Childhood Membranous Nephropathy, Circulating Antibodies to the 58-kD TIN Antigen, and Anti-Tubular Basement Membrane Nephritis: An 11-Year Follow-Up

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● Childhood membranous nephropathy (MNP) with anti–tubular basement membrane (anti-TBM) nephritis is a rare disorder that may have extrarenal manifestations. This article describes a new case to be added to the 10 previously reported. A renal biopsy specimen from a 1-year-old white boy with nephrotic syndrome, microhematuria, and hypertension showed MNP (granular global IgG, IgA and C3, and segmental IgM and C1q) associated with hypercellularity and granular deposits of IgM and C1q in the mesangium, arteriolar IgA, and linear TBM IgG, IgA, and C3. A biopsy at age 4 years showed MNP (IgG and C3) and linear IgG and C3 along the TBM. Six months later, temporary glucosuria suggested a mild tubular dysfunction. Biopsy at age 8 years showed sclerosing MNP (IgG and C3), linear TBM IgG and C3, and chronic active tubulointerstitial nephritis (TIN). Indirect immunofluorescence showed circulating anti-TBM antibodies, and the enzyme-linked immunosorbent assay (ELISA) approach verified strong reactivity with the 58-kd TIN antigen. Despite trials with steroids, chlorambucil, azathioprine, and cyclosporine, end-stage renal disease developed by the age of 9 years. At age 10 years, the patient received a cadaveric kidney transplant. With the patient now aged 12 years, the graft is still functioning well, without any clinical evidence of disease recurrence. Neurological, ocular, and abdominal symptoms, including nonbacterial diarrhea, were observed during the follow-up period. The pathophysiology of these extrarenal symptoms remains unclear. Serotyping and genotyping of HLA antigens (A2, A10, B12, B41, DR5 [1101, 1103-4, 1106 or 1108-1113], DR6 [1303, 1312, or 1413], DRB3 [*0101 and 0201-2 or 0301], DQA1 [*0501 homozygous], and DQB1 [*0301 homozygous]) did not indicate any HLA association similar to those decribed previously in childhood MNP with anti-TBM nephritis (HLA-B7 in four patients, HLA-DR8 in two patients). The presented case is the fifth in the literature that displays reactivity with the 58-kd TIN antigen, and for which data on HLA antigens are reported.
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INDEX WORDS: Membranous nephropathy; anti–tubular basement membrane nephritis; tubulointerstitial nephritis antigen; HLA class I and II antigens; renal transplantation; tubular dysfunction; end-stage renal disease.

MEMBRANOUS nephropathy (MNP) is infrequent in children, with an incidence below 5%.[1,2] Childhood MNP occasionally may be associated with linear[3-9] or granular[10,11] depos-

its of immunoglobulin G (IgG) and C3 along the tubular basement membrane (TBM). The linear immunodeposits indicate the presence of anti-TBM nephritis. Primary anti-TBM nephritis is characterized by linear TBM immunodeposits, interstitial mononuclear infiltrates, tubulitis, tubular damage/atrophy, interstitial fibrosis, the ultrastructural absence of electron-dense deposits in the TBM, circulating anti-TBM antibodies, a tubular dysfunction, and progressive azotemia.[12-14] Anti-TBM antibodies have been occasionally documented at times in a variety of renal diseases,[15] such as drug-induced tubulointerstitial nephritis (TIN),[16] anti–glomerular basement membrane nephritis,[17] renal allografts,[18] poststreptococcal glomerulonephritis,[19] lupus nephritis,[20] and MNP of children.[3-9] The latter association is the subject of the current communication.

CASE REPORT

A 10-month-old white boy was admitted with the nephrotic syndrome (proteinuria: 3.9 g/day, serum albumin level: 2.1 g/dL, edema), microhematuria, and hypertension

(130/80 mm Hg). Serum studies showed normal electrolytes, creatinine, and the third complement component (C3). Glucosuria and aminoaciduria were not detected. In response to a daily prednisone regimen of 60 mg/m^2 body surface area (BSA), the proteinuria decreased to 0.2 g/24 h, the hematuria disappeared, and the blood pressure normalized. Within 2 months, however, the patient became steroid dependent, and a percutaneous kidney biopsy was performed (March 1987). Results of tests for lupus erythematosus cell and anti-DNA antibody were negative. The treatment was continued with prednisone (1 mg/kg/d) and indomethacine (1 mg/kg/d), given alternately. At the age of 3 years, the patient had epileptic seizures, which were treated with carbamazepine. At the age of 4 years, the proteinuria became steroid resistant, and the nephrotic syndrome was manifested again (proteinuria: 6 g/d). Additional findings were microhematuria, a reduced urine concentrating capacity, hypertension (140/90 mm Hg), and normal serum creatinine and glucose levels. Glucosuria and aminoaciduria were still not observed. A new renal biopsy was performed (May 1990). Subsequently, a 6-week period of chlorambucil (0.2 mg/kg/d) and prednisone (40 mg/m^2 BSA every other day) was initiated, but without success.

Methylprednisolone pulse therapy (3 × 500 mg) was then tried, followed by a 6-week azathioprine (1 mg/kg/d) treatment. The proteinuria fluctuated between 0.5 and 6 g/24 h; the hematuria persisted. The hypertension was treated with an angiotensin-converting enzyme inhibitor, a Ca-channel blocker, and diuretics, and the hypercholesterinemia with bezafibrate. At the age of 4.5 years, glucosuria was observed (250 mg/L to 1.3 g/L), although the blood glucose levels were in the normal range. The glucosuria later disappeared. At the age of 5 years, the child suffered from frequent headaches, bulbar pain, visual disturbances associated with nausea, vomiting, tremor, a broad-based gait, abdominal pain, and nonbacterial diarrhea reminiscent of a lactase deficiency. The results of cranial radiograph, computed tomography scan, and ophthalmological investigations were negative. Electroencephalogram showed only a mild irregular cerebral activity. The explanation of these unusual symptoms remains unclear. The ocular and abdominal complaints slowly ceased. Because the laboratory tests constantly verified the nephrotic syndrome and azotemia appeared (serum creatinine 1.4 mg/dL), a low-protein diet and cyclosporine A (4 mg/kg/d) were initiated. The administration of cyclosporine was stopped 2 months later because the neurological symptoms had worsened; this was attributed to the side effects of the drug. At the age of 8 years, the serum creatinine was 2 mg/dL, and the creatinine clearance was reduced to 30 mL/min/m^2. Despite forced antihypertensive therapy, the patient had an elevated blood pressure (150/100 mm Hg). A further renal biopsy was performed (June 1994), and the serum of the patient was tested toward circulating anti-TBM antibodies. At the age of 9 years, chronic hemodialysis was started, and after 13 months of bicarbonate hemodialysis, the patient underwent a successful cadaveric kidney transplantation. The native kidneys were not removed. The child is now 12 years of age, and his allograft is functioning well, without clinical evidence of the recurrence of the disease. He is receiving cyclosporine, azathioprine, and steroid. The most recent parameters include the following: proteinuria below 0.5 g/day, no glucosuria, serum creatinine, electrolyte and acid-base levels normal, and blood pressure normal (100/70 mm Hg).

Morphological Studies

The renal biopsy specimens were processed for light microscopy, direct immunofluorescence (IF) (IgG, IgA, IgM, fibrinogen, C3 and C1q), and electron microscopy with standard methods. Indirect IF was performed on normal human kidney tissue to detect circulating anti-TBM antibodies.

Immunochemical Analysis

The serum obtained at the time of the third biopsy (1994) was used to test the reactivity of antibodies toward the 58-kd TIN antigen by enzyme-linked immunosorbent assay (ELISA), and other components of the TBM by Western blotting, as described.[5]

HLA Serotyping and Genotyping

Serologic HLA class I and class II typing was performed before renal transplantation, with standard methods. The genotyping of HLA-DRB, DQA1, and DQB1 alleles was performed in total cellular DNA isolates from peripheral blood leukocytes. For HLA-DRB analysis, the Amplicor kit (Hoffman-La Roche, Basel, Switzerland) was applied. The DQA1 typing was performed with a modified PCR-RFLP procedure,[21] and the DQB1 typing with the INNO-LiPA/DQB1 kit.

RESULTS

The renal biopsy findings are summarized in Table 1. MNP and linear staining with IgG along the TBMs are shown in Figs 1 and 2, respectively.

Indirect IF showed circulating anti-TBM antibodies at a concentration of 1:16 (Fig 3). Circulating anti-TBM antibodies were tested 1 and 2 years after transplantation, with negative results. The ELISA approach disclosed a high reactivity of the 58-kd TIN antigen at dilutions of 1:250, 1:50, and 1:10. Even at the 250-fold dilution, the reactivity was strong at 1 minute. In the Western blot experiment, no reactivity was detected.

The serotyping of HLA antigens showed A2, A10, B12, B41, DR5, and DR6 antigens. The genotyping verified DR5 (1101, 1103-4, 1106 or 1108-1113), DR6 (1303, 1312, or 1413), DRB3 (*0101 and 0201-2 or 0301), DQA1 (*0501 homozygous), and DQB1 (*0301 homozygous) alleles.

DISCUSSION

With the addition of the presented case (patient 11) to the previously described ones, 11

Table 1. Renal Biopsy Findings

Year		Light Microscopy	Direct Immunoflurescence	Electron Microscopy
1987	Glomerular tufts	Segmental thickening with spikes	Granular IgG, IgA and C3; segmental IgM and C3	MNP, stage II-III
	Mesangium	Foc-segm proliferation and increase of matrix	Granular IgM and C1q	Electron-dense deposits
	TIS	Normal	Linear IgG, IgA, and C3 along 60% of the TBMs	No deposits
	Vessels	Normal	One arteriole: IgA	Arterioles: no change
1990	Glomerular tufts	Diffusely thickened, spikes	Granular IgG and C3	Relapsing MNP, stage II-III
	Mesangium	No change	No deposits	No deposits
	TIS	Normal	Linear IgG and C3 along 70% of the TBMs	No deposits
	Vessels	No change	No change	Not available
1994	Glomeruli	Mainly sclerotic, open tufts: thickened, spikes	Granular IgG and C3 in patent glomeruli	Sclerotic
	TIS	ISF, TA, focal mononuclear infiltrates, 2+ tubulitis	Linear IgG and C3 along the TBM	No deposits
	Vessels	Arterioles with 2-3 smooth muscle layers	No change	Not available

NOTE. In 1987 and 1990, the tubular immunostaining was interpreted as pseudolinear. In 1994, the diagnosis of sclerosing MNP associated with chronic active anti-TBM nephritis was set up.

Abbreviations: MNP, membranous nephropathy; Foc-segm, focal and segmental; ISF, interstitial fibrosis; TA, tubular atrophy; 2+, 7 lymphocytes/profile; TBM, tubular basement membrane; TIS, tubulointerstitium.

cases of childhood MNP with anti-TBM nephritis have been published in the English literature (Table 2). The clinical features include a male preponderance, onset in early childhood (median age at renal biopsy, 3 years), nephrotic-range proteinuria, microhematuria, complete or incomplete Fanconi syndrome, circulating antibodies against the TBM, and renal insufficiency. Two patients responded to steroid treatment. Progression to end-stage renal disease was reported in six patients. Four patients received a renal transplant. The anti-TBM nephritis recurred in patient 5. Graft loss, however, was due to chronic rejection 3.5 years after transplantation.[5]

During the past few years, several autoantigens have been isolated from collagenase digests of the human TBM.[22-24] Among these, the 58-kd TIN antigen is a glycoprotein macromolecule[25,26] that promotes epithelial cell adhesion.[27,28] Immunofluorescence found that the TIN antigen had the highest expression in the BM of the proximal tubules. The expression was lower in the BM of the Bowman's capsules and distal tubules and
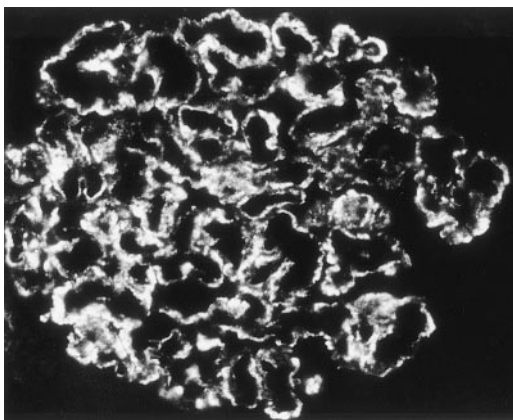

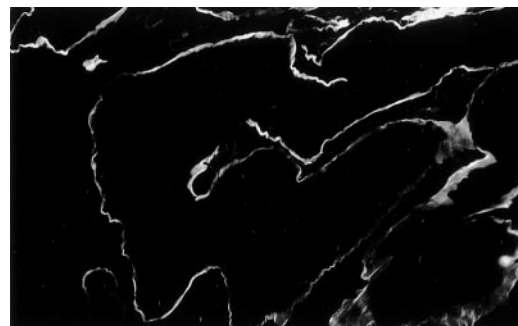**Fig 1.   Membranous nephropathy: Granular deposits of IgG along glomerular capillaries (original magnification ×160).**

Fig 2.   Linear immunostaining of IgG along tubular basement membranes (original magnification ×160).
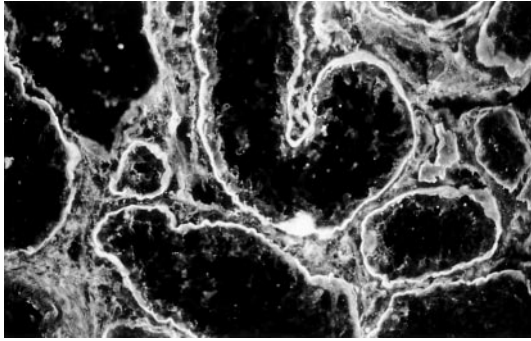
Fig 3. Normal human renal cortex incubated with the patient's serum (1:16) and stained with rabbit anti-human IgG: Linear tubular basement membrane deposition of IgG can be seen (original magnification ×160).

was absent from the glomerular BM and the mesangial matrix. In extrarenal tissues, the TIN antigen was localized in the small intestinal, corneal, and epidermal BMs.[29] In our patient, the ELISA approach showed that the patient's antibodies strongly recognize the 58-kd TIN antigen. The results from the immunoblotting approach were negative, and therefore nothing could be said as to whether the serum reacted with other TBM components besides the TIN antigen. The negativity may be because the autoantibodies are unable to recognize the 58-kd molecule in the conformation present after electrophoresis and blotting. In patients 3, 4, and 5, Western blotting showed a light stain for a 175-kd TBM protein, which could be the 58-kd form bound to another protein, or a trimer of the 58-kd form.[5] Because the anti-TBM antibodies strongly reacted with the 58-kd TIN antigen in all five patients tested so far (Table 2), the 58-kd form seems to be the primary target antigen in anti-TBM nephritis.

The first biopsy showed the coexistence of MNP, hypercellularity and granular immunodeposits of the mesangium, and linear immunostaining along the TBM. Mesangial-immunocomplex nephritis-like changes have not been observed in cases of childhood MNP with anti-TBM nephritis. The second biopsy, however, did not show the mesangial alterations seen in the first biopsy, either because of the intrinsic nature of the disease, or as a consequence of the therapy. The clinical picture in our patient was predominated by the nephrotic syndrome and hypertension. Although TBM immunodeposits were already present at the times of the first and second biopsies, the clinical and morphological signs of

anti-TBM nephritis were not manifested in the first 3 years of the disease. Later, temporary glucosuria was observed, indicating a mild tubular dysfunction, and the third biopsy, 7 years after the onset, showed chronic active TIN. Similarly to what was found in our patient, in patients 2, 6, and 8, the immunodeposits along the TBM were not associated with detectable defects in the tubular function at the time of the biopsy, and in patients 6 and 8, the TBM immunodeposits were not accompanied by light microscopic evidence of TIN. The first biopsy in patients 7 and 10 verified the MNP but did not show any light microscopic or immunomorphological change in the tubulointerstitium, and the renal symptoms at the time of the biopsy did not indicate tubulointerstitial disease. These data strongly suggest that in childhood MNP with anti-TBM nephritis, the glomerular disease is the primary lesion, and the formation of anti-TBM antibodies, their fixation to the TBM, and the development of TIN and tubular dysfunction are secondary phenomena. The manner in which MNP elicits the formation of anti-TBM antibodies is unclear. It may be interesting to mention that also in primary MNP associated with formation of anti-glomerular BM antibody, MNP—as characterized by long-standing nephrotic syndrome and granular immune deposits on the epithelial side of the glomerular BM—seems to precede the anti-glomerular BM response and the development of rapidly progressive, crescentic glomerulonephritis.[30,31] In our patient, the end-stage kidneys were not removed at transplantation. Because the MNP or anti-TBM nephritis did not recur after transplantation, the autoimmune process seemed to be "burned out" during the months of chronic hemodialysis.

Childhood MNP may exhibit extrarenal organ involvement, such as the intestinal villous atrophy in patient 8, or the lung hemorrhage in patients 1 and 9. In patient 8, high titers of circulating autoantibodies directed against the cytoplasm of the intestinal epithelial cells were verified. Direct IF, however, did not show immunoglobulin or complement deposition in the intestinal epithelium, which makes the role of the anti-intestinal epithelial cell antibody in producing intestinal injury uncertain.[7] The pathomechanism of the lung hemorrhage in patient 9 was unresolved. The nature of the extrarenal symp-

Table 2. Features of Childhood Membranous Nephropathy With Anti-TBM Nephritis

Patient	Biopsy (age in years)	Renal Symptoms	TIN	TBM IgG	Circulating Anti-TBM ABs	Renal Outcome	Extrarenal Involvement	Reference
1, Boy	3.8	Proteinuria, Fanconi syndrome, azotemia	Yes	Linear and granular	Positive	ESRD at 5 y	Lung infiltrates, anti-alveolar BM Abs	3
2, Boy	7	NS; incomplete Fanconi syndrome 1 year later	Yes	Linear	Positive	Not reported	Earlier: gluten-sensitive celiakia	4
3, Boy	3.7	NS, microhematuria, glucosuria	Yes	Linear	Positive*	ESRD at 13 y; Tx	Not reported	5
4, Boy	2.2	NS, microhematuria, glucosuria	Yes	Linear	Positive*		Not reported	5
	2.5	NS, azotemia	Yes	Linear	Positive	ESRD; Tx		
5, Boy	4.5	NS, microhematuria, Fanconi syndrome	Prob	Not reported	Positive after Tx*	ESRD at 11.5 y; Tx†	Not reported	5
6, Boy	1.7	NS, microhematuria; no tubular defects	No	Linear	Negative		Not reported	6
	6	Proteinuria, Fanconi syndrome, azotemia	Yes	Linear	Negative	Renal insufficiency		
7, Girl	10	NS, microhematuria; glucosuria later	No	No deposit	Negative		Not reported	6
	14	Proteinuria, tubular defects, azotemia	Yes	Linear	Negative	Renal insufficiency		
8, Boy	3	NS, microhematuria, no tubular defects	No	Linear	Positive	Responded to steroid	Malabsorption, villous atrophy	7
9, Boy	2.2	Proteinuria, azotemia; no tubular defects	No	No deposit	Not tested		Anemia, dyspnea	8
	3	NS, Fanconi syndrome, azotemia	Yes	Linear	Positive	ESRD at 8 y	Alveolar hemorrhage, no anti-alveolar BM Abs	
10, Boy	0.9	NS, microhematuria; no tubular defects	No	No deposit	Not tested			9
	2	NS, microhematuria, Fanconi syndrome	Yes	Linear	Positive*	Responded to steroid	Not reported	
11, Boy	1	NS, microhematuria, no tubular defects	No	Linear	Not tested		At 3 y: epilepsy, at 5 y: ocular, neurological, and abdominal symptoms	Presented case
	4	NS, microhematuria; glucosuria later	No	Linear	Not tested			
	8	NS, azotemia	Yes	Linear	Positive*	ESRD at 9 y; Tx		

Abbreviations: TBM, tubular basement membrane; Ab, antibody; NS, nephrotic-range proteinuria; TIN, tubulointerstitial nephritis by light microscopy; ESRD, end-stage renal disease; Tx, kidney transplantation; prob, probable.

*Reactivity with the 58-kd TIN antigen.

†The anti-TBM nephritis recurred in the graft.

toms in our patient also remained unexplored. Conceivably, the abdominal and ocular complaints could stem from a mild, temporary immune injury to the small bowel and cornea, as the basement membranes of these tissues also contain the TIN antigen. The neurological symptoms might be associated in part with the immune injury to the choroid plexus and the disturbed production of cerebrospinal fluid.[32] Because our patient has been on cyclosporine since renal transplantation, and the drug has not affected his neurological status adversely, the worsening of the neurological symptoms at age 7 was unlikely to have been attributable to a side effect of cyclosporine, as thought originally.

The HLA status has so far been examined in patients 3, 4, 5, and 10. All carried the B7 antigen, and patients 3 and 4 were also positive for the DR8 antigen, suggesting that childhood MNP with anti-TBM nephritis may be HLA-linked, and the B7 or DR8 antigens provide disease susceptibility. In healthy Hungarian individuals, the DQA1 *0501 and DQB1 *0301 alleles predominate,[33] and these alleles in our patient therefore belong to the normal profile. In patients with MNP from England, Germany, and France, the DR3 antigen has been found to be frequent, often in association with the A1 and B8 antigens.[34-37] In Hungarian patients with MNP, only the A1 and A3 antigens, but not the B8, DR2, or DR3 antigens, have been shown to have an increased incidence.[38] In conclusion, the HLA status of our patient differed from any association with HLA-antigens previously reported in childhood MNP with anti-TBM nephritis or primary MNP in whites.

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