Generalized vesiculo-bullous and pustular eruption in an adult man

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CLINICAL FINDINGS

A 35-year-old man was presented to our clinic with generalized bullous eruption since 3 weeks duration. The condition was associated with mild itching but sometimes it was marked. The lesions started initially on the trunk since 8 months with slowly progressive course and gradual spreading into the face and extremities. There were no lesions on the mucous membrane along this time. The general condition of the patient was good except in the last few weeks when the lesions started to spread into the whole body, the patient complained from fatigue, loss of appetite, joint pain and generalized weakness.

There was no family history or history of previous similar attacks of such lesions. The patient denied any relation between the skin eruption and any drug intake and there was no history of any systemic illness. The patient received various topical medications without improvement. Systemic steroids (40mg prednisone / day) showed mild improvement but complete cure was not achieved along the duration of the disease.

Clinical examination of the patient showed generalized vesiculo-bullous and pustular skin lesions more distributed on the trunk and extremities (Fig. 1) and to lesser extent in the face, neck, axillae and genitalia. Newly erupted lesions were formed of flaccid bullae that showed different sizes. Old lesions showed superficial erosion and crust formation while few lesions showed accumulation of sero-pustular fluid (Fig. 2). Some lesions were erupted on normal skin while others appeared on erythematous skin. There were no lesions on the oral cavity while the scalp showed some crusted lesions and nail dystrophy was observed in two fingernails.

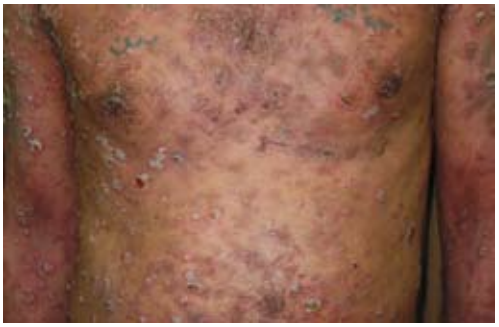

Fig. 1 Generalized vesiculo-bullous and pustular eruptions on the trunk and extremities.

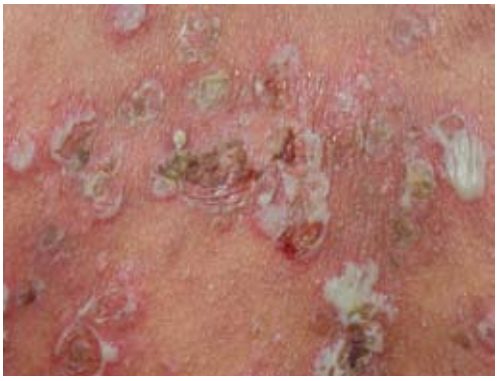

Fig. 2 Ruptured bullae with crust formation and intact flaccid bulla on the right side.

What is your clinical differential diagnosis?

Pemphigus vulgaris, IgA pemphigus, Pemphigus herpitiformis, Subcorneal pustualr dermatosis, Pemphigus foliaceus, linear IgA bullous dermatosis and acute generalized pustular dermatosis.

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Pathological findings

An incision skin biopsy was performed from the trunk. The biopsy included a newly eruptive blister with its adjacent skin. The skin specimen was bisected into 2 parts, the central part contained the blister while the peripheral part contained the adjacent skin. The central part was preserved in 10% formalin for routine H&E staining while the peripheral part was immediately freeze and processed for direct immunofluorescence examination.

Histological examination showed intraepidermal blister with dermal edema and superficial inflammatory infiltrate (Fig. 3). The roof and floor of the blister were formed of few layers of keratinocytes while the cavity was filled with inflammatory cells; mainly neutrophils with less number of eosinophils in addition to scattered acantholytic keratinocytes appeared as rounded cells with eosinophilic cytoplasm (Fig. 4). The dermal infiltrate was mainly superficial perivascular and showed considerable number of lymphocytes, neutrophils and eosinophils. The papillary dermis showed marked edema with few dilated blood vessels and minimal inflammatory infiltrate.

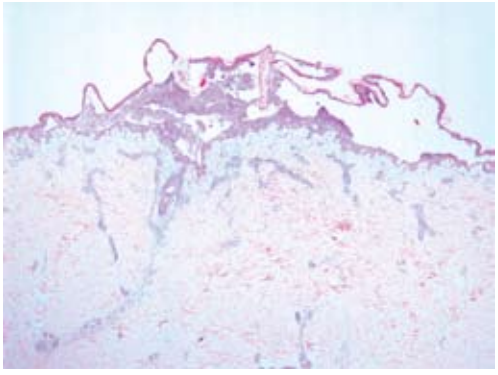

Fig. 3 Intraepidermal blister with dermal edema and superficial perivascular inflammatory infiltrate (H&E x40).

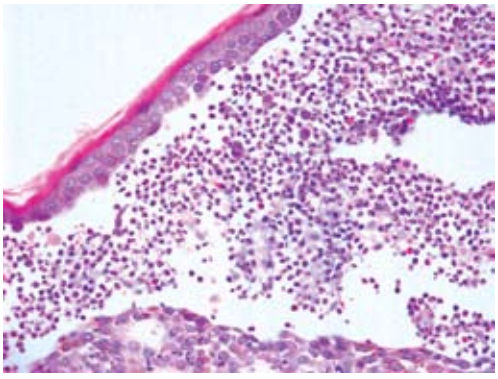

Fig. 4 The cavity of the bulla filled with neutrophils and eosinophils in addition to few scattered acantholytic keratinocytes (H&E x400).

Immunological findings

Direct immunofluorescence examination of the peri-lesional specimen revealed strong positive intercellular deposition of IgA in all epidermal layers (Fig-5) while IgG and C3 were weakly positive with focally faint staining.

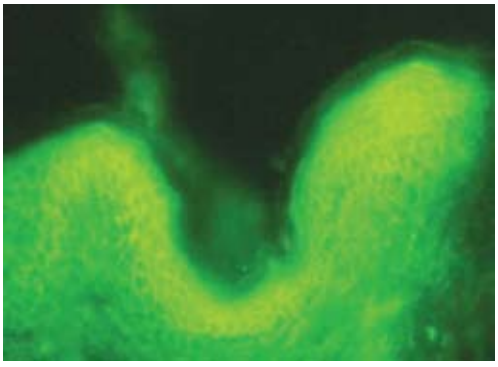

Fig. 5 Pan-dermal strong positive deposition of IgA in the intercellular spaces (DIF x100).

DIAGNOSIS

IgA Pemphigus

COMMENT

IgA pemphigus is a newly characterized immune-mediated intraepidermal blistering skin diseases which is related to pemphigus group but share some clinical and histological features with subcorneal pustular dermatosis. Many terms was suggested to describe this entity including IgA pemphigus, intraepidermal neutrophilic IgA dermatosis, IgA herpitiform pemphigus and intercellular IgA dermatosis. Although the immunological reactions in both diseases are different, still the

The clinicopathological challenges of IgA pemphigus

Diagnosis	Clinical	Pathological
Subcorneal pustular dermatosis	• More common in women during the 4th and 5th decades of life • It commonly involves the trunk, intertriginous areas, and the flexor aspect of the limbs • Face and mucous membranes are usually spared • The lesions are formed of flaccid pustules that may be surrounded by a transient zone of erythema	• A Subcorneal pustule filled with neutrophils with an occasional eosinophils • Acantholytic keratinocytes are not a feature of early lesions. • Spongiform pustules are not seen in the epidermis • DIF is usually negative
Pemphigus vulgaris	• More common in females • Oral blisters usually form the initial presentation • Presented with flaccid blisters on a normal or erythematous base • Commonly affect the trunk, groins, axillae, scalp, face, and pressure • Points • Positive Nikolsky's sign	• Suprabasal bullae with acantholysis • The basal cells giving a 'tombstone appearance' • The blister cavity usually contains acantholytic cells with eosinophils • The clefting may extend down adnexal structures • Eosinophilic spongiosis is common • IgG (class 1 & 4) and C3 deposits in the intercellular regions of all epidermis
Pemphigus foliaceus	• Usually presented with recurrent crops of flaccid bullae that readily rupture, resulting in shallow erosions and crusted erythematous plaques • Commonly affect the face and trunk • Generalized spreading is not uncommon • Mucosal involvement is rare • Stinging or burning sensation is sometimes present	• A Subcorneal blister with splitting of the granular or horny layer • The cavity of the blister contains fibrin, neutrophils and acantholytic cells • Eosinophilic spongiosis is uncommon but may be seen in African races • Neutrophilic spongiosis or pustules are rare • IgG and C3 deposits more localized to the upper layers of the epidermis
Dermatitis herpitiformis	• More common in males • Associated with intense pruritus • Presented with Flesh-colored–to–erythematous excoriated papules with small clustered vesicles. • Usually shows symmetrical distribution over extensor surfaces of the elbows, knees, buttocks, and shoulders. • Associated with gluten-sensitive enteropathy	• Papillary microabscesses is an important clue in the diagnosis • Collections of neutrophils and a varying number of eosinophils at the tips of edematous dermal papillae, • Subepidermal vesiculation with multilocularity • Acantholytic basal cell may also be found above the tips of dermal papillae • Intraepidermal collections of neutrophils may be present • IgA deposits in the dermal papillae as a granular pattern
Adult Linear IgA bullous dermatosis	• Drug-induced is common • Heterogeneous presentation including blistering, annular, crusted, herpitiform or hemorrhagic lesions • Usually affect the trunk and limbs • Pruritus or burning sensation are common symptoms • Mucosal involvement occur in 80%	• Subepidermal blister with neutrophils • Dermal papillary microabscesses may occur simulating DH • Eosinophils may be the predominant cells simulating BP but usually seen with drug-induced cases • IgA deposits in the basement membrane zone as a homogeneous linear pattern

relationship and overlap between both entities not fully identified.[1]

The frequency of the disease is not yet defined but it is more recorded in Japan, South America and Scandinavian countries. It usually shows a clinical course less severe than that of pemphigus vulgaris and adults are more affected without sex predilection.[2]

Clinically, the presence of both vesicular and pustular lesions are usually the commonest clinical presentation either arising on normal or erythematous skin. They usually distributed on the intertriginous areas but spreading into the trunk, extremities, face and scalp are common. The bullae are usually flaccid but flaccid pustules, verrucous plaques and oozing lesions may also present. Itching is a not common symptom in IgA pemphigus and mucosal involvement is rarely occurred.[3,4]

Histologically, the diagnosis is based mainly on the presence of intraepidermal blister filled with inflammatory cells, mostly neutrophils and mixed inflammatory cell infiltrate in the underlying dermis. However, the hallmark of the disease is the intercellular deposition of IgA in the epidermis. The classification of the disease into two distinct groups including subcorneal pustular dermatosis (SPD) type and intra-epidermal neutrophilic (IEN) type was proposed due to the presence of clinical, histological and immunological differences in both groups.[5,6]

SPD type is presented clinically with pustular lesions that may be confined to the intertriginous areas and histologically it shows subcorneal pustules with mild acantholysis and the deposition of IgA is usually limited to the upper layers of the epidermis. IEN type showed vesiculo-bullous lesions that rapidly evolve into eroded and crusted plaques which are more located on the trunk and extremities. This type showed intraepidermal blister with neutrophilic spongiosis and the deposition of IgA is usually present throughout the entire epidermis. The overlap of two groups was reported and this supports the notion that this is one disease with variable expression.[7-9]

The immunological studies of IgA pemphigus showed that circulating IgA antibodies could be detected only in 50% of cases while the combination of IgA and IgG may occur in some cases which are described as IgA/IgG pemphigus. The blister formation in IgA pemphigus is stimulated mainly by the intraepidermal accumulation of neutrophils caused by the specific binding of IgA autoantibodies for the monocyte/granulocyte IgA-Fc receptor (CD89). Desmocollin-1 has been identified as the target antigen in SPD type while desmogleins-1 or 3 were the implicated antigen in IEN type.[10-12]

Dapsone is the drug of choice in IgA pemphigus while response to systemic steroids is usually limited. Other therapeutic modalities that can be used alone or in combination with dapsone include Isotretinoin, clochicine, methotrexate, adalimumab and mycophenolate mofetil.[13-15]

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