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Perspective Article

Hylonome

Bone loss in chronic inflammatory conditions

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The rheumatic diseases include a diverse group of disorders that share in common their propensity to affect joint and periarticular structures. Inflammatory joint diseases, of which rheumatoid arthritis is the prototype, may produce marked alterations in remodeling of the joint components leading to loss of joint function and destruction of structural integrity. Although the disease mechanisms vary, in many instances the disorders are initiated by disturbances in immune regulation that involve complex interactions between unique host genetic susceptibility and specific environmental factor(s). In these disorders, skeletal tissues may be involved not only at juxtaarticular and subchondral sites, but in addition there is evidence that many of these conditions may produce generalized effects on bone remodeling that affect the entire skeleton.

Rheumatoid arthritis (RA) represents an excellent model for gaining insights into the effects of local as well as systemic consequences of inflammatory processes on skeletal tissue remodeling. Three principal forms of bone disease have been described in RA. The first is characterized by a focal process that affects the bone at the joint margins adjacent to the inflammatory synovial lesion. In RA, the synovial lining of diarthrodial joints is the target of an intense immunologic and inflammatory process that is associated with the proliferation of the synovial lining cells and infiltration of the tissue by inflammatory cells, including lymphocytes, plasma cells and activated macrophages. The proliferative synovial tissue (pannus) attaches to the immediately adjacent bone at the joint margins and induces a progressive focal osteolytic process that gives rise to the characteristic cystic bone "erosions" that can be detected radiographically[1,2]. Recent studies employing magnetic resonance imaging have shown that these erosions occur very early in the course of the disease and progress throughout the illness unless therapeutic interventions are employed[3,4].

Examination of the interface between the pannus and bone at the sites of erosions reveals the presence of resorption lacunae populated by multinucleated cells expressing the full repertoire of authentic osteoclasts, including the expression of tartrate resistant acid phosphatase, cathepsin K, and the calcitonin receptor[5-11]. Several groups have demonstrated that cells cultured from synovial tissues from RA patients or animal models of inflammatory arthritis can be induced to form osteoclasts, suggesting that the osteoclast-like cells at the bone-pannus interface are derived from precursors present within the inflamed synovial tissues[9-14]. Further evidence implicating osteoclasts in the pathogenesis of focal joint erosions is provided by two recent studies in which inflammatory arthritis was induced in animals lacking the ability to form osteoclasts. In the studies by Pettit et al.[15] receptor activator of NF-kB ligand knockout mice were employed and in the studies by Redlich et al., animals lacking the c-fos gene were utilized[16]. In both models, there was minimal evidence of focal bone erosions despite extensive pannus formation and cartilage destruction. These observations provide further evidence that osteoclasts represent the final common cellular pathway for bone resorption in inflammatory joint disease.

The unique propensity of the inflamed synovium in RA to induce bone resorption is likely related to its capacity to produce a variety of factors with potent osteoclast differentiation and activation activity, including receptor activator of NF-kB ligand (RANKL), interleukin-1, interleukin-6, interleukin-11, interleukin-15, interleukin-17, monocyte colony stimulating factor, tumor necrosis factor-α and parathyroid hormone related peptide, the factor implicated in the pathogenesis of humoral hypercalcemia of malignancy[10,17-26]. Particular attention has focused on RANKL because of its potent osteoclastogenic activity. In several different animal models of inflammatory arthritis, treatment with osteoprotegerin (the soluble receptor that inhibits its activity) results in marked suppression of bone erosions[16,22,27].

A second form of bone disease observed in patients with RA is the presence of juxta-articular osteopenia adjacent to inflamed joints. Histological examination of this bone tissue

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reveals the presence of frequent osteoclasts and increased osteoid and resorptive surfaces consistent with increased bone turnover[5,28]. Local aggregates of inflammatory cells, including macrophages and lymphocytes are often detected in the marrow space. It has been suggested that these cells are derived from the synovial lining and that they migrate into the marrow where they release local products that affect bone remodeling[5]. Decreased joint motion and immobilization in response to the joint inflammation likely represent additional contributing factors to this local bone loss.

The third form of bone disease associated with RA is the presence of generalized axial and appendicular osteopenia at sites that are distant from inflamed joints[29-31]. Although there are conflicting data concerning the effects of RA on skeletal mass, the presence of a generalized reduction in bone mass has been confirmed using multiple different techniques and there is compelling evidence that this reduction is associated with an increased risk of hip and vertebral fracture[32-36]. The conflicting data are in part related to the fact that most observations have been based on cross-sectional studies and have focused on patients late in the evolution of their disease when factors such as disability, corticosteroid and other treatments may confound the analyses. Histomorphometric analysis of bone biopsies from patients with RA indicate that, in the absence of corticosteroid use, the cellular basis of the generalized reduction in bone mass is related to a decrease in bone formation rather than an increase in bone resorption[37-39]. However, these conclusions differ from the results of more recent studies in which biochemical markers of bone turnover have been used to evaluate patients with RA and these studies indicate that there is increased bone resorbing activity. Higher rates of bone resorption were associated with more severe disease activity, especially in patients receiving chronic corticosteroids[40-44].

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