Annals Of Orthopaedics, Trauma And Rehabilitation
ISSN# 2833-2431

Research Article

Immunomodulation Enhancing Bone Synthesis: A Concept Emerging From a Clinical Case

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ARTICLE INFO

Received Date: January 15, 2024
Accepted Date: January 29, 2024
Published Date: February 27, 2024

KEYWORDS

Fracture; Bone repair; Immunomodulation; Malignancy

Citation for this article: George M. Weisz* MD, Anthony Marina- Portia and Michael Huang. Immunomodulation Enhancing Bone Synthesis: A Concept Emerging From a Clinical Case. Annals of Orthopaedics, Trauma And Rehabilitation. 2024; 7(1):148

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ABSTRACT

From the late decades of the previous century and progressively into the 21st century, the science of fracture repair has significantly changed. It moved from a simple metabolic/hormonal concept of bone regeneration to an inflammatory concept, to a more complicated immunological description. It was age dependant and related to diabetes, nutrition, hormone connection, autoimmune diseases, rheumatic arthritis, and nicotine. It was in the 21-st century that bone repair appeared as a branch of medicine, Osteoimmunology, not yet fully successful in promoting bone repair. Our interest surfaced from a patient who sustained a traumatic, non-metastatic, long bone fracture whilst under immunotherapy for prevention of a recurrent melanoma. Before presenting the clinical case, the authors propose to review some of the contradicting studies out of a vast literature on the topic. Indeed, the number of publications on bone genesis and immunology is staggering. We shall review only a dozen of them, with possible relevance to our clinical case. It is the aim of this presentation to introduce the theory of an enhanced bone repair under immune modulation.

INTRODUCTION

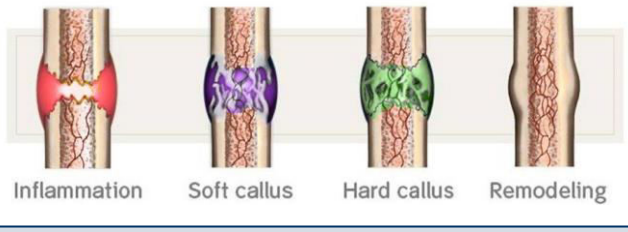
The authors intend to describe the pro- and anti-inflammatory cytokines' interplay during bone repair, resulting from the invasion of lymphocytes into the fracture zone. This indicated the importance of macrophages, or rather their more sophisticated form of the Osteomac, all originating in Mesenchymal cells. It was in 2020 that the team from Bethesda VA hospital gave a comprehensive description of the normal, delayed, or non-union fracture biology [1]. It described the cascades of bone healing, reviewing a previous thesis of 3 classic stages. It was extended further by Philips [2] and then as the "Diamond concept" of four stages by Giannoudis [3].

It occurred as follows:

In the process of fracture repair, an active immune system starts a cascade of stages: the first being the "inflammatory stage", a hematoma resulting from blood vessel disruption attracts platelets, neutrophiles, macrophages and cytokine secreting T cells. This process leads to the second stage in the "reparation" process, namely the soft (cartilaginous) and then the hard (osteogenic) callus and angiogenesis.

The dead tissues are removed by macrophages, themselves undergoing apoptosis. The last stage is the renewal or the remodeling stage, when bone tissue is regenerated and flooded with minerals, promoting osteogenesis.

Numerous attempts with various pharmaceutical, experimental and clinical trials did not lead to a significant shortening of healing time. The standard average healing time for a weight bearing, long bone closed fracture (uncompromised by diabetes, muscular dystrophy, malnutrition, nicotine dependence, renal disease, geriatrics, immune deficiency, polytrauma or fracture instability) was accepted as 17 weeks, and up to 35 weeks in a compromised patient [1].



Bone Healing

ON REVIEWING EXPERIMENTS ON BONE HEALING

In 2004, the authors were impressed by NAGAHAMA K, et al , for "Modulation of the Inflammatory Response and bone healing". This study clarified that deficiency in activating T-cells and depressing soft callus formation (osteoClasts), leads to osteoporosis, and indirectly allows for hyperactivity of osteoBlasts with resulting osteopetrosis [4]. In 2010, the authors were impressed by KOLAR, et al, for "The Early Fracture Hematoma and Its Potential Role in Fracture healing", describing Hematoma as the initial phase in the regeneration of chondral bone, leading to inflammation. This study emphasises the interplay between immune and bone cells, essential in the repair process [5]. In January 2011, the authors were impressed by TOBEN et al, for "Fracture healing is accelerated in the absence of the adaptive (active) immune system", suggesting the detrimental effect of cytokine, and by minimising the destructive effects of inflammation leading to enhanced osteoblastic effect and fracture repair [6].

In 2014, the authors were impressed by RAGGAT, et al, in "Fracture Healing via Periosteal Callus Formation Requiring macrophages..." In their impressive experiments, the scientists proved that: Macrophage depletion prevents ossification of cartilage into a bony matrix [7]. In 2015, the authors were impressed by SCHLUNDT for "Immune modulation as a therapeutic strategy in bone regeneration". They proved that hematoma to be indispensable for bone deposition, that cytokines have osteogenic potential and that under the influence of immune system, T and B cells interact on bone healing. Originating from mesenchymal sources, they influence both osteoclasts and osteoblasts [8]. In 2016 (September), the authors were impressed by GINALDI et al, for their description of "Osteoimmunology and beyond ", considering osteoporosis as a chronic inflammatory disease, and showing osteogenesis to be a balance between bone resorption and genesis, under immune system control [9]. In 2016(November), the authors were impressed by KALYAN, for "It May Seem Inflammatory, but some T Cells are Innately Healing the Bone". They reported dual action at times contradictory of T- cells, inflammatory and anti-inflammatory, showing the immunomodulatory effect on Bone Regeneration [10]. In 2017 , the authors were impressed by KHASSAWNA ET AL, for proving the influence of T-cell on the mineralization of the bone, in the organisation of collagen and the view that the lack of these cells leads to dysregulation in osteoblast distribution. In "T lymphocytes influence the mineralisation process of bone", they indicate bone without T- and B- cells would be much stiffer, but would lack elasticity [11].

In 2018 the authors were impressed by MOSELEY KF et al, for their thesis in "Immune-related adverse events with ICI affecting skeleton" in finding that Pembrolizumab (monoclonal antibody) induces adverse effect with multiple (non-metastatic) fractures when administered for Gr. IV melanoma [12]. In 2018, the authors were impressed by BAHT et al, in "The role of the Immune cells in bone healing" for once again proving the necessity of macrophages and cytokine secretions in modulating bone healing [13]. In 2020, the authors were impressed by WANG K, et al for the findings of "PD-1 blockade inhibits osteoclast formation..." by another monoclonal antibody nivolumab [14]. In 2021, the authors were impressed by HAWARY et al, for their thesis on 'Bone healing and Inflammation", showing a negative effect, namely, that immunosuppression depresses inflammation and interferes with bone repair [15].

In March 2021, the authors were impressed by FILIPPINI et al, for a clinical study on "Bone fracture as a novel immune related adverse event with immune check point inhibitors, resulting in bone resorption and osteoporotic fractures". This

negative effect of inhibitors, indeed important as they are used on daily basis, result in pathological fractures [16]. In 2022, the authors were impressed by PANTANO et al, (also a clinical study) in "Changes in bone turnover markers..." for reaffirming the crossroad between bone repair and immune system functions, suggesting a negative effect of ICI check point inhibitors on bone repair, leading to a delayed union [17]. In March 2023 the authors were impressed by TANG J, for their description of "Immune check point inhibitor: friend or foe for osteoporosis". Their final observation was that active anti-(PD1/PD-L1) check-point-inhibitor supports osteoClastic hyperactivity, leading to osteoporosis, but indirectly enhancing osteoBlasts activity, with resulting increased bone repair [18].

CASE REPORT

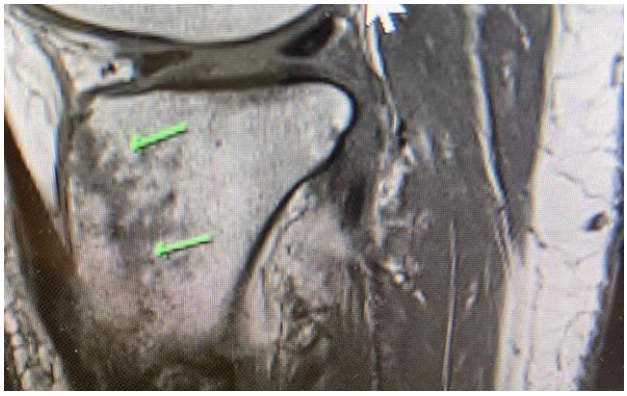


Figure 1a: Three weeks post trauma, lateral tibial view left knee.

The accident occurred on 2.12.21: a fall on the knee of a 73-year-old heavy built woman, 169 cm in height. She walked into the surgery two weeks later and was diagnosed with a vertical metaphyseal split and a transverse fracture, reaching horizontally into the lateral cortex of the tibia.(Gr. I-II in Schatzker fracture classification). She walked freely, unsupported, was able to drive and be active on stairs, and refused any conservative or surgical interventions. An enhanced bone healing time was recorded, despite the absence of immobilization, a lymphoedema on her leg was observed, the result of a previous groin dissection. She was receiving immunotherapy for the prevention of a melanoma recurrence, namely Pembrolizumab (MK-3475, a humanized Ig G4) monoclonal antibody. Subsequent radiological studies, plain x-ray, CT scans and MRI scans documented a full healing process within 32 days [19].

*Some of the radiological images were reproduced with permission from IMAJ.

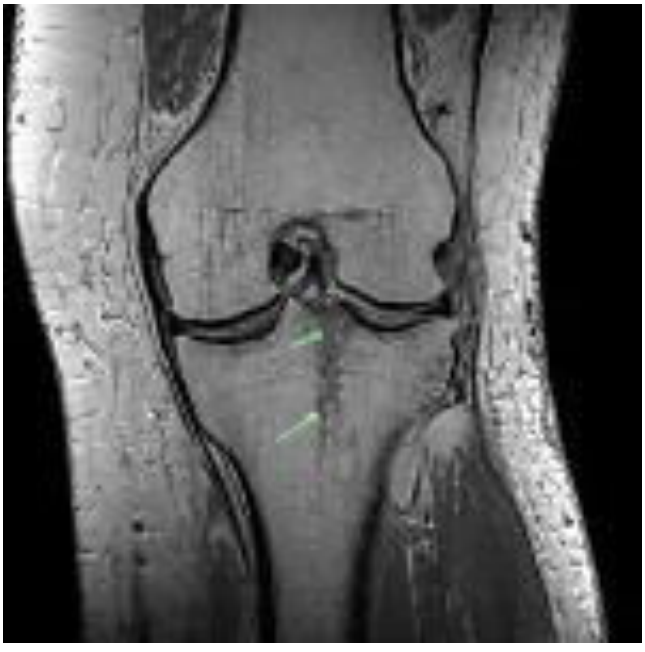


Figure 1b.

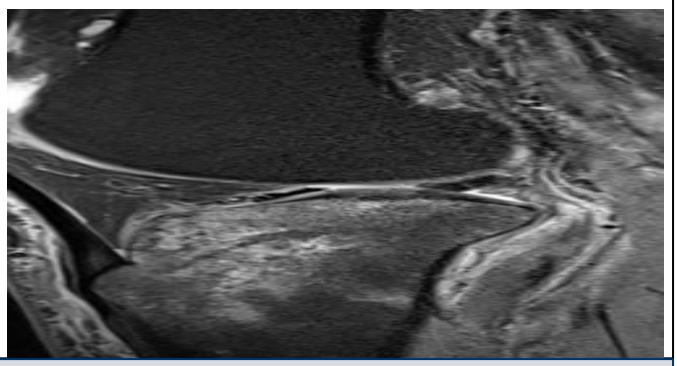


Figure 1c: Lateral view Indicating a bone structure oedema in the repairing stage, almost refilling the fracture space, 22.12.21.

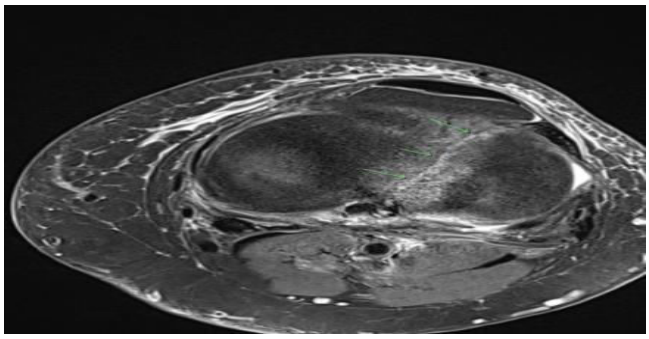


Figure 1d: Transverse view, obliterated fracture (soft callus?) 22.12.21.

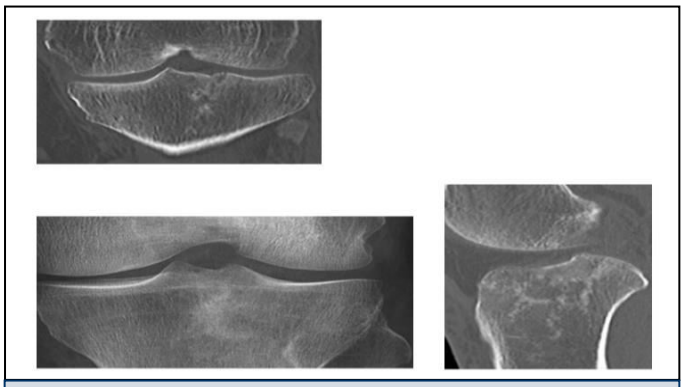


Figure 2a: Visualized almost full closure of fracture line.

Radiology report on 4.1.22: "Near complete healing of the previously demonstrated lateral tibial plateau fracture, with mature bony remodeling at the site of prior trabecular fracture and complete resolution of bone marrow oedema" [19].

DISCUSSION

The discussion should involve an analysis of the messages emerging from each of the above quoted publications. Reviewing over 100 publications in the literature (PubMEd, Google Scholar), from which 17 were quoted, the controversy is evident. Although the effect of immunomodulation on bone repair became obvious and the number of positive outcomes on bone repair is growing, there can be no final conclusion as yet [20].

The authors could not find a published clinical case of a traumatic long bone fracture under immunomodulation. For a clinician, the impressions on the mechanism of bone healing, the connections between bone genesis and the immune system, the essential role of the hematoma and the inflammatory process, the role of the cytokine secreting lymphocytes (T and B), the macrophages and the three stage cascade system of bone healing, all seem acceptable. The definite effect of the ICI proteins, i.e. mononuclear antibodies, in this case Pembrolizumab on bone genesis remains to be definitely determined, although it seems to be acceptable. Similarly remains the explanation of the essential value of hematoma during the internal fixation, when the primary hematoma is removed and a suction is applied, aiming to prevent a second collection. It remains a logical suggestion that depression of Soft Callus by osteoClastic activity indirectly allows for an increased OsteoBlastic emergence, with formation of a Hard Callus.

CONCLUSION

No definite conclusion could be determined by clinicians with their one clinical case, despite the clear logic. To prove such a concept would require confirmation with a full clinical trial. This is an observational report with suggestion of enhaced osteogenesis under immunomodulation.

It remains the task for immunologists to accept or deny the suggestions that in the Intermediate Stage of Bone Repair, a disbalance occurs between the two substages, namely a depressed osteoClastic event and the emergence of an enhanced osteoBlastic stage.

I ACKNOWLEDGE DISCUSSIONS ON THIS THEORY WITH MY COLLEAGUES

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