




Successful treatment of coexisting membranous nephropathy and immune thrombocytopenia by eradicating gastric *Helicobacter pylori* infection: a case report

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Abstract

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in middle-aged and older adults. MN etiology is mainly primary or idiopathic; however, it may also be secondary to infections, drugs, neoplasms, and autoimmune diseases. We present the case of a 52-year-old Japanese man with coexisting nephrotic MN and immune thrombocytopenic purpura (ITP). Renal biopsy revealed glomerular basement membrane thickening with immunoglobulin (Ig) G and complement component 3 deposition. Glomerular IgG subclass analysis revealed predominant IgG4 deposition with weak IgG1 and IgG2 deposition. IgG3 and phospholipase A2 receptor deposits were negative. Upper endoscopy revealed no ulcers, but histological examination demonstrated *Helicobacter pylori* infection in the gastric mucosa with elevated IgG antibodies. After gastric *Helicobacter pylori* eradication, the nephrotic-range proteinuria and thrombocytopenia of the patient were markedly improved without initiation of immunosuppressive treatment. Therefore, clinicians should consider the possibility of *Helicobacter pylori* infection in patients with coexisting MN and ITP. Further studies are required to demonstrate the associated pathophysiological aspects.

Keywords *Helicobacter* · Membranous nephropathy · Nephrotic syndrome · Thrombocytopenia

Introduction

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in middle-aged and older patients [1, 2]. In most cases, its etiology is idiopathic; however, it may occur secondary to several causes, including infections, drugs, neoplasms, and autoimmune diseases [3–5]. Recently, reports have indicated a pathogenic correlation between *Helicobacter pylori* infection and MN [6–8]. *Helicobacter pylori* antigens have been found in the glomeruli of MN patients [9], and successful *Helicobacter pylori* eradication reduced proteinuria [6, 7]. Additionally, immune thrombocytopenic purpura (ITP), an autoimmune bleeding

disorder characterized by platelet destruction and production inhibition [10], has a pathophysiological link with chronic *Helicobacter pylori* infections. This finding is based on the increased platelet count of patients with ITP after gastric *Helicobacter pylori* eradication therapy [11, 12].

Herein, we present the case of a 52-year-old Japanese man with coexisting MN and ITP whose nephrotic-range proteinuria and thrombopenia were markedly improved after the eradication of gastric *Helicobacter pylori* infection.

Case report

A 52-year-old Japanese man with a history of hypertension and dyslipidemia was admitted to our hospital. His annual health check-ups revealed no significant blood or urine test abnormalities besides dyslipidemia. However, 3 months before the admission, he developed edema in his lower limbs and high dipstick proteinuria (3+).

On evaluation, the patient was 168 cm tall and weighed 87 kg, which increased by 3 kg compared to before the edema appeared. He had a 128/84 mmHg blood pressure

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and an 84 bpm pulse with a regular rhythm. Lower limb edema with pinpoint-sized petechiae was evident. Neurological findings were unremarkable. He had no symptoms or findings suggesting autoimmune diseases, including systemic lupus erythematosus or Sjögren's syndrome. Table 1 demonstrates the laboratory findings on admission. His spot urinary protein-to-creatinine ratio was 7.6 g/g Cr with a decreased serum albumin concentration of 2.1 g/dL, leading to the diagnosis of nephrotic syndrome. Notably, his serum creatinine concentration was 0.60 mg/dL. His platelet count dropped to 54,000 / μ L, below the ITP diagnostic criterion of 100,000 / μ L.

Figure 1 illustrates the renal biopsy findings performed 1 day after admission. Light microscopy revealed 25 glomeruli without global glomerulosclerosis (Fig. 1a). The glomerular basement membrane (GBM) was thickened with a bubbly appearance and spike lesion. However, mesangial proliferation, endocapillary hypercellularity, extra-capillary proliferation, or segmental sclerotic lesions were not observed. Immunofluorescence staining revealed that the capillary walls were strongly positive for immunoglobulin (Ig) G and mild for IgA (Fig. 1d), complement component 3 (C3) (Fig. 1e), trace staining for IgM and C1q (Fig. 1f), and negative for phospholipase A2 receptor (PLA2R) (Fig. 1g). Glomerular IgG subclass analysis revealed predominant IgG4 deposition (Fig. 1k) but weak IgG1 and

IgG2 deposition (Fig. 1h, i). The IgG3 deposit was negative (Fig. 1j). Transmission electron microscopy revealed granular electron-dense deposits in the subepithelial regions of the GBM (Fig. 2). Additionally, signs of podocyte damage were observed, including diffuse foot process effacement and an increase in the number of actin filaments. These histological features were compatible with the diagnosis of secondary MN (Ehrenreich and Churg criteria stage II). Malignancy was almost ruled out using upper and lower gastrointestinal endoscopy and whole-body computed tomography scans. Upper endoscopy revealed no ulcers, but histological examination demonstrated *Helicobacter pylori* infection in the gastric mucosa. Table 1 reveals the negative test results for serum anti-hepatitis B surface antigen and anti-hepatitis C virus antibodies. The autoimmune screen revealed positive anti-nuclear antibodies, anti-Smith (Sm) antibodies (33.0 U/mL; normal range < 7.0 U/mL), and anti-Sjögren's-syndrome-related antigen A (SS-A) antibodies (> 240 U/mL; normal range < 7.0 U/mL), but was negative for double-stranded deoxyribonucleic acid and ribonucleic acid-polymerase-III antibodies. Complement levels and thyroid function tests were within their normal ranges without any subjective or objective findings associated with autoimmune diseases.

One week after the renal biopsy, the patient's platelet-associated-IgG and *Helicobacter pylori* IgG antibodies of

Table 1 Laboratory findings on admission

Urinalysis		Chemistry		Serology (normal range)	
Specific gravity	1.022	Total protein	5.5 g/dL	Rheumatoid factor	< 3.0 IU/mL (< 15 IU/mL)
pH	6.5	Albumin	2.0 g/dL	IgG	1136.8 mg/dL
Protein	(3+)	AST	21 IU/L	IgA	339.1 mg/dL
Glucose	(-)	ALT	16 IU/L	IgM	56.6 mg/dL
Occult blood	(2+)	LDH	188 IU/L	C3	123.4 mg/dL
Sediment		Total cholesterol	279 mg/dL	C4	33.2 mg/dL
RBC	20–29/hpf	Triglyceride	112 mg/dL	CH50	47.5 U/mL
WBC	1–4/hpf	BUN	12.7 mg/dL	ANA	40 \times (< 40 \times)
U-PCR	7.6 g/gCr	Creatinine	0.61 mg/dL	dsDNA	0.5 IU/mL (< 10 IU/mL)
U-NAG/Cr	14.3 U/gCr	eGFR	109 mL/min/1.73m ²	ssDNA	12 AU/mL (< 25 AU/mL)
U- β 2MG	0.20 μ g/mL	Cys C	0.70 mg/L	RNP	1.1 U/mL (< 5.0 U/mL)
Ccr	115.1 mL/min	Na	140 mEq/L	Sm	33.0 U/mL (< 7.0 U/mL)
		K	4.0 mEq/L	SS-A	> 240.0 U/mL (< 7.0 U/mL)
Peripheral blood		Cl	107 mEq/L	SS-B	0.7 U/mL (< 7.0 U/mL)
White blood cell	7120/ μ L	Ca	8.3 mg/dL	PA-IgG	53.0 ng/10 ⁷ cells (< 46 ng/10 ⁷ cells)
Red blood cell	385 \times 10 ⁴ / μ L	iP	2.7 mg/dL	Cryoglobulin	–
Hemoglobin	11.6 g/dL			HBs-Ag	–
Hematocrit	34.6%			HCV-Ab	–
Platelet	54 \times 10 ⁴ / μ L			C-reactive protein	0.88 mg/dl

hpf high power field, β 2MG β 2-microglobulin, Ccr creatinine clearance, AST aspartate aminotransferase, ALT alanine aminotransferase, LDH lactate dehydrogenase, ALP alkaline phosphatase, BUN blood urea nitrogen, ANA anti-nuclear antibody, MPO-ANCA myeloperoxidase-antineutrophil cytoplasmic antibody, PR3-ANCA Proteinase 3-antineutrophil cytoplasmic antibody, anti-GBM anti-glomerular basement membrane, ACE angiotensin-converting enzyme

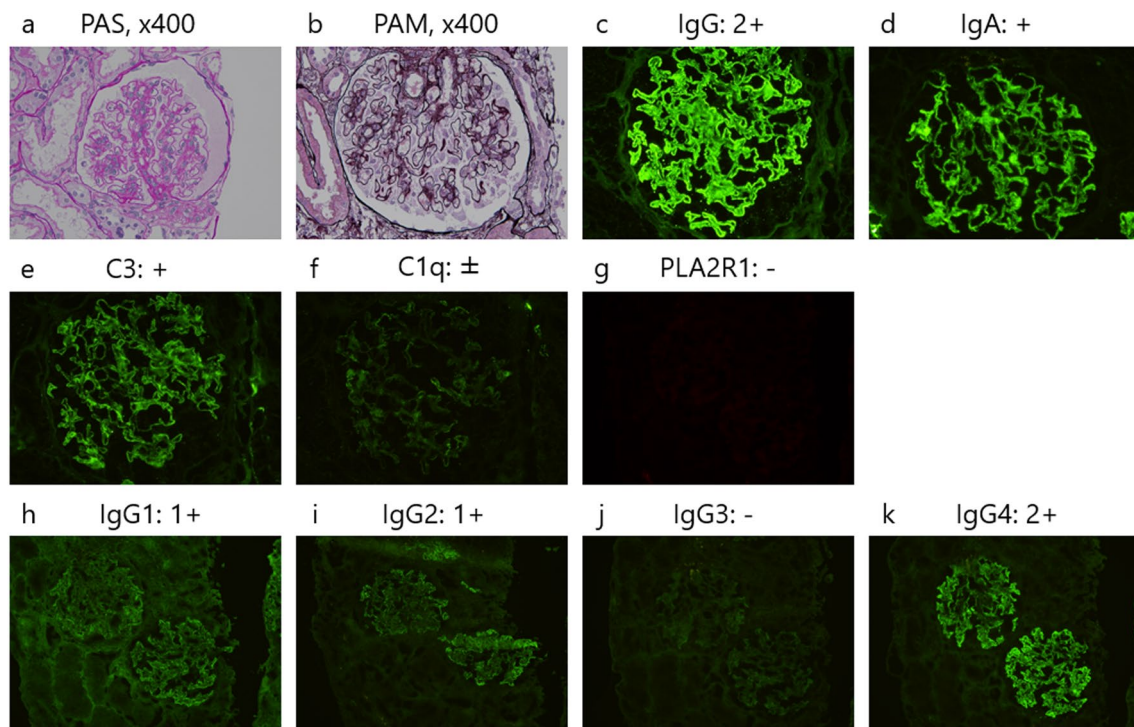
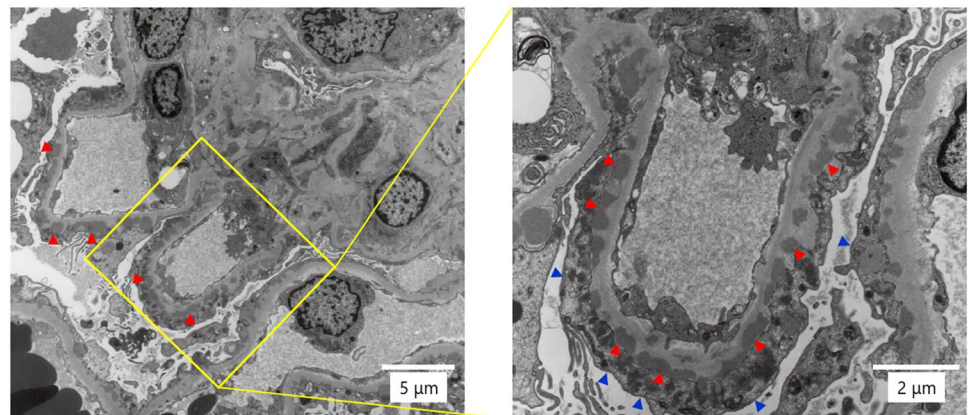


Fig. 1 Light microscopy and immunofluorescence findings of the renal biopsy. **a** Light micrograph reveals 25 glomeruli without global sclerosis (periodic acid–Schiff (PAS) staining, $\times 400$). No segmental sclerotic lesions can be observed. **b** The glomerular basement membrane was thickened with a bubbly appearance and a spike lesion (periodic acid–methenamine silver (PAM) staining, $\times 400$). **c–f** Immunofluorescence staining reveals deposition of IgG (**c**), IgA (**d**),

and C3 (**e**) and trace staining for C1q (**f**) in the glomerular basement membrane ($\times 400$). **g** Staining for PLA2R is negative ($\times 400$). **h–k** Immunofluorescence analysis of IgG subclasses indicates a predominance of IgG4 deposition (**k**) followed by IgG1 (**h**) and IgG2 (**i**) in a peripheral granular pattern ($\times 200$). The staining for IgG3 is negative (**j**). *Ig* immunoglobulin, *C3* complement component 3, *PLA2R* phospholipase A2 receptor

Fig. 2 Transmission electron microscopic findings of the renal biopsy. The transmission electron micrograph of the renal tissue reveals granular electron-dense deposits in the subepithelial regions of the glomerular basement membrane (red arrowheads). Diffuse podocyte effacement can be observed (blue arrows)

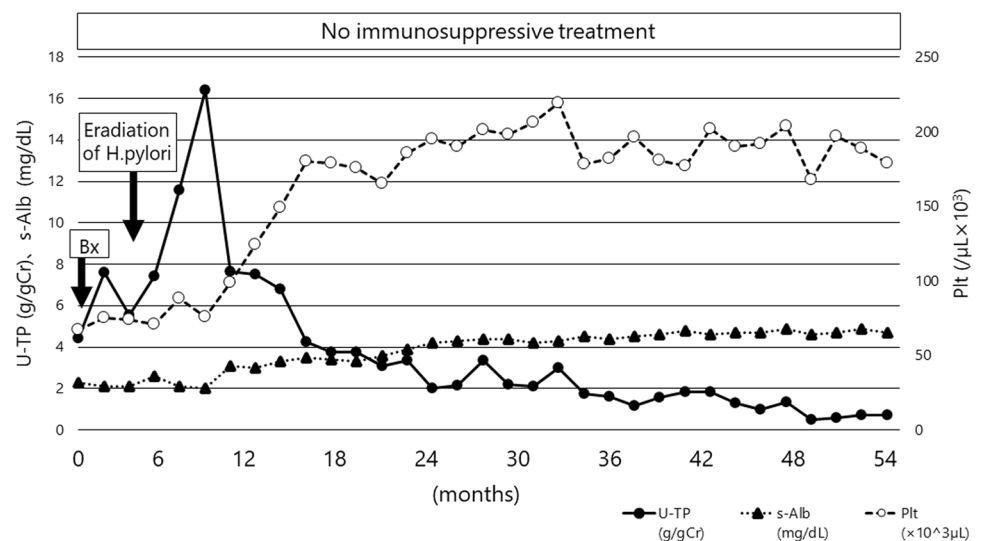


the patient were elevated at $53 \text{ ng}/10^7$ cells ($> 46 \text{ ng}/10^7$ cells) and $30.9 \text{ U}/\text{mL}$ ($> 9.9 \text{ U}/\text{mL}$), respectively. A bone marrow aspirate demonstrated normal cellularity, adequate megakaryocytes, and no evidence of malignancy. There were no other apparent thrombocytopenia causes including medications and food supplements. However, his 3-month platelet count of $67,000\text{--}88,000/\mu\text{L}$ indicated the presence of ITP. From these results, we speculated that *Helicobacter pylori*

infection caused secondary MN and ITP. The patient was started on triple therapy for his *Helicobacter pylori* infection (amoxicillin 1 g twice daily, clarithromycin 500 mg twice daily, and pantoprazole 40 mg twice daily for 14 days).

Four months after the *Helicobacter pylori* infection was eradicated, the proteinuria and thrombocytopenia of the patient improved without initiation of immunosuppressive treatment (Fig. 3). Furthermore, his serum

Fig. 3 Clinical course after admission to our hospital. Gastric *Helicobacter pylori* eradication causes a proteinuria decrease and a gradual platelet count increase. U-pro urinary protein, g/gCr urinary protein/creatinine ratio



albumin concentration increased to 4.0 g/dL, and proteinuria decreased within the normal range, indicating complete remission. Additionally, his platelet-associated IgG titer decreased within the normal range ($34 \text{ ng}/10^7 \text{ cells}$) after 4 months post-eradication. After 5 years post-eradication, although anti-nuclear, anti-Sm, and anti-SS-A antibodies were still positive ($40\times$, 13.0 U/mL , and $> 240 \text{ U/mL}$, respectively), the patient did not exhibit any symptoms of autoimmune disease or MN and ITP relapse. Therefore, we hypothesized that *Helicobacter pylori* infection was associated with the coexistence of MN and ITP.

Discussion

This study is the first case report to describe the successful treatment of coexisting MN and ITP solely through eradicating gastric *Helicobacter pylori* infection.

MN is the most common cause of nephrotic syndrome among adults, accounting for approximately one-third of cases. It is especially prevalent in Caucasian adults, with a 2:1 male preponderance and a peak incidence in individuals aged 50–60 years [5]. There is increasing evidence that autoimmune issues may cause idiopathic MN. Furthermore, this finding is supported by target antigens on the podocyte surface which have been found in most primary MN cases. These proteins are mainly PLA2R and rarely thrombospondin type 1 domain-containing 7A [5]. Serum PLA2R autoantibodies have been found in most (52–82%) patients with primary MN and are typically absent in those with secondary MN conditions [13]. Our patient tested negative for PLA2R in the immunofluorescence renal biopsy findings, indicating a possible secondary pathogenesis contributing to his MN. However, primary MN cannot be completely ruled out.

Furthermore, capillary wall positivity was present for IgG1, IgG2, as well as IgG4, and negative for IgG3. While autoimmune diseases, including systemic lupus erythematosus, have long been associated with MN, other vague autoimmune syndromes have also been reported, including inflammatory arthritis and ITP [14–16]. Additionally, an association between *Helicobacter pylori* infection and autoimmune diseases has been previously reported, including SLE, Sjögren's disease, and rheumatoid arthritis [17]. Although our patient did not exhibit a typical full-house pattern of immunoglobulin deposition in the glomerular basement membrane or any symptoms suggesting autoimmune diseases, including systemic lupus erythematosus or Sjögren's syndrome, he may have had an underlying autoimmune disease or overlapping syndrome because he was positive for anti-Sm and anti-SS-A antibodies even after 5 years post-eradication of his gastric *Helicobacter pylori*. The anti-Sm antibody is specific for systemic lupus erythematosus; however, its sensitivity is restricted [18]. The clinical significance of anti-Sm antibodies is still under debate. Furthermore, although we must monitor our patient for the possibility of late-onset systemic lupus erythematosus [18] or overlap syndrome [19], we successfully treated coexisting MN and ITP with gastric *Helicobacter pylori* eradication.

Several cases have previously reported a link between MN as well as ITP and were treated using prednisolone [19], a combination of prednisolone with immunosuppressive therapy [15, 16], rituximab [20], or low-density lipoprotein apheresis [21]. However, there are no reports on patients with coexisting MN and ITP whose condition improved after gastric *Helicobacter pylori* infection eradication. A recent meta-analysis on the effect of eradicating gastric *Helicobacter pylori* in patients with ITP, including 241 patients (125 in the eradication group and 116 in the control group) from 6 studies, demonstrated that those in the eradication

group had a significantly higher overall platelet response rate than those in the control group (odds ratio = 1.93, 95% confidence interval: 1.01–3.71, $P=0.05$) [22]. This finding indicates that *Helicobacter pylori* eradication has a significant therapeutic effect on patients with ITP. Considering the intrinsic desing limitation and sample size of the included studies, physicians in the clinical scenario should consider eradicating of gastric *Helicobacter pylori* in patients with coexisting MN and ITP.

Our study had several limitations. First, we could not provide a direct relationship and time course evidence between MN, ITP, and *Helicobacter pylori* infection. Patient symptoms developed several months before admission; however, deposit localization in electron micrographs (Ehrenreich and Churg criteria stage II) and strong IgG staining suggested a long-lasting immune abnormality causing membranous nephropathy. Second, we cannot completely exclude the possibility that the symptoms of the patient could have improved by spontaneous MN and ITP remission. Spontaneous complete proteinuria remission in patients with MN occurs in 5 to 30 percent patient at 5 years [23–25]. Furthermore, spontaneous remissions (presumed to be treatment independent) occur in up to 10–20% adults with ITP [26, 27]. These often occur within the first 6 months, but platelet count improvements years later have also been reported [27]. Third, serum PLA2R and thrombospondin were not tested, which can be considered a limitation in our report. Furthermore, multiple studies have found autoantibodies bound to podocyte antigens, predominantly belonging to the IgG4 subclass. These podocyte-specific autoantibodies can be present in the serum and glomeruli of patients [11].

In conclusion, clinicians should consider the possibility of *Helicobacter pylori* infection in patients with coexisting MN and ITP. Further studies are required to demonstrate the associated pathophysiology.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval This article does not involve any studies conducted on human participants or animals by any authors.

Informed consent Written informed consent was obtained from the patient for the publication of his clinical data.

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