Clinico-pathological analysis of autoimmune blistering disorders: experience in the central province of Sri Lanka

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Abstract

The knowledge about autoimmune blistering disorders has expanded significantly in the recent past. The management of this group of disorders has become easier with the new diagnostic methods and new treatment modalities which have emerged during the last decade. The studies on autoimmune blistering disorders are very sparse in Sri Lanka[1,2,3]. The aim of this study was to analyze the clinico-pathological profiles of patients with autoimmune disorders who attended the Dermatology unit, general hospital, Kandy over a period of 4 years from 1999 to 2003. This seems to be the largest sample of patients studied on the subject in Sri Lanka.

92 cases of autoimmune blistering diseases diagnosed on the basis of clinical, histological and direct immunofluorescence (DIF) were included in the study. The commonest auto immune blistering disease appeared to be pemphigus (P) (55.4%) with a mean age of 46 years. The disease was more common in females with a male: female ratio of 1:1.6. Bullous pemphigoid (BP) (25%) was the next common disease with a mean age of 54 years. In BP male to female ratio was almost equal. Linear Ig A disease (LAD) (14.1%) was the next common autoimmune disease observed in the study. LAD was the commonest auto immune blistering disease observed among children. Dermatitis herpetiformis(DH), Epidermolysis bullosa acquisita (EBA) and cicatricial pemphigoid (CP) were rare. A single case each from the above diseases was observed in this 4 year study. There were 2 cases of bullous LE (BSLE) during the study period. There was no cases of Herpes gestationis seen during this period. Majority of pemphigus patients were controlled with moderate doses of systemic steroids when combined with immunosuppressive agents.

Introduction

Immunobullous disorders are characterized by the presence of cutaneous and/or mucosal blisters, histologically by intraepidermal or subepidermal blister formation, and by immunopathology[4]. This group of disorders consists of pemphigus (P), bullous pem-phigoid (BP), epidermolysis bullosa acquisita (EBA), cicatricial pemphigoid (CP), pemphigus gestationis (PG), Linear IgA disease (LAD), dermatitis herpeti-formis (DH) and bullous systemic erythematosus (BSLE). This retrospective study covers 4 years from August 1999 to July 2003. The Dermatology Department in Teaching Hospital Kandy is the only hospital for dermatologic diseases in Central province of Sri Lanka, which has a population of 2.4 million.

Materials and method

The study sample consists of 92 patients of auto immune bullous diseases diagnosed clinically and confirmed by histopathologically and immunofluorescence at the department of oral pathology, Faculty of Dental Sciences, University of Peradeniya. Detailed clinical histories and treatment records were maintained for all patients. Direct immunofluorescence using IgG, IgA, IgM and C3 were performed on perilesional tissue. Salt split IF was performed for suspected cases of EBA.

Results

A total of 92 patients were diagnosed to have immunobullous disorders over a period of 4 years. Ages of these patients were ranging from 3 years to 87 years. There were 40 male patients and 52 female patients. All ethnic groups were represented in the study sample. There were 51 (55.4%) pemphigus patients, 23 (25%) bullous pemphigoid patients, 13 (14%) linear IgA patients and single case each of dermatitis herpetformis, Epidermolysis bullosa acquisita and cicatricial pemphigoid. There were 2 (2.2%) patients with bullous LE. Herpes gestationis was not observed during this period (Table 1).

Table 1. Spectrum of various AIBD: Total No: 92

Diagnosis	*No. of cases*	*% of total*
P	51	55.4
BP	23	25.0
LIAD	13	14.1
DH	01	1.1
EBA	01	1.1
CP	01	1.1
BLE	02	2.2
HG	00	00

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Table 2. Age and sex distribution of various AIBD

Diagnosis	*Mean age (Range) Years*	*Male: Female ratio*
P	46 (8-84)	1:1.6
BP	54 (3-87)	1:1.1
LIAD	20 (3-69)	2.2:1
DH	27	0: 1
EBA	16	0:1
CP	70	0:1
BLE	28 (25-32)	0:2
HG	-	-

Pemphigus. Pemphigus was found to be the most frequent autoimmune bullous disease during the 4 year study period. 51 patients with pemphigus were observed for the period of 4 years.

There were 20 male patients and 31 female patients with a male to female ratio of 1:1.5. All main ethnic groups were represented in our study.

In this study group of 51 pemphigus patients, pemphigus vulgaris (PV) was the commonest (48). Two patients had pemphigus foliaceus and one patient had IgA pemphigus. Age ranged from 8-83 years with a mean age of 45 years.

Duration of illness before diagnosis ranged from 1 week to 60 months with a mean of 6 weeks. IgA pemphigus was diagnosed initially as subcorneal pustular dermatosis. 5 years later, the diagnosis was confirmed as IgA pemphigus by DIP studies. All patients were treated with prednisolone with or without adjuvant therapy. Only 3 patients received prednisolone as monotherapy with an initial dose ranged from 45-60mg/day to control the disease. Ten (20%) patients were treated with Dapsone as adjuvant therapy which included two pemphigus patients and the IgA pemphigus patient. Azathiaprine was the commonest adjuvant therepy used in our patients. Twenty four (50%) patients who had generalized bullae were treated with Azathiaprine daily dose ranging from 50mg to l00mg/day in addition to prednisolone. Fourteen (27%) patients were treated with cyclophosphamide (50mg/day) and prednisolone. Seven (14%) patients with very severe disease were treated with monthly Dexamethasone and cyclophosphamide pulse therapy. Three patients who were young females of child bearing age group with severe disease were treated with Dexamethasone pulse therapy (without pulse cyclophosphamide) along with daily azathiaprine to control the initial disease.

Two patients were under complete remission at the end of 4 years. Number of relapses per patients ranged from 1-10. Commonest cause of relapse was found to be defaulting therapy.

Bullous pemphigoid. There were 23 (25%) Bullous pemphigoid patients included in this 4 year study. Twenty one (91%) BP patients had generalized disease and 2 (9%) had localized disease.

Duration before presentation ranged from 1 week to 12 months with a mean duration of 2 months. Oral mucosa was involved in 10 (44%) patients.

Histology revealed subepidermal blister formation. DIF was performed in all patients. Twenty patients showed linear deposision of IgG and C3 along the dermoepidermal junction. However 3 patients had only C3 positivity. IgA and IgM positivity seemed to be very rare.

A single patient has been treated with prednisolone as monotherapy. 17 patients were treated with Dapsone as an adjuvant therapy. Azathiaprine in 2 patients, cyclophosphamide in one patient and tetracycline in 2 patients were used as adjuvant therapy. Eight (34%) patients were in complete remission at the end of 4 years.

Linear IgA disease. There were 13 cases of LAD observed during the study period. This was the second commonest (32%) subepidermal bullous disorder in our study. There were 7 (54%) children under the age of 16 years. There were 6 (46%) adult patients. Duration of the disease at the time of presentation ranged from 1 week to 12 months. Two patients had oral mucosal involvement. DIP showed pathognomonic linear deposition of IgA at the dermoepidermal junction in all patients.

Ten patients were treated with prednisolone and Dapsone to control the initial disease. Prednisolone was gradually tapered and continued with Dapsone once the disease was under control. Two patients who were allergic to Dapsone were treated with prednisolone alone. Nine patients were at complete remission at the end of the study period.

Bullous systemic lupus erythematosus. Two patients had BSLE. Blisters were mainly on exposed sites. Both these patients had lupus nephritis with positive Anti-Ds DNA. Skin biopsy showed subepidermal blisters with mixed perivascular infiltrate. DIF showed Deposition of IgG, C3, IgA and IgM at the dermoepidermal

junction. With the increase of prednisolone dose and oral chloroquine therapy, rashes subsided within a few weeks.

Dermatitis herpetiformis. There was only a single case of DH. The patient presented with severely pruritic papules and vesicles. There were no symptoms of bowel involvement. Skin biopsy showed subepidermal blister formation with neutrophilic infiltration in the dermis. DIP showed granular positivity of IgA along basement membrane zone. Pruritus was subsided within few hours after starting Dapsone

Epidermolysis Bullosa acquisita. One patient presented with widespread blister formation with prominent post inflammatory leucoderma. There was evidence of oral and mucosal involvement. Skin biopsy showed subepidermal blister formation with mixed type of inflammatory cell infiltration in the dermis. Routine DIF studies showed Deposition of IgG, C3 and IgM deposition at the dermoepidermal junction. As we suspected EBA clinically, DIF was repeated with salt spilt skin. There was deposition of IgG, C3 and IgM on the dermal side of the salt split skin which confirmed the clinical diagnosis of EBA.

Cictricial pemphigoid. There was a single case of CP. There was only oral mucosal involvement. Skin biopsy showed subepidermal blister formation. DIF showed deposition of IgG, IgA and C3 at the demoepidermal junction. The disease was well controlled with cyclophosphamide and prednisolone therapy.

Discussion

Pemphigus

As in other Asian countries like India, China, and Malaysia pemphigus is the commonest autoimmune bullous disorder seen in Sri Lanka[5,6,7]. Previous studies done in Sri Lanka showed similar results[1,3]. This is in contrast to other reports from Western Europe and Singapore where bullous pemphigoid was the commonest auto immune blistering disorder[8,9,10]. Pemphigus vulgaris is the predominant variant as in India and other Asian countries[6,7]. Children were rarely affected by pemphigus. Definite female preponderance was observed as in previous study in Sri Lanka[1]. One patient had ocular myasthenia, while another developed SLE during follow up. There were no drugs or malignancies associated with our pemphigus patients.

Initial disease control was achieved with a lower dose of 30-75mg/day of prednisolone, compared to higher doses used in most other centers.

Azathioprine 50-100mg/day is an effective and relatively less toxic adjuvant in the treatment of PV. Monthly DCP pulse is effective in controlling the very severe disease and to reduce frequent relapses. Monthly dexamethasone without cyclophosphamide is a safe alternative in young females.

Steroid induced diabetes mellitus was the commonest adverse effect observed during therapy. Other adverse effects seen during therapy were hypertension, oral candidisis, psychosis, azathioprine induced hepatitis and pneumonia, cyclopospha mide induced febrile attacks and permanent amenorrhea.

Bullous pemphigoid

BP is the commonest subepidermal blistering disorder observed in the study. Approximately 6 new cases per year were seen at our hospital. More than 50% of our BP patient's onset of the disease was in fifth and sixth decade. In Most of the other studies onset of disease is around seventh decade. Oral involvement is commoner (43.5%) than the previous report from Sri Lanka. Sex incidence was almost equal. There were no associated malignancies in these patients.

Linear IgA dermatosis. LAD is less frequent than BP with more children involved. These figures are comparable to studies done in China[7]. LAD is rare in Western Europe and affecting mostly adults[8]. There was a clear male preponderance with a male to female ratio of 2: I was observed in our study. There was no history suggestive of drug induced disease. Unless the patient is sensitive to Dapsone it is the commonest drug used in our patients. Prednisolone was used in these patients to control the initial active stage of the disease.

Bullous systemic lupus erythematosus. BSLE is a transient blistering condition which occurs in the setting of SLE. Although BSLE is not related to the flare up of the systemic disease our patients had active disease with renal involvement.

Dermatitis herpetiformis. DH in association with celiac disease is rare in this population.

Epidermolysis bullosa acquisita. EBA is one of the rarest subepidermal blistering disorders in Western Europe is also rare in our study. Only a single patient was seen for the four year period.

Conclusion

Pemphigus is the most common autoimmune blistering disease with a definite female preponderance. Childhood pemphigus is rare. In majority of pemphigus patients moderate dose of systemic steroids in combination with immunosuppressive agents were adequate to control the initial disease.

Bullous pemphigoid is the commonest subepidermal blistering disorder affecting mainly around fifth and sixth decade. There were no associated malignancies. LAD is the commonest autoimmune blistering disorder in children. EBA, BSLE, CP and DH are less frequent while PG is very rare. Clinical and epidemiological features of autoimmune blistering disorders closely resemble those of other Asian countries than those of Western Europe.

It is compulsory to have advanced diagnostic techniques such as immunofluorescence in order to arrive at the definitive diagnosis as histopathological features may be similar in most subepidermal blistering disorders.

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