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Pemphigus Associated with Psoriasis Vulgaris: A Retrospective Study of Seven Patients and a Review of the Literature

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ABSTRACT The aim of this study was to analyze the characteristics and the treatment for patients with psoriasis who presented with subsequent pemphigus after their treatment. A retrospective study of seven patients with psoriasis associated with pemphigus was performed, including the clinical assessment and treatments. The patients with a median age of 74 (range from 54 to 85) were significantly older than those in previously reported cases, where the median age was 58 (range from 15 to 77) ($P<0.05$). Six out of seven patients were male, which represents a higher ratio than that reported in literature (10/20). The duration between the diagnosis of psoriasis and onset of pemphigus ranged from 4 to 30 years, and previous studies reported a much wider range that, from a few months to 52 years. Patients developed pemphigus after the treatments for psoriasis with ultraviolet light, steroids, or immunosuppressant. Our study represents a distinct subset of patients with psoriasis accompanied with pemphigus who share typical clinical characteristics. Among these patients, most are elderly men and the dominant subtype is pemphigus foliaceus. Our data suggests that no treatment for psoriasis specifically correlated with the development of pemphigus. The combination treatment of steroids with immunosuppressant lead to an improvement of the disease.

KEY WORDS: autoimmune disease, pemphigus, psoriasis, treatment for psoriasis

INTRODUCTION

Psoriasis vulgaris is a well-characterized chronic inflammatory skin disorder which has recently been considered a systemic disease rather than an isolated dermatologic disorder with systemic inflammation (1) and a significantly increased risk of cardiovascular diseases (2,3). Cases of psoriasis associated with other common autoimmune diseases such as arthritis, systemic lupus erythematosus (4), thyroiditis (5), multiple sclerosis, and inflammatory bowel disease (6) have been reported in previous studies. In 1978, Koerber *et al.* first reported some single instances of bullous disease associated with psoriasis (7). The most common types of autoimmune bullous diseases consist of bullous pemphigoid and pemphigus, and several clinical studies have revealed that bullous pemphigoid was the major type associated with psoriasis (8-11). In contrast, there are only some sporadic case reports of pemphigus (pemphigus vulgaris and pemphigus foliaceus) that link to psoriasis vulgaris (12,13). To our knowledge, comprehensive analysis of

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this "complication" of psoriasis is absent in the literature. Therefore, we investigated seven patients diagnosed with psoriasis and pemphigus to evaluate how pemphigus initiated and subsequently progressed in the context of psoriasis after their treatment, and we focused on their clinical features in particular. In addition, we reviewed and compared our findings in detail with the clinical case reports available in the medical literature. Furthermore, we will extend our study to assess the most effective treatments for these patients.

PATIENTS AND METHODS

Patients

Seven patients from Rui Jin Hospital presenting with psoriasis followed by pemphigus were analyzed. Diagnosis was established based on clinical manifestations, histopathology, immunofluorescence study, and enzyme-linked immunosorbent assay (ELISA) results of anti-Desmoglein 1 (Dsg1) and Desmoglein 3 (Dsg3) antibodies. The retrospective study was conducted at Rui Jin Hospital from January 2001 to December 2016. Our study abided by the principles expressed in the Declaration of Helsinki and was approved by the Ethics and Scientific Committees of Rui Jin Hospital.

Observed factors

Sex, age, course of psoriasis, prior treatment for psoriasis, subtype of pemphigus, histopathology, direct or indirect immunofluorescence results, titers of anti-Dsg autoantibodies by ELISA, and treatment for pemphigus of the seven patients were observed and summarized for analysis.

Literature review

Previous case reports of pemphigus associated with pre-existing psoriasis (20 individual cases) published from 1985 to 2016 and retrieved from PubMed were reviewed. Sex, age, course of psoriasis, prior treatment for psoriasis, subtype of pemphigus, and treatment for pemphigus of the cases reported in literature were summarized and compared with our cases.

Statistical analysis

SPSS14.0 statistical software (SPSS. Inc. Chicago, IL, USA) was used for data analysis. Mann-Whitney U test and Fisher's exact test were performed for quantitative data and qualitative data, respectively. $P \leq 0.05$ was considered statistically significant.

RESULTS

Clinical and laboratory characteristics of the patients

Seven patients were enrolled and were diagnosed with psoriasis and pemphigus in Rui Jin Hospital from 2001 to 2016. All cases were confirmed as pemphigus by the combination of the results of histology, immunofluorescence (direct immunofluorescence and/or indirect immunofluorescence) study, and serologic test of anti-Desmoglein 1/Desmoglein 3 antibodies by ELISA. The clinical and immuno-histopathologic features of a representative patient with psoriasis and pemphigus are shown in Figure 1. The scattered papules with scale and superficial erosion with a positive Nikolsky's sign were developed on his back. We performed a biopsy from each lesion, which were individually confirmed to be psoriatic and pemphigus lesion. Direct and indirect immunofluorescence showed that immunoglobulin G (IgG) was deposited between the keratinocytes.

Summary of the observations

Our patients had a median age of 74 (range from 54 to 85) (Table 1). The majority of them (6/7) were men (85.7%). The median duration of psoriasis was 10 years (range from 4 to 30). Three of the seven patients had pemphigus vulgaris (pemphigus vulgaris, 42.9%) and four presented with pemphigus foliaceus (pemphigus foliaceus, 57.1%). Two patients had a history of ultraviolet B irradiation (28.6%) and five patients had a prior history of glucocorticoid treatments before pemphigus developed (71.4%). Low-dose of glucocorticoids with immunosuppressive agents were efficient for treating their pemphigus. All of the seven patients with psoriasis vulgaris associated with pemphigus were treated with small doses of systemic glucocorticoid combined with an immunosuppressive agent, such as azathioprine or methotrexate. The majority of the symptoms were relieved within 2 weeks. With clinical improvement, the dose of glucocorticoid was slowly tapered to 5 mg/day and the immunosuppressive agent stopped. The disease condition of most of the patients improved during the tapering of the oral steroid. Only one patient's symptoms of psoriasis vulgaris worsened during the course of treatment, and the lesions were eventually controlled by the additional application of topical steroid ointment.

Literature review

We studied 20 individual previous case reports of patients with psoriasis and pemphigus (Table 2)

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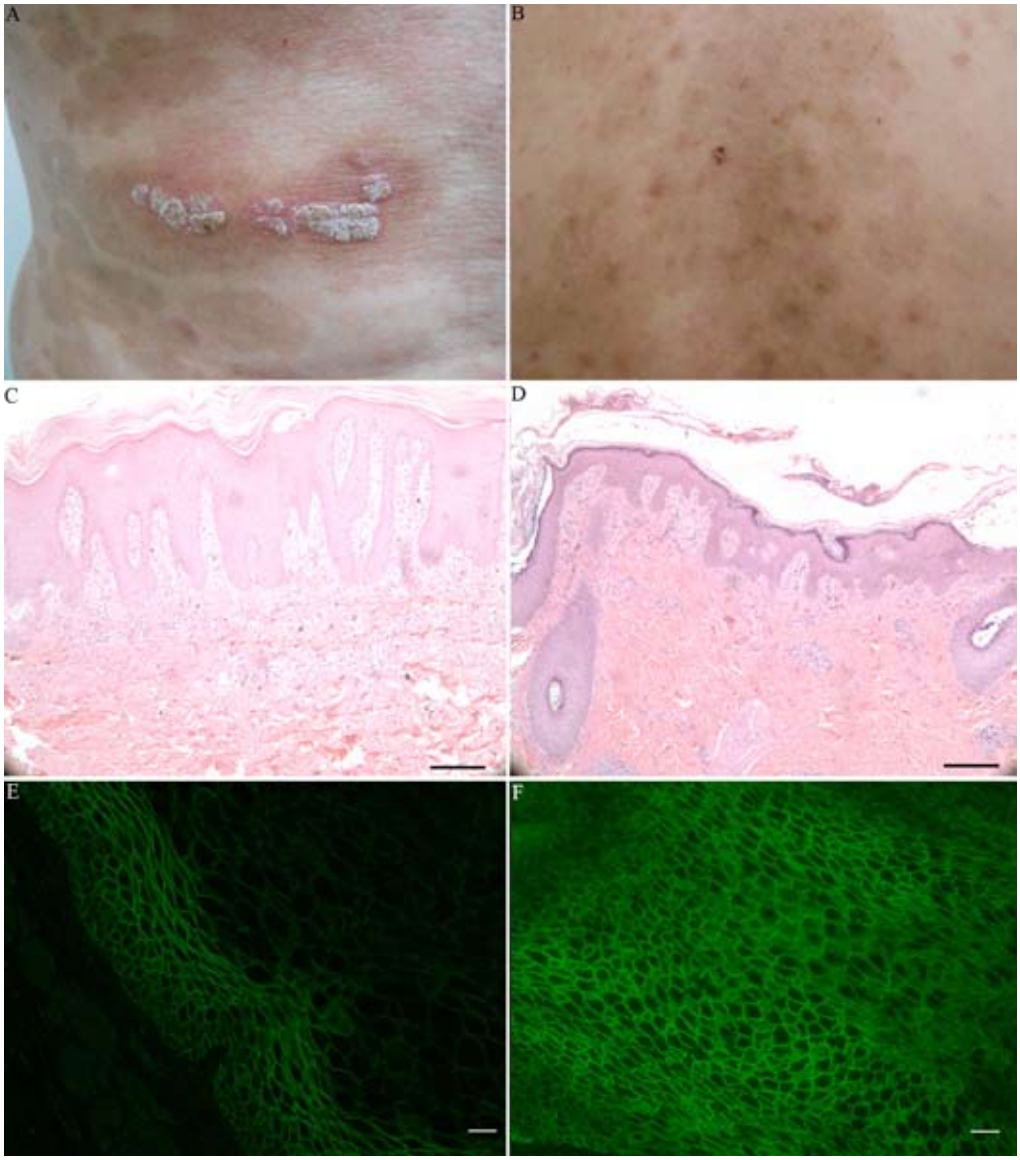

Figure 1. (a) The patient (the third patient in Table 1) presented with scattered papules on his lower back with scale; (b) The patient (the third patient in Table 1) had a typical pemphigus lesion on his back, which was characterized by superficial erosion and positive for Nikolsky sign; (c) The histopathologic features of the patient showed hyperparakeratosis, thinning and focal loss of the granular layer, and ectatic capillaries in the elongated dermal papillae which confirmed as psoriasis (hematoxylin and eosin (H&E), scale bar = 100 μm); (d) The histopathologic features of the patient showed acanthosis and partial separation of epidermis on one side of the sample with mild superficial lymphocytic perivascular infiltration that confirmed as pemphigus (H&E, scale bar = 100 μm); (e) Immunofluorescence of immunoglobulin G (IgG) deposited between keratinocytes via direct immunofluorescence assay (scale bar = 20 μm); (f) Immunofluorescence of immunoglobulin G (IgG) deposited between keratinocytes via indirect immunofluorescence assay (scale bar = 20 μm).

(12-29). The patients had a median age of 58 (range from 15 to 77) which was significantly younger than that observed in our patients ($P<0.05$). Ten cases were women (10/20, 50.0%) and ten cases were men (10/20, 50.0%), which showed no statistical difference from that of our patients ($P>0.05$). All the patients presented with onset of pemphigus after the treatment for psoriasis within a variable duration ranging from several months to 52 years. Only one patient was reported to be diagnosed with psoriasis and pemphigus concurrently. Fifteen of these patients had pemphigus foliaceus (15/20, 75.0%) and five patients developed pemphigus vulgaris (5/20, 25.0%). Six patients had a history of using ultraviolet radiation (psoralen ultraviolet A and ultraviolet B) (6/20, 30.0%) and four patients received glucocorticoid treatment for

Table 1. Summary of seven psoriasis patients associated with pemphigus.

Patients	Sex/age (years)	Course of psoriasis (years)	Prior treatments	Subtype of pemphigus	Histopathology	DIF/IIF	ELISA scores (U/ml) auto-antibodies (IgG)	Treatments
1	Male/79	4	Steroid ointment, UVB, telmisartan nifedipine, metformin	PF	Complied with psoriasis	IgG and C3 deposited in the intercellular spaces	0.16 (Dsg1)	Steroid ointment, tacrolimus ointment
2	Male/74	30	Steroid ointment, amlodipine	PF	Complied with psoriasis	N/A	9.93 (Dsg1)	Steroid ointment, prednisone, MTX
3	Male/54	5	Steroid ointment, UVB	PF	Complied with psoriasis and pemphigus	IgG deposited in the intercellular spaces	273.05 (Dsg1)	Prednisone, MTX
4	Female/58	30	Steroid ointment, tripterygium, acitretin, MTX	PF	Complied with pemphigus	N/A	66.60 (Dsg1)	Prednisone, cyclosporine
5	Male/81	20	N/A	PV	Complied with pemphigus	IgG deposited in the intercellular spaces	N/A	Tripterygium steroid ointment
6	Male/70	10	N/A	PV	Complied with pemphigus	N/A	N/A	Methylprednisolone azathioprine
7	Male/85	10	Steroid ointment	PV	Complied with pemphigus	IgG deposited in the intercellular spaces	N/A	Prednisone, MTX

Note: DIF: Direct immunofluorescence, IIF: Indirect immunofluorescence, UVB: Ultraviolet B, PF: Pemphigus foliaceus, PV: Pemphigus vulgaris, ELISA: Enzyme linked immunosorbent assay, MTX: Methotrexate, Dsg: Desmoglein, N/A: Information not available.

psoriasis (4/20, 20.0%). Three patients eventually developed pemphigus vulgaris after treatment with the immunosuppressant cyclosporine A (3/20, 15.0%).

Comparison of the cases

When combining data from the two tables (Table 1, Table 2), we found that all these patients (n=27) had a combined median age of 62 years (range from 15 to 85). About one-third of the patients were diagnosed with pemphigus vulgaris (8/27), while almost two-third of the patients developed pemphigus foliaceus (19/27) (Table 3).

DISCUSSION

Since the first report by Koerber *et al.* in 1978, case reports of bullous diseases that developed in patients with psoriasis have increased in number (7). This includes the predominant forms of bullous pemphigoid and the relatively rare forms of pemphigus, in which pemphigus foliaceus has been reported to be a more frequent disease than pemphigus vulgaris (8). Over the previous 20 cases, 15 of these patients presented with pemphigus foliaceus (15/20, 75.0%) and 5 patients developed pemphigus vulgaris (5/20, 25.0%). In order to clarify pemphigus onset and subsequent progression in the context of psoriasis after their treatment, we studied the clinical features of these patients with psoriasis vulgaris that following pemphigus after their treatment. Herein we reported seven cases of pemphigus arising in patients with psoriasis. Interestingly, in our seven cases, more than half of the patients also developed pemphigus foliaceus (4/7, 57.1%), which is consistent with what we found in the literature.

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Table 2. Reported cases of psoriasis associated with pemphigus.

Authors	Year of publication	Sex/age (years)	Time gap between psoriasis and pemphigus	Treatment for psoriasis before onset of pemphigus	Subtypes of pemphigus	Treatments for pemphigus
Lee *et al.*	1985	Female/34	Concurrent developed	None	PF	Prednisolone, azathioprine
Yokoo *et al.*	1989	Male/51	8 months	Topical treatments	PF	Prednisolone
Lee and Ro	1994	Female/40	10 years	Topical treatments	PF	Methotrexate
Fryer and Lebwohl	1994	Female/45	9 years	PUVA	PV	N/A
Perez *et al.*	1995	Male/38	N/A	Topical treatments	PF	Methotrexate
Aghassi and Dover	1998	Male/45	N/A	PUVA	PF	Prednisolone
Tomasini *et al.*	1998	Male/72	52 years	Topical treatment	PF	Prednisolone
Stavropoulos *et al.*	2003	Male/70	35 years	Topical treatment	PF	Hostacycline, prednisolone, betamethasone cream
Giomi *et al.*	2004	Female/77	7 years	Topical treatments	PF	Prednisolone
Hasse-Cieślińska *et al.*	2005	Female/15	N/A	UVB etanercept methotrexate	PF	Cyclophosphamide, prednisolone
Daulat *et al.*	2009	Male/51	30 years	Topical corticosteroid cyclosporine	PV	Cyclophosphamide, mycophenolate mofetil, prednisolone
Gurgen and Dorton	2010	Male/70	N/A	Betasol propionate	PV	Prednisone, mycophenolate mofetil
Caldarola *et al.*	2010	Male/60	32 years	Cyclosporine	PV	Prednisolone, azathioprine, topical treatment
Kwon *et al.*	2011	Male/53	13 years	Topical steroids UVB	PF	Prednisolone, azathioprine
Rallis *et al.*	2011	Female/71	3 years	Cyclosporine	PV	Cyclosporine
Grekin *et al.*	2012	Male/71	N/A	Mycophenolate mofetil	PF	Prednisolone, rituximab
Grekin *et al.*	2012	Female/74	3-4 years	UVB	PF	Prednisolone, topical corticosteroid, rituximab, mycophenolate mofetil, intravenous immunoglobulin
Kato *et al.*	2014	Female/56	20 years	Etretinate (topical steroid ointment)	PF	Cyclosporine betamethasone
Kurtzman DJ *et al.*	2015	Female/62	Several months	UVB	PF	Systemic corticosteroids, azathioprine.
Claus S *et al.*	2016	Female/63	Decades	N/A	PF	Systemic corticosteroids, azathioprine

Note: UVB: Ultraviolet B, PUVA: Psoralen ultraviolet A, PF: Pemphigus foliaceus, PV: Pemphigus vulgaris, N/A: Information not available.

A number of potential mechanisms have been proposed to account for this association. Several therapeutic options for psoriasis have been considered as independent triggers of pemphigus, including phototherapy (psoralen ultraviolet A and ultraviolet B), medication such as etanercept and enalapril, and topical medications such as dithranol and salicylic acid (14,25). However, removal of these treatments has rarely resulted in the relief of the bullous diseases.

We also found that ten patients in total (10/27) had a history of ultraviolet irradiation before pemphigus, suggesting that ultraviolet irradiation may play a role in pemphigus pathogenesis. Interestingly, we found that three patients who later developed pemphigus vulgaris had used cyclosporine A as the treatment for psoriasis (Table 2). Therefore, we predicted that cyclosporine A might have an effect on cell-cell adhesion in the skin epidermis, although the exact mechanism requires further investigation.

Table 3. Statistical analysis of patients with psoriasis and pemphigus.

Sex	Table 1	Table 2	P
Male	6 (6/7)	10 (10/20)	>0.05
Female	1 (1/7)	10 (10/20)	
PV	3 (3/7)	5 (5/20)	>0.05
PF	4 (4/7)	15 (15/20)	
Median age (min max)	74 (5485)	58 (1577)	0.019

Note: P<0.05 a statistical significance. PV: Pemphigus vulgaris, PF: Pemphigus foliaceus.

Additionally, pemphigus is regarded as an autoimmune disease mediated by pathogenic but not nonpathogenic autoantibodies against Desmoglein 3 and/or Desmoglein 1 in the serum of patients. As the association of pemphigus with many other immune disorders has been frequently reported (6), it is also believed that the hyperactivated immunologic/inflammatory status found in patients with psoriasis may cause the loss of the T- and B-cell self-tolerance to the pemphigus antigens, Desmoglein 1 and Desmoglein 3, and the presence of hypersensitive genetic factors may lead to the production of the autoantibodies and blister formation in pemphigus (30).

Another possible mechanism of the association is genetic predisposition. Several clinical studies have shown that patients with pemphigus had genetic susceptibility to pemphigus vulgaris. Several human leukocyte antigen class II alleles (such as DRB1*04, DRB1*08, and DRB1*14) have been reported to be related to pemphigus (31,32). Recently, in the humanized human leukocyte antigen-DRB1*04:02-transgenic mouse model, the human leukocyte antigen-DRB1*04:02-restricted CD4+ T-cells that are specifically reactive to human Desmoglein 3 epitopes were shown to help B-cells produce pathogenic pemphigus immunoglobulin G antibodies, indicating that genetic predisposition could be a major triggering factor for pemphigus in psoriasis (33). However, we would require further studies to confirm whether our patients with psoriasis have these associated human leukocyte antigen alleles.

On the other hand, the onset of pemphigus in psoriasis could also only be a coincidence. When combining our data with those from the literature, we found that the combined median age of 62 years (range from 15 to 85) was similar to the age of the overall pemphigus population (34). Interestingly, we also found that the ratio of the patients with pemphigus vulgaris and with pemphigus foliaceus was around 1:2 (8/27 vs. 19/27), which was not consistent with that of the overall distribution of pemphigus.

CONCLUSION

In addition to this analysis and comparison, we shared our clinical experience of the treatment for the co-existing diseases. We treated our patients with psoriasis associated with pemphigus with a combination of steroids and immunosuppressant, which resulted in a dramatic reduction of the psoriatic lesions. Moreover, careful examination of the triggering factors in our patients could lead to a significant finding, apart from the fact that five out of our seven patients had a prior history of steroid application.

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