INTERNAL MEDICINE

□ CASE REPORT □

Successful Corticosteroid Treatment for Purpura Fulminans Associated with Quinolone

Ikue Okamura[1], Yukitsugu Nakamura[2], Yuka Katsurada[3], Ken Sato[4], Takashi Ikeda[1] and Fumihiko Kimura[4]

Abstract

Purpura fulminans (PF) is a life-threatening syndrome comprising progressive hemorrhagic necrosis due to disseminated intravascular coagulation and dermal vascular thrombosis that leads to purpura and tissue necrosis. Various therapies have been used to arrest the progression of this disease, however, there is no established treatment because of the variety of underlying causes. We herein present an adult case of PF associated with leukocytoclastic vasculitis triggered by antibiotic (levofloxacin) intake. As a result of our rapid and accurate identification of the underlying cause, corticosteroid therapy successfully repressed the inflammatory process. As far as we know, this is the first report of levofloxacin-associated PF.

Key words: dermal vascular thrombosis, hypersensitivity vasculitis, intravascular coagulation, leukocytoclastic vasculitis, purpura fulminans

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Introduction

Purpura fulminans (PF) is a rare syndrome of intravascular thrombosis and hemorrhagic infarction of the skin that progresses rapidly and is accompanied by vascular collapse and disseminated intravascular coagulation (DIC) (1). It often requires surgical debridement, skin grafting or even amputation. The skin lesion is characterized by microvascular thrombosis in the dermis that ultimately results in perivascular hemorrhaging and necrosis with minimal inflammation (2). Inherited and acquired abnormalities of the protein C (PC) anticoagulant pathway are now believed to be responsible for the majority of patients with this clinical syndrome (2). Three distinct categories can be identified by the triggering mechanisms: i) acute infectious PF, which is the most common type; ii) neonatal PF associated with a hereditary deficiency of PC, protein S (PS), or antithrombin III (ATIII); and iii) idiopathic PF, which can be post-infectious or of unknown etiology (1). We herein report a case of drug-associated immune complex vasculitis presenting as idiopathic PF. As a result of our rapid and accurate identification of the underlying causes, corticosteroid therapy successfully repressed the inflammatory process. This is the first report of idiopathic PF that appeared to be triggered by levofloxacin intake.

Case Report

A previously healthy 22-year-old woman visited a general practitioner because, 2 weeks previously, she had developed abdominal pain, diarrhea (3 to 4 times per day), and a low-grade fever. She was prescribed levofloxacin, which she took for five days. She was admitted to our hospital because she developed bloody stool on the day following the first oral administration of levofloxacin, and also because of the sudden appearance of palpable purpura on her right foot four days later. After admission to our hospital, purpura rapidly progressed to ecchymoses on her trunk, with severe burning pain.

Upon hospital presentation, her consciousness was clear and vital signs were as follows: axillary temperature,

[1]Division of Hematology and Stem Cell Transplantation, Shizuoka Cancer Center, Japan, [2]Department of Hematology and Oncology, Dokkyo Medical University School of Medicine, Japan, [3]Department of Laboratory Medicine, National Defence Medical College Hospital, Japan and [4]Division of Hematology, Department of Internal Medicine, National Defence Medical College, Japan
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Correspondence to Dr. Takashi Ikeda, t.ikeda@scchr.jp

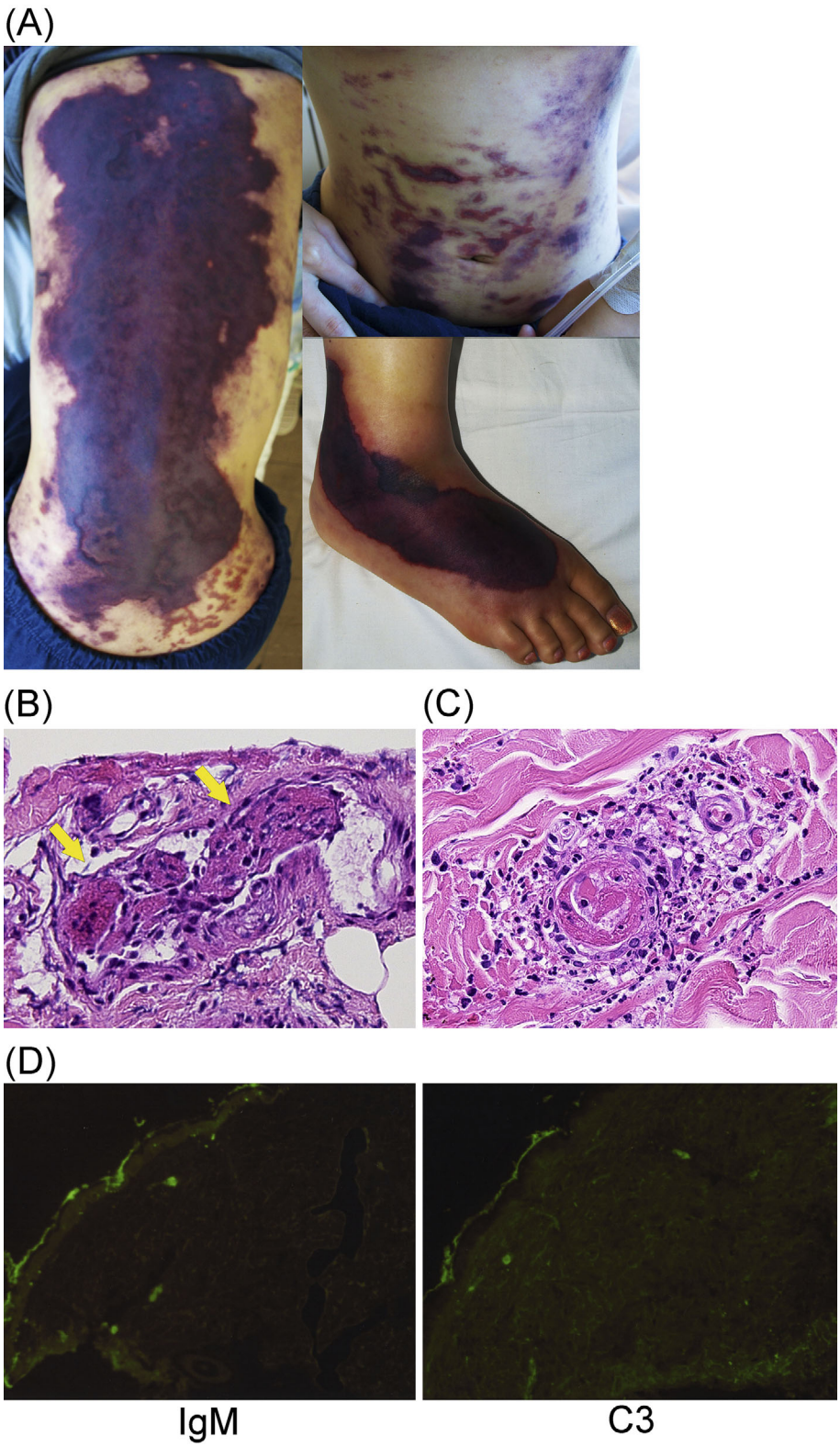

Figure 1. **Macroscopic and microscopic findings of the skin lesion. (A) Palpable purpura progressed rapidly into extensive ecchymoses on the back (left), trunk (right upper), and right foot and ankle (right lower). (B) A fascia biopsy of the right crus showing fresh fibrin thrombi (arrows), including neutrophils within a small dilated vessel [Hematoxylin and Eosin (H&E) staining; original magnification 20×]. (C) A skin biopsy showing infiltration of neutrophils with karyorrhectic nuclear debris, and extravasation of erythrocytes around small vessels in the dermis, leading to a diagnosis of leukocytoclastic vasculitis (H&E staining; original magnification 20×). (D) A skin biopsy showing immunoglobulin M and C3 deposition within the walls of a small vessel in the dermis (immunofluorescence stain; original magnification 20×).**

Table. Laboratory Data on Admission.

Complete blood counts	
White blood cell count	11,400/μL
Myelocyte	1.0%
Neutrophil (band form)	85.0% (42.0%)
Lymphocyte	5.0%
Monocyte	9.0%
Red blood cell count	447×10^4/μL
Hemoglobin	10.4 g/dL
Hematocrit	31.7%
Platelet count	11.6×10^4/μ
Coagulation	
Activated partial thromboplastin time (APTT)	29.4 sec (cont. 30.1 sec)
Prothrombin Time (PT)-INR	1.54
Fibrinogen	274 mg/dL
Fibrin degradation product (FDP)	31 μg/mL
D-dimer	21.1 μg/mL
Antithrombin III	78%
Plasmin-α2 plasmin inhibitor complex (PIC)	2.4 μg/mL
Thrombin antithrombin complex (TAT)	> 60.0 ng/mL
Coagulation factor XIII	37%
Protein C activity	65%
Protein C antigen	60%
Protein S activety	68%
Blood chemistry	
Total protein	4.8 g/dL
Albumin	2.1 g/dL
AST	16 IU/L
ALT	8 IU/L
LDH	311 IU/L
ALP	186 IU/L
γ-GTP	7 IU/L
creatine kinase	301 IU/L
BUN	4 mg/dL
Creatinine	0.5 mg/dL
Na	133 mEq/L
K	4.0 mEq/L
Cl	100 mEq/L
Serelogical studies	
C-reactive protein (CRP)	7.2 mg/dL
Immunoglobulin G	1,020 mg/dL
Immunoglobulin A	118 mg/dL
Immunoglobulin M	54 mg/dL

38.7°C; pulse, 130 beats per minute and regular; respiration, 14 breaths per min; and blood pressure, 111/83 mmHg. Upon physical examination, her abdomen was hard and tender with hypoactive bowel sounds. Palpable red-violet plaques were observed on the right lower limb, as were extensive ecchymoses on the trunk (Fig. 1A), and there was a dramatic progression from petechiae to confluent ecchymoses on the skin. Initial laboratory tests (Table) revealed a decreased hemoglobin concentration, a low platelet count, and an increased white blood cell count. Schizocytes were present on a peripheral blood smear. The coagulation system demonstrated elevated levels of plasma D-dimer, fibrin degradation product, thrombin antithrombin complex, and a decreased level of antithrombin III (ATIII), all of which were consistent with a diagnosis of DIC. A decreased level of fibrin stabilizing factor (FXIII) was also observed. Although there was no evidence of an inherited abnormality of PC or of PS—the activity levels of which were 65% and 68%, respectively—the presence of a slightly decreased functional level of PC was consistent with undergoing DIC-related consumption.

The results of serological testing for viral infections (including hepatitis B and C and HIV) were all negative. The levels of complement proteins C3 and C4 and of serum IgA were within the normal range, and no cryoglobulins were detected. The results of testing for double-stranded DNA antibodies, rheumatoid factor, anticardiolipin antibody, lupus anticoagulant, and antineutrophil cytoplasmic antibodies were all negative. Microscopic hematuria was observed, but proteinuria was not. Abdominal computed tomography revealed mural edematous thickening of the total colon, indicating severe inflammation. The clinical course and existence of DIC confirmed the diagnosis of PF.

Given the prognosis, immediate, intensive management was initiated, along with empiric therapy for PF (3). Empiric therapy consisted of anticoagulation therapy with the administration of low molecular weight heparin, along with broad-spectrum antibiotics (meropenem and clindamycin) and replacement of deficient blood components (fresh frozen plasma, ATIII, and FXIII). The day following the initiation of treatment, the patient's skin lesions continued to progress, her right crus became swollen, and the serum creatine kinase level elevated. In response to a suspicion of compartment syndrome, fasciotomy was performed on the fourth day following admission. This revealed effusion and inflammation in the subcutaneous tissue, but not in the muscle. The pathologic findings from the fascia biopsy revealed fresh fibrin thrombi including neutrophils in a small dilated vessel (Fig. 1B). These pathologic findings supported the clinical diagnosis of PF (2).

The patient continued to exhibit a fever and experienced purpura expansion and bloody stool, despite the treatment. Multiple cultures of blood, urine, and feces failed to yield any pathological organisms, indicating that bacterial infection had not triggered PF. According to these findings, we suspected that the underlying inflammatory process caused her hypercoagulable state, therefore, we inhibited the inflammatory process. On the fifth day after hospital admission, we began steroid pulse therapy with 1 g of intravenous methylprednisolone for three days, followed by gradual tapering off of steroid administration. This led to an immediate improvement, as evidenced by improved clinical and laboratory findings.

A skin biopsy from fresh purpura performed on the ninth day after hospital admission revealed infiltration of the neutrophils along with karyorrhectic nuclear debris and extravasation of erythrocytes around the small vessels in the dermis (Fig. 1C). An immunofluorescence examination revealed both immunoglobulin M (IgM) and C3 deposited within the wall of small vessels, but no immunoglobulin A (IgA) (Fig. 1D). Therefore, the patient was diagnosed to have leukocytoclastic vasculitis with IgM deposition. IgM deposition in blood vessels readily occurs in cases of vasculitis with circulating rheumatoid factor or monoclonal production of IgM, as found in cryoglobulinemic vasculitis or rheumatoid vasculitis (4). However, no cryoglobulins or rheumatoid factor was detected in the serum of the present patient. Fluoroquinolone-associated leukocytoclastic vasculitis has been previously reported, including levofloxacin in 4

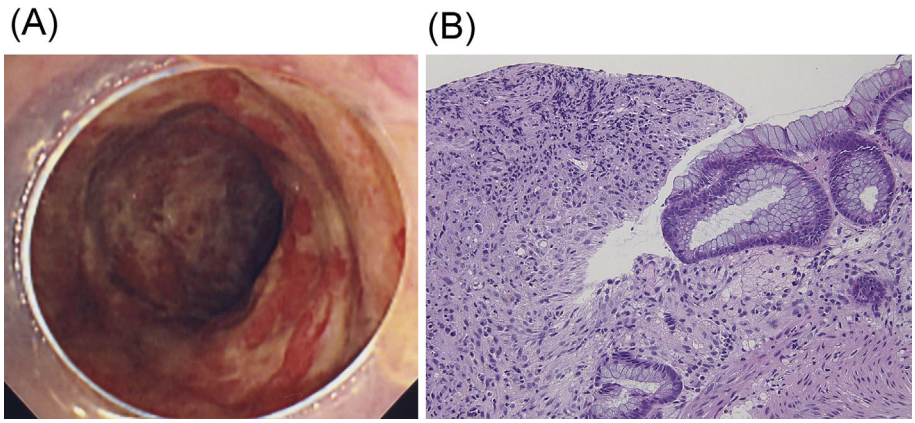

Figure 2. Macroscopic and microscopic findings of the colon lesion. (A) Colonoscopy showing widespread inflammation with multiple skip ulcers. (B) A colon biopsy showing colonic mucosa with slightly irregular-shaped, distributed crypts and granulation tissue (Hematoxylin and Eosin staining; original magnification 20×).

cases (5). Therefore, the present case could be diagnosed either as PF due to drug-associated hypersensitivity vasculitis (HV) [according to the 1990 American College of Rheumatology Classification Criteria (6)] or as drug-associated immune complex vasculitis [according to the Chapel Hill Consensus Conference 2012 Nomenclature (7)].

Total colonoscopy on the 17th day after hospital admission revealed widespread inflammation involving the entire colon, with multiple skip ulcers (Fig. 2A). A colon biopsy revealed non-specific colitis with ulceration (Fig. 2B). Corticosteroid administration was terminated two months after hospital admission, and thereafter no additional skin lesions developed while the purpuric skin lesions became necrotic. The patient was afebrile and had no abdominal complaints, with a normal coagulation state (PC and PS activity levels of 203% and 88%, respectively). Follow-up total colonoscopy performed on the 58th day after hospital admission revealed an almost normal mucosa with some scarring. We concluded that intestinal bleeding was a systemic sign of HV. Surgical debridement of the necrotic dermal tissue, followed by the application of skin grafts, was necessary on the 70th day after admission. One year after her initial presentation, the patient had fully recovered, without experiencing any disease recurrence.

Discussion

The factors central to the development of PF are thought to be abnormalities of the PC anticoagulant pathway (2). In acquired cases of PF, the common cause is severe bacterial infections (acute infectious PF), especially meningococcal disease. Idiopathic PF is rare and often follows an initiating febrile illness after a variable latent period (1). Acquired deficiencies of PC or PS are considered to be the pathogenesis of idiopathic PF. Furthermore, there are rarer cases of idiopathic PF, whose causes include antiphospholipid syndrome, ulcerative colitis, paroxysmal nocturnal hemoglobinuria, and systemic lupus erythematosus (2, 8-10), as well as drugs. Among the responsible drugs, acetaminophen and non-steroidal anti-inflammatory drugs have been reported (11-13). In the present case, the diagnostic possibilities initially considered were PF, thrombotic thrombocytopenic purpura, Henoch-Schönlein purpura, enterohemorrhagic *E. coli* infection, drug-associated immune complex vasculitis or post-infectious thrombocytopenic purpura. The diagnosis of PF in our patient was made according to the presence of purpuric necrotic skin lesions, coagulation abnormalities consistent with DIC, and the presence of thrombi in the dermal vessels. A history of diarrhea and low-grade fever suggested prior viral infection, which was compatible with idiopathic PF. On the other hand, there was a temporal relationship between the onset of clinical deterioration (from diarrhea to bloody stool and the sudden appearance of palpable purpura) and the administration of levofloxacin. Based on the medication administered at the disease onset and leukocytoclastic vasculitis with IgM deposition in the skin biopsy, the diagnosis of drug-associated immune complex vasculitis was made (7). The mechanism responsible for drug-associated immune complex vasculitis is unclear, however, from the immunofluorescence results we suggest that the drug is likely to stimulate an immune response by acting as a hapten. Therefore, leukocytoclastic vasculitis triggered by levofloxacin appears to have caused a hypercoagulable state that proceeded PF. Indeed, a previous case report described necrotizing vasculitis secondary to propylthiouracil presenting as PF (14).

Despite advances in intensive care monitoring and treatment, the rates of morbidity and mortality associated with PF remain high (15). Given the devastating prognosis associated with PF, a successful therapeutic outcome is most likely when there is early recognition of the underlying pathophysiological mechanism. In the present case, corticosteroid therapy suppressed the underlying inflammation process. It is important to stress that management strategies require rapid and accurate identification of the underlying cause.

The authors state that they have no Conflict of Interest (COI).

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