Hybrid Revascularization for Critical Limb Ischemia Triggered by Multiple Organ Dysfunction Due to Acute Pneumonia; Urgent Catheter Intervention Followed by Low-Density-Lipoprotein Apheresis and Elective Peripheral Bypass Surgery

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A 66-year-old man was referred for treatment of critical limb ischemia arising with multiple organ dysfunction due to acute pneumonia. Angiographic examinations demonstrated total obstruction of the bilateral external iliac arteries and the bilateral superficial femoral arteries with collateral circulation to the distal vessels. Urgent percutaneous transluminal angioplasty dissolved the obstruction of the left external iliac artery, and subsequent low-density-lipoprotein apheresis ameliorated his progressive ischemia in the lower extremities. Femorofemoral and bilateral femoro-popliteal bypasses were performed 31 days after the endovascular intervention, which achieved successful limb salvage with the relief of ischemic symptoms related to arteriosclerotic obliterans.

Keywords: arteriosclerotic obliterans, critical limb ischemia, low-density lipoprotein apheresis

Introduction

Critical limb ischemia (CLI) is categorized as an advanced stage of peripheral arterial occlusive disease (PAOD). Anti-platelet medication and prostaglandin infusion are usually ineffective in such conditions, and the most reliable treatment should be surgical or interventional revascularization in an urgent basis.1–3) However, the morbidity and mortality of surgical procedures are thought to be high for CLI patients with severe arteriosclerotic obliterans (ASO) because most of them have severe cerebrovascular obstruction and/or coronary artery disease.1,2) A large amount of patients might be subject to major amputation of the lower extremities without arterial revascularization therapy.2,3) Low-density lipoprotein (LDL) apheresis has become popular as a novel technique for reducing serum cholesterol in drug-resistant patients with severe hypercholesterolemia,4) and therapeutic LDL-apheresis has recently been applied to treat various microcirculation disturbances due to PAOD.4,5) In this report, we describe a patient whose severe PAOD in both lower extremities should be treated immediately after recovery from multiple organ failure (MOF). Instead of complete surgical revascularization in an
emergency basis, an urgent endovascular intervention was done for the left iliac artery followed by five sessions of LDL apheresis. Subsequent surgical bypass grafting achieved limb salvage without complicating systemic life-threatening disorders.

**Case Report**

A 66-year-old man with good activities of daily living was transferred to the emergency unit in Ishinkai Yao General Hospital for treatment of acute pneumonia. The patient suffered respiratory collapse accompanied by MOF, and received intensive care under the mechanical ventilation with the use of 0.2 mg/kg/hour of sivelestat sodium hydrate, 1000 mg/day of pазфлокацин mesilate and 0.5 g/day of doripenem hydrate. Despite severe liver and renal dysfunction in the immediate period, the patient could be weaned from the mechanical ventilation on the seventh day.

However, the patient complained of severe pain in the right lower extremity just after tracheal extubation. Peripheral arterial pulsations in the both groin and lower extremities were not detected, and severe cyanotic change was observed in the right toes. The patient had neither hypertension nor diabetes mellitus, and had not experienced any clinical symptoms related to myocardial ischemia or cerebrovascular disorders. Critical elevation of serum creatine phosphokinase was not observed, which denied the incidence of acute arterial embolization of the lower extremities. Not having experienced intermittent claudication before admission, the patient was clinically diagnosed as acute exacerbation of PAOD triggered by MOF. Medical treatment including 10 μg/day of alprostadil and 200 mg/day of cilostazol failed to relieve the progressive ischemic symptoms at all, and then the patient was referred to the Department of Cardiovascular Surgery for further treatment 6 days after the onset of CLI (Chest roentgenograms and laboratory data before the referral were shown in Figs. 1A–1C and 2).

Arterial-brachial systolic pressure index (ABI) was 0.46 for the left leg, and the measurement was not established in the right leg. Magnetic resonance imaging and angiography of the vessels in the lower extremities demonstrated the total obstruction of bilateral external iliac arteries and superficial femoral arteries (Fig. 1D). Digital subtraction angiography revealed small common femoral arteries supplied from both internal iliac arteries and medial circumflex femoral artery, with 12 cm defect in the right and 7.5 cm in the left (Fig. 1E). Bilateral popliteal arteries were depicted in delayed collateral circulation (Fig. 1E). Concomitant cardiac catheterization demonstrated that the left ventricular function was preserved without significant coronary artery stenosis.

Because the clinical symptoms were equivalent to Fontaine stage III, aorto-bifemoral bypass or axillo-bifemoral bypass in combination with bilateral femoro-popliteal bypasses should be done for limb salvage upon this pathology in an urgent basis. However, the patient had just recovered from life-threatening pneumonia and the family could not accept the perioperative risk in case of urgent complete revascularization. In addition, the obstructive lesion in the right lower extremity involved the common femoral artery and the bifurcation of the femoral artery in the infra-inguinal portion, so-called “no-stent zone”. Therefore, it was decided as a less invasive strategy that an urgent endovascular intervention was done for the left iliac artery followed by LDL apheresis if needed, and subsequent surgical bypass grafting was scheduled after an interval of antiplatelet medication.

Percutaneous transluminal angioplasty (PTA) using a 8 mm × 10 cm Iliac Stent System (S.M.A.R.T® CONTROL®; Cordis Co. Inc., Miami-Lakes, Florida, USA) was done for obstruction of the left iliac artery 8 days after angiographic diagnosis, followed by 10 μg/day of alprostadil and 40 mg/day of argatroban infusion. The ABI value for the left elevated to 0.55, but that for the right remained unmeasured. Concomitant oral medications were as follows: 200 mg/day of cilostazol, 300 mg/day of sarpogrelate hydrochloride, 100 mg/day of aspirin, 75 mg/day of clopidogrel, 1800 mg/day of ethyl-icosapentate, 2 mg/day of pitavastatin calcium, and 10 mg/day of ezetimide. Although the full complement of medication could ameliorated the progression of ischemic symptoms, cessation of infusion therapy resumed cyanotic deterioration and severe pain in the right lower extremity even in the rest period. Therefore, LDL apheresis was commenced 13 days after the endovascular intervention, using the Liposorber LA-15 System, including Liposorber LA-15 columns, Sulflux FP-08 Membrane Plasma Separator (Kaneka Medics Corporation, Osaka, Japan). Rapid relief of rest pain in the right leg was achieved, and 5 sessions...
of LDL apheresis was done before surgical revascularization. The ABI value for the left remained at 0.52, but that for the right could be measured at 0.29.

The summary of perioperative management is shown in Fig. 3A. The relief of critical ischemia and sufficient anti-platelet medication enabled an elective peripheral bypass surgery planned 32 days after the endovascular intervention. Inspection of the vascular lesion revealed severe arteriosclerotic changes in the femoral arteries and the popliteal arteries, and no significant blood flow was observed from the peripheral region of the bilateral popliteal arteries. Aggressive endoarterectomy for the deep femoral arteries and the popliteal arteries was applied to expect the long-term graft patency. Then, a femoro-femoral

Fig. 1 Chest roentgenograms (A) on admission, (B) at the weaning from mechanical ventilation, (C) on the referral. Angiographic examinations (D) magnetic resonance imaging, (E) digital subtraction angiography.
Fig. 2  Clinical course regarding laboratory data before the referral for limb ischemia. AST: asparate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CPK: creatine phosphokinase; WBC: white blood cell count; CRP: C-reactive protein; BUN: blood urea nitrogen; Crn: creatinine; PZFX: pazufloxacin mesilate; DRPM: doripenem hydrate.

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Fig. 3  (A) Clinical summary. (B) Three-dimensional enhanced computed tomography scan at 6 months after operation. PTA: percutaneous transluminal angioplasty; LDL-A: low-density-lipoprotein apheresis; FF: femoro-femoral; FP: femoro-popliteal.
bypass grafting using an 8 mm of PTFE artificial graft with a designed cuff (Advanta™ VS PTFE thin-Wall Straight Graft; Atrium Medical Corp., Hudson, New Hampshire, USA) and two femoro-popliteal bypass graftings using two 7 mm of ePTFE artificial graft (Dynaflo™ ePTFE Bypass Graft; Bard Co. Inc., Bryan, Ohio, USA) were done.

His ischemic symptoms in the lower extremities, such as rest leg pain and intermittent claudication, were dramatically disappeared after surgical revascularization. The ABI values were 0.98 for the right and 0.99 for the left just after the operation. Additional four sessions of LDL apheresis were done in expectation of further development of peripheral vascular bed. The patient was discharged on the 25th post-operative day when the ABI values were 1.02 for the right and 0.93 for the left. Computed tomography at 6 months after operation demonstrated good patency of the artificial grafts (Fig. 3B), and no recurrence of peripheral ischemia was observed during 3 years of follow-up period.

Discussion

The standard therapeutic strategy for CLI should be a kind of early revascularization procedures such as surgical bypassing and interventional angioplasty.1–3) The patient in this report had not experienced intermittent claudication before, and it is possible that abnormal coagulopathy due to multiple organ dysfunction might cause the obstruction of the collateral vessels and the acute exacerbation of peripheral ischemia. The family rejected surgical bypassing under general anesthesia just after recovery from acute critical pneumonia, and thus, we applied an urgent partial endovascular intervention followed by a scheduled complete surgical revascularization procedure in combination with strict medical treatment, including LDL-apheresis.

Although successful limb salvage was fortunately achieved in the end, it is unclear that optimal timing for LDL-apheresis should be earlier, just after the endovascular intervention for the obstruction of the left iliac artery. The initial endovascular intervention for the left iliac artery, which failed to increase the ABI value of the right leg, ameliorated local CLI symptoms under strict medical treatment. On the other hand, five sessions of LDL-apheresis contributed to an increase in the ABI value of the right leg, as well as the cessation of venous infusion of alprostadil and argatroban. Concomitant LDL-apheresis was unplanned in the first assessment, but might have ameliorated the ischemic conditions more effectively than venous infusion of alprostadil and argatroban. Early application of LDL-apheresis would provide more satisfactory effects in this patient with regard to rapid relief of CLI symptoms.

LDL-apheresis is thought to provide a rapid improvement of peripheral perfusion for patients with PAOD by attenuating red blood cell aggregation, which is attributed to the reduction of the whole blood viscosity and the improvement of red blood cell deformability.6) Previous studies suggested that LDL-apheresis induces the increase in vasodilative mediators such as nitric oxide and bradykinin.7) These hemorheological effects may also play a major role in the relief of CLI symptoms without complete revascularization. Therefore, LDL-apheresis can be a palliative therapy for patients with severe PAOD unsuitable for surgical and/or interventional complete revascularization.

Recent studies have suggested pleiotropic effects of long-term treatment with LDL-apheresis which may contribute to the morphological alterations of the vessel. Kojima, et al. and Kobayashi, et al. measured an increase in angiogenic activities in patients receiving LDL-apheresis.8,9) Utsumi, et al. demonstrated that LDL-apheresis reduced adhesion molecules and inflammatory cytokines in diabetic patients with PAOD.10) It is possible that LDL-apheresis enhances angiogenesis and attenuates inflammatory response in patients with PAOD, and thus, postoperative LDL-apheresis may play a promising role in developing the long-term patency for PAOD patients with poor peripheral vascular bed.

Conclusions

In summary, we successfully treated a patient suffering from acute exacerbation of PAOD in the bilateral lower extremities after recovery from critical pneumonia. Urgent partial endovascular intervention followed by LDL-apheresis ameliorated the critical ischemic conditions under strict medication, and a staged surgical revascularization achieved limb salvage with the relief of ischemic symptoms. Although the clinical indication of LDL-apheresis remains controversial, the present case may imply that periop-
operative LDL-apheresis could be effective as an adjuvant therapy for patients with severe PAOD requiring rapid improvement of peripheral circulation.

Disclosure Statement

All authors do not have any financial relationship with a biotechnology manufacturer, a pharmaceutical company, or other commercial entity that might pose a conflict of interest with the manuscript.

References


