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Case Report

Investigating Seronegative Phospholipase A2 Receptor Positive Primary Membranous Glomerulonephritis in a Young Adolescent Successfully Managed With Rituximab

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ABSTRACT

Membranous glomerulonephritis (MGN) is the most common cause of nephrotic syndrome in adults worldwide; however, it accounts for only 1.5% to 9% of cases of pediatric nephrotic syndrome. Detecting phospholipase A2 receptor (PLA2R) and thrombospondin domain containing 7A (THSD7A) among primary MGN patients has greatly transformed the diagnosis, treatment monitoring, and prognosis. These biomarkers are rarely undetected in the serum; however, renal tissue sent for histopathology is stained positive. Most of the previous reports of pediatric MGN are from adolescents approaching adulthood. We report a 9-year-old boy presenting with PLA2R-positive primary MGN who was seronegative and responded very well to 2 doses of rituximab after a failed steroid course.

Keywords: Membranous glomerulonephritis (MGN), Childhood nephrotic syndrome, Phospholipase A2 receptor (PLA2R), thrombospondin domain containing 7A (THSD7A), Rituximab

Introduction

Membranous glomerulonephritis (MGN) is a rare condition in children and accounts for less than 5% of cases of primary nephrotic syndrome [1]. On the contrary, it is responsible for 30-35% of cases of adult nephrotic syndrome and presents with asymptomatic proteinuria [2]. Histologically, it is characterized by the thickening of the glomerular capillary wall and immune complex deposits in the sub-epithelial region of the glomerular membrane. The disease is predominantly seen among adults aged 40–50 years, with a male-to-female ratio of 2 to 1. The mean age for pediatric MGN is 11.2 years in previous studies [3]. Phospholipase A2 receptor (PLA2R) and thrombospondin domain containing 7A (THSD7A) antibodies have been confirmed as effective tools in the diagnosis, monitoring and outcome of primary MGN cases. However, many times tissue PLAR2 positivity is not in sync with serum or urine PLA2R positivity which questions the reliability and efficacy of non-invasive serological testing in the diagnosis of primary MGN. Most of the reports of primary MGN in the pediatric age group are from adolescents or near-adult populations. We report one such case where a very young 9-year-old boy presented with nephrotic range proteinuria and microscopic hematuria that later was diagnosed as a case of PLA2R positive MGN although his serum PLA2R was undetectable. He achieved complete remission with 2 doses of rituximab after being unresponsive to 4 weeks of standard doses of steroids.

Case Presentation

A 9-year-old boy presented to the pediatric nephrology clinic with swelling of his legs for the last 6 months. For the last 15 days, he developed early morning facial puffiness and bilateral ankle edema. There was no history of fever, hematuria, oliguria, joint pain, rashes, photosensitivity, jaundice, diabetes, or any documented urinary tract infection. Meanwhile, there was no history of any non-steroid anti-inflammatory drug intake and he had not been on any kind of chemotherapy in the past. On examination, he had bilateral ankle edema and periorbital puffiness and his blood pressure was 104/70 mmHg (below the 90th percentile as per the American Academy of Pediatrics 2017 guidelines). His routine laboratory evaluations were as follows: Complete blood count (hemoglobin=11.9 g/dL, total leucocyte count=5310, platelet 3.32 L), kidney function test (urea=20.6 mg/dL, creatinine=0.73 mg/dL), thyroid profile (thyroid stimulating hormone=57.11 mIU/L, free T3=2.91 pg/mL, free T4=0.79 ng/dL), serum albumin=1.03 g/dL, and serum cholesterol=695 mg/dL. Meanwhile, the patient's urinalysis revealed the following items:

Albumin=4+, red blood cells=numerous/high power field and pus cells 3-4/high power field.

Urine culture showed the growth of Escherichia coli for which he was put on oral antibiotics as per the culture sensitivity reports. His repeat urinalysis after 2 weeks revealed albumin 4+, red blood count=25-30/high power field and pus=cells 3-4/high power field. A provisional diagnosis of acute glomerulonephritis was made and a workup was sent accordingly. His quantitative viral markers (antigen hepatitis B virus=0.01 IU/mL, anti-hepatitis C virus=0.13 index, human immunodeficiency virus=0.3 index) were negative. Serum C3 (0.95 gm/dL), serum C4 (0.11 g/dL), antinuclear antibody (2.75=AU/mL), anti dsDNA (0.21 AU/mL), anti-streptolysin O titer (<100 IU/mL), PR3 antineutrophil cytoplasmic antibodies (2.13 AU/mL), and MPO antineutrophil cytoplasmic antibodies (1.37 AU/mL) were within normal limits. His 24-h urinary protein was 7620 mg/day and his 24 h urine protein-creatinine ratio was equal to 11.78. Ultrasound whole abdomen revealed mildly enlarged bulky kidneys with raised cortical echogenicity and maintained corticomedullary differentiation. Anti PLA2R antibody level was negative (<2 RU/mL, bio ref interval <14 RU/mL), although anti-THSD7A could not be sent because of financial constraints. Percutaneous real-time Ultrasound-guided renal biopsy was performed in view of persistent nephrotic range proteinuria and microscopic hematuria. Light microscopy revealed membranous pattern glomerulopathy, tissue anti PLA2R positive with evidence of segmental tuft sclerosis in one of the sampled glomeruli (Figure 1). Direct immunofluorescence suggested immunoglobulin (Ig) A negative, IgG 2+ glomerular capillary wall, IgM negative, C3 negative, C1q negative, kappa 2+ capillary wall granular and lambda 2+ capillary wall granular. Electron microscopy revealed sub-epithelial electron-dense deposits with no defined substructure with thickened glomerular basement membrane and diffuse widespread effacement of visceral epithelial foot processes (Figure 2). In line with light microscopy and direct immunofluorescence findings, ultrastructural examination was consistent with stage-2 membranous nephropathy. He started on oral prednisolone (2 mg/kg/d) and enalapril as per the standard guidelines [4]. After 4 weeks of daily steroids, he had persistent nephrotic range proteinuria (urine protein 4+) with microscopic hematuria (RBC 18-20/high power field [hpf]). Prednisolone was stopped and he was continued on enalapril and daily home urine protein monitoring. After a 3 month follow-

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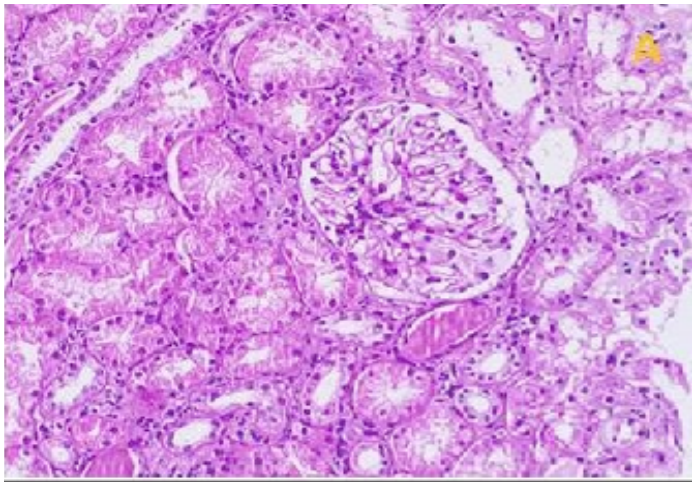

Figure 1. Light microscopy image showing membranous pattern glomerulopathy

up, his ankle edema persisted and his urine protein was 4+ with persistent microscopic hematuria (20-25/hpf), although his kidney function tests were normal. He was planned for rituximab infusion and 2 doses of rituximab were infused at 2 week intervals as per the standard protocols [4]. At a 1 month follow-up, his urinalysis revealed the following items: Albumin 1+, red blood count=2-3/hpf. Meanwhile, there was no ankle edema or periorbital puffiness. His 24 h urinary protein was reduced to less than 1 g/day. The child was counseled to perform daily urine protein monitoring at home and discharged on daily Enalapril with a close follow-up plan in the pediatric nephrology clinic.

Discussion

Membranous nephropathy is a very rare entity in children and often presents with nephrotic range proteinuria and microscopic hematuria. A total of 80 % of the subjects are primary MGN which are characterized by anti-PLA2R and anti-THD7A antibodies in the serum. The remaining 20% is secondary MN that is associated with other conditions, such as infections, malignancy, drug toxicity, and autoimmune diseases [5]. In comparison with adults, MN is uncommon in the pediatric population (about 0.1 cases per 100000 per year) [2]. The exact prevalence of primary MGN in younger children is underestimated as most of them are empirically treated with steroids without undergoing a biopsy. Contrary to adults where a clear male predisposition has been reported, no gender bias has been observed in the pediatric population with a ratio of males to females being 1:1 to 3:1 in various studies [6, 7].

Since the invention of PLA2R and THSD7A antigens, there have been remarkable changes in the diagnosis and

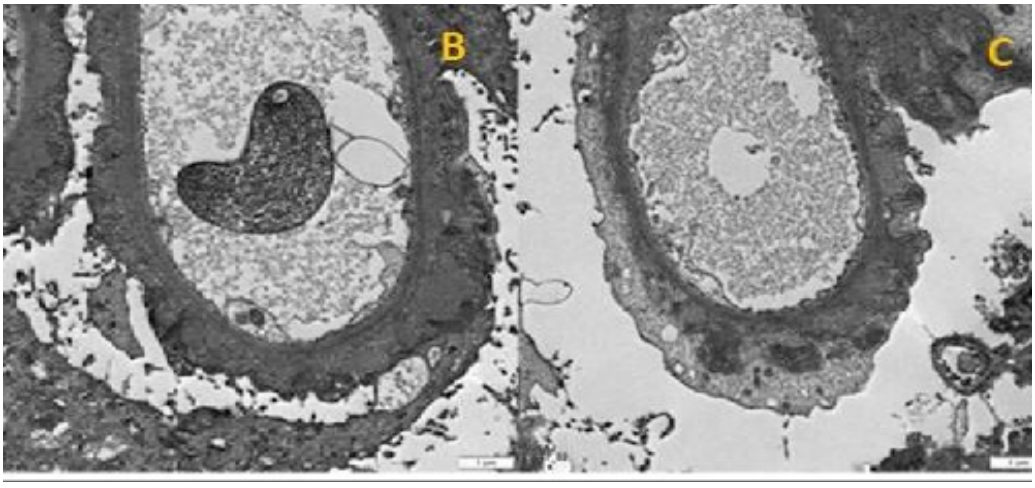

Figure 2. Electron microscopy revealed sub-epithelial electron-dense deposits with no defined substructure with thickened glomerular basement membrane and diffuse widespread effacement of visceral epithelial foot processes

treatment protocols for patients with primary MGN. A total of 70% to 90% of primary MGN patients show anti-PLA2R antibodies in their serum while anti-THSD7A have been reported in 2–3% of anti-PLA2R negative primary MGN patients [8]. However pediatric population has shown less PLA2R staining sensitivity as compared to adult patients. There has been variable sensitivity of PLA2R staining in serum and in glomerulus across many studies [9]. An overall sensitivity of 68% and specificity of 97% have been reported for serum anti PLA2R depending upon the employed technique [9]. Thus, serum anti-PLA2R has been recommended before renal biopsy in children with suspected primary MGN. However, in cases of serum anti-PLA2R negative patients, clinical presentation and biopsy must be considered before ruling out the diagnosis [9]. Multiple theories have been proposed for negative PLA2R antibodies in patients with primary MGN. This might be due to immunological remission following treatment or spontaneous remission. The immune sink phenomenon has been attributed as another hypothesis for seronegativity. The antigen needs to be saturated with immune complex deposition before it is detectable in serum. This leads to glomerular staining positivity for PLA2R antigen in a seronegative patient [10, 11]. Considering the very high specificity of PLA2R antibodies in primary MGN and its exclusive presence in only primary MGN conditions, all the recent guidelines recommend deferral of kidney biopsy in patients with the presence of PAL2R antibodies in serum.

In comparison with adults, pediatric MN patients with a diagnosis of nephrotic syndrome should be treated with steroids first and renal biopsy should be considered when they do not achieve remission even after 4 weeks of daily steroids. Anti PLA2R antibody testing may be performed in pediatric steroid-resistant nephrotic syndrome before a renal biopsy when secondary causes of MGN are ruled out. Pediatric patients mostly present with nephrotic-range proteinuria, microscopic hematuria, and steroid-resistant nephrotic syndrome.

Primary MGN in adolescent children can be treated as per the adult management protocols. Cyclophosphamide and calcineurin inhibitors (CNI) have been conventionally used in the management of primary MGN patients. Cyclophosphamide is not a favorable drug in adolescents due to its high risk of gonadal toxicity, malignancy, and myelotoxicity. Therefore, CNIs and or rituximab are increasingly recommended as first-line treatment for primary MGN. Patients with CNI have shown significant recurrences after its discontinuation. In recent trials, rituximab is superior to CNI in maintaining remission and lowering the risk of progression of disease [12, 13]. Although there has been no clear recommendation regarding the use of rituximab as a first-line treatment for pediatric patients with MN, the growing number of case series and case reports suggests rituximab as a promising agent to manage primary MN. Belimumab, a human IgG1 monoclonal antibody that inhibits B cell activating factor (BAFF), reduces PLA2R-Ab and subsequently proteinuria, important preludes to remission induction [14]. Very few cases of primary MGN have been reported in the pediatric age group and most of the reports are in adolescent children more than 10 years of age. Our case was exceedingly rare in terms of its age of presentation, seronegative but tissue PLA2R positive primary MGN, and achieving almost complete remission after 2 doses of rituximab.

Conclusion

Pediatric MGN imposes too many challenges in its diagnosis and management due to its rare occurrence, varied presentation, and inconsistent treatment response. Pediatric nephrologists have very limited experience in the treatment of pediatric MN patients because of the dearth of quality intervention trials. Adolescent patients are primarily managed by adult nephrologists while younger children are treated differently by pediatricians and pediatric nephrologists. The discovery of novel antigens such as PLA2R and TH7D7A has made remarkable progress in the diagnosis of adult MGN however its role in pediatric MGN is yet to be established because of diverse etiology. Renal biopsy is still the gold standard modality for diagnosis because of a high proportion of PLA2R seronegative primary MGN. Rituximab is becoming the first-line management option for pediatric primary MGNs who do not achieve spontaneous remission or after 4 weeks of steroid therapy. Refractory proteinuria and deranged renal function in a child with primary MGN warrant poor prognosis and unfavorable outcomes.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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