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Case report

Management of post-surgical Achilles tendon complications with a preparation rich in growth factors: A study of two-cases

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1. Introduction

The incidence of Achilles tendon ruptures is rising among active individuals regardless of age. Although operative reconstruction is a standard approach to rupture care, it is accompanied by a non-trivial risk of complications.[11] Overall, open repair is specially indicated for active people since it re-establishes fiber continuity, reducing re-rupture risk and improving long-term functional outcome.[16] When post-surgical complications arise, their management is demanding, particularly in extensively diseased tendons. Although relatively infrequent, deep infection along with tendon necrosis can be a devastating complication requiring repeated surgery. Determining optimal treatment for this entity is a significant challenge to the orthopaedic surgeon.[14,17]

The emergence of platelet-rich technologies has created new therapeutic opportunities by combining an understanding of the biology of tendon injury and repair with surgical principles.[6,22] Our group is investigating the use of the versatile autologous preparation termed preparation rich in growth factors (PRGF) in different medical conditions.[3,21] PRGF has been shown to enhance and accelerate soft tissue repair in cutaneous ulcers,[6] to improve bone repair in oral implantology[7] and non-unions in orthopaedics,[23] to ameliorate intra-articular conditions in select osteoarthritis (OA) patients[22] and to enhance soft tissue healing and remodeling in anterior cruciate ligament (ACL) reconstructive surgery as well as ruptured Achilles tendons in professional athletes.[20,23]

This report describes PRGF-assisted management of major complications in two recreational athletes after initial surgical management of acute Achilles tendon rupture. To our knowledge, this is the first article reporting the use of platelet-rich preparations in severe complications after primary Achilles repair. The biosafety, versatility and ease of preparation of platelet-based formulations in combination with our promising clinical results moved us to share our experience in hopes of inspiring awareness and further investigation of this novel therapeutic option.

2. Patients and methods

2.1. Case presentation

2.1.1. Case #1

A 52-year-old male recreational athlete with a history of Achilles tendinopathy and acute Achilles rupture at the calcaneous insertion was referred to our institution post-surgical therapy. He reported difficulty walking, impairment of ankle plantar flexion and sharp pain at the posterior aspect of his left ankle to superficial calcaneus palpation. Clinical evaluation disclosed a wound fistula in the distal region of the surgical scar, and a defect was palpated around the prominent superior tuberosity of the calcaneous. Complementary axial computerised tomography, magnetic resonance imaging and histology confirmed active osteomyelitis, interstitial tears and the presence of necrotic areas all along the entire length of the Achilles tendon (Fig. 1A). Microbial cultures ascertained the presence of Klebsiella both in tendon and calcaneus bone, prompting intravenous ciprofloxacin for 1 week and oral ciprofloxacin treatment for 2 more weeks.

2.1.2. Case #2

A 62-year-old male mountain medicine physician and professional mountaineer with asymptomatic degenerative tendinopathy (Fig. 1B) who had been previously operated on at our

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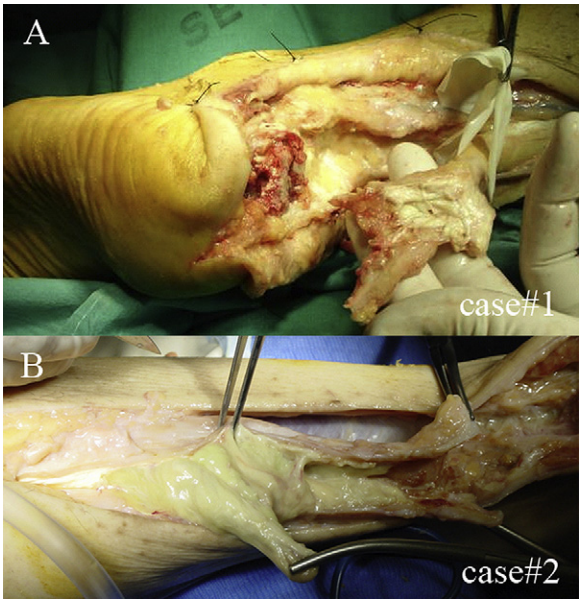

Fig. 1. Severe Achilles tendon disorders in case #1 (A) and case #2 (B).

institution for an acute mid-substance Achilles rupture returned 4 months later with a persistent infected fistula, possibly caused by an intolerance to the PDS suture (polydioxanone, Johnson&Johnson, Brussels, Belgium) used in the previous end-to-end repair. As microbial cultures identified the presence of *Streptococcus agalacticae*, oral cloxacilin three times a day was prescribed. After 3 weeks, the fistula was still active and required surgical debridement.

3. Treatment

A two-stage operation was planned for both cases. The first stage involved surgical debridement and use of PRGF technology as described below. Because the post-debridement defect between tendon and healthy tissue was larger than 8–10 cm, the second planned stage involved graft augmentation in both cases. In the end, graft augmentation was only performed in case #1.

3.1. PRGF preparation

For the preparation of PRGF, 80 ml of peripheral venous blood was drawn from each patient into 9 ml tubes containing 3.8% (w/v) sodium citrate. PRGF was prepared by centrifugation at 640 g for 8 min at room temperature (BTI System, Vitoria, Spain). In order to prepare the autologous fibrin membrane, 8–12 ml of plasma located at the top of the tubes was transferred to a glass bowl. After adding calcium chloride, the mixture was incubated for 30–40 min, allowing for the formation of a biocompatible fibrin membrane that promotes full epithelialisation of soft tissues. The 2 ml plasma fraction located just above the sedimented red cells, but not including the buffy coat, was collected in another tube. This fraction was injected in liquid form after activation or clotted ex vivo and immediately transferred to the bone defect as shown below.

3.2. Surgical debridement and PRGF application

3.2.1. Surgical debridement

In both cases, surgery involved extensive removal of the degenerated area.

In case #1, a single incision was made along the Achilles tendon, exposing the retrocalcaneal bursa and fat pad, which were completely excised. We found a surgical anchor around the calcaneous insertion that had been used for distal attachment during primary repair. Debridement included resection of this anchor as well as the necrotic distal tendon insertion onto the calcaneus and 8 cm of tendon extending proximally from tendon insertion (Fig. 2A).

In case #2, a 15 cm incision was made in line with the previous incision over the posterior aspect of the Achilles tendon. The tendon showed extensive degenerative changes, and the mucoid area was sharply dissected and removed (Fig. 2B). After debridement, only 2–3 cm of the distal tendon end was left, creating a tendon defect greater than 10 cm. A construct was made, approximating by traction the proximal thickened paratenon, fashioned into a tube and sutured in under strain to the 2–3 cm remaining distal tendon-end using FiberWire® (Arthrex Inc., Naples, FL, USA). At the end of surgery, a 1–2 cm gap persisted.

3.2.2. PRGF application

After cleaning the degenerated area, the different formulations of PRGF were applied as follows:

(i) In both cases, 3 ml of the activated liquid preparation was injected in the distal and/or proximal stump (Fig. 3A).
(ii) In case #1 PRGF, scaffolds were applied to entirely fill the tendon gap and the calcaneus tubercle defect.
(iii) In case #2, the paratenon construct was abundantly injected with PRGF, and the remaining 1–2 cm gap was filled with a PRGF clot.
(iv) In both cases, before closing the skin, the elastic PRGF membrane formed "ex vivo" was used to cover the treated areas as shown in Fig. 3B.

Patients were given prophylactic antibiotics and anti-thrombotics after surgery. A below-the-knee dorsal plaster splint was applied with the ankle in the equinus position. Patients were allowed to walk with elbow crutches without weight-bearing.

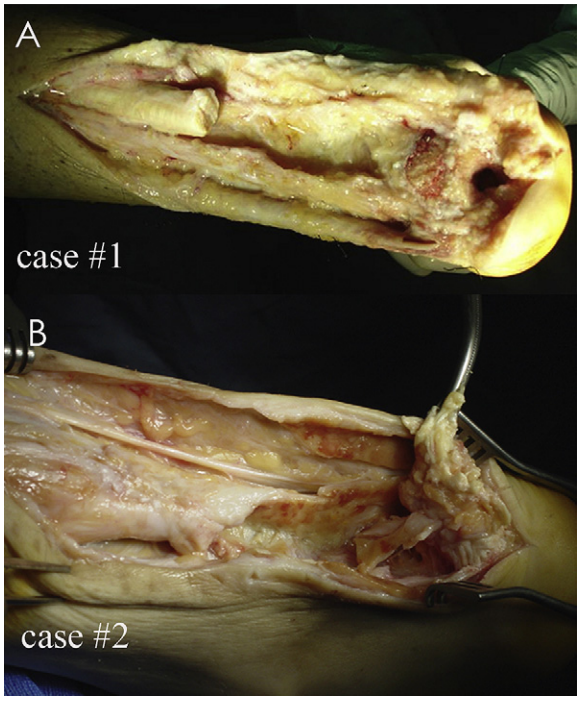

Fig. 2. Extensive tissue removal leaving 8–10-cm tendon gaps.

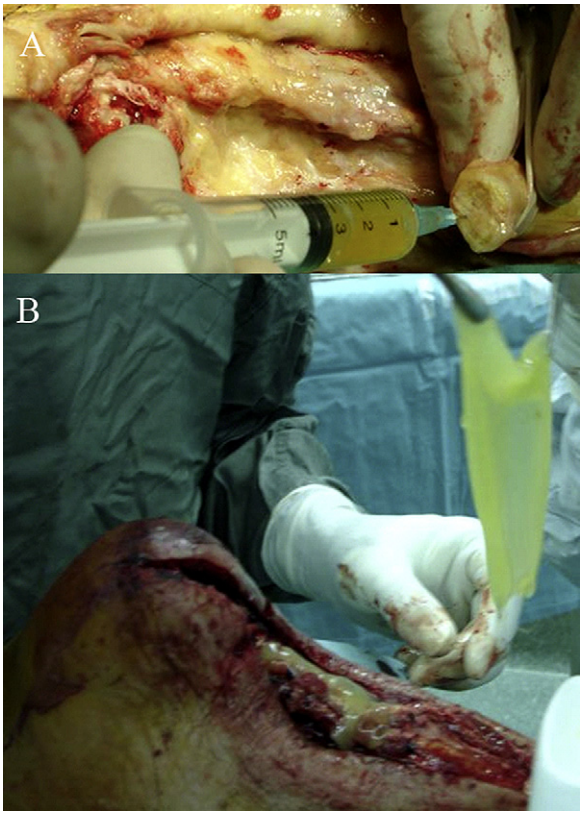

Fig. 3. PRGF infiltration within the proximal stump (A) and the application of an autologous fibrin membrane covering the entire area (B).

3.3. Graft augmentation

Initially, graft augmentation was planned for both patients. In case #1, tendon autograft was scheduled and carried out 3 weeks later. In case #2 the patient experienced good clinical recovery and had promising ultrasound scans during follow-up. As such, graft augmentation was delayed and eventually deemed unnecessary.

3.3.1. Case #1

Upon re-opening, we found interposed tissue bridging the gap all along the length of the tendon defect (Fig. 4). Surprisingly, pulling the proximal tendon-end induced plantar flexion. To further strengthen this tissue, 6 ml of activated PRGF was injected into the newly formed tissue. An autologous semi-tendinosus tendon was used to bridge the large Achilles defect to further reinforce and augment the repair site. To harvest the tendon, we made an incision over the pes anserinus and placed a PRGF scaffold at the donor site to help with healing (Fig. 5A). Before transplanting this tendon, small volumes of liquid PRGF were injected among the

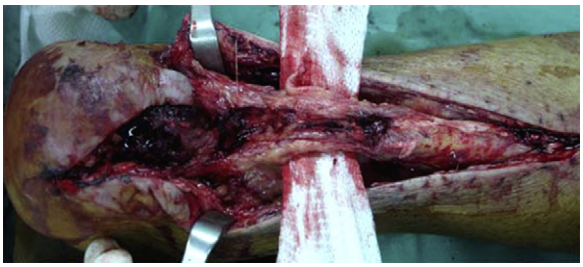

Fig. 4. The repair tissue formed 3 weeks after debridement and PRGF application in case #1.

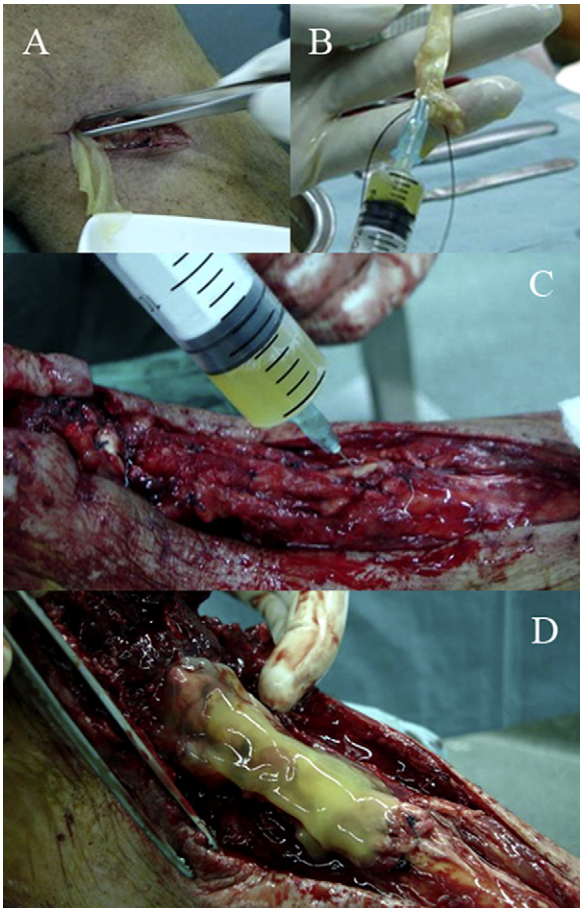

Fig. 5. PRGF-assisted grafting procedure: PRGF was applied at the donor site after harvesting the semitendinosus (A); activated PRGF is injected within the graft (B) and the reconstructed tendon (C); and the affected area is covered with the fibrin scaffold (D).

tendon fibres to activate tendon cells as previously described by Sanchez et al.[21] (Fig. 5B). The graft was then anchored to the calcaneus bone by drilling a bone tunnel and suturing to the proximal stump of the tendon. A number-0 Vycril locking suture was run along the underlying newly formed tissue to make a very solid construct (Fig. 5C). After closing the paratenon but before closing the overlying skin, the affected area was covered with a fibrin membrane (Fig. 5D).

4. Outcome and follow-up

4.1. Case #1

1 week after tendon grafting and PRGF application, patient #1 felt able to perform active ankle flexion-extension. At this point, assisted physical therapy was begun. The patient was instructed to do a small series of dorsal/plantar flexion exercises. A gradual increase of ankle angulations during flexion was achieved. The range of motion of the ankle was 8°/10° dorsal/plantar by the end of the first week and 15°/23° by the fourth week. At this point, partial weight bearing (50% of his weight) was allowed and increased to 70% by the sixth week. Full weight-bearing was achieved by the eighth week, at which point the range of motion was 20°/58°. Fifteen minutes of stationary bicycling and 1500 m progressive marching were included in physical therapy by week 10 with progressively increasing duration and intensity. The patient resumed football training activities by week 14. At the time

of writing, 11 months after graft augmentation, the patient is training and competing without any recurrence of symptoms.

4.2. Case #2

The plaster cast was removed after 14 days, and physical therapy was begun. This was followed by 4 weeks of partial weight-bearing as the patient felt able, using elbow crutches and a heel lift with the foot strapped into the equinus position using an adhesive bandage. After 6 weeks, the patient felt able to ambulate. Full weight-bearing and a complete range of motion was achieved by the end of the 10th week. The patient's functional result 1-year post-treatment is shown in Fig. 6. The patient resumed normal mountain climbing activities after 7 months without any recurrence of symptoms. Notably, 10 months after surgery, the patient was able to attempt climbing a peak over 7000-m high (Aconcagua, Argentina). MR imaging (Fig. 7) shows in detail the condition of the tendon at the time of writing, 5 years after PRGF-assisted surgical debridement. Although imaging abnormalities were found, the Achilles tendon has been functional and asymptomatic during this period. The healed Achilles tendon shows a thickened appearance and areas of increased signal intensity. The latter may be associated with some persistent age-dependent degenerative changes.

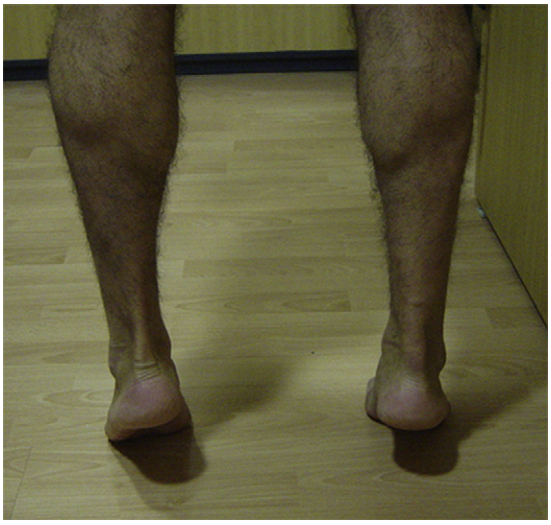

Fig. 6. Functional result of case #2 at 1 year.

5. Discussion

We report PRGF-assisted management of major post-operative complications such as infection and Achilles tendon necrosis in two recreational athletes. The two cases were challenging due to the critical length of the tendon defects (>8–10 cm) and the detached bone-tendon insertion in case #1. We used a two-step approach to manage these patients: (1) a surgical toilette to remove degenerated tissue and (2) a tendon augmentation to strength the tissue to deal with the large tensile forces generated by muscles. PRGF was used in both stages.

As the understanding of tendon biology and repair mechanisms improves, we have begun to better understand the molecular mechanisms underlying the benefit of PRGF.[9,10,12,13] In the surgical toilette, the PRGF scaffold served to establish the physical

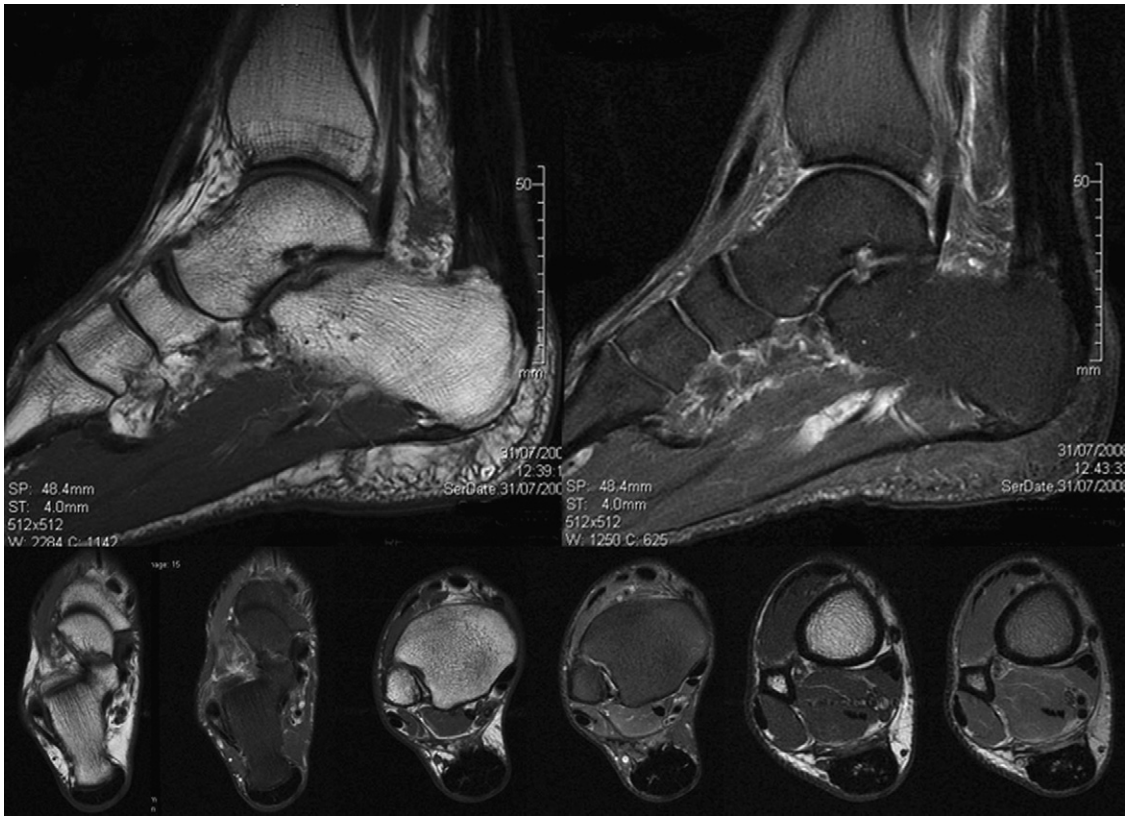

Fig. 7. Sagital T1-weighted fat-suppressed (A) and proton density fat saturation (PDFS) (B) MR images show thickening of the Achilles tendon. Internal signals can be seen consistent with background mucoid degeneration. Axial T1-weighted fat-suppressed (C) and PDFS (D) proximal, mid-substance (E and F) and distal (G and H) images show speckled appearance consistent with mucoid degeneration and loss of normal concave anterior margin.

continuity between the proximal tendon stump and the distal tendon insertion, providing a structure for cell migration and proliferation. This is thought to facilitate the formation of tissue with dense collagen fibres as well as proliferating fibroblasts and vessels.[18] By covering the area with a PRGF membrane, we likely facilitated an extrinsic repairing mechanism by which fibroblasts could move easily from the peripheral paratenon or external tissue sources to the healing site. This emphasises the importance of structures in close communication with the Achilles tendon, specifically the paratenon, skin barrier and subcutis.[15]

In addition to providing a fibrin scaffold, PRGF allows delivery of the necessary signalling molecules critical to a successful repair.[1,8] Platelets embedded in the scaffold secrete a large pool of proteins and factors including PDGF, TGF-β, VEGF, IGF-I, and HGF, among others to the local milieu.[19] In our previous work we have observed that this pool of released growth factors from PRGF increases the proliferation of human tendon cells and stimulates them to produce type I collagen and angiogenic factors such as HGF and VEGF.[2] The latter are critical for neovascularisation and maintenance of vasculature present in the endotenon and epitenon. HGF is a potent anti-fibrotic agent that could reduce scar formation around tendons.[5] Additional experiments conducted in a sheep model confirmed increased cellularity and vascularity as well as the absence of fibrosis after PRGF injection within Achilles tendons.[4] Other authors have shown that, during the initial repair process, growth factors such as IGF-I stimulate the migration and proliferation of fibroblasts to the wound site.[24,25] Based on these experimental results, we proposed a novel approach to create fully integrated bioactive grafts by injecting PRGF into the semitendinosus graft. We believed that this approach would add to the scaffold structure the necessary biological cues for cell migration, proliferation, angiogenesis and remodelling to result in better patient outcomes.

As research into tendon disorders continues, additional novel biological therapies are being translated into the clinic and operating room. When evaluating different therapeutic options, clinicians must weigh a treatment's versatility, biocompatibility and efficacy. PRGF application in combination with surgery represents an option that may meet these criteria for treatment of major complications from Achilles tendon rupture and repair. With its use, we were able to resolve major tendon problems that were causing marked morbidity and functional impairment.

6. Conclusions

Platelet-rich preparations fall into the novel biological armamentarium and offer new therapeutic opportunities in post-surgical complications of Achilles tendon rupture. This report describes the use of PRGF as an aid in healing after debridement and augmentation procedures. Our results indicate that a PRGF-assisted regenerative technique may be suitable in the management severe complications in Achilles tendon conditions.

Financial disclosure

Eduardo Anitua M.D. and Isabel Andia Ph.D work in the Research Department of Biotechnology Institute, a dental implant company that commercializes a system for preparing platelet-rich plasma for therapeutic use.

Mikel Sánchez M.D., Juan Azofra M.D., Alejandro Cole M.D. and Alejandra Da Silva M.D. declare that they have no competing interests.

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