Profile and outcomes of children presenting with infection-related glomerulonephritis

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ABSTRACT

Poststreptococcal acute glomerulonephritis (PSGN) was reported as the most common cause of GN in children. There has been, however, a marked shift in epidemiology in recent years with the decline in poststreptococcal cases. Various other bacteria and rarely viral and fungal infections are associated with GN. More cases are now being reported with ongoing infection at the time GN is diagnosed. Therefore, the term infection-related GN (IRGN) is now being used increasingly. We describe the clinical profile and outcomes of children presenting with IRGN at a tertiary care center in the past 1 year. 5 children presented with features of GN. Only 1 of the 5 had the course typically described in PSGN. Two patients also had a post-infectious course but with some unusual features. Another patient had an ongoing systemic infection in the form of pneumonia at the time of onset of features GN, while our fifth patient developed an infection-related GN with dengue illness.

Key words: *Glomerulonephritis, Infection related, Post-infectious*

Glomerulonephritis (GN) is a clinical syndrome of hematuria, hypertension, proteinuria, and edema [1]. Conventionally, poststreptococcal acute GN (PSGN) was believed to be the most common cause of GN in children with median age of presentation being 6–8 years. A typical patient had features of mild GN following a latent period of 7–21 days after the streptococcal infection with the absence of systemic features [2]. There has been, however, a marked shift in epidemiology in recent years with the decline in poststreptococcal cases [3]. Various other bacterial infections including Staphylococcal infections and rarely viral and fungal infections are associated with GN [4,5]. Furthermore, more cases are now being reported with ongoing infection at the time GN is diagnosed, rather than after a characteristic latent period. Therefore, the term infection-related GN (IRGN) is now being increasingly used [6].

We describe the clinical profile and outcomes of children who presented with acute GN with evidence of infection during or in the previous 1 month at a tertiary care center in past 1 year. The evidence of infection was either throat swab for Gram stain or culture positivity and/or clinical features of infection in the form of high fever with polymorphonuclear leukocytosis, raised C-reactive protein (CRP), or procalcitonin. Five children presented with features of GN following or during different infections during the study period January 2017–December 2018.

Patient I

A 6-year-old girl was brought into the hospital with periorbital edema and gross hematuria of 2 days duration with a history suggestive of sore throat 2 weeks back. On examination, the child had Stage I hypertension with urea of 58 mg/dl and creatinine 0.8 mg/dl. The serum C3 was 57 mg/dl. The serum antistreptolysin O (ASO) was raised (>200 IU/ml). However, there was no oliguria and the edema and hematuria resolved on its own over the next 5 days. The child became normotensive in the next 2 weeks with normal renal function tests. Her C3 was also found to be normal when repeated at the end of 12 weeks. She continues to be asymptomatic at follow-up with normal blood pressure and renal function tests.

Patient II

A 7-year-old boy had skin pustules over the lower back for which he was treated with oral amoxicillin for 5 days. 2 weeks after this episode, he developed gross hematuria with oligoanuria. His renal function tests were severely deranged (urea/creatinine of 184/7.6 mg/dl) and he had Stage II hypertension with anasarca. The C3 levels of the child and ASO repeated twice were normal. The patient underwent four sessions of intermittent hemodialysis due to persisting anuria and hyperkalemia. Renal biopsy was suggestive of diffuse proliferative GN with C3

and immunoglobulin G staining in a garland like a pattern on immunofluorescence studies as shown in Fig. 1

The child was also given 3 pulses of intravenous methylprednisolone and continued on 1 mg/kg/day of steroids for 4 weeks followed by an alternate day in view of persisting nephrotic range proteinuria and hypertension. At the end of 6 weeks, the 24 h urine protein was 2.4 g/day with urea and creatinine of 54 and 0.9 mg/dl, respectively, normal C3 levels and Stage I hypertension which was well controlled with 0.3 mg/kg/day of Amlodipine. He was started on Mycophenolate mofetil at 800 mg/m^2 which is planned to continue for 12–24 months. On follow-up, 1 year after the onset of the disease, the child had urea of 28 mg/dl, creatinine of 0.6 mg/dl, normal blood pressure, and urine protein creatinine (Up/Ucr) ratio.

Patient III

A 12-year-old boy presented with periorbital edema, mild pedal edema, and ascites along with gross hematuria. On examination, the child had Stage II hypertension with urea of 84 mg/dl and creatinine 0.9 mg/dl. The serum C3 was 26 mg/dl (normal 70–110 mg/dl). There was a history of coryza with a mild sore throat 10 days before, for which he had been treated symptomatically. The serum ASO and antinuclear antibody were normal. The Up/Ucr ratio was 3.4 mg/mg, and the 24 h urine collection for protein was 4.4 g. He was found to have oliguria in the hospital with urine output of 0.5 ml/kg/day for first 2 days after admission which improved over the next few days, and the edema and gross hematuria also resolved on its own over next 7–10 days. The child became normotensive after 4 weeks during which he was given Amlodipine @ 0.3 mg/kg/day. His renal function tests also recovered completely. The repeat 24 h urine collection for protein was 760 mg. His C3 was 72 mg/dl at the end of 12 weeks. He was asymptomatic at the last follow-up visit with normal blood pressure and renal function tests. The plan is to perform kidney biopsy in case of persistent proteinuria, low complement levels, or if the child develops hypertension.

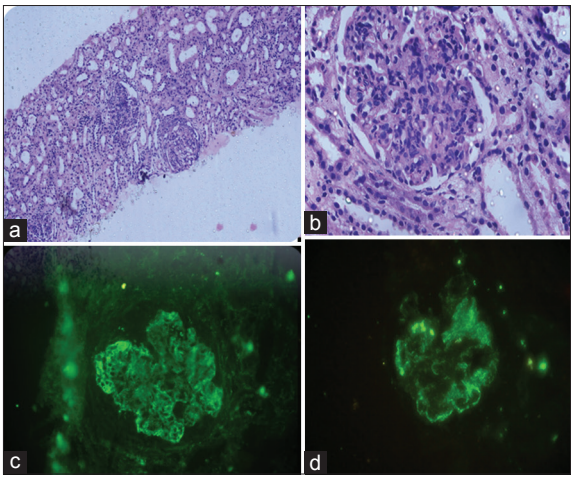

Figure 1: (a-d) Diffuse proliferative glomerulonephritis on light microscopy and strong C3 and immunoglobulin G staining on immunofluorescence on renal biopsy of patient 2

Patient IV

A 14-year- old girl presented with fever and cough of 7 days duration. She was found to have crepitations in the left middle and inferior axillary areas and mild periorbital edema. Her urine output in the first 24 h of admission was 0.9 ml/kg/day which reduced further to 0.4 ml/kg/day of cola colored urine over the next 24 h. Her investigations revealed in left middle zone consolidation on chest X-ray, a raised total leukocyte count of 18,600/mm^3 with 82% neutrophils, raised CRP and a urea/creatinine of 96/2.8 mg/dl (normal urea/creatinine 20–40/03 mg/dl). She was started on ceftriaxone along with fluid restriction and amlodipine. *Klebsiella pneumoniae* was found on blood culture and a C3 value of 36 mg/dl (normal >70 mg/dl). Her urine examination showed dysmorphic red blood cells, granular casts, and 3+ proteinuria.

On day 3, the child developed hyperkalemia with urea and creatinine of 156 and 4.2 mg/dl, respectively, as well as hypertension. The child was started on peritoneal dialysis (PD) using a stiff PD catheter. Her urine output began improving after 48 cycles of PD along with gradual improvement in renal function tests. She became afebrile after 7 days of intravenous antibiotics. At the end of 4 weeks of her illness her renal function tests improved (urea 48 mg/dl and creatinine 0.6 mg/dl) with normal C3 values of 76 mg/dl and a 24 h urine collection showing protein of 356 mg. She continues on a monthly follow to have a normal renal function with no hypertension or proteinuria.

Patient V

A 5-year-old boy was admitted with a history of fever, headache, and joint pains for 3 days. On examination, he had splenomegaly of 2 cm. Investigations revealed a platelet count of 100×10^3/mm^3 and a positive nonstructural protein 1 antigen and immunoglobulin M against Dengue virus. He was managed with oral paracetamol and oral fluids. Over the next 24 h, he developed cola colored urine with fall in his urine output to 0.9 ml/kg/day. The child, however, continued to be normotensive. Investigations revealed normal renal function tests, a hematocrit of 30% with a hemoglobin of 10 g% and platelet count of 1.22×10^3/mm^3. The serum C3 was found to be 62 mg/dl. There was no further fall in platelet count or hemoconcentration, and the child became afebrile after 48 h. His urine output also improved to >2 ml/kg/day with normal blood pressure and renal function tests. His C3 also normalized when repeated at the end of 12 weeks.

DISCUSSION

Post-infectious GN (PIGN) is an immunologically mediated glomerular injury triggered by an infection. Cases of PSGN with acute renal failure; usually as a result of a rapidly progressive course and crescentic GN, and represent 1% of the total number of cases of PSGN [7]. This was also seen in a study conducted in Indian children with PIGN in which only 3/72 cases progressed to AKI Stage III as per the AKIN criterion and only 1 required renal replacement therapy (RRT) [8]. At our center of all the children

who were admitted with IRGN, only one of the five had a course typically described in PSGN. This patient had a latent period of approximately 2 weeks following a sore throat with raised ASO titers, even though no organism was isolated, probably due to early administration of oral antibiotics. This patient had a mild course and resolved with conservative management alone.

Our second patient had PIGN with some unusual features and a severe course. At disease onset, we could not demonstrate low complement levels. Normal complement levels during a PSGN have been reported rarely during a PSGN [9]. The child also an unusually severe course with severe azotemia, hypertension, and fluid overload requiring RRT. This is seen in only approximately 1% of children with PSGN. His biopsy was suggestive of diffuse proliferative GN with no crescents. In view of the persistent nephrotic range proteinuria and severity of the disease, we continued the child on alternate day prednisolone and mycophenolate mofetil. The question that remains unanswered in such cases is whether it was truly a PIGN or an infection triggered disease of the unregulated alternative complement pathway activation, the C3 GN [10]. This would become more apparent by child's subsequent disease course and genetic testing for underlying mutations or deficiency in the complement proteins.

Similarly, our third patient though had a post-infectious course, but the preceding infection was only mild coryza, following which the patient developed nephrotic range proteinuria and very low C3 levels. He improved over the subsequent 8–12 weeks, but the plan is to monitor him closely for complete resolution failing which a biopsy will be planned. This is to rule out an infection triggered C3GN as mentioned above.

The fourth patient had an ongoing systemic infection in the form of pneumonia at the time of onset of GN. Her blood culture showed *Klebsiella pneumonia* which has only rarely been described to cause PIGN or IRGN [11]. She had a rapidly worsening azotemia with fluid overload and hyperkalemia necessitating RRT. However, the child improved as her systemic infection responded to antibiotics and showed a remarkably rapid renal recovery thereafter and has remained asymptomatic on follow-up with normal renal functions and normal blood pressure.

Our fifth patient developed an infection-related GN with Dengue illness, and while he only had a mild dengue disease, it triggered a typical IRGN in him with hematuria, proteinuria, and low C3. This child, however, had mild disease with no hypertension or azotemia and a self-resolving course. GN with dengue has been reported but is relatively rare with acute kidney injury due to acute tubular necrosis accompanying dengue shock syndrome being more common [12].

We acknowledge that being a referral hospital, our patients may represent the more severe or more unusual end of the spectrum. Nevertheless, they highlight the changing epidemiology of IRGN in children worldwide and emphasize the need for early diagnosis, appropriate management, and close follow-up even after apparent resolution, to identify children in whom infection may have triggered an immune or alternate complement pathway mediated GN.

CONCLUSION

Infection-related GN is relatively common in children and may be caused by various bacteria and viruses. Clinical severity maybe variable but good outcomes are observed with timely and appropriate interventions.

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