Case Report

Furosemide Induced Bullous Pemphigoid Associated with Antihistone Antibodies

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An 81 year old man developed tense blisters on his abdomen and thighs several months after starting oral furosemide. Routine histologic studies revealed subepidermal bullae filled with eosinophils and neutrophils typical of bullous pemphigoid. Direct immunofluoresence studies revealed weak linear deposits of IgG and trace C3 along the dermal-epidermal junction along with a striking in vivo ANA reaction. ELISA studies to BP180 and BP230 antigens were negative although a low titer of IgG4 was noted in the blister roof on 1M NaCl split skin. A homogenous pattern of ANA on Hep2 cells was detected at a titer of > 5120. Antibodies to histone were very high when detected with ELISA. The clinical and pathologic findings are consistent with drug induced bullous pemphigoid. The associated drug induced lupus erythematosus-like immunopathologic findings are unusual and illustrate the broad range of changes that may occur. Furosemide induced bullous pemphigoid and the significance of antihistone antibodies in drug induced autoimmune disease will be reviewed.

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INTRODUCTION

Cutaneous drug reactions are common and may present with a wide variety of primary lesions ranging from erythematous macules to extensive desquamation. As many as 11.6% of patients in a medical intensive care may develop a cutaneous drug reaction during the course of their hospitalization.[1] Bullous and vesicular drug reactions are uncommon but well recognized manifestations of drug reactions. Some blistering eruptions are associated with well defined immunopathologic changes. Vancomycin induced linear IgA disease is perhaps one of the most widely recognized examples.[2] Drug-induced lupus also may have cutaneous involvement but has a lower incidence of cutaneous involvement when compared to idiopathic lupus erythematosus.[3,4] When cutaneous lesions occur in the setting of drug induced lupus, they are usually comprised of erythematous macules, papules, and papulosquamous lesions. Characteristic serologic and immunopathologic findings such as the presence of anihistone antibodies and the presence of anti-ssDNA antibodies aid in diagnosis.[3,4,5]

Bullous pemphigoid is an acquired subepidermal blistering disease typically affecting older individuals that is associated with antibodies directed at hemidesmosomal antigens BP230 (BPag1) and BP180 (BPag2).[6] Routine histologic evaluation reveals a subepidermal blister filled with eosinophils and neutrophils. Direct immunofluorescence (DIF) highlights IgG, C3, and other immune components in a linear pattern along the dermal-epidermal junction.[6] Indirect immunofluorescence (IIF) on 1 M NaCl split skin reveals immunoreactants on the blister roof.[7]

Drug-induced bullous pemphigoid was first reported in association with salicylazosulfapyridine.[8] Many drugs are now known to be associated with bullous pemphigoid, and furosemide is one of the most commonly encountered culprits (**Table 1**).[8-15] Antibodies are typically directed at the same antigens associated with idiopathic bullous pemphigoid.

Table 1. Drugs that may induce Bullous Pemphigoid.

Adalimumab	Amoxicillin
Ampicillin	Anti-TNF therapy
Bumetanide	Captopril
Celecoxib	Chloroquine
Ciprofloxacin	Enalapril
Enoxaparin	Fluorouracil
Furosemide	Ibuprofen
Iodine	Levofloxacin
Lisinopril	Penicillamine
Penicillin	Phenacetin
Psoralen UVA phototherapy (PUVA)	Salicylazosulfapyridine
Serratiopeptidase	Spironolactone
Terbinafine	Tiobtarit
Valsartan	

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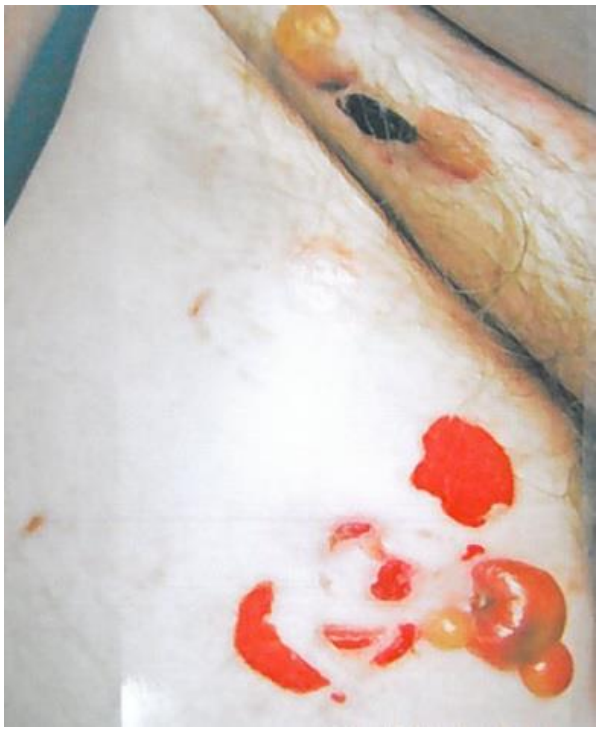

Figure 1. Tense bullae are noted in the groin area.

CASE REPORT

An 81 year old man presented for evaluation of an erythematous blistering eruption. His history was remarkable for diabetes, atrial fibrillation, cardiomyopathy, chronic obstructive pulmonary disease, chronic lymphocytic leukemia, pacemaker placement, and hip replacement surgery. His medications included warfarin sodium, losartan, digoxin, levothyroxine sodium, finasteride, tiotropine bromide inhaler, metformin, pantoprazole, atorvastatin, doxazosin, a daily multivamin, iron supplementation, and furosemide. He appeared ill, but was in no acute distress. He complained of pruritic lesions on the scrotum, penis, and chest. He had used nystatin cream for the lesions in the genital area without benefit. His height was 5'7" and his weight 77.7 kg. He was sent for dermatologic consultation where vesicles and bullae were noted on the chest, thighs, and groin area (**Figure 1**). Biopsy for routine histologic studies revealed a subepidermal blister with eosinophilia in a pattern typical of bullous pemphigoid (**Figure 2**). Therapy with oral prednisone at a dose of 30 mg daily was initiated in addition to epsom salt soaks.

Direct immunofluorescence revealed linear deposits of weak IgG and trace C3 at the dermal-epidermal junction as well as an in vivo ANA reaction, but a negative LE band test. Indirect immunofluorescence for IgG4 revealed antibodies binding to the epidermal roof of 1 M NaCl salt split skin (**Figure 3**). The dermal floor of the salt split skin was negative. Antibodies to BP180 were measured on an ELISA unit of 5.8. Antibodies to BP230 had a level of 8.1. Both of these were negative according to established controls in our laboratory.

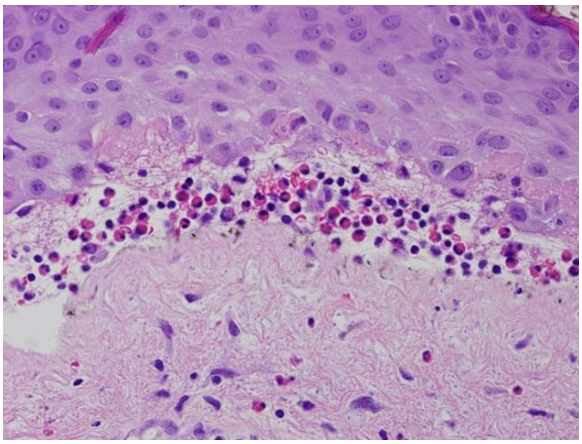

Figure 2. Biopsy reveals a subepidermal bulla filled with eosinophils. A few necrotic keratinocytes are noted and numerous eosinophils are evident in the blister cavity (Hematoxylin and eosin stained sections; original magnification 200x).

Laboratory evaluation revealed a positive antinuclear antibody (ANA) on HEp2 cells with a titer of > 5120 in a homogenous pattern (**Figure 4**). Mitotics were noted. Antibodies to histone were positive at 11.8 units on ELISA testing, but evaluation for antibodies to Ro (SSA) and La (SSB) were negative. Indirect immunofluorescence on monkey esophagus substrate revealed an ANA titer of > 1:80. Intercellular antibodies were negative.

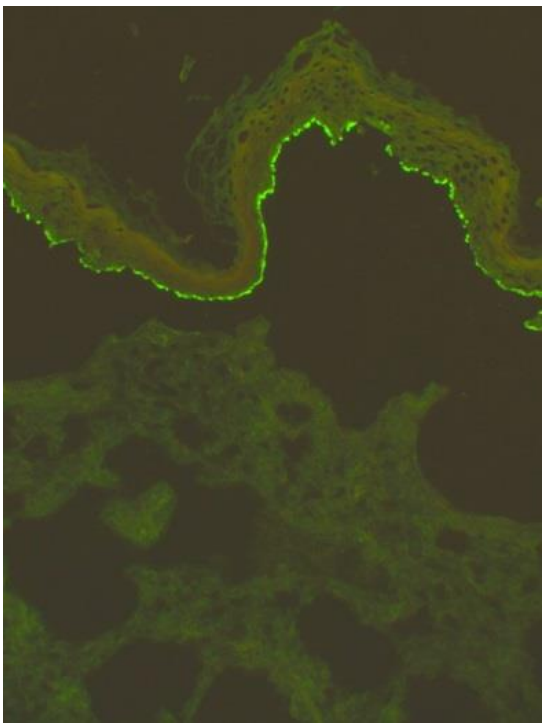

Figure 3. IgG4 split skin: Indirect immunofluorescence test for IgG4 antibodies on 1.0 M NaCl split skin revealing reactions with the epidermal roof. (original magnification 200x).

The clinical appearance of tense bullae on an erythematous base supported a diagnosis of bullous pemphigoid. Treatment with prednisone 30 mg daily for 6 days, and then 20 mg daily thereafter was associated with improvement.

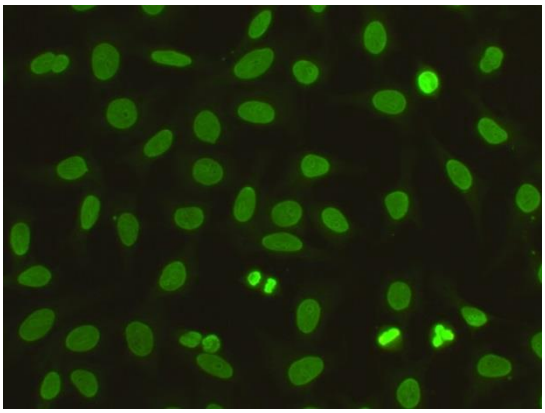

Figure 4. ANA test on HEp2 cells revealing a homogeneous pattern associated with mitotics. (original magnification 200x).

DISCUSSION

Drug induced bullous pemphigoid is associated with a variety of medications (**Table 1**). Although direct immunofluorescence findings are identical to those of idiopathic BP, routine histology may reveal a few subtle clues such as necrotic keratinocytes and increased intraepidermal vesicle formation when compared to the findings encountered in idiopathic BP.[16] The clinical course may vary. Some patients have their lesions resolve quickly after removal of the offending drug, whereas others have a protracted course that mimics idiopathic BP. Our patient showed good response to treatment and discontinuation of furosemide.

The striking ANA and high titer of antihistone antibodies noted in our patient are unusual. Although the immunopathologic findings raise the possibility that our patient might have drug induced lupus, his clinical picture, clinical course, and findings noted on routine histologic examination all indicate that he is best classified as having drug induced BP. Drug induced lupus is not only associated with antihistone antibodies and a positive ANA, typical cutaneous changes may be noted. Cutaneous findings may include leukocytoclastic vasculitis as well as a typical distribution of papulosquamous or annular lesions.[4] Drugs metabolized by acetylation have been most closely associated with drug induced lupus erythematosus.[4] Histone deacetylase inhibitors show promise as a treatment for lupus erythematosus.[17]

The presence of IgG4 antibodies in our case is interesting in the context of recent studies that illustrate type VII collagen antibodies present in a wide variety of autoimmune conditions.[18] Although drug induced bullous pemphigoid has typically been thought to exhibit identical immunopathologic findings with idiopathic BP, drug reactions are often complex and can be associated with varied autoimmune phenomena. Drug induced lupus (DIL) is more common in women, affects older individuals, and exhibits a predilection for African Americans.[4] Although ANA are often detected, ANA in DIL are much less likely to display complement fixing activity.[19] Epigenetic changes may play a role in how drugs impact the immune system. Histone acetylation and methylation of gene promoters can impact how genes are transcribed.[17]

The significance of the antihistone antibodies in our case is uncertain. The recent finding that the deacteylase inhibitor vironostat can be used to treat BP[17] indicates that the role of histone deacetylation and methylation of gene promoters may offer important insights into the pathogenesis of BP. The unusual findings noted indicate that additional immunologic changes may be occurring in some cases and that further study is needed to understand their significance.

CONFLICT OF INTEREST

There were no funding sources for this project.

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