BULLOUS PEMPHIGOID INDUCED BY DIPEPTIDYL PEPTIDASE-4 INHIBITORS. EIGHT CASES WITH CLINICAL AND IMMUNOLOGICAL CHARACTERIZATION

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ABSTRACT

Background

Dipeptidyl peptidase-4 (DPP-4) inhibitors have increasingly been identified as causative agents of bullous pemphigoid. The clinical and immunological characteristics of this pemphigoid variant are still unclear. The objective of our study was to analyze the clinical and immunological features of patients with pemphigoid induced by DDP-4 inhibitors.

Methods

All patients diagnosed with DPP-4 inhibitor-associated bullous pemphigoid at dermatology departments in three Spanish centers during the period 2013 to 2015 were included. ELISA assays for the NC16A domain of BP180 and BP230 were performed. Immunoblot studies using epidermal/dermal extracts and the C-terminal, NC16A and LAD-1 regions of BP180 were also carried out.

Results

A total of eight patients were identified (5 treated with vildagliptin, 2 with linagliptin and one with sitagliptin). Of these, 4 presented the classical inflammatory phenotype of bullous pemphigoid and 4 a non-inflammatory phenotype. The ELISA for BP180 (NC16A domain) was positive in 6 patients at diagnosis. Most patients reacted to more than one BP180 antigenic site (LAD-1 and/or C-terminal domain) on the immunoblot. Two patients showed no reaction against the NC16A domain of BP180 on either the ELISA or immunoblot but recognized either LAD-1 or both LAD-1 and the C-terminal domain. Only one of the NC16A-negative patients had a non-inflammatory subtype of bullous pemphigoid.

Conclusions

Patients with DPP-4 inhibitor-induced BP may present either an inflammatory or a non-inflammatory phenotype of BP. IgG response against other BP180 regions different from the NC16A domain, such as LAD-1 and the C-terminal domain, could be pathogenically relevant to the onset of DPP-4 inhibitor-induced BP.

KEY WORDS

Bullous pemphigoid; dipeptidyl peptidase 4 inhibitors; immunoblot; drug-induced bullous pemphigoid; LAD-1

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INTRODUCTION

Bullous pemphigoid (BP) is the most common cutaneous autoimmune blistering disease. It typically affects elderly patients and is associated with significant rates of morbidity and mortality.[1] Mucosal involvement is usually present in about 20 to 30% of patients.[1] The majority of patients with BP have circulating autoantibodies directed against one of two hemidesmosomal proteins (BP180 and BP230).[2] Antibodies directed against the extracellular NC16A domain of BP180 protein have been shown to play a relevant role in the pathogenicity of this disease.[2] Although in the vast majority of patients no causative agent is identified, in rare instances development of the disease has been linked to the use of certain drugs.[3] This drug-induced variant of BP usually shares common clinical, histopathological and immunofluorescence findings with conventional BP.[3] The intrinsic pathogenic mechanisms underlying this peculiar drug-related BP subtype are unknown, and only few studies that characterize the epitope specificities have been performed.[4]

Oral dipeptidyl peptidase-4 (DPP-4) inhibitors, so-called gliptins (vildagliptin, sitagliptin, linagliptin and saxagliptin), have been introduced in recent years for the treatment of type 2 diabetes mellitus in adults. They can be used in monotherapy or in combination with another antidiabetic medication (usually metformin). DPP-4 inhibitors have recently been implicated as potential causative agents in the development or exacerbation of BP.[3,5-8]

The objective of our study was to analyze the clinical, histopathological, and immunological

characteristics of a series of eight patients with DPP-4 inhibitor-induced BP (DI-BP) using enzyme-linked immunosorbent assays (ELISA) and immunoblot (IB) studies.

MATERIALS AND METHODS

Patients and sera

A retrospective study of all patients diagnosed with BP at the dermatology departments of three university hospitals in Spain during the period 2013-2015 was carried out. Those patients diagnosed with BP probably induced by DPP-4 inhibitors, according to the World Health Organization causality assessment system, were included in the study.[9] A diagnosis of BP was established on the basis of characteristic clinical, histopathological and immunological features, according to the Guidelines of the European Dermatology Forum.[10] Serum samples from 8 BP patients on DPP-4 inhibitors (except for one subject who had stopped taking the drug 2 months before) were collected at diagnosis. In 3 patients, successive periodical serum samples were obtained during different evolutionary phases of the disease. Approval to conduct this study was obtained from the center's ethic committee in accordance with the Helsinki Declaration of 1975, as revised in 1983.

ELISA for BP180 and BP230

ELISA analysis was performed for all patients. IgG antibodies directed against BP180 and BP230 proteins were evaluated using commercial kits (MBL International, Nagoya, Japan). The ELISA system for BP180 was specific for the NC16A domain. The results of the ELISA assays for BP180 were retrieved from the patients' reports, whereas the results of the ELISA for BP230 were obtained from frozen serum samples stored at - 80ºC.

IB studies

All of the IB studies were performed in Kurume University School of Medicine (Japan) using frozen serum samples stored at -80 ºC at the patients' respective hospitals.

IB of normal human epidermal extracts was performed according to the method described by Sugi et al.[11] For IB containing a recombinant form of BP180 NC16A, a fusion protein was prepared as previously described by Matsumura et al.[12]

In addition, IB using a recombinant protein corresponding to the carboxy-terminal (C-terminal) domain of BP180 was carried out. This fusion protein was obtained via the technique described by Nie et al.[13]

IB assays with concentrated supernatants of HaCaT cells culture medium for the LAD-1 120 kDa fragment, normal human dermal extracts and purified human laminin 332 (laminin 5) were also carried out following the methods previously described by Ishii et al and Hisamatsu et al, respectively.[14-16]

In one patient, only IB studies with normal human epidermal and dermal extracts could be conducted due to an insufficient amount of serum sample.

RESULTS

Patient demographics

Eight patients (4 females and 4 males), with a mean age of 80 years, were included (Table 1). At the time of their BP diagnosis, five patients were being treated with vildagliptin, 2 with

linagliptin and 1 with sitagliptin, all in combination with metformin. BP developed several months after the introduction of the DPP-4 inhibitor (median: 6.5 months; range: 4-48 months). Based on the Bullous Pemphigoid Disease Area Index (BPDAI),[10] 5 patients were classified as extensive BP and 3 as mild BP (patients 1, 3 and 8). Half of our patients (4 of 8) had an inflammatory subtype of BP. Oral mucosal involvement was present in 4 cases, 2 with mild involvement and 2 with extensive lesions along the palate and along the oral mucosa and pharynx, respectively (Fig. 1). In all patients, skin involvement predominated over mucosal involvement, and lesions healed without residual scarring.

Histopathological and immunofluorescence studies

Histopathological and direct immunofluorescence findings were identical to those observed in idiopathic BP. Indirect immunofluorescence on 1-molar salt-split skin revealed the presence of IgG against the epidermal side of the blister in the 8 patients (Fig. 2).

Response to treatment

Treatment with the DPP-4 inhibitor was stopped shortly after diagnosis of BP in all patients except 2. Treatment of one patient (No. 5) had been suspended two months before consultation and 4 months after the onset of symptoms. In another patient (No. 7) medication was discontinued 9 months after the first consultation.

Three patients were treated with topical clobetasol propionate alone following the regimen proposed by Joly P. et al.[17] The remaining patients received oral systemic treatments at low doses: dapsone (three patients) and cyclophosphamide (one patient), along with low doses of corticosteroids (0.5mg/kg/day) on a tapering-off regimen (four patients) (Table 1). Clinical remission was achieved after a median time of 3 months (range: 0.5-10) after DPP-4 inhibitor withdrawal. BP treatment was stopped in 7 out of 8 patients after a median time of 7 months

(range: 1-10), without subsequent clinical relapses during a median follow-up period of 9 months (range: 5-28).

Antibody profile

ELISA assays for BP180 were positive in 6 patients (75%) at diagnosis, although antibody titres were low in one of them (Table 1). In one patient, the ELISA was negative at diagnosis but became positive afterwards. ELISA for BP230 showed positive results in only one patient.

Four out of 8 patients' sera reacted with a band corresponding to BP180 on the IB at diagnosis. This had been negative at diagnosis but later became positive (along with the ELISA) in patient No. 4 (Table 1). Four out of 7 patients (57%) with a positive ELISA for BP180 antibodies turned out to have a positive band as detected by IB. In addition, sera from 2 patients reacted with a 190kDa-band, corresponding to periplakin.

Only 2 patients out of 7 that were tested exhibited reactivity with NC16A on the IB. The patient with stronger reactivity had also positive results for BP180 on the ELISA and IB with epidermal extracts. The patient with a weaker band showed a positive ELISA for BP180 at low titres, but a negative BP180 in the IB with epidermal extracts.

The IB with the C-terminal domain was positive in 3 out of 7 patients. Six out of the 7 BP sera analysed (86%) showed IgG reactivity with the 120-kDa LAD-1 band. None of the patients had IgA-class reactivity.

None of the sera reacted with normal human dermal extracts or purified laminin 332.

DISCUSSION

Drug-induced pemphigoid is a variant of classic BP that develops following the oral or topical administration of certain drugs. Since first being report in 1970, more than 50 different drugs have been implicated, a number that is constantly increasing with the introduction of new medications.[3] However, in case-control studies only two of these drugs (neuroleptics and aldosterone antagonists) have demonstrated a statistically significant association with BP.[18,19] In fact, identifying the responsible drug can often prove quite difficult, since many BP patients receive multiple medications.[3,18] In addition, given the considerable morbidity and mortality rates of this disease, re-challenge with the suspected therapy in question is not feasible.[3]

Since the introduction of DPP-4 inhibitors as a standard treatment for type 2 diabetes mellitus, several reports of patients developing BP following such treatment have been published.[3,5-8] Recently, the Bordeaux-based French Association of Regional Pharmacovigilance Centers reported 42 cases of BP induced by these drugs and demonstrated statistically the association of DPP-4 inhibitors with BP.[8]

As in our patients, the time periods described in the literature from the start of the drug intake to the onset symptoms are quite variable. In their study, Bene et al. reported a median time of 10 months, with a range from 8 days to 37 months.[8] Overall, clinical symptoms promptly resolved in our patients after the discontinuation of gliptins, without the need of any further systemic treatment (3 patients), or just requiring systemic drugs at low doses and over short periods of time (4 patients). This is in agreement with previous reports of DI-BP.[5-7] In three of our patients, sustained clinical remission was documented during a follow-up period of at least one year after discontinuation of anti-BP therapy.

Recently, Izumi et al. described the antibody's epitope profile and its correlation with the clinical phenotype in a series of 121 patients with BP, including 10 cases involving DPP-4 inhibitors therapy.[4] Fourteen of the BP patients showed a distinct clinical phenotype characterized by smaller blisters, milder erythema, and a limited distribution of skin lesions, which they termed non-inflammatory BP. Interestingly, half of the BP patients presenting non-inflammatory BP were receiving DPP-4 inhibitors. Moreover, this clinical phenotype was linked to a specific autoantibody profile, in which autoantibodies recognized the full BP180 molecule and its ectodomain mid-portion, but not the NC16A domain. Only a minority of their BP cases treated with DPP-4 inhibitors had a classical inflammatory subtype, with antibodies targeting both the full BP180 molecule and NC16A.

In contrast to the results from Izumi et al., only half of our patients (4 out of 8) had a non-inflammatory BP (Table 1). Of the four patients classified as non-inflammatory BP (Nos. 1, 3, 6 and 8), one had both negative ELISA and IB for NC16A, while another two had a negative or weakly positive IB with a positive ELISA at very low titres (Table 1). The three of them showed reactivity against the LAD-1 region, corresponding to the mid-portion of the BP180 ectodomain. The fourth patient, however, exhibited positive reactivity against NC16A in the ELISA and the IB. Moreover, in contrast to the autoantibody profile described by Izumi et al., only one of the NC16A negative/weak patients reacted against the full length BP180 molecule by IB. The observed differences in the results of full-length BP180 could be due to the technique employed and/or to the lower sensitivity of the IB compared with the ELISA.

Apart from the previously described NC16A-negative patient with non-inflammatory BP, we had an additional NC16A-negative case in our series. This particular patient presented an inflammatory BP with extensive urticariform lesions. Interestingly, the serum of this patient

obtained at diagnosis reacted exclusively against the LAD-1 molecule, and throughout the evolution of the disease this reactivity disappeared while both the ELISA and IB tests for NC16A became positive. This change in the autoantibody profile could be explained by an intramolecular epitope-spreading phenomena.[20]

Three patients (Nos. 5, 7 and 8), had a negative IB for NC16A despite having a positive ELISA for BP180 NC16A. One possible explanation for this could be the higher sensitivity of the ELISA compared with the IB in detecting autoantibodies against this fraction.[21,22] Interestingly, all of these patients also showed IgG reactivity to LAD-1. This region comprises amino acids 542 to 1,497 of the BP180 ectodomain. As NC16A overlaps with LAD-1 in amino acids 542 to 562, a positive result of the ELISA due to the LAD-1 reactivity of these patients cannot be ruled out.[23]

Importantly, IgG reactivity to LAD-1 (86%) in our series was more frequent than expected according to the previously published prevalence in BP (27%-67%).[24-26] When reviewing the literature, we have only found four BP patients, apart from our two cases and Izumi's cases, showing antibodies exclusively against the LAD-1 fraction.[27-30] Remarkably, 3 of these patients had non-inflammatory BP and two of them were being treated with DPP-4 inhibitors.

Contrary to Izumi et al.'s cases, which showed a negative reactivity against the C-terminal region of BP180, 50% of our cases reacted with it, a figure higher than expected according to previous studies on BP (23.5% to 33%).[4,22,31]

The main limitations of our study are the small number of patients, the absence of a control group and, because of ethical reasons, the lack of a drug rechallenge to confirm the drug association. Thus, although a clinical improvement was observed after discontinuation of the

DPP-4 inhibitors, we cannot confirm that these drugs are responsible for the development of BP in our cases, nor in similar cases previously reported in the literature.

In conclusion, herein we report the clinical and immunological findings of a series of 8 patients with DI-BP. We have been unable to demonstrate a clear-cut relationship between DI-BP and the non-inflammatory phenotype of BP. The association of this clinical subtype with a NC16A negative profile was also not observed in our series. It could be hypothesized that IgG response against other BP180 regions different from the NC16A domain, such as LAD-1 and the C-terminal domain, could be pathogenically relevant to the onset of DI-BP. Further molecular studies with a greater number of patients are needed to better characterize this drug-induced BP variant.

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TABLES

Table 1. Clinical characteristics of the patients and results of the ELISA and immunoblot studies.

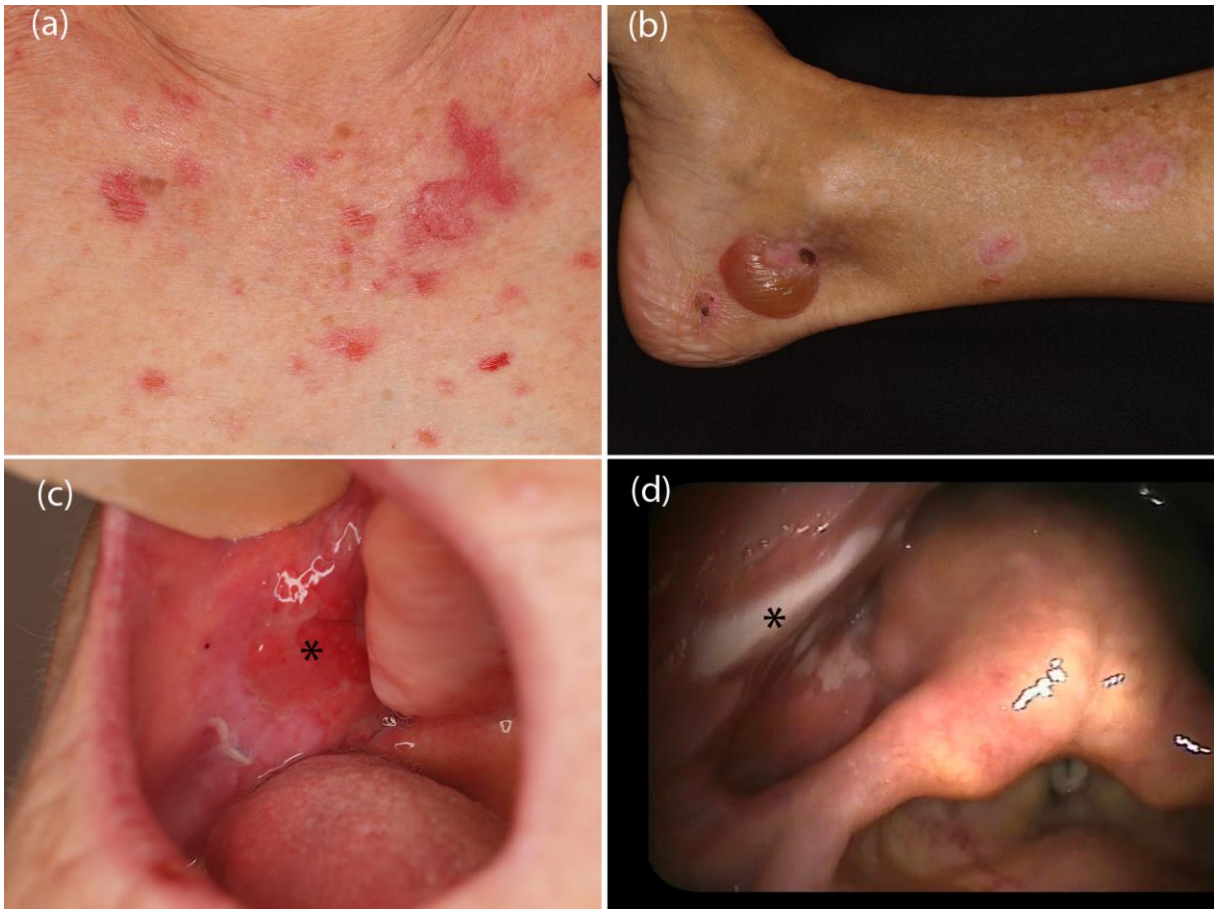
Patient Num/ gender /age (years)	**Drug**	**Time from the beginning of DPP-4i (mo)**	**Time from stopping DPP-4i* (mo)**	**BP involvement**		**IB-BP180**	**IB-BP230**	**IB-NC16A**	**IB-COOH**	**IB-LAD-1**	**IB-Periplakin**	**ELISA-BP180 (UI/ml)**	**ELISA-BP230 (UI/ml)**	**Treatment (along with suspension of DPP-4i)**	**BP outcome**	**Follow-up / Time in remission without therapy (mo)**
				Skin /Clinical subtype (NI vs I)	**Mucosa**											
1/F/78	Vildagliptin	8	0	Yes/NI	No	(-)	(-)	(+/-)	(+)	(+)	(+)	(+) 14.9	(-)	TCS	Sustained remission at 1 week	30 / 28
2/M/76	Sitagliptin	48	0	Yes/I	Yes	(-)	(-)	NA	NA	NA	(-)	(+) 63.3	(+) 24.92	TCS Oral methylprednisolone 16 mg/day Cyclophosphamide 50 mg/day	Absence of active lesions 2 weeks after starting cyclophosphamide	19 / 12
3/M/82	Vildagliptin	12	0	Yes/NI	Yes	(-)	(-)	(-)	(+/-)	(+)	(+)	(-)	(-)	TCS	Sustained remission 4 mo after starting therapy	9 / 5
4/F/65	Vildagliptin	7	0	Yes/I	No	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	TCS Dapsone 25 mg/day	Sustained remission at 9 weeks	24 / 17
		8	1	Yes/I	No	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)			
		11	4	No	No	(+)	(-)	(+)	(-)	(-)	(-)	(+)	(-)			
		12	5	No	No	(+)	(-)	(+)	(-)	(-)	(-)	(+)	(-)			

5/F/78	Vildagliptin	6 13 16 20	2 9 12 16	Yes/I Yes/I No No	No No No No	(+) NA NA (-)	(-) NA NA (-)	(-) NA NA (-)	(+) NA NA (-)	(+) NA NA (-)	(-) NA NA (-)	(+) 39 (+) 332 (+) 128 (+) 90	(-) NA NA NA	Prednisone 30 mg/day on a 1-month-tapering-off regimen Dapsone 75 mg/day	Sustained remission at 4 mo	18 / 9
6/M/83	Linagliptin	6 7	0 1	No Yes/NI	Yes No	(+) (+)	(-) (-)	(+) (+)	(-) (-)	(-) (-)	(-) (-)	(+) (+)	(-) (-)	Prednisone 30 mg/day on a tapering-off regimen, with relapse at low doses Dapsone at 25 mg/day was started 9 mo after the diagnosis	Sustained remission 1 mo after starting dapsone	14 / 5
7/F/89	Linagliptin	6	0	Yes/I	Yes	(+)	(-)	(-)	(-)	(+)	(-)	(+) 144	(-)	Prednisone 15 mg/day on a tapering-off regimen of 15 days plus TCS	Mild relapses of skin lesions controlled with TCS	17
8/M/87	Vildagliptin	4	0	Yes/NI	No	(+)	(-)	(-)	(-)	(+)	(-)	(+) 14	(-)	TCS	Sustained remission at 4 mo	11/ 7

BP, bullous pemphigoid; COOH: carboxy-terminal domain; DPP-4i: dipeptidyl peptidase 4 inhibitor; F, female; I: inflammatory; IB: immunoblot; M, male; mo: months; NA: not available; NI: non-inflammatory; TCS: topical corticosteroids (topical clobetasol propionate 20 g/day); (+): positive; (-): negative. * Time when sera were taken

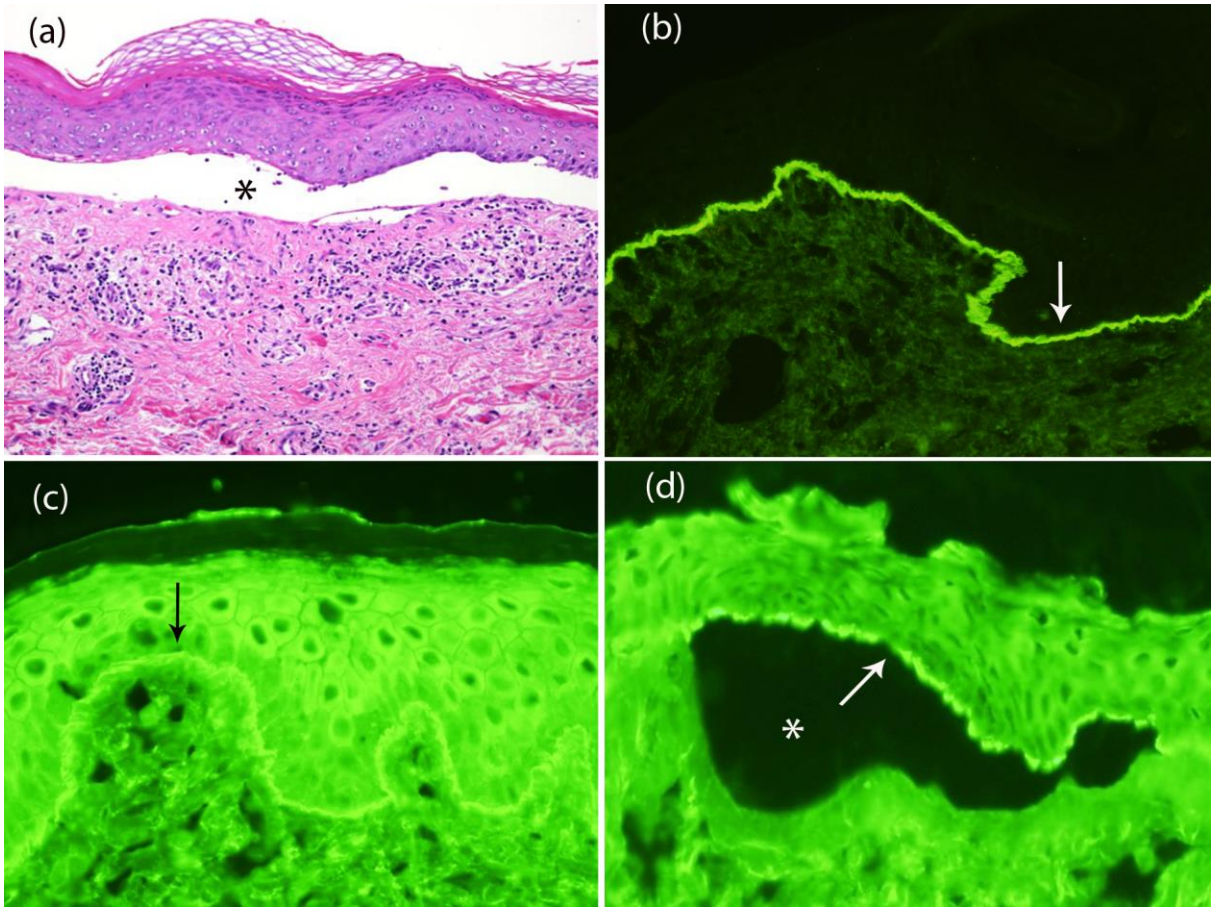
FIGURE LEGENDS

Figure 1.



Clinical manifestations. **(a)** Excoriated erosions on the trunk of patient No. 7. **(b)** Tense blister and superficial erosions on the foot and leg of patient No. 5. **(c)** Erosions on the right side of the buccal mucosa (asterisk) of patient No. 7. **(d)** Ulcerations on the lateral pharynx (piriform fossa) of patient No. 7.

Figure 2.



Histological and immunofluorescence studies. **(a)** Subepidermal blister and inflammatory infiltrate consisting of lymphocytes, neutrophils and eosinophils in the upper dermis (hematoxylin-eosin x200). **(b)** Direct immunofluorescence study demonstrating linear deposits of IgG along the epidermal basement membrane zone (arrow) (x200). **(c)** Indirect immunofluorescence study using normal human skin as substrate, demonstrating linear IgG deposition along the dermal-epidermal junction (arrow) (x200). **(d)** Indirect immunofluorescence study using salt-split normal human skin. Patient´s IgG autoantibodies are bound to the epidermal side (roof) of the split (arrow) (x200). An asterisk indicates the level of the artificially-induced cleft.