Case 1: Dermatitis Herpetiformis

Dr. M. H. Ho

Date:	8 July 1998
Venue:	Yaumatei Skin Centre
Organizer:	Social Hygiene Service, DH; Clinico-pathological Seminar

CASE SUMMARY

History

A 23-year old Chinese woman presented with a three year history of recurrent blistering eruption that is associated with mild itching. There was no history of photosensitivity or any other aggravating factors. She was seen in Shengzhan by traditional Chinese and Western doctors.

She was born in China as the eldest child of her family. Her siblings, including three sisters and one brother were all healthy. She had short stature that was investigated in China but no cause was identified. She had unilateral cleft lip with operation done when she was young.

Physical examination

Skin biopsy performed in August 1995 showed denseThere were multiple tiny vesicles on erythematous base, occurring in crops, on the trunk and limbs. The distribution was not limited to the extensor aspects. Erosions were also detected on the body, limbs and scalp (Figure 1, 2, 3). The mucosal surface was spared and the nails were normal.

Her height was 132 cm and the weight was 40 kg. She had not developed any secondary sexual characteristic features. Her mental development was normal but she received secondary school education up to Form one only.

Differential diagnoses

The differential diagnoses include dermatitis herpetiformis, Grover's disease, pemphigus foliaceus or erythematosus, bullous lupus erythematosus and other immunobullous diseases.

Investigations

The complete blood picture and ESR were normal. The liver and renal function tests showed elevated alkaline phosphatase and gamma glutamyl transferase, 116 (normal: 30-100iu/L) and 47 (normal: 8-35iu/L) respectively. The anti-skin antibody was negative. The

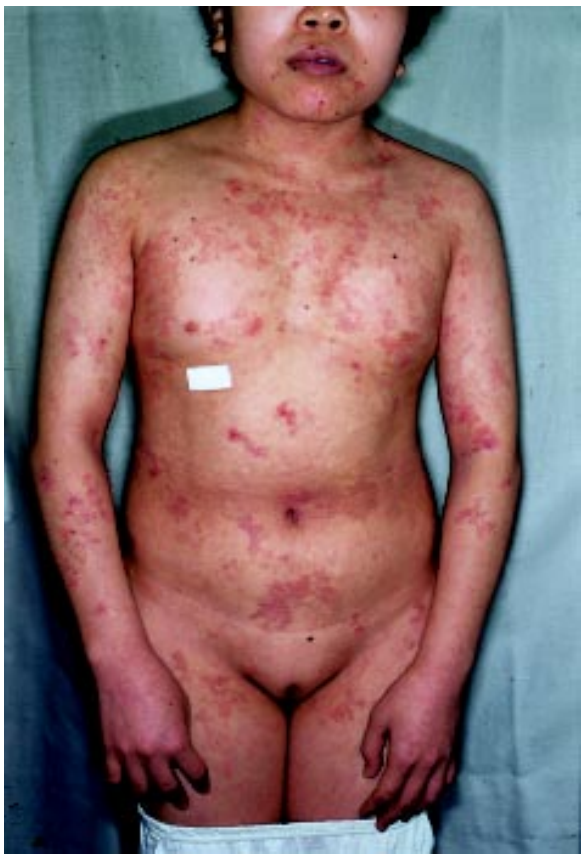

Figure 1: Bilateral symmetrically distributed rash and vesicles on the anterior trunk

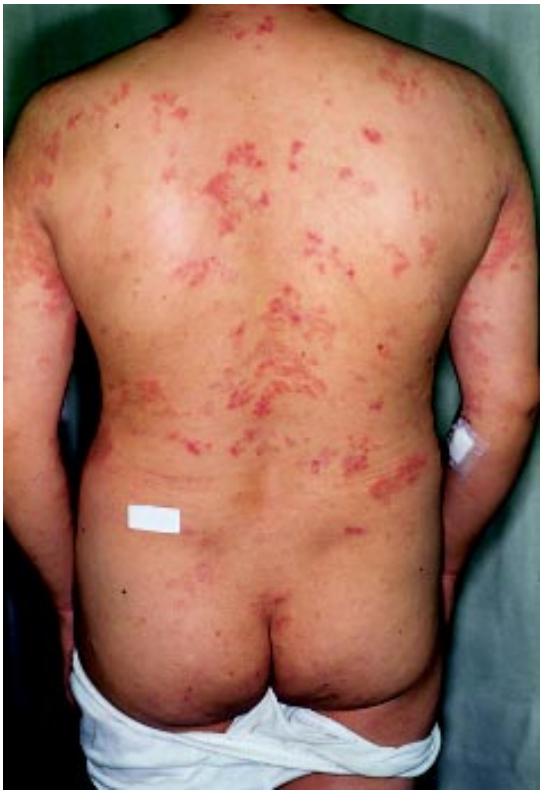

Figure 2: Rash and vesicles on the back

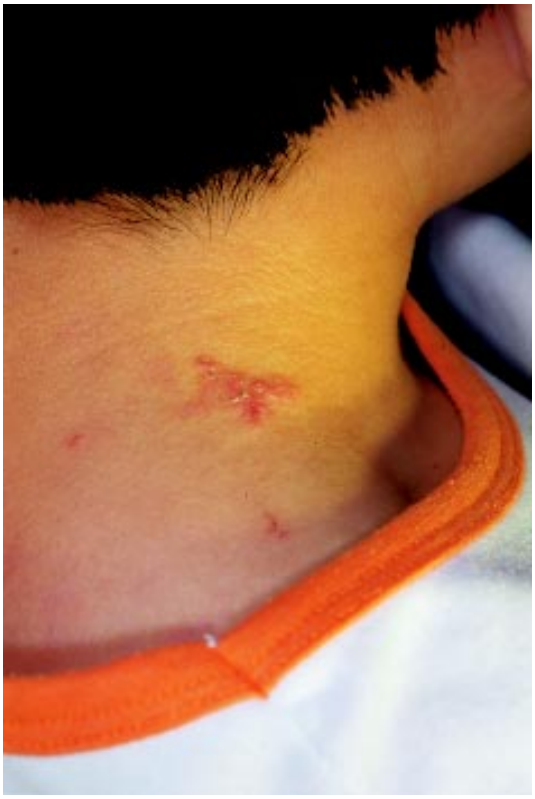

Figure 3: A close up view of the vesicular eruption on the side of the neck

other auto-immune markers (ANF, anti-ENA) were normal and complement levels were within normal limits. The immunoglobulin pattern showed elevated IgA 504 (normal: 90-450mg/dl). Anti-reticulin antibody and anti-endomysial antibody assay were arranged and the results were pending. Glucose 6 phosphate dehydrogenase level was normal and Hepatitis B surface antigen was negative. Mid-stream urine examination was normal.

Hormonal assays for her short stature were done. The thyroid function test revealed hypothyroidism with decreased free thyroxine 8.4 iu/L (normal: 9.1-23.8iu/L) and increased thyroid stimulating hormone 14.48 iu/L (normal: 0.4-3.2iu/L) levels. Other test results (growth hormone, spot cortisol, luteinizing hormone/follicle stimulating hormone, estrogen / testosterone) were pending.

Skin biopsy

The first biopsy was performed on the right forearm. It showed marked spongiosis and necrosis of keratinocytes forming a subepidermal bulla. The dermis was edematous with moderate amount of eosinophils, neutrophils and mononuclear inflammatory cells. IMF showed focal IgM deposits at the dermo-epidermal junction, C3 and fibrinogen within the bullous cavity. The impression was that of a subepidermal bullous disease.

The second biopsy was taken from fresh blister lesion on the neck. There were patchy focal accumulation of neutrophils and scanty eosinophils with fibrin at the dermal papillary tips. Microabscesses were seen at some of the dermal papillae. Multiloculated blisters containing fibrin were present in other areas. The epidermis was spongiotic in some areas. A few neutrophils, scanty eosinophils and a moderate number of mononuclear inflammatory cells infiltrated around blood vessels and skin appendages. IMF demonstrated focal granular deposit of IgA at dermal papillae. The findings were compatible with **dermatitis herpetiformis.**

Management

She was given dapsone 100mg and thyroxine 0.05mg daily. In addition she was referred to the gastrointestinal physician for exclusion of gluten

sensitive enteropathy, and to the dietitian for gluten free diet. She was also referred to the endocrinologist for investigation of short stature and primary amenorrhoea.

All lesions resolved and there was no new eruption after dapsone treatment.

REVIEW ON DERMATITIS HERPETIFORMIS (DH) [1]

DH is an uncommon dermatosis characterised by itchy, chronic, papulovesicular eruption distributed on extensor surfaces symmetrically. It is associated with gluten sensitive enteropathy (GSE) which can be asymptomatic. The first DH associated GSE was reported in 1966. This condition was rarely reported in Chinese. A large-scale survey in Singapore revealed only eight patients in the 2.5 million population who were diagnosed to have IgA dermatoses; three of them have granular Ig A deposit.[2]

Clinical features[1]

The age of onset is 20 - 40s but it can start at any age. Male is affected twice as common as female. Primary lesions take the form of erythematous papules, urticarial-like plaques or vesicles. It can be asymptomatic or cause severe burning and itching. The prodrome of localised stinging, burning, or itching sensation may occur 8-12 hours before the lesions appear. Herpetiform grouping is often present. Sometimes crusted lesions are present. They are symmetrically distributed over the extensor surfaces (buttock, knees, sacral area, elbows and shoulders), face and facial hair line, scalp and posterior nuchal area. Vesicles may be found on palms and are sometimes haemorrhagic.

Investigations

Histology[1]

In early non-vesicular skin lesions, histology is characterised by neutrophilic micorabscesses in dermal papillae. There are neutrophilic fragments and eosinophils. Papillary dermis is separated from the overlying epidermis. There is perivascular neutrophilic, eosinophilic and lymphohistiocytic infiltrate around upper and mid-dermal blood vessels.

The differential diagnoses include linear IgA disease, bullous lupus erythematosus, bullous pemphigoid and epidermolysis bullosa acquisita (neutrophil-rich form). In older lesions, there are subepidermal vesicles. The differential diagnoses include erythema multiforme, bullous pemphigoid and bullous drug eruption.

Direct IMF

The granular IgA deposits at dermal papillae is classical. IgA is unevenly distributed throughout the skin; being more dense near the active lesion.[3] The preferred biopsy site for immunopathologic diagnosis in DH is the normal appearing skin adjacent to an active lesion.3 IgA1 is the predominant subclass found.1 The IgA deposits are unaffected by drug treatment but decrease with adhesion to gluten free diet.

Site of blister[4]

It was thought that blistering occurred below lamina densa. Recent study using immunomapping technique instead of electron microscopy demonstrated that the cleavage took place above lamina densa within the lamina lucida. It has been proposed that neutrophils infiltrate dermal papilla and release lysosomal enzymes resulting in papillary edema. Further recruitment of neutrophils and release of enzymes cause enzymatic damage of the lower lamina lucida, leading to vesicle formation within the lower lamina lucida above lamina densa.

Cytokine[5]

Various cytokines have been shown to be involved in the pathogenesis of DH. ELAM (endothelial leucocyte adhesion molecules) expression was increased in the deep dermis. Interleukin-8 was elevated in basal keratinocytes. Granulocyte Macrophage-Colony Stimulating Factor was raised in the dermo-epidermal junction. These cytokines promote neutrophilic activation and infiltration. GM-CSF stimulated expression of IgA-Fc receptors on polymorphs. They account for the neutrophilic infiltration and activation, enzymes release and vesicles formation.

Indirect IMF[6,7]

The anti-gliadin antibodies are non-specific. The IgG anti-gliadin antibody is present in pemphigus, while IgA anti-gliadin antibody can be found in pemphigoid.

Anti-reticulin IgA is disease-specific while the anti-reticulin IgG is not. Anti-endomysial IgA is most specific for DH and GSE,[1, 6] and it correlates with the disease activity of GSE. The titre decreases with gluten free diet and is useful in monitoring the disease progress and compliance to diet.

HLA association

HLA B8 is detected in 77-87% of DH.[1] In addition, HLA DR3, Dqw2 are also associated the disease. However no significant association has been demonstrated in Chinese between HLA B8 , DR3 and DH.[8]

Differential diagnoses

The differential diagnoses include erythema multiforme, papular urticaria, neurotic excoriation, Grover's disease, bullous pemphoid and linear IgA disease. The diagnosis is confirmed by histological findings of granular deposit of IgA in normal appearing perilesional skin.

Association

Gluten sensitive enteropathy (GSE) in DH is often asymptomatic, but it may cause diarrhoea. Steatorrhoea occurs in less than 5% of cases. The histology consists of subtotal villous atrophy and crypt hypertrophy. However, no such association have been demonstrated in Chinese.[2] According to the literature, there is increased risk of intestinal lymphoma.

Management[1]

Diet

Gluten free diet is effective but takes five months to one year for its effect to become apparent.

Sulphones

Sulphone drugs cause rapid improvement of symptoms and signs, usually around three hours to few days after the first dose. This rapid response aids in making the diagnosis of DH. No new eruption develops after one to two days of treatment, but there may be exacerbation on withdrawal of drug. Dapsone 100-150 mg daily is used in Caucasian.[1] In Chinese, a lower dose of 25 to 50 mg daily is usually effective.[2] Sulfapyridine 1-1.5 gm daily is an alternative for patients intolerant to dapsone, the elderly, and those with cardio-pulmonary problems. Non-steroid anti-inflammatory drugs can cause exacerbation of DH even during dapsone treatment in these patients.

Combination Therapy (Diet and sulphone)

This has the advantage of reducing the maintenance dosage or even complete withdrawal of the drug, provided that the patient strictly adheres to the gluten free diet.

Learning points:

DH is a pruritic blistering eruption rapidly reponsive to dapsone. Exclusion of gluten sensitive enteropahy and gluten free diet may be helpful in long term management.

References

1. Katz SI. Dermatitis Herpetiformis. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF, editors. Dermatology in General Medicine. 4th edition. McGraw Hill 1993; 1: 56; 636-40.
2. Ratnam KV. IgA dermatosis in Adult Chinese Population. A 10-year study of Linear IgA and dermatitis herpetiformis in Singapore. Int J Dermatol 1988; 27(1):21-4.
3. Zone JJ, Meyer LJ, Peterson MJ. Deposition of granular IgA relative to clinical lesions in dermatitis herpetiformis. Arch Dermatol 1996;132(8): 912-8.
4. Smith JB, Taylor, Zone JJ. The site of blister formation in dermatitis herpetiformis within the lamina lucida. J Am Acad Dermatol 1992; 27:209-13.
5. Graeber M, Baker BS, Garioch JJ, et al. The role of cytokines in the generation of skin lesion in dermatitis herpetiformis. Br J Dermatol 1993; 129: 530-2.
6. Peters MS, McEvoy MT. Ig A antiendomysial antibodies in dermatitis herpetiformis. J Am Acad Dermatol 1989; 21: 1225-31.
7. Kuman V, Zane H, Kaul N. Serologic markers of Gluten-sensitive enteropathy in Bullous disease. Arch Dermatol 1992; 128: 1474-8.
8. Chan SH, Wee GB, Srinivasan N, et al. HLA antigens in three common populations in South East Asia: Chinese, Malay and Filipino. Tissue Antigens 1979; 13: 361-8.