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Bullous pemphigoid followed by pustular psoriasis showing Th1, Th2, Treg and Th17 immunological changes

Psoriasis vulgaris is occasionally accompanied by autoimmune bullous diseases, but the opposite is very rare. We document here the first reported case of generalized pustular psoriasis that appeared during steroid therapy for bullous pemphigoid. The serum cytokine levels and the results of an immunohistochemical study over the disease course suggest that the immunological state was consistent with a shift from Th2-dominance to Th1-dominance. IL-17-producing cells appeared in the skin lesions when each disease was most exacerbated and disappeared after remission. Thus, the present case demonstrated a dynamic immunological state in which the appearances of Th1 and Th2 as well as Th17 varied during the course of the disease.

Key words: pustular psoriasis, bullous pemphigoid, Th1, Th2, Th17

It has been reported that some patients with psoriasis, whose disease was improved by treatment such as phototherapy, occasionally suffered from bullous pemphigoid [1, 2]. These cases may be based on an immunological shift from T helper cell type 1 (Th1) to Th2 [3]. It has been suggested that Th1 plays a central role in the pathogenesis of psoriasis vulgaris as effector cells for keratinocytes, whereas a Th2-predominant immunological profile is observed in bullous pemphigoid [4-7]. However, it is unsatisfactory to explain the pathogenesis and course of autoimmune diseases such as psoriasis and bullous diseases simply within the scheme of the Th1/Th2 hypothesis [8].
There are other types of T lymphocytes: Regulatory T lymphocytes (Treg) can influence the expression and activation of helper T lymphocytes and are suggested to suppress autoimmunity [9]. Most recently, IL-17-producing T lymphocytes, Th17, have been accepted as a fourth type of CD4-positive T lymphocytes. Th17 appear to stimulate cytotoxic activity and exacerbate autoimmune diseases as a counterpart of Treg with opposite function [10-13].
Here, we report the first case of generalized pustular psoriasis that appeared during steroid therapy for bullous pemphigoid. We followed the dynamics of Th1, Th2, Treg, and Th17 changes over the disease course.

Patient and methods

Patient

A 37-year-old Japanese man was admitted to our hospital because of a sudden appearance of bullae and erythema on almost the whole body *(figures 1A, B)*. A direct immunofluorescence showed a linear deposition of IgG *(figure 1C)* and C3 (not shown) at the basement membrane zone. Indirect immunofluorescence detected IgG antibodies to the basement membrane zone in the patient's serum at a titer of 640, which reacted with the epidermal side of 1M sodium chloride split skin. Anti-BP180 IgG autoantibodies were detected on immunoblot analysis using the recombinant BP180 NC16a protein, which contains the most immunogenic regions of the BP180. We diagnosed the patient as having bullous pemphigoid. During treatment with oral betamethasone 5.5 mg daily and courses of plasmapheresis, systemic symptoms improved and erythema and bullae quickly disappeared.
After the betamethasone was tapered to 1.0 mg daily, erythema with pustules and severe edema appeared over the

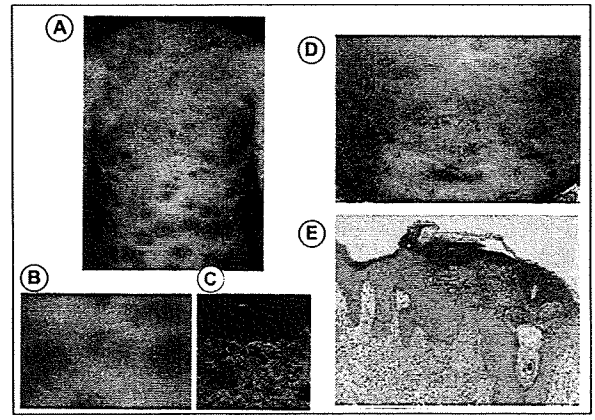

Figure 1. Clinical, histological and immunofluorescence manifestations of the present case. Bullae and erythema on the whole body seen at admission **(A, B)**. Direct immunofluorescence detected linear IgG deposition at the basement membrane zone **(C)**. Erythema with pustules and severe edema at the disease stage of pustular psoriasis **(D)**. Histopathology showed spongiform pustules in the upper epidermis **(E)**.

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body *(figure 1D)*, and fever with a temperature as high as 39 °C developed. Histopathologically, a specimen from the skin lesion showed Kogoj's spongiform pustules in the upper part of the epidermis and psoriasiform acanthosis with elongation of rete ridges *(figure 1E)*. Direct immunofluorescence showed a linear deposition of IgG and C3 at the basement membrane zone. Indirect immunofluorescence with the patient's serum showed IgG antibasement membrane zone antibodies at a titer of 10. Immunoblot analysis using epidermal extracts demonstrated that the patient's serum reacted with BP180. We diagnosed this patient as suffering from generalized pustular psoriasis accompanying bullous pemphigoid. Combination therapy with etretinate 20 mg daily and betamethasone 3.0 mg daily improved his skin lesions. Even after the steroid dose was tapered, a stable condition was maintained.

Quantification of serum interferon (IFN)-γ and tumor necrosis factor (TNF)-α

Serum samples were collected at the beginning and during the disease courses of both bullous pemphigoid and pustular psoriasis, and were stored at – 80 °C until use. Quantification of IFN-γ and TNF-α levels in the patient's sera was performed by enzyme-linked immunosorbent assays.

Immunohistochemistry

Skin biopsy samples were serially obtained from each lesion and stored at –80°C until use. The immunohistochemical procedures were carried out using first antibodies as follows: Mouse monoclonal anti-human IL-4 antibody, goat anti-human IL-17 antibody (R&D Systems, Inc., MN, USA), and mouse monoclonal antibody [236A/E7] to Foxp3 (Abcam, Cambridge, UK).

Results

In the present case, IFN-γ was not detectable (< 0.1 IU/mL) in any of the serum samples over the studied course of the disease *(table 1)*. Serum TNF-α was elevated at the time of the pustular psoriasis attack, and subsequently remained at a detectable level even after the remission *(table 1)*. Immunohistochemical analysis showed that both IL-4- and IL-17-producing cells, as well as Foxp3-positive cells, were detected in the upper dermis of the skin from a bullous pemphigoid lesion *(figure 2)*. On the other hand, the specimen from the psoriasis lesion showed no evidence of IL-4-producing cells or Foxp3+ cells. There were IL-17-producing cells not only in the dermis, but also in the epidermis. The skin specimen obtained at remission contained no IL-4- or IL-17-producing cells, or Foxp3-positive cells. The immunological dynamics over the course are summarized in *table 1*.

Table 1. The immunological dynamics over the disease course of the present case

		BP	Psoriasis	Remission
Serum: (pg/mL)	IFN-γ	n.d.	n.d.	n.d.
	TNF-α	n.d.	45	24
Skin :	IL-4	+	–	–
	IL-17	+	+	–
	Foxp3	+	–	–

ND: nod detected.

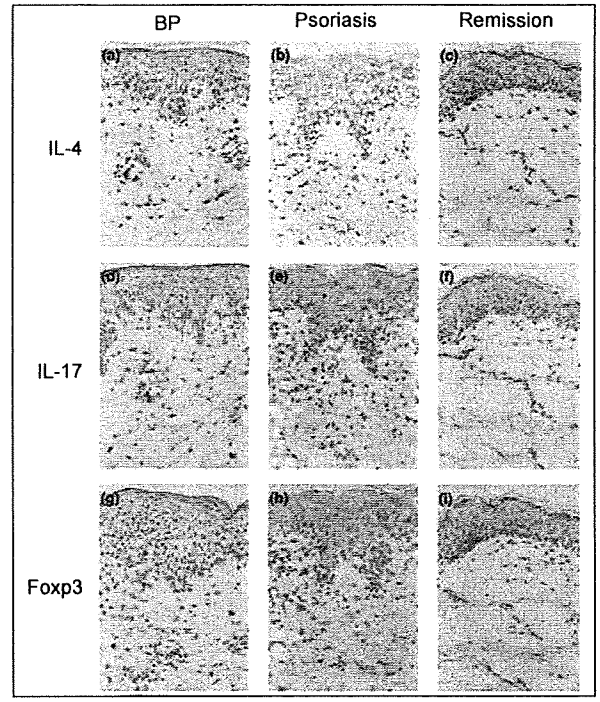

Figure 2. Immunohistochemistry over the disease course of the present case. IL-4-expressing cells (a) and Foxp3-positive cells (g) were detected in the skin at the onset of bullous pemphigoid. IL-17-producing cells appeared in the samples from the skin lesions of both bullous pemphigoid (d) and pustular psoriasis (e).

Discussion

We document the first reported case of generalized pustular psoriasis accompanying bullous pemphigoid. Although there was no published information available about the role of Th17 in autoimmune bullous diseases, accumulating evidence suggests that Th17 cytokines, including IL-22, play an important role in the pathogenesis of psoriasis [14-16]. We have recently confirmed that IL-17-producing lymphocytes were detected in the skin lesions of both bullous pemphigoid and pemphigus vulgaris (manuscript in preparation). The immunological profile of the present case was ideal to support the hypothesis that the immunological dynamics in autoimmune diseases should not be viewed as a one-dimensional interaction between Th1 and Th2, but as a multiple-level interaction among Th1, Th2, Treg and Th17.

The Th1/Th2 theory simply and elegantly explains various immunological states in mice and humans [8]. However, this theory is not suitable for understanding the pathogenesis of autoimmune diseases because the mechanism of exacerbation and amelioration cannot be simply explained as a switch from Th1 to Th2. Now we have information about two new players involved in the multidirectional immunological reactions: *i.e.*, Treg and Th17.

Accumulated evidence suggests that Treg is responsible for the third direction of an immunological reaction, and controls autoimmunity, tumor immunity and resolution of immune reactions. Th17 is accepted as a helper/effector cell subset responsible for cytotoxic reactions in autoimmunity, a function that could not be assigned by the Th1/Th2 hypothesis.

The role of Th17 in the lesional skin in bullous pemphigoid is unknown, but they may have a similar effector function to the one they have in several other autoimmune diseases. It is also conceivable that lesional Th17 may not be a cause but a result of the disease: *i.e.*, they may function in a non-specific protective and repair response following damage in the epidermis. It would be valuable to elucidate the precise mode of function of Th17.

It is, naturally, a limitation of this study that the immune parameters investigated in a single patient do not provide sufficient information to draw specific conclusions on the immune profile of autoimmune diseases. Nevertheless, the multidimensional immune reactions described here will help us to understand the pathogenesis of autoimmune diseases and to discover new therapies. ■

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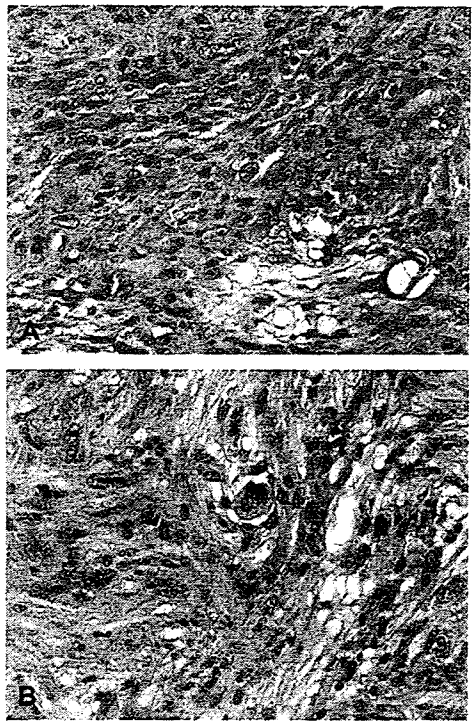

Fig 2. Myxoinflammatory fibroblastic sarcoma. High-power view showing large Reed-Sternberg–like cells (**A**) and mitotic figures (**B**).

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Refractory oral ulcers with multiple immunoglobulin G/immunoglobulin A autoantibodies without skin lesions

To the Editor: Current molecular diagnostics have characterized many new autoimmune bullous diseases that traditional descriptive dermatology would not have been able to define. Herein we report a case of refractory oral ulcers with immunoblots that were confusing, causing difficulty in making a definitive diagnosis.

Oral ulcers suddenly appeared in a 76-year-old male and were protracted over 8 months. He had been suffering from diabetes mellitus and hypertension, but had no history of malignancy. On the patient's first visit, very painful shallow ulcers and blisters with red halos were present over the palate, gingiva, labiogingival groove, buccal mucosa, and larynx (Fig 1, *A*). The conjunctivae, vermilion border of lips, glans penis, and anus were unaffected. There were no cutaneous lesions. A biopsy specimen of the buccal mucosa showed subepithelial blister formation with slight acanthosis and copious infiltration of lymphocytes and plasma cells in the submucosa, in which capillaries were dilated. There was no apparent acantholysis (Fig 1, *B*). Direct immunofluorescence examination showed linear deposition of both immunoglobulin G (IgG; Fig 1, *C*) and immunoglobulin A (IgA; Fig 1, *D*) antibodies along the basement membrane zone. Indirect immunofluorescence with the patient's serum using 1 M sodium chloride split-skin sections demonstrated IgG antibodies reactive with both epidermal and dermal sides (Fig 1, *E*) and IgA antibodies reactive with the epidermal side (Fig 1, *F*). The following antibodies were detected on immunoblot analysis: IgG and IgA to the BP180 NC16a domain (Fig 2, *A*), IgG and IgA to the 120-kDa linear IgA dermatosis antigen, LAD-1,[1,2] an ectodomain of the BP180 molecule (Fig 2, *C*), and

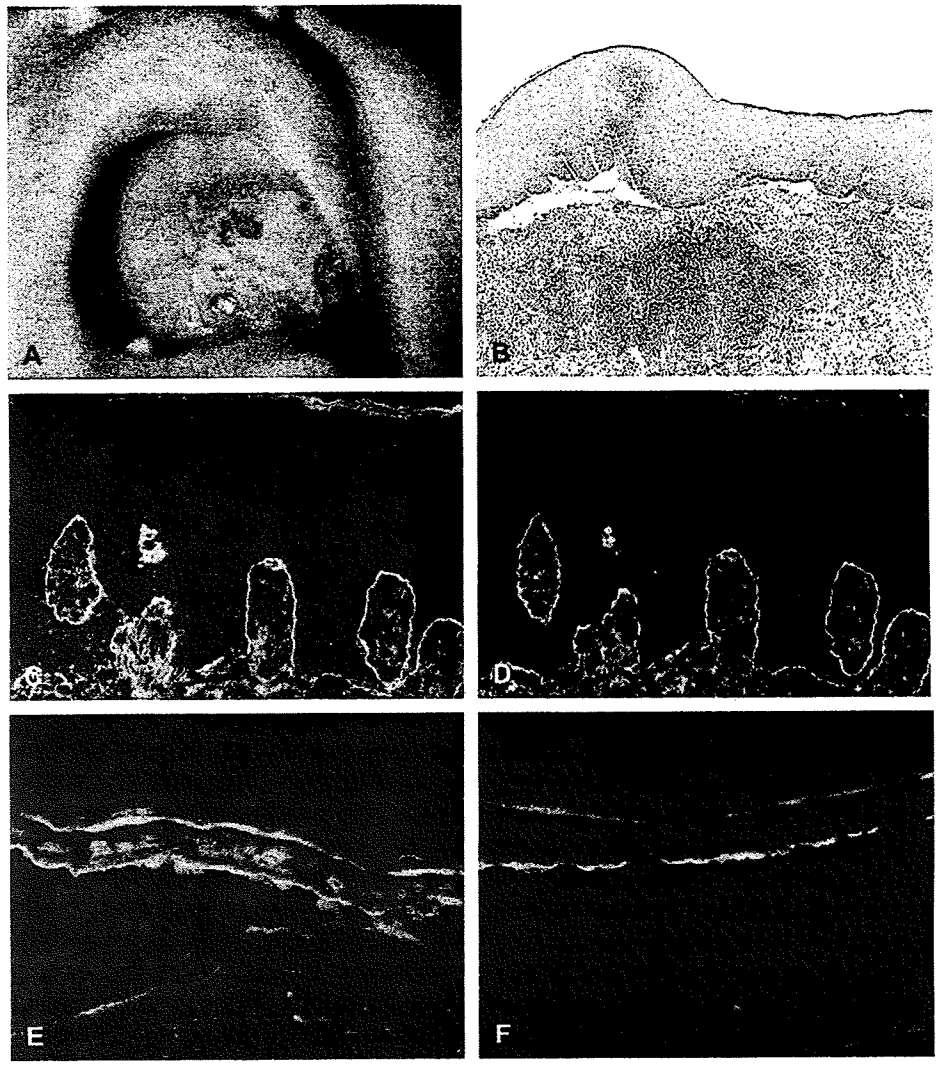
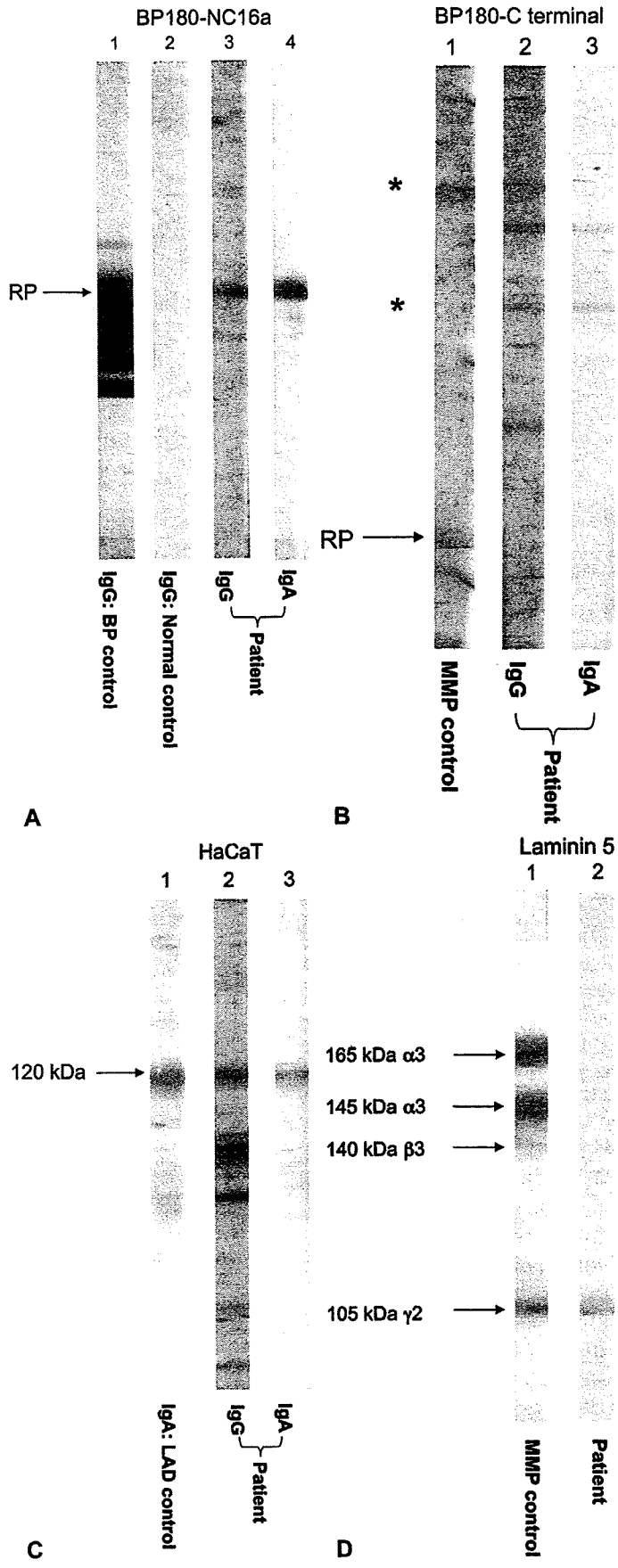


Fig 1. Oral lesions in the present case. **A**, Ulcers distributed on the palate. Histologic features of a biopsy specimen obtained from a lesion on the buccal mucosa, stained with hematoxylin–eosin (scale bar, 100 μm). **B**, The specimen showed subepithelial blister formation with infiltration of lymphocytes and plasma cells in the lamina propria. Direct immunofluorescence showed linear deposition of both (**C**) immunoglobulin G and (**D**) immunoglobulin A antibodies along the basement membrane zone. Indirect immunofluorescence with the patient's serum using 1M sodium chloride split-skin sections demonstrated (**E**) immunoglobulin G antibodies reactive with both epidermal and dermal sides and (**F**) immunoglobulin A antibodies reactive with the epidermal side.

IgG to the γ2 subunit of laminin 332 (Fig 2, *D*).[3] No IgG or IgA autoantibodies against BP230/BP180, 130-kDa desmoglein (Dsg) 3, 160-kDa Dsg 1, 210-kDa envoplakin, or 190-kDa periplakin were detected on immunoblot analysis using epidermal extracts (data not shown). By enzyme-linked immunosorbent assay, the index value of anti- BP180 NC16a domain of IgG antibody was 27.69 (normal range, <15). We ultimately diagnosed this case as mucous membrane pemphigoid complicated with linear IgA/IgG bullous dermatosis.[4] Daily administration of tetracycline hydrochloride 500 mg and nicotinamide 200 mg, relatively low doses because of the patient's advanced age, was partially effective, and lesions have been confined to the oral mucosa for 6 months. Systemic steroid administration was avoided because of his preexisting diabetes mellitus.

This is an unusual case of mucous membrane pemphigoid complicated with linear IgA/IgG bullous dermatosis. Extraoral involvement is common in patients with mucous membrane pemphigoid.[5,6]


BP180-NC16a
1
2
3
4
RP
IgG: BP control
IgG: Normal control
IgG
IgA
Patient
A
BP180-C terminal
1
2
3
*
*
RP
MMP control
IgG
IgA
Patient
B
HaCaT
1
2
3
120 kDa
IgA: LAD control
IgG
IgA
Patient
C
Laminin 5
1
2
165 kDa α3
145 kDa α3
140 kDa β3
105 kDa γ2
MMP control
Patient
D

Most patients with linear IgA bullous dermatosis show mainly cutaneous lesions, although mucous membrane lesions are predominant in a few cases.[7,8] Therefore, the present case cannot be simply explained as a confluence of various autoimmune bullous diseases with different characteristic autoantibodies. The patient should be monitored to determine whether extraoral lesions develop.

Even the current advanced molecular diagnostic technology cannot perfectly solve the highly complicated pathogenesis of cases such as ours. This rare case provides useful information for further investigations of unclassified autoimmune bullous diseases.

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Acquired combined nutritional deficiency presenting as psoriasiform dermatitis

To the Editor: Nutritional deficiency, a prevalent problem worldwide, remains rare in developed countries. In the United States, acquired nutritional deficiencies have been reported in patients with anorexia nervosa, malabsorption syndromes, those on long-term parenteral nutrition, and patients with food allergies.[1-4] Given the significant morbidity and sometimes mortality associated with certain nutritional deficiencies, their prompt recognition, diagnosis, and treatment by clinicians is of great importance.[1] Many nutritional deficiencies have classic cutaneous presentations that are valuable clinical diagnostic tools.[5] However, combined nutritional deficiencies often put forth a mixed clinical

Fig 2. Immunoblot analyses. **A**, Immunoglobulin G (IgG) antibodies of control bullous pemphigoid serum reacted with the recombinant protein (RP) of the BP180 NC16a domain (*arrow*; lane 1), while normal control serum did not react (lane 2). IgG (lane 3) and immunoglobulin A (IGA; lane 4) antibodies of the serum of the present case reacted with this recombinant protein. **B**, IgG antibodies of control anti-BP180 type mucous membrane pemphigoid serum reacted with the recombinant protein of BP180 C-terminus (*arrow*; lane 1), while IgG (lane 2) and IgA (lane 3) antibodies of the serum of the present case did not react with this recombinant protein. *Asterisks* show the nonspecific protein bands. **C**, IgA antibodies of control linear IgA bullous dermatosis serum reacted with the 120-kDa linear IgA dermatosis antigen LAD-1 (*arrow*) in cultured HaCaT cell supernatant. Both IgG (lane 2) and IgA (lane 3) antibodies of the serum of the present case also reacted with the LAD-1. **D**, IgG antibodies of control antilaminin 5 mucous membrane pemphigoid serum reacted with all of the 165-kDa α3, 145-kDa α3, 140-kDa β3, and 105 kDa γ2 subunits of laminin 332 (formerly laminin 5) in purified laminin 332 (lane 1). IgG antibodies of the serum of the present case reacted with the 105 kDa γ2 subunit (lane 2).

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High-Dose Intravenous Immunoglobulin (IVIG) Therapy in Autoimmune Skin Blistering Diseases

Norito Ishii · Takashi Hashimoto · Detlef Zillikens · Ralf J. Ludwig

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Abstract Treatment of autoimmune bullous skin diseases can often be challenging and primarily consists of systemic corticosteroids and a variety of immunosuppressants. Current treatment strategies are effective in most cases but hampered by the side effects of long-term immunosuppressive treatment. Intravenous immunoglobulin (IVIG) is one potential promising therapy for patients with autoimmune bullous skin diseases, and evidence of its effectiveness and safety is increasing. A number of autoimmune bullous skin diseases have been identified in which IVIG treatment may be beneficial. However, experience with IVIG in patients with autoimmune skin blistering disease is limited, where it is recommended for patients not responding to conventional therapy. The mode of action of IVIG in autoimmune diseases, including bullous diseases is far from being completely understood. We here summarize the clinical evidence supporting the notion, that IVIG is a promising therapeutic agent for the treatment of patients with autoimmune bullous skin disease. In addition, we review the proposed modes of action. In the future, randomized controlled trials are necessary to better determine the efficacy and adverse effects of IVIG in the treatment of autoimmune bullous skin diseases. In addition, insights into IVIG's mode of action might enable us to develop novel therapeutics to overcome the current shortage of IVIG.

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Introduction

Autoimmune bullous skin disorders (ABSDs) are a group of severe, potentially life-threatening diseases, clinically characterized by blisters and erosions of skin and/or mucous membranes. Patients with ABSDs develop autoantibodies reactive with the epidermal keratinocyte cell surfaces or the epidermal basement membrane zone which, in turn, induce separation between epidermal keratinocytes or at the dermal–epidermal junction [1, 2]. Based on histopathological, immunological, and clinical criteria, autoimmune bullous diseases are classified into two major groups associated with autoantibodies to desmosomal (pemphigus group) or hemidesmosomal proteins (subepidermal blistering diseases, e.g., pemphigoid diseases and epidermolysis bullosa acquisita (EBA)) [3–6]. Patients suffering from ABSDs are treated with high doses of systemic corticosteroids mostly in combination with other immunosuppressants [7, 8]. Although this treatment is in most cases efficient, long-term immunosuppression has been shown to be associated with increased morbidity and mortality. This includes systemic infections, gastrointenstinal disorders, hypertension, osteoporosis, hyperlipidemia, psychiatric disorders, moon face, diabetes mellitus, and obesity. Hence, there is a need for the identification of safe and effective alternatives for the treatment modalities of ABSDs. Recently, several new therapeutic agents and modalities have been reported and show promise in the treatment of patients with ABSDs [9–14].

Immunoglobulin G preparations, extracted from human blood, have been used as the treatment for patients with

antibody deficiencies and severe infections for more than half a century [15]. In addition, IVIG treatment has been established as an effective therapy for a number of autoimmune-inflammatory diseases, such as immune thrombocytopenia (ITP) [16], Guillain–Barr'e syndrome [17], multiple sclerosis [18], myasthenia gravis [19], and Kawasaki disease [20]. IVIG has also been demonstrated to be effective in autoimmune skin diseases like dermatomyositis, systemic lupus erythematosus as well as ABSDs [21]. Administration of IVIG is increasingly being used in patients with severe and recalcitrant ABSDs. However, the mechanism of action of IVIG for ABSDs is complex and is not fully understood. We here review the use of IVIG in ABSDs, including its efficacy and safety profile, its use in experimental animal models of ABSD, as well as its proposed modes of action.

Clinical use of IVIG in ABSDs

Pemphigus group

In pemphigus vulgaris (PV, desmoglein (Dsg 1) and Dsg 3 as auto-antigens) and pemphigus foliaceus (PF, Dsg1 as autoantigen) binding of autoantibodies to adhesion molecules of the epidermis results in intra-epidermal loss of adhesion (acantholysis). PV mainly affects mucous membranes in the oral cavity and the skin. Due to the low expression of Dsg 3 in the skin and low expression of Dsg 1 in the oral cavity, PF lesions are restricted to the skin. Both conditions are considered life-threatening. Systemic corticosteroids are the mainstay in the therapy of pemphigus, which has greatly improved survival. In patients with poor control of disease, various anti-inflammatory and immunosuppressive agents are added to the treatment regimen. Regarding IVIG around 100 reported patients with extensive treatment-resistant pemphigus have—in most cases successfully—been treated [22–44]. The vast majority of patients responded to treatment with high-dose IVIG (2 g/kg bodyweight) intravenously given at monthly cycles. Most commonly, the cumulative dose of 2 g/kg is given over a period of consecutive 5 days, i.e., IVIG 400 mg/kg/day [22–39]. In general, skin lesions quickly improve as soon as 1 week after initiation of IVIG. As IVIG is the only therapy that does not suppress the normal immunity, it can be used in patients whose immunity is considerably compromised. Therefore, IVIG may be ideally suited for the treatment of severe pemphigus (Fig. 1).

IVIG has so far only been used in few PF patients. These patients suffered from severe and widespread PF, resistant to conventional therapy. Similar to PV patients, IVIG treatment (1–2 g/kg/month) of PF patients with refractory disease has been reported to be most often successful. Interestingly, some of these patients remained in long clinical remission after discontinuation of IVIG [24, 28, 40–44].

Subepidermal blistering diseases

Bullous pemphigoid (BP) is a chronic autoimmune subepidermal blistering disease with autoantibodies directed against 180 or 230 kDa antigens that are components of the dermal–epidermal hemidesmosomal adhesion complex. Clinically, BP is characterized by blistering on erythematodous or apparently normal skin, primarily affecting the elderly. BP usually responds well to either systemic or topical treatment with corticosteroids. If required, dapsone or other adjuvants can be added. Despite a relatively good response to treatment, mortality in BP patients is high (20–25% within the first year after diagnosis), which is also due to treatment associated adverse events [45]. Hence, as outlined for pemphigus diseases, IVIG seems a good candidate to reduce the high treatment associated morbidity and mortality. Up to now, about 40 cases of IVIG treatment in BP have been described [24, 33, 46–50]. A review of literature revealed that most patients with extensive treatment-resistant BP benefit from IVIG therapy when IVIG was used at doses of 2 g/kg/monthly cycle for 3 months or more (until all previous lesions had healed and no new lesions appeared). Notably, IVIG was used as a monotherapy to sustain clinical remission in some patients [50]: in an open label trial including ten male Caucasian patients with BP, IVIG was used as a monotherapy. Patients received IVIG infusions at a dose of 2 g/kg/cycle. A cycle of IVIG therapy consisted of the total dose of IVIG divided into three equal doses and given on three consecutive days. Patients initially received infusions at 4-week intervals until an effective clinical response, defined as the complete healing of all lesions, was achieved. Once an effective clinical response was achieved, the interval between infusion cycles was gradually increased to 16 weeks. If no lesions were observed with a 16-week interval between two infusion cycles, IVIG therapy was discontinued. In all patients, circulating autoantibodies to BP180 and/or BP230 significantly declined. A statistically significant decline in the mean autoantibody titers was observed after 3 months of treatment, and became nondetectable after a mean period of 10–11 months. Serological remission was sustained for 7 months. The clinical response mirrored the serological findings: After 3 months of treatment, an effective response was observed, and all patients with serological remission also experienced a clinical remission, which lasted throughout the duration of the study [50].

Mucous membrane pemphigoid (MMP), previously termed as cicatirial pemphigoid, affects different mucous membranes and occasionally the skin. Oral, ocular, naso-

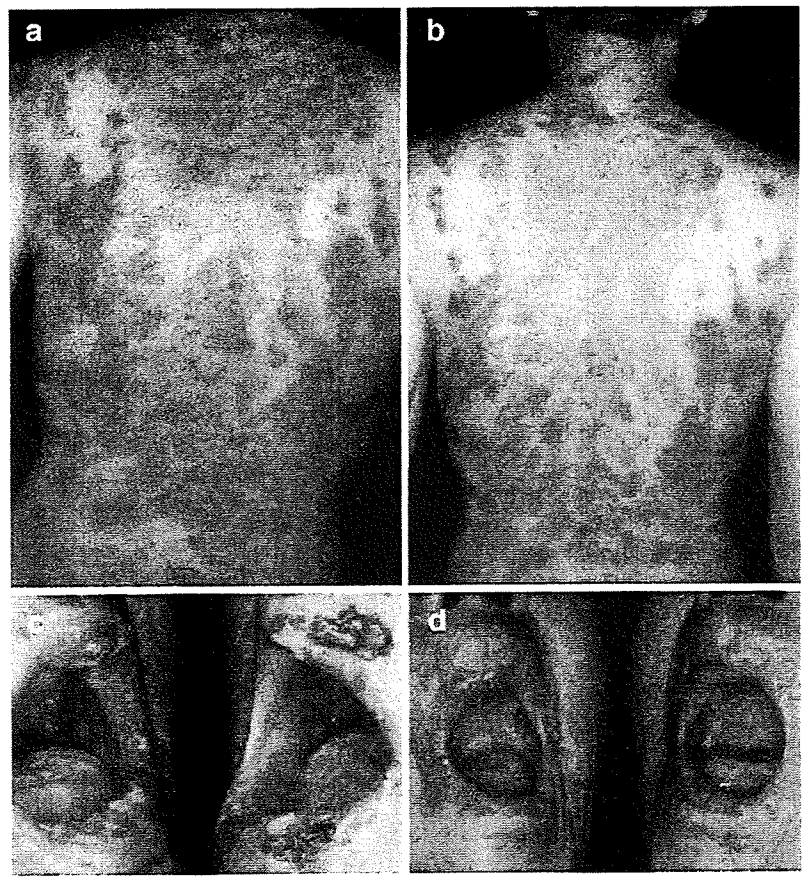

Fig. 1 Therapeutic efficacy of IVIG in patients with PV. Disseminated erosions on the back and oral mucosa before initiation of IVIG (**a**, **c**) and 1 month (**b**, **d**) thereafter in two patients with pemphigus vulgaris. The first patient (**a**, **b**) showed only a marginal improvement of corticosteroid therapy (prednisone; 20 mg/day) for 6 weeks without other immunosuppressants (**a**). Hence, treatment with IVIG was started (400 mg/kg/day for 5 days) combined with corticosteroid. Within 4 weeks after initiation of this therapy, a rapid clinical remission was achieved (**b**). This was accompanied by a reduction of circulating anti-Dsg 3 autoantibodies from 460 to 118 (normal<20). The second patient (**c**, **d**) had also showed only a marginal improvement of corticosteroid therapy (prednisone; 22.5 mg/day) for 3 months without other immunosuppressants (**c**). Hence, IVIG (400 mg/kg/day for 5 days) combined with corticosteroid was started. Within 4 weeks after initiation of this therapy, a rapid clinical remission was achieved (**d**). This was accompanied by a reduction of circulating anti-Dsg 3 autoantibodies from 1,213 to 102

phayngeal, and esophageal mucosa are typically involved. The blistering of affected areas is often followed by scarring. Hence, MMP affecting the eyes may lead to blindness. Overall, treatment of MMP is difficult, despite the use of corticosteroids combined with other immunosuppressants. At least 70 patients with severe widespread MMP resistant to conventional therapies were reported to be successfully treated with IVIG as adjuvant therapy [28, 50–58]. Most case reports have shown IVIG given at 2 g/kg/cycle initially every 2–3 weeks is a therapeutic option. IVIG therapy avoided progression of the disease and was more effective than conventional immunosuppressive treatment [56, 57]. In several patients who were already blind in one eye and had progression of disease despite conventional treatment, high-dose IVIG arrested the patients' disease and stabilized vision of the unaffected eye [56]. Likewise to BP patients treated with IVIG monotherapy, seven patients suffering from MMP which had contraindications for corticosteroids and other immunusuppressive agents were successfully treated with IVIG monotherapy. Serological and clinical remission in these patients was sustained for several months after cessation of IVIG infusions [49].

EBA is a chronic blistering disease of skin and mucous membranes characterized by subepidermal blisters and tissue-bound as well as circulating autoantibodies to the dermal–epidermal junction. The circulating IgG antibodies in EBA react with a 290 kDa dermal protein, type VII collagen, the main constituent of anchoring fibrils. Therapy of patients with EBA remains unsatisfactory and mainly relies on systemic corticosteroids and immunosuppressive agents, such as methotrexate, azathioprine, or cyclophosphamide [59–61]. A review of literature reveals 12 reported patients with extensive treatment-resistant EBA who had

been treated with IVIG [24, 28, 62–69]. The response was usually favorable, but further data are needed to establish the real potential of IVIG in EBA (Table 1).

Autoantibody levels during treatment with IVIG

Investigating the serological response to IVIG therapy demonstrated that after start of IVIG therapy a reduction of circulating autoantibodies could be detected [25, 35, 44, 70–72]. Hence, it was assumed that IVIG selectively decreases the concentration of circulating pathogenic autoantibodies in patients with ABSDs. Serum concentrations of the antibodies decrease by more than half within 1–2 weeks after initiation of treatment. Moreover, the decrease seems to be selective because total concentrations of IgG increase rather than decrease [35]. The decline of circulating autoantibodies (to Dsg 1, Dsg 3, or BP180 NC16A) correlates with improvement of disease activity in the majority of patients with PF, PV, and BP, respectively [70–72]. However, one has to critically reflect this specific decrease of circulating autoantibodies, as the patients receive 140 g of IgG (based on a body weight of 70 kg), which is a multiple amount compared to endogenous IgG (40–50 g). Hence, the observed reduction in pathogenic autoantibody concentration might be due to a diluting effect.

Corticosteroid-sparing effect

High-dose IVIG might become a therapeutic option in patients with corticosteroid-dependent ABSDs as an adjuvant steroid sparing agent [10, 34, 73]. The corticosteroid-sparing effect of IVIG was demonstrated in patients with corticosteroid-dependent ABSDs. Treatment with IVIG led to a marked reduction of corticosteroid doses which could be reduced after initiation of IVIG. The mechanism of molecular effect is currently under investigation, but published clinical experience has indicated a beneficial effect of IVIG as a steroid-sparing and even a disease-modifying agent. Common doses of concomitant corticosteroids and/or immunosuppressants could be considerably reduced during the post IVIG course of the disease. Again, this underscores the therapeutic efficacy of IVIG in the treatment of ABSDs.

Adverse events and limitations

The main advantage of IVIG over other steroid-sparing therapies is its excellent safety profile. Overall, IVIG treatment has limited adverse events [10, 74]. Adverse events are generally mild and reported side effects include headache, fever, chills, myalgia, flushing, hypotension, tachycardia, and gastrointestinal symptoms. Of these, the occurrence of headaches during IVIG infusion is most commonly reported. Thus, tension headache appears to be the single most common side effect from IVIG therapy, which may be more common in patients with an associated elevated blood pressure [74]. Headaches can be controlled by premedication or self limiting; severe adverse events are rare. After the introduction of strict regulations in the use of medications derived from blood donors, the risk of transmitting infectious diseases has been dramatically reduced. However, the limited supply of IVIG is a major obstacle for its broader application. This limited supply of IVIG is one of the reasons for the relatively high treatment costs. As far as cost is concerned, a recent study suggests that IVIG is a cost-effective treatment compared with conventional immunosuppressive therapy in patients with

Table 1 Summary of patients with EBA treated with IVIG

Patient #	Age/gender	Dose and frequency	Additional treatment	Outcome	Reference
1	16/M	0.4 g/kg/day for 5 days, 4 cycles	Adjunctive	Improved	[63]
2	37/M	2 g/kg/month, 8 cycles	Monotherapy	No improvement	[64]
3	55/M	0.4 g/kg/day for 5 days, 9 cycles	Adjunctive	Improved	[65]
4	36/M	0.4 g/kg/day for 5 days, 4 cycles	Adjunctive	Improved	[66]
5	60/M	0.4 g/kg/day for 5 days, 17 cycles	Monotherapy	Improved	[24]
6	18/M	0.4 g/kg/day for 5 days, 6 cycles	Monotherapy	Improved	[24]
7	37/M	0.4 g/kg/day for 5 days, 9 cycles	Adjunctive	Improved	[67]
8	43/F	0.4 g/kg/day for 5 days, 6 cycles	Adjunctive	Improved	[68]
9	63/M	0.5 g/kg/day for 3 days, 1 cycle	Adjunctive	Improved	[69]
10	54/F	2 g/kg/day/month, 4 cycles	Adjunctive	Improved	[70]
11	77/F	2 g/kg/day/month, 27 cycles	Adjunctive	Improved	[28]
12	38/F	2 g/kg/day/month, 10 cycles	Adjunctive	Improved, partial remission	[28]

References from selected publications were screened for additional reports on IVIG therapy in EBA. Overall, we identified the 12 publications. On January 14th, a Medline Search with the term (EBA or epidermolysis) and (IVIG or immunoglobulin) was performed

mucocutaneous blistering disease non-responding to first-line therapy [75]. On an annual basis, the mean total cost of IVIG therapy was significantly lower compared to the expenses of conventional immunosuppressive therapy during the entire course of the disease.

Mode of action of IVIG in ABSD

The mechanism of action of IVIG in ABSDs is still not determined precisely. It has been suggested that IVIG decreases serum levels of pemphigus autoantibodies by increased catabolism, and recent evidence in an animal model provides evidence that IVIG can inhibit the binding of anti-desmoglein 3 antibodies to recombinant desmoglein 3 in a dose-dependent manner in vitro as well as blistering in vivo in experimentally induced PV in newborn mice [76, 77]. In general, IVIG may mediate its effects through recognition and neutralization of specific, pathogenically relevant epitopes; e.g., neutralization of autoantibodies by anti-idiotype antibodies in the IVIG preparation [78, 79]. This, among several other antigen-specific therapeutic effects of IVIG, is mediated by the Fab fragment. More recent data indicated that the Fc fragments in IVIG preparations also have a significant impact on immune responses; e.g., inhibition of the neonatal Fc receptor [76].

The relative contribution of the Fc and/or Fab fragments to the therapeutic effects of IVIG has been addressed in several well-designed clinical trials and experiments: in patients with acute immune thrombocytopenic purpura, Fc fragments were as effective as IVIG [80]. In line with data from models of arthritis, nephrotoxic nephritis, and experimental autoimmune encephalitis, the Fc fragment was therapeutically effective while infusion of Fab fragments (when tested) were ineffective [80–85]. More recently, sugar moieties attached to the asparagine 297 residue of Fc fragments, e.g., sialic acid have been demonstrated to mediate most (if not all) therapeutic effects of IVIG. In brief, deglycosylated IVIG preparations lost its therapeutic effect, while hyperglycosylated lead to an increase in therapeutic efficacy [83]. Furthermore, recombinant hyperglycosylated Fc from IgG1, which can be recombinantly expressed, is also effective in the treatment of experimentally induced arthritis as well as in a model of autoimmune thrombocytopenia [86]. Subsequently, we will, therefore, focus on the proposed mechanisms induced by the Fc fragment (Fig. 2).

Neonatal FcR

The neonatal FcR (FcRn) is a crucial regulator of IgG half-life. Hence, saturation of the FcRn by IVIG, thus, shortening the half-life of all (including pathogenic) antibodies, is one possible mechanism by which IVIG could mediate its therapeutic effect. This assumption is supported by the notion of a decrease of pathogenic antibodies in patients receiving IVIG therapy [25, 35, 44, 70–72]. It remains to be investigated if this is a specific effect or if this is due to dilution. Mice lacking neonatal Fc-receptor expression were completely protected from blister formation induced by injection of autoantibodies into neonatal mice. In these mice, IVIG showed no therapeutic benefit. Hence, the authors concluded that neonatal Fc receptor exclusively mediates the therapeutic effects of IVIG in their model systems [76]. However, increasing the doses of pathogenic antibodies may overcome the complete protection from disease induction observed in mice lacking FcRn expression. This has recently been observed in experimentally induced EBA [87]. Therefore, assumption of a "complete dependency of IVIG on FcRn expression" [76] has to be critically revised. In line, in models of autoimmune thrombocytopenia, the effect of IVIG on platelet counts was evident before the detection of decreased platelet-specific autoantibodies [88].

Activating FcR

In most disease conditions, autoantibody-induced tissue damage is mediated by activating Fc receptors expressed by effector cells of the immune system. Hence, another compelling hypothesis on IVIG's mode of action is binding to activating Fc receptors, thus, inhibiting the binding of immune complexes. In most autoantibody-mediated autoimmune diseases, pathogenic effects are mediated through the low-affinity FcγRIII and the intermediate-affinity FcγRIV receptor [84, 89–93]. These latter receptors do not bind monomeric IgG, which is predominately present in IVIG preparations [94]. IgG dimers, which can be detected in aged IVIG preparations, have been shown to have an enhanced anti-inflammatory activity in ITP. Whether dimeric IgG inhibits antibody binding to activating Fc receptors has not been investigated [95]. Hence, at least at present, modulation of activating Fc receptors seems not the primary mechanism of IVIG activity.

Inhibitory FcR

In contrast, good evidence supports the notion that IVIG mediates its therapeutic effect through the inhibitory FcR (FcγRIIB) receptor: mice lacking FcγRIIB expression are no longer protected by IVIG treatment from disease induction [81, 82, 84, 96–98]. Moreover, IVIG therapy resulted in an increased expression of this molecule on effector macrophages, while leading to a downregulation of the activating FcγRIII receptor [96]. This assumption is further sustained by the notion that deglycosylated IVIG

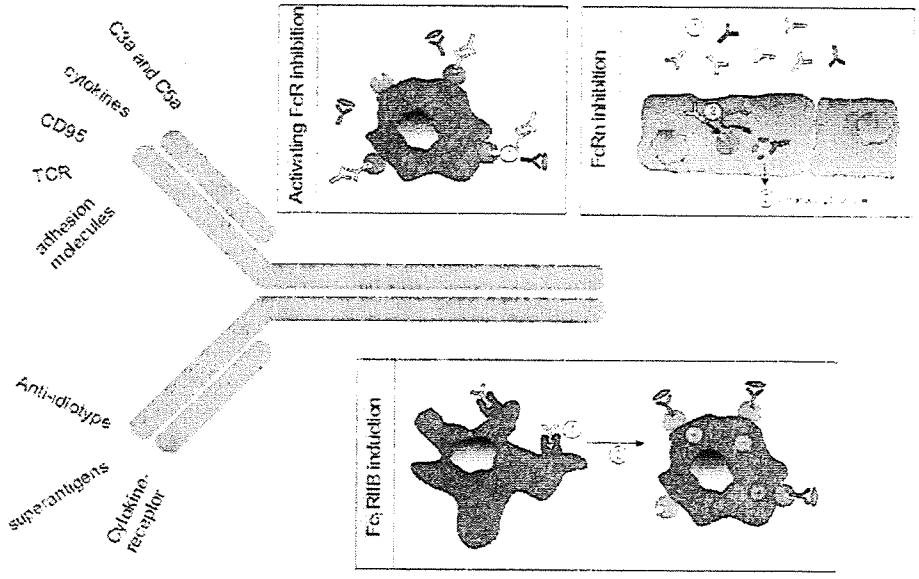

Fig. 2 Summary of IVIG's proposed modes of action. IgG present in the IVIG preparations consists of the Fab fragment (shown on *blue background*), allowing specific binding to antigens and the Fc fragment (shown on *yellow background*), which mediates pro-inflammatory effects after binding of the IgG to the antigen. Several Fab-mediated effects have been attributed to mediate the therapeutic efficacy of IVIG, including inhibition of the complement proteins *C3a and C5a*. Both complement proteins have been linked to mast cell activation. C3a- and C5a-induced rise in intracellular calcium in mast cells was dose-dependently inhibited by IVIG. This effect of IVIG was also achieved by Fab fragments, indicating the presence of anti-C3a and anti-C5a antibodies in the IVIG preparation [103]. Inhibition of *cytokines* and *cytokine receptors* has also been attributed to mediate the therapeutic effect of IVIG. For example, antibodies to IL-1α and IL-6 in IVIG preparations reduced the serum antiviral activity obtained from patients with autoimmune conditions treated with IVIG [104]. Presence of anti-CCR5 antibodies in IVIG preparations has been linked to a possible therapeutic use in HIV-infected patients [105]. However, anti-cytokine or anti-cytokine receptor activity has not yet been directly linked to the therapeutic effect of IVIG. The observation that IVIG inhibits T cell-mediated, Fas-induced apoptosis of keratinocytes [106] supports the notion that IVIG inhibits CD95L–CD95-induced apoptosis [107]. In the serum of healthy individuals (and, thus, also in IVIG preparations), naturally occurring antibodies to T cell receptors (*TCR*) are present. These antibodies are produced by patients with autoimmune diseases, which in turn modulate the activation of autoreactive T cells [108]. Since antibodies of these specificities are present in the polyclonal IVIG preparations, such antibodies might be responsible for the therapeutic effect of IVIG [109]. *Adhesion molecules* are expressed by endothelial cells and leukocytes and mediate the extravasation of leukocytes to the sites of inflammation [110, 111]. Thus, targeting the extravastion of leukocytes is a promising approach to treat the uncontrolled inflammatory response in autoimmunity [112, 113]. Through so far uncharacterized mechanisms, IVIG lead to decreased leukocyte rolling in vitro and in vivo, which could be attributed to inhibition of selectin function [114]. Experiments employing the neonatal mouse model of pemphigus [76] showed that IVIG as well as Fab fragments from the IVIG preparation inhibited disease induction [77]. This points towards the presence of *anti-idiotype* antibodies in IVIG preparations, which have been described to mediate the therapeutic effect of IVIG [78, 115]. *Superantigens* are products from certain bacteria leading to the stimulation of large numbers of T cells. There is good evidence for the involvement of superantigens in various disease conditions in which IVIG is used for therapy [116–118]. By ELISA and Western blotting, antibodies to superantigens were detected in IVIG preparations. Presence of these antibodies was functionally relevant, as IVIG was able to impair superantigen-induced T cell proliferation [119]. Yet, data from models of arthritis, nephrotoxic nephritis, and experimental autoimmune encephalitis clearly demonstrated that the Fc fragment was therapeutically effective, while infusion of Fab fragments (when tested) were ineffective [80–85]. Among the effects mediated by the Fc fragment is inhibition of immune complex binding to activating Fc receptors (shown *in red*), expressed by effector cells of the immune system, such as macrophages (shown *in blue*). (*1*) Dimerized IVIG (*green*) competitively inhibits autoantibody–autoantigen complex (*red and brown*) binding to activating Fc receptors (*red*). A second alternative to mediate the therapeutic effect of IVIG is inhibition of the neonatal Fc receptor (*FcRn*). (*1*) IVIG (*green*) and pathogenic autoantibodies (*red*) are circulating in the blood stream. (*2*) Once the antibodies are taken up by endothelial cells (*green/brown*), IVIG, and pathogenic antibodies compete in binding to the FcRn (*blue*). (*3*) As IVIG is given in excess, the half-life of pathogenic autoantibodies is dramatically shortened, leading to a decrease in autoantibody concentration. This proposed mode of action is supported by the notion of reduced autoantibody concentrations in pemphigus patients treated with IVIG. One more compelling hypothesis of IVIG's mode of action is induction of the inhibitory FcγRIIB. (*1*) Very recent work has identified the SIGN-R1 expressed by splenic macrophages (*blue*) as the receptor responsible to increase the expression of FcγRIIB [100]. (*2*) Binding of IVIG to SIGN-R1 leads through so far uncharacterized mechanisms to an upregulation of the inhibitory FcγRIIB (*green*). Thus, binding of immune complexes to the effector cells of the immune system are not activated and autoantibody-induced tissue damage is prevented

loses its therapeutic effect; deglycosylated IVIG does not bind to the FcγRIIB while retaining the binding ability to the FcRn and activating Fc receptors. In mice in which certain monocyte and macrophage subpopulations are absent due to lack of colony-stimulating factor-1 (op/op mice) [99], IVIG is not effective, while pathogenic antibodies are still able to induce disease [81]. Hence, IVIG seems to indirectly influence FcγRIIB expression. The receptor mediating the upregulation of FcγRIIB in mice has been recently identified. By use of splenectomized and specific ICAM-3 grabbing non-integrin-related 1 (SIGN-R1) deficient mice, SIGN-R1 expressing splenic macrophages must be considered as the primary cellular target of IVIG. Binding of IVIG to SIGN-R1 leads to an upregulation of FcγRIIB on effector cells through so far uncharacterized mechanisms [100].

IVIG in experimental autoimmune skin blistering diseases

While evidence for its therapeutic effectiveness in increasing, IVIGs mode of action remains the issue of an ongoing scientific discussion. With regard to ABSDs, two studies using IVIG have been published: Passive transfer of IgG from BP, PF, or PV patients or immunized rabbits induces the respective disease when injected into neonatal mice. In this model of passive antibody transfer, mice lacking neonatal Fc-receptor expression were completely protected from disease induction. In line, circulating levels of pathogenic IgG in FcRn-deficient mice were significantly reduced compared with those in wild-type mice. Administration of IVIG to wild-type mice also drastically reduced circulating pathogenic IgG levels and prevented blistering, while no additional protective effect was observed in FcRn-deficient mice. From these data, the authors concluded that the therapeutic efficacy of IVIG in these pemphigus and pemphigoid models dependents on FcRn expression [76]. However, these mice were completely resistant to autoantibody-induced blister formation. Hence, we believe that data of IVIG in diseased FcRn deficient mice is required to sustain this assumption. In addition, we have recently investigated the effect of IVIG in mice with experimentally induced EBA [101]. In a therapeutic treatment regime, IVIG significantly ameliorated clinical disease symptoms and reduced the inflammatory skin lesions. IVIG's mode of action in experimental EBA has, however, not been characterized [102].

Conclusions and perspectives

Based on the results of several case reports and experimental animal models, IVIG is an effective treatment for a number of ABSDs. IVIG is recommended in treatment-refractory cases or patients that do not tolerate standard treatment because of side effects. It is well accepted that IVIG efficiently modulates the activity of immune cells. However, the mechanisms by which this is achieved are still being characterized. Further work will aim at identifying the molecular mechanism of IVIG's therapeutic effects. In addition, the optimal doses for induction and maintenance still need to be explored. Further studies may also try to characterize which genes are modulated by IVIG in an effort to better predict the responders. Furthermore, the effect of combination therapy (i.e., with corticosteroids/or rituximab) needs to be studied, while pharmacoeconomic trials could evaluate the effect of IVIG on quality of life compared to the costs of other less expensive drugs, which may have more long-term side effects. Future studies should determine (1) the optimal number and dose of IVIG infusions required to induce remission, (2) the adequate adjuvant immunosuppressive medication, including initial dosage and tapering mode, (3) risk factors for developing severe adverse reactions, (4) the benefit of repeated IVIG infusion as maintenance therapy, and (5) determine the precise mode of action, allowing to recapitulate the therapeutic effect of IVIG.

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Broad histopathologic patterns of non-glabrous skin and glabrous skin from patients with a new variant of endemic pemphigus foliaceus-part 1

A prospective, controlled epidemiologic survey performed in El Bagre, Colombia revealed a new variant of endemic pemphigus disease, occurring in a gold mining region. The disease resembled Senear-Usher syndrome, and occurred in an endemic fashion. The aim of this study is to describe the most frequent histopathologic patterns in non-glabrous skin and in glabrous skin observed in these patients, and their clinical correlation. The study was performed on non-glabrous skin biopsies of 30 patients from the dominantly clinical affected areas (either on the chest, arms or face). Simultaneously, biopsies from the palms were obtained in 10 randomly chosen patients of the 30 total patients. The specimens were examined following hematoxylin and eosin (H&E) staining. The most common blisters observed were subcorneal, although in some cases intraspinous and subepidermal blisters were visualized. Our results showed a very heterogeneous pattern of histopathologic patterns in non-glabrous skin, which seemed to correlate with the clinical features. The most common pattern was typical pemphigus foliaceus-like, with some lupus erythematosus-like features. A non-specific, chronic dermatitis pattern prevailed in the clinically controlled patients taking daily corticosteroids. In the patients who have had the most severe and relapsing pemphigus, early sclerodermatous changes and scleredermoid alterations prevailed in their reticular dermis. In addition to the scleredermoid alterations, the reticular dermis showed a paucity of appendageal structures. On the contrary, in the palms, a similar pattern was seen in all cases, including thickening of the stratum corneum, hypergranulosis, edema in the papillary and reticular dermis and a dermal perivascular lymphocytic infiltrate. The direct immunofluorescence of the glabrous vs. the non-glabrous skin also showed some differences. We conclude that the histopathologic features of this new variant of endemic pemphigus are complex, therefore, classical histopathologic features previously described for superficial, endemic pemphigus cannot be used alone to diagnose this disease.

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Introduction

Endemic pemphigus foliaceus (EPF) is the only documented, endemic autoimmune-mediated disease observed in a relatively well-defined geographic region.[1–3] It is generally accepted that pemphigus foliaceus (PF) and Brazilian EPF, also known as fogo selvagem (FS), are characterized by acantholysis and blistering in the upper epidermis, with deposits of predominantly IgG4 autoantibodies in the intercellular spaces.[1–3] Biopsies from most FS patients with *acute* disease have shown subcorneal bullae with acantholysis and epidermal clefts.[3–6] In contrast, *chronic* lesions from FS patients have been reported to show acanthosis, mild papillomatosis, hyperkeratosis and keratotic plugging of hair follicle.[3 6] Within the dermis, vasodilatation and infiltration of lymphocytes and histiocytes are often reported.[1,3–6] In the group of patients with EPF from Tunisia, the presence of eosinophilic spongiosis with acantholysis was frequently noted histologically, with accompanying clinical features resembling pemphigus herpetiformis.[7,8]

We have identified a new variant of EPF in the areas around El Bagre, Colombia (El Bagre EPF).[9,10] Our studies resulted from an 11-year survey, and established that this geographic focus exhibits similar features to those described in pemphigus erythematosus, also known as Senear-Usher syndrome, a disease with combined features of lupus erythematosus and pemphigus.[11,12] El Bagre EPF predominantly affects 40- to 60-year-old males, as well as a few postmenopausal females; the patients are primarily miners who also work in agricultural activities.[9,10] In contrast, FS primarily affects children and young adults, with the highest incidence at 10- to 30- years of age and both sexes equally affected.[1–3,9,10] The principal aims of our study were to compile and classify the common histopathologic and direct immunofluoresence (DIF) patterns in skin biopsies from affected skin and clinically 'unaffected' palms of El Bagre EPF patients, and to correlate these findings with their respective clinical presentations.

Materials and methods

Subjects of study

We studied 30 patients who fulfilled the diagnosis of El Bagre EPF. Our 30 patients were chosen for the study after fulfilling a minimum five out of six of the following inclusion criteria. A clinical stage vs. histopathologic correlation was obtained. Written consents were obtained from all patients, as well as Institutional Review Board permission.

Skin sample

We tested 30 cases of El Bagre EPF previously diagnosed by us that fulfilled the following criteria. Specific criteria include (a) patient displays clinical features described for El Bagre EPF,[9,10] (b) patient lives in the endemic area, (c) patient serum displays cell surface staining between keratinocytes by either DIF or indirect immunofluorescence (IIF) (specifically, using Fluorescein isothiocyanate (FITC) conjugate monoclonal antibodies to human IgG4 or total IgG in glabrous skin),[9 11] (d) patient serum immunoprecipitates a Con-A affinity purified bovine tryptic 45-kDa fragment of PF antigen,[10–16] (e) patient serum is positive by immunoblotting (IB) for reactivity against desmoglein 1 (Dsg1), as well as for plakin molecules as previously described,[15,16] finally, (f) patient serum is positive using an enzyme-linked immunoabsorbent assay when screening for autoantibodies to PF antigens.[16]

For all the above determinations, serum from a well-characterized FS patient from Brazil and two PF sera from the endemic area were used as positive controls. A negative normal control from USA was also used. Following local anesthesia without epinephrine, skin biopsies were taken from the clinical predominantly lesions from affected areas on the chest, arms or face. Biopsies were fixed in 10% buffered formalin and processed for hematoxylin and eosin (H&E) staining. Biopsies from 10 randomly chosen patients out of 30 total patients were taken from the palms and split into two pieces; one was placed in Michel's medium for DIF and the other half was fixed in 10% buffered formalin and processed for H&E staining.

DIF and IIF

For IIF, sera from all subjects were titrated in calcium-supplemented buffer at 1 : 20 and 1 : 40 dilutions. We then incubated the substrate tissues with the serum. We next added the secondary antibodies; FITC conjugated rabbit anti-total IgG antiserum (Dako, Carpinteria, California) and FITC conjugated rabbit anti-human IgG4 (gamma chain) (Sigma Aldrich, Saint Louis, Missouri) at dilutions 1 : 20 and 1 : 40, respectively. For IIF, the antigen source was monkey esophagus. The samples were run with positive PF control sera and a negative control serum. For the DIF, we used FITC conjugated rabbit antisera to human IgG, IgA, IgM, C3, C1q, fibrinogen and albumin. Anti-human IgA antiserum (alpha chain) and anti-human IgM antiserum (mu chain) were obtained from Dako. Anti-human IgE antiserum (epsilon chain) was obtained from Vector Laboratories. The slides were counterstained with 4',6-diamidino-2-phenylindole Dapi (Pierce, Rockford, Illinois). Mouse anti-collagen IV monoclonal antibody (Invitrogen, Carlsbad, California) was used with a secondary donkey anti-mouse IgG (H + L chains) conjugated with Alexa Fluor 555 (Invitrogen).

Immunoblotting (IB)

Sera were tested for reactivity against Dsg1. This was carried out as previously described.[9,10,14] We used sodium dodecyl sulfate (SDS) extracts of human and bovine epidermis and fractionated by 7% SDS polyacrylamide gel electrophoresis (SDS-PAGE) according to the Laemmli method.[9,10,14] Gels were transferred onto nitrocellulose membranes.[5,10]

Superimposed microbiological infections

Based on the fact that our patients live in a tropical area in conditions of poverty and malnutrition and given the fact that we had previously detected some superficial subcorneal blisters in several El Bagre EPF patients,[9] we felt it necessary to discard samples displaying positive infection with bacteria and fungi. The presence of clinical microbiological infection was assessed by using a smear from the 4-mm skin punch biopsies before fixation in formalin. In addition, culture for fungi and mycobacteria were performed in accordance with the World Health Organization recommendations.[17]

Results

General histopathologic pattern and correlations with clinical presentations

Based on our experience of working with patients affected by this disease, we were able to observe very broad clinical patterns and histologically heterogeneous lesions. Indeed, approximately 50% of the El Bagre EPF patients had different morphologic clinical lesions at the same time. Superficial erosions with some oozing and marked crusting were noted in some patients. Other patients presented with ulcerated lesions on erythmematous skin with weeping yellowish serum surrounded by flaccid, easily ruptured vesicles. In some cases, the lesions were papulovesicles or papulopustules, arranged in arciform, annular or serpinginous patterns. Occasionally the lesions were discrete and localized, especially in more benign cases. Based on established dermatopathologic patterns, we divided our skin findings into several primary histopathologic prototype groups. In about 80% of patients, melanophages were present around the upper dermal vessels.

Typical PF-like histologic features

In about 25% of the cases, the histologic features of PF were observed (Fig. 1A). Clinically, as classically described in PF, the initial bullae are usually present on the trunk. The primary lesions were small superficial blisters (rarely observed clinically); because they are transient and quickly transform into erosions (Fig. 1B). Sometimes the bullae were localized at the basal membrane zone (BMZ) (Fig. 1C).

Lupus erythematosus-like histologic features

This pattern was seen in about 20% cases (Fig. 1D). Clinically, in these cases, discoid patches were clearly observed on the face (Fig. 1E). These cases were therefore clinically almost indistinguishable from classic cases of lupus erythematosus. Some histologic features included basal layer vacuolar change, active interface inflammation, epidermal atrophy, follicular plugging, deep perivascular and periadnexal inflammation as well as mucin deposition.

Chronic dermatosis pattern

In about 20% of the chronic cases, in which the patients were taking oral steroids varying between 20 to 40 mg/day and showing improvement in their clinical lesions, the biopsies showed histologic changes resembling those observed in chronic dermatoses (Fig. 1F,G). Clinically, most of these cases displayed lichenification of the skin with small plaques, papules and vesicles, especially in the chest. Occasionally, the only clinical finding was hyperpigmented or erythematosus macules, where previous inflammatory lesions had occurred (Fig. 1H). Of interest was the fact that in more senior patients (70 years or older) the chronic lesions became increasingly dry over time, with no vesicles, pustules or weeping. Instead, the main clinical lesions were confluent, hyperpigmented