 24.5 x 10⁴/cumm. Blood urea nitrogen (BUN) was 42mg/dl, serum creatinine was 4.8mg/dl, serum uric acid was 10.1mg/dl, serum albumin was 3.5g/dl and serum cholesterol was 81mg/dl. β2-microglobulin in sera was 10.2mg/dl (normal: 0.8-2.4mg/dl), and β2-microglobulin in urine was 960mg/dl (normal: 5-253mg/dl). The creatinine clearance was 12ml/min. Sodium was 138mEq, potassium 4.5mEq, chloride 108mEq, calcium 4.6mEq and inorg. phosphate 3.8mg/dl. The rest of the chemistry survey was within normal limits. Levels of serum C3 was 80mg (normal: 80-140mg/dl), C4 56mg (normal: 20-40mg/dl) and CH50 40.2U/ml (normal: 35.0-40.0U/ml). Levels of serum IgA was 676mg/dl (normal: 140-350mg/dl), IgG 2990mg/dl (normal: 1110-1820mg/dl), IgM 614mg/dl (normal: 50-180mg/dl). Angiogensin converting enzyme (ACE) was 21IU/L (normal: 12-36IU/L). Titer of ASO or ASK was not elevated, a throat culture was negative for β-hemolytic streptococci or acid-fast bacilli. Cultures of sputa or gastric juice were also negative for acid-fast bacilli, fungi or bacteria. Hepatitis-B surface antigen was nonreactive. Antinuclear antibody was negative. Urinalysis showed 1+ protein, 1-5 RBC/HPF and no WBC/HPF. 24-hr urine protein excretion was 0.25-0.5g. Urine culture showed no growth for 48 hours.

The size of both kidneys appeared to be diminutive. Tuberculin test was negative. The kveim reaction could not be done. Pulmonary function test was performed on January 26, 1983. DLco was 7.9ml/min. % DLco was 44%. The rest of the pulmonary function test was within normal limits. The results of blood gas analysis was shown as follows: pH 7.412, PO2 99.1mmHg, PCO2 38.5mmHg. O2 saturation 97.8% and BE -0.5.

Right open renal biopsy was performed without any complications on January 17, 1983. For light microscopy examination, 50 glomeruli were available for the study. The parenchyma was almost completely replaced by epitheloid cell granuloma surrounded by lymphocytes (Fig. 1). There were no caseation or necrosis in the kidney. The glomeruli which were not replaced by granuloma were totally sclerotic. Patchy areas of interstitial fibrosis and tubular atrophy were also observed. For immunofluorescence, 10 glomeruli were available for the study. No deposits of IgA, IgM, IgG, IgE
and C3 was observed in the kidney tissues. Deposits of fibrinogen was observed in the granulomatous lesions of the kidney tissues (Fig. 2). Rectal biopsy was performed at the same time. Epithelioid cell granuloma was also observed in the submucosal layers of the rectum.

Fig. 1  Epithelioid cell granuloma surrounded by lymphocytes and sclerotic glomeruli were observed in the kidney (×400).

Fig. 2  Immunofluorescent localization of fibrinogen in the epithelioid cell granuloma (×400)
Treatment with 30 mg/day (per os) of prednisolone and single shot injection of 48,000 IU of urokinase (Urokinase®, Green Cross Company, Osaka, Japan) was attempted after the diagnosis. Serum creatinine levels were elevated at the time of diagnosis and during the initial stage of corticosteroid and urokinase therapy at 4.8 mg/dl and 5.4 mg/dl respectively. The creatinine levels decreased to 3.2 mg/dl about 30 days after such therapy (Fig. 3). The levels of β2-microglobulin in sera, or in urine were 6.0 mg/dl, 960 mg/dl respectively. Creatinine clearance examined after such therapy was 15 ml/min (Table 1). 24-hr urine protein was not excreted at the same time. The amount of prednisolone was gradually tapered off to 15 mg every other day although urokinase therapy had been continued.

![Diagram](image)

**Fig. 3** The levels of serum creatinine were markedly decreased after the combined therapy with corticosteroid and urokinase.

**Table 1** Clinical data before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>before treatment</th>
<th>30 days after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>u-protein (g/day)</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>u-occult (RBC/HPC)</td>
<td>1.5</td>
<td>1&gt;</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>31.0</td>
<td>29.0</td>
</tr>
<tr>
<td>s-Cr (mg/dl)</td>
<td>5.4</td>
<td>3.2</td>
</tr>
<tr>
<td>β2-microglobulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>serum (mg/l)</td>
<td>10.2</td>
<td>6.0</td>
</tr>
<tr>
<td>urine (g/l)</td>
<td>960.0</td>
<td>960.0</td>
</tr>
<tr>
<td>Cr. Clearance (ml/min)</td>
<td>12.0</td>
<td>15.0</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Sarcoidosis is considered to be a systemic granulomatous disease although the pathogenesis of this disease is still obscure (3). The light microscopic and
immunofluorescent findings in this case are typical of renal granulomatous sarcoidosis. Although there are no BHL in this case, pulmonary function tests, especially DLco, were markedly impaired. Moreover, uveitis was observed at the time before occurrence of renal function impairment. It is suggested that corticosteroid therapy for the treatment of uveitis might modify the lung lesions in this case. Therefore, it was difficult to get a diagnosis of "systemic sarcoidosis" at the initial time when this was patient admitted. It is postulated that renal granulomatous lesions observed in this case are due to systemic granulomatous sarcoidosis. Rectal granulomatous lesions further support this diagnosis. However, it has been reported that granulomatous renal sarcoidosis with CRF is an apparently rare condition (1,5). In 1980, Muther et al (4) have reported the eleventh of granulomatous sarcoid nephritis and reviewed the previous literature. They indicated that granulomatous nephritis may be an important cause of morbidity and mortality in patients with sarcoidosis. Bolton et al. (1) and King et al. (2) have reported that the incidence of sarcoid granulomatous nephritis is low compared with that of calcium nephropathy due to sarcoidosis. In this case, no hypercalcemia and/or hyperuricemia were observed during the clinical course. Muther et al. (4) indicated the good response of granulomatous sarcoid nephritis to corticosteroids. Recently, we have reported that urokinase induced a significant defibrination of intraglomerular fibrin deposits in patients with IgA nephropathy and other glomerular diseases (6, 7). Since deposition of fibrinogen was detected in the granulomatous lesions of the kidney tissues in this case, a combined therapy with corticosteroid and urokinase has been continued. Such combined therapy was effective in improving proteinuria and impaired renal functions. It is suggested that administration of corticosteroid and/or urokinase may be useful for the defibrination of intragranulomatous fibrin deposits in patients with renal granulomatous sarcoidosis. Further examinations on fibrinolysis in renal tissues of granulomatous sarcoidosis are warranted.

REFERENCES