

CASE REPORT

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Vildagliptin induced cutaneous leukocytoclastic vasculitis: A case report

Serhat Sayin¹, Ethem Omeroglu², Semra Aslan Bilgin³

¹Department of Internal Medicine, Training and Research Hospital, Aksaray University, Aksaray, Turkey

²Department of Pathology, Training and Research Hospital, Health Sciences University, Konya, Turkey

³Department of Dermatology, Training and Research Hospital, Health Sciences University, Konya, Turkey

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Abstract

Vildagliptin is a new generation therapeutic agent of diabetes mellitus which belongs to dipeptidyl peptidase-IV inhibitor class acting via the incretin hormone system. It has moderate glycemic efficacy, a low propensity of causing hypoglycaemia and it is weight neutral. Overall, Dipeptidyl peptidase-4 (DPP-4) inhibitors are well tolerated. The use of DPP-4 inhibitors has been associated with a slightly increased risk of upper respiratory tract infections. In this article, we report a case of cutaneous leukocytoclastic vasculitis due to probable vildagliptin usage. Vildagliptin which is associated with cutaneous leukocytoclastic vasculitis was not described in the literature before. Physical examination revealed skin rash in the abdomen and thigh region in our patients due to use of the drug. Discontinuation of the drug eliminated the skin rash immediately.

Keywords: Vildagliptin, vasculitis, diabetes mellitus

Introduction

Incretin-based therapy is one of the new promising treatments for type 2 diabetes mellitus, and has recently become a first-line drug. Although the side effects do not often appear with this class of drug, several adverse events have been reported so far [1]. Here, we report a case of drug-induced skin eruption with strong itching nearly 9 months after initiation of vildagliptin.

Case Report

A 54-year-old male patient was followed-up with type 2 diabetes mellitus and coronary artery disease. The patient applied to our outpatient clinic for skin rash that developed in his body due to drug use. He had a type 2 diabetes mellitus diagnosis 4 years ago and premix insulin was started. He applied for glycemic control one year ago. He was using premix insulin at that time and HbA1c level was 11,3%. Intensive insulin therapy was started. In addition, metformin 1000 mg (twice a day) and vildagliptin 50 mg (twice a day) were added to the treatment. The patient continued to use drugs (Rosuvastatin 10 mg, ramipril 10 mg, acetylsalicylic acid 100 mg, bisoprolol 10 mg) for coronary artery disease and diet and exercise therapy. In the last 3 months, itchy maculopapular lesions developed in the thigh region and abdominal region (Figure 1). The patient cut out all the medication and he used and tested it individually.



Figure 1. Maculopapular lesions on the thigh and abdominal region

He noticed that the skin lesions and itchiness increased with the use of vildagliptin. The skin rashes and itching rapidly disappeared with the pill cut. He took vildagliptin several times in the last 3 months and skin rashes and itchiness increased every time. He applied for the regulation of his treatment. His physical examination was normal except for skin rashes. Hyperpigmented stains remained on the healing lesions. There was no fever and coughing. There was no different drug (Antibiotic, non-steroidal anti-inflammatory drug etc) used in the last 3 months. He did not use antihistamine drugs. There was no evidence of infection in the last 3 months (gastroenteritis, urinary system infection, upper respiratory tract infection). In laboratory tests: Fasting plasma glucose: 185 mg/dL, Creatinine: 0,99 mg/dL, HbA1c: 7,5 %, Wbc: 7,8 IU/L, HGB: 14,5 U/L (gr/dl), Plt: 360 103/μl, the percentage of eosinophil was 4,6 %. Tsh: 1,89 μIU/L, Crp: 3 mg/l, Sedimentation: 1 mm/hr, AST/ALT: 33/26 U/L, ANA (Anti nuclear antibody): Negative, Hepatitis serology (Hbsag, Anti HCV): Negative, Anti HIV: Negative, RF (Romatoid factor): Negative, Complement

*Corresponding Author: Serhat Sayin, Department of Internal Medicine, Training and Research Hospital, Aksaray University, Aksaray, Turkey
E-mail: drserhat_sa@hotmail.com

(C3, C4) level: Normal. The patient consulted a dermatologist and skin biopsy was suggested. Skin biopsy was performed with the patient's consent. The biopsy was compatible with cutaneous vasculitis. Vildagliptin was removed from the patient's treatment. The treatment was regulated as intensive insulin and metformin. Skin lesions and itchiness gradually decreased in follow-up.

Discussion

Vildagliptin is a highly selective and reversible substrate-like Dipeptidyl peptidase -4 (DPP-4) inhibitor. It increases concentrations of active GLP-1, promotes glucose dependent insulin secretion from pancreatic β cells and reduces glucagon secretion from α cells. It was demonstrated that the risk of weight gain and hypoglycemia was lower by means of vildagliptin plus metformin combination therapy. Besides, it was seen that this combination therapy reduced fasting plasma glucose, postprandial glucose and glycated hemoglobin (HbA1c) levels.

In our patient, with treatment change HbA1c decreased from 11,3 % to 7,5 %. There was no hypoglycemia.

Vildagliptin plus metformin combination therapy improves glycemic control in type II diabetic patients with favorable safety and tolerance levels [3,4]. Metformin may increase GLP-1 synthesis, whereas vildagliptin inhibits DPP-4 and increases activated GLP-1 levels. Therefore, the synergistic effect of vildagliptin and metformin maximizes activated GLP-1 levels and further increases insulin secretion and sensitivity [5].

Leukocytoclastic vasculitis was first described by Pearl Zeek in 1950 as vasculitis in small vessels after drug ingestion and it is called hypersensitivity vasculitis.

Leukocytoclastic vasculitis is a disease characterized by the inflammation of small vessels⁶. In the clinic, palpable purpura is a typical finding, especially in the lower limbs. Rarely, upper limb and trunk-localized lesions can be seen. Apart from palpable purpura, lesions such as necrosis, ulceration, vesicle, bullae, nodule, livedo reticularis are also seen [7].

In our patient, itchy maculopapular lesions have developed in the thigh and abdominal region. Vildagliptin associated cutaneous leukocytoclastic vasculitis was not described in the literature before but bullous pemphigoid was observed.

Leukocytoclastic vasculitis etiology includes various causes such as drugs, infections, malignancies, systemic inflammatory diseases. However, some of the cases can not be detected and these phenomena is evaluated as idiopathic.

Among the drugs that cause leukocytoclastic vasculitis are beta lactam group antibiotics, penicillins, sulfonamides, NSAIDs, allopurinol, thiazides, insulin, retinoids, quinolone group antibiotics, hydantoins [6,8]. Our patient did not use a different drug (Antibiotic, non-steroidal anti-inflammatory drug etc) for the last 3 months.

Infections leading to leukocytoclastic vasculitis include viral infections (hepatitis B, hepatitis C, HIV), bacterial infections (streptococcus, staphylococci, mycobacteria), fungal infections

(chlamydia, candida) and protozoal infections [9]. Our patient did not have an infectious (gastroenteritis, urinary system infection, upper respiratory tract infection) story for the past 3 months and also fever was never present. Hepatitis serology and Anti HIV was negative.

Histopathologically, fibrinoid deposits, endothelial swelling and erythrocyte extravasation are observed in the vein wall and around the perivascular neutrophilic infiltrate in the cutaneous postcapillary venules [10]. The skin biopsy of our patient: Histopathologically, extensive extravasated erythrocytes and fibrinoid thickening were observed in the wall and around the perivascular prominent lymphocytic infiltrate in the cutaneous superficial vessels (Figure 2,3).

It is necessary to pay attention to some points to associate the vasculitis tab with the drug. A short span of time should be taken to start the spillage, to cut the medication, to retract the spill, to report cases associated with the suspected drug, and if so, a similar spill with the provocation test [11]. We did not need some provocation tests on the grounds that our patient tested the drug several times. Every time the use of drugs increased skin rashes and itchiness.

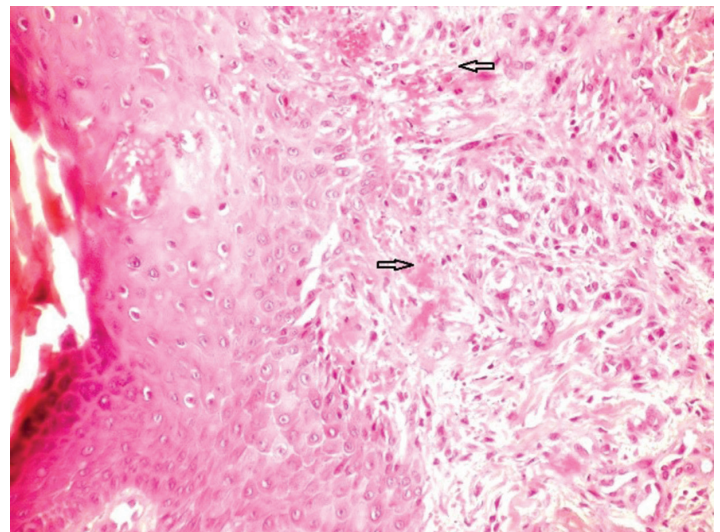


Figure 2. Erythrocytes extravasation in the upper dermis, HE X150

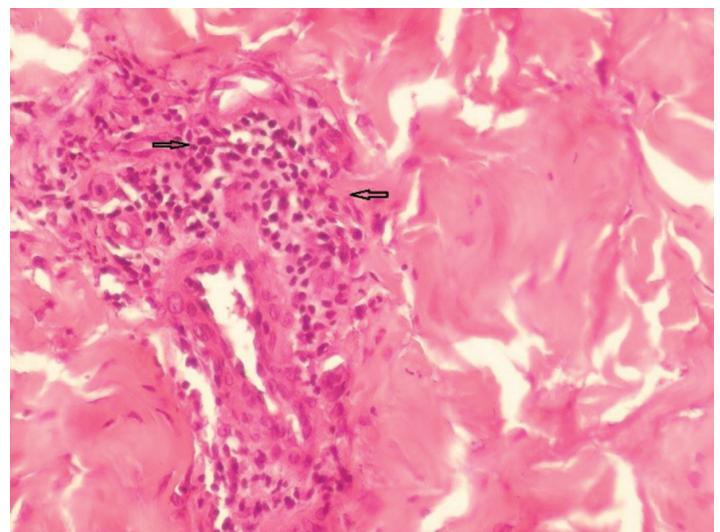


Figure 3. Perivascular lymphocytic infiltration and fibrinoid thickening in the vessel wall, HE X150

Cutaneous leukocytoclastic vasculitis generally has a good prognosis and is often seen as a self-limiting single attack. Therefore, bed rest, leg elevation, conservative approaches such as antihistamines for the itching and analgesics for the pain are suggested [9]. With conservative approaches, we gave antihistamines for the patient's itch.

Systemic steroid therapy is probably the most commonly used drug for cutaneous leukocytoclastic vasculitis. However, the efficacy has not yet been proven with randomized prospective studies. Studies have shown that treatment with leukocytoclastic vasculitis can be successfully treated with an initial dose of 0,5-1 mg/kg/day [9]. Dapsone is an anti-inflammatory drug that is used in various neutrophilic dermatoses and vasculitic diseases with its anti-neutrophilic effect [12]. Immunosuppressive agents (azathiopurine, mycophenolate mofetil, cyclosporin) that reduce steroid side effects in recurrent or chronic disease may also be treated [8-10,13]. Methotrexate is recommended especially in cases associated with connective tissue diseases. Intravenous immunoglobulin G and plasmapheresis are other treatment options recommended in selected treatment-resistant cases [7,9,14].

Conclusion

As vildagliptin is a widely used agent in type 2 diabetes mellitus treatment, physicians should be aware of the possibility of this rare but potentially serious adverse event.

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