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ORIGINAL ARTICLE

Clinicopathologic features of non-lupus membranous nephropathy in a pediatric population

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Abstract

Background Membranous nephropathy is an uncommon cause of nephrotic syndrome in pediatrics.

Methods We reviewed our kidney biopsy records for patients ≤ 20 years of age with membranous nephropathy without evidence of systemic lupus erythematosus within 6 months of biopsy (January 1995–September 2020). Staining for PLA2R, NELL1, THSD7A, SEMA3B, EXT2 (3 biopsies), and IgG-subclass were performed.

Results Sixteen children (≤ 12 years) and 25 adolescents (13–20 years) were identified. Four children and 15 adolescents showed autoantigen positivity: PLA2R+/SEMA3B- (13), SEMA3B+/PLA2R+ (2), SEMA3B+/PLA2R− (1), NELL1 (1), EXT2+ (2), and THSD7A (0). Co-morbidities associated with PLA2R positivity included IPEX syndrome, active hepatitis B, Von Hippel Lindau syndrome, solitary kidney, type 1 diabetes, hyperuricemia, pregnancy (1), obesity (3), type II diabetes, *H. pylori*, viral prodrome, and nephrolithiasis. The SEMA3B+/PLA2R− adolescent was pregnant, the NELL1+ adolescent was obese, and the two EXT2+ adolescents eventually met the clinical criteria for lupus (4, 9 years post-biopsy). Co-morbidities among the remaining 24 patients included remote hepatitis B (2), Down's syndrome, lysinuric protein intolerance, recurrent UTIs, hypothyroidism, pregnancy (3), and obesity (2). Follow-up data was available for 12 children and 16 adolescents. Of the 12 children, 6 achieved complete remission, 4 achieved partial remission, and 2 had no response to treatment (1 transplant). Of the 16 adolescents, 4 achieved complete remission, 4 achieved partial remission, and 8 had no response to treatment (3 transplants). A child with "full-house" immunofluorescence staining achieved spontaneous disease remission.

Conclusion Our non-lupus membranous nephropathy cohort represents one of the largest pediatric studies to date.

Keywords Pediatrics · Nephrotic syndrome · Kidney biopsy · Membranous nephropathy

Introduction

Membranous nephropathy (MN) describes a morphologic pattern of glomerular injury defined by subepithelial immune complex deposits, composed primarily of polytypic IgG, and often involving > 50% of the capillary loops. Although 15–30% of primary nephrotic syndrome in adults can be attributed to MN, it is a rare diagnosis in children 1–12 years of age (1–3%) with an increasing incidence in adolescents (18–22%) and young adults [1].

The etiology of MN has classically been classified as either primary, secondary, or idiopathic. Primary MN describes an autoimmune disease where pathogenic autoantibodies are targeted against intrinsic podocyte antigens. The 2009 discovery of the podocyte antigen phospholipase A2 receptor (PLA2R) as the autoantigenic target in ~ 70% of adult primary MN dramatically progressed our understanding of the pathogenesis of MN, including recognition of primary MN in the pediatric population [2–5] Alternatively, secondary MN describes a disease in which circulating antigens or antigen-antibody complexes, related to a systemic condition (infection, malignancy, systemic lupus erythematosus, etc.), deposit in the glomerular subepithelial space. Finally, idiopathic MN is reserved for cases where a target autoantigen is unknown and there is no apparent association with a secondary cause of MN.

Historical studies have found that secondary causes of MN, especially hepatitis B infection (HBV) and systemic lupus erythematous (SLE), are far more prevalent (up to 75%) than

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primary or idiopathic MN in the pediatric population [6, 7]. The predominance of secondary MN in children contrasts with that of the adult population, where 75–80% of MN has a primary etiology [3]. This observation has promoted the concept that primary MN is a disease of adults. However, recent case reports have described children and adolescents as young as 5 years old with PLA2R+ biopsies and corresponding serum anti-PLA2R autoantibodies, confirming primary MN does occur in children and adolescents [4]. In 2013, Cossey et al. described a cohort of 22 pediatric patients ages 4 to 17 with primary/idiopathic MN and found PLA2R positivity on biopsy in 10 patients (45%) ages 10 to 17 [8]. Additionally, a study from India found 83% PLA2R positivity in a cohort of 18 children and adolescents (ages 10 to 19) with primary/idiopathic MN [9]. These results indicate that PLA2R-associated MN is uncommon in childhood (especially in children < 10 years of age) but the incidence in adolescents may mirror that seen in the adult population.

In recent years, several additional podocyte antigens, including thrombospondin type-I domain-containing 7A (THSD7A), Semaphorin 3b (SEMA3B), neural epidermal growth factor-like 1 protein (NELL1), Exostosin 1/2 (EXT1/2), PCDH711, serine protease HTRA, TGFBR3, and CNTN1 have been described as autoantigenic targets in "primary" MN, with the discovery of other novel antigens accelerating [10–16]. Interestingly, several of these newly discovered autoantigens have associations with well-established causes of "secondary" MN. For example, it has been shown that both NELL1+ and THSD7A+ MN may be associated with malignancy and EXT1/2+ MN occurs predominately in women with clinical and/or serologic evidence of autoimmune disease, including systemic lupus erythematous (SLE) [14, 17, 18]. These observations have significantly blurred the distinction between "primary" and "secondary" MN.

Furthermore, in 2020, Sethi et al. described SEMA3B as a novel autoantigenic target in primary MN. Eight of the 11 SEMA3B-positive patients were children with an average age of 6.9 years; 3 of the children were under 2 years of age. The discovery of SEMA3B-positive MN in children suggests the podocyte autoantigens targeted in primary MN in children may be distinct from adults [11].

Despite major advances in our understanding of the pathogenesis of MN in adults, MN remains a heterogeneous and incompletely understood diagnosis in the pediatric population. In this retrospective cohort study, we describe our single institution experience with non-lupus membranous nephropathy in children and adolescents.

Methods

Patient selection This study was performed with IRB approval at our institution. The kidney biopsy archive at our academic medical center was searched from January 1995 to September 2020 for patients ages 20 or younger with a diagnosis of MN. We excluded patients with a known diagnosis of SLE at or within 6 months of their kidney biopsy. A total of 41 cases that met these criteria were identified. Clinical, laboratory, and outcome data were abstracted from the medical record. Outcome data, including treatment, disease progression, and remission was adequately collected for 28 patients, with incomplete or no follow-up data available for 13 patients. Statistical calculations were performed using Microsoft Excel (Microsoft, Redmond, WA).

Biopsy analysis Kidney biopsy tissue was processed and evaluated with standard methods for light, immunofluorescence, and electron microscopy. Light microscopic slides were reviewed, along with photomicrographs of immunofluorescence and electron microscopy. Frozen immunofluorescence sections were stained with fluorescein-conjugated antibodies from the Binding Site (San Diego, CA) against albumin, IgG, IgA, IgM, C3, C1q, fibrinogen, and kappa and lambda light chains. All cases with available preserved frozen tissue with glomeruli for examination were retrospectively stained for PLA2R and IgG subclasses (IgG1, IgG2, IgG3, and IgG4). Air-dried cryostat sections were incubated with PLA2R antibody (Sigma-Aldrich HPA012657, 1:5 dilution) for 60 min, followed by FITC labeled 2° antibody (Vector, FI-1000, in PBS buffered diluent) for 60 min with PBS rinse in between and after. All IgG subclass staining was performed at 1:10–1:20 dilution per validated protocol.

Immunohistochemical (IHC) staining was performed on routine formalin fixed paraffin-embedded kidney biopsy tissue with antibodies to PLA2R, THSD7A, NELL1, and SEMA3B. For PLA2R IHC, the deparaffinized formalin-fixed sections were subjected to antigen retrieval using citrate (pH 6), followed by incubation in 1% H_20_2 for 10 min and normal serum blocking (1:40) for 30 min. The sections were incubated with PLA2R antibody (Sigma-Aldrich, HPA012657) for 70 min (dilution 1:6000) and HRP (Vector MP-7401 anti-Rabbit IgG) reagent for 30 min with PBS washes in between. 3,3'-Diaminobenzidine (DAB) Liquid Substrate System was used followed by counterstaining with hematoxylin. Similar staining was performed with THSD7A (Atlas antibodies HPA000923, dilution 1:20) and SEMA3B (Abcam, ab48197, 1:800) antibodies after citrate antigen retrieval, serum (THSD7a 1:20 for 40 min) or protein block (SEMA3B, 12 min) and incubation with secondary HRP antibody (30 min).

NELL1 staining was performed using the Leica Bond III stainer. Unstained slides were subjected to Epitope Retrieval 2 and incubated with NELL1 primary antibody (rabbit polyclonal, Sigma #HPA051535; dilution 1:50). The detection system used was Polymer Refine Detection System (Leica Biosystems).

Unstained 4 µm sections were freshly cut from the FFPE blocks, and immunohistochemical staining for EXT2 was performed on 3 cases (Mayo Clinic, Rochester, MN). Staining for EXT1 was not performed as no cases with discordant EXT1 and EXT2 staining have been reported in the literature [14, 19].

Results

Demographic and clinical features The basic clinical features are summarized in Table 1. A total of 41 pediatric patients with non-lupus MN were identified, including 16 children (≤ 12 years of age) and 25 adolescents (13–20 years of age). Patient age ranged from 1.5 to 20 years with 18 males and 23 females (0.8:1 M:F ratio). Twenty-three patients were of Hispanic ethnicity, 6 were Asian, 4 were African American, and 3 were Caucasian. At the time of biopsy, only one patient had an elevated serum creatinine (2 mg/dL; case 41), 26 patients had nephrotic syndrome, and 25 patients had microhematuria. Three patients had a positive ANA (cases 7, 20, 39; 1:640, 1:160, and unknown titer). Co-morbidities included 4 patients who were diagnosed during pregnancy (10, 24, 26-week gestation, and one in the third trimester), 1 patient with active HBV infection, 2 patients with remote HBV infection, 8 patients with obesity, and 1 patient each with IPEX (Immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome, Von Hippel Lindau syndrome, Down syndrome, solitary kidney, lysinuric protein intolerance, recurrent urinary tract infections, hypothyroidism, viral prodrome, type 1 diabetes mellitus, type 2 diabetes mellitus, and hyperuricemia. Serum anti-PLA2R titers were negative in the three patients who were tested (cases 11, 12, and 22), which corresponded to the patients' negative tissue PLA2R staining (see below).

Kidney biopsy analysis The basic biopsy features are summarized in Table 1. Light microscopy (LM) was reviewed for all 41 patients. Sixteen biopsies had mesangial proliferation (> 3 cells/mesangial region), 12 had focal and segmental glomerulosclerosis (FSGS) lesions, and 1 had a single cellular crescent (case 1; see below). Thirty-five biopsies had < 5% interstitial fibrosis and tubular atrophy (IFTA), 3 had 10–20% IFTA, and 3 had > 50% IFTA (cases 11, 19, 31).

Adequate tissue for immunofluorescence microscopy (IF) was available on 39 biopsies, while 2 biopsies only had globally sclerosed glomeruli on the tissue submitted for IF. All 39 biopsies demonstrated granular capillary loop IgG staining. One biopsy showed "full-house" granular capillary loop staining for C1q, IgG, IgA, IgM, C3, Kappa, and Lambda (case 2; see below). Two patients showed tubular basement membrane (TBM) immune deposits (cases 1 and 7; Fig. 1). IgG subclass staining was performed on 39 biopsies and the results are shown in Table 1.

PLA2R IF and/or IHC staining was performed on 40 biopsies, based on tissue availability. Adequate tissue was available for IF staining for PLA2R and IgG subclasses on 34 biopsies, including 10 biopsies without tissue available for PLA2R IHC. Additionally, adequate tissue was available for PLA2R IHC for 30 biopsies, including 6 biopsies without tissue available for PLA2R IF. Granular capillary loop staining for PLA2R was seen on IF and/or IHC in a total of 15 biopsies (11 by IF only, 4 by IF and IHC, and 1 by IHC only).

Thirty biopsies had tissue available for IHC staining for NELL1, SEMA3B, and THSD7A. One biopsy demonstrated granular capillary wall staining for NELL1 (case 21), 3 biopsies were positive for SEMA3B (cases 1, 34, 37), and no biopsies were positive for THSD7A. Interestingly, 2 of the 3 biopsies that were positive for SEMA3B were also positive for PLA2R (cases 1, 38; see below) (Fig. 2). Given the association with SLE, one case with "full house" IF (case 2; see below) and the two cases with clinical SLE diagnosed 4- and 9-years post-biopsy (cases 17, 27; see below) were stained for EXT2. Cases 17 and 27 were EXT2+ and case 2 was EXT2−. The biopsy from the patient with active HBV was fixed in Zenker's solution, precluding IHC analysis for HBV antigens (case 10). The biopsy characteristics of autoantigen positive and autoantigen negative cases are summarized in Tables 2 and 3.

Electron microscopy (EM) was performed on 40 biopsies. All biopsies demonstrated capillary loop subepithelial and/or intramembranous immune complex deposits. The deposits were seen in a segmental distribution in 5 biopsies, all of which were negative for PLA2R, NELL1, THSD7A, and SEMA3B. The presence of mesangial deposits, subendothelial deposits, tubular basement membrane deposits, and endothelial tubuloreticular inclusions are summarized in Tables 1 and 3.

Clinical outcomes Clinical follow-up was available for 28 patients with an average of 67.4 months of follow-up (3 to 180 months). We defined treatment response as complete remission (resolution of proteinuria and/or microhematuria with preserved kidney function), partial remission (persistent subnephrotic proteinuria and/or microhematuria with preserved kidney function), or no response (persistent nephrotic range proteinuria and/or microhematuria with progression to kidney failure). Children had favorable outcomes with 50% (6 of 12) achieving complete remission, 33% (4 of 12) achieving partial remission, and 17% (2 of 12) with no response to treatment. By comparison, only 25% (4 of 16) of adolescents achieved complete remission, 25% achieved partial remission (4 of 16), and 50% (8 of 16) had no response to treatment. The average age of patients who achieved complete remission was 11 years (4–20 years, 5 children and 5

Table 1 Basic clinical and pathlogic features

ID	Age	Sex	Race	Hematuria/NS (+/-)	sCr (mg/dL)	Low C3/C4	ANA+/dsDNA+	Comorbidities/other	Outcome	%gs/%ss/%IFTA	PLA2R/NELL1/THSD7A/SEMA3B/EXT2	Positive autoantigen	IgG1/2/3/4 (0–3+)	Dominant IgG	C1q (>/= 1+)	E&C (I–IV)/S	Deposits: Mes/SE/TBM/TRI
1	1.5	M	H	+/+	0.2	-/-	-/NA	IPEX syndrome	PR	0/0/0	+/-/-/+/NA	PLA2R/SEMA3B	2/0.5/0/3	IgG4	-	III	+/-/+/-
2	4	F	H	+/-	<1	-/-	-/-	"Full house" IF	CR	0/0/0	-/-/-/-/-	-	2/0.5/3/0.5	IgG3	+	*S*	-/-/-/-
3	4	F	AA	+/+	0.3	-/-	-/-	None	CR	0/0/0	-/-/-/-/NA/NA	-	2/0.5/1/3	IgG4	-	III	-/-/-/-
4	4	F	AA	-/-	0.8	-/-	-/NA	LPI	PR	0/0/5	-/-/-/-/NA	-	1/1/0.5/0	IgG1/2	-	IV	-/-/-/+
5	6	F	NA	NA/NA	NA	NA	NA	Down's syndrome	NA	0/25/0	NA/-/NA/NA/NA	-	NA	NA	NA	I	NA
6	7	M	H	-/-	0.3	-/-	-/-	None	CR	0/0/0	-/-/-/-/NA	-	2/0.5/3/0.5	IgG3	-	III	-/-/-/-
7	9	F	C	+/-+	NA	-/-	+/NA	Recurrent UTI	CR	0/0/0	-/-/-/-/NA	-	3/0.5/3/0.5	IgG1/3	-	II	-/-/+/-
8	9	M	H	+/+	NA	NA	NA	None	CR	0/0/0	-/-/-/-/NA	-	NA	NA	-	II	+/+/-/-
9	9	M	AA	+/+	0.3	-/-	-/-	None	NA	0/0/0	-/-/-/-/NA	-	2/0.5/0.5/2	IgG1/4	-	II	-/+/-/+
10	10	M	A	+/+	<1	NA	NA	Active HBV	NA	0/0/0	+/-/-/-/NA	PLA2R	3/1/3/1	IgG1/3	-	II	+/-/-/+
11	11	F	H	-/-	1.5	-/-	-/NA	Remote HBV	NR	8/0/0	-/-/-/-/NA	-	NA	NA	NA	S	-/-/-/-
12	11	F	A	+/+	0.2	-/-	-/-	None	PR	0/0/0	-/-/-/-/NA	-	2/1/2.5/2.5	IgG3/4	-	IV	-/-/-/-
13	11	F	A	+/-	0.8	-/-	-/-	Solitary kidney	TX*	17/0/5	+/-/-/-/NA	PLA2R	0.5/0/2/0	IgG3	-	III	+/-/-/-
14	12	M	C	-/-	0.5	-/-	NA	None	PR	9/4/10	-/-/-/-/NA	-	0/0/0/0	NA	-	IV	-/-/-/-
15	12	M	A	+/+	0.5	-/-	-/-	Hypothyroidism	CR	0/0/5	-/-/-/-/NA	-	2/1/0/3	IgG4	-	II	+/-/-/-
16	12	M	H	+/+	<1	-/-	-/-	None	NA	0/0/5	+/-/-/-/NA	PLA2R	3/1/2/3	IgG1/4	-	III	-/-/-/-
17	13	M	H	+/+	0.7	+/-	-/-	SLE (9 years post)	NR	0/0/0	-/-/-/-/+	EXT2	3/3/1/3	IgG1/2/4	-	II	+/+/-/+
18	14	F	A	+/+	0.4	-/-	-/-	Viral prodrome	CR	0/23/5	+/-/-/-/NA/NA	PLA2R	1/1/1/3	IgG4	-	II	-/-/-/-
19	16	F	C	-/+	4.7	+/+	-/-	None	TX	75/40/50	-/-/-/-/NA	-	3/1/0.5/3	IgG1/4	-	III	-/-/-/-
20	16	F	A	+/-	0.7	-/-	+/-	Remote HBV	NA	20/0/0	-/-/-/-/NA	-	3/0/0.5/0.5	IgG1	-	S	-/-/-/+
21	16	F	H	-/+	0.3	-/-	-/-	Obesity	CR	0/0/0	-/+/-/-/NA	NELL1	2.5/2/0/2	IgG1	-	I	-/-/-/-
22	16	F	H	-/+	0.3	-/-	-/-	Pregnant, obesity	PR	0/0/0	-/-/-/-/NA	-	3/2/1/1.5	IgG1	-	II	-/-/-/-
23	16	M	H	-/+	NA	-/-	-/NA	DMI	TX*	0/4/0	+/-/-/-/NA	PLA2R	2/1/3/1	IgG3	-	III	-/-/-/+
24	16	M	H	-/-	<1	NA	NA	Obesity	CR	0/0/0	+/-/-/-/NA	PLA2R	1/0/0.5/0	IgG1	-	II	-/-/-/+
25	16	F	H	-/-	NA	-/-	-/-	Kidney stones	CR	0/0/5	+/-/-/-/NA	PLA2R	NA	NA	-	III	+/-/-/-
26	17	F	H	-/+	NA	NA	-/NA	VHL syndrome	NR	8/4/5	+/-/-/-/NA	PLA2R	3/2/2/3	IgG1/4	-	III	-/-/-/-

Table 1 (continued)

ID	Age	Sex	Race	Hematuria/NS (+/-)	sCr (mg/dL)	Low C3/C4	ANA+/dsDNA+	Comorbidities/other	Outcome	%gs/%ss/%IFTA	PLA2R/NELL1/THSD7A/SEMA3B/EXT2	Positive autoantigen	IgG1/2/3/4 (0–3+)	Dominant IgG	C1q (>/= 1+)	E&C (I–IV)/S	Deposits: Mes/SE/TBM/TRI
27	18	M	H	+/+	<1	-/-	-/NA	SLE (4-years post)	PR	0/0/0	-/-/-/+	EXT2	3/3/3/3	IgG1/2/3/4	-	III	-/-/-/-
28	18	M	NA	+/-	1	-/-	-/-	Obesity, hyperuricemia	PR	5/10/5	+/-/NA/NA/NA	PLA2R	1.5/0.5/0.5/2	IgG4	-	IV	+/-/-/-
29	19	M	H	-/+	NA	NA	NA	None	NA	0/0/0	-/-/-/-/NA	-	3/3/2/3	IgG1/2/4	-	II	-/-/-/-
30	19	F	NA	+/NA	NA	NA	NA	None	NA	0/11/0	-/-/- -/NA	-	2/0/3/2	IgG3	-	S	-/+/-/-
31	19	M	H	+/+	7	-/-	-/-	None	TX	55/46/95	-/-/-/-/NA	-	NA	NA	NA	IV	+/-/-/-
32	19	M	H	+/+	0.5	-/-	-/NA	None	NA	0/0/0	-/-/-/-/NA	-	3/3/0/3	IgG1/2/4	-	II	-/-/-/-
33	20	F	H	+/-	0.6	NA	-/NA	Pregnant	NA	11/5/0	-/-/-/-/NA	-	NA	NA	-	S	+/-/-/-
34	20	F	H	+/-	0.4	-/-	-/NA	Obesity, PCOS, asthma	NA	4/0/0	-/-/-/-/NA	-	1/0/1/4	IgG4	-	III	-/-/-/-
35	20	F	H	+/+	0.6	NA	-/-	Pregnant	NA	8/0/5	-/-/-/+/NA	SEMA3B	3/2/1/3	IgG1/4	-	II	-/-/-/-
36	20	F	H	-/+	0.7	-/-	-/-	Pregnant	NA	0/0/0	-/-/NA/NA/NA	-	3/0/1/3	IgG1/4	-	I	-/-/-/-
37	20	F	NA	+/NA	0.4	NA	NA	Pregnant, obesity	NA	0/0/0	+/-/-/-/NA	PLA2R	2/0.5/1/3	IgG4	-	II	-/-/-/-
38	20	F	H	NA/+	NA	NA	-/NA	DMII, obesity	PR	0/60/0	+/-/-/+/NA	PLA2R/SEMA3B	3/1/1/3	IgG1/4	-	IV	+/-/-/-
39	20	M	H	+/Na	1.1	-/-	+/-	Obesity	NR	9/26/20	+/-/-/-/NA	PLA2R	1/0/3/0.5	IgG3	-	III	-/-/-/-
40	20	M	NA	-/+	1.1	-/-	-/-	*H. pylori*	NR	0/0/5	+/-/-/-/NA	PLA2R	NA	NA	-	III	-/-/-/-
41	20	M	AA	+/+	2	-/-	-/NA	None	NR	20/20/10	+/-/NA/NA/NA	PLA2R	1/0.5/2/3	IgG4	-	III	-/-/-/-

H, Hispanic; AA, African American; C, Caucasian; A, Asian; O, other; (+), present; (-), absent; NA, not available; NS, nephrotic syndrome; sCr, serum creatinine; UTI, urinary tract infections; HBV, Hepatitis V virus; VHL, Von Hippel Lindau; LPI, lysinuric protein intolerance; DM1, type 1 diabetes mellitus RCC, renal cell carcinoma; PCOS, polycystic ovary syndrome; DMII, Type II diabetes mellitus; dsDNA, anti-double stranded DNA;PR, partial remission; CR, complete remission; NR, no response/kidney failure; TX, kidney transplant; TX*, transplant with recurrence; gs, global glomerulosclerosis; ss, segmental glomerulosclerosis; IFTA, % interstitial fibrosis and tubular atrophy; Mes, mesangial; SE, subendothelial; TBM, tubular basement membrane; TRI, tubuloreticular inclusions; IS, immunosuppression; SEMA3B, Semaphorin 3B; E&C, Ehrenreich and Churg stage; S, segmental

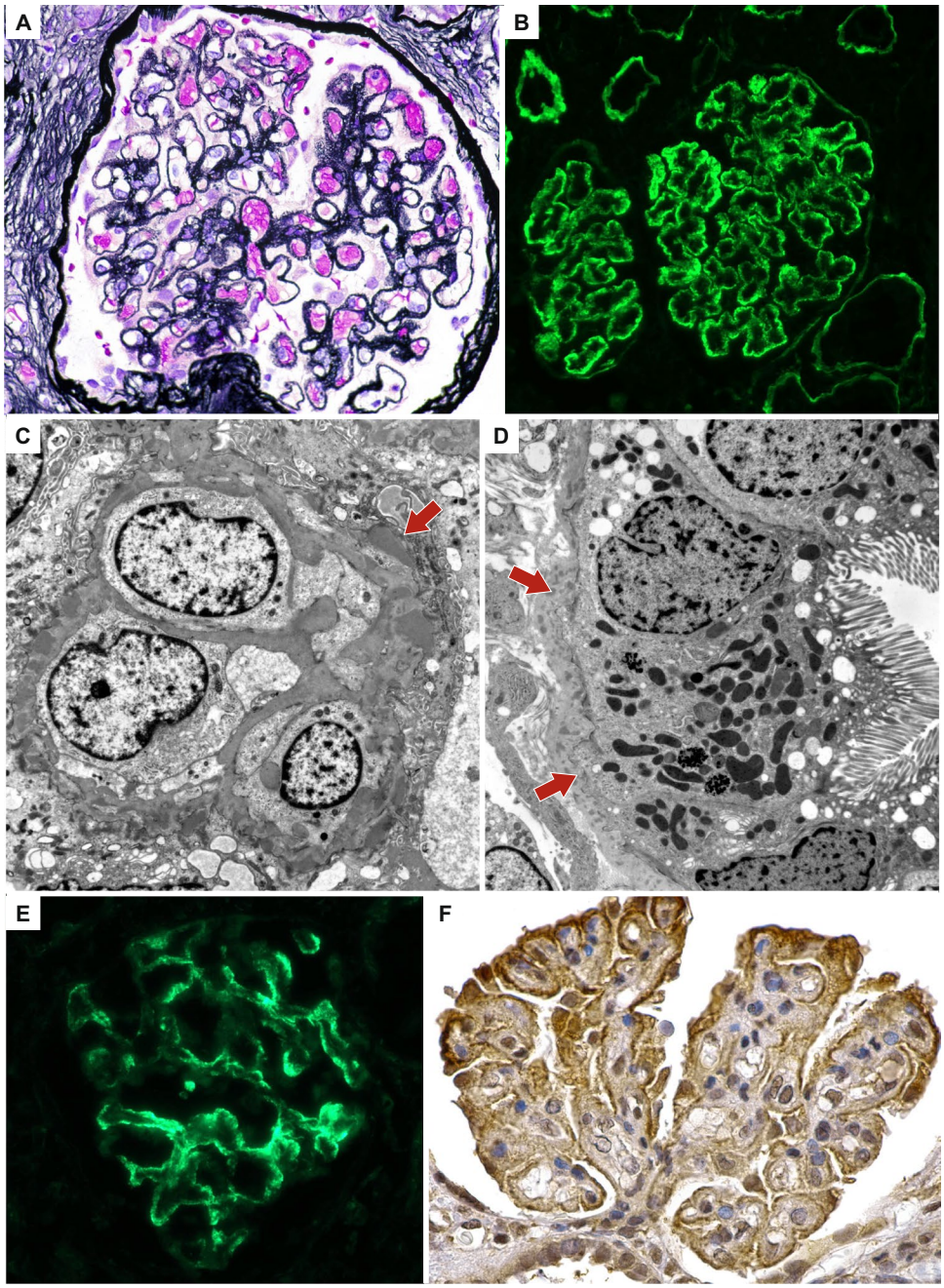

Fig. 1 Membranous nephropathy in a patient with IPEX syndrome: pathological features and ancillary staining. **A** Glomerulus with thickened basement membrane and spikes (methenamine silver, × 400). **B** IgG immunofluorescence stains granular glomerular capillary wall deposits. In addition, pseudolinear staining is observed along several tubular basement membranes. **C** Ultrastructural examination highlights subepithelial deposits (arrow) with associated glomerular basement membrane remodeling (× 6000). **D** Tubular basement membrane deposits (arrows) on electron microscopic examination (× 8000). **E** PLA2R immunofluorescence staining of the glomerular deposits (× 400). **F** SEMA3B immunohistochemical stain highlights granular capillary wall deposits (× 400)

adolescents) compared with the average age of patients who had no response to treatment of 16.2 years (11–20 years, 2 children and 8 adolescents). One child and three adolescents received a kidney transplant, 2 of which suffered disease recurrence (cases 13, 23). PLA2R was positive in 3 of the 10 patients (30%) who achieved complete remission compared with 6 of the 10 patients (60%) who had no response to treatment. The patient with NELL1 positivity achieved complete remission (case 21). The SEMA3B+/PLA2R+ cases achieved partial remission (cases 1, 38; see below) and the outcome of the SEMA3B+/PLA2R− case is unknown (case 35). The two EXT2+ patients were diagnosed with SLE 4- and 9-years post-biopsy (cases 17, 27; see below). The patient with "full house" staining on IF achieved spontaneous complete remission (case 2; see below). The patient with Von Hippel-Lindau syndrome required a bilateral nephrectomy for renal cell carcinoma (case 26; 120 months after MN diagnosis).

Notable cases

"Full house" immunofluorescence (case 2)

Case of a 4-year-old female with no significant co-morbidities who presented with a normal serum creatinine, nephrotic syndrome, and microscopic hematuria. At the

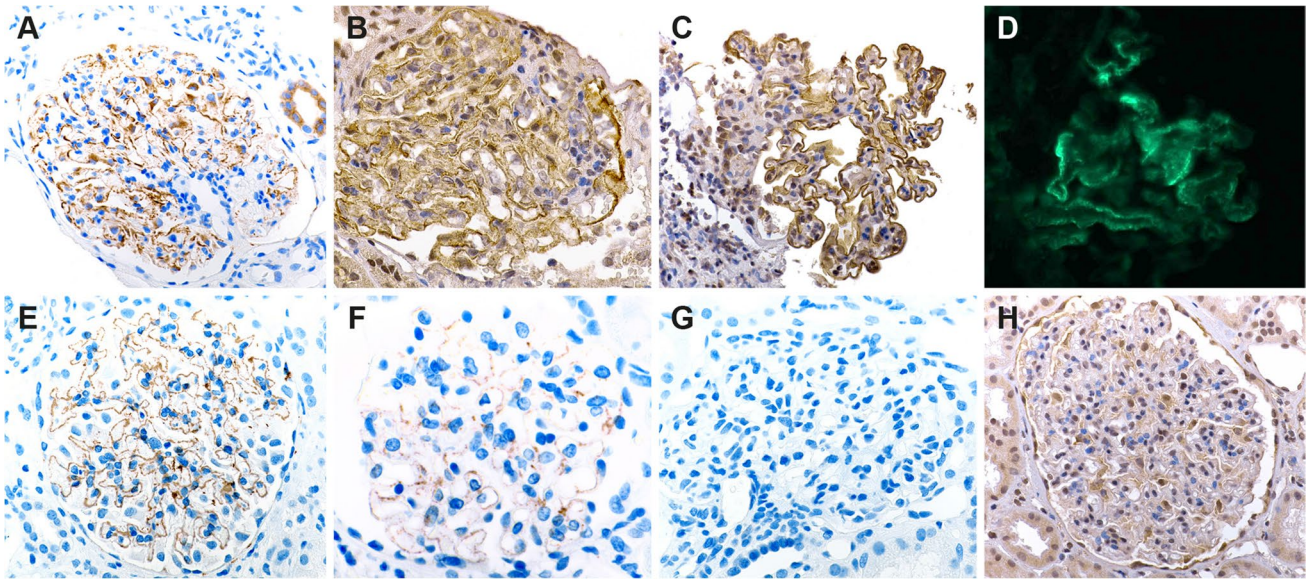

Fig. 2 Representative autoantigen staining. **A** NELL1 immunohistochemical stain highlights granular capillary wall deposits (case 21; × 400). **B**, **C** SEMA3B immunohistochemical stain highlights granular capillary wall deposits (cases 35 and 38; × 400). **D** PLA2R immunofluorescence staining of the glomerular deposits (case 38; × 400). **E**, **F** EXT2 immunohistochemical stain highlights granular capillary wall deposits (cases 17 and 27; × 400). **G** Negative EXT2 immunohistochemical stain (case 2; × 400). **H** Negative Semaphorin 3b immunohistochemical stain with background podocyte staining (case 21; × 400)

Table 2 Distribution of PLA2R/NELL/SEMA3B/THSD7A/EXT2 (autoantigen+) biopsy positivity in the study cohort

	Sex	Autoantigen+
Children (< 12 years old)	8 F, 8 M (50:50)	4/16 (25%)
Adolescents (12–20 years old)	14 F, 11 M (56:44)	15/25 (60%)

F, female; M, male

time of biopsy, the patient had negative autoimmune serologies (ANA, anti-dsDNA) and normal complement levels. Immunofluorescence microscopy demonstrated "full-house" granular capillary loop staining for C1q (3+), IgG, IgA, IgM, C3, Kappa, and Lambda. IgG subtype staining demonstrated IgG3 dominance. Ultrastructural examination demonstrated subepithelial deposits in a segmental distribution. No mesangial deposits, subendothelial deposits, or endothelial tubuloreticular inclusions were seen. Staining for PLA2R, NELL1, THSD7A, SEMA3B, and EXT2 was negative. The patient received no specific treatment for MN and at 37 months follow-up the patient had a normal serum creatinine, no microscopic hematuria, and no proteinuria. This was the only patient who achieved "spontaneous" resolution of MN in our cohort.

EXT2+ (cases 17 and 27)

Cases of 13- and 18-year-old males who presented with normal serum creatinine, nephrotic syndrome, and microscopic hematuria. At the time of biopsy, both patients had negative autoimmune serologies (ANA and anti-dsDNA); however, the 13-year-old patient had low complement level (C3). Both biopsies showed positive granular EXT2 immunohistochemical staining. Neither biopsy showed immunofluorescence "full house" staining or ≥ 1+ staining for C1q. However, the biopsy from the 13-year-old patient did show mesangial deposits, subendothelial deposits,

Table 3 Clinicopathological characteristics of patients based on PLA2R/NELL/SEMA3B/THSD7A/EXT2 (autoantigen+) staining on biopsy

	Mean age (range)	Gender	Dominant IgG4	Subendo deposits	Endothelial TRI	Mesangial deposits
Auto-antigen+	15.9 (1.5–20)	8 F, 11 M (2:3)	11/19 (57.9%)*	1/19 (5.3%)	5/19 (26.3%)	6/19 (31.6%)
Auto-antigen−	12.8 (4–20)	14 F, 8 M (3.5:2)	8/22 (36.4%)	3/22 (13.6%)	3/22 (13.6%)	4/22 (18.2%)

F, female; M, male; TRI, tubuloreticular inclusions; Subendo, subendothelial; Autoantigen+, PLA2R+/NELL1+/THSD7A+/SEMA3B+/EXT2+

*The NELL1+ case was IgG1-dominant, which is consistent with the reported literature [17]

endothelial tubuloreticular inclusions, and equal intensity IgG1/IgG2/IgG4 subclass staining, raising concern for lupus MN. This patient eventually met the diagnostic criteria for lupus ~ 4 years after his initial MN diagnosis. He was treated with steroids and mycophenolate mofetil but progressed to chronic kidney disease stage 5 and received a kidney transplant ~ 5 years after his initial MN diagnosis. The biopsy from the 18-year-old patient showed equal intensity IgG1/IgG2/IgG3/IgG4 subclass staining but no other histologic features suggestive of lupus MN (e.g., mesangial deposits, subendothelial deposits, or endothelial tubuloreticular inclusions). This patient did not receive specific treatment for MN but eventually met the diagnostic criteria for lupus ~ 9 years after his initial MN diagnosis. After 10 years of follow-up, the patient has persistent non-nephrotic range proteinuria, no hematuria, and a normal serum creatinine.

PLA2R+/SEMA3B+ (cases 1 and 38)

Case 1 Case of a 1.5-year-old male with IPEX syndrome who presented with a normal serum creatinine, nephrotic syndrome, microscopic hematuria, and several autoimmune/allergic manifestations of IPEX syndrome. Autoimmune serologies (ANA) were negative and complement levels were normal. Light microscopy demonstrated mesangial proliferation and a single cellular crescent. PLA2R and SEMA3B staining demonstrated granular capillary loop deposits and IgG subtype staining showed IgG4 dominance. Granular tubular basement membrane (TBM) deposits were seen on IF and EM. Ultrastructural examination also demonstrated mesangial deposits, however, no subendothelial deposits or endothelial tubuloreticular inclusions were seen. The patient underwent a bone marrow transplantation at 7 years of age. At ~ 11 years follow-up, the patient continues to have subnephrotic proteinuria but has no microscopic hematuria and a normal serum creatinine.

Case 38 Case of a 20-year-old female with obesity and type II diabetes who presented with nephrotic syndrome. Autoimmune serologies were negative. Light microscopy showed segmental sclerosis lesions and mild diabetic nephropathy in addition to the classic features of MN. PLA2R and SEMA3B staining demonstrated granular capillary loop deposits and IgG subtype staining showed IgG1/IgG4 co-dominance. Ultrastructural examination demonstrated mesangial deposits, however, no subendothelial deposits or endothelial tubuloreticular inclusions were seen. At ~ 11-year follow-up, the patient continues to have subnephrotic proteinuria and a normal serum creatinine.

Discussion

In this single center retrospective study, we described 16 children (≤12 years of age) and 25 adolescents (13–20 years of age) with non-lupus MN. Nineteen biopsies (46.3%) were positive for PLA2R, NELL1, THSD7A, SEMA3B, or EXT2 (EXT2 performed on only 3 biopsies). Of these patients, 15 were adolescents (60% of adolescents) and only 4 were children (25% of children). These results mirror the findings of previous studies in which the prevalence of autoantigen-associated/primary MN is low in childhood but approaches that of the adult population (~ 60%) in adolescents [8, 9, 20]. At least in our pediatric cohort, the traditional histological parameters such as mesangial or subendothelial deposits, tubuloreticular inclusions, IgG4 dominance, and tubular basement membrane deposits may not be entirely helpful in differentiating a podocyte antigen-directed autoimmunity ("primary")-associated MN from secondary causes of MN.

Of the 22 biopsies with negative autoantigen staining (negative for PLA2R, NELL1, THSD7A, SEMA3B, and EXT2), only 4 patients (cases 4, 5, 7, 15) had an identifiable potential etiological comorbidity (lysinuric protein intolerance, recurrent urinary tract infections, hypothyroidism**,** and Down's syndrome) [21–23]. The remaining 18 cases were best classified as idiopathic MN. The etiologies of idiopathic MN are likely varied and may include environmental or genetic risk factors that have yet to be elucidated. Additionally, it is possible that these cases represent primary MN related to an untested/unidentified podocyte antigen(s). As our understanding of pediatric MN progresses, it is likely that many of these cases will be reclassified as either autoantigen associated or secondary MN.

In adults, primary MN is about twice as prevalent in males compared to females [3]. In the pediatric population, there does not appear to be a male predominance. In a US study of 19 cases of pediatric MN, there was a ~ 1:1 male to female (M:F) ratio; a Chinese study of 44 cases of pediatric MN also showed a ~1:1 M:F ratio [24, 25]. Our cohort included 18 males and 23 females (~8:10, M:F), perhaps suggestive of a slight female predominance in pediatric MN. This difference likely reflects the distinct pathophysiology underlying pediatric MN.

Based on our review of the literature, PLA2R+ MN is an exceptionally rare diagnosis in children under 10 years of age [4, 8, 9, 26]. Of the 10 children in our study ages 10 or younger, only 2 patients demonstrated PLA2R positivity. It is notable that of these two children, one child had IPEX syndrome and the other had active HBV infection (cases 1 and 10). This finding suggests PLA2R+ MN may require a trigger or "second hit" in younger children. It has been established that PLA2R+ MN is strongly associated with single nucleotide polymorphisms in certain *HLA* loci and in the *PLA2R1* gene.

In a 2011 study, a predominately white European adult cohort showed a nearly 80-fold increased risk for primary MN if participants were homozygous for risk alleles in both the *PLA2R1* and *HLA-DQA1* genetic loci [27]. Children who carry similar genetic risk alleles may develop PLA2R+ MN early in life if exposed to specific environmental risk factors or underlying co-morbidities.

The youngest patient in our cohort (case 1, 1.5 years old) has IPEX syndrome, a disease caused by a loss-of-function mutation in *FOXP3*. FOXP3 normally functions as a transcriptional suppressor in CD4+/CD25+ regulatory T-cells and *FOXP3* mutations result in immune hyperactivity. In IPEX syndrome, the immune system fails to recognize self-antigens and overwhelming autoimmunity results in severe morbidity and mortality [28]. Kidney involvement is common in IPEX syndrome and MN, including a recently published case of PLA2R+ MN [29], is one of the most common manifestations. Our patient with IPEX syndrome demonstrated MN with positivity for both PLA2R and SEMA3B, TBM deposits, and a single cellular crescent. Interestingly, TBM staining was similarly found in young patients (< 2 years old) in the study that first described SEMA3B-associated MN [11]. The loss of peripheral immune tolerance in this patient appears to have resulted in MN with multiple autoantibodies, TBM deposits, and rare crescents.

We described a 10-year-old patient (case 10) with positive biopsy PLA2R staining and positive serum hepatitis B surface antigen (HBsAg) at the time of MN diagnosis. HBV is conventionally thought of as a cause of secondary MN; however, a recent study demonstrated that many (~ 64%) cases of HBV-associated MN are tissue PLA2R-positive. In rare cases, both PLA2R and HBsAg have been colocalized in the subepithelial deposits. It has been hypothesized that podocyte injury related to HBV-associated MN exposes PLA2R and results in autoantibody formation [30]. While the pathophysiology behind the association of HBV and PLA2R MN is not well understood, these observations reinforce the concept that the mechanisms underlying primary and secondary MN are not entirely distinct.

In addition to the patient with IPEX syndrome (case 1), a 20-year-old patient (case 38) with obesity and type II diabetes mellitus demonstrated dual positivity for PLA2R and SEMA3B. This finding underscores the fact that autoantibodies in primary MN are not mutually exclusive. In adults, it has been shown that epitope spreading within the PLA2R protein is common, however, epitope spreading between proteins (e.g., THSD7A and PLA2R) is a rarely described phenomenon [26, 31]. To our knowledge, dual PLA2R and SEMA3B positivity has not previously been reported and the frequency of dual autoantibody positive MN in pediatrics is unknown. Furthermore, it is unclear if both autoantibodies contribute to disease progression. Further studies are needed to elucidate the underlying pathophysiology in these rare cases.

A 4-year-old patient (case 2) demonstrated biopsy findings characteristic of lupus-like MN with negative lupus serologies and normal complement levels. A stain for EXT2 was negative. After 47 months of clinical follow-up, the patient did not develop clinical or serological evidence of lupus and was the only patient in our cohort who achieved spontaneous disease remission. In 2017, Bajema et al. described a cohort of 32 patients with non-lupus "full house" nephropathy (NLFHN). Twelve of the 32 patients had membranous deposits (including 1 PLA2R+ on biopsy) and none developed SLE after 20 years (mean) of follow-up [32] Despite these findings, NLFHN nephropathy represents a significant risk factor for the development of SLE and these patients should be closely monitored for disease progression [33].

Finally, we described 13- and 18-year-old patients (cases 17 and 27) who met the serologic and clinical criteria for SLE 4 and 9 years after their initial diagnosis of "idiopathic" MN, respectively. In 1976, Libit et al. described two pediatric patients who presented with idiopathic MN and developed SLE 1 and 3 years after the onset of nephrotic syndrome [34]. Since this initial report, there have only been a few additional reports of patients with idiopathic MN, without "full-house" IF staining, but who eventually went on to meet SLE diagnostic criteria [35, 36]. Interestingly, both biopsies in our cohort showed EXT2 positivity. EXT2 has a strong association with lupus MN and these results suggest positive staining may be a harbinger for future development of clinical SLE [14, 19]. Additional studies are needed to examine EXT1/2 in "idiopathic" MN as a predictive marker for the future development of SLE. It is important for clinicians to carefully follow patients with idiopathic MN, especially if biopsy features suggestive of lupus MN and/or EXT1/2 positivity are identified.

In conclusion, we describe the largest cohort of pediatric non-lupus membranous patients to date. Unfortunately, given the retrospective nature of this study, we were unable to obtain serum PLA2R status in the vast majority of our patients. Our study demonstrates that tissue PLA2R positivity, especially in children less than 12 years of age, is significantly lower than reported in adults. A clearly identifiable non-lupus secondary cause of MN is also infrequent, highlighting a need for further studies to improve our understanding of MN in children.

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