Hong Kong J. Dermatol. Venereol. (2015) **23**, 20-24

Views and Practice

Managing immunobullous disorders in hospitals

MM Chang 張苗

Introduction

Immunobullous disorders, or autoimmune blistering diseases, are a subgroup of blistering dermatoses due to the production of autoantibodies targeting epithelial proteins, causing intraepidermal or subepidermal cleavage. They have distinct pathological and clinical features, characterised by mucocutaneous blisters and erosions. The two prototypes are pemphigus vulgaris (PV) and bullous pemphigoid (BP). This article aims to discuss a few points in managing patients with such diseases in a hospital setting, focusing on BP as an example.

1. Epidemiology and patient demographics

Bullous pemphigoid is the most common immunobullous disorder, which typically affects the elderly after 70 years of age, though it may rarely be present in pregnant women, children and young adults.[1] With an ageing population, the incidence has increased globally. In Hong Kong, two university hospital cohorts of Chinese patients reflected a growing incidence of 9.2 to 11.2 per million per year.[2,3] In our ten-year retrospective cohort involving 121 Chinese, the majority of patients were found to be elderly with a mean age of 79.9 years, had a poor premorbid state (78% ADL-partially dependent or bed-bound) and multiple comorbidities.[3] BP accounted for 11% of inpatient dermatology consultations in the Prince of Wales Hospital in 2013-14.

Pemphigus vulgaris is the second most common autoimmune blistering disease in Hong Kong, though the exact incidence has not been thoroughly studied. Affected patients are younger (40-60 years) and are generally in better health. It accounted for 1-2% of inpatient dermatology consultations. There are no known ethnic, sexual or racial predilections in both diseases.

2. Clinical presentation and differential diagnosis

The hallmark of BP is pruritic tense blisters of variable sizes. They can be found on an erythematous or normal-looking skin, in a localised or widespread fashion. Mucosal involvement, mainly oral, is found in less than 10%. The classical form is distinctive although, in the early phase, eczematous or urticated plaques can be found (Figure 1). This non-bullous phase may last for weeks and is often misdiagnosed as

Division of Dermatology, Department of Medicine & Therapeutics, Prince of Wales Hospital, Hong Kong

MM Chang, MRCP, FHKCP

Correspondence to: Dr. MM Chang

9/F, Clinical Sciences Building, Department of Medicine and Therapeutics, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, New Territories

eczema, urticaria, drug eruption or scabies. In the late phase, excoriations and erosions very often predominate, mimicking pemphigus, staphylococcal scalded skin syndrome or toxic epidermal necrolysis, but without Nikolsky's sign (Figure 2). BP is typically non-scarring. It heals with post-inflammatory hyperpigmentation and sometimes milia formation. Other clinical variants, such as pretibial, erythrodermic, vesicular, vegetative, ulcerative, nodular and dyshidrosiform BP, are rare.

In the differential diagnosis, other non-autoimmune causes of tense blisters, such as acute contact dermatitis, insect bite reaction, infection, drug eruption, vasculitis, epidermolysis bullosa acquisita (EBA) or metabolic causes (diabetes, renal failure, porphyria) need to be considered. Other rare immunobullous diseases, such as cicatricial pemphigoid, linear IgA bullous dermatosis, dermatitis herpetiformis and paraneoplastic pemphigus, can be distinguished from BP by histological and immunological studies. Younger age and atypical presentation often suggest an alternative diagnosis.

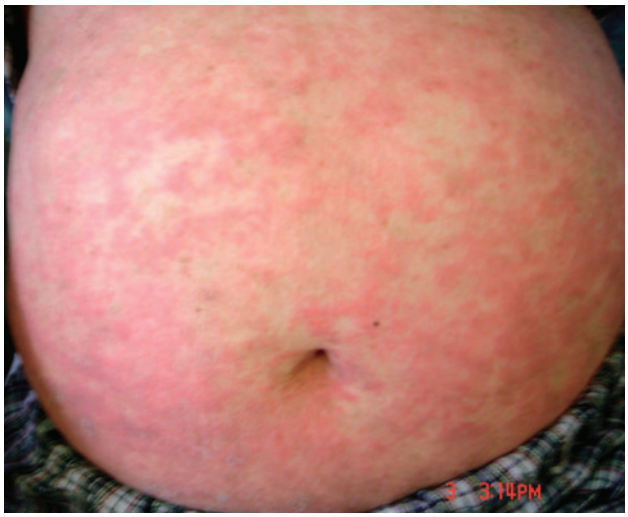

Figure 1. Urticated plaques in early phase of BP.

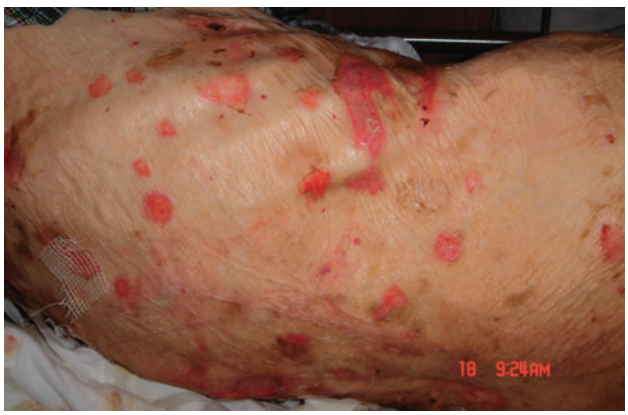

Figure 2. Erosions as a presentation in late-stage BP.

3. Investigation

The diagnosis of immunobullous disease hinges on classical clinical features, typical histology and direct immunofluorescence (DIF). In BP, this combination leads to a sensitivity of 90% and specificity of 83% and good positive-predictive value of 95 to 99%.[1]

A perilesional skin biopsy from a fresh blister stained with haematoxylin and eosin shows subepidermal cleft (blister) with variable infiltrates including eosinophils. Eosinophilic spongiosis without clefting is found in early lesions. On DIF, linear IgG and/or C3 deposits are found along the dermo-epidermal junction (DEJ). For PV, suprabasal split is found leaving basal keratinocytes in the form of a row of tombstone appearance; DIF with intercellular IgG and/or C3 deposits are found between keratinocytes. In both cases, DIF studies remain the gold standard for diagnosis.[1,4]

The specimen must include intact epidermis, and should be transported fresh and processed within 24 hours for DIF. Alternatively, transport in Michel's medium allows for a delay of processing up to two weeks.[4] In all cases, a diagnostic skin biopsy is crucial before the commencement of treatment (as it often involves a prolonged course of immunosuppressants) for clear documentation and medico-legal reasons; and to avoid subsequent non-diagnostic biopsies (empirical steroid treatment can give rise to false negative DIF). In cases when patients are not mentally fit to give their consent, it is strongly advised that a

biopsy under two doctors' consent be performed after informing their families or legal guardians.

In difficult cases, indirect immunofluorescence (IIF) or salt-split test, in which diseased human skin is incubated in 1M sodium chloride solution (antigen binding as roof-pattern of the epidermis in BP), can be considered.[1] Electron microscopy can also be used to differentiate BP from other subepidermal diseases, such as EBA. In Hong Kong, serum anti-skin antibodies (ASA, an IIF assay using monkey oesophagus as substrate) are sometimes tested for and 70% of BP are positive with stratified squamous epithelium (monkey oesophagus).[3] However, ASA does not reflect disease activity in BP, unlike that in pemphigus. Lately, measurement of anti-BP180 (NC16A domain) by enzyme-linked immunosorbent assays (ELISA) has been found to be a very specific and sensitive test for BP.[1] The diagnostic sensitivity can be increased up to 100% when BP180 and BP230 assays are used together,[1] and they may be useful in disease monitoring and prognostication.[5]

Other investigations before treatment include complete blood picture, liver and renal function tests, random serum glucose level, hepatitis B and C serology, chest radiography and early DEXA scan for osteoporosis screening. Malignancy screening is needed for paraneoplastic pemphigus but not for asymptomatic patients with BP or other forms of pemphigus in general.[1,4]

4. Associated conditions and malignancy

Bullous pemphigoid is noted to be associated with inflammatory skin dermatosis, diabetes and neurological disorders (cerebrovascular disease; multiple sclerosis; dementia and Parkinsonism, possibly due to cross-reactivity with neuronal BP 180/230 expressed in the brain).[1] Unlike paraneoplastic pemphigus, an association with malignancy is not yet established for BP. In fact, over 90% of the hospitalised BP patients have coexisting medical conditions (hypertension, followed by cerebrovascular disease, diabetes mellitus and dementia) which render them more prone to treatment–related complications and possibly higher mortality.[2,4]

5. Course and mortality

BP runs a waxing and waning course. Following corticosteroid therapy, the disease can be controlled with a median treatment period of two years and 50% remission within three years.[1,4,6] Spontaneous remission sometimes occurs in localised, and rarely, generalised forms. Untreated patients with active disease suffer from pain, skin infections, dehydration, electrolyte imbalance and sepsis.

Contrary to common belief, BP does carry significant morbidity and mortality. Large population-based studies showed significantly increased age-adjusted mortality rate for BP, but decreased for pemphigus.[7-9] The mortality rate of BP ranged from 15-41% in the first year and could reach up to 50% over five years.[1,6-9] The majority of deaths were due to sepsis. Poor prognostic factors include old age, low performance status, associated medical conditions, hypoalbuminaemia, anaemia and malignancy.[3,6,8] We also found that factors relating to clinical presentation, disease extent and choice of therapy did not affect the overall prognosis.[3,6,8]

6. Management

Treatment involves inducing and maintaining remission preferably with minimal side effects. Occasional blisters are acceptable, indicating that the patient is not overtreated.

For localised BP, topical treatment with high potency corticosteroids or tacrolimus is often successful.[4,10] For pemphigus and generalised BP, options are immunosuppressives or immunomodulating agents, anti-inflammatory agents and procedures to remove circulating pathogenic antibodies.[4] The first-line treatment for both diseases has been corticosteroids for more than 60 years.

In BP, both systemic steroid monotherapy and super-potent topical steroids are evaluated in controlled trials with good efficacy. In the literature, there is no well-evaluated induction dose. The UK guidelines recommend prednisolone (prednisone) 0.3-0.5 mg/kg/day for mild to moderate disease. For severe disease, dosages at 0.75-1.0 mg/kg/day achieve control within one to four weeks in 60-90% of cases.[4] Higher doses do not offer additional benefit but cause more complications.[10] Locally, we found that prednisolone at 0.5 mg/kg/day was effective in inducing remission within four weeks for most hospitalised Chinese patients (91.7%).[3]

Super-potent topical steroids (clobetasol proprionate cream 40g daily tapering over 12 months) were shown in a landmark study to be superior to prednisolone 0.5 mg/kg for extensive disease, with better side effect profile and overall survival but at the expense of systemic absorption.[11] Lately, a milder regimen of clobetasol 10 to 30g daily tapered over four months, was shown to be as efficacious, with less systemic absorption and a decreased risk of death.[12] However, the European practice was difficult to apply locally due to patient and carer factors.

In refractory cases, the following 'rescue therapy' can be considered: IVIG (2 g/kg spanned over 3-5 days), pulse intravenous methylprednisolone (15 mg/kg for 3 days), cyclophosphamide (100 mg daily with steroid), plasmapheresis, immunopheresis, or rituximab (375 mg/m^2 weekly for 4 weeks).[4] IVIG is most commonly used for its relatively good safety profile (lowest immunosuppressive risk). Plasmapheresis can be tried if the patient is haemodynamically fit and has little risk of infection (hospitalised BP patients are often colonised with pathogens). Like IVIG, plasmapheresis has to be followed by systemic steroids or immunosuppressants.

Initial induction of treatment is considered to be successful if there are no new inflammatory lesions or blisters after four weeks, with resolution of old lesions. Systemic steroids can then be tapered gradually by about 5-10 mg fortnightly with cautious tapering below 20 mg. The risk of disease flare has to be balanced against that of steroid-induced complications. In general, the lowest possible dosage that leads to fair disease control is recommended. However, steroid dosage has to be titrated (up 50% while on anti-TB medications) in patients on medications that affect steroid metabolism.

Osteoporosis preventive treatment (calcium, vitamin D supplementation and bisphosphonate) should be given when long-term steroids are initiated. Yearly DEXA scans are advised to monitor bone mineral density. Hepatology referral is recommended for patients with underlying hepatitis B and on immunosuppressants, though guidelines on routine antiviral use have not yet been established. Before stopping systemic steroid, evaluation for adrenal suppression through low dose short synacthen test is recommended.

Overall, adjuvant therapies such as azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, chlorambucil, dapsone, tetracycline and nicotinamide combination, or rescue therapy involving IVIG and plasma-exchange, were not shown to be superior to systemic steroid;[10,13] but may offer a steroid-sparing effect, thus reducing its side effects. Tetracyclines with nicotinamide were shown in a small randomised control trial to be efficacious and less toxic than systemic steroid.[4] Azathioprine is the second most common adjuvant therapy. Dapsone is often added for neutrophilic-rich BP with good response. Close monitoring is needed for adjuvant therapy. Mild transaminitis and leucopaenia after azathioprine, hypersensitivity syndrome or methaemoglobinaemia after dapsone have rarely been seen.

7. General medical and nursing care

During hospitalisation, patients on systemic steroids with extensive raw areas should be isolated to reduce cross-infection. Secondary

bacterial (MRSA, pseudomonas) or viral (herpes) infections can occur. Antimicrobials, rather than escalating immunosuppressants or use of IVIG, is effective. Routine monitoring of blood pressure, blood glucose level and sore prevention is necessary. Locally, we noted that complications (infections, worsening of diabetes or blood pressure, and pressure sores), were common (70%) shortly or within one year of commencement of systemic treatment in BP.[3] Complications should be monitored for and the immunosuppressants adjusted as indicated.

Blisters should be left intact if possible to prevent secondary infection. Large blisters should be aspirated with a sterile needle, keeping blister roof in place. Raw areas are cleansed by antiseptics or normal saline and covered by a non-adhesive dressing.[3] Excessive skin manipulation and trauma should be avoided in active PV (Nikolsky's sign). Patients with oral mucosal lesions should be given soft diet, soft tooth brushes, antiseptic gargles and prophylaxis against oral candidiasis. After prolonged hospitalisation, MRSA colonisation can occur. A 5-day decontamination regime with 4% chlorhexidine body wash and nasal mupirocin ointment can be considered when skin lesions resolve.

Conclusion

Hospitalised patients with BP have multiple comorbidities, often presenting with generalised involvement, more severe disease, recurrent relapses, higher morbidity and mortality (especially in the first year). Patients with poor prognostic factors (bed-bound status, anaemic, hypoalbuminaemic, with malignancy) should be monitored closely in a multidisciplinary approach. Close monitoring for side effects is needed when using systemic immunosuppressants.

References

1. Di Zenzo G, Della Torre R, Zambruno G, Borradori L. Bullous pemphigoid: from the clinic to the bench. Clin Dermatol 2012;30:3-16.
2. Chang MM, Yeung CK, Lo KK. Review of inpatient management of bullous pemphigoid in 2 university-affiliated hospitals in Hong Kong. Scientific forum of the Hong Kong Society of Dermatology and Venereology Annual Scientific Meeting, June 2011.
3. Chang MM, Choi CL, Luk NM, Lo KK. Bullous pemphigoid: a review of patients managed in hospital and its risk factors for poor prognosis and early mortality. Presented in Asian Dermatology Conference 2013.
4. Venning VA, Taghipour K, Mohd Mustapa MF, Highet AS, Kirtschig G. British Association of Dermatologists' guidelines for the management of bullous pemphigoid 2012. Br J Dermatol. 2012;167:1200-14.
5. Roussel A, Benichou J, Randriamanantany ZA, Gilbert D, Drenovska K, Houivet E, et al. Enzyme-linked immunosorbent assay for the combination of bullous pemphigoid antigens 1 and 2 in the diagnosis of bullous pemphigoid. Arch Dermatol 2011;147:293-8.
6. Joly P, Benichou J, Lok C, Hellot MF, Saiag P, Tancrede-Bohin E, et al. Prediction of survival for patients with bullous pemphigoid. Arch Dermatol 2005;141:691-8.
7. Risser J, Lewis K, Weinstock MA. Mortality of bullous skin disorders from 1979 through 2002 in the United States. Arch Dermatol 2009;145:1005-8.
8. Roujeau JC, Lok C, Bastuji-Garin S, Mhalla S, Enginger V, Bernard P. High risk of death in elderly patients with extensive bullous pemphigoid. Arch Dermatol 1998; 134:465-9.
9. Bernard P, Enginger V, Venot J, Bedane C, Bonnetblanc JM. Survival prognosis in pemphigoid. A cohort analysis of 78 patients. Ann Dermatol Venereol 1995;122: 751-7.
10. Culton DA, Diaz LA. Treatment of subepidermal immunobullous diseases. Clin Dermatol 2012;30:95-102.
11. Joly P, Roujeau JC, Benichou J, Picard C, Dreno B, Delaporte E, et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. N Engl J Med 2002;346:321-7.
12. Joly P, Roujeau JC, Benichou J, Delaporte E, D'Incan M, Dreno B, et al. A comparison of two regimens of topical corticosteroids in the treatment of patients with bullous pemphigoid: a multicenter randomized study. J Invest Dermatol 2009;129:1681-7.
13. Kirtschig G, Middleton P, Bennett C, Murrell DF, Wojnarowska F, Khumalo NP. Interventions for bullous pemphigoid. Cochrane Database Syst Rev 2010; CD002292.