

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS IN CHILDREN

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ABSTRACT

Rapidly progressive glomerulonephritis (RPGN) is a rare syndrome in children and one of the nephrology emergency which needs special attention. Rapidly progressive glomerulonephritis is determined by symptoms and signs of glomerulonephritis (GN); edema, hypertension, gross hematuria, and rapid loss of renal function. Early diagnosis and appropriate treatment play a critical role in saving renal function and preventing permanent glomerular damage. Diagnosis was made based on clinical and laboratory findings. We reported two cases of RPGN in an eleven year old boy and an eight year old boy. The patient came to the pediatric outpatient clinic at sanglah hospital with chief complaint dark "cola colored" urine. Laboratory work up showed proteinuria, erythrocyturia, decrease of C3 and normal C4 complement level, increased serum urea and creatinine level and loss of renal function in a few days with glomerular filtration rate decreased. Based on clinical and laboratory findings, the patient was diagnosed as rapidly progressive glomerulonephritis. The patient was given methylprednisolone pulses for 3 days, followed by high dose oral methylprednisolone. Prognosis of the patient was good. [MEDICINA 2015;46:46-51].

Keywords : rapidly progressive glomerulonephritis, children

GLOMERULONEFRITIS PROGRESIF CEPAT PADA ANAK

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ABSTRAK

Glomerulonefritis progresif cepat (GNPC) adalah sindrom yang jarang terjadi pada anak-anak dan merupakan salah satu kegawatdaruratan nefrologi yang perlu mendapat perhatian khusus. Glomerulonefritis progresif cepat ditentukan oleh gejala dan tanda glomerulonefritis (GN) yaitu edema, hipertensi, hematuria gross, dan turunnya fungsi ginjal. Diagnosis dini dan pengobatan yang tepat memberi peran penting dalam menyelamatkan fungsi ginjal dan mencegah kerusakan glomerulus permanen. Diagnosis dibuat berdasarkan temuan klinis dan laboratorium. Kami melaporkan dua kasus anak berusia sebelas tahun dan delapan tahun dengan keluhan buang air kecil berwarna gelap. Hasil laboratorium menunjukkan proteinuria, eritrosituria, penurunan C3 dan C4 komplemen tingkat normal, peningkatan urea serum dan kadar kreatinin dan hilangnya fungsi ginjal di beberapa hari dengan laju filtrasi glomerulus menurun. Berdasarkan temuan klinis dan laboratorium, pasien didiagnosis sebagai glomerulonefritis progresif cepat. Pasien diberi pulsa methylprednisolone selama 3 hari, diikuti dengan dosis tinggi metilprednisolon. Prognosis pada pasien ini baik. [MEDICINA 2015;46:46-51].

Kata kunci: glomerulonefritis progresif cepat, anak

INTRODUCTION

Rapidly progressive glomerulonephritis (RPGN) is a rare syndrome in children and one of the nephrology emergencies which needs special attention. Rapidly progressive glomerulonephritis is determined by symptoms and signs of glomerulonephritis (GN); edema, hypertension, gross hematuria, and rapidly progressing acute renal failure (severe decrease in glomerular filtration rate presents

as oliguria or anuria, and increased serum levels of BUN and creatinine). It also characterized by rapid loss of renal function (GFR<50% within 3 months) with histological finding of crescent lesion which usually involves >50 % of glomeruli. Early diagnosis and appropriate treatment play a critical role in saving renal function and preventing permanent glomerular damage.¹

Rapidly progressive glomerulonephritis is an uncommon disorder in children with unknown

precise incidence. Although adolescents are affected more commonly, RPGN may occur in younger children, including infant. The increase incidence of RPGN may be observed during large epidemic of streptococcal infection, since severe acute post-streptococcus glomerulonephritis may lead to RPGN.²

Rapidly progressive glomerulonephritis can be primary or secondary. Primary RPGN is an autoimmune disease which is divided into three immunopa-

thologic categories: Type 1; glomerulonephritis with antibodies directed against the glomerular basement membrane (GBM) (anti-GBM mediated GN), Type 2; immune-complex induced glomerulonephritis, Type 3; Antineutrophil cytoplasmic antibody associated glomerulonephritis (ANCA-associated glomerulonephritis or pauci-immune GN). Rapidly progressive glomerulonephritis type 1 and 2 are responsible for 10-20 % and 40 % of all cases respectively. Rapidly progressive glomerulonephritis type 2 can be found in different forms of systemic disease such as post infectious GN (PSGN), Ig-A nephropathy, Henoch-Schönlein purpura (HSP), SLE, membranous GN (MGN) or membranoproliferative GN (MPGN).³ Secondary form occur in any form of severe glomerulonephritis including membranoproliferative GN, IgA nephropathy, post infectious GN, and systemic lupus erythematosus (SLE). A few cases of idiopathic immune complex-mediated RPGN have been reported worldwide. We present one of pasien with RPGN as the possible diagnosis to know about underlying mechanism of the diseases.⁴

CASE ILLUSTRATION

Case I

PCS, an eleven year old boy came to the pediatric outpatient clinic at Sanglah hospital on February 11th, 2012 with chief complaint dark "cola colored" urine for four days. Previous health history was unremarkable until 14 days ago when he started to have sore throat and fever. Upon admission at our hospital, sore throat and fever have already resolved. He met a physician at that time and the symptoms subsided after taking oral antibiotic and paracetamol. Four days before his admission facial puffiness and edema were noted, but there was no edema of his

hands or genitalia. There was no history of nausea or vomiting. He had dark brown urine and he has not been voiding as much as usual, only 2 times in the past 24 hours. There was no dysuria and polyuria. His appetite had been poor although his liquid oral intake was well. He had complained of headache since four days before admission and constantly held his head, without any symptoms of decrease consciousness, seizure or hearing loss. There was no family history of hematuria, edema, hypertension nor renal failure.

He was born aterm vigorously and via spontaneous vaginal delivery at a local midwife, with birth weight of 3000 grams. There were no data of his birth height, head circumference, and thoracic circumference. No feasible abnormality was found. His mother was 33 year old (G2P1001). During her pregnancy, there was no history of fever, rash other serious disease, or taking medication. She had antenatal care at a local midwife regularly.

The immunization history was complete according to the recommended immunization plan by government. His growth and development were normal. He was fully breastfed for 6 months of age and began eat milk porridge upon 6 months old.

He was the youngest child in his family. None of his family member had the same complaint. The boy and his family lived in a permanent house. The father worked as a labor. He was loved and cared by his parents and siblings.

Patient was compos mentis on physical examination. Pulse rate was 100 times per minute and regular, respiratory rate was 28 times per minute, axillary temperature was 37°C and blood pressure was 150/100 mmHg. His body weight was 45 kgs body length was 140 cms and his ideal body weight was 32 kgs. Thus, according to the waterlow criteria his nutritional status was 140 %

(overweight). The head was normocephaly. The hair was fine and black. The conjunctiva was not anemic, the sclera was not icteric. There was periorbital edema. There was no abnormality on ears. There was no enlargement of lymph node nor nuchal rigidity.

The chest examination revealed no precordial bulging, ictus cordis was palpable on the 5th intercostal space on the left midclavicular line. There were no thrill and no right ventricular heave. On auscultation, the first and second heart sound were normal, without murmur. The movement of both sides of the chest was symmetrical. Vesicular respiratory sounds were noted, without wheezing or rales. The abdominal examination revealed no hepatomegaly and no splenomegaly, no distension, no ascites, and bowel sound was normal. There was no skin rashes nor impetigo scars. The extremities had pretibial edema and genitalia had scrotal edema.

Based on the clinical manifestations, the working diagnosis was nephritic syndrome et causa suspected of acute poststreptococcal glomerulonephritis dd/ postinfectious glomerulonephritis with second grade hypertension and overweight. We performed laboratory examinations (urinalysis and serology). Urinalysis showed proteinuria 500 mg/dl (+4) and erythrocyturia 250 ery/ul (+5) with granula cast. Complete blood count showed a normochromic normocytic anemia with hemoglobin level 9.8 g/dl, mean corpuscular volume (MCV) 75 fl and mean cell hematocrit concentration (MCHC) 33.4 g/dl. Serum sodium was 122 mmol, serum potassium 5.0 mmol, serum chloride 91.1 mmol, serum calcium 7.4 mmol. Plasma bicarbonate was 18 mmol. There was a decrease of glomerular filtration rate (17.4) with creatinine serum 4.31 mg/dl, blood urea nitrogen 54.5 mg/dl and albumin 1.7 mg/dl, decrease C3

complement level (23) and normal C4 complement level (34). Anti-streptolysin-O (ASO) <200. Throat swab found *Streptococcus viridans*.

Based on clinical and laboratory examination, the patient was diagnosed as nephritic syndrome et causa postinfectious glomerulonephritis with acute kidney injury and second grade hypertension and overweight. Further renal biopsy was not performed. The patient was given antibiotic therapy (cefotaxim injection), angiotensin-converting enzyme (ACE) inhibitors, and furosemid. In addition, the parents were given counseling regarding RPGN and its related issue, daily nutritional intake in order to avoid obesity, low salt diet and protein diet maintenance as a nutritional therapy. The patient was planned for urinalysis, vital sign and urine output monitoring.

On the second day of hospitalization, he had periorbital and pitting pretibial edema. His urine output decreased from 1.1 to 0.7 ml/hour and serum urea and creatinine level increased (60 mg/dl, 6.24 mg/dl, respectively) and glomerular filtration rate

decreased (12.3). Second grade hypertension persisted.

On the third day of hospitalization, he complained of headache (constantly held his head) without any symptoms of deteriorating consciousness, seizure, or hearing loss. Second grade hypertension was still noted until 5th day of hospitalization with the highest blood pressure was 150/100 mmHg. The glomerular filtration rate decreased each day with the highest (15.4) with creatinine serum 4.9 mg/dl, blood urea nitrogen 66 mg/dl. Urine output decreased until 0.6 ml/hour. The ultrasonography examinations was performed and showed mild right hidronefrosis and bilateral nephritis. The ultrasonograph features was presented below in **Figure 1**.

On the 4th day of hospitalization, the patient was diagnosed as rapid progressive glomerulonephritis with acute kidney injury and second grade hypertension and overweight. intravenous methylprednisolone (10 mg/kg/day) was given for RPGN treatment for 3 days. Further renal biopsy was not performed.

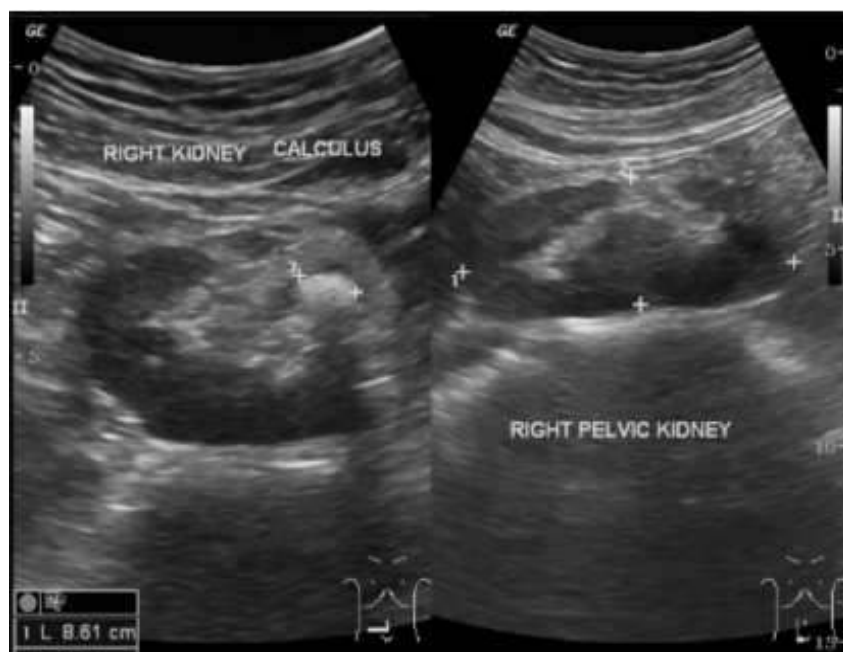


Figure 1. Ultrasonograph showing mild hidronefrosis and nephritis bilateral.

On the 7th day of hospitalization, oral methylprednisolon (2mg/kg/day) was given until 4 week and tapered 0.5mg/kg daily by 3 months and alternating day methylprednison for 6 to 12 months. Second grade hypertension was still persisted, without edema. Urinalysis showed proteinuria 25 mg/dl (+) and erythrocyte 0-1/lp.

He was discharged on the 12th day of hospitalization. At that time, first grade hypertension with normal glomerular filtration rate were still found. Angiotensin-converting enzyme inhibitors and furosemide was still given and blood pressure measurement was done daily. Four days after discharged, the patient came to Sanglah pediatric outpatient clinic and no hypertension, edema, or abnormality in urinalysis were found. Serum creatinine was normal. Oral antihypertension was gradually reduced. Nevertheless, blood pressure and hematuria were still monitored.

Three week after the RGPN symptoms appear, he complained of recurrent gross hematuria and first grade hypertension. Urinalysis showed abundant dysmorphic erythrocyte, proteinuria of 500 mg/dl (+4). Complete blood count found leukocytosis 14.4 K/ul, hemoglobin level 11.4 g/dl and platelet 315 K/ul. There was normal glomerular filtration rate with normal creatinine serum and blood urea nitrogen. He was treated at home with oral ACE inhibitors, diuretic, and he controlled to our outpatient clinic one week after with normal urinalysis and normal complete blood count. The prognosis of this patient was good.

Case II

KBW, an eight years old boy came to the pediatric outpatient clinic at Sanglah hospital on June 15th, 2014 with chief complain of oligouria since 10 hours before admission. He had dark brown

urine and he has not been voiding as much as usual, only 2 times in the past 24 hours. There was no dysuria and polacuria. He had intermittent fever since June 11th, 2014, no cough and no sore throat, he met a physician and was given oral antibiotic and paracetamol. He vomited 10 hours before admission, 4-5 times in a day, 5-10 ml each vomit, containing food and beverages that he consumed before. His parents said no edema of his orbita, extremities or genitalia. His appetite had been poor although his liquid oral intake was still well. He had complained headache since four days before admission and constantly held his head, without any symptoms of deteriorating consciousness, seizure or hearing loss. There was no family history of hematuria, edema, hypertension nor renal failure.

He was born at term, spontaneously, and vigorously at a local midwife, with birth weight of 3200 grams. There were no data of his birth height, head circumference and thoracic circumference. No feasible abnormality was found.

The immunization history was complete according to the recommended immunization plan by government. His growth and development was normal. He was fully breastfed 6 month of age and began eat milk porridge upon 6 months old, adult food since the age of 12 months.

He was the second child in his family. None of his family member had the same complain. The boy and his family lived in a permanent house. The father worked as a private employees. He was loved and cared by his parents and siblings.

On physical examination, he was compos mentis, pulse rate was 88 times per minute and regular, respiratory rate was 28 times per minute, axillary temperature was 36.7°C and blood pressure 120/70 mmHg. His body weight was 20 kgs, body length was 120 cm, and

his ideal weight was 23 kg. Thus, according to the waterlow criteria his nutritional status was 87% (underweight). The head was normocephaly, the hair was fine and black. The conjunctiva was not anemic, the sclera was not icteric. There was no periorbital edema. There was no abnormality on ears. There was no enlargement of lymph node nor nuchal rigidity.

The chest examination revealed no precordial bulging, ictus cordis was palpable on the 5th intercostal space on the left midclavicular line. There were no thrill and no right ventricular heave. On auscultation, the first and the second heart sound were normal, without murmur. The movement of both sides of the chest was symmetrical. Vesicular respiratory sounds were noted, without wheezing or rales. The abdominal examination revealed no hepatomegaly and no splenomegaly, no distension, no ascites, bowel sound was normal. There was no skin rashes or impetigo scars. There was no pretibial edema, genitalia was no scrotal edema.

Based on clinical manifestations, our working diagnosis was nephritic syndrome et causa suspect of acute poststreptococcal glomerulonephritis, first grade hypertension, acute kidney injury stadium failure and underweight. We did laboratory examinations; urinalysis and serology. Urinalysis showed proteinuria 500 mg/dl (+4) and erythrocyturia 250 ery/ul (+5) with granula cast. Complete blood count showed leukocyte 6,24 mg/dl, hemoglobin level 11.4 g/dl, thrombocyte 324 mg/dl, serum sodium 126 mmol, serum potassium 4.0 mmol, serum chloride 95 mmol. There was decrease of glomerular filtration rate (23.57) with creatinine serum 2.8 mg/dl, blood urea nitrogen 112 mg/dl and albumin 2.7 mg/dl, cholesterol total 194 mg/dl, decrease of C3 complement level (18) and normal C4 complement

level (35). Anti streptolysin-O was negative. Throat swab was not performed.

Based on clinical and laboratory examination, the patient was diagnosed as nephritic syndrome et causa postinfectious glomerulonephritis with acute kidney injury stadium failure with first grade hypertension and underweight. The patient was given antibiotic therapy (cefotaxim injection), ACE inhibitors, and furosemid. In addition, the parents was given counseling regarding RPGN and its related issue, daily nutritional intake to avoid malnutrition, low salt diet, and protein diet maintenance as a nutritional therapy. The patient was planned for daily urinalysis, vital sign and urine output for monitoring.

On the second day of hospitalization, he vomited 3 times, vomit contained food and beverages he had consumed, volume of 50 ml. His urine output decreased from 0.6 to 0.4 ml/hour and second grade hypertension persisted.

On the third day of hospitalization, he complained of headache, constantly held his head, without any symptoms of decrease consciousness, seizure, or hearing loss. First grade hypertension was still appeared until 5th day of hospitalization with the highest blood pressure was 130/80 mmHg. The glomerular filtration rate was decreased each day with the lowest (7.5) with creatinine serum 8.8 mg/dl, blood urea nitrogen 84 mg/dl. Urine output decreased until 0.4 ml/jam. The ultrasonography examinations was performed, showed acute bilateral nephritis and cystitis. The ultrasonograph presented features was presented below in **Figure 2**.

On the 4th day of hospitalization, the patient was assessed with acute kidney injury stadium failure et causa rapid progressive glomerulonephritis with first grade hypertension and

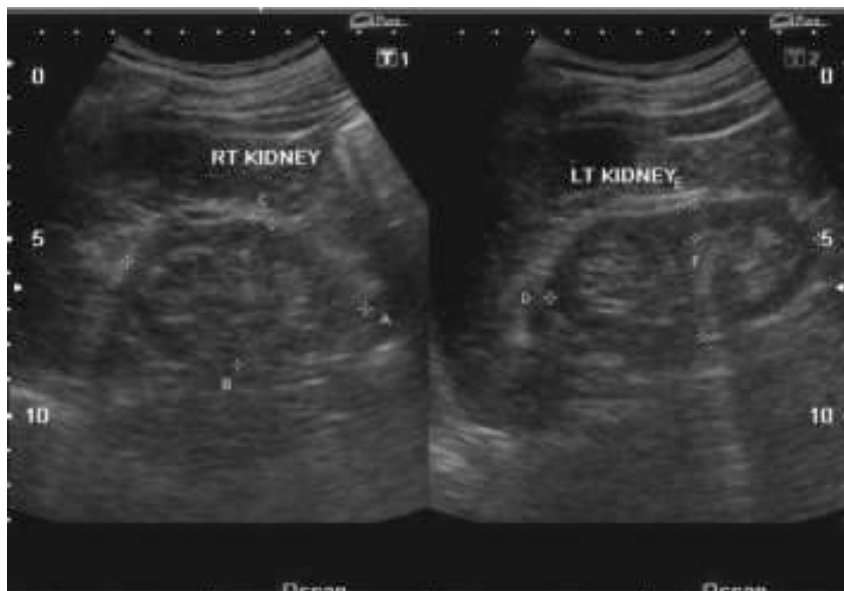


Figure 2. Ultrasonography showed acute bilateral nephritis and cystitis.

underweight and was given intravenous methylprednisolone (15 mg/kg/day) for RPGN treatment for 3 days. Further renal biopsy was not performed.

On the 7th day of hospitalization, oral methylprednisolone (1,5mg/kg/day) was given until 4 weeks and tapered 0.5mg/kg daily by 3 months and alternating day prednisone for 6 to 12 months. First grade hypertension was still found, without edema. Urinalysis showed proteinuria 25 mg/dl (+) and erythrocyte 0-1/lp.

He was discharged after 11 days of hospitalization. At that time, first grade hypertension with normal glomerular filtration rate were still found. Angiotensin-converting enzyme inhibitors and oral methylprednisolone were still given and blood pressure measurement was still done daily. He was treated at home with oral methylprednisolone, ACE inhibitors, and he visited our outpatient clinic one week after discharge. The prognosis of this patient was good.

DISCUSSION

Rapidly progressive glomerulonephritis is a rare syndrome in children, characterized by clinical features of glomerulonephritis (GN) and rapid loss

of renal function (50 %) decrease in GFR over days to weeks. The manifestation of RPGN varies included proteinuria and macroscopic hematuria (60%-90%), oliguria (60%-100%), hypertension (60%-80%) and edema (60 %-80%) or increased serum creatinine to life threatening renal failure.¹ The incidence of RPGN in children is not known. Crescentic glomerulonephritis comprises approximately 5% of unselected renal biopsies in children.²

Rapidly progressive crescentic glomerulonephritis causes vary widely as immune complex glomerulonephritis, postinfectious glomerulonephritis, poststreptococcal nephritis, infective endocarditis, staphylococcus aureus sepsis, systemic lupus erythematosus, henoch schonlein purpura, juvenile rheumatoid arthritis, pauci immune crescentic glomerulonephritis.^{1,3} In case I and II, the etiology of rapidly progressive crescentic glomerulonephritis at the time of admission was *Streptococcus viridans*. Pathogenesis of rapidly progressive crescentic glomerulonephritis are defined as the presence of two or more layers of cells in Bowman's space. The chief participants in

formation of crescent are coagulation protein, macrophages, T cells, fibroblast and parietal and visceral epithelial cells. Perturbations of humoral immunity as well as the Th1 cellular immune response contribute to the pathogenesis.⁴

The manifestation of rapidly progressive crescentic glomerulonephritis varies from asymptomatic proteinuria and hematuria, or increased serum creatinine to life threatening renal failure or hypertensive crisis. Nephritic features as edema, hypertension and gross hematuria, oliguria, proteinuria and rapid loss of renal function are also frequently present. Even in asymptomatic cases, progressive renal disease and declining kidney function is common. These 2 cases reported here illustrate these typical presentations, both the children had oliguria, nephritis, and acute kidney injury.^{1,3}

Diagnostic evaluation of RPGN are complete blood counts, peripheral smear for type of anemia, reticulocyte count, blood level of urea, creatinine, electrolytes, calcium, phosphate, urinalysis: proteinuria, microscopy for erythrocytes and leukocytes, casts, complement (C3,C4), antistreptolysin O, antinuclear antibody, antinuclear cytoplasmic antibodies (ANCA), renal biopsy (light microscopy, immunofluorescence, electron microscopy), low complement 3 (C3) is seen in postinfectious glomerulonephritis, SLE and membranoproliferative glomerulonephritis. Positive antistreptolysin O titers suggest streptococcal infection in the past 3 months. Elevated levels of ANCA suggest underlying vasculitis cause and are present in most patients with pauci-immune crescentic glomerulonephritis. Renal histological findings in various forms of crescentic glomerulonephritis are similar. Current classification of RPGN is based on nature of immune

deposits seen in the renal biopsy. It is categorized as: immune complex-mediated, anti-glomerular basement membrane (Anti-GMB) antibody mediated or pauci immune. Renal biopsy in immune complex mediated RPGN is characterized by the presence of glomerular immune complex that can be documented by immunofluorescence and electron microscopy. In case I, the complete blood counts showed normochromic normocytic anemia and antistreptolysin-O (ASO) <200. Throat swab found streptococcus viridians but in case II the complete blood counts showed normal, Anti streptolysin-O (ASO) negative. Throat swab was not done. In case I and II the diagnosis of rapid glomerulonephritis based upon clinical finding of nephritic syndrome and laboratory finding decrease of C3 level and normal C4 level, serum urea and creatinine level was increase and loss of renal function in a few days with glomerular filtration rate was decreased. However, laboratory antinuclear antibody, ANCA, and renal biopsy were not performed.^{1,2} The heterogeneity and unsatisfactory outcome of RPGN have led to the use of multiple treatments. Evidence based data are limited and specific treatment guidelines for children are based on data from case series and prospective study in adults.^{1,3}

The specific treatment of RPGN broadly comprises two phases: induction of remission and maintenance. Treatment includes intravenous pulses methylprednisolone (10-20 mg/kg/day) maximum 1g/day for 3 until 6 days, followed by high dose oral steroids (1-2mg/kg/day) for 4 weeks, with tapering to 0.5 mg/

kg/daily by 3 months and alternate day prednisone for 6 to 12 months, cyclophosphamide 500-750mg/m² IV every 3-4 weeks for 6 pulses, plasmapheresis on alternate days for 2 weeks.

The outcome for patients has improved in recent decades, such as that almost 60% to 70 % of patients recover renal function, which is maintained in the long term. The outcome is largely determined by the severity of renal failure at presentation and the promptness of intervention, renal histology and the underlying diagnosis. Patients with post streptococcal crescentic GN have a better prognosis, with most showing spontaneous improvement after supportive management.³ Both cases showed good long-term prognosis.

SUMMARY

We reported a two case of rapidly progressive glomerulonephritis in children. All had evidence of a preceding postinfection glomerulonephritis. The dominant clinical features were oliguria in a setting of nephritis syndrome, with a relentless progression to chronic renal failure. Therapy with steroids, guidelines to the monitoring of children with post-infection glomerulonephritis for the early detection of this uncommon complication are given. The prognosis of these cases were good.

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