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**LETTER TO THE EDITOR**

# Hemorrhagic bullous pemphigoid developing after linagliptin

## Linagliptin sonrası gelişen hemorajik büllöz pemfigoid

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To The Edıtor,

Diabetes mellitus (DM) is characterized by elevated blood glucose levels and impaired metabolic status. It is diagnosed in approximately 1 in 11 people worldwide[1,2]. Diabetes mellitus (DM) is a multifactorial condition managed through diverse treatment approaches. Crucial steps in its management include regular exercise, weight loss, and lifestyle adjustments[3]. Among the pharmacological treatments utilized for specific conditions, there are several well-established drug categories, including insulin, biguanides, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, glucagon-like peptide-1 agonists, dipeptidyl peptidase IV inhibitors (DPP-4 inhibitors), selective amylinomimetics, and sodium-glucose transporter-2 inhibitors. It is important to note that these drugs bring about varying mechanisms of action, and their use should be tailored according to specific metabolic needs[4].

Linagliptin is an orally administered inhibitor of the DPP-4 enzyme to treat patients with type 2 diabetes mellitus. It reduces hemoglobin A1C levels in patients who receive either monotherapy or combination therapy [5]. Some frequently seen side effects include a rise of 3% in urea levels and a three-fold increase in serum lipase levels. Nasopharyngitis happens at a rate of 7% while coughing is noted in 2% of occurrences. Furthermore, arthralgia, dermatological responses, cardiac failure, and hypersensitivity reactions are reported [5-7]. This report outlines a case where the intake of Linagliptin caused a side effect of hemorrhagic atypical bullous pemphigoid.

The emergency department received a 68-year-old woman complaining of itchy and swollen skin lesions on her body (Figure 1, 2). She had a medical history of type 2 diabetes mellitus, chronic kidney disease, and hypertension. The patient denied using alcohol or smoking and informed regularly using subcutaneous insulin, linagliptin, and propranolol. Linagliptin therapy commenced three weeks ago. Although not undergoing renal replacement therapy, she had stage 5 renal failure.

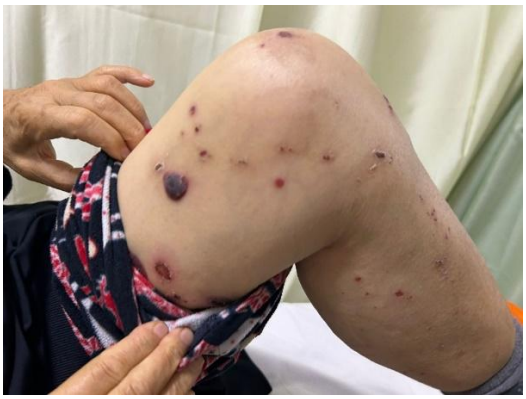

**Figure 1. Hemorrhagic bullous pemphigoid rash, lower extremity.**

Due to itching, the patient began treatment for suspected scabies at the dermatology clinic a week prior. The treatment administered comprised Goudron Vegetal and sulfur-containing ointment

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and shampoo. Additionally, the patient underwent oral ivermectin therapy.

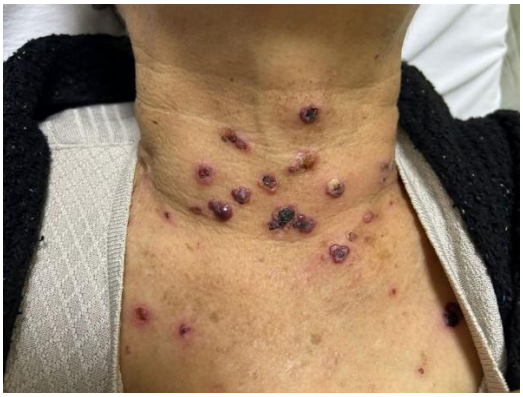

**Figure 2. Hemorrhagic bullous pemphigoid rashes, neck**

Upon admission, the patient's vital signs were recorded as follows: a systolic blood pressure of 100 mmHg, diastolic blood pressure of 70 mmHg, heart rate of 84 beats per minute, respiratory rate of 16 breaths per minute, and a body temperature of 36.9°C.

During the examination, fluid-filled lesions were identified on the neck, nape, trunk, and thigh regions. The oral and genital mucosa displayed a normal appearance. Eroded and hemorrhagic bullae were intermittently observed in the areas identified, and the Nikolsky sign was negative.

The patient's total blood count revealed a white blood cell count of 10.96 x10^3, hemoglobin of 7.9 g/dl, and platelets of 293 x103 microliters. The biochemical results exhibited INR of 1.2, CRP level of 45.6 mg/l, BUN level of 74 mg/dl and a creatinine level of 7.45 mg/dl.

Consultations with the dermatology and internal medicine departments were prompted by the patient's condition, which was considered a side effect of linagliptin usage. The dermatology department planned a biopsy for the lesion. The internal medicine unit decided to discontinue the medication and recommended outpatient follow-up. The punch biopsy yielded a sample of 0.2x0.2x0.1 cm. Subsequent examination by the pathology unit revealed subepidermal separation on microscopic sections, consistent with clinical findings indicative of bullous pemphigoid (Figure 3). To alleviate the patient's itching, they were discharged with a prescription for a topical ointment containing lidocaine and zinc oxide and oral tablets of diphenhydramine.

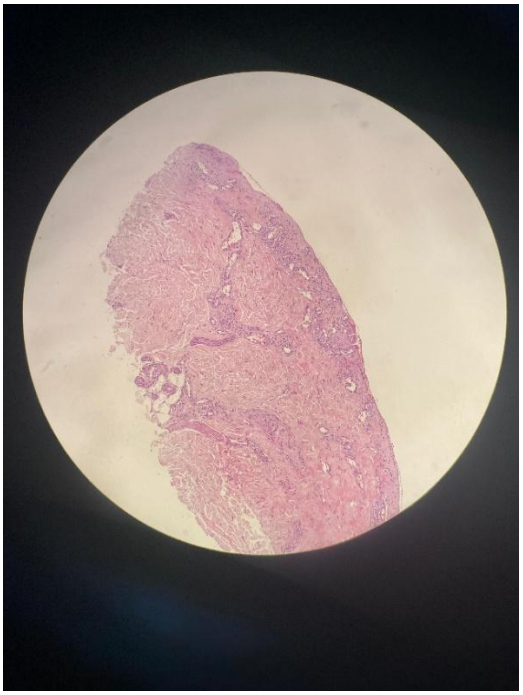

**Figure 3. Punch biopsy, microscopic view, bullous pemphigoid.**

Bullous pemphigoid is frequently observed among elderly individuals and manifests as tense, bullous lesions accompanied by widespread itching[8]. The condition usually lasts several months to five years and necessitates treatment for symptomatic patients. It can be triggered by infections or as a side effect of treatment. That can lead to severe and deadly outcomes[9].

Hemorrhagic bullous lesions have diverse causes due to their intricate formation. This condition presents a higher incidence of life-threatening consequences in comparison to other types of bullous lesions resulting from medications, infections, autoimmune disorders, and vascular issues[10].

Bullous pemphigoid has been reported as a side effect of DPP-4 inhibitors in numerous previously published case reports. This condition has been associated with elevated cytokine levels from skin cells and mechanisms relating to tissue differentiation and collagen[6,11]. In our case, the patient presenting to the emergency department with prolonged complaints demonstrates an atypical manifestation of

side effects related to the use of DPP-4 inhibitor. While bullous pemphigoid typically does not lead to mortal or morbid consequences unless there is an infection, this hemorrhagic form resulting from a subepidermal pathology might extend into a more morbid and mortal outcome with prolonged exposure. DDP-4 inhibitors like Linagliptin result in various skin lesions. However, it is worth noting that the effects of these drugs may not always match anticipated outcomes, and in certain instances, they could result in perilous consequences.

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