MADAM, autoimmune sub-epidermal blistering diseases include bullous pemphigoid, pemphigoid gestationis, linear IgA bullous dermatosis, mucous membrane pemphigoid (MMP), anti-p200 pemphigoid, epidermolysis bullosa acquisita (EBA) and bullous systemic lupus erythematosus.[1] Patients with EBA have IgG autoantibodies against type VII collagen while some MMP patients have autoantibodies to laminin-332.[2,3] We describe a juvenile case of sub-epidermal blistering disease with autoantibodies against both type VII collagen and laminin-332. The present case is unique because of its childhood-onset and successful remission requiring only topical steroid therapy.

Report of a case

A 12-year-old Japanese girl presented with pruritic eruptions on her scalp. A few weeks later, widespread pruritic vesicles gradually developed over her whole body. The vesicles were seen both on erythematous and normal skin (Figs 1a and b). Blisters and erosions also appeared in her oral mucosa, but there was no involvement of genital or ocular mucous membranes (Fig. 1c). Neither nail changes nor alopecia was observed. She had no family history of any blistering disorders or autoimmune disease. There was no preceding illness or history of medication/vaccination that might have triggered her disease.

General laboratory examinations revealed no apparent abnormalities except for an increased serum IgE level (668.8 IU/ml). A skin biopsy was taken from the edge of one blister in her right forearm. Light microscopy showed a

sub-epidermal blister with an inflammatory cell infiltrate consisting of mainly neutrophils in the upper dermis (Fig. 2a). Direct immunofluorescence of the patient's lesional skin showed *in vivo* linear deposits of IgG and C3 in the epidermal basement membrane zone (Fig. 2b). On the blistered area, deposition of IgG and C3 was demonstrated on be the dermal side of the separated skin (arrows, Fig. 2b). Indirect immunofluorescence with the patient's serum on 1M NaCl-split normal human skin showed IgG antibodies bound to the dermal side of the blister (Fig. 2c). Immunoblot analysis revealed that the patient's serum reacted with a 290-kDa protein in dermal extracts, and further with purified laminin-332 alpha3 protein (145-kDa, 160-kDa) (Figs 2d and e). Laminin-332 was obtained from human keratinocytes and was purified using an anti-laminin-332 affinity column as previously described.[7-8] Purified laminin-332 was a generous gift from Dr S. Amano, Shiseido Life Science Research Centre, Yokohama, Japan. The patient was diagnosed as having an autoimmune sub-epidermal blistering disease with circulating autoantibodies against type VII collagen and laminin-332.

The treatment was initiated with 20g of 0.05 % clobetasol propionate ointment daily to skin lesions, which healed within 9 days after the beginning of treatment, leaving residual pigmentations, scars and milia (Figs 1d and e). Blisters and erosions on the oral mucosa subsided without any topical therapy (Fig. 1f). The dose of topical corticosteroids was progressively decreased afterward, and no recurrence of skin lesions was observed. The titer of anti-basement-membrane antibodies in indirect immunofluorescence studies decreased from 1:320 to 1:40

over two months. We performed further immunoblot analyses on the patient's five serial serum samples obtained after her anti-basal membrane zone antibodies decreased. All five samples showed similar reaction bands to both 290-kDa protein in dermal extracts and purified laminin-332 alpha3 protein (145-kDa, 160-kDa) (data not shown). Hence it is difficult to speculate the major target antigen in this patient from these results. No local or systemic side effects of topical corticosteroids were noticed during the entire treatment duration.

EBA and MMP are distinct autoimmune bullous diseases that are both characterized by autoantibodies against dermo-epidermal junction components.[1] Detection of autoantibodies to either type VII collagen or laminin-332 differentiates these two diseases.[1] Interestingly, besides anti-type VII collagen antibodies, circulating anti-laminin-332 alpha3 antibodies were also found in our patient's serum. According to our survey of the literature, three other previous cases of sub-epidermal blistering disease with circulating antibodies against both type VII collagen and anti-laminin-332 have been reported (Table 1).[4-6] All of the reported cases are adult-onset cases, thus our report is the first juvenile case. Similar to our patient, these reported patients all presented with mucosal involvement.

Our case is very unique in its course and prognosis as well as onset-age. All of the previously reported cases needed systemic corticosteroid or immunosuppressant agents for proper disease control. In the studies by Jonkman et

al.[4] and Umemoto et al.[5], the bullous lesions of the patients relapsed after systemic prednisolone was tapered. The skin lesions of the patient reported by Baican et al.[6] were refractory to systemic prednisolone, azathioprine and dapsone. However, our juvenile case was successfully treated with only topical steroids, and no recurrence was observed in the following 6 months. Our case suggests that the treatment outcome and prognosis of juvenile cases are better than those of adult-onset cases. Further accumulation of similar juvenile cases is needed to confirm this hypothesis. The differences between childhood-onset and adult-onset cases seem to mirror those of EBA at different ages. Compared to adult cases, childhood EBA cases respond relatively better to treatment, and usually low-dose oral prednisolone and dapsone are effective and sufficient.[1]

In conclusion, we report the first juvenile case with autoantibodies to both type VII collagen and laminin-332, successfully treated with only topical steroid therapy. Our case suggests that juvenile cases have different characteristics from those of adult-onset cases in its course including treatment outcome, and prognosis. Since topical steroid therapy has several advantages over systemic corticosteroids due to less severe complications, we consider topical steroids as preferential to systemic steroids for childhood-onset autoimmune sub-epidermal bullous disease.

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Figure legends

Figure 1: Clinical manifestations of the skin and oral mucosa.

(a, b and c) Before topical steroid therapy. Erythema and tense vesicles on the left forearm and chest (a and b). Blister and erosions over the oral mucosa (arrows) (c).

(d, e and f) After topical steroid therapy. Skin lesions healed within 9 days of the beginning of treatment, leaving residual pigmentation, scars and milia (d and e). Blisters and erosions on the oral mucosa subsided (f).

Figure 2: Histopathological findings, immunofluorescence staining and immunoblot analyses

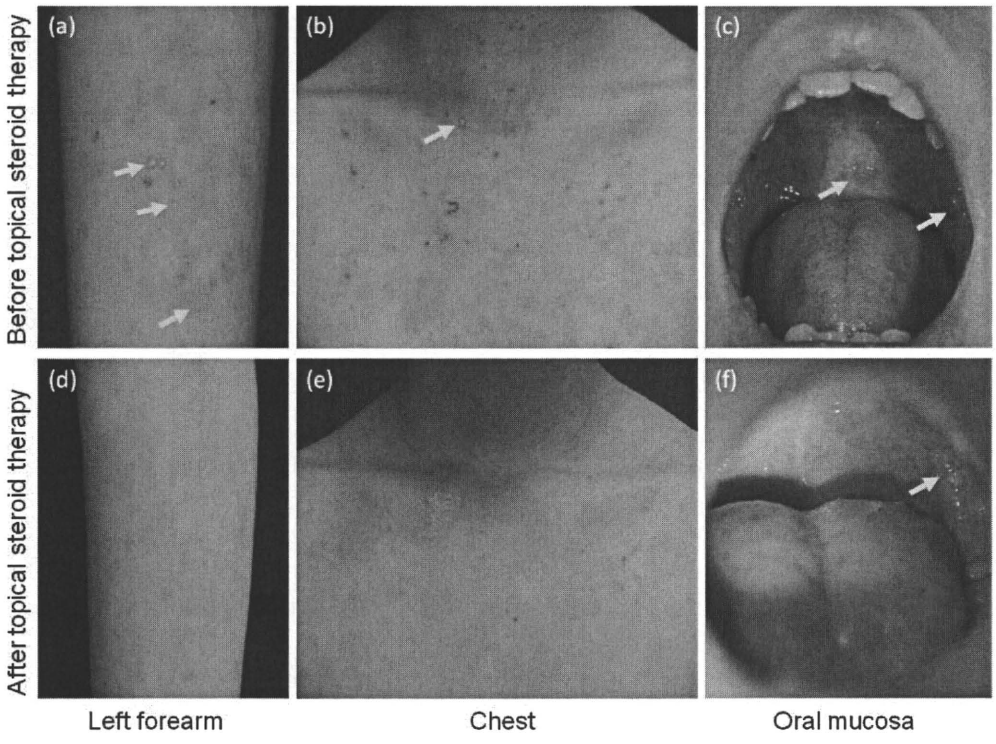
(a) A sub-epidermal blister with an inflammatory cell infiltrates mainly comprising neutrophils in the upper dermis. (Hematoxylin and eosin stain. Original magnification: x40)

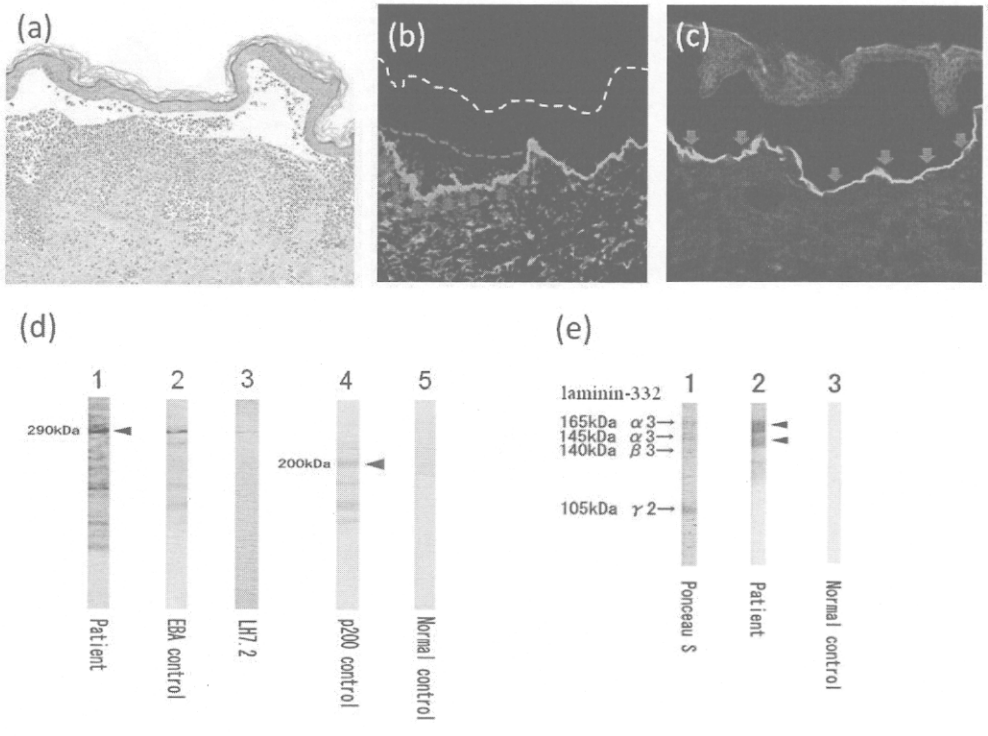
(b) Direct immunofluorescence showed *in vivo* linear deposits of IgG along the basement membrane zone. On the blister area, deposition of IgG was shown to be towards the dermal side of separated skin (arrows). (Original magnification: x40, White dotted line is the skin surface. Red dotted line is the roof side of separated skin.)

(c) Indirect immunofluorescence with the patient's serum on 1M NaCl-split normal human skin showed IgG antibodies bound to the dermal side (arrows). (Original magnification: x40)

(d) Immunoblot analysis revealed that the patient's serum (lane 1), like both serum from a reference EBA patient (lane 2) and monoclonal antibody LH7.2 to type VII collagen (lane 3), reacted with a 290-kDa protein in dermal extracts (arrowhead). Control anti-p200 serum did not react with the 290-kDa but with a 200-kDa protein (red arrowhead) (lane 4). Normal control serum (lane 5) showed reactivity with neither.

(e) In immunoblotting of purified laminin-332, lane 1 showed Ponceau S stain (protein staining using amido black) sample. Reactivity with 145-kDa and 160-kDa purified laminin-332 alpha3 protein (arrowheads) was indicated in the patient's serum (lane 2), but not in the normal control serum (lane 3).


Before topical steroid therapy
After topical steroid therapy
(a)
(b)
(c)
(d)
(e)
(f)
Left forearm
Chest
Oral mucosa


(a)
(b)
(c)
(d)
1
2
3
4
5
290kDa
200kDa
Patient
EBA control
LH7.2
p200 control
Normal control
(e)
laminin-332
165kDa α3
145kDa α3
140kDa β3
105kDa γ2
1
2
3
Ponceau S
Patient
Normal control

Comparison of 4 reported cases with circulating anti-type VII collagen and anti-laminin332 antibodies

case	Age/Sex	Skin lesion	Mucosal Involvement	Treatment	Outcome	Immunoblot Analysis	Reference
1	64F	blisters and erythema on the hands and feet	oral/genital	oral prednisolone 80mg/day	Lesions resolved without scars/milia. Mild replapse occurred when tapering to prednisolone 5mg/day per os.	type VII collagen laminin 332 α3	Jonkman et al.[4]
2	46M	erythematous plaque, blisters, erosions and crusts on the trunk and extensor aspects of extremities	oral	oral colchicine 1.5mg/day (refractory to prednisolone, azathioprine, and dapsone)	Previous lesions healed with milia and scars. Free of new blisters but erythematous plaque persisted with erosions and crusts.	type VII collagen laminin 332 α3,Y2	Baican et al.[6]
3	35F	vesicular lesions on the face, neck and upper back	oral/genital	oral prednisolone 40mg/day	Lesions resolved without scars/milia. Mild replapse occurred when tapering to prednisolone 25mg/day per os. (mild relapse when tapering to prednisolone 25mg/day per os)	type VII collagen laminin 332 α3, β3	Umemoto et al.[5]
4	12F	blisters, erosions, and erythema on the face, trunk, hands and feet	oral	topical clobetasol propionate ointment 20g/day	Lesions resolved with scars and milia.No recurrence was found. (no recurrence found)	type VII collagen laminin 332 α3	Our patient

thickness of the mucous layer of small intestines, resulting in the inhibition of small intestinal absorption.[4] In addition, PGE1 increases blood flow in the stomach and upregulates the digestion in the stomach. During the provocation test in our case, serum gliadin levels were not increased by administering misoprostol. However, sodium cromoglicate, a mast cell stabilizer commonly used to treat allergic rhinitis, allergic conjunctivitis, and asthma, could not affect serum gliadin levels in the provocation test, and therefore allowed the symptoms to occur. We consider that the effects of misoprostol on the alimentary tract are crucial for the prevention of FDEIA. Our observation indicates that the exacerbating effect of aspirin in FDEIA comes from the inhibitory effects of aspirin on PGE1 in the gastrointestinal milieu. Thus, misoprostol would be a promising prophylactic drug for FDEIA.

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Type XVII collagen ELISA indices significantly decreased after bullous pemphigoid remission

The major pathogenic epitope of bullous pemphigoid (BP) is known to be the noncollagenous extracellular domain (NC16A) of type XVII collagen (COL17).[1] Here we investigated indirect immunofluorescence (IIF) and COL17 NC16A domain enzyme-linked immunosorbent assay (ELISA)[2–5] data before treatment and after remission to evaluate the usefulness of ELISA analyses as indicators for BP disease activity.

We included ten consecutive BP patients [eight women and two men: between 33 and 80 years old (mean; 59 years old)] who showed typical clinical features before treatment and were successfully treated, resulting in complete or partial remission at our institute. The first day of each patient visit was within the last three years. In all patients, the diagnosis was confirmed by histopathological observation and immunofluorescence study, i.e. histopathological subepidermal blister formation was observed and direct and IIF studies revealed the presence of autoantibodies along the dermal–epidermal junction. All patients were successfully treated with oral prednisolone therapy of 30–50 mg/d with or without azathioprine or a combination therapy using tetracycline and nicotinamide. Treatment periods from initial diagnosis to remission ranged from four months to 35 months (mean; 14.6 ± 10.8 months). Serum samples were obtained for ELISA and IIF at least twice during the disease course for each patient.

Concentration of autoantibodies in the patients' sera directed against the NC16A domain of COL17 was measured using the COL17 NC16A ELISA kit following the kit's instructions.[6] IIF staining and evaluation were performed as previously described using normal human skin as a substrate.[7]

In all the cases, the ELISA indices showed a decrease during the successful treatment course. ELISA indices after remission were significantly reduced compared with those before treatment ($P < 0.0001$) (Fig. 1a). IIF titers also decreased after remission in six cases, but the titers were not apparently reduced in the other four cases, although a statistically significant reduction in combined IIF titer was observed after remission compared with those before treatment ($P < 0.05$) (Fig. 1b).

Positive correlation between ELISA indices and BP disease activity has been reported previously in the literature. Di Zenzo *et al.*[8] demonstrated that disease severity before treatment was well correlated with ELISA indices in BP patients. Izumi *et al.*[9] described ELISA indices and alteration of disease activity of five BP patients during various treatments. In this study, we compared the ELISA

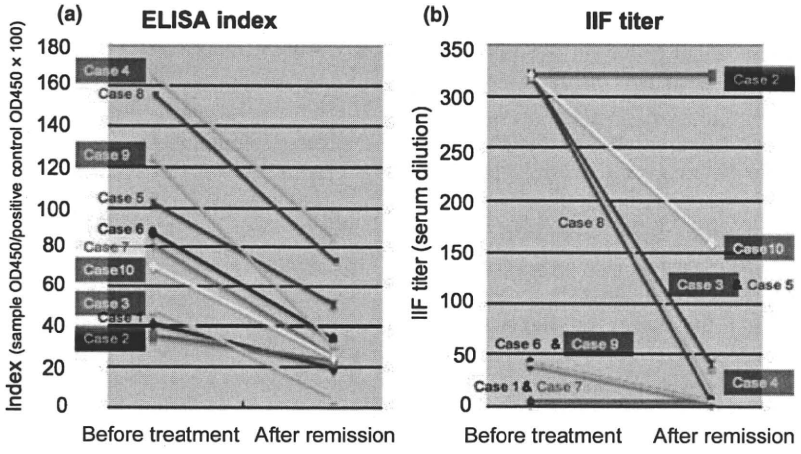

Figure 1 ELISA indices and indirect immunofluorescence (IIF) titers before treatment and after remission. (a) ELISA indices of successfully treated BP patients. Disease remission was defined as when erythema, bullae and erosions had completely healed (complete remission) or no more than three bullae or erythema were seen in a week (partial remission) and only a low dose of oral prednisolone (<5 mg/d) or no treatment was needed to maintain this condition. As ELISA indices after remission, we adopted ELISA indices at the time when each patient's disease activity was evaluated as being in "complete remission" or "partial remission" (as defined above) for the first time after treatment. Mean ELISA index of the 10 patients before treatment was 91.3 ± 45.7 (range: 35.6–165.6) and the mean index after remission was 37.4 ± 25.3 (range: 6.0–86.4). After complete or partial remission, the ELISA indices were significantly reduced ($P < 0.0001$). (b) IIF titers of the same patients. Apparent decreases in IIF titers after remission were seen only in six patients. Mean IIF titer of the 10 patients before treatment was 201 ± 154 (range: 5–320) and the mean titer after remission was 60.5 ± 102.8 (range: 5–320). A statistically, significant reduction was observed in combined IIF titers after remission compared with those before treatment ($P < 0.05$). Colors of the lines are specific for each patient in both figures (a) and (b)

indices before treatment and after remission in our BP patient cohort and clearly demonstrated that ELISA indices significantly decreased after remission. Feng *et al.*[10] reported similar results on correlation of ELISA indices with disease course in BP patients, although the time points for ELISA after treatment were just before the decrease in corticosteroid and when the dosage of corticosteroid was successfully decreased to half the initial dose in the report. In this study, we employed ELISA indices at the time when each patient's disease activity was evaluated as "complete remission" or "partial remission" for the first time after treatment. Thus, this study is unique in the point that we evaluated exact correlation between ELISA indices and disease remission.

In conclusion, the present results further support the idea that the COL17 NC16A ELISA indices demonstrate a correlation with the BP disease remission more accurately than IIF titers and are a useful tool to detect BP disease remission and to assess the efficacy of BP treatment.

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Case letter

Subepidermal blistering disease with three distinct autoantibodies: anti-BP230, anti-laminin gamma-1, and anti-laminin-332

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Key words: autoimmune blistering disease; anti-p200 pemphigoid; bullous pemphigoid; mucous membrane pemphigoid; laminin 332; laminin γ1; BP230

To the Editor: A 25-year-old Japanese female presented with pruritic tense blisters involving the lips, forearms, fingers and soles (Fig 1A, B, and C). No mucosal involvement was observed. Skin biopsy from a bulla on her left forearm demonstrated subepidermal separation with eosinophilic inflammatory infiltrate in the dermis (Fig 2A). Direct immunofluorescence (IF) microscopy of the lesion showed linear deposition of C3 and IgG at the dermo-epidermal junction (Fig 2B, C). Indirect IF on sodium-split skin revealed linear IgG deposition on both the epidermal and the dermal sides (titer 1:20; Fig 2D). Enzyme-linked immunosorbent assay (ELISA) using bacterial recombinant protein of the NC16a domain of COL17 (MBL, Nagoya, Japan) was negative. ELISA using bacterial recombinant proteins of the N- and C-terminal domains of BP230 (MBL, Nagoya, Japan) was also negative. Immunoblot analysis with epidermal and dermal extracts derived from normal human skin and purified laminin-332 was performed. The results showed the presence of circulating IgG autoantibodies against BP230, laminin γ1, and the γ2 chain of laminin-332 (Fig 2E, F, G). 40 mg/day of oral prednisolone (PSL) failed to alleviate the symptoms. With the addition of 75 mg/day of oral diaphenylsulfone (DDS), the cutaneous lesions rapidly healed with postinflammatory hyperpigmentation. PSL and DDS were

tapered without relapse of skin lesions. At 10 months after referral, she discontinued PSL and was taking DDS at 25 mg daily.

Previously, antibodies against laminin-332 were detected in about 10% to 20% of mucous membrane pemphigoid (MMP) patients. The majority of the patients have antibodies reactive with the α3 subunit of the protein. However, our case showed reactivity only with the γ2 subunit. The mucosal involvement that is typically seen in MMP was not observed in our case.

Circulating antibodies against BP230 were detected in the serum of a patient by immunoblot analysis but not by BP230 ELISA (MBL, Nagoya). This ELISA system utilizes the N- and C- terminal domains of BP230 but not the central-rod domain.[1] Therefore, the autoantibodies against BP230 that were detected in our immunoblot study may have reacted with the central-rod domain of the BP230 antigen. Autoantibodies against BP230, an intracellular protein, are clearly associated with bullous pemphigoid (BP), but have not been shown to be involved in the initiation of the disease. A marked improvement with the administration of DDS and the absence of erythematous plaques in the patient were not typical of the BP clinical course and manifestations.

Autoantibodies against laminin γ1 are characteristic of anti-laminin γ1

pemphigoid.[2] Blisters involving the lips, and therapeutic improvement with DDS are compatible with the clinical features of anti-laminin γ1 pemphigoid. Based on these findings, the diagnosis of anti-laminin γ1 pemphigoid may be appropriate.

It is possible that the unusual autoimmune profile of the patient also developed as a result of epitope spreading. Although several cases of autoimmune blistering disease with distinct autoantigens have been reported,[3-5] this is the first case report describing a patient with IgG autoantibodies for three different antigens to the basement membrane zone: BP230, laminin γ1 and the γ2 subunit of laminin-332.

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