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Authors

Gutierrez, Yasmin

Sample, Hannah

Abdullahi, Gezman

et al.

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CLINICAL VIGNETTE

Not All Tense Blisters are Bullous Pemphigoid

Yasmin Gutierrez, MD^{1,2}, Hannah Sample, BS³, Gezman Abdullahi, MD¹ and Yang Yu, MD⁴

¹UCLA-Olive View Medical Center, Department of Internal Medicine

²USC Keck School of Medicine, Department of Dermatology

³University of California, Los Angeles, David Geffen School of Medicine

⁴UCLA-Olive View Medical Center, Division of Dermatology

Introduction

Linear IgA bullous dermatosis (LABD) is a rare immunobullous disease that may be idiopathic, or drug induced. LABD affects patients of all ages with a bimodal distribution in adolescence and the sixth decade of life.¹

LABD is characterized by urticarial plaques that often progress to tense vesicles and bullae on an erythematous base. Lesions are typically widespread involving the trunk, face, and extremities.¹ Clinical presentation may resemble bullous pemphigoid with tense bullae on an erythematous base or dermatitis herpetiformis with grouped vesicles.^{2,3}

The diagnostic gold standard for LABD is histopathologic direct immunofluorescence (DIF) which characteristically exhibits linear IgA antibody deposition in the basement membrane.⁴ Drug induced LABD also demonstrates a dispersed neutrophilic papillitis and may form neutrophil rich subepithelial blisters and involve eosinophils.⁴ Medications implicated in drug induced LABD include phenytoin, vancomycin, trimethoprim-sulfamethoxazole, captopril, and aminopenicillins, among several others.⁵ Management of LABD depends on patient factors, e.g. age, medical comorbidities, disease severity. Common reported agents include topical and systemic corticosteroids, dapsone, rituximab, IVIG, sulfonamides, and omalizumab.⁶

We present a case of vancomycin induced LABD in a patient with recent history of herpes zoster, emphasizing the importance of clinicopathologic correlation in the evaluation of bullous lesions.

Case Description

A 62-year-old man presented to our emergency room for evaluation of recurrent fevers for two weeks. He was previously seen at an outside clinic for fevers and a single dermatome herpes-zoster infection of the right flank for which he received acyclovir and three doses of cefazolin.

On presentation, vitals were significant for blood pressure of 82/49, heart rate of 130, and temperature to 38.5°C. Physical

examination revealed diffuse erythema of the upper trunk and lymphadenopathy. Initial laboratory studies were remarkable for leukocytosis and eosinophilia. Given suspicion for soft tissue infection, the patient was admitted and started on vancomycin on hospital day (HD) one, followed by acyclovir and aztreonam on HD two. Cephalosporins were avoided given a low suspicion for cefazolin-induced drug reactions including serum sickness and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. The patient remained febrile despite broad-spectrum antimicrobials, which were discontinued. Non-infectious testing was negative, including a lymph node biopsy for possible malignancy. On HD eight, new tense vesicles and bullae on an erythematous and urticarial base along the left flank and bilateral medial upper arms were noted (Figure 1). Clinical suspicion for disseminated zoster was high and acyclovir was restarted. Varicella zoster virus (VZV) and herpes simplex virus (HSV 1 and 2) PCRs were sent from vesicle fluid. The next day, numerous new tense bullae with an erythematous urticarial base were noted involving the medial bilateral aspects of upper arms, bilateral flanks, inguinal folds, scrotum, and lower extremities. Findings were concerning for immunobullous disease and dermatology was consulted.

Shave biopsies of the right upper medial arm bullae and the perilesional skin were obtained and sent for hematoxylin and eosin (H&E) staining and DIF, respectively. PCRs for VZV and HSV 1 and 2 were not detected. H&E staining revealed subepidermal vesicles with numerous neutrophils (Figure 2). DIF displayed a linear basement membrane zone staining pattern with anti-serum to IgA, granular basement membrane zone staining pattern with anti-serum to C3, and negative staining to IgG and IgM, characteristic of LABD.

The diagnosis of drug induced LABD was made based on the clinical course and histopathology with vancomycin recognized as the culprit drug. Upon diagnosis of LABD, vancomycin had already been discontinued and the patient was started on Dapsone 100 milligrams daily and a systemic steroid taper. Topical skin management included clobetasol 0.05% ointment to the extremity lesions and hydrocortisone 1% cream to the groin lesions. Two weeks after hospital discharge, the patient was

evaluated in outpatient dermatology with noticeable healing of existing lesions and no new bullae. At most recent follow up, the patient remained in remission off steroids and dapsone.

Discussion

LABD's vesicular lesions may mimic a herpetiform arrangement while its tense blisters may resemble bullous pemphigoid.⁷ Our patient's vesiculobullous eruption presented a unique diagnostic challenge given the patient's recent history of herpes zoster infection and initial concern for immunosuppression. While a viral etiology was initially suspected, VZV and HSV 1 and 2 PCR viral swabs of the lesions were negative. Given our patient's age and tense bullae on exam, bullous pemphigoid was on our differential diagnosis. The tense bullae of bullous pemphigoid and LABD can be indistinguishable, however, the grouped bullae of LABD classically form an annular or arciform pattern and is sometimes described to look like a "crown of jewels."

Given the broad differential for immunobullous disease, histopathology was crucial in making the final diagnosis. DIF of LABD classically shows IgA antibodies at the basement membrane, while H&E stains exhibit subepidermal blisters with predominant neutrophils which were both visualized in our patient's biopsy.^{3,4,8}

The pathogenesis of drug induced LABD has not been clearly elucidated, though lesions have been reported to erupt as early

as one day after initiation of vancomycin.⁷ Given that onset may be rapid and acute, it has been hypothesized by Yamagami et al. that vancomycin may enhance preexisting IgA autoreactivity. In our patient, eruption was noted eight days after exposure to vancomycin. Although several medications have been implicated in drug induced LABD, vancomycin is reported as the most common culprit drug and accounts for approximately 50% of cases.⁵ Consequently, aztreonam and acyclovir were attributed as less likely causes of our patient's LABD.

Treatment of drug induced LABD involves withdrawal of the suspected agent which commonly leads to remission. Our patient presented with lesions after discontinuation of vancomycin therefore adjunct treatments, including topical and systemic corticosteroids as well as dapsone, were utilized with good clinical response. Alternative medications such as rituximab and IVIG have also been reported to be effective particularly for patients who cannot tolerate or do not respond to dapsone.⁶

Conclusion

Our patient's skin eruption demonstrates the importance of a broad differential diagnosis for bullous eruptions in hospitalized patients receiving antibiotics and a high clinical suspicion for antibiotic induced LABD. Early diagnosis is crucial in management of drug induced LABD as discontinuation of the culprit drug is the mainstay of treatment.



Figure 1: Left - Vesicles and bullae on an erythematous base along the medial upper arm and trunk. Right - Black arrow showing the pathognomonic "Crown of Jewels".

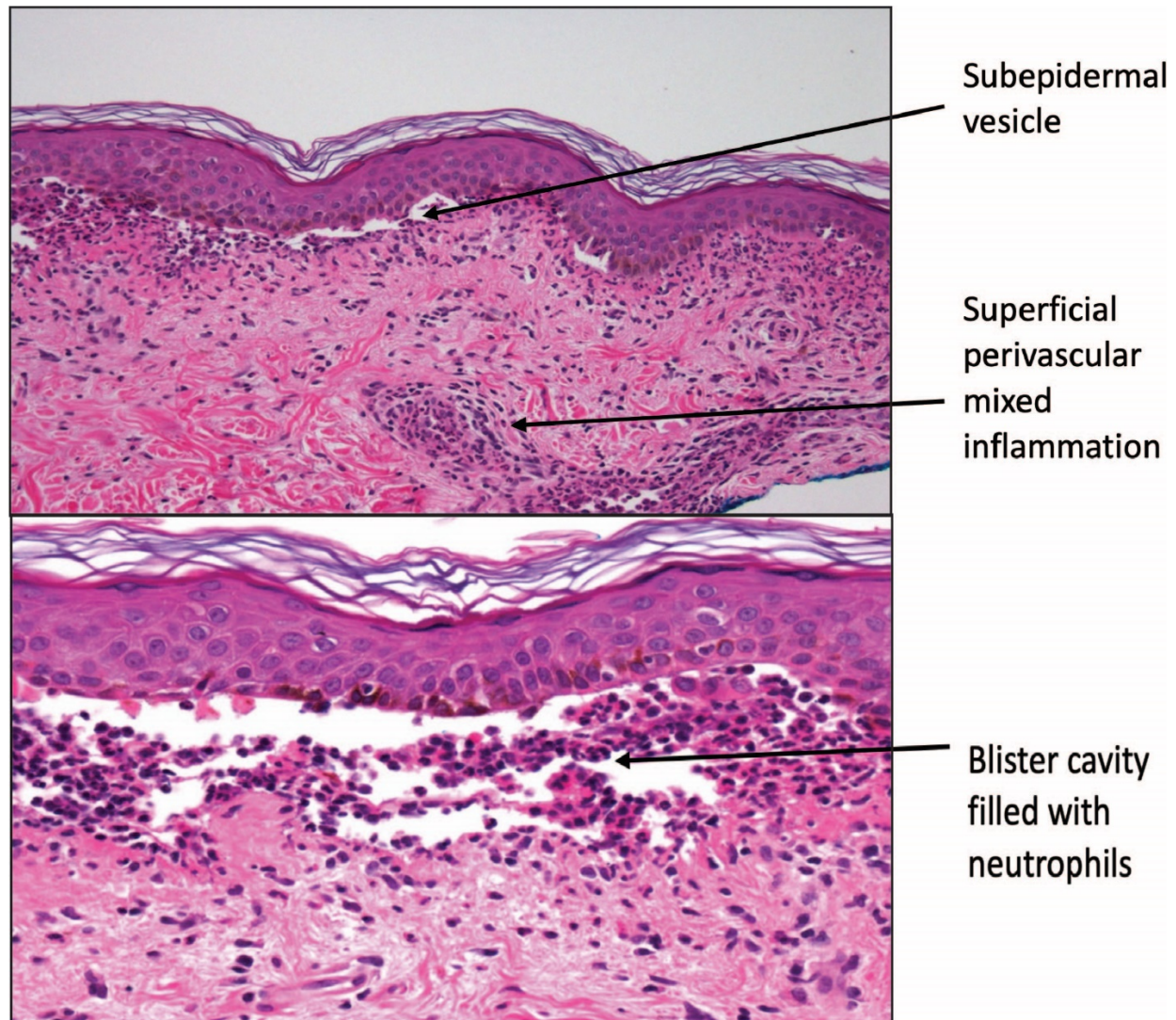


Figure 2: Top - Subepidermal cleft. Bottom - Numerous neutrophils within the subepidermal cleft.

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