

Foreign Bodies Associated With Peri-Implantitis Human Biopsies

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Background: Peri-implantitis is an inflammatory condition that can lead to implant loss. The aim of this descriptive retrospective study is to describe the histopathologic findings in soft tissue biopsies of implants with peri-implantitis.

Methods: Thirty-six human peri-implantitis biopsies were analyzed using light microscopy (LM) and scanning electron microscopy (SEM). The composition of foreign materials found in the tissues was assessed using an energy dispersive x-ray spectrometer.

Results: At the LM level, the inflammatory lesion of peri-implantitis was in most cases a mixture of subacute and chronic inflammation dominated by plasma cells. At the SEM level, radiopaque foreign bodies were identified in 34 of the 36 biopsies. The predominant foreign bodies found were titanium and dental cement. These foreign materials were surrounded by inflammatory cells.

Conclusions: At present, the exact mechanism for introduction of these materials and their role in peri-implantitis is unknown. Further research is warranted to determine their etiology and potential role in pathogenesis. *J Periodontol* 2015;86:9-15.

KEY WORDS

Dental cements; dental implants; microscopy, electron, scanning; pathology, oral; peri-implantitis; titanium.

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This descriptive pilot study examines the soft tissues from human biopsies obtained from patients diagnosed with peri-implantitis. This pathologic condition is characterized by clinical signs of inflammation and progressive bone loss (BL) and is a leading cause of implant failure.¹ Some authors have described the etiopathogenesis of this problem as being similar to that of periodontitis. However, there are differences in the inflammatory infiltrates in the two types of lesions.² Differences in host response may explain the progression of the lesions.³ As an example, ligature-induced periodontitis in animals is self-limiting in most cases after removal of the ligature, whereas rapid progression of the lesion is usually seen around implants.² It has also been argued that peri-implantitis is a foreign body response not dependent on the presence of bacteria.⁴

A recent systematic review and meta-analysis found that the frequency of peri-implantitis was 18.8% of patients and 9.6% of implants.⁵ Even if these numbers are exaggerated, further elucidation of the pathogenesis of implant failure is needed to deal with this problem.

One of the contributing factors of peri-implantitis has been shown to be excess dental cement.⁶ Some authors have even described a specific condition, cement-related peri-implant disease, and shown high correlation between excess cement and peri-implantitis.^{7,8}

The removal of excess cement usually results in resolution of inflammation. However, it is important to note that in some cases it takes years before an infection related to the excess dental cement is detected.⁶ Independent of the technique used for cementation⁹ and irrespective of the diameter and location of the implants, there is always excess cement, despite meticulous cleaning of the abutment/crown, after cementation.¹⁰ The amount of undetected cement increases significantly as the restoration margins are located deeper subgingivally.⁸ Excess dental cement has been associated with bleeding on probing, suppuration, and peri-implant attachment loss and BL.⁷ The effect of cement seen histologically has not been described; that is the aim of this paper.

MATERIALS AND METHODS

In this descriptive retrospective study, archival biopsy material was analyzed. Soft tissue biopsies were taken during flap surgery around implants with peri-implantitis. Peri-implantitis in this group of patients was characterized by clinical signs of inflammation, including bleeding on probing, suppuration, increased probing depth, abscess formation, pain, erythema, and edema, accompanied by radiographic signs of severe progressive BL. After written informed consent was obtained, 36 biopsies of peri-implant tissues obtained from 31 patients diagnosed with peri-implantitis and requiring surgical intervention were submitted for histopathologic analysis to the Oral Pathology Division at Baylor College of Dentistry, Texas A&M University. The paraffin blocks containing the peri-implant tissues were used for microscopic analysis in this study. All of these implants were restored with a cemented single-unit fixed partial denture. Approval from the Institutional Review Board of Baylor College of Dentistry, Texas A&M University, was obtained.

Histomorphometric Analysis: Light Microscopy

Tissues obtained from the implant areas were routinely processed for light microscopy (LM) analysis. Sections were cut at 5 μm and stained with hematoxylin and eosin. The composition of the inflammatory infiltrate was analyzed.

Scanning Electron Microscopy and Energy Dispersive X-Ray Spectrometry

The individual paraffin blocks containing the tissues were imaged with scanning electron microscopy (SEM)[¶] equipped with an energy dispersive x-ray spectrometer detector (EDS) to characterize the morphology and elemental composition of the foreign material. The specimens were analyzed with sample settings of organic, non-conductive, low-vacuum, EDS mode, under accelerating electron

voltages of 10 to 20 kV power, and at varying magnifications to identify regions for further analysis. Regions of interest in the paraffin blocks contained foreign materials that resembled particles or particle agglomerations (referred to here as particles) in the samples that were radiopaque. These areas were further inspected by increasing the magnification to $\times 1,000$. Once enlarged, each area of interest in the biopsy was analyzed using point EDS. This technique permitted determination of the elemental composition (in mass %) of the point of the tissue under analysis. The number of analyzed areas from each biopsy sample ranged from five to 15 depending on the number of radiopaque particles visualized.

Control EDS measurements were taken of the paraffin where the tissues were embedded to establish a baseline for comparison with areas of the sample containing the peri-implant tissues. Areas of paraffin only contained high concentrations of the elements carbon (C) and oxygen (O). Areas displaying an elemental composition of C, nitrogen (N), sodium (Na), potassium (K), and O were recorded as tissue controls, as this material was purely organic in nature. Samples displaying foreign bodies with additional non-organic elements such as titanium (Ti), zirconium (Zr), aluminum (Al), and silicon (Si) were analyzed further. These particles were imaged and measured, and the total mass percentage of the represented elements from the point EDS analysis was recorded for each specimen.

RESULTS

LM

Histopathologic review of the specimens revealed non-specific inflammatory changes in all specimens. The overlying epithelium occasionally showed degenerative changes, but more often demonstrated proliferative activity associated with the underlying inflammation. In some cases, the epithelium had morphologic characteristics that most closely resembled sulcular epithelium. The inflammatory infiltrate in most cases was chronic (Fig. 1A). Occasional cases showed only subacute inflammation, whereas in some instances a mixture of subacute and chronic inflammation was present in varying areas of the specimen (Fig. 1B). In approximately one third of the cases, the chronic inflammatory infiltrate was heavily dominated by plasma cells. When the inflammation was predominantly plasmacytic, apoptotic debris was sporadically noted. Bacterial colonies were also identified in about one third of the cases. In four

¶ JSM-6010LA, Jeol, Peabody, MA.

cases, granulomatous inflammation with foreign body–type giant cells was identified (Fig. 1C). Foreign material resembling dental cement was noted in eight cases, and in nine additional cases, a foreign material that did not appear to be dental cement was seen. In seven cases, the connective tissue harboring the inflammation was very dense and hypocellular, suggesting scar formation. In general, the LM findings were consistent with chronic inflammation. Histologically, the epithelium showed some thickening of the spinous cell region with elongation of the rete pegs. Russell bodies were evident occasionally, demonstrating that plasma cells were actively producing immunoglobulins (Fig. 1D). No peri-implant malignancy was identified.

SEM and EDS

The mean proportion and SD of the elements found in the 36 blocks are presented in Table 1. The mean percentages represent the composition of the elements found in all the areas evaluated in each biopsy. Therefore, in each sample, elements were averaged across five to 15 areas of the biopsy. To identify the composition of foreign bodies, two control areas were identified: paraffin and tissue with no evident presence of foreign bodies. The paraffin areas contained a high percentage of C, ranging from 93.5% to 98.1%, and O, ranging from 1.9% to 6.6% (Fig. 2). The analysis of tissue-containing areas in the sample with

no contaminants presented C (81.1% to 84.2%), O (4.4% to 10.6%), and N (6.3% to 11.6%). Any particle in the biopsies that presented elements other than C, O, and N were considered foreign bodies and were further characterized.

Radiopaque foreign particles were found in 34 of the 36 samples. EDS analysis revealed elements that differed from the control areas; namely, paraffin and tissue with no apparent foreign body embedded. To facilitate analysis, the main particles of interest were grouped according to: 1) titanium presence (group 1) and 2) presence of dental cement–related elements (Zr, Si, and Al) (group 2).

Morphologic analysis of the biopsies using SEM revealed the presence of radiopaque particles (diameter varying from 9 to 54 μm) with characteristic features of titanium debris in some of the biopsies. Further analysis demonstrated that seven biopsies contained group 1 particles, with Ti peaks. These peaks confirmed the presence of titanium in the tissues (Figs. 3A and 3B). The elemental composition of Ti in the biopsies inspected varied from 0.13% to 9.45%. The EDS analysis of the radiopaque particles in the other biopsies revealed the presence of group 2 particles in 19 biopsies. Group 2 contained particles of Zr (3.56% to 1.05%), Si (1.8% to 8.6%), and Al (0.4% to 6.3%). Zr, Si, and Al are elements characteristically present in commercial dental cements (Figs. 3C and 3D).

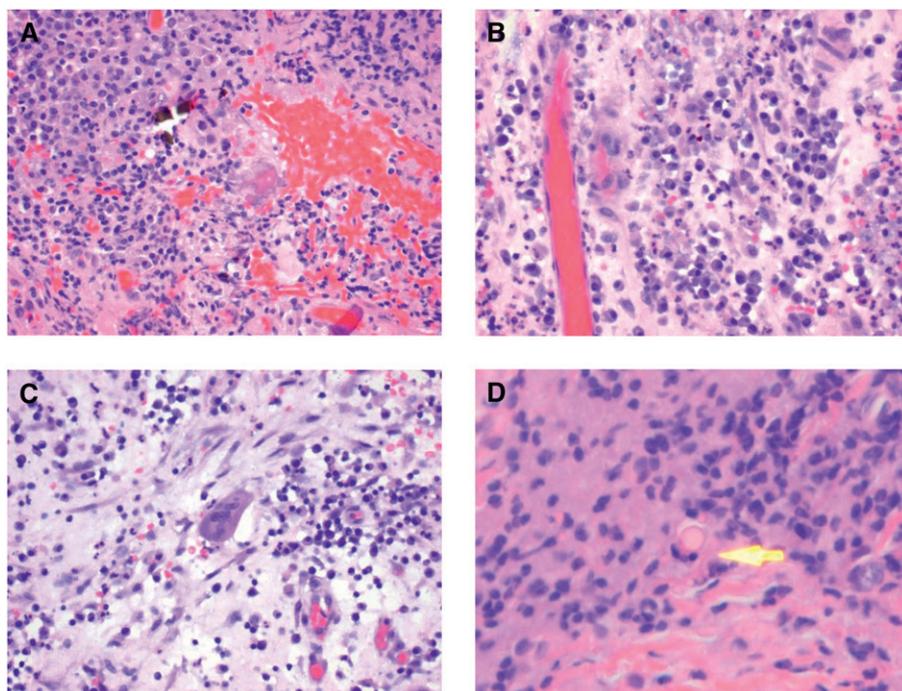


Figure 1.

Histologic slides under LM. (H&E staining; original magnification $\times 20$.) **A**) Chronic inflammatory infiltrate. **B**) Subacute inflammatory infiltrate. **C**) Focal granulomatous infiltrate with giant cells. **D**) Russell body.

DISCUSSION

This descriptive analysis of the biopsies of 36 peri-implantitis specimens demonstrated the presence of foreign bodies surrounded by chronic inflammatory infiltrates. The predominant foreign bodies were titanium and dental cement.

The histologic analysis of the biopsies demonstrated the presence of chronic inflammatory infiltrates and foreign bodies of different elemental composition. The infiltrate was heavily dominated by plasma cells. This has been shown in other case reports.^{11,12} In the cases reported here, some showed subacute inflammation exclusively. This has been shown in experimental peri-implantitis in animals in which the infiltrates present large amounts of polymorphonuclear cells and macrophages, which has been determined to be one of the main differences between infiltrates in

Table 1.
Mean Proportions (%) of the Elements Found in the Peri-Implantitis Biopsies

Element	Mean	SD
C	71.51	11.38
O	17.04	8.27
Ca	1.96	2.37
N	1.72	3.60
Na	1.67	1.89
P	1.51	1.40
Si	1.37	1.46
Al	1.08	1.40
Ti	0.60	1.79
F	0.42	2.28
Zr	0.40	0.48
Cl	0.40	0.99
K	0.34	0.57
Fe	0.27	0.94
Zn	0.26	0.93
Pt	0.22	1.31
S	0.19	0.37
Mg	0.12	0.34
Br	0.12	0.24
Pb	0.10	0.56
Ni	0.09	0.55
Ba	0.09	0.34
Bi	0.09	0.52
La	0.02	0.13
Cu	0.00	0.03
Ir	0.00	0.02
As	0.00	0.02

C = carbon; O = oxygen; Ca = calcium; N = nitrogen; Na = sodium; P = phosphorus; Si = silicon; Al = aluminum; Ti = titanium; F = fluorine; Zr = zirconium; Cl = chlorine; K = potassium; Fe = iron; Zn = zinc; Pt = platinum; S = sulfur; Mg = magnesium; Br = bromine; Pb = lead; Ni = nickel; Ba = barium; Bi = bismuth; La = lanthanum; Cu = copper; Ir = iridium; As = arsenic.

periodontitis and those in peri-implantitis.¹³⁻¹⁵ In the current study, multinucleated giant cells were seen in the biopsies, similar to those frequently found in the infiltrated connective tissue in direct contact with

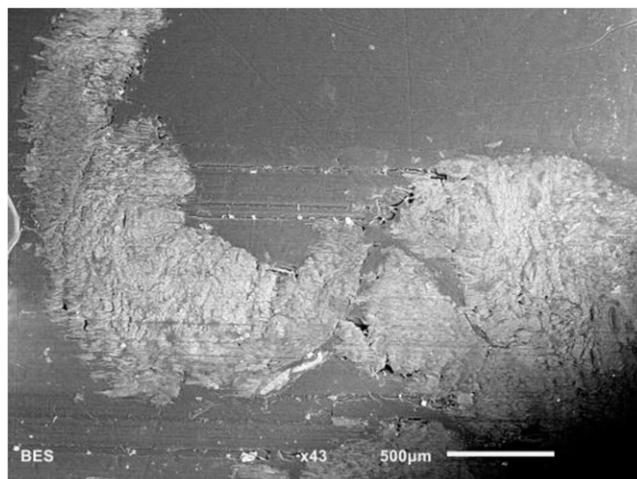


Figure 2.
SEM micrograph of the biopsy block areas that were used as controls: paraffin and tissue.

biofilms or pus in peri-implantitis in dogs.¹⁴ At the LM level, some tissues showed particles that appeared to be residual bone. These bone particles could be there as a result of rapid osteoclastic activity reported in peri-implantitis lesions¹⁵ or could have been removed from the bony lining of the lesion when the soft tissue biopsy was obtained. These bone fragments could correspond to the particles observed with the SEM/EDS with high content of Ca and P.

It has been argued by many that peri-implantitis is an inflammatory reaction initiated by bacteria; however, chronic inflammation can also be seen in foreign body responses without bacteria. In fact, some have suggested that osseointegration is a foreign body response to the implant, with a chronic inflammatory response, and that crestal BL around implants is not primarily related to biofilm-mediated infectious processes as in periodontitis.⁴

In this study, Ti found with EDS was confirmed to be surrounded by inflammatory cells under LM in seven of the 36 biopsies. Elemental concentrations of Ti ranged from 2% to 43% and varied in diameter from 9 to 54 µm.

How did the titanium get into the soft tissues? One possible mechanism is deposition of titanium due to friction against the bone at implant placement. However, a recent non-published study (Sathyanarayanan Sridhar, Department of Bioengineering, University of Texas at Dallas, Richardson, Texas; Thomas G. Wilson, Jr., Private practice of Periodontics, Dallas, Texas; Pilar Valderrama, Private practice of Periodontics, Dallas, Texas; Pilanda Watkins-Curry, Department of Chemistry, University of Texas at Dallas; Julia Y. Chan, Department of

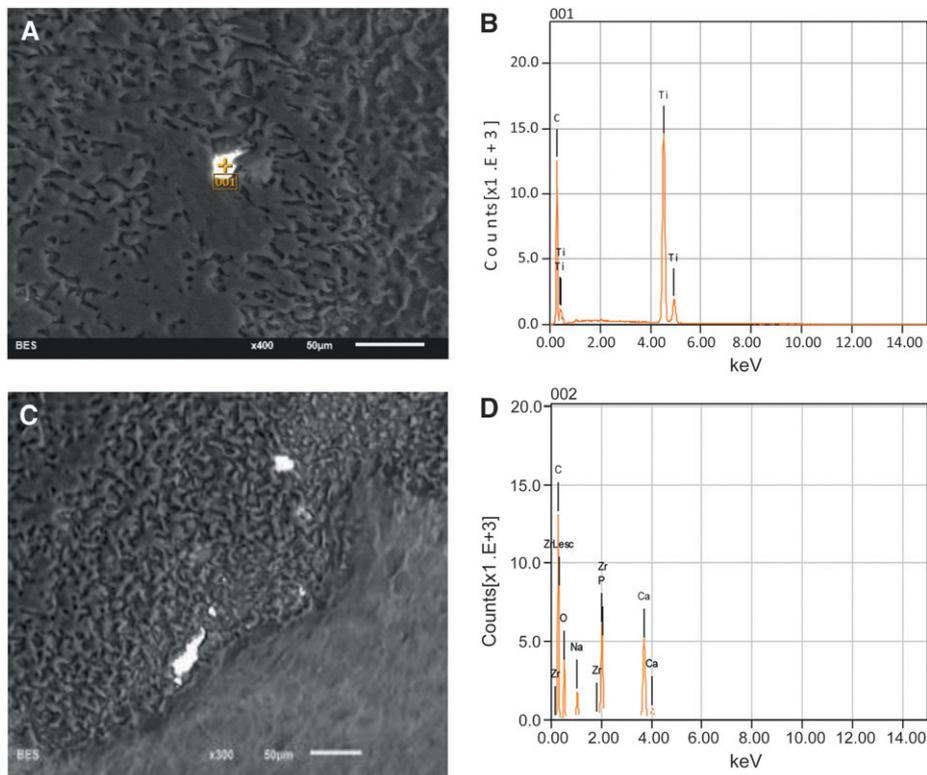


Figure 3.

A) SEM micrograph of a Ti particle. **B)** Spectrum demonstrating the elements present in the particle shown in panel A. **C)** SEM micrograph showing the contaminating particles containing Zr (white spots). **D)** Example of a spectrum demonstrating the elements present in the particles shown in panel C.

Chemistry, University of Texas at Dallas; Danieli C. Rodrigues, Department of Bioengineering, (University of Texas at Dallas; unpublished data) that used sawbone of various densities found no titanium deposition at implant insertion. Additionally, these particles could have come from restorative sources. The Ti ions and debris could also be a result of wear produced during debridement of implants at maintenance visits or previous surgical attempts to control the BL.^{16,17}

A third possibility is that these particles appear in the soft tissues as a result of corrosion, which triggers surface degradation and leaching of metal ions and debris. In the oral environment, the combination of an acidic (corrosive) medium and micromotion, resulting from occlusal forces, can lead to disruption of the oxide layer protecting the titanium surface (namely titanium oxide, TiO_2). A similar phenomenon has been previously observed around failing hip prostheses, in which the synergistic effects of micromotion and corrosion have been reported to cause failure¹⁸ and other related foreign body reactions.¹⁹ A previous retrospective study of failed dental implants due to peri-implantitis showed clear signs of corrosion on the rough and smooth interfaces of the implants. This suggests that corrosion can be con-

sidered a factor to explain the appearance of titanium particles in the tissues.²⁰

In vitro studies have shown that Ti ions can significantly decrease the viability of osteoblasts, osteoclasts, and epithelial cells.²¹ However, these do not always affect the expression of genes similarly, and osteoblasts can retain their normal function in some cases.²² On the other hand, bacterial endotoxins and host enzymes can adhere to Ti wear particles, which can accelerate inflammatory host responses and osteolysis.²³ Toll-like receptors (TLRs) present in the oral peri-implant tissues could contribute to the cellular interaction with Ti wear particles in the same way that aseptic loosening happens with orthopedic implants.²⁴

Higher numbers of T and B lymphocytes, higher values of microvessel density, increased expression of vascular endothelial growth factor, and high expression of matrix metalloproteinase (MMP)-8 and -9 have been observed in peri-implant soft tissues around titanium healing abutments.²⁵ These inflammatory cells and cytokines could be the normal response of the body during early healing around implants, but if there is persistent activation of the immune system, there is a potential risk for tissue breakdown around the implant.

How did cement become embedded in the peri-implant tissues? The material may have been introduced at cementation²⁶ or during attempts to remove excess cement at maintenance visits.²⁷ Using the dental endoscope, the authors have observed (TGW; unpublished data) that sonication results in deposition of small particles in the peri-implant tissues. In this study, several cases presented with foreign-body giant cells around the dental cement particles. At the LM level, these particles were surrounded by granulomatous infiltrate and bacterial colonies, suggesting that they induce inflammation and favor biofilm colonization and infection. There is evidence associating excess dental cement and peri-implant disease.⁶⁻⁸

Zirconium was found in some of the tissues using EDS/SEM (0.1% to 5.8% on average per biopsy). Zirconium found in the tissues could be part of the

zirconium dioxide used as radiopaque additives in dental cements and endodontic sealing materials. Barium and sulfur also found in these biopsies are commonly used for the same purpose in cements as barium sulfate (BaSO_4). It has been demonstrated in vitro that dental cements containing these opacifiers stimulate the release of pro-osteolytic tumor necrosis factor (TNF)- α and interleukin (IL)-6 from a monocytic cell line, in a dose-dependent fashion.²⁸ In vivo, these particles of cement appear to promote osteolysis at the bone-implant interface, and this effect is most marked when BaSO_4 is used as the radiopaque agent.²⁹ Zirconium could have also originated from zirconia abutments. One possible mechanism could be the “settling” of a zirconia abutment inside a titanium implant. Titanium implants connected with zirconia abutments have shown higher wear at the implant interface following cyclic loading compared with titanium abutments.³⁰ This could result in particles within the tissues. Furthermore, it could explain some cases in which there is a mismatch of materials, with the zirconia wearing the titanium of the implant internally/marginally, which can cause the abutment screw to loosen. Zirconia micro- and/or macrofractures may occur, releasing particles in the peri-implant soft tissues.³¹ Once in the peri-implant tissues, an inflammatory response may be initiated. Cultured macrophages in contact with commercially pure particles of zirconia have shown increased messenger RNA for TLRs 2, 3, 4, and 9 and their adaptors myeloid differentiation 88, Toll/IL-1R-domain-containing adaptor-inducing interferon- β , and nuclear factor- κB and increased production of TNF- α , IL-1 β , and IL-6.³² These findings suggest that peri-implantitis could be enhanced by the presence of excess dental cement.

CONCLUSIONS

The microscopic analysis of soft tissue biopsies taken from around implants with cemented restorations suffering from peri-implantitis revealed a mixture of subacute and chronic inflammation dominated by plasma cells.

Foreign bodies primarily consisting of titanium and dental cement were found to be associated with an inflammatory infiltrate in 34 of the 36 biopsies analyzed in this study. These initial findings argue for further research into the nature of peri-implantitis and the role of foreign bodies in this process.

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