Boletín Médico del
Hospital Infantil de México

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CLINICAL CASE

Linear IgA bullous dermatosis in a latin adolescent treated with cyclosporine and prednisone

Andrea Ríos-Sánchez[1], Juan A. Godínez-Chaparro[2], Marissa de J. Quintal-Ramírez[3], and Ixchel R. Ramírez-Ricarte[4]*

[1]National School of Medicine and Homeopathy, National Polytechnic Institute; [2]Pediatric Dermatology Service, High Specialty Medical Unit of the Dr. Gaudencio González Garza General Hospital, La Raza National Medical Center, Mexican Social Security Institute; [3]Department of Pathology, La Raza National Medical Center, Mexican Social Security Institute; [4]Pediatric Dermatology Service, General Hospital of Mexico Dr. Eduardo Liceaga, Ministry of Health. Mexico City, Mexico

Abstract

Introduction: *Linear IgA bullous dermatosis (LABD) is a rare autoimmune disease. Although dapsone is the initial treatment, other immunomodulators are used in resistant cases or when dapsone is unavailable.* **Case report:** *A 12-year-old Mexican child, with no relevant medical history, developed in May 2023 a disseminated dermatosis affecting all body segments, including mucous membranes, characterized by erythematous patches and plaques evolving into the formation of serous and serosanguinous blisters and vesicles, distributed in a "string of pearls" pattern. LABD was suspected and confirmed by skin biopsy, which showed a subepidermal blister with neutrophilic infiltration and linear Immunoglobulin A deposits at the dermo-epidermal junction by direct immunofluorescence.Treatment with prednisone (2 mg/kg/day) and cyclosporine (5 mg/kg/day) resulted in improvement and lesion remission within 2 weeks. Both drugs needed to be discontinued for 3 months due to intermittent blistering. Cyclosporine was continued as maintenance therapy at a dose of 4 mg/kg/day for 8 months.* **Conclusions:** *The report highlights the use of cyclosporine as an alternative immunomodulator for DAAL, an immunosuppressive agent used in autoimmune disorders. Few cases, including this one, have described complete remission and control of the dermatosis with cyclosporine, accompanied by prednisone at the start of treatment.*

Keywords: *Linear immunoglobulin A bullous dermatosis. Prednisone. Cyclosporine. Case report.*

Dermatosis ampollosa por IgA lineal en un adolescente latino tratado con ciclosporina y prednisona

Resumen

Introducción: *La dermatosis ampollosa por IgA lineal es una enfermedad autoinmunitaria rara. Aunque la dapsona es el tratamiento inicial, se usan otros inmunomoduladores en casos resistentes o cuando la dapsona no está disponible.* **Caso clínico:** *Un niño mexicano de 12 años, sin antecedentes relevantes, desarrolló en mayo de 2023 una dermatosis diseminada a todos los segmentos corporales, incluyendo las mucosas, caracterizada por manchas y placas eritematosas que evolucionaron hacia la formación de ampollas y vesículas serosas y serohemáticas, distribuidas en forma de «cadena de perlas». Se sospechó dermatosis ampollosa por IgA lineal y se confirmó mediante biopsia cutánea, que mostró una ampolla subepidérmica con infiltrado neutrófilo y depósitos lineales de IgA en la unión dermoepidérmica mediante*

***Correspondence:**
Juan A. Godínez-Chaparro
E-mail: alberto.godinezch@gmail.com

Date of reception: 24-03-2024
Date of acceptance: 24-07-2024
DOI: 10.24875/BMHIM.24000043

Available online: 02-10-2024
Bol Med Hosp Infant Mex. 2024;81(5):305-310
www.bmhim.com

inmunofluorescencia directa. El tratamiento con prednisona (2 mg/kg al día) y ciclosporina (5 mg/kg al día) resultó en mejoría y la remisión de las lesiones a las 2 semanas. Fue necesario dejar ambos fármacos durante 3 meses debido a la aparición intermitente de ampollas. Se dejó ciclosporina como terapia de mantenimiento a dosis de 4 mg/kg al día por 8 meses. **Conclusiones:** *El reporte destaca el uso de ciclosporina como inmunomodulador alternativo para la dermatosis ampollosa por IgA lineal, un agente inmunosupresor utilizado en trastornos autoinmunitarios. Pocos casos, incluido este, han descrito la remisión completa y el control de la dermatosis con ciclosporina, acompañada de prednisona al inicio del tratamiento.*

Palabras clave: *Dermatitis ampollosa por IgA lineal. Prednisona. Ciclosporina. Reporte de caso.*

Introduction

Linear IgA bullous dermatosis (LABD), also known as chronic bullous disease of childhood, is a rare autoimmune subepidermal vesiculobullous disease that affects mucocutaneous tissues. The disease derives its name from the linear deposition of autoantibodies, primarily immunoglobulin A (IgA), along the dermoepidermal junction[1]. LABD has an annual incidence of 0.5-2.3 cases per million people and is more prevalent in Asian and African populations. This bullous disease represents the most common autoimmune form in childhood and follows a chronic course[2-4].

The initial and maintenance management of LABD is with dapsone; however, this drug is difficult to access and unavailable in certain countries. In addition, there are cases that have shown resistance to first-line treatment, which includes dapsone and prednisone. Furthermore, there is a lack of randomized controlled trials on the treatment of LABD; therefore, the described management options are mostly anecdotal[2]. This article presents the case of a Latin patient with LABD whose disease onset occurred during adolescence and was treated with ciclosporin and prednisone. The patient responded favorably to the initial treatment with ciclosporin and prednisone and achieved adequate therapeutic control solely with ciclosporin in the following months.

Clinical case

A 12-year-old male patient, native and resident of Mexico City, presented with no significant personal or family medical history. He has completed age appropriate immunizations. His current condition began in May 2023 when he suddenly developed a localized dermatosis on the trunk characterized by patches and wheals. In the following weeks, tense vesicles and blisters appeared, causing intense itching. The dermatosis spread to involve all body segments, including oral and genital mucosa, in the following days. The patient consulted multiple physicians, but no clinical diagnosis was issued. He received treatment with antihistamines, steroids, and topical drying agents for 2 weeks without clinical improvement.

In June 2023, he presented to the pediatric dermatology service at La Raza National Medical Center, Mexican Social Security Institute. Initial somatometry measurements were as follows: weight 41.4 kg, height 1.50 cm, blood pressure 100/60 mmHg, heart rate 91 bpm, respiratory rate 18 rpm, and oxygen saturation 91%. On physical examination, he exhibited a disseminated dermatosis affecting all body segments, including oral and genital mucosa. It consisted of erythematous patches that coalesced, annular, and serpiginous erythematous plaques, with tense vesicles and blisters containing serous and serosanguineous fluid. The distribution pattern resembled a “string of pearls,” with erosions and hemorrhagic crusts forming on rupture (Fig. 1). The rest of the physical examination was unremarkable. Laboratory studies revealed a complete blood count with a hemoglobin level of 13.6 g/dL, hematocrit of 42.6%, leukocytosis of 12,115 K/uL with neutrophilia of 8660 K/uL, and platelet count of 323,000 K/uL. Renal function tests, including serum creatinine, were within normal limits.

On clinical suspicion of LABD, a skin biopsy was performed. Histopathology with hematoxylin and eosin staining revealed a subepidermal blister with a predominance of neutrophilic infiltration in the papillary dermis (Fig. 1). Direct immunofluorescence showed linear deposits of IgA at the dermoepidermal junction (Fig. 1). The diagnosis of LABD was confirmed, and treatment was initiated with prednisone at 2 mg/kg/day and cyclosporine at 5 mg/kg/day. Improvement and lesion remission were observed within 2 weeks of therapy initiation. Both medications had to be continued for 3 months due to the intermittent appearance of blisters during this period. Finally, cyclosporine was continued as maintenance therapy at a dose of 4 mg/kg/day for 8 months without any recurrence of blisters reported up to the time of this publication. No adverse drug effects were reported.

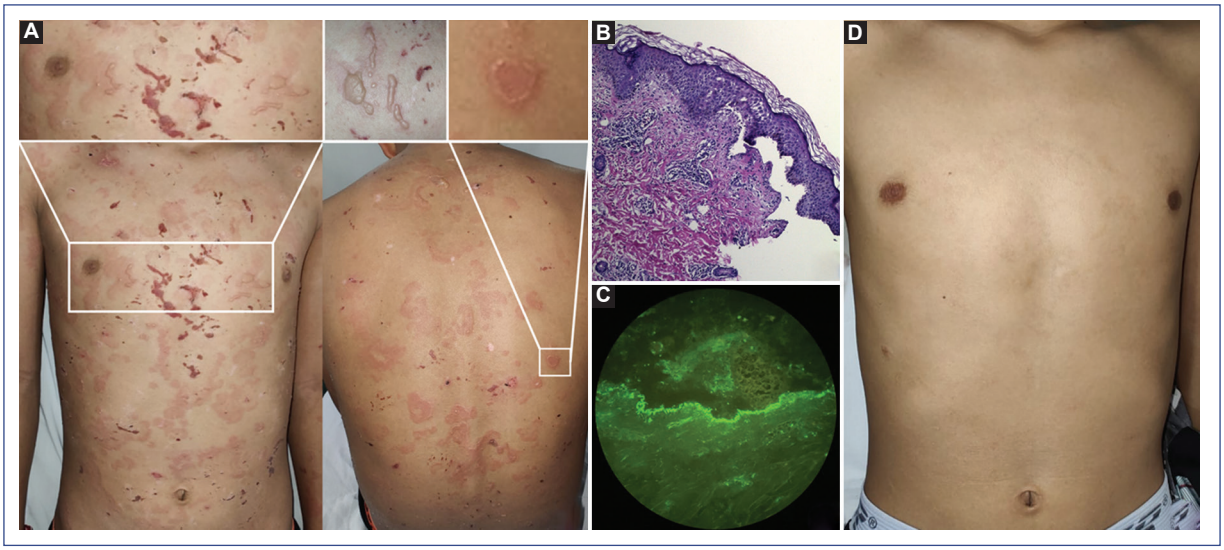

Figure 1. A: dermatosis with annular patches and serpiginous wheals, vesicles, and blisters forming a "string of pearls" pattern and hemorrhagic crusts due to scratching. **B:** subepidermal blister edge with neutrophilic infiltrate in the papillary dermis. **C:** direct immunofluorescence showing linear deposits of immunoglobulin A at the basement membrane. **D:** healthy skin after treatment.

Discussion

LABD involves circulating IgA antibodies against the basement membrane, identified by immunoelectron microscopy in the lamina lucida and sublamina densa. Onset can be triggered by infections, vaccinations, autoimmune diseases, oncological processes, and medications. In some cases, especially in children, no triggering factors are identified[4-6].

The infantile variant of LABD begins in the abdominal and perioral areas and progresses to the rest of the body. It presents with transparent or serohematic vesicles and blisters on normal, erythematous, or target lesion skin, causing itching, excoriations, and blood crusts. New blisters characteristically form at the periphery of resolving lesions, creating a ring pattern known as a "crown of jewels" or "string of pearls."[4] Mucous membranes may be affected. The Nikolsky sign and large skin erosions are more common in drug-induced LABD than in the idiopathic type[5].

The confirmatory diagnosis of LABD is established through the comprehensive evaluation of clinical, histopathological, and immunological findings. Two diseases that can be confused with this condition are dermatitis herpetiformis and bullous pemphigoid (Table 1)[4].

The treatment of choice for managing LABD is dapsone at a dose of 0.5-2 mg/kg/day, often complemented with systemic corticosteroids to control the dermatosis[2,6]. In regions with limited access to dapsone, such as Mexico, other immunosuppressants are used. In cases of glucose-6-phosphate dehydrogenase deficiency, sulfa allergy, therapeutic failure, or unavailability of the drug, and systemic corticosteroids at doses of 0.5-1 mg/kg/day are recommended. If the clinical response is unsatisfactory, alternative drugs such as antibiotics (penicillins, erythromycin, or tetracyclines), intravenous immunoglobulin, colchicine, rituximab, the combination of nicotinamide/niacin + tetracycline, mycophenolate mofetil, methotrexate, cyclosporine, tumor necrosis factor-α inhibitors, omalizumab, sulfasalazine, azathioprine, and thalidomide have been used, though their efficacy is primarily based on case reports rather than clinical studies[2].

Cyclosporine is an immunosuppressant used in autoimmune disorders, including dermatological conditions, by inhibiting the proliferation of activated T lymphocytes through the blockade of Interleukin-2 production[15]. It has been used in severe and resistant cases of LABD along with other immunomodulators like dapsone and corticosteroids[16-19]. In addition, as a steroid-sparing drug, it allows for the reduction or discontinuation of steroids or dapsone, serving as a maintenance option to prevent recurrences over prolonged periods.[4]

Table 1. Comparative table of linear IgA bullous dermatosis of childhood compared to its main differential diagnoses

Variable/disease	Linear IgA bullous dermatosis	Dermatitis herpetiformis	Bullous pemphigoid
References	Yang et al.[3], Mori et al.[4], Bernett et al.[6], Díaz et al.[7], Schultz and Hook[8]	Schultz and Hook[8], Mirza et al.[9], Tekin et al.[10], Reunala et al.[11]	Schultz and Hook[8], Patsatsi et al.[12], Oranje and van Joost[13], Bernard and Borradori[14]
Global incidence (per million population annually)	0.5-2.3 cases	0.8-1.8 cases	6-13 cases
Pediatric onset age	Rare in childhood. Most cases occur in preschoolers aged 3-5 years (mean onset age of 4.5 years).	Rare in children (4% of cases). It is more common between the ages of 2 and 7 years.	Rare in children. Two groups: (a) childhood (under 12 years with a mean onset age of 8.3 years) and (b) juvenile cases (13-18 years, mean age 14.9 years).
Etiology	Autoimmune Autoantibodies mainly IgA Association with HLA haplotypes B8, DR3, DQ2, Cw7	Autoimmune Genetic association with HLA-DQ2 and HLA-DQ8. First-degree relatives have a higher risk. Gluten and tissue transglutaminase are important environmental factors.	Autoimmune Association with alleles DQB1*0301, DRB1*04, DRB1*1101 and DQB1*0302
Physiopathology	Autoantibodies IgA directed against the basement membrane zone. Microscopy identifies two types: one in the lamina lucida and another in the sublamina densa.	Formation of circulating IgA-transglutaminase 3 immune complexes originating from the intestine and deposited in the dermis.	Autoantibodies IgG and/or IgA against specific antigens in the hemidesmosomes that damage the adhesion structure of the dermoepidermal basement membrane zone.
Target antigens (morphological structures)	– LAD Antigen (Anchoring filaments) – BP230/BPAG1e (Hemidesmosomal plaque) – BP180/BPAG2/Collagen XVII (Hemidesmosomal plaque/ Anchoring filaments) – Type VII collagen (Anchoring fibrils)	– Transglutaminase	– BP180/BPAG2/Collagen XVII (Hemidesmosomal plaque/ Anchoring filaments) – BP230/BPAG1e (Hemidesmosomal plaque)
Morphology	Tense vesicles and blisters in a polycyclic configuration over an erythematous annular background resembling a "crown of jewels" or "string of pearls."	Pruritic eruption consisting of blisters, papules, and erythema. Symmetrical lesions. Acral purpura is more common in children.	Tense blisters, sometimes hemorrhagic, on normal, erythematous, or urticarial skin. The blisters exhibit an arciform or rosette pattern. May or may not involve mucous membranes.
Topography	Trunk at abdominal level and proximal extremities. Progresses to the rest of the body. Affects mucous membranes.	Extensor surfaces of forearms, knees, and buttocks followed by back, abdomen, and face.	All body segments. Predilection sites include the face, neck, skin folds, palms, and soles of the feet. Mucous membranes may be affected as well.
Itchiness	Intense	Intense	Intense
Histopathology	Subepidermal blisters with an inflammatory infiltrate composed of neutrophils, some eosinophils, and lymphocytes in the underlying dermis.	Subepidermal blisters with a predominance of neutrophilic infiltrate or formation of microabscesses in the dermal papillae.	Subepidermal blister with infiltration of scattered eosinophils within the blister accompanied by a perivascular infiltrate of neutrophils, numerous eosinophils, and lymphocytes.
Direct immunofluorescence	Linear deposits of IgA at the dermoepidermal junction	Granular deposits of IgA in the dermal papillae.	Linear deposits of IgG and/or C3 along the basement membrane in a "chicken wire" pattern.

(Continues)

Table 1. Comparative table of linear IgA bullous dermatosis of childhood compared to its main differential diagnoses *(continued)*

Variable/disea-se	Linear IgA bullous dermatosis	Dermatitis herpetiformis	Bullous pemphigoid
Treatment	Choice: Dapsone 0.5-2 mg/kg/day. Other options include antibiotics, other immunomodulators such as steroids, cyclosporine, and azathioprine.	Gluten-free diet, dapsone at 0.5 mg/kg/day at the beginning of treatment, and sulfonamide.	Topical steroids or systemic prednisone at a dose of 1-2 mg/kg/day in combination with immunomodulators such as dapsone, azathioprine, mycophenolate mofetil, or erythromycin/nicotinamide.
General associations	Triggers: infectious agents, drugs, other associated autoimmune conditions (systemic lupus erythematosus, rheumatoid arthritis, psoriasis), oncological processes, autoimmune lymphoproliferative syndrome, and gastrointestinal pathology (celiac disease, Crohn's disease, ulcerative colitis).	Celiac disease T-cell or B-cell lymphoma associated with enteropathy. Other autoimmune diseases such as diabetes mellitus, atopic dermatitis, alopecia areata, vitiligo, and thyroid diseases.	Autoimmunity, primary immunodeficiencies, transplant patients. Vaccinations as possible triggers.

IgA: immunoglobulin A; IgG: immunoglobulin G; BP230/BPAG1e: bullous pemphigoid antigen 1; BP180/BPAG2: bullous pemphigoid antigen 2.

Only two anecdotal cases have been documented in the pediatric population where cyclosporine was used with other immunomodulators to treat LABD[16,17]. Ikeya et al., reported a 12-year-old adolescent with LABD following HPV vaccination, who did not improve with erythromycin and required oral prednisolone and cyclosporine[16]. Tate et al., described a 5-year-old child with LABD without identified triggering factors, whose difficult-to-control disease required treatment in a burns unit, receiving dapsone, prednisolone, and cyclosporine[17].

Conclusion

Cyclosporine is a useful pharmacological alternative for controlling LABD. Publishing positive clinical experiences in rare diseases is crucial to generate more scientific evidence, evaluate its efficacy and safety in the disease in the future, and develop standardized therapies.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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