Mesangiolytic Glomerulopathy after Radiotherapy and Chemotherapy of Gastric Lymphoma

Junko Yoshimura, Seiya Kato, Kiyoshi Tamaki, Keisuke Kohno, Utako Kaneyuki, Mitsuhide Maeda, Yuiko Saikusa-Itoh, Ayako Hayashida, Shuji Iida, Hiroaki Suefuji and Seiya Okuda

Abstract

Mesangiolytic glomerulopathy is an uncommon complication of irradiation and chemotherapy of THP-COP [pirarubicin, cyclophosphamide (CPA), vincristin (VCR), predonisolone (PSL)] and CHOP (CPA, Doxorubicin, VCR, PSL). We report a case of 63-year-old man 7 months status post radiation, and 10 months post chemotherapy for gastric lymphoma. The patient showed proteinuria and mild renal insufficiency. Renal biopsy revealed marked mesangiolysis in the glomeruli without any immune depositions. After the administration of angiotensin II receptor blocker, the patient’s renal function remained stable for over two years. Mesangiolysis was thought to be a characteristic glomerular lesion in this patient treated with both chemoagents and radiation.

Key words: nephritis, angiotensin II receptor blocker, PBC, sarcoidosis

(introduction)

Since Warthin first reported autopsy findings in the kidneys of two leukemic patients who received irradiation therapy, radiation nephropathy has been known as an uncommon but potentially devastating complication of irradiation (1, 2). Early studies demonstrated that acceptable renal tolerance is 20-23 Gy (3). Although subsequent improvement in radiotherapeutic techniques has reduced the radiation dose to which kidneys are exposed, concurrent combination of chemotherapy and radiation may increase the incidence of radiation nephropathy (4). Here, we describe a patient with gastric lymphoma who developed mesangiolytic glomerulopathy 7 months after radiotherapy and 10 months after chemotherapy.

Case Report

A 63-year-old man was referred to our clinic with mild renal insufficiency (serum creatinine, 1.62 mg/dl) and proteinuria (0.42 g/g-Creatinine) in June 2004. The patient had been in his usual state of good health until 2001, when a chest X-ray abnormality was observed, and he was diagnosed as pulmonary sarcoidosis. Since the case of sarcoidosis was limited to the bronchopulmonary lymph nodes, the patient did not require medication. In March 2002, he developed upper gastrointestinal discomfort and lost appetite. Endoscopic biopsy led to a diagnosis of non-Hodgkin’s lymphoma (diffuse large B-cell type, Lugano staging system for gastrointestinal lymphomas; stage I) of the stomach. Before the initiation of chemotherapy, laboratory evaluation revealed a serum creatinine level of 1.0 mg/dl, no proteinuria, and no other abnormal laboratory findings. In July 2002, treatment was initiated with two cycles of the THP-COP
Table 1. Laboratory Findings on Admission

<table>
<thead>
<tr>
<th>Urinalysis</th>
<th>Complete blood count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Occult blood</td>
</tr>
<tr>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood chemistry</td>
</tr>
<tr>
<td></td>
<td>GOT</td>
</tr>
<tr>
<td></td>
<td>GPT</td>
</tr>
<tr>
<td></td>
<td>LDH</td>
</tr>
<tr>
<td></td>
<td>ALP</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>γ-GTP</td>
</tr>
<tr>
<td></td>
<td>TP</td>
</tr>
<tr>
<td></td>
<td>Alb</td>
</tr>
<tr>
<td></td>
<td>T.Chol</td>
</tr>
<tr>
<td></td>
<td>BUN</td>
</tr>
<tr>
<td></td>
<td>Cr</td>
</tr>
</tbody>
</table>

regimen (Pirarubicin (THP) 75 mg, day 1; Cyclophosphamide (CPA) 1,100 mg, day 1; Vincristine (VCR) 2 mg, day 1; and prednisolone (PSL) 100 mg, day 1-5), and one cycle of the CHOP regimen (CPA 1,100 mg, day 1; Doxorubicin (ADM) 75 mg, day 1; VCR 1.0 mg, day 1; and PSL 100 mg, days 1-5). Chemotherapy was completed on September 4, and radiation therapy was initiated in October (total: 40.5 Gy). During the administration of irradiation, the patient’s serum creatinine levels remained at 0.7-0.9 mg/dl, no proteinuria or abnormal urinary sediments were observed, and his blood pressure (BP) remained within the normal range (systolic BP: 92-106 mmHg). The patient was discharged in November 2002, since his gastric lymphoma was in complete remission, and the patient had exhibited no evidence of relapse. In March 2003, a diagnosis of primary biliary cirrhosis (PBC) was made, with abnormal liver function (AST 119 U/l, ALT 147 U/l, T.Bil. 0.55 mg/dl, ALP 499 U/l, IgM 389 mg/dl, γ-GTP 207 U/l, T.Chol 170 mg/dl, ANA(-), anti-mitochondrial antibody>320) and pruritus. The patient was administered ursodeoxycholic acid, after which, his liver function tests improved. Nephrological evaluation in May 2003 revealed that the serum blood urea nitrogen (BUN) level was 29.3 mg/dl, and the creatinine (Crea) was 1.13 mg/dl; in December 2003, the levels were as follows: BUN 26.9 mg/dl, Crea 1.67 mg/dl, and the estimated level of proteinuria was 0.42 g/g-Creatinine. Physical examination revealed no abnormalities (i.e., the patient’s BP was normal, as were the results of heart, pulmonary, and abdominal examinations. No peripheral lower limb edema was observed). However, the patient’s renal function tests did not improve over the next six months. In June 2004, when the patient was admitted to our hospital, his creatinine clearance was 54.2 ml/minute, his 24 hour urine protein level was 0.78 g, and no microscopic hematuria was observed. Additional laboratory tests revealed the following (Table 1): Angiotensin converting enzyme level of 26.2 IU/L/37°C (normal: 8.3-21.4) and lysozyme level of 18.7 mg/ml (normal: 5.0-10.2) were both elevated, which was most likely due to sarcoidosis. Cardiac ultrasound data was within the normal range (AoD/LAD 36.2/31.9, IVST/PWT 11.5/11.5, LVdD/LVds 44.2/23.5, EF 78.4%). Left renal biopsy was performed in June 2004.

Light microscopic examination enabled the identification of 24 glomeruli, 8 of which were globally sclerotic, and one of which was segmentally sclerotic. Most of the glomerular tufts were lobulated and enlarged, with an expansion of the mesangial matrix, mesangial cell proliferation, and segmental double contour of the basement membrane. The size of glomeruli was within normal range. Some glomeruli displayed mesangiolysis with endothelial cell dropout and a widening of the capillary loops (Fig. 1A-C). No capillary loops exhibited thrombosis. Mild arteriolar thickness was seen, but hyalinization was not observed. Tubular atrophy, interstitial edema, fibrosis, and chronic inflammatory cell infiltration were present surrounding the sclerotic glomeruli (Fig. 1D). There were no findings of sarcoidosis, vasculitis, amyloid deposition, or malignant cells. Upon immunofluorescence microscopy, glomerular staining for fibrinogen, immunoglobulin (Ig) A, IgG, IgM, C3, C4, and C1q were negative (data not shown). Electron microscopy showed endothelial cell swelling, leukocytic adherence to endothelial cells, partial mesangial interposition with double contours of the basement membrane, and a thinning of the basement membrane in part, whereas the podocytes exhibited fewer abnormalities. No electron-dense deposits were identified (Fig. 2). Thus, the patient was diagnosed as having mesangiolytic glomerulopathy due to radiotherapy and chemotherapy.

The patient was treated with ARB (angiotensin II receptor blocker: losartan potassium) after the renal biopsy. As his systolic blood pressure was 92-106 mmHg, the dose of ARB was initially 25 mg/day, and was then gradually increased to 50 mg/day. The patient maintained normal blood pressure during the subsequent follow-up period, and his renal function has remained stable for over two years, in spite of the
Figure 1. Light microscopic findings of renal biopsy. Most of the glomeruli showed mesangial proliferation and segmental double contour of the basement membrane (arrows). Mesangiolysis and massive expansion of the subendothelial space (*). A: Periodic acid-Schiff (PAS) stain, ×200, B: Periodic acid-methenamine stain, ×200. C: Tubulointerstitium shows fibrosis. Azan stain, ×200. D: Tubular atrophy, interstitial edema, mild fibrosis, and chronic inflammatory cells (mainly lymphocytes) were seen. PAS stain, ×200.

Discussion

Domagk described a 9-year-old girl who received abdominal irradiation for tuberculous mesenteric lymph nodes, and died 6 months later with symptoms of renal failure (5). The autopsied renal specimens showed glomerular hyalinization or thickening of Bowman’s capsule, tubular atrophy or necrosis, and hyaline material in the arterial walls. Thus far, the histology of radiation nephropathy has been well characterized as including the following features: endothelial injury, mesangiolysis, and glomerular basement membrane expansion (6, 7). Irradiation produces toxic oxygen species, a process which is believed to be an important initiator of glomerular endothelial injury, followed by the detachment of the endothelium from the basement membrane and mesangiolysis (8). Mesangiolysis is characterized by the attenuation or dissolution of the matrix and by the degeneration of mesangial cells (8). In cases of radiation nephropathy, the endothelial damage occurs via the attachment of leukocytes to the glomerular capillary endothelium; the endothelial cells subsequently swell, which in turn leads to exudation of the plasma components (including leukocytes, erythrocytes, and platelets) into the subendothelial and mesangial compartments (8). In the present case, the pathological findings were compatible with radiation-induced mesangiolytic glomerulopathy. In cases of thrombotic microangiopathy, though all patients had some impairment of renal function, some patients had entirely negative urinalysis or proteinuria (9). Thus, mesangiolysis does not always lead to the severe renal laboratory abnormalities.

The present patient had primary biliary cirrhosis (PBC), sarcoidosis, and a malignant lymphoma. Moreover, he received chemotherapy and radiotherapy for gastric lymphoma. Many of the patients who have received radiation therapy have also received chemotherapy, so it is not easy to determine which factor is responsible for the subsequent nephropathy. Most of the clinical data on this topic comes from patients who have received total irradiation and chemotherapy in preparation for bone marrow transplantation. Some report have shown that shielding of the kidneys from irradiation decreases bone marrow transplant nephropathy (10). It is generally accepted that some chemotherapeutic agents make the kidney more vulnerable to nephrotoxicity due to total body irradiation. The pathogenesis is still unclear. Tubulointerstitial nephritis (11, 12), and membranous nephropathy (MN) (13) have been described in some cases of PBC. In cases of sarcoidosis, histologic varieties of glomerulonephritis [e.g., MN, focal glomerulosclerosis (14), and membranoproliferative glomerulonephritis (15)] have also been reported. In the present case, we did not observe any immunocomplex deposition in the basement membrane.
Figure 2. Transmission-electron microscopic findings of renal biopsy. A: Thinning of the basement membrane (**). ×6000. B: Endothelial cell swelling (†) and leukocytic adherence (††) to an endothelial cell. ×2000. No electron-dense deposits were observed, which was in accord with the negative immunofluorescence findings (data not shown).

Figure 3. Clinical course and major treatments. Serum creatinine level (Crea; mg/dl, open circles) increased gradually after radiation therapy for gastric lymphoma, and remained stable for over one year with the administration of angiotensin II receptor blocker (ARB; losartan potassium 25-50 mg/day, p.o.). The changes in urinary protein levels [U-Pro; g/g-Cr (Creatinine)] are also illustrated.
or mesangial matrix by either immunofluorescence or electron microscopy. Chemotherapeutic regimens such as mitomycin C have been reported to induce hemolytic uremic syndrome (HUS) (16), the present case, however, did not present with any clinical symptoms of HUS. Thus, we considered that the best diagnosis in this case was mesangiolysis related to radiotherapy and chemotherapy.

Radiotherapy was first used to treat malignant lymphoma of the stomach in the 1980s, and nephropathy has been reported in patients who have received this treatment (17). The National Cancer Institute workshop (Bethesda, Maryland) also reported that radiation nephropathy is a possible complication of radionuclide therapy (18). Arneil et al reviewed nine cases of radiation nephropathy in children, and cautioned that irradiation and cytotoxic chemotherapy, when applied together, may be much more hazardous than either treatment alone (19). It has also been suggested that patients with collagen vascular diseases tolerate radiotherapy less well than other patients (20). In the present case, the relationship among radiation, chemotherapy, and co-existing autoimmune diseases is unclear with respect to an increased tendency to induce renal injury. The incidence of complications in such a population appears to require the attention of oncologists.

Radiation nephropathy can be treated with angiotensin converting enzyme inhibitor (ACE-I) or ARB (18, 21). It has been reported that oxidative stress plays a role in the radiation-induced late effect on organs in the development of radiation nephropathy (8, 22). A novel signaling mechanism for angiotensin II has been identified involving the angiotensin II type I receptor-mediated production of superoxide generated by NADH/NADPH oxidase, and an increase in intracellular hydrogen peroxide; it is therefore expected that ARB reflects inhibition of angiotensin II-mediated oxidative stress (23). In an experimental model, angiotensin II receptor blocker protects the kidney from the development of radiation-induced fibrosis (21). In the present case, the renal function and proteinuria levels remained stable for at least two years with the administration of ARB. The blockade of angiotensin II-mediated signaling may exert beneficial effects against the progression of chemotherapy and radiation-induced glomerular injury.

References