CASE REPORT

Previously misdiagnosed linear IgA dermatosis resolved with dapsone

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SUMMARY

This is the case of a 25-year-old African American woman with a 3-week history of itching with burning, blistering lesions on her torso and extremities. Medical history was unremarkable. Medical treatments included three visits to urgent care, where she was treated with antivirals, oral and topical steroids, antibiotics and antifungals unsuccessfully. We performed a skin biopsy, and immunofluorescent studies revealed a linear deposition of IgA antigen at the basement membrane. The clinical diagnosis of linear IgA dermatosis (LAD) was established, with no eliciting cause, other than potential occupational exposure to *Chlamydomonas psittaci* via her employment in a pet store. This is the first case to our knowledge to report such an association. However, confirmation of the exposure would only establish correlation, not causality. Resolution of symptoms and blisters was achieved with dapsone treatment. Accordingly, we highlight the crucial importance of reviewing exposures, along with the potential aetiology of LAD.

BACKGROUND

LAD is a rare autoimmune blistering disease, characterised by linear deposition of IgA antibodies at the dermoepidermal junction of the skin. The typical clinical presentation consists of annular or grouped vesiculobullous lesions, often associated with pruritus and involvement of mucous membranes. Autoimmune blistering diseases include pemphigus vulgaris, epidermolysis bullosa acquisita, paraneoplastic pemphigus, cicatricial pemphigoid, dermatitis herpetiformis, bullous pemphigoid and LAD.¹ The bullous rash lesions of LAD presents as pruritic annular papules, vesicular bullae that usually manifest on extensor surfaces, buttocks and torso.² Histopathology demonstrates collections of neutrophils along the basement membrane and dermal papillary tips. Diagnostic workup includes serological tests, including indirect immunofluorescence, direct and immunoblotting. Direct immunofluorescence demonstrates deposition of IgA in a linear pattern along the basement membrane, and occasionally there may be deposition of IgG and C3.³ The prevalence of LAD in the USA is highest in Utah, estimated as 0.6 per 100 000 adults and mostly affecting women. Internationally, LAD has been commonly reported in Southern England, Tunisia and France.^{4,5} LAD is an autoimmune disease, however, documented cases have been reported with prodromal exposure to vancomycin,⁶ influenza vaccination,⁷ *Chlamydia*

and other infections, myeloproliferative disorders.⁸ Gluten sensitivity has not been associated with LAD. Evidenced-based guidelines for management of bullous skin lesions associated to LAD or bullous pemphigoid suggests no gold standard treatment.⁹ However, pharmacological treatment with systemic corticosteroids should be considered first, with doxycycline, dapsone, nicotinamide, azathioprine or sulfapyridine for mild to moderate disease.¹⁰ Dapsone has been reported as one of the most effective agents for LAD. Doses of 50–150 mg/d in adults have shown to be rapidly effective, and lesions may begin to resolve within 72 hours.¹⁰ Sulfapyridine, for example, has also been shown effective and with a milder side effect profile.¹¹ Other treatment alternatives that are less substantiated include prednisone, colchicine, tetracyclines and nicotinamide.¹⁰ In fact, several cases report bullous skin lesions similar to LAD that can mimic bullous pemphigoid, dermatitis herpetiformis, erythema multiforme, severe eczema¹² and toxic epidermal necrolysis.¹³ Therefore, the purpose of this case is to report the successful diagnosis and treatment outcome after consecutive failed treatments and misdiagnosis of a case of LAD, which is a rare condition easily misdiagnosed and improperly treated. Additionally, this case discusses the importance of appropriate differential diagnosis and the need to define a consensus around diagnostic criteria for bullous skin lesions.

CASE PRESENTATION

This is the single case of a 25-year-old African American woman who presented to a specialty clinic with a 3-week history of blister-like skin lesions, burning pain, itchy rash along her torso, upper back and lower extremities. The patient's medical treatment history included prescription of acyclovir and benadryl a few days after the onset of symptoms without improvement. Additionally, treatment history included use of oral and topical steroids, antifungals and antihistamines with consecutive visits to the emergency room and urgent care on several occasions, without symptomatic relief. Medical history was unremarkable prior to onset of symptoms, without skin trauma, new medications or significant changes to her daily routine. Specifically, there was no history of travelling, illicit drug, alcohol use, vancomycin use or any other medications. She had mild respiratory symptoms weeks earlier but did not seek medical care. The patient was a full-time college student and worked part time at a pet store. Importantly, she reported cleaning bird cages repetitive during

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Figure 1 'Cluster-of-jewels' sign—upper torso-posterior.

her shifts, but most recent, a few days prior to the onset of symptoms.

On full dermatological physical examination, the patient was alert, oriented and cooperative. Skin findings revealed multiple annular rings of blisters with erythematous bullous base throughout the posterior torso and both upper and lower extremities noted. Close-up examination of the bullous lesions revealed a classic string of pearls sign or a tight cluster-of-jewels sign (figureS 1 and 2).

Figure 2 Blisters—lower extremities.

Table 1 Most common target antigens and associated diseases with immunofluorescence findings

Disease	Main target antigens
Bullous pemphigoid	BP180, BP230
Mucous membrane pemphigoid	BP180, BP230, $\alpha 6\beta 4$ integrin, laminin-332
Pemphigoid gestations	BP180, BP230
Linear IgA dermatosis	BP180, BP230
Lichen planus pemphigoides	BP180, BP230
Anti-p200 pemphigoid	Laminin c1

INVESTIGATIONS

On patient's written and verbal consent, a punch biopsy was performed and the diagnosis of LAD was confirmed with the presence of subepithelial bulla and papillary microabscess with high neutrophil predominance. Furthermore, direct immunofluorescence studies confirmed the diagnosis with the presence of IgA deposits along the basement membrane zone (BMZ) in a linear pattern.

DIFFERENTIAL DIAGNOSIS

Bullous skin lesions are common skin findings for several dermatological conditions; therefore appropriate medical history, occupational history, physical examination and differential diagnosis are essential for successful treatment. Pemphigus vulgaris, bullous pemphigoid, paraneoplastic pemphigus, dermatitis herpetiformis, erythema multiforme, severe eczema and toxic epidermal necrolysis are a few of the most common differential diagnosis for bullous skin lesion. Furthermore, this patient had a potential prodromal occupational exposure to *Chlamydophila psittaci*, which may cause pneumonia, and one case has been reported¹⁴ for a possible association between pneumonia and bullous skin lesion presentation. Although postinfective LAD usually peaks a few weeks after the original infection, this association cannot be overlooked. Additional differential diagnoses include: mucous membrane pemphigoid, pemphigoid gestations, lichen planus pemphigoides and anti-p200 pemphigoid.¹⁵ A rigorous skin examination biopsy, and moreover, detection of tissue-bound and circulating autoantibodies is necessary to separate bullous pemphigoid lesions from each other, and current guidelines still consider immunofluorescence the gold standard for the diagnosis.¹⁶ Table 1 below describes the most common target antigens and associated diseases with immunofluorescence findings.¹⁵

TREATMENT

The pharmacological treatment used in this case report after the appropriate confirmatory diagnosis of LAD was oral dapsone 50mg twice a day and oral prednisone 60mg loading followed by 40mg daily for a 5-day period. Dapsone and sulfapyridine are usually given for skin lesions in LAD and low-dose prednisone can initially be used to suppress blister formation. Due to the haemolytic nature of dapsone, haemoglobinuria, methaglobinuria and glucose-6-phosphate dehydrogenase deficiency diagnosis should be excluded prior to dapsone therapy.¹⁷ The prognosis of LAD is variable and in some cases can spontaneously regress or the condition may persist for several years even with appropriate treatment.³ Currently, there are no available published data regarding evidenced-based guidelines for treatment of bullous skin lesions associated to LAD. However, the clinical consensus is that pharmacological treatment with dapsone, sulfapyridine and low-dose prednisone should be initiated on establishment of the LAD diagnosis by skin biopsy.

Figure 3 Four weeks post-treatment.

OUTCOME AND FOLLOW-UP

At the end of the 4-week treatment plan, the patient was asymptomatic and with complete resolution of the rash and blisters (figure 3). The patient was re-evaluated by a rheumatologist and dermatologist, who both acknowledged maximal medical improvement and complete resolution of initial chief complaint with occasional necessity for additional treatment. A 6-month re-evaluation visit revealed that the patient had remained asymptomatic, without skin blister flare-up and did not require additional or maintenance treatment.

DISCUSSION

Linear IgA has a bimodal age of onset and as in this case; age at presentation is considered an important prognostic factor influencing the clinical course of the disease. Adult onset varies from 14 to 80 years, most commonly autoimmune on the younger and drug-induced disease in the elderly.⁹ Typical skin manifestations include multiple vesicles, blisters and erythema erosions along the extensor surfaces and torso. Histopathologically, LAD is characterised by neutrophilic infiltration and subepidermal blister with the presence of continuous linear IgA deposits at the BMZ.¹⁵ IgA autoantibodies in LAD were shown to target most characteristically the antigens proteins 97 and 120 kDa extracellular domains of BP180 (collagen XVII), termed the LAD antigen 1 (LABD97) and LAD-1, respectively.^{15 17} Anti-BMZ isotype reactivity sounds found an association with IgA autoantibodies for younger patients and IgG for older patients.³ HLA-B8, HLA-DR3 and HLA-DQ2 rates increase in these patients.¹⁵ The mechanism for blister formation is not fully understood; however, it has been thought to be associated to IgA and complement-mediated neutrophil chemotaxis with autoantibodies producing neutrophil-rich infiltrates and subepidermal vesicles along the BMZ and linear IgA deposits, but IgG (25% of cases) and C3 can be detected.^{3–15} The most common cases documented with a prodromal exposure include drug induced to captopril, lithium, furosemide, vancomycin and phenytoin. Postinfection LAD is rare; however, cases with prior exposure to influenza vaccination, poststreptococcal glomerulonephritis, *Chlamydia* and myeloproliferative disorders have also been reported.^{8 15} Typically, lesions arise within 7 to 14 days of onset of the offending trigger. Dapsone has been established as one of the most effective pharmacotherapies for LAD with remission of symptoms in 3 days; however, dapsone should be used carefully due to the risk

of haemolysis and methemoglobinaemia (which are dose dependent), motor neuropathy, neutropaenia and hepatitis. Therefore, blood count, liver enzymes, methemoglobin and haptoglobin must be regularly monitored.¹⁵ Our qualitative literature review comprised several peer-reviewed articles, including case reports and reviews; however, this is the first case to our knowledge that the bullous skin lesions related to LAD are potentially associated to a possible occupational exposure to *C. psittaci* and to consecutive misdiagnosis of severe eczema, dermatitis herpetiformis and fungal infection, as well as inappropriate treatments. This patient had mild upper respiratory symptoms weeks earlier to onset of LAD; however, she did not seek medical care and no confirmatory diagnosis was established for her respiratory symptoms. However, confirmation of the exposure would only establish correlation, not causality. Finally, this research has potential limitations, considering it is the report of only one case. This is one of the few cases in the literature reporting a potential infectious aetiology of LAD. Therefore, with this single case report, we emphasise the importance of differential diagnosis of bullous skin lesions, including proper medical and occupational history, biopsy, immunofluorescence imaging and appropriate treatment, highlighting the need to define a consensus on diagnostic criteria and treatment for bullous skin lesions differentials, including rare aetiologies of LAD.

Learning points

- ▶ Bullous skin lesions are a common physical finding of several dermatological diseases; therefore, differential diagnosis is essential for appropriate treatment and a successful outcome.
- ▶ Skin biopsy with immunofluorescence is considered the gold standard diagnostic method and should be performed early in the course to avoid inappropriate treatment and misdiagnosis, as reported by this single case.
- ▶ Appropriate differential diagnosis should be contemplated, especially considering that LAD is potentially associated to environmental triggering factors and drug interactions, such as drug-induced, myeloproliferative-induced, and infectious-induced LAD.

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