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A Case Report of Dapagliflozin-Induced Nodular Vasculitis

Dapagliflozin İlişkili Nodüler Vaskülit Olgu Sunumu

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Abstract

Nodular vasculitis (NV), first described by Montgomery in 1945 for erythema induratum-like lesions, is a rare form of panniculitis that is particularly localized on the calves. Characterized by plaques and erythematous nodules, NV may often show ulceration and draining. It is known as a reactive disease associated with many causative factors. Several NV cases due to infectious or non-infectious causative factors have been reported, but no case of NV due to sodium-glucose cotransporter-2 inhibitors (SGLT2i) has yet been reported. In this case report, we presented a case diagnosed with NV, who presented with tender, erythematous, eroded plaques with hemorrhagic-purulent discharge on both legs during treatment with dapagliflozin (an SGLT2i).

Keywords: Nodular vasculitis; dapagliflozin; antinuclear antibodies; sodium-glucose cotransporter-2 inhibitors; diabetes mellitus

Özet

İlk olarak 1945 yılında Montgomery tarafından eritema induratum benzeri lezyonlar için tanımlanmış olan nodüler vaskülit (NV), özellikle bacaklarda lokalize olan ve nadir görülen bir pannikülit formudur. NV, plaklarla ve eritematöz nodüllerle karakterize olup, zaman zaman ülsere ve akıntılı hâle gelebilir. Birçok nedensel faktörlerle ilişkili reaktif bir hastalık olarak bilinmektedir. Enfeksiyöz ya da enfeksiyöz olmayan nedenlere bağlı birçok NV vakası bildirilmiştir, ancak sodyum glukoz ko-transporter 2 (SGLT2) inhibitörlerine bağlı bir NV vakası henüz bildirilmemiştir. Bu olgu sunumunda, dapagliflozin (bir SGLT2 inhibitörü) tedavisi esnasında her iki bacağında gelişen hassas, eritemli, erode ve hemorajik-pürülan akıntılı plaklarla başvuran ve NV tanısı konulan bir olguyu sunduk.

Anahtar kelimeler: Nodüler vaskülit; dapagliflozin; antinükleer antikorlar; sodyum glukoz ko-transporter 2 inhibitörleri; diabetes mellitus

Introduction

Nodular vasculitis (NV) was first mentioned by Montgomery in 1945 for erythema induratum-like lesions (1). NV is a rare form of panniculitis and is usually localized on the calves. Characterized by plaques and erythematous nodules, NV may occasionally show ulceration and draining. It is considered a reactive disease associated with many causative factors (2). Some of the infectious causereported in previous studies for NV are Tuberculosis, Nocardia, Fusarium, Pseudomonas, Chlamydia, and hepatitis C virus (3-5). Some cases of NV have also been found associated with non-infectious conditions such as drugs (6,7), inflammatory bowel diseases (8), several autoimmune diseases (9), and rare malignant diseases (10,11).

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are oral antidiabetic drugs that in-

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hibit glucose reabsorption by binding to SGLT2 channels of proximal tubules of the kidney. The fact that this mechanism is insulin-independent makes these drugs promising in the treatment of type 2 diabetes mellitus (T2DM) (12,13). Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are the SGLT2i approved until December 2017 by the United States Food and Drug Administration (FDA) (14). Several studies have revealed that SGLT2i drugs remarkably reduce the risk of cardiovascular events. Despite these promising results, some serious side effects and complications, such as increased amputation rates, ketoacidosis, and acute kidney injury associated with SGLT2i (15-17), have been reported. To the best of our knowledge, NV associated with SGLT2i has not been reported so far. In this paper, we present a case of nodular vasculitis associated with dapagliflozin, an SGLT2i.

Case Report

A 36-year-old male patient presented to our hospital with tender, erythematous lesions on both legs that appeared 15 days before. He stated that within a few days, the lesions became enlarged and draining. His previous medical history included T2DM and obesity. He was a smoker. While he was using only metformin 1,000 mg twice a day before, 20 days prior to his presentation, he started dapagliflozin 10 mg orally daily for T2DM. Followings were his vital signs recorded on his admission:

Blood pressure, 125/75 mmHg; pulse rate, 80 beats/min; respiratory rate, 16 breaths/min; pulse oximetry (SpO_2), 98% on room air. His height, weight, and BMI were 171 cm, 138 kg; 47.3 kg/m^2, respectively. Physical examination of the patient revealed eroded plaques with erythematous, violaceous edges measuring 8x9 cm on the medial aspect of the right leg and 10x15 cm on the posteromedial aspect of the left leg (Figure 1). The plaques showed central crusts, erosions, and a hemorrhagic-purulent discharge. All other physical examinations were found normal. Initial laboratory investigations revealed white blood cell (WBC) count of 17.9×10^9/L (4-11) with 82% neutrophils, hemoglobin of 12g/dL (13-18), platelets of 448×10^9/L (140-450), erythrocyte sedimentation rate (ESR) 66 mm/h (0-20), C-reactive protein (CRP) 189.28 mg/L (normal 0-5 mg/L), creatinine 0.7 mg/dL (0.7-1.2), normal partial thromboplastin time and prothrombin time, normal liver function tests, and normal electrolytes. Viral hepatitis and human immunodeficiency virus serological results were all negative. The patient was hospitalized; dapagliflozin treatment, started 20 days ago, was discontinued. From his wound cultures, *Staphylococcus aureus* (SA) was isolated, and he was started on cefuroxime and teicoplanin were started. Testing for antinuclear antibodies (ANA) and antiphospholipid antibodies (aPL) were negative in investigations with suspicion of vasculitis. Myeloperoxidase antibodies and proteinase 3 antibodies were both negative. C3 and C4 Complement levels were within normal limits. Histopathological findings of biopsy samples taken from the lesions showed compatibility with NV. Then we started 25

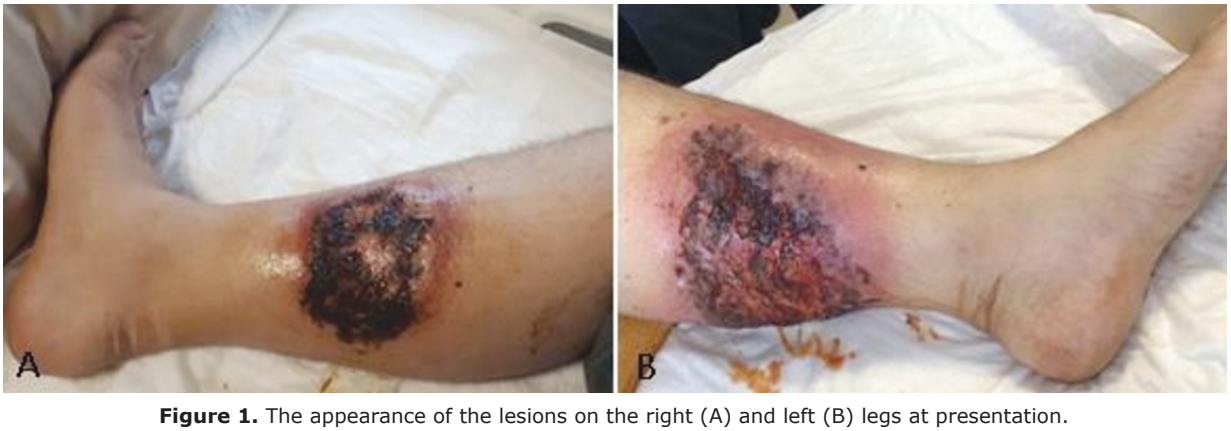

Figure 1. The appearance of the lesions on the right (A) and left (B) legs at presentation.

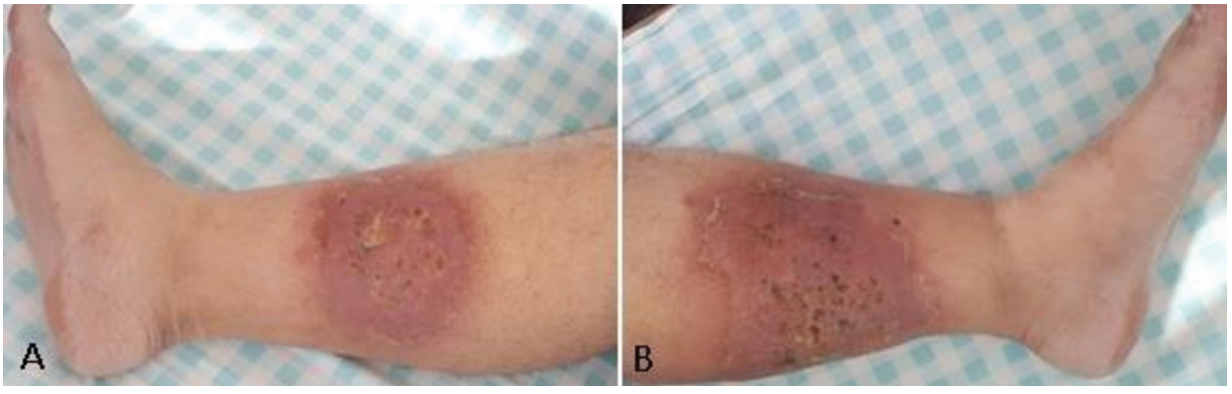

Figure 2. The appearance of the lesions on the right (A) and left (B) legs 20 days after dapagliflozin discontinuation.

mg of dexketoprofen trometamol orally twice a day. With the discontinuation of dapagliflozin treatment, the addition of dexketoprofen trometamol, and antibiotic treatment, his lesions reduced within days, and on the 20th day of his admission, his wounds were healed by leaving depressed scars (Figure 2). On the 20th day of the treatment, laboratory investigation showed a WBC count of 13.6×10^{9}/L (4-11) with 66% neutrophils, CRP of 19 mg/L (normal 0-5 mg/L), ESR of 60 mm/h (0-20). There was no recurrence within nine months after the patient's skin lesions were resolved.

Discussion

This is the first case of NV reported in the literature associated with dapagliflozin. Literature search to study the relationship between SGLT2i and vasculitis showed only one previously reported case of empagliflozin-associated cutaneous polyarteritis nodosa (PAN) (18). NV associated with any SGLT2i has never been previously reported.

Drug-induced NV has been rarely reported, and one case related to propylthiouracil and another case related to etanercept have been described (6,7). However, to date, there are no case reports of dapagliflozin as a cause of NV or other types of vasculitis. Hereby, we report the first case of dapagliflozin (even the first SGLT2i) as a possible cause of NV.

In the Canagliflozin cardioVascular Assessment Study (CANVAS), canagliflozin was shown to be associated with a significant reduction in the risk of cardiovascular events; however, it doubled the amputation risk in patients with T2DM in a study (15). Importantly, very rare side effects may remain undetected during studies before the drug approval and can only be detected in a large patient population after the drug has been approved. Also, phase IV studies are required to reveal these uncommon side effects and to understand their safety profile better.

This case initially presented with erythematous, tender nodules with central crusts, localized on the calves, and showed depressed scars during the recovery period. Also, the histopathological features of the biopsy samples taken from the lesions were found compatible with NV. Significant improvement was noticed in skin lesions within days following dapagliflozin discontinuation. Therefore, we believed that NV disease was caused by dapagliflozin in our case. This case suggests the possible relationship between dapagliflozin and NV and the immediate appearance of lesions after the initiation of dapagliflozin treatment and improvement within days after dapagliflozin discontinuation is the most notable feature. However, in the mechanism of NV that occurs during treatment with dapagliflozin, the role of an SGLT2i remains unknown. More case reports and clinical studies are needed in this context.

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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: Muhammet Kocabaş; Design: Melia Karaköse; Control/Supervision: Mustafa Kulaksızoğlu, Feridun Karakurt; Data Collection and/or Processing: Zeliha Yarar; Analysis and/or Interpretation: İlker Çordan, Mustafa Can; Literature Review: Harun Aydemir; Writing the Article: Muhammet Kocabaş, Mustafa Can; Critical Review: Melia Karaköse; References and Fundings: Mustafa Can; Materials: Hatice Çalışkan Burgucu.

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