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Conservative management of distal leg necrosis in lung transplant recipients

F. Aigner [a], M. Husmann [b], L.C. Huber [a], C. Benden [a], M.M. Schuurmans [a, *]

[a] Division of Pulmonology, University Hospital of Zurich, Switzerland
[b] Division of Angiology, University Hospital of Zurich, Switzerland

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ABSTRACT

Critical limb ischemia (CLI) with distal leg necrosis in lung transplant recipients (LTR) is associated with a high risk for systemic infection and sepsis. Optimal management of CLI has not been defined so far in LTR. In immunocompetent individuals with leg necrosis, surgical amputation would be indicated and standard care. We report on the outcome of four conservatively managed LTR with distal leg necrosis due to peripheral arterial disease (PAD) with medial calcification of the distal limb vessels. Time interval from lung transplantation to CLI ranged from four years (n = 1) to more than a decade (n = 3). In all cases a multimodal therapy with heparin, acetylsalicylic acid, iloprost and antibiotic therapy was performed, in addition to a trial of catheter-based revascularization. Surgical amputation of necrosis was not undertaken due to fear of wound healing difficulties under long-term immunosuppression and impaired tissue perfusion. Intensive wound care and selective debridement were performed. Two patients developed progressive gangrene followed by auto-amputation during a follow-up of 43 and 49 months with continued ambulation and two patients died of unrelated causes 9 and 12 months after diagnosis of CLI.

In conclusion, we report a conservative treatment strategy for distal leg necrosis in LTR without surgical amputation and recommend this approach based on our experience.

1. Introduction

Long-term survival rates for lung transplant recipients (LTR) are improving with 53% and 31% surviving five and 10 years, respectively [1]. With improved long-term survival cardiovascular complications are encountered more often as a consequence of the negative effects of the immunosuppression on arteriosclerotic risk factors [2,3]. Deaths due to cardiovascular disease occur in 8.7% after more than five years [1]. To date, the management of cardiovascular complications in LTR is not standardized. The incidence of cardiovascular diseases in LTR will increase with increasing age at transplantation. There are no recommendations for management of critical limb ischemia (CLI) in LTR. Because of one fatal outcome in one of our patients dying two days after lower limb amputation, the optimal therapy remained a matter of debate. Since outcome of this complication appears to be underreported, it is unclear whether non-amenable peripheral vascular angiopathy contributes to wound healing complications and what therapeutic strategy is best. We report on four cases of LTR with CLI due to a peripheral arterial disease (PAD) with toe and forefoot necrosis that were managed withholding extensive debridement or surgical amputation with favorable outcomes.

We retrospectively reviewed the medical records of four consecutive patients with distal leg necrosis in our cohort. In general, the patients were managed according to our standards described previously [4] and international guidelines for peripheral artery disease [5,6]. Limited bed-side debridement of non-viable and fibropurulent tissue is done by wound or ward nurse whereby dry necrotic areas are left untouched. Gentle irrigation of wound with physiologic saline solution (for wet wounds). Wound coverage with wet-to-damp hydrofiber dressings, which support autolytic debridement, absorb exudate, and protect surrounding normal skin. For dry wounds we use dry gauze as protection only. For exudative and infected wounds we use absorptive dressings, such as (ionicsilver) hydrofiber dressings. On the margins of infected wounds we sometimes also use a polyvinylpyrolidone iodine non-adherent dressing despite known cytotoxic effects. For bandaging of challenging anatomic areas (eg, around the heel) we

* Corresponding author. University Hospital, University of Zurich, Division of Pulmonology, Rämistrasse 100, 8091, Zürich, Switzerland.
E-mail address: mace.schuurmans@usz.ch (M.M. Schuurmans).

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Abbreviations

ANA	antinuclear antibodies
ANCA	anti-neutrophil cytoplasmic antibodies
CF	cystic fibrosis
CLI	critical limb ischemia
ESRD	end stage renal disease
LTR	lung transplant recipient
PAD	peripheral artery diseases
PTA	percutaneous transluminal angioplasty
PTH	parathyroid hormone

use a highly conformable foam dressing and generally loose bandages (no compression therapy). We compared assessment, therapeutic interventions and outcome of the cases. Primary end-point was the overall survival and secondary end-point the evolution of the necrosis.

2. Cases

2.1. Case 1

At age of 24 years, a male patient with end-stage lung disease due to cystic fibrosis (CF) received a lung transplant. Three years prior to the transplant, three ischemic cerebral insults and a splenic infarction were diagnosed. Because of a heterozygous factor V Leiden and protein S type 2 mutation, the patient received anticoagulation with phenoprocumon. Almost 13 years after lung transplantation, CLI with bilateral necrosis of the toes developed (Table 1). The examinations before lung transplantation had shown no signs of PAD. Before initial presentation of CLI, no symptoms of PAD existed. Dialysis for end stage renal disease (ESRD) had been started three months before presentation for CLI. Initially, red discoloration of the toes developed, followed by necrotic lesions at the tip of the toes. Over the next six weeks the red-livid discoloration extended over the forefeet with livedo reticularis and petechial bleeding [7]. The first toe and the lateral foot margin on the right side and the second toe on the left became necrotic initially followed by oval skin and soft tissue necrosis of the forefoot (Fig. 1). Mediacalcinosis with diffuse involvement of the distal arteries of the lower limb with multiple stenoses was found. Focal arteriosclerotic plaques of the larger vessels were not visible. Hepatitis C serology, ANA and ANCA were negative. Therapy with iloprost was performed, in addition to heparin, acetylsalicylic acid and broad-spectrum antibiotic therapy to cover gram-negative and positive bacteria. The calcium-phosphate product was 4.11 $mmol^2/l^2$. PTH was 146.6 ng/l (range 15–65 ng/l) four months before onset of necrosis, and PTH was 100.5 ng/l at presentation of necrosis. Calciphylaxis was considered in this patient because of ESRD, immunosuppression with prednisone, anticoagulation with phenoprocumon and a hypercoagulable state due to protein S mutation. Therefore, therapy with sodium thiosulfate was initiated. A skin biopsy was not performed. PTA of the anterior tibial artery and the dorsal artery of the foot were performed without success. Cardiovascular risk factors were managed (Table 2), pain treated and wound care performed [5,6]. Necrosis slowly progressed over the next 12 months (Fig. 1) with mummification. As a complication, an erysipela developed on the right lower extremity. Initially local wound swab showed C. glabrata, S. maltophilia, Enterococcus species, P. aeruginosa, and P. putida. About eight months later, A. vesicolor and C. uniguttulatus grew from local swabs at the boarder of the necrosis. Antifungal therapy with amphotericin B was initiated and broad-spectrum antibiotic therapy was continued leading to control of infection. Ambulation was maintained for 10 months. After two months of reduced mobility, abdominal pain occurred and an intestinal obstruction with stool retention was suspected since the patient no longer passed stools. The patient refused to be treated longer for this condition and discontinued immunosuppression requesting palliation. The patient died within hours, one year after first manifestation of CLI with necrosis. The family refused an autopsy.

2.2. Case 2

At age 27, a female patient with CF underwent lung transplantation for end-stage lung disease. The patient was examined 51 months before the diagnosis of CLI because of bilateral pretibial pain without claudication. Oligosymptomatic PAD, Rutherford classification 0/0, was diagnosed because of hemodynamically non-relevant obstructions and no claudication. First symptomatic PAD was manifested by claudication in the left calf 13 months before CLI due to 80% stenosis of the A. superficialis femoris which was successfully treated by PTA. Ten years after lung transplantation, pain of the right forefoot and the first to third toes developed (Table 1). PTA of the popliteal artery was performed (Fig. 2) The distal vessels could not be opened. The pain at rest resolved completely. Claudication of the calves and the right foot persisted. About one month later, CLI with pain at rest and discoloration of the big toe developed. PTA of the anterior and posterior tibial arteries was performed without success. No change in perfusion could be documented after PTA. Surgical treatment with amputation was evaluated and considered as high risk due to persistent vascular compromise and immunosuppression. A conservative treatment with iloprost, clopidogrel and heparin and empiric antibiotic therapy was performed. Gangrene of the toes developed with mummification and progression to the forefoot (Fig. 3). Also progressive renal failure developed. Dialysis was started 132 months (11 years) after lung transplantation and living-related donor renal transplant was performed 14 months later. Special orthopedic shoes were fitted to prevent pressure being exerted on the forefoot during ambulation. The patient performed practically all wound care herself having a nursing background. The necrotic area became mobile, meaning it was moveable but still attached. Efforts were made not to disconnect the necrotic part until it fell off spontaneously. A glove-like part of the forefoot was autoamputated after four years and surprisingly exposed toe-like bony structures (Fig. 3). Wound healing is still in progress and the forefoot remains free of pressure to allow this process to continue.

2.3. Case 3

At age 38, a female patient with CF-related end-stage lung disease underwent bilateral lung transplantation. Almost four years after transplantation, the patient presented with livid coloration and acral necrosis of the right second finger with associated dys- and paresthesia. Duplex sonography showed a significant distal stenosis of the radial artery with diffuse medialcalcinosis of all distal arteries of the upper extremity. A successful PTA was performed. Demarcation and healing was observed over four months with complete healing after six months. The necrosis was due to peripheral embolization from the radial stenosis probably due to repeated arterial punctures. 38 months after transplantation pain in the toes developed. The right second and third toe and left first to fourth toes discolored. The angiography showed diffuse involvement of all the lower leg arteries with massive mediacalcinosis. A PTA would not be successful and bypass surgery was considered not

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