



CASE REPORT

Piperacillin–Tazobactam-Induced Linear IgA Bullous Dermatitis Supported by a T-Cell Activation Assay

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Linear immunoglobulin (Ig) A bullous dermatosis (LABD) is a rare subepidermal autoimmune blistering disease characterized by linear IgA deposits at the basement membrane zone visualized with direct immunofluorescence (DIF). Most cases of LABD are idiopathic, but some are drug-induced with vancomycin being the most common causative agent. We herein report a patient presenting with blisters and erosive lesions, primarily in the intertriginous and flexor areas, consistent with a diagnosis of piperacillin–tazobactam-induced LABD based on the patient's clinical course and histopathology, DIF, and *in vitro* T-cell activation assay (TAA) findings. Only one case of piperacillin–tazobactam-induced LABD has been previously reported. In addition to its rarity, our case was also unique in that the skin lesions occurred in the intertriginous and flexor areas, uncommon locations for typical adult patients with LABD, and TAA strongly suggested an association with the causative drug. (**Ann Dermatol 30(5) 588~591, 2018**)

-Keywords-

Linear IgA bullous dermatosis, Piperacillin-tazobactam, T-cell activation assay

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INTRODUCTION

Linear IgA bullous dermatosis (LABD) is a subepidermal autoimmune bullous disease characterized by linear IgA deposition at the basement membrane zone (BMZ). LABD typically presents with a widespread annular eruption of vesicles and tense bullae¹. In adults, the skin lesions usually occur on the trunk, extensor extremities, buttocks, face², and rarely in the intertriginous and flexor areas³. Involvement of the intertriginous and flexor areas is more commonly seen in children⁴.

LABD is usually idiopathic, but it may be related to infection or medication⁵. Multiple drugs have been implicated, and vancomycin is the most common offending medication^{1,5}. Only one case of piperacillin-tazobactam-induced LABD has been previously reported¹. Also, to the best of our knowledge, conventional lymphocyte transformation test (LTT) has been performed in only two previous case reports of drug-induced LABD⁶. Some recent reports have suggested that T-cell activation assays (TAA) are more sensitive than LTT for the detection of drug-specific responses in patients with a diagnosis of drug hypersensitivity⁷⁻¹⁰. We herein report a patient presenting with blisters and erosive lesions, mainly in the intertriginous and flexor areas. The diagnosis of piperacillin–tazobactam-induced LABD was finally made based on the patient's clinical course and histopathology, direct immunofluorescence (DIF), and TAA findings.

CASE REPORT

A 59-year-old Taiwanese male was admitted to the hospital with a diagnosis of right lower lung pneumonia. He had a history of insulin-dependent diabetes mellitus, hypertension, end stage renal disease presumed secondary

to diabetic nephropathy, peripheral occlusive arterial disease, chronic osteomyelitis of the left foot, and chronic hepatitis C infection. He had no known history of drug allergy and denied recently taking any new medications.

Empirical antibiotic therapy was administered soon after admission with cefuroxime for 1 day. The next day cefuroxime was discontinued and moxifloxacin was administered. Moxifloxacin was discontinued after 3 days, and a 10-day course of piperacillin-tazobactam was begun. In addition, a 7-day course of teicoplanin was added 2 days after the start of piperacillin-tazobactam administration for suspected recurrent osteomyelitis of the left foot. An erythematous skin rash first appeared 3 days after the initial dose of piperacillin-tazobactam, and subsequently the patient developed multiple intense pruritic vesicles, bullae, and erosions primarily on the thighs, axillae, groins, finger webs, and popliteal fossae over the next 7 days. Because of a suspected drug eruption, all antibiotics were discontinued.

Physical examination revealed numerous clear tense bullae with erosions and crusts on the thighs, axillae, groins, finger webs, and popliteal fossae (Fig. 1A~C). Some lesions were arciform in appearance (Fig. 1D). The ocular, nasal, and genital mucosal membranes were spared. A skin biopsy obtained from an intact blister revealed a subepidermal blister with dense neutrophils, nuclear dust, and eosinophils in the dermis (Fig. 2A, B). DIF demonstrated a continuous linear deposition of IgA and a weak linear deposition of C3 along the BMZ (Fig. 2C, D). Type IV collagen staining showed the subepidermal blister to be

above the basement membrane. Indirect immunofluorescence examination failed to demonstrate anti-keratinocyte cell surface or anti-basement membrane zone antibodies.

TAA was performed 7 days after discontinuation of all antibiotics. At that time, the skin lesions were in clinical remission. In brief, peripheral blood mononuclear cells were isolated using density gradient centrifugation. The cells were then incubated in culture media containing cefuroxime, moxifloxacin, piperacillin/tazobactam, teicoplanin, or solvent control. Culture supernatants were collected on days 7, 14, and 21, and the levels of cytokines granulysin and granzyme B were measured with Enzyme-Linked Immunosorbent Assay. The levels of granulysin and granzyme B were the highest in the piperacillin/tazobactam culture supernatant (granulysin, 6 times higher than the solvent control and granzyme b, 31.2 times higher than the solvent control), followed by moxifloxacin (granulysin, 3.4 times higher than the solvent control and granzyme B, 7.7 times higher than the solvent control). There were no significant increases in the cytokine levels in the cefuroxime and teicoplanin culture supernatants.

Based on the timing and duration of antibiotics usage, disease course, histopathological findings, and DIF, we suspected a diagnosis of drug induced-LABD most likely triggered by piperacillin-tazobactam. This was supported by the TAA results suggesting piperacillin/tazobactam as the main culprit drug. After cessation of the antibiotics, oral prednisolone 10 mg three times daily was begun, but was



Fig. 1. (A~C) Photographs showing numerous clear fluid-filled tense bullae with erosions and crust formation on the axillae, thighs, groins and popliteal fossae; (D) some lesions are arciform in appearance.

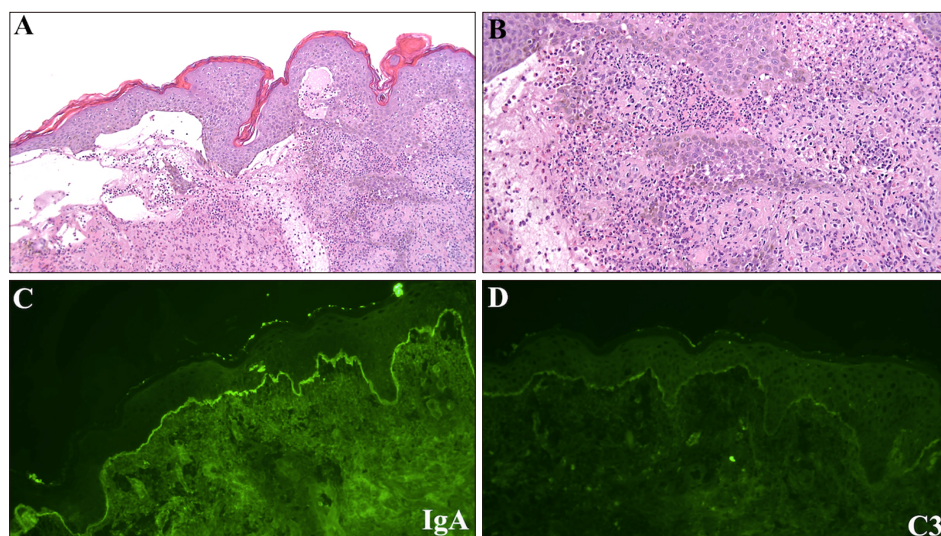


Fig. 2. Photomicrographs of the patient's cutaneous biopsy specimen demonstrate subepidermal blister with dense neutrophils, nuclear dust, and eosinophils in the dermis (A: H&E, $\times 40$; B: H&E, $\times 100$). Photomicrographs of direct immunofluorescent staining of the skin biopsy specimen demonstrated continuous linear deposition of IgA and weak linear deposition of C3 along the basement membrane zone (C, D: $\times 100$).

discontinued after one day because the patient developed tarry stools. Topical therapy included antimicrobial barrier dressings to the areas of erosion and clobetasol propionate (0.05%) ointment to areas of intact erythematous skin. The patient's symptoms improved rapidly. At follow-up two weeks later, there was near complete resolution of all skin lesions.

DISCUSSION

LABD is a rare disease with an incidence of 0.23~2.3 cases per million person-years¹. LABD has a bipolar age distribution, afflicting mostly children aged 6 months to 10 years or adults over 60 years old⁵.

Patients with LABD may have lesions on the skin and/or mucous membranes⁴, and typically present with a widespread skin eruption of vesicles and bullae on inflamed or non-inflamed skin¹. The acute onset of annular or arcuate blisters resembling a string or cluster of pearls has been reported to strongly suggest a diagnosis of LABD^{3,4}. The trunk, extensor extremities, buttocks, and perioral areas are the most common lesion sites in adults². Unlike our patient, adult patients usually do not manifest lesions in the body folds and flexor areas³.

LABD is usually idiopathic but may be related to infection or medication⁵. Vancomycin is the most common medication reported to induce LABD^{1,5}. Other implicated medications include penicillins, cephalosporins, angiotensin converting enzyme inhibitors, and nonsteroidal anti-inflammatory drugs⁵. However, penicillins have been rarely implicated in LABD. Piperacillin-tazobactam-induced LABD is less common, and only one case has been previously reported and that patient presented with Stevens-Johnson

syndrome (SJS) and toxic epidermal necrolysis (TEN) like findings¹.

Cytotoxic mechanisms are involved in most forms of drug-induced skin disease^{9,11}. Granulysin, a secretory protein produced by cytotoxic T lymphocytes and natural killer cells, plays a key role in disseminated keratinocyte death in SJS/TEN^{7,8} and various cutaneous adverse reactions (CAR)^{9,11}. Other mediator, such as granzyme B, is expressed in epidermal T cells at the dermoepidermal junction and mediates drug-specific cytotoxicity in T-cell lines and clones derived from patients with different CARs^{9,11}. Since increased concentrations of granulysin and granzyme B are significantly correlated with CARs⁷⁻⁹, a positive TAA result has been defined as a 2-fold increase in cytokine expression compared with that of the solvent control⁸. In our case, the TAA showed a strong reaction to piperacillin-tazobactam and provided evidence useful for identifying the causative drug. Larger studies of similar cases are necessary to justify the use of TAA for the detection of causative drugs.

The primary treatment of patients with drug-induced LABD is withdrawal of the offending agent⁵. Other accepted treatments include dapsone, sulfonamides (sulfapyridine and sulfamethoxypyridazine), colchicine, and topical and oral corticosteroids⁵. In our case, spontaneous resolution of the skin eruption several days after discontinuation of piperacillin-tazobactam strengthened our suspicion that piperacillin-tazobactam was the culprit drug. In conclusion, piperacillin-tazobactam can occasionally induce LABD. Unlike the first case report describing a patient with SJS/TEN-like skin lesions, our case presented with annular or arciform blisters mainly in the intertriginous and flexural areas. If possible, LTT or TAA should

be performed to potentially identify the causative drug.

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We received the patient consent form about publishing all photographic materials.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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