Case Report

Nephrotic Syndrome Secondary to Primary Membranoproliferative Glomerulonephritis in a 27 Years Old Nigerian Male

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Abstract: Membranoproliferative glomerulonephritis (MPGN) is not a common cause of nephrotic syndrome (NS) in adults unlike in children. It is commonly steroid-resistant in adults unlike in children. Tissue diagnosis needed for effective management could be unavailable due to cost, particularly in resource poor settings. Patient was examined, had urine analysis, serum biochemistry assay, kidney scan and a kidney biopsy for histological diagnosis.

The patient had generalized oedema, with ascites, elevated blood pressure (156/90 mmHg) and massive proteinuria (4.6 g/day). The haemogram showed haematocrit of 32%, with absolute lymphocytosis (72%). Fasting lipids showed hypercholesterolemia (533 mg/dl), elevated LDL (274 mg/dl), low HDL (27 mg/dl) and hypertriglyceridemia (302 mg/dl). Ultrasound showed enlarged kidneys. Histological findings were mesangial hypercellularity, double-contour formation along the glomerular capillary wall (tram track appearance) and endocapillary proliferation. He was managed with intravenous methylprednisolone, (followed by gradually reducing oral doses), frusemide, atorvastatin, antibiotics and had daily weighing. He responded well to treatment. He was counselled on good compliance and has been on follow-up visits. His clinical and laboratory parameters have been normal.

Nephrotic syndrome from MPGN should be looked out for in adults presenting with NS and their treatment with steroids could be very beneficial.

Keywords: Membranoproliferative glomerulonephritis, Nephrotic syndrome, Kidney biopsy, Histology, Proteinuria, Hypercholesterolemia.

INTRODUCTION

Membranoproliferative glomerulonephritis (MPGN) often referred to as mesangiocapillary glomerulonephritis, commonly manifest with nephrotic syndrome (NS) in children [1]. First described as a separate form of glomerulonephritis in the early 60s, MPGN involves thickening of the glomerular basement membrain [as is found in membranous glomerulonephritis (MGN)], and mesangial thickening, unlike in MGN [2]. The disease was initially described predominantly in children, and of unknown aetiology [3]. Idiopathic or primary MPGN has been a term used to delineate typical histological markers of MPGN, that are not secondary to any known aetiological condition such as collagen vascular diseases (CVD) or infections [4]. Due to its rarity in adults, management could be hampered particularly when histological diagnosis is unavailable (as is commonly seen in resource poor nations), coupled with the fact that the NS that commonly complicates it is mostly steroid resistant in adults.

This case report discusses the management of a 27 year old Nigerian male who had a histologically confirmed MPGN, complicated by NS which was steroid sensitive.

CASE REPORT

He was a 27 year old student who presented at the emergency section of the University College Hospital, Ibadan, on account of recurrent generalised oedema and low grade fever of two months, and progressive reduction in urine output of a week duration. There was no change in urine colour nor dysuria. He had some difficulty with breathing of a week duration, not associated with orthopnoea nor paroxysmal nocturnal dyspnoea (PND). Body swelling started from the face, it was worse on waking up, and it later progressed to involve the whole body- Body swelling temporary resolves after frusemide use. He also gave a history of passage of frothy urine. He had a similar illness 4 years prior to presentation during which he received oral frusemide, and prednisolone 60 mg which was gradually tapered to l0 mg daily over 3 months at the referral hospital. He was worked up for a kidney biopsy which he refused at the referral centre. He had a history of chronic use of herbal remedies. He had no personal nor family history of hypertension, diabetes or kidney disease. He had generalised oedema but wasn't dys-

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pnoeic nor pale. He weighed 102.5 kg, had tachycardia and his blood pressure was 156/90 mmHg. The abdomen was grossly distended but not tender. The intra-abdominal organs were not palpably enlarged, ascites was demonstrated by fluid thrill, and there were no significant central nervous system examination findings.

PROVISIONAL ASSESSMENT: Relapsed Nephrotic Syndrome

Urinalysis showed proteinuria 3+ and 24-hour urine protein was 4.5g (Spectrophotometry). Full blood count analysis showed haematocrit (32%), leucocytosis (13.6 109/L) with absolute lymphocytosis (72%), Blood film showed normocytic, normochromic anaemia. Fasting lipids showed hypercholesterolemia (533 mg/dL), elevated LDL cholesterol (274 mg/dL), low HDL cholesterol (27 mg/dL) and hypertriglyceridemia (302 mg/dL). Serology was negative for the hepatitis viruses and HIV. Blood culture yielded no growth. Anti-nuclear antibody (ANA) and double stranded DNA (dsDNA) were negative, and C-reactive protein (CRP) was not elevated. Renal scan revealed the right and left kidney length of 14.7 cm and 15.1 cm respectively, both without pelvicalyceal dilatation (Table **1**).

Table 1. Serum Biochemistry.

Day	Sodium mmo/L	Potassium mmol/L	Bicarbonate mmol/L	Calcium mmol/L	Phosphate mmol/L	Urea mmol/L	Creat umol/L	Protein g/dL	Albumin g/dL
AD 0	136	3.6	22	2.2	1.4	6.8	111	58	18
AD 8	138	3.8	23	2.3	1.1	5.6	89	64	24

Creat: Creatinine, AD: Admission day.

TREATMENT

He was commenced on intravenous (IV) Frusemide 100 mg 12 hourly, daily oral doses of Lisinopril 2.5 mg, Aspirin 75 mg, Atorvastatin 20 mg and Albendazole 400 mg stat.

He also had subcutaneous (sc) Clexane 40 mg daily, antibiotics and IV Methylprednisolone 500 mg daily for three days. Methylprednisolone was changed to oral prednisolone 60 mg daily for 4 weeks (with Rabeprazole 40 mg twice daily). This was gradually tapered to 5 mg daily with regular urinalysis check for proteinuria at each clinic visit. As a result of the large kidneys detected during renal ultrasound, coupled with the fast response to steroid treatment, the possibility of an acute glomerulonephritis was also entertained, further justifying the need for tissue diagnosis. He consented to, and had a renal biopsy before discharge.

Histological findings (Fig. **1**) included mesangial hypercellularity, endocapillary proliferation, and double-contour formation along the glomerular capillary wall (tram track appearance).

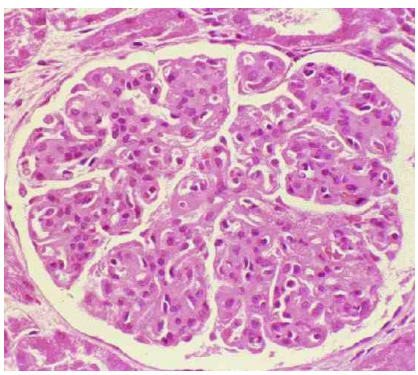

Fig. (1). Photomicrograph showing renal histological findings in a 27 year old man with membranoproliferative glomerulonephritis. Haematoxylin and Eosin (x60).

DEFINITIVE DIAGNOSIS: Nephrotic Syndrome Secondary to Membranoproliferative Glomerulonephritis

He had a progressive decline in weight, abdominal girth and level of proteinuria, and was counselled on full compliance before he was discharged after 4 weeks on admission. His follow up visits revealed he had sustained clinical and laboratory improvement. The frusemide was stopped, the prednisolone was tapered to 5 mg daily, and he achieved his pre illness weight of 72 kg.

DISCUSSION

Membranoproliferative glomerulonephritis (MPGN) is majorly a childhood condition that can be associated with nephrotic syndrome due to its involvement of the glomerular basement membrane (GBM), as is also seen with MGN [3]. Proteinuria induced hypoalbuminemia stimulates hepatic lipoprotein synthesis, accounting for the hypercholesterolemia in NS as was found in the index patient. The diagnosis of primary MPGN was made as we were able to exclude the mentioned underlying diseases through history and absence of some laboratory markers of these underlying diseases like ANA, dsDNA, and viral screening. Though the index patient had a very fast recovering, with good blood pressure control, and large kidneys, we made a diagnosis of primary membranoproliferative glomerulonephritis (histologically confirmed) because of the recurrent symptoms.

Typical of MPGN is immune complexes and complement factors deposition in the masangium and subendothelial space, seen with electron microscopy (EM) which could also reveal intramembranous and subepithelial deposits [5]. Its diagnostic hall mark on light microscopy (LM) is the “double contour formation” that results from remodelling of the capillary wall, as was found in the index patient (Fig. **1**). Early histologic findings are mesangial hypercellularity and endocapillary proliferation with eventual lobular accentuation of the glomerular tufts [6].

In a 10 year study involving participants from 2-60 years of age, at Ile-Ife, Nigeria, MPGN (21.9%) and MCD (22.9%) were the two most common histologic patterns in people less than 17 years with nephrotic syndrome. However, in the 17-50 years subgroup, MGN and FSGS were more common. The limited availability of special stains in resource poor nations has been a major setback in the effective diagnosis, classification and treatment of glomerular conditions, and renal diseases in general [7]. Glomerular diseases were earlier reported to make up about 52% of causes of CKD in Africans, however, in recent studies, hypertension has become the leading cause of CKD among Africans [8]. Challenges in histological diagnosis and effective treatment have remained in low resource nations like Nigeria. The use of adjuvant treatment modalities like effective blood pressure control and proteinuria reduction has remained good alternative measures in these nations, and this becomes important considering the high cost of immunosuppressants, their side effects profile and the lack of effective monitoring of their plasma concentrations in these nations [9].

Histologic classification of MPG using EM include types I, II, III, and secondary MPGN [5, 6]. We were unable to precisely classify the MPGN lesion in this index patient as we lack facilities Schiff (PAS), immunofluorescences (IF) and EM staining. Secondary MPGN could complicate infections, result from infections particularly hepatitis C, collagen vascular diseases and cancers particularly, lymphoproliferative disorders [10]. The most common, MPGN type I, on IF, shows strong C3 staining with or without immunoglobulins (Ig), and on EM shows subendothelial deposits with evidence of double contour formation. The C-3 nephritic factor is found in Type II disease, the "dense deposit disease" MPGN type III on IF shows C3 staining similar to MPGN type I, but unlike MPGN type 1, it shows both subepithelial and subendothelial deposits on EM [11]. The three types of MPGN manifest hypocomplementemia, however with different complement activation mechanisms. MPGN accounts for not more than 10% of all histologically classified glomerulonephritis, the sixth leading cause of end-stage kidney disease (ESKD) among the glomerulonephritides but fifth among primary glomerular diseases. It is most common in childhood though it can be seen across all ages [10].

A declining incidence of MPGN has been reported from the most developed countries with 6-12% reported in the US [11]. The predominant histopathologic subtype in children with nephrotic syndrome is similar in Turkey and Nigeria [12, 13]. Primary MPGN is most common between 8 and 30 years [14]. The index patient was first seen at the age of 23 which supportively makes the diagnosis of idiopathic MPGN more likely. Adults commonly present with secondary MPGNs, in the US, with type I reported more in females unlike type II which seems to show no gender bias [11]. Nephrotic syndrome from MPGN (as was seen in the index patient) is seen in about 40-70% cases. Acute nephritic syndrome with, haematuria and asymptomatic proteinuria is found in 20–30%; and recurrent gross haematuria in 10–20%. Asymptomatic renal disease often progresses slowly to ESRD, post-transplant recurrence is very common in type II MPGN [14].

Poor prognostic markers of MPGN are old age, and presence of nephrotic syndrome, hypertension, and reduced kidney function (GFR) at 1 year [14, 15]. Crescent formation, interstitial fibrosis, tubular wall dilatation and atrophy, and multiple sclerotic glomeruli are histological markers of poor treatment outcome.

Fifty percent of MPGN type I complicated by nephrotic syndrome progresses to ESKD after 10 years while ninety percent of the remaining half develop ESRD after 20 years. Persons with non-nephrotic range proteinuria has a 10-year renal survival rate of 85% in type I while type II with a median renal survival of 5-12 years tends to be more aggressive than type I disease [16].

The use of steroids in the index patient proved efficient, as remission was attained relatively early on the two occasions it was used. Hopefully, with the counselling patient received, compliance would be improved upon to ensure sustenance of remission. Mycophenolate mofetil (MMF) with corticosteroid is documented to reduce proteinuria and preserve kidney function in idiopathic MPGN [17]. Cyclosporine has also been used in corticosteroid-resistant primary MPGN [18]. The empirical treatment of these patients with inhibitors of the renin angiotensin aldosterone system (RAAS), as was the case in the index patient, is recommended, as first choice in treating hypertension, decreasing proteinuria and retarding disease progression. Nephrotic syndrome at presentation, low GFR, hypertension or crescents are predictors of poor treatment outcome. Some patients with these signs at presentation can however undergo spontaneous remission [19]. Bearing this in mind, the importance of strict clinic follow up and monitoring was well explained to the patient and his family.

CONCLUSION

Membranoproliferative glomerulonephritis is most commonly found in children, and when found in adults, it is commonly described as steroid resistant. Histopathologic diagnosis is essential for effective characterization and treatment. Despite being commonly described as steroid resistant in adults, optimized steroid use, inclusion of effective supporting measures like the use of ACEIs or ARBs for blood pressure and proteinuria control, and compliance with treatment regimen can help in achieving and sustaining remission.

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