A Morbilliform Variant of Vancomycin-Induced Linear IgA Bullous Dermatosis

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Background: Linear IgA bullous dermatosis is an autoimmune blistering disease characterized clinically by the presence of small tense blisters and immunologically by the presence of IgA at the dermal-epidermal junction. Idiopathic, systemic disease–related, and drug-related versions of this disorder have been described, with the latter most commonly associated with vancomycin.

Observations: We describe 2 patients with vancomycin-associated linear IgA bullous dermatosis who presented with a morbilliform eruption that lacked blistering. Lesional and perilesional tissue from each patient was examined by light microscopy and direct immunofluorescence. Histopathologic examination findings revealed vacuolar interface dermatitis with a mixed inflammatory infiltrate and occasional eosinophils, consistent with a drug eruption. Direct immunofluorescence revealed IgA deposited in a linear pattern at the dermoeipidermal junction. In both patients, the results of indirect immunofluorescence using both IgG and IgA were negative.

Conclusions: These cases highlight the existence of a new form of linear IgA bullous dermatosis presenting as a morbilliform drug eruption. Both patients were following extensive medication regimens, including use of multiple antibiotics. The diagnosis of linear IgA bullous dermatosis allowed us to target vancomycin as the likely allergen and begin treatment. In light of these findings, direct immunofluorescence may be a useful diagnostic adjunct in determining the cause of drug eruptions.

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Linear IgA Bullous Dermatosis (LABD) is classically described as an acquired autoimmune blistering eruption that may be idiopathic, related to systemic disease, or associated with exposure to various medications. The usual clinical presentation is tense vesicles and bullae, erythematous patches, and occasional erosions. The eruption occurs predominantly on the patient's trunk and extremities, but it may involve the palms, soles, and mucous membranes.1,6 Drug-induced LABD is thought to be a distinct clinical and histopathologic entity because the course of disease, response to treatment, and histopathologic findings differ from those of idiopathic LABD.7 This entity has been associated most frequently with vancomycin, although a list of frequently inciting medications also includes penicillins, cephalosporins, and captopril.1 The lesions of drug-induced LABD typically appear within 7 to 14 days of starting use of the offending agent and resolve within 3 weeks after the drug therapy is discontinued.2,7,8 Although the lesions typically resemble those of idiopathic LABD, drug-induced LABD may resemble erythema multiforme10 or toxic epidermal necrolysis.11 The diagnosis of drug-induced LABD is generally confirmed by finding linear deposition of IgA at the dermoeipidermal junction (DEJ) on direct immunofluorescence.1 Weak deposition of C3 and IgG at the DEJ has been observed less frequently.1 Histopathologic findings are frequently characterized by subepidermal blisters and basal cell vacuolization with a predominantly neutrophilic infiltrate.1,3 Corticosteroids and dapsone have been used as adjunctive treatments while use of the offending medication is discontinued, but they are not thought to hasten resolution.1,3 Rechallenge typically results in return of the eruption.1

With the approval of the Mayo Clinic institutional review board, we describe 2 patients with complicated conditions who were taking numerous medications and developed a morbilliform eruption typical of a drug-induced rash. The offending medication was identified by the pattern noted on immunofluorescence as vancomycin, and the diagnosis was vancomycin-induced LABD.

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A 70-year-old man with a recent history of laparoscopic bilio-pancreatic division with duodenal switch for morbid obesity was admitted with postoperative perihepatic abscess and sepsis. He was initially treated with a several-day course of vancomycin and 3 drains. Cultures yielded methicillin-resistant *Staphylococcus aureus* and enterococcal species. His antibiotics were switched to levofloxacin and metronidazole. A dermatology consultation was requested after numerous erythematous macules developed on his trunk and upper extremities. A biopsy specimen from his right upper arm revealed superficial lymphocytic perivascular inflammation consistent with a drug eruption. Because of the temporal relation of the erythematous macules and the initiation of levofloxacin and metronidazole therapy, the antibiotics were changed to vancomycin and etrapenem. Vancomycin was not suspected as the cause of the eruption because its use had been discontinued previously. The eruption improved during the next 2 days with the use of trimcinolone acetoneide cream. However, at discharge 2 weeks later, according to the nursing notes, a skin eruption was again developing in the patient; this eruption markedly worsened after discharge to a skilled nursing facility.

On readmission 5 days later because of hypotensive shock and severe neutropenia, an additional computed tomographic scan showed no evidence of active abcess. The patient was afebrile, and his white blood cell count was low. His skin eruption consisted of numerous erythematous macules and occasional papules coalescing into large patches over his trunk and extremities, sparing the mucous membranes (**Figure 1A** and B). Nonpalpable purpura was also present on his lower legs, and the primary clinical service was concerned about vasculitis. No blisters were evident anywhere on his skin. Treatment with meropenem, linezolid, and caspofungin acetate was initiated on readmission. Clinically, the dermatology service favored the diagnosis of a morbilliform drug eruption caused by etrapenem or vancomycin. We believed that the purpura of the lower extremities was purpura simplex, but we needed to rule out leukocytoclastic vasculitis. Additional biopsy specimens were obtained, including those from direct immunofluorescence studies from the right thigh and right abdomen. Use of all antibiotics was discontinued for 1 day, pending results.

Biopsy specimens from the right side of the abdomen (**Figure 1C**) and the right thigh revealed lichenoid interface dermatitis. Direct immunofluorescence revealed continuous strong linear deposition of IgA along the DEJ (**Figure 1D**). The results of indirect immunofluorescence were negative for IgG or IgA at the DEJ, and the results of enzyme-linked immunosorbent assay testing for antibodies against bullous pemphigoid antigens 1 and 2 were negative.

With the diagnosis of LABD, the probability emerged that vancomycin was the offending agent all along. The patient then started taking meropenem and linezolid again.

Because of the patient’s persistent skin eruption, neutropenia, and hypotension, the collaborative decision was made to start the use of dapsone, 50 mg/d, and methylprednisolone sodium succinate, initially at 125 mg/d. Both his skin eruption and systemic symptoms improved during the next 3 days. Use of dapsone was discontinued, use of methylprednisolone was tapered, and the patient was discharged from the intensive care unit. A specimen from a subsequent biopsy performed as part of a hospital admission 1 month later failed to show any evidence of immunoglobulin deposition at the DEJ.

**CASE 2**

A 61-year-old woman with a history of systemic lupus erythematosus, subsequent kidney disease, and living related kidney transplant in 1993 was treated with sigmoidectomy and diverting loop ileostomy for diverticulitis. Postoperative complications included acute renal failure and abdominal wound infection, for which the patient received meropenem and vancomycin. The patient was discharged to a skilled nursing facility to continue receiving intravenous antibiotics and was later readmitted with worsening infection. She had received 13 days of vancomycin therapy before readmission, when she presented with blotchy erythema on her chest, back, and buttocks (**Figure 2A** and B). Meropenem therapy was discontinued, and she started taking levofloxacin and metronidazole. The erythematous eruption continued to spread, and a dermatology consultation was requested, at which time diffuse morbilliform erythema was almost entirely confluent on her back and chest and involved more than 50% of the skin of her extremities. She had no blisters, targetoid lesions, or papules, and the palms, soles, and mucous membranes were not involved.

A biopsy specimen obtained from involved skin of the left side of her back revealed vacuolar interface dermatitis and mixed dermal inflammation with occasional eosinophils (**Figure 2C**). Direct immunofluorescence revealed continuous strong linear IgA deposition along the DEJ without evidence of deposition of other immunoglobulins (**Figure 2D**). The results of indirect immunofluorescence were negative for IgG or IgA at the DEJ, and the results of an enzyme-linked immunosorbent assay for antibodies against bullous pemphigoid antigens 1 and 2 were negative.

A diagnosis of LABD was made, and vancomycin therapy was discontinued. The patient was treated only with topical corticosteroids, and the erythema markedly improved by discharge 6 days later.

**COMMENT**

Drug-induced LABD is a diagnosis usually entertained when the typical skin lesions of vesicles and blisters are present. Alternative cutaneous patterns that have been recognized as drug-induced LABD include patterns suggestive of erythema multiforme and toxic epidermal necrolysis. To our knowledge, only 1 other case report has been published of drug-induced LABD occurring without evidence of blistering. This case involved...
erythematous papules in a patient with somatostatin-induced LABD.

The underlying pathogenesis of drug-induced LABD has not yet been delineated. However, several possible contributing factors have been suggested. One factor is drug-induced activation of T cells. Yawalkar et al.\textsuperscript{12} found an increased number of CD8\textsuperscript{T} T cells in the peripheral blood and increased levels of interleukin 5 in the lesional skin of a patient with LABD. Interleukin 5, along with other cytokines, has been shown to influence IgA expression.\textsuperscript{2,13} T-cell–derived cytokines may also contribute to tissue damage and allow for exposure of previously protected antigens followed by initiation of immune response and blister formation.

The 2 patients described herein highlight the need to consider a diagnosis of drug-induced LABD in patients displaying only morbilliform erythema. Both patients fit the typical LABD patterns of cutaneous eruption within 7 to 14 days of exposure to the offending drug and improvement after withdrawal of use of the drug. The condition of patient 2 improved with only topical corticosteroids, whereas patient 1 was treated with systemic immunosuppressive agents after vancomycin therapy was withdrawn. Both patients also had strong linear IgA deposition at the DEJ on direct immunofluorescence. Neither patient had circulating antibodies on indirect immunofluorescence; however, in contrast to idopathic LABD, patients with drug-induced LABD can frequently lack circulating antibodies on indirect immunofluorescence.\textsuperscript{3,7,9} When circulating antibodies are present, they have been shown to clear after therapy with the offending agent is withdrawn and the eruption

Figure 1. Patient 1: blanchable erythema on the chest (A), morbilliform erythema on the anterior left lower extremity (B), lichenoid infiltrate and mild perivascular inflammation (hematoxylin-eosin, original magnification $\times 20$) (C), and linear deposition of IgA at the dermoepidermal junction by direct immunofluorescence (original magnification $\times 40$) (D).
fades. Similarly, sequential biopsy specimens have been reported to show resolution of IgA deposits after withdrawal of the drug therapy despite lack of adjunctive therapy. Patient 1 received adjuvant treatment, and a second biopsy specimen obtained during a later hospitalization failed to show linear IgA deposition at the DEJ.

The lack of blistering in these 2 patients is unexplained. In patient 2, a chronic immunosuppressive state may have prevented the degree of antibody production necessary to induce a blistering response. Another consideration is that the target antigen that caused the antibody production in these 2 patients may not have led to blister formation. Immunologic target antigens in LABD are thought to be heterogeneous and include 180-, 230-, and 285-kDa proteins that correspond to bullous pemphigoid antigen 2, bullous pemphigoid antigen 1, and 285-kDa linear IgA disease antigen, respectively, the same antigens previously implicated in idiopathic LABD. Another question is whether the specific lots of vancomycin used to treat these patients may have influenced their unique eruptions. In previous studies, the development of vancomycin-induced LABD did not depend on lot number or company of origin. We have identified 4 additional patients with morbilliform drug eruptions who were taking vancomycin in addition to other antibiotics at our institution during the past 9 months and who did not have linear deposition of IgA on direct immunofluorescence testing.

The findings of linear IgA deposition at the DEJ in our patients allowed us to target the likely offending agent, vancomycin, and discontinue its use quickly. This tactic proved useful because both patients were ill and had been taking multiple other antibiotics when their skin eruptions occurred. In the case of patient 1, meropenem had already been blamed for his eruption and its use discontinued, with continued worsening of the skin eruption before the biopsies. Direct immunofluorescence and identification of a nonblistering form of vancomycin-induced LABD allowed us to treat these patients appropriately and should be considered when evaluating a drug eruption in patients receiving multiple antibiotics.

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