Volume 21 Number
September 2015

Case report

Generalized linear IgA dermatosis with palmar involvement

Ivy N Norris MD[1], M Tye Haeberle MD[2], Jeffrey P Callen MD[2], Janine C Malone MD[2]

Dermatology Online Journal 21 (9): 1

[1]University of Louisville School of Medicine

[2]Division of Dermatology, Department of Medicine, University of Louisville School of Medicine, Louisville, Kentucky

Correspondence:

Dr. Tye Haeberle
3810 Springhurst Blvd
Louisville, KY 40241
mthaeb01@louisville.edu

Abstract

Linear IgA bullous dermatosis (LABD) is a sub-epidermal blistering disorder characterized by deposition of IgA along the basement membrane zone (BMZ) as detected by immunofluorescence microscopy. The diagnosis is made by clinicopathologic correlation with immunofluorescence confirmation. Differentiation from other bullous dermatoses is important because therapeutic measures differ. Prompt initiation of the appropriate therapies can have a major impact on outcomes. We present three cases with prominent palmar involvement to alert the clinician of this potential physical exam finding and to consider LABD in the right context.

Introduction

Linear IgA bullous dermatosis (LABD) is a sub-epidermal blistering disorder characterized by deposition of IgA along the basement membrane zone (BMZ) as detected by immunofluorescence microscopy. Patients present most often with bullae mimicking bullous pemphigoid or with blisters that can have a herpetiform arrangement. Patients may exhibit widely scattered lesions, mucosal lesions, or expanding annular plaques arranged in a “cluster of jewels” [1] pattern of polycyclic groupings of bullae with central crusting. Koebner’s isomorphic response can often be seen with the lesions of LABD. The disease most often develops from an autoimmune response toward the 120kDa or 97 kDa fragment of bullous pemphigoid antigen 2 (BPAG2, a 180kDa protein also known as collagen XVII), termed LABD97 [2]. A subtype with antibody deposition in the sublamina densa has been described and shown to have reactivity towards type VII collagen [3,4], p200 antigen [5], and more recently laminin-332 [2]. However, similar to the clinical heterogeneity of LABD, the condition also exhibits antigenic heterogeneity, although other target antigens have not yet been fully elucidated [6].

Infections, malignancies, and systemic autoimmune diseases have been reported to co-exist with LABD. Additionally, many drugs have been implicated in causing the disease of which the most common culprit is vancomycin. Vancomycin is a glycopeptide antibiotic with strong gram-positive effect that has seen a recent increase in use secondary to the rise in beta-lactam-resistant bacteria. Vancomycin works by inhibiting bacterial cell wall synthesis. The mechanism by which this drug leads to loss of self-tolerance in LABD is not fully understood.

To our knowledge, only two patients have previously been reported in the literature, which highlight isolated palmar involvement as the patient's clinical presentation of LABD [1,7]. Herein, we report three patients with linear IgA bullous dermatosis exhibiting significant palmar involvement in addition to generalized disease suggesting that palmar involvement may serve as a marker for LABD, either as an isolated finding or in conjunction with blisters in a generalized distribution.

Case synopsis

Case 1:

A 69-year-old man with a recent diagnosis of metastatic prostate cancer was admitted to an outside hospital for treatment of pneumonia. Antibiotic therapy was empirically initiated. The patient developed pruritus and bullae involving his trunk one day following drug initiation. Over concern for Stevens-Johnson syndrome, the patient was transferred to a university burn unit. The dermatology department was consulted. Medications at the time of consult were hydromorphone, ondansetron, and topical bacitracin. The patient had been on pantoprazole, fondaparinux, benzonatate, dutasteride, aspirin, methylprednisolone, and biclutamide, as well as vancomycin, levofloxacin, and piperacillin plus tazobactam prior to transfer from the referring hospital.

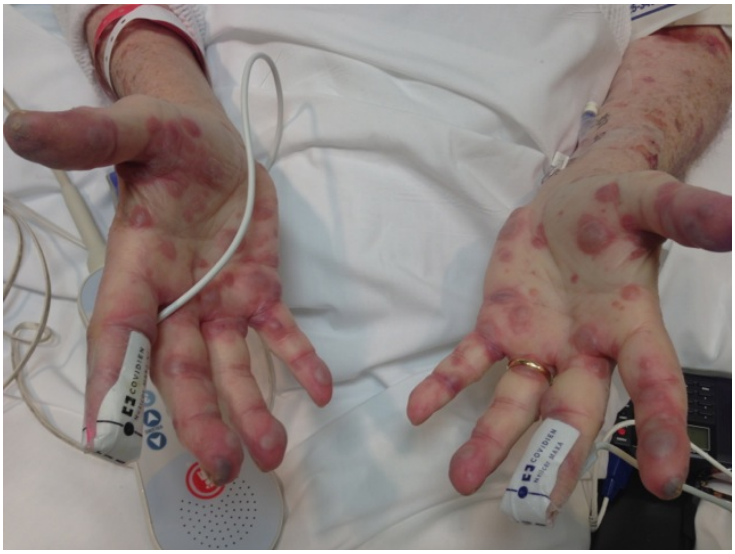
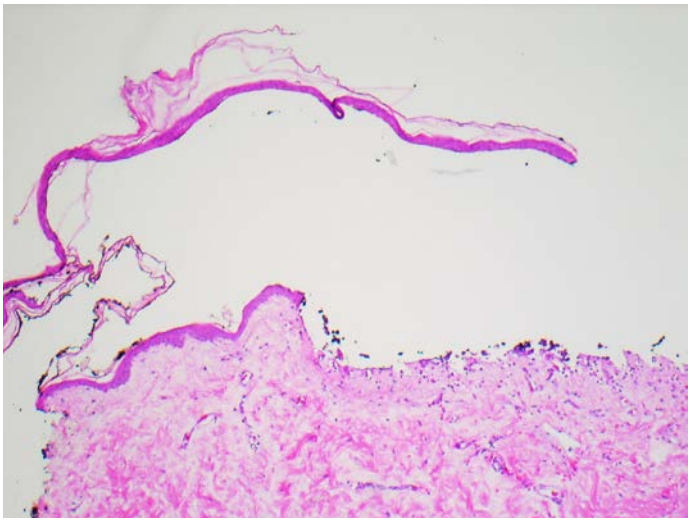


Figure 1. Erythematous bullae involving bilateral palms

Examination revealed bullae on an erythematous base involving much of his back, legs, face, arms, palms (Figure 1), and his oral, ocular, penile, and rectal mucosae. Biopsies revealed sub-epithelial bullae with a mixed inflammatory infiltrate (Figure 2). Immunofluorescence microscopy revealed 3+ linear IgA deposition along the basement membrane, consistent with LABD (Figure 3).



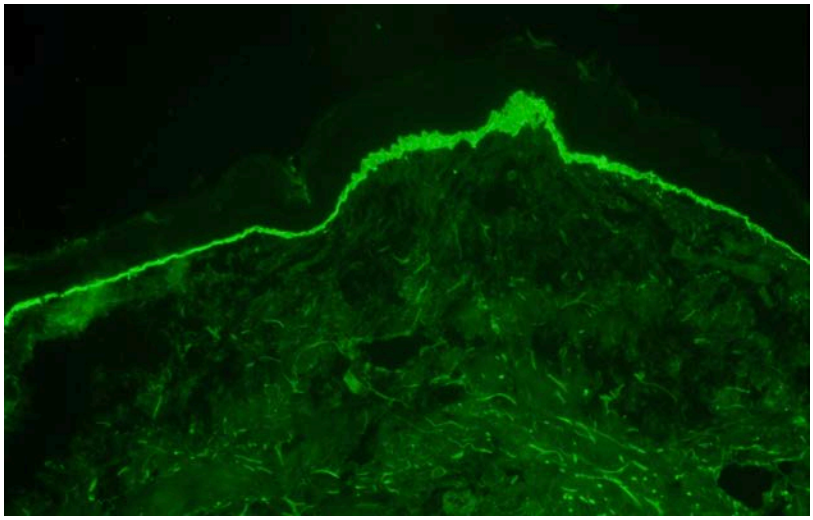


Figure 2. Subepidermal Bullous with mixed inflammatory component. **Figure 3**. IgA Direct Immunofluorescence shows linear deposition along the basement membrane.

The patient was started on systemic steroids and dapsone. He developed significant anemia over three days and dapsone was discontinued. The lesions slowly began to heal with continued systemic steroids in conjunction with local wound care. The patient was discharged to a skilled nursing facility in good condition.

Case 2:

A 68-year-old male with a four-year history of chronic bullous disease with severe ocular involvement and of a variable and recurrent course presented to the dermatology clinic for follow-up. Previous biopsies evaluated with direct immunofluorescence (DIF) had shown multiple immunoglobulins deposited along the BMZ and he also exhibited elevated serum levels of IgA. The patient had symblepharon of both conjunctiva and blisters involving his trunk and right palm (Figure 4).

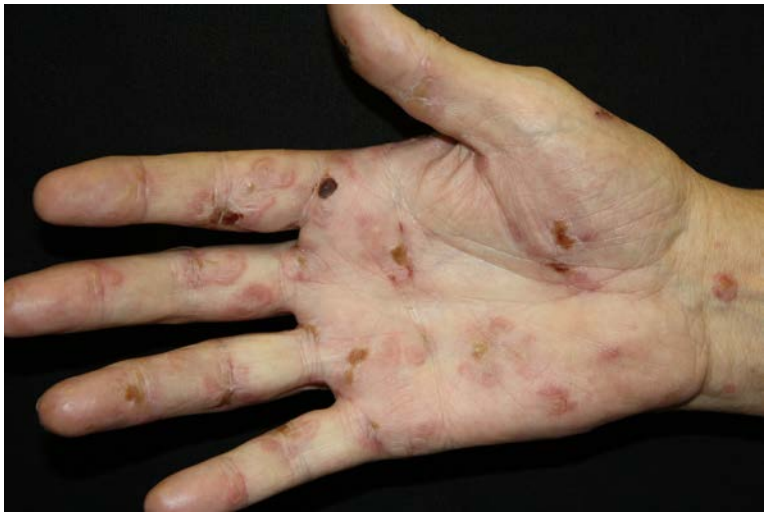


Figure 4. Erythematous vesicles and bullae as well as erosions on the palmar surface

At the time of presentation, the patient had been on a daily regimen of 100 mg dapsone with intermittent rituximab infusions when his disease flared. Owing to the previous somewhat equivocal DIF biopsy and only moderate response to dapsone, a second biopsy was performed of the left index finger, which showed a neutrophil-rich sub-epidermal vesicular dermatosis consistent with LABD.

He was continued on dapsone therapy at 100 mg daily and was offered prednisone or further rituximab but declined. At follow-up visits, chlorambucil 4 mg daily was added to his dapsone regimen. The patient has begun to see improvement with fewer flares.

Case 3:

An 84-year-old woman, status post-C3-C4 vertebral discectomy and subsequent healthcare-associated pneumonia (HCAP) treated with meropenem and vancomycin, reported an increase in shortness of breath and was found to have a saddle pulmonary embolism. The patient was transferred to a university tertiary hospital for care. On day one of admission, the patient completed her course of antibiotics. On day four, having been transferred to step-down care, the patient reported generalized pruritus and palmar and plantar pain. Her itching increased throughout day four at which time she began to develop bullae atop erythematous bases. Following a dermatology consultation, she was noted to have developed multiple erythematous patches on her palms and soles (Figure 3). Additionally, several Koebnerized lesions in the configuration of a previously removed adhesive bandage were noted involving her trunk (Figure 4).

Biopsy revealed sub-epidermal clefting with a predominantly neutrophilic infiltrate (Figure 5). DIF showed linear deposition of IgA along the basement membrane zone. The etiology of this patient’s LABD was suspected to be secondary to the vancomycin she had received.

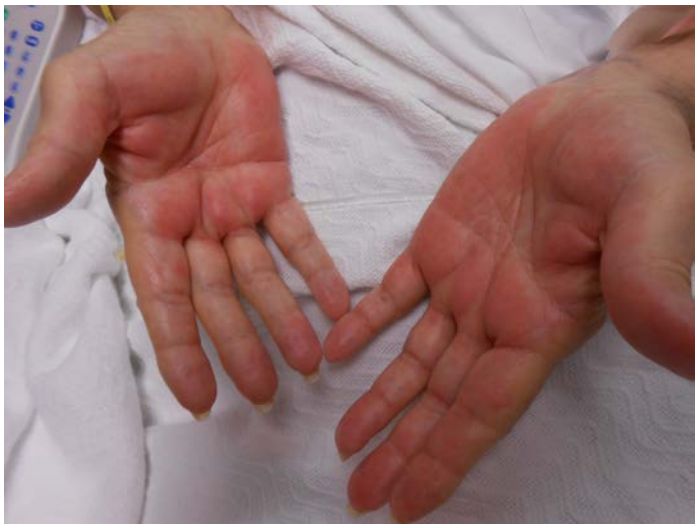


Figure 5. Erythematous patches involving the palms

It was elected to treat with potent topical corticosteroids rather than systemic therapy. Gradual resolution of her lesions had begun when the patient transferred to a sub-acute rehabilitation facility. Several months later, follow-up revealed significant improvement in her condition.

Discussion:

Although vancomycin is a commonly recognized etiology of drug-induced LABD, the typical clinical presentation is that of widespread cutaneous involvement with a predilection for the trunk and extremities. As such, LABD may mimic other bullous diseases such as erythema multiforme, dermatitis herpetiformis, bullous pemphigoid, or toxic epidermal necrolysis. A patient with vancomycin-induced LABD (VILABD) similar to ours, which manifested with localized palmar involvement has been reported [7]. The clinical histories of our patients 1 and 3 are consistent with VILABD but both notably demonstrated a rarely reported presentation of generalized disease with especially prominent palmar involvement. In acute presentations of VILABD as in patients 1 and 3, cessation of the antibiotic is typically sufficient to augment gradual resolution of disease. Although vancomycin is one of the more commonly reported drugs causing LABD, others that have been described include isoniazid, metronidazole, loperamide, diclofenac, captopril, lithium, amiodarone, phenytoin, cyclosporine and furosemide [8,9] and the clinician should consider ceasing these if LABD is diagnosed. Patient 3 exhibited an isomorphic response that has been previously been described as a manifestation of VILABD [10].

Table 1 serves to compare the various features of the disease and its course among the example patients with LABD and palmar involvement. Patients in this case series as well as those described in the literature are included. Gender and age were variable but all but one of the patients were greater than 65 years of age. The sites of involvement are compared among patients to highlight the marked involvement of palmar surfaces. Of course, LABD manifests on the trunk and extremities not uncommonly, but it is the predilection for palmar surfaces that is the focus of this paper. The most variable aspect among patients highlighted in this table is the response to therapy. Dapsone remains first line therapy. However, response varies and is often ultimately seen in conjunction with steroids, rituximab, or other immunosuppressants. Of note, ELISA was not noted in all patients, but in those tested all were negative for BP180 antigen antibodies, specifically cases 1 and 2 in the paper by Cauza, et al.

Table 1 Comparison of cases of LABD with palmar involvement

Patient	Case 1	Case 2	Case 3	Case 1 (Cauza, et. al[1])	Case 2 (Cauza, et. al[1])	Case 1 (Walsh[7])
Age	69	68	84	38	84	76
Sex	Male	Male	Female	Female	Female	Male
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Drug-related vs. idiopathic	Drug-related (vancomycin)	Idiopathic	Drug-related (vancomycin)	Idiopathic	Idiopathic	Drug-related (vancomycin)
Sites of involvement	Palms, mucosae, trunk, extremities	Palms, trunk, conjunctiva	Palms, soles, trunk	Palms, soles, buttocks	Palms, wrists	Palms
Isomorphic phenomenon	No	No	Yes	No	No	No
H&E	Subepithelial bullae with mixed inflammatory infiltrate	Neutrophil-rich subepidermal vesicular dermatosis	Subepidermal clefting with neutrophil-predominant infiltrate	Non-specific inflammatory infiltrate in papillary dermis; minimal junctional blistering with neutrophils, and eosinophils in dermis	Edema of papillary dermis and neutrophils along DE junction	Subepidermal vesicular dermatosis with neutrophils
DIF	3+ linear IgA deposition along BMZ	IgA deposition along BMZ	Linear IgA deposition along BMZ	Band-like deposition of IgA and C3 along BMZ	Linear IgA deposition along BMZ	Linear IgA and C3 deposition along BMZ
Treatment	Prednisone and dapsone	Rituximab, dapsone, chlorambucil	Topical corticosteroids	Dapsone, mycophenolate mofetil, cyclophosphamide; finally IVIG+ methylprednisolone+ dapsone	Dapsone	Hemodialysis to remove vancomycin, cessation of drug, and topical clobetasol
Response to therapy	Dapsone not tolerated, adequate response to steroids	Gradual improvement	Gradual improvement	Improvement with IVIG and steroids with dapsone but no total disease clearance	Improvement with six-month limited course	Resolution within one month of onset

Linear IgA bullous dermatosis patients marked by a recurrent course over the span of years, as in the presentation of the second patient, are more likely to be idiopathic. Standard treatment for these patients includes dapsone therapy. This was used with

limited long-term efficacy in our patient with chronic LABD. For patients who respond sub-optimally to monotherapy with dapsone, rituximab or intravenous immunoglobulin therapy may be used [11]. Chlorambucil has been used successfully in bullous disorders [12] and thus far has, in concert with dapsone, shown some efficacy in our patient with chronic LABD. Thus, alternative therapies warrant particular consideration in patients who may be refractory to standard treatments or in patients with an atypical clinical presentation.

Table 2

Differential Diagnosis for Palmar Erythema/Bullae
Dishydrosiform dermatitis [13]
Palmoplantar psoriasis
Toxic epidermal necrolysis [14] [15]
Dermatitis herpetiformis [16]
Erythema multiforme (bullous) [17]
Bullous pemphigoid

Conclusion:

We present these patients specifically to highlight involvement of the palmar region in both idiopathic and vancomycin-induced LABD. There are only a few patients with LABD reported in the medical literature with involvement of the palmar surfaces, all of which report exclusively acral involvement. We report three occurrences of LABD in which the patients presented with generalized bullae in addition to prominent involvement of the palmar surfaces. We stress that LABD is an important consideration in the differential diagnosis of vesiculobullous disease with prominent palmar involvement, whether blisters remain localized to the palmar surfaces or in the event that a generalized blistering eruption also shows prominent palmar involvement.

References

1. K. Cauza, G. Hinterhuber, S. B and e. al., "Unusual Clinical manifestation of linear IgA dermatosis: a report of two cases," J Am Acad Dermatol, vol. 51, pp. S112-7, 2004.
2. S. Izaki, J. Mitsuya, T. Okada and e. al., "A Case of Linear IgA/IgG Bullous Dermatosis with Anti-laminin-332 Autoantibodies," Acta Derm Venereol, vol. 95, pp. 359-360, 2015.
3. S. Wakelin, J. Allen, S. Zhou and e. al., "Drug-induced linear IgA disease with antibodies to collagen VII.," Br J Dermatol, vol. 134, pp. 310-314, 1998.
4. T. Hashimoto, A. Ishiko, H. Shimizu and e. al., "A case of linear IgA bullous dermatosis with IgA anti-type VII collagen autoantibodies.," Br J Dermatol, vol. 134, pp. 336-339, 1996.
5. K. Wozniak, T. Hashimoto, S. Fukuda and e. al., "IgA anti-p200 pemphigoid.," Arch Dermatol, vol. 147, pp. 1306-1310, 2011.
6. C. Paul, P. Wolkenstein, C. Prost and e. al., "Drug-induced Linear IgA disease: target antigens are heterogenous.," Br J Dermatol, vol. 136, no. 3, pp. 406-411, 1997.
7. S. Walsh, K. Kerchner and O. Sangueza, "Localized palmar vancomycin-induced lienar IgA bullous dermatosis occuring at supratherapeutic levels," Arch Dermatol, vol. 145, no. 5, pp. 603-4, 2009.
8. K. Lings and A. Bygum, "Linear IgA Bullous Dermatosis: a retrospective study of 23 patients in Denmark," Acta Derm Venereol, vol. 95, pp. 466-471, 2015.
9. R. Hall and C. Rao, "Uptodate: Linear IgA bullous dermatosis," 03 January 2014. [Online].
10. H. Mcdonald, N. York and A. Pandya, "Drug-induced linear IgA bullous dermatosis demonstrating isomorphic phenomenon," J Am Acad Dermatol, vol. 62, no. 5, pp. 897-8, 2010.
11. I. Khan, K. Bhol and A. Ahmed, "Linear IgA bullous dermatosis in a patient with chronic renal failure: response to intravenous immunoglobulin therapy," J Am Acad Dermatol, vol. 40, no. 3, pp. 485-8, 1999. PMID: 10071325
12. T. Chave, N. Mortimer, D. Shah and e. al., "Chlorambucil as a steroid-sparing agent in bullous pemphigoid," Br J Dermatol, vol. 151, no. 5, pp. 1107-8, 2004. PMID: 15541099
13. N. Levine, A. Freilich and P. Barland, "Localized pemphigoid simulating dyshidrosiform dermatitis," Arch Dermatol, vol. 115, no. 3, pp. 320-1, 1979. PMID: 373634
14. R. Kakar, H. Paugh and C. Jaworsky, "Linear IgA bullous disease presenting as toxic epidermal necrolysis: a case report and review of the literature," Dermatology, vol. 227, no. 3, pp. 209-13, 2013. PMID: 24135381

15. R. Dellavalle, J. Burch, S. Tayal and e. al., "Vancomycin-associated linear IgA bullous dermatosis mimicking toxic epidermal necrolysis," J Am Acad Dermatol, vol. 48, no. 5, pp. S56-7, 2003. PMID: 12734475
16. D. Navi, D. Michael and N. Fazel, "Drug-induced linear IgA bullous dermatosis," Dermatol Online J, vol. 12, no. 5, p. 12, 2006. PMID: 16962027
17. A. Armstrong, A. Fazeli, S. Yeh and e. al., "Vancomycin-induced linear IgA disease manifesting as bullous erythema multiforme," J Cutan Pathol, vol. 31, no. 5, pp. 393-97, 2004. PMID: 15059226