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Alarming Sign to Physician on Prescribing Diabetic Medication (Gliptin with Metformin) which Causes Bullous Pemphigoid

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Abstract

Bullous pemphigoid is the most common autoimmune bullous disorder which mainly affects elderly individuals. BP classically manifests with tense blister over urticarial plaques on trunk and extremities accompanied by intense pruritis. It occurs when your immune system attacks a thin layer of tissue below your outer layer of skin. Since 2011, a growing number of observations has been reporting cases of BP in Type2 DM patients. Reason for abnormal immune response is unknown, although it sometimes can be triggered by taking certain medications. For several decades, metformin has used as an oral hypoglycemic agent, being the first line agent in the treatment of type 2 Diabetic Mellitus (DM) and use of new category of antidiabetic drug called dipeptidyl peptidase inhibitor (DPP-4i) or gliptins are also causing BP. A old male patient with known diabetic mellitus was presented to the inpatient department with complaints of seizure like activity with a history of itching, fluid filled blisters since 3months over lower limbs and gradually progressed to upper limb, face and abdomen. He was treated with corticosteroid local applicant, anti-histamine, vitamin supplement. Induced bullous pemphigoid has been associated with several drugs, but metformin is not one of them and combination of drug with gliptin where gliptin was a causative agent for drug-induced BP. Here I have reporting one such case of metformin with gliptin induced Bullous Pemphigoid (BP).

Keywords: Bullous Pemphigoid, Diabetic mellitus, Metformin, Gliptin, Corticosteroids.

Introduction

Bullous Pemphigoid is the most common type of sub epidermal autoimmune bullous disease characteristically affect the elder people. The etiology for what precipitates this disease is not entirely clear. Kridin and Ludwig (2018) the reported global incidence ranges between 2.4 and 21.7 new cases per million population per year, with many studies suggesting a rising incidence in the past two decades (De et al., 2023) the pathogenesis of BP can be explained by the presence of a dysregulated Tcell immune response and the synthesis of IgG and IgE autoantibodies against hemidesmosomal proteins (BP180 and BP230) involved in derma-epidermal cohesion ,leading to neutrophil chemotaxis and degeneration of basement membrane. Diagnosis may relay on clinical assessment and positive direct immunofluorescence microscopy and the quantification of circulating autoantibodies against BP180and BP230 using ELISA (Chouchane et al., 2021) .As it is a serious pathology requiring systematic and continuous treatment and its evolution is chronic and variable. The usual duration of period was 5 years, but mortality rate linked to this disease and its treatment. Its aggressiveness and treatment response may widely vary, there are no precise studies on the effect that BP may have on patients' lives (Molina-Guarneros et al., 2020) Type 2 diabetic mellitus is a chronic condition that is characterized by high blood sugar, insulin resistances. The body either doesn't produce enough insulin or it resist insulin (Attaway et al., 2014). BP induced by many drug, one of them is gliptin category, but metformin inducing are few (Wikipedia, (n.d.); Lashkar et al., 2020) which are anti -hyperglycemic agent of DPPI-4i and biguanide class, stimulate the release of insulin and reduce secretion of glucagon. (Yang et al., 2021) Dipeptidyl peptidase-4 inhibitors (DPP-4-i) can be used as monotherapy when metformin is contraindicated or not tolerated and some studies have shown benefits of metformin-DPP-4 inhibitor combination therapy in special populations. However, most often, they are prescribed in combination with metformin (Molina-Guarneros et al., 2020). Alone gliptin can induce BP where combination with metformin and prolong use even may have higher risk of dermatological reaction like BP.

Case Report

A 68year old male patient was presented with the chief complaints of seizure like activity -jerking of right upper and lower limb, frothing from mouth, mouth deviation to left, duration of 30mints, weakness in right upper and lower limb since 15 days with history of itching, fluid filled blisters since 3months over lower limbs and gradually progressed to upper limb, face and abdomen and he was treating on OP basis local territory hospital of Warangal region.

Collecting upon history noted that patient has Hypertension, Diabetic around 30yrs and on DM medication of Tab. ISTAMET [sitagliptin and metformin [50/500mg], Seizure disorder since 2yrs, old CVA -Rt hemiparesis since 2015, Psychiatric disorder around 3yrs.

Finding On Examination

General examination

On examination -patient was drowsy, arousable, afebrile, BP – 100/60mmhg,

PR- 103b/min, GCS – E4V1M4, pupils- B/L 3mm reactive.

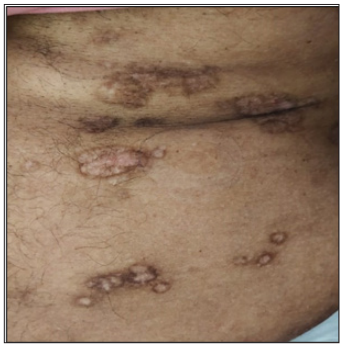
Laboratory Findings

All the routine investigations were performed and revealed Hemoglobin – 14.5 gm%, TLC- 12,500/L, Sr. K – 3.1, RBS – 162mg/dl.

Cutaneous examination

Was found to be healing bullae over body, lower limb and new blisters over face and noted eczematous rashes over thigh and scrotal region.

Below diagram I,II,III,IV shows healing of Bp over abdomen, Lt and Rt thigh ,Rt arm. V and VI diagram shows eczematous rashes over Lt thigh and Rt wrist region.



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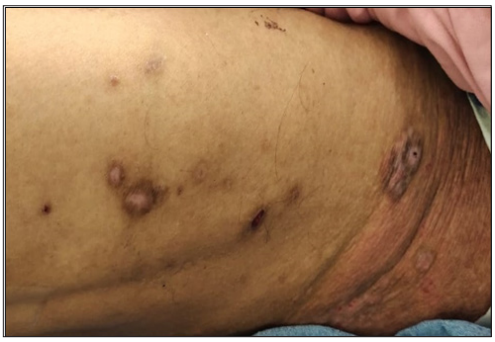

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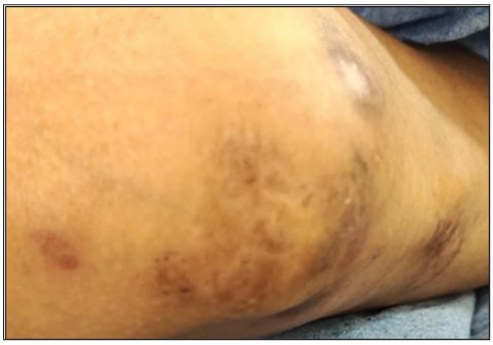

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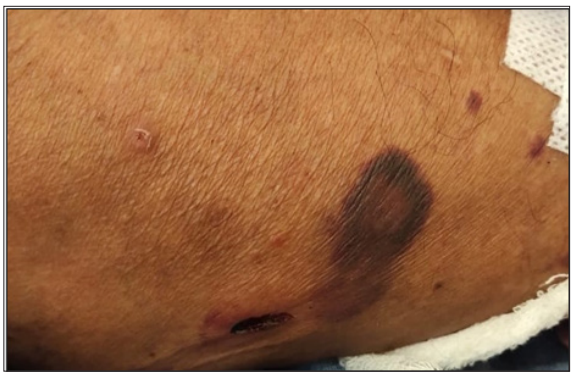

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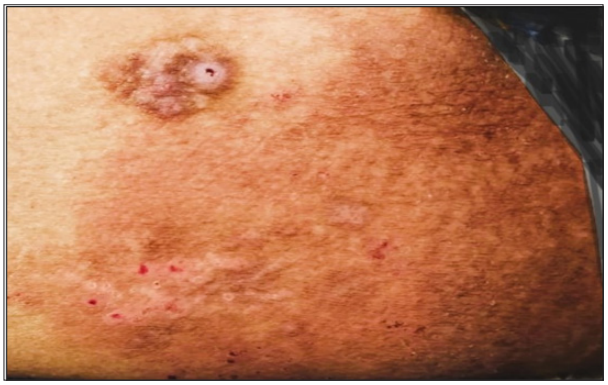
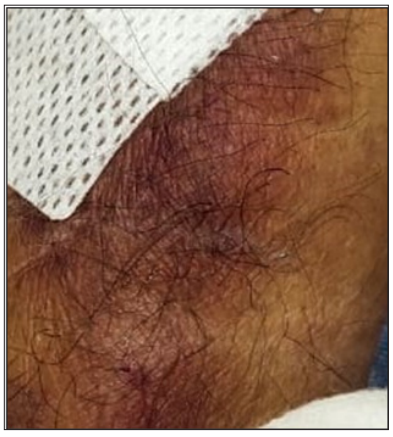


V



VI

Patient was on regular medication -on Tab. istamet more than 20year and changed into insulin human mixtard 26units SC OD since 1months.

During the course of hospital dermatology opinion was taken for new blisters and eczematous rash. Management of blisters include Tab. Atarax 10mg o.d, Tab .Ivepred 4mg b.i. d, Oint. Petrogel with clopinate gm local applicant t.i.d.

Day to day examination of GRBS was found to be on 2nd day-148mg/dl, 3rd day -163mg/dl, 4th day - 137mg/dl maintaining sugar levels with no oral and insulin correction.

Patient relieved from symptoms, no further seizure activity sensorium improved, blisters and rashes are healing well, he was discharged with advice to continue steroid, antibiotic creams and cetirizine, antiepileptic. On follow up visit, after a week the blister are healed without any scarring.

Disscussion

Bullouspemphigoid(BP)isablisteringskindiseasecharacterized by dysregulated T cell immune response and synthesis of IgG and IgE auto antibodies against 2-hemidesmosomal protein (BP-180 and BP-230) within in the dermal-epidermal junction. This disease develops characteristically in older people greater than 50years (Kridin & Ludwig, 2018). BPAG1 and BPAG2 resulting in deposition of IgG in basal cell-basement membrane region in a linear fashion way. BP is a serious pathology requiring systematic and continuous treatment (Lashkar et al., 2020). Drug induced bullous pemphigoid is difficult to differentially diagnose from its idiopathic counterpart, as the clinical picture and histopathological findings in both condition may only have subtle differences (Stavropoulos et al., 2014). The mechanism which is responsible for the development of BP has not yet been elucidated. Several drugs that induced BP are loop diuretics, spironolactone, penicillin, beta blockers, neuroleptics, and gliptins. But metformin has not been reported to cause BP only few case report has been suggested still now (Mukherjee, 2015; Cima, (n.d); Lashkar et al., 2020). DPP4 inhibitors are second line antidiabetic agent is a cell-surface glycoprotein with enzymatic activity that is expressed throughout the body including the skin. Various cell types, including keratinocytes and T cells, express DPP4, and its inhibition can increase the activity of numerous proinflammatory cytokines, leading to cutaneous eosinophil activation and blister formation (Forssmann et al., 2008). The underlying pathogenesis of metformin could be related to increase level of transforming growth factor beta (TGF β), increase in esnophilia level. Wikipedia (n.d.) Several reports suggested that BP is caused by gliptin, however it must be noted that patients who were also taking metformin along with gliptins can trigger BP and have higher risk (Skandalis et al., 2012). The latency period between the onset of BP and usage of the Tab. Istamet was relatively long in our patient, and this was also mirrored in previous pharmacovigilance studies ranging from 5 to 25 months (García et al., 2016). So this make a sense that physician and health care provider should be very caution while prescribing the combination or alone antidiabetic drug. If we neglect to monitor patient sugar levels or not taking proper history this will subsequently lead to a delay in diagnosis and delay in withdrawing the offending trigger (Armanious & AbuHilal, 2021). And also it make us to prescribe oral l form to IV insulin. Initially it raises the question of whether this is a drug-induced or drug-exacerbated phenomenon in those who are susceptible. Usage of correct dosage form of diabetic drug and regular checkup of glucose level, educating patient regarding drug complication and their side effects will help the physician to avoid such complications, if not diagnosed ultimate outcome could be fatal (Randhawa et al., 2020).

Conclusion

This report suggest the proposed association between gliptin with metformin and BP. The main drug of choice to treat type2 diabetes is metformin which is the safest drug but it can also cause rare complication like bullous pemphigoid with greater implication also many research articles were present regarding gliptin induced BP. Combination of both drug is even more worse for T2DM patient considering with their age. Furthermore, the elapsed time between initiate of the treatment with suspected drug and onset of skin manifestations varies considerably from case to case. Refinement of the lesions after withdrawal of the suspected drug confirms the diagnosis of drug-induced BP. Physician should be aware of this potential adverse effect. Early withdrawal of offending drug and timely detection can lead to swift improvement and decline morbidity. Abbreviations: BP – Bullous pemphigoid, BPAG –Bullous Pemphigoid Antigen, TGF β -Tissue Growth Factor Beta, DPP4- Dipeptidyl peptidase 4 inhibitor, GRBS – Glucose Random Blood Sugar, RBS – Random Blood Sugar, Tab – tablet , Oint – ointment, Inj – injection,T2DM- type 2 diabetic mellitus.

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Conflict Of Interest

The author declare no conflict of interests.

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