Cryoglobulinemic Glomerulonephritis: A Case Report

Nuntawan Piyaphanee, M.D.*, Sivaporn Chaiyaumporn, M.D.*, Boonyarit Cheunsuchon, M.D., Achra Sumboonnanonda, M.D.***

**Department of Pediatrics, **Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Cryoglobulinemic glomerulonephritis (CG) is rare in children. We report a 13-year-old Thai boy who presented with acute nephrotic nephritis syndrome, arthralgia, and purpura. Renal pathology revealed membranoproliferative glomerulonephritis and CG. No secondary causes of CG were found. He responded well to 12 weeks of oral cyclophosphamide plus low dose prednisolone and azathioprine for maintenance. He was doing well at 31 weeks but long term follow up is required as chronic renal failure and neoplasia were reported.

Keywords: Membranoproliferative glomerulonephritis; cryoglobulin; cryoglobulinemic glomerulonephritis (Siriraj Med J 2017;69: 211-213)

INTRODUCTION

Membranoproliferative glomerulonephritis (MPGN) is characterized by mesangial and endocapillary proliferation and capillary wall remodeling forming double contours due to deposition of immunoglobulins (Ig), immune complexes and/or complement proteins in the mesangium and/or along the capillary wall of the glomerulus. Clinical presentation can be asymptomatic hematuria and proteinuria, acute nephritic syndrome, nephrotic syndrome, chronic kidney disease or rapidly progressive glomerulonephritis.[1,2] MPGN is classified into immune-complex-mediated form and complements alternative pathway-mediated form. Immune-complex-mediated MPGN results from immune complex deposition in the glomeruli and kidney pathology typically shows Ig and complement.[1,3] Chronic viral infections are important causes as well as bacterial, fungal and parasitic infections. MPGN can also be associated with autoimmune disease and monoclonal gammopathy.[4-6] Cryoglobulinemia is the presence of serum Ig that precipitates at a cold temperature, classified according to the component of cryoprecipitate into type I, II and III. Cryoglobulinemia can cause an immune complex mediated vasculitis characterized by purpura, weakness, arthralgia and many organs involvement, particularly kidneys.[7] Cryoglobulinemic glomerulonephritis (CG) usually gives a MPGN pattern.[8]

To our knowledge, this is the first case report in Thailand.

CASE REPORT

A 13-year-old boy had generalized edema for 4 days and transient mild arthralgia of both knees and ankles. There were no oral ulcer, rash, alopecia, respiratory tract or skin infection. Hypertension was noted (BP 139/78 mmHg). Weight and height were normal for age. Puffy eyelids, ascites, pitting edema 3+ of both legs and 2 small purpura lesions at both hands were noted. Complete blood count (CBC), blood urea nitrogen (BUN) and serum creatinine were normal for age. Urinalysis: specific gravity 1.026, protein 4+, blood 1+, wbc 3-5, and rbc 10-20/hpf. Urine protein per creatinine ratio (UPCR) showed nephrotic range proteinuria (6 mg/mg). Serum albumin was 2.4 g/dl and cholesterol 334 mg/dl. Acute nephrotic nephritis syndrome was diagnosed, and further investigation performed as follows.

Correspondence to: Achra Sumboonnanonda
E-mail: achrasu@gmail.com
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Anti-Streptolysin O, Anti-DNase B, ANA, and Anti-dsDNA were negative. Complement(C) 3 and C4 were 70.1 mg/dL (normal 83-177) and 15.6 mg/dL (normal 15-45). Liver enzymes were normal. Hepatitis B surface antigen (HBsAg) and Anti-Hepatitis C virus (HCV) were negative. Hemoculture and urine culture were negative.

Initial treatment included fluid restriction, low salt diet, furosemide (1 mg/kg/dose) and enalapril (0.1 mg/kg/day). Prednisolone 60 mg once daily was prescribed. Renal biopsy performed at 2nd week contained 11 glomeruli. All showed lobular pattern with endocapillary hypercellularity (Fig 1). Double contour of glomerular capillary walls with mesangial interposition was noted in all glomeruli (Fig 2). The tubules, interstitium and blood vessels were unremarkable. Immunoperoxidase study showed moderate (2+) IgM staining along capillary walls (Fig 3) and mild C3 staining in similar pattern. Electron microscopy showed subendothelial and mesangial deposits with characteristic microtubular substructure (Fig 4). The biopsy finding showed MPGN compatible with CG.

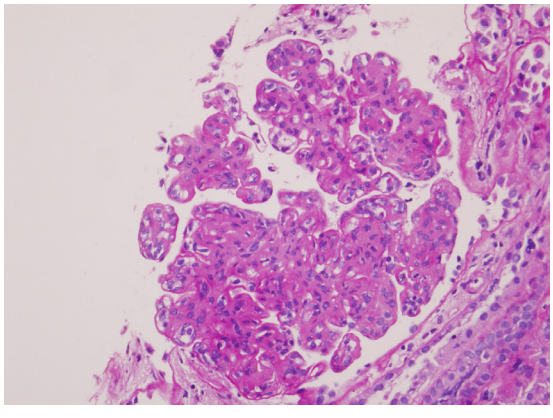

Fig 1. Glomerulus showing lobular pattern with endocapillary hypercellularity (periodic acid-Schiff).

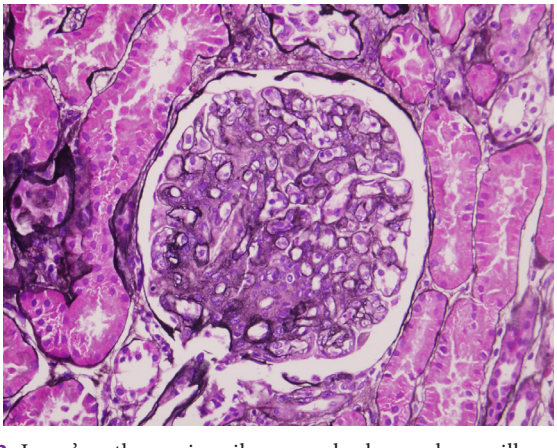

Fig 2. Jones' methenamine silver reveals glomerular capillary wall double contour and mesangial interposition.

Investigations for CG revealed negative Cryocrit. Serum protein electrophoresis showed no monoclonal gammopathy. Rheumatoid factor was 8.45 (normal less than 4.5) U/ml. HCV RNA, Hepatitis E virus (HEV) IgM, HEV IgM, anti-HIV, Epstein-Barr virus (EBV) IgM, EBV IgG were negative. Anticardiolipin IgM and IgG, lupus anticoagulant and anti Beta2 Glycoprotein 1 IgM and IgG were negative. CH 50 was 71 U/mL (normal at least 75), anti-Sm, anti-nRNP, anti-Ro, anti-La, and ANCA screening were negative.

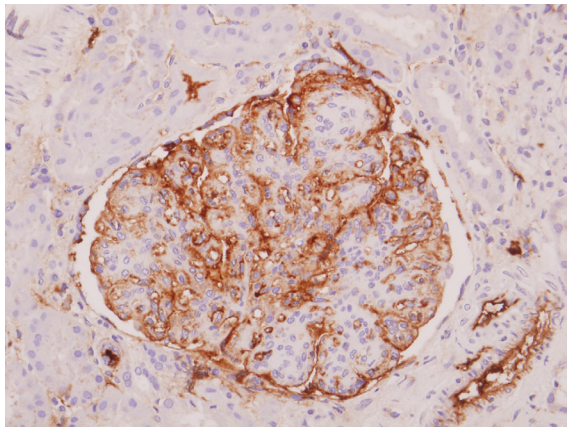

Fig 3. IgM staining positive along glomerular capillary walls (immunoperoxidase stain)

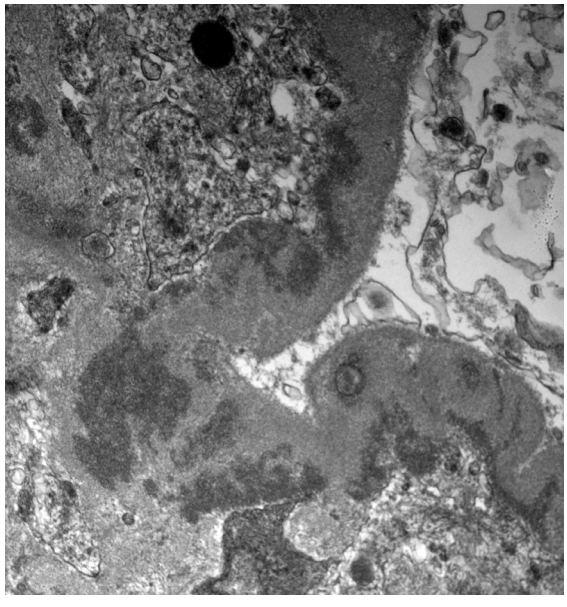

Fig 4. Electron microscopy shows deposits with microtubular substructure in subendothelial space.

Generalized edema, hypertension, and marked proteinuria persisted despite 4 weeks of prednisolone, enalapril and furosemide. 12 weeks of cyclophosphamide 100 mg/d and spironolactone were added. Nephrotic syndrome improved after 12 weeks. Serum C3 and C4 also returned to normal levels. Diuretics were discontinued and prednisolone tapered. After 16th week and gradually increased dose of enalapril, hypertension improved. At 29th week, UPCR decreased to 0.5 mg/mg and no hematuria. Azathioprine was started for maintenance while further tapering prednisolone. Amlodipine was added. At the last follow up (31st week), he was doing well and had

no hypertension. Medications included prednisolone 5 mg/d, azathioprine 100 mg/d, amlodipine 10 mg/d and enalapril 30 mg/d.

DISCUSSION

Studies from various countries revealed MPGN in 1.8-7.5% children with primary nephrotic syndrome.[9-11] A diagnosis of CG generally requires MPGN and positive cryoglobulin, but histological findings specific to CG have been reported.[8,12-15] Although cryoglobulin test is simple, it requires careful temperature regulation and handling of sample to avoid false negative.[7,16,17] Prognosis of cryoglobulinemic disease varies according to organs' damage, underlying diseases and comorbidities. A long term follow up of MPGN (7.7± 5.3 years) showed that 4 of 9 patients in cryo-positive group died from B-cell lymphoma and liver failure and 1 developed ESRD versus no death in cryo-negative group (n=26) and 4 patients developed ESRD.[1] Associated infections, especially HCV are associated with CG and treatment should be given. This patient had acute nephrotic nephritis, hypertension, arthralgia and purpura with positive rheumatoid factor and decreased C3 and CH 50 levels compatible with CG. However, extensive investigations failed to find a cause for CG in this boy. Clinical, treatment and prognosis of non-infectious CG were reported.[18, 19] Immunosuppressants, mainly glucocorticoids and cyclophosphamide are considered first line therapy in severe cases. Apheresis may also be useful in life-threatening disease.[17] In our patient, the clinical response of nephrotic syndrome was slow, but satisfactorily controlled with 12-week oral cyclophosphamide and gradually tapering dose of prednisolone. Long term follow up is required as chronic renal failure and neoplasia were reported.[13,17]

CONCLUSION

CG is a rare cause of acute nephrotic nephritis. We report here the first case in Thai children. Histopathological findings, especially electron microscopy, were essential in the diagnosis of this patient. In short term outcome, clinical improvement was achieved with immunosuppressive treatment.

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