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AUTOIMMUNE BULLOUS DISEASES IN DERMATOLOGY CLINIC, SARAWAK GENERAL HOSPITAL.

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ABSTRACT

Background: Autoimmune bullous diseases (ABDs) are organ-specific autoimmune diseases characterized by erosions, vesicles, or bullae formations on the skin or mucous membranes. The study aimed to demonstrate demography, clinical features, co-morbidities, laboratory findings, and treatment modalities for ABDs in Sarawak patients. **Materials and methods:** This was a cross-sectional, observational retrospective study on ABDs treated at the dermatology clinic of Sarawak General Hospital over eight years. **Results:** Seventy-nine ABD patients in this study consisted of bullous pemphigoid (75.9%), pemphigus vulgaris (13.9%), pemphigus foliaceous (7.6%), IgA dermatosis (1.3%) and pemphigoid gestationis (1.3%). Malays were the most commonly affected ethnic group. Bullous pemphigoid predominantly affects the elderly and females. In contrast, pemphigus vulgaris were mostly younger age group with a male predilection. Clinical manifestations of bullous pemphigoid and pemphigus differed in terms of its lesion extent, location, and mucosal involvement. ABDs especially bullous pemphigoid was associated with multiple co-morbidities and polypharmacy. Direct immunofluorescence aided the ABD histological diagnosis. IgG and C3 were common deposits. One-third of bullous pemphigoid patients had peripheral blood eosinophilia. Corticosteroid was the mainstay treatment for ABDs. The majority of ABD patients achieved remission although pemphigus patients took a longer duration compared to pemphigoid (mean 17 months vs 4 months). **Conclusion:** The study illustrated an overview of the demography and characteristics of ABDs, which facilitated a detailed understanding of the disease among primary healthcare personnel. The overall clinical outcome served as a foundation to refine treatment strategy befitting the standards of clinical care.

Keywords: Autoimmune bullous disease, Bullous pemphigoid, Pemphigus Vulgaris, Demography, Immunofluorescence

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DEMOGRAPHICS AND CLINICAL FEATURES OF AUTOIMMUNE BULLOUS DISEASES IN SARAWAK GENERAL HOSPITAL.

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ABSTRACT

Background: Autoimmune bullous diseases (ABDs) are organ-specific autoimmune diseases characterized by erosions, vesicles, or bullae formations on the skin or mucous membranes. The study aimed to demonstrate demography, clinical features, co-morbidities, laboratory findings, and treatment modalities for ABDs in patients in Sarawak, Malaysia. **Materials and methods:** This was a retrospective cross-sectional study of patients with ABDs treated at the dermatology clinic of Sarawak General Hospital over an eight years period. **Results:** A total of 79 patients with ABD were included in this study. ABD consisted of bullous pemphigoid (75.9%), pemphigus vulgaris (13.9%), pemphigus foliaceous (7.6%), IgA dermatosis (1.3%) and pemphigoid gestationis (1.3%). Malay ethnicity were the most commonly affected group. Bullous pemphigoid predominantly affected the elderly and female gender. In contrast, pemphigus vulgaris were more common in younger age group with a male predilection. Clinical manifestations of bullous pemphigoid and pemphigus differed in terms of its lesion extent, location, and mucosal involvement. Bullous pemphigoid was associated with multiple co-morbidities and polypharmacy. One-third of bullous pemphigoid patients had peripheral blood eosinophilia. Corticosteroid was the mainstay treatment for ABDs. The majority of ABD patients achieved remission although pemphigus patients took a longer duration compared to pemphigoid (mean 17 months vs 4 months). **Conclusion:** The study illustrated an overview of the demography and characteristics of ABDs, which facilitated a detailed understanding of the disease among primary healthcare personnel. The overall clinical outcome served as a foundation to refine treatment strategy befitting the standards of clinical care.

Keywords: Autoimmune bullous disease, Bullous pemphigoid, Demography, Immunofluorescence, Pemphigus Vulgaris.

INTRODUCTION

Autoimmune bullous diseases (ABDs) are a group of organ-specific diseases defined by pathogenic autoantibodies directed at target antigens that function in cell wall adhesion in the epidermis or between stratified squamous epithelium to dermis mesenchyme.[1] It is characterized by erosions, vesicles, or bullae formations on the skin or mucous membranes. Each subgroup of ABDs demonstrates a unique pattern of natural history, and epidemiology and varies according to geographic regions.[2] It is classified according to the target structures and depth of blister formation. The

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two main categories are (i) Intra-epidermal (Pemphigus group) and (ii) Sub-epidermal (Pemphigoid, dermatitis herpetiformis, and acquired epidermolysis bullosa). Bullous pemphigoid and Pemphigus vulgaris are the most common subgroups among the ABDs, although they are overall rare.[3,4]

While ABDs have been well studied and reported in the literature, Asian population data are still considerably limited. This uncommon group of diseases is associated with severe and potentially fatal outcomes. Only two local university-based studies have reported these dermatological disorder in Malaysia.[3,5]

This current study evaluates the epidemiological background of ABDs in Kuching, a diversified multi-ethnic city of the largest state of Sarawak in East Malaysia, Borneo.

METHODOLOGY

This was a cross-sectional, retrospective chart review study on autoimmune bullous diseases treated in Sarawak General Hospital's dermatology clinic, from January 2013 to December 2020. All patients clinically with a confirmed skin biopsy diagnosis of ABD were included in the study. The study was approved by the National Medical Ethics Committee for Sarawak.

Patients' medical records were retrieved and patients' demographic background, disease profile (clinical presentation, duration of symptoms, and extent of disease), and laboratory results (direct immunofluorescent, histopathology examination, and blood eosinophil counts) were extracted for analysis. Treatment modalities, remissions, and relapse were also recorded. Data were tabulated into Microsoft Excel. Patients' identifiable details were keep confidential and cross reference to study ID.

Data analysis was done by using IBM SPSS Statistics. Descriptive statistics such as mean with standard deviation or frequency with percentage were used to determine the demography, characteristics and outcome of the disease. Univariate analysis Perason's Chi -square test was applied to determine the association between laboratory tests and bullous disease. $P \leq 0.05$ was considered significant.

RESULTS

Demogprahic & characteristics

79 patients with ABDs sought consultation at the dermatology clinic, Sarawak General Hospital from 2013 to 2020. We treated approximately ten cases per year. 60 patients had bullous pemphigoid (75.9%), followed by 11 pemphigus vulgaris (13.9%) and 6 pemphigus foliaceous (7.6%). We had one linear IgA dermatosis and pemphigus gestationis each. The majority were Malay and Chinese, which accounted for more than two-thirds of the patients. Ibans were significantly less although being the major ethnic group in Sarawak. Forty-two patients were female, and 37 were male. The male to female ratio of 1: 1.26 in bullous pemphigoid and pemphigus foliaceous indicated a female preponderance. On the other hand, more males were seen with pemphigus vulgaris (M: F, 1.75:1). In our series, the patient age ranged from 14 to 94 years old. The mean age for bullous pemphigoid was 71 years. The youngest bullous pemphigoid patient was 41 years, and the oldest was 94 years. On the contrary, pemphigus vulgaris patients were younger, with a mean age of 45. The patients were mostly in the age group of 30 to 49 years. Four patients were diagnosed with pemphigus foliaceous. Patients with pemphigoid gestationis and linear IgA dermatosis were rare and affected the younger ager group (Table I).

ABDs presented with localised or generalised blisters and erosions. Pemphigus le-

Table I: Demographic and Characteristics of Bullous diseases in Dermatology Clinic, Sarawak General Hospital.

Category	Bullous pemphigoid n (%)	Pemphigus vulgaris n (%)	Pemphigus foliaceous n (%)	Linear IgA dermatosis n (%)	Pemphigoid gestationis n (%)
Histopathology (HPE)	60 (75.9)	11 (13.9)	6 (7.6)	1 (1.3)	1 (1.3)
Gender					
Male	28 (46.7)	7 (63.6)	2 (33.3)	0 (0.0)	0 (0.0)
Female	32 (53.3)	4 (8.9)	4 (66.7)	1 (100)	1 (100)
Race					
Malay	27 (45.0)	6 (54.5)	3 (50.0)	-	-
Chinese	17 (28.3)	4 (36.4)	1 (16.7)	-	-
Iban	8 (13.3)		1 (16.7)	1 (100)	-
Bidayuh	7 (11.7)		1 (16.7)	-	1 (100)
Indian	1 (1.7)	-	-	-	-
Age (years)					
10-19	-	-	1 (16.7)	-	-
20-29	-	-	-	1 (100)	1 (100)
30-39	-	5 (45.5)	3 (50.0)	-	-
40-49	4 (6.7)	3 (27.3)	-	-	-
50-59	5 (8.3)	2 (18.2)	1 (16.7)	-	-
60-69	16 (26.7)	-	-	-	-
70-79	21 (35.0)	1 (9.1)	-	-	-
80-89	11 (18.3)	-	1 (16.7)	-	-
90-99	3 (5.0)	-	-	-	-
Site					
Generalised	38 (63.3)	7 (63.6)	4 (66.7)	1 (100.0)	1 (100.0)
Head or neck	2 (3.3)	2 (27.3)	1 (16.7)	-	-
Trunk	5 (8.3)	1 (9.1)	1 (16.7)	-	-
Limbs	15 (25.0)	-	-	-	-
Clinical features					
Localised blisters	27 (20.3)	2 (6.9)	1 (7.7)	-	-
Generalised blisters	32 (24.1)	7 (24.1)	4 (30.8)	1 (50.0)	1 (33.3)
Blisters & erosions	54 (40.6)	9 (31.0)	6 (46.2)	1 (50.0)	1 (33.3)
Urticated plaque	12 (9.0)	-	-	-	1 (33.3)
Non specific rash	2 (1.5)	1 (3.4)	1 (7.7)	-	-
Oral mucosa involved	6 (4.5)	10 (34.5)	1 (7.7)	-	-
Duration (Days)					
< 3 months	48 (81.4)	48 (81.4)	3 (75.0)	1 (100.0)	1 (100.0)
3 to 12 months	8 (13.6)	8 (13.6)	1 (25.0)	-	-
> 12 months	3 (5.1)	3 (5.1)	-	-	-
Mean ± SD	75.1 ± 142.7	259.6 ± 642.9	82.5 ± 70.9	10.0	6.0
Min - Max	1 - 730	2 - 2190	30 - 180	10 - 10	6 - 6

sions were more often located on the trunk, head and neck with mucosa involvement. Meanwhile, urticarial plaque and localised cutaneous lesions involving the limbs were seen only in bullous pemphigoid in our series (Figure 1). The majority of cases (80.3%) were diagnosed within three months from the onset of symptoms, although the mean duration of symptoms before dermatology consultation was 100.5 days. We had four cases diagnosed after one year, and one almost six years later. Mild, gradual onset and localised involvement were the reasons behind the delay in seeking consultation in our clinic.

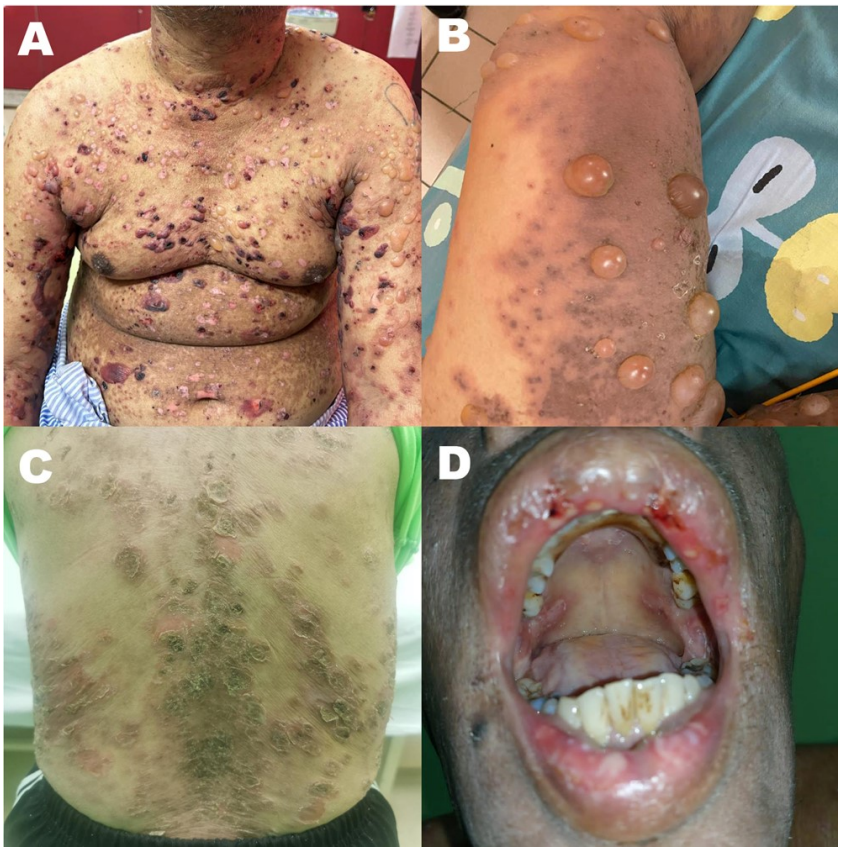

Figure 3: Clinical pictures of autoimmune bullous disease. (A) Bullous pemphigoid manifested as tense blisters with erosion of the torso. **(B)** Pemphigoid gestationis showed tense shinny blisters in late pregnancy. **(C)** Pemphigus foliaceous presented with crusted erosions at the back of body. **(D)** Pemphigus vulgaris seen as erosions in mucous membrane of oral cavity.

Co-morbidities and medications

In this cohort, 65 patients (82.3%) were associated with multiple co-morbidities including chronic diseases such as hypertension (64.5%), diabetes mellitus (43.0%), and dyslipidaemia (31.5%). More patients in the bullous pemphigoid group (85.0%) had co-morbidities than the pemphigus group (70.5%). Neurological disorders like stroke (16.7%), Parkinson's (6.7%), and dementia (5.0%) were seen in the bullous pemphigoid group. There were two patients with pemphigoid disease with concomitant psoriasis. Colon and breast cancer occurred in two of the pemphigoid patients. None of the patients from Pemphigus had malignancy. Our patients with IgA dermatosis and pemphigoid gestationis was not associated to any co-morbid diseases (Figure 2).

Most of the patients especially bullous pemphigoid (84.9%) were taking medications related to their co-morbidities before the onset of bullous disease; 46.2% of pemphigus vulgaris patients had previous medications. Eleven patients did not have records on their medications. The most common medication taken was amlodipine (43.6%). Others included Simvastatin, Metformin, Gliclazide, Perindopril and Aspirin. The list of medications was summarised in Figure 3.

Direct immunofluorescent (DIF) and laboratory findings

Direct immunofluorescent staining was performed on the skin biopsies. Bullous pemphigoid showed linear pattern of deposits along the dermal-epidermal junction. In pemphigus vulgaris and pemphigus foliaceous, granular pattern of deposits was seen at the intra-epidermal layer. IgG and C3 were the predominant deposits in pemphigus and pemphigoid diseases. IgA was found deposited in linear IgA dermatosis, pemphigus vulgaris and bullous pemphigoid. None of the DIF staining in our series detected IgM. For laboratory tests, one-third of bullous pemphigoid patients had peripheral blood eosinophilia.

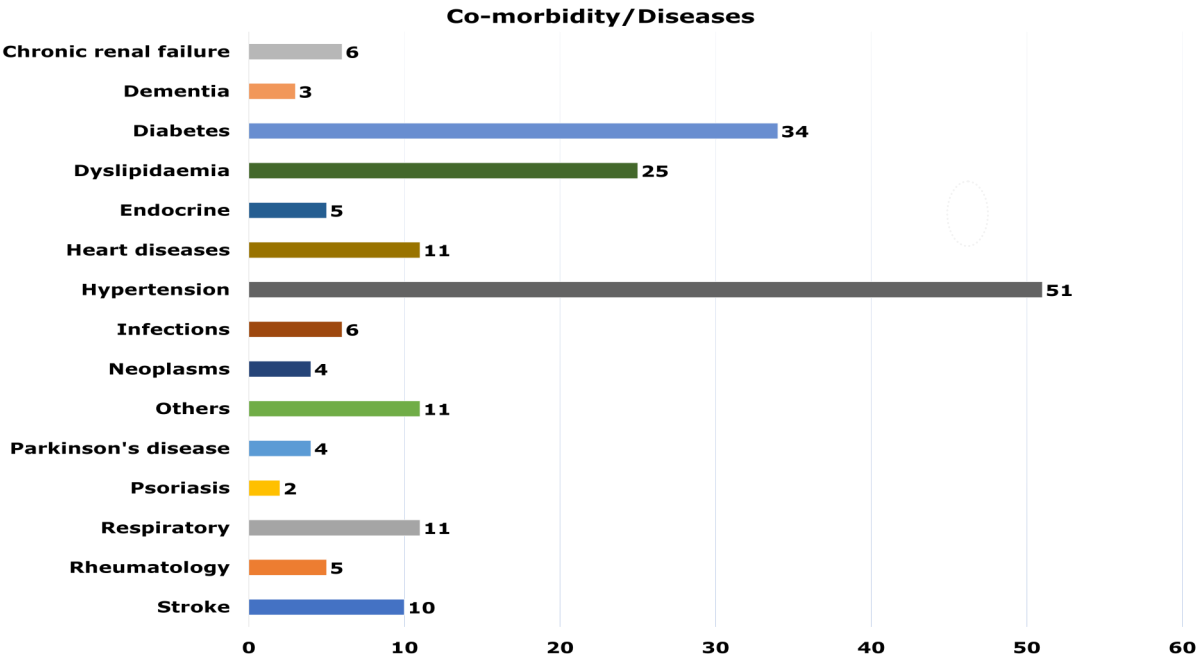

Figure 2: The number of all ABD patients with co-morbidity/diseases. Heart diseases: Coronary artery disease (6), Cardiac arrhythmia(4), Valvular hear disease (1); **Respiratory:** Bronchial asthma(7), Chronic pulmonary obstructive disease (4); Endocrine: Hyperthryoidism(1), Hypothyroidism(1), Polycystic Ovarian Syndrome(1), Osteoporosis(2); **Rheumatology:** Osteoarthritis(3), Gouty arthritis(3); **Neoplasms:** Colon cancer(1), Breast cancer(1), Uterine fibroid(2); **Infections:** Listeria meningitis(1), Pleural Tuberculosis(1), Hepatitis B, Syphilis(3); **Others:** Orbital pseudo-tumour(3), Schizophrenia(1), Alopecia totalis(1), Deep vein thrombosis(1), Submacular haemorrhage(1), Diverticulitis(1), Benign prostate hyperplasia(1), Cataract(1), Fatty liver(1).

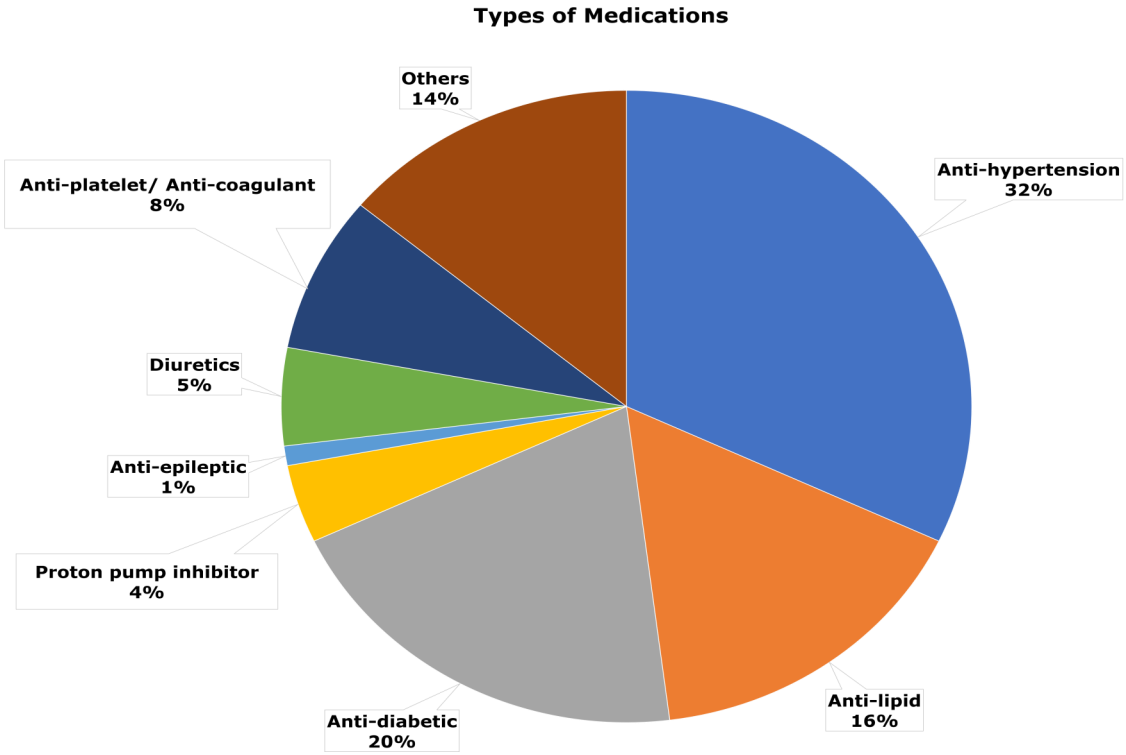

Figure 3: List of medications (%). Anti-hypertension: Amlodipine(31), Perindopril(11), Enalapril(1), Ramipril (1), Metoprolol(7), Atenolol(3), Bisoprolol(3), Carvedilol(1), Prazocin(2), Losartan(3), Valsartan(2); **Diuretic:** Frusemide(5), Hydrochlorothiazide(4), Spironolactone(1); **Anti-diabetic:** Vildagliptin(6), Metformin(19), Gliclazide(15), Empagliflozin(1); **Anti-lipid:** Simvastatin(23), Atorvastatin(8), Lovastatin(1); **Anti-platelet/ Anti-coagulant:** Aspirin(9), Cardiprin(3), Clopidogrel(1), Apixaban(2), Dabigatran(1), Warfarin(1); **Proton Pump Inhibitor:** Pantoprazole(2), Esomeprazole(2); **Anti-epileptic:** Gabapentin(1), Levetiracetam(1), Phenytoin(1); **Others:** Sodium nitrate, Digoxin, Neurobion, Tramadol, Gemfibrozil, Tamsulosin, Iberet, Fluroxamine, Donepezil, Resperidone, Finasteride, Pramipexole, Baclofen, Benserazide, Entacapone, Lecodop, Theophylline, MDI Salbutamol/ Seretide, MDI Atrovent/ Seretide

Table II: Direct immunofluorescent and other tests of bullous disease.

	Bullous pemphigoid n (%)	Pemphigus vulgaris n (%)	Pemphigus foliaceous n (%)	Linear IgA dermatosis n (%)	Pemphigoid gestationis n (%)	*p*-value
Direct IF*						
Positive	21 (67.7)	3 (9.7)	6 (19.4)	1 (3.2)	-	***0.007****
Negative	7 (87.5)	-	-	-	1 (12.5)	
NA	32 (80.0)	8 (20.0)	-	-	-	
C3						
Positive	19 (90.5)	3 (100.0)	4 (66.7)	-	-	0.051
Negative	2 (9.5)	-	2 (33.3)	1 (100.0)	-	
IgG						
Positive	20 (95.2)	2 (66.7)	6 (100.0)	-	-	0.055
Negative	1 (4.8)	1 (33.3)	-	1 (100.0)	-	
IgM						
Positive	-	-	-	-	-	
Negative	21 (100.0)	3 (100.0)	6 (100.0)	1 (100.0)	-	
IgA						
Positive	4 (19.0)	1 (33.3)	-	1 (100.0)	-	0.123
Negative	17 (81.0)	2 (66.7)	6 (100.0)	-	-	
ANA						
Positive	7 (11.7)	-	1 (16.7)	1 (100.0)	-	0.052
Negative	13 (21.7)	6 (54.5)	3 (50.0)	-	-	
NA	40 (66.7)	5 (45.5)	2 (33.3)	-	1 (100.0)	
Eosinophilia						
Positive	18 (30.0)	-	2 (33.3)	-	1 (100.0)	***0.001****
Negative	16 (26.7)	10 (90.9)	3 (50.0)	1 (100.0)	-	
NA	26 (43.4)	1 (9.1)	1 (16.7)	-	-	

* Statistical Significance.

patients had peripheral blood eosinophilia. Antinuclear antibody (ANA) was positive in seven cases of bullous pemphigoid, one case of pemphigus foliaceous and linear IgA dermatosis each. Hepatitis B, C and HIV screenings were negative in all patients. We had four positive cases of latent syphilis in bullous pemphigoid (Table II).

Pattern of treatment modalities and outcome

Corticosteroid was the most commonly used therapy for ABDs in our centre. Most of the patients responded (81.0%) to steroids, although some required immuno-suppressants. Methotrexate was the preferred choice of immunosuppressive agent.

Among the 64 patients that achieved remission, eight had partial response (six were pemphigus and two were pemphigoid disease). In pemphigoid, 77.8% of patients achieved remission within six months; and three had remission after one year of therapy. Mean duration to remission was four months. Pemphigus patients generally took an extended period to remit with a mean duration of 17 months, although 69.2% of pemphigus patients still achieved remission by six months. Relapse occurred in 12 patients (15.2%) due to non-compliance or rapid reduction of systemic steroid (Table III) .

DISCUSSION

Bullous pemphigoid was the most common ABD in our series. This is in contrast to the literature published in the '90s, where most

Table III: Treatment pattern and outcome.

	Bullous pemphigoid n (%)	Pemphigus vulgaris n (%)	Pemphigus foliaceous n (%)	Linear IgA dermatosis n (%)	Pemphigoid gestationis n (%)
Treatment					
Topical steroid only	5 (8.3)	1 (9.1)	1 (16.7)	1 (100.0)	-
Systemic steroid only	16 (26.7)	4 (36.4)	2 (33.3)	-	-
Both	38 (63.3)	6 (54.5)	3 (50.0)	-	1 (100.0)
No steroid	1 (1.7)	-	-	-	-
C3					
Azathioprine	-	2 (18.2)	4 (66.7)	-	-
Methotrexate	11 (18.3)	3 (27.3)	3 (50.0)	-	-
Cyclosporin	-	1 (9.1)	1 (16.7)	-	-
IV Ig	-	2 (18.2)	1 (16.7)	-	-
Rituximab	-	1 (9.1)	1 (16.7)	-	-
Acitretin	-	-	1 (16.7)	-	-
Dapsone	-	-	-	1 (100.0)	-
Duration to remission (days)					
Mean ± SD	125.9 ± 122.6	248.1 ± 484.4	1056.8 ± 630.0	60.0	14.0
Median	90.0	75.0	630.0	-	-
Min: Max	7: 510	30: 1440	14: 3650	60: 60	14: 14
Relapse					
Yes	9 (75.0)	3 (25.0)	-	-	-
No	51 (76.1)	8 (11.9)	6 (9.0)	1 (1.5)	1 (1.5)

Asian studies reported pemphigus vulgaris as the commonest ABD.[3,4,6] The first local study (Malaysia) on ABDs in 1992, found pemphigus was commoner than bullous pemphigoid.[3] However, our findings were consistent with Hong Kong and other Western countries that pemphigoid disease was more prevalent than other autoimmune bullous diseases.[7-10] In our series, bullous pemphigoid affected predominantly the older age group of 60-89. The number of pemphigoids has been rising over the years in our clinic. A shift in the pattern of ABDs in Malaysia reflects the rising aging population due to improvements in the health care system nationwide with increased life expectancy.[11] The female predilection in our series of ABDs was following other studies, which reported the ratio ranged from 1:27 to 1:1.34.[2,6,12]

ABDs were highest among Malays in Sarawak. The local university study in west Malaysia showed that more Indians had chronic bullous disease.[3] This could be due to the distinct and unique population in Sarawak compared to its Peninsular counterpart. The major ethnic groups in Sarawak include Iban (28.3%), Malay (26.4%), and Chinese (24.2%). Indians accounted for 0.3% of the population in Sarawak, while the major ethnicities in Peninsular Malaysia are Malays (66.7%), Chinese (23.9%), and Indian (8.3%).[11,13]

The disease is also known to be associated with multiple co-morbidities in the literature.[14-16] Co-morbidities were more prevalent in our pemphigoid cohort. Some studies found neuropsychiatric disorders and diabetes mellitus were statistically higher in bullous pemphigoid than other ABDs.[14,15] The study also reported hypertension and autoimmune diseases were more common in pemphigoid. Our current study showed that ABDs were associated with other autoimmune diseases notably psoriasis and a positive ANA.

A recent systemic review and case-controlled studies revealed that neurological disease was significantly higher in bullous

pemphigoid patients. [5,17-19] An Iranian study reported that 19.5% of bullous pemphigoids had at least one neurological disease, namely dementia, stroke, and movement disorder.[17] A retrospective local study showed that bullous pemphigoid patients were significantly (3.5 times) more likely to have associated neurological disease.[5] Dementia was the most common neurological disease that had a profound association with bullous pemphigoid. Stroke, Parkinson's disease, and epilepsy were also more prevalent among bullous pemphigoid patients in a systemic review.[19]

The overall event rate of malignancy was higher in the autoimmune bullous diseases.[20-22] Two Japanese studies found that the incidence of internal malignancy was 5 to 11.2% in pemphigus and 5.8 to 10.4% in pemphigoid patients, respectively.[21,22] Rate of malignancy was 11% in bullous pemphigoid in a meta-analysis.[20] The occurrence of malignant disease for our pemphigoid patients could be related to old age and both were 78 years old. Hence, malignancy screening needs to be considered in patients with ABDs.

Drugs have been linked to ABDs, and over 90 medications were associated with drug-induced bullous pemphigoid.[23] The drugs with substantial evidence were gliptins, PD-1/PD-L1 inhibitors, loop diuretics, penicillin, and derivatives. In our series, vildagliptin, frusemide, aspirin, and enalapril were among the drugs that were likely associated with ABD. Evidence of association in amlodipine was uncertain, although it was the most common medication taken by ABD patients in this study. Clinicians are encouraged to check through the patient's medications and cease potentially triggering drugs whenever ABD is suspected.

Apart from direct immunofluorescent (IF) microscopy being the diagnostic gold standard to date, peripheral blood eosinophilia was observed in 22.1% to 50% of the bullous pemphigoid patients in various studies.[12,17,18,24] Our findings showed that 30% of our bullous pemphigoid patients had raised peripheral eosinophil. Elderly patients presenting with an itchy rash or blisters with a raised peripheral blood eosinophilia should raise suspicion of bullous pemphigoid as a differential diagnosis.

Corticosteroids have been the mainstay of treatment in autoimmune bullous diseases since its introduction in 1959, which significantly reduced morbidity and mortality of the patients suffering from these diseases.[25] However caution must be applied when using corticosteroids, especially in the elderly, as previous studies reported complications and even fatal outcomes from systemic corticosteroids usage.[26] One study showed that 16% of elderly patients on systemic corticosteroids had significant risks of infections.[16] In our series, most bullous pemphigoid patients, achieved remission on a low dose of oral prednisolone (0.1 - 0.5mg/ kg/kg) or with topical corticosteroids alone in mild localised cases. Pemphigus patients were generally less responsive to steroid therapy alone and took a longer duration to achieve remission than bullous pemphigoid. Many of them had refractory or persistent disease requiring multiple lines of therapy. Additional immunosuppressive agents were needed in pemphigus. Intravenous Immunoglobulin and Rituximab were used in three of our recalcitrant pemphigus patients. Dapsone was effective in treating the only patient with linear IgA dermatosis.

CONCLUSION

Autoimmune bullous diseases are not uncommon in the Malaysian population, including East Malaysia. This study has illustrated a better understanding of the disease's local demography and associated features in East Malaysian state of Sarawak. It emphasized the need for precise diagnosis and confirma-

tion by immunofluorescence to outline better treatment strategies of each subgroup. Each subtype demonstrates different response to treatment, prognosis and disease association. Our series has drawn a comprehensive outlook on treatment patterns and clinical outcomes that would enhance future primary care for betterment of patient care in local community.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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