Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4149-24
Intern Med Advance Publication
http://internmed.jp

【 CASE REPORT 】

Critical Limb Threatening Ischemia Due to Severe Polyarteritis Nodosa—A Case Report—

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Abstract:

A delayed diagnosis of polyarteritis nodosa may lead to critical limb-threatening ischemia (CLTI). A 74-year-old woman presented with left-foot pain and was treated with oral vasodilators and antiplatelet agents. However, the distal ischemia progressed to CLTI, including gangrene of the fingers and toes, and bilateral foot dropping appeared because of peroneal nerve paralysis. Angiography of the extremities revealed obstruction and stenosis of medium-sized arteries. Based on the progressive distal gangrene, mononeuropathy multiplex, and pathological findings of necrotic vasculitis, polyarteritis nodosa was diagnosed, and the patient's condition improved. A biopsy and neurological examination are essential for the appropriate diagnosis of PAN and immediate treatment.

Key words: Vasculitis, Digital gangrene, Mononeuropathy multiplex, Polyarteritis nodosa

(Intern Med Advance Publication)
(DOI: 10.2169/internalmedicine.4149-24)

Introduction

Polyarteritis nodosa (PAN) was defined in the Chapel Hill Consensus Conference as "necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules" (1). The overall prognosis of this disease has improved in recent decades, primarily because of its early diagnosis and the efficacy of immunosuppressant treatment (2). However, delays in the diagnosis and treatment of PAN may result in critical limb-threatening ischemia (CLTI), including distal necrotic lesions or gangrene. We herein describe a case of CLTI of gangrene of the fingers and toes that occurred due to severe PAN.

Case Report

A 74-year-old woman presented to the hospital with pain in the toes of the left foot 3 months before presentation (Fig. 1A). Oral prostanoids and antiplatelet agents were administered due to peripheral circulation insufficiency. She had experienced difficulty in walking because of a drooping left foot, which had persisted for one month. She then experienced digital pain in the right 5th finger and left 2nd and 3 rd fingers. No other preceding symptoms, such as fever, body weight loss, dizziness, skin symptoms (purpura, livedo reticularis), arthralgia, or myalgia, were observed. She had diabetes, dyslipidemia, and hypertension, and had been taking metformin, rosuvastatin, amlodipine, and valsartan for years. The patient had no history of allergy or smoking. Treatment did not improve her symptoms, and necrotic lesions of the tip and toe of her foot and her fingers pro-

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Received: May 18, 2024; Accepted: July 31, 2024; Advance Publication by J-STAGE: October 4, 2024
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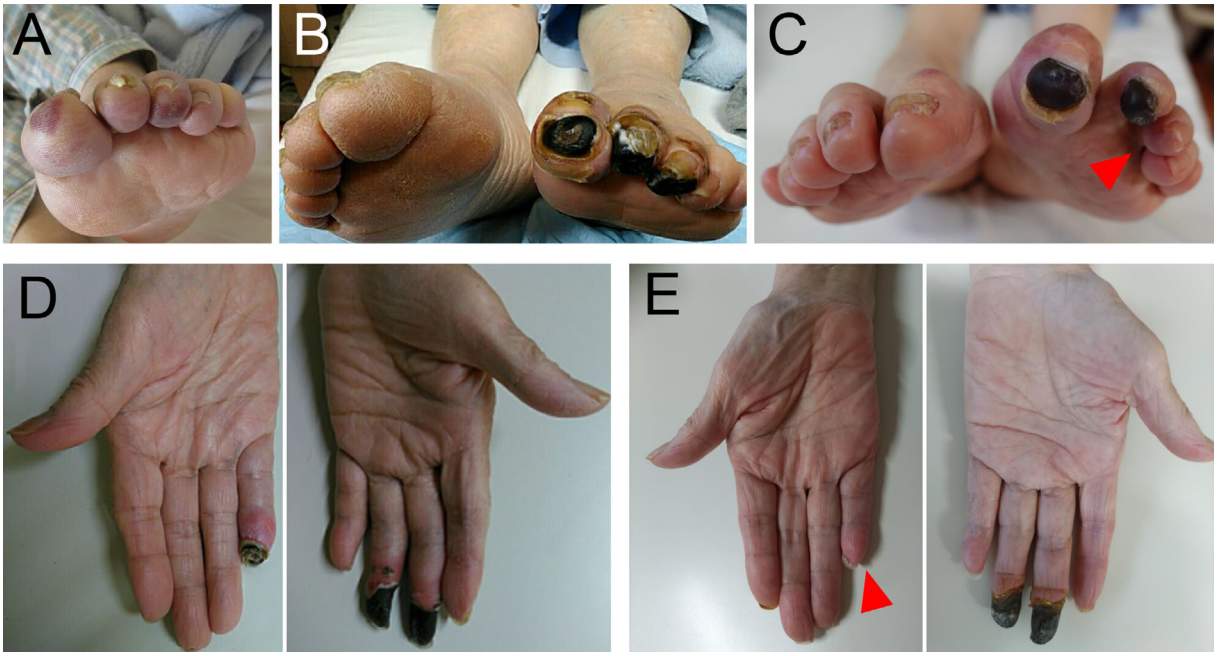

Figure 1. Images of the skin lesions. A: Ischemic lesions of the left toes 3 months before admission. B: Gangrene of the 1st to 3rd toes on admission. C: Gangrene of the 3rd toe (red arrow) disappeared 3 months after treatment initiation. D: Digital gangrene on admission. E: Digital gangrene of the 5th right finger (red arrow) disappeared 3 months after treatment initiation.

gressed; thus, the patient was transferred to our hospital for CLTI treatment. A physical examination revealed the following results: height, 147.6 cm; body weight, 43.9 kg; body mass index, 20.2 kg/m^2; blood pressure, 112/72 mmHg; and body temperature, 36.2°C. The bilateral ankle-brachial index was 1.0. Contrast-enhanced computed tomography (CT) revealed no obstruction or stenosis of the large arteries. Laboratory data upon admission revealed the following: leukocyte count, 6,800/μL; eosinophil rate, 3%; C-reactive protein level, 0.7 mg/dL; D-dimer, 3.4 μg/mL; low-density lipoprotein-cholesterol level, 36 mg/d; serum creatinine 0.67 mg/dL; estimated glomerular filtration rate 64 mL/min/1.73 m^2; IgA, 567 mg/dL; blood glucose level, 128 mg/dL; glycated hemoglobin level, 6.1%. Her levels of complement components and active proteins C and S were normal, and lupus anticoagulant and cryoglobulin tests were negative. Tests for autoimmune antibodies were all negative, including antinuclear antibodies, myeloperoxidase, proteinase 3 antineutrophil cytoplasmic antibodies, anti-RNP, Sm, SS-A, SS-B, Scl-70, Jo-1, double-stranded DNA, centromere, cardiolipin, cryoglobulin, and antiphospholipid antibodies. Hepatitis B surface antigen and hepatitis C antibody tests were negative. Intravenous prostanoids alprostadil (60 μg/day) was ineffective against finger and foot pain. Moreover, the ulcers on her fingers and toes progressed, resulting in gangrene (Fig. 1B, D), and foot dropping appeared in the right foot. Angiography of the left upper and lower extremities revealed obstruction of the left ulnar artery and insufficient distal circulation in the hands and feet (Fig. 2). Magnetic resonance imaging of the head revealed no abnormalities. The patient had no chest symptoms and no significant electrocardiographic or echocardiographic findings; thus, coronary angiography was not performed. Nerve conduction studies revealed bilateral peroneal neuropathies. Hematoxylin and eosin staining of a biopsy specimen from the left third toe revealed leukocytoclastic vasculitis in the corium and sub-corium deep plexus, showing neutrophil infiltration with nuclear fragmentation, fibrin deposition, and blood clots in medium-sized vessels, suggesting necrotizing vasculitis (Fig. 3). Based on the symptoms, including mononeuropathy multiplex, vasculitis with organ-threatening manifestation of digital ischemia, and pathological findings, the patient was diagnosed with severe PAN (1, 3). The 5-factor score for assessing the prognosis and severity was calculated as 2 points for age >65 years, absence of ear nose throat manifestations, and no evidence of renal insufficiency, gastrointestinal involvement, or cardiac insufficiency (4). On day 10 of hospitalization, prednisolone (50 mg/day) was administered. Three months after the start of treatment, the necrotic area in the left 3rd foot toe and right 5th finger disappeared (Fig. 1C, E), and bilateral foot dropping gradually improved. The prednisolone dose was tapered to 10 mg/day with 50 mg of azathioprine. The patient's symptoms were stable with no progression of gangrene or neuropathy in the outpatient setting.

Discussion

We report a case of severe PAN with progressive gangrene and polyneuropathy that required immunosuppressive therapy. Clinically, PAN is suspected in patients with marked constitutional symptoms and multisystem involve-

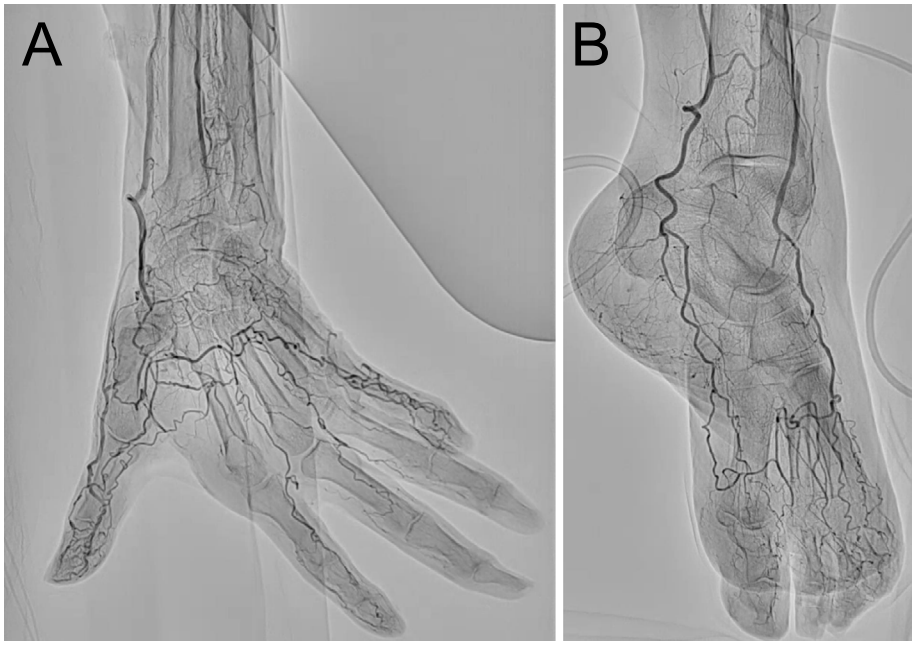

Figure 2. Angiography of the left hand reveals ulnar artery obstruction (A), and angiography of the left foot reveals peripheral arterial insufficiency (B).

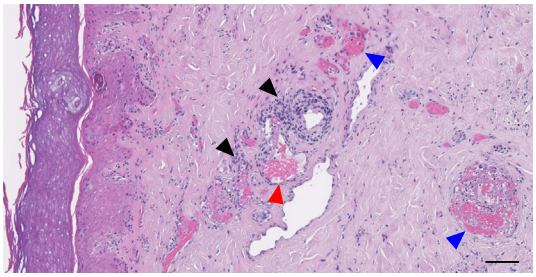

Figure 3. Hematoxylin and Eosin staining of the biopsy specimen from the left third finger. Leukocytoclastic vasculitis in the corium and sub-corium deep plexus shows neutrophil infiltration with nuclear fragmentation (black arrows), fibrin deposition (blue arrows), and blood clots in medium-sized vessels (red arrow).

ment (2). In this case, there were no obvious systemic symptoms, including fever and body weight loss; however, foot drop and gangrene were observed. The characteristics of patients with PAN have been reported in different cohorts. In two previous reports, distal necrosis was reported in 6.3% and 22% of patients with PAN (5, 6). Delays in the diagnosis and treatment of PAN may result in CLTI including distal necrotic lesions or gangrene. Thus, PAN should be included as a differential diagnosis in patients with CLTI of unknown etiology.

The differential diagnoses of CLTI include atherosclerotic disease, arterial embolism, vasospasm, Buerger's disease, and vasculitis of medium-sized arteries. Systemic vasculitis includes granulomatosis with microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss), immunoglobulin A vasculitis (Henoch-Schönlein purpura), cryoglobulinemic vasculitis, and vasculitis secondary to connective tissue diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis) (1). Our patient had diabetes, which is a strong risk factor for atherosclerosis and peripheral neuropathy. However, the angiographic and pathological findings suggested vasculitis. The corkscrew collateral appearance on angiography shown in the case mimicked Buerger's disease, and is one of the diagnostic criteria for Buerger's disease (7). Buerger's disease is a non-atherosclerotic segmental inflammatory disease that most commonly affects the small- and medium-sized arteries, veins, and nerves of the arms and legs (7, 8). Sometimes, patients with unknown causes of CLTI are diagnosed with Buerger's disease. However, our patient had no history of smoking; thus, CLTI was unlikely to have been caused by Buerger's disease. Human leukocyte antigen (HLA) typing (i.e., HLA-A9, HLA-B5, and HLA-B54) is related to the pat hogenesis of Buerger's disease; however, in our patient, HLA typing was not included in pathogenetic typing (9). Once Buerger's disease is diagnosed, the patient has no chance of receiving immunosuppressive therapy, and the diagnosis should be carefully and comprehensively confirmed by clinical symptoms and pathological findings from biopsy of a clinically affected organ. Bilateral foot dropping was a clue that raised the suspicion of PAN, with bilateral peroneal nerve paralysis based on nerve conduction studies. Pathological examination of a finger biopsy specimen showed necrotizing vasculitis, indicating vasculopathy from PAN. Thus, we comprehensively diagnosed the patient with PAN and administered immunosuppressive therapy.

Glucocorticoids (prednisone 1 mg/kg daily) are the first-line therapy for the treatment of PAN, with the addition of either azathioprine (2 mg/kg daily) or methotrexate (20 to 25 mg once weekly) for at least 1 year recommended in pa-

tients who are refractory or who are unable to receive adequate glucocorticoids due to adverse effects (3). Untreated PAN has a poor prognosis with a 5-year survival rate of 13% (10, 11); however, with treatment, the recent 5-year survival rate for PAN has improved to approximately 80% (4, 12). Therefore, an early diagnosis and immediate treatment are needed to improve the prognosis.

In patients with finger and/or toe ischemia (e.g., ulcers from unexplained causes), PAN should be considered as a differential diagnosis, and a biopsy of the affected organs and neurological examination should be performed immediately to prevent a delay in the diagnosis.

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

Disclosure Statement

The authors declare no conflicts of interest in association with the present study.

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