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

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Abstract

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.

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 children, the assumption is that cryoglobulins in both adult and pediatric patients share similar etiologic mechanisms.

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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 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.

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. Creatinine clearance was normal, and urine protein was absent.

DISCUSSION

Cryoglobulinemia is rarely reported in the pediatric literature and is not commonly included in the differential for causes of glomerulonephritis in children. To our knowledge, the rhomboid crystals supporting the diagnosis of cryoglobulin-induced kidney injury have never been reported in a child.

These crystals were first reported in an adult in a 1969 case report of a 36-year-old woman with cryoglobulinemia, glomerulonephritis, nephrotic syndrome, and paraproteinemia.[6] A review of the literature suggests that these crystalloid inclusions may present in patients with cryoglobulinemic kidney disease, proximal tubular cells of patients with plasma cell dyscrasia, and patients with juxtaglomerular cell tumors, and there is an isolated report of these inclusions in a patient with perchloroethylene ingestion.[7–10] Our patient had no additional kidney pathological state and no history of ingestions.

The first clinical report of the mixed or essential form of cryoglobulinemia was described by Lerner and Watson[11] in 1947. In 1980, Meltzer described the clinical aspects of 40 patients with mixed cryoglobulinemia.[12] Consistent with widespread deposition of cryoglobulin into tissues, he noted that 100% had purpura, 72.5% had polyarthralgias, hepatomegaly occurred in 70%, and 55% had kidney involvement. The combination of purpura, arthralgias, and weakness, the so-called Meltzer triad, often is associated with multisystem organ dysfunction in patients with cryoglobulinemic vasculitis.[13] Vascular tissue damage results from deposition of cryoglobulins in multiple vascular beds, leading to inflammation and occasionally blood vessel thrombosis and occlusion. The diversity of the vascular beds affected accounts for the variability in clinical presentation.[4,12,14]

Given this diversity, making the diagnosis of essential cryoglobulinemic vasculitis can be difficult. There are no standardized diagnostic criteria. Ferri et al[15] suggested the diagnostic parameters of serum mixed cryoglobulins, low C4 level, skin purpura, and leukocytoclastic vasculitis. There were no pediatric patients in the group of patients used to establish these proposed criteria.

Although our patient had cryoglobulins and low complement levels, he did not undergo skin biopsy of the ecchymoses to confirm that he had leukocytoclastic vasculitis.

An extensive infectious, serological, and radiological workup failed to find a cause for a secondary cryoglobulinemic process. Significantly, he did not have hepatitis C or B, chronic liver disease, or connective tissue disease, such as systemic lupus erythematosus or Sjögren syndrome.[15] Table 1 lists all other tests performed to rule out secondary forms of cryoglobulinemia. The pancytopenia triggered a concern for bone marrow suppression from a viral illness or lymphoproliferative process. However, neither of these was found to be present by using serological testing, culture, or bone marrow biopsy. The patient's bone marrow was not consistent with a plasma cell dyscrasia. Total body computed tomography and positive emission tomographic scan showed no aggregates of abnormal tissue

suggesting neoplasm or infection. He had monoclonal IgG λ and IgM λ proteins in the blood and κ and λ light chains in urine, which have been reported previously in patients with cryoglobulinemia, but are of unclear significance.[2,12,16,17] The cryoglobulin content in this case is not typical for type II cryoblobulinia because there were several different monoclonal components in addition to the polyclonal IgM protein. Atypical cryoglobulins have been reported previously.[18]

Given the association between viral infections and cryoglobulins, it is interesting to note that our patient had a low positive Epstein-Barr virus viral load. The timeline of his disease process coupled with negative IgM and positive IgG Epstein-Barr virus antibodies makes the relevance of this viral load doubtful. Epstein-Barr virus has been reported in the setting of cryoglobulinemia; a causal relationship has not been established.[19,20]

In general, cryoglobulinemic vasculitis is considered to be a relapsing and remitting disease in adults. A long-term study of 105 adult patients with essential cryoglobulinemia with kidney involvement showed that 14% developed chronic kidney failure and 49% died, most commonly of cardiovascular disease, liver disease, or secondary infection. Most patients who survived tended to have relapsing courses, with only 2% experiencing complete remission and 15% with remission of kidney symptoms only.[5] There are no long-term pediatric data available. In contrast to this reported adult series, our patient has had no evidence of relapse and continues to be without systemic disease more than 20 months after the initial presentation.

This is an unusual case because cryoglobulinemia is rarely reported in children. To our knowledge, cryoglobulinemia-associated membranoproliferative glomerulonephritis and the rhomboid crystals supporting the diagnosis of cryoglobulin-induced kidney disease have never been reported in a child.

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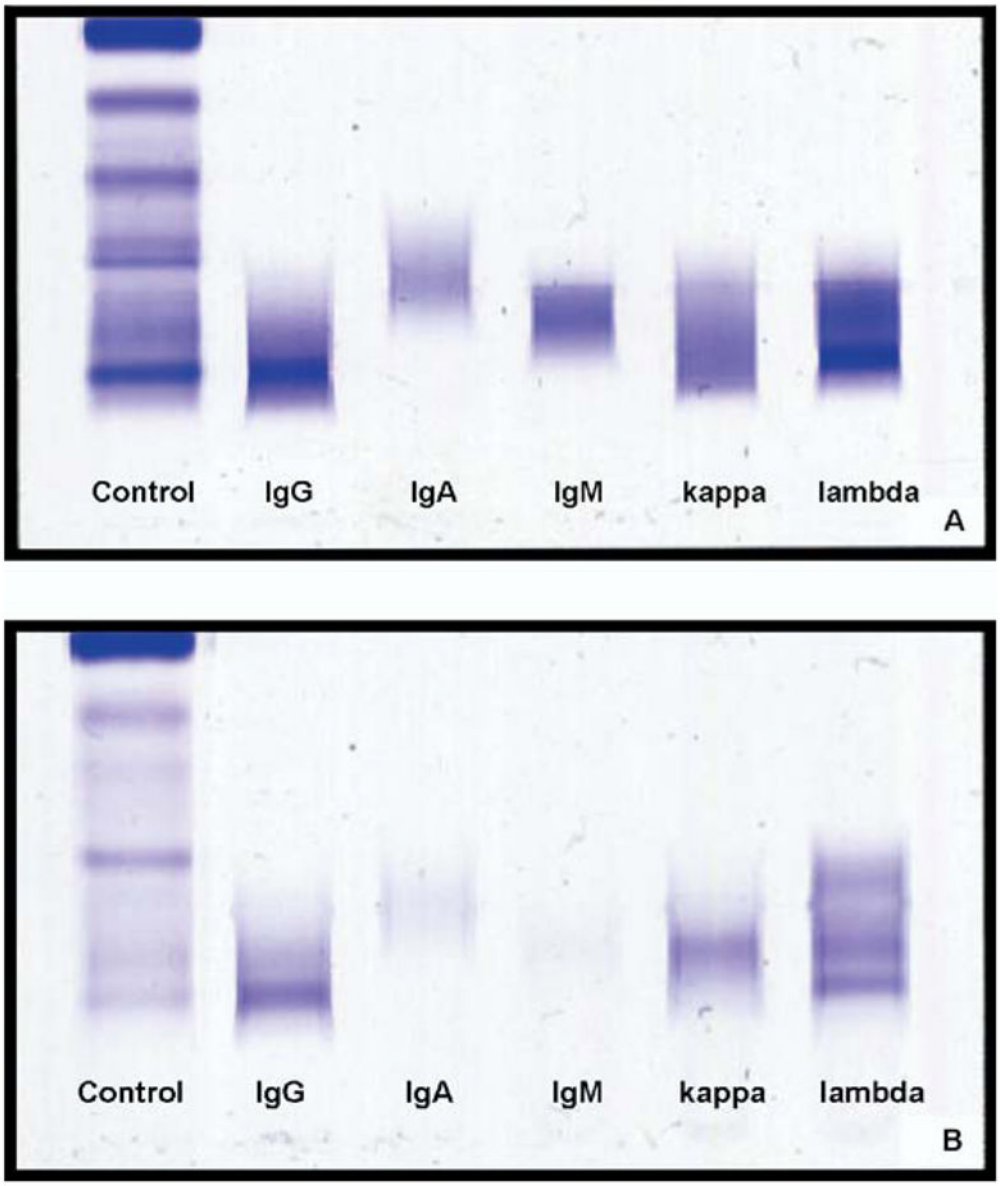

Figure 1.
Immunofixation electrophoresis of the patient's (A) serum and (B) urine showed (A) monoclonal components typed as immunoglobulin M (IgM) λ and IgG λ and (B) a monoclonal IgG λ protein and monoclonal free λ and κ light chains.

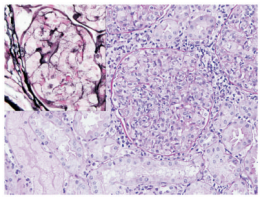

Figure 2.
Light microscopy. Glomeruli show global hypercellularity with dilatation of capillaries. Crescents are not present. The interstitium shows only minimal patchy mononuclear inflammatory cell infiltrates. Tubules are without significant abnormalities. (Periodic acid–Schiff stain; original magnification ×25.) Insert: a markedly dilated glomerular capillary filled with mononuclear cell elements shows remodeling phenomena, including rudimentary new basement membrane formation. (Methenamine silver incubation; original magnification ×40.)

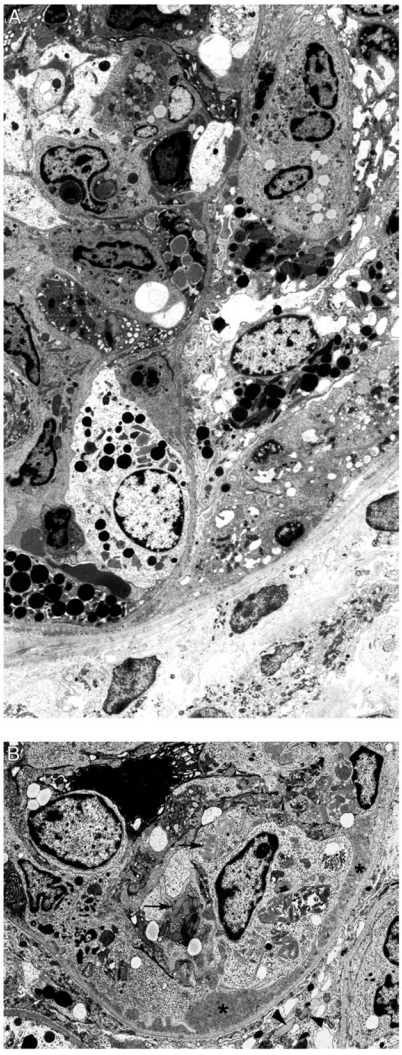

Figure 3.
Electron microscopy. (A) Low magnification shows a peripheral glomerular capillary tuft dilated by abundant mononuclear cell elements, some with large dense intralysosomal storage products that are also seen in podocytes. (Original magnification ×2,000.) (B) Higher magnification shows marked endocapillary hypercellularity and accumulation of subendothelial electron-dense deposits along the lamina rara interna (asterisks). Mononuclear cell elements contain intracytoplasmic crystalloid inclusions (arrows) that are also seen in podocytes (arrowheads). (Original magnification ×5,000.)

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.