Chronic bullous dermatosis in Hong Kong

RCW Su, LY Chong

The medical records of patients with chronic bullous dermatosis who have attended the Social Hygiene Service in Hong Kong were reviewed retrospectively. All skin biopsy reports in the Social Hygiene Service (Dermatology) for patients with a diagnosis of vesiculo-bullous disease were retrieved along with the respective medical records for the period from January 1985 through December 1992. The epidemiology, treatment, course, and prognostic data were reviewed. Of 234 patients with chronic bullous disease, the three most common diagnoses were bullous pemphigoid (n=149, 63.7%), pemphigus vulgaris (n=38, 16.2%), and pemphigus foliaceus (n=23, 9.9%). Only six patients (2.6%) had dermatitis herpetiformis, and another six had linear immunoglobulin A disease (2.6%). Systemic steroids (40-80 mg/day) were the mainstay of therapy for pemphigus and pemphigoid patients. The most common steroid-sparing agent employed was azathioprine. Dapsone was the treatment of choice for dermatitis herpetiformis and gluten-free diet was not employed for control of the skin condition in these patients.

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Key words: Pemphigoid, bullous; Skin diseases, vesiculobullous; Autoimmune diseases; Hong Kong

Introduction

Chronic bullous dermatosis includes a variety of bullous diseases. Some, such as pemphigus and pemphigoid are not uncommon, yet are serious and potentially fatal conditions. These diseases have an autoimmune aetiology, with auto-antibodies directed against the epidermis or dermo-epidermal junction; hence, they may be treated with immunosuppressive agents, which reduce mortality and morbidity. Chronic bullous dermatoses deserve close attention and study and a better understanding of their epidemiology, natural history, and prognosis is needed.

While chronic bullous dermatosis has been extensively studied in western countries, there are only a few published studies from Southeast Asia. No such study has been published in Hong Kong before. The Social Hygiene Service offers most of the dermatology and genito-urinary medical services for the public in Hong Kong. In this study, the records of individuals with chronic bullous dermatosis seen by the unit from January 1985 through December 1992 were reviewed in an attempt to obtain some epidemiological data for this locality.

Materials and methods

All skin biopsy reports in the Social Hygiene Service from January 1985 through December 1992 were screened.

Medical records were retrieved for study if the histopathological report (and direct immunofluorescent study) of skin biopsy had been reported as one of the following: pemphigus, pemphigoid, herpes gestationalis, linear IgA bullous dermatosis, chronic bullous dermatosis of childhood, dermatitis herpetiformis, or epidermolysis bullosa.

Data were abstracted according to a pre-designed questionnaire that included patient age, sex, race, site of disease, duration of disease before first attendance, histological diagnosis, and the results of immunofluorescent staining. The treatment (drug names, doses, duration), complications, progress (outcome after start of treatment, cure or death, if any) were also recorded where available.

Results

A total of 234 patients were studied; all were ethnic

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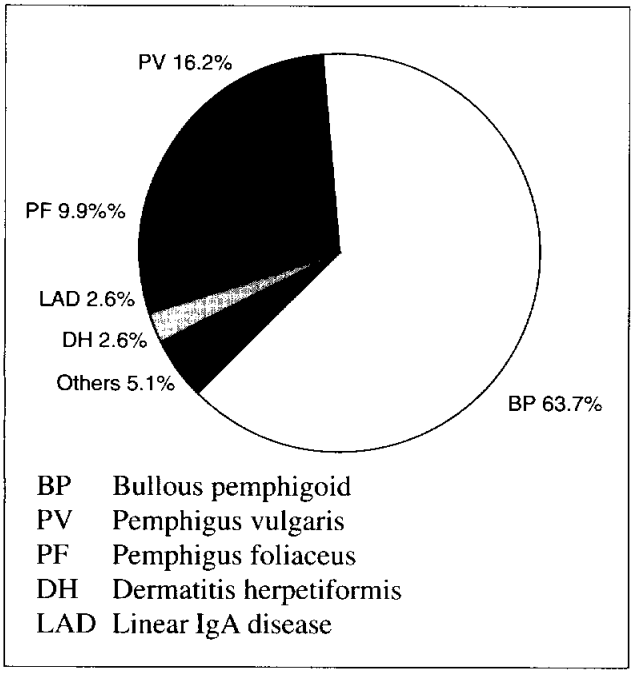
Table 1. Site of lesions

Site	Bullous pemphigoid No.(%)	Pemphigus vulgaris No.(%)	Pemphigus foliaceus No.(%)	Dermatitis herpetiformis No.(%)	Linear IgA disease No.(%)
Generalised	8 (5)	1 (3)	0	1 (17)	1 (17)
Head/neck	28 (19)	24 (63)	11 (48)	1 (17)	1 (17)
Trunk	97 (65)	37 (97)	20 (87)	4 (67)	5 (83)
Limbs	137 (92)	21 (55)	1 (4)	4 (67)	4 (67)

Chinese. The three most common diagnoses were bullous pemphigoid (n=149, 63.7%), pemphigus vulgaris (n=38, 16.2%), and pemphigus foliaceus (n=23, 9.9%). There were six cases (2.6%) of dermatitis herpetiformis and six cases of linear IgA disease (Fig 1). There were only a few cases of pemphigus erythematosis (n=3), benign familial pemphigus (n=3), epidermolysis bullosa (n=3), pemphigoid gestationalis (n=2), and pemphigus vegetans (n=1).

In this series, there was a predominance of men, especially in the patients with dermatitis herpetiformis (M:F, 5:1), pemphigus foliaceus (M:F, 1.6:1), and pemphigus vulgaris (M:F, 1.4:1) [Fig 2]. The mean age of presentation of bullous pemphigoid was 70 years (SD 15 yr), whereas the mean age for pemphigus vulgaris was 57 years (SD 14 yr) and for pemphigus foliaceus was 63 years (SD 13 yr) [Fig 3]. The age distribution of dermatitis herpetiformis (presenting at 17, 49, 58, 61, 69, and 78 years) was quite scattered. Linear IgA disease appeared to have a bimodal age distribution, with the childhood form presenting at 3, 4, 9, and 12 years, and the adult form presenting at 51 and 65 years. There were, however, not enough cases for any definite conclusions to be drawn.

Fig 1. The different type of chronic bullous dermatosis seen



BP Bullous pemphigoid
PV Pemphigus vulgaris
PF Pemphigus foliaceus
DH Dermatitis herpetiformis
LAD Linear IgA disease

The lesions in bullous pemphigoid were more commonly located on the limbs and extremities. In contrast, pemphigus lesions were more often located on the trunk, head, face, and mouth (Table 1).

Direct immunofluorescent staining was performed on the skin biopsies (Table 2). Pemphigus vulgaris and pemphigus foliaceus showed a granular pattern of deposits in the epidermis. Bullous pemphigoid and linear IgA disease showed a linear pattern of deposits at the dermo-epidermal junction. Dermatitis herpetiformis showed a granular or linear (continuous granular) pattern of deposits in the papillary dermis. In pemphigus and pemphigoid, immunoglobulin G (IgG) and occasionally, immunoglobulin M (IgM) was the predominant immunoglobulin deposited. In linear IgA disease and dermatitis herpetiformis, IgA was the predominant immunoglobulin deposited.

The majority of bullous disorders in this series were diagnosed within two to three months of the onset of skin lesions. A minority of cases were not diagnosed for more than one year, however, after the first appearance of skin lesions (Table 3). In these patients, an insidious onset with localised involvement occurred, hence, they did not present to a dermatologist early in the course of their illness.

Steroids were the mainstay of therapy for pemphigus and pemphigoid patients. The mean dosage of prednisolone employed in these patients were as follows: pemphigus vulgaris, 48 mg (SD 25 mg), pemphigus foliaceus, 36 mg (SD 17 mg), and bullous pemphigoid, 32 mg (SD 11 mg). The maximum dose of prednisolone used in pemphigus was 120 mg/day, but much lower doses were often employed together with ster-

Table 2. Direct immunofluorescent studies

Immunofluorescent studies	Bullous pemphigoid No.(%)	Pemphigus vulgaris No.(%)	Pemphigus foliaceus No.(%)	Dermatitis herpetiformis No.(%)	Linear IgA disease No.(%)
Positive	128 (86)	36 (95)	22 (96	3 (50)	6 (100)
C3	117 (79)	28 (74)	16 (70)	1 (17)	3 (50)
IgG	108 (72)	35 (92)	21 (91)	0	1 (17)
IgM	12 (8)	2 (5)	3 (13)	0	1 (17)
IgA	10 (7)	2 (5)	4 (17)	2 (33)	6 (100)
Negative	21 (14)	2 (5)	1 (4)	3 (50)	0

Table 3. Duration of lesions prior to diagnosis

Duration (m)	Bullous pemphigoid No.(%)	Pemphigus vulgaris No.(%)	Pemphigus foliaceus No.(%)	Dermatitis herpetiformis No.(%)	Linear IgA disease No.(%)
< 3	112 (86)	19 (53)	18 (78)	3 (60)	5 (83)
3 - 12	14 (11)	17 (47)	4 (17)	0	1 (17)
> 12	4 (3)	0	1 (4)	2 (40)	0

oid-sparing agents. The immunosuppressives used as steroid-sparing agents included azathioprine, cyclophosphamide, and cyclosporin. Azathioprine was the first choice and the most frequently used steroid-sparing agent. The dosage of azathioprine employed was 100-150 mg/day for pemphigus and 50-200 mg/day for pemphigoid. Cyclophosphamide, 100 mg/day was employed together with steroids for one patient with pemphigus vulgaris. Cyclosporin, 250 mg/day was employed with steroids for one patient with bullous pemphigoid. Dapsone was used to control dermatitis herpetiformis and linear IgA disease, and occasionally used in bullous pemphigoid as well. The most frequently used dosage of dapsone was 100 mg/day, but it varied from 50-200 mg/day. The adoption of a gluten-free diet was not necessary for the control of dermatitis herpetiformis in these patients.

In this series, the complications recorded could be divided into those due to infective or non-infective causes. Infectious complications, which may be caused by immunosuppressive therapy, included pneumonia (n=1), pulmonary tuberculosis (n=1), herpes zoster (n=4), cellulitis (n=2), and tinea cruris or pedis (n=6). Non-infectious complications included diabetes mellitus (n=2), Cushing's syndrome (n=2), acne (n=4), and myopathy (n=2). These complications were mostly related to the steroid given in the treatment of pemphigus and pemphigoid. One of the pemphigus patients had bronchogenic carcinoma, but none of the pemphigoid patients was recorded as having any internal malignancy.

The pemphigus patient had preceding inoperable bronchial adenocarcinoma at the left hilar region, with left vocal cord palsy and left hemidiaphragm paralysis before a generalised, blistering eruption developed on the face, trunk, and limbs. Clinically, the skin condition was diagnosed as pemphigus vulgaris and the skin biopsy showed features of pemphigus. Immunofluorescence showed the epidermal intercellular deposition of IgG, which is consistent with pemphigus. The patient was initially given prednisolone, 80 mg/day, which was rapidly increased to 120 mg/day due to his unsatisfactory response.

Discussion

Bullous pemphigoid was found to be more common than pemphigus in this series. This agrees with studies from the West, but contrasts with findings from other Southeast Asian countries where the reverse is true.[1-3] The reason for this is unclear. Bullous pemphigoid often occurs in the elderly (70-90 years), while pemphigus tends to occur at a younger age. Possibly, the Hong Kong population has a similar life expectancy and age demographics to the West, with a significant proportion of senior citizens. By contrast, other more recently developed Asian countries have younger populations, which accounts for pemphigus being more common. In Hong Kong, the average life expectancy in 1990 for men and women was 75 years and 81 years, respectively. In Malaysia and China, the corresponding figures were 65 and 70 years, and 68 and 70 years, respectively.

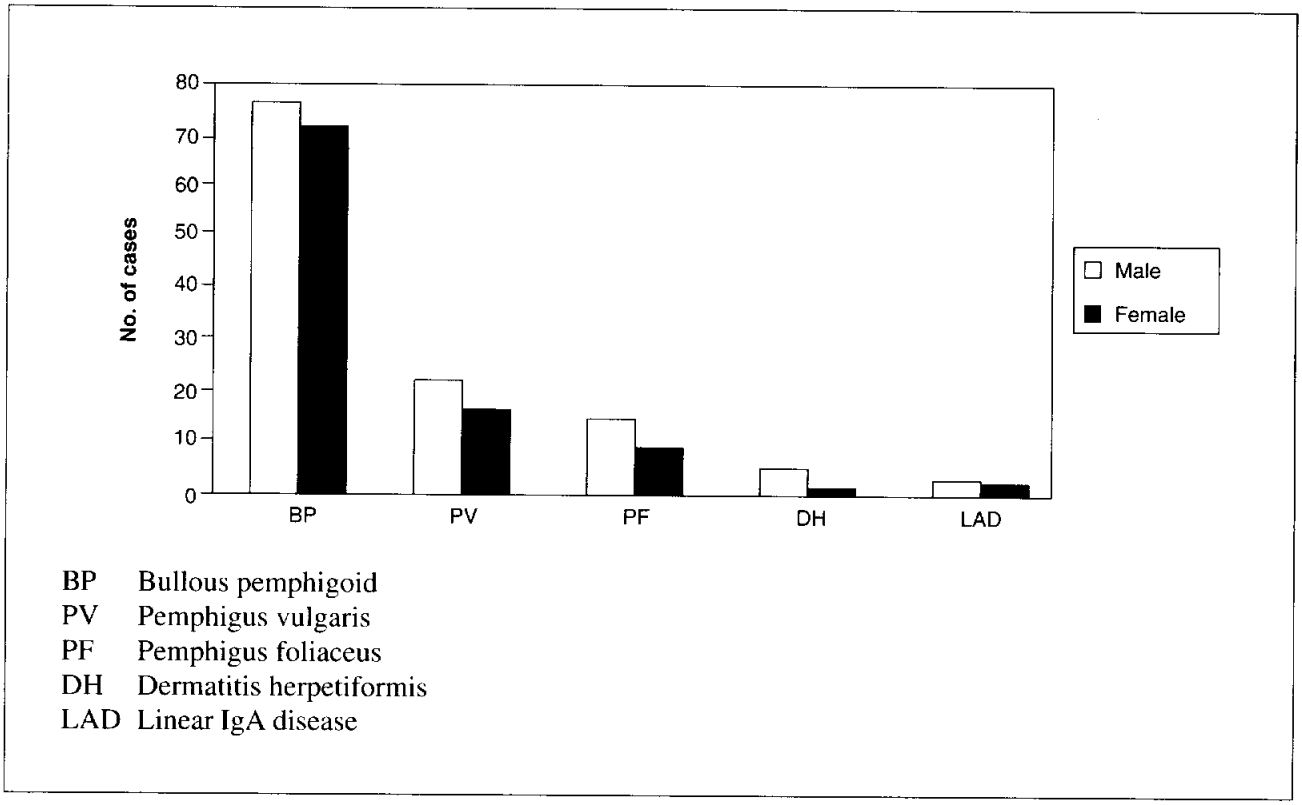


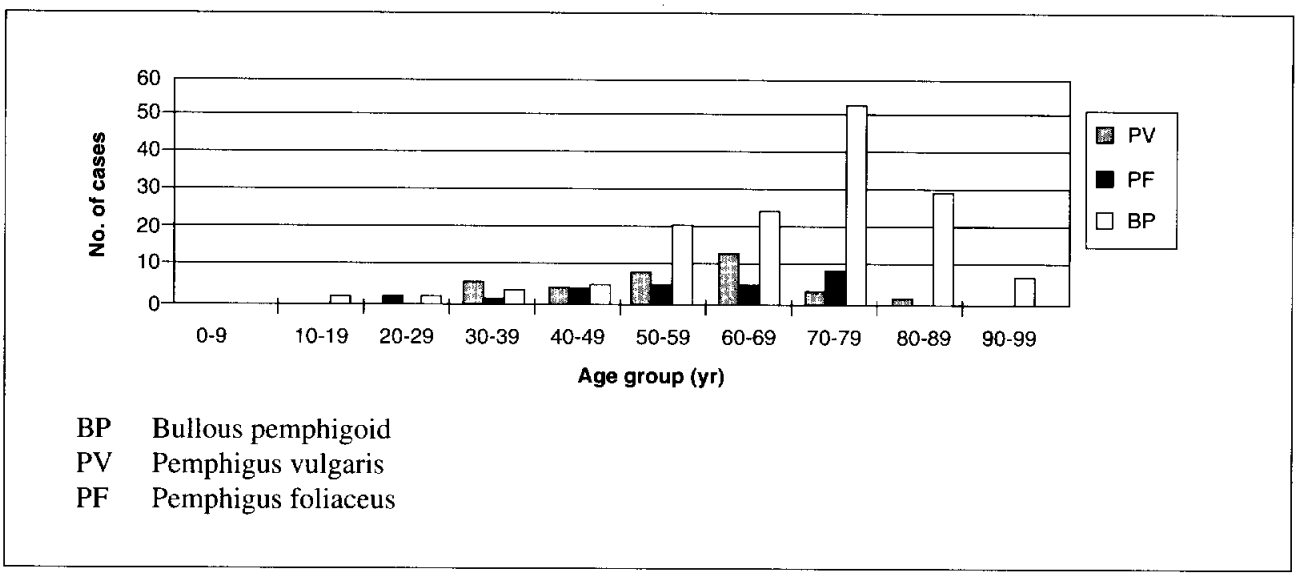
Fig 2. Sex distribution of patients with different types of bullous dermatosis

There was a sharp fall in mortality from bullous disease in the United States and the United Kingdom during the 1950s. The timing of improvement in mortality fits well with the introduction of systemic steroids for general use. The rate decreased to approximately one-third of the pre-steroid level.[4] Pemphigus in the pre-steroid era was usually fatal, but overall mortality fell to 50% with the introduction of steroids.[5] Pemphigoid not treated with steroids has a mortality rate of approximately 30%, and this has improved with steroids to as low as 5%.[6] Nevertheless, pemphigus and pemphigoid are both important causes of death. There is still debate as to the best line of management. Lever and White found a greater fall in mortality when very high initial doses of steroid (120-200 mg/day) were given, which can subsequently be reduced once control has been achieved.[7] Conversely, Ryan found mortality to be lower when moderate steroid doses were used. Over-vigorous regimens can carry severe side-effects that outweigh the benefits.[8]

In the majority of pemphigus patients, both the starting and maximum dose of prednisolone used were in the range of 40-80 mg/day only. The reason for this may be twofold. Firstly, steroid-sparing agents were introduced early, and the early use of these agents enables moderate doses of steroids to achieve disease control.[1,2] Secondly, the average body weight of southern Chinese patients tends to be lower compared with patients in the West, hence, correspondingly lower doses of steroid were needed for control. The maximum dosage of prednisolone required to control pemphigus vulgaris was only 120 mg/day. One recent study indicated no clear long term advantage with a high dose prednisolone regimen (>120 mg/day) in pemphigus therapy, nor was the time taken to achieve initial control significantly shortened.[9] Studies from other countries in the region also show that steroid-sparing agents should be used, and that the steroid dosage should not be too high.[1,2]

It was difficult to analyse the prognostic data from this survey, as some patients had been lost to follow up. Patients with fatal medical illnesses often end up in medical wards under the care of physicians experienced in the management of medical complications. Savin examined the factors adversely affecting the length of survival in pemphigus patients.[10] He found that age at onset of disease was important, with older patients dying significantly more quickly than do younger ones. In addition, a short pre-treatment phase signified a fulminating course in pemphigus vulgaris, and correspondingly, a shorter survival time.

Krain found the mortality in pemphigus patients to be related more to intercurrent disease other than pemphigus.[5] Mortality was not directly related to the



BP Bullous pemphigoid
PV Pemphigus vulgaris
PF Pemphigus foliaceus

Fig 3. Age distribution of patients with chronic bullous dermatosis

severity of pemphigus, or to the maximum daily dose of steroid required to bring about remission. However, steroid administration was associated with substantial morbidity. Complications were higher in patients older than 50 years, and for those requiring more than six months of therapy. The complications noted were similar to those found in our series.[5]

It has been stated in dermatology textbooks that pemphigus foliaceus often responds well to topical steroids and if the control is inadequate, prednisolone, 20-40 mg daily is usually sufficient.[11] This was not always borne out by our experience. Even with the concomitant use of steroid-sparing agents, we found that some pemphigus foliaceus patients required large doses of prednisolone (40-80 mg/day), as with pemphigus vulgaris, to achieve control.

The salt split-skin technique was developed to split the skin along the dermo-epidermal junction at the level of the lamina lucida. It is used in conjunction with immunofluorescent studies to distinguish epidermolysis bullosa acquisita from bullous pemphigoid.[12] Epidermolysis bullosa acquisita is a recently described and relatively rare condition that can resemble bullous pemphigoid clinically. Both bullous pemphigoid and epidermolysis bullosa acquisita show immune deposits at the dermo-epidermal junction but these are directed at different target antigens. With the salt split-skin technique, bullous pemphigoid shows immune deposits at the epidermal side of the split, whereas epidermolysis bullosa acquisita shows immune deposits at the dermal side of the split.

This technique is not routinely available in Hong Kong. Private communication with dermatopathologists suggests that local results of this laboratory procedure have not been consistent. This technique either was not mentioned or found to be unreliable in studies undertaken in other Asian countries. Epidermolysis bullosa acquisita is likely when the bullous lesions are acrally distributed, particularly over areas of friction, and are unresponsive to steroids. However, this condition is relatively rare and will not significantly affect the epidemiology of bullous pemphigoid in this locality.

The natural course of bullous pemphigoid tends to be self-limiting, with eventual remission; the mean duration of disease is approximately 3.3 years.[13] Patients often die from causes unrelated to bullous pemphigoid or its treatment. Those who die from causes relating to bullous pemphigoid or its treatment do so within weeks after the onset of disease. The relationship between bullous pemphigoid and internal malignancy is controversial. Both conditions occur more frequently in elderly patients, and old age seems to be the confounding factor for their association. Pemphigoid has also been associated with diabetes mellitus. Bullous pemphigoid is an autoimmune disorder, and diabetes mellitus is known to be associated with autoimmune disease. The onset and course of diabetes appears not to be affected by the treatment of pemphigoid with steroids.[13] In this series, no significant association between bullous pemphigoid and malignancy was found. A prospective study is needed to clearly define the course and prognosis of these pemphigoid patients.

The term paraneoplastic pemphigus describes when an underlying neoplasm (usually lymphoma, leukaemia, thymoma or sarcoma) associated with painful mucosal ulcerations and polymorphous skin

lesions, progresses to a blistering eruption of the trunk and extremities.[14] Clinically, skin lesions resembling pemphigus with positive Nikolsky's sign are seen, but they can also resemble erythema multiforme or bullous pemphigoid. There is also mucosal involvement including oral, oesophageal, and bronchial epithelium. Histological examination shows vacuolisation of epidermal cells, keratinocyte necrosis, and suprabasal acantholysis. Immunofluorescent studies reveal pemphigus-like intercellular epidermal or epithelial antibodies, as well as basement membrane antibodies in perilesional epithelium and serum. These bind to four polypeptides with molecular weights of 250 kd (desmoplakin 1), 230 kd (bullous pemphigoid antigen), 210 kd (desmoplakin 2), and 190 kd (unidentified antigen). The prognoses of these patients is generally poor and their skin condition is difficult to control unless the underlying neoplasm can be cured.

One patient had clinical, histological, and immunofluorescent features of pemphigus vulgaris with coexisting bronchial neoplasm. There were no laboratory facilities available for us to investigate whether or not the pemphigus antibodies were reactive against the above-named antigens. The lesions of nearly all pemphigus patients seemed well controlled with prednisolone, 80 mg/day or less, but this particular patient required prednisolone, 120 mg/day or more.

Gastrointestinal disease has been described in patients with dermatitis herpetiformis in the West.[15] The small bowel changes of villous atrophy are secondary to gluten sensitivity, which is indistinguishable from coeliac disease.[16] However, coeliac disease is virtually unheard of in the southern Chinese. Dermatitis herpetiformis is relatively uncommon in southern Chinese[1] and none of the patients with dermatitis herpetiformis had gastrointestinal symptoms; their skin condition readily responded to moderate doses of dapsone without a change to a gluten-free diet. These findings are similar to the Malaysian experience.[2]

In the West, a gluten-free diet is recommended for dermatitis herpetiformis patients to control skin and gastrointestinal symptoms, as well as to prevent the development of gastrointestinal lymphoma, despite the fact that a gluten-free diet is poorly tolerated by most patients and takes nine to 12 months to make an impact. It remains to be seen whether local dermatitis herpetiformis patients also have asymptomatic gluten-sensitive enteropathies. There may be a need for dermatitis herpetiformis patients in Hong Kong to undergo gastrointestinal investigations and have endomysial antibody assays done.

Conclusion

This retrospective survey was an attempt to obtain epidemiological data on chronic bullous dermatosis in this locality. Bullous pemphigoid was found to be the most common bullous disorder, followed by pemphigus. This contrasts with data published from other Southeast Asian countries, but is in agreement with data from the West. Steroid in doses of 40-80 mg/day was the mainstay of therapy for pemphigus and pemphigoid patients. Azathioprine was the most frequently used steroid-sparing agent. A prospective study with better follow up is needed to understand the prognosis and chances of survival of chronic bullous dermatosis in this locality.

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