Coexistence of Immunoglobulin M Nephropathy and Autoimmune Hemolytic Anemia
Two Rare Entities

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Immunoglobulin M (IgM) nephropathy is described as mesangial proliferative glomerulonephritis with diffuse mesangial IgM deposition. We report a patient diagnosed with IgM nephropathy and concomitant autoimmune hemolytic anemia syndrome associated with cold-reacting autoantibodies. Complete remission was achieved with systemic corticosteroid and plasmapheresis.

INTRODUCTION

Immunoglobulin M (IgM) nephropathy is described as mesangial proliferative glomerulonephritis with diffuse mesangial IgM deposition. Although the pathogenesis of the disease is not fully interpreted, presence of deposits of complements C1q and C4 along with IgM in the glomerular mesangium suggests that there may be an immuno-complex mediated activation of the complement cascade.¹ Autoimmune hemolytic anemia syndromes associated with cold-reacting autoantibodies, also known as cold autoimmune hemolytic anemia (CAIHA), occur as the result of strongly activated classical complement pathway, which is usually triggered by IgM type autoantibodies. Infection and lymphoproliferative disorders are the predominant causes in secondary cases.² We aimed to report a patient diagnosed with IgM nephropathy and concomitant CAIHA, both of which characterized by complement activation.

CASE REPORT

A 69-years-old woman was admitted with flank pain to the emergency service. On physical examination, she had bilateral pretibial edema (2+). The findings of remaining physical examination were unremarkable. Laboratory investigations revealed a hemoglobin level of 9 g/dL, a serum urea of 220 mg/dL and a serum creatinine of 12.2 mg/dL. She also had a high potassium level, a low serum albumin level, and a high lactate dehydrogenase level. Three to 4 leukocytes and 15 to 20 isomorphic erythrocytes were detected per high-power field in the urinary sediment. Urine protein-creatinine ratio was 8.8 mg/mg. The remaining laboratory tests were within normal range (Table). Her serum creatinine level had been 1.09 mg/dL a month earlier.

Renal ultrasonography results were unremarkable. Light microscopy of a renal biopsy specimen demonstrated mesangial cellular proliferation and normal glomerular basement membranes; mild mixed-type interstitial inflammation and tubulitis; hemosiderin pigment depositions and casts in tubular epithelial cells; and necklace-like...
erithrocytes in tubule lumens. Immunofluorescence microscopy revealed 3+ granular mesangial IgM deposition, while it was negative for IgA, IgG, C3, and C1q (Figure). The histological findings were interpreted in favor of IgM nephropathy and intravascular hemolysis.

Within 5 days, a rapid fall of hemoglobin occurred, which was noted 2 days before renal biopsy. Leucocyte and platelet counts were stable. There was no evidence of bleeding. The patient was diagnosed with CAIHA, based on existence of schistocytes on the peripheral blood smear, high reticulocyte account and serum lactate dehydrogenase levels, decreased haptoglobin level, and a positive direct coombs test with 4+ anti-C3d antibodies. Laboratory and radiological investigations for Chlamydia pneumoniae, Mycoplasma pneumoniae, tuberculosis, Legionella, syphilis, cytomegalovirus, Ebbstein-Barr virus, and lymphoproliferative disorders were negative. Systemic lupus erythematosus and other connective tissue diseases were ruled out via medical history and laboratory examination. There were no medication that possibly responsible for hemolysis.

Folbiol, 5 mg/d, and methylprednisolone, 60 mg/d, were started. On the 7th day of treatment, the patient no longer needed hemodialysis, but hemoglobin level decreased to 6.5 g/dL. Thereupon, therapeutic plasma exchange with 1.5 plasma volume fresh frozen plasma per procedure was performed. After 4 sessions of plasmapheresis, hemoglobin level increased to 9.2 g/dL and plasmapheresis was stopped. At 3 months of follow-up, when her serum creatinine was 1.2 mg/dL and hemoglobin was 12 g/dL, steroid was discontinued.

**DISCUSSION**

The frequency of IgM nephropathy reported in renal biopsy series in adults in the literature has varied from 2% to 45%. This wide variation in the prevalence of IgM nephropathy may be due to varying biopsy indications, varying definitions used for the diagnosis, and genetic or environmental factors. Common biopsy indications are nephrotic syndrome and hematuria in the cases diagnosed with IgM nephropathy. Our patient presented with acute kidney injury, nephrotic-range proteinuria, and hematuria. Acute kidney injury might have occurred as a result of acute tubular injury caused by intravascular hemolysis in our patient.

Although histological findings are seen in a wide spectrum, diffuse and globally mesangial IgM staining is the characteristic feature.
on immunofluorescence study. Mesangial IgM deposition may be solely or accompany predominantly to other depositions.\textsuperscript{5,6} Renal biopsy findings were consistent with the diagnosis of IgM nephropathy in our patient.

Treatment of IgM nephropathy is highly uncertain. Although steroid is known as first-line treatment, steroid resistance was reported in up to 52\% of patients in the literature.\textsuperscript{6} As acute kidney injury started to resolve on the 7th day of methylprednisolone treatment, the patient was thought to be steroid-responsive.

Cold autoimmune hemolytic anemia occurs as the result of strongly activated classical complement pathway which usually triggered by IgM type auto-antibodies. The first step in the treatment of CAIHA is to keep the patient warm and to treat the underlying disease in secondary forms of the disease. The response to systemic corticosteroid therapy and plasmapheresis are considered to be mostly not effective.\textsuperscript{2} Cold autoimmune hemolytic anemia was resolved after plasmapheresis in our patient, who failed to respond to steroid therapy.

Although pigment nephropathy is the common form of acute kidney injury, tubulointerstitial nephritis coexisting with drug-induced and infection-related immun hemolytic anemia or postinfectious glomerulonephritis coexisting with immun hemolytic anemia are rarely reported.\textsuperscript{7,8} As well as pigment nephropathy findings were shown in renal biopsy, immunofluorescence investigation was consistent with IgM nephropathy in our patient. To the best of our knowledge, this is the first case report of IgM nephropathy coexisting CAIHA. In conclusion, it is conceivable that similar mechanisms including IgM-type antibodies and complement pathway may lead to CAIHA and IgM nephropathy.

**CONFLICT OF INTEREST**
None declared.

**REFERENCES**


