Simultaneous Occurrence of Collagen Type III Glomerulopathy and Immunoglobulin A Nephropathy: A Rare Case Report

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Patient: Male, 35-year-old
Final Diagnosis: Glomerulonephritis
Symptoms: Arthralgia • body aches • hematuria • swelling
Clinical Procedure: Kidney biopsy • ultrasonography
Specialty: Nephrology • Pathology

Objective: Rare disease
Background: Collagen type III glomerulopathy (CG) is a rare disease with poorly understood pathogenesis, usually identified by abnormal collagen type III accumulation in glomeruli and manifesting as progressive deterioration of kidney function with nephrotic-range proteinuria. Immunoglobulin A nephropathy (IgAN) is the most prevalent glomerulopathy worldwide and is a leading cause of end-stage renal disease as a result of progressive fibrotic changes. Fibrosis is primarily caused by collagen type III deposition, which may explain the simultaneous occurrence of IgAN and CG.

Case Report: A young man presented with clinical and laboratory evidence of chronic kidney injury, including long-term nephrotic-range proteinuria and microscopic hematuria. Partial improvement in proteinuria was achieved with steroid therapy and conservative management. As the non-invasive workup was inconclusive, and a complete recovery of kidney function was not achieved, a kidney biopsy was done. Histopathological microscopic examination revealed advanced IgA nephropathy, Oxford classification M0E1S1T2C0, with features highly suggestive of type III collagen glomerulopathy.

Conclusions: We described a case of collagen type III glomerulopathy, also known as collagenofibrotic glomerulopathy, and its association with concurrent immunoglobulin A nephropathy in a healthy man presenting with chronic proteinuria and microscopic hematuria. As the number of reported cases in the Middle East is rising, we present this report to improve understanding and greater recognition of such cases.

Keywords: Collagen Type III • Glomerulonephritis, IGA • Glomerulonephritis, Membranoproliferative • Fibrosis • Saudi Arabia

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Collagen type III glomerulopathy (CG) is a rare non-immune disease defined by depositions of collagen type III in glomeruli, mainly in mesangial and subendothelial areas. Usually, type III collagen is not found in glomeruli but rather occurs in interstitium and vessels. Initially, it was believed to be part of nail-patella syndrome (NPS), but further studies showed it appeared to be a discrete entity. CG can present at any age; in childhood, it suggests a familial form of autosomal recessive inheritance, while in adults, it manifests as a sporadic disorder. It affects males and females equally [1-3].

Clinically, patients usually present with nephrotic-range proteinuria, hypertension (HTN), and progressive chronic kidney disease that can advance to end-stage kidney disease (ESRD) in 10 years. In addition, several cases were reported concerning extra-renal involvement, mainly hemolytic uremic syndrome. Rare associations with Hodgkin’s Lymphoma and hepatic perisinusoidal fibrosis were also described [2-4].

Immunoglobulin A nephropathy (IgAN) is common in people of all ethnicities, and Korea and Japan have the highest rates recorded. It has a benign course in most cases, with approximately 25-30% of patients developing ESRD in 10 years. Progressive disease is linked to several risk factors, which include male sex, HTN, proteinuria >1 g per day, and chronic microscopic hematuria [5].

Microscopic examination of renal biopsy tissue is needed to diagnose CG, including immunofluorescence and electron microscopy studies. Immunohistochemistry for type III collagen is occasionally necessary to support the diagnosis [4].

Most reported CG cases were noted in Asian patients, mainly of Japanese origin, including the first description of CG by Arakawa and Yamanaka in 1979 as being a variant of NPS, which later was clarified to be a different entity and a new form of glomerulopathy. Their report involved 2 individuals, with renal biopsy of both patients demonstrating collagen fibers, primarily in the mesangial area, without NPS-related skeletal findings. The first biopsy was for a 34-year-old woman who developed HTN and increased proteinuria during pregnancy, and the second biopsy involved a 65-year-old man with proteinuria of non-nephrotic range and HTN. In 1995, the World Health Organization added CG to the classification of glomerular diseases [4,6].

IgA nephropathy is one of the major causes of end-stage renal disease and is the commonest glomerulopathy globally [7]. Histological findings in kidney biopsy used for prognosis prediction in patients with IgA nephropathy include the extent of interstitial fibrotic and tubular atrophic changes [8,9]. One of the most prevalent collagen types in fibrotic kidneys is type III, the most abundant type found in urinalysis of patients with chronic kidney disease (CKD) [10-12]. These facts based on past scientific research may have contributed to the coexistence of CG and IgA nephropathy in our patient.

Of the few cases reported [13], especially in the Middle East, we present the first CG case with concurrent IgA nephropathy in a previously healthy man.

Case Report

A 35-year-old man presented with a history of generalized bone and multiple joint pain with lower-limb (LL) swelling. Laboratory workup done at the time showed hemoglobin 155 g/L, hematocrit 45.4%, and white blood cell count 6.22 (×10^9/L), with normal differentials. An abnormal renal function test (RFT) result consistent with chronic kidney injury was noted; serum levels of total protein 55 g/L, albumin 30 g/L, creatinine 137 umol/L, estimated glomerular filtration rate 54 ml/min/1.73 m², blood urea nitrogen 6.4 mmol/L, and uric acid 478 umol/L. In addition, urinalysis and microscopy were positive for excretion of blood (0.03 mg/dL) and protein (300 mg/dL), with urine creatinine of 14.6 mmol/L, macroalbuminuria >2000 mg/L, and urine albumin/creatinine ratio of >137 mg/mmol. Electrolytes, blood glucose, and hemoglobin a1c were within normal limits.

In a more detailed history, the patient had chronic proteinuria and microscopic hematuria for 10 years with no other significant urinary tract-related findings. He also had chronic on-off bilateral LL edema lasting for 2-3 days with a history of 1 attack of gross hematuria during the last few months prior to presentation. In the previous month, there was worsening of the LL swelling, lasting longer periods with associated periorbital edema, accompanied by pain in both ankles and wrists. Persistently high blood pressure (BP) readings were also noted recently, with the last reading of 152/87 mmHg. The rest of the medical/surgical background and systemic review were unremarkable, with a negative history of smoking, illicit drug use, recurrent urinary tract infection, and personal or family renal conditions. The patient’s presentation was highly suggestive of glomerulonephritis with the impression of query IgA nephropathy; thus, a more extensive workup was done.

Renal ultrasound (US) was unremarkable. However, labs were still demonstrating abnormal RFT with serum creatinine of 130 umol/L, e-GFR of 58 ml/min/1.73 m², uric acid 474 umol/L, and albumin level of 34 g/L; 24-h urine protein was also high at 7.97 g/day. Serological tests for hepatitis B, C, and HIV antibodies were negative. Perinuclear anti-neutrophil cytoplasmic antibodies, cytoplasmic anti-neutrophil cytoplasmic antibodies, anti-nuclear antibodies, anti-glomerular basement
membrane antibodies, anti-double-stranded deoxyribonucleic acid antibodies, and complement 3 and 4 were also all negative. C-reactive protein and cyclic citrullinated peptide were unremarkable; however, rheumatoid factor 24 IU/ml and erythrocyte sedimentation rate 35 mm/h were high.

The need for a kidney biopsy was discussed with the patient and agreed on. The pathology report of the collected specimen from the left native kidney was inconclusive as the biopsy specimen was insufficient, with only 5 glomeruli demonstrating a mild focal mesangial hypercellularity and mesangial matrix expansion; 2/5 glomeruli showed global sclerosis and 1/5 displayed segmental sclerosis. In addition, small blood vessels had mild subintimal sclerosis, moderate interstitial fibrosis, and tubular atrophy. Immunofluorescence and electron microscopy studies were not done due to the insufficient sample.

A steroid-based Pozzi protocol and conservative treatment, which included fish oil, calcium, and vitamin D, were initiated, with the impression of IgA nephropathy as suggested by clinical presentation, microscopy findings of nephrotic-range proteinuria, and the initial pathology report. After 6 months of treatment, the proteinuria had improved, and 24-h urine protein was trending down from 7.97 (g/day) to 3.1 (g/day). Well-controlled BP readings and stable serum creatinine levels (100-130 umol/L) were also achieved. Then, steroid treatment was tapered over approximately 3 months, and stable chronic kidney disease stage 3 was recorded after 1 month off steroids.

Although partial response to steroid and conservative treatment was noted, complete resolution of proteinuria was not obtained, with the last 24-h urine protein level of 3.8 g/day, and the risk of progression could not be ruled out. Therefore, the necessity of a re-biopsy was explained to the patient, who agreed. The second specimen was also collected from the left native kidney, which revealed advanced IgA nephropathy, Oxford classification M0E1S1T2C0, with features highly suspicious for type III collagen glomerulopathy. Global sclerosis was found in 16/24 glomeruli, and severe interstitial fibrosis, and tubular atrophy, mild arterial sclerosis and arterioles hyalinosis were also appreciated. The biopsy specimen was sent to Mayo Clinic Medical Laboratories for a second opinion and possible further studies to confirm the presence of collagenofibrotic glomerulopathy, an extremely rare condition.

Mayo Clinic Medical Laboratories found collagenofibrotic glomerulopathy type III, which was confirmed by mass spectrometry. Glomeruli showed positivity for IgA and lambda. Ultrastructurally, on light microscopy, para-mesangial deposits and a few subendothelial granular electron-dense deposits were seen, without significant glomerular hypercellularity. These findings were also consistent with concomitant IgA nephropathy. On light microscopy (Figure 1), 16/24 glomeruli were globally sclerotic; the remaining glomeruli appeared enlarged with abundant deposition in the mesangium and globally in the subendothelial zone of PAS-weak and silver-negative material, associated with duplication of the glomerular basement membranes. There was only mild segmental mesangial hypercellularity. One glomerulus showed segmental sclerosis. No crescents or fibrinoid necrosis were identified. There was moderate tubular atrophy and interstitial fibrosis involving >50% of...
the cortex sampled, accompanied by a mild interstitial inflammatory infiltrate mainly composed of mononuclear cells. There was no significant tubulitis. Some non-atrophic tubules exhibited mild acute injury with luminal ectasia and epithelial simplification. Focal interstitial foam cells were seen and mild-moderate arteriosclerosis was appreciated.

On immunofluorescence (Figure 2), 1/3 of glomeruli showed global sclerosis, and there was 2+ mesangial staining for IgA and lambda with weak non-specific staining for IgM, C3, C1q, and kappa. Glomeruli were negative for IgG and albumin.

On electron microscopy (Figure 3), there was marked global mesangial and subendothelial deposition of thick curved collagen fibrils with a banded pattern. Para-mesangial deposits and a few subendothelial granular deposits were also seen. In addition, mesangial and para-mesangial electron deposits were evident. No endothelial tubuloreticular inclusions were identified. There was widespread duplication of the glomerular basement membranes, with cellular interposition. Podocytes displayed segmental foot process effacement involving about 40-50% of the peripheral capillary surface area. Tubules showed intracytoplasmic protein and lipid resorption droplets.

Based on clinical, histopathological, and laboratory findings, we determined the patient had both IgA nephropathy and CG glomerulopathy. Fortunately, maintenance of a stable CKD stage 3 and static level of proteinuria, with last 24-h urine protein of 3.2 (g/day), was achieved through a combination of sodium-glucose cotransporter 2 inhibitor, angiotensin-converting enzyme inhibitor, calcium channel blocker, and antigout. Furthermore, the patient was educated about lifestyle modification for weight reduction with a low-protein diet suitable for his condition. Finally, the patient was recommended to continue the same management with regular follow-up appointments for any deterioration or relapse.

**Discussion**

CG is a relatively new entity of unknown pathology; in our case, the patient had a concomitant IgA nephropathy with advanced features and positivity of IgA complexes in glomeruli [6]. Collagen type III glomerulopathies include 2 main types – NPS...
and CG. NPS is an autosomal dominant disorder in which mesangial and mottled glomerular basement membrane (GBM) deposits are noted, described as moth-eaten lamina densa. CG deposits are found in mesangial and subendothelial spaces, but not in the lamina densa [14]. This atypical glomerular deposition of collagen type III can occur in proliferative, non-proliferative, immune, and non-immune glomerular diseases [13].

In India, an extensive study of CG involving 10 128 renal biopsies, collected from 2011 to 2015, was conducted at the Center for Renal and Urological Pathology (AAK); however, only 8 patients were diagnosed with CG and were included in the study – 5 males and 3 females, with an average age of 38 years. All patients who had serological tests done had negative results, and serum levels of C3 and C4 were normal. No family history of renal diseases, hemolytic uremic syndrome, and no signs or symptoms of nail-patella syndrome were noted [4].

There are a few reports of concomitant hemolytic uremic syndrome and type III collagen glomerulopathy with associated deficiency of factor H, which can contribute to endothelial injury via complements assisted damage, allowing access and accumulation of type III collagen within the subendothelial area [3].

The criterion standard in diagnosing CG is pathological examination of a renal biopsy. Light microscopy reveals a mesangial matrix expansion and weak PAS-positive material with or without increased mesangial cellularity. GBM shows double contour, tubular atrophy, and vascular and interstitial sclerosis, which are potentially non-specific findings. Also, nodular or lobular glomerular contours can be mistaken for diabetic Kimmelstiel-Wilson nodular lesions, as well as amyloid or thrombotic microangiopathy (TMA) [2,3].

Diagnosis of CG depends on ultrastructural evidence of type III collagen curvilinear bundles with frayed edges and cross striations. On EM, unlike the typical parallelly arranged collagen fibrils of 64-nm periodicity, CG has randomly arranged curvilinear collagen bundles longitudinally curled in subendothelial and mesangial areas with variable periodicity (40-64 nm). Also, podocyte effacement is usually present. Additionally, a crucial difference detectable in EM distinguishing NPS from CG is the lamina densa of the GBM, which is spared from collagen depositions in CG but not in NPS [1,2,14].

Immunofluorescence studies for immunoglobulins and complements are typically negative except for type III collagen, which displays a strong stain in mesangium and GBM [2]. Immunohistochemistry can be used adjunctly for diagnosis confirmation or, if EM is unavailable, utilizing antibodies against collagen type III. In addition, special staining (eg, silver stain and PAS) and Congo red could be used to help exclude TMA, amyloid, and diabetes [3].

The most frequently diagnosed glomerulonephritis globally is IgAN, usually with presentation at late stages of the condition, as it does not manifest with apparent symptoms in early stages. A study conducted in Saudi Arabia showed that despite occurring in people of all ages, the higher incidence was seen in males, with the most common presentation being hematuria and proteinuria [15]. It is an immune-complex-mediated disease mainly affecting glomeruli; as the condition progresses, persistent inflammation and subsequent fibrotic changes occur, with collagen deposition as a vital part of the fibrosis process.

In our case, evidence of IgAN was found in histopathological analysis, in addition to features of CG. We believe that IgAN resulted in a subsequent incidence of CG, which is not always an outcome perceived with the progression of IgAN. The rarity of concomitant case reports in our literature review evidences this. Usually, complements and immunoglobulins in CG patients are negative; glomerular C3 and IgM might be present due to subendothelial deposit of hyaline; however, it is not an indicator of an immune-mediated activity. Nonetheless, CG with immune complexes deposition has been described in the literature [6].

Although the exact trigger of CG occurrence in our patient is unclear, it might be attributed to this concomitant deposition of collagen type III in the preliminary presence of IgAN in the mesangial area, as well as segmental and focal fibrosis with curled collagen fibers in the mesangium, as described in a previous case report [16]. In addition, activation of mesangial cells can be another effect of the inflammatory reaction triggered by IgA complexes and endothelial injury, which consequently allows the accumulation of collagen type III within the glomeruli [5].

Specific markers of fibrosis are still lacking; presently, detecting chronic renal disease progression is done through proteins related to the remodeling of the extracellular matrix. Previously, PIIP was studied as a potential marker, as it was detected in various nephropathies, reflecting renal collagen type III accumulation. Results suggested that increased turnover of collagen type III was noted during the progression of the fibrotic changes in IgA nephropathy patients. Hence, higher disease severity was also associated with this progression [17].

Findings such as accelerated HTN, proteinuria in the nephrotic range, and proliferative pathology reflect the severity of IgA nephropathy, and immunosuppressive treatment should be considered if these are present [5]. Thus, our patient was started on steroid therapy with only a partial response by the end of the course, possibly explained by the presence of a coexisting IgA nephropathy and its associated inflammation on top of CG, which might have been the result of an immune-mediated process in this case.
Conclusions

We report the first case in the Middle East of the association between CG and concomitant IgA nephropathy and emphasize the importance of a careful pathological examination. While the course of CG is variable, with no well-defined risk or predictive factors, the disease usually progresses, and patients may eventually develop ESRD. Although the precise trigger of IgAN was unknown in our patient, we believe it preceded CG occurrence, eventually leading to glomerular deposition of collagen type III as part of the inflammatory reaction and fibrosis process. However, not all IgAN cases end with CG; thus, the exact etiology of such concomitant cases still needs further research. Steroid therapy was administered initially, which only resulted in a partial response. However, as there is not yet a definitive treatment for CG, the patient is currently stable on supportive management targeting BP control and proteinuria reduction or maintenance as the primary treatment goals to preserve kidney function. Despite CG being a rare and under-diagnosed disease, a growing number of cases are being reported from Middle Eastern countries. Thus, it should be regarded as an essential proteinuria differential. We hope this report contributes to better understanding of this condition.

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References: