.Case Report

Buerger's disease manifesting nodular erythema with livedo reticularis

Tetsuo Takanashi*, **, Reiko Horigome***, Yasuaki Okuda*, Masato Nose****
Masayuki Matsuda**, Shu-ichi Ikeda**

*Department of Internal Medicine, Center for Rheumatic Diseases, Dohgo Spa Hospital
**Department of Internal Medicine (Neurology and Rheumatology), Shinshu University School of Medicine
***Department of Dermatology, Iida Municipal Hospital
****Department of Pathology, Ehime University School of Medicine

Footnotes: Buerger's disease with nodular erythema

Correspondence to:
Dr. Masayuki Matsuda
Department of Internal Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan
Tel +81-263-37-2673, Fax +81-263-37-3427
Email: matsuda@hsp.md.shinshu-u.ac.jp

Abstract

We report a patient with Buerger's disease (BD) who showed painful nodular erythema with livedo reticularis as an initial symptom. The patient developed this cutaneous manifestation in both lower extremities, and a skin biopsy demonstrated perivascular infiltration of mononuclear cells in the border zone between the dermis and subcutaneous tissue. Both nodular erythema and livedo reticularis were successfully treated with oral prednisolone, but both feet developed necrosis with ulcerations and had to be amputated 1.5 years later because of acute gangrene. Histopathology of the amputated tissue showed acute inflammation and multiple thrombi with recanalization in the posterior tibial arteries, leading to a diagnosis of BD. This disease should be considered as a possible diagnosis in refractory patients with nodular erythema and livedo reticularis, particularly when ulcerations and necrosis rapidly worsen.

Keyword: Buerger's disease, corticosteroid, livedo reticularis, nodular erythema

Introduction

Buerger's disease (BD, thromboangitis obliterans) is a peripheral vascular disorder characterized clinically by progressive necrosis ascribed to ischemia in the extremities, particularly in the distal parts, and pathologically by segmental formation of thrombi with acute and chronic inflammation in intermediate and small arteries (1, 2). As this disease occurs preferentially in male heavy smokers, the carbon monoxide in cigarette smoke is considered to play an important role in the pathogenesis, although the precise mechanisms remain unclear (1-3). Migrating phlebitis is often seen in patients with BD (1, 4, 5), but other cutaneous manifestations are very rare (6). Here, we report a patient with BD who showed nodular erythema with livedo reticularis in both legs as an initial symptom. Oral prednisolone was effective for this skin manifestation, but both feet gradually showed necrosis and ulcerations due to ischemia and required amputation 1.5 years later despite intensive administration of vasodilators. We suggest that BD should be considered as a possible diagnosis in refractory patients with nodular erythema and livedo reticularis, particularly when ischemic lesions suggestive of involvement of intermediate arteries are present.

Case report

A 33-year-old male smoker (30 cigarettes/day for 15 years) suddenly developed painful nodular erythema and livedo reticularis in both lower extremities with no precipitating cause, significant family history or habit of alcohol intake. When he visited our hospital, laboratory tests demonstrated no increase in inflammatory reactions, including C-reactive protein (CRP) and white blood cells (WBC). A skin biopsy showed perivascular infiltration of mononuclear cells predominantly in venules around the border zone between the dermis and subcutaneous tissue (Fig. 1A), occasionally with involvement of the neighboring arterioles (Figs. 1B, C and D). There was neither fibrinoid necrosis nor a granulomatous lesion. These skin symptoms were successfully

treated with oral prednisolone at a dose of 20 mg/day and non-steroidal anti-inflammatory drugs (NSAIDs). Three months later the patient developed an ulcer on his left elbow and purplish bullous lesions with severe pain in the second and third toes of the left foot while tapering oral prednisolone. Painful bullous lesions soon developed in the other foot also, and these symptoms fluctuated in parallel with inflammatory reactions in his serum despite an increased dose of oral prednisolone and coadministration of vasodilators, such as prostaglandin and vitamin E (Fig. 2).

At the age of 35 he suddenly became unable to walk because of severe pain in both feet 3 months after the development of intermittent claudication, and was admitted to our hospital. Physical examination showed gangrene of the toes, several ulcers with pyorrhea in both legs (Fig. 3), and multiple petechiae in both upper limbs. No pulsation was palpable in the bilateral dorsal pedal and posterior tibial arteries. Laboratory data demonstrated positive inflammatory reactions (CRP 10.55 mg/dl, normal <0.1 mg/dl; WBC 23100/mm^3, normal 3500-9500/mm^3) and a slight increase in hepatic indices (AST 57 U/l, normal 12-37 U/l; ALT 168 U/l, normal 7-45 U/l). Electrolytes, renal indices (blood urea nitrogen 11.2 mg/dl, normal 9-22 mg/dl; creatinine 0.6 mg/dl, normal 0.6-1.0 mg/dl), complements and immune complexes in serum were within normal limits, and autoantibodies such as anti-cardiolipin and anti-neutrophil cytoplasmic antibodies were all negative. There were no abnormal findings in urinalysis. Angiography showed segmental stenosis in the left posterior tibial artery and both fibular arteries without the irregularities of vascular wall suggestive of atherosclerosis (Fig. 4). Soon after admission, intensive treatment to improve hemoperfusion in both feet was started using methylprednisolone pulse therapy and vasodilators, such as kallidinogenase and sarpogrelate hydrochloride, in addition to morphine sulfate, NSAIDs and antibiotics for severe pain. Nevertheless, the gangrene gradually worsened, and both feet were finally amputated one month after admission. Histopathology of the amputated tissue demonstrated multiple thrombi with recanalization (Figs. 5A and B)

and infiltration of leukocytes, including neutrophils (Figs. 5C and D), in the posterior tibial arteries. The patient has since been in good general condition with a low dose of oral prednisolone, although scleritis and nodular erythema in both legs sometimes appear in conjunction with an increase in inflammatory reactions.

Discussion

The present patient clinically showed necrosis with ulcerations ascribable to ischemia in both legs, and administration of vasodilators and corticosteroids failed to relieve these symptoms. Histopathology of the amputated tissue demonstrated multiple thrombi with acute and chronic inflammation in both posterior tibial arteries, which showed segmental stenosis on angiography, leading to a definite diagnosis of BD (1, 2). The clinical background of our patient was compatible with that of typical BD with regard to being a young male adult with a history of heavy smoking. CRP and WBC showed marked increases along with drug-induced elevation of hepatic indices on admission to our hospital possibly because of necrosis with infection, although these inflammatory reactions usually remain within normal limits in BD. Considering that painful bullous lesions fluctuated for approximately 1 year before the development of gangrene, the ischemia in both lower legs may have progressed insidiously.

The most interesting point about the present patient is that nodular erythema with livedo reticularis responsive to corticosteroids preceded necrosis of both feet. BD does not usually show this skin manifestation ascribable to the involvement of arterioles. On the basis of the gross appearance of skin lesions in our patient, polyarteritis nodosa (PN), particularly a cutaneous form, was suspected as a possible diagnosis at onset, but there were no inflammatory reactions and two pathological findings were incompatible with this disease. One is that the fibrinoid necrosis and predominant infiltration of polymorphonuclear cells characteristic of PN could not be found in any vessels examined (7). The other is that the primarily affected vessels in our patient were

considered to be venules. PN primarily affects arteries, while our patient showed more predominant perivascular infiltration of mononuclear cells in venules than in the neighboring arterioles. Considering that BD often affects veins as a form of migrating phlebitis (1, 4, 5), the cutaneous manifestation in our patient might have been ascribed to this disease itself. The reappearance of nodular erythema and livedo reticularis even during treatment with corticosteroid after amputation of both feet in conjunction with an increase in inflammatory reactions also supports this hypothesis. Small-vessel involvement has been shown to complicate BD in one clinical report (6). Implantation of bone marrow stem cells or omental transplantation may prevent progressive necrosis in BD (8-10), and early diagnosis using angiography is important if this disease is suspected as a cause of nodular erythema and livedo reticularis.

In conclusion, BD may clinically manifest with skin symptoms ascribable to small-vessel involvement as seen in PN. Even though a cutaneous manifestation responds well to corticosteroids, BD should be considered as a possible diagnosis when there are clinical signs or symptoms suggestive of involvement of intermediate arteries, such as progressive necrosis with ulcerations in the extremities.

Acknowledgements

This work was supported by a grant from Neuroimmunological Disease Division, the Ministry of Public Health, Labor and Welfare, Japan.

References

1. Olin JW. Thromboangitis obliterans (Buerger's disease).N Engl J Med **343**: 864-869, 2000.
2. Olin JW, Shih A. Thromboangiitis obliterans (Buerger's disease). Curr Opin Rheumatol **18**: 18-24, 2006.
3. Young C, Beynon H, Haskar D. Buerger's disease (thromboangitis obliterans): a reversible cause of upper limb digital infarcts. Br Soc Rheumatol **39**: 442-443, 2000.
4. Mishima Y. Thromboangitis obliterans (Buerger's disease). Int J Cardiol **54** (Suppl): S185-187, 1996.
5. Stone JH, Nousari HC. "Essential" cutaneous vasculitis: what every rheumatologist should know about vasculitis of the skin. Curr Opn Rheumatol **13**: 23-34, 2001.
6. Fernandez Ballesteros A, Roldan Montaud A, Diaz de Entresosotos FZ, Jimenez Jimenez J, Parra Perez C, Sanchez del Charco M. Thromboangitis obliterans associated with small-vessel vasculitis. Med Clin (Barc) **93**: 781-783, 1989 (in Spanish).
7. Herbert CR, Russo GG. Polyarteritis nodosa and cutaneous polyarteritis nodosa. Skin Med **2**: 277-285, 2003.
8. Miyamoto M, Yasutake M, Takano H, et al. Therapeutic angiogenesis by autologous bone marrow cell implantation for refractory chronic peripheral arterial disease using assessment of neovascularization by ^{99m}Tc-tetrofosmin (TF) perfusion scintigraphy. Cell Transplant **13**: 429-437, 2004.
9. Agarwal VK. Long-term results of omental transplantation in chronic occlusive arterial disease (Buerger's disease). Int Surg **90**:167-174, 2005.
10. Puechal X, Fiessinger JN. Thromboangiitis obliterans or Buerger's disease: challenges for the rheumatologist. Rheumatology **46**: 192-199, 2007.

Figure legends

Figure 1: Skin biopsy from the right lower leg, showing perivascular infiltration of mononuclear cells (arrow) with no fibrinoid necrosis in the border zone between dermis and the subcutaneous tissue (A: HE staining, bar=100 μm). Higher magnification shows more predominant infiltration in venules (arrows) than in neighboring arterioles (arrowheads) (B: HE staining, bar=100 μm, C: elastica van Gieson staining, bar=100 μm, D: HE staining, bar=50 μm).

Figure 2: Clinical course of the patient. Change in skin symptoms is subjectively demonstrated on the basis of inspection. CRP: C-reactive protein, NSAIDs: non-steroidal anti-inflammatory drugs.

Figure 3: The left foot showed necrosis of toes with severe excoriation of the skin on admission to our hospital.

Figure 4: Angiography showed segmental stenosis (arrows) in the left posterior tibial artery and both fibular arteries. There were no irregularities in the vascular wall suggestive of atherosclerosis.

Figure 5: Histopathology showed thrombi with recanalization and marked infiltration of inflammatory cells, including neutrophils, in the right (A, B) and left (C, D) posterior tibial arteries, respectively. (A, C: HE staining, bar=100 μm, B, D: elastica van Gieson staining, bar=100 μm)

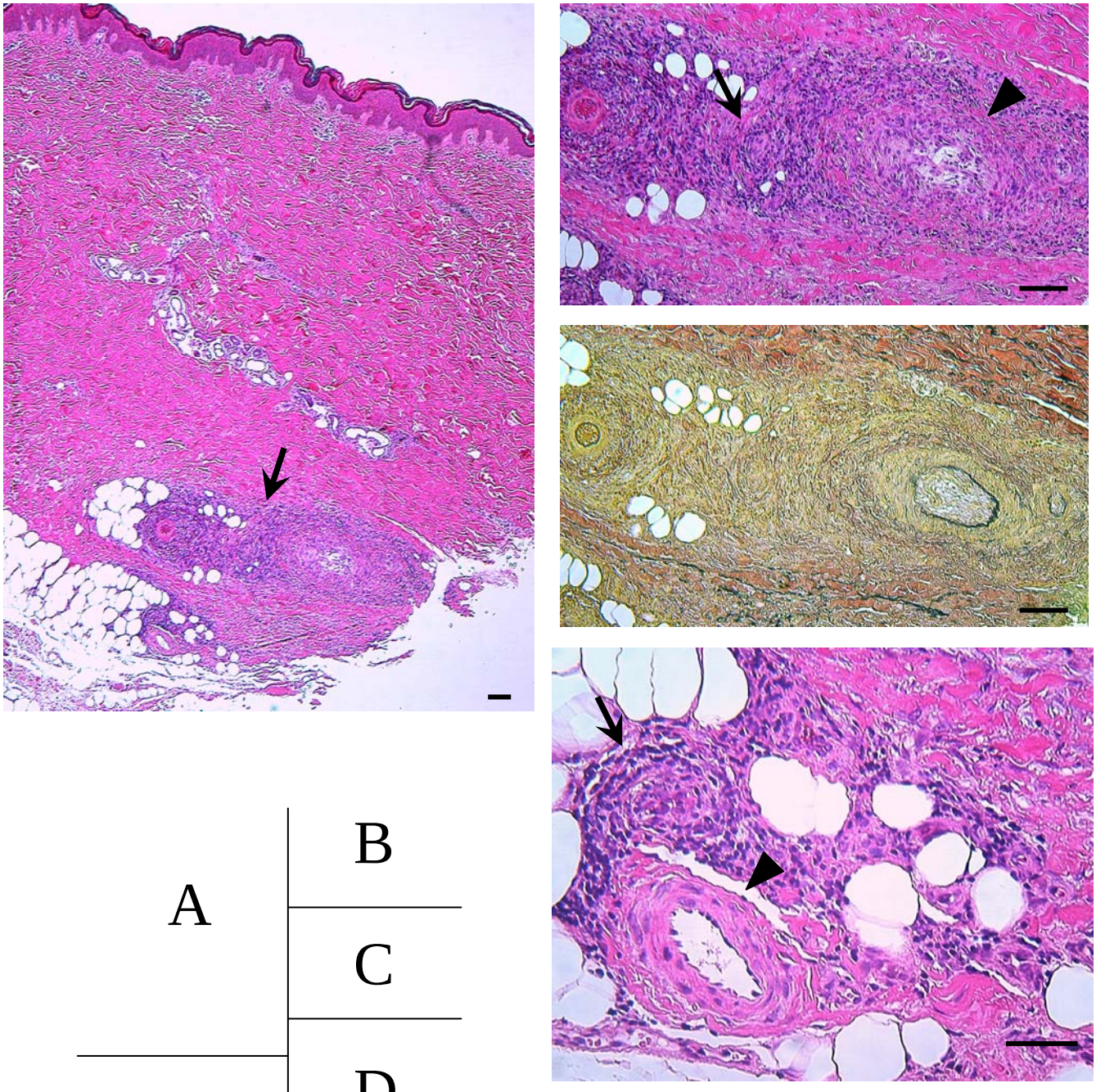

Figure 1

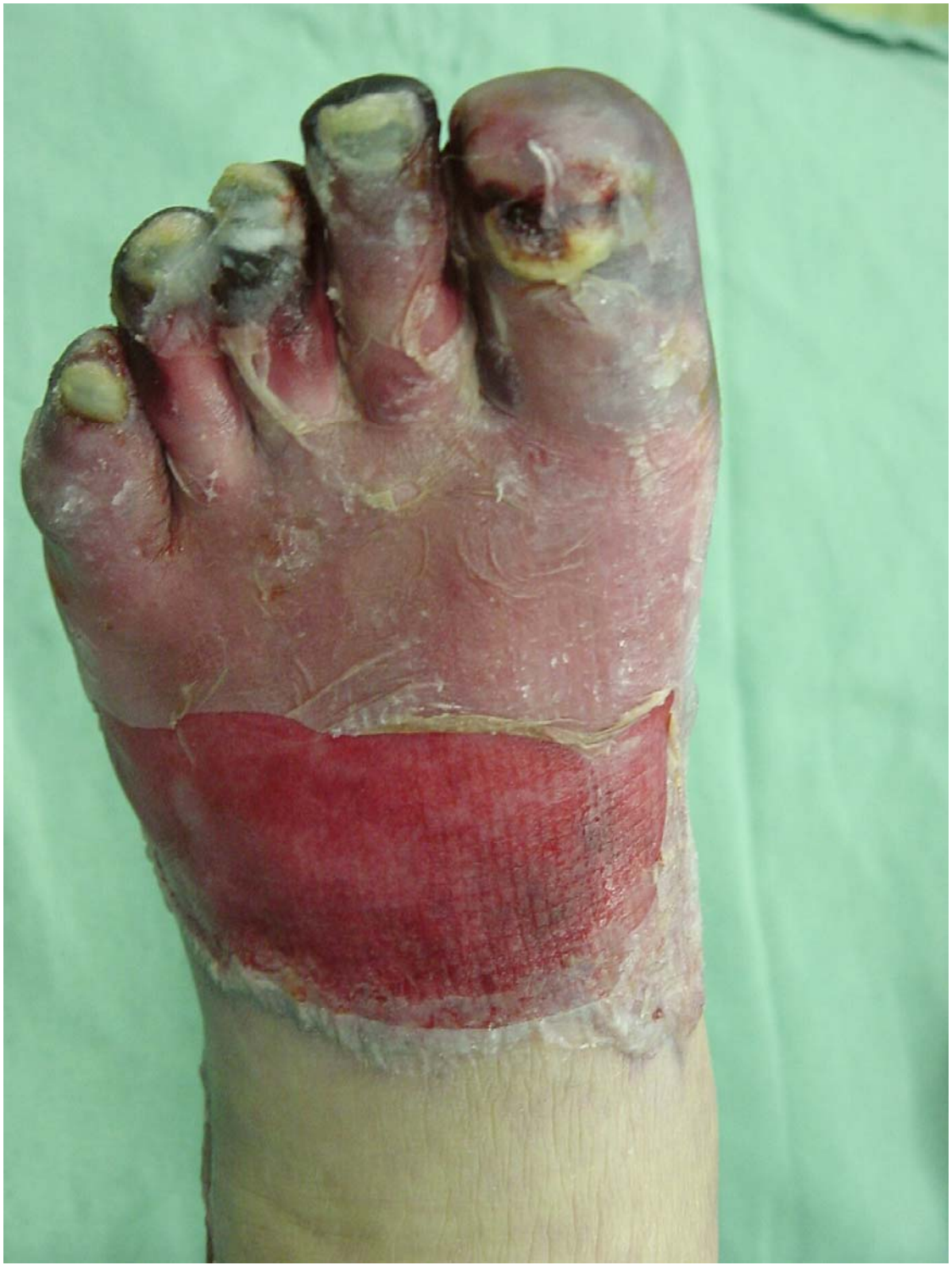

Figure 3

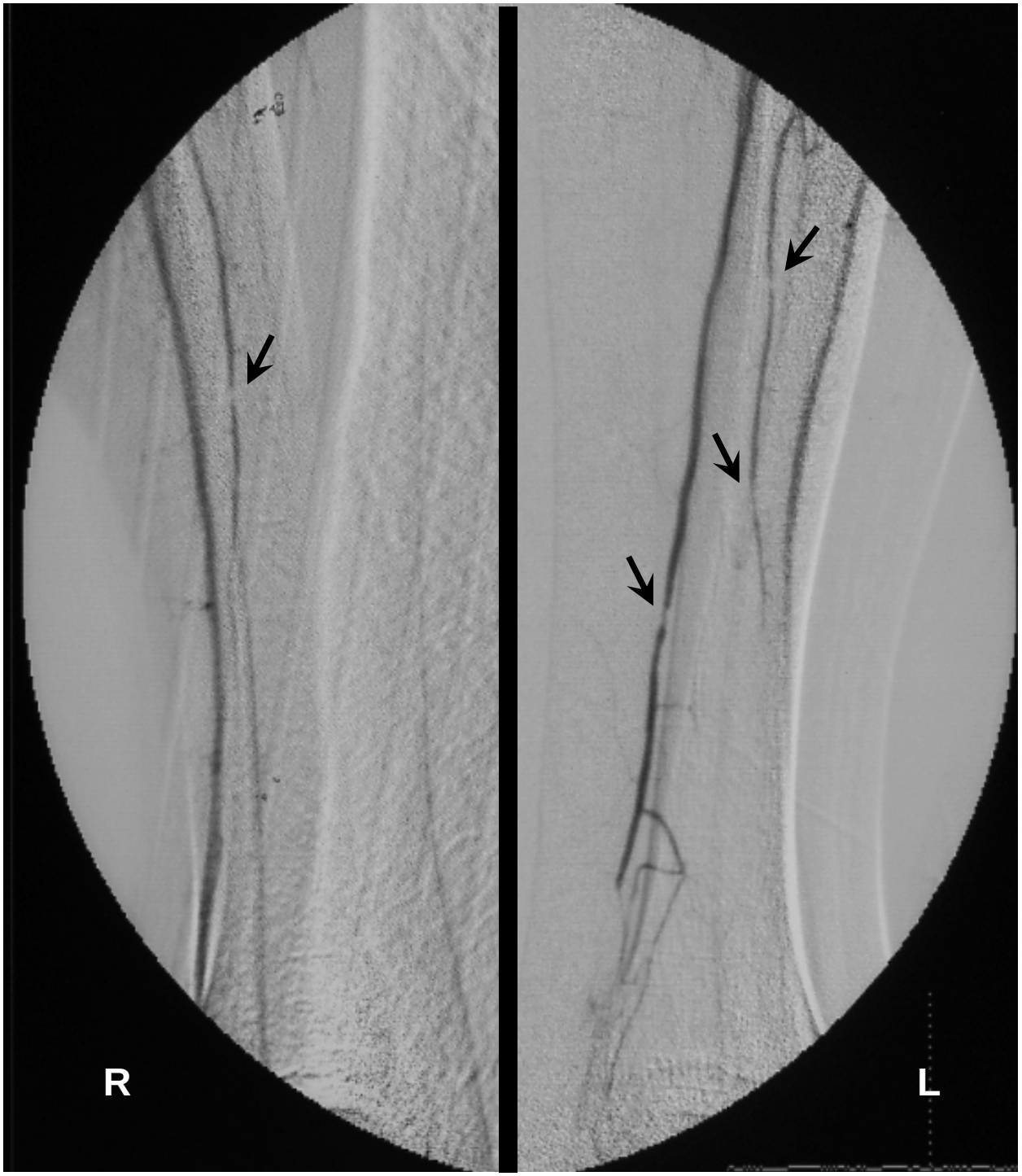

Figure 4

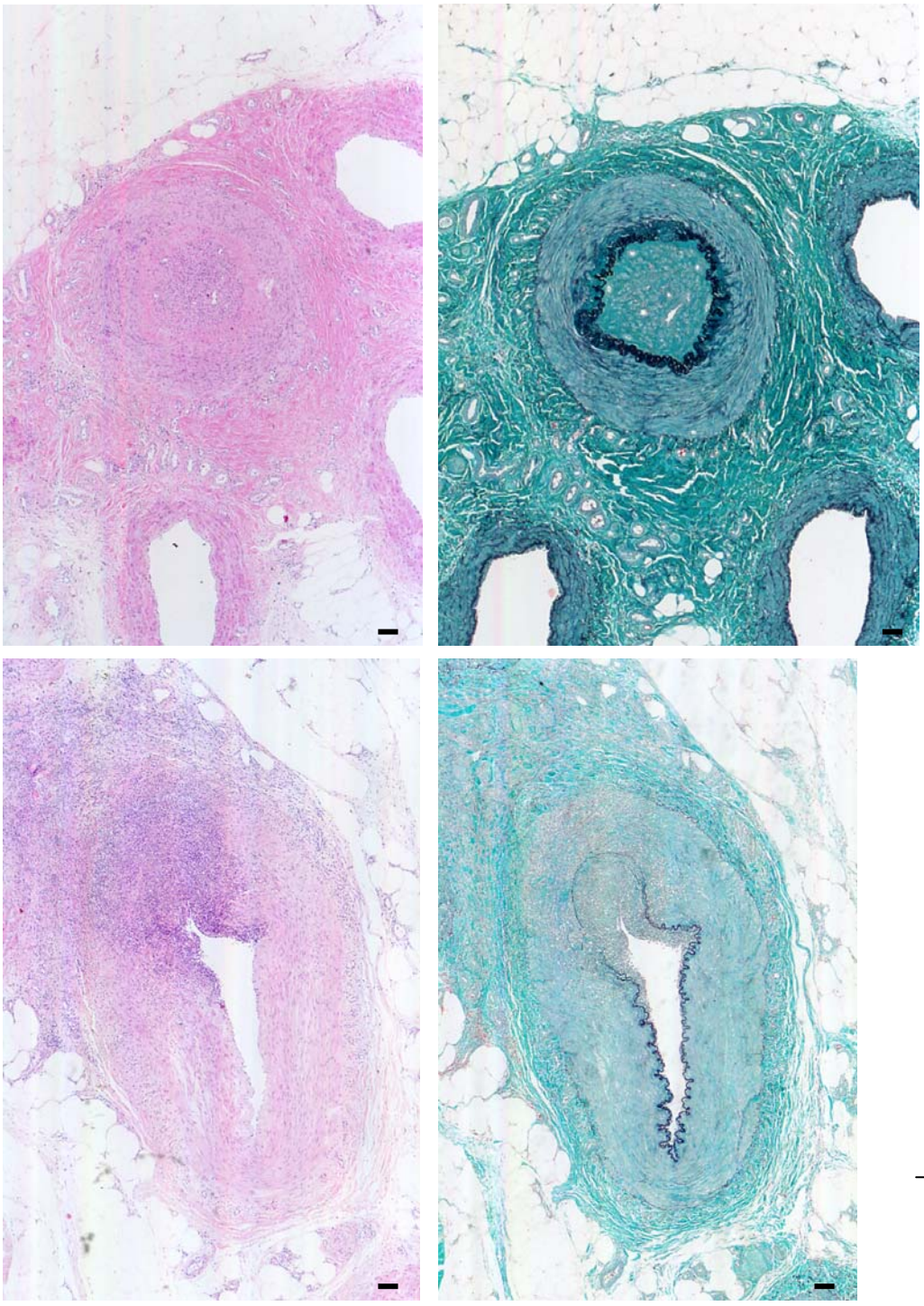

Figure 5

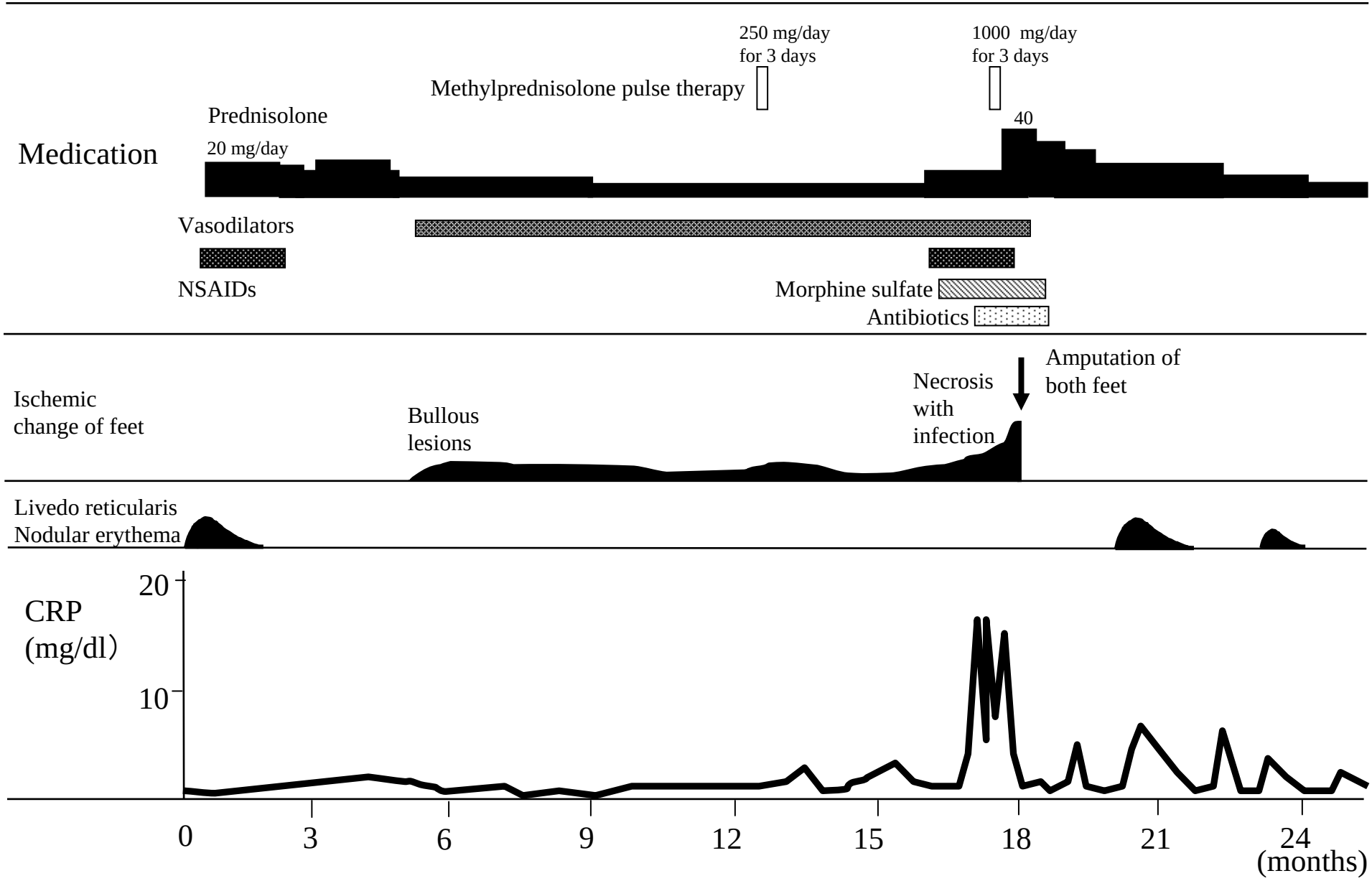
250 mg/day
for 3 days
1000 mg/day
for 3 days
Methylprednisolone pulse therapy
Prednisolone
20 mg/day
40
Medication
Vasodilators
NSAIDs
Morphine sulfate
Antibiotics
Ischemic
change of feet
Bullous
lesions
Necrosis
with
infection
Amputation of
both feet
Livedo reticularis
Nodular erythema
CRP
(mg/dl)
20
10
0
3
6
9
12
15
18
21
24
(months)

Figure 2