

## THROMBOMODULIN OVEREXPRESSION SURROUNDING A SUBEPIDERMAL BULLOUS ALLERGIC DRUG ERUPTION

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### Abstract

Blistering drug eruptions and drug-induced anaphylaxis and hypersensitivity syndromes are among the most serious types of adverse drug reactions. We report a 69 old female patient who was using multiple medications and presented with a two month history of recurrent blisters, pustules and crusts. The patient was evaluated by a dermatologist, and biopsies for hematoxylin and eosin (H&E) examination, as well as for direct immunofluorescence (DIF) and immunohistochemistry (IHC) were performed. The H&E examination revealed a subepidermal blister with numerous luminal eosinophils, as well as a dermal superficial and deep, perivascular infiltrate of lymphocytes, histiocytes and eosinophils. The DIF revealed a linear positive staining on the subepidermal interior of the blister with IgG, IgA, IgM, IgD, Complement/C4, lambda light chains, fibrinogen, and albumin; staining was noted in the basement membrane zone, and also focally present around dermal blood vessels and eccrine glands. The dermal staining colocalized with anti-p0071 (Plakophilin 4). We also observed overexpression of thrombomodulin in adjacent epidermal keratinocytes, as well as in the upper dermal blood vessels; its presence may be linked to mitigation of inflammation. With the increased medications that many patients are taking orally and are using topically, overall drug reaction patterns seem to be more complex than previously described.

**Key words:** subcorneal blisters; drug reaction; drug-drug interactions

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### Introduction

Bullous or blistering drug eruptions and drug-induced anaphylaxis and hypersensitivity syndromes are among the most serious types of adverse drug reactions, especially within the senior patient population. Based on the underlying mechanisms, bullous drug eruptions has been previously classified into the following categories: spongiotic or eczematous, acute generalized exanthematous, fixed, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis [1-3].

### Case Report

A 66 year old female patient was seen by the dermatologist for a three month history of recurrent healing patches, and focal pain in her foot. The patient also reported itchy blisters, pustules and crusts on her back, extremities and foot dorsum for about two months. This patient was taking several oral medications for hypertension, diabetes, depression, hypercholesterolemia and osteoarthritis. Specific medications she was taking included pioglitazone hydrochloride (antidiabetic, Actos®), atorvastatin calcium (Lipitor®), alprazolam, aspirin 80 mgs /

day, tetracycline, clindamycin, and Diovan® HCT (valsartan/hydrochlorothiazide).

Skin biopsies for hematoxylin and eosin (H&E) examination, as well as for direct immunofluorescence (DIF) and immunohistochemistry (IHC) were performed.

Processing of biopsies for H&E examination, DIF and IHC was performed as previously described [4-6]. In addition to DIF antibodies with FITC conjugated markers, we also used an anti-multiepitope cocktail to p0071 from Progen, Germany, with goat anti-mouse Texas red conjugated goat anti-mouse IgG (H & L) as its secondary. Our case was IRB exempt because no patient identifiers were recorded, and no clinical pictures were taken.

Immunohistochemistry (IHC) staining was performed as previously described [4-6], utilizing antibodies obtained from Dako, including monoclonal mouse anti-thrombomodulin. We tested for this molecule based on the fact that it has been implicated in keratinocyte differentiation and wound healing.

In addition, thrombomodulin also acts to create activated protein C, generated from the cleavage of protein C by thrombin coupled to thrombomodulin [7,8].

Examination of the H&E tissue sections demonstrated a subepidermal blistering disorder, with partial re-epithelialization of the blister base. Within the blister lumen, numerous eosinophils were present, with occasional lymphocytes also seen. Neutrophils were rare. Dermal papillary festoons were not observed. Within the dermis, a moderately florid, superficial and deep, perivascular infiltrate of lymphocytes, histiocytes and eosinophils was identified. No evidence of an infectious, or a neoplastic process was seen.

DIF studies demonstrated the following results: IgG (+++, epidermal stratum corneum/acrosyringium and +, linear base membrane zone (BMZ); IgA (+++, epidermal stratum corneum/acrosyringium); IgM (+++, epidermal stratum corneum/acrosyringium); IgD (+++, epidermal stratum corneum/acrosyringium); IgE (+, focal papillary dermal perivascular and perineural); complement/C1q(+++,epidermal stratum corneum/acrosyringium); complement/C3(+++, epidermal stratum corneum and +, papillary dermal perivascular and perieccrine); Complement/C4 (+++, epidermal stratum corneum/acrosyringium); kappa light chains (+++, eccrine acrosyringium and surrounding epidermal stratum corneum); lambda light chains (+++,epidermal stratum corneum/acrosyringium); albumin (+++,epidermal stratum corneum/acrosyringium) and fibrinogen (+, epidermal stratum corneum, linear BMZ and papillary dermal perivascular, perineural and perieccrine) (Fig. 1, 2).

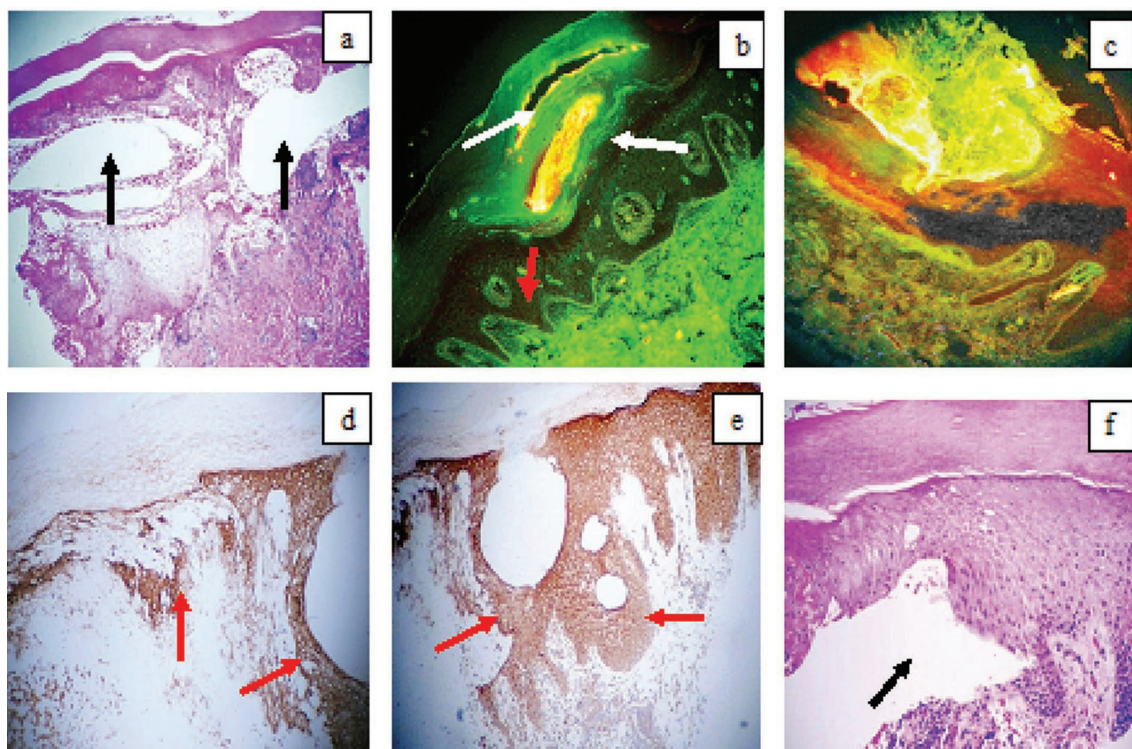
Following workup, the patient was instructed to visit her primary case physician, to try to decrease and/or change the

medications she was receiving. In addition, the patient was treated with topical Lidex® (fluocinonide) cream 0.05%, Diprosone (bethamethasone dipropionate) 0.05% cream, and Protopic(tacrolimus) 0.1% ointment, with satisfactory results.

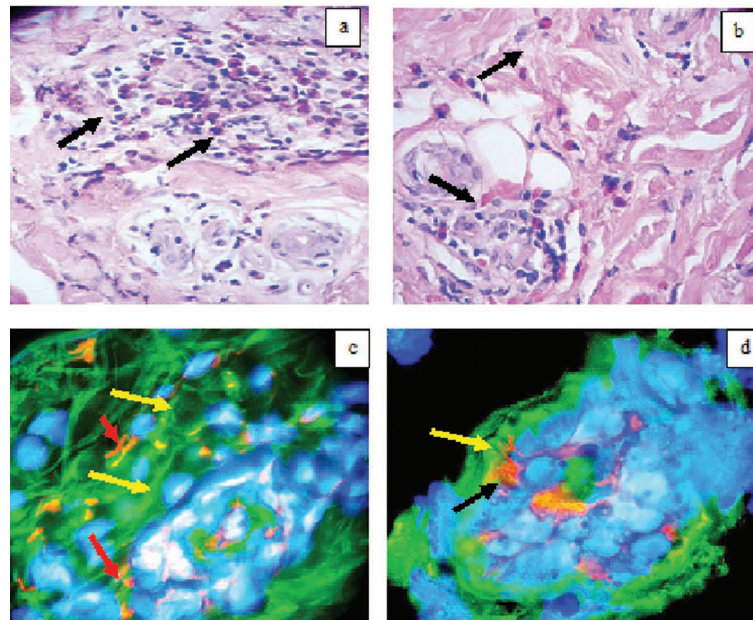
## Discussion

Allergic reactions may be serious and potentially life-threatening, and may cause injury to tissues throughout the body. Some people have hypersensitive immune systems that overreact to otherwise minor stimuli such as bee stings, foods, medications, and latex [2,3]. As the number of elderly patient's rises in many countries, drug-related iatrogenic complications are becoming increasingly important, and thus age-related changes in pharmacokinetics and pharmacodynamics of common medications is prevalent [1,4-6].

In drug reactions, significant localized inflammation is often present as well as recruitment of additional leukocytes. Scant investigation has focused on the role of thrombomodulin in allergic drug reactions. Thrombomodulin represents an endothelial cell surface glycoprotein, that inhibits the activities of thrombin and accelerates activation of anticoagulant protein C. Thrombomodulin has been associated with inhibition of leukocyte recruitment during acute inflammation. In our case, we were able to demonstrate the presence of thrombomodulin surrounding the inflammatory process. Thus, we suggest that in our case, the patient immune system is attempting to begin to decrease the in situ inflammation.



**Figure 1.** a H&E stain shows the large blisters (black arrows). b. DIF positive stain with FITC conjugated IgG demonstrates positive staining in a subcorneal blister (yellow staining; white arrows), some stain at the basement membrane zone as well as around the upper dermal blood vessels (green staining; red arrow). c. Utilizing DIF double staining with FITC conjugated IgG and rhodamine conjugated anti-IgA, the subcorneal blister was also positive for FITC conjugated IgG (yellow staining) and positive stain with rhodamine conjugated IgA (orange/pink staining). d and e. IHC positive staining with anti thrombomodulin demonstrates positive staining in the epidermis around the blister, and in the upper dermal vessels (brown staining; red arrows). f. H&E staining shows a subepidermal blister at intermediate magnification (200X)(black arrow).



**Figure 2. a and b.** H&E staining demonstrates an inflammatory infiltrate around dermal blood vessels and eccrine glands respectively, with multiple eosinophils present (black arrows). **c and d.** DIF positive staining around the upper dermal blood vessels using FITC conjugated anti kappa light chains (green staining; yellow arrows). The black arrow highlights an eccrine sweat ductus. We also used the antibody to p0071 conjugated to rhodamine to show colocalization with the blood vessels (red/orange staining, red arrows).

Moreover, thrombomodulin has been shown to be present in normal skin tissue, but appears limited to keratinocytes of the epidermal spinous layer [9]. In our case, thrombomodulin appears to be focally overexpressed; we suggest further study of this molecule and its role in additional allergic drug reaction cases.

All medical providers are thus encouraged to regularly review all medications, taken both systemically and topically, before adding new medications; especially in senior patients, these reviews will help to prevent cutaneous blistering allergic drug reactions [10].

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