Linear IgA Bullous Dermatosis: Not so “straight” forward.

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Objectives

- Case discussion
- Review pathogenesis of Linear IgA Bullous Dermatosis (LABD)
- Discuss Epidermolysis Bullosa Aquisita (EBA) variant
- Review treatment options
Case Background

- **CC**: 10 year old male with “blisters” of entire body x 2 years

- **HPI**: Patient had extensive bullae and erosions involving entire body for past two years. He admitted to associated pruritus and pain. Caretaker stated these lesions waxed and waned but never resolved.

- **PMHx**: Asthma

- **FMHx**: Denied any family history of blistering disorder.
Case Background cont.

- Medications: Albuterol prn
- Allergies: NKDA
- ROS: Positive for pain and pruritus of skin lesions. Denied any fever/chills or developmental delay.
Physical Exam

- Multiple bullae, vesicles, and erosions grouped in an annular pattern involving the trunk, extremities, face, and genitals

- Many lesions exhibited honey-colored crusts and excoriations
Histopathology

- Neutrophils, along with fewer numbers of eosinophils, aligned along the dermoepidermal junction and aggregated within the papillary dermal tips. There was basal vacuolization with subepidermal blister formation.
On direct immunofluorescence there was a thick linear IgA deposition along the epidermal basement membrane zone.

The thick linear fibrillar staining of IgA localized mostly at the dermal floor of the subepidermal blister. There was no IgG, C3, C5b-9, or fibrinogen deposition.

The findings were diagnostic of linear IgA bullous dermatosis favoring the epidermolysis bullosa acquisita/type VII collagen variant.
Treatment Course

- Our patient was started on Dapsone 50mg daily with a low dose of oral steroids. He initially cleared but after two months he began to develop new bullae and vesicles.

- At his follow up, mycophenolate mofetil 500mg bid and topical triamcinolone 0.1% ointment bid were started.

- During this time he was treated for multiple secondary bacterial infections, including MRSA, and was treated with clindamycin and trimethoprim/sulfamethoxazole.
After 8 months there was no improvement in his condition.

After being presented at a grand rounds, it was decided to treat him based on a study by Kwatra and Jorizzo and he was started on a combination of methotrexate 7.5 mg weekly and prednisone 30 mg daily.

On follow up two months later, he had marked improvement but much of his body surface was still involved. His prednisone dose was lowered to 20 mg daily and methotrexate was increased to 10 mg.
One month later, the patient was 80% clear.

Despite this at his next follow up appointment 3 months later he was flaring with at least 50% worsening of skin lesions.

He was referred to Drs. Schachner (pediatric dermatology) and Nousari (immunobullous) in Miami and after much evaluation the joint group of physicians have decided to try treatment more consistent with EBA.
LABD Overview

- Linear IgA Bullous Dermatosis (LABD) is a rare, autoimmune, subepidermal vesiculobullous disease that is characterized immunopathologically by the linear deposition of IgA at the basement membrane zone (BMZ).

- There are two variations of LABD, adult-onset and childhood-onset (also called Chronic Bullous Dermatosis of Childhood).

- LABD can be idiopathic or drug-induced.

- Antibodies bind to the epidermal side of the BMZ characterizing classic LABD as well as antibodies binding to the dermal side of the BMZ characterizing IgA mediated-Epidermolysis Bullosa Acquisita (IgA-EBA).
Rare disease, 0.1 to 2.3 cases per million individuals per year

Bimodal age of onset: 6 months to 6 years and > 60 years old

No clear gender predilection
LABD Causes

- Idiopathic
- Drug related: Most commonly vancomycin but also reported with phenytoin, amiodarone, captopril, and NSAIDs
- Possible infectious etiology: upper respiratory tract infections, typhoid, brucella, tetanus, varicella-zoster, and gynecologic infections
- Increased frequency of HLA Cw7, B8, DR3, and DQ2
LABD Pathogenesis

- It is not fully understood but many studies demonstrate both humoral and cellular mechanisms.
- It is an inflammatory process that starts with activation of the complement cascade and recruitment of neutrophils.
- Neutrophils release proteolytic enzymes resulting in separation of the dermo-epidermal junction.
- The IgA antibodies are thought to contribute directly to the destruction of the basement membrane zone, recruit neutrophilic infiltrate, and activate complement.
Most patients have autoantibodies against the BP-180 antigen but many other antigens have been documented.

Type VII collagen has classically been described as the antigen targeted in epidermolysis bullosa acquisita by IgG antibodies.

When Type VII collagen is targeted by IgA antibodies it is classified as IgA-EBA. Some authors believe this to be a subset of LABD while others believe it to be a subset of EBA.

Many studies attribute the heterogeneous nature of this disease to the multiple antigens targeted.
LABD consists of a combination of annular bullae, vesicles, and/or papules found in groups.

Subepidermal bullae are tense and often form a “cluster of jewels” or rosette pattern.

Children often have lesions on face, lower abdomen, perineal, and anogenital regions with generalization to the trunk extremities, hands, and feet.

Pruritus is common.

Mucosal involvement has been noted in up to 80% of adult patients but varies in children.
IgA-EBA Clinical Manifestations

- Lesions vary and resemble those of classic LABD.
- Lesions have been described as erythematous urticarial plaques, vesicles, bullae, and erythema-multiforme-like.
- Scarring and milia may occur.
**Diagnosis**

- Difficult due to similarity of many immunobullous diseases
- Requires hematoxylin-eosin stained biopsies with direct and indirect immunofluorescence studies
- Histology: subepidermal blister with a primarily neutrophilic infiltrate in the superficial dermis
- DIF: linear deposition of IgA along the basement membrane
- IIF: circulating IgA antibodies to antigens on the BMZ but only positive in 30-50%
Diagnostic Dilemma

- Most antibodies in LABD bind to the 97kDa and 120kDa antigens, fragments of the BP180 hemidesmosomes in the lamina lucida
  - This causes mapping to the epidermal side of the salt-split skin

- Another pattern found was antibodies binding to both sides of the lamina densa creating a “mirror image”

- Cases like ours have documented IgA antibodies binding to collagen type VII in the lamina densa and sublamina densa causing mapping to the dermal side of the salt-split skin
Treatment

- There are no large, randomized, controlled trials on the treatment of LABD in adults or children to date.

- Successful treatment has been based on previous case studies and observations.
Historically, Dapsone is the treatment of choice due to its anti-inflammatory and immunomodulatory effects.

It is thought to inhibit lysosomal activity, myeloperoxidase mediated iodination, and adherence of neutrophils to the basement membrane zone.

Dose of 50-200mg/day for adults and 0.5-2mg/kg/day for children have been documented.

The response is usually fast and causes long-lasting remission.
Treatment: Dapsone cont.

- Side effects: Most patients experience a benign hemolysis that partially corrects itself with a compensatory reticulocytosis.

- Potentially fatal side effects: hepatotoxicity, dapsone hypersensitivity syndrome, agranulocytosis, and aplastic anemia.

- Other side effects: methemoglobinemia, peripheral motor neuropathy, paresthesias, and weakness.

- Monitoring: screen for G6PD deficiency, baseline CBC with differential and liver function tests, weekly CBC x 1 month then monthly for 6 months.
Treatment cont.

- Other treatments include:
  - Sulfonamides: sulfapyridine, sulfasalazine
  - Oral antibiotics: tetracycline
  - Immunomodulants: corticosteroids, tacrolimus, mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, cyclophosphamide, immunoadsorption, rituximab, and IVIg
  - Adjunctive treatments: colchicine and thalidomide

- IgA-EBA demonstrates mixed results with dapsone
  - Others: colchicine, sulfapyridine, cyclophosphamide, methotrexate, and plasmapheresis have all been used
Our Patient

- Failed Dapsone with corticosteroids
- Failed mycophenolate mofetil with corticosteroids
- Failed methotrexate with corticosteroids
- Due to patient compliance and economic burden, IVIg could not be tried
- After consultation with Drs. Schachner and Nousari in Miami we feel the next best course of action is rituximab infusion.
Treatment: Rituximab

- Chimeric monoclonal antibody targeted against CD 20, a receptor located on B-cells
- CD20 contributes to B-cell activation and differentiation
- Originally used to treat B-cell tumors and autoimmune diseases
- Lozinski et al successfully treated a patient with classic LABD with rituximab
- There are no current case reports of IgA-EBA treated with rituximab but many exist demonstrating clearance of classic forms of EBA.
- Most common side effects: mild to moderate infusion-related reactions but there is risk of sepsis with cases of *Pneumocystis carinii* and *Pseudomonas* reported
Treatment: Rituximab cont.

- Three studies: Weekly infusions x 4 weeks
- Another: weekly infusions at lowered dose x 5 weeks due to poor health of the patient
- All had concomitant use of adjunctive treatments such as corticosteroids or immunomodulatory agents.
- Our patient will begin Rituximab and continue mycophenolate mofetil.
Not all immunobullous diseases are “straight” forward diagnoses.

Immunofluorescence with serration mapping is important to distinguish between diseases such as classic LABD and IgA-EBA.

Not all diseases with a self-remitting prognosis self-remit. Treatment resistance can always happen.

Every immunobullous patient is unique and their treatment should be tailored to them specifically.
References

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Thank You!