Linear IgA bullous dermatosis: a clinical study of 16 cases at National Taiwan University Hospital

I-Chen Tsai1, Chia-Yu Chu2*, Hsiang-Jung Chen2, Li-Fang Wang2, Hsien-Ching Chiu2

1Department of Dermatology, China Medical University Hospital, Taichung, Taiwan
2Department of Dermatology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

ABSTRACT

Background Linear immunoglobulin A bullous dermatosis (LABD) is a rare autoimmune subepidermal bullous disease. It is defined by continuous linear deposition of IgA in the basement membrane zone on direct immunofluorescence microscopy. The clinical presentations of LABD may mimic other diseases, and data in Taiwanese populations are still lacking. The current study aims to examine LABD status in Taiwan.

Methods We reviewed the database at our institute from 1995 to 2008. The gold standard for the diagnosis of LABD is based on continuous linear depositions of IgA in the basement membrane zone on direct immunofluorescence.

Results A total of 16 LABD patients were identified. Mean age at diagnosis was 55 years, and most (>80%) occurred after the fourth decade. The trunk was most commonly involved (76%). However, in contrast to previous reports, the mucosal involvement was rare in our series (18%). Initial impressions were dermatitis herpetiformis in 8 patients (50%), bullous pemphigoid in 4 patients (25%), and vasculitis, varicella, and pemphigus vulgaris in the remaining 4 patients (25%). Four patients reported a history of drug ingestion shortly before the onset of the disease, and all recovered after discontinuing the offending drugs. One of them had griseofulvin-associated LABD, a case not reported previously. The other three drugs were rifampin, vancomycin and gemcitabine. Among the various regimens, dapsone (100mg) twice a day achieved the best treatment response in the five treated patients.

Conclusion The rare and diverse presentations of LABD highlight the importance of our study results in aiding clinical diagnosis and planning treatment strategies.

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KEYWORDS
Direct immunofluorescence microscopy
Linear immunoglobulin A bullous dermatosis
Griseofulvin

Introduction

Linear IgA bullous dermatosis (LABD) is a rare autoimmune subepidermal blistering disorder defined by the presence of homogenous linear deposits of IgA in the cutaneous basement membrane zone (BMZ). LABD was first discussed in 1901, with the description of 15 children having nonpruritic blistering eruptions.1,2 However, it was not recognized as an entity separate from dermatitis herpetiformis until 1979, based on the findings of immunopathology, and the lack of consistent association with a gluten-sensitive enteropathy.2

The clinical manifestations of LABD are heterogeneous. Patients may have some features similar to both DH and bullous pemphigoid.2–4 Thus, it is difficult for clinicians to make the diagnosis of LABD with confidence. The causes of LABD are not clear. Certain drugs, autoimmune diseases, infection, chronic renal insufficiency and malignancies have all been reported to be associated with this disease.2–4 Since LABD is such a rare disease with diverse clinical manifestations and etiologies, reviewing our local data is crucial to providing clinicians with useful diagnostic clues. Here, we performed a retrospective analysis and collected cases of direct immunofluorescence (DIF)-proven LABD from our...
institutional database to define the clinical features, pathological findings, potential etiologies, treatment responses and clinical outcomes in a Taiwanese population.

**Materials and methods**

From 1995 to 2008, a total of 16 patients were identified from our institutional database. The gold standard for the diagnosis of LABD is based on the DIF of perilesional skin, which reveals continuous linear depositions of IgA in the BMZ. Medical records were reviewed to obtain information on gender, age and location at onset, interval between disease onset and diagnosis confirmation, clinical manifestations, symptoms, drug associations, underlying systemic diseases, preceding infections and treatment responses. “Drug association” was defined as new drug intake identified by history from 1 to 14 days before the eruption onset. “Effective treatment” was defined as no new blister formation and healing of old lesions during tapering of medication. If disease activity increased once medications were tapered, but could still be controlled after resuming the previous dosage, the response to treatment was defined as “stationary”. Continuous progression in disease severity in spite of persistent medical treatment was regarded as “ineffective” treatment response. “Remission” was defined as no relapse of the disease after complete discontinuation of the medications. Clinical follow-up outcomes were assessed at clinic visits and/or by telephone interviews for those who couldn’t come to our clinic due to living a long distance from the clinic or remission of the disease.

**Results**

**Patient characteristics**

Demographic data are presented in Figure 1 and Table 1. Of the 16 patients, 8 were males (50%). There was no gender difference in our patient cohort. The mean age at diagnosis was 55 years (median, 57 years; range, 24–80 years).

![Figure 1 Age distribution of disease onset.](image-url)

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age at onset (yr)</th>
<th>Mucosal lesion</th>
<th>Interval between onset and diagnosis (d)</th>
<th>Clinical feature</th>
<th>Histopathology</th>
<th>Immunopathology</th>
<th>Treatment/response</th>
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<td>–</td>
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<td>35</td>
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<td>+ (weak)</td>
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</table>

M=male; F=female; NA=not available; SE=subepidermal; PMN=polymorphonuclear neutrophils; Eos=eosinophils; DC=discontinued; R=remission; E=effective; S=stationary; SR=spontaneous remission; FU=follow-up.
Most patients (>80%) had LABD after the fourth decade of life. The interval between disease onset and diagnosis confirmation by DIF varied. The mean interval was 58 days, however, two patients had an extremely long period before accurate diagnosis was made. One patient (No. 12) had been diagnosed as generalized eczema until she was referred to our institute, where a biopsy with DIF was performed. Several biopsies were performed on one patient (No. 6) until the confirmation of the diagnosis was made.

**Clinical manifestations**

The distribution of the eruptions is shown in Figure 2. The trunk was involved in 12 (76%) patients, the extremities in 10 (62%) and perineum in 2 patients (12%). Eight (50%) patients presented with a combination of annular or grouped papules, vesicles, and bullae. Thus, the initial impression of the symptoms of these eight patients was a diagnosis of dermatitis herpetiformis (Figure 3). Four patients (25%) presented with tense and large blisters on the erythematous base, and hence were initially diagnosed with bullous pemphigoid. Pemphigus vulgaris-like lesions were noted in three of these patients, and the remaining patient presented with vasculitis-like lesions.

Fourteen (90%) patients complained of pruritus before the onset of eruptions or during the occurrence of eruptions. There were no concurrent constitutional symptoms, such as fever, arthralgia or muscle weakness. In our series, mucous

![Figure 2](image2.png) Distribution of the involved areas.

![Figure 3](image3.png) (A) Clinical pictures of patient No. 15. Symmetrically grouped erythematous papules, vesicles and bullae arranged in an annular pattern on the upper chest, which is similar to the presentation of dermatitis herpetiformis. (B) Vesicles and blisters superimposed at the edge of annular lesions, creating a typical “string of beads” sign. (C) Clinical pictures of patient No. 10. Erythematous, slightly edematous plaques studded with large, tense bullae on the lateral aspect of trunk which is easily misdiagnosed as bullous pemphigoid. (D) Classical “clusters of jewels” appearance: cluster tense blisters on the erythematous base.
membrane with the presence of erosion on the lips and/or buccal mucosa occurred in only 3 patients (18%).

**Association with drugs and systemic diseases**

Four patients (25%) reported a history of drug ingestion shortly before the onset of the disease, including rifampin, vancomycin, gemcitabine, and griseofulvin. One had a recurrent urinary tract infection before each episode of LABD. Three patients had chronic renal insufficiency before the onset of LABD.

**Histopathology and immunopathology**

A total of 19 tissue specimens from the 16 patients were reviewed. Subepidermal blisters were seen in 15 patients; polymorphonuclear neutrophil infiltration in the upper dermis predominated in 12 patients; both polymorphonuclear neutrophil and eosinophil infiltrations were observed in three patients, and mainly eosinophil infiltration in two patients (Figure 4).

The immunopathological findings are summarized in Table 1. In 10 patients (62.5%), IgA was the only positive immunoreactant (Figure 5), while in the remaining 6 patients, IgG or C3 were also weakly positive in addition to IgA.

**Treatment and clinical response**

Medications and treatment responses are summarized in Table 1. Treatment responses were not available in two patients who were lost to follow-up. Spontaneous remission without any treatment was noted in one patient. In the four patients with drug-associated LABD, all eruptions resolved completely after discontinuing the offending drugs with \( n=1, \) prednisolone 0.5–1 mg/kg/day) or without \( n=3 \) concurrent use of systemic medications. In the patient with urinary tract infection-related LABD, the eruptions subsided after the administration of systemic antibiotics and low dose prednisolone. In the remaining eight patients, prednisolone was used as the initial medication in two patients, resulting in a good response. Dapsone was used in the other six patients with five responding excellently to medical treatment, and with one patient having an adverse effect (dapsone hypersensitivity syndrome). The treatment was then shifted to prednisolone and combination therapy with hydroxychloroquine to control the disease activity.

**Discussion**

In the present study, we retrospectively reviewed the clinical and pathological features of DIF-proven LABD in a Taiwanese population. We found a low incidence of mucosal involvement as well as fair recovery after discontinuing the offending medication in drug-related LABD. The rare and diverse presentation of this disease highlights the

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**Figure 4** Histopathology of skin biopsy on the upper chest lesion from patient No. 15. (A) A subepidermal blister with intact epidermis (H&E, 20×). (B) Prominent neutrophils with few eosinophils in the dermal papillary tips (H&E, 200×).

**Figure 5** Direct immunofluorescence microscopy performed on the perilesional skin biopsy specimen (200×). Continuous linear IgA deposition in the basement membrane zone was noted.
importance of our study results in aiding clinical diagnosis and planning treatment strategies.

Although the incidence of LABD varies in different published reports, it is certainly a rare disease worldwide. The estimated incidence is 0.26, 0.52 and 0.22 per million populations per year in Singapore, France and Germany, respectively.7 To the best of our knowledge, there is no previous report of incidence of bullous diseases in Taiwan. A calculation of all cases receiving DIF examinations during the same study period revealed that there were 226 cases of bullous pemphigoid, 91 cases of pemphigus (including pemphigus vulgaris and pemphigus foliaceus), while only 16 cases of LABD confirmed by DIF examinations. Comparing with previous reports from Germany and France,6,7 the incidences of pemphigus were around 0.98–1.7 cases per million inhabitants per year, while the incidences of LABD were 0.22–0.52 cases per million inhabitants per year. Therefore, the relative incidences between LABD and pemphigus were around 0.22–0.34 fold in Germany and France. In our hospital, the relative case numbers of LABD and pemphigus (16 vs. 91, 0.18 fold) during the study period were similar to that of previous reports, indicating that LABD is also a rare disease in Taiwan. The lack of racial difference in disease incidence suggests that extrinsic factors such as drugs and systemic illness play much more important roles in the etiology of LABD than do ethnic and genetic considerations.

Comparisons of epidemiological and clinical data reported by Weng et al,8 Leonard et al1 and our present study are summarized in Table 2. Gender difference was not significant in our series. However, Weng et al8 reported a male predominance (2.4:1), while a slight predominance of females was observed by Leonard et al (1:1:6).3 Although the mean age of disease onset was relatively older in our series, most of our patients were older than 40 years, in line with previous reports.2,3 Similar to other series,2–4 cutaneous manifestation was also heterogeneous in our study (8 with dermatitis herpetiformis-like skin lesions, 4 with bullous pemphigoid-like lesions, 2 with pemphigus vulgaris-like lesions, 1 with a varicella-like lesion and 1 with a vasculitis-like lesion). Therefore, LABD should be considered as a potential diagnosis in patients presenting with blisters in an annular distribution. Pruritus before or during the disease course was also a common finding both in our patients and previous series.2,4,9 However, mucous membrane involvement occurred only in 3 patients (18%) in our study, while studies by Weng et al8 and Guide and Marinkovich9 demonstrated a much higher proportion of mucosal involvement (47% and 80%, respectively). The low incidence of mucosal involvement is probably a unique feature in Taiwanese patients with LABD.

Similar to dermatitis herpetiformis, the histopathology of LABD reveals subepidermal bullae with a superficial dermal neutrophilic infiltration.2,3,9 Occasionally, there are eosinophils mixed with neutrophils, and thus LABD can also be indistinguishable from bullous pemphigoid. These pathological findings were all observed in our series. For an accurate diagnosis, DIF is considered as the gold standard diagnostic modality.10 The occurrence of continuous linear IgA deposition in the BMZ is a specific finding in LABD, while a papillary granular IgA deposition is suggestive of dermatitis herpetiformis; continuous linear IgG deposition in the BMZ is typical in bullous pemphigoid.9,10 Although a linear distribution of BMZ-specific IgA antibodies on DIF is the gold standard for diagnosis of LABD, other immunologic factors can also be involved in LABD.2,10 In our study, five patients showed depositions of IgG antibodies in addition to IgA antibodies on DIF. Chan et al10 suggested that LABD and bullous pemphigoid can usually be separated based on the greater fluorescence intensity of one of the antibodies, either IgG or IgA, in combination with clinical and immunopathologic features. In the four patients whose immunostaining showed a presence of both IgA and IgG antibodies, all had a greater fluorescence intensity for IgA antibody. It has been proposed that the deposition of IgA antibody might lead to neutrophil chemotaxis and complement activation with eventual loss of adhesion at the dermal-epidermal junction and subepidermal blister formation.2

A subset of patients has been described with drug-induced LABD.11–13 Intravenous vancomycin is the most common offending drug.13 While its mechanism is still unclear, it has been proposed that drug-specific T cells may release Th2 cytokines such as interleukin IL-4, IL-5, IL-6, IL-10 and transforming growth factor-β which would then stimulate the production of IgA antibodies.12,14 The importance of drugs as the causative agent for LABD lies in that the eruptions resolve completely upon discontinuation of the offending drugs.11,12 Therefore, a detailed medication history is crucial in the diagnosis and treatment of LABD. In our study, four patients had drug-related LABD, and all experienced fair recovery after withdrawal of the offending medications. Of particular note is that one case was related to griseofulvin, which has not been reported previously to be associated with LABD.

Traditionally, the treatment of choice for LABD is dapsone.2,9 Treatment responses in our patients also supported this previous experience since all patients who received dapsone had excellent recovery except for one with adverse

Table 2 Comparisons of epidemiological and clinical data in three series of linear immunoglobulin A bullous dermatosis.3,6

<table>
<thead>
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<th>Our series</th>
<th>Leonard et al1</th>
<th>Weng et al8</th>
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<tr>
<td>Case number</td>
<td>16</td>
<td>34</td>
<td>17</td>
</tr>
<tr>
<td>Male-to-female ratio</td>
<td>1:1</td>
<td>1:1.6</td>
<td>2.4:1</td>
</tr>
<tr>
<td>Mean age</td>
<td>55</td>
<td>45</td>
<td>47</td>
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<tr>
<td>Mucosal involvement</td>
<td>3/16 (18%)</td>
<td>NA</td>
<td>8/17 (47%)</td>
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</table>

NA = not available.
effect. Dapsone should be prescribed with caution because of its complications.9 The most common adverse effect is hemolytic anemia, which can be severe in patients with glucose-6-phosphate dehydrogenase deficiency.9 Potentially fatal side effects include hepatotoxicity and dapsone hypersensitivity syndrome, which often occur within the first 3 months. Important measures to prevent these adverse effects include checking a baseline complete blood count, liver enzymes, and glucose-6-phosphate dehydrogenase levels before and during the administration of dapsone. Alternative medications such as sulfapyridine, corticosteroid, colchicine, tetracycline and nicotinamide, have also been reported to be beneficial for LABD treatment.2,9

Since this study is based on a retrospective chart review with some clinical follow-up data obtained by telephone interview, treatment strategies may change over time and there may be bias from interviewers and patients. In addition, the case number was limited. Further multicenter collaborations to establish our local database may be needed to confirm results from our present study.

References


