

Case Reports of Linear IgA Bullous Dermatitis of Childhood

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Abstract

Linear IgA bullous dermatosis of childhood (LADC) is an uncommon acquired blistering skin disorder which affects young children. It is characterised by a linear band of IgA at the epidermal basement membrane on direct immunofluorescence. From 1984 to 1988 at the previous skin centre at Middle Road Hospital, and 1989 to 1997 at the present National Skin Centre, a total of 4 cases were seen. All the patients were female and their ages ranged from 5 to 14 years (mean 8 years). There were 2 Chinese, 1 Caucasian and 1 Malay. All presented with an acute onset of blistering of 1 to 3 weeks' duration. Their skin biopsies showed subepidermal bullae with neutrophils, with /without eosinophils and direct immunofluorescence tests revealed linear deposits of IgA along the dermoepidermal junction. All were treated with prednisolone and dapsone with good results. One patient developed dapsone-induced haemolysis and treatment was changed to colchicine. We review the epidemiology, aetiology, current concepts and treatment modalities of this condition.

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Introduction

Linear IgA bullous dermatosis of childhood (LADC) is an acquired subepidermal blistering disorder of young children which is characterised by the unique finding of linear deposits of IgA along the dermoepidermal junction. It usually occurs acutely in pre-school children and has been described in association with a variety of infections. Clinically, the blisters are tense and clear; they are typically arranged in an annular fashion described as a "crown of jewels" or "string of pearls". In the past, it has been known by various terms such as juvenile dermatitis herpetiformis, bullous pemphigoid of childhood and chronic bullous dermatosis of childhood. Recently these terms have been replaced by its more accurate current name as increasing evidence suggest clinical and immunopathologic similarities between it and the adult form of linear IgA dermatosis.

Case Reports

These are the reports of the 4 cases of LADC, 2 of whom were seen at Middle Road Hospital (1984-1988) and the other 2 at the National Skin Centre (1989-1997) (Table I).

Case 1

OAL, an 8-year-old Chinese girl, was seen in 1984 with blisters over the trunk, perineum and arms for one week. The vesicles were clear and some were arranged in an annular pattern (Fig. 1). An initial diagnosis of bullous

impetigo was made and she was treated with several courses of antibiotics. As the blisters recurred over the next 3 months, a biopsy of a vesicle was taken. The histology showed a subepidermal bullae containing neutrophils. The direct immunofluorescence of perilesional skin showed smooth linear deposits of IgA along the dermoepidermal junction while the indirect immunofluorescence was negative. Swab cultures grew *Staphylococcus aureus*. The ANA was negative; G6PD was present. The history suggested a possible relationship to gluten diet e.g. malt drinks. However, a jejunal biopsy performed in 1986 showed no evidence of enteropathy.

She was started on dapsone 50 mg daily and prednisolone 15 mg daily for 2 weeks. There was initial difficulty with control and dapsone had to be increased to 100 mg daily with prednisolone at 15 mg daily over 4 months because of continued blistering. At 6 months of treatment, haemolysis was detected and dapsone was replaced by sulphapyridine. The reticulocyte count increased from 2.5% to 8.1% with the haemoglobin maintained at about 11 g/dL. By then the patient had developed mild Cushingoid facies from the corticosteroids. Finally, after 7 months, the problem was found to be poor compliance with the medication, as she quickly went into remission in 10 days under inpatient supervised therapy with low doses of prednisolone and dapsone. However, the patient remained non-compli-

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TABLE I: REVIEW OF CASES OF LINEAR IgA BULLOUS DERMATOSIS OF CHILDHOOD FROM 1984 TO 1997

No.	Age (years)	Sex	Race	Duration (weeks)	Sites of blisters	IIF	DIF	Treatment	Side effects
1.	8	F	Chinese	1	Trunk, perineum and arms	-	+	Dapsone, prednisolone, sulphapyridine	Haemolysis
2.	5	F	Caucasian	2	Trunk and arms	Not done	+	Dapsone, prednisolone	None
3.	14	F	Chinese	3	Limbs and perineum	Not done	+	Dapsone, prednisolone	None
4.	5	F	Malay	1	Limbs, trunk and face	+	+	Dapsone, prednisolone, colchicine	Haemolysis

IIF: indirect immunofluorescence; DIF: direct immunofluorescence

ant with treatment. The patient was prescribed dapsone 50 mg daily and prednisolone 5 to 10 mg daily at intervals with frequent clinical relapses. She defaulted follow-up in 1992.

Case 2

KNM, a 5-year-old Caucasian girl, presented in 1988 with 2 weeks’ of blistering over the whole body. The histology showed a subepidermal bulla containing erythrocytes, neutrophils and eosinophils. Smooth linear IgA deposits were detected along the dermoepidermal junction on direct immunofluorescence of perilesional skin. She was treated with dapsone 50 mg daily and prednisolone 15 md daily, with remission achieved in 2 weeks. She subsequently left the country and was lost to follow-up.

Case 3

LLF, a 14-year-old Chinese girl, had blisters over the arms, legs and around the genitals and anus for 3 weeks in 1988. The vesicles were clear and arranged in an annular fashion. A biopsy showed a subepidermal bulla containing neutrophils and faint traces of linear IgA deposits were seen along portions of the dermoepidermal junction on direct immunofluorescence. The ANA was negative and G6PD was present. She was treated with prednisolone 15 mg daily and dapsone 75 mg daily with clinical remission within2 weeks. There were no complications with dapsone. The disease was controlled with dapsone 50 mg daily and prednisolone 5 mg daily. Treatment was stopped by one year. She remained in remission until her discharge from follow-up in 1990.

Case 4

NNBZ was a 5-year-old Malay girl seen in 1997 for one week’s duration of blistering. One month prior to this, she was diagnosed to have hand-foot-mouth disease by her general practitioner along with several other children in her nursery. This cleared with symptomatic treatment. Clinically, there were tense vesicles and bullae over the trunk (Fig. 2), limbs and face. Many were arranged in an annular pattern. The biopsy showed a subepidermal bulla with eosinophils and neutrophils

(Fig. 3) and the direct immunofluorescence showed linear IgA along the dermoepidermal junction. The split skin indirect immunofluorescence was positive for IgA, showing a roof pattern and titre of 1:10. A swab culture from the blister grew *Staphylococcus aureus*. The herpes culture and serology were negative. G6PD was present. She was started on dapsone 50 mg daily and prednisolone 20 mg daily with remission occurring in 5 days.

Two months later, she developed haemolysis. The haemoglobin fell from 13.8 g/dL to 6.9 g/dL with an increase of reticulocyte count from 2.9% to 7.6%. The dapsone was stopped until the haemoglobin level normalised. She was then treated with colchicine 0.5 mg bd and remission was achieved within 2 weeks. Presently the patient is still in remission a year later at a dosage of 0.5 mg daily. So far, there have been no side effects. During this period, the patient’s mother attempted to take off the colchicine against our advice, resulting in prompt recurrence of the blisters within a few days. The lesions resolved with continuation of colchicine.

Discussion

LADC is a rare immunobullous disorder of the skin which causes blistering in young children and is characterised by linear deposits of IgA along the dermoepidermal junction. In 1901, Bowen¹ reported 15 children with large blisters involving mainly the face and genitalia. At that time, they were considered to be a variant of dermatitis herpetiformis unique to children. In retrospect, they were probably the first report of LADC. In 1961, Kim and Winkelmann² were the first to separate LADC from dermatitis herpetiformis on clinical grounds, and they proposed the term “bullous pemphigoid of childhood”. In 1970, Jordan et al³ investigated 6 children with subepidermal blisters with direct immunofluorescence tests using anti-IgG conjugates. They were all negative, proving that they were not bullous pemphigoid as previously described. However, the tests were not performed with anti-IgA conjugates. Jordan et al called the disease “chronic bullous dermatosis of childhood”. One year later, Jablonska et al,⁴ using both anti-IgG and anti-IgA, characterised the direct immunofluorescence patterns of bullous pemphigoid (linear

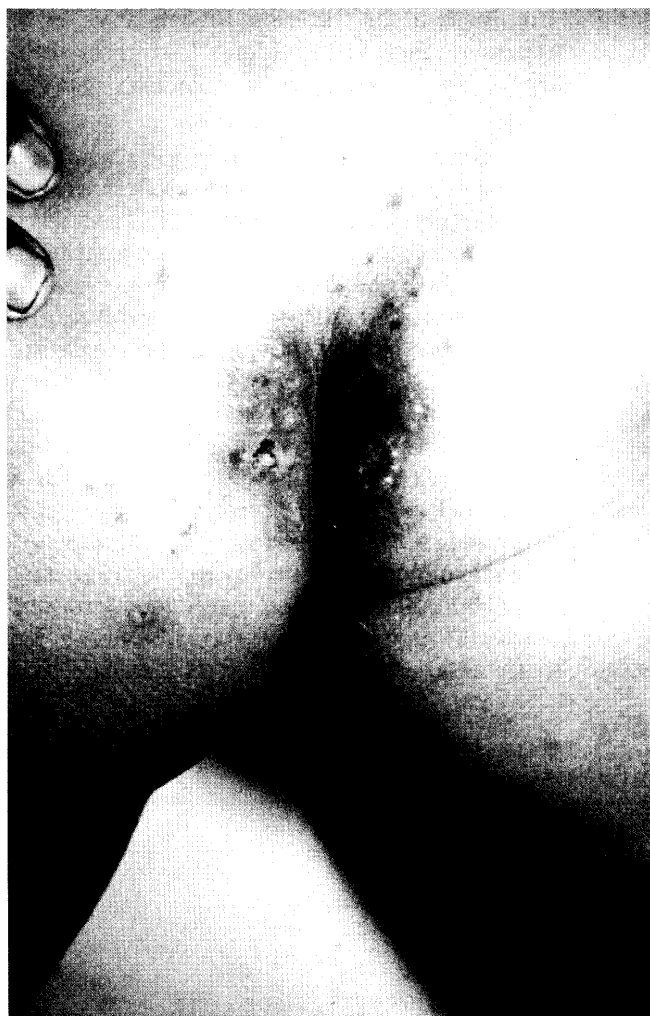


Fig. 1. Case 1. Annular vesicles over the perineum ("crown of jewels" appearance).



Fig. 3. Histology showing subepidermal bulla with eosinophils (Haematoxyline-eosin stain, original magnification x40).

IgG), dermatitis herpetiformis (granular IgA) and LADC (linear IgA). The term "linear IgA bullous dermatosis of childhood" was proposed by the same authors in 1979 and has been the preferred name ever since.⁵

The incidence of LADC is unknown but it has been reported worldwide. The mean age of onset is 4 to 5

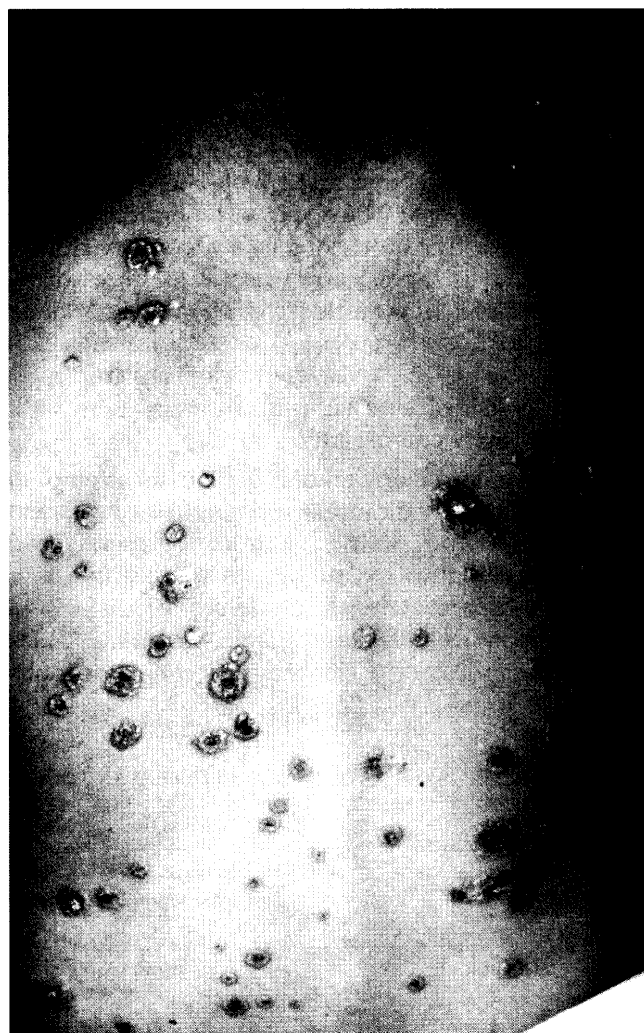


Fig. 2. Case 4. Small tense blisters over the back.

years with an age range of 6 months to 14 years in one study.⁶ There is a slight female preponderance of 1.6:1 which is reflected in our series. There is no familial tendency, but there is an association with HLA B8 in 76%.⁶

The onset is acute with mild to moderately pruritic blisters. The lesions are usually distributed over the face, hands and feet and perineum. The blisters are tense and large, they may be clear or haemorrhagic on a normal or erythematous base. There are often new blisters forming around a healed lesion giving rise to the "crown of jewels" appearance. In Wojnarowska's review, 72% had facial lesions, 60% peri-oral, 84% perineal and 80% hand and feet involvement. Mucous membrane lesions were reported in 64% in the same study but this was not seen in our series.⁶ Differential diagnoses of blisters in a child include bullous impetigo, insect bite reactions, erythema multiforme, lupus erythematosus, childhood bullous pemphigoid and dermatitis herpetiformis.

LADC is similar to the adult counterpart, linear IgA

bullous dermatosis of adults, in both histology and immunofluorescence. The biopsy shows a subepidermal bulla with either a predominantly neutrophilic or eosinophilic infiltrate. The indirect immunofluorescence is diagnostic, showing linear deposits of IgA along the dermoepidermal junction. These have been shown to be of the IgA1 subclass.⁷ The direct immunofluorescence can remain positive for as long as 4 years after clinical remission and is therefore not useful for monitoring activity.⁸ Indirect immunofluorescence was reported to be positive in 72% in Wojnarowska's study but only 31% in another study.⁵ IgA levels are normal and currently there is no evidence to support an association with gluten sensitivity enteropathy.⁶

There have been many studies done in an attempt to localise and identify the target antigens in the basement membrane zone using immunoblotting and immunoprecipitation techniques. So far, multiple antigens in the sublamina densa, intralamina lucida or both with molecular weights ranging from 97 kDa to 290 kDa have been implicated.⁹⁻¹³ This may reflect heterogenous

antigen involvement or differing investigative techniques. At present, there is no evidence to suggest prognostic differences from differing molecular weights antigens.

LADC has been associated with a preceding infection or drug in 38%.⁶ Table II shows the associated conditions which have been reported so far with LADC and compares it with its adult counterpart. Most of the conditions reported in LADC are viral infections whereas the adult form is mostly associated with drugs, autoimmune disease and malignancy. Many questions regarding the pathogenesis of LADC remain. Why is IgA involved and why is there an adult form? It is believed that an exogenous antigen, either infective, malignant or dietary, enters an immunologically susceptible person via a mucosal route such as the gastrointestinal tract, triggering production of IgA which cross react with an antigen(s) in the basement membrane zone.³¹ Different triggering antigens like various viruses or drugs may produce antibodies of different molecular weights, hence the heterogeneity of target antigens identified so far.

TABLE II: ASSOCIATIONS OF CHILDHOOD AND ADULT LINEAR IgA DISEASE

	Childhood linear IgA disease	Adult linear IgA disease
Gastrointestinal disease	Ulcerative colitis ¹⁴ Gluten sensitivity enteropathy ¹⁵	Ulcerative colitis ²¹ Gluten sensitivity enteropathy ²² Gastric hypochlorhydria ²¹
Infections	Herpes simplex virus ¹⁶ Chicken pox ¹⁷ Ebstein Barr virus ¹⁸ Salmonella enteritis ¹⁹ Upper respiratory tract infection ⁶ Urinary tract infection ⁶ Measles ⁶ Typhoid ⁶ Gastroenteritis ⁶	Herpes zoster ²³ Streptococcal infection ²⁴
Drugs	Penicillins ⁶	Penicillin G ²⁵ Vancomycin ²⁶ Non-steroidal anti-inflammatory drugs (NSAIDs) ²⁷ Lithium** Phenytoin ²⁹
Autoimmune		Thyrotoxicosis ³⁰ Hypothyroidism ³¹ Vitiligo ³¹ Lupus erythematosus ³² Dermatomyositis ³³ Rheumatoid arthritis ³⁴ Immune nephritis ³⁵ Autoimmune haemolytic anaemia ³⁶
Malignancy		Lymphoma ³⁷ Polycythaemia rubra vera ²¹ Carcinoma of bladder ³⁸ , oesophagus ³⁹ , thyroid ⁴⁰ , kidney ³¹ , uterus ³¹
Others	Vaccination ²⁰	

The effective drug of choice of LADC is dapsone at 1 to 2 mg/kg/day. Adverse side effects include haemolysis (especially in G6PD deficiency), agranulocytosis, methaemoglobinaemia, hepatitis, headache, gastrointestinal symptoms and peripheral neuropathy. An alternative to dapsone is sulphapyridine at 60 to 150 mg/kg/day. Adverse side effects include haemolysis, rashes, nausea and vomiting. Oral corticosteroids can be given alone or in combination with dapsone or sulphapyridine. Recently colchicine 0.5 mg bd has been used with success by Zeharia et al⁴¹ and Banodka et al.⁴² Colchicine is believed to exert its anti-inflammatory action by inhibiting chemotaxis of neutrophils, leukocyte adhesion and lysosomal degranulation, and has been used successfully in the treatment of some inflammatory dermatoses in which neutrophils are predominant in the pathogenesis, such as Behcet's disease, dermatitis herpetiformis and cutaneous vasculitis. Colchicine in low doses is safe and has a low rate of side effects. We used an empiric dose of colchicine 0.5 mg twice daily for 3 months, decreasing to 0.5 mg daily thereafter. Higher doses, in our experience, tend to result in gastrointestinal disturbance. The drug was well tolerated with no side effects seen. Toxic effects are usually due to overdosage and include nausea, vomiting, abdominal pain and diarrhoea. The complete remission and the absence of relapse during therapy, together with exacerbations when the drug was stopped inadvertently in our patient suggests that colchicine exerts a therapeutic effect. Other treatment modalities like cotrimoxazole with dapsone,⁴³ and dicloxacillin⁴⁴ have been cited in anecdotal reports.

Most cases of LADC resolve by puberty. Clinical remission is reported in 64%, usually within 2 years.⁶

Conclusion

Our experience with 4 female children with linear IgA disease over a period of 13 years shows that a valuable clinical clue to the diagnosis of linear IgA disease of childhood is the "crown of jewel" appearance of the vesicles, with confirmation by linear deposits of IgA on direct immunofluorescence. The patients are easily controlled with dapsone or oral corticosteroids. Colchicine should be considered as an alternative therapy for G6PD deficient patients or in the event of haemolysis.

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