Membranous glomerulonephropathy in a patient with bullous pemphigoid

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Abstract Bullous pemphigoid (BP) is a common autoimmune blistering disease that can be complicated by autoimmune disorders. We describe a patient with BP who developed membranous glomerulonephropathy (MN). Proteinuria decreased during the clinical course as anti-BP180 antibody titers decreased. This finding suggested an association between the pathogenesis of these two diseases in terms of immunological disorders.

Keywords Autoimmune skin disease · Nephrotic syndrome

Introduction

Bullous pemphigoid (BP) is an autoimmune blistering skin disease that usually develops in elderly persons. The etiology of BP is associated with immunological abnormalities that are characterized by a chronic course of sub-epidermal bullous skin lesions with linear IgG and C3 deposition at the cutaneous basement membrane zone [1, 2] and frequently elevated serum basement membrane zone antibodies (BP180, 230) [3]. Patients with autoimmune diseases and malignancies often develop BP, and some are

complicated by kidney diseases, such as membranous glomerulonephropathy (MN) [2–4].

Here, we describe MN that developed in a patient with BP. Steroid therapy helped to decrease proteinuria and heal skin lesions while concomitantly lowering BP-specific autoantibodies.

Case

A man who had been diagnosed with impaired glucose tolerance in his early 60s developed chronic prurigo in his 70s and was hospitalized in his early 80s (June 2012) with nephrotic syndrome. The skin rash had worsened during April 2012, with tense blisters, particularly on the flexor side of the arms, the proximal thighs, and trunk. Around this period, leg edema developed and he gained 4 kg. A physical examination revealed obvious edema in the bilateral lower extremities and massive tense blisters, crusted eruptions, and edematous erythema over the extremities and trunk. Laboratory findings revealed low levels of total protein (5.3 g/dL) and serum albumin (1.7 g/dL), high levels of IgM (1034 mg/dL) and IgE (5531 U/mL), and an IgG value of 1126 g/dL. Levels of IgG2, 3, and 4 were within normal ranges, whereas that of IgG1 was low (Table 1). Urinalysis revealed severe proteinuria (5.6 g/day) and a selectivity index of 0.62. No findings suggested active infections or malignancies (Table 1). A renal biopsy obtained on day 8 showed mild thickening of the capillary walls (Fig. 1) and diffuse granular IgG (+), IgG2 (±), IgG4 (++), and C3 (±) deposits along the glomerular capillary loops (Fig. 2). Deposits of IgG1 and IgG3 were undetectable. Electron microscopy showed small sub-epithelial deposits and mild thickening of the glomerular basement membrane (Fig. 3). These findings

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Table 1 Laboratory data

Complete blood count		Biochemical test		Immunological test	
WBC	7000/mm ³	TP	5.3 g/dL	IgG	1126 mg/dL
Neutrophil	64.6%	Alb	1.7 g/dL	IgG1	231 mg/dL
Lymphocyt	21.2%	BUN	13.1 mg/dL	IgG2	450 mg/dL
Monocyt	8.5%	Cr	0.76 mg/dL	IgG3	27.1 mg/dL
Eosinophil	5.4%	UA	5.7 mg/dL	IgG4	54.1 mg/dL
Basophil	0.3%	Adjusted Ca	9.9 mg/dL	IgA	352 mg/dL
RBC	332 × 10 ⁴ /mm ³	P	4.1 mg/dL	IgM	1034 mg/dL
Hb	12.7 g/dL	T-bil	0.8 mg/dL	IgE	5581 IU/mL
Ht	36.6%	D-bil	<0.1 mg/dL	C3c	139.0 mg/dL
Plts	14.0 × 10 ⁴ /mm ³	AST	41 IU/L	C4	32.9 mg/dL
PT	96%	ALT	35 IU/L	CH50	50 CH50
APTT	34.8 s	ALP	166 IU/L	IC-C1q	≤1.5 µg/mL
		γ-GTP	33 IU/L	RF	<7.0 IU/mL
Urinalysis		LDH	269 IU/L	ANA	(–)
Protein	5.6 g/day	T-chol	450 mg/dL	MPO-ANCA	<10 EU
Occult	(–)	LDL-chol	290 mg/dL	PR3-ANCA	11 EU
Sugar	(–)	HDL-chol	46 mg/dL	Cryoglobulin	(–)
RBC	1–4/HPF	TG	233 mg/dL	CEA	2.5 ng/mL
WBC	1–4/HPF	Glu	97 mg/dL	CA19-9	9.2 U/mL
Granular cast	5–9/HPF	Na	140.5 mEq/L	PSA	0.406 ng/mL
NAG	19.0 U/L	K	4.0 mEq/L	ASO	105 IU/mL
β2MG	4085 µg/L	Cl	109.8 mEq/L	HBs ag	(–)
Selectivity index	0.62	HbA1c	6.3%	HCV ab	(–)
				Wa-R	(–)

Fig. 1 Light microscopy findings. Mild thickening of the capillary walls (PAM ×80)

suggested that MN (stage 1–2) was the cause of the nephrotic syndrome.

The cutaneous symptoms with tense blistering suggested an autoimmune bullous disease, such as pemphigus and

BP. Drugs were not the cause of the bullous pemphigoid, because the patient was not under regular medication before admission. We measured antibodies to BP antigens 1 and 2 (BP230 and BP180, respectively) and desmoglein (Dsg) 1 and 3. Anti-BP180 antibody was significantly elevated at 76.6 U/mL (reference range, <9 U/mL), whereas other autoantibodies were undetectable. Therefore, the skin disease was diagnosed as BP, although a skin biopsy was unobtainable at the time as the blistering had worsened. Scores for erosions/blisters by bullous pemphigoid disease area index (BPDAI) indicated severe lesions, while urticaria/erythema and mucosal lesions were mild.

Oral prednisolone (PSL) was started at 30 mg/day (0.5 mg/kg/day) from day 15. The initial dose of PSL was decided based on disease activity by BPDAI and the fact that the patient was elderly. This therapeutic strategy effectively treated the BP and MN, while improving the proteinuria and cutaneous symptoms. Furthermore, proteinuria decreased as the disease activity of BP improved. Proteinuria decreased to 2.1 g/day by day 60 and was undetectable by day 320 (Fig. 4). The anti-BP180 antibody titers on days 60 and 320 were 26.4 and 5.8 U/mL, respectively (Fig. 4).

Fig. 2 Immunofluorescence microscopy findings. Granular deposition of IgG (+; **a**), C3 (+/–; **b**), IgG2 (+/–; **c**), and IgG4 (++; **d**) is evident along capillary walls

Fig. 3 Electron microscopy findings. Sub-epithelial electron-dense deposits are visible along glomerular basement membranes ($\times 5000$)

Fig. 4 Clinical course

Discussion

We described a patient who developed BP and MN. Bullous pemphigoid was diagnosed based on the presence of BP-specific antibodies and cutaneous symptoms. To clinically distinguish BP, pemphigus can be difficult. However, several studies have confirmed the disease sensitivity and specificity of a serodiagnosis of BP and pemphigus. Although anti-Dsg1 and 3 antibodies are a feature of patients with pemphigus, anti-BP180 and 230 antibodies are elevated in those with BP. In particular, anti-BP180 antibody reactivity is closely associated with BP, as it is detectable with absolute accuracy in almost all patients with BP [5–7]. Moreover, serum levels of anti-BP180 antibody correlate with disease activity [8].

Bullous pemphigoid has been associated with various renal lesions, and many studies have found that the severity of skin lesions parallels that of kidney disease. The occurrence of immune disorders involving two basement membranes of the skin and kidney is not merely coincidental [4]. The cutaneous phenomenon of BP does not always occur ahead of MN, and in fact, it sometimes arises secondary to MN [2, 4].

Topically or systemically administered steroids comprise the foundation of treatment for moderate to severe BP and 0.5–1.0 mg/kg/day of PSL is often administered [9]. We systemically treated both BP and MN in the present patient with PSL (0.5 mg/kg/day). The initial dose was decided according to BP severity based on the BPDAI and in consideration of the patient being of advanced age. This dose was effective against both diseases. However, some cases of BP with MN have required higher doses of steroid than our patient or other types of immunosuppressants [3, 10].

The pathological mechanisms of BP and MN seem alike, because deposition at the cutaneous basement membrane zone and the glomerular basement membranes is similar.

Electron microscopy of biopsy specimens identified purely sub-epithelial deposits in the present patient. These are more characteristic of primary, rather than secondary MN, in which immunoreactants localize on the mesangium and subendothelium as well as subepithelium. However, the findings in our patient were similar to those of MN that develops in patients with BP [2–4]. Thus, immunoreactant deposition on the glomeruli of patients with BP might not be the same as that associated with secondary MN.

More IgG4 than IgG2 was deposited along the capillary walls in our patient. Which IgG subclasses that were deposited along capillary walls were not estimated in previous studies [1–4], and thus, the typical deposition of IgG subclasses along the capillary walls in BP associated with MN has remained uncertain. Usually, IgG4 is predominantly deposited in primary MN, whereas IgG1, 2, and 3 are deposited in secondary MN [11, 12]. On the other hand, several studies have determined that the serum IgG subclasses of anti-BP180 antibody in patients with BP differ among the disease stages of BP [13–16]. IgG1 is more prevalent in patients at the early stage of BP than IgG4, but IgG4 increases in patients with chronic BP. Ujiie et al. reported that autoantibodies to BP induced blister formation in the absence of complement activation and that IgG4 was predominantly elevated and associated with the induction of blister formation in BP [17]. Our patient developed MN secondarily to blister formation during the chronic stage of BP. Thus, the disease stage might influence the deposition of specific IgG subclasses in the capillary walls of patients with MN.

We could not localize anti-BP180 antibody along capillary walls. However, proteinuria decreased as the skin condition improved and levels of autoantibody to BP180 decreased. Thus, the two diseases might have been associated with the same immunological disorders involving the basement membrane as previously suggested [1–4]. Sonia et al. speculated that several immunological mechanisms lie

behind the two diseases, for example, circulating immune complexes of antibodies to BP that mediate secondary MN, such as lupus nephritis, immunological cross reactions to common epitopes in both cutaneous and renal basement membranes, such as Goodpasture's syndrome, and multi-system autoimmune triggering events that are associated with kidney disease [3]. Neonatal Fc receptor (FcRn) promotes the formation of sub-epithelial immune complexes [18], and when combined with IgG, it allows the passage of IgG through the renal basement membrane; this is thought to play a key role in transcytosis within many organs and to maintain IgG homeostasis in the circulation [19]. Neonatal Fc receptor is associated with glomerulonephritis as well as BP [18, 20, 21], and it has high affinity for IgG4 [22]. Thus, we speculated that the IgG4 of anti-BP180 antibody bound to FcRn was associated with immune reactions of podocytes in glomeruli during the course of autoimmune triggering events of BP in our patient. However, further studies are required to confirm an association between FcRn and BP related to MN.

Conclusion

Our findings of a patient with MN and BP suggest that these two diseases are associated in terms of immunological dysfunction.

Compliance with ethical standards

Conflict of interest We have no conflicts of interest to declare.

Human rights This article does not contain any studies with human participants performed by any of the authors.

References

- Esterly NB, Gotoff SP, Lolekha S, Moore ES, Smith RD, Medenica M, Furey NL. Bullous pemphigoid and membranous glomerulonephropathy in a child. *J Pediatr*. 1973;83:466–70.
- Simon CA, Winkelmann RK. Bullous pemphigoid and glomerulonephritis. Report of four cases. *J Am Acad Dermatol*. 1986;14:456–63.
- Soine EJ, Nelson PS, Nesbitt LT Jr. A patient with coexistent bullous pemphigoid and primary membranous glomerulonephropathy. *J Am Acad Dermatol*. 2009;60:1042–4.
- Ross EA, Ahmed AR. Bullous pemphigoid-associated nephropathy: report of two cases and review of the literature. *Am J Kidney Dis*. 1989;14:225–9.
- Thoma-Uszynski S, Uter W, Schwietzke S, Hofmann SC, Hunziker T, Bernard P, Treudler R, Zouboulis CC, Schuler G, Borradori L, Hertl M. BP230- and BP180-specific auto-antibodies in bullous pemphigoid. *J Invest Dermatol*. 2004; 122:1413–22.
- Sitaru C, Dähnrich C, Probst C, Komorowski L, Blöcker I, Schmidt E, Schlumberger W, Rose C, Stöcker W, Zillikens D. Enzyme-linked immunosorbent assay using multimers of the 16th non-collagenous domain of the BP180 antigen for sensitive and specific detection of pemphigoid autoantibodies. *Exp Dermatol*. 2007;16(9):770–7.
- Feng S, Lin L, Jin P, Wu Q, Zhou W, Sang H, Shao C. Role of BP180NC16a-enzyme-linked immunosorbent assay (ELISA) in the diagnosis of bullous pemphigoid in China. *Int J Dermatol*. 2008;47:24–8.
- Feng S, Wu Q, Jin P, Lin L, Zhou W, Sang H, Shao C. Serum levels of autoantibodies to BP180 correlate with disease activity in patients with bullous pemphigoid. *Int J Dermatol*. 2008;47:225–8.
- Joly P, Roujeau JC, Benichou J, Picard C, Dreno B, Delaporte E, Vaillant L, D'Incan M, Plantin P, Bedane C, Young P, Bernard P, Bullous Diseases French Study Group. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med*. 2002;346(5):321.
- Kawakami T, Fujita A, Shirai S, Kimura K, Soma Y. Therapeutic effect of mizoribine on bullous pemphigoid associated with membranous nephropathy. *J Am Acad Dermatol*. 2009;60:523–4.
- Lai WL, Yeh TH, Chen PM, Chan CK, Chiang WC, Chen YM, Wu KD, Tsai TJ. Membranous nephropathy: a review on the pathogenesis, diagnosis and treatment. *J Formos Med Assoc*. 2015;114:102–11.
- Kuroki A, Shibata T, Honda H, Totsuka D, Kobayashi K, Sugisaki T. Glomerular and serum IgG subclasses in diffuse proliferative lupus nephritis, membranous lupus nephritis, and idiopathic membranous nephropathy. *Intern Med*. 2002;41:936–42.
- Shirakata Y, Shiraishi S, Sayama K, Miki Y. Subclass characteristics of IgG autoantibodies in bullous pemphigoid and pemphigus. *J Dermatol*. 1990;17:661–6.
- Döpp R, Schmidt E, Chimanovitch I, Leverkus M, Bröcker EB, Zillikens D. IgG4 and IgE are the major immunoglobulins targeting the NC16A domain of BP180 in bullous pemphigoid: Serum levels of these immunoglobulins reflect disease activity. *J Am Acad Dermatol*. 2000;42:577–83.
- Modre B, Allen J, Wojnarowska F. Does class switching contribute to remission in bullous pemphigoid? *Acta Derm Venereol*. 1999;79:127–31.
- Laffitte E, Skaria M, Jaunin F, Tamm K, Saurat JH, Favre B, Borradori L. Autoantibodies to the extracellular and intracellular domain of bullous pemphigoid 180, the putative key autoantigen in bullous pemphigoid, belong predominantly to the IgG1 and IgG4 subclasses. *Br J Dermatol*. 2001;144:760–8.
- Ujiie H, Sasaoka T, Izumi K, Nishie W, Shinkuma S, Natsuga K, Nakamura H, Shibaki A, Shimizu H. Bullous pemphigoid autoantibodies directly induce blister formation without complement activation. *J Immunol*. 2014;193:4415–28.
- Olaru F, Luo W, Suleiman H, St John PL, Ge L, Mezo AR, Shaw AS, Abrahamson DR, Miner JH, Borza DB. Neonatal Fc receptor promotes immune complex-mediated glomerular disease. *J Am Soc Nephrol*. 2014;25:918–25.
- Hayamann JP, Levraud JP, Bouet S, Kappes V, Hagège J, Nguyen G, Xu Y, Rondeau E, Sraer JD. Characterization and localization of the neonatal Fc receptor in adult human kidney. *J Am Soc Nephrol*. 2000;11:632–9.
- Li N, Zhao M, Hilario-Vargas J, Prisayan P, Warren S, Diaz LA, Roopenian DC, Liu Z. Complete FcRn dependence for intravenous Ig therapy in autoimmune skin blistering diseases. *J Clin Invest*. 2005;115:3440–50.
- Akilesh S, Huber TB, Wu H, Wang G, Hartleben B, Kopp JB, Miner JH, Roopenian DC, Unanue ER, Shaw AS. Podocytes use FcRn to clear IgG from the glomerular basement membrane. *PNAS*. 2008;105:967–72.
- Vidarsson G, Dekkers G, Rispens T. IgG subclasses and allotypes: from structure to effector functions. *Front Immunol*. 2014;5:520.