

A retrospective study on 464 bullous pemphigoid patients in Northeast China

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To the Editor: Bullous pemphigoid (BP) is a chronic autoimmune blistering disease characterized by the association with autoantibodies to two hemidesmosomal proteins (BP180 and BP230) interfering with the adhesion of basal epidermal keratinocytes. The global incidence of BP is 2.5 to 75 cases/million per year.^[1] Genetic, environmental, and stochastic factors contribute to the susceptibility to BP. We performed a retrospective study on BP in Northeast China to evaluate its clinical characteristics. The data of BP patients from Shenyang Seventh People's Hospital between January 2015 and January 2020 were analyzed, including 464 BP patients from Northeast China. All patients met the BP diagnostic standard. This study was approved by the Institutional Review Board of Shenyang Seventh People's Hospital (No. 2015-WQ-01).

The data on epidemiological and clinical characteristics, auxiliary examination, complication, and treatment of BP patients were collected from the hospital. The body surface area (BSA) involvement was an indicator of the disease severity (mild: skin lesions < 10% of BSA; severe: skin lesions > 30% of BSA; and moderate: between mild and severe).

All data were presented as mean \pm standard deviation or mean \pm standard error of the mean. Data analysis and graphing were conducted using GraphPad Prism 5.0. Statistical analyses were performed with unpaired two-tailed Student's t test; a *P* value < 0.05 was considered statistically significant.

The patients aged from 14 to 97 years, with an average age of 73.14 ± 2.32 years, a male-female (M/F) ratio of 1.32:1,

accounting for 0.73% (464/63,969) of dermatology inpatients which was stable per year; their average hospital stay was 24.93 ± 6.21 days; 73 (15.73%) patients had mucous membrane and 35 (7.54%) had fever. The main characteristics of BP patients are summarized in Table 1. The temperature fluctuated between 37.5°C and 38.5°C. Fever and blood eosinophils were correlated with the severity of BP.

All BP patients had undergone histopathological examinations before or after hospitalization, indicating pathological features of subcutaneous blisters and eosinophilic granulocyte infiltration. The routine examination after hospitalization showed higher leukocytes in 98 (21.1%) patients, eosinophils > 5% in 89 (19.2%) patients, hemoglobin < 110 g/L in 109 (23.5%) patients, hypoalbuminemia in 79 (17.0%) patients, and blood electrolyte disorder in 64 (13.8%) patients. Direct immunofluorescence (DIF) examination indicated a higher BP positive rate compared with the indirect immunofluorescence (IIF) examination, with no significant difference. The level of anti-BP180 antibody or anti-BP230 antibody was positively correlated with BP severity. A total of 278 patients had one or more systemic diseases and 34 patients had other skin diseases such as eczema, psoriasis, and lichen planus.

In this study, diamino diphenyl sulfone was ineffective in four patients. Two patients took oral cyclosporine and most rashes faded away 4 to 5 days later, but blisters appeared continuously for a long time before the combined use of glucocorticoid; 58 patients receiving intravenous immune globulin achieved the desired effect; plasmapheresis was effective in 11 patients; glucocorticoid cream, antibiotic ointment, and He-NE laser were used onto topical skin.

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Table 1: Characteristics of 464 patients with BP in Northeast China.

Variables	Cases	Percentage (%)
Gender		
Male	264	56.9
Female	200	43.1
Recurrence	81	17.5
Misdiagnosis	24	5.2
DIF IgG or C3 (+)	384	82.8
IIF IgG or C3 (+)	363	78.2
Treatment effect Cured	114	24.6
Improved	305	65.7
Unimproved	45	9.7
Concomitant disease		
Neurological system	101	21.8
Circulatory system	71	15.3
Respiratory system	53	11.4
Motor system	33	7.1
Immune system	30	6.5
Urinary system	17	3.7
Digestive system	12	2.6
Blood system	7	1.5
Genital system	5	1.1
Death cause		
Respiratory failure	7	1.5
Circulatory failure	6	1.3
Alimentary tract hemorrhage	1	0.2
Severe infections	2	0.4
Sudden death because of unknown etiology	1	0.2
Disease severity		
Mild	83	17.9
Moderate	269	58.0
Severe	112	24.1

BP: Bullous pemphigoid; DIF: Direct immunofluorescence; IIF: Indirect immunofluorescence.

Blood-cooling detoxification decoction (adding or subtracting ingredients appropriately) was used to treat toxic-heat type patients suffering from acute paroxysm, rapid blister multiplication, fever and thirst, dry stool, dark urine, and red tongue. The effectiveness and safety of traditional Chinese medicine (TCM) in the early treatment of patients with moderate BP were investigated. The patients were randomly assigned into the TCM group (28 patients receiving combined Western and Chinese medicine) and the control group (20 patients receiving Western medicine). The time from the beginning of treatment to the occurrence of blisters disappearing and dry erosive surface in the experimental group was significantly shorter than that in the control group, with a statistically significant difference.

This study showed that misdiagnosis rate, main therapeutic drugs, accompanying diseases, and death causes of this disease were consistent with the literature, with great differences in M/F ratio, fever and blood eosinophil, TCM treatment, and 1-year mortality compared with the literature. Some retrospective studies confirmed that the

prevalence of BP is higher in females than males (M/F ratio 1:2.1), but this study showed an opposite situation, with M/F ratio of 1.32:1, indicating a statistically significant difference. BP mainly affects elderly individuals, including those suffering from other systemic illnesses, especially neurological diseases. Various studies have shown that BP antigen is expressed in the skin and central nervous system, with a correlation between BP and neurological disease.^[2] A study on sex differences in stroke incidence revealed that 45.3% of 720 stroke patients were men, with M/F ratio of 1:2.1. However, the stroke incidence in Northeast China is higher in men than in women and that may be the reason why the M/F ratio is different from the literature.

Fever is uncommon in BP, but this study showed 35 (7.5%) patients had fever with increased blood eosinophils, flushing, rashes, and severe pruritus. The medical history showed that some patients had been prescribed drugs such as quinolones, antibiotics, nonsteroidal drugs, and angiotensin converting enzyme inhibitors before the occurrence of BP. Fever and increased blood eosinophils were correlated with BP severity and the occurrence of other signs such as increased leukocytes and blood electrolyte disorder indicated a severe disease state. The DIF and IIF examinations showed that the findings of typical histological features were similar to those in classic BP. Although no direct correlation between drugs and BP had been determined, these patients were prone to be diagnosed with drug-induced BP.^[3] The oral involvement of BP is common (15.7%), which is consistent with the literature.

Typical BP has significant pathological features, while it may present as eczematoid erythema in the early stage, leading to a misdiagnosis rate of 5.17%. Thus, multiple biopsies are required for making a definite diagnosis. Increased blood eosinophils in the superficial dermis layer were an important diagnostic clue to this disease in the early blister forming stage.

Glucocorticoids remain the most effective treatment for BP, especially in recurrent cases. Many domestic experts believe that a dose of corticosteroid for controlling BP should be less than that for controlling pemphigus, while this study indicated that a larger-dose corticosteroid is required for impact therapy in severe patients. Minocycline, nicotinamide, and *Tripterygium wilfordii* are effective in mild patients with frequent recurrences 2 to 3 years later. Although immunosuppressors such as cyclosporine have significant effects on BP, it is not the preferred treatment option. Intravenous immune globulin can effectively neutralize various pathogenic factors, and rapidly enhance the anti-infection ability and immunomodulating function of the body. Plasmapheresis can remove the disease-related autoantibodies and reduce the dose of glucocorticoids, but it is only used in severe patients because of the exorbitant price when other therapies are ineffective.

TCM doctors hold that disease onset is correlated with months. The distribution of disease onset of 464 patients in this study indicated that June and December are the

most common months for BP onset. TCM has been widely applied in dermatologic therapy. In this study, TCM exerted a good effect in the early treatment of BP without adverse events. The fiery syndrome such as rapidly increased blisters, red tongue, and yellow moss could be effectively treated by antipyretic-alexipharmic drugs, which deserves further research.

Severe patients suffer from extensive surface erosion leading to hypoproteinemia and skin infection. He-NE laser, antibiotic ointment, hormone cream, and nursing are essential for topical treatments in this study.

The death causes are mostly system illnesses and glucocorticoid-induced side effects, which often require multidisciplinary treatment. Although there are many effective drugs, the author deems that the appropriate use of drugs can control this disease and reduce its side effects.

A recent systematic review demonstrated a 1-year combined BP mortality rate of 6% to 40%, that is, 26.7% in Europe, 20.5% in Asia, and 15.1% in the United States.^[4] BP mortality rate was 4. % in this study; this lower mortality rate was not attributed to the diagnosis criteria. Alleles and haplotypes may be genetic markers associated with BP. Major histocompatibility complex (MHC) class II alleles are the strongest risk factors associated with autoantibody-mediated diseases. Human leukocyte antigen (HLA)-DR5 is higher in French BP patients. A significant association between HLA-DQA1*03:01 and 05:05 alleles was documented in Japanese BP patients. Recent study in Chinese populations DRB1*08 allele conferring protection against BP. HLA-DRB1* 10:01 is associated with susceptibility to BP, while DRB1*07:01 allele is associated with protection against BP.^[5] The activation of antigen-specific B cells and

secretion of autoantibodies in BP depend on the interaction between T-cell receptors and classical MHC class II molecules. Differences in alleles lead to diverse pathogenesis, which further leads to diversity in BP severity and clinical manifestations, and thus affects differences in 1-year combined mortality. Although this study shows a potential correlation among these factors, many mechanisms remain to be further investigated.

Conflicts of interest

None.

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