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Zaheri, F; Pas, H H; Bremer, J; Meijer, J M; Bolling, M C; Horvath, B; Diercks, G F H

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Paraneoplastic pemphigus. A detailed case series from the Netherlands revealing atypical cases.

Zaheri F., MD[1], Pas H.H. [1], PhD, Bremer J. [1,3], PhD, Meijer J.M. [1,3], MD, PhD, Bolling M.C. [1,3], MD, PhD, Horvath B. [1,3], MD, PhD, Diercks G.F.H., MD, PhD[1,2,3]

[1] Department of Dermatology, Expertise Center for Blistering Diseases, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

[2] Department of Pathology and Medical Biology, Division of Pathology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

[3]ERN-SKIN expertise center

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Correspondence:
Dr. G.F.H. Diercks, Department of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, P.O. Box 30 001, 9700 RB, Groningen, The Netherlands. E-mail: g.f.h.diercks@umcg.nl

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Abstract

Background

Paraneoplastic pemphigus (PNP) is an extremely rare life-threatening blistering autoimmune disease that is associated with an underlying neoplasm. There is a set diagnostic criterion for PNP, which is primarily based on a severe stomatitis and the detection of specific antibodies against envoplakin, periplakin and alpha-2-macroglobulin-like protein 1. However, it has becoming increasingly evident that there are patients with PNP that do not meet all the diagnostic criteria requirements.

Objectives

The aim of this study was to analyse our cohort of Dutch patients and to define the atypical cases that did not meet the diagnostic criteria.

Methods

A retrospective case study of all known Dutch PNP patients of the past 25 years. Patients' clinical and immunological variables were thoroughly analysed and described.

Results

Twenty-four patients were included in this study. The results revealed several atypical patient cases that did not completely meet the set diagnostic criteria. Of the 24 patients, two patients presented without a stomatitis, in three patients an underlying neoplasm could not be detected, and in two patients the presence of specific autoantibodies could not be demonstrated, although all other criteria for PNP were met. Finally, three out of the 24 patients survived the disease.

Conclusion

Although our findings showed similarities to previous studies and most of the patients met the criteria, there were a few atypical patient cases; highlighting the importance of not strictly adhering to the set criteria when making a diagnosis, as this can lead to a missed or late diagnosis. Thus, it is of crucial importance to combine clinical and elaborate laboratory results to confirm the diagnosis of PNP in suspected patients. Although PNP harbours an unfavourable prognosis in most cases, it might be resolved by timely treatment of the underlying cause.

Introduction

Paraneoplastic pemphigus (PNP) is a life-threatening autoimmune disease; it is a consequence of an underlying neoplasm. It is a heterogeneous disease that mainly affects the skin and/or mucosa, but also involves multiple other organs and is therefore also called paraneoplastic autoimmune multiorgan syndrome (PAMS). The first case of PNP was reported in 1990. [1] The disease mainly affects those aged between 40 and 75 years, with the average age of onset being 60 years. [2, 3] It is a rare condition, with approximately only 500 cases described in the literature.

PNP is characterised by heterogenous cutaneous lesions and the presence of severe stomatitis. Some cases also involve ocular complications and muscle weakness. [4] In 30-90% of cases, the respiratory epithelium is affected, which can result in bronchiolitis obliterans. [4] Bronchiolitis obliterans results from damage to the small airways of the lungs and is one of the main causes of death in PNP patients. [5]

Approximately 84% of PNP cases are associated with a haematologic neoplasm. [2] Lymphoproliferative diseases are most associated with PNP, with non-Hodgkin's lymphoma (NHL) associated with most of the cases. Other diseases associated with PNP include chronic lymphocytic leukaemia, Castleman's disease, thymoma, Waldenstrom's macroglobulinemia, Hodgkin's lymphoma, monoclonal gammopathies and carcinomas. However, in 30% of the cases, a neoplasm is discovered after the diagnosis of PNP [2], which emphasizes the need for early recognition.

For the diagnosis of PNP Anhalt et al. [1] originally stated five criteria that patients must meet: 1) a severe stomatitis and polymorphous skin lesions in the context of a neoplasm, 2) specific histologic changes, e.g., acantholysis or interface dermatitis, 3) direct immunofluorescence showing an intercellular and linear deposition of immunoglobulins, 4) positive indirect immunofluorescence on columnar epithelium, e.g., rat bladder and 5) a positive immunoblot (IB) for envoplakin and periplakin. Later studies also revealed that anti-alpha-2-macroglobulin-like-1 protein (anti-A2ML1) autoantibodies shown on immunoprecipitation (IP) are specific for PNP. [6] However, there have been patients diagnosed with PNP who did not meet the above-mentioned criteria completely. The reason for these atypical presentations of PNP is unclear, but such patient cases can easily lead to missed or late diagnosis. With a disease such as PNP, a timely diagnosis is of life-saving importance. Thus, the aim of this study was to retrospectively analyse our cohort of typical and atypical PNP patients to define possible clinical and diagnostic clues to aid in achieving faster diagnosis. We thoroughly analysed the clinical and immunological variables of all patients.

Materials and Methods

Inclusion Criteria

In total 27 patients were identified over a period of 25 years; all patients were diagnosed with PNP at the University Medical Center Groningen Expertise Center for Blistering Diseases, which is a tertiary referral centre in the Netherlands and recognized by the European Reference Network-Skin. Due to missing data, three patients were excluded. In order not to miss any "atypical" cases the inclusion criteria did not strictly adhere to the ones described by Anhalt et al [1]. The diagnosis of PNP was established as a combination of 1) appropriate clinical symptoms, i.e., severe stomatitis and/or cutaneous symptoms, 2) the presence of a malignancy, 3) the presence in patients' sera of anti-envoplakin and anti-periplakin autoantibodies in IB and/or the presence of anti-A2ML1 autoantibodies in IP and/or a positive rat bladder [7,8]. Patients were included if two out of three criteria were present. All samples were collected before treatment was initiated and while patients had active lesions.

Variables analysed included: age, sex, symptoms, clinical course, underlying neoplasm, treatment, and prognosis. Furthermore, we assessed multiple immunological variables such as immunoprecipitation and immunoblot results. This study is in line with the guidelines of the ethical review committee in the UMCG. Some of these patients have already been described in separate case reports. [9-16]

Immunoblot, Immunoprecipitation, Immunofluorescence and ELISA

IB was performed for all patients during the diagnosis of the disease. IB was carried out exactly as it is described in Pas et al. [17] IB reveals the target protein antigens in patients; with molecular weights of 250, 210 and 190 kD. These correlate to desmoplakin I and II, envoplakin and periplakin. [4] Antibodies against A2ML1 cannot be detected by the IB, and therefore IP was also performed during diagnosis, as it does reveal the presence of anti-A2ML1 autoantibodies. IP was also performed for every patient in the study. IP is described in Poot et al. [7] In IP a typical set of five protein bands with molecular weights of 250, 210, 190 and 170 kD can be detected. These protein bands correlate to desmoplakin I and II, envoplakin, periplakin and A2ML1. [4]

Direct immunofluorescence (DIF) was performed on 14 patients as described in Poot et al. [9] IIF using the monkey oesophagus was performed on 22 patients, whereas rat bladder as a substrate was used on all 24 patients. IIF using monkey oesophagus and rat bladder as a substrate was performed in this study exactly as described in Poot et al. [8]

ELISA was performed as according to the protocol of the manufacturer (MBL, Nagoya, Japan) to measure the anti-desmoglein 1 and anti-desmoglein 3 antibody titres in all patients. Any value above 20 for both index values was considered positive.

Histopathology

The HE stained biopsy specimens of seven patients were examined histologically.

Results

Patients' characteristics

The 24 patients consisted of 15 (62%) men and 9 (38%) women. The age at diagnosis ranged from 7 to 87 years but most of the patients (71%) were diagnosed after the age of 50.

Clinical Characteristics

Mucosal Surfaces

All but one patient (96%) had mucosal lesions during the disease. Of the 24 patients, two patients presented without a stomatitis. One patient did not develop any mucosal lesions (patient #22), whereas the other patient (#7) only presented with ocular lesions. Some patients developed mucosal lesions later in the disease course, but most presented initially with a mucosal lesion (Table 1).

Cutaneous Symptoms

Nineteen out of the 24 (79%) had cutaneous lesions. Most commonly, patients experienced erosions, blisters, lichenoid lesions, and erythema. Eight out of these 19 patients had blisters in different areas of the body. Four patients suffered from erosions and one patient from diffuse lichenoid lesions all over the body. Five patients had different types of erythema. Two patients experienced desquamation of the hands. Other cutaneous symptoms included pruritus, dermal necrosis, and other non-specific symptoms (Table 2).

Bronchiolitis Obliterans

Nine patients out of 24 (37%) developed bronchiolitis obliterans, 11 did not develop bronchiolitis obliterans (46%) and from four patients (17%) it was unknown. From the nine patients that had bronchiolitis obliterans, eight were positive for anti-A2ML1 autoantibodies. The one remaining patient (#20) that was not positive for anti-A2ML1 autoantibodies, was also negative for all autoantibodies in the IP and IB.

Underlying Neoplasm

Ten out of the 24 (42%) patients had an underlying lymphoma; three of these 10 patients had follicular NHL, two had a large B-cell NHL, one had a low-grade NHL, one had an unknown type of NHL, and three others had a follicular dendritic sarcoma (FDCS). Other patients were diagnosed with leukaemia (n=2), Castleman's disease (n=2), sarcoma (n=1), laryngeal carcinoma (n=1), retroperitoneal fibroblastic tumour (n=1), oesophageal carcinoma (n=1), a carcinoid (n=1), inflammatory myofibroblastic tumour (n=1) and post-transplantation lymphoproliferative disease (n=1). Three patients presented without an underlying neoplasm. Of these two patients died within a month of their diagnosis and for one patient no underlying neoplasm could be detected within one year of the initial diagnosis (Table 2).

Disease course

The treatment varied per patient; treatment included varying (high) doses of prednisone alone or in combination with either dexamethasone, azathioprine, rituximab, plasmapheresis, or intravenous immunoglobulins. Eighteen out of the 24 patients (75%) were treated with systemic corticosteroids; high dose prednisone. Six of these patients received a combination of prednisone with rituximab (#4, #12, #13, #19, #20, #21). One patient received a combination with plasmapheresis (#6) and another patient received a combination with intravenous

immunoglobulins (#21). Few patients also received azathioprine or dexamethasone in addition to only prednisone or to a combination of treatments. Two patients (#13 and #21) required surgery to remove the tumour. Two patients had no treatment due to unknown reasons and two patients refused treatment. One patient was diagnosed post-mortem; sera was being assayed at the UMCG when the patient died. Finally, for one patient no information on treatment was available.

Despite the high rate of treatment, 21 out of the 24 (88%) patients died and three survived (13%). The cause of death was bronchiolitis obliterans in eight patients, cardiac failure in three, treatment refusal in two, respiratory insufficiency in one, acute lung bleed in one, fatal sepsis in one (also had bronchiolitis obliterans) and finally, cerebrovascular accident in one. Of the remaining four patients died the cause of death was unknown.

Patients #8, #13 and #16 were the survivors; two of them had Castleman's disease and #13 had an inflammatory myofibroblastic tumour, which was removed. All three patients presented with different clinical features (Table 2). #8 and #16 were positive for anti-A2ML1 autoantibodies and both were negative for antidesmoglein-1 and positive for antidesmoglein-3 autoantibodies. Patient #13 was positive for anti-envoplakin and anti-periplakin autoantibodies, but negative for anti-A2ML1 autoantibodies and for antidesmoglein-1 and antidesmoglein-3.

Diagnosis of PNP (Table 3)

Histology

Histopathological findings were obtained from seven patients. Four patients presented with lichenoid dermatitis. Other findings included suprabasal acantholysis (n=1), ulcerative inflammation (n=1) and non-specific lymphocytic dermatitis (n=1).

Direct Immunofluorescence

Of the 13 patient skin biopsies for DIF, 10 patients (77%) had IgG deposition in an epidermal cell-surface pattern (ECS). Seven out of 10 of these patients also had IgG deposition in their basement membrane zone (BMZ), in a linear (n=3), a granular (n=2), a mixed linear/granular pattern (n=1) and a focal pattern (n=1). Three patients solely had a BMZ linear (n=2) or mixed linear/granular (n=1) IgG deposition without ESC involvement. No patient biopsies showed an IgA deposition in an ECS pattern but there were three biopsies that had IgA deposition along the BMZ.

Immunodiagnostics

Immunoblot

Nineteen out of 24 (79%) patients met the criteria for anti-envoplakin and anti-periplakin autoantibodies. One patient was positive for anti-envoplakin only (Table 3). Additionally, IB revealed that four patients were positive for anti-desmoplakin I and anti-desmoplakin II autoantibodies. Finally, for two out of 24 patients (#19 and #20) no antigens could be detected, despite that the rat bladder IIF was positive.

Immunoprecipitation

IP revealed that 15 out of 24 patients (63%) were positive for anti-A2ML1 autoantibodies amongst other PNP-antibodies. From these, 2 patients were positive only for anti-A2ML1 autoantibodies. The same two patients (#19 and #20) that were negative in IB, were also negative for all antigens in IP (Table 3).

Regarding both immunoblot and immunoprecipitation, there was one patient that showed negative for IB but was positive for antibodies to desmoplakin I, envoplakin and A2ML1 in the IP.

ELISA

Five out of 24 patients (21%) had a positive anti-desmoglein 1 antibody index value. For anti-desmoglein 3 antibodies, 19 out of 24 (79%) were positive.

Indirect Immunofluorescence

In the indirect immunofluorescence, 19 out of 24 (79%) showed a positive response for anti-cell surface IgG autoantibodies for the rat bladder. Two patients showed an inconclusive result. With regards to IIF on monkey oesophagus, circulating IgG anti-cell surface autoantibodies were found in 16 out of the 22 patients (73%); one patient showed an inconclusive result. Circulating IgG anti-BMZ autoantibodies were negative in all tested patients.

DISCUSSION

Anhalt et al. has proposed a set criterion for the diagnosis of PNP. [1] There are, to date, few case series published in existing literature, most likely due to the rare prevalence of the disease. Ohzono et al. is the largest case series; it includes a population of 104 patients all diagnosed with paraneoplastic pemphigus. [5] Most of the patients in our case series met the diagnostic criteria of Anhalt et al. [1], described in the introduction, and our findings were like that of Ohzono et al. Although our study mainly showed similarities to that of Ohzono et al., and other previous case series, certain patients in our series did not fully meet the set diagnostic criteria that is described in the literature. These patients were, however, diagnosed with paraneoplastic pemphigus, which raises questions as to what precisely makes these patient cases atypical. These patients that did not adhere to these criteria are discussed below.

Mucosal lesions, mainly oral lesions, have become a defining characteristic of the disease and are usually one of the earliest features of the disease. [1] In total, 92% of our patient group from this series had oral mucosal lesions. These findings were like those reported in Ohzono et al. [5], where 82 out of 88 patients (93%) had oral mucosal involvement. Although involvement of the oral mucosa is one of the set criteria in establishing the diagnosis, we had two patients in our series with no oral mucosal lesions. These two patients were, however, diagnosed with PNP as they had fulfilled all other criteria for PNP, e.g., skin lesions with an underlying malignancy, a positive rat bladder and a positive IB for envoplakin and periplakin. The reason for this anomaly within these patients is unknown. It has been reported in previous literature that anti-desmoplakin autoantibodies might be involved in the development of oral lesions; [18] one of these patients was negative for desmoplakin, however, the other was positive, so the reason for this atypical presentation remains unclear. In this respect also DSG3, the antigen involved in mucosal pemphigus, was positive in one patient and negative in the other. The mucosal lesions might likely be attributed to another yet unknown autoantigen than desmoplakin and DSG3.

A major characteristic of PNP is its association with an underlying neoplasm. However, in our series, an underlying neoplasm was not found in three of the patients, although they met the other set criteria for PNP. Two of these patients died soon after the diagnosis, one from bronchiolitis obliterans (#14) and the other (#18) due to treatment refusal. In the third patient (#23) no neoplasm could be detected, even though she presented with severe involvement of the oral mucosa and a positive IB for envoplakin and periplakin. The patient also died quite soon after diagnosis, approximately one year, from unrelated cardiac complications. We suspect that these patients may have been developing an underlying malignancy, which was not yet detectable. Ohzono et al. reported similar findings in 12 of their patients. [5] These cases and those of Ohzono et al. support the theory that some patients do not have detectable neoplasms (at least not at the beginning of the disease) and are in fact at the beginning of developing an underlying malignancy, which can perhaps be overlooked due to the limits of diagnostic imaging.

PNP is a life-threatening disease with a highly lethal disease course. In this case series, 21 of the 24 patients died. BO was the highest cause of death. Only three of the patients survived. The first was a young patient with an inflammatory myofibroblastic tumour. Removal of the tumour helped in subsiding the PNP symptoms, and the patient ended up surviving. The other two, also young patients, had Castleman's disease. It could be hypothesised that the autoreactive dysregulated IL-6 is involved in the autoantibody production that eventually leads to the clinical features, and thus,

resolving the disease is resolving the PNP symptoms. In this respect, PNP patients have shown a markedly elevated serum IL-6 levels, especially in Castleman's disease. [3]

Another criterion set out in Anhalt et al. is a positive IB for envo- and periplakin in combination with a positive rat bladder on indirect immunofluorescence. Seventy-nine percent (19 out of 24) of our patients were positive for the rat bladder and positive on IB for envo- and periplakin. Moreover, 63% of patients showed autoantibodies against A2ML1, a recently described antigen associated with PNP. However, two of the patients were negative for envo- and periplakin on IB and for A2ML1 on IP. (Table 3) These two patients both presented with severe stomatitis, and were both diagnosed with non-Hodgkin's lymphoma, they also had increased anti-desmoglein titres and a positive rat bladder. One patient also died of BO. This was considered as sufficient to diagnose these patients with PNP and indicates that these specific autoantibodies cannot be found in every PNP patient. The importance of IP is highlighted by the fact that two patients were negative for PNP antigens on IB, while IP revealed antibodies against envo- and periplakin and A2ML1.

PNP histology is mentioned in the original series by Anhalt et al.; histological images of PNP usually show a lichenoid or acantholytic reaction pattern. [1] Our series also showed similar reaction patterns although the sensitivity is not high since we found two biopsies with non-specific changes. In addition, one should be aware that the clinical and histological picture of PNP resembles that of graft-versus-host disease. [19] In the case of patient #24 from our series who presented with severe mucosal and cutaneous lesions, it was unclear whether the patient had graft-versus-host disease or PNP as he had undergone a recent allogeneic stem cell transplant. Further laboratory examinations showed that IB was positive for envo- and periplakin, which led to the diagnosis of PNP and resulted in a different treatment schedule and prognosis.

The limitation of our study is the retrospective character bridging over 3 decades with only 24 cases over the time due to the rarity of PNP. Moreover, our centre is the only reference centre for autoimmune bullous diseases in the Netherlands. Therefore, cases might have been missed due to referral bias. However, despite the long timeframe, we could perform new diagnostic methods retrospectively on the old samples from our biobank. Based on the detailed description and the novel diagnostics we were able to reveal and add some new results to the knowledge of this rare, but potentially lethal disease.

This study revealed that, in most cases, PNP is characterized by severe mucosal lesions, polymorphous skin lesions and the presence of specific laboratory findings. However, our study has also highlighted the fact that PNP does not always present typically and that it is of crucial importance to not strictly adhere to the set diagnostic criteria of Anhalt et al. as it can result in missed diagnosis. It is of crucial importance to combine clinical and elaborate laboratory results to make the diagnosis of PNP in suspected patients. Although PNP harbours a worse prognosis, it might be resolved in certain cases by timely treatment of the underlying cause.

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Site of Mucosal Lesions	Patients' n/N (%)	Lesions
Total	23/24 (96%)	
Oral	22/24 (92%)	Erosions (56%)
		Blisters (23%)
		Cheilitis (32%)
Ocular	8/24 (33%)	Erosions (13%)
		Conjunctivitis (50%)
		Blepharitis (25%)
		Blurred Vision (13%)
		Painful Eyes (13%)
Nasal	1/24 (4%)	Erosions (100%)
Genital/Urogenital	11/24 (46%)	Erosions (64%)
		Blisters (18%)
		Pain (9%)
		Skin Discolouration (9%)

Table 1: Mucosal lesions and their prevalence in this case series. The mucosal lesions are each divided further into categories such as erosions and blisters. These different types of lesions present either solely or in combination with each other.

Patient	Gender/Age	Malignancy	Mucosal Lesions				Cutaneous Lesions
			Oral	Ocular	Nasal	Anogenital	
1[14]	M/75	Large B-cell NHL	+	-	-	-	Blisters on palms and soles, erythema on trunk and limbs
2[13]	F/56	Epithelioid Leiomyosarcoma	+	-	-	-	None
3[11]	M/61	Chronic lymphoid leukemia	+	+	-	+	Erosions of upper eyelids
4[9]	M/70	Follicular NHL	+	-	-	+	2 brown spots, all over skin lesions
5	F/48	Low-grade NHL	+	-	-	-	None
6[15]	M/60	Follicular dendritic cell sarcoma	+	+	-	-	Superficial blisters of trunk, face, and upper limbs
7	M/42	Follicular NHL	-	+	-	-	Dermal necrosis, erythema, and blisters
8	F/29	Castleman's disease	+	-	-	+	Erosions
9	F/73	Follicular B-cell NHL	+	+	-	-	Pruritus, erosions, and erythematous lesions all over body
10	M/86	Larynx Carcinoma	+	-	-	-	Diffuse blisters on extremities
11	M/57	Carcinoid w/ lymph and liver metastases	+	-	-	-	Diffuse lichenoid lesions all over the body
12[12]	M/53	NHL	+	-	-	+	Pruritic erythematous skin, erosions, blisters, and desquamation of hands
13	M/18	Inflammatory Myofibroblastic Tumour	+	+	-	+	None
14	M/72	No neoplasm	+	+	-	+	Erythematic erosions, blisters
15	M/73	Follicular dendritic cell sarcoma	+	-	-	+	None
16	F/32	Castleman's disease	+	-	-	+	Blisters all over the body
17	M/54	Retroperitoneal Fibroblastic Tumour	+	+	-	+	Pruritic skin on trunk
18	M/87	No neoplasm	+	-	-	-	None
19[16]	F/7	Post-transplantation EBV positive lymphoproliferative disease	+	-	-	-	Blister on buttocks
20	M/59	Large B-cell NHL	+	-	+	+	Light red macula over entire body
21[10]	F/36	Follicular dendritic cell sarcoma	+	+	-	+	None
22	F/73	Oesophageal carcinoma	-	-	-	-	Blisters all over the body
23	F/71	No neoplasm	+	-	-	-	Pruritus
24	M/67	Chronic myeloid leukemia	+	-	-	-	Back erosions, face erosions

Table 2: patient characteristics. NHL=non-Hodgkin's lymphoma

Patient No.	IP	IB	DSG 1	DSG 3	DIF	IIF Oesophagus	IIF Rat Bladder
1	DSP, EP, PP, A2ML1	EP, PP	1	207	N.A.	+	+
2	EP, PP, A2ML1	DSP, EP, PP	>150	>150	N.A.	+	-
3	DSP, EP, PP, A2ML1	DSP, EP, PP	98	245	N.A.	+	-
4	DSP, EP, PP	DSP, EP, PP	2	186	ECS	+	+
5	DSP, EP	DSP, EP, PP	3	54	ECS, BMZ (linear)	+	+
6	EP, PP, A2ML1	EP, PP	2	42	N.A.	+	+
7	DSP, EP, PP, A2ML1	EP, PP	7	114	BMZ (linear)	N.A.	+
8	A2ML1	EP, PP	3	158	ECS, BMZ (granular)	+	+
9	DSP, EP, A2ML1	DSP	0	94	ECS	Inconclusive	+
10	DSP, EP, PP, A2ML1	EP, PP	164	136	ECS, BMZ (linear)	+	+
11	DSP, EP, A2ML1	-	1	50	ECS, BMZ (granular)	-	+
12	A2ML1	EP, PP	57	145	ECS	+	Inconclusive
13	EP, PP	EP, PP	3	3	BMZ (linear)	+	+
14	EP, PP, A2ML1	EP, PP	6	87	ECS, BMZ (linear/granular)	+	+
15	EP, PP	EP, PP	5	132	N.A.	-	+
16	EP, PP, A2ML1	EP, PP	5	97	N.A.	-	+
17	EP, PP, A2ML1	EP, PP	11	30	N.A.	+	+
18	EP, PP, A2ML1	EP	2	1	N.A.	+	+
19	-	-	10	142	N.A.	+	+
20	-	-	129	135	ECS, BMZ (focal)	+	+
21	EP, PP, A2ML1	EP, PP	3	8	ECS, BMZ (linear)	+	+
22	EP, PP	EP, PP	11	2	N.A.	-	+
23	EP, PP	EP, PP	6	4	N.A.	-	-
24	EP, PP	EP, PP	18	3	BMZ (granular/linear)	N.A.	Inconclusive

Table 3: patient immunological results. IP=immunoprecipitation, IB=immunoblot, DSG=desmoglein, DIF =direct immunofluorescence, IIF=indirect immunofluorescence, DSP=desmoplakin, EP=envoplakin, PP=periplakin, N.A.=not available