Journal of Urology and Renal Diseases
Costich M. et al. J Urol Ren Dis 07: 1244.
www.doi.org/10.29011/2575-7903.001244.
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Case Report

A Case Report on a Successful Treatment of Profound Proteinuria in a Pediatric Patient with Membranous Nephropathy Secondary to Systemic Lupus Erythematous

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Citation: Costich M, Abdul-Aziz R, Huang Y, Tarsi S, Waz WR, et al. (2022) A Case Report on a Successful Treatment of Profound Proteinuria in a Pediatric Patient with Membranous Nephropathy Secondary to Systemic Lupus Erythematous. J Urol Ren Dis 07: 1244. DOI: 10.29011/2575-7903.001244

Received Date: 05 February, 2022; **Accepted Date:** 14 February, 2022; **Published Date:** 18 February 2022

Abstract

Membranous Nephropathy (MN) is a leading cause of nephrotic syndrome in adults. The common etiology of MN in adults is primary form in which approximately 70% of patients express circulating antibodies against Phospholipase A2 Receptor (PLA2R), a podocyte antigen. Although primary MN is relatively uncommon in children, secondary MN occurs in 20% of the children with systemic lupus erythematous nephropathy. Systemic Lupus Erythematous (SLE) is an autoimmune disorder affecting multiple organ systems. Renal involvement is seen in approximately 60-80% of patients. Class V Lupus Nephritis is characterized by nephrotic range proteinuria. Here we discuss the case of a 14-year-old girl born in Thailand with a past medical history of hypothyroidism and Nonalcoholic Steatohepatitis (NASH) who presented to the Emergency Department with anasarca and 25 kg of weight gain in several months. Patient was hypertensive. Physical examination revealed abdominal skin striae, hyperpigmented papules on her arms bilaterally, exanthem on the face and wrists, arthritis and alopecia of the scalp. Laboratory blood work showed patient had an anemia (Hgb of 6.6 g/dL), high levels of Anti-Nuclear Antibody (ANA) (1:2560), low complement C3 (48 mg/dL) and C4 (8.2 mg/dL), and positive dsDNA antibodies. Urine analysis revealed nephrotic range of proteinuria. Renal biopsy revealed negative PLA2R in glomeruli, but positive and diffuse granular/pseudolinear IgG staining along the glomerular capillary loops by immunofluorescence, the pathologic diagnosis consistent with secondary form of MN due to class V membranous lupus nephritis.

Patient started on diuretics and ACE inhibitor for edema and hypertension; steroid, CellCept and Plaquenil for SLE. 4 months after therapy, patient had significant improvement with 25 kg of weight loss. Her 24 hr urine protein decreased from 24 g/day to 3.5 g/day. 8 months after therapy, proteinuria was further reduced to 1 g/day after rituximab infusion.

Keywords: Autoantibodies against phospholipase A2 receptor (PLA2R); Class V lupus nephritis; Cellcept; Exotosin 1 (EXT1); Exotosin 2 (EXT2); Membranous nephropathy; Neural EGF-link 1 protein (NELL-1); Pediatrics; Proteinuria; Rituximab; Systemic Lupus Erythematous; Thrombospondin type 1-domain-containing 7A (THSD7)

Introduction

Membranous Nephropathy (MN) is a leading cause of nephrotic syndrome in adults but it is an uncommon disorder in children [1,2]. It is an immune complex glomerulonephritis characterized by thickened Glomerular Basement Membrane (GBM) in the presence of subepithelial immune deposits of

Immunoglobulin G (IgG) and complement C3. Jones silver-stained renal biopsy shows typical "spikes" of morphology. The most common cause of MN in adults is primary or idiopathic form in which approximately up to 60-70% of patients express circulating autoantibodies against Phospholipase A2 Receptor (PLA2R) [3] and thrombospondin type 1-domain-containing 7A (THSD7) [4], both are podocyte antigens. Recently, new antigens of MN were described: Exotosin 1 (EXT1) and Exotosin 2 (EXT2), Neural EGF-Link 1 Protein (NELL-1) [5]. Although primary MN is relatively uncommon in children, secondary MN occurs in 20% of children with Systemic Lupus Erythematous (SLE) nephropathy [6]. In patients with secondary MN, PLA2R is often not expressed [3]. Whether antibodies to other podocyte antigen, such as NELL1, EXT1, EXT2 or THSD7, expressed in pediatric patients remain unknown. Systemic Lupus Erythematous (SLE) is a multi-organ system autoimmune disorder with multiple clinical manifestations. Juvenile SLE has an incidence of 0.3-0.9/100,000 children per year and a prevalence of 3.3-8.8/100,000 children [7]. Lupus Nephritis (LN) is seen in 60-80% of children at presentation [8]. The mortality rate for children with LN remain 19x that of the healthy pediatric population and among pediatric patients undergoing treatment for End-Stage Renal Disease (ESRD), the 5-year mortality may reach 22% [8]. Here we report an unusual case of MN secondary to class V LN.

Case Report

Here we report a 14 y/o girl who was born in Thailand and immigrated to the US at age 4, presented to the hospital with abdominal pain and anasarca, and 25 kg of weight gain in the past few months. Past medical history includes hypothyroidism diagnosed at age 13 on levothyroxine and Nonalcoholic Steatohepatitis (NASH). In the Emergency Department she was tachycardic at 111 bpm and hypertensive with blood pressure measured at 148/104 mmHg. Physical exam revealed severe anasarca, abdominal skin striae, hyperpigmented papules on her arms bilaterally, arthritis, alopecia of the scalp. Blood work showed patient had anemia with a Hgb of 6.6 g/dL (nl 12-15 g/dL), high Anti-Nuclear Antibody (ANA) titer (ratio of 1:2560, nl <1:40), low complement C3 (48 mg/dL, nl 80-175 mg/dL)) and C4 (8.2 mg/dL, nl 14-40 mg/dL) and positive dsDNA antibody (Table 1). Urine analysis revealed nephrotic range of proteinuria: 24 g/day (nl 0-0.15 g/day) per 24 hour urine collection and urine p/c ratio 7.4 (nl < 0.2) on random spot urine collection (Table 1).

Blood Tests	At the time of diagnosis	4 months after induction therapy	Reference ranges
Hemoglobin (g/dL)	6.6	12.5	12-15
Albumin (g/dL)	1.1	4.0	3.5 – 5
ANA	1:2560		< 1:40
dsDNA (IU/mL)	45.1	< 9.8	< 35
C3 (mg/dL)	48	136	80 – 175
C4 (mg/dL)	8.2	26	14 – 40
Urine test			
Total protein (g/day)	24	3.5	0 – 150
Spot urine p/c ratio	7.4	0.6	< 0.2

Table 1: Biochemistry profile at the time of diagnosis and 4 months after therapy. As indicated, patient had significant anemia, hypoalbuminemia, high ANA, Hypocomplimentemia (C3 and C4), and positive dsDNA at the time of diagnosis. Her nephrotic range of proteinuria was as high as 24 g/day and urine p/c ratio up to 7.4. Such changes were resolved after 4 months of therapy. C3, complement protein 3; C4, complement protein 4; ANA, anti-nuclear antibody.

Renal biopsy of the right kidney showed diffuse capillary loop thickening with strong granular/pseudolinear staining of IgG and C3. Further PLA2R and IGG subtypes immunofluorescence study were pursued. The result was negative for PLA2R antibodies in the glomeruli (Table 2). The glomeruli show semi linear and fine granular capillary loop staining with IgG1 (segmental 1+), IgG2 (global 1+), IgG3 (global 2+) and IgG4 (global 3+). There is also focal granular tubular basement membrane staining with IgG4 (1+). In addition, DNA analysis was performed to look for the presence of 4 alleles commonly associated with primary MN: NELL1, EXT1, EXT2 and THSD7A. Genetic testing for EXT1, EXT2, and THSD7A showed no significant sequence or variants identified and while NELL1 returned as heterozygous; this is of unknown significance (Table 2). The combined features suggested a secondary form of membranous nephropathy. Electron microscopic study showed numerous and variably sized electron dense immune-type deposits in the subepithelial, intramembranous, mesangial, and subendothelial positions (Figure 1).

Kidney biopsy	At the time of diagnosis	Comment
PLA2R	• PLA2R is negative in glomeruli • There are numerous and variably sized electron dense immune-type deposits in the subepithelial, mesangial and subendothelial positions	• Ultrastructure findings confirm SLE Class V membranous glomerulopathy
Genetic testing		
NELL1	• Heterozygous	• Unknown significance
EXT1	• No clinically significant sequence or variants were identified	
EXT2	• No clinically significant sequence or variants were identified	
THSD7A	• No clinically significant sequence or variants were identified	

Table 2: Results of testing for phospholipase A2 receptor antibodies in the kidney biopsy as well as genetic testing performed to identify the alleles most commonly associated with primary membranous nephropathy.

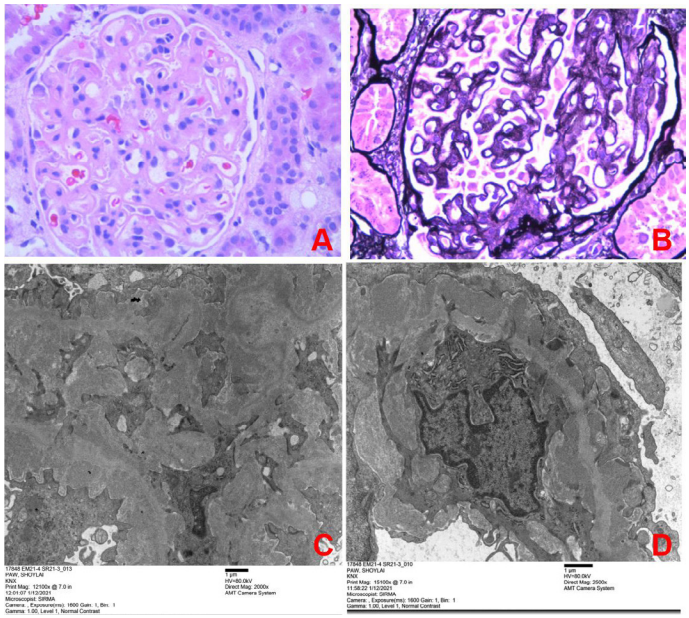

Figure 1: Renal Biopsy, clockwise from top left: **A.** an H&E stain of the renal biopsy showing diffuse basement membrane thickening; **B.** A silver stain that highlights silver positive "spikes" along basement membrane; **C** and **D.** Electronic microscope images that reveals numerous electron dense deposits in subepithelial intramembranous, mesangial, and subendothelial positions; the ultrastructural findings consistent with secondary membranous nephropathy.

The patient was started on diuretics, ACEi for edema and hypertension, and an IV Solu-Medrol pulse (1 g daily x3) which was then followed by once a week for 4 weeks. Plaquenil (Hydroxychloroquine) 400 mg daily as well as CellCept (Mycophenolic acid) 1 g BID were added as induction therapy for SLE. The patient began showing significant improvement. 4 months after therapy, the alopecia of her scalp and the rashes on her forearms have drastically improved. Blood pressure, complements (C3 and C4) and Hgb returned to normal (Figure 2). Proteinuria improved and serum albumin returned to normal (Figure 3A). Her 24 hr urine protein excretion decreased from 24 g/day to 3.5 g/day (nl 0-0.15 g/day) (Figure 3B). As result of anasarca and fluid overload evolvement, her total weight loss was

up to 25 kg (Figure 4). 8 months after therapy, the patient received a rituximab infusion (750 mg/m^2, x2 on day 0 and day 15) for persistent proteinuria. Proteinuria was further reduced to 1.0 g/day (Figure 3B).

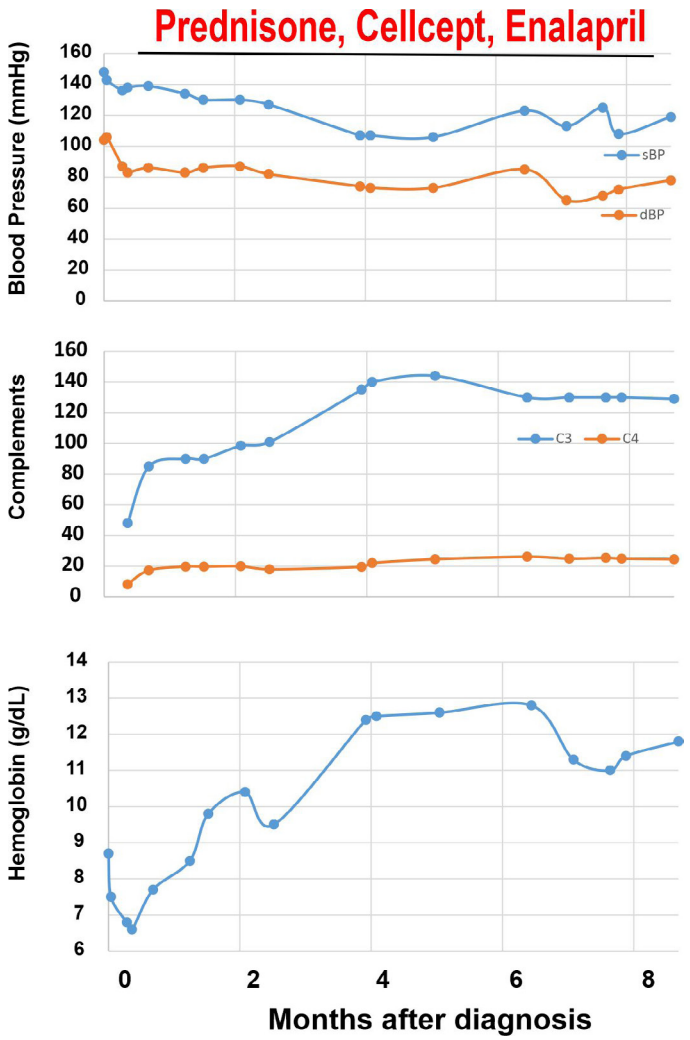

Figure 2: Changes in blood pressure, complement proteins, and hemoglobin in response to prednisone, Cellcept, and enalapril. As indicated, 4 months of therapy, blood pressure, complements (C3 and C4) and Hgb returned to normal. sBP, systolic blood pressure; dBP, diastolic blood pressure; C3, complement protein 3; C4, complement protein 4.

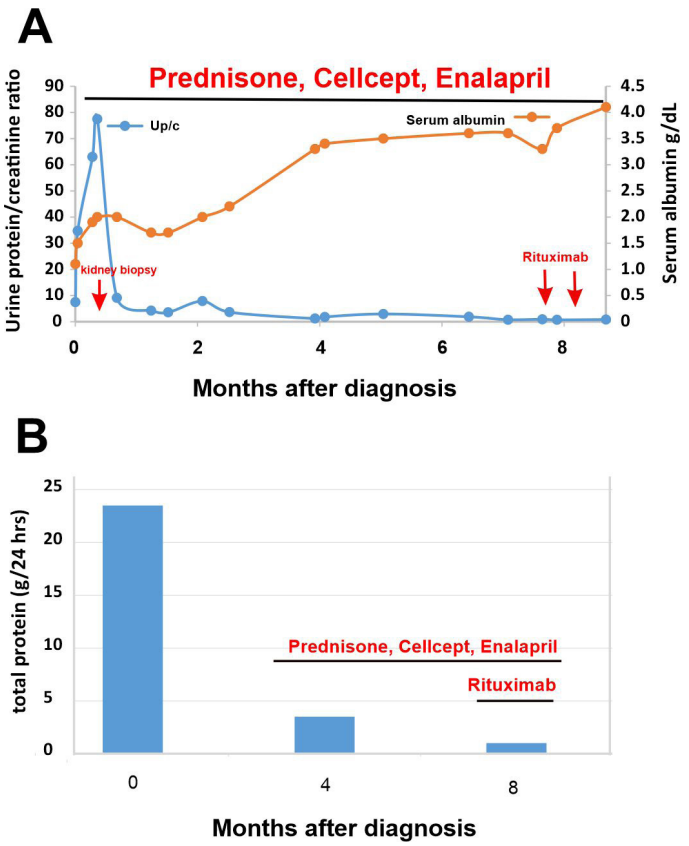

Figure 3: Changes in urine protein/creatinine ratio, serum albumin, and total urine protein in response to therapy. **A.** 4 months of induction therapy, proteinuria improved significantly and serum albumin returned to normal. **B.** 24-hour urine protein excretion decreased from 24 g/day to 3.5 g/day in response to therapy. The 24-hour urine protein excretion was further decreased to 1.0 g/day after infusion of Rituximab (750 mg/m^2, x2 on day 0 and day 15).

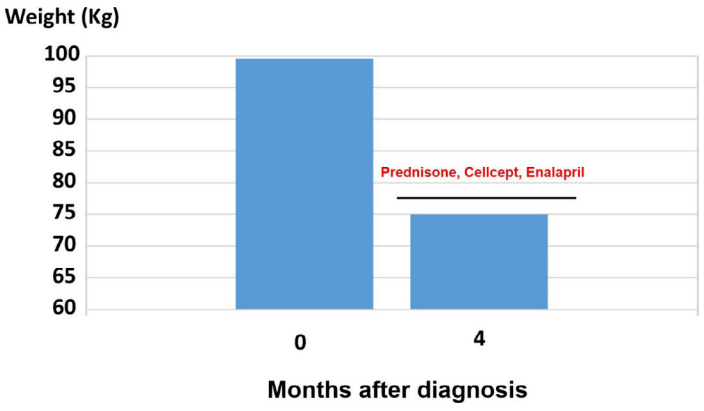

Figure 4: Change in body weight (kg) in response to therapy. 4 months after therapy, patient lost 25 kg in weight. Most of the loss can be attributed to a resolution to her volume overloading and resolution of profound proteinuria.

Discussion

Membranous Nephropathy (MN) is an uncommon disorder in children. Although the idiopathic form of this disorder is much more common adults, secondary disorder, such as SLE, is a common cause of membranous nephropathy in children [8]. Nephrotic range of proteinuria is the clinical hallmark and is associated with low serum albumin in almost all patients. MN occurs in 20% of the children with SLE nephritis. Here we report a pediatric patient with MN secondary to class V LN.

In 1959, Heymann et al used an animal model and described MN being an autoimmune response to an antigen [9]. It was not until 2009 Beck et al first identified a causal antigen, PLA2R, in primary MN [3]. Soon in 2014, a second antigen THSD7A was identified in primary MN [4]. PLA2R-associated and THSD7A-associated primary MN, both podocyte antigens, accounted for up to 70% of primary MN in adults. Recently, new antigens, NELL1, EXT1/EXT2, THSD7A, were described responsible for primary MN [5]. These groundbreaking discoveries and clinical findings appear distinctive in adult patients with primary MN [10]. However, in pediatric patient such as in the case we described here, PLA2R staining was negative in glomeruli (Table 2). Furthermore, Genetic testing for NELL1, EXT1/EXT2, and THSD7A showed no significant sequence or variants identified and while NELL1 returned as heterozygous, this is of unknown significance (Table 2). This is consistent with the MN being secondary to another disorder and not from a primary MN.

There are multiple different diagnostic criteria for SLE. In children, the SLICC criteria has been found to be more sensitive. It requires 4/17 criteria with a minimum of 1 clinical and 1 immunologic criteria [11] or proven LN by biopsy by which the patients will be distinguished proliferative LN (class III, IV, III/IV +V) from membranous LN (class V) [12]. In our case, patient met the diagnosis of SLE by 3 clinical (synovitis, chronic cutaneous lupus, and nonscarring allopecia) and 3 immunologic (high ANA, low complements C3 and C4, positive dsDNA) criteria plus biopsy-proven LN (class V).

The treatment for lupus nephritis is informed by the pathophysiology present in the renal biopsy. All patients with SLE and LN should be treated with supportive measures including dietary modifications to limit salt and protein intake, ACE inhibitors or similar hypertensive control, anticoagulation, and lipid-lowering therapy. Patients with proliferative LN often start with Intravenous (IV) Solu-Medrol followed by a high-dose corticosteroid taper and either Mycophenolate Mofetil (MMF) or cyclophosphamide for induction therapy. Induction therapy continues for 3-6 moths and is it followed by maintenance therapy with either MMF or azathioprine. After 12-18 months of treatment, if complete remission is achieved, slow taper of maintenance therapy is considered. If partial remission is achieved, continue treatment indefinitely but consider repeat biopsy to determine whether active lesions are still present. If no response to initial treatment, switch to the alternative induction therapy [12]. From renal standpoint, patients with proliferative LN are at highest risk developing ESRD and requiring for renal replacement therapy.

Patients with membranous LN (class V) often present uncontrolled nephrotic syndrome with severe proteinuria. Because most of patients present with normal serum creatinine, treatment is not as clearly defined as that for the proliferative lesions, further no randomized trials have been published [8]. The low risk of ESRD from class V membranous lupus nephritis approximately 5-10% at 10 years has encouraged less aggressive treatment as compared to proliferative lupus nephritis.

In our case, uncontrolled nephrotic syndrome with profound proteinuria (24 g/day), if untreated, could accelerate atherosclerosis, thrombosis, infection. Therefore, intervention remains necessary. In this regard, rituximab and velocycloprin are the therapeutic agents which have been recommended. B cell anomalies play a role in the pathogenesis of membrane nephropathy so B cell depletion with rituximab has been considered as a treatment for inducing and maintaining a complete or partial remission [13], as seen in our case (Figure 3B). Voclosporin is a next generation of Calcineurin Inhibitor (CNI) developed using a pharmacodynamic approach for indications of systemic, pulmonary, dermatologic autoimmune disease. It is structurally similar to cyclosporin except for modification of a functional group on amino acid -1 of the molecule. This allows Voclosporin to binds calcineurin, leading to an increase in potency connection [14].

Conclusion

This is an unusual case of MN secondary to SLE (class V LN). A 14-year old female with history of hypothyroidism and NASH who presented with anasarca and profound proteinuria (24 g/day) with normal kidney function. After 4 months of therapy with ACEi and immunotherapy (steroid, CellCept) urinary protein excretion reduced significantly from 24 g/day to 3.5 g/day, which was further reduced to 1.0 g/day with infusion of rituximab.

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