Review

Linear IgA bullous dermatosis

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Introduction

Linear immunoglobulin A (IgA) bullous dermatosis (LABD) is a unique immunobullous disease characterized by vesicles, bullae, and erosions. It was first recognized as an entity distinct from dermatitis herpetiformis (DH) or bullous pemphigoid (BP) on the basis of the immunopathologic finding of linear IgA deposits in the basement membrane zone (BMZ) on direct immunofluorescence (DIF) by Chorzelski *et al*. In 1979.[1] Synonyms for LABD include linear IgA disease, IgA pemphigoid, and linear DH. There is a childhood variant of LABD termed chronic bullous dermatosis of childhood (CBDC). CBDC has a somewhat different mode of clinical presentation than that of LABD, but they share identical histologic and immunopathologic characteristics, and thus are considered by most experts to be different clinical presentations of the same disease. Synonyms for CBDC include juvenile DH and juvenile pemphigoid. LABD is an uncommon dermatosis with an estimated incidence of 0.22 and 0.5 per million of the population per year in Germany and France, respectively.[2,3]

Definition

LABD may be diagnosed based on the following three criteria.

1 The presence of a vesicular or bullous eruption, usually confined to the skin, but which may involve the mucous membranes.
2 The presence of a subepidermal vesicle with a predominantly neutrophilic infiltrate on histology of lesional skin.
3 The presence of BMZ-specific IgA antibody deposited in a linear pattern in the absence of other immunoglobulins on DIF of perilesional skin.

Clinical features

The clinical features of LABD may resemble those of DH, with a primarily pruritic papulovesicular eruption involving extensor surfaces symmetrically. More commonly, however, the clinical features are more like those of BP with tense vesicles and bullae developing *de novo* or on an urticarial base.[1,4] The bullae of LABD may be somewhat linear or "sausage" like in shape. The torso and limbs are most frequently involved. Involvement of the hands, feet, perineum, and face may also be seen. Occasionally, there can be generalized blistering of the body. The age of peak incidence of this disease is 60–65 years with a slight female predominance.[5] Mucous membrane involvement has been reported to occur in up to 80% of patients.[6–8] Cicatricial pemphigoid may also have IgA antibodies deposited at the BMZ in addition to IgG antibodies. A dual circulating antibody response with both IgA and IgG antibodies predicts a worse response in this subset of cicatricial pemphigoid patients.[9]

There are two main clinical differences between adult-onset LABD and childhood-onset LABD or CBDC. First, CBDC occurs in children with a peak incidence of about 4.5 years, while LABD is a disease of adults.[5] Second, in CBDC, there is a typical localization on the lower abdomen and perineum, while the distribution of LABD may have one of two distinct patterns:[4,5] (i) involvement of extensor surfaces with grouped papulovesicles similar to the clinical picture of DH; or (ii) flexural and truncal involvement with scattered vesicles and bullae similar to BP. In CBDC, the blisters on the lower abdomen and perineum area frequently occur in a configuration known as a "cluster of jewels" (Fig. 1), where new lesions occur at the periphery of older blisters. The torso, hands, feet, and face may also be involved. Mucosal involvement in CBDC has been reported to occur in up to 64% of patients. Occasionally, LABD

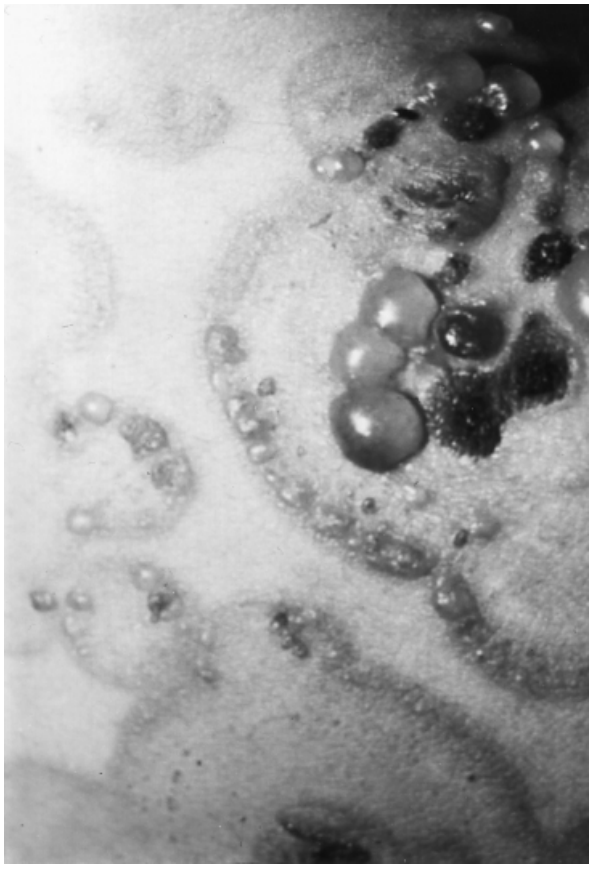

Figure 1 Blisters in a "cluster of jewels" configuration in a patient with CBDC

may develop an atypical eruption resembling erythema multiforme.[10,11]

As LABD has been recognized as a distinct entity for only 20 years, it is difficult to assess the long-term prognosis in this disease. Chorzelski *et al.*[12] have reported a mean disease duration of 5.6 years before resolution in adults. Jablonska *et al.*[13] have reported a mean duration of 3.9 years before resolution of CBDC. CBDC can have relapses and remissions with continuation of the disease as LABD into adulthood. It is interesting to note that, during pregnancy, LABD spontaneously improves with no adverse fetal outcome observed in a series of 19 pregnancies[14] For the purposes of the rest of this review, the term LABD includes both the adult and childhood variants of this disease.

Histopathology

Biopsy of a lesion reveals a subepidermal bulla with a superficial dermal infiltrate of neutrophils. There may be papillary microabscesses composed of neutrophils, as is typical of DH, but usually the neutrophils tend to be scattered more evenly along the BMZ in LABD (Fig. 2). Occasionally eosinophils may be admixed among the neutrophilic infiltrate as may be seen in some cases of BP. These findings sometimes may all be seen on different sections of the same biopsy. It is often difficult to distinguish LABD from DH or from the bullous eruption of systemic lupus erythematosus on histology alone.[15–17]

Immunopathology

Immunofluorescence

The *sine qua non* for the diagnosis of LABD is the presence of BMZ-specific IgA class antibody in a linear distribution on DIF of perilesional skin in the absence of other immunoglobulins (Fig. 3a). Without this finding a diagnosis of LABD cannot be made. Cases of LABD with IgG antibodies in addition to IgA antibodies deposited in a linear fashion at the BMZ have been reported.[18–23] These cases immunopathologically represent an overlap of LABD and BP. These patients do not meet the strict criteria for the definition of LABD needed for the research setting. It would seem prudent, however, to treat these cases as either LABD or BP depending on which antibody response is predominant. Prospective studies are needed on these patients with BMZ antibody overlap to further define their clinical course.

Complement may occasionally be present at the BMZ in addition to IgA. There does not seem to be a significant regional variation of the deposition of antibodies in LABD.[24] Early studies suggested that circulating antibodies could be detected in only a minority of patients using indirect immunofluorescence (IIF).[1,5,19,25–27] These studies used intact human skin or esophageal substrates (Table 1). The limiting titers are usually low at 1 : 10–1 : 80, but much higher titers are occasionally seen. It has been shown that the use of BMZ-split human skin, as described by Gammon *et al.*, is a more sensitive substrate for the detection of these circulating IgA class antibodies.[28–30] This technique separates skin in the lower lamina lucida and the tissue is then used for standard immunofluorescence. The majority of these antibodies bind to the epidermal side of BMZ-split human skin with a minority of these antibodies binding to the dermal side (Fig. 3b). Occasionally, antibody binding to both sides of the split is observed. The antibodies are usually IgA1 subclass, but IgA2 BMZ-specific antibodies have also been described in a minority of cases.[31–33] Free antibody has also been detected using IIF in LABD blister fluid.[34]

Western immunoblot

In LABD, specific antibody binding has been found to various antigens on Western immunoblot (Table 2). The most well characterized of these antigens is a 97-kDa antigen found in a modified epidermal extract (LABD97).[35]

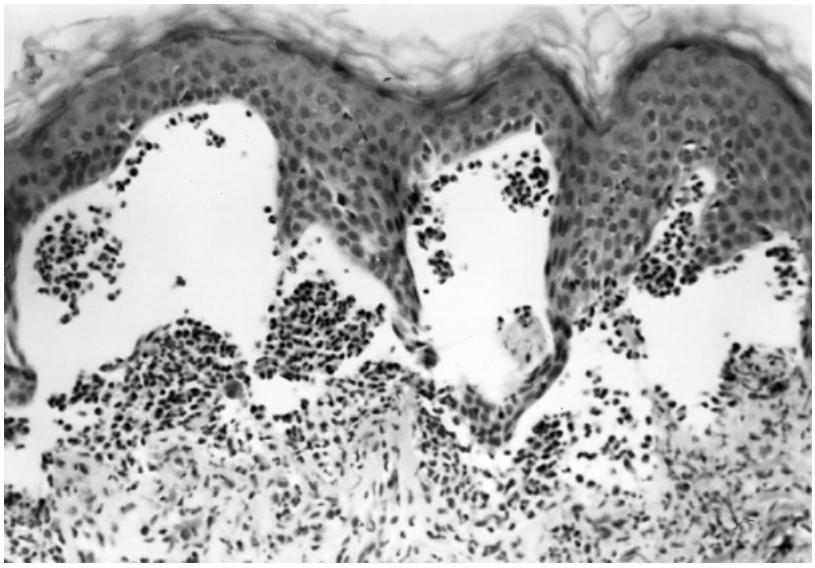

Figure 2 Histology of LABD demonstrating a subepidermal blister with stuffing of the dermal papillary tips with neutrophils (hematoxylin and eosin; original magnification, 200×)

This antigen is recognized by adult and childhood LABD sera that bind to the epidermal side of BMZ-split skin.[36] It has been shown that this antigen is identical to a portion of the extracellular domain of the 180-kDa antigen recognized by circulating IgG antibodies in BP (BPAg2).[37] The LABD97-specific IgA antibodies do not cross-react with epidermal extracts containing BPAg2, unlike the IgG BPAg2-specific antibodies which can cross-react with LABD97.[38] The LABD97-specific antibodies do cross-react with a 120-kDa antigen produced in keratinocyte culture.[39,40] It may be that the LABD97 is an alternative splicing product of BPAg2 or, more likely, a proteolytic cleavage product with a new conformational epitope being formed secondary to the cleavage of BPAg2. Alternatively, LABD97 may represent a product of protein processing of BPAg2 by tissue proteases.

Specific binding of LABD sera that react with the dermal side of BMZ-split skin to collagen VII has been described in case reports.[41–43] Only a minority of the dermal binding sera are, however, specific for collagen VII. We examined the sera of 17 LABD patients who had dermal binding of IgA on IIF and none reacted with collagen VII on Western immunoblot (Egan and Zone, unpublished data, 1999). IgA antibodies in LABD sera have been reported to bind to the 230-kDa bullous pemphigoid antigens (BPAg1) and BPAg2.[44] Other less well-characterized antigens that have been reported as being specifically recognized by IgA antibodies in LABD patients' sera include antigens of 100 kDa, 110–120 kDa, 145 kDa, 160–180 kDa, 200 kDa, 220 kDa, 255 kDa, and 285 kDa (where collagen VII was 250 kDa).[28,43,45–47]

Immunoelectron microscopy

Unlike the immunofluorescent findings, where the majority of circulating antibodies bind to the epidermal size of BMZ-split skin suggesting reactivity with an antigen(s) in the lamina lucida, there are many different patterns of antibody deposition discernible on immunoelectron microscopy (IEM). Prost *et al.*[48] described the localization of IgA deposits in the majority of patients studied in a "mirror image" pattern on each side of the lamina densa, i.e. the lamina lucida and sublamina densa. Other studies have not routinely found this pattern, but have found IgA deposition in the lamina lucida, lamina densa, sublamina densa, in the hemidesmosome, or on the basal surface of the keratinocytes (Table 3). Indirect IEM using LABD sera with high titers of antibodies specific for LABD97 has demonstrated binding of these antibodies in the lamina lucida.[54,55] Indirect IEM using LABD sera with high titers of antibodies specific for collagen VII shows binding to the anchoring fibrils.[42,56]

Disease associations

Numerous case reports link LABD to Hodgkin's disease[58] and other B-cell lymphomas;[59,60] whether this is a real association such as is seen in DH or simply fortuitous has yet to be determined (Table 4). Transitional cell cancer of the bladder has also been reported in association with LABD, as has esophageal cancer.[61,62] The association of LABD and systemic lupus erythematosus (SLE) is unclear. IgA can be deposited at the BMZ as part of a lupus band seen in SLE. Also, bullous SLE is characterized by IgG antibodies reactive with collagen VII, and there may well

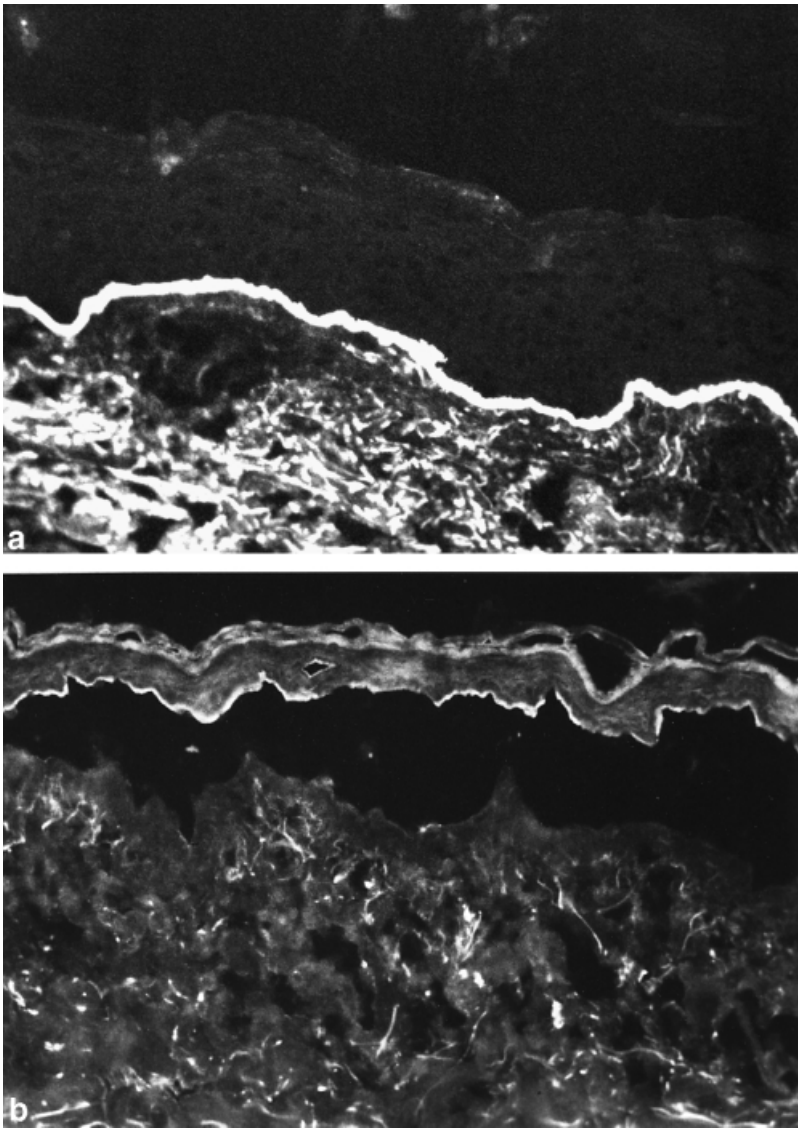

Figure 3 Immunofluorescence findings in LABD. (a) DIF demonstrating linear deposition of IgA at the BMZ. (b) IIF demonstrating IgA antibodies from a patient's serum binding to the epidermal side of BMZ-split human skin

Table 1 Detection of circulating antibodies in LABD

Study	Substrate	No. of patients with circulating antibodies
Yaoita and Katz[25]	Non-split human skin	LABD 2/6
Chorzelski *et al.*[1]	Monkey esophagus	LABD 3/37
Leonard *et al.*[19]	Non-split human skin	LABD 1/34, CBDC 13/13
Mobacken *et al.*[26]	Monkey esophagus	LABD 1/9
Bhogal *et al.*[27]	Non-split human skin	LABD 2/15
Wojnarowska *et al.*[5]	Non-split human skin	LABD 5/25, CBDC 18/23
Dmochowski *et al.*[28]	BMZ-split human skin	LABD 35/46
Wojnarowska *et al.*[29]	Non-split human skin	LABD/CBDC 18/59
Wojnarowska *et al.*[29]	BMZ-split human skin	LABD/CBDC 34/59

Table 2 Antigens recognized by LABD patients' sera

Study	Molecular weight of antigen
Zone *et al.*[35]	97 kDa (LABD97)
Yamane *et al.*[45]	100 kDa
Collier *et al.*[46]	110–120 kDa
Marinkovich *et al.*[39]	120 kDa
Yamane *et al.*[45]	145 kDa
Collier *et al.*[46]	160–180 kDa
Ghohestani *et al.*[44]	180 kDa (BPAg2)
Allen *et al.*[43]	200 kDa
Collier *et al.*[46]	220 kDa
Ghohestani *et al.*[44]	230 kDa (BPAg1)
Wojnarowska *et al.*[47]	285 kDa (collagen VII is 250 kDa in this report)
Zambruno *et al.*[41]	290 kDa (collagen VII)

Table 3 IgA antibody localization at the basement membrane zone in LABD

Study	Location of antibody
Yaoita and Katz[25]	LL 1/2, AF 1/2
Dabrowski *et al.*[49]	SLD/AF 1/1
Horiguchi *et al.*[50]	LL/SBK 1/1
Bhogal *et al.*[27]	SLD 31/31
Prost *et al.*[48]	LL 3/16, LD/SLD 3/16, LL/SLD 11/16
Rusenko *et al.*[51]	SLD 3/3
Onodera *et al.*[52]	LL/SBK 1/1
Zone *et al.*[35]	LL 2/2
Karpati *et al.*[53]	LL/SBK 1/2, SLD/AF 1/2
Haftek *et al.*[54]	LL/HD 6/6
Zambruno *et al.*[41]	SLD/AF 1/1
Hashimoto *et al.*[42]	SLD/AF 1/1
Ishiko *et al.*[55]	LL 5/5
Allen *et al.*[43]	SLD/AF 2/2
Caux *et al.*[56]	SLD/AF 1/1
Zhou *et al.*[57]	LL 1/5, LD 1/5

LL, lamina lucida; AF, anchoring fibrils; SBK, sub-basal keratinocytes; SLD, sublamina densa; HD, hemidesmosome; LD, lamina densa.

be overlap with an IgA response developing to collagen VII in some cases.[63] LABD has been reported to develop in the setting of DH.[12] There seems to be a real association between ulcerative colitis (UC) and LABD, although the reason for this association is unknown; one study found UC to be present in five out of 70 (7.1%) LABD patients, a prevalence much higher than expected; spontaneous remission of LABD coincident with a total colectomy for UC has also been described.[64,65] Other disease associations include multiple sclerosis,[66] dermatomyositis,[67] Crohn's disease,[68] hydatidiform mole,[69] and rheumatoid arthritis.[70] LABD developing after a cardiac transplant while the patient was on high-dose immunosuppressive therapy has also been described.[71]

Table 4 Diseases and drugs associated with LABD

Diseases associated with LABD

Hodgkin's disease[58]
B-cell lymphoma[59]
Dermatitis herpetiformis[12]
Bladder cancer[61]
Esophageal cancer[62]
Systemic lupus erythematosus[63]
Ulcerative colitis[64]
Multiple sclerosis[66]
Dermatomyositis[67]
Crohn's disease[68]
Hydatidiform mole[69]
Rheumatoid arthritis[70]

Drugs associated with LABD

Amiodarone[76]
Ampicillin[77]
Captopril[78]
Cefamandole[79]
Childhood vaccinations[80]
Diclofenac[81]
Glibenclamid[82]
Interferon gamma[83]
Interleukin-2[84]
Iodine[85,86*]
Lithium carbonate[87]
Penicillin G[88]
Phenytoin[89]
Piroxicam[90]
Rifampin[91]
Somatostatin[91]
Sodium hypochlorite[92*]
Trimethoprim–sulfamethoxazole[91]
Vancomycin[72–75]

*After topical contact.

Drug-induced LABD

A striking characteristic of LABD is the fact that it is frequently precipitated by drugs and that it may remit once the offending drug is stopped (Table 4). The drug most frequently implicated in precipitating LABD is vancomycin,[72–75] although other drugs have been implicated.[76–92] The mechanism by which these drugs stimulate an IgA antibody response to produce anti-BMZ antibodies with subsequent formation of clinical blisters is unknown.

Differential diagnosis

Although any infectious, autoimmune, or genetic blistering skin disease can enter into the differential diagnosis of

LABD, LABD needs to be differentiated clinically and pathologically usually from only two blistering skin diseases, DH and BP. The differential diagnosis from BP may be difficult clinically as both may present with tense blisters; however, on DIF, BP has linear IgG BMZ deposition, while LABD has linear IgA deposition. BP usually has a more intense infiltrate of eosinophils under the subepidermal blister with neutrophils being less prominent; the reverse is true for LABD. Distinguishing LABD from DH is usually not difficult clinically as only a minority of LABD cases present with a DH-like eruption of intensely pruritic papulovesicles and erosions on extensor surfaces. The histology of LABD and DH can be identical with neutrophils packing the dermal papillae under subepidermal blisters. Because both diseases are characterized by IgA deposits on DIF, it is easy to understand why it took so long to separate LABD as a clinical entity from DH. There are some important differences between the two diseases: (i) DH is associated with a gluten-sensitive enteropathy in almost all cases which responds to a gluten-free diet,[93] whereas in LABD there is no such association and no improvement with a gluten-free diet;[94] (ii) DH is closely associated with the HLA-B8-DR3 haplotype but there is no association with LABD;[95] (iii) the IgA found in the skin of DH patients is in granular deposits in the dermal papillae and no circulating BMZ-specific antibodies have been detected in DH.[96] Thus while DH and LABD share some features, they differ significantly with regard to immunopathology.

Treatment

As with DH, the therapy of choice in LABD is dapsone. It should be started at a low dose (25 mg/day adults, 6.25 mg/day children) and increased as tolerated at weekly intervals to a maintenance dose (100–200 mg/day adults, 25–50 mg/day children). Dapsone exhibits good bioavailability, but serum levels can have a wide variation; therefore, measuring serum dapsone levels as a guide to therapy has little value. There is wide variability in the half-life of dapsone (10–50 h), but the vast majority of patients are best managed on a single daily dose. Hemolysis is the most common side-effect of treatment. Dapsone is a strong oxidizer and produces a dose-related oxidant stress on normal aging red cells. Initial reduction of hemoglobin by 2–3 g is common, but subsequent partial compensation by reticulocytosis is the rule. It may produce severe hemolysis in patients with glucose-6-phosphate-dehydrogenase (G-6-PD) deficiency. Blacks, Asians, and Caucasians of southern Mediterranean descent should be screened for G-6-PD deficiency before starting dapsone therapy.

Methemoglobinemia is seldom a problem and is usually less than 15%; it can serve as an indicator of compliance to therapy as it produces cyanosis imparting a blue color to the lips and extremities. At higher doses (>200 mg/day), it may become symptomatic with the development of weakness, headaches, and tachycardia. Other dose-related side-effects include a sensory and motor neuropathy which is usually reversible, toxic hepatitis and cholestatic jaundice, and hypoalbuminemia. These are rarely seen at doses of less than 200 mg/day. Idiosyncratic reactions include psychiatric symptoms, an infectious mononucleosis-like syndrome, exfoliative dermatitis, erythema multiforme, erythema nodosum, and urticaria. The most feared idiosyncratic reaction is aplastic anemia which usually occurs in the first 2–12 weeks of therapy.

Patients on dapsone therapy should have the following laboratory follow-up: (i) baseline complete blood count (CBC) and liver function tests and a G-6-PD level if indicated; (ii) the CBC should be checked weekly for the first month, monthly for the next 5 months, and semiannually thereafter; (iii) a chemistry profile should be obtained at 6 months and then annually to monitor for possible hepatotoxicity, changes in renal function, and hypoalbuminemia; (iv) patients should be made aware of the development of cyanosis and hemolytic anemia to allay anxiety when these expected side-effects occur.

If the patient is intolerant of dapsone, sulfapyridine may be used, usually at a dose of 1.0–1.5 g/day; however, its absorption is erratic, reducing its clinical usefulness. It is often worthwhile to use small doses of corticosteroids (5–15 mg/day) in addition to dapsone or sulfapyridine in cases where high-dose dapsone or sulfapyridine alone do not adequately control the disease.[1,97,98] Other therapies that have been reported to be of benefit in LABD include colchicine,[99] and a combination of tetracycline and nicotinamide.[100]

Conclusions

LABD is a unique immunobullous skin disease characterized by the linear deposition of BMZ-specific IgA on DIF. Clinically, it can be separated into an adult and childhood form. Immunopathologically, the IgA antibodies have been reported to react with numerous basement membrane antigens. The best characterized of these antigens are LABD97 and collagen VII. LABD is often precipitated by drugs. LABD needs to be differentiated from BP and DH clinically and immunopathologically. The therapy of choice for LABD is dapsone.

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Letter to referring physician – 1938

Dr. James Martin,
Hamilton, Arizona.

Dr. Richard Holmes,
1842 Medical Sciences Building,
Grand River, Arizona

Dear Doctors:

I examined your patient, Mr. G. H. Pennock, on November 13th, with a great deal of interest. Mr Pennock has, I should say, almost unquestionably a chronic dermatophytosis of the nails and the skin of both hands and feet, complicated by what at this present age, looks like a grade three ichthyosis; by excessive irradation; by what looks very much like a rosacea syndrome with low blood pressure; a neurogenous factor in the form of tension and overload; a high carbohydrate, relatively avitaminotic diet; and septic teeth. The teeth, of course, I cannot be sure of without dental and X-ray study. I might point out also that he had a predisposing infection in the form of a pneumonia which occurred four years ago. He is, moreover, an extremely heavy man of the type, who, while he may present no abnormalites of blood sugar to the ordinary examination, is pretty apt to show what Urbach called "skin diabetes" — in other words, a defect in carbohydrate metabolism which only shows itself in the maintenance of unduly high levels during a glucose tolerance test.

I might commit myself or, in other words, stick out my neck, by saying that I think Mr. Pennock incurable, and then have him promptly get well. I think I can say that at least the condition is an extremely resistant one under the circumstances, and that there is some question in my mind whether with the amount of attention he is likely to give it, Mr. Pennock can ever be gotten well. The finger nails in particular impress me as dermatophytic to a degree that makes them practically incurable, and they will serve as a focus for recurrences under the various predisposing and exciting influences which I have enumerated.

His ichthyosis can be helped by the systematic inunction of grease, and this can afford the rest of his skin some protection against infection. His rosaceal and seborrheic background can be helped by sharp restriction of carbohydrate, the addition of considerable amounts of vitamins B and A, and the taking over a long period of time of liberal doses of dilute hydrochloric acid and calcium gluconate by mouth.

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