

Severe Vancomycin-Induced IgA Bullous Dermatitis Case Report

Mohamad Malek Bawadkji (✉ malek.bawadkji7@gmail.com)

MedStar Research Institute: MedStar Health Research Institute <https://orcid.org/0000-0002-1508-1144>

Sai Deepika Potluri

MedStar Union Memorial Hospital

Raj Dangol

MedStar Union Memorial Hospital

Michael Man Kit Siu

MedStar Union Memorial Hospital

Rabin K Shrestha

MedStar Georgetown University Hospital

Marcos A Wolff

MedStar Franklin Square Medical Center

Christopher J. Haas

MedStar Georgetown University Hospital

Research Article

Keywords: Linear IgA Bullous Dermatitis (LABD), Drug-induced LAB, Vancomycin, Vesiculobullous disorder

Posted Date: November 1st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-559809/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Linear IgA Bullous Dermatitis is a rare autoimmune blistering disease with an incidence of about 0.5 to 2.3 cases per million individuals per year. Although multiple reports have documented drug exposure as a precipitating factor, formal studies validating the existence of drug-induced LABD are lacking. A 49-year-old man with history of intravenous drug use presented with left hip pain of three weeks duration after sustaining a fall. On presentation he was hemodynamically stable and physical examination was notable for poor dentition, gingivitis, stigmata of IV drug use with associated cellulitis on right antecubital fossa and proximal left thigh tenderness with stiffness and limited range of movement. Laboratory diagnostics were remarkable for elevated inflammatory markers, with no evidence of leukocytosis. CT scan without contrast of the left lower extremity that demonstrated severe left hip osteoarthritis without fracture or dislocation. Blood Cultures were collected and empirically started on Vancomycin and Piperacillin/Tazobactam for right elbow cellulitis. The patient continued to experience severe pain, prompting incision and drainage of the left hip along with acetabuloplasty, removal of the femoral head, and Stage I hip replacement with placement of prophylactic prosthetic cement spacer with Vancomycin and Tobramycin. Within twenty-four hours of surgery, he developed multiple distinct maculopapular/bullous lesions of his torso and medial thigh that rapidly progressed, involving the oral mucosa, scrotum, glans, hands, and feet with associated periorbital edema. Punch biopsy was performed and due to involvement of ~20% body surface area and transferred to a tertiary center. H&E and immunostaining of the histological sample demonstrated IgA bullous disease. The patient's bullous lesions improved two weeks after discontinuation of Vancomycin and initiation of therapy. This case demonstrates the importance of early recognition of the rare adverse effects of commonly used medications. Vancomycin is currently used more frequently given the recent rise in the prevalence of methicillin-resistant *Staphylococcus aureus* infection. Further studies are needed to understand the pathophysiology, genetic predisposition, and disease penetrance.

Introduction:

Linear IgA Bullous Dermatitis (LABD) is a rare autoimmune blistering disease with an incidence of about 0.5 to 2.3 cases per million individuals per annum [1,2]. It is characterized by linear deposition of IgA at the dermo-epidermal junction. The etiology is primarily idiopathic, drug-related, or infection-related. Although multiple reports have documented drug exposure as a precipitating factor, formal studies validating the existence of drug-induced LABD are lacking. Vancomycin has been reported as a potential inciting drug in most reports [3,4]. Here, we report a case of a 49-year-old man who developed a severe, circular, maculopapular rash and bullous lesions during his hospital course while receiving Vancomycin. The rash involved approximately 20% of the total body surface area including the back, groin, palms, soles, eyes, oral mucosa and glans. The diagnosis of Linear IgA Bullous Dermatitis was confirmed histologically.

Case Presentation:

A 49-year-old man with history of intravenous (IV) drug use and diverticulitis presented with left hip pain of three weeks duration that developed after sustaining a fall while running. His symptoms were initially mild, characterized as a mild limp with generally preserved range of motion and ambulation. During this time, he continued to use IV drugs and suffered an episode of transient overdose that rendered him unconscious approximately twenty-four hours prior to presentation. Upon awakening the following morning, he reported anesthesia of the left hip and refractory pain that left him bedbound. He denied fevers, chills, new rash, or open wounds. On presentation he was noted to be hemodynamically stable and physical examination was notable for poor dentition, gingivitis, proximal left thigh tenderness and stiffness with limited range of movement, but no erythema nor effusion was noted. The stigmata of IV drug use with an associated cellulitis of the right antecubital fossa were appreciated [Figure 1]. Laboratory diagnostics were only remarkable for severe iron deficiency anemia (Hemoglobin 5.4 gm/dL, Ferritin 21.2 ng/mL and Iron Saturation 6%) and elevated inflammatory markers (ESR 110 mm/hr and CRP 75.80 mg/L), with no evidence of leukocytosis. Diagnostic imaging included a Computed Tomography (CT) scan without contrast of the left lower extremity that demonstrated severe left hip osteoarthritis without fracture or dislocation. Blood cultures were collected, the patient was transfused a single unit of packed red blood cells, and empirically started on Vancomycin and Piperacillin/Tazobactam for right elbow cellulitis, that was later narrowed to Vancomycin monotherapy within twenty-four hours.

Unfortunately, during the patient's hospital course his left hip pain failed to improve with conservative management and Magnetic Resonance Imaging (MRI) was performed. MRI demonstrated findings consistent with septic arthritis and osteomyelitis of acetabular roof and femoral head. Intervention Radiology joint aspiration was attempted but was unsuccessful and Orthopedics was consulted for incision and drainage. A scant amount of purulent material was expressed that was sent for culture and a drain was placed. The patient continued to experience severe pain that was accompanied by decreased range of motion, prompting repeat incision and drainage of the left hip along with acetabuloplasty, removal of the femoral head, and Stage I hip replacement with placement of prophylactic prosthetic cement spacer containing Vancomycin and Tobramycin. He was not a candidate for placement of permanent articulating hip implant due to active IV drug use and poor dentition.

Within twenty-four hours of surgery (eight days since admission), he developed multiple distinct maculopapular/bullous lesions of his torso and medial thigh that rapidly progressed, involving the oral mucosa, scrotum, glans, hands, and feet with associated periorbital edema [Figure 2, 3]. Vancomycin was thought to be the inciting factor and it was discontinued with transition to IV Cefazolin as cultures from the purulent aspirate grew methicillin-sensitive *Staphylococcus aureus* (MSSA). Blood cultures from admission continued to be negative. Stevens-Johnson Syndrome (SJS) was suspected and he was immediately started on cyclosporine therapy (150 mg IV x 1 and 150 mg P.O. BID). Punch biopsy was performed and due to involvement of 15-20% body surface area, he was transferred to a burn unit at a tertiary center.

At the tertiary center, Cefazolin was discontinued given its association with SJS and he was initiated on Linezolid. Repeat skin biopsy was obtained and Prednisone therapy was added to cyclosporine for management of SJS. H&E and immunostaining of the histological sample demonstrated IgA bullous disease [Figure 4]. Dapsone, a medication considered to be a first line therapy for LABD, was deferred in the setting of the patient's baseline anemia. He was continued on Prednisone which was gradually tapered and Doxycycline therapy (100mg BID) was added for anti-inflammatory effects. The prophylactic prosthetic cement spacer with Vancomycin and Tobramycin remained *in situ*. The patient's bullous lesions improved two weeks after discontinuation of Vancomycin and initiation of therapy. He subsequently transitioned from Linezolid to Daptomycin due to risk of marrow suppression with prolonged Linezolid use. The patient completed a four-week course of Daptomycin and was subsequently discharged on a tapering dose of Prednisone, Doxycycline, and Nicotinamide for pain management with recommendation to follow up in the dermatology clinic.

Discussion:

Linear IgA Bullous Dermatitis (LABD) is a rare, sub-epidermal, vesicular bullous disease with an incidence of about 0.5 to 2.2 cases per million individuals per year [1, 2]. LABD occurs in bimodal age distribution, with a drug-induced etiology as a frequent underlying cause [1]. Adult patients typically experience an abrupt onset of skin lesions with a diverse spectrum of clinical presentations including tense bullous lesions, erythematous plaques, string of pearl-like configurations, and target or target-like lesions [5] that generally involve the trunk, extremities, palms, soles, and rarely mucosal areas manifesting within 1 to 15 days of drug initiation [6]. Mucosal lesions usually present as erosions or ulcers with the oral mucosa and peri-orbital area most commonly affected. Atypical features such as large erosions mimicking Toxic Epidermal Necrolysis (as seen in our patient) and positive Nikolsky's sign were significantly more frequent in the drug-induced form compared to the idiopathic form of the disease [15], which should raise index of suspicion and encourage prompt discontinuation of any presumed offending agents.

Physical examination might be suggestive of LABD, however formal diagnosis relies on confirmatory physical and histological characteristics demonstrating subepidermal bullae, perivascular inflammation with predominant neutrophils, and linear IgA deposition in the basement membrane [11]. While Vancomycin is one of the most associated drugs [3,4,9], multiple classes of medications including Penicillins, Cephalosporins, Sulfonamides, ACE inhibitors, NSAID's are also common culprits [2]. In the case of Vancomycin, the severity of the reaction does not appear to correlate with serum Vancomycin levels. Although multiple case reports have documented drug exposure as a precipitating factor, further research and studies that aims to understand the mechanism of drug-induced LABD are lacking.

The pathophysiology of LABD is believed to be due to autoimmune production of circulating IgA anti-basement membrane zone antibodies that target 97 kDa antigen and a 120 kDa antigen. Both antigens comprise the extracellular portion of bullous pemphigoid antigen 2 [BP 180/type XVII collagen], which plays a canonical role in the epidermal-dermal adhesion [13]. The cleavage of BP180 antigen results in

exposure of neoepitopes on the 15th collagenous domain that react with IgA autoantibodies [16]. In contrast, in Vancomycin-induced LABD, type VII collagen appears to be the target [17], but exact mechanism is yet to be fully understood. Genetic factors appear to play a contributory role with associations with several genetic loci - HLA B8, HLA Cw7, HLA DR3, HLA DQ2 and TNF-2, but the exact role requires further evaluation [14].

The management of LABD focuses primarily on discontinuation of the offending agents with adjunctive use of Dapsone as first line therapy [12]. For severe and refractory cases, immunosuppressants like Dapsone, Sulfonamides [Sulphapyridine and Sulfamethoxyipyridazine], Colchicine, and topical or oral Corticosteroids should be considered [13]. The prognosis for patients with Vancomycin-induced LABD is excellent, with prompt improvement without residual skin lesions following recovery [7,8]. Upon Vancomycin re-exposure, a more severe recurrence with a shorter latency period and longer course of recovery has been reported [7].

In this case, the patient was started on Vancomycin and Piperacillin/Tazobactam upon hospital admission, that was later narrowed to Vancomycin. He underwent Stage I hip replacement with placement of prophylactic prosthetic cement spacer containing Vancomycin and Tobramycin. One day after surgical intervention, the patient developed the noted skin findings. While it remains possible that the Vancomycin-infused spacer may have contributed to the patient's presentation, it is more likely, specifically given the local concentrations of drugs from spacers, that the systemic Vancomycin was sufficient to stimulate an autoimmune response given the noted temporal relationship between drug administration and rash (eight days after admission and starting Vancomycin). Clinical improvement was noted to correlate with Vancomycin discontinuation and initiation of immunosuppressive therapy.

Conclusion:

This case demonstrates the importance of early recognition of the rare adverse effects of commonly used medications. Vancomycin is currently used more frequently given the recent rise in the prevalence of methicillin-resistant *Staphylococcus aureus* infection. Skin manifestations like Red Man Syndrome, Type I hypersensitivity reactions, drug reaction with eosinophilia and systemic symptoms (DRESS), and progression to severe symptoms that may mimic TEN and SJS may all occur in the setting of Vancomycin use, yet drug-induced LABD in patients with new onset vesiculobullous disorder should be considered. Alternative differentials include pemphigus vulgaris, bullous pemphigoid, dermatitis herpetiformis and erythema multiforme [5,10]. Early suspicion, prompt discontinuation of the offending drug, and initial punch biopsy with hematoxylin and eosin staining and direct immunofluorescence testing helps to confirm the diagnosis. Further studies are needed to understand the pathophysiology, genetic predisposition, and disease penetrance.

Declarations:

Acknowledgment: The authors would like to acknowledge Jeffrey Iding, M.D., Clinical and Laboratory Pathologist of Medstar Health and Jaroslaw Jedrych, M.D., Assistant Professor, Department of Dermatology, Division of Dermatopathology at Johns Hopkins School of Medicine for providing skin biopsy pathology slides.

I- Funding: None

II- Conflicts of Interest/Competing Interests: None

III- Ethics Approval: Not applicable

IV. Consent to Participate: Verbal and written consent obtained from the patient.

V. Consent for Publication: O Verbal and written consent obtained from the patient.

VI. Availability of Data and Material: Not applicable

VII. Code Availability: Not Applicable

VIII. Author's Contribution:

M. Malek Bawadkji M.D: Performed chart review, literature review, obtained consent and wrote the first draft of the manuscript.

Sai Deepika Potluri M.D: Chart and literature review.

Raj Dangol M.B.B.S: Chart and literature review.

Michael Man Kit Siu M.D: Chart and literature review.

Rabin K Shrestha M.D: Reviewed the manuscript.

Marcos A Wolff M.D: Reviewed the manuscript.

Christopher J Haas M.D, Ph.D: Oversaw he project and wrote the manuscript with Mohamad Malek Bawadkji.

All Authors gave input on the manuscript.

References:

1. L. A. Baden, C. Apovian, M. J. Imber, and J. S. Dover, Vancomycin-induced linear IgA bullous dermatosis, *Archives of Dermatology*, vol. 124, no. 8, pp. 1186–1188, 1988.
2. J. M. Whitworth, I. Thomas, S. A. Peltz, B. C. Sullivan, A. H. Wolf, and A. S. Cytryn, "Vancomycin-induced linear IgA bullous dermatosis (LABD)," *Journal of the American Academy of Dermatology*,

- vol. 34, no. 5, pp. 890–891, 1996.
3. Onodera H, Mihm MC Jr, Yoshida A, Akasaka T. Drug-Induced linear IgA bullous dermatosis. *J Dermatol*. 2005;32:759–764.
 4. Fortuna G, Salas-Alanis JC, Guidetti E, Marinkovich MP. A critical reappraisal of the current data on drug-induced linear immunoglobulin A bullous dermatosis: a real and separate nosological entity? *J Am Acad Dermatol*. 2012 Jun;66(6):988-94. doi: 10.1016/j.jaad.2011.09.018. Epub 2011 Dec 9. PMID: 22169257.
 5. Armstrong AW, Fazeli A, Yeh SW, Mackoll BT, Liu V. Vancomycin-induced linear IgA disease manifesting as bullous erythema multiforme. *J Cutan Pathol*. 2004;31:393–397.
 6. B. D. Wilson, E. H. Beutner, V. Kumar, T. P. Chorzelski, and S. Jablonska, "Linear IgA bullous dermatosis: an immunologically defined disease," *International Journal of Dermatology*, vol. 24, no. 9, pp. 569–574, 1985.
 7. Bogdan I, Neugebauer BI, Negron G, Pelton S, Plunkett RW, Beutner EH, et al. Bullous skin disease: An unusual allergic reaction to vancomycin. *Am J Med Sci*. 2002;323:273-278.
 8. Whitworth JM, Thomas I, Peltz SA, Sullivan BC, Wolf AH, Cytryn AS. Vancomycin-induced linear IgA bullous dermatosis (LABD). *J Am Acad Dermatol*. 1996;34:890-891.
 9. Piperacillin-tazobactam-induced linear IgA bullous dermatosis presenting clinically as Stevens-Johnson syndrome/toxic epidermal necrolysis overlap. Adler NR, McLean CA, Aung AK, Goh MS. *Clin Exp Dermatol*. 2017 Apr; 42(3):299-302.
 10. A Rare Case of Vancomycin-Induced Linear Immunoglobulin A Bullous Dermatitis. *Case Rep Dermatol Med*. 2017; 2017:7318305. doi: 10.1155/2017/7318305. Epub 2017 Jan 10. PMID: 28168063
 11. Linear IgA bullous dermatosis. Shireen V. Guide MD, M. Peter Marinkovich MD. *Nov-Dec 2001*;19(6):719-27. doi: 10.1016/s0738-081x (00)00185-1.
 12. Linear IgA dapsone responsive bullous dermatosis. Wojnarowska et al. PMID: PMC1437485
 13. Linear IgA bullous dermatosis of adults. Chorzelski TP, Jablonska S, Maciejowska E. *Clin Dermatology* 1991;9(3):383. PMID: 1806226
 14. Adult linear IgA disease and chronic bullous disease of childhood: the association with human lymphocytes antigens Cw7, B8, DR3 and tumor necrosis factor influences disease expression. Collier et al. *Br dermatology*. 1999;141(5):867. PMID: 10583169
 15. Linear IgA bullous dermatosis: comparison between the drug-induced and spontaneous forms. Chanal J et al. *Br Dermatology*. 2013;169(5):1041. PMID: 23815152
 16. C-Terminal Processing of Collagen XVII Induces Neoepitopes for Linear IgA Dermatitis Autoantibodies. Ellen Toyonaga et al. PMID: 28842325

Figures



Figure 1

Pertinent physical exam findings on the day of admission. (A) Left elbow non-painful chronic ulcer with no discharge or granulosomatous tissue secondary to intravenous [IV] drug use. (B) Right elbow non-painful chronic ulcer with no discharge or granulosomatous tissue secondary to intravenous [IV] drug use. (C) Right antecubital fossa erythema and tenderness consistent with acute cellulitis secondary to intravenous [IV] drug use.



Figure 2

Maculopapular/bullous lesions eight days after admission and within twenty-four hours of Stage I hip replacement surgery. (A) Maculopapular rash on the back. (B) Maculopapular rash with a singular bullous lesion on the left lateral torso. (C) Bullous lesion on the left medial thigh. (D) Patient reported bilateral wrist pain, but no rash was noted at that time.



Figure 3

Progression of the skin lesion over the next twenty-four hours after it was first noted. (A) Worsening of the maculopapular and bullous lesions on the left lateral torso. (B) Extension of the maculopapular and bullous lesions on the back. (C) Maculopapular and bullous lesions on the right lateral torso. (D) Bullous lesions on the right and left medial thighs. (E) Bullous lesions on the right wrist. (F) Bullous lesions on the left wrist. (G) maculopapular lesions on the right foot sole. (H) Maculopapular lesions on the left foot sole.

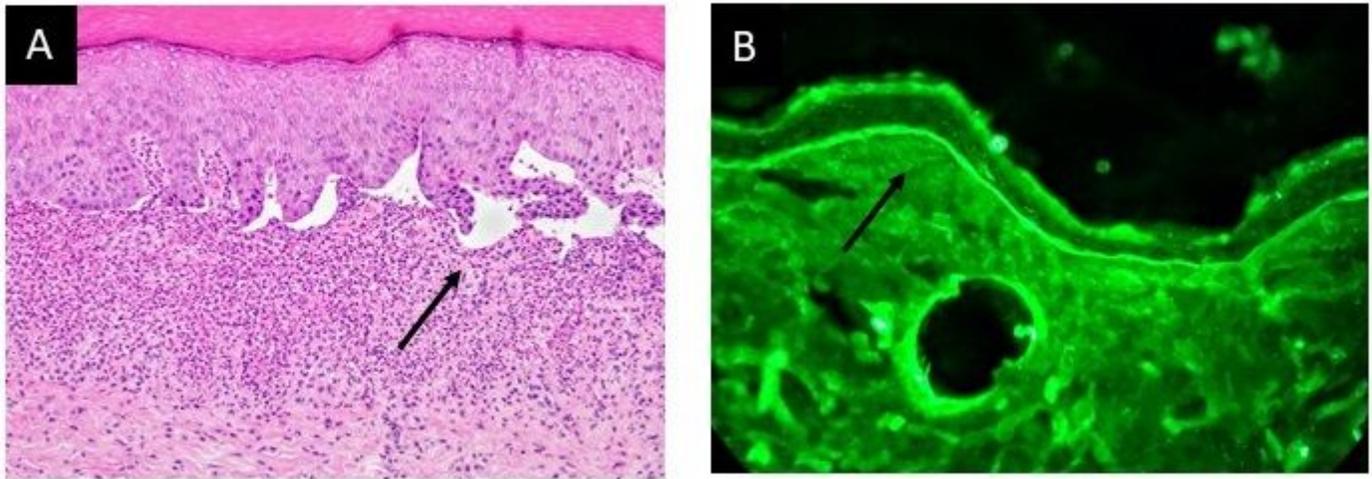


Figure 4

Diagnostic pathology slides. (A) Low magnification H&E stain showing subepidermal bullous dermatosis with neutrophils. (B) Low magnification immunohistochemical staining showing linear deposition of IgA along epidermal basement membrane with negative IgG, IgM, C3 and Fibrin.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CAREchecklistIgABullousDermatosisBawadjki102021.docx](#)