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ANATOMY

HISTOPATHOLOGY ASSIGNMENT

OSTEOARTHRITIS

T lymphocytes in the pathogenesis and progression of osteoarthritis

Osteoarthritis (OA) is the most common type of arthritis (Lazaros *et al.*, 2007). The prevalence of symptomatic OA is at least 12.1% in both sexes, whereas the prevalence of radio-graphically defined OA is much higher and increases with age (Lazaros *et al.*, 2007) OA is a heterogeneous disease, and its classification leaves much to be desired. Primary OA, which has no apparent predisposing factor, and secondary OA, in which the patient has a prior trauma or condition related to OA, are the 2 most common subsets. Primary OA is called generalized OA when it affects many joints, nodal OA when it exhibits as nodes over interphalangeal joints and erosive inflammatory OA when it exhibits as erosions in distal interphalangeal joints (Lazaros *et al.*, 2007). Erosive inflammatory arthritis, which is characterized by flares of inflammation in joints and the presence of inflammation markers in peripheral blood, may represent the far end of the spectrum of generalized OA. Current treatments for OA are purely palliative, and the need for novel therapies is obvious. The etiology of primary OA is not known. Unidentified genetic factors have been implicated in the development of OA and a genetic component is supported by studies of families and twins (Lazaros *et al.*, 2007). Clonal chromosome aberrations, such as the gain of chromosomes were observed in the synovial membrane of certain patients with OA (Lazaros *et al.*, 2007). Alpha1-antitrypsin 1-antichymotrypsin, gene polymorphisms, and HLA alleles have been associated with generalized OA, whereas type II precollege gene polymorphisms have been associated with precocious OA with mild chondrodysplasia (Lazaros *et al.*, 2007)

T cells may play an important role in the pathogenesis and progression of OA as follows.

1. CD3 T cells infiltrate the synovial membrane of patients with OA

Several groups of investigators, including our own have reported the presence of mononuclear cell (MNC) infiltrates consisting of T cells and macrophages in the synovial membrane of 50% of patients with OA. MNC infiltrates may be diffuse or per vascular nodular (Lazaros *et al.*, 2007). We have observed angiocentric infiltrates composed primarily of CD3 T cells in the synovial membrane of patients with OA, in a pattern similar to that observed in RA (ref. 25, and Sakkas LI, et al: unpublished results). Trans mural CD3T cells infiltrating the vessel wall were evident, although they were located mainly in perivascular areas. Many vessels were compressed and occluded, and endothelial cells were strongly positive for E-selectin, in a manner similar to that observed in RA (ref. 25, and Sakkas LI, et al: unpublished results). All of these observations in patients with OA are in addition to the findings in patients with the relatively uncommon type of erosive inflammatory disease, which clearly shows a strong inflammatory component (Lazaros *et al.*, 2007). In certain patients with OA, the MNC infiltrates resemble those observed in the synovial membrane of patients with RA (Lazaros *et al.*, 2007).

Nodular lymphocytic aggregates were observed in 14% of patients with early OA and in 37% (22) to 65% of patients with advanced OA at the time of joint replacement surgery (Lazaros *et al.*, 2007). The presence of T cells may play an important role in the pathogenesis and progression of OA as follows. 1. CD3 T cells infiltrate the synovial membrane of patients with OA. Several groups of investigators including our own have reported the presence of mononuclear cell (MNC) infiltrates consisting of T cells and macrophages in the synovial membrane of 50% of patients with OA. MNC infiltrates may be diffuse or perivascular nodular, We have observed angiocentric infiltrates composed primarily of CD3 T cells in the synovial membrane of patients with OA, in a pattern similar to that observed in RA (ref. 25, and Sakkas LI, et al: unpublished results) (Lazaros *et al.*, 2007). Transmural CD3 T cells infiltrating the vessel wall were evident, although they were located mainly in perivascular areas. Many vessels were compressed and occluded, and endothelial cells were strongly positive for E selection, in a manner similar to that observed in RA (ref. 25, and Sakkas LI, et al: unpublished results). All of these observations in patients with OA are in addition to the findings in patients with the relatively uncommon type of erosive inflammatory disease, which clearly shows a strong inflammatory component (Lazaros *et al.*, 2007). In certain patients with OA, the MNC infiltrates resemble those observed in the synovial membrane of patients with RA (Lazaros *et al.*, 2007).

2. T cells infiltrating the synovial membrane of patients with OA express early, intermediate, and late activation antigens.

We previously demonstrated that in the majority of patients with advanced OA, T cells infiltrating the synovial membrane express early activation antigens (CD69), intermediate activation antigens (CD25, CD38), and late activation antigens (CD45RO, HLA class II) (Lazaros *et al.*, 2007). These activation antigens were expressed on T cells and other MNCs infiltrating the synovial membrane of both patients with OA and patients with RA, although their proportions were significantly higher in patients with RA than in those with OA (Lazaros *et al.*, 2007). Although it could be argued that CD45RO T cells may extravasate from peripheral blood, the expression of CD69, an

early activation antigen, suggests that activation occurs in situ, in the synovial membrane (Lazaros *et al.*, 2007). CD38 and the CD43, which are detected in the synovial membrane of patients with OA mediate adhesion to vascular endothelium and binding to intercellular adhesion molecule 1 (ICAM-1), respectively. Leukocytes and endothelial adhesion molecules are also expressed in the synovial membrane of patients with OA, although to a lesser degree than in patients with RA. B cells are also activated in patients with OA (Lazaros *et al.*, 2007)

B lymphocytes in the pathogenesis and progression of osteoarthritis

Cellular infiltrates in the inflamed OA synovium have been reported to contain activated B cells along with other cell types (Abdul and Tariq 2013). A clonal analysis of B cells in OA synovium revealed their oligoclonal nature suggesting an antigen driven activation instead of non-antigenic activation (Abdul and Tariq 2013). Moreover, several studies found antibodies against cartilage components highlighting the activation of humoral adaptive immune response in OA. When cartilage cell surface proteins were used as substrate in an ELISA and sera from OA patients were applied, an elevated antibody titer was detected compared to controls (Abdul and Tariq 2013). Similarly, auto antibodies were found in OA patients against cartilage derived proteins osteopontin, cartilage intermediate layer protein (CILP), YKL-39, fibulin-4 and collagen. Anti-CCP antibodies were detected in 7 out of 136 OA patients, while another group also detected them in OA patients but at significantly lower levels compared to RA patients (Abdul and Tariq 2013). Antibodies against native G1 domain of aggrecan core protein were found in synovial fluid of OA patients (Abdul and Tariq 2013). Using proteomic approach, Xiang et al identified triosephosphate isomerase (TPI) as an important antigen with autoantibodies present specifically in OA but not in RA (Abdul and Tariq 2013). Other studies have reported autoantibodies in animal models of OA including horses and dogs (Abdul and Tariq 2013). The role of the auto antibodies against cartilage components in development of OA has been further highlighted by studies showing their deposition and cytotoxic effects on cartilage, which may be one of the mechanisms playing important role in cartilage degeneration in OA (Abdul and Tariq 2013).

OSTEOMYELITIS

The term Osteomyelitis encompasses a broad group of infectious diseases characterized by infection of the bone and/or bone marrow. The pathogenesis of these diseases can follow acute, sub acute or chronic courses and involves a range of

contributory host and pathogen factors. A commonly used aetiological classification distinguishes between three types of Osteomyelitis: acute or chronic haematogenous disease seeded by organisms in the bloodstream, local spread from a contiguous source of infection and secondary Osteomyelitis related to vascular insufficiency. Acute haematogenous Osteomyelitis acute haematogenous Osteomyelitis refers to infection of bone resulting from bacteria in the bloodstream. This is seen most often in children, with initial infection thought to occur in the richly vascularised metaphyseal region (Gutierrez, 2005). Children are thought to experience frequent episodes of bacteraemia, often with no apparent symptoms, leading to seeding and development of osteomyelitis (Conrad, 2010). The pathogenesis of this process has been theoretically described. Inoculation of the metaphyseal vessels occurs at the transition point from the arteriolar vessels to the venous sinusoids, slowing blood flow and increasing vascular turbulence (Jansson et al., 2009). These sites of turbulence may be predisposed to bacterial infection by providing an opportunity for local invasion. Although rarely seen in developed countries, haematogenous osteomyelitis may take on a chronic course within bone if left untreated. Sequelae of this devastating condition may include chronic sinuses with exposed bone, loss of structural integrity and growth disturbances (Beckles et al., 2010). Local trauma to bone in the setting of bacteraemia may also be a contributing factor. Animal studies have shown significantly increased rates of haematogenous osteomyelitis when direct injury to bone was combined with intravenous bacterial seeding. (Kabak et al., 1999; Morrissy & Haynes, 1989).

T lymphocytes in the pathogenesis and progression of Osteomyelitis

The goal of immune responses in infectious diseases is to eliminate pathogens through inflammatory reactions without collateral damage (Shreemanta *et al.*, 2015). T cells are not only the key mediators of adaptive immune responses, but they also orchestrate the delicate balance of immune responses between nonproductive and exaggerated inflammation. CD4⁺ antigen-specific responses are found in humans 3–8 weeks following infection with *Mtb*, corroborated by the tuberculin skin test or interferon gamma (IFN- γ) release assay (IGRA) in humans. The role of CD4⁺ cells, as well as interleukin (IL) 12 and IFN- γ , have been well documented by studies of the syndrome of Mendelian susceptibility to mycobacterial diseases, defined by a selective vulnerability to weakly virulent mycobacterial species (BCG and environmental mycobacteria) due to mutations in the IL-12 and IFN- γ receptors. Reactivation of latent infection with *Mtb* to clinical disease during TNF- α antagonist therapy in the first year of treatment suggests that TNF- α contributes to contain *Mtb* infection, which had been observed previously in murine models; TNF- α antagonist therapy also removes terminally differentiated TNF- α ⁺ (CD45RA⁺CCR7⁻) immune effector CD8⁺ T cells, which underlines the role of *Mtb*

specific CD8⁺T cells in clinical tuberculosis, along with the observation that CD8⁺ immune effector functions, including cytokine production and cytotoxic abilities, may be impaired. Concepts in targeted cellular therapy that are already used in clinical trials for viral targets or malignant cells may cross fertilize directed cellular therapy for the treatment of tuberculosis (Shreemanta *et al.*, 2015)

B lymphocytes in the pathogenesis and progression of Osteomyelitis

Acute Osteomyelitis presents as a suppurative infection accompanied by edema (Jason and Shirliff, 2009), vascular congestion, and small vessel thrombosis (Jason and Shirliff, 2009). In early acute disease, the vascular supply to the bone is decreased by infection extending into the surrounding soft tissue. Large areas of dead bone (sequestra) may be formed when the medullary and periosteal blood supplies are compromised. Acute Osteomyelitis can be arrested before dead bone develops if treated promptly and aggressively with antibiotics and surgery (if necessary). In an established infection, fibrous tissue and chronic inflammatory cells form around the granulation tissue and dead bone. After the infection is contained, there is a decrease in the vascular supply to it, inhibiting an effective inflammatory response. Chronic Osteomyelitis is the result of the coexistence of infected, nonviable tissues and an ineffective host response.²⁰ Bacteria have been shown to persist within glycoalyx-enclosed microcolonies adherent to the bone and to prosthetic devices in cases of osteomyelitis. (Jason and Shirliff, 2009). Biofilms are typically composed of cells embedded in a highly hydrated polysaccharide matrix with nucleic acids and proteins throughout. These biofilms are associated with the refractory nature of chronic infections such as Osteomyelitis (Jason and Shirliff, 2009). It has been reported that concentrations of antimicrobial agents required for the eradication of bacteria in biofilms are more than 50 to 1000 times higher than those needed for killing of the free-floating planktonic cells. Usually, that level of antibiotics is impossible to achieve because of patient toxicity. In the bones, this is further complicated by questionable penetration of antibiotics into infected and ischemic areas leading to subpotent antibiotic concentrations (Jason and Shirliff, 2009). The reason for the reduced ability of antimicrobial agents to eradicate these infections is due to the reduced antibiotic penetration and the very slow growth rate and differential upregulation of stress response genes by cells within the biofilm (Jason and Shirliff, 2009).

Pathologic features of chronic osteomyelitis are the presence of necrotic bone, the formation of new bone, and the exudation of polymorphonuclear leukocytes joined by large numbers of lymphocytes, histiocytes, and, occasionally, plasma cells. New bone forms from the surviving fragments of periosteum and endosteum in the region of the infection. An encasing sheath of live bone, an involucrum, surrounds the dead bone under the periosteum (Jason and Shirliff, 2009). The involucrum is irregular and is often perforated by openings through which purulence may track into the surrounding soft tissues and eventually drain to the skin surfaces, forming a chronic sinus. The

involucrum may gradually increase in density and thickness to form part or all of a new diaphysis. New bone increases in amount and density for weeks or months, according to the size of the bone and extent and duration of infection. Endosteal new bone may proliferate and obstruct the medullary canal (Jason and Shirliff, 2009). After host defense or operative removal of the sequestrum, the remaining cavity may fill with new bone, especially in children. However, in adults, the cavity may persist or the space may be filled with fibrous tissue, which may connect with the skin surface via a sinus tract (Jason and Shirliff, 2009)

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