A 55-year-old Chinese man presented with acute onset of a vesicobullous rash on his face, axillae, genitalia and trunk. The skin biopsy showed a subepidermal bulla. The diagnosis was made by direct immunofluorescence of the perilesional skin which revealed characteristic linear deposition of IgA along the dermoepidermal junction. He was successfully treated with dapsone initially but subsequently developed erythema multiforme, possibly due to dapsone. Linear IgA dermatosis should be considered in patients presenting with bullous lesions, even when the distribution of the rash is atypical. Alternative diagnoses should be entertained when patients experience an unexpected relapse whilst on treatment. We highlight the important points in the clinical presentation, diagnosis and the problems encountered in the treatment of this uncommon skin disorder.(Dermatol Sinica 24: 27-31, 2006)

Keywords: Bullous disease, Dapsone, Erythema multiforme, Linear IgA dermatosis
INTRODUCTION

Linear IgA dermatosis is an uncommon autoimmune vesicobullous disease in Singapore.1 It is characterized by linear deposition of IgA autoantibody at the basement membrane zone. We report a patient with linear IgA dermatosis who responded briefly to dapsone therapy but later developed a drug reaction, in the form of erythema multiforme.

CASE REPORT

A 55-year-old Chinese man presented with a two week history of an itchy vesicobullous rash. The rash started on the face and lips, and then spreading to the trunk and axillae. It first presented as papules which progressed to become vesicles. He denied any form of topical treatment on the body. Systemic review did not reveal any other symptoms.

There was no history of previous episodes of skin problems and he did not have any family history of skin diseases. He had not taken any medications but confessed to drinking herbal tea from Chinese medical halls intermittently for the past one year. He had otherwise no past history of note. He worked as a hawker assistant.

Physical examination revealed a vesicobullous eruption with symmetrical flexural distribution including the axillae and genitalia. The bullae were tense and the Nikolsky sign was negative (Fig. 1). There were no mouth lesions and the rest of the physical examination was unremarkable. Because of the atypical distribution, the provisional clinical diagnosis was linear IgA disease but bullous pemphigoid could not be excluded on clinical grounds.

Histological examination of the skin biopsy showed a subepidermal bulla containing fibrinous exudate with an admixture of neutrophils and occasional eosinophils (Fig. 2). The dermis contained a perivascular lymphocytic infiltrate. Direct immunofluorescence studies showed predominant linear deposits of IgA, with IgG and C3 in the basement membrane zone and in the floor of the bulla (Fig. 3). Indirect immunofluorescence examination of the patient's serum showed no anti-basement membrane or anti-intercellular substance antibodies.

The diagnosis of linear IgA disease was made and he was started on prednisolone 50mg once daily. The patient was reviewed 2 weeks later. He had run out of prednisolone for 4 days...
and there were active bullous lesions on the axillae and face. Prednisolone was reintroduced and the dose was increased to 60 mg per day. He was also started on dapsone 50mg a day, his glucose-6-phosphate dehydrogenase status having been found to be positive. Other blood investigations including full blood count, renal and liver function tests were normal. One week later, his skin lesions were improved with dried vesicles. Over the next 2 weeks, prednisolone was tailed down to 40mg a day and dapsone increased to 100mg a day. 3 weeks later, he presented to clinic with generalised erythema and swollen palms with generalized target-like skin lesions. He was admitted with a diagnosis of an erythema multiforme-like drug eruption possibly secondary to dapsone.

Examination at this time revealed a symmetrical erythematous maculopapular and targetoid rash on the arms, trunk and legs and vesicles on the left arm. There was no mucosal involvement. Dapsone was withdrawn and he was maintained on prednisolone 40mg a day. A biopsy of a targetoid skin lesion showed interface dermatitis compatible with early lesions of erythema multiforme (Fig. 4). Blood investigations were unremarkable except for mild anaemia of 11.8g/dL (14.0-18.0), which could be secondary to dapsone therapy. The renal and liver function tests were normal. The rash subsided after five days, but he developed new vesicles in the axillae and trunk, possibly a relapse of the linear IgA disease. He was discharged with an increased dose of prednisolone 50mg a day. On review a week later, he did not have new bullae and the dose of prednisolone was gradually tapered. The haemoglobin levels normalized spontaneously 1 month after discharge and had since remained stable.

DISCUSSION

Linear IgA dermatosis is one of the rarest subepidermal blistering diseases in Western Europe and is more common in China. It is surprisingly not common in Singapore, where the majority of the population is Chinese.1 Typically, it occurs in patients over thirty years of age, with the average age of onset after sixty years old and is more common in females.2 The disease is characterized by annular or grouped papules, vesicles or bullae on a normal or erythematous base. The lesions are typically distributed symmetrically along the extensor surfaces and are often pruritic.

Linear IgA dermatosis may mimic dermatitis herpetiformis or bullous pemphigoid, but it is a separate disorder that is both immunopathologically and immunogenetically distinct.2, 3 There may also be mucosal involvement, clinically indistinguishable from cicatricial pemphigoid.3 Chronic bullous disease of childhood is an immunopathologically similar disease which differs only in age of onset and that it typically resolves within 2 to 4 years of onset.2, 3

Most cases of linear IgA dermatosis are idiopathic, although it has been associated with infections, malignancies4 and drugs, including vancomycin,5 fruosemide6 and captopril.7 There are also two reports of ultraviolet light induced IgA dermatosis.4 Our patient denied taking any drugs around the time his skin lesions appeared. It is unlikely that the Chinese herbal tea was responsible for inducing his disease.

Subepidermal bullae containing predominantly neutrophils seen in linear IgA disease
can be indistinguishable from dermatitis herpetiformis on light microscopy. Those with a predominant infiltrate of eosinophils may mimic bullous pemphigoid. The type of inflammatory infiltrate present may depend on the age of the lesion and the time of the biopsy. In our own patient, histological examination revealed a sub-epidermal bulla with predominant neutrophils and direct immunofluorescence of perilesional skin showed linear deposits of IgA along the dermoeidermal junction. Indirect immunofluorescence on sodium chloride split skin, which was not done in our patient, yields variable results with immunoreactants mapping to the roof or floor of the split or both. There is evidence of antigenic heterogeneity in idiopathic linear IgA dermatosis as demonstrated by Western immunoblotting. Target antigens involved include BP230/BPAG1, BP180/BPAG2, LAD antigen, type VII collagen and a 97kDa antigen representing a cleaved ectodomain of BPAG2 (BP180). IgG autoantibodies may also be involved. Linear IgA deposits have been reported in a few other conditions, including cutaneous varicella-zoster infection.

A rare group of bullous pemphigoid patients may also have IgA, IgG/C3 deposits along the basement membrane zone and distinction between linear IgA disease may be challenging. The classification of these patients has been debated upon. Some authorities classify only patients with IgA deposits as linear IgA disease while others categorize patients with both IgG and IgA on the basis of the predominant immunoglobulin on the direct immunofluorescence. The diagnosis of bullous pemphigoid would be more convincing if there were circulating anti-basement membrane autoantibodies against BP180 or type VII collagen. These tests were not performed in our patient. It can be argued that the erythema multiforme-like rash correlated well with the administration and withdrawal of dapsone. It is also unlikely that the patient's linear IgA disease should flare without other exacerbating triggers, after having good initial response to dapsone. The patient also subsequently developed more characteristic linear IgA vesicles, reminiscent of his initial presentation, after dapsone was withdrawn.

Linear IgA dermatosis has a variable course and may last for years with spontaneous resolution in some patients. Patients with linear IgA dermatosis respond favourably to dapsone, but some require low dose prednisolone to suppress blister formation. Our patient developed erythema multiforme whilst on dapsone, which may have been due to this drug. Adverse reactions to dapsone are more likely to occur in patients with a slow acetylator phenotype. Cutaneous reactions to dapsone are well recognized and include the dapsone hypersensitivity syndrome, toxic epidermal necrolysis and Stevens-Johnson syndrome. Dapsone remains one of the most effective drugs for treatment of linear IgA dermatosis and intolerance to dapsone may impede the future management of his skin condition.

In conclusion, we have described a patient with linear IgA dermatosis who developed erythema multiforme possibly due to dapsone. This complication should be considered in any patient with linear IgA bullous dermatosis who develops an otherwise unexplained flareup during dapsone treatment.

REFERENCES