Paraneoplastic Pemphigus-Mixed Bullous Disease Type –Report of a Rare Blistering Condition with IgA Deposition

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A male patient of 55 years with generalized lymphadenopathy was diagnosed as Non-Hodgkin's lymphoma. After treatment with four cycles of combined chemotherapy of Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisolon (CHOP) the patient developed blistering lesions all over the body. Histological examination of lesional skin showed both suprabasal and subepidermal bullae. Direct immunofluorescence (DIF) test of perilesional skin revealed linear deposition of IgA, C3 and fibrin along the basement membrane zone (BMZ); and deposition of IgG both in the epidermal intercellular substance and along BMZ. Indirect immunofluorescence (IIF) test using patient's serum on normal human skin and Long-Evans rat urinary bladder showed linear deposition of circulating IgA along the BMZ. Protein electrophoresis on cellulose acetate membrane showed increased Gamma globulin fraction. This is a case of paraneoplastic pemphigus-mixed bullous disease type showing strong reactivity to IgA, which has not been described in literature.

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Introduction

The term 'pemphigus' refers to mucocutaneous diseases that are characterized by intraepithelial blisters, caused by a loss of normal cell-cell adhesion (acantholysis), and are associated with autoantibodies against cell-surface proteins of stratified squamous epithelium.[1] Blisters in patient with high titres of autoantibody with underlying neoplasms, most frequently lymphoma, are referred as paranneoplastic pemphigus. A case with clinical features, histologic and immunofluorescence abnormalities of pemphigoid and pemphigus with IgM paraprotein having underlying cancer was described as paraneoplastic mixed bullous disease.[2] A patient with paraneoplastic pemphigus-mixed bullous disease type showing strong reactivity to IgA is presented below.

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Case History

A 55 years old man from Munshiganj district, Bangladesh was admitted at the Medicine ward of the Bangabandhu Sheikh Mujib Medical University (BSMMU) Hospital, Dhaka on the 23rd June 2001 with complaints of multiple neck and axillary swellings. Physical examination of the patient revealed mild anaemia with generalized lymphadenopathy. The lymph nodes were discrete and non-tender.

The laboratory investigations showed haemoglobin 9.5 g/dL, platelet count $300x10^9$/L, blood urea 22 mg/dL and serum creatinine 0.7 mg/dL. X- Ray Chest (P/A view) showed left sided pleural effusion but sputum for AFB was negative and Tuberculin test also was insignificant. Ultrasonography of whole abdomen revealed lymphadenopathy. Fine needle aspiration cytology (FNAC) of cervical lymph node (June 26, 2001) showed features of non-Hodgkin's lymphoma (NHL), small cell type, and subsequently by histopathological examination of left axillary node confirmed as NHL, low grade (July 08, 2001).

The patient was treated with four cycles of Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisolon (CHOP) and six month later he presented with vesiculo-bullous lesion all over the body and clinically was suspected as a case of paraneoplastic pemphigus (Figure 1).

Histopathological tests done from lesional and perilesional skin for routine examination and direct immunofluorescence (DIF) test, respectively. Routine Hematoxylin and Eosin (H & E) stained sections revealed suprabasal clefts with few acantholytic cells and a small subepidermal bulla containing fibrin, neutorphils and small number of eosinophils (Figure 2 & 3). On DIF test, cryostat sections incubated with rabbit antihuman sera conjugated with FITC made by Medic Italy, showed linear deposits of IgA (++), C3 (+), fibrin (+) and focal deposits of IgM at basement membrane zone (BMZ). Faint deposits of IgG at BMZ and in epidermal intercellular substance were also seen. In indirect immunofluorescence (IIF) test, incubation of normal human skin with serum of the patient showed strong linear deposition of IgA and faint deposit of IgM along the BMZ. IIF test on Long-Evans rat urinary bladder sections also showed linear deposition of IgA along the BMZ (Figure 4). Protein electrophoresis on cellulose acetate membrane at pH 8.8 revealed raised gamma globulin level (27% , normal 12-18%).

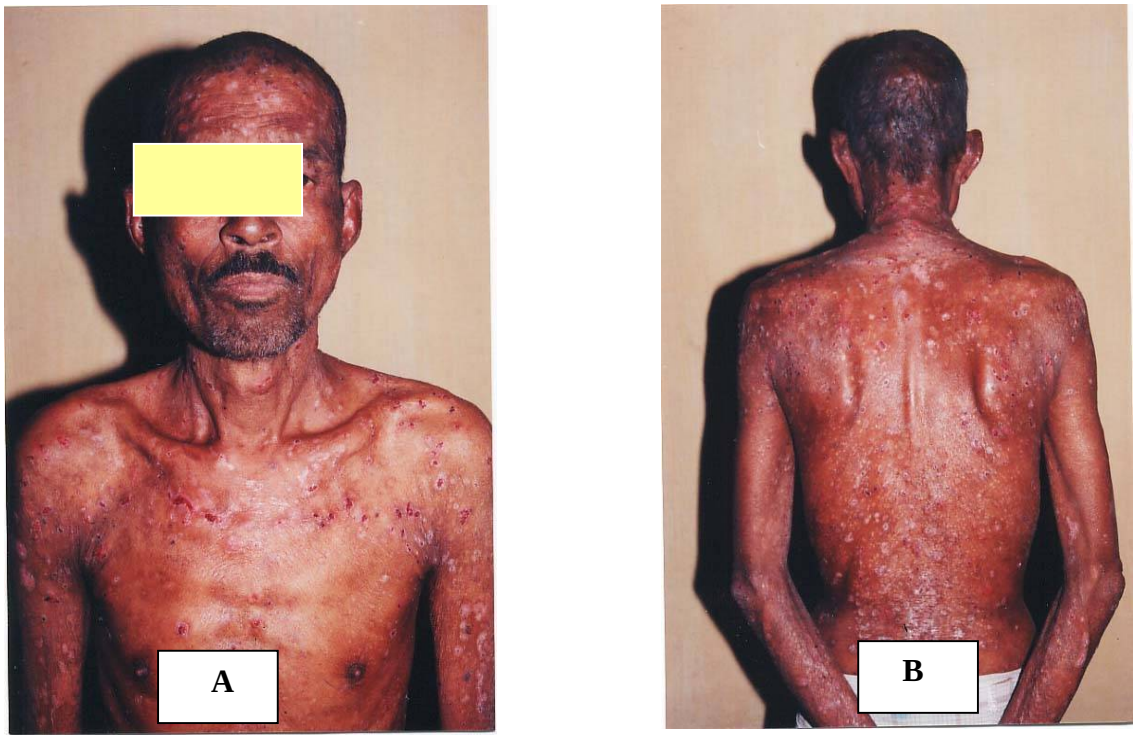

Figure 1. Blisters(healed) on front (A) and back (B) of the body

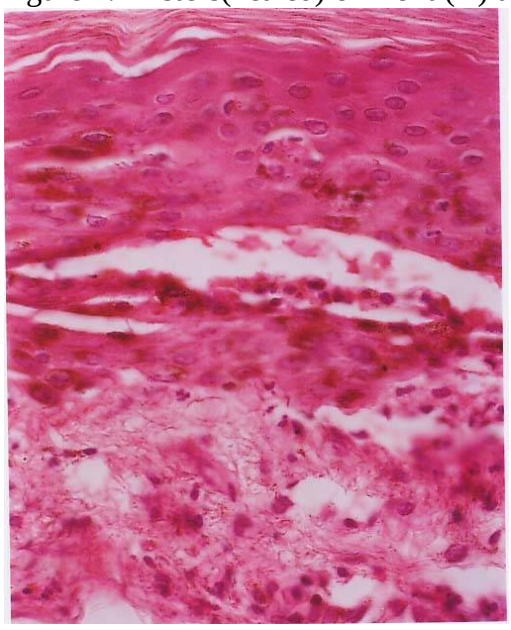

Figure 2. Small intra epidermal bulla with few acantholytic cells

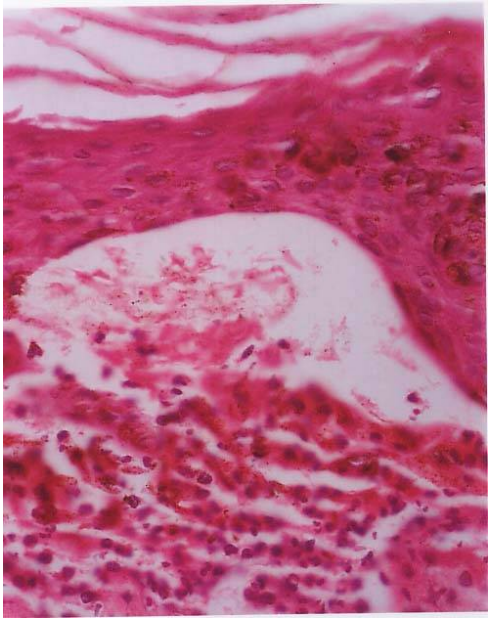

Figure 3. Sub-epidermal bulla containing fibrin, neutrophils and eosinophils

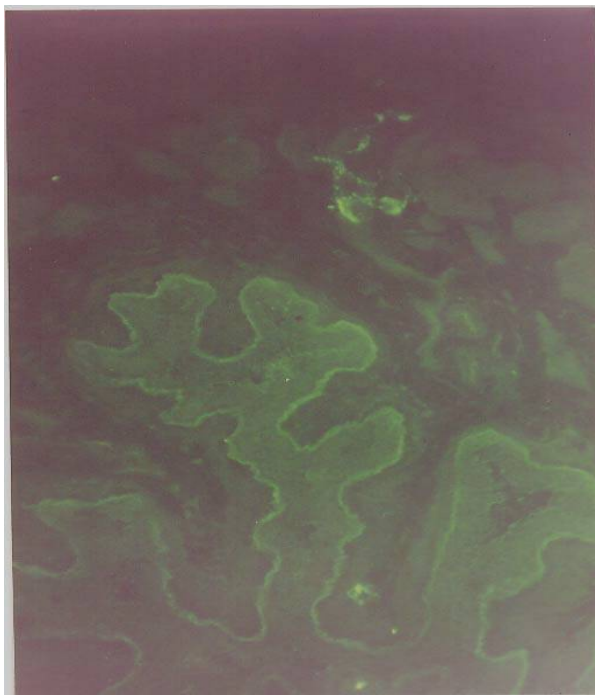

Figure 4. IgA along the sub-epithelial BMZ of Long - Evans Rat Urinary bladder

Discussion

Pemphigus is the disease, characterized by intraepithelial blisters, caused by a loss of normal cell-cell adhesion, and are associated with autoantibodies against cell-surface proteins of stratified squamous epithelia. Anhalt et al[1] first described paraneoplastic pemphigus in 1990. The authors reported five patients with underlying neoplasms, who developed oral erosions and bullous skin eruptions and described as paraneoplastic pemphigus. They suggested five criteria to define paraneoplastic pemphigus 1) Painful mucosal erosions, sometimes with a skin eruption that eventually results in blisters and erosions, in the setting of confirmed or occult malignancy 2) Histopathologic changes of acantholysis, keratinocyte necrosis, and interface dermatitis 3) DIF observation of immunoreactants, typically IgG and complement (C3) within the epidermal intercellular space as well as at the epidermal basement membrane 4) IIF observation of circulating antibodies specific for stratified squamous or transitional epithelia 5) Immunoprecipitation of a complex of proteins with molecular weights of 250, 230, 210 and 190-kd. The 250-kd and 230-kd antigens correspond with desmoplakin- I and bullous pemphigoid antigen respectively. Identities of 210-kd and 190-kd antigens were not known. They used rodent urinary bladder epithelium for the screening of paraneoplastic pemphigus as antigens of pemphigus vulgaris and pemphigus foliaceus are not expressed in this tissue. Later in 1993 Camisa and colleague proposed major and minor criteria for the diagnosis of neoplasia induced pemphigus.[3]

These are:

<u>Major criteria</u>

Polymorphous muco-cutaneous eruption

Concurrent internal neoplasia.

Characteristic serum immunoprecipitation findings

<u>Minor criteria</u>

Positive cytoplasmic staining of rat bladder epithelium by IIF

Intercellular and basement zone immunoreactants on DIF of perilesional tissue.

Acantholysis in biopsy specimen from at least one anatomical site of involvement.

A patient should be considered to have the neoplasia induced pemphigus if all three major or two major and two or more minor criteria are met.

In paraneoplstic pemphigus the tumour antigens evoke an immune response that is primarily humoral. The neoplasm does not appear to produce the autoantibodies in paraneoplastic pemphigus. Non-neoplastic B lymphocytes are probably responsible, as invivo-bound immunoglobulins are polyclonal.[3]

In the present case the lesions were polymorphous, crusted and vesicular eruptions all over the body and developed after treatment of

Non-Hodgkin's lymphoma. The lesions were both suprabasal with acantholytic cells and subepidermal representing mixed bullous lesion of pemphigus and pemphigoid. Bystryn and colleagues described a case with mixed bullous disease exhibiting combined features of cicatrical pemphigoid and pemphigus and associated with a B-cell lymphoma producing IgM paraprotein.[2] In DIF testing of present case faint deposition of IgG was seen in intercellular substance and along BMZ. Deposition of IgA was strong but it was seen along BMZ. The combination of intercellular and subepidermal deposition of immunoreactants is a clue to the diagnosis of paraneoplastic pemphigus.[4] Because circulating antibodies that bind to the cell surface of stratified squamous epithelia are common to all forms of pemphigus, other substrates, such as rodent bladder, is useful in distinguishing paraneoplastic pemphigus from pemphigus vulgaris or pemphigus foliaceus. Binding to rat bladder transitional epithelium is specific for circulating autoantibodies from patients with paraneoplastic pemphigus with a specificity of 83%. However, testing on rat bladder has a sensitivity of only 75%[4]. In present case the important antibody deposition was IgA and located along BMZ of rat urinary bladder, but no deposit is seen at intercellular space of bladder epithelium. These features are indicative of new entity not yet described previously. Bystryn and colleagues found that the IgM paraprotein was deposited to intercellular antigen of human skin but did not react to mammalian bladder in their case. In the present case two major and almost three minor criteria, for the diagnosis of paraneoplastic pemphigus proposed above, are met. We believe that this condition represents a novel bullous disease, and diagnosed as paraneoplastic pemphigus (mixed bullous disease type). Though the immunoprecipitation analysis is a standard diagnostic procedure for paraneoplastic pemphigus because it has higher specificity and sensitivity than IIF testing,[4] unfortunately as it is not widely available, is not done in this case.

Conclusion

Paraneoplastic pemphigus may present with variable features. The present case of paraneoplastic pemphigus has distinct features with autoantibody – IgA to some components of BMZ. Strong reactivity of IgA to BMZ illustrates a distinct bullous disease associated with paraneoplastic syndromes and at least one possible mechanism for such eruption is the production of anti-skin antibodies in patient with malignant B cells. However, definite nature of antigens remains to be explored and the full spectum of bullous disease associated with underlying cancers remains to be determined. As possibility of underlying malignancy including lymphoma is present in a small proportion of patients of pemphigus, complete physical examination and laboratory investigations are mandatory in cases of blistering disease[5] and IIF test with rat urinary bladder may be included in the suspected cases.

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