Percutaneous injection of autologous platelet-rich gel in a patient with an infected nonunion of the tibia. A case report and review of the literature

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Abstract
In the treatment of infected nonunions, the goals are to eliminate the infection while stimulating bony union. Platelet-rich gel (PRG) enrich with growth factors represents novel autologous treatment option that could be applicable in the treatment of disturbances of the healing processes. Despite tibial infected nonunion with fistula after percutaneous autologous PRG grafting into gap bone and soft tissue defect was healed.
This case is the first report of the application of PRG in an infected nonunion. In our opinion PRG is inductive biomaterial with antimicrobial activity, which might be used in the treatment of local bone and wound infection.
Key words: Platelet-rich gel, Growth factors, Nonunion, Infected fracture

INTRODUCTION

Despite advances in surgical techniques and fixation procedures, the treatment of open fractures continues to be associated with high rates of delayed union and nonunion. When fracture healing is delayed, a secondary intervention may be required. Secondary operations to promote union of unhealing fractures are associated with high rates of patient morbidity and reduced quality of life [1]. Fractures with an open wound, soft tissue loss, severe comminution and displacement or bone loss are more prone to nonunion. Infection and insufficient immobilization are the primary causes of nonunion. Merle D'Aubigne reported a union rate of only about 50% after grafting nonunited infected tibial fractures. He and others advocated the use of bone grafting with no metal fixation [1,2]. Novel grafting techniques that increase initial union rates have inherent value in the fracture treatment.

Cytokines are critical mediators of fracture healing. Previous studies showed that local application of bone morphogenetic protein-7 is capable of increasing gap healing in clinical use [3]. Application of autologous platelet-rich gel (PRG) represents a novel approach to the treatment of open fractures. Upon platelet activation, platelet a-granules release over 30 cytokines including platelet-derived growth factor (PDGF), transforming growth factor-b (TGF-b), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), \epidermal growth factor (EGF) [4] and also antimicrobial proteins [5]. In a recent clinical study, PRP was capable of increasing bone regeneration in mandibular defects in combination with bone marrow [6].

In the present case study, we report the influence of PRG on healing of an infected nonunion. To our knowledge, this is the first report of PRG application in an active infection site.

CASE REPORT

A fifty-five-year old man using a welding can with petrol experienced double open fracture of the cruris (fig. 1) on 31.01.2003. Both legs had been treated with external fixation. In the left leg delayed union occurred and in the right leg an infected nonunion with fistula developed. After 6 months the left leg was treated with intramedullary nailing and within 4 months union occurred. In the right leg methicillin-sensitive *Staphylococcus aureus* (MSSA), *Proteus mirabilis* and *Enterobacter cloace* were detected in the wound. On 30.04.2004 MSSA was still present and radical debridement was performed: the fibrous tissue of the nonunion site was removed and the gap filled with a gentamicin sponge. Further microbiological examination was still positive for MSSA in the fistula and impaired bone healing persisted.

On 19.08.2004 percutaneous autologous platelet-rich gel (PRG) injection at the nonunion site was performed. 12ml of PRP was obtained using gravitational platelet concentration system (GPS I, Biomet, USA) and mixed with 3ml of 1600 U/ml bovine thrombin in a 10% calcium chloride solution at room temperature to form PRG. Under general anesthesia an 18-gauge needle was introduced into the gap of nonunion using fluoroscopic guidance (fig. 2). PRG was then injected into the gap via a peppering technique. PRG was applied to the nonhealing wound at two times following injection into the nonunion (fig. 3). No bacteria were detected in the wound during the wound healing process. However, MSSA was still detected at the pin site. After 5 months, union occurred and the stabilizer was removed (fig. 4). The wound of the fracture site was healed (fig. 5). On 7.11.2005 the patient reported acute the right lateral ankle pain, which developed into phlegmone after 2 weeks. The nonhealing wound characterized by excuding purulent material developed. The microbiological examination detected methicillin-resistant *Staphylococcus aureus* (MRSA). Currently, the patient does not experience the episodes of phlegmone.

DISCUSSION

Several factors influence the outcome of nonunion. These include the localization of the fracture site, type of fracture, skill of surgeon, and infection. Efficacy of the treatment of bone healing disturbances is dependent on many factors, including type of nonunion, use of osteoinductive and osteoconductive biomaterials, method of stabilization in secondary intervention, active infection

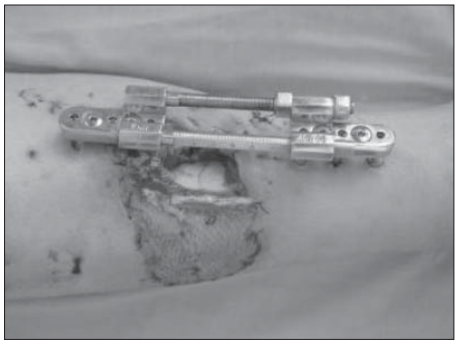

Fig. 1. The right cruris open fracture treated with external fixation (KoD)

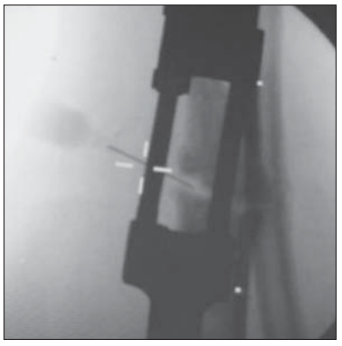

Fig. 2. Percutaneous PRG injection into the nonunion gap of the right cruris under fluoroscopic guidance

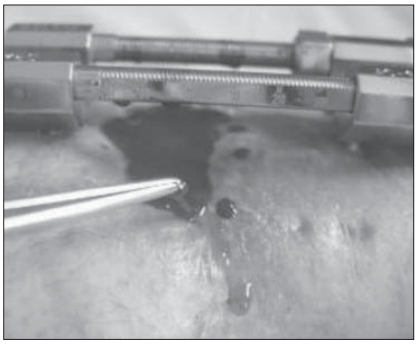

Fig. 3. The nonhealing wound covered by PRG

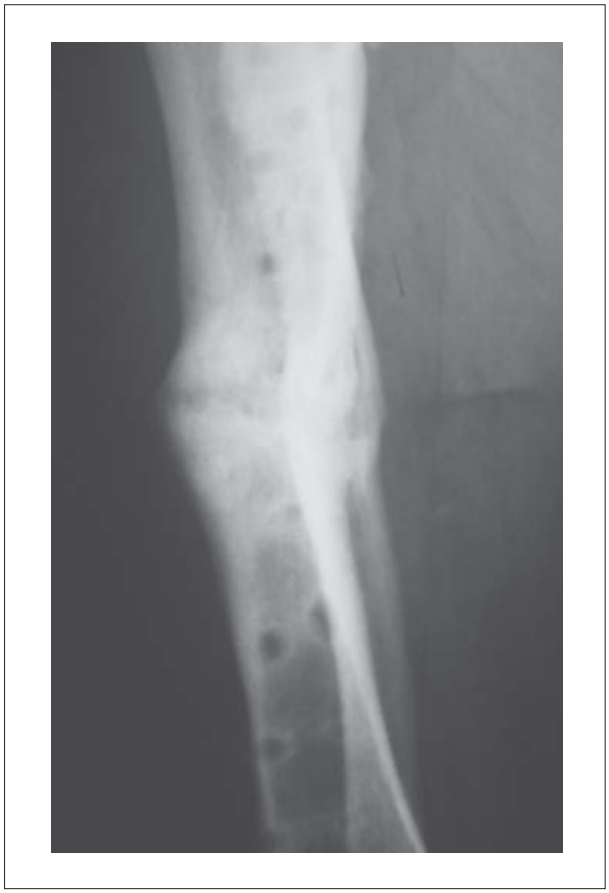

Fig. 4. X-ray after the stabilizer removing

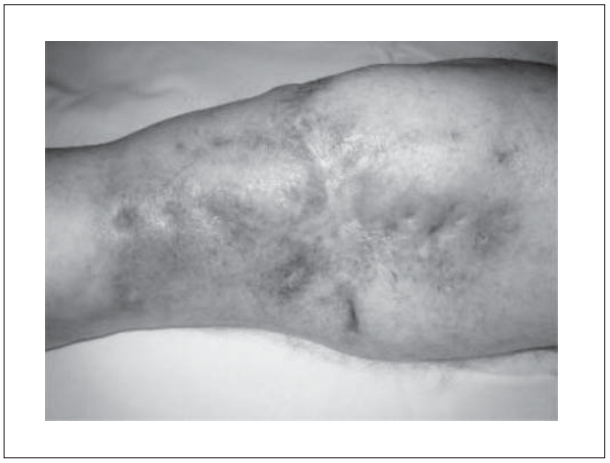

Fig. 5. Clinical appearance of the limb – medial site. 10 months after PRG injection

and general patient health status. Poor union rates in infected tibial fractures have been reported in many articles, with a variety of surgical procedures advocated for management. Infected tibial nonunions cause many psychological, economic, and social problems, not only through functional inadequacy, but also extended antibiotic therapy. Infected nonunions of tibia commonly arise post-trauma, unrelated to hematogenous osteomyelitis [1,2]. In the treatment of infected nonunions, the goals are clearly to resolve the infection, and obtain union. Generally speaking, there are two different strategies of treatment. One is to resolve the infection prior to managing the nonunion. This is done by removal of all internal fixators followed by a thorough debridement of the fracture site. An external stabilizer is frequently inserted. Systemic or local antibiotics are used to control deep infection. After the deep infection is controlled, microbiological examinations detecting no bacteria, a variety of grafting materials are used to promote fracture healing. This involves an additional surgical procedure that can induce a flare up of the controlled infection [1,2,7]. For this reason, some osteoconductive synthetic materials are coated with antibiotics. The second treatment method is concomitant local drainage of the infection site with retention of internal fixation. The advantage of this approach is that it is minimal-invasive, however the success rate is low. Accordingly, most authors consider radical debridement and stable external fixation necessary for good results. However, infections that are resistant to surgical management have been reported [1,7]. Due to the issues associated with these conventional treatment methods more effective alternatives are needed for treatment of infected nonunions.

Previously, Bielecki et al. performed microbiological examination of PRG on 20 healthy volunteers [8,9]. In this study, they could demonstrate a strong activity of PRG against MSSA, which was comparable to gentamicin and oxacillin. They also found weak activity against MRSA and Escherichia coli. We did not find any reports about antibacterial properties of PRG in available literature and the mechanism of antibacterial effect of PRG is not yet fully discovered. Platelets are known to actively participate in healing processes by delivering growth factors and other active molecules to the site of injury [10,11,12,13]. Subsequent evidence suggested that platelets have antimicrobial properties directly interacting with microorganisms, contributing to clearance of pathogens from the bloodstream, and participating in antibody dependent cell cytotoxicity against microbial pathogens [14,15,16,17]. Tang et al. reported the isolation and tentative identification of several antimicrobial peptides from human platelets after thrombin stimulation: fibrinopeptide A, fibrinopeptide B, thymosin â-4, platelet basic protein, connective tissue activating peptide 3, RANTES and platelet factor 4 [5]. PRP also contains significant numbers of leukocytes. The others found markedly increased leukocyte counts (more than sevenfold) as compared to baseline levels [13,18]. This concerned both neutrophils, which are involved in direct bacteria killing as well as lymphocytes responsible for antigen-specific immune response [19,20]. During antibiotic treatment PRP antimicrobial properties are enhanced by antibiotics concentrated in plasma [21]. Our patient was treated with intravenous Cloxacillin (Syntarpen).

Unfortunately, 15 months later the patient developed MRSA(+) phlegmone of the lateral ankle, however, the opposite of the previous soft tissue defect site. The fact that one wound colonised with MSSA and another colonised with MRSA suggests that the infection never resolved, and that chronic infection was present throughout the treatment. However, despite infection after local PRG application bone and soft tissue defect was healed.

It is justifiable to conclude that PRG is inductive biomaterial, which might posses local antimicrobial activity [6,22,23]. This is probably reason that in injection site MSSA was not detected, but in pin site still was observed. Despite infection after PRG application the bone healing processes were achieved.

This case is, to our knowledge, the first report of the application of PRG in an infected tibial nonunion. The nonunion was reached, but chronic infection was not resolved following application of the PRG material in combination with conventional antibiotic therapy. Further clinical investigations into the efficacy of PRG application in sites exhibiting active infection and impaired healing are warranted.

Acknowledgements

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