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Causative drug detection by drug-induced lymphocyte stimulation test in drug-induced linear IgA bullous dermatosis

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SIR: Linear IgA bullous dermatosis (LABD) is a rare autoimmune blistering skin disorder characterized clinically by the presence of small tense blisters and immunohistologically by the deposition of immunoglobulin A (IgA) at the dermal-epidermal junction.[1] It is occasionally induced by drugs, internal malignancies and infections. Only one case of generalized LABD induced by ampicillin/sulbactam has been reported, as far as we know.[2] We encountered a case of LABD probably induced by ampicillin/sulbactam, and positive drug-induced lymphocyte stimulation test for ampicillin/sulbactam supported the diagnosis.

A 72-year-old Japanese woman was admitted to the Division of Surgery at our hospital with peritonitis due to gastric perforation. Immediately after admission, ampicillin/sulbactam was administered for 10 days, after which the antibiotics were changed to meropenem. Three days later, multiple erythemas appeared on the trunk, and the patient visited us 4 days after the onset of the skin symptom. Under the clinical diagnosis of drug eruptions, we treated her with topical steroids. The surgeon changed the antibiotics from meropenem to piperacillin/tazobactam. From 4 days thereafter, blistering lesions appeared on her auricles, neck, axillae, groin, legs, palms and soles (Fig 1a, b). Histological examination of a lesional skin biopsy specimen showed a subepidermal blister with neutrophilic infiltration (Fig 2a). Direct immunofluorescence staining demonstrated linearly distributed deposition of IgA at the dermal-epidermal junction in the perilesional skin (Fig 2b). No staining for IgG was detected. Indirect immunofluorescence examination using normal skin sections did not show anti-keratinocyte cell surface antibodies or anti-basement membrane zone antibodies. Indirect immunofluorescence staining on 1M NaCl-split normal human skin sections demonstrated that circulating IgA autoantibodies in the patient's serum reacted with the dermal side of the split skin. Immunoblot analysis using human epidermal and dermal extracts, the recombinant NC16a domain of 180-kD bullous pemphigoid antigen (BP180,

type XVII collagen), the recombinant C-terminal domain of type XVII collagen, concentrated conditioned medium of HaCaT cells, and purified human laminin 332 as substrates showed no reactivity. Enzyme-linked immunosorbent assays (ELISA) showed the patient's serum to be negative for both type XVII collagen and 230-kD bullous pemphigoid antigen (BP230, dystonin-e). Drug-lymphocyte stimulation tests (DLSTs) were performed with calculation of [H^3]-thymidine uptake of lymphocytes obtained from the patient's peripheral blood by SRL Inc. (Tokyo, Japan). The lymphocytes were isolated by density gradient centrifugation and resuspended. They were stimulated by culture with each drug or vehicle (negative control). [H^3]-thymidine was added, and the lymphocytes were harvested. [H^3]-thymidine uptake was calculated with a scintillation counter. Stimulation indices were defined as count per minute (cpm) of the stimulated lymphocytes/ cpm of the negative control. Stimulation indices for ampicillin/sulbactam, piperacillin/tazobactam and meropenem were 568%, 410% and 89%, respectively. Based on her clinical features and laboratory data, we diagnosed the case as sublamina densa-type LABD induced by ampicillin/sulbactam and piperacillin/tazobactam. After cessation of intravenous piperacillin/tazobactam, she was treated with intravenous injection of betamethasone at 4 mg daily. However, the blistering lesions expanded to the buttocks. 40 days after the initial use of ampicillin/sulbactam, her peritonitis was controlled and her intestinal condition recovered enough for her to take oral medication. Thus, oral diaminodiphenyl sulfone (DDS) at 50 mg daily was administered. Then, her skin condition improved, and neither erythemas nor blisters newly developed. We tapered the betamethasone, and finally discontinued it 19 days after the introduction of DDS. At present, she continues to take DDS at 25mg daily, and the lesions have not recurred.

LABD is divided into two subgroups: the lamina lucida type and the sublamina densa type. By indirect immunofluorescence staining, sera from patients with the lamina lucida type and the sublamina densa type react with the epidermal and dermal sides of 1M

NaCl-split normal human skin, respectively.[3] Most lamina lucida-type LABD sera react with the 97-kD and 120-kD LAD-1 truncated domains of type XVII collagen.[4,5] In contrast, type VII collagen is the major autoantigen for sublamina densa-type LABD.[6,7] From the results of indirect immunofluorescence staining with 1M NaCl-split skin, we regard the present case as the sublamina densa type, although we were unable to identify the autoantigen by immunoblot analysis.

Drug exposure is an important triggering factor of LABD. Vancomycin is the most common causative medication, although diclofenac, piroxicam, lithium and others have also been reported as triggers of drug-induced LABD.[1] From the disease course, her medical history and the DLST result, we considered that the patient had drug induced-LABD triggered by ampicillin/sulbactam and exacerbated by piperacillin/tazobactam. In the literature, we found only one case of drug-induced LABD in which DLST was performed, although the result was negative.[8] In our case, we obtained very important supporting information for the diagnosis from the DLST. The present case suggests that DLST might give us helpful information on a causative medicine in drug-induced LABD. Further accumulation of similar cases will be necessary to clarify the significance of DLST for the detection of causative drugs.

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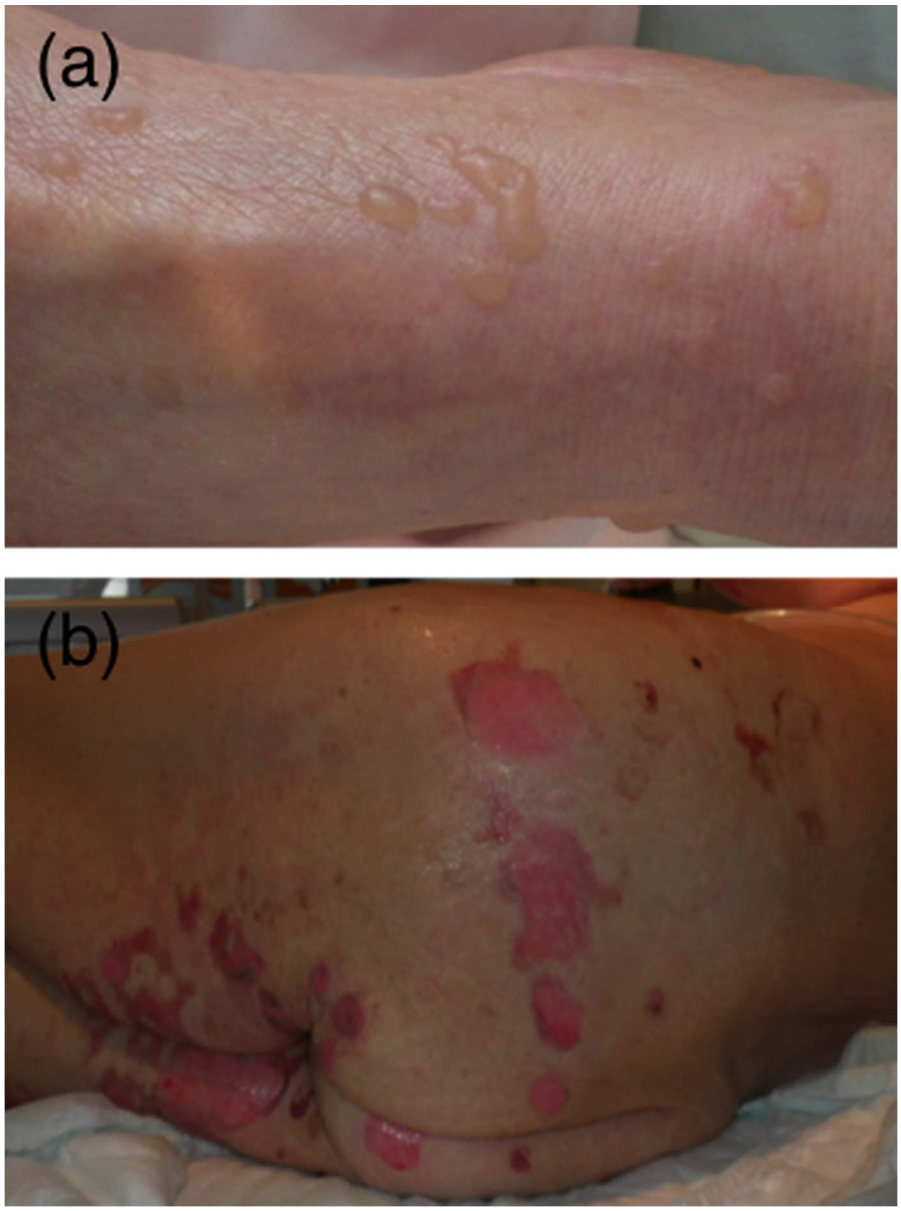
Figure legends

Figure 1. Clinical features of the patient. (a) Tense vesicles in her left leg. (b) Erosions in her buttocks and thighs.

Figure 2. Histopathology and direct immunofluorescence staining of a skin biopsy specimen. (a) A skin biopsy specimen shows subepidermal blisters with inflammatory cell infiltration mainly consisting of neutrophils (haematoxylin and eosin stain, x400). (b) Direct immunofluorescence staining (fluorescein isothiocyanate, green) of a skin biopsy specimen reveals linear deposits of IgA at the dermo-epidermal junction (x200).



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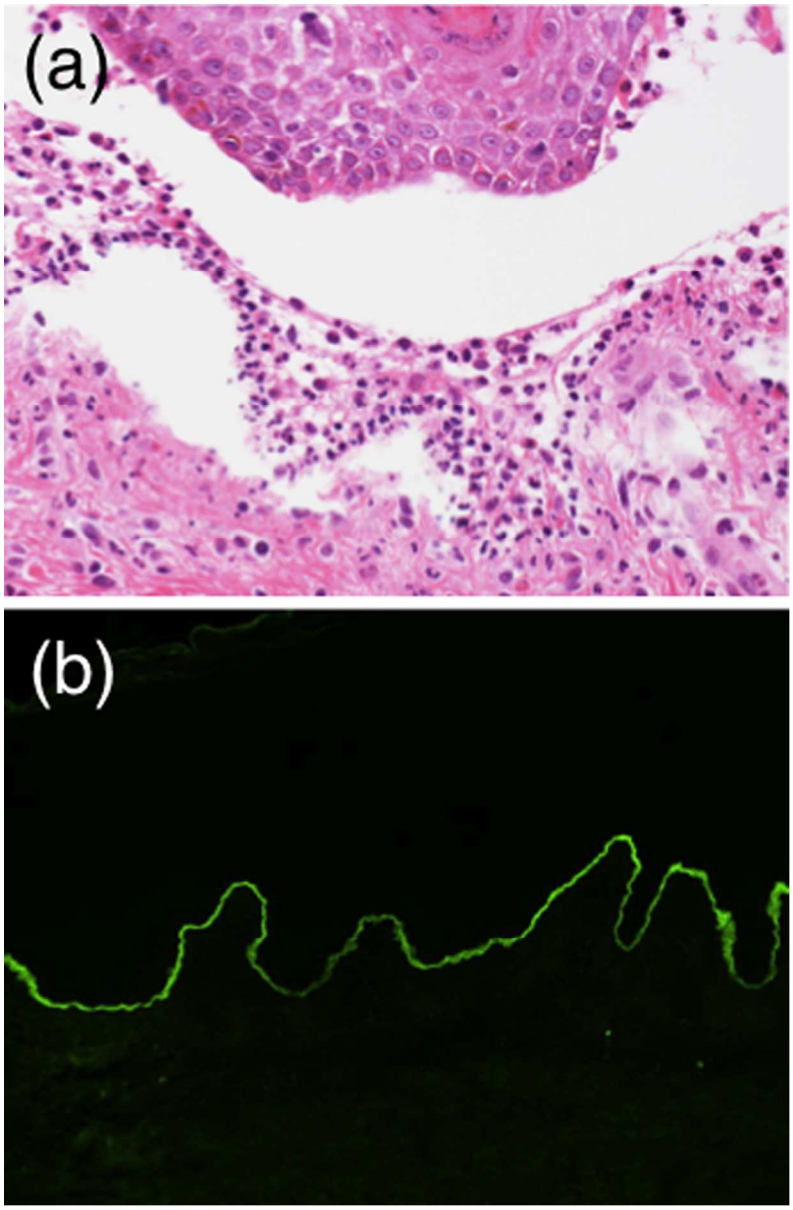

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