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Juvenile Blistering Diseases : the Problems of Diagnosis and Treatment

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SUMMARY **Correct clinical diagnosis in cases of chronic, relapsing, non-hereditary, blistering diseases in childhood could not be made without the aid of histopathology and immunofluorescence, since the morphology and the distribution of the lesions of bullous pemphigoid (BP), linear IgA bullous dermatosis (LAD) and dermatitis herpetiformis (DH) may be similar. Histopathology was helpful in about half of the cases. The results of immunopathology were very useful for the final diagnosis. Of twenty-one cases of juvenile blistering diseases, two cases which showed IgG on direct test with circulating antibodies were BP; three cases with deposition of IgG but without circulating antibodies were probably BP; three cases were either BP or LAD (IgG and IgA on direct test without circulating antibodies); nine cases were definite LAD (linear IgA only); one case which showed granular IgA in the dermal papillae and linear IgA was DH; and the last three cases were probably LAD and BP with non-immunoreactant deposits. Regardless of the diagnosis, dapsone and co-trimoxazole controlled eight cases and could be discontinued without relapse, while the other six cases were maintained on dapsone therapy alone. Prednisolone, when added in cases of poor response to either dapsone or co-trimoxazole, caused remission and was discontinued in three out of the five cases. Two cases were lost to follow up.**

Chronic non-hereditary blistering diseases in childhood include bullous pemphigoid (BP), dermatitis herpetiformis (DH) and linear IgA bullous dermatosis (benign chronic bullous dermatosis). Linear IgA bullous dermatosis differs from dermatitis herpetiformis by the absence of associated small-bowel disease and the presence of linear deposition of IgA only, at the dermo-epidermal basement membrane zone (BMZ).[1-3] Histopathologically, diffuse infiltration with neutrophils in the basal vacuoles, along the BMZ and involving the tip of the rete pegs, favor LAD diagnosis whereas microaggregates of neutrophils in dermal papillae with basal vacuolization favors dermatitis herpetiformis.[3] BP in childhood is rare. Results from histopathological and immunofluorescent studies are similar to those for the adult type.[4]

However, in our practice for the last five years a number of cases of vesiculobullous eruption in childhood were misdiagnosed clinically as determined by histopathology and immunofluorescence. This was also observed by Chlorzelski *et al.*[5] Dapsone or co-trimoxazole was given to determine its efficacy in these patients.

MATERIALS AND METHODS

Patients

Thirteen boys and eight girls, 1-10 years old, with an average age of 5.2 years and with histories of recurrent, chronic vesiculobullous eruptions on the skin surface for many months were admitted to the Institute of Dermatology, Thailand between 1980-1984. Cases of epidermolysis bullosa or bullous eruption with scar formation were excluded from this study. There were no other symptoms except severe pruritus in some cases. None of the cases had gastrointestinal symptoms. Initial diagnosis was made based on the skin morphology which was characteristic for the specific diseases, *i.e.*, large tense bullae (BP), grouping

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of vesicles and small bullae on urticarial rashes (DH), and rosette patterns (the classical feature of LAD).

Skin biopsies were taken from urticarial lesions or from tiny vesicles for routine histopathological examination and periodic acid-Schiff stain. Half of the tissues were tested for direct immunofluorescence, and the sections were stained with fluorescein conjugated rabbit antihuman IgG, IgA, IgM, C3 and fibrinogen. The F/P molar ratios were 2.27, 2.73, 2.25, 2.47, and 2.92, respectively. The sections were examined with an Olympus epi-illuminating microscope.

Sera were also tested for IgG and IgA circulating anti-basement membrane zone antibodies. Normal human skin specimens were used as the substrate. In the follow up study and in cases where negative results were obtained, skin biopsies and immunofluorescent tests were repeated.

Other laboratory tests were also performed as needed, *i.e.*, fluorescent antinuclear antibody tests, C3 level tests, liver function tests, LE cell preparation tests and G-6-PD deficiency tests.

Treatment

Dapsone was initiated at a dosage of 1-2 mg/kg/day in all diagnoses except in G-6-PD deficient patients for whom co-trimoxazole syrup (trimethoprim-sulphamethoxazole, 40-200 mg/day) was prescribed. Some cases of bullous pemphigoid responded to dapsone in 3 weeks.[6] Therefore, in

Table 1 Grading of response to dapsone or co-trimoxazole

Grade of effectiveness	Onset of clearing	Percentage of skin clearing	Dapsone treatment
excellent (4^+)	in 1 week	100%	D/C in 1 month, no relapse
good (3^+)	over 2 weeks	80 - 100%	D/C in 4 months, no relapse
moderate (2^+)	over 3 weeks	50 - 80% (partially controlled)	Continued treatment for years and still continuing
poor (1^+)	over 4 weeks	0 - 50%	Prednisolone was added

Table 2 Immunofluorescent studies and treatment in juvenile blistering diseases

Final diagnosis (age/sex)	Direct IF to BMZ No. of positive (pattern)			Indirect IF to BMZ No. of positive (titer)		No.of treated case			Response to treatment (cases)			
	IgG	IgA	C3	IgG	IgA	DDS	Cot	+Pred	1^+	2^+	3^+	4^+
Juvenile BP (IM, 9M, 6F, 3M, 5M)	5 (T/HL/GL)	–	3 (T/HL)	2 (1:20, 1:80)	–	5*	–	1	1	1	2	–
BP or LAD (6F, 10F, 5M)	3 (T/HL/GL)	3 (HL)	3 (T/HL)	–	–	3	–	-	–	1	2	–
LAD (5M, 4M, 8M, 3F, 2F, 5M, 3F, 3M, 8F)	1 (HL)	9 (HL/GL)	2 (HL)	–	3 (1:10,1:20, 1:80)	8*	1	2	2	2	–	4
DH (7M)	–	1 (GP & HL)	–	–	–	1	–	–	–	1	–	–
Non-Ig deposit (5M 9F, 2M)	–	–	–	–	–	2	1	2	2	1	–	–

F = female
M = male
DDS = Dapsone
+Pred = Prednisolone was added
Cot = Cotrimoxazole
T = tubular pattern
HL = homogeneous linear pattern
GL = granular linear pattern
GP = granular deposits in dermal papillae
*lost 1 case

this study, if the eruptions did not respond in three to four weeks, prednisolone 1 mg/kg/day was added. The grading system used to determine the efficacy of dapsone and co-trimoxazole is shown in Table 1.

RESULTS

There were no sites of predelection in these cases of bullous eruptions, since the bullae predominated on the scalp, face, neck, back, pelvic regions, and upper and lower extremities. The mucous membrane was involved in six cases. The morphology of the lesions, which included rosette patterns, urticaria with vesicle formation and scattered tense bullae, was typical in many cases but was misdiagnosed in others, as determined by immunofluorescent studies (Table 2). Examples of problem cases for clinical diagnosis were a case with small and large tense bullae in a rosette-like pattern (Fig.1) and with tubular IgG at the BMZ (Fig. 2), and a case with scattered large tense bullae on the legs (Fig. 3) and with homogeneous linear IgA at the BMZ (Fig. 4).

Immunofluorescent findings

The results were classified into 5 categories :

1. IgG in a tubular pattern, with either positive or negative C3 deposition at the BMZ and with circulating IgG anti-BMZ antibodies present in two cases. These were cases of classical juvenile BP.

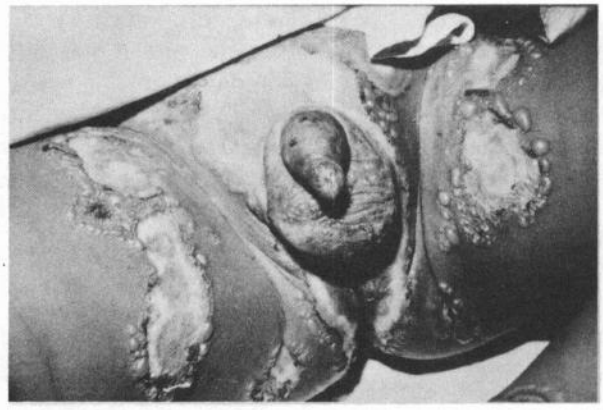

Fig. 1 Small and large tense bullae in a rosette-like pattern. Clinical diagnosis------LAD

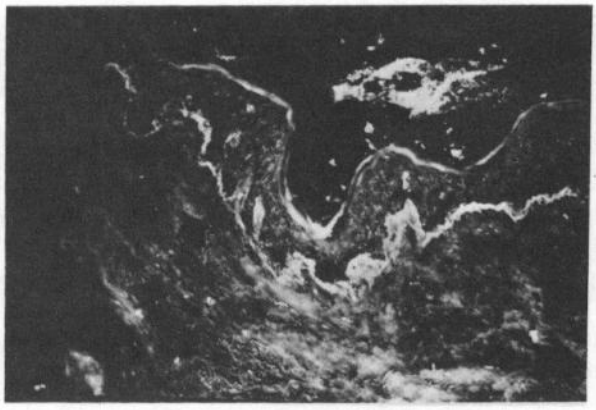

Fig. 2 Immunopathology revealed tubular IgG at the BMZ (x 200); final diagnosis, BP

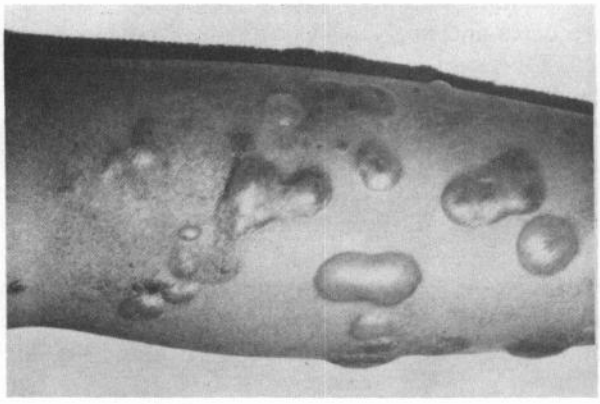

Fig. 3 Scattered large tense bullae on the legs. Clinical diagnosis-----BP

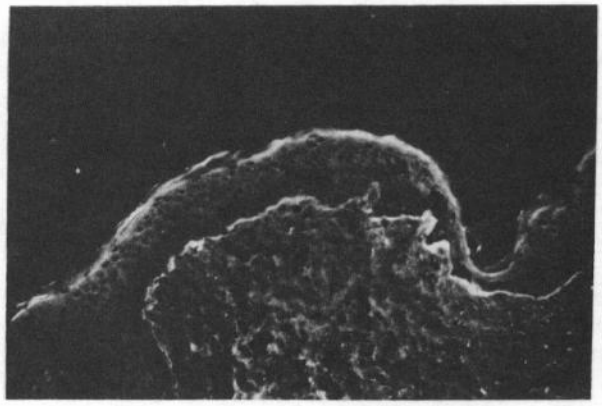

Fig. 4 Immunopathology revealed linear IgA at the BMZ (x 200); final diagnosis, LAD

2. IgG in homogeneous or granular, linear and tubular patterns, with negative circulating antibodies noted in six cases. Linear IgA was noted in 3 cases, and C3 in 5 cases. Three cases were probably BP while the other three cases may have been BP or LAD (see discussion).

3. a) IgA with negative IgG, in a homogeneous linear pattern at the BMZ in five cases.

b) IgA alone in a granular, linear pattern at the BMZ, not in dermal papillae in one case.

c) IgA in mixed homogeneous and granular, linear patterns at the BMZ, not in dermal papillae in 2 cases.

d) IgA with positive IgG, both in granular, linear patterns at the BMZ in one case.

Three of these 6 cases also had low titers of circulating IgA anti-BMZ antibodies. These were definite case of LAD.

4. Immunoglobulins were not deposited in three cases although repeated skin biopsies and tests were performed.

5. One case showed linear IgA deposits at the BMZ and granular IgA in the dermal papillae. This was a case of DH. The combined deposits may be seen often in DH.

Pure granular IgA in dermal papillae was not observed in this series. Circulating antibodies became negative after treatment.

The histopathological examination using the criteria of Smith *et al*[3] confirmed the diagnosis of LAD in 7 cases with immunoreactant deposits and 2 cases with non-immunoreactant deposits. Vacuolization of epidermal basal cell layers infiltrated with neutrophils were observed in seven LAD cases while tips of the rete pegs were infiltrated with neutrophils in one case (both criteria were observed in one case). However, one or both criteria were seen in one case of BP, two cases of BP or LAD, one case of DH, and two cases of non-Ig deposits.

Papillary microabscesses with neutrophils, which are characteristic for DH, were also observed in 1 case of BP, 3 cases of BP or LAD, 4 cases of LAD, and 1 case of non-Ig deposits. The presence of eosinophils in subepidermal bullae may suggest BP, but the other cellular infiltration was not helpful in making the diagnosis of any disease because it did not correlate to the results of immunofluorescent tests. This was the problem of definite diagnosis.

Treatment

The results of treatment are shown in Table 2.

In five cases of BP, three cases were controlled by dapsone in 2 months (3+) while in another case prednisolone was added. Medications were discontinued after 4 months in two cases and no relapse was observed. One case is still on maintenance therapy with dapsone. One case was lost to follow up.

In three cases of BP or LAD, dapsone controlled the eruptions in two and was discontinued in 2-4 months. One case is still on maintenance therapy with dapsone.

In nine cases of LAD, two cases were controlled by dapsone and two cases by co-trimoxazole in 1 week. Discontinuation of medications caused no relapse. Two cases are still on maintenance therapy with dapsone alone (5-10 mg/day). Prednisolone (15 mg/day) was added in two other cases and the treatment has continued up to the time of this writing. One case was lost to follow up. Only one patient developed methemoglobinemia, but dapsone was reduced to half dose and she tolerated it very well. Bullous eruptions could also be controlled.

In three cases of non-Ig deposits, two showed a histological picture of LAD and another of BP. One case with a histopathological diagnosis of LAD is on maintenance therapy with dapsone alone. Prednisolone was added in two cases, one of which was on co-trimoxazole, and it was discontinued without relapse.

In the case of DH, dapsone has been continued at a maintenance dosage with only a few vesicles seen.

DISCUSSION

Based on immunofluorescent studies, there was one case of juvenile DH. This is not surprising because Thai food is almost a gluten-free diet and gastrointestinal symptoms were absent in all cases. Adult cases of DH are also rare in Thai patients (personal observation).

Six cases were questionable for diagnosis of BP because circulating antibodies could not be detected. The histology favored BP because of the presence of eosinophilic subepidermal bullae in two cases. It favored DH because of neutrophilic abscesses in one case and it favored LAD because of basal vacuolization and rete tip involvement with neutrophilic infiltration in two cases. The remaining case might have been a cell-poor type of BP. However, neutrophilic

micro-abscesses may be seen in BP.[1,5] Three of these six cases also had linear IgA at the BMZ. Faber and van Joost[6] preferred to interpret such findings as cases of BP while Katz considered them as LAD.[7] Beutner *et al* [8] suggested that finding C3 and more strongly positive IgG deposits indicated a diagnosis of BP while finding more strongly positive IgA deposits and an absence of C3 pointed to a diagnosis of LAD. These three cases may be either BP or LAD. Two cases dramatically responded to dapsone and it could be discontinued in 4 months. One is still on dapsone. The response of BP to dapsone was not susprising since our juvenile[4] and adult BP cases[9] and cases reported by Marsden[10] also responded to dapsone. However, it should be noted that cases with a diagnosis of BP or suspicious of BP (by histology) did not respond very well or responded slowly to dapsone.

In cases of LAD and non-Ig deposits, seven cases responded moderately or poorly to dapsone. At the present moment, three cases are still on maintenance therapy of dapsone. When prednisolone was added in four cases, it was able to control the vesicular eruption in all cases and could be discontinued in 2 cases. Our study confirmed the effectiveness of dapsone in some cases of LAD as studied by Marsden.[10] Because of the high incidence of the association of HLA-B8 typing in both DH and LAD,[1] a study regarding this matter was not performed.

In conclusion, regardless of the clinical, histopathological or immunopathological diagnosis, definite diagnosis could not be made in many cases. Eight cases (BP 2; BP or LAD 2 ; LAD 4) responded well to dapsone or co-trimoxazole and six cases have been on maintenance doses of dapsone up to the time of this writing. In five cases, prednisolone was added and was discontinued in three cases without relapse. Two cases were lost to follow up.

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