
Case report

A successful challenge in a patient with vancomycin-induced linear IgA dermatosis

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Background: Linear IgA bullous dermatosis (LABD), a subepidermal, blistering skin disease, is generally believed to be idiopathic. It has been reported in association with multiple medications, including vancomycin. In each case, complete clearance of the skin lesions occurred with discontinued use of the drug. A subsequent rechallenge reproduced the eruption within hours to days.

Objective: To present a patient with vancomycin-associated LABD who underwent a successful challenge with the antibiotic 4 years after the initial reaction.

Methods: The patient developed blistering lesions over her trunk and extremities 10 days after the initiation of vancomycin for sepsis. A biopsy specimen of a skin eruption was consistent with linear IgA dermatosis. Following discontinued use of the drug, her skin lesions resolved. Four years later, she required vancomycin for osteomyelitis.

Results: The patient underwent a vancomycin-graded challenge of 5 doses over 5 days. On day 1, she received 10 mg, and this was increased in a semilog fashion to 1,000 mg on day 5. She had no recurrence of her skin lesions.

Conclusions: This is the first case, to our knowledge, to show a successful rechallenge in a patient with drug-associated LABD. Since the patient did not have a reaction to the challenge, it is possible that the IgA antibodies responsible for drug-induced LABD are only present transiently and diminish over time.

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INTRODUCTION

Linear IgA bullous dermatosis (LABD) is a subepidermal, bullous, blistering disease characterized by linear deposition of IgA at the dermal-epidermal junction. In the idiopathic form, IgA autoantibodies are directed against antigens that have molecular weights of 120 and 97 kDa. These appear to be fragments of type XVII collagen.¹ The pathogenesis, however, is not clearly defined.

Other than the idiopathic form, LABD has also been reported in association with exposure to drugs, including vancomycin, lithium, and diclofenac.² In previously reported cases of drug-induced LABD, complete clearance of skin lesions occurred with discontinued use of the drug.^{2–12} In one case, rechallenge with the implicated drug reproduced the skin eruption within 36 hours.³ We present a patient with vancomycin-induced LABD who subsequently tolerated a graded challenge with the antibiotic 4 years following the initial reaction.

CASE REPORT

Eight days after a total vaginal hysterectomy, a 48-year-old woman presented with abdominal pain that was later diagnosed as a pelvic abscess. Following a sigmoid colectomy

and abscess drainage, the patient remained febrile. Blood cultures were positive for *Staphylococcus aureus*. She began taking vancomycin and eventually the bacteremia cleared. Approximately 10 days following the initiation of vancomycin, the patient developed multiple blisterlike lesions over her trunk and extremities. The only new medications in her regimen included furosemide and vancomycin. Despite discontinued use of the furosemide, the blistering lesions progressed. A biopsy specimen of involved skin demonstrated bullous pemphigoid (Fig 1), and direct immunofluorescence revealed linear IgA deposits at the dermal-epidermal junction. Vancomycin was believed to be the causative agent, and its use was stopped. Subsequently, no new lesions were noted, and after a few days the patient's bullous skin eruptions resolved. She was diagnosed as having vancomycin-induced LABD and was told to avoid this antibiotic in the future.

The patient was again admitted 4 years later with fevers and back pain. She was subsequently diagnosed as having oxacillin-resistant *S aureus* sepsis secondary to T12 and L1 spine osteomyelitis. The bacteremia was successfully cleared with linezolid therapy, but the osteomyelitis continued to progress. An infectious disease consultant recommended vancomycin for effective clearing of the infection. After obtaining informed consent, the patient began a 5-day graded challenge of vancomycin as follows: day 1, 10 mg; day 2, 30 mg; day 3, 100 mg; day 4, 300 mg; and day 5, 1,000 mg. She

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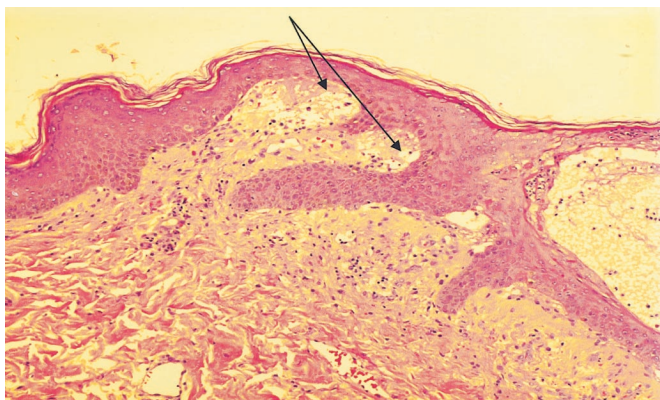


Figure 1. Involved skin from the patient shows areas of subepidermal bullous changes (arrows) at the dermal-epidermal junction. There is also an inflammatory cell infiltrate (hematoxylin-eosin, original magnification $\times 10$).

tolerated the challenge and became afebrile. Ten days later she was transferred to a long-term care facility without a recurrence of the LABD lesions.

DISCUSSION

LABD is an autoimmune skin disease characterized by IgA deposits at the cutaneous basement membrane zone. Clinically, the lesions may mimic dermatitis herpetiformis, erythema multiforme, and bullous pemphigoid. A biopsy specimen is diagnostic, because direct immunofluorescence of perilesional tissue reveals linear deposition of IgA at the dermal-epidermal junction. The autoantibodies are directed against a 120-kDa protein secreted from keratinocytes and a 97-kDa protein from the epidermis and dermis.¹

LABD has also been associated with exposure to many medications, such as vancomycin, captopril, diclofenac, and phenytoin.² A thorough patient history, including the chronological order of any drug initiated, can be beneficial in identifying the culprit. Features of previous reports of vancomycin-induced LABD suggest a relatively constant delay of 7 to 15 days between drug exposure and the formation of skin lesions.¹ In one case, a single full dose of vancomycin was readministered 11 days after such therapy had been discontinued. In 36 hours, the patient developed a recurrence of the generalized bullous eruption.³ This suggests that challenge shortly after an initial reaction results in rapid development of the skin lesions.

Our case is the first, to our knowledge, to show a successful challenge in a patient with vancomycin-induced LABD. We performed a 5-day, graded challenge of vancomycin starting with 10 mg and increasing in a semilog manner to 1,000 mg. By performing the graded challenge, we were able to evaluate for a recurrence of the skin eruption before giving the full dose. Since the previous report of a challenge with vancomycin described the development of LABD lesions within 36 hours, it was thought that any reaction to the antibiotic would occur during our build-up phase. Since 10%

to 50% of lesions in the autoimmune form resolve spontaneously, it is possible that this is what the patient had.² However, the timing of her symptom onset and resolution in relation to vancomycin administration is consistent with the drug-induced form. It is not clear why this patient did not react on re-exposure; however, a better understanding of the mechanism of the drug-induced form of this disease may provide clues. Although the pathogenesis is not clear, it has been speculated that this form of LABD, as in the idiopathic form, is autoantibody driven. It is believed that the IgA antibody is specific for an antigenic site on the implicated drug, which is similar to one in the basement membrane and thus cross-reacts with it.¹³

A similar mechanism has been postulated for drug-induced bullous pemphigoid-like lesions with linear deposits of IgG at the dermal-epidermal junction. Kashihara et al¹⁴ suggested that the implicated medication changes the antigen structure or exposes a previously hidden antigenic site. Clinically, LABD resembles bullous pemphigoid in appearance and the pathogenesis of the 2 drug-induced forms may be similar, only differing in the immunoglobulin subclass deposited at the basement membrane zone. If it is indeed the case that the autoantibody is specific for an antigen on the medication but cross-reacts with a similar one in the dermal-epidermal junction, then it is possible that this specific IgA is present only transiently. This theory would explain why early re-exposure to vancomycin results in a recurrence of the bullous eruption, whereas the same is not true 4 years after the initial reaction as in our case. Our case suggests that the specific IgA antibody in drug-induced LABD may diminish over time and thus allow for successful readministration of the implicated drug.

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