Case Report and Literature Review of the Sequential Treatment Involving Percutaneous Transluminal Angioplasty (PTA), Tissue-engineered Skin Graft (ADM), Autologous Skin Graft and Negative Pressure Wound Therapy (NPWT) in Chronic Limb-threatening Ischemia (CLTI) Patients with Extensive Ulcers in the Donor Site after Coronary Artery Bypass Graft Surgery

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Research Article

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Abstract

This case report describes a 63-year-old male, who was admitted to the hospital due to "the ulceration in his left lower limb for more than 1 month and the pain exacerbation for 2 weeks". The patient was diagnosed with "cerebral infarction, coronary heart disease and type 2 diabetes" nine years ago and subsequently treated with coronary artery bypass graft surgery. This time, he was admitted with an ulcer in the size of 4*45cm on the inner side of his left lower limb, with the wound covered by a dark scab, and the skin was red and swollen around the part where the pus percolated. According to the occlusion in the initiating terminal of his left superficial femoral artery, and the extensive stenosis and occlusion in popliteal and infrapopliteal arteries, this patient was diagnosed with arteriosclerosis obliterans of lower limbs, as shown by the Digital Subtraction Angiography (DSA). Therefore, on the basis of supportive medical treatment and local debridement, he underwent two endovascular operations to open the "straight bloodstream" towards the affected part. Then, the 4-month sequential treatment of split-thickness skin and tissue-engineered skin grafts combined with Negative Pressure Wound Therapy (NPWT) was performed for wound repair. Finally, the wound healed completely, recovering the patient's ability to walk with a walking aid. This was the first time that the sequential treatment, including Percutaneous Transluminal Angioplasty (PTA), autologous skin and tissue-engineered skin grafts, and negative pressure suction, was successfully used to cure a refractory ulcer in the donor site after the patient with critical limb ischemia received the coronary artery bypass graft surgery.

Introduction

The cardiac surgery can cause various postoperative wound complications, such as infection, dehiscence, delayed healing, etc., which has become a pressing issue in related industries. Thereinto, the complications at the chest and in the donor site of lower limb blood vessels have their respective incidence rates of 24%[1−2] and 3%~25%[3]. The sternal dehiscence and wound infection are common risks faced by patients receiving a cardiac surgery concerning sternotomies, such as coronary artery bypass graft, heart valve replacement, and heart transplant. According to statistics, the patients suffering from sternal dehiscence accounted for 3%~8%; those with superficial wound infection accounted for 8%; those with deep wound infection accounted for 2%[4]. Among these patients, 3%~40% of them died of sternal wound infection and mediastinitis[5−6]. However, the ulcers along the trend of great saphenous veins in lower limbs are rarely reported. As an increasing number of patients suffer from arteriosclerosis obliterans of lower limbs, especially Chronic Limb-threatening Ischemia (CLTI), the problem of refractory ulcers in lower extremities occurring after coronary artery bypass graft surgery has attracted more and more attention. The infection and pain caused by these ulcers may lead to transfemoral amputation and even death.

In Peripheral Artery Diseases (PAD), the lower limb ischemia occurs most commonly in clinical practice. It refers to the arterial stenosis or occlusion and insufficient blood perfusion in lower limbs caused by various factors, which will lead to intermittent claudication, pain, ulcer, gangrene or other ischemic manifestations in lower extremities[7].

CLTI is the severest stage of ischemia during the progression of PAD in lower extremities, with its typical clinical manifestations including reduced walking ability, rest pain for over 2 weeks, ulcer, and gangrene. In this stage, the bloodstream will be inhibited due to the arterial occlusion in lower limbs, which seriously affects the patients' quality of life and sometimes may lead to amputation or death[8].

PAD, with a worldwide prevalence of 3%~10%[9], may develop into CLTI in 10%~20% of PAD patients[10−12]. The annual incidence of CLTI is estimated to be 220 ~ 3500 per 1 million people in the United States, the United Kingdom, and many other countries, with the incidence being 1% in adults. CLTI often occurs in the severest stage of PAD, showing a high mortality rate (higher than 50% within 5 years)[13].

In this report, we presented a CLTI patient who developed a refractory ulcer in the donor site after receiving the coronary artery bypass graft surgery. Based on the literature review on related case reports (Table 1), we finally focused on the patients with extensive refractory ulcers in the donor site of lower limbs. By studying this case, we recognized the positive role played by the integrated sequential treatment involving Percutaneous Transluminal Angioplasty (PTA), autologous skin or artificial dermis grafts, Negative Pressure Wound Therapy (NPWT), and other suitable techniques. Given that there are few reports about similar cases, this case must be documented and reported to provide precise references for the subsequent treatment of similar patients.

Table 1
Literature review of similar case reports on wound repair in the donor site of blood vessels after coronary artery bypass graft surgery

Case No.	Years of age/gender	Chief complaint	Wound features	Medical history	Some examination results	Wound treatment	Healing time (d)
1	75/male	The wound in lower limbs cannot heal within 40 days after the cardiac surgery.	A longitudinal wound extends from the tibial plateau on the inner side of the left lower leg to the site 30 cm above the medial malleolus, with a thick scab covering the wound. The gray inactive fat can be found below the scab.	The coronary artery bypass graft surgery was performed 40 days ago (the great saphenous vein in the left lower limb was removed). The patient has suffered from coronary atherosclerotic heart disease and diabetes for 1 year.	At admission: CRP 9 mg/L; PCT 0.35 ng/ml; WBC $5.12×10^9$ /L; HGB 69 g/L; ALB 31 g/L; fasting blood glucose (FBG) 6.7 mmol/L. Bacterial culture on the wound: No bacteria.	The wound dressing is changed every two days. Methods: debridement, washing the wound with normal saline, filling the wound with nano-silver sterile gauze, packing the wound with aseptic dressing.	40

Notes: CRP: C-reactive protein; PCT: procalcitonin; WBC: white blood cell count; HGB: hemoglobin; ALB: albumin

Case No.	Years of age/gender	Chief complaint	Wound features	Medical history	Some examination results	Wound treatment	Healing time (d)
2	67/female	The wound on the inner side of both upper legs cannot heal within 2 months after the cardiac surgery.	The longitudinal wounds are located on the inner side of both upper legs. Thereinto, the wound on the right upper leg is about 15 cm long and 2 cm deep; the wound on the left upper leg is about 20 cm long and 1 cm deep. These wounds are covered by hard scabs, and the gray adipose tissues can be found below these scabs.	The right coronary artery stent implantation and coronary artery bypass graft were performed 2 months ago. The patient has a 37-year history of hypertension, a 20-year history of diabetes, and a 10-year history of cerebral infarction.	At admission: CRP 9 mg/L; PCT 0.35 ng/ml; WBC 13.32×10^9 /L; HGB 115 g/L; ALB 34 g/L; fasting blood glucose (FBG) 11.79 mmol/L. Bacterial culture on the wound: No bacteria.	Ditto	65

Notes: CRP: C-reactive protein; PCT: procalcitonin; WBC: white blood cell count; HGB: hemoglobin; ALB: albumin

Case No.	Years of age/gender	Chief complaint	Wound features	Medical history	Some examination results	Wound treatment	Healing time (d)
3	63/male	The wound on the inner side of the left lower limb cannot heal within 1 month after the cardiac surgery.	There is an ulcer in the size of 4*45cm on the inner side of the left lower limb, which is covered by a dark scab. The skin is red and swollen around the part where the pus percolates. The gray adipose tissues can be found below the scab.	The coronary artery bypass graft surgery was performed 1 month ago. The patient has sequelae of cerebral infarction, coronary atherosclerotic heart disease, and type 2 diabetes.	The patient's both feet, with toenail hypertrophy, are pale in color under a low skin temperature, and the fine hair on the feet has fallen off. There is a symptom of pulselessness in the left femoral artery and arteries below this one. Glycosylated hemoglobin: 8.3. Echocardiography: EF 32%. ABI: 0.3 on the left side and 0.7 on the right side. DSA: occlusion in the initiating terminal of the left superficial femoral artery, and extensive stenosis and occlusion in popliteal and infrapopliteal arteries.	The endovascular operation is performed twice to open the "straight bloodstream" towards the affected part. The wound is sequentially repaired by debridement, split-thickness skin graft, tissue-engineered skin graft, and negative pressure treatment.	8 months
Notes: CRP: C-reactive protein; PCT: procalcitonin; WBC: white blood cell count; HGB: hemoglobin; ALB: albumin							

Manifestation

1. Medical history and physical examination

A 63-year-old male patient was presented to hospital in December, 2020 due to "the ulceration in his left lower limb for more than 1 month and the pain exacerbation for 2 weeks". He was diagnosed with "cerebral infarction, coronary atherosclerotic heart disease, and type 2 diabetes" nine years ago and underwent coronary artery bypass graft surgery one month ago.

According to the physical examination at admission, the patient's both feet, with toenail hypertrophy, were pale in color under a low skin temperature, and the fine hair on the feet had fallen off. An ulcer in the size of 4*45cm was observed on the inner side of his left lower limb, and the wound was covered by a dark scab. The skin was red and swollen around the part where the pus percolated. There was a symptom of pulselessness in the left femoral artery and arteries below this one. The laboratory examination showed the glycosylated hemoglobin of 8.3, and the Ejection Fraction (EF) was measured to be 34% by echocardiography. The Ankle-Brachial Index (ABI) was 0.3 on the left side and 0.7 on the right side. It was found from the digital subtraction angiography (DSA) that this patient suffered from occlusion in the initiating terminal of his left superficial femoral artery, and extensive stenosis and occlusion in popliteal and infrapopliteal arteries, based on which, he was diagnosed with arteriosclerosis obliterans of lower limbs combined with CTLI.

2. Process and outcome of the wound treatment

Phase I: In the first week, the PTA was performed to open the occluded superficial femoral artery, with a self-expanding stent implanted into this artery. The popliteal and infrapopliteal arteries were expanded by endovascular drug-coated balloon dilatation to make the blood flow from the main artery to the affected part. (Fig. 1)

Phase II: In the second week, the scab and necrotic tissues were removed on the basis of autolytic debridement, which was followed by the NPWT. When fresh granulation tissues were observed on the wound, the autologous split-thickness skin could be grafted, and consequently, the wound healed. (Fig. 2) The ulcer and extensive skin defect that subsequently occurred on the back of the lower leg were treated by expanding the area of debridement and resecting part of the muscle tendon. Then, the negative pressure treatment and split-thickness skin graft were performed. Finally, the wound healed, and the patient was discharged. (Fig. 3)

Phase III: Three months after hospital discharge, the patient developed ulcers in the lateral malleolus and tendo calcaneus, which were complicated with coldness, numbness, and pain in the lower limbs. The DSA showed extensive stenosis and occlusion in the infrapopliteal artery of the left lower limb, and the aortic blood flow was not detected on the foot. Therefore, the patient was readmitted and treated with PTA to open the “straight bloodstream” towards the foot, particularly towards the diseased region. (Fig. 4)

Phase IV: After the surgery, part of the exposed necrotic tendo calcaneus was removed from the heel. Then, the tissue-engineered skin graft combined with negative pressure treatment was performed, during which the tissue-engineered skin, which had been soaked in the sterile normal saline for 3-4min, was trimmed into the shape of the wound. With the collagen layer appressed to this wound, the stent was sutured along the edge of the wound under tension-free conditions. Then, the sterile vaseline gauze was put on the silica gel layer for negative pressure treatment, and the postoperative dressing change was provided for the patient regularly. After the collagen layer was completely vascularized, the silica gel layer was removed by tweezers. The tissue-engineered skin graft was repeated until the wound healed. (Fig. 5) Similarly, the ulcer in the lateral malleolus was also repaired by tissue-engineered skin graft combined with negative pressure treatment. (Fig. 6)

Discussion

1. Treatment of the hard-to-heal wound in lower limbs after coronary artery bypass graft surgery

It has become a pressing clinical problem to manage the wound complications after cardiac surgery, such as infection, dehiscence, and mediastinitis. These complications were featured with difficult wound healing and long healing duration, with the average healing time lasting 16.0 ± 3.1 weeks. In addition to the traditional debridement, the wound can also be managed by NPWT, autologous platelet-rich plasma, new bioengineered skin, flap coverage, and other methods. Besides, physical therapies, for example the Low-intensity Shockwave Therapy (LiSWT), are also adopted in some cases to promote wound healing. However, these new methods are greatly restrained in clinical application due to the need of adequate wound bed preparation and the limitation of strict indications. In particular, it is challenging to rapidly and effectively repair the ulcer wound in the donor site of lower limb blood vessels.

2. Formulation of therapeutic schemes

The current treatment methods for CLTI primarily include drug therapy, endovascular operation, surgical intervention, and other tentative schemes, such as gene therapy and stem cell transplantation. Although the progression of arterial occlusion in lower limbs can be slowed down by drug therapy, the vascular stenosis and occlusion caused by arteriosclerosis obliterans cannot be cured fundamentally. Therefore, CLTI patients are preferentially treated with revascularization through endovascular operation or surgical intervention. This is because the “straight bloodstream” can be supplied to the surgical site by vascular surgery, thus guaranteeing wound healing.

3. Mechanism of the heel ulcer repair with tissue-engineered skin

Using the collagen matrix and medical silicone rubber membrane, Yanns et al.[14] prepared the artificial composite dermis in 1982, which was successfully used to repair the deep burn wound as a dermal regeneration template. In 2017, China’s first double-layer tissue-engineered skin was researched and developed, achieving good results in departments of burn, plastic surgery, hand and foot surgery, etc.[15] At present, the tissue-engineered skin has been highly recognized by domestic and foreign clinicians due to its good therapeutic effect in deep burn, traumatic skin defects, chronic skin ulcer, wound repair caused by tumor resection, and scar plastic surgery[16–17].

According to different structures, materials and preparation methods, the dermal substitute is referred to as tissue-engineered skin, tissue-engineered skin matrix, artificial skin, and artificial dermis in some references at home and abroad. However, it is essentially used to substitute the defective dermal tissues by inducing the regeneration of the dermis through a dermal stent template, thus optimizing the skin appearance and function after wound healing.

In this case, the double-layer tissue-engineered skin was grafted. Thereinto, a semipermeable silicone rubber membrane used for medicine was adopted as the upper layer, which was like the epidermis that controlled the evaporation of water and inhibited the invasion of microorganisms. The spongy dermal stent layer constructed by collagen-chondroitin sulfate was the lower layer, showing high biocompatibility and low immunogenicity[18–19]; playing the role of a cell proliferation stent, this layer promoted the intrusive growth of vascular endothelial cells and Fibroblasts (Fb) in the graft site to form a stent-new capillary-cell composite. Two or three weeks later, the vascularization was adequate, based on which the autologous split-thickness skin was grafted[20]. Last, the dermal stent was degraded gradually and replaced by new dermal tissues.

The domestic and foreign research indicates that the tissue-engineered skin has been successfully applied to the treatment of diabetic, vascular and pressure ulcers, given that it can accelerate the wound healing of chronic ulcers[21–23]. To avoid infection, the repeated debridement is needed during the repair of chronic ulcer wounds using tissue-engineered skin, and this graft operation can only be performed under the conditions of the clean wound and sufficient basal blood supply. Besides, the autologous skin cannot be grafted before the adequate vascularization of tissue-engineered skin on the wound caused by chronic ulcers, which may take two or more weeks.

To repair the deep wound, the tissue-engineered skin can be grafted repeatedly to make the new dermis thicker, which has been applied to this case. That is, the patient underwent the tissue-engineered skin graft repeatedly to repair the heel ulcer, with the result that the wound healed before skin grafting. Although this graft technique has been reported in the clinical treatment of diabetic foot ulcers and other lower limb ulcers[24–26], there is no report about its use to repair refractory ulcers in the donor site of patients with ischemic diseases after coronary artery bypass graft surgery. (Table 1)

Conclusion

The growth and cell factors can be transferred to the wound via the tissue-engineered skin that contains natural extracellular matrices, protogenous growth factors, and living cells[27], thus accelerating the healing process[28]. Meanwhile, the tissue-engineered skin can induce dermal regeneration and inhibit the scar hyperplasia[29–32]. Thus, the wound elasticity and flexibility are recovered; the skin appearance and function are improved[33–34]. Furthermore, the tissue-engineered skin graft can replace the traditional flap transposition by directly covering the exposed bone and muscle-tendon in part of wound repair[35–36].

The sequential treatment, involving PTA, autologous skin or/and tissue-engineered skin grafts, and NPWT, can be used to repair the extensive hard-to-heal wound in the donor site of CTLI patients who have undergone the coronary artery bypass graft surgery. However, it is still a tough clinical issue to accelerate wound healing effectively.

Abbreviations

DSA: Digital Subtraction Angiography; NPWT: Negative Pressure Wound Therapy; PTA: Percutaneous Transluminal Angioplasty; CLTI: Chronic Limb-threatening Iischemia; PAD: Peripheral Artery Diseases; EF: Ejection Fraction; ABI: Ankle-brachial Index; DSA: Digital Subtraction Angiography; LiSWT: Low-intensity Shockwave Therapy; Fb: Fibroblasts

Declarations

Ethics approval and consent to participate

This study was approved by the Ethical Committee of the Affiliated Hospital of Qingdao University (No. QDZYYYECPJ-2020-003-01).

Consent for publication

All authors have read and agreed the publication of this manuscript.

Availability of data and materials

Not applicable

Competing interests

The authors have no competing interests to declare

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Figures

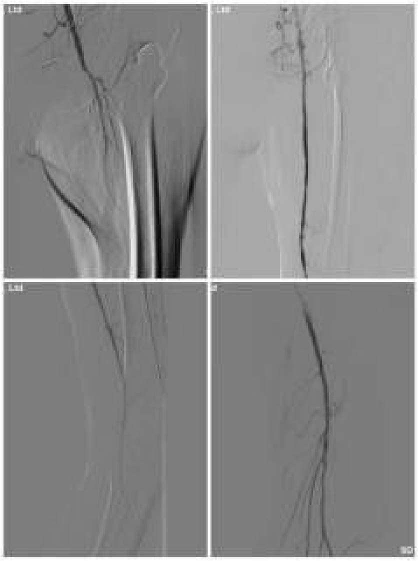

Figure 1

DSA: a occlusion in the initiating terminal of the left superficial femoral artery; b image after the revascularization in the left superficial femoral artery; c extensive stenosis and occlusion in popliteal and infrapopliteal arteries; d image after the PTA

Figure 2

a ulcer in the donor site of blood vessels on the inner side of the left lower limb; b photo after the autolytic debridement; c wound improvement after the PTA; d photo after the split-thickness skin graft; e wound healing

Figure 3

a ulcer on the back of the left lower leg; b photo after the removal of partial muscle tendon; c exposed tendo calcaneus; d photo after the tissue-engineered skin graft; e wound healing

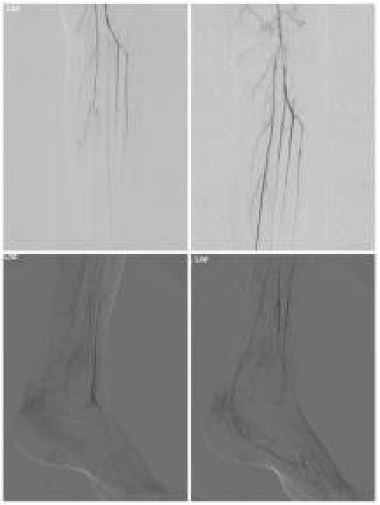

Figure 4

DSA: a extensive stenosis and occlusion in the infrapopliteal artery of the left lower limb; b image after the PTA; c occlusion of the main artery on the foot; d image after the PTA; e improved bloodstream on the foot

Figure 5

a ulcer in the lateral malleolus of the left foot; b photo after the autolytic debridement; c photo after the split-thickness skin graft; d epithelization on the wound base; e wound healing

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Figure 6

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