CASE REPORTS

Cryoglobulinemia and Glomerular Rhomboid Inclusions in a Child With Acute Kidney Injury

Carla M. Nester, MD,[1,2] Eric J. Benner, MD, PhD,[3] Mathieu Latour, MD,[4] Volker Nickeleit, MD,[4] Harvey Hamrick, MD,[3] and William Primack, MD[5]

Cryoglobulinemia is rarely reported in children, and kidney failure secondary to cryoglobulinemia is even more uncommon. We report the case of a 7-year-old boy with cryoglobulins and a systemic illness, including persistent fever, arthralgias, rash, hypocomplementemia, and acute kidney injury associated with nephritic urine sediment. An extensive workup showed no infectious, neoplastic, or rheumatological cause of his kidney injury. The kidney biopsy specimen showed membranoproliferative glomerulonephritis type 1 with electron microscopic evidence of rhomboid crystalloid inclusions. These inclusions have rarely been reported in adult patients with cryoglobulinemia. The patient underwent spontaneous remission, including full recovery of kidney function, and required no immune suppression. The patient's course is consistent with cryoglobulinemia-associated kidney injury, which supports the inclusion of essential cryoglobulinemia in the differential diagnosis of pediatric patients with hypocomplementemic glomerulonephritis.

Am J Kidney Dis 53:866-870.

INDEX WORDS: Membranoproliferative glomerulonephritis; mixed cryoglobulins; hypocomplementemia; pediatric.

Cryoglobulins, first described in 1933 by Wintrobe and Buell,[1] may be found in low levels in healthy individuals and likely represent endogenous immune complexes on the pathway to clearance by the reticuloendothelial system.[2] Greater concentrations sufficient to cause disease are presumed to result from chronic immune stimulation, lymphoproliferative diseases, and/or defective clearance. In adults, hepatitis C accounts for more than 80% of patients with cryoglobulinemia. The remainder of cases are either idiopathic or associated with chronic inflammatory diseases.[3] Although relatively few cases have been reported in children, the assumption is that cryoglobulins in both adult and pediatric patients share similar etiologic mechanisms. Kidney disease associated with cryoglobulinemia usually manifests histologically as type I membranoproliferative glomerulonephritis.[4,5]

We present the case of a 7-year-old child with hypocomplementemia, acute kidney injury, and cryoglobulinemia in whom no identifiable systemic disease was found.

CASE REPORT

A previously healthy 7-year-old boy was admitted to the hospital for evaluation of a 2-week history of intermittent fever to 40°C, abdominal pain with guaiac-positive stools, and migratory arthralgias involving major and minor joints. Several days before admission, he developed periorbital and peripheral edema, as well as pancytopenia. Admission blood pressure was normal. Physical examination showed an erythematous confluent macular rash on the left cheek, conjunctival injection, edema of the face and lower legs, upper abdominal tenderness, hepatomegaly, and scattered ecchymoses over the ankles. Abnormal admission laboratory study results included the following values: white blood cell count, 3.3×10^9 cells/L; hemoglobin, 9.0 g/dL (90 g/L); platelet count, 36×10^9 platelets/L ($36 \times 10^3/\mu$L); reticulocyte count, 2.8%; erythrocyte sedimentation rate, 47 mm/h; C-reactive protein, 6.5 mg/dL; serum creatinine, 1.3 mg/dL (115 μmol/L); urine protein-creatinine ratio, 2.7; total protein, 4.9 mg/dL (49 g/L); serum albumin, 1.7 g/dL (17 g/L); lactate dehydrogenase, 214 U/L; C3, less than 40 mg/dL (<4 g/L); C4, less than 8 mg/dL (<0.8 g/L), and urinalysis with

From the Departments of [1]Internal Medicine and [2]Pediatrics, Division of Nephrology, University of Iowa Carver College of Medicine and Children's Hospital, Iowa City, IA; [3]Department of Pediatrics and [4]Department of Pathology and Laboratory Medicine, Nephropathology Unit, University of North Carolina; and [5]University of North Carolina School of Medicine, UNC Kidney Center, Chapel Hill, NC.

Received March 11, 2008. Accepted in revised form January 13, 2009. Originally published online as doi: 10.1053/j.ajkd.2009.01.015 on March 23, 2009.

Address correspondence to Carla M. Nester, MD, Departments of Internal Medicine and Pediatrics, Divisions of Nephrology, The University of Iowa Hospitals and Clinics, 200 Hawkins Dr, T308GH, Iowa City, IA 52242-1081. E-mail: carla-nester@uiowa.edu

0272-6386/09/5305-0019$36.00/0
doi:10.1053/j.ajkd.2009.01.015

3+ protein, 3+ blood, 12 to 16 dysmorphic red blood cells/high-power field, and hyaline casts. Transaminase levels were normal. Peripheral smear did not show schistocytes.

During the first week of hospitalization, our patient developed hypertension with blood pressure of 150/81 mm Hg, creatinine level increased to 2.8 mg/dL (248 μmol/L), and he had nephrotic-range proteinuria. Lactate dehydrogenase level increased to 2,495 U/L, and he continued to experience daily fever spikes. During his febrile period, while cultures and serological test results were pending, he was empirically treated with vancomycin, doxycycline, and ceftriaxone. He required 1 blood transfusion for anemia. Multiple imaging and diagnostic studies were negative for occult sites of infection, malignancy, or rheumatological disease (Table 1). Serum and urine protein electrophoresis showed distinct bands of restricted mobility, suggesting the presence of monoclonal proteins (Fig 1). Serum immunofixation electrophoresis showed monoclonal components typed as immunoglobulin M (IgM) λ and IgG λ at 1 g/dL. Urine immunofixation electrophoresis showed a monoclonal IgG λ protein and monoclonal free λ and κ light chains. Analysis of cryoglobulins present in serum showed monoclonal IgG λ protein, monoclonal IgM λ protein, monoclonal free κ protein, and polyclonal IgM protein. Epstein-Barr virus viral load showed 200 copies/μg of DNA (IgG antibody positive, IgM antibody negative). The patient underwent bone marrow biopsy that showed a nonspecific hypocellular marrow.

Table 1. Laboratory Studies Performed

Study	Results
Blood culture	No growth
Urine culture	No growth
Fecal culture	No growth
Throat culture	No growth
Rare pathogen blood culture	No growth
Rocky Mountain spotted fever	Serology negative
Ehrlichia	Serology negative
Leptospira	Serology negative
Hepatitis B virus	Serology negative (hepatitis B surface antigen, hepatitis B core IgG and IgM immunoassay)
Hepatitis C virus	Serology negative, viral load undetectable by PCR
Cytomegalovirus	Serology negative, viral load undetectable by PCR
Epstein-Barr virus	200 copies/μg of DNA by PCR; IgG positive, IgM negative
HIV	Serology negative, HIV PCR negative
Parvovirus B19	Serology negative
Bartonella henselae	IgG 1:128, IgM negative
Bartonells quintana	Serology negative
Arbovirus screen	Serology negative
Febrile agglutinins	Negative

Abbreviations: HIV, human immunodeficiency virus; Ig, immunoglobulin; PCR, polymerase chain reaction.

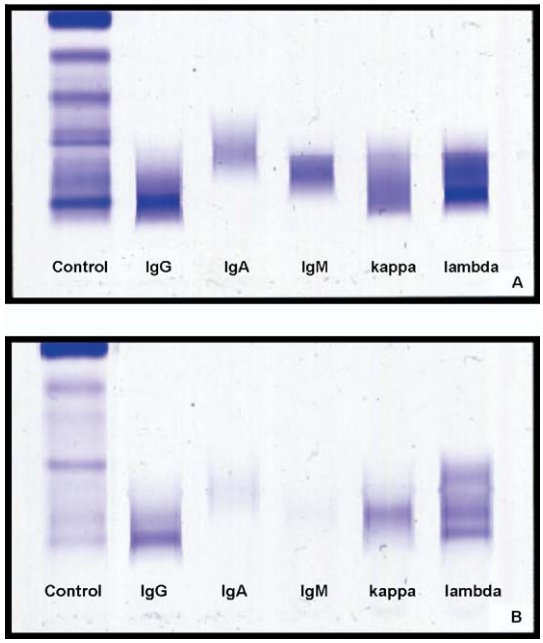

Figure 1. Immunofixation electrophoresis of the patient's (A) serum and (B) urine showed (A) monoclonal components typed as immunoglobulin M (IgM) λ and IgG λ and (B) a monoclonal IgG λ protein and monoclonal free λ and κ light chains.

A percutaneous kidney biopsy was performed on hospital day 15. The biopsy specimen showed diffuse and global endocapillary hypercellularity with abundant mononuclear cells and basement membrane remodeling with duplication and cell interposition. Proteinaceous intracapillary thrombi were not seen. The interstitial compartment showed patchy minimal mononuclear inflammatory cell infiltrates. Tubules, arteries, and arterioles were without diagnostic abnormalities (Fig 2). Immunofluorescence studies showed trace granular accumulation of IgG, IgM, C1q, and κ and λ light chains along the peripheral glomerular capillary walls. C3 staining was negative.

Electron microscopy showed glomerular capillaries distended by mononuclear cells with areas of basement membrane remodeling and segmental accumulation of electron-dense deposits along the lamina rara interna (Fig 3A). Also present were unusual rhomboid intracytoplasmic inclusions with a crystalloid substructure (Fig 3A and 3B). A diagnosis of membranoproliferative glomerulonephritis type 1 was rendered.

During the next 14 days, the patient's fever resolved and all key laboratory markers returned to normal. No immune suppression was administered. At 2 months after discharge, his blood pressure, creatinine, and complement levels were normal, and the child reported feeling well. Urine showed 1^+ protein but otherwise was normal. At a 20-month follow-up, all serological test results continued to be negative.