

Dermatology quiz: an old man with skin rash

皮膚科猜謎：一名有皮疹的老翁

KH Man 萬景雄 and CM Lo 盧礎文

Case

A 71-year-old man with good past health attended our emergency department with complaint of itching skin rash for two weeks. There was no precipitating factors or events before the onset of rash. He was labelled by other doctors as chickenpox and non-specific skin rash in previous consultations. His blood pressure was 220/134 mmHg, pulse rate 86 beats per minute and temperature 36.2°C. The systems review was unremarkable. The skin rashes were illustrated in Figures 1 to 4.



Figure 1. Rash of the patient.



Figure 2. Rash over the elbow.



Figure 3. Rash over both hands.



Figure 4. Closer look of the rash over the hand.

Correspondence to:

Man King Hung, MBChB, FHKCEM, FHKAM(Emergency Medicine)
Kwong Wah Hospital, Accident and Emergency Department,
25 Waterloo Road, Yau Ma Tei, Kowloon, Hong Kong.
Email: drmankh@hotmail.com

Lo Chor Man, FRCP(Irel), FHKCEM, FHKAM(Emergency Medicine)

Questions

1. Describe the rash.
2. What is the likely diagnosis?
3. What is the management?

Answers

1. Multiple blisters and raw areas over the face, both upper limbs and trunk.
2. Bullous pemphigoid.
3. Take skin biopsy. Consider starting steroid after skin biopsy. Co-morbid conditions of the patient have to be taken into account in the decision making.

Discussion

Blister is defined as an elevation of skin containing fluid. It is called bulla when the size is greater than 5 mm. Blister or bulla is a common skin rash in all age groups and there is a wide variety of differential diagnoses. Some of the blister skin lesions are associated with potentially fatal conditions such as Steven-

Johnson syndrome and toxic epidermal necrolysis. Some other lesions such as bullous pemphigoid, pemphigus vulgaris and erythema multiforme, although rare and less lethal, still carry a significant mortality or morbidity if one cannot recognise and offer proper management.

The initial assessment of blister lesions, like other skin diseases, should base primarily on the history and physical examination without the need of complex investigations. History such as age, sex, occupation, duration, progress, itchiness, preceding illness or erythema, drug and past health are relevant and important. On physical examination, apart from the appearance of the rash, the distribution of the blister can help considerably in making the correct diagnosis. The differential diagnoses of blister eruptions are summarised in Table 1.¹

Table 1. Characteristics and differential diagnosis of common blister eruptions

	Characteristics
Widespread blisters	
Pemphigoid	Elderly patients, trunk and flexures affected; preceding erythematous lesions, deeply situated and tense blister, sometimes itchy
Pemphigus	Adults, superficial blisters, mucous membranes affected, Nikolsky sign positive
Erythema multiforme	Erythematous and target lesions; infection, drugs, malignancy, pregnancy and rheumatologic disorder related
Steven-Johnson syndrome	More severe and extensive vesiculobullous rash with mucous membranes affected, systemic involvement, acute onset
Toxic epidermal necrolysis	Tender erythema, bullae formation, and subsequent exfoliation; mucous membrane affected, systemic toxicity; Nikolsky sign positive
Dermatitis herpetiformis	Itchy, extensor surface, persistent
Chickenpox	Crops of blisters, self-limiting, prodromal illness
Pityriasis lichenoides	Crops of pink papules, varioliform, no infective agent isolated
Drug eruptions	History of drugs prescribed, e.g., barbiturates, tranquillisers
Localised blisters	
Eczema	Pompholyx blisters on hand and feet, itchy
Allergic reactions	Topical medication, insect bites, acute onset
Psoriasis	Deep, sterile, non-itchy, on palms and soles
Impetigo	Localised, staphylococci and streptococci isolated, acute
Herpes simplex	Itchy, turbid blisters, preceding redness

Bullous pemphigoid

This disorder is a rare, autoimmune, chronic skin disorder characterised by blister lesions. It occurs most frequently in elderly people in the fifth through seventh decades of life and is rarely fatal. Male and female are equally affected.

Causes

Bullous pemphigoid is thought to occur because IgG immunoglobulin and activated T lymphocytes attack components of the basement membrane, particularly a protein known as antigen BP180, or less frequently BP230. These proteins are within the NC16A domain of collagen XVII. BP180 is also called Type XVII collagen. These are associated with the hemidesmosomes, structures that ensure the epidermal keratinocyte cells stick to the dermis to make a waterproof seal.^{2,3} In many patients, skin antibodies can also be detected circulating in the blood stream (positive indirect immunofluorescence). The serum levels of the auto-antibodies are also correlated to disease activity.^{4,5}

Symptoms

The first symptom of bullous pemphigoid is usually redness of the skin surrounding a lesion, scar, or the navel. Within weeks, thin walled blisters with clear fluid centres (bullae) appear mainly on the undersurfaces of the flexural aspects of the limbs and trunk.

The blisters are usually tense and contain clear or blood-tinged fluid; they do not rupture easily. If the blisters do rupture, pain may occur but healing is usually rapid. If untreated, the disease can persist for months or years, with periods of spontaneous remissions and exacerbations.

Bullous pemphigoid usually itches and in its early phase, itching and hive-like patches may be the only symptoms. Unlike pemphigus, bullous pemphigoid blisters usually do not affect the mucous membrane lining of the mouth.

Diagnosis

Bullous pemphigoid is usually recognised by its characteristic blisters. However, it is not always easy to distinguish from pemphigus and other blistering conditions. In most cases the diagnosis will be confirmed by skin biopsy of a typical blister. The lesion

is located in the sub-epidermal region when seen under the microscope. Direct immunofluorescence staining highlights antibodies along the basement membrane that lies between the epidermis and dermis.

Treatment

As in other autoimmune bullous diseases, the goal of therapy is to decrease blister formation, to promote healing of blisters and erosions, and to determine the minimal dose of medication necessary to control the disease process with minimal adverse side effect. If the pemphigoid is very widespread, hospital admission may be advised so the blisters and raw areas can be expertly dressed. Antibiotics may be required for secondary bacterial infection.

The proper treatment of bullous pemphigoid depends on the severity of the disease. For localised disease, topical steroids plus systemic anti-inflammatory agents (tetracycline and nicotinamide) may be sufficient. The effects of monotherapy with nicotinamide are unknown. Very potent topical steroids are effective and safe treatment for bullous pemphigoid. However, their use in extensive disease may be limited by side effects and practical factors.

Systemic corticosteroids are the best established treatment. Systematic review of the Cochrane Database regarding the intervention for bullous pemphigoid by Khumalo et al concluded that lower doses of oral steroid may be adequate for disease control and this could reduce the incidence and severity of adverse reactions.⁶ Starting doses of prednisolone greater than 0.75 mg/kg/day do not seem to give additional benefit. The effectiveness of the addition of azathioprine or plasma exchange to corticosteroids has not been established.

Azathioprine, an immunosuppressive agent, is used to suppress the production of pathogenic antibodies. It is mostly employed as an adjunct to systemic corticosteroids for its presumptive steroid-sparing effect. However, the efficacy of azathioprine as a steroid-sparing agent in bullous pemphigoid has been addressed in only two randomised controlled trials, with conflicting results. One randomised controlled trial by Burton et al reported a 45% reduction in cumulative prednisolone dosage over a 3-year period.⁷ Conversely, a larger randomised controlled trial by Guillaume et al found no difference in remission rates

at six months in patients treated with corticosteroids only compared with those receiving combination treatment with prednisolone and azathioprine.⁸ It is recommended that azathioprine is only considered as a second-line treatment to prednisolone where response has been inadequate and either the disease is not suppressed or the side-effects are troublesome and unacceptable.⁹

Plasmapheresis (plasma exchange) removes pathogenic antibodies and inflammatory mediators. There have been only two randomised controlled trials by Guillaume et al and Roujeau et al^{8,10} studying the use of plasmapheresis in the treatment of bullous pemphigoid. The regimens used, the additional therapy, and the results have been very variable. There is no evidence to support the use of plasmapheresis in routine treatment of bullous pemphigoid, although at low corticosteroid doses a steroid-sparing effect was seen. There may be a limited role for plasmapheresis in resistant cases of bullous pemphigoid where side-effects are a major issue.⁹

Mortality and morbidity

Patients with aggressive or widespread disease, those requiring high doses of corticosteroids and immunosuppressive agents, and those with underlying medical problems have increased morbidity and risk of death. Because bullous pemphigoid usually occurs in elderly patients, they frequently have other co-morbid conditions, thus making them more vulnerable to the adverse effects of corticosteroids and immunosuppressive agents such as peptic ulcer disease, gastrointestinal bleeding, agranulocytosis, and diabetes. These may be fatal, particularly in patients who are debilitated. The proximal causes of death are infection with sepsis and adverse events associated with treatment.

Progress of our patient

This gentleman was admitted into our medical ward and the dermatologist was consulted. With regard to his clinical features including old age, persistent and long duration of lesions, symptoms of itching, and its distinctive morphology and distribution, the diagnosis

of extensive bullous pemphigoid with active disease was made. Oral prednisolone 40 mg daily, tetracycline and cetirizine were started and topical potassium permanganate and clobetasol propionate were given as well.

Investigations results were as follows: the erythrocyte sedimentation rate and C-reactive protein were elevated. Anti-nuclear antibodies and anti-neutrophil cytoplasmic antibodies were negative. Urine porphyrin was also negative. The skin biopsy result was compatible with bullous pemphigoid with the immunofluorescence staining showing linear deposits over the dermal-epidermal junction.

His skin lesions gradually dried up and crusted with no more new bulla eruption. His blood pressure was well controlled by antihypertensive drugs. He was eventually discharged from hospital on day 10 and prednisolone was tapered down gradually. When he was reviewed at the outpatient clinic at week 4, there were no new skin lesions and only residual scars with hyper-pigmentation left.

References

1. Buxton PK. Blisters and pustules. ABC of dermatology. Hot climates edition. London: BMJ Books; 1999. Ch 8, p. 38-41.
2. Sitaru C, Schmidt E, Petermann S, Munteanu LS, Brcker EB, Zillikens D. Autoantibodies to bullous pemphigoid antigen 180 induces dermal-epidermal separation in cryosections of human skin. *J Invest Dermatol* 2002;118(4):664-71.
3. Thoma-Uszynski S, Uter W, Schwietzke S, Schuler G, Borradori L, Hertl M. Autoreactive T and B cells from bullous pemphigoid (BP) patients recognize epitopes clustered in distinct regions of BP180 and BP230. *J Immunol* 2006;176(3):2015-23.
4. Schmidt E, Obe K, Bröcker EB, Zillikens D. Serum levels of autoantibodies to BP180 correlate with disease activity in patients with bullous pemphigoid. *Arch Dermatol* 2000;136(2):174-8.
5. Feng S, Wu Q, Jin P, Lin L, Zhou W, Sang H, et al. Serum levels of autoantibodies to BP180 correlate with disease activity in patients with bullous pemphigoid. *Int J Dermatol* 2008;47(3):225-8.
6. Khumalo N, Kirtschig G, Middleton P, Hollis S, Wojnarowska F, Murrell DF. Interventions for bullous pemphigoid. *Cochrane Database Syst Rev* 2005;(3):CD002292. [DOI:10.1002/14651858. CD002292.

- pub2].
7. Burton JL, Harman RR, Peachey RD, Warin RP. Azathioprine plus prednisone in treatment of pemphigoid. *Br Med J* 1978;2(6146):1190-1.
 8. Guillaume JC, Vaillant L, Bernard P, Picard C, Prost C, Labeille B, et al. Controlled trial of azathioprine and plasma exchange in addition to prednisolone in the treatment of bullous pemphigoid. *Arch Dermatol* 1993; 129(1):49-53.
 9. Wojnarowska F, Kirtschig G, Highet AS, Venning VA, Khumalo NP. British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002;147(2):214-21.
 10. Roujeau JC, Guillaume JC, Morel P, Crickx B, Dalle E, Doutre MS, et al. Plasma exchange in bullous pemphigoid. *Lancet* 1984;2(8401):486-8.