A toxic epidermal necrolysis-like presentation of linear IgA bullous dermatosis treated with dapsone

Julie K Nguyen¹, Misha V Koshelev¹ MD PhD, Bartley J Gill¹ MD PhD, Jessica Boulavsky¹ MD, Abdul Hafeez Diwan² MD, Harry Dao¹ Jr MD

Affiliations: ¹Department of Dermatology, Baylor College of Medicine, Houston, Texas, ²Department of Pathology & Immunology, Baylor College of Medicine, Houston, Texas

Corresponding Author: Harry Dao Jr., M.D., Assistant Professor of Dermatology, Baylor College of Medicine, Email: hdao@bcm.edu

Abstract

Linear IgA bullous dermatosis is a rare autoimmune vesiculobullous disease characterized by linear deposition of IgA along the basement membrane zone. It is classically idiopathic, but may also arise secondary to drug exposure. A heterogeneous spectrum of clinical features has been described, including a rare, morbid variant mimicking toxic epidermal necrolysis. Herein, we present a case of vancomycin-induced linear IgA bullous dermatosis that manifested clinically as toxic epidermal necrolysis and resolved with dapsone therapy.

Keywords: IgA bullous dermatosis; drug-induced linear IgA; toxic epidermal necrolysis; vancomycin; dapsone

Introduction

Linear IgA bullous dermatosis (LABD) is an autoimmune blistering disease characterized by a subepidermal vesiculobullous eruption with variable mucous membrane involvement. The lesions can resemble those of other blistering and inflammatory skin disorders, posing a diagnostic challenge for clinicians. Direct immunofluorescence (DIF) microscopy reveals the hallmark linear IgA deposition along the basement membrane zone (BMZ), [1]. Most cases of LABD arise spontaneously, but associations with medications, infections, lymphoproliferative disorders, and internal malignancies have been reported [2, 3]. We report a case of vancomycin-induced LABD that presented clinically as a life-threatening cutaneous drug reaction, toxic epidermal necrolysis (TEN).

Case Synopsis

A 56-year-old man with a history of alcohol abuse and recurrent pancreatitis was admitted for a pancreatic pseudocyst. His hospital course was complicated by septic shock and respiratory failure necessitating intubation and transfer to the intensive care unit (ICU). Medications started on admission were vancomycin, meropenem, and micafungin. Vancomycin and meropenem were discontinued on day 6 of administration because of the development of a blistering skin rash on the anterior trunk. Over the next 24 hours, the patient developed large areas of erythema and scattered bullae on the posterior trunk, prompting a dermatology consult for evaluation of possible TEN.

Physical examination was notable for erythematous papules over the anterior trunk coalescing into a confluent erythematous patch over the upper chest and neck. More remarkable was diffuse erythema with multiple tense bullae and large areas of skin detachment over the posterior trunk and buttocks (Figure 1a). The Nikolsky sign was positive. Tense vesicles and bullae were noted on the anterior neck, antecubital fossae, and axillae. There was no conjunctival, oral, or anogenital mucous membrane involvement. The face and acral skin were spared. Over the following days, the patient developed more extensive erosions on the back. The rash spread caudally to the lower abdomen, flanks, thighs, and popliteal fossae, affecting 50% of the body surface area (BSA). New bullae were noted on the bilateral flanks and inguinal folds (Figure 1b).
Based on the clinical history and appearance, we favored LABD and considered TEN and bullous pemphigoid in the differential diagnosis. A skin biopsy sample sent for frozen section was negative for epidermal necrosis. Histological examination revealed subepidermal vesicles with neutrophils and focal neutrophilic papillary microabscesses (Figure 2a). Scattered eosinophils and lymphocytes were also evident. DIF of perilesional skin demonstrated linear IgA deposition at the dermal-epidermal junction (Figure 2b). Staining for IgG, IgM, C3, albumin, and fibrinogen was negative. Testing for circulating antibodies by indirect immunofluorescence (IIF) was not performed.

Based on the DIF results and close temporal association with drug administration, we diagnosed this case as vancomycin-induced LABD. Given the progression of the eruption following vancomycin withdrawal, oral dapsone (100 mg daily) was initiated while awaiting results for a quantitative glucose-6-phosphate dehydrogenase (G6PD) assay, which was normal (10.9 U/g Hb). It was felt that the benefits of timely systemic therapy outweighed the possible risk of dapsone-induced hemolysis, particularly as the patient's ICU setting easily facilitated frequent laboratory monitoring with twice daily complete
blood counts. No new blisters developed and clinical improvement was noted within 72 hours on dapsone (Figure 3a). Lesions resolved completely without scarring by 3 weeks and dapsone was tapered without event (Figure 3b).

Case Discussion
LABD is an autoimmune subepidermal vesiculobullous disease that has a wide spectrum of clinical manifestations. In adults, LABD manifests as tense vesicles and bullae that coalesce to form annular or polycyclic plaques on normal skin, often with an erythematous base [2]. It can resemble bullous pemphigoid, dermatitis herpetiformis, cicatricial pemphigoid, pemphigus vulgaris, lichen planus, or TEN [3–5]. Lesions preferentially affect the trunk and extensor surfaces, but can localize to any area of the body. Oral cavity and ocular involvement may also be noted.

Histologically, LABD is characterized by subepidermal blistering with papillary microabscesses and a predominantly neutrophilic dermal infiltrate [3, 6]. Because it is difficult to distinguish LABD from other vesiculobullous diseases by clinical and histologic findings alone, immunopathological testing is essential for definitive diagnosis. The gold standard for LABD diagnosis is DIF of perilesional skin, which in all patients reveals linear IgA deposits along the BMZ. The concomitant deposition of other immunoreactants in the same pattern occurs less frequently [7]. Immunoelectron microscopy studies have discerned various ultrastructural patterns of IgA deposition, demonstrating the lamina lucida as the major site [6, 8, 9]. Circulating anti-BMZ IgA autoantibodies may be detected by IIF, but there is variable positivity in the sera of LABD patients [2, 3].

The pathophysiology of LABD involves autoantibodies of the IgA1 subclass directed against various target antigens in the BMZ [2,7, 10]. Although the fundamental role of IgA in LABD pathogenesis is well established, the exact etiology of the autoimmune response is incompletely understood. Both humoral and cellular immune responses mediate tissue injury, contributing to dermal-epidermal separation and blister formation. A passive transfer mouse model showed that IgA is responsible for the inflammatory infiltrate beneath the BMZ, likely by promoting

Figure 3. A) Erosions with a thin serosanguineous crust over previous areas of blistering. B) Faint pink patches in previous areas of desquamation on the posterior trunk.
The major target antigens of LABD include proteins of 97 kDa (LABD97) and 120-kDa (LAD-1), although antibodies directed against many other BMZ components have been identified [2, 6, 9, 12]. Both LABD97 and LAD-1 are proteolytic products of the extracellular domain of BP180 (BPAg2/collagen XVII), the bullous pemphigoid antigen [13, 14]. A 285-kDa protein (LAD285) has been identified as a major dermal antigen, but its pathogenic role has yet to be elucidated [2, 15]. Immunoblot analyses in drug-induced LABD have detected antibodies reacting to BP180, LAD285, BP230 (BPAg1), collagen VII, and laminin-332 [8, 12, 16, 17]. The multiplicity of target antigens implicated in LABD may be a result of intermolecular epitope spreading and may explain the clinical heterogeneity of the disease [12, 18, 19].

Most cases of LABD are idiopathic, but some are associated with recent drug administration. The pathophysiologic mechanism of drug-induced LABD remains unknown. The most frequently implicated agent in drug-induced LABD is vancomycin [7, 20]. Less common culprit drugs include beta-lactam antibiotics, captopril, phenytoin, nonsteroidal anti-inflammatory drugs, and amiodarone [2, 21].

The onset of blisters in drug-induced LABD typically occurs within 7-15 days of starting the offending medication, but shorter latency periods have been observed [4,21]. Withdrawal of the causative drug generally results in spontaneous regression of lesions within 2-7 weeks, as well as clearance of IgA deposits from the BMZ [2, 22]. Although most cases of vancomycin-induced LABD arise during vancomycin therapy, the eruption may appear as late as 2 weeks after drug cessation [21].

Historically, idiopathic and drug-induced LABD were understood to be clinically and histologically indistinguishable. However, recent efforts to compare the two forms have identified some significant differences. One study found that a positive Nikolsky sign and large erosions were more frequent in drug-induced than idiopathic LABD, with no differences in the morphology of lesions, location, mucosal involvement, or histological features [23]. The authors attributed these findings to a variant of drug-induced LABD that is more severe, with lesions that mimic TEN and can pose life-threatening risk of infection.

We report a patient who, following vancomycin administration, developed large areas of skin detachment with tense bullae on a background of erythema. Despite the clinical resemblance to TEN, epidermal necrosis was absent on frozen section. Histologic identification of a subepidermal blister with neutrophils combined with DIF visualization of linear IgA deposition at the BMZ yielded the diagnosis of LABD. This case of drug-induced LABD presenting as a TEN-like eruption highlights the importance of immunopathology in the workup of a fulminant blistering rash.

A review of the literature revealed 19 previously reported cases of drug-induced LABD mimicking TEN, all of which were diagnosed by DIF [4, 5, 8, 23–34]. Including our patient, 15 cases are summarized in Table 1. The 5 patients identified in the retrospective cohort study by Chanal et al. were not included since they were not described in detail [23]. Notably, the only mortality in their series of 28 LABD cases was a patient with drug-induced LABD and large TEN-like erosions who died of sepsis.

The most commonly implicated drug in cases of drug-induced LABD manifesting as TEN was vancomycin (11/15), followed by phenytoin (4/15). In our patient, the chronology of vancomycin initiation and its history as a classic trigger of drug-induced LABD strongly implicated it as the etiology of our patient’s eruption. To our knowledge, meropenem has never been reported in association with LABD. In cases of TEN-like LABD, males and females have been affected equally and the average patient age was 59 (range 41 to 91). Where reported, mucous membrane involvement was present in 7 of 14 cases, the Nikolsky sign was positive in 7 of 8 cases, and BSA involvement ranged from 15-90%. Among survivors, complete resolution or healing of skin lesions was noted in 2-3 weeks following discontinuation of the implicated medications. However, six patients died of their comorbidities (40% mortality rate), four of whom died before clinical resolution of the lesions was achieved. Interestingly, the 3 cases with greater than 75% BSA involvement were fatal.
Table 1. Reported cases of drug-induced LABD presenting as TEN.

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Comorbidities</th>
<th>Implicated medication(s)</th>
<th>Latent period (days)</th>
<th>Morphology &amp; distribution of lesions</th>
<th>MM, Nickolsky, BSA affected</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>71/female</td>
<td>Low back pain</td>
<td>Diclofenac</td>
<td>29</td>
<td>Multiple clear vesicles and bullae on erythematous skin; widespread bullae on limbs, palms, soles, nipples, buccal mucosa, larynx</td>
<td>Positive NR NR</td>
<td>DC diclofenac</td>
<td>Resolved in 2 weeks</td>
<td>1997</td>
<td>Paul et al. [8]</td>
</tr>
<tr>
<td>87/female</td>
<td>CVA, UTI</td>
<td>Vancomycin, phenytoin</td>
<td>11</td>
<td>Tense bullae and denudation of skin on back and posterior legs; erythema-based vesicobullae on back, perineum, extremities; no palmoplantar lesions</td>
<td>Positive NR NR</td>
<td>DC vancomycin and phenytoin; topical therapy</td>
<td>Resolved in 2 weeks</td>
<td>2000</td>
<td>Mollf et al. [26]</td>
</tr>
<tr>
<td>77/male</td>
<td>CVA, urosepsis</td>
<td>Vancomycin, phenytoin, enalapril</td>
<td>13</td>
<td>Generalized erythema of back, buttocks, and posterior thighs with erosions and small vesicles; exfoliation of back; bullae on scrotum; targetoid lesions on palms and soles</td>
<td>Negative 15%</td>
<td>DC vancomycin and phenytoin</td>
<td>Died of intracranial hemorrhage</td>
<td>2001</td>
<td>Hughes and Callen [25]</td>
</tr>
<tr>
<td>74/male</td>
<td>CVA, pneumonia, sepsis</td>
<td>Vancomycin, piperacillin, tazobactam, ciprofloxacin</td>
<td>4</td>
<td>Erythematous, macular eruption started on abdomen; tense bullae on abdomen and arms</td>
<td>Positive NR 90%</td>
<td>DC antibiotics</td>
<td>Died of septic shock</td>
<td>2003</td>
<td>Dellaralle et al. [5]</td>
</tr>
<tr>
<td>60/female</td>
<td>Glossoptasia multififorme</td>
<td>Phenytoin</td>
<td>7</td>
<td>Widespread areas of patchy erythema with large, flaccid, confluent bullae affecting the trunk, extremities, palms, soles</td>
<td>Negative Positive 40%</td>
<td>DC phenytoin; supportive care</td>
<td>Healed over 2 months</td>
<td>2003</td>
<td>Tran et al. [27]</td>
</tr>
<tr>
<td>77/male</td>
<td>CABG, respiratory failure, acute renal failure, atrial fibrillation, sepsis</td>
<td>Vancomycin</td>
<td>6</td>
<td>Tense bullae on erythematous base in groin and axillae; hemorrhagic bullae on trunk, thighs, and extremities; diffuse desquamation of trunk, groin, buttocks, upper arms</td>
<td>Negative Unclear 46%</td>
<td>DC vancomycin, wound care; oral dapsone 25 mg twice daily</td>
<td>Healed over 3 weeks; died of cardiac complications</td>
<td>2004</td>
<td>Waldman et al. [4]</td>
</tr>
<tr>
<td>67/female</td>
<td>Pneumonia, rheumatoid arthritis (on prednisolone)</td>
<td>Vancomycin</td>
<td>13</td>
<td>Tense bullae with surrounding erythema on arms, hands, breasts, back, lower legs, buttocks, perineum; annular maculo-papules and desquamation on trunk</td>
<td>Negative Positive 40%</td>
<td>Intravenous methylprednisolone</td>
<td>Resolved in 2 weeks</td>
<td>2006</td>
<td>Coelho et al. [26]</td>
</tr>
<tr>
<td>54/male</td>
<td>Influenza</td>
<td>Azithromycin, zanamivir, rimantadine</td>
<td>Unclear</td>
<td>Generalized erythema; widespread bullae on trunk, extremities, scrotum; erosions in intertriginous areas</td>
<td>Positive Normal 40%</td>
<td>DC azithromycin and antivirals; prednisone; pentoxifylline</td>
<td>Healed on 16th day</td>
<td>2007</td>
<td>Cummings et al. [26]</td>
</tr>
<tr>
<td>57/female</td>
<td>Perforated sigmoid colon, lung and splenic abscesses, sepsis, CVA</td>
<td>Vancomycin, phenytoin</td>
<td>Unclear</td>
<td>Large, flaccid, confluent bullae with background erythema and denudation; palms and soles affected</td>
<td>Negative Positive 75%</td>
<td>DC phenytoin; antibiotics; supportive care; IVIG</td>
<td>Improved within 48 hours; died of CVA</td>
<td>2009</td>
<td>Khan et al. [29]</td>
</tr>
<tr>
<td>49/male</td>
<td>CVA, pneumonia</td>
<td>Vancomycin</td>
<td>Unclear</td>
<td>Erythroderma; flaccid and tense bullae on upper extremities, flanks, thighs; large erosion on arm; bullae and wet cigarette paper-like epidermis</td>
<td>Negative Normal 20%</td>
<td>DC vancomycin, methylprednisolone</td>
<td>Resolved in 3 weeks</td>
<td>2010</td>
<td>Trufant et al. [30]</td>
</tr>
<tr>
<td>91/female</td>
<td>CAD, colon adenocarcinoma</td>
<td>Verapamil</td>
<td>13</td>
<td>Maculopapular lesions with rosettes on trunk; large sheets of superficial peeling of back</td>
<td>Positive Normal 20%</td>
<td>DC verapamil; clofertazol; cyclosporine</td>
<td>Resolved in 12 days</td>
<td>2011</td>
<td>Schroeder et al. [31]</td>
</tr>
<tr>
<td>41/female</td>
<td>Bacterial meningitis</td>
<td>Vancomycin, ceftriaxone</td>
<td>10</td>
<td>Multiple tense bullae on erythematous base on trunk and limbs; palms and soles spared</td>
<td>NR Positive 50%</td>
<td>DC vancomycin and ceftriaxone</td>
<td>Resolved in 2 weeks</td>
<td>2011</td>
<td>Zheng-Wei et al. [32]</td>
</tr>
<tr>
<td>91/female</td>
<td>ESRD on hemodialysis, diabetes, Crohn’s disease, cholecystoduodenal fistula, sepsis</td>
<td>Vancomycin, piperacillin/tazobactam, ceftazidime, ampicillin/sulbactam, augmentin</td>
<td>Unclear</td>
<td>Large flaccid bullae and skin sloughing on trunk, extremities, palms, soles</td>
<td>Positive Normal 75%</td>
<td>Supportive care</td>
<td>Died of comorbidities</td>
<td>2013</td>
<td>Kakar et al. [33]</td>
</tr>
<tr>
<td>76/male</td>
<td>RCC, pneumonia</td>
<td>Vancomycin, piperacillin/tazobactam</td>
<td>8</td>
<td>Yellow, tense bullae over erythematous base on trunks, palms, soles; erosions with hemorrhage and crusting</td>
<td>Positive Normal NR</td>
<td>DC antibiotics</td>
<td>Resolved in 2 months; died of metastatic RCC</td>
<td>2014</td>
<td>Nair et al. [34]</td>
</tr>
<tr>
<td>56/male</td>
<td>Pancreatic pseudocyst, respiratory failure, sepsis</td>
<td>Vancomycin</td>
<td>6</td>
<td>Diffuse erythema with large areas of skin sloughing; tense vesicles and bullae on trunk, extremities, buttocks, inguinal folds</td>
<td>Negative Positive 50%</td>
<td>DC vancomycin and meropenem; oral dapsone 100 mg daily</td>
<td>Resolved in 3 weeks</td>
<td>2016</td>
<td>Current patient</td>
</tr>
</tbody>
</table>

Drug-induced LABD is regarded as a benign condition that resolves with appropriate intervention and does not increase mortality [2]. However, it appears that older patients with severe comorbidities who develop this variant of drug-induced LABD mimicking TEN are more likely to have negative outcomes.

Treatment of drug-induced LABD involves discontinuation of the offending medication, which is typically sufficient for clinical remission. Refractory cases may require systemic therapy. Therapeutic options include sulfones, sulfonamides, corticosteroids, antibiotics, immunosuppressants, intravenous immunoglobulin (IVIG), and immunoadsorption [2]. Although systemic therapy is not required to treat most cases of drug-induced LABD, therapeutic agents were used in 7 of 15 cases in our review. They included dapsone, methylprednisolone, prednisone, pentoxifylline, IVIG, and cyclosporine. That systemic treatment was considered and implemented so frequently suggests that this variant of LABD has a severe clinical evolution compared to other forms.

The conventional first-line treatment for LABD is dapsone, which is effective in the therapy of autoimmune bullous diseases and neutrophilic dermatoses [2, 35]. Dapsone works as an anti-inflammatory and immunomodulatory agent, possibly by inhibiting neutrophil adherence to IgA class BMZ antibodies, and produces clinical improvement within 24-48 hours of initiation [36]. Dapsone therapy requires careful laboratory monitoring due to its dose-dependent adverse effects of hemolysis and methemoglobinemia, particularly in the first 3 months when the risk of hematologic toxicity is greatest [37, 38]. Rare side effects include agranulocytosis, peripheral neuropathy, and hypersensitivity syndrome [37].

It is remarkable that aside from our patient, only one other reported patient with TEN-like LABD received dapsone, the mainstay of therapy for LABD and a far less immunosuppressive alternative to steroids. That patient had vancomycin-induced LABD, presenting as hemorrhagic bullae and diffuse exfoliation, in the setting of bacteremia and multi-organ dysfunction [4]. He was treated in the burn unit, where all antibiotics were discontinued and dapsone 25 mg twice daily was administered with complete re-epithelialization over 3 weeks. There was no mention of G6PD testing or discussion about why dapsone was chosen. Dapsone treatment was proposed in another patient, but comfort care measures were favored instead [33].

In our patient, dapsone was initiated before confirming normal G6PD activity owing to his worsening clinical status and severity of the eruption. Screening for G6PD deficiency is recommended before starting oxidant drugs to avoid precipitating hemolytic anemia in susceptible G6PD-deficient individuals, although a low G6PD level is not an absolute contraindication to dapsone therapy [37, 39]. Currently there are no consensus guidelines regarding the initiation of dapsone without G6PD testing. Screening is more relevant in patients considered to be at higher risk for the enzyme deficiency, particularly males of African, Asian, or Mediterranean descent [6, 39]. The qualitative fluorescent spot test is useful for rapid population screening, whereas a quantitative spectrophotometric analysis provides definitive diagnosis [40, 41].

Most patients on dapsone, regardless of G6PD status, have some degree of hemolysis that does not produce clinically significant anemia [38]. Even in G6PD-deficient individuals, dapsone-induced hemolysis is usually a mild self-limiting process and a dose of 100 mg daily may be safely administered [40]. Hemolysis may be detected clinically within 24-72 hours of drug administration, characteristically presenting as hemoglobinuria, whereas anemia worsens until days 7-8 [41].

Although our patient had anemia during his hospital course, he had no signs or symptoms of acute hemolysis before the eruption or after dapsone initiation. Since infection is the most common precipitating factor for hemolysis in G6PD-deficient individuals, it can reasonably be presumed that any clinical evidence of enzyme deficiency likely would have manifested before dapsone initiation [41]. Considering the low morbidity of most G6PD variants, it may be judicious in certain clinical scenarios – such as the desire to avoid immunosuppressive drugs in an ill patient who requires prompt systemic treatment for LABD – to start dapsone before G6PD results are
available.

Systemic therapy, particularly dapsone, should be more strongly considered in LABD mimicking TEN to avoid rash progression and subsequent risk of sepsis, especially if there is no improvement with drug discontinuation alone.

Conclusion

We have identified a patient with drug-induced LABD presenting clinically as TEN, treated successfully with dapsone. This rare variant appears to be more severe than other forms of LABD. Clinicians should include LABD in the differential diagnosis when evaluating patients with a fulminant blistering or erosive dermatosis in the setting of recent drug exposure and pursue immunopathological testing. Dapsone as systemic therapy should be strongly considered in this variant to avoid disease progression and potentially fatal complications.

References


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