Renal Intravascular Large B-cell Lymphoma Localized Only within Peritubular Capillaries Report of a Case

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Abstract

We report a 35-year-old Japanese woman with intravascular large B-cell lymphoma diagnosed by percutaneous renal biopsy. The patient was referred to our institution for further examination of fever of unknown origin. She had renal dysfunction with a creatinine clearance of 44.1 mL/min, and daily urinary excretion of 0.22 g of protein and 21.5 mg of beta 2 microglobulin. Computed tomography showed markedly enlarged kidneys bilaterally. Percutaneous renal biopsy showed that an island-like atypical lymphoid cell accumulation was encircled with the peritubular capillary walls in many areas of the tubulo-interstitium, resulting in marked destruction of tubular structure. However, almost all the glomeruli were intact. Immunohistochemical analysis confirmed the diagnosis of intravascular large B-cell lymphoma. Shortly after diagnosis, she was treated with rituximab, cyclophosphamide, hydroxydaunomycin, oncovin, and prednisolone, and her renal function and size improved.

Renal involvement by lymphoma has been classified into two categories: intraglomerular intravascular lymphoma and tubulointerstitial diffuse invasion type that is distinct from intravascular lymphoma. For the latter cases with renal dysfunction and marked bilateral nephromegaly but without proteinuria, intravascular lymphoma within intra-peritubular capillaries should be considered as a possible diagnosis.

Key words: intravascular large B-cell lymphoma (IVLBCL), peritubular capillary, renal lymphoma, kidney biopsy

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Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare variant of large B-cell lymphoma that is characterized by proliferation of malignant lymphoid cells only in the small vessels of several organs such as the central nervous system, skin, kidneys, adrenals, lungs, and liver (1-4). Neurologic and skin involvement have been encountered clinically, while fever of unknown origin without weight loss is a common non-specific symptom. Since Jothy et al (5) reported the first case of IVLBCL in kidney tissue after a percutaneous biopsy in 1981, 12 additional case presentations have been published (6-15). All of these cases had malignant lymphoid cells localized only within the intraglomerular capillaries.

Here, we report a case of IVLBCL, in which a biopsy specimen from a markedly enlarged kidney showed localization of lymphoma cells only within the intraperitubular capillaries.

Case Presentation

A 35-year-old Japanese woman was referred to our hospital with a chief complaint of fever of unknown origin in July 2004. Her father died of malignant lymphoma 7 years earlier. There was no additional family history. She had lived in a boarding school in the United Kingdom in the
past, but she had not been exposed to any known infectious disease in the weeks prior to her presentation. She had symptoms suggestive of a common cold at the end of April 2004. In May, she developed a nonproductive cough, fever to 38.5°C, and lower left chest pain. Although antibiotics were started, her fever persisted. There were no findings suggesting infection, and chest radiography was unremarkable. She was admitted to our hospital in Japan for further studies in July 2004.

On admission, the patient was 169 cm tall and weighed 54 kg. Her blood pressure was 126/70 mm Hg, and her temperature was 38.2°C. Bilateral kidney enlargement and splenomegaly were detected by palpation, but no enlarged lymph nodes were palpated. Inspiratory and expiratory sounds were normal to auscultation. There was no pedal edema. Her neurologic and skin examinations were normal.

Laboratory findings were as follows: erythrocyte count was $3.78 \times 10^6/\mu L$; hemoglobin, 10.1 g/dL; hematocrit, 32.8%; leukocyte count, 8,400/µL; and platelet count, 12.3 x $10^4/\mu L$. Her total serum protein concentration was 6.8 g/dL; albumin, 2.6 g/dL; blood urea nitrogen, 18 mg/dL; creatinine, 0.9 mg/dL; and uric acid, 3.8 mg/dL. Her serum sodium was 140 mmol/L; potassium, 3.9 mmol/L; chloride, 104 mmol/L; and total cholesterol, 140 mg/dL. Her total bilirubin was 0.5 mg/dL; aspartate aminotransferase (AST), 19 (IU/L); alanine aminotransferase (ALT), 127 (IU/L); lactate dehydrogenase (LDH), 1199 IU/L; alkaline phosphatase (ALP), 339 (IU/L); gamma-glutamyl transpeptidase (γGTP), 106 (IU/L); and C-reactive protein, 12.6 mg/dL. The erythrocyte sedimentation rate was 74 mm/hr. Her serum IgG concentration was 1,530 mg/dL; IgA, 105 mg/dL; IgM, 37 mg/dL; and IgE, 30 U/mL (normal range less than 350). The soluble interleukin-2 receptor (sIL-2R) concentration was elevated at 5,040 U/mL (normal range 250 to 590). Resting arterial blood gases on room air showed a PaO$_2$ level of 100 mmHg, and a PCO$_2$ level of 37 mmHg. The urine dipstick pH was 5.5; the glucose, protein, and occult blood were negative. The urinary sediment contained less than 1 erythrocyte per high-power field (HPF). No Bence-Jones protein was detected in the urine. A 24-hour urine collection contained 0.22 g of protein and 21.5 mg of beta 2 microglobulin (MG). Her 24-hour creatinine clearance was 44.1 mL/min.

Bone marrow aspirate was performed in smear and clot section, and revealed a hypercellular marrow, but there was no heteromorphism in the myeloid and lymphoid series, and no finding of hemophagocytosis. Bone marrow biopsy was not done. Immunophenotypic analysis of bone marrow was performed by means of flow cytometric analysis, and revealed that CD19 positive B cell was 21%. $\kappa$ positive B cell was 8.75% and $\lambda$ positive B cell was 5.69%, and there was no significant laterality between $\kappa$ and $\lambda$ chain.

Diagnostic imaging studies using ultrasound, computed tomography (CT) and magnetic resonance image (MRI) revealed marked enlarged kidneys bilaterally, mild splenomegaly. However, no lymphadenopathy or other organ involvement (including the liver and brain) was apparent (Fig. 1A). A chest radiograph and CT scan revealed only a small right pleural effusion, and no interstitial shadow. The pleural effusion was so small, that thoracentesis was not done. Gallium scan was not performed.

Two days after admission, percutaneous renal biopsy was performed.

**Renal Biopsy Specimen Findings**

Light microscopic examination of a renal specimen containing 20 glomeruli revealed a mild increase in the mesangial matrix, but no mesangial cell proliferation or capillary wall thickening in the glomeruli (Fig. 2). In the tubulointerstitial, severe cell infiltration was apparent and marked destruction of both the proximal and distal tubular structures associated with interstitial edema was observed (Fig. 3A). A high power examination showed island-like accumulations.
Figure 2. Light microscopic examination of a renal specimen revealed a mild increase in the mesangial matrix, but no mesangial cell proliferation or capillary wall thickening in the glomeruli were seen. (HE; × 40).

Figure 3. Hematoxylin and eosin staining (A) confirmed that in the tubulointerstitium, severe cell infiltration was apparent and marked destruction of both the proximal and distal tubular structures with interstitial edema were observed. And immunohistochemical staining using CD20 (B) showed the island-like cell accumulation; these were positive for CD20. (A-B; ×10).

Figure 4. A higher power magnification shows an island-like accumulation of large atypical lymphoid cells with hyperchromatic nuclei (arrow) in many areas of the interstitium. (HE; × 40).

of large atypical lymphoid cells with hyperchromatic nuclei in many areas of the interstitium (Fig. 4). Periodic acid methenamine (PAM) silver staining and immunohistochemical staining using anti CD34 confirmed that this cellular accumulation was encircled with peritubular capillary walls. These lymphoid cells were positive for CD79a, CD20, and CD5, but negative for CD3 and CD10 (Fig. 3B, Fig. 5A-D). A diagnosis of intravascular large B-cell lymphoma localized only within the peritubular capillaries was made. The cells infiltrating between each island area in the interstitium were determined to be mainly reactive T-cell lymphocytes because of their positively for CD3 (Fig. 5E). Immunofluorescence did not reveal any glomerular immune deposits. Electron microscopic findings did not detect any electron dense deposits, but a cluster of atypical lymphocytes encircled by a peritubular capillary wall was observed (Fig. 6).

Clinical Course

Immunohistochemical analysis of the renal specimen confirmed the diagnosis of intravascular large B-cell lymphoma. The stage was above IIIB, and the international prognostic index was high risk.

The patient was initially treated with a combination of rituximab (600 mg/day) and CHOP therapy (cyclophosphamide, hydroxydaunomycin, oncovin and prednisolone) in late July and received a second cycle 3 weeks later. Four weeks after her second treatment, CT examination showed improvement in her kidney (Fig. 1B) and spleen size, and the pleural effusion disappeared, no more cough. Her serum creatinine fell to 0.5 mg/dl, and her urinary beta 2 MG decreased to 154 μg/day. Her 24-hour creatinine clearance in-
Figure 5. Periodic acid methenamine (PAM) silver staining (A) and immunohistochemical staining using CD34 (B) confirmed that this cell accumulation was encircled with peritubular capillary walls (arrow), and positive for CD20 (arrow) (C), CD5 (arrow) (D). Cells infiltrating diffusely between each island area in the interstitium were mainly reactive T-cell lymphocytes because of their CD3 positivity (arrow) (E). (A-E; × 40).

creased to 78.4 mL/min. Her mild renal dysfunction, serum LDH and soluble IL-2 receptor concentrations were all normalized.

She was discharged on August 10, 2004. She was treated with rituximab-CHOP therapy in 6 cycles, attaining complete remission. She underwent autologous peripheral blood stem cell transplantation in January 2005. Now she is in complete remission, and still alive.

**Discussion**

Non-Hodgkin lymphoma forming an intravascular tumor has been called intravascular large B-cell lymphoma (16), characterized by clusters of large B-cell lymphocytes within vessels. Once the vasculature is occluded in association with thrombosis, clinical manifestations such as neurologic, pul-

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monary, or skin lesions are frequently encountered. Although almost all cases have been diagnosed postmortem, pre-mortem cases diagnosed by percutaneous renal biopsy have been published. The renal involvement with lymphoma has been classified by Tornroth et al (14) into the two categories of intraglomerular growth and tubulointerstitial invasion. Cases with the intraglomerular growth type were grouped as one renal manifestation of IVLBCL, while the tubulointerstitial type had been considered as another type distinct from IVLBCL, because the lymphoma cells had invaded diffusely into the tubulointerstitium. From the viewpoint of this literature, the mechanism of renal dysfunction, in the present case, may more closely those proposed in the tubulointerstitial type of lymphoma, ie, obstruction of peritubular capillaries with increased postglomerular vascular resistance, compression of tubule, or modulation of the tubuloglomerular feedback mechanism. However, the pathological findings of this case are more similar to that of IVLBCL.

Since Jothy et al (5) presented the first patient with IVLBCL diagnosed by kidney biopsy in 1981, 12 such cases (6-15) have been reported, and the pathologic finding common to these cases was localization of the lymphoma cells only within the lumina of the glomerular capillaries. Clinical findings associated with IVLBCL were reported to be acute renal failure (ARF) in 5 of 11 cases, or nephrotic-range proteinuria in 6 of 11 cases. The ARF might be caused by the obstruction of glomerular circulation due to the invasion of the lymphoid cells (14), as has been suggested in acute proliferative glomerulonephritis (17), resulting in a loss of renal function. In these cases, the higher the proportion of glomeruli affected by the infiltration of tumor cells, the more the renal function had deteriorated, consistent with the view that the presence of tumor cells had impaired glomerular function. In the IVLBCL cases with nephrotic range proteinuria, histology of the renal biopsy revealed minimal glomerular lesions because of the absence of immune deposits in the glomeruli. Because remission of the nephrotic syndrome was often observed after successful therapy for the lymphoma, it has been suggested that lymphoma cells may release a cytokine which enhances the glomerular membrane permeability (14).

The predominant clinical manifestation in patients with tubulointerstitial lymphoma has been reported to be ARF in 39 of 44 cases (14), but no nephrotic syndrome. Increased interstitial pressure due to the proliferation of lymphoma cells may cause ischemia, tubular obstruction, compression of the peritubular capillaries with increased post glomerular vascular resistance, or modulation of the tubuloglomerular feedback mechanism, resulting in renal failure, as has been suggested in interstitial nephritis (14, 18). Bilateral marked nephromegaly is the other major clinical feature in patients with the tubulointerstitial type of disease. Renal size has been reported to improve rapidly in response to chemotherapy (14).

Based upon these prior publications, one might consider that the present patient, with renal dysfunction (but without proteinuria) as well as bilateral marked nephromegaly that responded to chemotherapy, should be diagnosed as having the tubulointerstitial type of renal lymphoma. However, close investigation of the histology was more consistent with the diagnosis of IVLBCL within the peritubular capillaries. Although it is unclear whether this finding might also have been present in the previously published cases of the tubulointerstitial type of renal lymphoma, a report by Sepandj et al (19) supports our diagnosis. They presented a patient who was diagnosed IVLBCL by percutaneous kidney biopsy, and the pathological finding was that most lymphoma cells appeared to be in the peritubular vessels. However, some were noted outside the vessel wall. Because they did not use immunohistochemical staining, they could not precisely identify whetheer or not the localization of tumor cells was only within the peritubular capillaries.

In the present case, the tumor cell accumulation was encircled with peritubular capillary walls, by anti-CD34 staining. And these lymphoid cells were positive for CD5, which is an important marker for IVLBCL patients. In Japanese IVLBCL patients, CD5 positivity is 38%, and it is associated with higher prevalence of bone marrow involvement and thrombocytopenia and a lower frequency of neurological abnormalities among negative CD10 IVLBCL patients (20).

The cause of highly selective peritubular capillary localization of the lymphoma cell was unclear. The size of lymphoma cell was so large that the entrapment of tumor cells was more likely within the glomerular than peritubular capillaries, and a mechanism of passive trapping may be excluded.

Hitherto no specific receptors or other mechanisms which would account for the selective glomerular localization of the intravascular lymphoma cells have been described, but there may be some interaction between the endothelial cell of peritubular capillary and the lymphoma cell.

In conclusion, when tubulointerstitial cell infiltration is
found in a patient with bilateral marked nephromegaly and renal dysfunction without proteinuria, intra-peritubular capillary lymphoma should be considered as a possible diagnosis.

References


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