

Drug-induced Linear IgA Bullous Dermatitis in a Patient With a Vancomycin-impregnated Cement Spacer

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PRACTICE POINTS

- Linear IgA bullous dermatosis (LABD) is an autoimmune mucocutaneous disorder characterized by linear IgA deposits at the dermoepidermal junction.
- A substantial number of cases of LABD are drug related, with vancomycin most commonly implicated.
- While antibiotic-impregnated cement spacers deliver high concentrations of local medications, systemic reactions are still possible.
- Dapsone is the first-line treatment for LABD.

Linear IgA bullous dermatosis (LABD) is an autoimmune blistering rash caused by IgA autoantibodies against the epidermal basement membrane zone. It commonly is drug induced, often in association with systemic vancomycin. We report a case of a previously healthy 77-year-old man who developed a diffuse macular rash and hemorrhagic bullae on the left leg 10 days after placement of a vancomycin-impregnated cement spacer (VICS) during a revision knee arthroplasty and initiation of postoperative treatment with intravenous (IV) vancomycin. The lesions initially were limited to the leg in which the hardware was placed, but the patient later developed painful palmoplantar and oropharyngeal blisters as well as edematous, erythematous plaques on the back and buttocks. A punch biopsy from a lesion on the left thigh revealed neutrophil-rich subepidermal bullae, and immunofluorescence revealed linear IgA and C3 deposition along the dermoepidermal junction, confirming a diagnosis of LABD. This report illustrates the importance of considering antibiotic-impregnated cement spacers, which frequently are

used to manage prosthetic joint infections, as potential culprits in patients with cutaneous eruptions.

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Case Report

A 77-year-old man was admitted to the general medicine service at our institution for treatment of a diffuse macular eruption and hemorrhagic bullae 12 days after undergoing left-knee revision arthroplasty during which a cement spacer impregnated with vancomycin and tobramycin was placed. At the time of the surgery, the patient also received intravenous (IV) vancomycin and oral ciprofloxacin, which were continued postoperatively until his hospital presentation. The patient was recovering well until postoperative day 7, when he developed painful swelling and erythema surrounding the surgical wound on the left knee. Concerned that his symptoms indicated a flare of gout, he restarted a former allopurinol prescription from an outside physician after 2 years of nonuse. The skin changes progressed distally on the left leg over the next 48 hours. By postoperative day 10, he had developed serosanguinous blisters on the left knee (Figure 1A) and oral mucosa (Figure 1B), as well as erythematous nodules on the bilateral palms. He presented to our institution for emergent care on postoperative day 12 following progression of the eruption to the inguinal region (Figure 2A), buttocks (Figure 2B), and abdominal region.

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FIGURE 1. Scattered serosanguinous blisters with erythematous bases localized on the left knee (postoperative day 14)(A) and blistering of the anterior soft palate with epithelial sloughing visible on the right hard palate and buccal mucosa (postoperative day 12)(B) that developed after placement of a vancomycin-impregnated cement spacer during a revision knee arthroplasty.

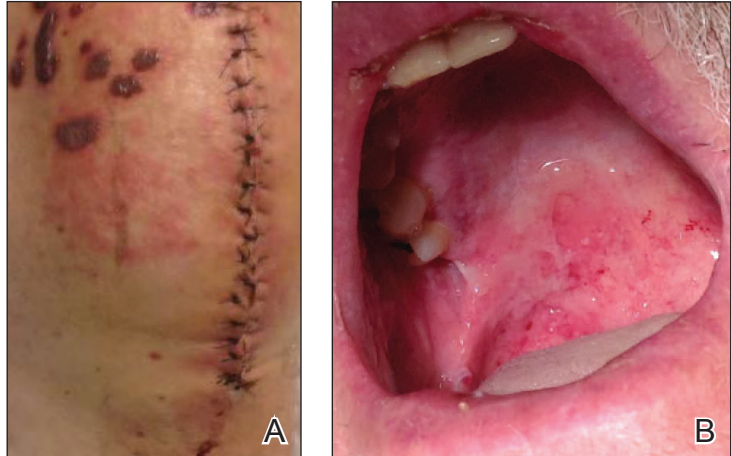


FIGURE 2. Annular erythematous plaques with centralized bullous formation in the inguinal region (postoperative day 14)(A) and buttocks (postoperative day 18)(B) following placement of a vancomycin-impregnated cement spacer during a revision knee arthroplasty.

Due to concerns about a potential drug reaction, the IV vancomycin, oral ciprofloxacin, and oral allopurinol were discontinued on hospital admission. A dermatology consultation (D.A.D., J.A.Z., E.T.) was obtained, and a punch biopsy from a lesion on the left thigh revealed a neutrophil-rich subepidermal bulla with scattered eosinophils (Figure 3A). Direct immunofluorescence demonstrated linear IgA (Figure 3B) and C3 deposition along the dermoepidermal junction, which confirmed a diagnosis of drug-induced linear IgA bullous dermatosis (LABD). Vancomycin was suspected as the causative agent.¹ An initial vancomycin trough level drawn 48 hours after discontinuation (postoperative day 13) was still therapeutic at 14 $\mu\text{g}/\text{mL}$ (reference range, 10–20 $\mu\text{g}/\text{mL}$ in adults). This was substantially higher than the predicted value of 3 $\mu\text{g}/\text{mL}$ based on renal excretion. Similarly, 5 additional serum levels obtained during the patient's hospital course were greater than those predicted, and follow-up trough levels remained detectable at 1 $\mu\text{g}/\text{mL}$ 2 weeks after discontinuation.

Oral prednisone 60 mg once daily and oral dapsone 25 mg once daily were initiated on hospital days 4 and 6 (postoperative days 15 and 17), respectively. A 6-week course of oral ciprofloxacin 750 mg twice daily and daptomycin 8 mg/kg once daily was initiated for bacterial coverage on hospital day 5 (postoperative day 16). Topical triamcinolone and an anesthetic mouthwash also were used to treat the mucosal involvement. The lesions stabilized on the third day of steroid therapy, and the patient was discharged 7 days after hospital admission (postoperative day 18). Dapsone was rapidly increased to 100 mg once daily over the next week for *Pneumocystis jirovecii* pneumonia prophylaxis. An increase in prednisone to 80 mg once daily was required 3 days after the patient was discharged due to worsening oral lesions. Five days after discharge, the patient was readmitted to the hospital for 3 days due to acute kidney injury (AKI) in which his baseline creatinine level tripled. The cause of renal impairment was unknown, resulting

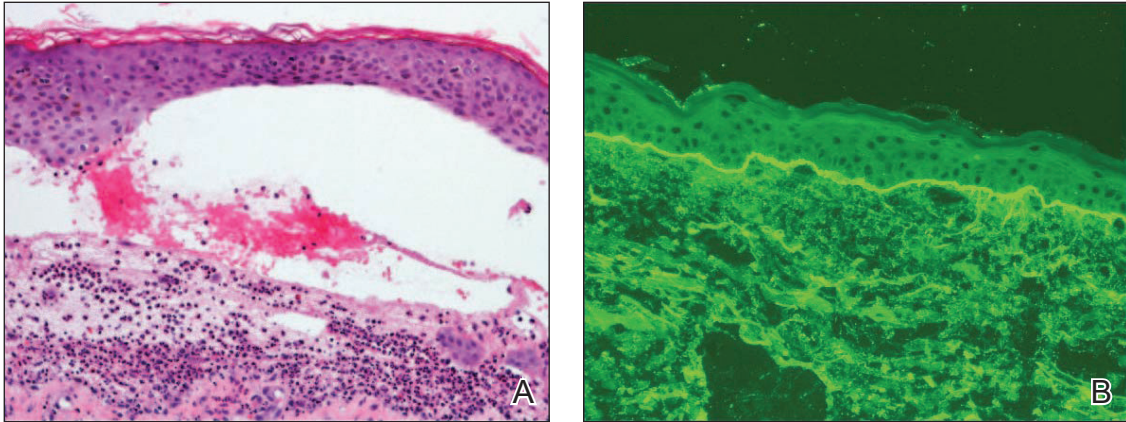


FIGURE 3. A neutrophil-rich subepidermal bulla with scattered eosinophils was noted on staining with hematoxylin and eosin (A)(original magnification $\times 20$), and direct immunofluorescence demonstrated linear IgA deposition along the dermoepidermal junction (B)(original magnification $\times 20$).

in empiric discontinuation of dapsone on postoperative day 27. Prophylaxis for *P jirovecii* pneumonia was replaced with once-monthly inhaled pentamidine. Prednisone was tapered 20 days after the original presentation (postoperative day 32) following gradual improvement of both the skin and oral lesions. At dermatology follow-up 2 weeks later, doxycycline 100 mg twice daily was added for residual inflammation of the left leg. A deep vein thrombosis was discovered in the left leg 10 days later, and 3 months of anticoagulation therapy was initiated with discontinuation of the doxycycline. The patient continued to have renal insufficiency several weeks after dapsone discontinuation and developed prominent peripheral motor neuropathy with bilateral thenar atrophy. He did not experience any skin eruptions or relapses in the weeks following prednisone cessation and underwent successful removal of the cement spacer with full left-knee reconstruction 4 months after his initial presentation to our institution. At 9-month dermatology follow-up, the LABD remained in remission.

Comment

Linear IgA bullous dermatosis is a well-documented autoimmune mucocutaneous disorder characterized by linear IgA deposits at the dermoepidermal junction. The development of autoantibodies to antigens within the basement membrane zone leads to both cellular and humoral immune responses that facilitate the subepidermal blistering rash in LABD.^{2,3} Linear IgA bullous dermatosis affects all ages and races with a bimodal epidemiology. The adult form typically appears after 60 years of age, whereas the childhood form (chronic bullous disease of childhood) appears between 6 months and 6 years of age.³ Medications—particularly vancomycin—are responsible for a substantial portion of cases.¹⁻⁴ In one review, vancomycin was implicated in almost half (22/52 [42.3%]) of drug-related cases of

LABD.⁴ Other associated medications include captopril, trimethoprim-sulfamethoxazole, phenytoin, and diclofenac.^{3,4} Vancomycin-associated LABD has a substantially shorter time to onset of symptoms, with a mean of 8.6 days compared to 63.8 days for other causative agents.⁴ Resolution of symptoms also occurs more quickly, with remission occurring in 66.7% (16/24) of cases at a mean time of 13 days compared to a 39.2% (11/28) resolution rate with a mean time of 18.9 days following discontinuation of other implicated medications.⁴ While idiopathic LABD involves the mucous membranes in up to 80% of cases, drug-induced LABD is less commonly associated with mucosal lesions. In an earlier systematic review from 1966 to 2002, 32% (7/22) of reported cases of vancomycin-induced LABD were reported to have mucosal involvement.^{5,6} In 2012, one group found that most published cases of drug-induced LABD do not use standardized algorithms, such as the Naranjo algorithm, to definitively tie LABD onset to medication use.⁴ The Naranjo algorithm, devised in 1981, consists of 10 questions that determine the probability of adverse drug reactions.⁷ In our case, a Naranjo score of 5 suggested a probable adverse drug reaction due to vancomycin use; however, we cannot completely exclude ciprofloxacin in our case in light of a case report of LABD in the setting of IV vancomycin and ciprofloxacin use.⁸ In our patient, ciprofloxacin had a Naranjo score of 2, which suggested a possible adverse drug reaction. Allopurinol, which does not have any published association with LABD, also had a Naranjo score of 2 in our patient.

The initial treatment of drug-induced LABD is immediate discontinuation of the suspected agent(s) and supportive care.⁹ Although future avoidance of vancomycin is recommended in patients with a history of LABD, there are reported cases of successful rechallenges.^{4,10} The early removal of our patient's cement spacer was discouraged by both the orthopedics and infectious disease

consultation services due to potential complications as well as the patient's gradual improvement during his hospital course.

Dapsone is considered the standard systemic treatment for LABD. Sulfapyridine is an alternative to dapsone, or a combination of these 2 drugs may be used. Corticosteroids can be added to each of these regimens to achieve remission, as in our case.² Although dapsone was discontinued in the setting of the patient's AKI, the vancomycin in the dual-eluting spacer was more likely the culprit. A review of 544 postoperative outcomes following the use of an antibiotic-impregnated cement spacer (AICS) during 2-stage arthroplasty displayed an 8- to 10-fold increase in the development of AKIs compared to the rate of AKIs following primary joint arthroplasty.¹⁰ While our patient's AKI was not attributed to dapsone, his prominent peripheral motor neuropathy with resultant bilateral thenar atrophy was a rare complication of dapsone use. While dapsone-associated neuropathy has been reported in daily dosages of as low as 75 mg, it typically is seen in doses of at least 300 mg per day and in larger cumulative dosages.¹¹

Despite having a well-characterized vancomycin-induced LABD in the setting of known vancomycin exposure, our patient's case was particularly challenging given the continued presence of the vancomycin-impregnated cement spacer (VICS) in the left knee, resulting in vancomycin levels at admission and during subsequent measurements over 2 weeks that were all several-fold higher than the renal clearance predicted.

Vancomycin-associated LABD does not appear to be dose dependent and has been reported at both subtherapeutic¹⁻³ and supratherapeutic levels,⁵⁻⁹ whereas toxicity reactions are more common at supratherapeutic levels.⁹ The literature on AICS use suggests that drug elution occurs at relatively unpredictable rates based on a variety of factors, including the type of cement used and the initial antibiotic concentration.^{12,13} Furthermore, the addition of tobramycin to VICSs has been found to increase the rate of vancomycin delivery through a phenomenon known as passive opportunism.¹⁴

As AICS devices allow for the delivery of higher concentrations of antibiotics to a localized area, systemic complications are considered rare but have been reported.¹³ Our report describes a rare case of LABD in the setting of a VICS. One clinical aspect of our case that supports the implication of VICS as the cause of the patient's LABD is the concentration of bullae overlying the incision site on the left knee. A case of a desquamating rash in a patient with an implanted VICS has been documented in which the early lesions were localized to the surgical leg, as in our case.¹⁵ Unlike our case, there was a history of Stevens-Johnson syndrome following previous vancomycin exposure. A case of a

gentamicin-impregnated cement spacer causing allergic dermatitis that was most prominent in the surgical leg also has been reported.¹⁶ An isomorphic phenomenon (Köbner phenomenon) has been suggested in the setting of vancomycin-induced LABD lesions that intensified at a site of adhesive tape application,¹⁷ but the Köbner phenomenon did not appear to be a major factor in our patient. The removal of the patient's cement spacer was performed to prevent development of a chronic autoimmune response or autoreactivity state against the skin basement membrane zone structural antigen.

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