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Case Report / Olgu Sunumu

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Metformin-induced systemic vasculitis: A rare case report and literature review

Metformine ilişkili sistemik vaskülit: Nadir bir olgu sunumu ve literatür taraması

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Abstract

Leukocytoclastic vasculitis is a cutaneous small-vessel vasculitis characterized by inflammation and necrosis of the vessel wall. It is usually limited to the skin but may rarely affect organs such as the kidney. A 58-year-old female patient presented with palpable petechiae-purpura on the skin after initiating metformin for type 2 diabetes mellitus. Renal biopsy was performed due to hematuria and proteinuria. The renal biopsy showed proliferative glomerulonephritis. After other causes of vasculitis were excluded, a diagnosis of metformin-induced vasculitis was considered. The patient was started on methylprednisolone and azathioprine treatment. Skin findings disappeared completely after two months, and glomerulonephritis resolved at 9 months.

Keywords: Glomerulonephritis, diabetes, metformin, systemic, skin, vasculitis

Öz

Lökositoklastik vaskülit, damar duvarında enflamasyon ve nekroz ile karakterize kutanöz küçük damar vaskülitidir. Genellikle deri ile sınırlıdır, ancak nadiren böbrek gibi organları etkileyebilir. Elli sekiz yaşında kadın hasta, tip 2 diabetes mellitus için metformin kullandıktan sonra ele gelen peteşi-purpura ile başvurdu. Hematüri ve proteinüri nedeniyle böbrek biyopsisi yapıldı. Renal biyopsi sonucu proliferatif glomerülonefrit ile uyumlu bulundu. Hastada diğer vaskülit nedenleri dışlandı. Metformin ilişkili vaskülit düşünüldü. Hastaya metilprednizolon ve azatiopürin tedavisi başlandı. İkinci ayda deri bulguları tamamen kayboldu. Dokuzuncu ayda böbrek bulguları tam remisyona girdi.

Anahtar Kelimeler: Glomerülonefrit, diyabet, metformin, sistemik, deri, vaskülit

Introduction

Leukocytoclastic vasculitis (LCV) denotes a histopathological finding of hypersensitivity vasculitis (HSV). It is a cutaneous small-vessel vasculitis characterized histologically by inflammation and necrosis of the blood vessel walls and accompanied by various skin lesions such as palpable purpura, necrosis, ulcer, nodule, urticaria, livedo reticularis.[1] Although often confined to the skin, LCV can also affect organs such as the kidney. Various infections, drugs, serum sickness disease, connective tissue diseases (CTD), and malignancies are the most common causes for LCV. However, the etiology is unclear in many cases. The most prominent clinical finding is palpable purpura which is frequently observed in the lower extremities, in feet, ankles, around hydrostatic pressure-dependent areas, or at vascular bifurcations.[2] Less commonly, it can occur in the abdomen, arms, or hips. Many drugs have been reported to cause LCV, such as propylthiouracil, phenytoin, guanidine, sulphonamides, penicillins, granulocyte-macrophage colony-stimulating factors, non-steroidal anti-inflammatory drugs, antiaggregants and anticoagulants, certain antiepileptics, and allopurinol.[3]

Metformin is an oral drug belonging to the biguanide class of antidiabetics which is widely used to treat diabetes mellitus (DM) and generally well tolerated.[4] Cutaneous side-effects such as rash, urticaria, photosensitivity, and

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lichenoid and psoriasiform drug eruption due to metformin use have been rarely reported.[5] Here, we present a case of metformin-induced LCV with renal involvement.

Case Report

A 58-year-old female patient presented with red dots on her anterior lower extremities that had appeared 2 months prior, subsequently spreading to the hip, abdomen, and arms. The patient tried 1% topical methylprednisolone (MP) and oral desloratadine 5 mg therapy. Then she was referred to our rheumatology clinic due to increased acute-phase reactants, petechiae, palpable purpura, and proteinuria. Her medical history revealed that she had been on metformin 1 gr/day for type 2 DM. Her BMI was 36 kg/m^2. There was no history of asthma, CTD, and systemic infection. On skin examination, red and brown colored, old and new petechiae, and palpable purpura were identified on all four limbs and abdominal region (Figure 1A, 1B). Fundoscopic examination revealed no signs of diabetic retinopathy or uveitis. The Schirmer's test (15/14 mm) result was normal. The rest of the physical exam was unremarkable.

The patient's laboratory test results are shown in Table 1. Screening tests for vasculitis and CTD were negative. There was no serological evidence of infection. Coagulation tests, protein electrophoresis and levels of serum complement, immunoglobulin (IgA, IgE, IgM, IgG), and creatinine were normal. The eosinophil count was normal in the blood. The urinalysis showed 2+ proteinuria, 30 erythrocytes/hpf and 14/hpf leukocytes with negative urine culture.

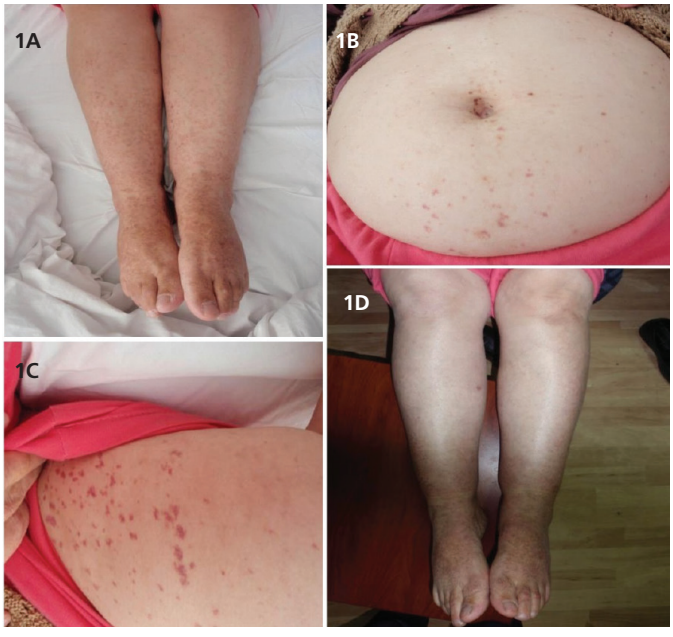

Figure 1A. Petechiae and purpura, **1B.** Petechiae and purpura in the abdomen, **1C.** New petechiae and purpura in the thigh, **1D.** Post-treatment control

The patient was screened for malignancy. The following test and clinical examination results were normal/negative: fecal occult blood test, gynecological examination and smear test, otorhinolaryngological examination and endoscopy, chest and neck X-ray, abdominopelvic ultrasound (USG); bilateral mammography and breast USG. Venous and color Doppler USG of the lower extremity arteries were normal. Fasting and postprandial blood glucose screening also revealed normal glucose levels. Both the HbA1c value of 5.9% (4.8 to 6) and urine microalbumin levels were within the normal limits. We discontinued metformin due to suspicion of drug-induced vasculitis. A skin biopsy was performed, which showed mild to moderate keratosis in the epidermis, and congestion in the dermis, as well as sparse mild perivascular lymphocytic infiltrates (Figure 2A). Immunofluorescence (IF) test results were negative, which did not imply active vasculitis. These findings suggested that the biopsy could have been taken from inactive lesions

Table 1. Laboratory tests

Parameters	Results	Normal
Leukocyte (u/L)	7.05	4.3-10.3
Haemoglobin (gr/dL)	**12.8**	13.6-17.2
Platelet (u/L)	245	156-373
CRP (mg/L)	**14**	0-6
ESR (mm/Hour)	33	0-20
ASO (IU/mL)	25	0-200
RF (IU/mL)	10	<25
ANA (IF)	Negative	Negative
Anti dsDNA (IF)	Negative	Negative
ANCA (IF)	Negative	Negative
Hepatitis B and C test	Negative	Negative
Salmonella test	Negative	Negative
Brucella test	Negative	Negative
HIV test	Negative	Negative
Cryofibrinogen	Negative	Negative
Cryoglobulin	Negative	Negative
ACA-IgM (U/mL)	2	0-12
ACA-IgG (U/mL)	6	0-12
C3 (mg/dL)	176	89-187
C4 (mg/dL)	27	16.5-38
Creatinin (mg/dL)	0.5	0.8-1.2
BUN (mg/dL)	7	5-20
AST (IU/L)	22	<31
ALT (IU/L)	17	<31
aPTT (sec)	11.13	10.5-13.2
INR	0.95	0.85-1.2

ANA: Antinuclear antibodies, anti-dsDNA: Anti-double stranded DNA antibodies, ANCA: Antineutrophil cytoplasmic antibodies, ACA: Anticardiolipin antibodies, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, aPTT: Activated partial thromboplastin time, ASO: Antistreptolysin-O, BUN: Blood urea nitrogen, C3-C4: Complement, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, INR: International Normalization Rate, RF: Rheumatoid factor, HIV: Human immunodeficiency virus

or that a vasculitis could have been masked by the topical steroid and antihistamine therapy.

Over the course of the outpatient follow up, lower extremity skin lesions improved, but new lesions had appeared on the thighs (Figure 1C). The patient refused a biopsy from the new lesions. Her 24-hour urine sample had 2.5 g/day proteinuria as well as eosinophilia (10%). A renal biopsy was performed due to non-nephrotic range proteinuria and abnormal urinary sediment findings. Among the 12-13 glomeruli specimens, we saw complete sclerosis in 1 glomerulus; segmental mesangial cell proliferation, polymorphonuclear leukocyte infiltration, nuclear dust, and adhesions between the glomerular tuft and Bowman's capsule in 3 glomeruli, and enlargement and congestion in the rest. Focal fibrosis (5%), tubular atrophy, and mononuclear cell infiltration were detected in the interstitium, scattered hyalinization and thickening in some vessel walls, and hyaline and erythrocyte casts in the tubular lumen. Crystal violet stain showed no amyloid deposition. IF staining were negative. Histopathological and immunohistochemical findings were consistent with focal proliferative glomerulonephritis (FPGN) (Figure 2B). In addition to glomerulonephritis findings, mild interstitial nephritis findings were also found on renal biopsy.

We excluded primary or other secondary vasculitis, CTD, infection, and malignant diseases and considered the patient as having metformin-induced systemic vasculitis based on clinical and laboratory findings, drug use, and eosinophiluria. We did not restart metformin because metformin-induced vasculitis cases have been reported in the literature and the HbA1c and glucose levels of the patient were normal. We also did not initiate supportive therapy including ACE inhibitors and statins.

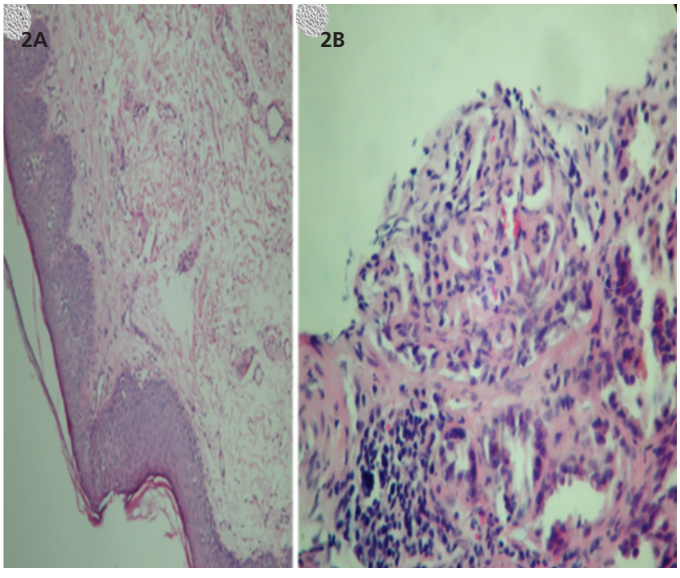

Figure 2A. Skin biopsy (HE 100x). Rare perivascular lymphocytes, **2B.** Kidney biopsy (HE 200x). Segmental mesangial cell proliferation and Polymorphonuclear leukocytes infiltration in the glomeruli

Oral MP 1 mg/kg/day and azathioprine (AZA) 100 mg/day were started due to relapsed/refractory skin findings and renal involvement. Skin findings disappeared completely in follow-up (Figure 1D). Then we reduced the dose of oral MP and continued AZA therapy. At 3-month follow-up visit, C-reactive protein and erythrocyte sedimentation rate had returned to normal levels. Proteinuria levels decreased to 2500 mg/day, 1218 mg/day, 1000 mg/day, and 120 mg/day at 0, 3, 6, and 9 months, respectively. Currently, the patient continues using MP 4 mg/day and AZA 100 mg/day.

Discussion

LCV is a histological term commonly used to refer to manifestations such as neutrophil-rich exudate involving postcapillary venules, endothelial dysfunction, fibrin deposition, and leukocytoclasia. LCV can be primary (idiopathic) without an identifiable cause or secondary to identifiable causes. In the latter, typical causes include skin involvement of systemic vasculitis, CTD, infectious diseases, and lymphoplasmacytic malignancies. More than 30% of malignant cases are reported to be hematologic (IgA monoclonal gammopathy). However, the cause remains obscure in many cases.[6] Cutaneous vasculitis affects all ages but is less common in children than adults and slightly more in females than in males.[3] Characteristic lesions are nonpruritic petechiae and palpable purpura, and are more prevalent in the lower extremities.

The pathogenic mechanism of drug-induced vasculitis is not fully defined and varies depending on the underlying causes. Immune complexes are considered responsible for the pathogenesis of LCV. An immune-mediated adverse reaction occurs against a triggering antigen. Some studies have attempted to establish the correlation of deposition of immune complexes and complement activation inside the vascular walls with LCV.[7] In a study on 61 patients by Khetan et al.[8], HSV (37.7%), Henoch-Schönlein purpura (HSP) (26.2%), drugs (19.7%), infections (11.4%), and CTD (6.5%) were implicated in the etiology of cutaneous vasculitis. Currently, there is no laboratory method or pathological finding to distinguish drug-induced vasculitis from the other types. In drug-induced LCV, symptoms mostly resolve after the discontinuation of the causative agent. Lesions recur in only 10% of cases. LCV is often limited to the skin but may also show systemic involvement. Drug-induced vasculitis accounts for approximately 10-20% of all cases.[9]

Metformin is a biguanide-derivative oral antidiabetic drug widely used in managing type 2 DM and particularly preferred in overweight patients. Cutaneous side-effects such as rash, urticaria, photosensitivity, and lichenoid and psoriasiform drug eruption have been rarely reported due to metformin use.[5] These findings usually disappear days to weeks after the discontinuation of the drug. However, in most cases, the findings recur after metformin is restarted. The diagnosis of drug-induced LCV requires the exclusion of other potential causes. In our case, IF staining was not observed in the renal biopsy. There was no finding suggesting lupus nephritis, diabetic nephropathy, pauci-immune GN, or HSP. The findings were consistent with FPGN. We suspected renal involvement due to metformin-induced LCV. We started AZA because of non-nephrotic proteinuria and non-severe clinical findings. FPGN and skin symptoms responded well to combination therapy with MP and AZA.

The diagnosis of drug-induced LCV is quite difficult as it is based on the history of drug exposure, the exclusion of other types of vasculitis, and disappearance/reappearance of lesions after discontinuation/restarting of the drug.[6] In our case, skin biopsy was not typical for LCV, but histopathological findings might have regressed as the patient's rashes had appeared 2 months earlier. When she had initially presented to our clinic, she was using topical steroid cream and antihistamine. This may explain the sparse distribution of lymphocytes detected in the biopsy performed later. Besides, her skin lesions initially recurred on the thighs but totally resolved after the combination therapy.

In literature (PubMed, Scopus, and Google Scholar), only 3 cases with metformin-induced LCV have been reported so far. The first was a 59-year-old female patient. She had developed skin rash and pneumonitis during DM treatment with metformin. Metformin was discontinued. Her skin biopsy was compatible with LCV. Oral prednisone was started for the treatment of pulmonary symptoms. The findings subsequently regressed. In her follow-up, metformin had been restarted 2 weeks after prednisolone was discontinued and the skin findings reappeared. They disappeared after the discontinuation of metformin once more.[10] The second case was a 33-year-old female patient using metformin 850 mg/day to lose weight. She had developed skin lesions. When metformin was discontinued, they disappeared. However, in her follow-up visit, the findings had recurred after resuming the metformin.[11] The third case was a 60-year-old female patient. She had developed bullous skin lesions in the lower extremities after using metformin 850 mg/day for DM. Her skin biopsy was compatible with LCV, and IF test results were negative. No etiology of vasculitis other than metformin was found. Topical and systemic steroids were started after the discontinuation of metformin. In her follow-up visit two months later, the skin lesions had completely disappeared.[12] The comparison of the characteristics of our case and 3 metformin-induced vasculitis cases reported so far are given in Table 2.

The common feature of these three cases is that skin findings had occurred after metformin use. In the first two cases, skin findings recurred after reinitiating the metformin. Metformin-induced rashes usually occur within the first week of drug use, but this period may go up to months or even years. The durations of vasculitis development due to metformin use in all cases are given in Table 2.

Conclusion

Our case is the first published metformin-induced proliferative GN. Currently, it is the fourth reported case of metformin-induced LCV. Drug-induced LCV often resolves with the discontinuation of the drug and rarely requires systemic treatment. Metformin rarely causes LCV and systemic findings may occur as in our case. Further studies are needed to establish the relationship between metformin and LCV.

Table 2. Cases of metformin-induced vasculitis

Patients	Age/Sex	Purpose	Skin rash	Semptoms	Period**	Biopsy	Treatment
Case-1	59-F	T2DM	Purpuric papules	Pneumonitis	4 month	LCV	Oral prednizolon
Case-2	39-F	Weight loss	Palpable purpura	No	5 day	LCV	Topical chlorhexidine and aqueous eosine
Case-3	60-F	T2DM	Hemorrhagic papules, Vesicles, and Bullae	No	1 month	Bullous LCV	Topical corticosteroids and antibacterials Oral prednisone
Present Case	58-F	T2DM	Petechiae Palpable purpura	Leukocyturia Hematuria Proteinuria	2 month	Perivascular lymphocytic infiltrates in skin biopsy. Focal proliferative GN	Oral MP Azathioprine

DM: Diabetes mellitus, GN: Glomerulonephritis, LCV: Leukocytoclastic vasculitis, MP: Methylprednisolone.

***The time between initiation of metformin and development of vasculitis*

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: F.Y., B.K., E.E., Design: F.Y., B.K., E.E., Data Collection or Processing: F.Y., B.K., E.E., Analysis or Interpretation: F.Y., B.K., E.E., Literature Search: F.Y., B.K., E.E., Writing: F.Y., B.K., E.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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