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Case Report

Metformin induced bullous pemphigoid - A rare case report

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Abstract Bullous Pemphigoid (BP) is a chronic, acquired autoimmune skin disease. Exact etiology of this autoimmune process is not known. Certain drugs such as furosemide, penicillins, sulfonamides, ciprofloxacin, penicillamines, Angiotensin Converting Enzyme(ACE) inhibitors, chloroquine, etanercept, and phenacetin were reported to cause BP. Metformin is also a rarer one to cause BP. This is a case report of a 58-year-old female recently diagnosed with Type 2 Diabetes Mellitus (T2DM), started on Metformin, presented with the formation of few cutaneous tense bullae on both distal forearm. Clinical finding of skin lesions and direct immunofluorescence (DIF) finding were consistent with BP. To our best knowledge, this is among the very few cases of Metformin induced BP in the literature.

Key words
Bullous pemphigoid, Metformin, Direct immunofluorescence.

Introduction

Bullous pemphigoid (BP) is a chronic, autoimmune, sub-epidermal, blistering skin disease that occurs primarily in the elderly and is characterized by large tense blisters with immunopathological findings of linear deposits of C3 and IgG at the basement membrane zone (BMZ). The mechanism that leads to BP is not fully understood, but it is most likely to be an autoantibody-mediated damage to the epithelial BMZ, a complex structure that mediates adhesion, permeability, and cellular organisation and differentiation. Autoantibodies against two principal hemi-desmosomal proteins, bullous pemphigoid antigen 180 (BP180) and bullous pemphigoid antigen 230 (BP230), are strongly linked to the clinical disease.[1]

Autoimmune reactions triggered by exposure to certain drugs may thus be a cause of BP, as a result of the drug acting as an antigen in the basement membrane zone. Even though the strength of this association is uncertain,[2] many drugs, namely Furosemide, Nonsteroidal anti-inflammatory drugs (Ibuprofen), Captopril, Phenacetin, Penicillamine, Etarnacept, oral antibiotics,[3,4] gliptins and metformin[5,6,8] have been associated with BP. Metformin is an oral hypoglycemic agent of Biguanide class, which is the first drug of choice for the management of type 2 diabetes mellitus.[6] For the diagnosis of BP, clinical examination should be aided by histopathological examination, but a definitive diagnosis can be achieved only using Direct immunofluorencence (DIF).[7] Here we have reported a rare case of metformin induced confirmed by DIF.

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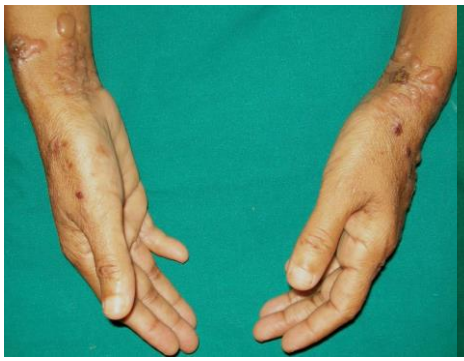

Figure 1 Showing few tense fluid filled and ruptured bullae on distal forearm around wrist area.

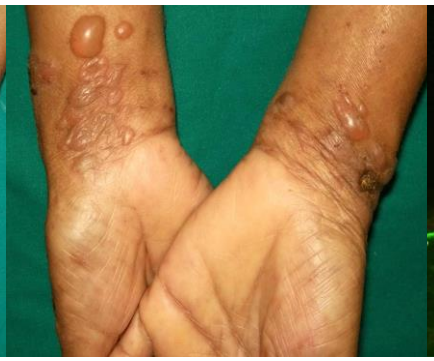

Figure 2 Showing few tense fluid filled and ruptured bullae on distal forearm around wrist area.

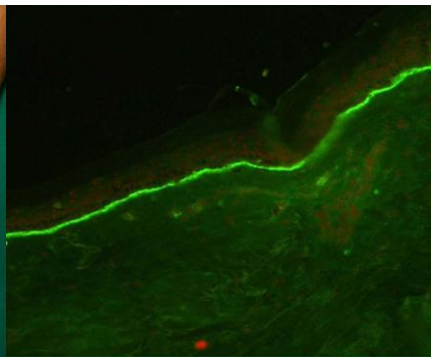

Figure 3 BP – DIF showing Linear basement membrane zone (BMZ) deposits of IgG.

Case Report

A 58-year-old female without other comorbidities diagnosed recently with Type 2 DM presented with few itchy tense bullae on erythematous base and few ruptured bullae with crusting over both distal forearm around wrist area and dorsum of hand **(Figure 1,2)** healed without scarring. There was no lesion on face, neck, oral mucosa or other parts of body. Two weeks back, she was started on Tab. Metformin 500mg twice daily after diagnosing diabetes mellitus. Her fasting blood sugar (FBS) was 160mg/dl, post prandial blood sugar (PPBS) was 240mg/dl and HbA1C was 8.2%. Complete haemogram was within normal limits. Lipid profile, Liver and Renal function tests were within normal limits. Urine routine and microscopic examination was normal. Her vitals were stable. She was not taking any other medication apart from the advised one. She had no prior history of any drug allergy.

A perilesional 4mm skin punch biopsy was taken from bulla on forearm and sent in Phosphate buffered saline (PBS) to the Department of Pathology where it was stained and examined under immunofluorescence microscope. DIF showed a linear deposit of immunoglobulin IgG along the basement membrane zone **(Figure 3)** confirmed our clinical diagnosis of BP. She was then started on topical clobetasol and oral doxycycline. Metformin was stopped and she was started on Gliclazide. The lesions regressed following the treatment. After a month of discontinuation of metformin, she reported remarkable improvement, all the lesions had resolved without any residual scarring.

Discussion

BP is an acquired autoimmune disease, characterised by sub-epidermal blistering,[3] that affects mainly the elderly people in the fifth to seventh decade of life with an average age of onset being 65 years. The incidence is between 0.2 and 3 per 100,000 person years. There is no known ethnic, racial, or sexual predilection.4 The mechanism that leads to BP is not fully understood, but it most likely involves autoantibody-mediated damage to the epithelial basement membrane zone, a complex structure that mediates adhesion, permeability, and cellular organisation and differentiation. Autoantibodies against two principal hemi-desmosomal proteins, antigen BP180 and BP230, are strongly linked to the clinical disease.[1]

Although in most cases the causative agent remains unidentified, certain medications have been implicated in the pathogenesis of the disease. The drug induced variant of BP follows

the oral or topical administration of specific drugs. It is difficult to differentiate clinically from classic BP. Hence, Drug induced BP must always be considered as a possible diagnosis in the elderly who have been started on new medications.[3] Several drugs have been implicated for the causation of BP that includes furosemide, nonsteroidal anti inflammatory drugs (NSAIDs; ibuprofen), captopril, phenacetin, penicillamine, etanercept, systemic antibiotics, gliptins and metformin in medical literature so far.[3-5] Metformin, being the first preferred and effective agent for the management of type 2 DM, is widely used. Metformin is not known to cause very severe adverse effects, apart from mild gastro intestinal upset and lactic acidosis. Several reports earlier have mentioned association of BP with gliptins however it must be noted that those patients were also taking metformin along with gliptins.[6,8]

Lesions in BP usually appear as tense bullae on normally appearing skin, or on an erythematous or even urticarial base. They may be accompanied by erythema multiforme type of lesions such as target lesions on palms and soles.[3] It predominantly involves the scalp, abdomen, extremities, axilla, and groin. Patients with BP may experience an episode or a recurrent bouts of lesions.[8] The bullae are usually filled with clear fluid but may be hemorrhagic. There is rarely oral and ocular mucosal involvement. The bullae usually heal with post-inflammatory pigmentary changes, and there is no scarring or milia formation.[4]

Patients with localized lesions of BP may be treated with high-potency topical steroids, such as clobetasol or betamethasone. Patients with more extensive disease require use of systemic corticosteroids alone or combined with immunosuppressive drugs such as azathioprine, cyclophosphamide, mycophenolate or rituximab. Patients with moderate disease can be treated with dapsone or tetracycline, doxycycline, or minocycline, which may be combined with niacinamide, minimizing the use of sterioids.[9,10]

Conclusion

In our clinical practice, the differential diagnosis of rarer entity of drug induced BP needs to be considered. The medical history especially the drug history, clinical acumen supported by DIF finding of linear deposits of IgG and C3 will help to clinch the rarer diagnosis. With discontinuation of the culprit medication, most patients respond rapidly to treatment and do not experience relapses. Several earlier reports have mentioned association of BP with gliptins, however it must be noted that those patients were also taking metformin along with gliptins6,8 and as in our case report, only metformin use has been rarely reported to cause BP in diabetes patient in medical literature.

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