Cutaneous leukocytoclastic vasculitis induced by continuous erythropoietin receptor activator

Hyeok-Jin Kwon, MD, Jung-Hwan Kim, MD, Dong-Wha Yoo, MD, Tae-Hoon Kim, MD, Jung-Ho Yoon, MD, and Ki-Ho Kim, MD, PhD
Busan, Republic of Korea

Key words: continuous erythropoietin receptor activator; cutaneous leukocytoclastic vasculitis; immunogenicity; polyethylene glycol; type III hypersensitivity.

INTRODUCTION

Cutaneous leukocytoclastic vasculitis (CLCV) is characterized by the inflammation of superficial small vessels of the skin that clinically presents as a palpable purpura.[1,2] Type III hypersensitivity, wherein immune complexes play a significant role, is considered a key mechanism underlying CLCV pathophysiology.[1] Numerous factors promote CLCV, although infection and drugs are etiologically dominant.[1,2]

Erythropoiesis-stimulating agents have been commonly used for anemia treatment in patients with chronic kidney disease (CKD).[3,4] However, there are emerging concerns that these recombinant human proteins exhibit immunogenicity, which can induce autoantibodies that form immune complexes that impair drug effectiveness.[5,6] Continuous erythropoietin receptor activator (CERA) is a type of erythropoiesis-stimulating agent that contains polyethylene glycol (PEG), which is generally considered to decrease immunogenicity.[3,7,8] Herein, we report a case of CLCV that occurred after CERA injection.

Abbreviations used:

CERA:	continuous erythropoietin receptor activator
CKD:	chronic kidney disease
CLCV:	cutaneous leukocytoclastic vasculitis
PEG:	polyethylene glycol

CASE REPORT

A 74-year-old Korean woman with stage 5 CKD who had been treated with hemodialysis for 2 years was prescribed a subcutaneous injection of 150-μg CERA (Mircera, Roche) every 4 weeks for the treatment of anemia (hemoglobin level, 8.3 mg/dL). Ten days after the first injection, palpable purpuric lesions appeared on the lower extremities before spreading to the arms a few days later (Fig 1, *A* and *B*). Despite several medications being administered (itopride, deflazacort, ilaprazole, and raloxifene), the patient had not experienced any adverse effects prior to this incident. Initially, we performed blood tests to differentiate not only coagulation disorders and rheumatologic diseases but also vasculopathies that can result in cutaneous purpura; we evaluated the complete blood cell count, liver and kidney function, prothrombin time, activated partial thromboplastin time, complement levels, cryoglobulin levels, fibrinogen levels, fibrinogen degradation product, antithrombin III, D-dimer, rheumatoid factor, antinuclear antibody, anti–double-stranded DNA antibody, and antineutrophil cytoplasmic antibody. However, these tests did not reveal any considerable findings, except for the known CKD and anemia. Hence, a pathologic evaluation was necessary to make an accurate diagnosis. A skin biopsy was performed on the leg using a 3-mm punch. Perivascular inflammatory cells were observed in the dermis, mainly comprising neutrophils, in addition to some eosinophils and lymphocytes (Fig 2, *A*). Under higher magnification, we discovered prominent vascular damage demonstrated by extravasated erythrocytes, nuclear dust, and vascular wall destruction (Fig 2, *B*).

From the Department of Dermatology, College of Medicine, Dong-A University, Busan.
Funding sources: None.
IRB approval status: Not applicable.
Correspondence to: Ki-Ho Kim, MD, PhD, Department of Dermatology, College of Medicine, Dong-A University, Busan 49201, Republic of Korea. E-mail: khkim@dau.ac.kr.

JAAD Case Reports 2021;16:101-4.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.08.027

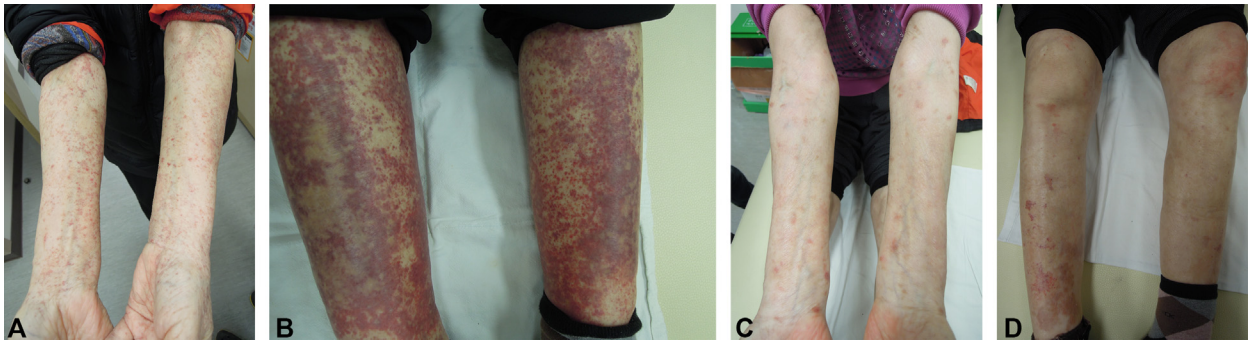

Fig 1. Cutaneous purpuric lesions after the first continuous erythropoietin receptor activator injection. **A** and **B**, Diffuse erythematous-to-violaceous purpura on the legs and arms of the patient. **C** and **D**, Cutaneous manifestations after treatment with topical and systemic corticosteroids.

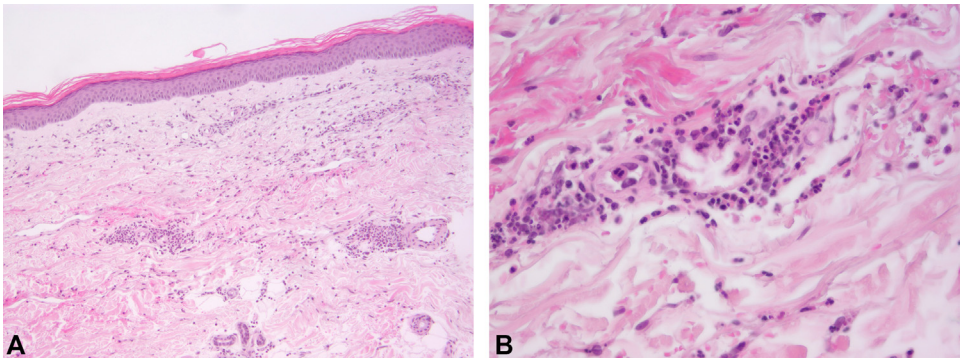

Fig 2. Histopathologic findings of the initial purpuric lesions on the leg. **A**, Hematoxylin-eosin staining showing superficial deposition of perivascular inflammatory cells. **B**, Typical findings of leukocytoclastic vasculitis with dermal infiltrates dominantly composed of neutrophils; neutrophilic nuclear dust, extravasated erythrocytes, and vascular endothelial wall destruction were observed. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×100; **B**, ×400.)

Furthermore, immunoglobulin and complements were deposited along the vascular walls, as observed by direct immunofluorescence (Fig 3, *A* to *C*).

Based on clinical and histologic findings, the patient was diagnosed with CLCV caused by CERA injection; topical 1% hydrocortisone lotion, olopatadine 10 mg daily (5 mg twice a day), and methylprednisolone 8 mg daily (4 mg twice a day) were administered. Two weeks after treatment, the purpuric lesions were found to be significantly ameliorated (Fig 1, *C* and *D*). However, to address the anemia, erythropoietin injections were needed; therefore, subcutaneous 150-μg CERA injections were resumed. One week after the second injection, the patient was referred to the dermatology department due to a recurrence of purpuric lesions on the extremities (Fig 4, *A* and *B*). We applied the same therapeutic modalities, and the lesions were ameliorated (Fig 4, *C* and *D*). Since the cutaneous lesions repeatedly developed following CERA injection, we recommended continuous prophylactic treatment with low-dose systemic steroids (methylprednisolone 4 mg twice a day). Although mild cutaneous lesions persisted, the patient tolerated successive injections.

DISCUSSION

Cutaneous vasculitis can be induced by numerous factors such as infection, drugs, and systemic diseases.[1] Leukocytoclastic vasculitis is pathologically defined as neutrophilic vascular damage comprising extravasated erythrocytes, neutrophilic nuclear dust, and vascular wall degeneration that clinically presents with erythematous-to-violaceous lesions on the skin.[1] Consequently, immune complexes are formed through antigen-antibody interactions, which are deposited along the dermal vascular walls, thereby inducing successive inflammatory pathways that destroy the vascular structures.[1]

Drugs are considered a principal cause of CLCV, with countless agents being reported.[1,2] Although the pathogenesis of drug-induced vasculitis is not

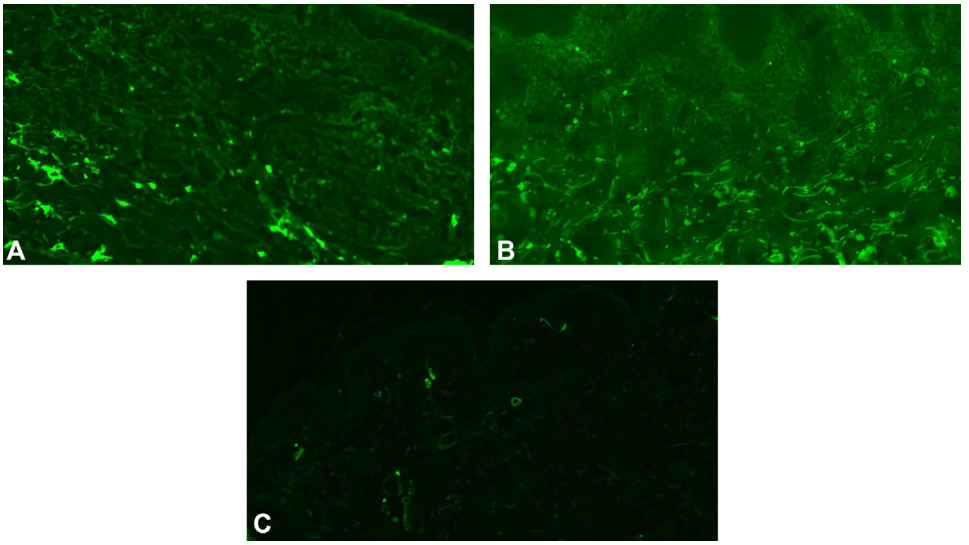

Fig 3. Immunoglobulins and complements were detected along the vascular walls by direct immunofluorescence. **A**, IgG. **B**, C3. **C**, Immunoglobulin M. (Original magnifications: **A**, ×200; **B**, ×200; **C**, ×200.)

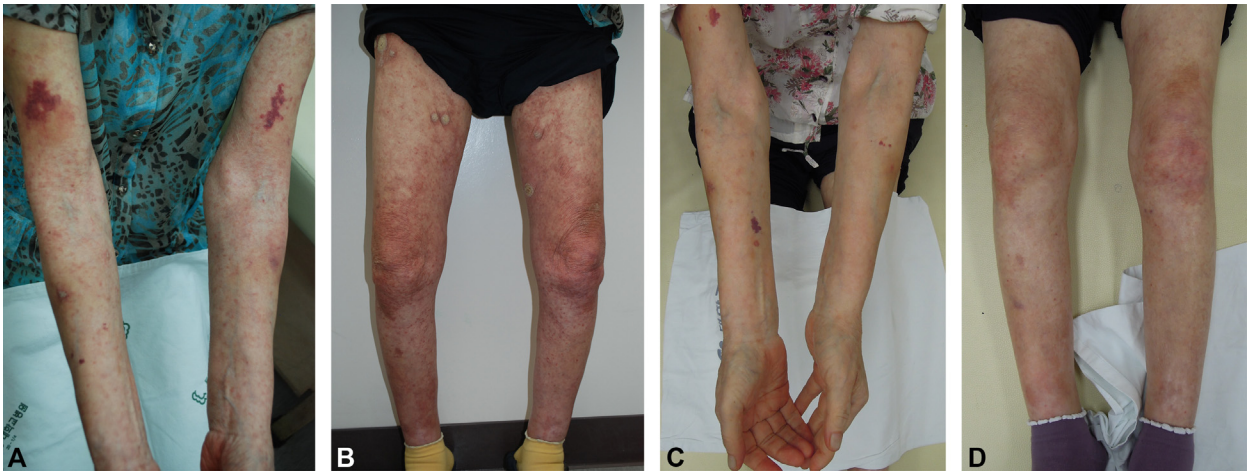

Fig 4. Recurrent purpura after the second continuous erythropoietin receptor activator injection. **A** and **B**, Worsened purpuric lesions on the extremities. **C** and **D**, Improved cutaneous findings upon the administration of the same therapeutic modalities as on the first incidence.

fully understood, it is believed that drug molecules act as haptens that can display immunogenicity when attached to large carrier proteins and serve as epitopes.[2] Hapten molecules induce the activation of B cells, which in turn produce selective antibodies.[2] Therefore, immune complexes are produced as a result of drug-derived haptens.

Chronic intractable anemia in patients with CKD is a major concern because erythropoietin, a vital hormone that stimulates erythropoiesis, is mainly produced in the kidney. To address this symptom, several recombinant erythropoiesis-stimulating agents have been introduced,[3,4] which are integral to CKD-induced anemia treatment; however, immunogenicity associated with these biopharmaceuticals has become a major issue, as it impacts their efficacy.[5,6]

CERA (methoxy polyethylene glycol-epoetin beta) injections have a long-acting efficacy, which can help clinicians extend injection intervals owing to its added PEG molecules.[4,5] Overall, PEG molecules not only stabilize the active therapeutic agent but also reduce its potential immunogenicity.[3,4,7,8] However, PEGylated drugs have been known to induce antibody production, including anti-PEG immunoglobulin M and IgG antibodies.[7,8] Although

the biologic effects of these antibodies are still debatable, we hypothesized that anti-PEG immunoglobulin M and IgG antibodies target the PEG molecules in CERA.[7,8] Anti-PEG antibodies against PEGylated drugs can induce reduced drug efficacy and hypersensitivity.[7] Indeed, several cases of anaphylaxis and pure red cell aplasia have been reported, indicating that CERA can also promote biopharmaceutical-related immune responses.[9,10]

In this case, although the clinical course of the patient improved after the first (hemoglobin range, 8.3-10.1 mg/dL) and second (hemoglobin range, 9.3-10.9 mg/dL) CERA injections, we concluded that the presented cutaneous lesions were a response to CERA injections, based on the patient's clinical history and response to treatment. Regarding the pathogenesis of CLCV and biopharmaceutical immunogenicity, both are associated with immune complex–mediated reactions.[1,5,6] Our histologic findings highlighted the deposition of immunoglobulin and complements along the vascular walls, suggesting the clinical manifestation of biopharmaceutical-induced immunogenicity, which is a possible evidence of the existence of anti-PEG antibodies.[1,5-8]

In conclusion, this case report provides clues that CERA displays immunogenicity that clinically presents as CLCV. Additionally, this case provides clinical evidence of PEG immunogenicity; hence, we propose in-depth studies focusing on the precise mechanism underlying PEG immunogenicity, which remains controversial.

The authors acknowledge and are grateful for the patient's permission to publish the herein described clinical information.

Conflicts of interest

None disclosed.

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