CASE REPORT

Intramedullary application of bone morphogenetic protein in the management of a major bone defect after an Ilizarov procedure

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We describe a patient with insufficient bone regeneration of the tibia after bone transport over an intramedullary nail, in whom union was ultimately achieved after exchange nailing and intramedullary application of rh-bone morphogenetic protein-7 at the site of distraction.

The Ilizarov technique is widely used in the treatment of patients with leg-length discrepancy, deformity of an extremity and for bone defects after resection of tumours or surgical debridement for infection. In most patients, bone regenerates uneventfully during distraction or transport through an osseous defect, and then consolidates successfully. For the occasional failure, different solutions such as shortening of the bone or cancellous grafting have been used. We present such a patient in whom union was eventually achieved after exchange nailing and the use of a morphogenetic protein at the site of distraction.

Case report

A 12-year-old girl developed a pleomorphic rhabdomyosarcoma of the proximal right tibia. A wide local excision, radiation therapy including the whole lower leg and chemotherapy were undertaken at another hospital. Activity of the proximal tibial growth plate ceased after the radiation and the proximal tibia became necrotic over at least 5 cm. She suffered a fatigue fracture of the proximal tibia two years after the initial treatment. This was treated with an above-knee plaster cast. The tibia healed with a significant varus deformity. Six months later, the deformity was corrected with a valgus osteotomy and stabilised with a broad medial buttress plate, which was retained for 2.5 years. A second fatigue fracture occurred, four months after removal of this plate. This was also treated in a cast, but failed to heal leading to a stiff atrophic pseudarthrosis (Fig. 1). On several occasions, bone biopsies were taken. Histological examination showed large areas of bone necrosis, but no local recurrence of the tumour.

She presented to us for the first time at the age of 19. At that time, she had 3.5 cm of shortening of the right lower leg, severe muscle wasting and a varus deformity of 10° at the level of the atrophic pseudarthrosis. She limped significantly, and was unable to participate in sports or dancing.

We recommended staged surgical procedures to solve the problems of atrophic pseudarthrosis, varus deformity and shortening, beginning with complete resection of the...
necrotic bone, correction of the varus deformity and stabilisation with an intramedullary nail. We also planned to fill the defect by a bone transport at a later stage and to continue tibial lengthening.

During the first operation, nearly 7 cm of the proximal tibia was resected and consisted mostly of necrotic bone. The remaining part of the proximal tibia contained only the medial and lateral condyles and the tuberosity, and was 4 cm long. In order to enable correction of the deformity, a fibular osteotomy was carried out 8 cm below the proximal end of the fibula, with resection of 1 cm of bone. A custom-made intramedullary nail was implanted to hold the fragments in their correct positions (Fig. 2). Interlocking screws were introduced into the proximal 5 cm of the nail and were directed in three different planes at 45° oblique towards the medial condyle, 45° oblique towards the lateral condyle and in the sagittal plane from the tibial tuberosity towards the popliteal fossa. The posterior cortices were not perforated. The screws fitted tightly into the nail to create high stability in all planes. The distal end of the nail also had three interlocking screws. Wound healing was uneventful. Six weeks later, a midshaft corticotomy was performed and an external fixator placed with two Schanz screws in both the intermediate and the distal fragments. No bridging external fixation was placed across the ankle joint. A week later, transport of the segment was begun at 1 mm per day from distal to proximal. When the transported segment reached the proximal tibial docking site, a cancellous bone graft was added to promote healing. Since the leg was still 3.5 cm short, distraction of the regenerated segment was continued with the same external fixator. This required removal of the three distal interlocking screws. Because of the rigidity of the crural musculature, lengthening of only 2.5 cm was obtained (Fig. 3). A rigid pes equinovarus deformity developed which was corrected by lengthening of the tendo Achillis and the tendon of tibialis posterior, together with release of the capsule of the ankle. Complete correction could not be achieved and the amount gained was maintained with a plaster cast for six weeks. After lengthening, the nail was locked again with three distal screws, three months after the beginning of the lengthening procedure.

She was allowed to mobilise with half of her body weight on the right leg. Bone remodelling progressed very slowly in the distraction zone. There was still incomplete filling of the area with new cortical bone, although she was asymptomatic 1.5 years later. Since further bone formation had ceased, an exchange nailing was carried out. Five consecutive reamings

Fig. 2
Radiographs following resection of 7 cm of necrotic bone and stabilisation of the proximal and distal fragments with an unreamed intramedullary nail prior to callus distraction.

Fig. 3
Following lengthening, the distal interlocking screws have been removed. The tip of the intramedullary nail is now situated 2.5 cm above the ankle joint (arrows). Cancellous bone grafting has been performed at the docking site to encourage bony healing. Callus can be seen on the dorsolateral site of the diaphyseal defect.
were carried out using heads increasing from 9 mm to 11 mm in steps of 0.5 mm. All the reaming debris were carefully collected, the volume being about 10 cm$^3$. It was then mixed with one dose of rh-bone morphogenetic protein (BMP)-7 (Osigraft, OP-1 Stryker Biotech, Hopkinton, Massachusetts). A tube and an impactor were used to place the mixture carefully in the intramedullary canal in the most proximal part of the bone defect. Its position was checked with image intensification. The nail was then smoothly introduced with small rotary movements. Although some distal migration of the mixture was seen, most remained at the level of the bone defect. The nail was locked with three screws both proximally and distally (Fig. 4). Regeneration of cortical bone then resumed and healing appeared complete six months later. There was a slight but acceptable collapse of the medial plateau after removing of a loose medial oblique locking screw.

At 2.5 years from the final intervention, the patient has no complaints. She is able to walk without crutches, has normal knee function but limited movement in the ankle. The tibia remains 1 cm short, is fully united and has radiological evidence of remodelling (Fig. 5). Due to the rigidity of the foot in slight equinovarus, sport and dancing are still limited.

**Discussion**

This patient presented with a complex surgical problem. Resection of the tumour at the level of the proximal tibia followed by irradiation and chemotherapy was curative, but at the cost of destruction of the growth plate and necrosis of the metaphysis and the proximal part of the shaft. The first osteotomy using fixation with a broad plate probably increased the local bone necrosis. As with post-traumatic or chronic osteomyelitis, resection of necrotic bone was required in order to restore viable bone with potential for healing. An Ilizarov procedure with distal corticotomy and retrograde transport of the intermediate fragment seemed to be the best solution to fill the large defect. A custom-made intramedullary nail and three interlocking screws in the proximal and distal fragments provided enough stability for the Ilizarov procedure. We carried out the transport corticotomy in the shaft instead of the biologically more favourable distal metaphysis in order to avoid problems with fixation of a short distal segment. Retrograde bone transport occurred without problems. Subsequent leg lengthening was limited by the development of a rigid pes equinovarus, which persisted in spite of tendon lengthening.

Recombinant bone morphogenetic protein-7 promotes and accelerates healing in persistent nonunion in long bones. The BMPs have a great osteoinductive capability as they promote the differentiation of pluripotential mesenchymal cells into osteochondrogenic lineage cells. They can be placed together with blood and cancellous bone grafts in the fracture gap. In our patient, the size of the
defect was such that the volume of the mixture of BMP, blood and cancellous bone grafts would have been too small to completely fill the existing defect. Intramedullary application of rh-BMP-7 offered a promising solution in that it allowed placement of the bone reamings at the level of the defect,\textsuperscript{17} giving an intramedullary rather than an external bone graft.\textsuperscript{18,19} Some benefit has also been shown in a rabbit model.\textsuperscript{16} Exchange nailing is an accepted procedure to promote healing in long bone pseudarthrosis but is not always successful.\textsuperscript{20-22} However, the use of rh-BMP-7 in combination with exchange intramedullary nailing was associated with rapid bone regeneration. We do not know whether the combination of reaming, enhanced mechanical stability and rh-BMP-7 application, or one of these factors alone was responsible for the healing in the presented case, but each can make a contribution to bone healing.\textsuperscript{8,10-12,17,22}

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References