Case Report

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Regenerative Medicine

The role of the cord blood platelet gel in the management of a diabetic foot with tendon exposure

Mafalda Massara*[,1], Giulia Pucci[2], Giuseppe Stilo[1], Antonino Alberti[1], Rosangela Surace[2], Giovanni Foti[2] & Pietro Volpe[1]

[1]Unit of Vascular & Endovascular Surgery, Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria, 89124, Italy

[2]Calabria Cord Blood Bank, Service of Immunohaematology & Transfusion Medicine, Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria, 89214, Italy

*Author for correspondence: Tel.: +39 347 798 6948; drmafaldamassara@gmail.com

Diabetic foot infection is frequent in diabetic patients and is due to neuropathy, trauma or peripheral arterial disease. The presence of an abscess requires urgent drainage and specific antibiotic therapy. Patients with critical limb ischemia need revascularization and, subsequently the intervention of a plastic surgeon is often required in cases of exposure of tendons and ligaments. During the COVID-19 pandemic, a patient was refered to our department with an abscess on the dorsum of the left foot. After urgent drainage with tendon exposure, he started specific antibiotic therapy and underwent tibial vessels angioplasty. After infection healing cord blood platelet gel was applied, accelerating the healing process, with injection of its liquid part into the exposed tendons, thus retaining the vital functions of the tendons.

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Background

Patients affected by diabetes mellitus often develop various infections, in particular, foot infections due to neuropathy, trauma, a peripheral arterial occlusive disease or a combination of these factors. The presence of an abscess generally requires an urgent operation of drainage, with large incisions and frequent surgical debridements, accompanied by a specific antibiotic therapy and specific dressings. Patients with concomitant critical limb ischemia (CLI) need an examination of the lower limbs arteries and often require a peripheral revascularization. Dressing of the diabetic foot must be adapted to the local state and often the exposure of ligaments and tendons require the intervention of a plastic surgeon.

In this paper, we report our experience regarding the management of an infected diabetic foot with tendon exposure, after urgent abscess drainage and peripheral revascularization, during the COVID-19 pandemic.

The use of cord blood platelet gel (CBPG), with local application and injection of its liquid part into the exposed tendons kept the tendons alive and accelerated the healing process with complete coverage of tendons, avoiding limb and functionality loss.

The patient gave his verbal written informed consent for the inclusion of his medical history within this case report.

Presentation of case & initial diagnosis

A 66-year-old man was admitted to the emergency room of our hospital with fever, glycemic decompensation and an abscess on the dorsum of the left foot (during the complete lockdown due to the COVID-19 pandemic). He was also affected by hypertension, diabetes mellitus (on insulin therapy), dyslipidemia and had an history of peripheral arterial disease. He has been already undergone a venous bypass of the femoropopliteal below the knee on the right lower limb due to rest pain 3 years prior and amputation of II-III-IV-V fingers of the left foot due to infection

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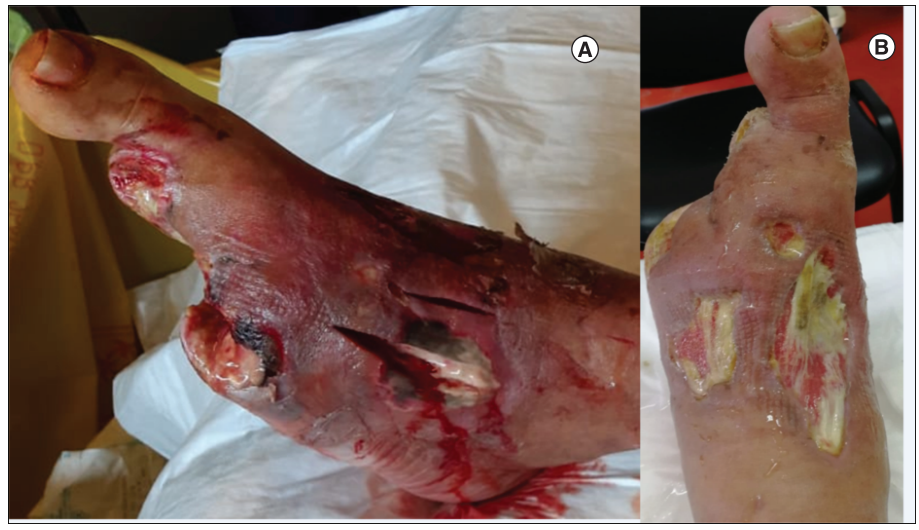

Figure 1. Abscess drainage. (A) Deep incision with abscess drainage on the dorsum of the left foot. **(B)** Large exposition of tendons on the dorsum of the left foot.

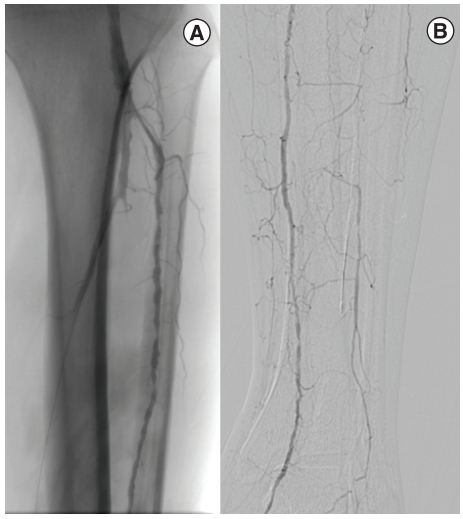

Figure 2. Pre- and post-treatment angiography. (A) Angiography showing the tibial vessels disease on the left lower limb. **(B)** A positive final result after posterior tibial artery angioplasty.

2 years prior. After clinical evaluation, the patient was submitted to an eco-color duplex that showed the regular patency of the left arterial femoropopliteal axis and a flow reduction on tibial vessels, especially on retromalleolar posterior tibial artery (10 cm per s).

Therefore, he was promptly admitted to the Vascular Surgery Department and he was submitted to an urgent routine blood draws, CRP and procalcitonin assay and a blood culture sampling.

Treatment

After making the withdrawals, the patient underwent urgent abscess drainage through deep incisions on the dorsum of the foot (with subsequent exposure of left foot tendons [Figure 1A & B]), specific antibiotic therapy based on microbiological results after 3 days of broad spectrum antibiotic therapy and a further blood collection for blood culture that, along with the first collection, showed negative results. Based on ultrasonography performed on the day of admission, 1 day later the patient underwent angiography of the left lower limb under local anesthesia (Figure 2A) that confirmed the regular patency of the femoropopliteal axis and of the tibial-peroneal trunk. After cannulation of the posterior tibial artery, the vessel was submitted to angioplasty with a 2 mm diameter balloon (Figure 2B), with subsequent improvement of the peripheral blood flow, demonstrated with an ultrasonographic

Figure 3. Cord blood platelet gel application. (A) Local application of cord blood platelet gel on the lesions. **(B)** Injection of the liquid part of cord blood platelet gel into the exposed tendons.

intraoperative check (from 10 to 50 cm per s). He continued oral therapy with acetylsalicylic acid and we added clopidogrel 75 mg per day for 3 months.

Outcomes & implications

Two weeks later, the microbiological examination of a tissue sample from the wound showed a negative result. The possibility of sending the patient to a specific plastic surgery center was temporary excluded due to the COVID-19 pandemic. Therefore, we decided to treat the two lesions on the dorsum of the foot (lesion A: 3 × 3.5 cm; lesion B: 2.5 × 6.2 cm) recurring to CBPG, with local application of the gel covered through fatty gauze and sterile gauze and injection of its liquid part into the exposed tendons, in order to avoid necrosis due to large exposure (Figure 3A & B). The CBPG protocol of our center [1] consisted of platelet gel application twice a week for 4 weeks and then once a week for an additional 4 weeks. The healing process was monitored by direct ulcer dimension tracing onto clear plastic sheet and subsequent computerized planimetry.

At the end of the 8 weeks, we observed the complete healing of lesion A (Figure 4A), with complete coverage of tendons, and a reduction of lesion B to 1.8 × 3.9 cm (Figure 4B), with complete coverage of tendons. Lesion B continued to be treated using fatty gauze.

Discussion

Diabetes mellitus represents a risk factor for the development of infections, especially in patients with uncontrolled levels of glycemia [2,3].

In regard to diabetic foot infections, many factors can contribute such as immunopathy, peripheral neuropathy (that involves sensory, motor and autonomic parts of the nervous system), trauma and vasculopathy [4,5].

According to the Infectious Diseases Society of America guidelines, an empirical treatment of antimicrobial agents should be applied on the basis of infection severity [6], with special attention for gram-positive cocci and in particular methicillin-resistant *Staphylococcus aureus*, gram-negative *bacilli* and enterococcus and anti-anaerobic therapy for gangrenous wounds.

Mild and severe diabetic foot infections require intravenous-specific antibiotic therapy for 2–4 weeks, accompanied by abscess drainage, aggressive incisions and frequent soft tissue and bone debridement.

In addition, in diabetic patients with peripheral arterial disease, a revascularization is often required to improve the process of wound healing and avoid limb loss.

In the last decade, wound debridement was accompanied by adjuvant therapies used to improve the process of wound healing such as negative pressure wound therapy, spinal cord stimulation, hyperbaric oxygen treatment, use of antibiotic impregnated beads and local application of autologous platelet-rich plasma (PRP) and CBPG [1,7–15].

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Figure 4. Clinical Results. (A) Complete tendons coverage and healing of the lesion B. **(B)** Size reduction of lesion B at the end of 12 applications of cord blood platelet gel.

In our hospital, autologous PRP is prepared by colleagues of Calabria Cord Blood Bank, from a large amount of peripheral blood from the patient obtained through a venipuncture (90 ml), however, very often blood sampling in diabetic patients (also affected by peripheral arterial disease and other serious comorbidities, is problematic due to anemia and poor nutrition.

The use of allogenic blood products such as CBPG can overcome these disadvantages of autologous PRP. In addition, CBPG presents a higher concentration of growth factors than autologous gel obtained from adult platelets.

CBPG is obtained by cord blood when it is unsuitable for use for transplantation of hematopoietic cells. It is also produced in the Calabria Cord Blood Bank of our Hospital [1].

At first, an aliquot is removed to determine the count 'ABO' cord group. Then the cord blood units are transferred to triple top and bottom blood bags and are centrifuged at 210 rpm for 10 min at 10°C to decompose the whole blood in packed red cells and PRP. The centrifuged products are separated with a manual bag press and are separated into top blood bags (PRP) and bottom blood bags (whole blood into packed red blood cells) of the mother bag (triple blood bags), in order to value the volumes and platelet concentrations of both products.

Subsequently, PRP is submitted to a second centrifugation at 2000 × g for 15 min at 10°C, with production of platelet concentrate (CP) endowed with a concentration of platelet of 0.8/1.2 × 106 per ml and platelet-poor plasma (PPP). The CP is cryopreserved in Maco Biotech Freezing EVA bags (Macopharma, London, UK), at -80°C. An aliquote of PPP is used for the detection of bacteria and fungi, according to standard blood component culture procedures.

Finally, the CP is transferred in a sterile Petri plate with the addition of about 20% of calcium gluconate and incubated for about 30 min, to obtain the CBPG ready for application [1].

PRP has been widely used to treat tendon-, muscle-, ligament- and cartilage-based conditions [16–18], as well as, ulcers in patients with CLI and Rutherford 6 lesions, after peripheral revascularization [12], to enhance the healing process. CBPG can be used in several clinical conditions. Tadini *et al.* [19,20] demonstrated its benefits in children suffering from epidermolysis bullosa that presented skin lesions. Rosso *et al.* [21] tested the *in vitro* and *in vivo* tissue repair capability mediated by CBPG compared with the standard culture conditions using human primary mesothelial cells, to treat prolonged air leak after pulmonary resection. The authors demonstrated that CBPG accelerates the repair of pleural damage and stimulates the development of pleural adhesions, with reduction of inflammation. In addition, it was used for the treatment of inherited epidermolysis bullosa and to treat oral ulcerations in patients with epidermolysis bullosa [22,23].

Our group used CBPG to improve the process of wound healing in a group of ten diabetic patients with peripheral ulcers and CLI, after endovascular or surgical peripheral revascularization. The other ten patients, also

affected by CLI, underwent revascularization and the peripheral diabetic ulcers were treated with standard wound care, patients treated with CBPG had a more rapid wound healing [1].

More recently, CBPG was used to improve the healing process of a deep surgical site dehiscence after a peripheral bypass in a diabetic patient, with a good final result [24].

In our patient, after an urgent abscess drainage, a peripheral angioplasty with improvement of blood flow on tibial vessels was considered necessary, in order to avoid limb loss and favor the process of healing.

Our patient needed frequent debridements with exposure of dorsum foot tendons. After the exclusion of local and systemic infection, an alternative to plastic surgery (not present in our hospital), was judged temporarily inappropriate due to the COVID-19 pandemic. Instead, CBPG was applied locally, with an injection of the liquid part into the exposed tendons, in order to avoid necrosis due to long and large exposure.

Until now there are no studies in the current literature regarding the results of CBPG injection into exposed tendons.

Regardless of the presence of tendon lesions in our patient, the large and complete exposure could have caused their necrosis or general damage. We believe that the injection of CBPG (which is rich in growth factors) into the tendons, has been protective, helping to keep the tendons alive and functional.

Conclusion

CBPG has been widely used to treat skin and oral lesions caused by epidermolysis bullosa and to favor the process of pleural tissue repair. More recently, it has been used to improve the process of wound healing in diabetic patients with peripheral ulcers and CLI after endovascular or surgical peripheral revascularization, but there are no studies in the current literature about the results of its injections into exposed tendons.

In our patient, we obtained a good final result, with complete coverage of the exposed tendons that have also retained their functionality. However, larger studies are required to confirm our results regarding the effects of CBPG injection into exposed tendons.

Executive summary

- Diabetes mellitus often is responsible for foot infections, due to neuropathy, vasculopathy or trauma.
- Patients with peripheral arterial occlusive disease need revascularization.
- Abscesses require urgent drainage and specific antibiotic therapy.
- Cord blood platelet gel applied to the lesions improves the process of wound healing.
- The injection of the liquid part of cord blood platelet gel into exposed tendons keep vital and functional the tendons.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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