Sublamina densa-type linear IgA bullous dermatosis with IgA autoantibodies specific for type VII collagen: a case report and clinicopathological review of 32 cases

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Abstract

Linear IgA bullous dermatosis (LABD) is a rare autoimmune bullous disorder characterized by linear deposits of IgA at the basement membrane zone (BMZ) and/or by circulating IgA anti-BMZ antibodies. Comparing with other immuno-bullous diseases, LABD represents a heterogeneous disease entity with diversity of pathogenic IgA autoantibodies to different hemidesmosomal antigens and an association with malignancies and occasional drug use. We herein present an 82-year-old Japanese man with LABD, whose indirect immunofluorescence using 1M NaCl-split skin showed positive staining for IgA at the dermal side alone. Fluorescence overlay antigen mapping using laser scanning confocal microscopy (FOAM-LSCM) was employed to examine the in vivo bound patient's IgA, which was specific for type VII collagen (COL7), a prominent antigen of the sublamina densa. One year later, he developed malignant lymphoma, suggesting the diagnosis of paraneoplastic LABD. We reviewed 32 cases of sublamina-densa type LABD with anti-COL7 IgA antibodies thus far reported in the literature to compare the clinicopathological characteristics of this rare disease variant and emphasize that COL7 is the main autoantigen in sublamina densa disease.

Keywords: paraneoplastic linear IgA bullous dermatosis, sublamina densa, type VII collagen, malignant lymphoma

Introduction

Linear IgA bullous dermatosis (LABD) is a rare acquired subepidermal blistering disorder, which presents with urticarial plaques, papules, vesicles, and bullae affecting the skin and mucous membranes. Cutaneous lesions typically heal without scarring, but mucosal involvement, the most common manifestation in the disease, may cause stricture or conjunctival and corneal scarring [1, 2], leading to morbidity. Although the etiopathology of LABD has yet to be fully understood, it may be provoked by infection, certain drugs (especially vancomycin hydrochloride and diclofenac) or malignancies, mostly lymphoproliferative disorders [3, 4].

LABD is characterized by in vivo linear IgA deposition at the basement membrane zone (BMZ) and can be divided into two immunopathological subgroups: the lamina lucida-type and sublamina densa-type. The former includes the vast majority of LABD and in this form, the pathogenic IgA autoantibodies react with the epidermal side of 1M NaCl-split normal human skin, targeting BP230 and 97-kDa LABD-97, or 120-kDa LAD-1 antigens that are distinct proteolytic fragments of the BP180 extracellular portion; pathogenic antibodies react less frequently with the NC16a epitope of BP180 [2, 4, 5]. However, only limited evidence has been available for the sublamina densa-type of LABD and clinically, patients with anti-sublamina densa IgA antibodies tend to be more refractory to the standard treatments [6].

This report describes a case of lymphoma-associated LABD with in vivo bound/circulating IgA autoantibodies reactive with the dermal side

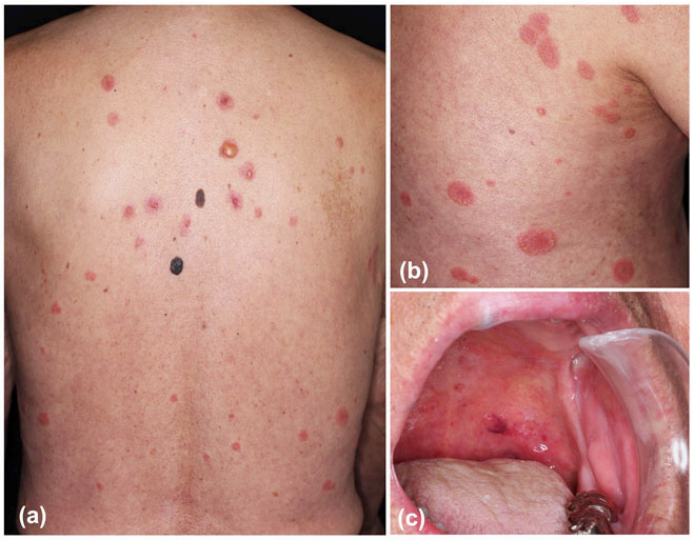

Figure 1. *A) Fingertip-sized oval edematous erythema with tense bullae were distributed on the trunk and limbs. B) Annular array vesicles lined the inner border of erythema on the lateral trunk. C) Oral ulceration and bullae on the soft palate and buccal mucosa.*

of 1M NaCl-split skin. Fluorescence overlay antigen mapping using laser scanning confocal microscopy (FOAM-LSCM) demonstrated that the patient's IgA reactivity corresponded specifically to COL7, a major sublamina-densa antigen. We further summarize 32 reported cases of sublamina densa-type LABD with IgA antibodies to COL7, to look for the clinicopathological signature of this extremely rare disease entity.

Case Synopsis

An 82-year-old Japanese man who had a three years' history of multiple tender-itchy vesicles on the trunk, extremities, palms, and oral mucosa, was admitted to our hospital because of the sudden onset of splenic infarction with a fever of 38.9 degrees. He also complained of exacerbation of the skin and mucous lesions. His complex medical history included bladder and gastric cancers, thymoma, controlled hypertension, coronary spastic angina, pulmonary emphysema, autoimmune hepatitis complicated by chronic hepatitis C, and nonerosive reflux disease, for

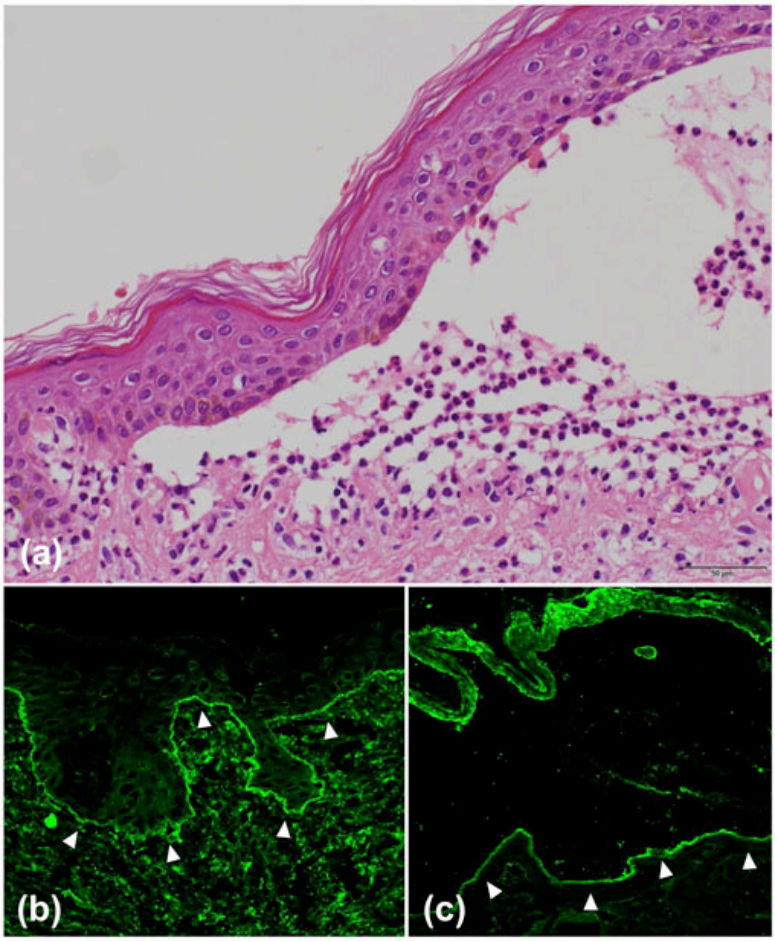

Figure 2. *A) Histopathology of the lesional back skin showed a subepidermal blister containing eosinophils, neutrophils, and plasmacytes, with inflammatory infiltrates in the upper dermis (H&E, 200%). B) Direct immunofluorescence revealed a fine granular deposition for IgA along the BMZ (arrows, 400%). C) Indirect IF using 1M NaCl-split skin showed positive IgA reactivity at the dermal side of the BMZ alone (arrows, 200%).*

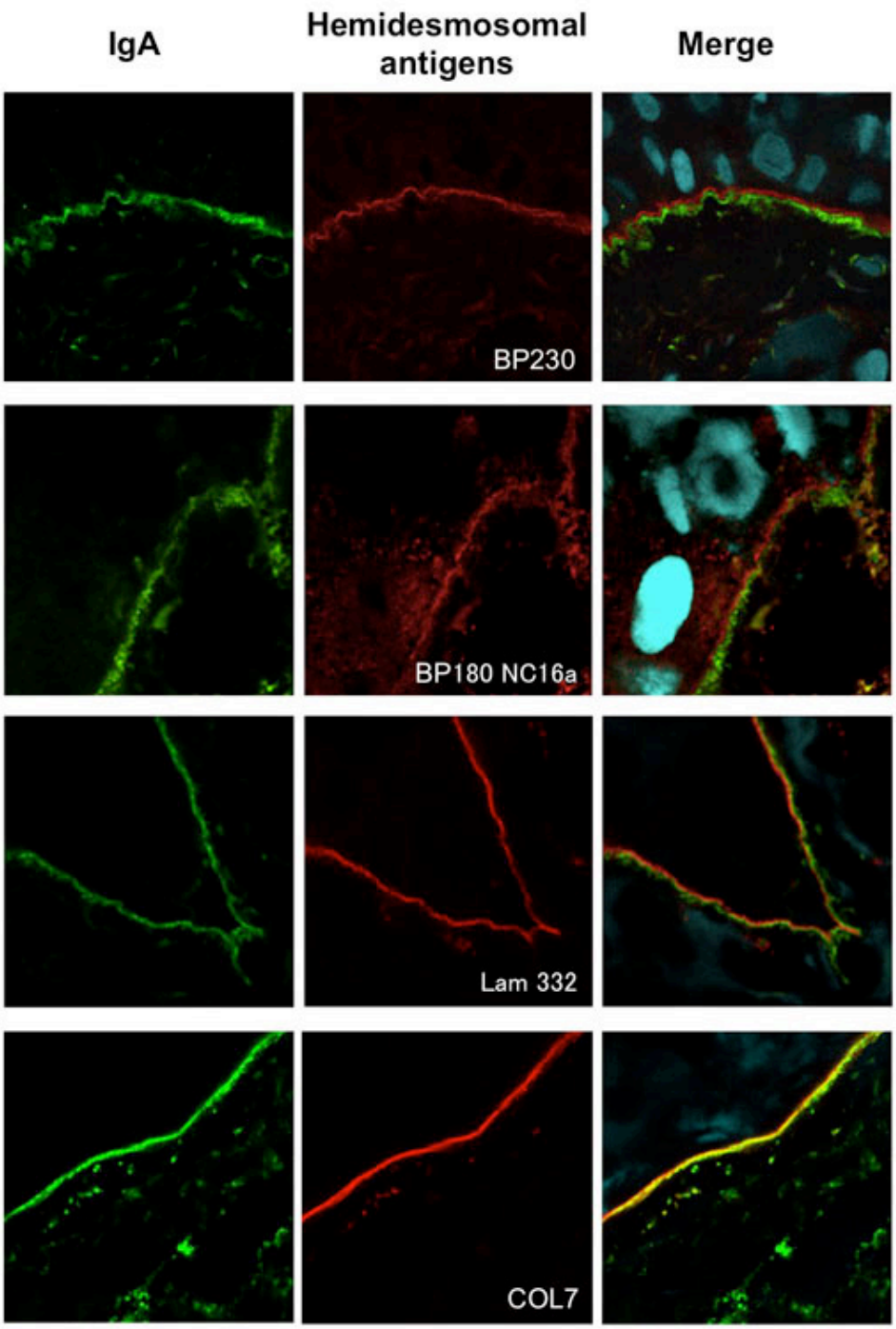

Figure 3. *On a FOAM-LSCM, the linear BMZ immunoreactivity of patient's serum IgA localized below those of mouse monoclonal antibodies to BP230 and laminin-332 (Lam 332), (1,800% and 5,000%, respectively), and a BP patients' serum that was positive for BP180 NC16a-ELISA (3,000%). Note that the patient's IgA signal merged completely with monoclonal antibody to COL7 (5,000%).*

which he received antihypertensive, antianginal, and anticoagulant agents, lipid-modifying agents, and proton pump inhibitor.

On examination, fingertip-sized oval edematous erythemaatous papules and plaques with tense bullae were distributed on the trunk and limbs (**Figure 1**A). Notably, annular arrays of vesicles lined the inner border of erythema on the lateral trunk (**Figure 1**B). Nikolsky sign was not evident. Oral ulceration and bullae were present on the posterior wall of the pharynx, soft palate, and buccal mucosa (**Figure 1**C). Blood examination disclosed elevated values of soluble IL-2 receptor (1385 U/mL; normal, 127-582), IgG (3287 mg/dL; normal, 870-1700), IgA (1125 mg/dL; normal, 110-410), IgM (225 mg/dL, normal, 33-190), antinuclear antibody (% 320; normal, < % 40), and particularly 4.5% atypical lymphocytes. Serum

anti-desmogleins 1 and 3 and anti-BP180 antibodies were all negative. Histopathology of the lesional back skin showed a subepidermal blister containing eosinophils, neutrophils, and plasmacytes, with numerous inflammatory infiltrates in the upper dermis (**Figure 2**A). Direct immunofluorescence revealed a fine granular deposition for IgA along the BMZ (**Figure 2**B), but was negative for IgG, IgM, and C3. Indirect immunofluorescence (IIF) using 1M NaCl-split skin showed positive IgA reactivity at the dermal side of the BMZ alone (**Figure 2**C).

To characterize the in vivo bound and serum IgA autoantibodies reactive with the dermal side of BMZ, we performed fluorescence overlay antigen mapping using laser scanning confocal microscopy (FOAM-LSCM) on normal human skin section as a substrate: a bullous pemphigoid (BP) patient's serum that was positive for BP180 NC16a-ELISA, and mouse monoclonal antibodies to BP230 (NU-01-BP1; Cosmo Bioantibody Collection, Tokyo, Japan) and laminin-332 (P3H9-2; Abcam, MA) displayed the linear immunoreactivity that stained above the patient's IgA reactivity at the BMZ (**Figure 3**, right, top-third). This indicates that the antigen(s) targeted by patient's IgA localized at least below the lower lamina densa. Further double staining revealed that the immunoreactivity of patient's IgA co-localized specifically with that of monoclonal antibody to COL7 (LH7.2; Abcam, MA), (**Figure 3**, right, bottom). Based on these findings we diagnosed LABD with IgA autoantibodies directed against COL7.

Upon admission, he was initially treated with piperacillin/tazobactam for splenic infarction and subsequently with 30mg daily of oral prednisolone (0.53 mg/kg/day). His mucocutaneous lesions improved rapidly and the daily dose of oral prednisolone was tapered to 2.5mg/day over approximately 1-year without flare-up. He has been in remission for at least one-year after administration of oral prednisolone. Thereafter, he had a continuous feeling of fatigue and anorexia with elevated serological markers of inflammation, including C-reactive protein (3.34 mg/dL; normal, <3.0 mg/dL), soluble IL-2 receptor (12,568 U/mL), and 9.0% atypical lymphocytes. He underwent fluorodeoxyglucose positron emission tomogramphy scanning that visualized multiple fluorodeoxyglucose-avid lesions involving cervical, axillary, mediastinal, and inguinal lymph nodes. A diagnostic lymph node biopsy revealed numerous atypical lymphocytes with positive immunostaining for CD3, CD20, CD79, PAX5, and bcl-2, was suggestive of T-cell/histiocyte-rich large B-cell lymphoma.

Case Discussion

LABD appears in a variety of clinical settings, particularly hematological malignancies, infections, autoimmune disease, and drugs. In addition to the heterogeneous disease backgrounds, the clinicopathology of LABD is highly variable and almost indistinguishable among the distinct causative origins, albeit vancomycin can be the most incriminated drug (40-42% of all the drug-induced cases), [4, 7].

Our present case represents a rare sublamina densa type of LABD associated with malignant lymphoma. In our patient serum IgA antibodies react specifically with COL7, a major component of the anchoring fibrils in the dermal-epidermal junction. This structural antigen has been well known to be recognized by serum autoantibodies in patients with epidermolysis bullosa acquisita (EBA) and bullous systemic lupus erythematosus [6]. Sublamina densa-type LABD can be a distinct immnopathological entity; the disease prevalence is lower than the prevalence of dermal-binding disease in all LABD cases (8.7-16.8%), [2, 8].

To address the immunopathology of sublamina densa-type LABD, we performed a retrospective review of the English literature up to January 2017, as follows; the search terms included "linear IgA bullous dermatosis," "sublamina densa," "anchoring fibril," and "type VII collagen." This survey was reviewed separately by two different reviewers (N.U. and N.O.), and consisted of 20 studies comprising 76 cases [2, 4, 5, 7-23], including ours'. Of these, 32 cases had serum autoantibodies directed against COL7, as conducted by the eligibility criteria, including positive IgA at the dermal side of 1M NaCl split-skin and any combination of the following findings; i) positive bands for monomeric and/or dimeric COL7 on immunoblotting using human dermal substrates [2, 4, 5, 8-10, 13, 14, 22, 23], ii) immunodeposits specific for anchoring fibrils on immunoelectron microscopy [9, 13, 22], iii) negative indirect IF on recessive dystrophic

epidermolysis bullosa skin (a COL7-knockout human skin), [11, 12], iv) in vivo bound IgA signal overlying with COL7 on FOAM-LSCM, like our present case [7, 10], or v) positive COL7-specific ELISA [12]. Considering the serum antibodies below the detection sensitivity on indirect immunofluorescence, the 2 studies using FOAM-LSCM on the patient's skin were allowed to be included in our review [7].

Among 32 cases with anti-COL7 IgA autoantibodies, their ages ranged from 1.5 to 82.0 years old (median; 58.2 ± 27.5) and the male to female ratio was 3: 2. In addition, there were only four cases associated with drugs (12.5%); two cases were caused by penicillin and one case by vancomycin [2, 4, 5, 7-23]. Overall clinical details suggest no gender/age predilection and no particular drug usage for developing anti-COL7 IgA antibodies in the disease. Interestingly, of the 32 COL7-reactive IgA sera, five (15.6%) had an immunoreactivity with other dermal antigen(s), [2, 7]. Of these 5 sera, two had IgA antibodies to laminin-332 or BP180 in each; the latter case may be the reactivity in close proximity to the COOH terminus of BP180, the antigen mostly localized in the lamina densa [2, 7]. The remaining 3 sera did not identify the IgA reactivity to the exact dermal antigen(s), and may harbor the immunoreactivity to laminin-332 and/or laminin gamma 1, or their native conformational epitopes. Both of these are potentially difficult to characterize on conventional immunoblotting [4, 5, 10]. Although we excluded the remaining 44 cases with unconvincing immunoreactivity to COL7, our retrospective review supports that COL7 can be the main autoantigen targeted by IgA in sublamina densa-type LABD. Further updated evidence will hopefully define development of IgA autoantibodies to multiple dermal antigens in this disease entity. One may account for the debatable concept whether the 32 cases could be diagnosed as; i) LABD with IgA autoantibodies to COL7 or ii) LABD-like immunophenotypic variant of EBA with exclusive or predominant IgA autoantibodies to COL7 [24], although their direct and/or indirect IF did not show IgG deposits along the BMZ. The pathogenic impact of anti-COL7 IgA antibodies in EBA cases may be responsible in part for the ocular involvement [25, 26], a concept that has emerged by demonstrating the epidermal-dermal separation ex vivo [27]. However, it remains difficult to discriminate this rare immunopathological entity of EBA from LABD.

Another unique observation in our case was a complication of hematological malignancy. Our retrospective review did not evaluate the interrelationship between the development of a humoral autoimmune response to COL7 and the incidence of malignancy. The underlying paraneoplastic reaction responsible for the particular immuno-phenotypes of LABD remains unclear. More importantly, recommended treatment regimen are generally similar between the lamina lucida and sublamina densa diseases. This may in part be attributable to the difficulty of determining anti-COL7 IgA autoantibodies throughout the clinical course of both immune-phenotype diseases. Accumulating evidence concerning precise antigen mapping in each LABD case will thus help guide further understanding of the immunopathogenic diversity of LABD, particularly in sublamina-densa type disease.

Conclusion

Our case report and retrospective review of 32 relevant cases has shown that COL7 is the main autoantigen recognized by IgA in sublamina densa-type LABD. Further updated evidence concerning the complication of certain malignancies and detailed medical histories is warranted to assist in our understanding of this rare disease.

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