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Original Article

Pemphigus foliaceus: a clinical study of 32 cases in Hong Kong

落葉性天疱瘡：香港的 32 宗病例研究

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This is a cross-sectional, retrospective study of 32 Hong Kong Chinese patients with pemphigus foliaceus from the year 1993 to 2003. The incidence was 0.48 per million population per year. There were 24 males and 8 females and the mean onset age was 55. Seventeen patients presented with generalised disease and one with erythroderma. There was a correlation of anti-skin titre versus disease severity. Twenty-seven patients required systemic prednisolone with a mean dose of 36 mg daily for the first disease remission. Dapsone was not an effective treatment. When azathioprine was used as an adjuvant, the mortality and remission rates were 0% and 40% respectively. Disease or treatment related deaths occurred within the first three months. The average onset age for the deceased was 73.7 in compare with 52.4 for the survivors.

本報告為 32 例香港華人落葉性天疱瘡自 1993 至 2003 年的回顧性剖面研究。發病率為每年每百萬人口 0.48 宗。男患者 24 名，女患者 8 名。平均發病年齡為 55 歲。 17 名患者有泛發性病損。另一名有全身紅皮症。抗皮膚抗體滴度與病情呈相關性聯繫。 27 名患者需口服強的松龍，誘導首次緩解劑量平均每日 36 毫克。氨苯碸無確切療效。以硫唑嘌呤為輔助治療，死亡率與緩解率分別為 0% 及 40% 。因治療或疾病本身所致的死亡均於發病後三個月發生。死亡病例的平均發病年齡為 73.7 歲，於存活病例則為 52.4 歲。

Keywords: Hong Kong Chinese, pemphigus foliaceus

關鍵詞：香港華人、落葉性天疱瘡

Introduction

Pemphigus foliaceus (PF) is an autoimmune disease characterised by blistering high in the epidermis, either in the granular layer or just beneath the stratum corneum, and was first described by Cazenave of France (1802-1877) in 1844. Pemphigus is a disease showing two geographic settings: a sporadic and an endemic form. The superficial blisters are extremely fragile and tend to affect the seborrhoeic areas of the face, scalp and chest. Immunologically, pemphigus foliaceus antigen is a 160-kDa desmoglein (Dsg) 1 glycoprotein that binds more to the superficial epidermis. There is still debate

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on the best line of management. Pemphigus foliaceus is described as a chronic benign disease and responds well to treatment.[1]

Objectives

The present study includes the period of January 1993 to May 2003 and is set to examine the local epidemiology, clinical characteristics, treatment and prognosis of pemphigus foliaceus. In addition, the following correlations are studied:

1) Presentation to treatment interval versus time to first remission and
2) Clinical severity at follow up versus anti-skin titre.

Clinical remission is defined as total clearance of cutaneous lesions noted by the attending dermatologist. Relapse is defined as a recurrence of cutaneous lesions documented by the attending dermatologist. A simple severity score was adopted from Harman et al[2] (skin score: 0, quiescent; 1, minor activity of less than five discrete lesions; 2, moderate activity of more than five but less than 20 discrete lesions; 3, severe, more than 20 discrete lesions or extensive, confluent areas of eroded skin).

Method

A manual and computer search through the biopsy records were performed for the period of January 1993 through May 2003 in all the Hong Kong Social Hygiene Service (SHS) clinics. The inclusion criteria were proven histopathology from skin biopsy and confirmed by direct immunofluorescence (DIF) study.

These patients were invited for an interview for their medical history and skin condition. For those who were unable to attend or deceased, they or their relatives were interviewed over the telephone. Patient medical records, histology slides and, if available, DIF studies were reviewed. The literature review was based on Pubmed search and compared with the present study.

Results

Epidemiology

There was an average of 1.64 pemphigus foliaceus cases per 10,000 new skin cases in the Social Hygiene Service from 1993 to 2003. This study reflected an incidence of 0.48 per million population per year. There were 32 patients diagnosed with pemphigus foliaceus during the study period with 24 males and 8 females giving a male to female ratio of 3:1 (Figure 1). A binomial test showed that the difference was significant, $p < 0.05$. The mean age at diagnosis for males was 56.4 (range from 17 to 82) and for females it was 50.9 (range from 10-75). An independent sample t-test indicated that the age difference between male and female patients were not significant, $t = -0.66$, $p > 0.05$. All the affected patients were Chinese. There was no family history.

Clinical characteristics

Table 1 summarises the clinical symptoms, sites of involvement and aggravating factors of PF. The mean duration from the disease onset to diagnosis was 10.07 months (range: 0.5-75). The average

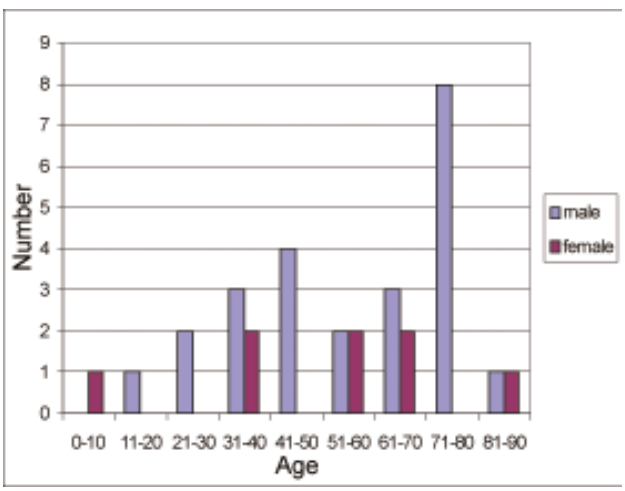

Figure 1. Age and sex of patients at presentation.

Table 1. Symptoms, site of involvement and aggravating factors of PF

	No. of cases (%)
Symptoms	
None	8 (25)
Itch	22 (69)
Pain	8 (25)
Burning	4 (13)
Site of involvement	
Head & Neck	6 (18.7)
Trunk	15 (46.9)
Limbs	4 (12.5)
Generalised	17 (53.1)
Erythroderma	1 (3.1)
Aggravating factors	
Heat	7 (21.9)
Sunlight	7 (21.9)
Humidity	1 (3.1)
Stress	1 (3.1)
Acid food	1 (3.1)

duration from the onset to the presentation of disease was 8.4 months. Hence, the average time from the presentation to diagnosis was 1.67 months.

Two patients were not included for the time to remission, duration of the first remission, number of relapses and number of relapses per year. One had poor compliance with treatment and another had no disease remission and passed away four months later.

The average time to the first remission in 30 patients was 1.58 months (SD: 1.33, range: 0.25-6). The mean duration of first remission was 16.75 months (SD: 24.24, range: 0.5-98). The ratio of total remission during follow up versus duration of follow up in all 32 patients was 0.6 (SD: 0.34, range: 0-1). The average number of relapses per year in 30 patients was 1.03 (SD: 1.62, range: 0-8). The average duration of follow up was 30.95 months (SD: 28.43, range: 1.5-108). Figure 2 shows the time to first remission

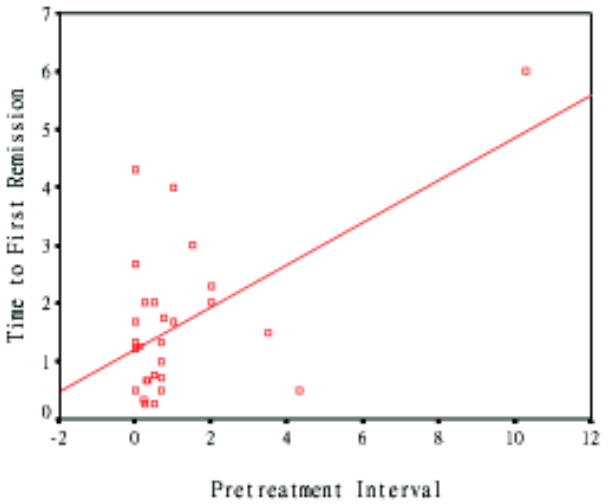

Figure 2. Relationship between presentation to treatment interval versus time to first remission.

correlating with presentation to treatment interval ($p = 0.001$).

Among the group of PF patients, co-existing disorders included rheumatoid arthritis, psoriasis, non-Hodgkin's lymphoma and lung carcinoma. Transition to pemphigus vulgaris was noted in one patient.

Diagnosis

Among the 32 patients, histopathology showed that the level of splitting was high up in the epidermis, 56% were in the subcorneal layer and 44% were in the subgranular layer. Acantholysis and dyskeratosis were present in all patients. Table 2 showed DIF staining properties.

The mean anti-skin titre at diagnosis of 29 patients was 1/120. The mean anti-skin titre at follow up

Table 2. DIF staining in PF patients

	No. of cases (%)
IgG	30 (94)
IgM	2 (6)
IgA	1 (3)
C3	23 (72)
Negative	1 (3)

of 20 patients was 1/100. The mean severity score was 1.43.

There was a positive correlation of antibody titre against severity score as illustrated by 20 patients who had blood tests at the follow up visit (Figure 3).

Treatment

Figure 4 summarised treatment given to the patients. The average initial dose of oral prednisolone in 27 patients required for disease remission was 36 mg per day (SD: 14, range: 20-60). At interview, 15 patients were taking oral prednisolone and the average dose was 9.7 mg per day (SD: 10.56, range: 2.5-40) (one patient had poor compliance with treatment and was excluded). The average duration to disease remission in 25 patients was 1.23 months (SD: 0.83, range: 0.25-3.2). The ratio of average duration of steroid treatment versus duration of follow up was 0.81 (SD: 0.31, range: 0.07-1). Adjuvants were given to 11 patients for disease remission. For azathioprine, two out of five patients were taking treatment and two were in remissions at interview. For dapsone, two out of four were on treatment and three had active disease at interview; one died.

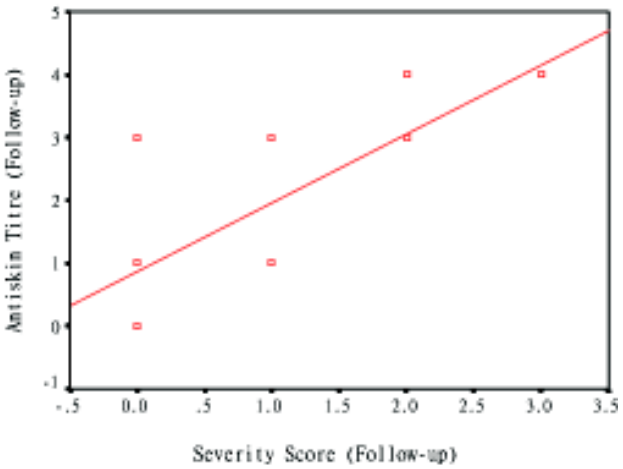

Figure 3. Pearson correlation between clinical severity and anti-skin titre at follow-up visit.

Complications of treatment can be divided into two groups, infective and non-infective. Treatment side effects were common. Nineteen out of 27 patients (70%) taking oral prednisolone versus four out of five (80%) put on azathioprine were affected; one patient taking azathioprine suffered from cryptococcal meningitis and treatment was changed to dapsone. Three out of four patients (75%) taking dapsone had haemolytic anaemia. One patient suffered from a sudden drop of haemoglobin from 15 g/dl to 9.5 g/dl and after stopping treatment, haemoglobin increased to 12.8 g/dl. None of the four patients received antibiotics encountered any problem.

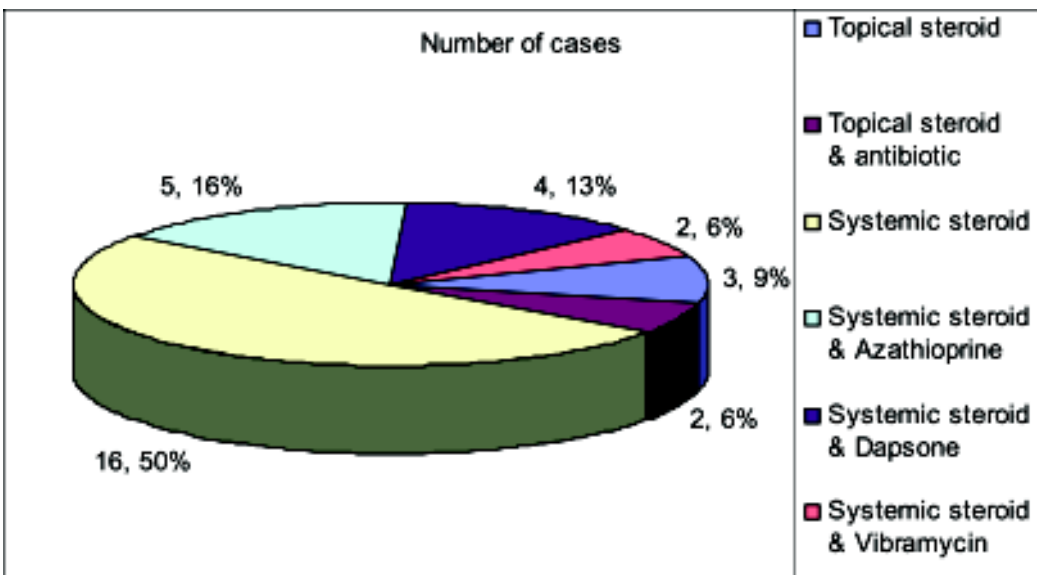

Figure 4. Treatment given to PF patient.

Prognosis

At interview, nine patients were in remission with no treatment, whereas four patients required a mean oral prednisolone dosage of 8.75 mg daily for disease control; one patient also received azathioprine 50 mg daily. Twelve patients had active disease and required a mean oral dosage of prednisolone 12.5 mg daily; in addition two of these patients required dapsone 100 mg daily and one required azathioprine 100 mg daily. Three patients had active disease but on no treatment. Four patients had passed away (Figure 5).

The mean onset age for the deceased was 73.7 years in comparison with 52.4 for the survivors. There were four deceased during the follow up period (Table 3).

Discussion

Epidemiology

The average incidence was 0.48 per million population per year in Hong Kong and was comparable with the sporadic form in the United States[3] and Western Europe.[4,5] Although the Social Hygiene Service is taking care of the majority of dermatology patients in the territory, this is likely to be an under estimation.

All the affected patients were Chinese and mostly in their fifties, 56.4 for males and 50.9 for females. There was a male preponderance with a ratio of 3:1. There was no clear explanation. There is no regional difference for the age of presentation in Singapore,[6] Hong Kong,[7] or China.[8] The sporadic form in United States[3] and Western Europe[4,5] was more prevalent between the fifth and sixth decade of life, whereas the endemic form in Brazil affected the second and third decades of life.[9] An equal sex predisposition has been reported in North America,[3] Finland,[4] France,[5] Brazil,[9] Singapore,[6] Hong Kong[7] and China.[8]

Clinical characteristics

The mean duration from the onset to diagnosis was 10.07 months. Six patients (18.75%)

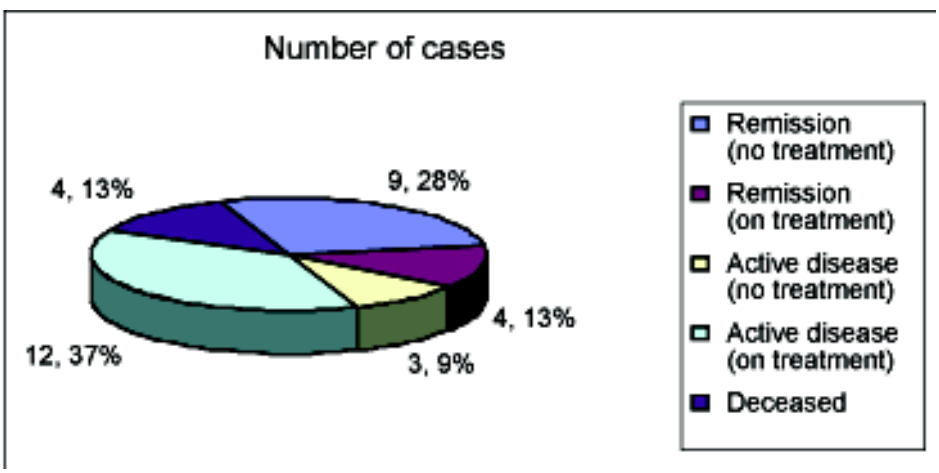

Figure 5. Disease outcome at interview.

Table 3. Details of the deceased

Age	Sex	Survival from onset (months)	Survival from diagnosis (months)	Cause of death
62	M	7.3	3	Chest infection
77	M	74.3	28	Lung carcinoma
74	M	12.25	10.25	Myocardial infarction
82	M	4.75	2.5	Pneumonia

presented after a year. The delay was due to mild disease, late presentation to dermatologist, low index of suspicion among general practitioners, coexistence of other skin disease and attitude of patient towards the disease. When they presented to the dermatologist, the diagnosis was made promptly. The average time from the presentation to diagnosis was 1.67 months. The average time to the first remission was short (1.58 months). They enjoyed a long duration of first remission of 16.75 months. The disease tended to become chronic and lead a fluctuating course as evidenced by a ratio of 0.6 of total remission time during follow up versus duration of follow up. The number of relapses per year is also a reflection on the course of the disease with a mean of 1.03. Most patients were followed up on a long term basis with an average follow up time of 30.95 months. However, there were seven defaulters and four patients were deceased. Only one patient was discharged.

There was a correlation of time to first remission versus pre-treatment interval in this study. It makes sense that the earlier a patient is treated, the shorter the time it takes to remission.

Pemphigus foliaceus has been reported in association with autoimmune disease and malignancy by Rosenberg et al.[10] The patient who developed rheumatoid arthritis was never treated with penicillamine. Similarly, the non-Hodgkin's lymphoma patient was not treated with immunosuppressive therapy at any stage. Finally, one patient showed a transition to pemphigus vulgaris after 17 months, an uncommon phenomenon known as an epitope-spreading.[11]

Diagnosis

All the dermatopathologists agreed that pemphigus foliaceus is a straight forward diagnosis. DIF is a reliable test for diagnosis and is positive for IgG and C3 in both affected and normal skin in early disease. Hernandez et al[12] and Jiao et al[13] reported these results in their studies. One patient had a negative test due to lesional skin specimen. Another negative test for IgG was positive for C3, but the dermatopathologist pointed out to the diagnostic features of PF.

There was a correlation between anti-skin titre and disease severity. Similar results were reported by Judd et al[14] and Fitzpatrick et al.[15] However, as the correlation was not perfect, clinical follow up and assessment were equally important. In Hong Kong, the substrate employed for the anti-cellular antibodies is monkey oesophagus.

In comparison with a study in Singapore by Goon et al,[6] the yield for positive histology was higher in Hong Kong. This may reflect on the severity of the disease at presentation, high pick up rate by our pathologists or cases selection at the beginning of the study. Since the average of IIF titre was also higher, this represented a group of patients with more severe disease activities. However, the percentage of positive DIF was the same in both countries.

Treatment

Pemphigus foliaceus is a rare disease. There is no large controlled trial.[1,16-18] Pemphigus foliaceus is described as a chronic benign disease and responds to potent topical steroids.[1] In this aspect, it differs from the results of this study. Out of the 32 patients, only five responded to topical therapy and 27 were treated with oral prednisolone for disease remission. The average dose was 36 mg daily. As the build and body weight of local Chinese are lighter and adjuvants are introduced early, this is considered as a large dose, especially in the older patients. Unfortunately, the body weight of these patients was not available for comparison. Pemphigus foliaceus responded quickly to treatment in our patients. The average time to the first remission was short (1.23 months). The disease ran a chronic fluctuating course and required a low maintenance dose. This was reflected by disease free duration versus follow up time and the number of relapses per year. At

interview, 15 patients received oral prednisolone at an average dose of 9.7 mg daily.

In the Social Hygiene Service, the adjuvants employed were mainly tetracyclines, dapsone and azathioprine. There was no mortality for those taking azathioprine. Two out of five patients were in remissions (40%), in compare with a 28% reported by Bystryn et al.[16] For dapsone therapy, three out of four patients (75%) had active disease at interview and one had passed away. This implied that dapsone is not an effective drug. Four patients were put on antibiotic. Two responded and two required systemic prednisolone. As this study is uncontrolled, it is possible that a selection bias towards patients with a tendency of milder disease or spontaneous remission.

Prognosis

In this study, 6.25% of the patients died of the disease or treatment related causes. A similar result of 6.2% was reported by Bystyrn et al.[16] These patients passed away within three months of treatment. This was also reported by Rosenberg et al,[10] Seidenbaum et al[19] and Ahmed et al[20] in their studies. Therefore, when the disease was prolonged, the prognosis was better. The mean onset age for the deceased was 73.7, in sharp contrast to the 52.4 years for those who survived treatment. This means that the older patients have a less favourable prognosis. This was reported by Savin.[21] 40.6% of the patients were in remission, in compare with the 28.9% reported by Bystryn et al.[16]

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