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**The Involvement Of T and B Lymphocytes In The Pathogenesis and Progression of Osteomyelitis and Osteoarthritis**

**Osteomyelitis**

Osteomyelitis is inflammation of the bone caused by an infecting organism which leads to bone destruction and loss .Although bone is normally resistant to bacterial colonization, events such as trauma, surgery, the presence of foreign bodies, or the placement of prostheses may disrupt bony integrity and lead to the onset of bone infection. Osteomyelitis can also result from hematogenous spread after bacteremia. When prosthetic joints are associated with infection, microorganisms typically grow in biofilm, which protects bacteria from antimicrobial treatment and the host immune

response.

Pathogenesis and Progression

Staphylococcus Aureus remains the most common pathogen, but the percentage of, hematogenous osteomyelitis due to S. aureus has declined from 80 % to 90 % of cases to 40% to 605 in recent years.

Staphylococcus Epidermidis causes approximately 5% or fewer cases of disease. Because inadvertent contamination of cultures by the organism is frequent, its role as a pathogen in unknown.

Group A Streptococci isolates cause disease in children and occasionally in adults. Group B Streptococci. Its common in neonates and may be more common pathogen in this age group than are Staphylococci.

Group B Streptococci also occur in diabetic patients (Edward *et al*, 1978).

Haemophilus Influenza is now an infrequent cause of osteomyelitis in the United States due to widespread usage of polysaccharide vaccine Gram negative enteric bacilli mostly Escherichia coli, Salmonella and Klebsiellaspecies, most often occur in adults and account for 10% to15% of cases of hematogenous osteomyelitis. Gram negative infections are common in certain predisposed hematogenous osteomyelitis e.g. Neonates (Enterobacteriacae), patients with sickle cell disease (Salmonella), and intravenous drug users (Pseudomonas). Patients with underlying chronic illness, including chronic renal disease, alcoholism,diabetes, andmalignancy, also have an increased risk of gram- negativeinfections.

Anaerobes are uncommon cause of hematogenous osteomyelitis. Infections with multiple organisms (multiple infections) are not uncommon.

Mycobacterium Tuberculosis Tuberculous osteomyelitis should be suspected in any of vertebral osteomyelitis or osteomyelitis at any site that has not responded to antibiotic therapy. One third of human immunodeficiency virus (HIV)-infected individuals with tuberculosis have extra pulmonary disease with or without pulmonary involvement (Watts and Lifeso, 1996).

Fungal Osteomyelitis Osteomyelitis can result from invasive infections due to a number of fungal pathogens, including Candidaspecies.

Sporothrixschenckii, Coccidioidesimmitis, Blastomycesdermitidis, Histoplasmacapsulatum, Cryptococcusneo formans, and variety of less commonly encountered pathogens. Fungal osteomyelitis should be considered in any indolent osteomyelitis that has not responded to routine measures or in any patient with evidence of disseminated fungal disease.

Therapy is generally complex and prolonged (Johnson and perfect, 2001).

Diabetic Foot Infections The organisms isolated are related in part to the severity of underlying disease, which has been divided into mild non –limb threatening infections and more severe limb-threatening infections (Caputo *et al*, 1994). Patients in both groups frequently receive multiple courses of different antibiotics. Recent receipt of antibiotics increases the likely hood of atypical or drug-resistant organisms, particularly MRSA, but also enterococcus and Pseudomonas

The pathology of osteomyelitis is characterized by severe inflammation, impairment of vasculature, and localized bone loss and destruction. In an attempt to overcome the infective microorganisms, leukocytes produce inflammatory cytokines and enzymes that break down the infected and surrounding tissue. Purulence consisting of dead leukocytes and host/bacterial cells can fill intercellular spaces around the infection and form an abscess. In chronic infection, abscesses can impair blood flow and strip the periosteum, creating an area of vascularized, necrotic bone called a sequestrum (Healy and Freedman, 2006). Vascular impairment makes the foci of chronic infection impervious to the immune system and systemic antibiotics. The sequestrum is indicative of a chronic infection and compromises the bone's integrity. Often the formation of new bone—an involucrum—occurs, which forms from remaining intact fragments of the periosteum and functions to provide axial support to weight-bearing bones and prevent pathological fracture. Exudate or purulence from the infection may escape through an opening in the bone called a sinus tract.

**Osteoathritis**

Osteoarthritis occurs when the cartilage that cushions the ends of bones in your joints gradually deteriorates. Cartilage is a firm, slippery tissue that enables nearly frictionless joint motion. Eventually, if the cartilage wears down completely, bone will rub on bone.

Osteoarthritis is the most common form of arthritis, affecting millions of people worldwide.

It occurs when the protective cartilage that cushions the ends of your bones wears down over time.

Although osteoarthritis can damage any joint, the disorder most commonly affects joints in your hands, knees, hips and spine.

Pathogenesis and Progression

Osteoarthritis is traditionally thought of as a ‘wear and tear’ disease which occurs as we age. However, recent research suggests otherwise.

The pathogenesis of OA involves a degradation of cartilage and remodelling of bone due to an active response of chondrocytes in the articular cartilage and the inflammatory cells in the surrounding tissues.

The release of enzymes from these cells break down collagen and proteoglycans, destroying the articular cartilage. The exposure of the underlying subchondral bone results in sclerosis, followed by reactive remodelling changes that lead to the formation of osteophytes and subchondral bone cysts. The joint space is progressively lost over time.

Osteoarthritis (OA) results from an imbalance between breakdown and repair of the tissues in the synovial joints. Risk factors include trauma, overuse, obesity, and genetic predisposition. The etiopathogenesis of osteoarthritis has been divided into 3 stages.

In stage 1, proteolytic breakdown of the cartilage matrix occurs. Chondrocyte metabolism is affected, leading to an increased production of enzymes, which includes metalloproteinases (eg, collagenase, stromelysin) that destroy the cartilage matrix. Chondrocytes also produce protease inhibitors, including tissue inhibitors of metalloproteinases (TIMP) 1 and 2, but in amounts insufficient to counteract the proteolytic effect.

Stage 2 involves the fibrillation and erosion of the cartilage surface, with a subsequent release of proteoglycan and collagen fragments into the synovial fluid.

In stage 3, the breakdown products of cartilage induce a chronic inflammatory response in the synovium. Synovial macrophage production of metalloproteinases, as well as cytokines such as interleukin (IL) 1, tumor necrosis factor (TNF)-alpha, occurs. These can diffuse back into the cartilage and directly destroy tissue or stimulate chondrocytes to produce more metalloproteinases. Other proinflammatory molecules (eg, nitric oxide [NO], an inorganic free radical) may also be a factor in stage 3.

**The involvement of T and B Lymphocytes**

Activated T cells are known to enhance osteoclastogenesis and bone resorption. Because CD28 is expressed constitutively on T cells and its expression is down-regulated by chronic exposure to the inflammatory environment, we characterized co-stimulatory molecule expression on T cells from chronically infected patients. Cytofluorometric techniques are used to phenotypically characterize T cells, its co-stimulatory molecules and perforin secretion from infected and non-infected human bones. A higher T cell activation [human leucocyte antigen D-related (HLA-DR+)] is shown in infected compared to non-infected bones. Chronically infected human bones are characterized by an increase of CD28-negative CD4+ T cells, indicating long-term activated cells with cytotoxic ability. Therefore, this alteration of co-stimulatory molecules may modify interactions with osteoclasts and impact bone resorption.

B cells not only participate in proinflamatory reactions.They also play a role in regulation of immune responses. Regulatory B (Breg) cells are specific subsets that have an ability of immune response suppression.They contribute to maintenance of peripheral tolerance and inhibition of immune reaction to specific self-antigens, mainly by producing of

interleukin-10 (IL-10) but also by transforming growth factor (TGF-β), Fas ligand, and expressing of TNF-related apoptosis-inducing ligand (TRAIL)

Breg cells are important in preventing the disease onset and also in sup-

pressing the disease symptoms. Primarily, Breg cells are

able to change T cell differentiation in behalf of a regulatory phenotype. It is considered that related interactions between Breg cells and T cells control the induction of T regulatory (Treg) cells and are important in maintaining Treg cell compartment recent findings, Breg cells have an ability to inhibit Th1immune responses by the production of IL-10 during

chronic infections Furthermore, they are capable of indirect suppression of Th1 and Th17 cells differentiation by suppressing production of pro-inflammatory cytokines by dendritic cells.

In conclusion, bone tissue in humans appears to be a site of T cell activation and proliferation, the latter being decreased in chronic bacterial infections. Bone infections are associated with a high percentage of CD28− CD4 T cells exhibiting a cytotoxic phenotype as well as an up-regulated CD40/CD40L pathway on T cells. As activated T cells are already known to express RANKL, which is a crucial factor for osteoclastogenesis, our results suggest a creative line of work on the mechanisms of bone resorption in human BI. Moreover, we assume that biotherapies targeting co-stimulatory molecules might have significant but variable effects on bone resorption, depending on their membrane expression.

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