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Case Reports

A Newer Approach to the Management of Membrano Proliferative Glomerulonephritis – Experience from A Tertiary Level Hospital, Bangladesh

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Introduction:

Idiopathic Nephrotic Syndrome (INS) is regarded as proteinuria, hypoalbuminemia, generalized oedema and hyper lipidemia[1]. Minimal change disease (MCD) is the commonest (76.6%) histological variant of INS and 90% of them respond with adequate dose of steroid which have normal renal function over the long term[2,3]. Though 3-5% cases of MCD is responsive to steroid initially, but subsequently becomes resistant[4]. Approximately 10% INS are steroid resistant[4]. In the landmark study by International Study of Kidney Diseases in Children (ISKDC); MCD (Minimal Change Disease), FSGS (Focal segmental glomerulous Sclerosis) and MPGN (Membrano Proliferative Glomerulonephritis) each are accounted for about a quarter of children with steroid resistant nephrotic syndrome[2]. Though they are associated with atypical clinical and laboratory findings like hypertension, hematuria, renal insufficiency, low complement level etc with significant glomerular lesion; but during initial episodes, other histological variant of INS may not give any clinical and laboratory clue regarding histological variant. Usually these cases are referred to Pediatric Nephrologist after 4 weeks of steroid therapy, where as the case deserves much earlier attention. The treatment of patients with histological variant other than MCD is more complicated[5]. Till now, no ideal regimen has been identified to treat such type of INS. Different authors have been trying with different regimens and number of medications such as methyl prednisolone, cyclophosphamide, cyclosporine, mycophenolate mofetil with varying results. Recent reports have showed remission rates ranging from 20 to 70% by using these drugs[6]. But, these drugs are associated with various complications and ultimately progress to end stage renal disease[6].

MPGN is a rare variety of childhood nephrotic syndrome, which accounts 5-14% on renal biopsy series and its modalities of treatment and prognosis is also guarded[7,8]. Various studies showed that 52-90% patients developed end stage renal disease (ESRD) within 10-20 years[8]. In 2011, the authors managed three cases of MPGN in the Department of Paediatric Nephrology, BSMMU with injection methyl prednisolone, oral cyclophosphamide along with oral prednisolone. All three patients are still in remission and their renal function status is within normal limit. In Bangladesh, no case report of MPGN is formally studied. So, these three case-scenarios are reported here to increase awareness among the pediatricians regarding rare histological variants of nephrotic syndrome that may behave like MCD initially and also choosing treatment regimen in MCGN cases.

Case Summary:

Case 1:

A 3-year old boy presented with the complaints of generalized swelling, scanty micturation, high fever with cough and cold and respiratory distress. He was second issue of non related parents. His birth history was uneventful, other sibs were in good health. His past history was uneventful.

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On examination (O/E) patient was febrile (temp-102ºF), dyspnoeic (respiratory rate-44/min) edematous and normotensive. His weight (wt) was 16kg (within 75th centile) and height (ht) was 96cm (within 50th centile). Bed-side urine albumin was 4+. Ascities and scrotal edema was present, Crepitations and rhonchi were present on auscultation of chest. Laboratory investigations showed significant proteinuria (albumin ++++) on urine routine examination. 24-hours urinary protein was 3.2gm/m^2/day and neutrophilic leukocytosis (WBC-18,000/cm^3, N-80%) was present on blood picture. Serum Albumin was 12gm/L, serum cholesterol level was 480mg/dl. Chest x-ray was suggestive of pneumonia. Tuberculin test was negative. Complement level and serum creatinine were within normal level. HBsAg and ANA were negative. Findings of ultrasonography of Kidney, Ureter, and Bladder region was normal. Diagnosis was NS (1st attack) with pneumonia.

Case 2:

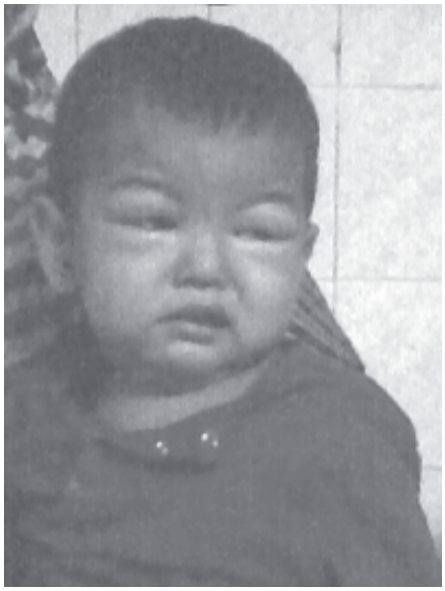
A 2 years and 7 months old girl presented with generalized swelling, scanty micturation, abdominal pain and high grade fever. She was the first issue of non-consanguinous parents. Her birth history was uneventful with insignificant past history. O/E patient was febrile (Temp-103^{0}F), dyspneic, edematous and normotensive. Her weight was 15kg (75th centile) and height was 94cm (within 50th centile). Tenderness was present all over abdomen. Renal angle was non tender and bowel sound was sluggish. Investigation showed: significant proteinuria (albumin ++++), no hematuria or casts on urine R/M/E. 24-hour UTP was 5gm/m^2/day. Blood picture showed neutrophilic leukocytosis (WBC-28,000/cmm, N-88%) Blood culture sensitivity showed no growth. Serum Albumin was 11gm/L and serum cholesterol level was 620 mg/dl. Tuberculin test was negative. Complement level and serum creatinine were within normal level. HBsAg and ANA were negative. No mentionable observation was made from chest x-ray. Findings of ultrasonography of kidney, ureter, and bladder region was normal. Diagnosis was NS (1st attack) with peritonitis.

Case 3:

A 1.5 years' boy presented with generalized swelling, scanty micturation and high grade fever with vomiting. His Birth history was uneventful with insignificant past illness.

O/E patient was febrile, edematous and normotensive. His weight was10.5kg (just above 50th centile) and height was 77cm (within 50th centile) .On Abdomen palpation, mild tenderness was present over flank and renal angle were tender and kidneys were non ballotable. Ascities and scrotal edema was present. Laboratory investigations showed urine Albumin 3+, pus cell-20-25/HPF on urine R/E, urine C/S showed no growth. 24hour UTP was 5gm/day. Complete blood picture showed neutrophilic leukocytosis (WBC 18,000/mm, neutrophil 74%) and serum albumin was 13gm/L. Tuberculin test was negative. Complement level and serum creatinine were within normal level. HBsAg and ANA were negative. No mentionable observation was made from chest x-ray. Findings of ultrasonography of Kidney, Ureter, and Bladder region was normal. Our diagnosis was NS with UTI.

All these three patients were treated with injectable antibiotics, infusion 20% human albumin and other symptomatic drugs along with angiotensin converting enzyme inhibitor. After controlling infection with appropriate antibiotic, oral prednisolone was given in 60mg/m^2/day in divided doses. But none of them showed any response even after four weeks of therapy. After excluding secondary causes of nephrotic syndrome (complement level, anti nuclear antibody, HBsAg and HCV), renal biopsy was done in all three patients and their histopathological findings were compatible with Type-1 Membranoproliferative Glomerulonephritis. As secondary causes were excluded, our histopathological diagnosis was MPGN Type-1 variant of INS. After taking permission from ethical board in BSMMU and proper counseling of the parents, these patients were treated with injection Methyl prednisolone alternate day for 6 pulses. When they were in remission, oral cyclophosphamide (12 weeks), and alternate day oral prednisolone (1.5 mg/kg), was administered that was gradually tapered over 6 month.



Case one underwent in remission after giving 6th pulses of injection methyl-prednisolone (30 mg/kg) on alternate day. Second care was in remission after 3rd dose of alternate day injection methyl-prednisolone. Third care was in remission after 5th dose of injection methyl-prednisolone. Now all three patients are in remission and they are in our follow up clinic.

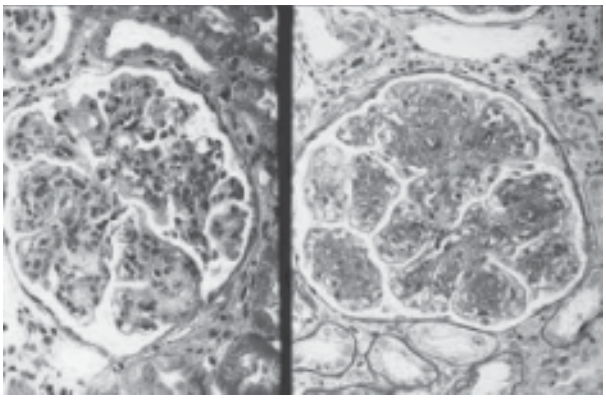


Figure: *Histopathological findings of MCGN Type I (proliferation of mesangial cells with tuft of capillary)*

Discussion:

MPGN is commonly occurs in late-childhood and early adulthood. Diagnosis before six years of age is uncommon[9]. On the contrary, reported three children were within 1.5-3 years of age. Clinical and laboratory findings vary in individual patients with MPGN, which has a progressive course. In many cases patients may be asymptomatic. In 60-80% cases child may present with nephrotic syndrome[10]. Three patients under study were presented with typical clinical features of MPNS. Some authors reported, macroscopic hematuria is more frequently present in MPGN than hypertension and activation of complement system with reduced renal function are the hallmark of MPGN. In 75% cases, complement level is low though clinical features are not the indicators for progression of diseases[10,11]. Cases under study had not any atypical features like as hematuria, hypertension, low complement level or renal insufficiency.

For diagnosis of MPGN, secondary causes should be excluded such as hepatitis B or C, or Lupus nephritis, HIV etc. In cases under study, hepatitis B or C, ANA were negative and complement (3 and 4) level was normal. Adequate randomized controlled trials have yet been reported to give sufficient evidence for treatment of MPGN[12]. Idiopathic asymptomatic MPGN does not require any treatment [10]. Children with MPGN when present with nephrotic syndrome and/or impaired renal function, pulses methyl-prednisolone (PMT) therapy based treatment protocol, would effectively induce more rapid remission[13,14].

Various treatment trials included alternate day steroids, intravenous ($^1/_v$) boluses of steroids or a

combinations of i/v and oral therapy and duration of treatment ranging from 6 month to 12 months[15]. Mendoza and co-workers reported a response rate of 65% in patient with SRNS when treated with a regimen of i/v methyl-prednisolone, with alternate day steroid with an oral alkylating agent[16]. Based upon this experience (Mendoza & Tune) we have treated our three patients. Though the efficacy of oral cyclophosphamide in SRNS patients is limited[17], intravenous cyclophosphamide has been used in resistant patient with response rate 40% to 100%[18]. Three patients under study received oral cyclophosphamide, but they were on remission and one patient developed alopecia. No complications like leucopenia, hemorrhagic cystitis etc were noticed.

Management through combination of cyclophosphamide and alternate day steroid therapy has not been found beneficial in resistant cases[17,19]. Fortunately patients under study, who were getting this regimen at that time, were in remission. No difference observed in renal functions of these patients before and after the end of the pulses methylprednisolone therapy (PMT). One, out of these three patients, developed hypertension which was treated with calcium channel blocker, weight gain was observed in all three patients during the first courses of PMT therapy. None of 3-patients under study developed acute rise in blood pressure, hemorrhagic cystitis, striae, aseptic necrosis, diabetics or gastrointestinal bleeding etc. During treatment period, supportive treatments like nutritional support, albumin infusion, ACE-inhibitor were given as required. All three patients are in remission and leading a normal life with good health.

Conclusion:

Management of patient with MPGN is difficult in developing countries with limited resources. No regimen can guarantee a complete cure. We should keep in mind that in absence of any atypical feature, child may be diagnosed as MPGN and can show better response with combined immunosuppressive therapy.

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