

Linear IgA bullous dermatosis: a rare side effect of vancomycin

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Following a motor vehicle accident, a 70-year-old white female was admitted with lower limb fractures that required operative repair. The postoperative course was complicated by sepsis. Vancomycin and piperacillin/tazobactam were initiated empirically. Five days later, she developed a pruritic maculopapular rash in the groin and axilla. The rash progressed to a non-hemorrhagic vesicles and bullae on an erythematous base and spread to involve the trunk, palms and the inner aspects of the lips. Skin biopsy and direct immunofluorescence testing were consistent with vancomycin-induced linear IgA bullous dermatosis. Vancomycin was stopped with complete resolution of the lesions in the subsequent 2 weeks. Being aware of vancomycin-induced linear IgA bullous dermatosis in patients who develop a blistering skin rash while receiving this antibiotic should lead to timely interventions. Stopping vancomycin promptly and encouraging early skin biopsy to confirm the diagnosis will prevent disease progression and avoid unnecessary costs and suffering.

Physicians across all aspects of medicine prescribe vancomycin for suspected or proven Methacillin-resistant *Staphylococcus aureus* and other resistant gram-positive bacterial infections. Physicians are well acquainted with vancomycin-induced red man syndrome and its potential nephrotoxicity. However, there are other potential side effects that are less well recognized. Due to the fact that vancomycin is not often suspected to be the cause of such manifestations, awareness of these rare reactions is crucial.

Vancomycin-induced linear IgA bullous dermatosis (VILABD) is a rare autoimmune vesicobullous mucocutaneous disease with a broad differential diagnosis.¹ It affects people of all ages with two peaks: one before the age of 5 years and the second after the age of 60 years.² Vancomycin is the most common cause of drug-induced linear IgA bullous dermatosis (LABD).³ Being aware of this side effect, prompts early biopsy and direct immunofluorescence testing, which confirms the diagnosis preventing disease progression and avoiding unnecessary costs and procedures. We report a case of LABD in a 70-year-old white woman caused by intravenous vancomycin therapy.

CASE

Following a motor vehicle accident, a 70-year-old white female with type 2 diabetes mellitus was admitted with lower limb fractures but no internal organ damage. The patient required operative repair followed by mechanical ventilation. On Day 3 of the hospital stay, fever with no localizing symptoms was reported. Appropriate samples for Gram stain and culture were obtained and vancomycin and piperacillin/tazobactam were initiated empirically. On day 8 of the hospital stay (day 5 of antibiotic therapy) she developed a pruritic maculopapular skin rash in the groin and axilla. Over the following 2 days, the lesions progressively transformed into vesicles and bullae and spread to involve the trunk, scalp, palms and the inner aspects of the lips (Figure 1). The patient reported eye grittiness and excessive lacrimation.

On examination, the patient was afebrile with stable vital signs. Skin examination showed nonhemorrhagic vesicles and bullae on an erythematous base with a diameter that ranged between few millimeters up to 3 centimeters. Intact blisters were tense. The lesions that developed on the palm had a target shape (Figure 2). There was no surrounding cellulitis or pustules. The lesions involved the inner aspects of the lips but not the



Figure 1. Photographic image showing tense pruritic vesicles and ruptured bullae with erythematous base in the axilla ("cluster of jewels").



Figure 2. Photographic image showing target lesions on the palm.

palate or pharynx. There were no genital lesions and no lymph node enlargement. The antibiotics were stopped and she was started on oral antihistamines. No steroids or antivirals were initiated.

Laboratory results showed a white blood cell count of $8.4 \times 10^9/L$ (normal range, $4.0-10.6 \times 10^9/L$), with 7.6% eosinophils (normal range, 0%-5.0%), and a hemoglobin of 9.1 g/dL (normal range, 14.5-17.7 g/dL). Platelets count, kidney function tests and liver func-

tion tests were within normal limits. A swab from the base of one of the vesicles was sent for human herpes virus (HSV) and varicella zoster virus (VZV) PCR testing, which came back negative. A skin punch biopsy showed subepidermal infiltration with neutrophils and eosinophils. Direct immunofluorescence (DIF) study revealed linear, widespread deposits of IgA (Figure 3) along the basement membrane zone (BMZ) with no traces of IgG or C3 deposits. Based on histopathology, immunofluorescence testing and the negative viral studies, a diagnosis of VILABD was made.

DISCUSSION

Up to two-thirds of LABD cases are drug-induced, and about half of drug-induced LABD are caused by vancomycin.^{3,4} Other disease processes that might provoke LABD include infections and malignancies.⁵ Drugs reported to induce LABD include amiodarone, ampicillin, captopril, cefamandole, cyclosporine, diclofenac, interferon- γ , interleukin 2, lithium, penicillin G, phenytoin, piroxicam, somatostatin, mefenamic acid and trimethoprim/sulfamethoxazole.^{6,7} In VILABD, lesions usually develop 1 to 15 days after starting vancomycin with a median of 9 days.⁸ The disease may appear as long as 2 weeks after the drug is discontinued.⁹

The pathophysiology of LABD entails autoantibody interaction with numerous basement membrane antigens.¹⁰ Drugs may cause LABD by cross-reaction with target epitopes, by altering the conformation of epitopes or by exposing previously sequestered antigens to the immune system. The diagnosis of VILABD is suspected on clinical grounds and is confirmed by histopathological examination and DIF testing of skin biopsy showing linear IgA deposition in the BMZ. Although the clinical presentation of VILABD is highly variable, most cases present with vesiculobullous mucocutaneous eruptions on an erythematous base, with characteristic annular arrangement of bullae, popularly known as "clusters of jewels" (Figure 1).¹¹ Mucus membrane involvement occurs in up to 40% of cases and ranges in severity from mild oral ulcers to severe pharyngeal and conjunctival disease.¹²

The clinical differential diagnosis includes bullous pemphigoid, Stevens-Johnson syndrome, erythema multiforme, viral infection, toxic epidermal necrolysis and dermatitis herpetiformis.¹³ DIF testing that reveals linear deposits of IgA distinguishes between drug-induced LABD and other bullous skin diseases where predominantly IgG deposits are seen in the BMZ.¹² IgA-mediated epidermolysis bullosa acquisita is a subtype of LABD.¹⁰ In this entity the IgA autoantibodies are specifically directed against type VII collagen in the

BMZ.¹⁰ Irrespective of different terminology, both have a similar clinical presentation and prognosis.¹⁰

Treatment of drug-induced LABD includes discontinuing the offending agent and supportive measures. Reports have shown that VILABD has spontaneous remission after stopping vancomycin.¹⁴ Once discontinued, it takes a median of 2 days before the development of new lesions stop and 14 days until resolution.⁷ In VILABD, corticosteroids and dapsone do not affect prognosis and are usually not indicated.¹¹ Challenging a patient with vancomycin shortly after developing VILABD results in the rapid relapse of skin lesions.⁹ However, a successful graded challenge with the antibiotic years following the initial reaction has been reported.¹⁵

Although vancomycin is a commonly prescribed antibiotic, linear IgA bullous dermatosis is an under-recognized potential side effect. The onset of vesicles and bullae after the administration of this antibiotic should raise suspicion of this blistering skin disease. Early diagnosis through skin biopsy and DIF testing followed by the prompt discontinuation of vancomycin could shorten the pain and suffering of the affected patient.

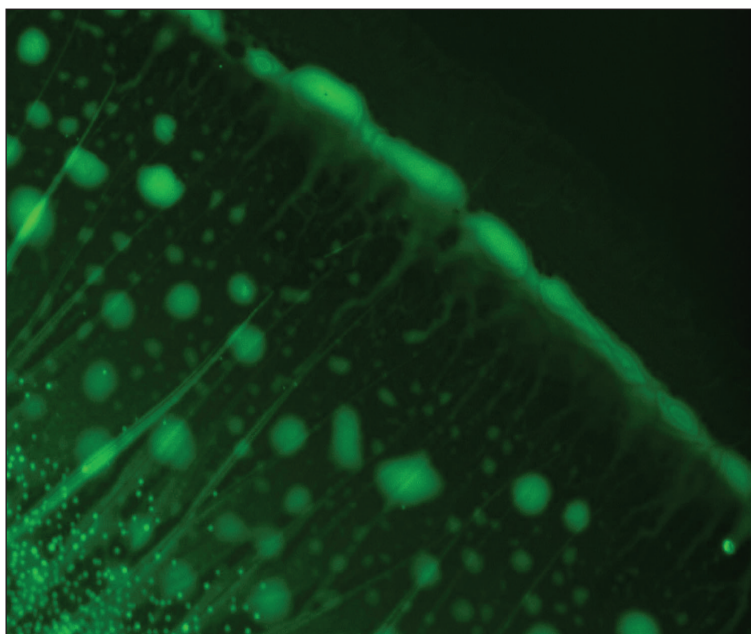


Figure 3. Direct immunofluorescence of perilesional skin showing linear IgA deposits on the dermal side of the basement membrane zone.

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