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Title: Clinical and immunological features of pemphigus relapse

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What's already known about this topic?

Pemphigus frequently recurs through the disease course.

What does this study add?

Most patients of mucocutaneous pemphigus vulgaris with relapse were taking less than 1mg/kg of initial prednisolone and pemphigus recurred when tapered to around 0.1mg/kg of prednisolone.

Abstract

Background: More than half of pemphigus patients experience relapse during the disease course. However, the risk factors and clinical and immunological characteristics of relapse remain largely unclear.

Objective: To elucidate risk factors and clinical features of pemphigus relapse

Methods: Retrospective review of the clinical records of 42 pemphigus cases in a single center.

Results: 61.9% of cases experienced relapse, usually when oral prednisolone was tapered to around 0.1mg/kg. In mucocutaneous pemphigus vulgaris (mcPV), the initial doses of prednisolone were significantly lower in cases with relapse (0.78 ± 0.24 mg/kg) than without relapse (1.01 ± 0.01 mg/kg). At relapse, mcPV shifted to mucosal dominant PV (mPV) (40%), pemphigus foliaceus (PF) (20%) or others (20%). In contrast, the relapsing mPV and PF had the same clinical phenotypes as the initial phenotypes. Patients with both anti-Dsg1 and anti-Dsg3 antibodies at onset had recurrence with anti-Dsg3 antibodies alone (40%), with both anti-Dsg1 and Dsg3 antibodies (30%) or with anti-Dsg1 antibody alone (20%), or were subthreshold (10%).

Conclusion: mcPV shows transitions in clinical phenotype and autoantibody profile at relapse. At least 1mg/kg/day of prednisolone, especially for mcPV cases, and prudent tapering around 0.1mg/kg may lead to better outcomes.

Introduction

Pemphigus is an autoimmune blistering disease characterized by circulating autoantibodies to desmosomal molecules of cell-cell adhesion in the epidermis and/or mucous membrane, followed by blistering or erosion. The clinical phenotypes of pemphigus are defined by the clinical manifestations and the anti-desmoglein (Dsg) antibody profile.[1] It is mainly classified into two major types: pemphigus vulgaris (PV) and pemphigus foliaceus (PF). Patients with PV present with erosions and blisters of the skin and/or mucosa, with the histological feature of suprabasal acantholysis. These are caused by anti-Dsg3 autoantibodies or anti-Dsg1 and anti-Dsg3 autoantibodies. In contrast, PF is characterized by scaly and crusted erosions of the skin with subcorneal acantholysis caused by anti-Dsg1 antibodies.[2]

The mainstream therapies for pemphigus are corticosteroids and immunosuppressive agents.[3–5] The goal of treatment is to achieve the absence of new lesions with minimal or no therapy. However, many patients experience several relapses and it is often difficult for them to achieve remission. The risk factors and clinical/immunological characteristics of relapse remain largely unclear.

To find indicators of optimal initial treatment and to predict relapse, we retrospectively investigated clinical findings such as the age of onset, the clinical phenotypes at onset and relapse, the initial dose of prednisolone (PSL), the disease severity at onset, the time course of anti-Dsg antibody titers and the clinical outcomes precisely in a single center. The novel findings in this study may provide valuable information for pemphigus management.

METHODS

Patients

We retrospectively examined patients with pemphigus attending the Department of Dermatology at Hokkaido University Hospital between 2001 and 2017. Forty two patients with at least a 9-month-period of observation and for whom the following information was available from clinical records were selected: age at onset, gender, date of onset of skin and/or mucosal lesions and initiation of systemic PSL, disease severity at onset, period of administration of initial dose of PSL, date of achievement of PSL 10mg, doses of PSL and titers of anti-Dsg1 and/or -Dsg3 antibodies at onset, at the first relapse and at the latest physician office visit, and with or without adjuvant treatment. The patients without relapse were enrolled only by the achievement of tapering PSL to 10mg or less during observation period. Anti-Dsg antibody titers at onset indicated the latest titers before the start of PSL treatment. This study was approved by the local ethics committee and the Institutional Review Board of Hokkaido University.

Diagnosis, definition of clinical phenotypes and clinical outcomes

The clinical diagnosis was made based on the clinical features, histopathology, direct immunofluorescence test and serological tests. The serological tests included indirect immunofluorescence and/or ELISA or chemiluminescent enzyme immunoassay (CLEIA).[3] Patients with mucosal dominant PV (mPV) predominantly had oral erosions with limited skin involvement, defined as no more than 5 or 6 scattered or isolated erosions or blisters no larger than 5 cm in diameter. Patients with mucocutaneous PV (mcPV) presented oral involvement in addition to more than 6 erosions or blisters on the skin larger than 5 cm in diameter.[1] PF patients had cutaneous lesions with anti-Dsg1 antibodies but no mucosal lesions or anti-Dsg3 antibodies.

Disease severity was evaluated based on PDAI (pemphigus disease area index) with reference to the clinical records or clinical pictures at onset.[6] Disease severity during the clinical course was arbitrarily evaluated on a scale of 0-3 with reference to the clinical

records. Cutaneous severity was graded according to the body surface area (BSA) involvement of erythema, vesicles, bullae or erosions as follows: 0, no lesions; 1, up to 5% BSA involvement; 2, up to 15% BSA involvement; 3, ≥ 15% BSA or extensive involvement. Oral severity was graded according to the oral surface area (OSA) involvement of vesicles, bullae, or erosions as follows: 0, no lesions; 1, up to 5% OSA involvement; 2, up to 30% OSA involvement; 3, ≥ 30% OSA or extensive involvement.

The definitions of therapeutic response were based on the consensus statement for pemphigus.[7] Briefly, relapse was defined as the appearance of ≥ 3 new lesions/month that did not heal spontaneously within one week or the extension of established lesions in patients who had achieved disease control. The remission mentioned in this study was defined as including complete and partial remission, as stated in the consensus statement for pemphigus. [7] That is, patients who were taking PSL at ≤ 10 mg/day and/or minimal adjuvant therapy with the absence of new or established lesions, or the presence of transient new lesions that healed spontaneously within one week.

Statistical analysis

GraphPad Prism ver. 6.00 for Windows (GraphPad Software, San Diego CA) was used for statistical analyses. The Mann-Whitney rank sum test was used to determine differences in various clinical features between patients with relapse versus without relapse or differences in anti-Dsg antibody at relapse between clinical phenotypes. The Dunn's multiple comparisons test was performed to determine differences in clinical phenotypes. The Wilcoxon matched-pairs signed-rank test was used to determine the differences in the anti-Dsg antibody titers at onset versus at relapse. The Fisher's exact probability test was used to determine differences in relapse rate. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical features and anti-Dsg antibody profile at pemphigus onset

Of the 42 patients, 27 (64.3%) were diagnosed with PV and 15 (35.7%) were diagnosed with PF. The PV patients consisted of 12 mPV (28.6%) and 15 mcPV (35.7%). The patients' age at onset, the period between onset and the initiation of oral PSL were not statistically different between clinical phenotypes. The female:male ratios for mPV, mcPV and PF were 10:2, 6:9 and 6:9, respectively. The gender ratios in previous reports were various,[8–16] and the female:male ratio of mPV in our study was remarkably high. The observation periods of mPV, mcPV and PF were 89.5 ± 64.6, 66.9 ± 47.1 and 47.6 ± 32.0 months, respectively. Initial doses of PSL were higher for mPV (0.86 ± 0.2 mg/kg) and mcPV (0.85 ± 0.2 mg/kg) than for PF (0.51 ± 0.1 mg/kg) (Table 1).

Next, we examined the autoantibody profiles at onset. For mPV, 3 of 12 cases (25%) had both anti-Dsg1 and anti-Dsg3 antibodies and 9 of 12 cases (75%) had anti-Dsg3 antibodies alone at onset. In contrast, in mcPV, 13 of 15 cases (86.7%) had both anti-Dsg1 and anti-Dsg3 antibodies at onset and 2 of 15 cases (13.3%) had anti-Dsg3 antibodies alone at onset. All 16 PF patients had anti-Dsg1 antibodies alone (Table 2). It is noteworthy that 2 of 11 cases (18.2%) with anti-Dsg3 antibodies alone presented as mcPV. As expected, anti-Dsg1 antibody titers were significantly higher in mcPV (161.8 ± 230.8 index value) and PF (327.8 ± 385.2 index value) than in mPV (13.8 ± 23.0 index value). Interestingly, anti-Dsg3 antibody titers were similar in mPV (329.0 ± 288.7 index value) and mcPV (392.1 ± 372.3 index value). These results confirm that anti-Dsg1 antibodies and anti-Dsg3 antibodies strongly correlate with the development of cutaneous lesions and mucosal lesions, respectively.

A possible risk factor for pemphigus relapse

The relapse rates of mPV, mcPV and PF were 50%, 66.7% and 66.7%, respectively (Table 3). We compared clinical indexes of patients with relapse versus without relapse. Notably, in mcPV, the initial doses of PSL were significantly lower in cases with relapse (0.78 ± 0.24

mg/kg) than without relapse (1.01 ± 0.01 mg/kg) (Figure 1a). The duration of initial dose of PSL or the cumulative dose of PSL to 10mg did not significantly differ between patients with relapse versus without relapse (Figure 1b, c). This indicates that the pace of reduction did not differ between patients with relapse and patients without relapse. Adjuvant therapies were used in a few cases with relapse before first relapse or without relapse before the reduction to PSL 10mg (Table3). The relapse rate was similar in patients with versus without adjuvant therapies, although statistical analysis could not be performed due to the small number of patients with adjuvant therapy. There were no significant differences in the period between onset and the administration of oral PSL (data not shown) and in the age or anti-Dsg antibody titers at onset between patients with relapse versus without relapse (Figure 1d-f). The disease severity at onset did not significantly differ between patients with relapse versus without relapse (Figure 1g). Thus, a lower initial dose of PSL is a possible risk factor for mcPV relapse.

Clinical findings at first relapse

Next, we analyzed the clinical data at first relapse. The durations between the initiation of PSL and first relapse in mPV, mcPV and PF were 28.7 ± 11.6, 19.1 ± 9.4 and 15.9 ± 12.8 months, respectively. Importantly, the doses of PSL (mg/kg) at first relapse were similar among mPV (0.11 ± 0.09), mcPV (0.12 ± 0.07) and PF (0.14 ± 0.09) (Figure 2a). It is worth noting that most of the patients experienced relapse when taking around 0.1mg/kg of PSL irrespective of clinical phenotype. Patients who relapsed at PSL >10mg/day numbered one each for mPV, mcPV and PF. Anti-Dsg1 antibody titers at first relapse were higher in PF (115.0 ± 104.8 index value) than in mcPV (36.5 ± 37.8 index value), but the difference was not statistically significant (Figure 2b). Anti-Dsg3 antibody titers at first relapse were similar between mPV (181.2 ± 326.9) and mcPV (109.6 ± 176.5) (Figure 2c). In Japan, the method for measuring anti-Dsg antibodies shifted from ELISA to chemiluminescent enzyme immunoassay (CLEIA) in 2013. To appropriately compare anti-Dsg antibody titers at onset to those at first relapse, we extracted the cases in which the titers were examined by ELISA

alone or CLEIA alone in the 2 timepoints. In PV and PF cases, anti-Dsg1 antibody titers were higher at onset (216.3 ± 336.7 index value) than at first relapse (58.2 ± 65.6 index value) (Figure 2d). Similarly, in PV, anti-Dsg3 antibody titers were significantly higher at onset (273.5 ± 250.9 index value) than those at first relapse (33.7 ± 34.4 index value) (Figure 2e). Most of the patients experienced a relapse when the antibody titers were less than those at onset. The average ratio of anti-Dsg1 and Dsg3 antibody titers at relapse to those at onset were 0.81 and 0.3, respectively (Figure 2f).

Transitions of clinical and immunological phenotypes at first relapse

At first relapse, clinical phenotype and autoantibody profile were changed from initial presentation in some patients. Although mPV and PF patients developed the same clinical phenotypes as the initial phenotypes at first relapse, mcPV patients (n=10) shifted to mPV (40%), mcPV (20%), PF (20%) or others (20%) (Table 4). In mcPV patients, there were two patients who had only cutaneous lesions with both anti-Dsg1 and anti-Dsg3 antibodies at first relapse. Although they could be possibly classified as cutaneous PV or PF, we classified them as “others” because of unverified histopathology of those lesions at relapse. Of note, no patients with mucosal lesions alone at onset developed cutaneous lesions at relapse, and vice versa. For example, mPV cases did not shift to mcPV or PF. Next, we analyzed the time course of autoantibody titers in cases with relapse. Patients with both anti-Dsg1 and anti-Dsg3 antibodies at onset (n=10) showed anti-Dsg3 antibodies alone (40%), both anti-Dsg1 and anti-Dsg3 antibodies (30%) or anti-Dsg1 autoantibodies alone (20%), or were subthreshold (10%) at first relapse. In contrast, patients with anti-Dsg3 antibodies alone at onset (n=6) had anti-Dsg3 antibodies alone (83.3%) or were subthreshold (16.7%) at first relapse. Patients with anti-Dsg1 antibodies alone at onset (n=10) had anti-Dsg1 antibodies alone (80%) or were subthreshold (20%) at first relapse (Table 4 and 5).

In this study, clinical phenotype shifted from mcPV to PF in four of the cases by the end of the observation period. In 3 of those cases, anti-Dsg1 and anti-Dsg3 antibodies were both positive at onset and only anti-Dsg1 antibodies were detected in the PF phase. One of

the cases initially presented as mcPV with anti-Dsg3 antibodies alone, relapsed as mPV with slightly elevated anti-Dsg3 antibody titers and finally developed into PF with anti-Dsg1 antibodies alone. In contrast, none of the cases shifted from PF to PV. The time course of disease severity and autoantibody titers in representative cases with clinical transition from mcPV to mPV and from mcPV to PF are shown in Figure 3.

Clinical outcomes and anti-Dsg antibody titers at the end of observation period

The remission rates of mPV, mcPV and PF were 83.3%, 80% and 73.3%, respectively. When the patients who achieved remission before relapse were included, the remission rates for mPV, mcPV and PF were 91.7%, 93.3% and 93.3%, respectively. Of the patients with at least one relapse, the remission rates of mPV, mcPV and PF were 66.7%, 70% and 60%, respectively. The patients who were finally off PSL accounted for 8.3%, 20% and 6.7% of the mPV, mcPV and PF cases, respectively (Table 3). Anti-Dsg antibodies became negative in most cases during the disease course. Anti-Dsg3 was more prone to be negative in mcPV (80%) than in mPV (41.7%) (Table 6).

DISCUSSION

Nowadays, systemic corticosteroids are the mainstay treatment for pemphigus. In Japan, 1mg/kg of PSL is recommended for moderate to severe cases.[3] At our institute, most cases are started with PSL at 1mg/kg for PV and at 0.5mg/kg for PF. Notably, less than 1mg/kg of initial PSL in mcPV cases were associated with relapse. mcPV is reported to be less responsive to treatment than mPV and PF.[17] A report on 155 patients with pemphigus showed the initial dose of corticosteroids to have no significant effect on the prognosis.[16] However, all of the patients in the study were treated with systemic corticosteroids at more than 1mg/kg. It also has been reported that dosages higher than 1mg/kg have no advantage over dosages of 1mg/kg in terms of the time to disease control [13] and that stratifying the initial dose of PSL according to PV disease severity at presentation is important.[18] From these findings, we consider that a sufficient dose of PSL (1mg/kg) is important for the initial treatment, especially for mcPV cases.

Interestingly, there was no significant difference in relapse rate between PF and PV, even though the initial dose of PSL for PF was roughly half that for PV. PF is considered to have a better prognosis than PV.[10] Therefore, the recommended dose of PSL might differ according to the clinical phenotype. It is intriguing that the dose of PSL at first relapse is roughly same around 0.1mg/kg regardless of clinical phenotype.

PV disease severity correlates with anti-Dsg antibody titer.[1,17,19–22] It is noteworthy that anti-Dsg1 and anti-Dsg3 antibody titers at onset did not significantly correlate with relapse in this study. Because of the substantial differences of anti-Dsg antibody titers among individuals, these autoantibodies can be used to monitor the disease course within a given individual but not to compare disease severity between patients.[23] Anti-Dsg antibody titers were lower at first relapse than at onset in this study. In most cases, it took some time after onset until anti-Dsg antibodies were analyzed. Therefore, the primary autoantibody titers, which were evaluated before the initiation of systemic PSL, might have been higher than those at true onset. Thus, we should be careful to manage when autoantibody titers appear to increase even if those are lower than the levels at onset.

This study has shown cases with a transition of anti-Dsg antibody profile associated with changes of clinical phenotype at first relapse. Several reports have described the transition of clinical phenotype between PV and PF.[24–32] The transition from PF to PV is less common than that from PV to PF. In cases with a clinical transition from PV to PF, the change of antibody profile showed two patterns: a shift from anti-Dsg3 antibodies alone to anti-Dsg1 antibodies alone,[24,28,29] or a shift from both anti-Dsg1 and anti-Dsg3 antibodies to anti-Dsg1 antibodies alone.[24,25,27] In contrast, cases with a clinical transition from PF to PV showed the change of antibody profile from anti-Dsg1 antibodies alone to both anti-Dsg1 and anti-Dsg3 or to anti-Dsg3 antibodies alone.[26,31] On the other hand, a case with a clinical transition from mPV to mcPV had only anti-Dsg3 antibodies at the mPV phase with the late development of anti-Dsg1 antibodies.[33] These cases were explained by the 'epitope spreading' hypothesis.[34] However, the epitope spreading phenomenon is regarded as being rarely seen in PV and PF,[35] and the mechanism remains controversial.

Clinical relapse is commonly seen in pemphigus. The relapse rates have ranged between 13% and 82%.[12–16,36–38] We found that none of the clinical factors, such as age, clinical phenotype or disease severity at onset had an impact on the occurrence of relapse. The study of 134 patients with pemphigus indicated that those with mucosal involvement and younger age (< 61 years) at presentation were more likely to achieve complete remission off therapy.[38] In contrast, other reports have suggested that young age at diagnosis (< 40 years), mucosal involvement at diagnosis or higher anti-Dsg1 or anti-Dsg3 antibody titers related to higher likelihood of recurrence.[8,12,16,36,39] Thus, there are no factors that consistently relate to clinical outcomes.

Complete or partial remission rates have been reported as ranging 50% and 100%. The patients with off therapy varies from 1.4 to 75% and with minimal therapy varies from 13 to 94.4%.[12,14–16,18,36,38,40] The variability between the reports may be due to differences in disease severity, follow-up period or relapse definition. In our study, the remission rate was 65% in PV and PF cases with relapse and of whom 15.4% could be off PSL. The remission

rate could be higher with prolonged observation period, and the incidence of relapse may not necessarily lead to poor outcome.

In conclusion, at least 1mg/kg dose of PSL is important for preventing relapse, especially for mcPV. In addition, when the dose of PSL is tapered to roughly 0.1mg/kg, we should carefully monitor for elevated anti-Dsg antibody titers and for clinical appearance, which can differ from that at onset.

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410 **Figure legend**

411 **Figure 1.** The clinical findings for each clinical phenotype with or without relapse. (a) Initial
412 dose of PSL. (b) Duration of initial dose of PSL. (c) Cumulative dose of PSL to 10mg. (d)
413 Age at onset. Anti-Dsg1 (e) and anti-Dsg3 (f) antibody titers at onset. (g) Disease severity at
414 onset. The bar indicates the median for each value. $^{*}P < 0.05$.

415

416 **Figure 2.** Dose of PSL and titers of antibody at first relapse. (a) Dose of PSL at first relapse.
417 Anti-Dsg1 (b) and anti-Dsg3 (c) antibody titers at first relapse. The titers of anti-Dsg1 (d) and
418 anti-Dsg3 (e) at onset and first relapse. (f) The ratio of antibody titers at relapse to those at
419 onset. The bar indicates the median for each value. $^{*}P < 0.05$, $^{**}P < 0.01$. NS, not significant.

420

421 **Figure 3.** The transition of clinical and anti-Dsg antibody profiles through the disease course.
422 The patients with mcPV at onset shifted to mPV (a) or PF (b). The cutoff values of anti-Dsg
423 antibodies changed in April 2014 at our facility.

424

425 **Table Legend**

426 **Table 1**. Summary of epidemiological data of the pemphigus patients

427 **Table 2**. Clinical phenotypes and anti-Dsg antibody profiles

428 **Table 3**. Clinical phenotype and disease outcome

429 **Table 4**. Transition of clinical phenotype at first relapse

430 **Table 5**. Transition of anti-Dsg autoantibody profiles at first relapse

431 **Table 6**. Rate of negative anti-Dsg antibody at the end of observation period

Tables

Table 1. Summary of epidemiological data of the pemphigus patients

Subtype	Clinical phenotype at onset	N	Gender	Age (years)		Onset to initial treatment (months)	Observation period (months)	Initial dose of PSL (mg/kg)
			Female:Male	mean ± SD	range	mean ± SD	mean ± SD	mean ± SD
PV	mPV	12	10:2	58.6 ± 8.7	43-76	6.9 ± 5.8	89.5 ± 64.6	0.86 ± 0.2
	mcPV	15	6:9	51.5 ± 13.4	24-73	7.1 ± 5.1	66.9 ± 47.1	0.85 ± 0.2
PF	PF	15	6:9	50.9 ± 14.5	14-69	8.5 ± 10.5	47.6 ± 32.0	0.51 ± 0.1
total		42	22:20	53.3 ± 13.1	14-76	7.5 ± 7.7	66.5 ± 51.3	0.74 ± 0.2

PV, pemphigus vulgaris; PF, pemphigus foliaceus; mPV, mucosal dominant PV; mcPV, mucocutaneous PV; PSL, prednisolone; SD, standard deviation

Table 2. Clinical phenotypes and anti-Dsg antibody profiles

Clinical phenotype at onset	Both Dsg1&3 n (%)	Dsg3 alone n (%)	Dsg1 alone n (%)
mPV (n=12)	3 (25.0)	9 (75.0)	0
mcPV (n=15)	13 (86.7)	2 (13.3)	0
PF (n=15)	0	0	15 (100)

mPV, mucosal dominant pemphigus vulgaris; mcPV, mucocutaneous pemphigus vulgaris; PF, pemphigus foliaceus; Dsg, desmoglein

448 Table 3. Clinical phenotype and disease outcome”

Clinical phenotype at onset	Relapse n (%)		Remission[1] n (%)		PSL off[2] n (%)		Adjuvant treatments[3]		
							mPSL pulse n (%)	IVIG n (%)	Azathioprine n (%)
mPV (n=12)	(+)	6/12 (50.0)	4/6 (66.7)	10/12 (83.3)	0	1/12 (8.3)	1/6 (16.7)	2/6 (33.3)	1/6 (16.7)
	(-)	6/12 (50.0)	6/6 (100)		1/6 (16.7)		0	1/6 (16.7)	2/6 (33.3)
mcPV (n=15)	(+)	10/15 (66.7)	7/10 (70.0)	12/15 (80.0)	3/10 (30.0)	3/15 (20.0)	0	2/10 (20.0)	0/10 (0)
	(-)	5/15 (33.3)	5/5 (100)		0		0	1/5 (20.0)	1/5 (20.0)
PF (n=15)	(+)	10/15 (66.7)	6/10 (60.0)	11/15 (73.3)	1/10 (10.0)	1/15 (6.7)	1/10 (10.0)	1/10 (10.0)	2/10 (20.0)
	(-)	5/15 (33.3)	5/5 (100)		0		0	1/5 (20.0)	1/5 (20.0)
Total (n=42)	(+)	26/42 (61.9)	17/26 (65.4)	33/42 (78.6)	4/26 (15.4)	5/42 (11.9)	2/26 (7.7)	5/26 (19.2)	3/26 (11.5)
	(-)	16/42 (38.1)	16/16 (100)		1/16 (6.3)		0	3/16 (18.8)	4/16 (25.0)

449 mPV, mucosal dominant pemphigus vulgaris; mcPV, mucocutaneous pemphigus vulgaris;

450 PF, pemphigus foliaceus; PSL, prednisolone; mPSL, methylprednisolone; IVIG, intravenous

451 immunoglobulin

452 [1]Cases in remission as of the end of observation period

453 [2]Cases in which oral PSL had been stopped by the end of observation period

454 [3]Adjuvant treatments before first relapse in patients with relapse or achievement of PSL

455 10mg in patients without relapse

456 Table 4. Transition of clinical phenotype at first relapse

Onset	First relapse	n (%)
mPV (n=6)	mPV	6 (100)
mcPV (n=10)	mPV	4 (40.0)
	mcPV	2 (20.0)
	PF	2 (20.0)
	Others[1]	2 (20.0)
PF (n=10)	PF	10 (100)

457 mPV, mucosal dominant pemphigus vulgaris; mcPV, mucocutaneous pemphigus vulgaris;

458 PF, pemphigus foliaceus

459 [1]Others: only cutaneous lesions with both anti-Dsg1 and anti-Dsg3 antibodies.

460

461

462

463 Table 5. Transition of anti-Dsg autoantibody profiles at first relapse

Onset	First relapse	n (%)
Dsg3 (n=6)	Dsg3	5 (83.3)
	Subthreshold	1 (16.7)
Dsg1/3 (n=10)	Dsg3	4 (40.0)
	Dsg1/3	3 (30.0)
	Dsg1	2 (20.0)
	Subthreshold	1 (10.0)
Dsg1 (n=10)	Dsg1	8 (80.0)
	Subthreshold	2 (20.0)

464 Dsg, desmoglein

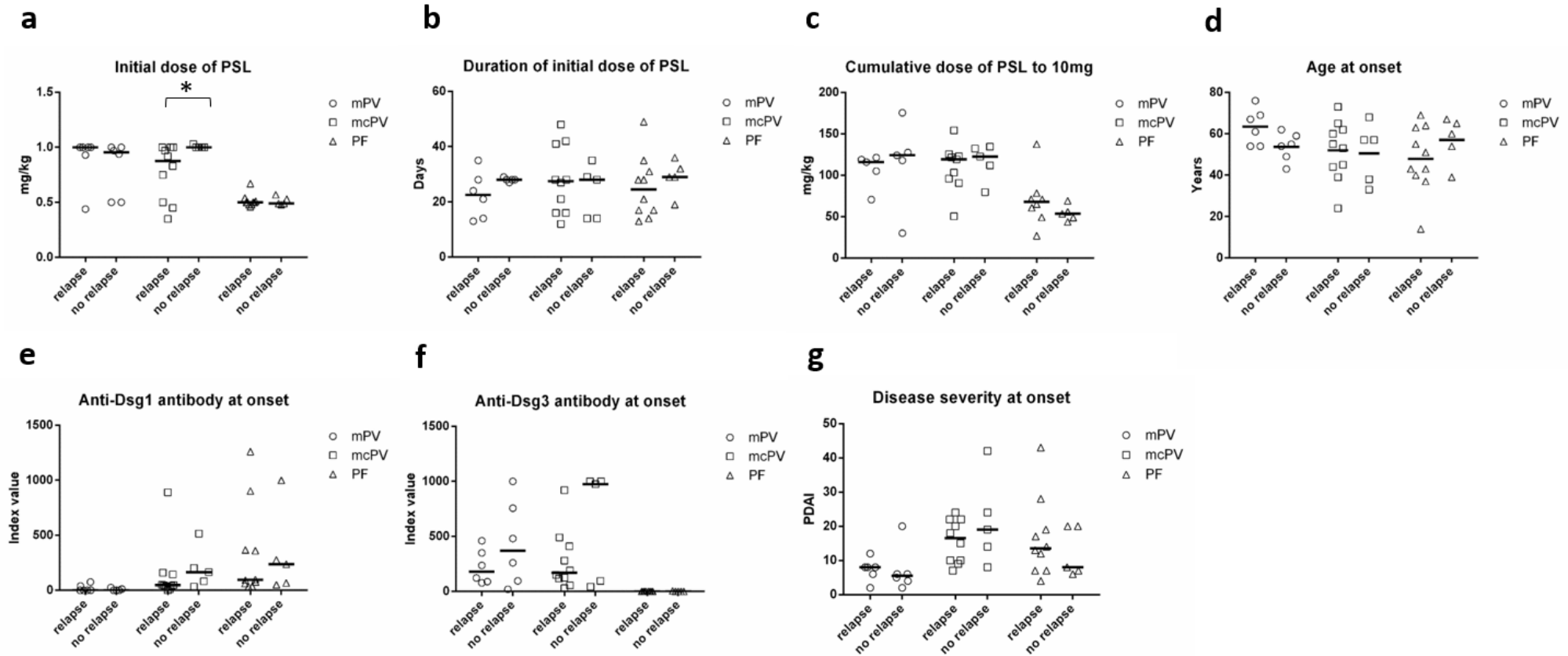
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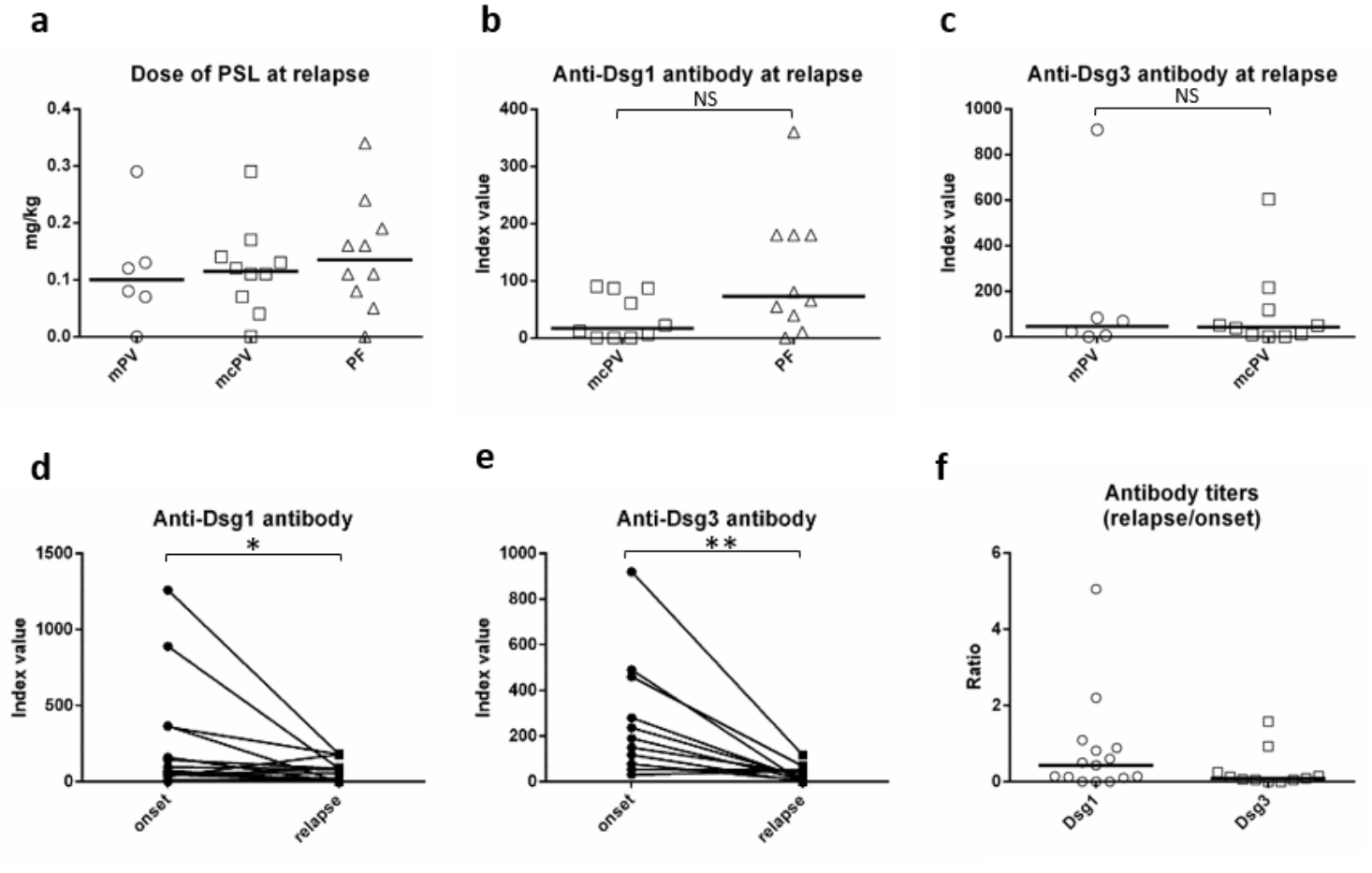
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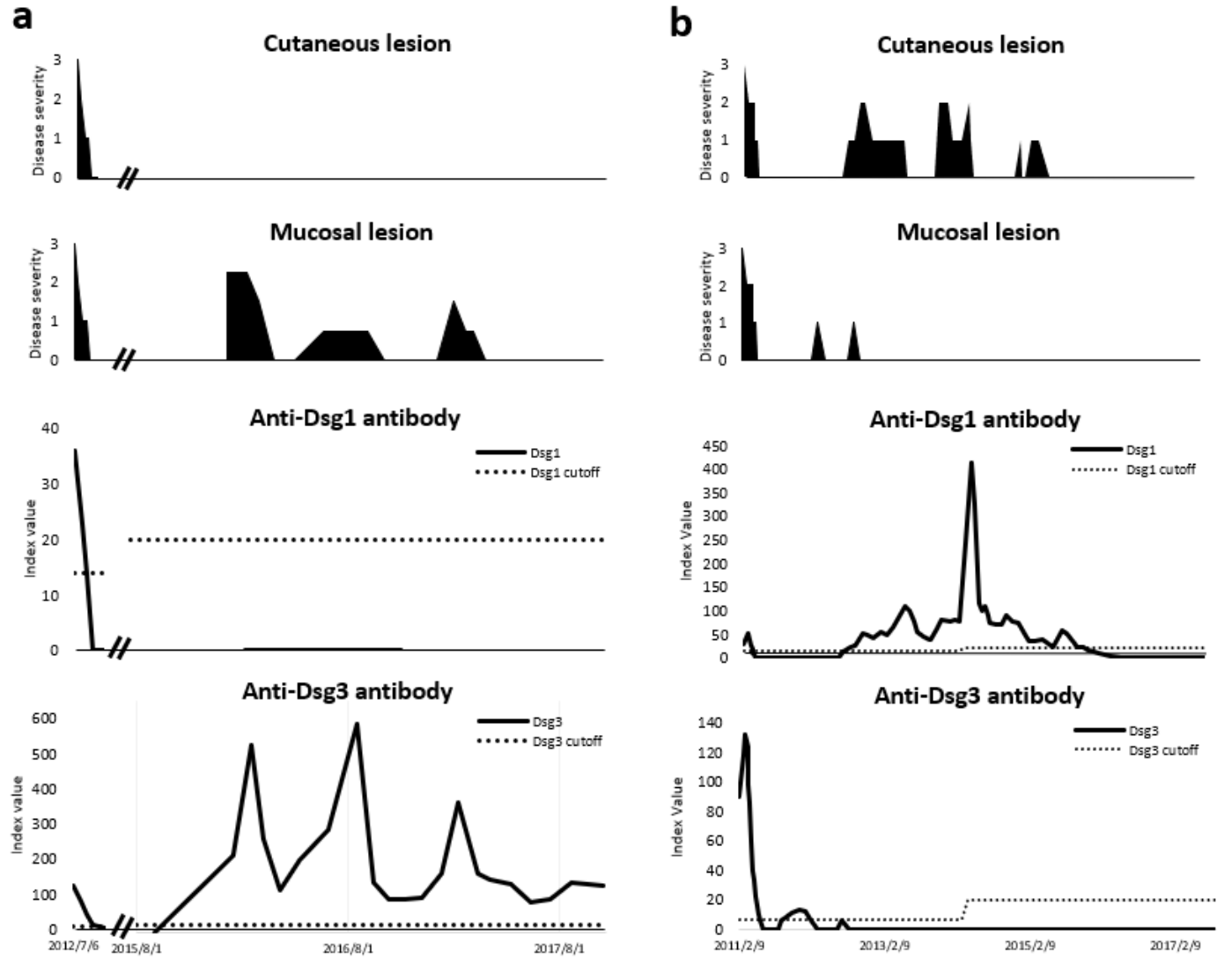
Table 6. Rate of negative anti-Dsg antibody at the end of observation period

Clinical phenotype at onset	Anti-Dsg antibody	Positive at onset n (%)	Turned negative n (%)
mPV (n=12)	Dsg1	3/12 (23.1)	3/3 (100)
	Dsg3	12/12 (100)	5/12 (41.7)
mcPV (n=15)	Dsg1	13/15 (86.7)	11/13 (84.6)
	Dsg3	15/15 (100)	12/15 (80.0)
PF (n=15)	Dsg1	15/15 (100)	9/15 (60.0)
	Dsg3	0	-

mPV, mucosal dominant pemphigus vulgaris; mcPV, mucocutaneous pemphigus vulgaris; PF, pemphigus foliaceus; Dsg, desmoglein


a
Initial dose of PSL
mg/kg
1.5
1.0
0.5
0.0
*
relapse
no relapse
mPV
mcPV
PF
b
Duration of initial dose of PSL
Days
60
40
20
0
c
Cumulative dose of PSL to 10mg
mg/kg
200
150
100
50
0
d
Age at onset
Years
80
60
40
20
0
e
Anti-Dsg1 antibody at onset
Index value
1500
1000
500
0
f
Anti-Dsg3 antibody at onset
Index value
1500
1000
500
0
g
Disease severity at onset
PDAI
50
40
30
20
10
0


a
Dose of PSL at relapse
mg/kg
0.4
0.3
0.2
0.1
0.0
mPV
mcPV
PF
b
Anti-Dsg1 antibody at relapse
NS
Index value
400
300
200
100
0
mcPV
PF
c
Anti-Dsg3 antibody at relapse
NS
Index value
1000
800
600
400
200
0
mPV
mcPV
d
Anti-Dsg1 antibody
*
Index value
1500
1000
500
0
onset
relapse
e
Anti-Dsg3 antibody
**
Index value
1000
800
600
400
200
0
onset
relapse
f
Antibody titers
(relapse/onset)
Ratio
6
4
2
0
Dsg1
Dsg3


a
Cutaneous lesion
Disease severity
Mucosal lesion
Disease severity
Anti-Dsg1 antibody
Index value
Dsg1
Dsg1 cutoff
Anti-Dsg3 antibody
Index value
Dsg3
Dsg3 cutoff
2012/7/6
2015/8/1
2016/8/1
2017/8/1
b
Cutaneous lesion
Disease severity
Mucosal lesion
Disease severity
Anti-Dsg1 antibody
Index Value
Dsg1
Dsg1 cutoff
Anti-Dsg3 antibody
Index Value
Dsg3
Dsg3 cutoff
2011/2/9
2013/2/9
2015/2/9
2017/2/9