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Understanding Peri-implantitis: Cellular Mechanisms and Microbiological Analysis

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ABSTRACT

Peri-implantitis is the one of the main reasons for a dental implant failure leading to a cascade of other oral problems to follow. The inflammatory lesions causing implant failure also make the surrounding bone to resorb, sometimes making re-implant placement impossible. This article discusses about the events that occur at the cellular and histopathological level. This article also discusses the histopathological difference between periimplantitis and periodontitis.

Keywords: peri-implantitis, inflammation, histopathology, microbiology

INTRODUCTION

Peri-implantitis is a common cause of implant failure, accounting for 10% of cases[1]. This progressive disease affects both hard and soft tissues, leading to bone resorption, decreased osseointegration, pocket formation, and purulence. It is classified into early, moderate, and advanced peri-implantitis based on probing depth, bleeding, and bone loss[1]. Early implant loss occurs before prosthetic loading, causing osseointegration issues and preventing the implant from anchoring the denture. Causes include bacterial infections, surgical mistakes, or overloading. Primary osseointegrated implants can lose their connection to the surrounding bone, leading to peri-implant mucositis and bone resorption[2].

Local inflammation that occurs over the course of peri-implant illnesses is the primary cause of this loss of crestal bone around an implant. These conditions, which include peri-implant mucositis and peri-implantitis, are characterized as inflammatory lesions of the tissues surrounding the implant[3]. An inflammatory lesion that is restricted to the mucosa surrounding an implant is known as periimplant mucositis, whereas an inflammatory lesion of the mucosa that affects the supporting bone and results in osseointegration loss is known as peri-

implantitis. Although the current epidemiological data are limited, peri-implant mucositis has been reported to affect 80% of the subjects with dental implants and 50% of the implants, whilst peri-implantitis affects 28–56% of the subjects and 12–43% of the implants[4].

MATERIAL AND METHOD

A male patient aged 44 years reported at the dental clinic with mobile teeth. On intraoral inspection and complete history taking it was recorded that he got implants placed 2 year back at a dental clinic at the lower anterior region which were now mobile and he was diagnosed as a case of peri-implantitis. Clinically, peri-implantitis was managed according to the protocol, for histopathological examination swab/soft tissue were sent for examination.

For duration of 24 to 48 hours, the soft tissue that overlaid was immediately fixed using neutralized buffered formalin solution. The standard laboratory protocol for tissue processing was followed, which includes dehydration, washing, and paraffin wax infiltration. The preparation and embedding of the tissue block was done with paraffin wax. Sections that were 3 microns thick were stained with hematoxylin and eosin in accordance with the usual protocol outlined in Bancroft's textbook. Using an Olympus BX53 research microscope, low-and high-power digital photographs (Olympus EPL3) were obtained and the slides were inspected. Long, thin rete ridges of parakeratinizd startified suamous epithelium are visible over the gingival core, and beneath it is a strong collagenous stroma containing few inflammatory cells, mostly lymphocytes.

RESULTS

Histopathology of Peri-Implantitis

Histological comparison of tissue samples from periodontitis, peri-implant mucositis, and healthy gingiva reveal large inflammatory cell infiltrates that dominate the specimen region from peri-implantitis locations[5]. The lesions are consistently bigger at peri-implantitis locations and extend apical to the pocket epithelium in investigations comparing to samples from periodontitis and peri-implantitis. Although the majority cell type in both lesions are usually plasma cells, the densities of neutrophil granulocytes, macrophages, and plasma cells are substantially higher at the peri-implantitis site than at the periodontitis location. **(Figure 1)** According to a human histological examination of dental implants that were recovered, periimplantitis-affected implants exhibit high bacterial counts, a bone sequestrate, and a correlated inflammatory infiltrate. Studies comparing lesions from mucositis and periimplantitis revealed higher percentages of B cells and elastase-positive cells in the former. Gross histological sections of implants removed because of periimplantitis reveal that the apical region of the implant frequently has the sole bone-encapsulated fibrous tissue.

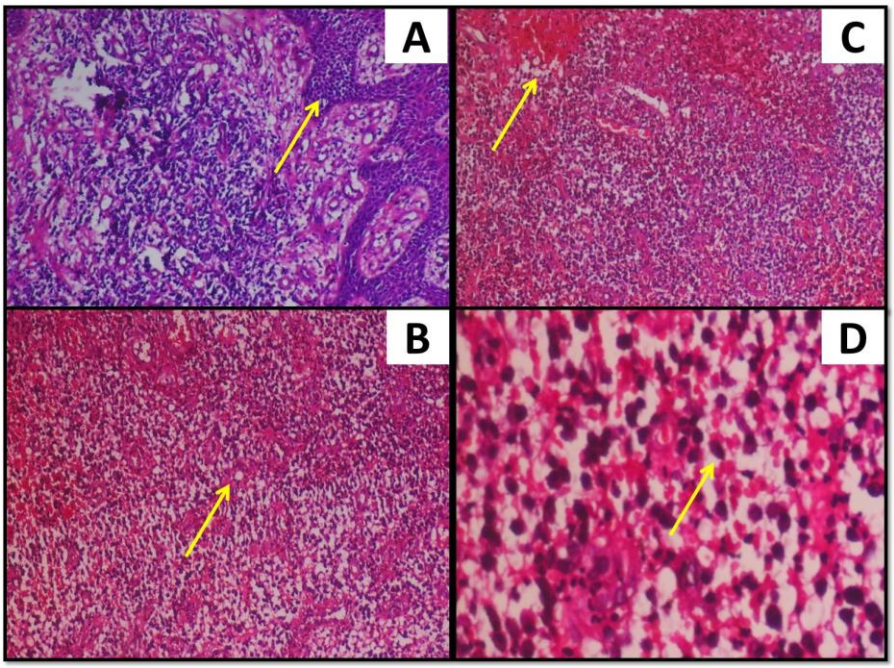

Figure 1: showing higher number of inflammatory cells in cases of peri-implantitis. A) Hyperplastic epithelium with underlying dense inflammatory infiltrate (H and E, 10x), B) Dense inflammatory infiltrate with a background of hemorrhage (H and E, 40x), C) Thickened vessels with engorged RBCs (H and E, 40x), D) Chronic inflammatory cells chiefly composed of plama cells and lymphocytes (H and E, 100x).

DISCUSSION

Cellular and Molecular Mechanisms Involved

According to a study on the activation state of macrophages in the infiltrated connective tissue, peri-implantitis lesions have a higher number of macrophages undergoing M1-polarization. M1 macrophages, also called classically activated macrophages, are polarized by lipopolysaccharide (LPS), either alone or in combination with Th1 cytokines, such as interferon (IFN)-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF)[6]. Studies on the functional characteristics of cells show that peri-implantitis lesions have different mRNA signatures and higher mRNA levels for certain cytokines, such TNF-a, IL-8, CCR5, and CXCR3, compared to periodontitis lesions. When taken as a whole, the differences in the main inflammatory cell densities and architectures of Infiltrated Connective Tissue (ICT) between the two types of lesions show the characteristics of a dysregulated local host response in peri-implantitis. The ICT extends significantly apically to the pocket epithelium and toward the crestal bone. Additionally, there is no epithelial lining between the ICT and the submarginal biofilm in the pocket area, and neutrophil and macrophage recruitment to the ICT is increased and continues[7].

A recent study found that human fibroblasts from lesions with periimplantitis generated more proinflammatory chemokines than fibroblasts from gingiva in health. A separate study found that periimplantitis-related lesions had altered extracellular matrix, especially with regard to collagen V, tenascin, and matrix metalloproteinase. Research has demonstrated that gingival samples from patients with peri-implantitis include osteoclast-activating cytokines, the most prevalent of which is interleukin 1 alpha. These results support the hypothesis that inflamed

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peri-implant tissues may be more susceptible to disintegration and provide possible explanations for why this process is so harmful under these conditions. Studies conducted on animals to evaluate the peri-implantitis caused by an artificial ligature have shown that the infiltration of inflammatory cells can be observed in close proximity to the bone marrow spaces8. The lesion may get worse as the alveolar bone isn't separated from it by a healthy connective tissue fiber compartment. This is not the case with the periodontitis, where the inflammatory lesion and the intact supracrestal connective tissue fiber compartment are separated[8].

Microorganisms such as P. gingivalis and F. nucleatum produce pro-inflammatory cytokines such as interleukin (IL)-1b, tumour necrosis factor (TNF)-a, and inducible nitric oxide synthase (iNOS). These cytokines have been demonstrated to play a major role in hypoxia-related inflammation. Consequently, it has been noted that inflammatory gingival tissues show more hypoxia whereas healthy tissues maintain normal oxygen levels. Furthermore, human gingival and periodontal ligament cells are inhibited by hypoxia in their migration, proliferation, and differentiation. Under hypoxic conditions, the tissues' fight against hypoxia is regulated by hypoxia-inducible factor (HIF)-1 alpha. HIF-1alpha is rapidly degraded by prolyl hydroxylase at normal oxygen levels (PH). Because PH is an oxygen-dependent enzyme, low oxygen levels prevent it from functioning. HIF accumulates as a result, and HIF degradation is stopped. The periodontal ligament is one of the most significant blood and oxygen supply systems and is essential to the periodontium's defense against dysbiotic bacteria. Consequently, the lack of a periodontal ligament may lead to insufficient vascularization and an increased inflammatory state in the periodontium. Peri-implant tissues have been suggested to be more prone to inflammation and collagenase activity than periodontal tissues. The immune cells implicated in peri-implantitis lesions vary from those in periodontitis lesions.

In peri-implantitis lesions, pro-inflammatory cytokines and chemokine receptors were increased, influencing wound healing, complement activation, and cell adhesion. Peri-implant connective tissues have increased levels of IL-10, TIMP-2 (tissue inhibitor of MMPs), and receptor activator of nuclear factor jB (RANKL) in comparison to connective tissue samples[9].

Nevertheless, a few studies have also demonstrated that in situations of severe periodontitis or peri-implantitis, the "inner zone" (ICT-1) next to the pocket epithelium in both types of lesions has higher densities of inflammatory cells than the "outer zone" (ICT-2). Compared to periodontitis samples, peri-implantitis specimens had greater densities of iNOS-, NOX2-, MPO-, and PAD4/MPO-positive cells in the NCT (non-infiltrated connective tissue) compartment. These cells serve as indicators of both antibacterial nitric oxide and DNA damage. The overall picture of a broad tissue reaction at peri-implantitis sites is enhanced by the identification of tissue reactions that extend beyond the lateral border of the ICT[10].

Microbiology of Peri-Implant Infections

Periodontopathic bacteria can cause infection in saliva that is close to implants. It was shown that the oral environment's aging process contributes to the colonization of oral bacteria and their succession in the peri-implant sulci. **Figure 2** shows the shift from normal to pathologic bacteria in cases of peri-implantitis[11,12]. Implant-related microbiota contains a small number of bacteria, including A. odontolyticus, E. corrodens, H. actinomycetemcomitans, P. micros, C. sputorum, and L. buccalis. Although these bacteria have the ability to cause periodontal

diseases, implant failure is mostly dependent on their early colonization. Elevated amounts of spirochetes, P. gingivalis, P. intermedia, and other infections are observed with failing or unsuccessful implants. The presence of teeth had no bearing on the likelihood of implant infection, as seen by the greater concentrations of Eikenella corrodens around implants with mucositis. The co-occurring networks for peri-implant mucositis comprised Porphyromonas gingivalis, Tannerella forsythia, and Prevotella intermedia. As in adult or refractory periodontitis, gram-negative anaerobic bacteria, such as Fusobacterium nucleatum, Treponema denticola, Tannerella forsythia, and "black-pigmented bacteria," were prevalent in peri-implantitis. Tannerella forsythia, Treponema, Desulfobulbus, Fretibacterium, and Pseudoramibacter alactolyticum were linked to late failures[13].

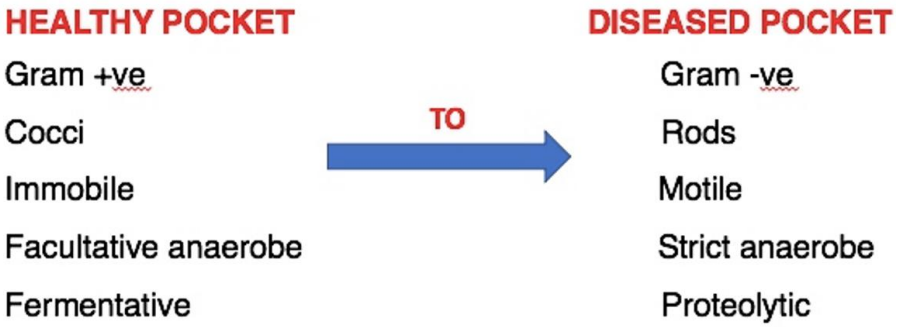

Figure 2: Shift from normal to pathologic bacteria

CONCLUSION

The majority-titanium nature of dental implants may have an impact on the peri-implantitis sites' local host reactions. Methods such as synchrotron radiation, SEM-EDX, and μ-PIXE are employed to assess metal microparticles in soft tissues around implants. While histological examination maintains the orientation and architecture of the tissue, immunohistochemistry has several technological drawbacks. Proteomics and transcriptomics represent novel "omics" avenues for future research, however sample sizes and resource allocation need to be balanced. Conducting an analysis of host-parasite interactions can enhance our comprehension of the involvement of microorganisms in peri-implantitis. Technologies such as checkerboard DNA–DNA hybridization, fluorescent in situ hybridization, 16S rRNA gene-based PCR, and qPCR have been used to investigate the function of the peri-implant microbiota in health and disease, including peri-implantitis. By adding surface-modifying end groups (SMEs) or altering the chemical composition of the substrates, biomaterials' surface chemistries can be altered to reduce or halt biofilm development.

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