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Characteristics of Intravascular Large B-Cell Lymphoma Limited to the Glomerular Capillaries: A Case Report

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Key Words
Intravascular large B-cell lymphoma, kidney-limited · Glomerular capillary · Kidney biopsy

Abstract
A 65-year-old woman was admitted to our hospital for the evaluation of rapidly progressive renal dysfunction with serum creatinine of 2.7 mg/dl and urinary protein of 1.5 g daily. C-reactive protein (CRP) was 0.1 mg/dl. Kidney-limited intravascular large B-cell lymphoma (IVL) localized to the glomerular capillaries was diagnosed because the intraglomerular cells were positive for CD20 and CD79a, while there was no positivity in the extraglomerular kidney and extrarenal organs. Treatment with rituximab, cyclophosphamide, hydroxydaunomycin, vincristine, and prednisolone was started, and the patient has since been doing well. When IVL is limited to the intraglomerular capillaries, CRP may not be elevated.

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Introduction

According to the current WHO classification, intravascular large B-cell lymphoma (IVL) is a rare type of non-Hodgkin's lymphoma characterized by the selective growth of tumor cells within the lumens of the small vessels in various organs, including the kidney [1, 2]. In 2003, Tornroth et al. [3] reviewed renal involvement by IVL based upon previous reports and their own cases and concluded that this disease can be divided into an intraglomerular type and a type with tubulointerstitial invasion. They stated that the latter type features diffuse invasion of lymphoma cells into the tubulointerstitial region. In 2007, Sawa et al. [4] reported the first case of tubulointerstitial IVL limited to the peritubular capillaries. In 2009, Kameoka et al. [5] reported that kidney-limited IVL was very rare. In fact, the majority of patients who have been reported with renal involvement by IVL also had extrarenal lesions in addition to renal ones.

We encountered a 65-year-old Japanese woman with kidney-limited IVL localized to the glomerular capillaries in whom C-reactive protein (CRP) was negative. Here, we review the relation between kidney-limited IVL and CRP based on this case and previous reports.

Case Report

A 65-year-old Japanese woman was admitted to our hospital for the evaluation of rapidly progressive renal dysfunction. At the age of 60 years (April 2000), hypertension was detected, and treatment with amlodipine was started. Subsequently, proteinuria (41 mg/dl) was noted, and serum creatinine (Cre) was 0.94 mg/dl. On September 3, 2005, edema of the bilateral lower extremities was noted with exacerbation of hypertension (200/110 mm Hg). She was admitted to hospital 2 days later on September 5.

On admission, her height was 154 cm, her weight was 48.2 kg, her blood pressure was 152/92 mm Hg, and her temperature was 35.9°C. No enlarged lymph nodes were palpable. Inspiratory and expiratory sounds were normal on auscultation. Both neurological examination and cutaneous examination revealed no abnormalities. There was pitting edema of the bilateral lower extremities. Laboratory findings are shown in table 1. Urea nitrogen was 41 mg/dl, and Cre was 2.7 mg/dl. CRP was 0.1 mg/dl, and the erythrocyte sedimentation rate was 53 mm/h. Soluble interleukin-2 receptor was elevated to 1,680 U/ml (normal range: 250–590). Urine sediment contained 6–10 erythrocytes per high-power field. Examination of a 24-hour urine specimen revealed excretion of 1.51 g of protein.

Computed tomography showed a normal liver and spleen with no lymphadenopathy. Both kidneys were small with a long axis of 9 cm bilaterally (fig. 1a). Echogenicity of the renal cortex was increased on ultrasonography (fig. 1b). Scintigraphy with ^{67}Ga-citrate only showed positive uptake by the kidneys.

Renal Biopsy Findings

Renal biopsy was performed. Light microscopy of a specimen containing 12 glomeruli revealed global sclerosis in 2. There was mild fibrosis and atrophy, as well as very slight cellular infiltration, in the tubulointerstitial region (fig. 2a). Six of the 12 glomeruli were enlarged (fig. 2b), and the glomerular capillaries were filled with large atypical cells that had atypical nucleoi (fig. 2c). There was no increase in the mesangial matrix or mesangial cell proliferation. Immunohistochemical staining detected atypical large lymphoid cells in the glomerular capillaries that were positive for CD20 (fig. 3a) and CD79a (fig. 3b), but negative for CD3 (fig. 3c) and CD10. Lymphocytes in the tubulointerstitium were positive for CD3, but negative for CD20 and CD79a. Immunostaining was negative for IgG, IgA, IgM, and C3. Elec-

tron microscopy revealed numerous atypical cells with large nuclei, large nucleoli, masses of chromatin in the outer zones of the nuclei, and an abundance of endoplasmic reticulum (fig. 4). No deposits of immunoglobulins/complement components were detected. Bone marrow aspiration and flow cytometric analysis did not detect any abnormal cell populations. Endoscopy of the upper and lower gastrointestinal tract showed no abnormal findings. Based on these findings, kidney-limited IVL localized to the glomerular capillaries was diagnosed.

Clinical Course

Treatment with CHOP regimen, including cyclophosphamide of 1,000 mg (750 mg/m^2), hydroxyl doxorubicin of 70 mg (50 mg/m^2), and oncovin (vincristine) of 2 mg (1.4 mg/m^2) intravenously for 1 day and prednisolone of 100 mg orally daily for 5 days was started. Constipation-related ileus occurred after the first cycle of this therapy. This symptom was considered due to motor neurological dysfunction, probably related to an overdosage of vincristine. Thus, at the second cycle, this drug was switched to vindesine of 3 mg, and rituximab of 600 mg was added (as R-CHOP therapy), and a total of 6 cycles were performed at 4-week intervals. Her serum creatinine decreased from 3.2 to 1.4 mg/dl, and urinary protein became negative immediately after the end of the R-CHOP therapy. Two months after completing 6 courses of therapy, relapse occurred with an increase in lactate dehydrogenase. She then received 3 courses of rituximab of 600 mg, cyclophosphamide of 850 mg, cytosine arabinoside of 1,400 mg for 2 days, etoposide of 70 mg for 3 days, and dexamethasone of 40 mg for 3 days (R-CHASE therapy) as salvage chemotherapy, and complete remission was achieved. After 108 months, she is doing well with a Cre of 1.21 mg/dl, daily urinary protein excretion of 0.21 g, CRP of 0.01 mg/dl, and lactate dehydrogenase of 197 IU/l.

Discussion

IVL was first reported in 1959 by Pfleger and Tappeiner [6] as 'angioendotheliomatosis proliferans systemisata'. According to the latest WHO classification, IVL is a rare type of extranodal diffuse large B-cell lymphoma [7]. Patients with IVL usually have no lymphadenopathy, and tumor cells involve the small vessels of many organs, such as the bone marrow, central nervous system, skin, lungs, liver, kidneys, and intestinal tract [8]. IVL is very aggressive, and the prognosis is usually extremely poor [9], but chemotherapy including a chimeric anti-CD20 monoclonal antibody (most commonly rituximab) has been reported to achieve a relatively good response [10], and autologous stem cell transplantation can also lead to good outcomes [11].

The serum level of CRP is known to be a nonspecific simple test that may become positive for numerous inflammatory conditions. However, this test can be a useful prognostic marker for non-Hodgkin's lymphoma and Hodgkin's lymphoma associated with interleukin-6 overproduction [12]. We reviewed reports about CRP in patients with IVL and found the following. Tornroth et al. [3] reported 5 patients with diffuse bilateral renal lymphoma. All 5 patients showed elevation of CRP. Among them, 2 patients had bone marrow involvement, and 1 patient showed skin lesions. One patient had the interstitial type of IVL sparing the glomeruli. Renal biopsy showed the intraglomerular type in 1 patient, but autopsy demonstrated minute lymphoma aggregates in the peritubular capillaries as well as intraglomerular tumor cells. Wood et al. [13] reported a case of IVL of the intraglomerular type. CRP was 16.2 mg/dl, and only occasional interstitial tumor cells were detected. Subsequently, involvement of the lymph nodes, liver, spleen, lungs, and bone marrow became apparent in this patient. Kameoka et al. [5] reported a 40-year-old Japanese woman with intraglomerular IVL. CRP was normal at 0.02 mg/dl, and extrarenal involvement was not detected.

In conclusion, we managed a patient with intraglomerular IVL limited to the intraglomerular capillaries, without extraglomerular or extrarenal involvement. CRP was not elevated. When IVL is confined to the intraglomerular capillaries, CRP may be normal. However, elevation of CRP may occur in patients who have renal IVL with interstitial involvement or extrarenal lesions. Because CRP is a systemic inflammatory marker that indicates overproduction of interleukin-6, elevation of CRP may be involved in the process by which the disease progresses from the intraglomerular capillaries to the systemic vessels [12].

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Disclosure Statement

The authors report no conflicts of interest.

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Table 1. Laboratory data of the present case on admission to our hospital

	Values	Normal range
Urinalysis		
Protein, g/day	1.51	0.0
Sugar	negative	negative
Erythrocytes (n/high-power field)	6–10	<1
β_2-Microglobulin, μg/day	2,391	<400
N-acetyl-β-D-glucosaminidase, IU/day	18	<90
Bence-Jones proteinuria	negative	negative
Blood count		
White blood cells, n/μl	4,100	3,300–8,800
Red blood cells, n/μl	353×10^4	430–550
Hemoglobin, g/dl	11.0	13.5–17.0
Hematocrit, %	33.1	39.7–51.0
Platelets, n/μl	32.5×10^4	13.0–35.0
Erythrocyte sedimentation rate, mm/h	53	<10
Serum chemistry		
Total bilirubin, mg/dl	0.5	0.3–1.1
Aspartate aminotransferase, IU/l	22	13–33
Alanine aminotransferase, IU/l	11	8–42
Lactate dehydrogenase, IU/l	362	103–109
Alkaline phosphatase, IU/l	185	117–350
γ-Glutamyl transpeptidase, IU/l	19	9–109
UN, mg/dl	41.0	8–22
Cr, mg/dl	2.7	0.60–1.00
UA, mg/dl	7.0	3.6–7.0
Na, mEq/l	141	135–149
K, mEq/l	4.6	3.5–4.9
Cl, mEq/l	105	96–108
TP, g/dl	7.7	6.7–8.3
Alb, g/dl	3.9	4.0–5.0
T-chol, mg/dl	140	128–219
Glucose, mg/dl	88	69–109
HbA1c, %	4.7	4.3–5.8
Immunological findings		
CRP, mg/dl	0.1	0.0–0.3
IgG, mg/dl	1,428	870–1,700
IgA, mg/dl	145	110–410
IgM, mg/dl	95	33–190
CH50, U/ml	57	32–47
C3, mg/dl	115	65–135
C4, mg/dl	47	13–35
Antinuclear antibody	negative	negative
Anti-ds-DNA antibody, IU/ml	<12	<12.0
MPO-ANCA, EU	<10	<2
PR3-ANCA, EU	<10	<10
Anti-GBM Ab, EU	<10	<10
Soluble interleukin-2 receptor, IU/l	1,680	250–590

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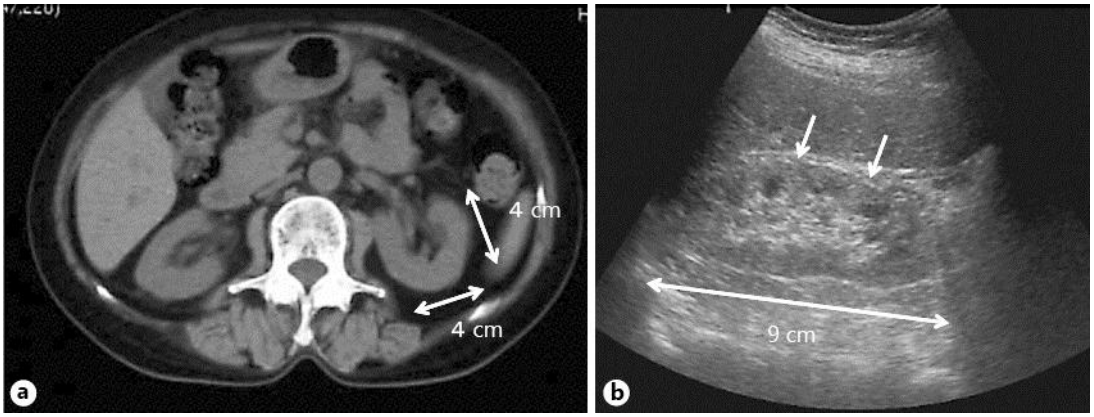

Fig. 1. Imaging findings. **a** Computed tomography showed a decrease in kidney size with a long axis of 9 cm and a short axis of 4 × 4 cm bilaterally. **b** Ultrasonography demonstrated increased echogenicity (arrows) of the renal cortex.

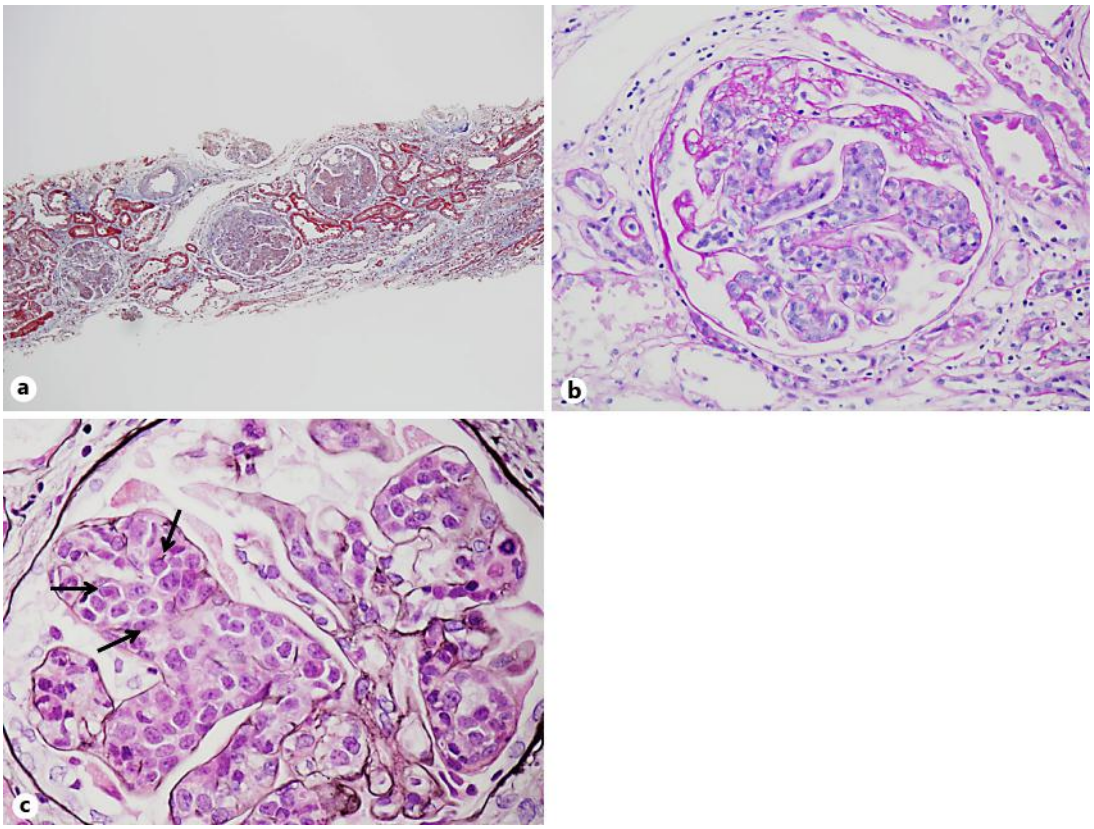

Fig. 2. Light microscopy of the renal biopsy specimen, which contained 12 glomeruli, with 2 showing global sclerosis. **a** There was mild fibrosis and atrophy and very slight cellular infiltration in the tubulointerstitial region (Masson trichrome stain). **b** Six of the 12 glomeruli were enlarged (PAS stain). **c** Glomerular capillaries were filled with atypical large cells that had atypical nucleoi (arrows; PAM stain).

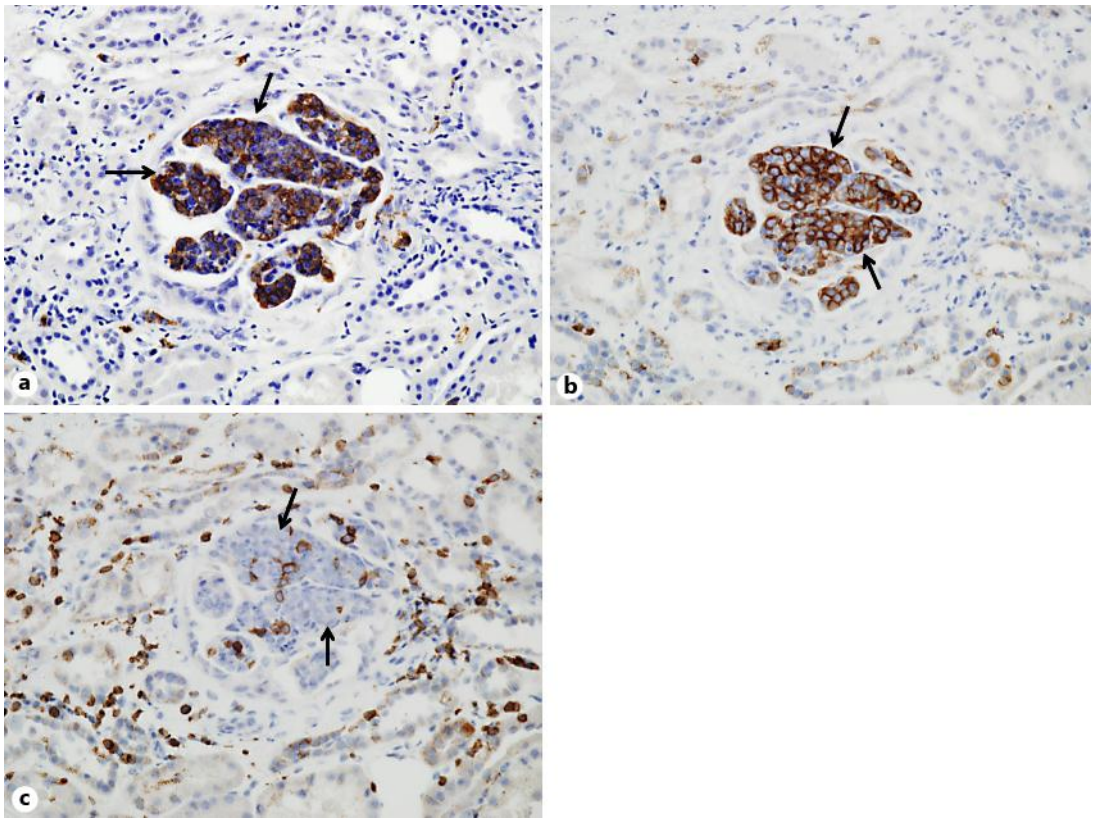

Fig. 3. Immunohistochemical staining. Atypical large lymphoid cells inside glomerular capillaries showed positivity for CD20 (arrows; **a**) and CD79a (arrows; **b**), but were negative for CD3 (arrows; **c**).

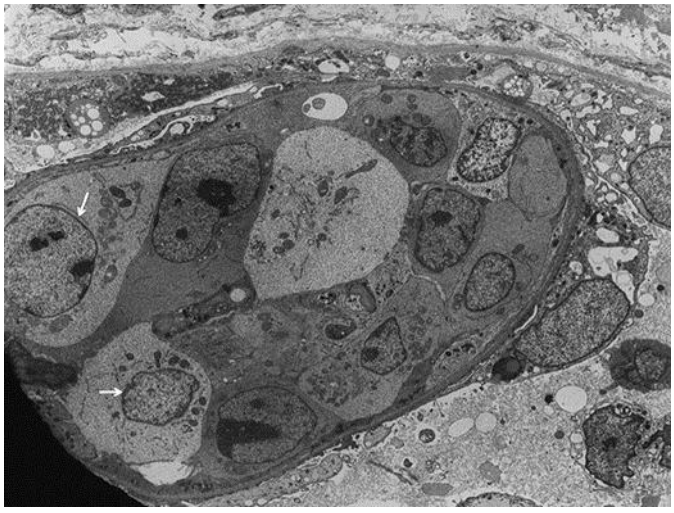

Fig. 4. Electron microscopy showed an increase in atypical cells with large nuclei (arrows), large nucleoli, masses of chromatin in the outer nuclear zone, and abundant endoplasmic reticulum in the cytoplasm.