Relapse or Worsening of Nephrotic Syndrome in Idiopathic Membranous Nephropathy Can Occur even though the Glomerular Immune Deposits Have Been Eradicated

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Relapse of membranous nephropathy • Salt intake •
Eradication of GBM deposits

Abstract

Background: Relapse or worsening of nephrotic syndrome (NS) in idiopathic membranous nephropathy (IMN) is generally assumed to be due to recurrent disease. Here we document that often that may not be the case. **Subjects and Methods:** This is a prospective study of 7 consecutive IMN patients whose renal status improved, then worsened after completing a course of immunosuppressive therapy. Each underwent detailed testing and repeat kidney biopsy. **Results:** In 4 patients (group A), the biopsy showed recurrent IMN (fresh subepithelial deposits). Immunosuppressive therapy was begun. In the other 3 patients (group B), the biopsy showed that the deposits had been eradicated. However, the glomerular basement membrane (GBM) was thickened and vacuolated. Immunosuppressive therapy was withheld. Groups A and B were comparable except that group B had very high intakes of salt and protein, based on 24-hour urine testing. Reducing their high salt intake sharply lowered pro-

teinuria to the subnephrotic range and serum creatinine stabilized. **Conclusion:** This work is the first to demonstrate that relapse/worsening of NS can occur in IMN even though the GBM deposits have been eradicated. High salt and protein intake in combination with thickened and vacuolated GBM appears to be the mechanism. Copyright © 2011 S. Karger AG, Basel

Introduction

In idiopathic membranous nephropathy (IMN) the recommended approach to manage those who fail immunosuppressive therapy is to consider another course of immunosuppressive therapy, usually with a different immunosuppressive drug [1–3]. Objective assessment of salt and protein intake and strategic use of repeat kidney biopsy is not mentioned. In addition, the recent prospective observational study of the risk factors for progression of conservatively managed IMN did not include or mention assessment of salt and protein intake or repeat kidney biopsy [4]. These measures also were not mentioned in the detailed editorial that accompanied the

IMN observational study [5]. It is well established that salt and protein intake influence proteinuria in proteinuric glomerular diseases (discussed later). However, these influences have largely been ignored in the development of recommendations for the management of proteinuric renal disease.

The herald case that led to the present insights involved an IMN patient who was first seen in 1998 with nephrotic syndrome (NS). He was then lost to follow-up until 2005 when he re-presented with NS. We discovered that, contrary to our 1998 recommendation to follow the Ponticelli protocol (3 months of oral cyclophosphamide) [6], he received 1 year of oral cyclophosphamide therapy at 100–150 mg daily. His edema cleared. His apparent recurrent NS after 1 year of oral cyclophosphamide was surprising because of our consistently favorable experience with shorter courses of oral cyclophosphamide, e.g. 3–4 months [7]. To determine whether further immunosuppressive therapy was warranted, kidney biopsy was repeated. The glomerular basement membrane (GBM) was thickened and vacuolated but there was complete eradication of the GBM electron-dense deposits. Apparently, the cyclophosphamide therapy had been successful. What was not successful was control of his hypertension, and control of his salt and protein intakes both of which were very high based on 24-hour urine testing. We hypothesized that his heavy proteinuria was the consequence of both his structurally abnormal GBM, and conditions that promote glomerular hypertension, specifically high salt intake [8, 9], high protein intake [10–12], and his systemic hypertension [10, 13].

Since the herald case, we have prospectively studied all of the IMN patients presenting to our program with relapse of NS ($n = 6$). Each underwent detailed testing including 24-hour urine testing for salt and protein intake, and repeat kidney biopsy. The herald case and the 6 subsequent cases are the basis for this report.

Subjects and Methods

Patient Population

Our 7 cases are stratified according to whether the repeat kidney biopsy showed recurrence of IMN (group A, $n = 4$) or no recurrence of IMN (group B, $n = 3$). Group A and group B patients are all of the IMN patients evaluated by our nephrology program since 2005 because of relapse of their NS. At presentation with NS, each patient was assessed for secondary membranous nephropathy by history and physical exam, chest X-ray, renal ultrasound and laboratory testing that included a complete blood cell count,

antinuclear antibody, complement C3 and C4, routine liver function studies, and screening for hepatitis C and hepatitis B. All of the studies were normal or negative.

Group A

Case 1 is a 46-year-old European-American (EA) non-smoker who was in good health until early 2000 when he developed edema associated with NS. He received a 5-month course of oral cyclophosphamide therapy along with a tapering dose of prednisone beginning at 80 mg daily. His 24-hour urine protein/creatinine (P/C) ratio decreased by about 50% but he remained nephrotic for the next 6 months. At this point he was entered into a double-blind, randomized trial sponsored by Alexion in which he received periodic infusions of eculizumab or placebo, along with ramipril and atorvastatin. One year later he was in complete remission (24-hour urine P/C ratio <0.3). He remained in complete remission until mid-2005 when his 24-hour urine P/C ratio increased to 3.3 despite maximally tolerated doses of ramipril, candesartan, furosemide, and simvastatin. Mycophenolate 1,000 mg twice daily and prednisone 5 mg daily was given for a period of 6 months. Nephrotic-range proteinuria persisted. Kidney biopsy was repeated.

Case 2 is a 66-year-old EA non-smoker who was in good health until 1992 when he presented with NS that did not respond to enalapril and hydrochlorothiazide therapy. Lower extremity deep vein thrombosis developed. He received warfarin for 1 year. He also received prednisone for 6 months starting at 120 mg every other day. By 6 months his 24-hour urine P/C ratio decreased to 0.6. In 2003, he developed type 2 diabetes. Proteinuria was stable. However, in 2008 his proteinuria gradually increased to nephrotic levels despite benazepril, chlorthalidone, and simvastatin therapy. In early 2009, kidney biopsy was repeated.

Case 3 is a 50-year-old EA male smoker with seasonal allergies who presented in 1996 with difficult to control hypertension and nephrotic-range proteinuria while receiving lisinopril, hydrochlorothiazide, and labetalol. He received cyclophosphamide therapy 125 mg daily for 3 months. By early 1998, 24-hour urine P/C ratio was <0.2 . Serum creatinine remained at 1.5 mg/dl. He was lost to follow-up until mid-2001 when he presented with a 24-hour urine P/C ratio of 3.3. Serum creatinine was 1.2 mg/dl. He was enrolled in the Alexion study (see case 1). One year later his 24-hour urine P/C ratio was 1.2. He was again lost to follow-up until early 2009 when he presented with edema and a marked increase in proteinuria. He continued to smoke. Chest X-ray was negative. Kidney biopsy was repeated.

Case 4 is a 76-year-old EA male non-smoker who was in good health when he presented in 1998 with edema and nephrotic-range proteinuria which persisted despite 4 months of lisinopril and furosemide therapy. He received cyclophosphamide 100 mg daily. By 6 months of this therapy he achieved a 24-hour urine P/C ratio 0.6. Relapse of NS developed 6 months later. He then received a second course of cyclophosphamide 100 mg daily, this time for 4 months, followed by azathioprine 100 mg daily for another year. One year after the start of the second course of cyclophosphamide, he was in complete remission (undetectable proteinuria). He remained in complete remission until early 2008 when his proteinuria increased progressively to nephrotic levels despite benazepril, chlorthalidone, and a statin. Kidney biopsy was repeated.

Group B

Case 1 (the 'herald' case) is a 41-year-old EA male non-smoker who was in good health until 1998 when he was presented with nephrotic-range proteinuria and hypertension. He was treated with lisinopril and furosemide but proteinuria persisted and his serum creatinine began to increase. Cyclophosphamide 150 mg daily and prednisone 20 mg daily was begun with the intention to treat with cyclophosphamide for 3 months, however he was lost to follow-up. Through his primary care physician he received cyclophosphamide 100 mg daily for another 9 months. He re-presented to our program in September of 2002 with heavy proteinuria and increased serum creatinine. He was receiving quinapril, diltiazem extended release, metoprolol, and furosemide. Azathioprine 100 mg daily was begun. His proteinuria did not improve and serum creatinine continued to increase. Kidney biopsy was repeated.

Case 2 is a 45-year-old EA non-smoking male with sleep apnea who presented in early 2003 with lower extremity edema. ACE inhibitor did not improve the proteinuria. Cyclophosphamide 150 mg daily was begun along with prednisone 10 mg daily for 3 months. Proteinuria decreased to <3.0 g/day but by late 2004 proteinuria had increased to >20 g/day. He then received a second course of 3 months of cyclophosphamide 100 mg daily along with prednisone 10 mg daily but heavy proteinuria persisted. Kidney biopsy was repeated.

Case 3 is a 38-year-old EA male who presented in September 2002 with proteinuria. He received losartan and quinapril therapy but heavy proteinuria persisted. In March 2004, cyclophosphamide 150 mg daily was begun along with prednisone starting at 40 mg daily. This was followed by improving and then worsening proteinuria despite good blood pressure control with telmisartan and furosemide. He received a second 3-month course of cyclophosphamide followed by mycophenolate 1,000 mg twice daily. Heavy proteinuria persisted. Kidney biopsy was repeated.

Definitions

Nephrotic-range proteinuria was defined as 24-hour proteinuria >3.5 g. Relapse/worsening was defined as either a change in 24-hour proteinuria from the sub-nephrotic to the nephrotic range, worsening of 24-hour proteinuria, or persistence of nephrotic-range proteinuria accompanied by an increase in serum creatinine level.

Analytic Studies

Laboratory testing was performed at The Ohio State University Medical Center, or at the community hospitals where the patients also received care.

To standardize the results of 24-hour urine testing, the proteinuria results are expressed as the P/C ratio of intended 24-hour urines that were at least 50% complete based on their creatinine content [14, 15]. 24-Hour urine sodium (Na) and urea nitrogen (UUN) excretion were adjusted according to the completeness of the 24-hour collection. Urine Na is expressed as mm/day. UUN is expressed as g/day. To estimate completeness of the intended 24-hour collections, for each collection the expected creatinine content was estimated using Cockcroft-Gault $[(140 - \text{age}) \times \text{weight in kg} \times 0.2 \times 0.85 \text{ (if female)} \times 1.21 \text{ (if black race)}]$ [11]. Completeness of an intended 24-hour collection was taken as the ratio: (measured creatinine content)/(expected creatinine content).

Statistical Analysis

Because of small sample sizes, results are presented as the mean of the individual values and their range.

Results

Table 1 shows the key clinical characteristics of the group A and B patients at presentation with NS, and at time of their most recent relapse/worsening. Table 1 and the case narratives (see Methods) show that group A and B were generally similar. The only major difference was the abnormally high intakes of salt and protein of group B.

Figure 1 shows key aspects of the clinical course for each group B patient. As shown, heavy proteinuria persisted despite repeat courses of immunosuppressive therapy. The repeat kidney biopsies showed that their IMN was no longer immunologically active. Thus, the patients received no further immunosuppressive therapy. Instead, reduction in salt and protein intake and blood pressure control with angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers. These recommendations were never achieved in case 1. Improved diet compliance, however, was achieved in cases 2 and 3 on most occasions. This reduced proteinuria to the sub-nephrotic range, and stabilized serum creatinine levels. Note that the proteinuria data are reported as the P/C ratio of intended 24-hour urine collections (see Methods). This is the most reliable way to monitor proteinuria trends in individual patients, as we have previously shown [14–16]. To convert the P/C ratios to 24-hour proteinuria, the P/C ratios of cases 1, 2, and 3 are multiplied by 1.8, 2.3, and 2.4, respectively.

Figure 2 shows for each group B patient the association between 24-hour urine Na and P/C ratio. These are all of the 24-hour collections taken in the group B patients after the onset of their most recent relapse/worsening of NS. As shown, in general, higher 24-hour Na was associated with greater proteinuria. Also examined was the association between 24-hour urine UUN and P/C ratio, using the same format as that of figure 2. Greater 24-hour UUN was not associated with greater 24-hour urine P/C ratio (data not shown). However, likely this is explained by failure of these patients to change their protein intakes from the high levels shown in table 1.

Figure 3 shows electron photomicrograph of the kidney biopsy at initial presentation and then at the time of relapse/worsening in a representative group B patient (case 2). Figure 4 shows representative electron photomi-

Table 1. Clinical characteristics for group A and group B patients at initial presentation of IMN and at the time of their most recent relapse of NS

Pa- tient No.	Scr mg/dl	24-Hour urine			UA RBC/ HPF	Weight kg/BMI	BP mm Hg	Scr mg/dl	24-Hour urine			UA RBC/ HPF	Weight kg	BP mm Hg	Interval years
		P/C	Na mM	UUN g					P/C	Na mM	UUN g				
Group A at initial presentation								Group A at relapse							
1	0.9	9.4	ND	ND	1	77/24	104/70	1.01	3.3	79	10.2	3	77	98/60	5
2	1.2	6.3	ND	ND	2	86/27	134/80	1.67	4.4	170	8.8	1	88	140/82	16
3	1.5	2.4	360	ND	4	92/27	135/90	1.83	5.4	137	9.1	0	104	130/84	12
4	1.3	6.1	ND	ND	3	73/22	120/80	1.40	3.2	179	10.1	3	78	130/82	11
Mean	1.2	6.0				82		1.48	4.1	141	9.6		86.7		11
Range	0.9–1.5	2.4–9.4				73–86		1.01–1.83	3.2–5.4	79–179	8.8–10.2		77–104		5–16
Group B at initial presentation								Group B at relapse							
1	1.3	6.6	ND	ND	7	90/29	134/74	3.0	10.3	459	15.7	2+ blood	90	198/98	7.4
2	1.2	8.2	ND	ND	1	149/37	108/70	1.23	4.5	280	16	ND	144	108/70	2.2
3	0.6	3.8	ND	ND	10	113/32	130/90	1.0	2.4	321	15.3	6	113	115/74	3.3
Mean	1.0	6.2				110		1.74	5.73	353	15.67		115.7		4.3
Range	0.6–1.3	3.8–8.2				90–149		1.0–3.0	2.4–10.3	280–459	15.3–16.0		90–144		2.2–7.4

Scr = Serum creatinine; P/C = Protein/creatinine ratio; Na = sodium; UUN = urine urea nitrogen; UA RBC/HPF = red cells/high-power field in urine sediment or dipstick blood; BP = blood pressure systolic/diastolic; Interval = years since initial presentation with IMN.

As discussed in the case study narratives, group A patients 3 and 4, and group B patient 3 each experienced one relapse of NS between initial presentation and the most recent relapse (described above). ND = Not done.

crographs from the repeat kidney biopsies of group B cases 1 and 3. The key findings are that in the repeat kidney biopsies the GBM electron-dense deposits were either eradicated or were rare and surrounded by GBM, indicating that the deposits had formed in the remote past [17].

Table 2 provides a semiquantitative assessment of the light, immunofluorescence, and electron microscopy renal biopsy [18] in group A and group B. The key finding is that at relapse/worsening electron-dense deposits were eradicated in group B.

Discussion

Although relapse of NS in IMN is common, about 30% or more of patients relapse after treatment [1, 2], to the best of our knowledge our work is the first to systematically study IMN relapse by objectively assessing salt and protein intake, and by repeat kidney biopsy. We found that in 4 of the 7 cases (group A), relapse of heavy proteinuria was caused by recurrence of the IMN. However, in 3 of the 7 cases (group B), relapse was not attributable to recurrence of IMN. There was complete or nearly complete eradication of electron-dense GBM deposits.

Evidence that abnormally high salt intake was causally related to recurrence of heavy proteinuria in group B is that reducing salt intake to about 200 mmol/day or less resulted in reductions in proteinuria to the sub-nephrotic range and stabilization of serum creatinine levels.

We could not demonstrate an association between protein intake (24-hour UUN) and proteinuria in the group B patients. However, it is well established that increased protein intake increases proteinuria in chronic kidney disease (CKD) [10, 12]. Our failure to detect an association may be explained by the narrow range of high protein intakes in the group B patients (table 1).

Other studies have also shown that increased salt intake can substantially increase proteinuria in non-diabetic CKD [8, 9]. For example, an increase of salt intake from 50 or 100 mmol/day to 200 mmol/day can increase proteinuria from <3 g/day to >8 g/day [8] even though the patient was receiving an ACE inhibitor or an angiotensin receptor blocker [8, 9]. With regard to the ability of dietary protein to influence proteinuria in CKD, it has been shown that decreasing dietary protein intake from normal (1.0–1.3 g/kg/day) to 0.7 g/kg/day decreases 24-hour proteinuria by about 50% in those with NS, even if they are receiving an ACE inhibitor [11]. Increased salt intake also increases microalbuminuria, especially in hyperten-

Fig. 1. Clinical course of the group B patients. **a** Case 1. The key points are that the patient received cyclophosphamide at 150 mg daily for 3 months, then 100 mg daily for 9 months. The latter course occurred when he was lost to follow-up by us. After he re-presented with NS relapse, we were unable to achieve control of blood pressure or dietary salt and protein intake. He progressed to end-stage renal disease. **b** Case 2. The key points are that nephrotic-range proteinuria (>11.0 g/day) persisted despite two courses of cyclophosphamide. However, decrease in proteinuria to the sub-nephrotic range was achieved when dietary salt intake

was reduced (see fig. 2). This was instituted shortly after the second kidney biopsy. Additional information is not available because the patient has been lost to follow-up. **c** Case 3. The key points are that nephrotic-range proteinuria (>6.0 g/day) persisted despite two courses of cyclophosphamide. However, decrease in proteinuria to the sub-nephrotic range was achieved when control of salt intake was reduced (see fig. 2). This was instituted shortly after the second kidney biopsy. His serum creatinine remains stable at the levels shown in table 1 and proteinuria remains improved on a regimen of better control of salt and protein intake.

sive diabetics [19, 20] and those receiving losartan [21]. A positive association of sodium intake with proteinuria was also noted in the patients of the African American Study of Kidney Disease and Hypertension (AASK), who generally had proteinuria levels <500 mg/24 h [22].

With regard to the pathogenesis of the glomerular changes in the group B patients, we suggest the following

scenario. The immunosuppressive therapy (or natural suppression) of the pathogenic antibodies in IMN resulted in cessation of new GBM deposits. Under favorable circumstances, the deposits would eventually resolve and the GBM would remodel towards normal [23]. However, because of the glomerular hypertension/hyperperfusion resulting from high dietary salt and protein intake (cases

Fig. 2. Association of 24-hour urine Na excretion with 24-hour urine P/C for the group B patients. Note that for each patient, in general, greater salt intake was associated with greater proteinuria. The values shown are all of the 24-hour testing results on each patient.

Fig. 3. Group B, case 2 electron microscopy findings from the first and second biopsy. The first biopsy (a) shows abundant subepithelial electron-dense immune-type deposits. The second biopsy (b) shows prominently thickened GBM with electron-lucent areas, but no discrete electron-dense immune-type deposits.

Fig. 4. Group B case 1 and case 3 electron microscopy findings of their second kidney biopsies. Case 1 (a) shows irregularly thickened GBM with numerous electron lucencies. No discrete electron-dense immune-type deposits are seen. Case 3 (b) shows irregularly thickened GBM with numerous electron lucencies. Only rare deposits are seen.

Table 2. Semiquantitative analysis¹ of the light, immunofluorescence and electron microscopy findings in each of the group A and group B patients based on their original kidney biopsy (first biopsy) and the repeat biopsy done at the time of their most recent relapse (second biopsy)

		Light microscopy			Immunofluorescence		Electron microscopy		
		glom cap thickening	glomerular sclerosis	interstitial fibrosis	glomerular capillary		glomerular basement membrane		
					IgG	C3	electron dense dep	irregular thickening	electron lucencies
<i>Group A</i>									
1	1st biopsy ²	NA ³	NA	NA	NA	NA	NA	NA	NA
	2nd biopsy	2	0	+/-	3+	1+	3+	3+	2+
2	1st biopsy ⁴	3+	1+	1+	NA	NA	NA	NA	NA
	2nd biopsy	3+	2+	2+	2+	1+	2+	3+	3+
3	1st biopsy	1+	0	0	3+	2+	3+	1+	0
	2nd biopsy	3+	2+	2+	3+	0	3+	3+	3+
4	1st biopsy	1+	0	0	3+	2+	3+	1+	0
	2nd biopsy	2+	1+	2+	3+	1+	3+	3+	2+
<i>Group B</i>									
1	1st biopsy	2+	0	1+	3+	3+	3+	2+	2+
	2nd biopsy	3+	2+	2+	1+	0	+/-	3+	3+
2	1st biopsy	2+	0	1+	3+	1+	3+	2+	+/-
	2nd biopsy	3+	0	1+ to 2+	1+	+/-	+/-	3+	3+
3	1st biopsy	1+	0	0	3+	0	3+	1+	0
	2nd biopsy	2+	1+	1+	2+	+/-	1+	3+	3+

cap = Capillary; dep = deposits; glom = glomerular.

¹ 0 absent; +/- minimal; 1+ mild; 2+ moderate; 3+ proteinuria (see Results). ² Performed at an outside institution, which did not perform digital images of the electron microscopy ³ Not available. ⁴ Only paraffin sections were available.

1–3), and inadequate blood pressure control (case 1), the GBM remained thickened, vacuolated, and excessively porous to plasma proteins.

Additional harmful effects of high salt intake include stimulation of the tissue RAAS, induction of TGF- β with adverse effects on endothelial nitric oxide, and increased activation of the aldosterone receptor increasing the pro-fibrotic effects of aldosterone [24]. These effects of high salt intake appear to be exaggerated in patients with high body mass index (BMI) [24] (cases 2 and 3 of group B). High BMI itself is also associated with proteinuria. Usually, the proteinuria level is sub-nephrotic [25, 26]. Thus, high BMI could have contributed to some of the very heavy proteinuria of group B, cases 2 and 3.

Despite the potent effects of high salt and protein intake on proteinuria in patients with proteinuric CKD, these dietary parameters are rarely routinely monitored in IMN clinical trials. Thus, the efficacy of immunosup-

pressive therapy in randomized trials may have been underestimated. Some of the patients who received immunosuppressive treatment may have eradicated the glomerular immune deposits but because of excessive dietary salt and protein intake (or inadequate blood pressure control), their proteinuria was sustained at high levels spuriously suggesting that the immunosuppressive therapy had failed. On the other hand, in uncontrolled IMN trials [27] therapeutic efficacy may have been overestimated because some of the reported decreases in proteinuria may have been due to better compliance with diet and other measures, which commonly occurs when patients enroll in clinical trials [28].

A further implication of this work is that proteinuria change alone should not be relied upon to assess therapeutic efficacy of immunosuppression in clinical trials, as has been suggested [29–31]. Clearly, this requires further study [32]. Those studies should include measure-

ment of 24-hour urine Na and UUN in order to more accurately interpret change in proteinuria.

The present study does not make clear how often relapse/worsening of IMN is the result of recurrence of IMN or failure to control 'hemodynamic factors'. That would require a much larger study. However, the present report suggests that this is not a rare occurrence. The present study does, however, provide an estimate of when the level of salt intake can mimic recurrence of IMN. For example, as shown in table 1, it would appear that 24-hour urine sodium excretion <170 mEq is not sufficient for hemodynamic factors to mimic recurrence of IMN. Also, the group B patients achieved sub-nephrotic proteinuria when the 24-hour urine for sodium was <200 mmol/24 h (fig. 2).

The implications of our findings with regard to patient management seem clear. IMN patients who experience relapse should first be tested to see whether the relapse can be accounted for by hemodynamic measures (high blood pressure, or high intake of salt or protein, or the use of DH-CCB) [11, 33, 34]. If these factors can be excluded, likely recurrence of IMN has occurred. Additional immunosuppressive therapy may then be indicated. On the other hand, if high intake of salt and/or protein is found, or if hypertension is poorly controlled, a trial to correct these measures is warranted. This should include reduced salt and protein intake to the levels discussed above, and blood pressure control using antihypertensive medications that do not worsen glomerular hypertension

[12, 35]. If these measures markedly improve proteinuria, a trial of conservative therapy (no immunosuppressives) seems appropriate. If these measures do not substantially reduce proteinuria, a repeat kidney biopsy or, perhaps, testing for antibodies to M-type phospholipase A₂ receptor [36], would be appropriate to determine whether the patient has recurrence of IMN [37].

In summary, the present study provides unequivocal evidence that heavy proteinuria can recur in IMN patients even though the electron-dense deposits have been eradicated. Implications of these findings are substantial with regard to individual patient care, and to interpretation of past clinical trials and design of future clinical trials.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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