

# Intravascular Large B-Cell Lymphoma of the Kidney



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## INTRODUCTION

Intravascular large B-cell lymphoma (IVLBCL) is a rare and aggressive non-Hodgkin lymphoma with a nonspecific protean clinical phenotype; therefore its diagnosis can be missed or delayed until tissue sampling. This disease has been recognized by the 2008 World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues, and has previously been termed angiotropic large cell lymphoma, intravascular lymphomatosis, and malignant angioendotheliomatosis.<sup>1</sup> An incidence of 0.095 per 1,000,000 in the United States has been reported, with increasing incidence from 2000 to 2013 likely ascribable to increased recognition.<sup>2</sup> Tissue damage and the clinical phenotype are likely related to occlusion of the vasculature by the intraluminally sequestered neoplastic cells. We describe a patient who presented with a protracted course of a combination of constitutional symptoms, neurological abnormalities, and splenomegaly, but initially without a clear underlying etiology to explain the clinical findings. Only after significant worsening of proteinuria and hematuria (which was confounded by a recent ureteral stone removal), and the new finding of granular casts and white blood cell casts on urine microscopy, was a kidney biopsy performed, the diagnosis of IVLBCL made, and therapy initiated, thereby illustrating the need for consideration of this neoplasm in the differential diagnosis of acute kidney failure in patients with a constellation of symptoms, and the importance of tissue sampling for diagnosis.

## CASE PRESENTATION

### Clinical History and Initial Laboratory Data

A 59-year-old El Salvadoran man presented with a protracted course of clinical and laboratory findings of

unclear and undetermined etiology. The patient initially presented 1 year prior with a 20-pound weight loss, fatigue, and fever, and was empirically treated for presumed infection; however, the febrile state persisted, and he developed over the following month night sweats, weight loss, fatigue, and intermittent hypotension. Medical history was notable for diabetes mellitus, hypertension, nephrolithiasis, gastritis, and fatty liver disease. Pertinent laboratory values from the initial presentation included serum creatinine 0.77 mg/dl, blood urea nitrogen 20 mg/dl, lactate dehydrogenase 592 U/l, C-reactive protein 51.3 mg/l, and urine protein-to-creatinine ratio 300 mg/g, and urinalysis showed 1+ proteinuria. A complete blood count showed a normocytic anemia (hemoglobin 10.7 g/dl) with a normal platelet and leukocyte count but with an absolute lymphocytopenia and a monocytosis. Physical examination revealed a palpable spleen tip 5 cm below the left costal margin, decreased vibration and proprioception in the lower extremities, and a sensory deficit extending proximally to the upper calves. Strength was 4 to 5 out of 5 in the lower extremities, and a cranial nerve examination was normal. Splenomegaly was noted on computed tomography. A bone marrow biopsy showed hypercellular marrow but without increased blasts or involvement by a lymphoproliferative disorder, and with a 2:1 myeloid-to-erythroid ratio. Flow cytometry performed on the bone marrow aspirate showed no immunophenotypic evidence of abnormal myeloid maturation, increased blasts, clonal B-cell population, or an abnormal T-cell population. The marrow did not show a cause for the patient's anemia or monocytosis. Repeated and more extensive workups for an infectious etiology were negative. Heavy metal and toxicology screens were negative.

Two weeks prior to the emergent presentation, hospital admission, and the subsequent kidney biopsy,

the patient presented with lower extremity weakness and numbness for 2 weeks with difficulty ambulating. A few days later, he was found to have an impacted ureteral calculus and underwent lithotripsy and stone removal. The patient's medication list at this time included metformin, atorvastatin, omeprazole, and tamsulosin. A kidney biopsy was obtained and reviewed at our institution. Pertinent laboratory values included serum creatinine 1.14 mg/dl (estimated glomerular filtration rate 68.1 ml/min per 1.73 m<sup>2</sup> by the Modification of Diet in Renal Disease [MDRD] equation), blood urea nitrogen 23 mg/dl, serum albumin 2.2 g/dl, urine protein-to-creatinine ratio 2200 mg/g, C-reactive protein 226 mg/l, and lactate dehydrogenase 2012 U/l, and urinalysis revealed granular and white cell casts, and both dysmorphic and non-dysmorphic red blood cells. A complete blood count showed a normocytic anemia (hemoglobin 9.0 g/dl), thrombocytopenia (112 × 10<sup>9</sup>/l), and normal white blood cell count but with an absolute monocytosis. Serum protein electrophoresis did not show evidence of a monoclonal protein. Cerebrospinal fluid showed a normal cell count but elevated protein; lumbar spine magnetic resonance imaging findings were normal; and electromyography revealed an axonal sensorimotor polyneuropathy. Serologic testing of the cerebrospinal fluid was negative for Purkinje cell cytoplasmic antibody, anti-Hu, anti-Yo,  $\alpha$ -fetoprotein, and oligoclonal bands, but there was increased cerebrospinal fluid myelin basic protein (29.7 ng/ml). With a concern for Guillain-Barré syndrome as a possible explanation for the neurologic symptoms, i.v. Ig therapy was initiated. Ultrasound examination results of the kidneys were normal.

### Kidney Biopsy

A total of 40 glomeruli were present, 3 of which were globally sclerosed. Frequent glomerular capillary loops were distended and occluded by proliferations of large atypical mononuclear cells. The glomerular capillaries of uninvolved loops were of normal thickness and texture, with many distinctive double contours of the basement membranes. Extracapillary proliferations were not seen in the glomeruli. The mesangium was mildly expanded by extracellular matrix and increased numbers of mesangial cells. Tubular epithelium was diffusely flattened, and many tubules showed prominent clear vacuolar changes of the cytoplasm. The parenchyma showed mild tubular atrophy and interstitial fibrosis. Large atypical cells were also frequently seen occluding peritubular capillaries. Arteries showed moderate sclerosis, and arterioles show mild sclerosis.

There was evidence of an atypical, intravascular population of cells, prominently within glomerular and

peritubular capillaries (Figure 1). The cells were large and featured vesicular chromatin. The atypical population showed positive staining for CD20, B-cell-specific activator protein, multiple myeloma oncogene 1 (MUM-1), Bcl-6, and Bcl-2, and negative staining for CD10 and CD30. The neoplastic B-cells were negative for Epstein-Barr virus-encoded RNA by *in situ* hybridization. This population was found exclusively within the vasculature, as highlighted by coimmunostaining of B-cell-specific activator protein with CD34, an endothelial marker. CD3 and CD5 stain-reactive T-cells did not stain the neoplastic population. The neoplastic population exhibited a high proliferation index as illustrated by Ki-67 staining (>90% positive), correlating with the presence of frequent mitotic figures and numerous apoptotic bodies.

Immunofluorescence microscopy showed fine granular mesangial deposits staining for IgA (2+ on a scale of 0 to 4+), IgM (1+), C3 (trace), and  $\kappa$  and  $\lambda$  light chains (1+). The interstitium revealed scattered fibrin deposits, but no immune deposits. There was no difference in reactivity between  $\kappa$  and  $\lambda$  light chains in the glomeruli, tubular casts, and background of the tissue.

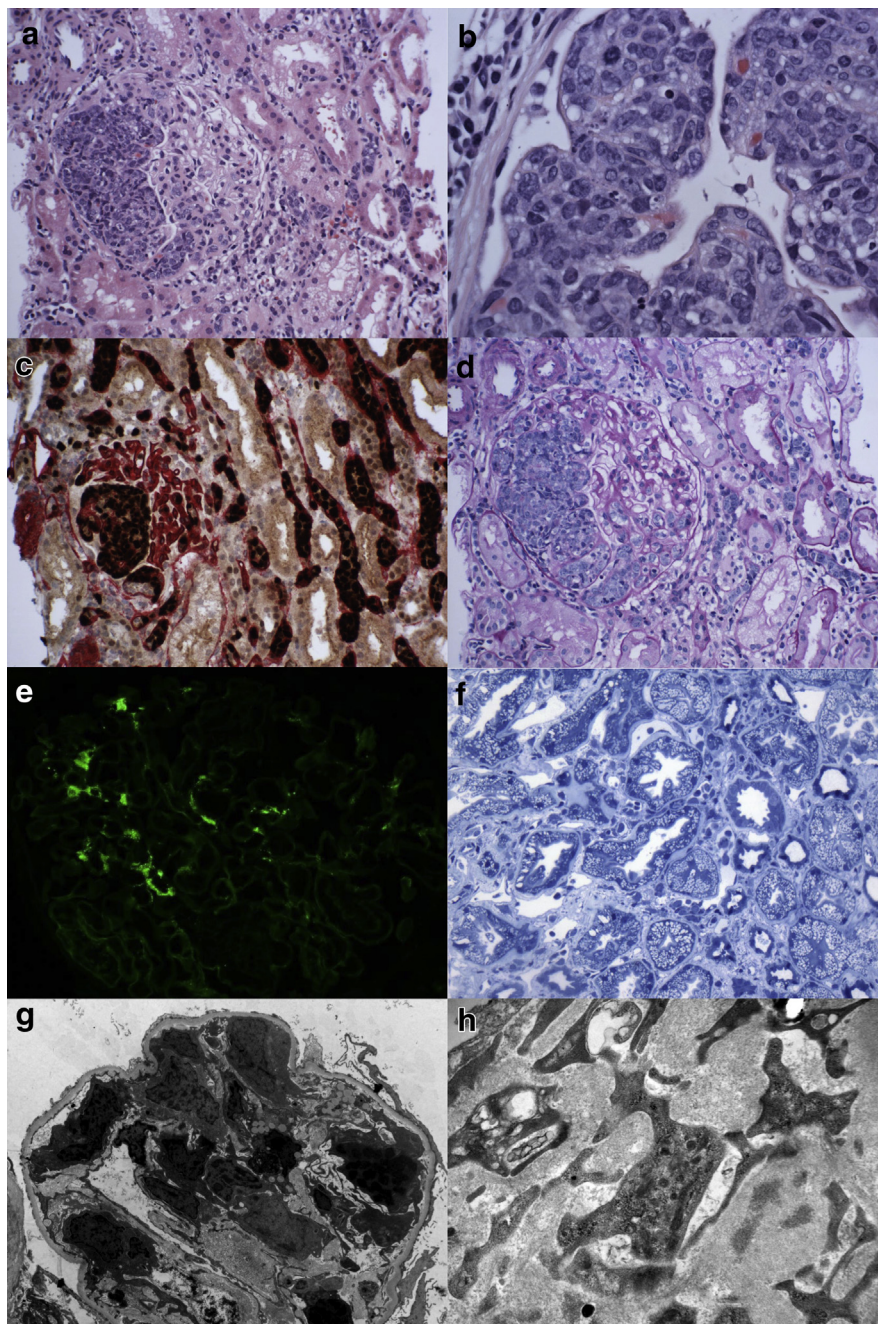
The glomerular visceral epithelial cells revealed extensive effacement of their foot processes. A new layer of basement membrane material was formed under the displaced endothelium in several places (double contours). The glomerular basement membranes were irregularly thickened and segmentally wrinkled. The endothelial cells showed focal swelling and a loss of fenestrations. Several glomerular capillary lumens were occluded by atypical mononuclear cells and cellular debris. The mesangium revealed normal cellular elements and a mildly increased amount of matrix that contained few finely granular electron-dense deposits. There were no electron-dense deposits along the tubular basement membranes or within the interstitium. Tubules contained increased clear cytoplasmic vacuoles. The peritubular capillaries contained atypical mononuclear cells.

### Diagnoses

Diagnoses were made of intravascular large B-cell lymphoma present in glomerular and peritubular capillaries of the kidney, acute tubular injury with prominent vacuolar changes of the proximal tubules as seen with osmotic tubulopathy, IgA nephropathy (IgAN), and mild chronic changes of the parenchyma.

### Clinical Follow-up

After pathologic examination of the patient's kidney biopsy results, treatment with high-dose methotrexate and folate was initiated. Although a regimen of



**Figure 1.** (a) By light microscopy, the glomerular capillary loops and peritubular capillaries contain large atypical cells (hematoxylin and eosin); (b) at higher power, the large intraluminal neoplastic cells show frequent mitotic activity and apoptosis (hematoxylin and eosin). (c) The neoplastic cells were exclusively found within the vasculature, as highlighted by coimmunostaining of the B-cell–specific activator protein with CD34. (d) On a periodic acid–Schiff–stained section, the segments of the glomerulus not distorted by the neoplastic cells showed mild mesangial expansion by the matrix and a mild increase in cellularity; some proximal tubules show vacuolar change. (e) By immunofluorescence, the glomeruli showed granular staining for IgA in the mesangium, and with equally intense staining for  $\kappa$  and  $\lambda$  light chains (light chain studies are not shown). (f) A semithin Toluidine blue–stained epoxy section of tissue processed for electron microscopy highlighted the prominent vacuolar change exhibited by many tubules. (g,h) By electron microscopy, many glomerular capillary loops contained circulating neoplastic cells characterized by overall large size and irregularly shaped nuclei; the finely granular electron-dense deposits were present in the mesangium. Original magnification (a,b,c,e,f)  $\times 200$ , (d)  $\times 600$ , (g)  $\times 3000$ , and (h)  $\times 20,000$ .

cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (R-CHOP) is typical for the management of IVLBCL, methotrexate was favored with the concern that the former treatment would offer less central nervous system penetration. Magnetic resonance imaging of the brain performed after the kidney biopsy

showed a 1.8-cm area of T2/FLAIR abnormal hyperintensity in the right frontal lobe without associated enhancement or local mass effect. Unfortunately, the patient's clinical status deteriorated rapidly, and he ultimately expired less than 1 month after the kidney biopsy.

## DISCUSSION

The presented case illustrates the challenge of determining the underlying etiology of the variable clinical and laboratory features of IVLBCL, and how the rendering of a diagnosis is contingent upon tissue sampling (Table 1). In this case, an antecedent bone marrow biopsy was performed and did not show evidence of involvement by a lymphoproliferative disorder. Only after a sudden worsening of proteinuria and hematuria, with new granular casts and white blood cell casts on urine sediment, was a kidney biopsy performed, in which the IVLBCL was discovered, in addition to an IgAN (there was no clinical evidence to support the presence of Henoch–Schönlein purpura) and acute tubular injury with prominent vacuolar change. Without tissue sampling, a definitive determination of the processes underlying the protean clinical and laboratory features would not have been possible. The clinical differential diagnosis secondary to the nonspecific nature of IVLBCL can include vasculitis, sepsis, transient ischemic attack, leukemia or a lymphoproliferative disorder, sarcoidosis, multiple sclerosis, and others.<sup>3</sup>

Two generalized phenotypes of IVLBCL have been described, based on the largest series investigating the entity—those diagnosed in Asian and those from non-Asian, Western countries (sometimes referred to as “classical” or European). Overall, IVLBCL is usually widely disseminated and has been described to involve any tissue site; however, typically it does not involve lymph nodes or the peripheral circulation.<sup>1,4</sup> The kidney can be the only determined site of involvement, and this has been noted in 5% of cases.<sup>5</sup> The Western type is characterized by neurologic and cutaneous involvement, whereas the Asian variant is typified by bone marrow involvement, fever, hepatosplenomegaly, anemia, thrombocytopenia, bone marrow involvement, dyspnea, and hemophagocytic syndrome.<sup>4</sup> Neurological symptoms include both sensory and motor deficits, paresthesias, hypostenia, aphasia, hemiparesis, seizures, myoclonus, altered consciousness, and others.<sup>5,6</sup> These variants have, however, been described in patients of varying background, with Asians diagnosed with the “classical,” Western variant, and *vice versa*.<sup>3</sup>

**Table 1.** Teaching points regarding renal involvement by intravascular large B-cell lymphoma (IVLBCL)

1	IVLBCL is a rare and aggressive lymphoma with a nonspecific protean clinical phenotype
2	The clinical differential diagnosis secondary to the nonspecific nature of IVLBCL can include vasculitis, sepsis, transient ischemic attack, leukemia or a lymphoproliferative disorder, sarcoidosis, multiple sclerosis, and others
3	IVLBCL has been rarely described to directly involve the kidney
4	Diagnosis of IVLBCL is contingent upon tissue sampling

Overall survival ranges from 25% to 42.7% at 3 years, with most treatment regimens in the United States consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab.<sup>3,5,7</sup> Limited data suggest that the addition of rituximab to anthracycline-based regimens improves clinical outcomes.<sup>8</sup> Survival is significantly better when IVLBCL is limited to cutaneous involvement, use of anthracycline-based chemotherapies, younger age (<60 years), female sex, a normal platelet count, and not stage III/IV at the time of diagnosis.<sup>2,5,7</sup> The description of direct renal infiltration has been mostly in the form of isolated case reports (>40 to date), with direct renal involvement proved by a tissue diagnosis ranging from 2% to 21% of cases.<sup>3,5,7</sup> In kidney-proven cases of IVLBCL, renal failure, proteinuria, and fever have been described variably.<sup>9</sup>

The histopathologic features of IVLBCL include intravascular growth and distribution of neoplastic cells that express B-cell antigens (CD20, B-cell–specific activator protein), CD79a, multiple myeloma oncogene 1 (MUM-1), Bcl-6, Bcl-2, and variably CD5 and CD10.<sup>3,7</sup> The neoplastic cells are found generally limited to within the lumina of small vessels, a feature proposed to be secondary to their lacking surface proteins involved in transvascular migration/diapedesis (including CD29, CD54, and CD49d), or the combined effect of neoplastic cells with aberrant expression of CXCR3 and aberrant expression of its ligand CXCL9 by endothelial cells.<sup>10</sup>

The biopsy also revealed the additional findings of an IgAN and acute tubular injury with prominent vacuolar changes of the proximal tubules as seen with osmotic tubulopathy. In this case, the IgAN was characterized by few glomerular immune deposits, and, aside from the neoplastic cells plugging the glomerular capillaries, evidence of an active immune complex–mediated glomerulitis with endocapillary proliferation, cellular crescent formation, or fibrinoid necrosis of the tuft was lacking. Osmotic tubulopathy is a nonspecific morphologic pattern of injury that can be seen in the setting of administration of i.v. Ig preparations, mannitol, dextrans, contrast media, hydroxyethyl starch, and other solutes that accumulate within proximal tubular vacuoles.<sup>11</sup> Proximal tubular function, however, is not necessarily altered in this setting. In this case, the administration of i.v. Ig shortly before the biopsy was performed can be implicated in part to the tubular changes observed. Overall, the findings of an IgAN and osmotic tubulopathy likely contributed only to a small degree to the patient’s renal dysfunction.

The lymphomatous cells appear to congest much of the microvasculature of the kidney, and in addition,

the glomeruli also appear to show both evidence of podocyte and endothelial injury. The podocyte effacement was extensive, albeit not diffuse and global, and these changes would contribute to the proteinuria observed. That said, the proteinuria seemed to increase at a relatively gradual rate (from 300 to 2200 mg/g over the span of a year) and was never nephrotic range (this all in the setting of normal-range serum creatinine, and therefore decreased filtration cannot be implicated if one would expect a greater degree of proteinuria); the degree of proteinuria and the chronologic trend in proteinuria is not in keeping with minimal change disease. It is likely that the podocyte effacement reflects ischemic changes secondary to the numerous lymphomatous cells within the microvasculature. In cases of IVLBCL involving the kidney, most present with proteinuria and some with nephrotic-range proteinuria.<sup>9</sup> The evidence of endothelial focal swelling and the formation of a new layer of basement membrane material under the endothelium (double contours, and without associated subendothelial electron-dense deposits) suggests acute and chronic endothelial injury; however, it is not entirely clear as to whether this process (in part or at all) is secondary to the lymphomatous cells in the microcirculation and/or another primary vascular disease present. Thrombotic angiopathies are associated with monoclonal Igs in the setting of a lymphoproliferative disorder or plasma cell neoplasm; however, our patient never had a paraprotein detected to which to ascribe the endothelial injury.<sup>12</sup> It is possible that the lymphomatous cells directly or indirectly induce injury to the endothelium.

The diagnosis of IVLBCL is hampered by heterogeneous clinical findings, with a large series noting 25% of cases diagnosed at the time autopsy: obviously better recognition and consideration of this entity is required.<sup>3</sup> A diagnosis of IVLBCL was eventually made in this patient after a protracted clinical course, and whether a better clinical outcome would have been achieved with earlier initiation of appropriate chemotherapy is unclear. The additional IgAN and osmotic tubulopathy are interesting and novel coinciding lesions to be found in a kidney biopsy specimen, illustrating direct involvement with IVLBCL; however, their contribution to the patient's clinical course is likely of far less impact than that of the lymphoma.

## DISCLOSURE

All the authors declared no competing interests.

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