Nephrotic syndrome in Sickle Cell Disease of Western Odisha, India: A case report of five cases


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ABSTRACT: Background- Sickle cell disease causes a distinct pattern of glomerular dysfunction. Subjects with sickle cell disease (SCD) are known to develop many potential functional and structural renal abnormalities. Glomerular hypertension and hyper filtration are thought to play a major role in the development of glomerular disease in subjects with SCD. We reported 5 unusual cases of sickle cell disease presenting as nephrotic syndrome.

KEYWORDS- Nephrotic syndrome, sickle cell disease.

I. INTRODUCTION

Sickle cell Anemia is a monogenetic hemoglobin disorder caused by transversion mutation on 6th codon (GAG>GTT) of beta globin gene of 11th chromosome q arm. As a result on deoxygenise condition hemoglobin tetramer become polymerise to form a rod like structure which make the shape of RBC membrane forming sickle shape. In India prevalence of Sickle Cell Disease is of 1-40 % and The State of Odisha falls in the high prevalence zone (21 -40%) [1, 2].

Many structural and functional abnormalities of the kidney are observed in subjects with sickle cell disease (SCD) [3]. These abnormalities are observed along the entire length of the nephron from the glomerulus to the papillary tip. Because the rate of oxygen consumption by the kidney is very high, a rate exceeded only by that of the heart [3], the kidney is especially sensitive to the vaso-occlusion-induced hypoxia that can result from red cell sickling and/or from sickle cell-endothelial cell adhesion. The environment of the renal medulla is characterized by acidosis, hypertonicity, and hypoxia. These factors tend to promote haemoglobin S polymerization and red cell sickling, thereby making this area of the kidney particularly susceptible to changes in oxygen delivery. [4]

The kidneys of young SCD subjects with normal renal function tend to hypertrophy, generally exhibiting a smooth capsular surface. As these subjects age, there is an increasing frequency of chronic renal failure that is associated with scarred, shrunken kidneys, the capsular surface ranging from coarsely granular to grossly distorted and scarred . Enlarged glomeruli are noted both at autopsy and at biopsy where they can sometimes be seen with the naked eye. In SCD subjects, glomerular size tends to increase with age. By contrast, in normal individuals after early childhood, little relationship is seen between age and glomerular size. On histological examination, these enlarged markedly hypercellular glomeruli exhibit lobulation of the glomerular tuft. Not uncommonly, glomerular changes indistinguishable from those of proliferative glomerulonephritis may occur in SCD subjects who have no apparent renal disease [5]. Reduplication of the basement membrane and mesangial proliferation are also seen in this subject population, changes that occur with increased frequency as SCD subjects age. In addition, older subjects exhibit progressive glomerular fibrosis. On electron microscopy of the glomeruli from SCD subjects [6], even those without evidence of renal dysfunction, have revealed some effacement of the foot processes and local thickening of the basement membrane. These changes tend to be much more prevalent in cases of SCD associated with the nephrotic syndrome. The earliest lesions in sickle cell nephropathy include glomerular enlargement, perihilar focal segmental glomerulosclerosis, and hemosiderosis [7].
Proteinuria is becoming a common finding in subjects with sickle cell anemia, and results from damage to the glomerulus (sickle cell glomerulopathy). It may occur in up to 27% of adults with hemoglobin SS and in 5-8% of adults with other sickle hemoglobinopathies. Despite the paucity of associated clinical findings, it may herald the development of progressive renal insufficiency, and lead to end-stage renal disease and, therefore, should be thoroughly investigated [8]

II. MATERIALS AND METHODS

The study was conducted in Sickle Cell Clinic, Odisha Sickle Cell Project (NHM), Veer Surendra Sai Institute of Medical Science & Research (VIMSAR), Burla. After obtaining necessary written consent from the subject, blood samples were collected in K2 EDTA Vaccumtainers (BD Peripherals, Franklin Lales, NJ USA). Basic laboratory investigations like Sickling reduction slide test, Complete Blood Count (CBC) using Sysmex KX 21 (Sysmex Corporation, Kobe, Japan), alkaline agarose gel electrophoresis (pH- 8.6), biochemical parameters such as serum creatinine (CRT-J), serum urea (UREA), serum bilirubin (BIL-T & BIL-D), Aspartate Aminotransferase (ASTL), Alanine Aminotransferase (ALTL) using Cobas Integra 400 Plus (Roche Diagnostics Ltd., Rotkreuz, Switzerland) were performed as per the manufacturer’s instruction and standard protocols. Cation exchange high performance liquid chromatography (HPLC) by VARIANT-II hemoglobin testing system using the CDM 5.1 TM software (Bio-Rad Laboratories, Hercules, CA, USA) was used to detect and quantify various Hb fractions based on individual retention time (RT). 24 hour urinary Protein and Sr. albumin were done in RDC (regional diagnostic centre), VIMSAR. Kidney biopsy was done in the hospital. The side of biopsy was prepared with antiseptic solution and sterile drapes were applied. The biopsy was performed while the subjects were awake. After the site was prepared, the local anaesthetic was injected into the skin, through subcutaneous tissue and down to and around the kidney. After a few seconds, a small 1-2mm incision is made to allow insertion of the biopsy needle. A loud click was heard as the spring loaded biopsy needle was fired into the kidney to obtain a tissue sample. When enough kidney tissue was obtained, pressure was applied to the biopsy site. After a period of time, site was cleaned and dressed. Sutures were not required. Following the biopsy, the subjects were asked to lie flat on their back for 4–6 hours to minimise the risk of bleeding. Blood pressure and urine were frequently monitored to ensure the subject does not suffer from any bleeding complications. Mild-moderate pain was managed with simple analgesics. Intra and post procedural events were uneventful. 2 Tissue samples were sent to higher centre for evaluation.

III. CASE SERIES

Five cases, all males, screened, four were Sickle Cell Anemic cases and one was Sickle-Beta thal compound heterozygote case were admitted to our hospital with complaints of generalised swelling of body (anasarca) and were on hyroxyurea (HU) therapy and continuing. There was no past history of (h/o) breathlessness, cough, fever, yellowish discoloration of eyes or urine, chest pain or bone pains, malaena, hematemesis, throat or skin infections in recent past. One subject had similar complaints 3 years back which subsided without medications and another subject had recurrent history of anasarca. No past h/o hypertension (HTN), diabetes mellitus(DM) or Chronic kidney disease. Clinical examination revealed facial puffiness, pallor, pedal edema, parietal edema, ascitis, bilateral pleural effusion without any cardiac abnormality. Investigations revealed nephrotic range proteinuria in all 5 cases with decreased serum albumin and moderate elevations of serum creatinine in 4 cases. Hb was moderately decreased in all cases with insignificant liver parameters. Serum electrolytes were normal. None of the cases showed hypercholesterolemia and none were found to be diabetic. Serological test were normal for infections (hepatitis, HIV, etc.), paraproteinemia, autoimmune diseases which may cause glomerular involvement. We have briefly described their clinical, biochemical, hematological profile in Table 1 and 2. Ascitic fluid analysis was transudative. Size of Kidney was normal with normal corticomedullary differentiation on USG-Abdomen. 2D ECHO of heart was normal in all cases. Angiotensin converting enzyme (ACE) Inhibitor (ramipril 5 mg) and low dose diuretics were started without steroids in all 5 cases. All cases were subjected to imaging-guided percutaneous Kidney biopsy with pre-procedure evaluation of BT, CT, TPC, PT/INR, aPTT and with informed consent. Renal biopsy was performed by a nephrologists in our hospital. The biopsy was planned with the assistance of ultrasound to visualise the location and depth of the kidneys immediately before the biopsy. One was immunofluorescent(IF) specimen and other light microscopy (LM) specimen with their respective solutions. Biopsy report revealed features of membrano-proliferative glomerulonephritis (MPGN) in 2 cases and focal segmental glomerulosclerosis (FSGS) in 3 cases without any immune complex deposition.

ACE inhibitor, diuretics and HU were continued in all cases along with folic acid therapy. Cases were discharged and reviewed every month with regular follow-up. General condition improved with resolution of anasarca and proteinuria. None of the subject developed renal failure. ACE inhibitor and diuretics were discontinued gradually and HU with folic acid therapy were continued. Till date all cases are doing well and there is no relapse.
Nephrotic syndrome in Sickle Cell Disease...

TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
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<td>38/M</td>
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<td>SS</td>
<td>SS</td>
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<td>Sr. Albumin (g/dl)</td>
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<tr>
<td>Sr. Creatinine (mg/dl)</td>
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<td>FSGS</td>
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Note: Membrano-Proliferative Glomerulo Nephritis (MPGN), Focal Segmental Glomerulo Sclerosis (FSGS)

TABLE 2

<table>
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<th>CASE</th>
<th>WBC</th>
<th>RBC</th>
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<th>MCV</th>
<th>MCH</th>
<th>MCHC</th>
<th>PLT</th>
<th>SGOT</th>
<th>SGPT</th>
<th>BIL-D</th>
<th>BIL-T</th>
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Note. WBC: white blood cells; RBC: red blood cell; HGB: hemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular Hb; MCHC: mean corpuscular Hb distribution width; PLT: platelet; SGOT: Serum glutamic oxaloacetic acid; SGPT: Serum glutamic pyruvic trasaminase; BIL-D: bilirubin direct; BIL-T: bilirubin total; LDH: Lactate Dehydrogenase;

IV. DISCUSSION

Unlike hematuria, proteinuria is more commonly encountered in subjects homozygous for sickle cell (HbSS) than in other hemoglobinopathies. Nephrotic syndrome is now well recognized, although its frequency in sickle cell nephropathy has not been well studied. Structural glomerular abnormalities are seen in subjects with SCA but not in heterozygotes. The morphologic lesions most frequently identified are focal segmental glomerulosclerosis (FSGS) and membranoproliferative glomerulonephritis-like (MPGN-like) disease without immune complex deposits. Homozygous sickle cell disease does seem to predispose to the development of the nephrotic syndrome and those that do develop nephrotic syndrome exhibit some special characteristics, when compared to non-sicklers with nephrotic syndrome. These include adult age of onset of the nephrotic syndrome except one case of 5 year (4th case), normal cholesterol levels. Drugs such as prednisone and cyclophosphamide are ineffective for the treatment of subjects with nephrotic syndrome. Angiotensin converting enzyme inhibitors decrease proteinuria, but their long-term effect in preventing the progression of glomerular disease has not been established. Chronic renal failure, although infrequent, may be one of the manifestations of this disease. Primary treatment being ACE inhibitor but there are no long-term studies that establish the effectiveness of ACE inhibition in slowing progression of sickle cell glomerulopathy [9]. ACE inhibitors should be used cautiously because they may cause hypotension, hyperkalemia and increased renal tubular acidosis.

VII. CONCLUSION

The incidence of nephrotic syndrome is rare in sickle cell disease subjects but this disorder must be investigated in every case of SCD presenting with anasarca. A nephrology evaluation is necessary to rule out conditions such as diabetes mellitus, hypertensive nephrosclerosis, membranous nephropathy, and amyloidosis that cause a clinical presentation almost indistinguishable from sickle cell glomerulopathy. A low protein diet may reduce proteinuria and slow down progression. A long term follow up is required in such subjects owing to the pathological nature of underlying disease.
CONFLICT OF INTEREST:
The authors declare there is no conflicting interest

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