J Musculoskelet Neuronal Interact 2011; 11(4):320-323

Hylonome

Clinical Quiz

Atrophic femoral bone nonunion treated with 1-84 PTH

D. Paridis, Th. Karachalios

Orthopaedic Department, University Hospital of Larissa, Mezourlo region, 41110, School of Health Sciences, Faculty of Medicine, University of Thessalia, Larissa, Hellenic Republic and the Institute of Biomedical Research and Technology, BIOMED/CERETETH, Larissa, Hellenic Republic

Keywords: Long Bone Nonunion, Fracture Fixation, 1-84 PTH

Case

A 48 year old male patient (heavy smoker) sustained a high energy, two level, comminuted fracture (pertrochanteric and mid-diaphyseal), of his right femur in a road traffic accident. He initially underwent internal fixation of both fractures with a hip sliding screw and a dynamic compression plate, at an emergency basis. Despite several surgical attempts at fixation (plates and external fixators) and biological enhancement of the nonunion environment (autologous bone grafting in combination with bone morphogenetic protein 7), the mid-diaphysis femoral fracture failed to unite and structural failures of the materials of internal fixation were observed (Figure 1). During the treatment course, smoking, high energy of both bone and soft tissue envelope trauma, fracture comminution and iatrogenic technical fixation errors were recognized as causative factors for the development of nonunion. Alternative anabolic treatment strategies for fracture healing were considered following a thorough literature search. An "off label", daily dose of PTH 1-84, was administered to the patient for a period of two months. At the end of the second month, satisfactory radiological callus formation was observed and the patient was allowed to walk full weight bearing. At one year follow up, the patient regained painless, full range, motion of the adjacent joints and walked with a mild limp due to a minor leg length discrepancy.

Commentary

According to the U.S. Food and Drug Administration (FDA), nonunion is considered when union has not been achieved 9 months after the fracture and there is no trace of progress of fracture healing in the fracture site for three consecutive months. The rate of nonunion and delayed union in long bone fractures ranges between 5-10%.

Despite the rich blood supply of both femoral bone and thigh soft tissue envelop, some fractures may not unite due to extrinsic and instrinsic factors (e.g. severity of injury, devatilization of bone fragments, insufficient fixation, smoking etc). Complex fractures of the lower limb such as femoral and tibial fracture, and bipolar femoral fractures, constitute the 2.5 to 6% of all fractures, are usually the result of high energy trauma (traffic accident, fall from a height, etc) while 47-67% of them are either open or communited[1-2].

Depending on the viability and potential healing of the bone fragments at the fracture site, nonunions (pseudarthroses) can be divided into those having a potential of biological response (viable-vital) and those lacking this potential (none viable-avital). Vital nonunions can be further subdivided into hypertrophic (elephant foot), slightly hypertrophic (horse hoof) and oligotrophic nonunions. Avital nonunions can be divided into dystrophic (torsion wedge), necrotic (crash), those with a bone defect, and atrophic nonunions. In hypertrophic nonunions rich callus is present. In these cases insufficient stabilization or premature loading of a reduced fracture with viable edges is recorded. Depending on the degree of motion at the fracture site, the nonunion is either soft or stiff. In the slightly hypertrophic type poor callus is present. It typically results following insufficient fracture fixation with plates and screws. These nonunions may be soft or stiff, as well. Callus is absent in oligotrophic nonunions. This type occurs when the fracture ends are rigidly fixed with a distance gap between the fragments. Dystrophic nonunions are characterized by the presence of a small bone fragment section in which the blood supply is reduced or lost. It is typically found in fractures of the tibia which have been treated with plates and screws. Necrotic nonunions (crash type) are characterized by the presence of avascular fragments of intermediate size. Structural failure of fixation materials is often seen in this type of nonunion. Nonunions with bone defect are considered as recent fractures in which a large or a small fragment of a shaft is absent. Sim-

The authors have no conflict of interest.

Corresponding author: Th. Karachalios, MD, DSc, Professor in Orthopaedic Surgery, Orthopaedic Department, University Hospital of Larissa, Mezourlo region, 41110, School of Health Sciences, Faculty of Medicine, University of Thessalia, Larissa, Hellenic Republic
E-mail: kar@med.uth.gr

Edited by: P. Makras
Accepted 15 November 2011

Figure 1(a-f). a) anteroposterior view of the right femur showing structural failure of the initial plate fixation, **b)** lateral view, after the second attempt for fixation with a long locking plate, showing the extended avital fracture area, **c)** anteroposterior view of the femur following the second structural failure of the plate (broken screws and pain), **d)** lateral view of the nonunion area following the application of a Spatial Taylor Frame with autografting and BMP-7, **e)** anteroposterior and **f)** lateral view showing the consolidation of the fracture nonunion following a 2 months administration of 1-84 PTH.

ilar nonunions are the result of bone substance loss due to infection (volcrum) or excision of neoplasmatic tissue. In these cases bone fragments are viable, but the defect zone is biologically inactive and radiological atrophy of the bone ends appears at later stages. Atrophic nonunions are actually the final result of the above three types of avital nonunions. Fragment edges are absorbed after a long period of treatment and scar tissue without any osteogenic capacity is found between them.

Although delayed unions or nonunions of fractures can occur without an obvious reason, in many cases several factors affecting fracture healing can be identified:

1. Factors associated with trauma (injury)

Severity of injury. Both the communited fracture pattern and the biological integrity of soft tissue envelop at the fracture site have been shown to affect the rate of fracture healing. Sufficient blood supply with intact soft tissue envelope are essential for the formation of external callus.

Open fractures. Damage of the soft tissue envelope and severe bone fracture patterns are more important in the open than in the closed fractures. Apart from the impaired blood supply and the tissue's viability there is an additional risk of infection which further increases the risk for nonunion.

Interposition of soft tissue. The process of healing can be delayed or nonunion can eventually occur when soft tissue structures such as muscles, tendons, nerves, fascia and periosteal flaps are found between the main fracture fragments.

2. Factors associated with patient

Age. Age is considered as the most important factor affecting the healing of fractures. In children, most fractures consolidate quickly due to the presence of high numbers of progenitor mesenchymal stem cells at the fracture site and the intense osteoblastic activity of the periosteum.

Nutrition. A high-calorie diet enriched in proteins, calcium and Vitamin D helps bone healing. In specific, sufficient food supply include or be accompanied with a calcium intake of 1000-1500 mg/day and 400-800 I.U./day of Vitamin D.

Smoking. Smoking is an unfavourable, dose dependent, factor in the process of healing. Recent studies suggest that there is a consistent nicotinic activation of nAChR in osteoblast cells which has a broad role affecting cellular physiology through modulation of gene expression[3].

Factors related to hormone levels. Thyroid hormone, calcitonin, insulin and anabolic steroids have been reported to accelerate healing in animals. In contrast, diabetes, hypervitaminosis D and rickets have been also shown to inhibit bone healing in animals.

Bone disease. Osteoporosis, osteomalacia, neoplasms, bone cysts, osteogenesis imperfecta, fibrous dysplasia, hyperparathyroidism, infections and Paget's disease are conditions associated with low energy pathological fractures. Apart of the management of the fracture, treatment of the underlying disease is also necessary.

3. Factors associated with treatment

The choice of appropriate treatment is based on the pattern of fracture. Developments in system fixation with plate, external fixation and those of intramedullary nailing, have succeeded in providing anatomic reduction, sufficient stability with vital surrounding tissue that is necessary for fracture healing. Specifically for the diaphyseal area of long bones, the prevalence of static intramedullary-nailing greatly reduces the occurrence of nonunion, but also contributes effectively to the treatment of nonunion with a cure rate of 95-98%.

In the past few years much has been done in the management of nonunions using human bone morphogenetic proteins (BMP) and other factors (Growth Factors)[4]. Other advances in the treatment of nonunions have been the use of improved electric and electromagnetic stimulation treatment modalities.

PTH peptides are likely to play an important role in future management of delayed nonunion and aseptic nonunion of long bones. Teriparatide has shown improved callus characteristics in different animal models[5]. There is also level I evidence data suggesting that both Teriparatide and PTH 1-84 improve fracture healing of recent fractures in different skeleton sites[6-8]. There is only one report of a nonunion case of the humerus successfully treated with PTH 1-84[9].

References

1. Lambiris E, Megas P, Karioris G, Giannikas D. Combined femoral shaft and proximal femoral fractures treared with intramedullary nailing. Osteosynthese International 2000; 8(Suppl.1):155-7.
2. Bennett FS, Zinar DM, Kilgus DJ. Ipsilateral hip and femoral shaft fractures.Clin Orthop Relat Res 1993; (296):168-77.
3. Rothem DE, Rothem L, Soudry M, Dahan A, Eliakim R. Nicotine modulates bone metabolism-associated gene expression in osteoblast cells. J Orthop Trauma 2010; 24(9):543-6.
4. Nauth A, Giannoudis PV, Einhorn TA, et al. Growth factors: beyond bone morphogenetic proteins. J Orthop Trauma 2010;24(9):543-6.
5. Oteo-Alvaro A, Moreno E. Atrophic humeral shaft nonunion treated with teriparatide (rh PTH 1-34): a case report. J Shoulder Elbow Surg 2010;19(7):22-8.
6. Holzer G, Majeska RJ, Lundy MW, Hartle JR, Einhorn TA. Parathyroid hormone enhances fracture healing. A preliminary report. Clin Orthop Relat Res 1999;366:258-63.
7. Aspenberg P, Genant HK, Johansson T, et al. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized double blind study of 102 postmenauposal women with distal radial fractures. J Bone Miner Res 2010;25:404-14.
8. Peichl P, Holzer L, Maier R, Holzer G. Parathyroid Hormone 1-84 accelerates fracture healing in pubic bones of elderly osteoporotic women. J Bone Joint Surg 2011; 93A:711-9.
9. Oteo-Alvaro A, Moreno E. Atrophic humeral shaft nonunion treated with teriparatide (rh PTH 1-34): a case report. J Shoulder Elbow Surg 2010;19(7):22-8.

Questions

1. Which factors affect nonunion of long bones?
A. High energy soft tissue trauma
B. Open fracture
C. Smoking
D. Fracture pattern (severe comminution)
E. All the above

Critique

Negative prognostic factors associated with fracture healing are high energy trauma, open fracture (injury pattern), comminuted fracture pattern and smoking (patient habit).
The correct answer is E.

2. Which factors have shown a clinically proven positive action on healing of a fracture nonunion?
A. Bone morphogenetic proteins
B. Growth factors
C. Biphosphonates
D. PTH peptides
E. Vit. D and Ca

Critique

There are no level I or II studies, that clinically prove the action of PTH, biphosphonates, and Vit. D in combination with calcium for the treatment of nonunions of long bones. There is evidence based data (level I studies) which shows that bone morphogenetic proteins (especially 2 and 7) are effective in the management of nonunion.
The correct answer is A.

3. Which is the "gold standard" surgical procedure for the fixation of closed diaphyseal long bones fractures of the lower limp?
A. Intramedullary nailing
B. Internal fixation with conventional plates
C. External fixation
D. Internal fixation with locking plates
E. Skeletal Traction

Critique

There is evidence based data which indicates that intramedullary nailing shows superior clinical results and less complications compared to other fixation techniques.
The correct answer is A.