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Dapagliflozin-Induced Vulvovaginitis in an Atopic Patient with Type 2 Diabetes Mellitus

Tip 2 Diabetes Mellituslu Atopik Hastada Dapagliflozin Kaynaklı Vulvovajinit

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Abstract

Dapagliflozin, an oral anti-diabetic agent, is a recently discovered sodium-glucose co-transporter receptor-2 inhibitor, which improves glycemic control by facilitating the renal excretion of glucose. Urinary and genital tract infections are common in type-2 diabetes mellitus. Vulvovaginal candidiasis is an infection of the vaginal vestibular area. We present a case of vulvovaginal candidiasis associated with the use of dapagliflozin. A 48-years-old female patient having type-2 diabetes mellitus for the past eight years was admitted to our outpatient clinic. Her medical history was remarkable for atopic dermatitis. She was using metformin and sulfonylurea. Her hemoglobin A1c was 7.8%. A daily dose of 10 mg dapagliflozin was added to her treatment. On the 12th day of dapagliflozin therapy, she noted vulvovaginal pruritus, which was reported three days later, after the symptoms worsened. Physical examination revealed widespread erythema on vulvar, vaginal, and perineal regions of the genitourinary area. The vaginal culture was positive for *Candida albicans*. Thus, the patient was diagnosed with vulvovaginal candidiasis. The symptoms of vulvovaginal candidiasis were managed through the topical application of clotrimazole. Three days later, the clinical manifestations worsened, and dapagliflozin was discontinued. This led to the regression in signs and symptoms of vulvovaginal candidiasis. Hence, an appropriate diagnosis and management of vulvovaginal candidiasis were essential to provide optimal genital and metabolic health. We believe that this case will be highly relevant among atopic patients at potential risk of vulvovaginal candidiasis and recommend that a drug withdrawal may be considered in such patients.

Keywords: Type 2 DM; dapagliflozin; vulvovaginitis

Özet

Dapagliflozin, sodyum-glukoz kotransporter reseptör-2 inhibitorü olarak adlandırılan yeni geliştirilmiş bir oral antidiyabetik ajan olup; glisemik kontrolü, glukozun böbreklerden geri emilmesini inhibe edip glukozürik etki göstererek sağlamaktadır. Tip 2 diabetes mellitus seyrinde üriner ve genital enfeksiyonlar sıklıkla görülmektedir. Vulvovajinal kandidiyaz vajinal vestibüler alanın infeksiyonu ile karakterizedir. Çalışmamızda dapagliflozin kullanımı ile ilişkili bir vulvovajinal kandidiyaz olgusu sunulmaktadır. Kırk sekiz yaşındaki, sekiz yıllık Tip 2 diabetes mellitus öyküsü olan kadın hasta polikliniğimize kabul edildi. Öz geçmişinde atopik dermatit öyküsü mevcuttu. Hemoglobin A1c %7,8 idi. Metformin ve sülfonilüre tedavisi almakta iken tedavisine günlük dapagliflozin 10 mg eklendi. Dapagliflozin tedavisinin 12. gününde vulvovajinal pruritus şikâyeti olup, bundan üç gün sonra şikâyetlerinde artış meydana geldi. Fizik muayenesinde, genitoüriner alanın vulvar, vajinal ve perineal bölgelerinde geniş eritem saptandı. Vajinal kültüründe *Candida albicans* üremesi saptanıp, vulvovajinal kandidiyaz tanısı konuldu. Topikal klotrimazol ile vulvovajinal kandidiyazis tedavisi yapıldı. Ancak, tedavi başladıktan üç gün sonrasında klinik bulgularında kötüleşme olması üzerine dapagliflozin tedavisi kesildi. Topikal klotrimazol tedavisine devam edildikten sonra vulvovajinal kandidiyazis belirti ve bulguları geriledi. Optimal genital ve metabolik iyileşmeyi sağlamak için vulvovajinal kandidiyazisin uygun tanı ve tedavisi şarttır. Vulvovajinal kandidiyazis için potansiyel risk taşıyan atopik hastalarda ilaç bıraktırmanın yararlı olabileceği göz önünde bulundurulmalıdır.

Anahtar kelimeler: Tip 2 DM; dapagliflozin; vulvovajinit

Introduction

The prevalence of type–2 diabetes mellitus (T2DM) is ever-increasing, and it presently affects at least 285 million people worldwide (1). The first line of treatment for patients with T2DM is modification of the lifestyle, including diet, exercise, and weight reduction as required (2). The development of new therapeutic agents for the treatment of T2DM is continuously undertaken to achieve optimum HbA1C levels. New drugs with

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different mechanisms of managing various conditions in the etiopathogenesis of diabetes are still being developed. The sodium-glucose cotransporter receptor-2 (SGLT2) inhibitors are recently discovered oral antidiabetic (OAD) agents that improve glycemic control by facilitating the renal excretion of glucose. SGLT2 inhibitors are known to have benefits such as weight loss, reduction in systolic blood pressure, and low hypoglycemic risk. However, they are also known to cause urinary and genital tract infections more commonly than other antidiabetic agents (3). Vulvovaginitis (VV) is a genital infection which could be a complication of T2DM. Vulvovaginal candidiasis (VVC) is an infection of the vaginal vestibular area, which can also spread to the outer parts of the labia minora and labia majora, and the intercrural and perineal regions (4). Herein we present a case of VVC associated with the use of dapagliflozin.

Case Report

A 48-year-old woman with T2DM for the past eight years was admitted to the endocrinology clinic for routine follow-up. Her body mass index was 33.7 kg/m^2. Her past medical history was remarkable for atopic dermatitis since childhood but she was having arterial hypertension for five years. She had been using metformin and sulfonylurea to manage T2DM, while her blood pressure was controlled with 80 mg valsartan daily. She was a non-smoker but had a positive family history for T2DM. Her initial laboratory results were as follows: fasting plasma glucose= 131 mg/dL, HbA1c= 7.5%, low-density lipoprotein (LDL)= 101 mg/dL, alanine aminotransferase (ALT)= 21 U/L, creatinine= 0.72 mg/dL, GFR >60 mL/min, and spot urinary microalbumin/creatinine ratio= 28.8 µg/mg, TSH: 2.3 µU/mL (normal range: 0.27-4.2), free T4:1.1 ng/dL (normal range: 0.87-1.7. White blood count results were 7800 10^3/µL. A daily dose of 10 mg dapagliflozin was added to her treatment schedule. On the 12th day of dapagliflozin therapy, she noted vulvovaginal pruritus. Three days later, she complained of increased severity of symptoms and was admitted to our clinic for further management. Physical examination revealed widespread erythema on vulvar, vaginal, and perineal regions of the genitourinary area. Spot urine glucose excretion level was not checked at fasting, but the urinalysis showed glucose to be 1+. Four leukocytes and 15 erythrocytes per high power objective field were detected in the urine sediment through microscopy. Although the urine culture was negative, the vaginal culture was positive for *Candida albicans*. Thus, the patient was diagnosed with VVC. The blood sedimentation rate was normal and leukocytosis was not observed, but C-Reactive Protein (CRP) level was observed to be 30 mg/L (normal range 0–5 mg/L). For the treatment of VVC, topical application of clotrimazole cream was prescribed. Dapagliflozin and metformin treatment was continued. However, upon worsening of the clinical manifestations three days later, dapagliflozin was discontinued, the patient was switched to vildagliptin, and topical clotrimazole therapy was continued. The symptoms of VVC regressed after two days, and the patient had no further complaints.

Discussion

Dapagliflozin is an SGLT2 inhibitor which can be used singly or as a part of combined therapy in patients whose hyperglycemia is ineffectively controlled by other antidiabetic medications. It is proven that glucosuria facilitates the growth of bacteria and increases their adherence to the uroepithelium and vaginal epithelial cells, which might be linked with the increased incidence of genital infections (5).

It is known that SGLT2 inhibitors are insulin-independent glucose-lowering agents which function by inhibiting GLUT–1 and GLUT–2 renal glucose transporters (6).

Dapagliflozin provides moderate weight loss and blood pressure reduction in T2DM (7). The advantages are a low risk of hypoglycemia, weight loss, decreased blood pressure, and association with lower incidences of cardiovascular failure and mortality in patients with cardiovascular disease. Disadvantages include genitourinary infections, polyuria, volume depletion, and transient elevation of creatinine levels. Urinary tract infections can progress to urosepsis and pyelonephritis (8). Signs, symptoms, and events suggestive of genital infection were reported in ≥1% of women being treated using dapagliflozin. Vaginal pruritus and tenderness, vulvovaginal erythema, dyspareunia, dysuria, and vaginal discharge are common symptoms. In this case, severe pruritus with erythema at the vulvovaginal area indicated the occurrence of VV. A study analyzing 12 clinical trials involving 4545 patients with T2DM summarized that once-daily treatment regimens of 2.5 mg, 5 mg, or 10 mg dapagliflozin accompanied an increased risk of VV or balanitis related to the induction of glucosuria. Most of them resolved spontaneously or

after standard antimicrobial therapy; the infections rarely required discontinuation of treatment. Urinary glucose appears to be a risk factor for the development of genital infection; however, the amount of urinary glucose does not necessarily correlate directly with the rates of infection (9). The drug class of SGLT2 inhibitors includes dapagliflozin, canagliflozin, and empagliflozin. It was reported that canagliflozin was associated with an increase in the vaginal colonization of *Candida* sp. and VV in women with T2DM (10).

Vulvovaginal candidiasis is most frequently caused by *Candida albicans*, and all diabetic individuals should be treated to prevent further complications (4). Diagnosis must be confirmed by a wet preparation (saline, 10% KOH) or gram stain of the vaginal discharge which shows budding yeasts, hyphen or pseudohyphae, and a positive culture (11). In case of uncontrolled diabetes, VV cannot be treated successfully, entailing a careful re-evaluation of anti-diabetic medications by physicians. SGLT2 inhibitors are usually associated with genital mycotic infections of mild-to-moderate severity, and thus do not necessarily need to be discontinued on the basis of a single VV episode (12). Women with atopic diathesis and type-1 allergies are significantly more prone to vaginal candidiasis than others (13). The clinical symptoms of vaginal candidiasis such as redness and itching suggest an expression of allergy, particularly in recurring cases (14). Its higher frequency in patients with atopy suggests an association between allergy and vaginal candidiasis. Since our patient had a history of atopic dermatitis, we assume that she tends to get VVC more often than the normal population. For the treatment of widespread VVC, an antimycotic skin cream (clotrimazole) is recommended BID for around a week (4). The combination of intravaginal treatment for acute VVC, with an additional cream for the vulva, appears to yield better treatment results than intravaginal treatment alone. Therefore, in the light of the association between glucosuria and VV, medical treatments such as SGLT2 inhibitors that stimulate glucosuria should be evaluated to determine the risk of genital infection in individuals having a personal history of atopy.

Summary

Vulvovaginitis is a frequently encountered acute and recurrent complication of diabetes mellitus, which tends to be exacerbated by poor glycemic control. Appropriate diagnosis and management are essential to provide optimal genital and metabolic health. The analysis of this patient's history, physical examination, and pathological findings implicates dapagliflozin in the induction of VV. We believe that this case will be highly relevant among atopic patients with potential risk for VVC during usage of these medications. Drug withdrawal may be considered in such patients.

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Author Contributions

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