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Case Report Open Access

Possible Dual Immunoreactivity for Laminin-332 and Type VII Collagen in a Case with Vancomycin-Induced Linear Iga Bullous Dermatosis Manifesting as Erythroderma

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Summary

We report a unique case of vancomycin-induced linear IgA bullous dermatosis (LABD) presenting as erythroderma. Direct immunofluorescence showed a linear IgA deposition at the dermal side of the basement membrane zone (BMZ), and double immunostaining using patients' skin as a substrate revealed that the *in vivo* IgA signal co-localized with laminin-332 and type VII collagen. Our case is the first documentation of vancomycin-induced LABD, in which the pathogenic IgA deposit would concomitantly recognize the two distinct antigens at the dermal BMZ.

Keywords: Linear Iga bullous dermatosis; Erythroderma; Vancomycin; Laminin-332; Type VII collagen

Introduction

Linear IgA bullous dermatosis (LABD) is a rare autoimmune subepidermal bullous disease characterized by linear IgA deposition at the basement membrane zone (BMZ), and often shows considerably variable clinical presentation. Although the etiopathology of LADB is unknown, increasing evidences have suggested an occasional drug exposure in a substantial number of the patients. Among the causative drugs, vancomycin hydrochloride, a glycopeptide antibiotic agent, has frequently been reported [1-6], and the rare clinicopathology of the drug-induced LABD can be a noteworthy updating to assist the awareness of the underlying disease cause. We herein report the first case of vancomycin-induced LABD presenting as erythroderma, whose *in vivo* IgA deposit reacted with both laminin-332 and type VII collagen.

Report

An 81-year-old Japanese man had a 1-month history of unknown-origin fever and appetite loss. Because his sputum culture identified methiillin-resistant Staphylococcus aureus infection, physicians gave him an intravenous vancomycin hydrochloride (2 g/day). His medical history included stable ischemic heart disease and hypertension, treated uneventfully with calcium antagonist and anticoagulant for several years. Otherwise he had no previous history of drug eruptions and allergy. On the 10th day of the vancomycin treatment, pruritic skin rash appeared on the lower legs and then spread to the almost entire body. On physical examination, severe confluent erythema was more than 80% of the body surface, and relatively weak erythema almost covered the remaining skin, suggestive of erythroderma (Figure 1a). In addition, finger tip-sized tense bullae were distributed on the lateral trunk (Figure 1b), but without mucosal lesions and Nikolsky's sign. A skin biopsy from the lesional bulla showed a subepidermal split with neutrophilic and lymphocytic infiltrates in the upper dermis (Figure 1c). Direct immunofluorescence showed a homogeneous linear IgA deposition alone at the dermal side of the BMZ (Figure 2a). Repeated indirect immunofluorescence using salt-split and non-split normal human skin was negative. To determine the circulating IgA autoantibodies reactive with dermal BMZ antigen(s), we performed immunoblotting with two different substrates, dermal extracts from normal human skin and extracellular matrix from HaCaT keratinocyte cultures, but obtained negative results.

We further characterized the *in vivo* IgA deposit at the dermal BMZ by immunostaining using the patients' skin section as a substrate: three bullous pemphigoid patients' sera, which were positive for BP180

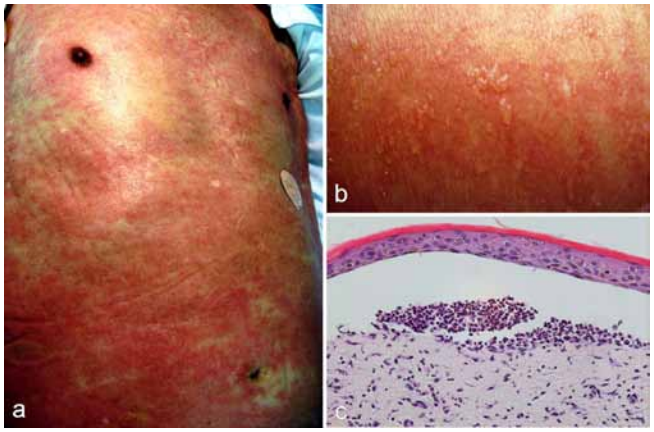

Figure 1a: Pruritic, confluent erythema appeared more than 80% of the body surface, and relatively weak erythema almost covered the remaining skin. **b**: Diffuse erythema combined with multiple small-sized, tense bullae on the lateral aspect of the trunk. **c**: A subepidermal blister containing numerous neutrophils and lympho-neutrophilic infiltration in the upper dermis.

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NC16a-ELISA, demonstrated the linear epidermal BMZ staining (Figure 2b), but inversely mouse monoclonal antibodies to laminin-332 (GB3, Acris GmbH, Germany) and type VII collagen (LH 7.2, Dako, Denmark) stained the dermal BMZ (Figure 2c and 2d). This suggests that the dermo-epidermal separation occurred at the narrowed region between the lower lamina lucida and upper lamina densa. Double immunostaining revealed that the linear IgA deposit in the patients' skin co-localized with laminin-332 and type VII collagen (Figure 2e and 2f). The overall clinicopathology was consistent with vancomycin-induced LABD. After the cessation of vancomycin, he was treated intravenously with hydrocortisone sodium succinate 200 mg/day for 3 days and subsequently with 100 mg/day for 3 days. His skin rash and bullae regressed dramatically and never recurred without medications during 4-months of follow-up.

The diagnostic difficulty of LABD may include a controversial clinical presentation mimicking simply dermatitis, herpes infection, bullous pemphigoid, erythema multiforme, and most significantly toxic epidermal necrolysis [2-6]. Likewise, LABD has been associated with a variety of disease settings; solid and hematological malignancies, infections, autoimmune basis, and drugs [7-11]. In addition to the heterogeneous disease backgrounds, a recent literature review has documented that the clinicopathology of drug-induced LABD is highly variable and almost indistinguishable from the idiopathic form [9]. Moreover, the cause-effect relationship has tended to be unclearly reported, albeit vancomycin can be the most incriminated drug (42% of all the drug-induced cases). In our case, i) personal and medical histories did not suggest underlying drug and allergic reactions, ii) the timing of vancomycin start and onset of skin rash is highly susceptive for the event, iii) the rapid improvement of the skin lesion after discontinuation of vancomycin and no recurrence thereafter suggest an association of the drug, although we did not apply re-challenge test, and iv) the Naranjo's algorithm, a questionnaire-designed scoring for determining the likelihood of adverse drug reaction [11], was judged as "probable" (score 7).

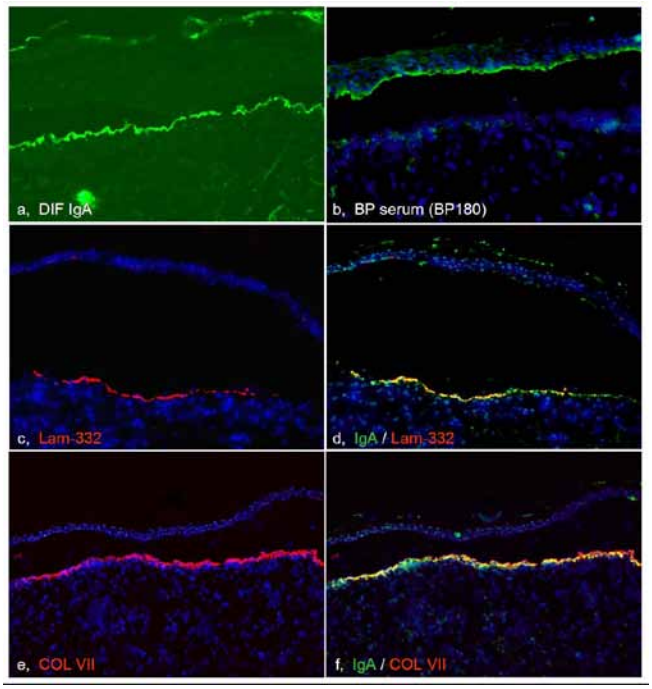

Figure 2: Direct immunofluorescence showing linear IgA deposit at the dermal side of the separated BMZ (**a**). Immunostaining using the patients' skin section revealed the epidermal BMZ labelling with a BP serum (targeting BP180 NC16a; **b,** *green*), but inversely showed the dermal BMZ labelling with laminin-332 (**c,** *red*) and type VII collagen antibodies (**e,** *red*). These two antigens overlay partially with the *in vivo* IgA deposit (*yellow*, **d** and **f**). DAPI was used for the nuclear staining (*blue*, **b-f**).

To our knowledge, this is the first documented case of vancomycin-induced LABD to establish erythroderma, in which the *in vivo* IgA deposit would concomitantly recognize two distinct dermal BMZ antigens, laminin-332 and type VII collagen. The linear dermal BMZ immunofluorescence in our case raises another possibility that the skin-bound IgA may in part target p200/laminin gamma-1, an antigen recognized by anti-laminin gamma-1 pemphigoid sera [10]. Intriguing observation is that despite the severe and extensive skin lesion our patient had no mucosal involvements. Considering no different frequencies of mucous lesions between idiopathic and drug-induced LABD, [9] no mucosal involvements in our case would support the finding of the rare autoimmunity against to type VII collagen and/or laminin 332. However, the lack of detectable circulating IgA antibody in the patients' serum caused the potential difficulty for determining the exact pathogenic antigen(s), as was in the most cases reported thus far (~8% positivity on indirect IF) [9]. Currently there is no available concern about the reasons why vancomycin can frequently develop LABD and also why drug-induced LABD represents the lack of association between variable clinical presentations and immunopathology. Nevertheless, the evidence that after withdrawal of vancomycin the rapid clearance of the skin lesions has been demonstrable in the most affected cases (~70%) may thus alert us to the likelihood cause of the drug in LABD.

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