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Case Report

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Slowly Progressive Immunoglobulin A Nephropathy With Isomorphic Hematuria and Without Significant Proteinuria: A Case Report and Follow-Up for 9 Years

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ABSTRACT

Immunoglobulin A nephropathy has variable clinical presentations of asymptomatic hematuria to rapidly progressive glomerulonephritis. It may also present with hypertension and a slow decrease in glomerular filtration rate over months or even years which can easily be attributed to hypertensive target organ damage. Here, a 9-year follow-up of 45-year-old male with a history of hypertension, obesity, and smoking history was discussed. During his follow-up, he had intermittent isomorphic urinary erythrocytes and slow progression in decrement of kidney functions without significant proteinuria. After 3 years of slow progression which was formerly thought be caused by hypertension, smoking, and obesity-related kidney disease, he had a rapid decrease in glomerular filtration rate. Kidney biopsy revealed immunoglobulin A nephropathy with hypertensive nephrosclerosis. Treatment with methylprednisolone improved and slowed his kidney disease progression. We would like to remind clinicians to be aware of slowly progressive immunoglobulin A nephropathy with isomorphic hematuria and without significant proteinuria. The presence of other risk factors such as smoking, hypertension, and obesity should not blur silent increases in serum creatinine levels in order not to delay kidney biopsy as untreated immunoglobulin A nephropathy leads to uncontrolled hypertension, which increases irreversible kidney injury.

Keywords: Hematuria, hypertension, nephritis

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INTRODUCTION

Immunoglobulin (Ig) A nephropathy, first recognized by Berger and Hinglais in 1968, was reported as the most prevalent glomerulonephritis in most of the countries.[1] It has various clinical courses that differ from one patient to another, and even intra-individual variations may occur.[2] The main pathogenetic mechanisms consist of abnormalities in IgA1 (one of the monomers of IgA) production and metabolism.[3] Clinical features range from asymptomatic glomerular hematuria to proteinuria, hypertension, kidney failure, and repeated events of macroscopic hematuria induced by infections such as gastroenteritis and tonsillitis.[2] Progression to chronic kidney disease G5 usually occurs in 33%-40% of patients in a period of approximately 15 years, depending on the severity of proteinuria.[2,4] Male gender, age under 30 years old, diastolic hypertension, severe proteinuria, mild hematuria, low serum albumin levels, and high serum creatinine levels were reported as the poor prognostic predictive factors of kidney survival for 10 years.[4,5]

Herein, a male patient—who had intermittent isomorphic hematuria, controlled hypertension, and insidious loss of kidney functions without significant proteinuria (<500 mg/day) and who was finally diagnosed with IgA nephropathy—and his medical follow-up of nearly 9 years will be presented.

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CASE PRESENTATION

A 45-year-old male with arterial hypertension diagnosed 8 months ago presented to our department in March 2012. He had been taking perindopril (4 mg) plus indapamide (1.5 mg) till then. At the time of admission, his blood pressure was 140/90 mmHg, his body mass index was 29.7 kg/m^2, and he was a heavy smoker (30 packs/day). His initial serum creatinine level was 1.33 mg/dL. Hyperuricemia (serum uric acid = 7.96 mg/dL), hypercholesterolemia (serum low-density lipoprotein cholesterol = 201 mg/dL), left ventricular hypertrophy, thoracic aortic aneurysm, and hypertensive retinopathy were found. Ultrasonography revealed mildly hyperechogenic normal-sized kidneys. Isomorphic intermittent erythrocyturia [2-20 red blood cells/high power field (HPF)] was observed at his follow-up visits for the next 3 years. Cystourethroscopy revealed normal results for prostate and bladder pathology. He had proteinuria ranging between 200 and 400 mg/day and albuminuria ranging between 30 and 68 mg/day. He was diagnosed with metabolic syndrome and advised to take medications of atorvastatin 10 mg/day, allopurinol 150 mg/day, perindopril 5 mg/day, and benipin 4 mg /day, get pneumococcal and influenza vaccine, and cease smoking. He had difficulty quitting smoking and following the diet. The course of his blood pressure was around 120/70 mm Hg, serum creatinine levels fluctuated between 1.5 and 2 mg/dL, and estimated glomerular filtration rates (CKD–EPI-cre based) of the patient were between 56 and 40 mL/min/1.73 m^2 throughout the next 3 years. In October 2015, after an episode of diarrhea, his serum creatinine level, the number of erythrocytes (isomorphic) in urine, and proteinuria and albuminuria levels rapidly increased to 3.55 mg/dL, 35 red blood cells/high power field (HPF), 1.33 g/day, and 680 mg/day, respectively. As diarrhea had ceased before hospitalization, no was needed treatment. The deterioration in kidney functions was resistant to fluid resuscitation. Serum complement level 3 was 104 mg/dL (normal: 90-180), complement level 4 was 21.8 mg/dL (normal 10-40), antinuclear antibody, anti-double stranded DNA, and cytoplasmic antineutrophil cytoplasmic autoantibodies (ANCA) tests were negative. Perinuclear ANCA was mildly (titer of 1/100) positive. Globally sclerotic 5 glomeruli, ischemic 2 glomeruli, segmental mesangial cellular proliferation in 6 glomeruli,

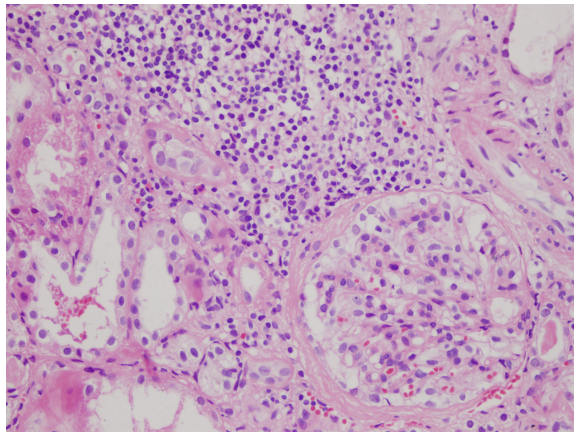

Figure 1. Kidney biopsy which presents glomerular mesangial cellular proliferation, enhanced mesangial matrix, and periglomerular fibrosis with nearby tubular inflammatory infiltration, H&E: ×200.

arteriolar hyalinosis, interstitial fibrosis, tubular atrophy, and tubulointerstitial inflammation in 50% of the cortical sample were observed in light microscopic evaluation of kidney biopsy (Figure 1). Immunofluorescence microscopy revealed Ig A deposition (severity degree of +2) and mild degree (+1) of complement 3 deposition (Figure 2). The patient was diagnosed with smoking-related hypoxic kidney injury, hypertensive glomerulosclerosis, and IgA nephropathy (CRESCENT [MEST-C] score was M1, E1, S1, T2, C0). There was no clinical or laboratory sign of celiac disease, HIV infection, and cirrhosis. Fish oil, methylprednisolone 32 mg/day, and calcium 600 mg + vitamin D3 400 IU were added to his prevalent treatment. After 2 months, the dosage was tapered gradually to 4 mg/day and prescribed for 1 year. His serum creatinine level decreased to 1.9 mg/dL 6 months later. He quit smoking and lost 8 kg in weight. His kidney functions were stable for 1 year after cessation of methylprednisolone treatment. However,

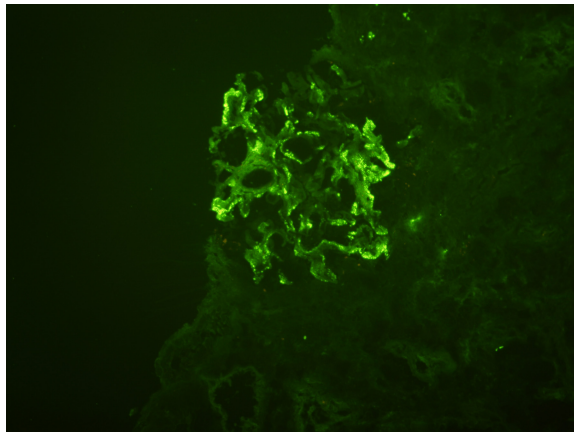

Figure 2. Granular and dominant immunoglobulin A deposition with severity index of +2 located along the mesangial area on immunofluorescence microscopy at ×200.

MAIN POINTS

- Immunoglobulin (IgA) nephropathy could be present with isomorphic hematuria, without significant proteinuria.
- If the patient's blood pressure is under control and still even a small decrease in glomerular filtration rate is noticed, a kidney biopsy decision should not be delayed.
- The recommendation for optimum treatment choices and duration of treatment for IgA nephropathy changes over years. For the present case, methylprednisolone treatment had to be given for nearly 4 years (as an on-and-off therapy) in order to preserve kidney functions.

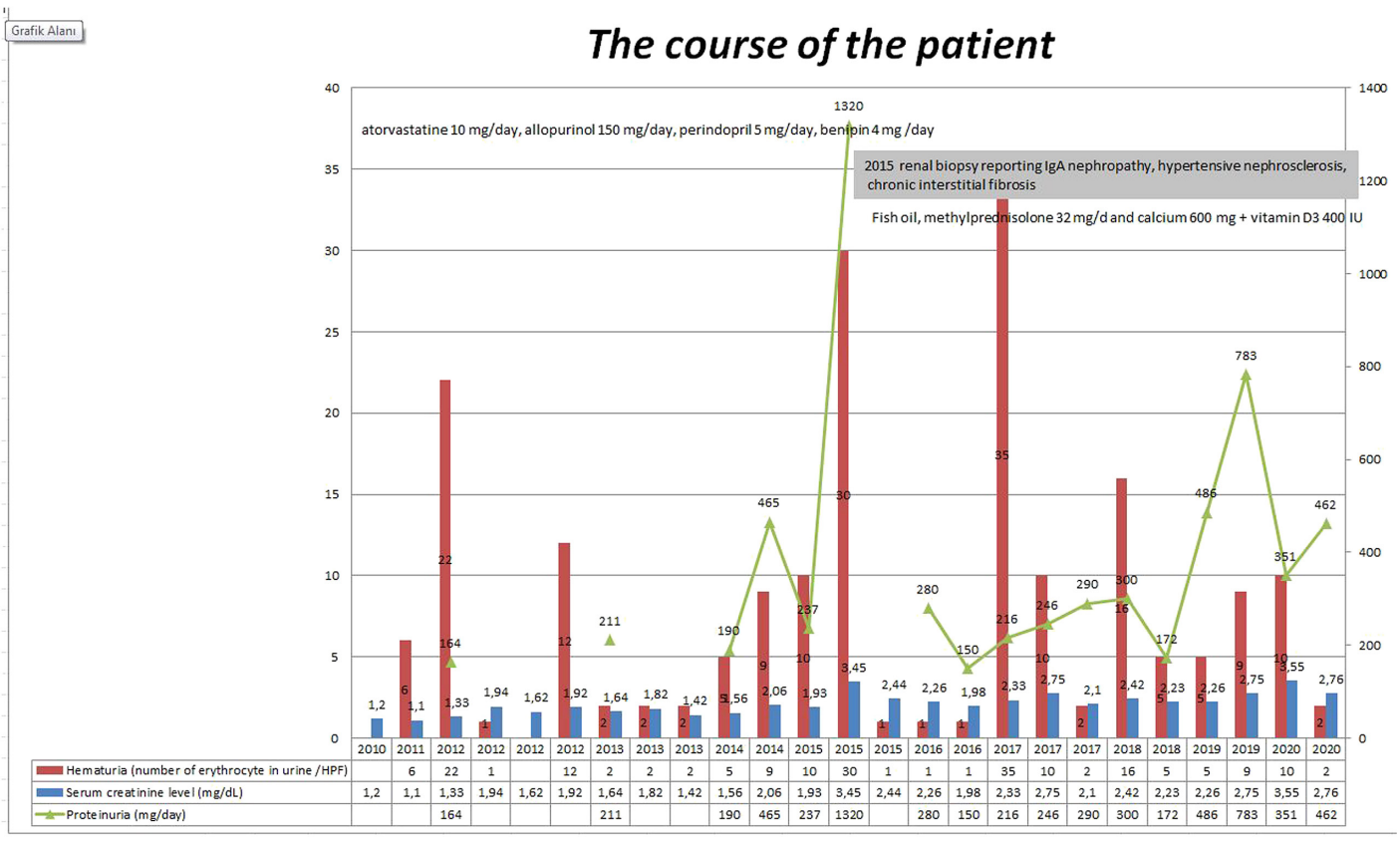

Figure 3. The course of the patient during 9 years of follow-up.

a small increase in his serum creatinine level was observed from 1.9 to 2.35 mg/dL in year 2017 together with an increase in erythrocyturia (35 red blood cells/HPF) after an episode of upper airway infection (Figure 3). Azathioprine was administered at a daily dose of 100 mg. Due to side effects (nausea) and increase in serum creatinine level to 2.75 mg/dL, azathioprine was stopped, and methylprednisolone treatment was restarted. For the last 3 years, whenever methylprednisolone treatment was tapered, a profound increase in serum creatinine level, increase in urinary erythrocyte number, and decrease in glomerular filtration rate were observed. This made it necessary to continue glucocorticoid therapy. After 9 years of follow-up, the patient is doing well with a glomerular filtration rate of 27 mL/min.

DISCUSSION

Although kidney biopsy is the gold standard to diagnose IgA nephropathy, and the consensus about the proper indications for this procedure has changed.[6,7] As isolated hematuria usually predicts a more benign course, kidney biopsy is indicated when there is persistent proteinuria of >500-1000 mg/day or elevation of serum creatinine levels. With this case, we learned that IgA nephropathy could present and progress without dysmorphic hematuria and significant and persistent proteinuria. Importance of early kidney biopsy in patients with intermittent microscopic isomorphic hematuria, proteinuria of <500 mg/day, and progression of chronic kidney disease even with well-known other risk factors like smoking and obesity were emphasized.

Treatment of IgA nephropathy includes non-immunosuppressive treatment (angiotensin-converting enzyme [ACE] inhibitors and fish oil) and immunosuppressive treatment for persistent proteinuria above 1 g/day, increasing creatinine, and proliferative and necrotizing glomerular pathology.[8] Because of rapid increase in serum creatinine levels despite the absence of crescent and necrosis in kidney biopsy, immunosuppressive treatment added to non-immunosuppressive treatment (ACE inhibitors and fish oil) of our patient led to improvement in kidney functions. Immunosuppressive treatment includes 6 months of methylprednisolone therapy and combined medications of other immunosuppressive agents for crescentic forms.[8] Immunosuppressive treatment is not recommended for patients with chronically elevated serum creatinine levels and glomerulosclerosis in kidney pathology. Still, Kidney disease improving global outcomes (KDIGO) guidelines 2021 for glomerulonephritis suggest immunosuppressive drugs for patients who remain at high risk of progressive chronic kidney disease with estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m^2 despite maximal supportive therapy, an offer to enroll in a clinical trial and detailed discussion about the risks and benefits of the

immunosuppressive treatment.[9] In this present case, even though glomerulosclerosis and tubular atrophy in kidney pathology and slow progression in kidney disease were present, treatment with methylprednisolone improved and slowed his kidney disease progression. Whenever an attempt to stop methylprednisolone therapy was made, the decrement in glomerular filtration rate worsened, making it difficult to stop therapy in 6 months.

One of the predictors for the slow progression of IgA nephropathy to kidney failure is the absence of proteinuria or the presence of little proteinuria.[8] However, in this case, we would like to remind the clinicians to be aware of progressive IgA nephropathy without significant proteinuria and dysmorphic hematuria. The presence of other risk factors such as smoking and obesity should not blur silent increases in serum creatinine levels in order not to delay kidney biopsy.

Informed Consent: Written informed consent for publication of this case report was taken from the patient.

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