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FIVE-YEAR-OLD MALE WITH IGA NEPHROPATHY INITIALLY PRESENTING WITH ADVANCED CHRONIC CHANGES IN RENAL BIOPSY FINDINGS

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Abstract:

Background:IgA nephropathy is a common glomerular disease worldwide. However, in children, it is rare for IgA nephropathy to present with advanced chronic histological changes on renal biopsy. Here, we present the case of child who was found to have IgA nephropathy with chronic changes in renal biopsy findings.

Case Presentation: A 5-year-old male presented with hematuria preceded by upper respiratory infection for 23 days. Based on his initial urine analysis and serum creatinine, we presumed that he had acute kidney injury secondary to post-streptococcal glomerulonephritis.Renal biopsy was preformed and he was diagnosed with IgA nephropathy with global sclerosis and interstitial fibrosis.Immunosuppressive medications with steroid and mycophenolate mofetil were administered, but there was little improvement after 3 months and the patient was diagnosed with chronic kidney disease stage 3.

Conclusions: Although this is rare, IgA nephropathy in children can initially present with advanced chronic renal disease. The distinction of acute versus chronic IgA nephropathy is crucial as the two clinical entities require different pharmacological management strategies and approaches.

Key words: IgA nephropathy, Pediatric, Chronic kidney disease.

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INTRODUCTION:

IgA nephropathy is a common glomerular disease worldwide[1]. Most children present clinically with gross hematuria 2-3 days following upper respiratory infections. Some children with IgA presented initially with severe acute kidney injury due to the presence of crescentic glomerulonephritis.In these patients, early diagnosis and the initiation of immunosuppressivemedications can help to preserve renal function. However,it is quite rare in children to initially present with advanced stage of chronic kidney disease. In such patients, the response to immunosuppressive regimen is poor and patients will most likely progress to end-stage renal disease within a few years. In this case we present a 5-year-old male who presented initially with acute glomerulonephritis presumed to be due to post-streptococcal glomerulonephritis with elevated creatinine. However renal biopsy showed IgA nephropathy with global sclerosis and moderate interstitial fibrosis. To our knowledge, this the first pediatric case that presented with IgA nephropathy and chronic changes in renal biopsy findings at initial clinical presentation.

CASE PRESENTATION:

A 5-year-old male patient from Jeddah,Saudi Arabia presented to the emergency department with chief complaints of sore throat and hematuria. He developed hematuria on the second day after he experienced sore throat. His pharyngotonsillitis was treated with antibiotics without a throat swab at a publichospital. He was then referred to another public hospital, where he underwent initial work-ups and the following results were obtained: creatinine level of 1.4 mg/dLand urea level of121.4 mg/dL.Urinalysis showed: protein, +1;and red blood cells (RBCs), 14 /HPF (High Power Field). Serum ASO titers were 600 IU/l (mildly elevated). Based on these examinations, the patient was diagnosed with post-streptococcal glomerulonephritis. The patient was referred to KAUH's pediatric nephrology clinic and was admitted with a working diagnosis of post-streptococcal glomerulonephritisdue to his history of sore throat. On presentation at the clinic, he had an elevated blood pressure of 130/80 mmHg, a weight of 15.5kg, and height of 92 cm, which is below the fifthpercentile.

On admission, the patient had a creatinine level of 110 µmol/L, glomerular filtration rate (GFR) of 33.45mL/min/1.73 m^2,and a high urea level of 11.2 mmol/L. Serum albumin was 28 g/L.Urinalysis showed +1 protein level, a white blood cell (WBC) count of 3, and RBC count of 17 / High Power Field. Random urine protein/creatinine ratio was 1.4, C3 level was 1.21 g/L (normal), and C4 level was 0.43 g/L (normal).Serum antinuclear antibody and antineutrophil cytoplasmic antibodies (ANCA) were negative.

Kidney ultrasound was performed, and results showed echogenic kidneys with loss of cortical medullary differentiation.

Due to elevated serum creatinine and normal serum complement, we decided to perform a renal biopsy to determine alternative diagnoses.

A kidney biopsy was performed, whichshowed the presence of immunoglobulin (Ig) A, IgG (only podocyte staining was seen with very large glomerulus), mild segmental C3, rare intramembranous deposits in some segments, many mesangial deposits without capillary deposits in another glomerular segment, reabsorbing lucent deposits, and intramembranous deposits.

Findings of light microscopy were as follows: there were nine glomeruli—four showed global sclerosis and two showed segmental glomerulosclerosis; only one glomerulus with mesangial hypercellularity, respectively. There was also moderate interstitial fibrosis and tubular atrophy.

The patient was administered iron, active vitamin D sodium bicarbonate, and calcium gluconate. For hypertension, he was prescribed amlodipin1 mg . He was then started on pulse methylprednisolone with threesubsequent doses followed by oral prednisolone 60 mg/m^2/day every other day. The patient continued on oral prednisolone 60 mg/m^2/day and started on mycophenolate mofetil 1200 mg/m^2/day and enalapril upon discharge.The patient had a blood pressure of 114/81 mmHg.

Three months, later laboratory investigations were repeated, and they showeda creatinine level of 134 µmol/L, GFR of 31.34mL/min/1.73 m^2,and urea level of 11.2 mmol/L. Urinalysisshowed an RBC count of 6.16, and+1 protein level.The patient was diagnosed with chronic kidney disease stage 3. The immunosuppressive regimen was stopped and the patient continued on supportive treatment.

DISCUSSION:

Although IgA nephropathy is the most common type of glomerulonephritis in the Western world, rapid progression to end-stage renal disease (ESRD) is uncommon (<10%) [1]. In this case, there was a rapid clinical deterioration of kidney function, and the presence of chronic changes with a very few active lesions in renal biopsy. This case exemplifies a small percentage of patients with IgA nephropathy that can rapidly progress towards ESRD. There is one case of a20-year-old Latin American male who had a similar course, reported by Akkad et al.in2016[2].

Huang et al. conducted a study among 14 patients with IgA nephropathy and serological positive ANCA. The study was conducted in order to describe the clinical and histological characteristics of patient subpopulations and to assess if ANCA in seropositive patients has higher odds of determining the rapid progression of deteriorating kidney function. Huang et al.concludedthat patients with IgA nephropathy and pathogenic ANCAs commonly show clinical features of rapidly deteriorating kidney disease [3]. ANCA serology was conductedon this patient and the resultwas negative for both cytoplasmic and perinuclear features, which indicated that more significant prognostic factors need to be identified.

Another study byLv et al. [4]recruited 113 Chinese patients with crescenticIgA nephropathy,from eightkidney centers across China.It was found that patients with crescenticIgA nephropathyhada poorer prognosis, and nearly 70% of these patients progressed to ESRD in 5 years, including those who received immunosuppressive therapy. It was found that the initial serum creatinine (SCr) concentration was the strongest risk factor for kidney failure. Using logistic curves, the previous studies developed a simple model based on SCr concentration to predict the outcomes of crescenticIgA nephropathy. In this model, a plot of the association between the probability of ESRD and the initial SCr formed an S-shaped curve. Patients with early stage disease (SCr<2.7 mg/dL, the first turning point) had a good prognosis, with <25% of patients progressing to ESRD during follow-up. In contrast, patients with SCr>6.8 mg/dL (600 μmol/L, the second turning point) were less likely to recover from chronic dialysis, even after aggressive immunosuppressive therapy. Our patients had an initial serum creatinine level of 1.2 mg/dl. However, GFR is children is calculated differently than in adults.In addition, there was a difference in the type of IgA nephropathy as he did not have crescentic IgA, making the S-shaped curve less applicable to our patient.

Upon presentation to our hospital, the patient had a GFR of 33.45 and a high urea level of 11.2 mmol/L. Urinalysis showed +1 protein, and a WBC count of 3 and RBC count of 17. C3 level was 1.21 g/L and C4 level was at 0.43 g/L. First, we hypothesized that this elevation in creatinine level was due to blood clots in the renal glomeruli as we started the patient on double maintenance to dilute the urine and reverse the cause of post-renal kidney failure.Unfortunately, this was not the case as kidney ultrasonography showed evidence of end-stage kidney disease (ESKD)because of the loss of cortical medullary differentiation bilaterally, and kidney biopsy showed diffuse global sclerosis with diffuse fibrosis in>90% of kidney tissues, which supports our hypothesis that the patient would develop chronicity. Biopsy findings were classified according to the Oxford classification as MO E0 S1 T2. Mesangial cells and endocapillary hypercellularity were very few , which may be because the biopsy was performed when chronic changes had already occurred. Despite these unfavorable findings from the kidney biopsy, we preferred to initiate a trial of immunomodulation therapy to preserve any remaining kidney tissue. Thus, the patient was started on pulse methylprednisolone, with three subsequent doses followed by oral prednisolone 60 mg/m^2/day and mycophenolate mofetil every other day for 5 months. However, there was no indication of improved kidney function as his last SCr level was 1.5 mg/dL. Therefore, this supports our initial hypothesis that the patient developed chronic kidney Stage 3B. The patient is now on supportive therapy for chronic kidney disease, including anti-hypertensives.

In the comparison between our case andthe case reported by Akkad et al., we observed the following differences:

Domain of comparison	**Case reported byAkkad et al. (2016)**	**Our case (2018)**
Biopsy finding	Cellular/fibrocrescents, fibrinoid necrosis, and global sclerosis were suggestive of active glomerular injury in a background of cortical chronic injury.	Presence of IgA, IgG (only podocyte staining was seen along with a very large glomerulus), mild segmental C3, rare intramembranous deposits, many mesangial deposits without capillary deposits, reabsorbing lucent deposits, and intramembranous deposits.
ANCA	+	-
SCrlevel upon presentation:	>16 mg/dL	1.2 mg/dL
Age of patient at presentation:	**20 years old**	**5 years old**

There are some clinical and laboratory parameters that aid in the classification of disease severity, and in our patient, the predictors of poor prognosis are high SCr, decreased GFR, as well as elevated blood pressure (>140/90 mmHg), and persistent proteinuria. In a study of 2,270 patients with IgA nephropathy in Japan, the 7-year cumulative incidence of ESRD was markedly increased in patients with high SCr at diagnosis (P value <0.001) [5].
Clinical features also play a major role in the prognosis of the disease, as some renal biopsy findings are linked to progressive disease.The concurrent use of Oxford histologic classification system with renal biopsy may help in the identification of patients with less favorable renal prognosis [6]. The Oxford classification estimates the risk of developing ESRD at 5 years [7].

The optimal approach forthe treatment of IgA nephropathy is still uncertain [2]. There is no cure for IgA nephropathy despite its clear pathogenesis, and unfortunately, only a few randomized, controlled clinical trials have been carried out on this topic [8].

The treatment of patients with normal blood pressure and who have no major urinary abnormalities is usually unnecessary, as approximately 23% will achieve full remission over the years, with only follow-ups as necessary [2].

The available treatments for patients at risk of renal insufficiency, such asthose with high blood pressure and/or proteinuria (>1g/dL), include angiotensin-converting enzyme inhibitors for the control of hypertension. Corticosteroids are administeredto patients with proteinuria >1 g/dL, as these were shown to increase renal survival. Immunosuppressive medications are only recommended for patients with rapidly progressive disease. Although the benefits of fish oil are not significant, they remain an option for patients at risk of progression or who have slowly progressing renal failure. Anticoagulant and antiplatelet drug use are not evidence-based but are still better than no treatment, as found in some studies [9].In conclusion, IgA nephropathy is a common glomerular disease worldwide. However, it is rare for IgA nephropathy to present as chronic kidney disease at initial clinical presentation. The presence of chronic changes should be considered when there is a rapid deterioration of renal function and renal biopsy should be done to elicit acute and chronic changes because this will aid in decision-making for optical pharmacological treatment and prognostication.

DECLARATIONS:

Ethical approval and consent to participate:
Permission to conduct the study was granted by the Biomedical Ethics Research Committee of King Abdulaziz University. Detailed written informed consent was obtained from the parents/caregivers prior to inclusion.

Consent for publication:
Detailed written informed consent was obtained from the parents/caregivers prior to publication.

Availability of data and materials:
No data have been submitted to any open access databases. All data supporting the study are presented in the manuscript or available upon request.

Competing of interest:
The authors declare that they have no competing interest regarding the publication of this paper.

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Authors' contribution:
AA: wrote the discussion; BB: wrote the clinical presentation; RA: helped to write the clinical presentation; MF: helped to organize the manuscript and references; WA helped to review the literature and collect the clinical data; OS: a senior author who reviewed and revised the manuscript

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