Diffuse vesiculobullous eruption with systemic findings

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Abstract
Drug induced linear IgA bullous dermatosis (LABD) is a rare blistering disease that has been shown to be associated with the use of various medications. Although rarely seen together, some of the medications associated with LABD can lead to the syndrome drug reaction with eosinophilia and systemic symptoms (DRESS), which presents with fever, cutaneous eruption, and multi-organ involvement. We present a patient who developed fever and a generalized vesiculobullous eruption after recently starting amlodipine and meloxicam. Initial laboratory tests demonstrated elevated liver function tests, leukocytosis, and eosinophilia. Histopathologic examination of the punch biopsy revealed a bulla with sub-epidermal split and numerous neutrophils. Direct immunofluorescence demonstrated broad deposition of IgA along the dermal-epidermal junction. These findings were consistent with an overlap between LABD and DRESS. Drug induced LABD and DRESS are independently both rare diseases. It is even more uncommon to see the two concurrently in the same patient. In this patient, these two conditions were thought to be triggered by either amlodipine or meloxicam. Given the high mortality rate associated with DRESS, it is important to recognize the presentation and initiate the appropriate treatment plan as soon as possible.

Keywords: diagnosis, drug eruptions, drug hypersensitivity syndrome, fluorescent antibody technique, linear iga bullous dermatosis

Introduction
Linear IgA bullous dermatosis (LABD) is an uncommon drug induced or idiopathic autoimmune blistering disease that presents as generalized erythematous plaques, vesicles, or bullae and which can affect both skin and mucosal membranes [1, 2]. Linear IgA bullous dermatosis derives its name from the visualization of continuous linear IgA deposits in the basement membrane zone under direct immunofluorescence microscopy [1].

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe reaction which presents 2-8 weeks after the offending drug is initiated with fever, rash, lymphadenopathy and multi-organ involvement [3, 4]. The incidence rate is reported to vary from 1:1000 to 1:10,000 drug exposures with a fatality rate of 5-10%, typically related to hepatic failure [3, 5].

Both drug induced LABD and DRESS have independently been reported to be associated with a wide range of medications to include antibiotics, non-steroidal anti-inflammatory drugs, and anti-hypertensive medications [1-7]. To the best of our knowledge, we present the first case report of a patient with drug induced LABD with clinical features of DRESS related to either amlodipine or meloxicam.

Case Synopsis
A 61-year-old woman presented to the emergency department with three days of a generalized
vesiculobullous eruption including oral and vaginal mucosa. Symptoms of fever, sore throat, and fatigue were also reported. Her medical history was pertinent for hypertension with recent addition of amlodipine approximately six weeks prior. She was also recently re-started on meloxicam, which she had intermittently used in the past for osteoarthritis-related joint pain. Physical examination demonstrated crusted papules and bullae of varying sizes on the extremities and trunk (Figure 1). Erosions with peripheral erythema were present on the undersurface of tongue and buccal mucosa (Figure 2). Initial labs revealed elevated liver function tests to include alkaline phosphatase at 219 U/L, alanine aminotransferase at 117 U/L, and aspartate aminotransferase at 77 U/L. Additionally, her white blood cell count was increased to 16.3 x 10^3/mcL with an increase of eosinophils to 13% and the presence of atypical lymphocytes at 1%. Punch biopsy of a representative lesion (Figure 3) and direct immunofluorescence (Figure 4) was performed. Histopathologic examination of the initial punch biopsy demonstrated bulla with sub-epidermal split and abundant neutrophils. Special stains for microorganisms were negative. Direct immunofluorescence demonstrated broad deposition of IgA along the dermal-epidermal junction. Staining for IgG, IgM, C3, and fibrin was not appreciated. These findings were all consistent with LABD. Given the clinical presentation and lab findings discussed above, an overlap diagnosis of DRESS was made.

It was thought that the patient’s presentation was medication-induced with either amlodipine or meloxicam being the most likely cause. Both medications were discontinued and the patient was placed on a prolonged prednisone taper starting at 40mg daily for the first three weeks, which was then decreased by 10mg every two weeks subsequently, for a total of nine weeks total on oral corticosteroid. Given the diagnosis of LABD, the patient was also
started on 50mg of dapsone daily, which was continued for a total of six months. Following discharge from the hospital, the patient’s skin disease progressively cleared with only residual hyperpigmentation. At three-month follow-up, laboratory values had normalized to include alkaline phosphatase at 75 U/L, alanine aminotransferase at 16 U/L, aspartate aminotransferase at 14 U/L, white blood cell count at 10.9 x 10^3/mcL, eosinophils at 3.8%, and no atypical lymphocytes. Since that time, the patient has intermittently used meloxicam again without any known sequela. Re-challenge with amlodipine has not been done.

**Case Discussion**

Linear IgA bullous dermatosis presents with heterogeneous cutaneous manifestations and clinical findings similar to other bullous diseases including bullous pemphigoid, dermatitis herpetiformis, and Stevens-Johnson syndrome/toxic epidermal necrolysis. The histopathologic findings of LABD are sub-epidermal blisters with a neutrophil predominant dermal infiltrate, which overlaps with dermatitis herpetiformis and bullous lupus erythematosus [1]. The gold standard for diagnosis of LABD is direct immunofluorescence microscopy demonstrating deposition of IgA in a linear pattern along the basement membrane [1, 2, 6, 7].

Linear IgA bullous dermatosis is typically idiopathic, but may also be induced by medications, occur following an infection, or appear in association with inflammatory bowel disease or malignancy [1, 2]. Our case was thought to be related to either amlodipine or meloxicam. The fact that the patient has rechallenged with meloxicam without ill effect makes this less likely as the causative factor. Amlodipine induced LABD has previously been described at the case report level [7]. Of the non-steroidal anti-inflammatory drugs (NSAID), diclofenac, piroxicam, and naproxen induced LABD have all been reported [1, 2, 6]. The theorized pathophysiologic mechanism of drug induced LABD proposes that drug specific T-cells release cytokines that lead to the production of IgA autoantibodies targeted against several basement membrane antigens [1, 6]. Binding of these antigens leads to complement activation, inflammatory mediator release, and infiltration of inflammatory cells, which release proteolytic enzymes that damage the basement membrane resulting in bulla formation [6].

Our patient had drug induced LABD which presented with clinical manifestations of DRESS. There is large variability in the presentation of DRESS, although common findings include cutaneous eruption, hematologic abnormalities, lymphadenopathy, and internal organ involvement [2-5]. It typically presents with a high fever followed by skin rash and lab abnormalities approximately two to eight weeks after the offending drug is started [3]. The liver is the most frequent internal organ affected and the reaction manifests with mild elevations in liver function tests. Other common laboratory abnormalities include eosinophilia and atypical lymphocytosis [3].

Drug reaction with eosinophilia and systemic symptoms is usually associated with aromatic anticonvulsants and sulfonamides, although other medications including amlodipine and NSAID, such as ibuprofen and celecoxib, have been described [2-5]. A review of literature revealed no cases of DRESS associated with meloxicam. Although the pathogenesis is not well understood, DRESS is thought to be related to malfunctions in drug specific metabolic pathways and reactivation of...
human herpesvirus type-6, 7 and Epstein-Barr virus [2, 3].

Treatment for both entities requires immediate discontinuation of the suspected medication. A prolonged steroid taper is required for DRESS and the addition of dapsone for LABD may be necessary [1-7]. In patients who do not tolerate dapsone or in whom it is contraindicated, other agents such as sulfapyridine, colchicine, prednisone, or other corticosteroid sparing agents can be used as second line therapies [8-10]. Patients with DRESS typically see complete resolution of symptoms within weeks to months, although periods of remissions and relapses have been described [3]. Fatalities occur in 5-10% of patients regardless of treatment, with hepatic necrosis reported as the primary cause of death [3, 10].

**Conclusion**

Given the unique findings of LABD on direct immunofluorescence, the diagnostic markers of this disease are well accepted. In contrast, DRESS is a challenging diagnosis to reach given its variable pattern of cutaneous and organ involvement and extended time frame between drug initiation and symptom onset. This case is significant as it is the first reported association between amlodipine or meloxicam and LABD with clinical manifestations of DRESS. The presentation of these entities was recognized early on and appropriate therapy was initiated. The patient had complete clearing of her skin disease and resolution of organ involvement.

**References**