Can immunotherapy improve fracture healing?

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TO THE EDITOR:

A review of the literature on the effect of immune modulation on the skeleton shows disappointing results.

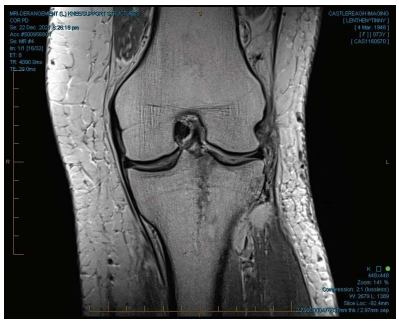
In the process of fracture repair, an active immune system starts a cascade of repair stages. The first stage is the inflammatory stage, when a hematoma resulting from blood vessel disruption attracts platelets, neutrophiles, and macrophages. In addition, lymphocytic T cells secrete cytokines. This pathology leads to the second stage in the reparation process, namely the soft, cartilaginous stage that soon becomes hard. This stage includes the recruitment of mesenchymal stem cells to generate angiogenesis remodeling and callus formation, namely revascularization and calcification (angiogenesis and osteoblasts), while the dead tissues are removed by macrophages, which undergo apoptosis (resorption). The last stage is the renewal or the remodeling stage, when the bone tissue is regenerated and saturated with minerals, thus promoting osteogenesis [1-3]. The result is a fully restored normal bone structure.

The inflammatory stage could be shortened or eliminated entirely by fracture fixation with a compression plate. With that treatment, healing begins immediately with osteogenesis. The inflammatory stage could be assisted by immune T cell secretion, a process scarcely reviewed in the literature, and mostly in animal studies. These animal studies suggest some positive effects of immune cells. Experimental studies have found that lack of macrophages or lack of cytokine secretion by T cells could delay the bone repair process [4,5].

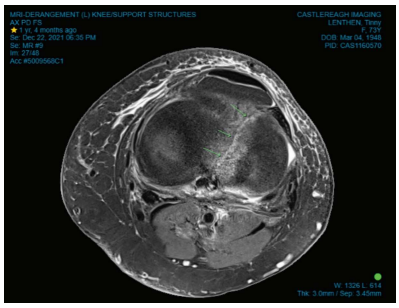
This theory of the effect of immunomodulation on bone genesis remains clinically unproven but is suggested by self-plasma therapy. The question is whether treatment of traumatic long bone fracture, treated in parallel with an immune modulator such as pembrolizumab, could be advantageous.

Figure 1. Magnetic resonance imaging (MRI) and computed tomography (CT) scans of a tibial condyle fracture taken 02 December 2021

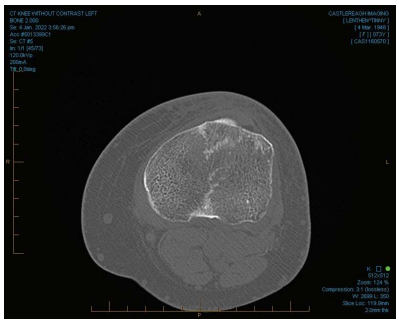
[A] MRI 2 weeks post-fracture



[B] MRI of tibial plateau 20 days post-trauma



[C] CT scan of tibial plateau taken 4 January 2022 showing healing 32 days post-trauma, note the wide lymphoedema



How could immune modulation increase osteogenesis? Would pembrolizumab promote macrophage and T-cells activity in callus? Would cell multiplication by secretion of cytokines shorten the inflammation stage like metallic fixation, thus promoting osteoblastic remodeling and increasing osteogenesis?

A case of rapid bone healing, namely fracture through tibial condyle with bone cortex involvement but with no cortex separation, was radiologically found to heal within 32 days [Figure 1]. This result, despite full weight bearing and full mobilization with minimal discomfort in a leg, but with lymphoedema resulting from inguinal dissection conducted for melanoma prevention, which included weekly pembrolizumab infusions. Such rapid healing of a long bone without protection has not yet been reported to the best of our knowledge. In fact, we have not encountered such rapid healing in more than 40 years of trauma surgical practice.

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