Furosemide-Induced Cutaneous Leucocytoclastic Vasculitis: Case Report

Furosemide Bağlı Kutanöz Lökositoklastik Vaskülit

Mustafa ÜNÜBOL, MD,[a]
Ceyhun CEYHAN, MD,[b]
Taşkın ŞENTÜRK, MD,[a]
Canten TATAROĞLU, MD[c]

Departments of
[a]Internal Medicine,
[b]Cardiology,
[c]Pathology,
Adnan Menderes University
Faculty of Medicine, Aydın

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Yazışma Adresi/*Correspondence:*
Ceyhun CEYHAN, MD
Adnan Menderes University
Faculty of Medicine,
Department of Cardiology, Aydın,
TÜRKİYE/TURKEY
ceyhunceyhan@yahoo.com

ABSTRACT Leucocytoclastic vasculitis is the most commonly seen form of vasculitic syndromes. We present a rare case of cutaneous leucocytoclastic vasculitis. A 55-year-old male patient with diagnosis of dilated cardiomyopathy received furosemide intravenous (IV) infusion therapy because of congestive symptoms. On the 4th day of treatment, skin lesions developed on lower extremities as palpable purpura. Furosemide infusion was decreased gradually and stopped. Histological examination of a skin biopsy was consistent with leucucytoclastic vasculitis. The lesions were resolved completely after seven day of the metilprednisolone treatment. Best to our knowledge, urticarial skin lesions in which furosemide might presumably be the etiological factor has been reported very uncommon in the literature.

Key Words: Diuretics; vasculitis, hypersensitivity

ÖZET Lökositoklastik vaskülit, vaskülitik sendromların en sık olan şeklidir. Biz nadir bir kutanöz lökositoklastik vaskülit olgusunu sunmaktayız. Dilate kardiyomiyopati tanılı 55 yaşında erkek hastaya konjestif semptomlarının olması nedeniyle furosemid intravenöz infüzyon tedavisi uygulandı. Tedavinin dördüncü gününde, alt ekstremitelerde palpe edilebilen purpura şeklinde deri lezyonları gelişti. Furosemid infüzyonu kademeli olarak azaltılıp kesildi. Deri biyopsisinin histolojik incelemesi lökositoklastik vaskülit ile uyumlu bulundu. Lezyonlar metilprednizolon tedavisinin yedinci gününden sonra tamamıyla kayboldu. Bilgilerimize göre, literatürde furosemidin olası etyolojik faktör olabileceği ürtikeryal deri lezyonları oldukça nadir olarak bildirilmiştir.

Anahtar Kelimeler: Diüretikler; vaskülit, hipersensitivite

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Leucocytoclastic vasculitis (LCV) is a disorder of small cutaneous vessels, characterized by deposition of immune complexes.[1] LCV is the most commonly seen form of vasculitic syndromes. More than 70% of the LCV cases appear due to drug usage, infectious diseases, malignancy, connective tissue disorders or primary vasculitis. Drug-induced etiology is implicated approximately 10-24% of cases of LCV.[2] The most frequently implicated agents in this syndrome presenting with non-thrombocytopenic purpuric skin eruptions are diphenylhydantoin, propylthiouracil, allopurinol, sulfonamides and penicilins.[3] Cutaneous leucocytoclastic vasculitis presents as palpable purpura most often localized in the lower extremities, often accompanied by abdominal pain, arthralgia and renal involvement.

The clinical diagnosis of leucocytoclastic vasculitis is confirmed histopathologically by skin biopsy. Furosemide is a loop diuretic. So named because of their predominant site of action in the nephron, they produce natriuresis and diuresis primarily by blocking sodium chloride reabsorption at the loop of Henle.[4] It is used as treatment for hypertension, acute pulmonary oedema, heart failure and hypervolemia. Cutaneous LCV was developed in our patient after we started furosemide infusion for the treatment decompensated heart failure.

CASE REPORT

55 years old male patient with the diagnosis of dilated cardiomyopathy applied to the hospital with congestive symptoms. The patient's physical examination revealed that, the respiratory sounds were decreased in both basal lung areas. S3 was positive; liver was enlarged and handled at 5 cm of right midclavicular line. Bilateral severe peripheral edema was present. Cardiothoracic ratio was increased (0.75) and there was bilateral massive pleural effusion on X-ray examination. In the echocardiography, ejection fraction was low (30%) and there were findings compatible with dilated cardiomyopathy. The patient was using 3 x 12 unit insulin aspart and 16 unit insulin detemir therapy at nights for five years with diagnosis of type 2 diabetes mellitus. Because of hyperpotasemia and renal dysfunction angiotension converting enzyme inhibitor or angiotensin reseptor blocker and tiazide diuretics were not given to the patient. Continuous IV furosemide infusion with dosage of 10 mg/hour was given to the patient. On the second day of IV infusion treatment it was increased to 20 mg/hour. On the 4th day of treatment, skin lesions developed on both lower extremities as palpable purpura (Figure 1). Histopathologically analysis of biopsy material collected from skin lesions, focal spongios was seen on upper derma and also mixed inflammation that contains moderate perivascular neutrophile was seen on upper and intermediate derma (Figure 2). Perivascular diffuse fibrinogen, C3, focal IgA, IgM accumulation was determined by direct immunofluorescence

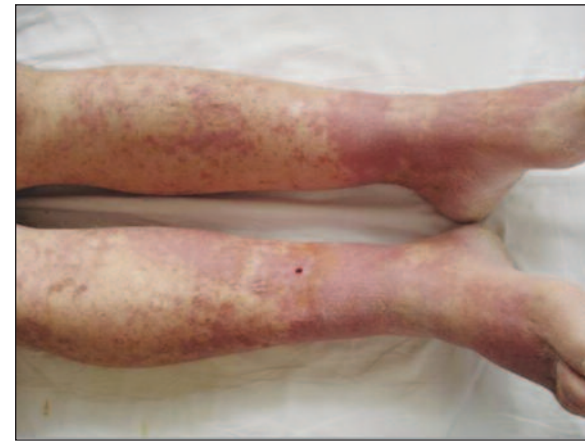

FIGURE 1: Purpuric nonblanching rash on patient's lower extremites.

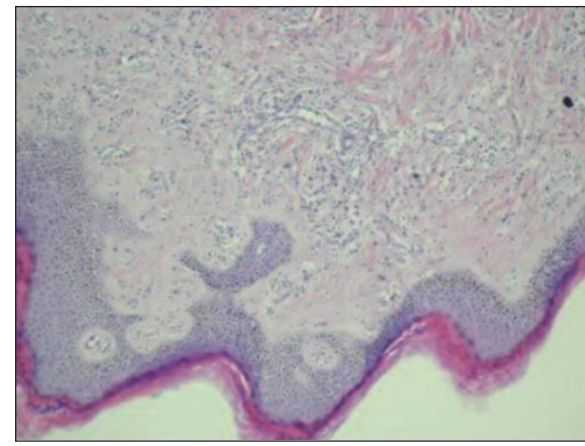

FIGURE 2: Focal spongios was seen on upper derma and also mixed inflammation that contains moderate perivascular neutrophile was seen on upper and intermediate derma (Hematoxylin and eosin staining, x400).

method. These findings were compatible with leukocytoclastic vasculitis. Rheumatoid factor, TSH, antinuclear antibody and auto antibodies to neutrophilic cytoplasmic antigens (ANCA) were found as negative and serum C3 level was determined as normal. There was no finding compatible with systemic infection and malignant disease. Urine microscopy was also normal. Laboratory findings were as follows; white blood cell (WBC) 10.400/mm^3, hemoglobin 11.5 g/dl. Erythrocyte sedimentation rate was found as 75 mm/hour, C-reactive protein level was determined as 76 mg/dl. Furosemide-induced leucocytoclastic vasculitis was thought. Furosemide infusion was decreased gradually and stopped. After this drug discontinu-

ation, skin lesions did not disappear completely and 40 mg/day metilprednisolone was added to patient's treatment. The lesions were resolved completely after seven day of the new treatment. Metilprednisolone with decreasing dosage was discontinued at first month. The patient's lesions were not observed during the follow-up.

DISCUSSION

Furosemide has been found to produce cutaneous reactions in fewer than 5% of patients.[5] These reactions can range from eczematous and psoriasis-like to bullous.[6] Upon looking for any previous reports of substituting bumetanide for furosemide-even through bumetanide was also a sulfonamide loop diuretic, like furosemid- there were only two previously documented cases, in which there was no cross-allergy between the two drugs.[7] Urticarial skin lesions associated with the drug are uncommon but to our knowledge, there are reports of vasculitic skin lesions in the literature uncommon, which might be caused by furosemide.[8]

Cutaneous LCV is a from of cutaneous angiitis mostly presenting with palpable purpuric skin lesions localized on the lower extremities without any systemic involvement other than skin.[9] Approximately 40% of all cutaneous vasculitis are in the form of cutaneous LCV and the annual incidence is 15-30 per million.[10] In order to determine the cause of the disease, depending on the patient's history, complete blood cell count, RF, ANA and ANCA and complement (C3, C4) should be checked.[2] Drugs and viral upper respiratory tract infections are the most common triggers, whereas no etiological agents can be identified in the majority of cases.[11] If possible, the underlying cause should be treated or removed, for example discontinuation of drugs.

The most common drugs and agents implicated as the cause of cutaneous LCV are diphenylhydantoid, propylthiouracil, allopurinol, antibiotics (penicillins, sulfonamides, tetracyclin, erythromycin, gentamicin), non-steroidal anti-inflammatory drugs (acetylsalycylic acid, naproxen), food additives (tartrazine), herbicid and insecticides.[3] The interval between the first exposure to the drug and appearance of symptoms for drug-induced vasculitis may vary from hours to years.[12] The pathogenesis of drug-induced cutaneous LCV is generally through type III immune complex hypersensitivity reactions. Some drugs that act by the modulation of cytokine secretion, in particular down-regulation of tumor necrosis factor-alpha, may also induce vasculitis disorders.

Leucocytoclastic vasculitis is the most commonly seen form of vasculitic syndromes. Drug-induced etiology is implicated approximately 10-24% of cases of LCV. Drug-induced hypersensitivity vasculitis is a diagnosis of exclusion and requires a history of drug use and absence of underlying systemic conditions. Both local and systemic intermediate–type insulin allergy as well as delayed-type cutaneous reactions to human insulin have been reported. In addition, production of antibody to human insulin and secondary LCV in B cell clonal diseases has been reported.[13] Although these reports, insulin related LCV had not been considered as a primary etiological factor because of patient's long times of usage.

In conclusion, we present a rare case of cutaneous leucocytoclastic vasculitis in which furosemide might presumably be the etiological factor.

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