Sri Lanka College of Dermatologists (SLCD) Oration – 2008

# Autoimmune blistering diseases – a personal odyssey

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I deeply appreciate the honour bestowed upon me on being invited to deliver the SLCD oration this year. It was with some trepidation that I agreed to fulfill it. Today I consider it a privilege and I wish to thank the President and the council of the SLCD for extending this invitation. When I was asked to choose a topic, I reflected upon what I have been doing over the years.

I opted to do dermatology in early 1984, after completing my M.D. examination in Medicine in 1983.When I changed over from Medicine to Dermatology, I realized a difference. Instead of treating 'urgent' or 'stamped' patients I was looking after a set of patients with longstanding health problems and chronic suffering. Most skin diseases though not life threatening, result in long term suffering, disability and have an adverse effect on the quality of life.

There are few skin diseases which are potentially life threatening. Autoimmune diseases belong to this category. Though these diseases are comparatively uncommon, patients with these diseases were found in the Dermatology Ward of the General Hospital, Colombo (presently National Hospital of Sri Lanka) at any time of the year. Sometimes these conditions were severe and the management was problematic.

During that period, histology was the only helpful diagnostic tool available for the diagnosis of these diseases in Sri Lanka. However, in developed countries immunodermatology was a rapidly evolving subspecialty which included immunological diagnostic methods. This made me to select immunodermatology as my area of special interest when I applied for overseas training. I appreciate the encouragement that I received from Dr. D. N. Atukorale in making this decision.

Before sharing my experiences in immunological blistering diseases with you, I like to mention few facts about blistering diseases in general. A blister is defined as "circumscribed elevation of the skin containing fluid". Blisters can be located superficially or deeply in the skin or mucous membranes. Blisters can be caused by immunological or non immunological causes. The latter includes physical forces, infections, allergic reactions, drug reactions and hereditary conditions.

Immunological blistering diseases are a rare distinct group of blistering disorders. The onset of an autoimmune blistering disorder can be abrupt, causing anxiety to the patient and the family. Often these diseases run a prolonged course, characterized by exacerbations and remissions. Some of these diseases have a high mortality even at present. The gravity of the treatment related health problems also is significant. In autoimmune diseases the body produces antibodies against it's constituents. Autoimmune blistering diseases are organ specific autoimmune diaeases, where autoantibodies are directed against various constituents of the skin.

At this point, my memory goes back to my early days of training at the Department of Dermatology, John Radcliff and Slade Hospitals, Oxford, U.K. I remember Dr. (now Prof) Fenella Wojnarowska handing over an article from a journal to me. It was an article on epidermal basement membrane[1]. She emphasized the importance of understanding it well. At that time there was a remarkable interest in ultrastructure of the skin; various new molecules and antigens were still being identified.

The epidermal cells are joined to one another through desmosomes. In pemphigus antibodies are directed against desmosomal proteins. In all other autoimmune blistering diseases antibodies are directed at the constituents of the basement membrane. In bullous pemphigoid, autoantibodies react with 2 hemidesmosomal antigens. Target antigen in epidermolysis bullosa acquisita is located in the deepest part of the basement membrane, known as the sublamina densa. The precise location of some of the target antigens was not known at that time. By incubating in 1M Nacl, skin can be made to split consistently through lamina lucida[2]. Antibodies binding antigens in hemidesmosomes and upper lamina lucida can be differentiated from those that bind to antigens in sublamina densa by performing indirect immunofluorescence on split skin.

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**Linear IgA disease (LAD)**

This disease has been originally described as a separate clinical entity in 1975[3]. It shares features with other subepidermal blistering disorders. Childhood form of the disease known as chronic bullous dermatosis of childhood (CBDC) has an abrupt onset associated with fever and arthralgia, predilection for perioral and perineal regions and rosette shaped arrangement of blisters. In the adult form of the disease (LAD) annular arrangement of blisters is observed, but the abrupt onset and pattern of distribution noted in CBDC are not observed.

At that time it was not known whether these 2 forms of the disease share the same autoantigen or different antigens. Previous studies done in this regard had produced diverse results. In some studies LAD antigen resembled bullous pemphigoid (BP) antigen; in others it resembled epidermolysis bullosa acquisita (EBA) antigen.

With this background knowledge a research project was planned to study the tissue distribution and species expression of the antigens in CBDC and LAD, in comparison with those of BP and EBA. This project was carried out in the Department of Dermatology of Oxford and the Department of Immunofluorescence, Institute of Dermatology, London, U.K. It was with the kind permission of Prof. Martin Black that I was able to visit the Institute of Dermatology, London. The chief scientific officer there, Dr. Balbir S. Bhogal was of immense help to me in carrying out this project.

Indirect immunofluorescence using sera of adult LAD, CBDC, BP and EBA was performed using various human and animal tissues as suibstrates. Normal human sera were used as controls. This procedure was repeated several times to ensure the consistency of the results. Conclusions derived from the results of the research project showed that the adult IgA disease and chronic bullous dermatosis both share a common antigen. Further it was clear that it differs from antigens of BP and EBA.

Findings of this study was presented at many scientific meetings. A poster presentation based on this study received the "Gold Award" at the meeting of the American Academy of Dermatology in 1986. Subsequently it was published in the British Journal of Dermatology[4].

My interest in linear IgA disease continued. After I returned from U.K, for 2 years I worked at Teaching Hospital, Kandy, as acting Consultant Dermatologist. At that time a short paper on CBDC was presented at the sessions of Kandy Society of Medicine[5]. Subsequently another presentation on blistering diseases in Sri Lankan children was made by me at the meeting of the International Society of Dermatology held in Oxford, U.K.[6].

It described 13 children with blistering diseases; 11 CBDC, 1 BP&1 EBA. Children with CBDC were mostly of the preschool age group. Among the 11 children with CBDC, 3 had mucosal lesions. As immunofluorescent tests were not available in Sri Lanka at that time specimens of skin and sera were sent to the Institute of Dermatology, London. Direct immunofluorescence was positive in all 11. Indirect immunofluorescence was positive in 8. These findings were later included in a poster presentation titled "CBDC around the world"[7]. The findings of the recent series described from the Lady Ridgeway Hospital, Colombo are somewhat similar[8].

Adult LAD is comparatively rare. This too tends to remit in several years like CBDC. Drug induced LAD also is found in Sri Lanka. Unusual patients with LAD in my series include a young girl with dermal binding IgA disease who had mechanobullous features and a young male whose illness was associated with hepatospleenomegaly, anaemia, osteosclerosis and renal failure. The latter died several years after the onset of the disease.

**Epidermolysis bullosa acquisita (EBA)**

Within few months of my returning from U.K. in 1986, I was requested to give a lecture to the Sri Lanka Dermatology Association, on a topic of my choice. I selected EBA as my topic.

The first patient with EBA in Sri Lanka was diagnosed at that time. He was a 11-year old boy who presented with generalized tense blisters and oral erosions. Initially he had been treated as CBDC and BP, but the response had been poor. IMF studies (done in U.K.) confirmed the diagnosis of EBA. His antibody titre was very high. Inflammatory blistering gradually stopped and mechanobullous features appeared. After about 1 year the disease remitted. He never had any more relapses. Presently he is a healthy adult.

Subsequently I came across a series of patients with this condition. Disease associations found in my series include carcinoma of lung, autoimmune haemolytic anaemia, lupus erythematosus, and goiter. Like in U.K. EBA is a heterogenous disease in Sri Lanka also. In a poster presentation at the world congress of dermatology in 1992, I discussed EBA in Sri Lanka[9].

**Bullous pemphigoid (BP)**

Bullous pemphigoid accounts for 37% of all the patients in my present series of patients with autoimmune blistering diseases. When compared with the previous review[10] in 1997, there is a clear increase in the prevalence of BP. Though it is described as a disease of elderly 30% of our patients were less than 50 years of age. A slight female preponderance was noted. Association with malignancy was not evidenced. After undergoing skin grafting for a leg ulcer, an elderly patient developed BP, on the grafted skin and donor site.

Most patients were treated with daily oral steroids with tetracycline as an adjuvant. Irregular clinic attendance was common in this group. A considerable number was lost to follow up. Severe pemphigoid can be even fatal in the active blistering stage. EBA can mimic BP at this stage. Split skin immunofluorescence is of value in distinguishing between these 2 conditions. We treated some patients with severe BP with IV pulses of dexamethasone and cyclophosphamide. The response was satisfactory. These patients were more regular in follow up and experienced lesser side effects due to steroids.

**Pemphigoid gestationis**

During the period that I was working in Kandy I encountered a female with this exceedingly rare blistering disease. She started developing blisters in the third trimester. She gave birth to a healthy baby but experienced a severe postpartum exacerbation of the disease. It was successfully controlled with steroids and 2 months later she was free of disease. Both direct and indirect immunofluorescence done in U.K. were positive. Indirect test revealed high titre of IgG antibodies. This case too was presented at the Academic Sessions of the Kandy Society of Medicine[11]. Subsequently another patient with this rare condition was reported by Katugampola et al[12].

**Cicatricial pemphigoid**

An elderly female with this rare condition was seen in the General Hospital Colombo in 1987. She was having recurrent tense blisters in the submental region and longstanding visual loss due to corneal scarring. The skin lesions promptly responded to steroids but the visual loss was permanent. This was included in the dermatology case histories described in the *Ceylon Medical Journal*[13].

**Pemphigus**

This is the most common autoimmune blistering disease among Sri Lankan adults. It accounted for 59% of all autoimmune blistering diseases in 1996. However, in my recent series it accounts for 47%.

Out of the total of 261 recorded patients (from different stations where I worked) 227 were having pemphigus vulgaris. Pemphigus foliaceus is the next common type. There was a clear female preponderance. Most patients were in 30-60 year age group, 20% of the patients were less than 20 years of age.

Pregnancy is known to aggravate pemphigus. Postpartum exacerbations in pemphigus are well known. Over the years, several pregnant women with pemphigus were successfully managed. A 20-year old woman in the third trimester of her first pregnancy developed severe pemphigus. She was successfully managed with high dose steroids and repeated transfusions of fresh frozen plasma. She delivered a normal baby and is in remission 3 months later. Another mother with pemphigus gave birth to a baby with large flaccid blisters. The baby's general health was good and the skin lesions disappeared in 2 weeks time. This is the first time neonatal pemphigus was observed in Sri Lanka.

A young woman with severe muco cutaneous lesions of pemphigus was unresponsive to steroids. Investigations revealed an abdominal tumour. Indirect immunofluorescence on rat bladder confirmed the diagnosis of paraneoplastic pemphigus (PNP). Histology of the abdominal growth revealed an inflammatory myofibroblastic tumour. This was the first known case of PNP occurring in association with this rare tumour. It was reported in the *International Journal of Dermatology*[14].

Dexamethasone-cyclophosphamide pulse (DCP) therapy for pemphigus which was originally described in India[15] is increasingly used in Sri Lanka also since 1995. According to the drugs used and the time frame it is divided into stages. Stage 4 denotes total remission while stages 2 and 3 indicate partial remission. Stage 1 indicates disease that is still active.

Over the past 6 years 43 patients with pemphigus were treated with this regime at the NHSL. High dose intra venous cyclophosmide was not given in the case of younger patients who have not completed the families. The patients with less severe disease were managed on daily oral steroids. This group mostly consisted of those with mucosal dominant disease who were having recalcitrant skin lesions even after several years of treatment.

During a 6 year follow up period of 56 patients with pemphigus in NHSL, 4 deaths were recorded. Mortality of pemphigus ranges from 5-10%[1]. Those who died were found to have comorbid conditions such as diabetes and hypertension even before the onset of the disease. During the course of the disease they experienced multiple complications. One female with severe disease was treated with mycophenolate mofetil and plasmapheresis in addition to DCP. She developed recurrent venous thrombosis and died of a CVA, 3 years after the onset of the disease.

Management of autoimmune blistering diseases is a team work. For a long time histopathology was the only helpful investigation available for diagnosing these diseases. Over the years consultant pathologists have extended their support to us in this regard.

Immunofluorescence (IMF) was started in the Department of Immunology, Medical Research Institute (MRI) Colombo, In 1994. The Oral Pathology Department of the Dental Hospital, Peradeniya commenced the IMF in 1999. In 2005 SLCD organized a workshop on IMF, prior to the academic sessions of that year. Dr. Balbir Bhogal, the chief scientific officer of the IMF Department of the Institute of Dermatology, London was the chief resource person. A large number of consultants and trainees in dermatology and pathology participated in that. At present MRI receives a large number of specimens from a wide area of the country. At present only the direct IMF is done. The enthusiasm shown by Dr. Rajeewa de Silva, Consultant Immunologist and his team in organizing this service is commendable.

Now I have reached the end of my presentation. To end my narration on blisters I like to present this true story from the history of Buddhism[17].

A wealthy youth by the name of Tissa, became a monk with the idea of practicing meditation. He was staying at the Jethawana monastery where Lord Buddha also was residing, but he could not meditate as he became sick. Small boils or blisters of the size of mustard seeds appeared on his skin and enlarged to the size of *beli* fruits. Later those ruptured discharging fluid. His robes became sticky with blood and pus giving rise to an offensive smell. For this reason he was known as Putigatta Tissa (Tissa with a stinking body). Fellow monks abandoned him. Having noted his sorrowful plight, Lord Buddha approached him. He personally boiled some water to wash the clothes; soon other monks also joined and the sick monk was given a bath and his robes also were washed. After the bath, dressed in a clean robe the sick monk felt comfortable. Lord Buddha delivered a short sermon. The sick monk concentrated well and achieved Arahanthood. Shotly after he passed away. Very likely, Venerable Tissa would have been suffering from a severe blistering disease.

To conclude my oration I would like to emphasize the importance of care and attention necessary for the patients with blistering diseases. Timely intervention is crucial in saving them. Careful longterm management will enable them to live useful lives. In addition to advanced investigative facilities and better therapeutic options commitment of the dermatologists is vital in achieving this goal.

At this moment, it is with gratitude that I like to mention those who helped me. I thank Dr. D. N. Atukorale for his guidance and advice which created an interest in blistering diseases in me. Prof. Fenella Wojnarowska who introduced me to research in blistering diseases, and Dr. Balbir Bhogal who helped with IMF on many occasions deserve special thanks. I greatly appreciate the training that I received from my clinical teachers during my internship, post intern years, and the period of postgraduate training. I wish to thank the generations of medical officers and the other staff of the stations that I worked, for their kind assistance. Finally I wish to thank my family members for their unstinted support towards my academic activities over the years.

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