Case Report
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Case Report: Fixed Drug Eruption Caused by Dapagliflozin

Vaka Sunumu: Dapagliflozine Bağlı Fiks İlaç Erüpsiyonu

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Abstract

Type 2 diabetes mellitus (T2DM) is a global health concern. It has multifactorial pathophysiology and its incidence is increasing day by day. The treatment is mainly targeted at maintaining cardiovascular and renal functions. Administration of sodium-glucose co-transporter-2 (SGLT2) inhibitors is one of the emerging medications for T2DM. It improves glycemia by employing insulin-independent mechanisms that increase urinary glucose excretion. The authors hereby report a case of a 62-year-old male with T2DM, who was referred to our outpatient clinic for glycemic control. The patient was taking metformin and gliclazide for five years in addition to dapagliflozin, an SGLT-2 inhibitor, for one year. Physical examination revealed a few, sharply-demarcated erythematous plaques on the patient's forearm for fifteen days. The patient previously had psoriasis, and to rule out this diagnosis a skin punch biopsy was taken from one of the lesions. The histopathological evaluation was found to be compatible with drug eruption; however, skin patch test performed with dapagliflozin was non-reactive. After performing oral provocation test with dapagliflozin, new erythematous plaques appeared around the same sites on the forearm. On withdrawing dapagliflozin, the lesions resolved completely. This case gives an insight that dapagliflozin may also cause drug eruptions, which should be kept in mind, especially in a patient with psoriasis.

Keywords: Dapagliflozin; fixed drug eruption; sodium-glucose co-transporter-2 inhibitors; type 2 diabetes mellitus

Özet

Tip 2 diabetes mellitus (Tip 2 DM), global bir sağlık problemidir. Patofizyolojisi multifaktöriyeldir ve insidansı günden güne artmaktadır. Tedavide temel hedef, kardiyovasküler ve renal fonksiyonların korunmasıdır. Sodyum glukoz ko-transporter-2 (SGTL2) inhibitörleri, Tip 2 DM tedavisinde yeni ortaya çıkan ilaçlardan biridir. SGLT-2 inhibitörleri, insülinden bağımsız mekanizma ile üriner glukoz atılımını artırarak glisemiyi düzeltmektedir. Bu çalışmada, glisemik kontrol amaçlı polikliniğimize başvuran 62 yaşındaki Tip 2 DM'li erkek hasta sunulmuştur. Hasta beş yıldır metformin, gliklazid; beraberinde bir yıldır da dapagliflozin tedavisi almakta idi. Fizik muayenesinde, ön kol üzerinde keskin sınırlı eritematöz plaklar saptandı. Psöriyazis tanısı olan hastada, psöriyazisi ekarte etmek için lezyonlardan birinden deri biyopsisi alındı. Histopatolojik değerlendirme ilaç erüpsiyonu ile uyumlu bulunmasına rağmen, dapagliflozin ile yapılan deri yama testi reaktif değildi. Dapagliflozin ile oral provokasyon testi yapıldığında, ön kolda eski lezyonların yerlerinde eritemli yeni plakların ortaya çıktığı gözlendi. Dapagliflozin tedavisinin kesilmesi ile lezyonlar tamamen düzeldi. Bu hasta, dapagliflozinin fiks ilaç erüpsiyonuna neden olabileceği ve önceden psöriyazis tanısı almış olsa bile bu hastalarda akılda tutulması gerektiği konusunda fikir vermektedir.

Anahtar kelimeler: Dapagliflozin; fiks ilaç erüpsiyonu; sodyum glukoz ko-transporter-2 (SGTL2); tip 2 diyabetes mellitus

Introduction

The latest treatment modality for T2DM includes SGLT2 inhibitors, which exert an insulin-independent action by blocking the re-absorption of filtered glucose in kidneys. Dapagliflozin, an SGLT2 inhibitor, is consumed orally, once-daily, and has a half life of about 17 hours. SGLT2 inhibitors cause the loss of calories, helping in subsequent weight loss (1). Weight loss is associated with the reduction of visceral or subcutaneous fat. SGLT2 inhibitors provide cardio-

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vascular protection with other beneficial effects like weight loss, decrease in blood pressure and triglycerides, and also diminish the progression of kidney diseases (2). SGLT2 inhibitors are generally well-tolerated; yet, the typical adverse effects include genital mycotic infections and lower urinary tract infections (3). The available current literature does not report any case of fixed drug eruption caused by SGLT2 inhibitors. Only a few cutaneous adverse events such as intense and severe pruritus (4), an increased rate of vaginal colonization by candida species, and vulvovaginal adverse events in women with T2DM caused by canagliflozin (5) have been reported.

Drug eruptions can either result from immunological or non-immunological mechanisms. In immunologically mediated drug eruptions, drugs or their metabolites may act as haptens, thus causing either a specific cell-mediated or humoral response. Fixed drug eruptions (FDE) are the cell-mediated, delayed type of drug reactions. It may present as a single or a few, round, sharply demarcated erythematous and edematous plaques anywhere on the body. After re-administration of the causative drug, the lesions recur at exactly the same sites. Patch testing and oral provocation have been used to identify the suspected agent and check for cross-sensitivities to medications. Management starts with the withdrawal of the suspected drug (6).

Case Report

The authors hereby report a case of a 62-year-old male having coronary artery disease, with a history of T2DM for 20 years, who was referred to our outpatient clinic for glycemic control. He was on metformin and gliclazide for five years, and dapagliflozin was given for one year. His initial anthropometric measurements were weight: 81 kg, height: 163 cm, and body mass index (BMI): 30.4 kg/m². His blood test showed: fasting blood glucose:118 mg/dL, creatinine: 1.0 mg/dL, serum alanine aminotransferase: 22 U/L, HbA1c: 7.1%. After treatment with dapagliflozin for 12 months, the patient has lost 6 kg. Physical examination revealed a few, sharply-demarcated erythematous plaques on his forearms, present for fifteen days (Figure 1). The patient's past medical history revealed that he had been affected with psoriasis, and to rule out this diagnosis a skin punch biopsy was performed on one of the lesions. Histopathological evaluation showed parakeratosis, loss in granular layer, subcorneal neutrophilic infiltration, irregular acanthosis and spongiosis, perifollicular and perivascular eosinophilic and lymphocytic inflammation. Though the skin biopsy was compatible with drug eruption (Figure 2); however, skin patch test performed with dapagliflozin was observed to be non-reactive. After oral provocation test with dapagliflozin, new erythematous plaques appeared near the same sites on the forearms (Figure 3). When dapagliflozin was withdrawn, the lesions resolved completely in seven days. No lesion was observed after one month of withdrawal of the drug (Figure 4).

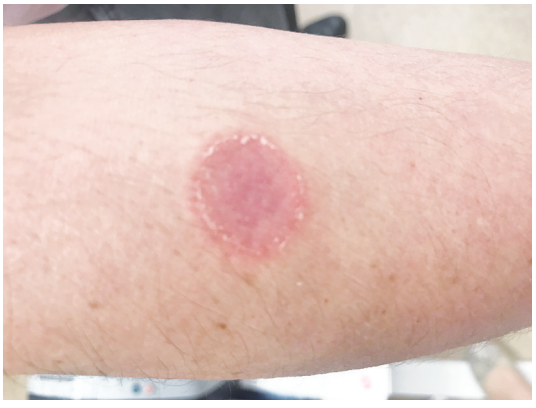

Figure 1: Erythematous plaques on his forearms.

Discussion

SGLT2 inhibitors like dapagliflozin, canagliflozin, empagliflozin, and ipragliflozin form the novel therapeutic approach for T2DM. The most common adverse effects of these drugs include female genital mycotic infections and benign urinary tract infections (7). These drugs can be classified as 'nutrient load reducer's' group among the antihyperglycemic agents, which have been shown to improve cardiovascular and renal outcomes, with low hypoglycemia risk (8). Despite all these beneficial effects, skin lesions which may develop due to SGLT2 inhibitors should not be overlooked. To the best knowledge of the authors, this study is the first report showing fixed drug eruption

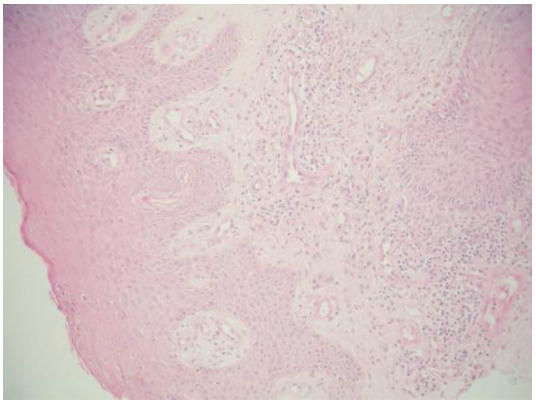

Figure 2: Psoriasiform epidermal hyperplasia and dermal perivascular inflammation with eosinophilic infiltration (40X HE).

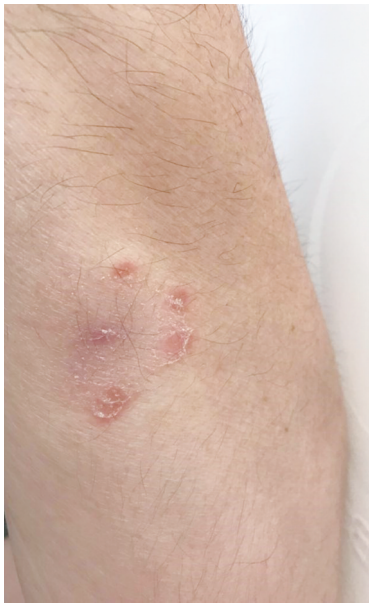

Figure 3: Recurrens after oral provocation test near the same sites of former lesions

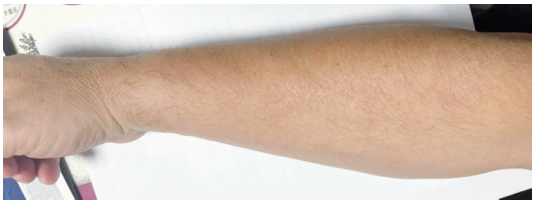

Figure 4: No lesion was observed after one month of dapagliflozin withdrawal.

caused by dapagliflozin. Drug eruption mechanisms with dapagliflozin have not been investigated earlier. In a previous study on Japanese population, six SGLT-2 inhibitors have been evaluated for possible skin reactions wherein serious generalized rashes, eruptions, urticaria, erythema, and eczema and subcutaneous tissue disorders with ipragliflozin alone were observed. Ipragliflozin is stored in the skin tissue, and interacts with melanin; therefore skin reactions might be related to the disturbed skin tissue homeostasis (9). Such reactions, however, were not observed with dapagliflozin in the present study.

Recent studies have also reported fixed drug eruptions with SGLT2 inhibitors (10), for example, drug eruptions with ipragliflozin (11) and Fournier's gangrene with empagliflozin, though not with dapagliflozin (12). U.S. Food and Drug Administration (FDA) recently issued a safety warning about a rare, but serious, skin infection in patients treated with SGLT2 inhibitors, i.e., necrotizing fasciitis (gangrene) of the perineum on and around the genitals, also referred to as Fournier's gangrene (13). Adverse cutaneous drug reactions are recognized as major health problems worldwide, causing a considerable financial burden for the healthcare systems. SGLT2 inhibitors are in use in Europe since only a few years, and their adverse effects are yet to be clarified. The authors suggest that FDE must be added to the list of side-effects of SGTL2 inhibitors as a rare cutaneous reaction. Though drug eruption caused by dapagliflozin is a rare condition, this possibility should be kept in mind, especially while dealing with psoriasis patients.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Müge Keskin; Design: Müge Keskin, Arzu Or Koca; Control/Supervision: Müge Keskin, Derun Taner Ertuğrul; Data Collection and/or Processing: Müge Keskin, Mustafa Altay; Analysis and/or Interpretation: Müge Keskin, Arzu Or Koca; Literature Review: Müge Keskin, Murat Dağdeviren; Writing the Article: Müge Keskin, Derun Taner Ertuğrul; Critical Review: Müge Keskin, Murat Dağdeviren; References and Fundings: Müge Keskin, Mustafa Altay.

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