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MATRIC NUMBER: 16/MHS01/075

DEPARTMENT: ANATOMY

LEVEL: 400

COURSE CODE: ANA 404 (HISTOPATHOLOGY)

TOPIC: DISCUSS THE INVOLVEMENT OF T- AND B-LYMPHOCYTES IN THE PATHOGENESIS AND PROGRESSION OF OSTEOMYELITIS AND OSTEOATHRITIS

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**PATHOGENESIS AND PROGRESSION OF OSTEOMYELITIS**

The term osteomyelitis encompasses a broad group of infectious diseases characterized by infection of the bone and/or bone marrow (Mayank Roy et al, 2012). Osteomyelitis is inflammation of the bone caused by an infecting organism. 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(Mayank Roy et al, 2012). 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. The pathogenesis of these diseases can follow acute, subacute or chronic courses and involves a range of contributory host and pathogen factors(Mayank Roy et al, 2012). 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(Mayank Roy et al, 2012).

**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.

**Vertebral osteomyelitis**

Osteomyelitis involving the spine is also most commonly caused by haematogenous seeding of bacteria into the vertebrae (Tay et al., 2002). The pathophysiology of this condition reflects the unique vascular structures of the spine. The venous anatomy of the spine, originally investigated for its role in cancer metastasis, allows retrograde flow from the pelvic venous plexus due a lack of valvular structures, providing an opportunity for haematogenous deposition of bacteria (Batson, 1967). Fine arteriolar structures surrounding the vertebral end plate may also represent a location at which bacteria can become trapped (Wiley & Trueta, 1959). Infections are predominantly localized to the lumbar and thoracic spine, with significantly less frequent involvement of the cervical spine (Beronius et al., 2001). In children, a markedly different disease process has been observed in infections of the spine. Blood vessels in the paediatric spine pass through the physeal cartilage and terminate within the intervertebral disc, allowing for seeding of infection from the osseous vasculature (Tay, et al., 2002). This results in a direct extension of infection into the disc that is not seen in adult patients. For this reason, this condition is referred to by some authors as paediatric discitis rather than osteomyelitis.

**Osteomyelitis secondary to contiguous infection**

In adult patients, the majority of osteomyelitis cases are due to inoculation from contiguous infection. Sources can include direct contamination at a site of injury, iatrogenic contamination at the time of an invasive procedure, or invasive infection from surrounding soft tissue. The epidemiology of contiguous infection osteomyelitis is biphasic, with young patients suffering trauma and related surgery and older patients suffering decubitus ulcers (Mader et al., 1999). Chronic infection often results, with clinical courses complicated by loss of bone structural integrity and soft tissue envelope disturbance.

The progression of disease in localized osteomyelitis is characterized by a cycle of microbial invasion, vascular disruption, necrosis and sequestration. As a result of this, cortical bone undergoes necrosis and is detached from surrounding live bone, creating an area known as a sequestrum. This provides a fertile environment for further bacterial invasion and progression continues.

**Host factors**

The pathogenesis of osteomyelitis is a complex process involving interactions between a host and an infectious agent. The host’s inflammatory response to a pathogen can further the physical spread of disease by clearing space in bone. Predisposing genetic differences in immune function are increasingly seen as an aetiological factor in some cases of osteomyelitis. Acquired factors such as diseases causing immune or vascular compromise and implantation of foreign materials are frequently involved in the disease process as well(Mayank Roy et al, 2012).

**Pathogen factors**

The initial event in the localization of infection appears to be adhesion of the bacteria to the extracellular matrix (ECM). Various factors govern this adhesion process. Once a bacteria reaches the biomaterial surface by haematogenous route they acquire a conditioning film of ECM proteins. Osteoblast play an active role in the internalization of the bacteria. Subsequently a multi-layered biofilm is made by the bacteria, which protects it from phagoctytosis and antibiotics(Mayank Roy et al, 2012).

**PATHOGENESIS AND PROGRESSION OF OSTEOARTHRITS**

Osteoarthritis (OA) is the most common type of arthritis. The prevalence of symptomatic OA is at least 12.1% in both sexes, whereas the prevalence of radiographically defined OA is much higher and increases with age (Lawrence RC et al, 1998). OA is a heterogeneous disease, and its classification leaves much to be desired (Altman R et al, 1986). 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. 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 (Holderbaum D et al, 1999), and a genetic component is supported by studies of families and twins (Stecher RM et al 1953). Clonal chromosome aberrations, such as the gain of chromosomes 5 and 7, were observed in the synovial membrane of certain patients with OA. Alpha1‐antitrypsin, α1‐antichymotrypsin, gene polymorphisms, and HLA alleles have been associated with generalized OA, whereas type II procollagen gene polymorphisms have been associated with precocious OA with mild chondrodysplasia (Lazaros et al, 2007).

Although the pathophysiology of OA is poorly understood, it is widely believed that primary OA is predominantly a disease of articular cartilage that may be caused by a biomechanical alteration, i.e., abnormal forces acting on normal cartilage or normal forces acting on abnormal cartilage (Lazaros et al, 2007). Articular cartilage consists of chondrocytes and extracellular matrix (ECM). ECM contains water and certain macromolecules, including collagen, proteoglycans, and hyaluronic acid. Microscopic examination has revealed a loss of proteoglycans and proliferation of chondrocytes in the cartilage of patients with early OA. As the disease progresses, loss of chondrocytes and calcification occurs (Lazaros et al, 2007).

The pathogenic mechanisms that lead to cartilage destruction and bone proliferation are not known. Point mutations of ECM macromolecules in articular cartilage have been reported (Lazaros et al, 2007). The structure of ECM molecules can also be altered by mutations in enzymes that cause posttranslational modification of collagen and the side chains of proteoglycan . Mutations in collagen or its modifying enzymes may cause subtle defects in cartilage. In that event, environmental factors, such as repetitive joint stress, may be responsible, at least in part, for the manifestation of OA. Proteolytic enzymes such as matrix metalloproteinases (MMPs) and their inhibitors appear to play a significant role in cartilage matrix degradation (Lazaros et al, 2007). However, changes in OA are not restricted to cartilage. In subchondral bone, there are early changes such as increased trabecular bone and stiffness (Lazaros et al, 2007), as well as late changes such as the presence of cysts and osteophytes, which are the hallmarks of OA. Furthermore, considerable inflammation occurs in the synovial membrane. Although OA has been considered by rheumatologists, in general, to be a noninflammatory disease, accumulating evidence suggests that this is not the case. Inflammation in the synovial membrane of at least 50% of patients with OA is well documented.

THE ROLE OF T AND B-LYMPHPOCYTE IN THE PATHOGENESIS AND PROGRESSION OF OSTEOMYELITIS AND OSTEOATHRITIS

**T lymphocytes**

T lymphocytes originate from precursor stem cells in fetal liver and bone marrow and differentiate into mature cell types after migration to the thymus [Yang Q et al 2010]. T lymphocytes may be categorized based on their distinct function into cytotoxic T lymphocytes (expressing the surface protein cluster of differentation (CD) 8 and responsible mainly for immune defence against intracellular pathogens and for tumour surveillance) and helper T lymphocytes (expressing the surface protein CD4) [Abbas AK et al, 1996]. Helper T cells (naïve CD4+ T lymphocytes) are triggered when they are presented with peptide antigens by MHC (major histocompatibility complex) class II molecules, which are expressed on the professional antigen-presenting cells (APCs) surface. Both are necessary for production of an adequate immune response [Romagnani S, 2006]. T cells have on their surface T cell antigen receptors (TCR) responsible for recognition of an antigen/major histocompatibility complex (HLA complex), immunological accessory molecules identifying HLA determinants, and adhesion molecules recognizing their counterpart ligands on APCs [Kronenberg M et al 1986-1988].

Once activated, helper (CD4+) T cells can be subdivided into at least three main functional subtypes according to releasing cytokines, the Th1 subset (mainly involved in cell–mediated tissue-damaging reaction), the Th2 subset (driving B cells to produce antibodies in the humoral immune response), and Th17 cells (playing a role in immune responses to infectious agents and maintenance of autoimmune diseases) (Marta Rydzewska et al, 2018). Th 1 cells produce tumor necrosis factor-β (TNF- β), interferon gamma (IFN-γ), and interleukin (IL) 2,;Th 2 cells secrete mainly IL-4, IL-5, IL-6, and IL-13, and Th17 secrete IL-17 (Fig. [1](https://thyroidresearchjournal.biomedcentral.com/articles/10.1186/s13044-018-0046-9#Fig1)) (Marta Rydzewska et al, 2018). Moreover, some CD4+ T cells produce both Th1 and Th2 cytokines and have been termed Th0. Determination of Th subtype is activated during an immune response, which depends on the type of antigen and its concentration, the nature of the initial antigen-presenting cell, and, probably, on ill-defined genetic and environmental influences. We recognize also set of T cells that can suppress these inflammatory responses, described as regulatory T cells (T regs) (Marta Rydzewska et al, 2018).

 

*The differentiation of CD4+ cells into specific T cell subsets. Cytokines play crucial roles in determining Th cell differentiation and the combination of cytokines is required for the differentiation of each subset*

### B lymphocytes

B lymphocytes develop from hematopoietic stem cells. Maturation of B cells takes place in bone marrow, whereas their activation occurs in the secondary lymphoid organs such as lymph nodes and the spleen [Kondo M., 2010].

B cells can also serve as APCs. They have a transmembrane receptor, called BCR (a surface immunoglobulin), which enables them to identify specific antigens, against which they initiate an immune response and synthesize antibodies, and present fragments of these antigens to CD4+ T cells using MHC class II molecules [Kambayashi T. et al, 2014]. When the antigen is uncommon, B cells may be the dominant APCs as they have an ability of up-concentration antigens on the cell due to the presence of BCR in the cell membrane [Kristensen B. et al,2016]. T helper (Th) cells reciprocally support activation of B cells. Particular attention was paid to sequencing of thyroid antibodies and defining B cell epitopes in TSH receptor. This, in turn, could enable further understanding of the pathogenesis of GD, which is a cause of triggering TSHR leading to development of this disease. However, the pace of the autoimmune reaction in AITD is usually slow, which leads its proliferation and differentiation involving many different polyclonal B and T cells [Ramos-Leví AM, et al, 2016].

On the ground of a number of data, Breg cells are important in preventing the disease onset and also in suppressing the disease symptoms. Primarily, Breg cells are able to change T cell differentiation in behalf of a regulatory phenotype (Marta Rydzewska et al, 2018). 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. There are studies showing that population of Treg cells is reduced in mice with B cell deficiency (Marta Rydzewska et al, 2018). According to recent findings, Breg cells have an ability to inhibit Th1 immune 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 (Marta Rydzewska et al, 2018).



*Schematic representation of Breg cells function. Through the production of IL-10 and TGF-β Breg cells can suppress the differentiation of pro-inflammatory lymphocytes and maintain of self-tolerance. DC, dendritic cells, IL-10, interleukin-10; TGFb, transforming growth factor β; TNF, tumor necrosis factor.*

**REFERENCES**

Mayank Roy, Jeremy S. Somerson, Kevin G. Kerr and Jonathan L. Conroy. (2012) Pathophysiology and Pathogenesis of Osteomyelitis. DOI: 10.5772/32171

Conrad, D. A. (2010). Acute Hematogenous Osteomyelitis. Pediatrics in Review, Vol. 31, No.

11, pp. (464-471),

Gutierrez, K. (2005). Bone and Joint Infections in Children. Pediatric Clinics of North America,

Vol. 52, No. 3, pp. (779-794),

Jansson, A., Jansson, V., & von Liebe, A. (2009). [Pediatric osteomyelitis]. Der OrthopÃ¤de,

Vol. 38, No. 3, pp. (283-294)

Tay, B. K. B., Deckey, J., & Hu, S. S. (2002). Spinal Infections. J Am Acad Orthop Surg, Vol. 10,

No. 3, pp. (188-197),

Batson, O. V. (1967). The vertebral system of veins as a means for cancer dissemination.

Progress in Clinical Cancer, Vol. 3, No., pp. (1-18)

Beronius, M., Bergman, B., & Andersson, R. (2001). Vertebral Osteomyelitis in Goteborg,

Sweden: A Retrospective Study of Patients During 1990-95. Scandinavian Journal of

Infectious Diseases, Vol. 33, No. 7, pp. (527-532)

Wiley, A. M., & Trueta, J. (1959). The vascular anatomy of the spine and its relationship to

pyogenic vertebral osteomyelitis. The Journal of Bone and Joint Surgery. British

Volume, Vol. 41-B, No., pp. (796-809)

Mader, J. T., Shirtliff, M., & Calhoun, J. H. (1999). The host and the skeletal infection:

classification and pathogenesis of acute bacterial bone and joint sepsis. Best Practice

& Research Clinical Rheumatology, Vol. 13, No. 1, pp. (1-20),

Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998; 41: 778– 99.

Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al, for the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis Rheum* 1986; 29: 1039– 49.

Holderbaum D, Haggi TM, Moskowitz RW. Genetics and osteoarthritis: exposing the iceberg. *Arthritis Rheum* 1999; 42: 397– 405.

Stecher RM, Hersh AH, Solomon WM, Wolpaw R. The genetics of rheumatoid arthritis: analysis of 224 families. *Am J Hum Genet* 1953; 5: 118– 38.

Lazaros, Sakkas, Chris D., Platsucas, The role of T cells in the pathogenesis of osteoarthritis. 2007. [Volume56, Issue2](https://onlinelibrary.wiley.com/toc/15290131/2007/56/2). <https://doi.org/10.1002/art.22369>

Yang Q, Jeremiah Bell J, Bhandoola A. T-cell lineage determination. Immunol Rev. 2010;238:12–22.

Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. Nature. 1996;383:787–93.

Romagnani S. Regulation of the T cell response. Clin Exp Allergy. 2006;36:1357–66.

Kronenberg M, Siu G, Hood LE, Shastri N. The molecular genetics of the T-cell antigen receptor and T- cell antigen recognition. Annu Rev Immunol. 1986;4:529–91.

Isakov N. Cell activation and signal initiation. Immunol Today. 1988;9:251–2.

Kondo M. Lymphoid and myeloid lineage commitment in multipotent hematopoietic progenitors. Immunol Rev. 2010;238:37–46.

Kambayashi T, Laufer TM. Atypical MHC class II-expressing antigen-presenting cells: can anything replace a dendritic cell? Nat Rev Immunol. 2014;14:719–30.

Kristensen B. Regulatory B and T cell responses in patients with autoimmune thyroid disease and healthy controls. Dan Med J. 2016;63(2):B5177.

Ramos-Leví AM, Marazuela M. Pathogenesis of thyroid auto- immune disease: the role of cellular mechanisms. Endocrinol Nutr. 2016;63:421–9.

Marta Rydzewska, Michał Jaromin, Izabela Elżbieta Pasierowska, Karlina Stożek& Artur Bossowski. Role of the T and B lymphocytes in pathogenesis of autoimmune thyroid diseases. Article number: 2 (2018)