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Histopathological observations of human periimplantitis lesions

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Abstract

Objective: The aim of the present study was to analyze some characteristics of advanced and progressive periimplantitis lesions in man.

Material and methods: Soft tissue biopsies were obtained from 12 implants in six patients. The implants had been in function between 4 and 21 years and were, with one exception, located in the maxilla. The radiographic examination performed prior to biopsy revealed that all sites exhibited advanced bone loss. Further, clinical signs of severe inflammation, such as suppuration, swelling and/or fistula formation were detected in the majority of sites and seven of the 12 implants were found to be mobile at biopsy. Each biopsy was following fixation embedded in epoxy resin and sections were prepared for histometric and morphometric analysis.

Results and conclusion: It was demonstrated (i) that all soft tissue units harbored large inflammatory cell infiltrates (ICT) that extended to a position apical of a pocket epithelium and (ii) that about 60% of the lesions were occupied by inflammatory cells, among which plasma cells dominated. Numerous amounts of PMN cells occurred not only in the pocket epithelium and adjacent connective tissue areas, but were also present in peri-vascular compartments in more central areas of the ICT.

Key words: biopsy, dental implants, inflammation, morphometry

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Biological complications that occur in implant therapy may compromise the quality as well as the quantity of soft and hard tissues surrounding the implant. Such complications include soft tissue inflammation, bone resorption and, eventually, the loss of the implant. In a recent systematic review, Berglundh et al. (2002) reported on the incidence of implant loss and different soft tissue complications including periimplantitis. Meta-analysis of 51 studies indicated that implant loss prior to functional loading occurred in about 2.5% of all implants placed, while about 2–5% of implants were lost during the first 5 years of function. Berglundh et al. (2002) further stated that biological complications were reported in only 40–60% of the studies evaluated and that only limited information was available regarding periimplantitis and resulting bone loss.

Periimplantitis was defined as a condition that includes ''inflammatory reactions in the periimplant tissues and loss of supporting bone around an implant in function'' (Albrektsson & Isidor 1994). While some reports on the incidence of periimplantitis exist, limited information is available regarding its clinical and radiographic characteristics. In addition, most information on hard and soft tissues of periimplantitis was obtained from experimental studies in dogs and monkeys (Lindhe et al. 1992, Lang et al. 1993, Schou et al. 1993, Marinello et al. 1995). In such experimental models, plaque formation was allowed and ligatures were placed in a submarginal position around the neck of implants. The ligatures were removed when the ensuing inflammatory response in the periimplant tissues had mediated advanced bone destruction and biopsies were subsequently obtained at different time intervals. The histological analysis of the biopsy material revealed the presence of large inflammatory lesions in the periimplant mucosa but also that these lesions extended to the alveolar bone. Lindhe et al. (1992) suggested that the periimplant tissues, in contrast to the periodontal tissues, are poorly organized to resolve progressive, plaque-associated lesions.

Histopathological characterization of periimplant tissues at failed implants in humans has documented the presence of inflammatory lesions in the periimplant mucosa (e.g. Sanz et al. 1991, Piattelli et al. 1998), while in other reports inflammatory cell infiltrates (ICT) were claimed to be virtually absent (Esposito et al. 2000). Further, histological analysis of periimplant tissues at retrieved implants have frequently been confined to the bone tissue, despite identified clinical symptoms of inflammation in the periimplant mucosa at the time point of implant removal (Sennerby et al. 1991, Albrektsson et al. 1993).

The aim of the present study was to further analyze the periimplantitis lesion

in man as it presents in biopsies obtained from implant sites exhibiting clinical signs of inflammation and progressive bone loss.

Material and Methods

Subjects and implants sites

The study protocol was approved by the Human Research Ethics Committee of Göteborg University. Soft tissue biopsies were obtained from 12 implant sites in six patients (Table 1). The implants had been in function between 4 and 21 years and were, with one exception, located in the maxilla. The clinical and radiographic examination performed prior to biopsy revealed that all sites exhibited advanced bone loss. Further, clinical signs of severe inflammation, such as suppuration, swelling and/or fistula formation were detected in the majority of sites (Figs. 1 and 2) and seven of the 12 implants were found to be mobile at biopsy.

For different reasons, such as implant mobility or extensive bone loss, some implants were scheduled for explantation. In such cases of implant failure, biopsy sampling was performed together with the removal of the implant (subject BS, SS, and GL; implant failure group), while in the remaining sites (subject SL, ES and BA; periimplantitis treatment group) the soft tissue biopsies were collected in conjunction with surgical treatment that included pocket elimination or regenerative procedures.

Biopsy sampling and histological processing

A soft tissue biopsy was obtained from either the mesial or the distal aspects of the implants in the periimplantitis treatment group. In the group of implant failures, the biopsy procedure included the dissection of a 4–5 mm wide soft tissue collar adjacent to the implant and the bone. This tissue was removed concomitant with the implant (Fig. 3). Each biopsy was placed in a fixative consisting a mixture of glutaraldehyde (5%) and formaldehyde (4%) buffered to pH 7.2 (Karnowski 1965). The implant was removed following fixation and the remaining soft tissue was divided into several units, each repre-

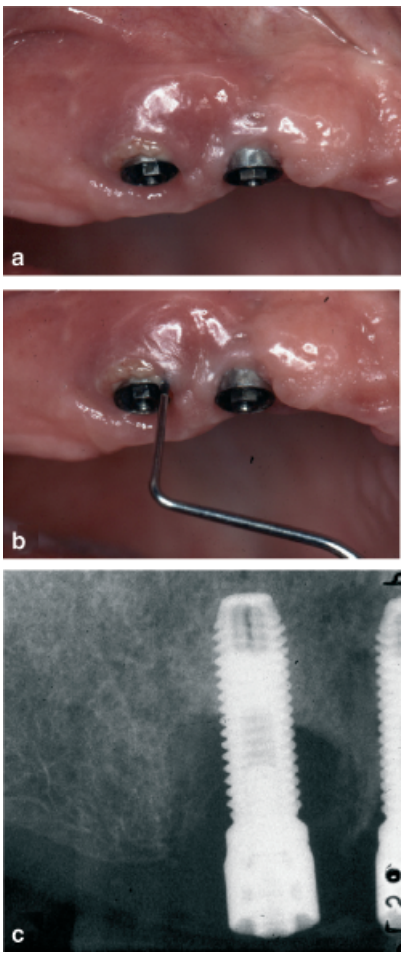

Fig. 1. Clinical symptoms of periimplantitis site R3 of subject BA. Note the swelling (a), the suppuration during probing (b) and the crater-shaped bone defect in the radiograph (c).

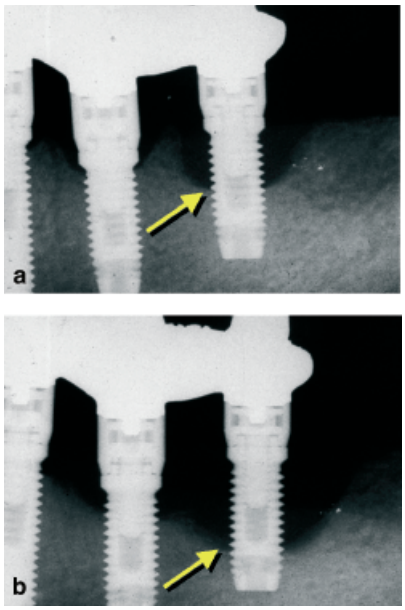

Fig. 2. Radiographs illustrating progressive bone loss at implant sites in subject ES. The radiograph in (b) was obtained one year later than in (a).

Table 1. Clinical data on subjects and implant sites

Subjects	Implant sites	Function time (years)	Biopsy sampling	Clinical features other than symptoms of soft tissue inflammation and excessive bone loss
BS (48 years)	maxilla; L2, L3	4	explantation + biopsy	implant mobility at explantation
SS (59 years)	maxilla; R1, L1	9	explantation + biopsy	suppuration, fistula, implant mobility at explantation
GL (74 years)	maxilla; R3, L2, L3	21	explantation + biopsy	implant mobility at explantation non-mobile implant
	maxilla; R1, L1	21	explantation + biopsy	non-mobile implant
SL (73years)	maxilla; L1	7	biopsy during surgical therapy	swelling, abscess formation
ES (65years)	mandible; L2	6	biopsy during surgical therapy	swelling, suppuration, bleeding on probing, non-mobile implant
BA (70 years)	maxilla; R3	7	biopsy during surgical therapy	swelling, suppuration, abscess formation, bleeding on probing, non-mobile implant

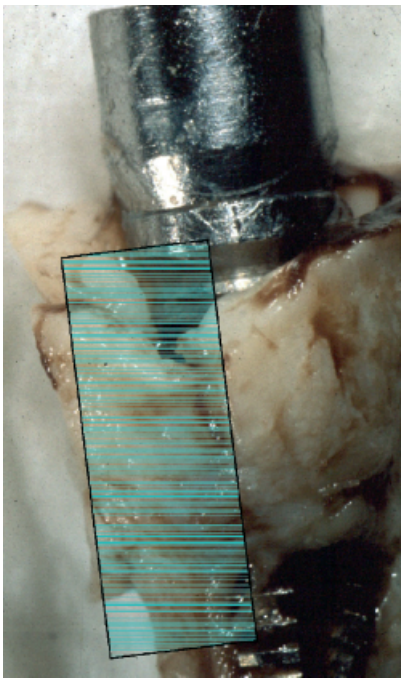

Fig. 3. Soft tissue collar adjacent to an explanted implant. The outlined area depicts section region illustrated in Fig. 4.

senting various aspects of the implants (i.e. mesial, distal, buccal or lingual). Following dehydration and secondary fixation in OsO_4 the tissue units were embedded in epoxy resin (EPON® 812 substitute, Fluka GmbH, Buchs, Switzerland) (Schroeder, 1969). Sections were produced from each unit with the microtome set at 3 μm and stained in periodic acid–Schiff (PAS) and toluidine blue (Schroeder, 1969). Three sections from each tissue unit, i.e. 12 sections in all from each biopsy, were selected for histometric and morphometric analysis.

Histological analysis

The following landmarks were identified and used for the linear measurements; the marginal portion of the periimplant mucosa (PM), the apical termination of the junctional/pocket epithelium (aJE), the coronal (cICT) and the apical level of the infiltrated connective tissue (aICT). The width of the ICT was assessed at 3 levels and the size of the lesion was determined using a mouse cursor at a magnification of $\times$ 100.

Morphometric measurements were performed with a computerized image analysis system using a Leitz DM-RBE microscope (Leica, Wetzlar, Germany) equipped with a Leica Q-500 MC® image system at a magnification of $\times$ 1000. A point counting procedure (Schroeder & Münzel-Pedrazzoli 1973) was used to describe the percentage of the ICT occupied by collagen (Co), vessels (V), fibroblasts (Fi), macrophages (Mø), lymphocytes (Ly), plasma cells (Pc), polymorphonuclear cells (PMN) and residual tissue (R). Mean values and standard deviations for each variable were calculated for each implant unit and a group mean was calculated for all implants.

Results

Gross histological observations and histometric measurements

The lesions that were included in biopsies from the implant failure and periimplantitis treatment groups (including mobile and non-mobile implants at removal) had similar histopathological characteristics (Fig. 4). Thus, in all specimens a large ICT occupied almost the entire connective tissue portion. The size of this varied between 0.84 and 8.50 mm^2 and was on the average 3.61 $\pm$ 2.49 mm^2 (Table 2). A keratinized oral epithelium outlined the marginal portion of the biopsy and was continuous with a pocket epithelium. The marginal aspect of the pocket epithelium was wide and exhibited rete ridges that projected into the infiltrated connective tissue. The apical portion of the pocket epithelium, however, was frequently thin and ulcerated. In most sections the inflammatory cell infiltrate reached a position that was apical of the pocket epithelium (5.93 $\pm$ 1.37 versus 5.27 $\pm$ 2.08 mm; Table 2). The lateral dimension of the lesion, i.e. the width of the ICT (wICT; Table 2) was on the average 0.97 $\pm$ 0.55 mm.

The composition of the ICT was not uniform with respect to densities of collagen, vascular structures and inflammatory cells in different compartments of the lesion. Thus, in the marginal portion of the ICT comparatively large numbers of collagen fibers occurred together with numerous lymphocytes and plasma cells (Figs. 5 and 6). Few, but large vascular units occupied the central part of this marginal portion of the lesion, while numerous small vessels were present in an area lateral to the pocket epithelium. In the central and apical portions of the ICT, collagen fibers were few or in some specimens

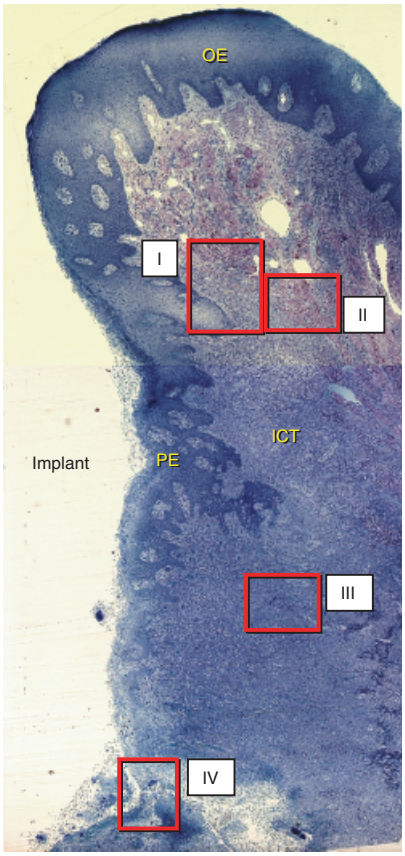

Fig. 4. Cross-section of periimplant mucosa at explanted implant shown in Fig. 3. PAS and tolouidine blue. Original magnification $\times$ 25. OE: oral epithelium, PE: pocket epithelium, ICT: infiltrated connective tissue. ''Implant'' indicates pocket area towards the implant. Outlined areas I, II, III and IV indicate Figs. 5–8.

virtually absent, while inflammatory cells and vascular units dominated the lesion. Plasma cells occupied a large area of this ICT portion and PMN cells, mostly neutrophilic granulocytes, occurred in larger numbers not only in the pocket epithelium and associated connective tissue areas but also in perivascular compartments distant from the implant surface (Fig. 7).

The results from the morphometric assessments of the composition of the inflammatory cell infiltrate for each subject and site are reported in Table 3. Plasma cells outnumbered other connective tissue constituents and occupied on the average 38.8 $\pm$ 5.1% (range: 29.2–44.8%) of the ICT volume. The proportions of collagen and vascular structures were 10.0 $\pm$ 3.6% and 9.3 $\pm$ 3.5%, respectively, while the tissue fraction of the remaining cell groups varied between 4.2% and 6.6%.

Table 2. Results from the histometric measurements

Subject	Site	Size ICT (mm^2)	PM–aJE (mm)	PM–cICT (mm)	PM–aICT (mm)	wICT (mm)
BS	L2	0.84	3.89	2.13	4.52	0.34
	L3	2.71	3.50	1.76	6.25	0.96
SS	R1	1.68	7.28	2.80	7.80	0.53
	L1	3.98	8.56	6.13	8.53	0.40
GL	L1	2.59	4.78	2.23	5.95	0.95
	L2	8.50	–	–	–	1.56
	L3	3.46	4.71	1.57	4.85	1.22
	R1	8.17	3.97	1.40	6.03	2.04
	R3	2.50	6.10	1.24	4.72	0.77
SL	L1	1.27	7.89	3.00	6.75	0.28
ES	L2	2.63	5.63	2.22	5.62	0.96
BA	R3	4.87	1.62	0.56	4.31	1.54
Group mean		3.61 ± 2.49	5.27 ± 2.08	2.28 ± 1.46	5.93 ± 1.37	0.97 ± 0.55

Mean values for each site and group mean ± SD.
ICT, inflammatory cell infiltrate; PM, periimplant mucosa, aJE, apical termination of the junctional/pocket epithelium; cICT, coronal level of ICT; aICT, apical level of ICT; wICT, width of the ICT.

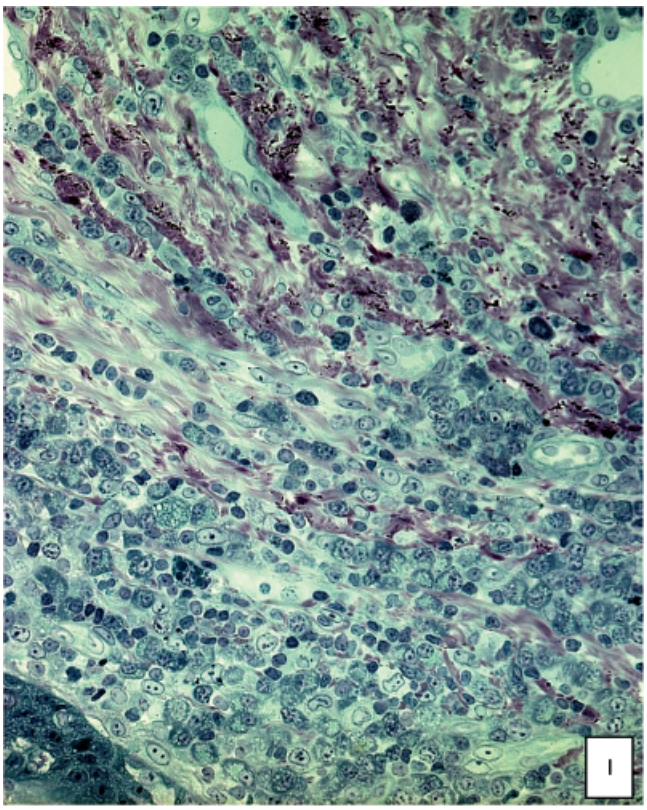

Fig. 5. Area I illustrated in Fig. 4. Collagen fibers intermingled with numerous lymphocytes and plasma cells. PAS and tolouidine blue. Original magnification × 400.

The most apical portion of the ''pocket area'' of the soft tissue was comprised of an uncovered and severely infiltrated connective tissue. In such areas and also in more marginally located ulcerated portions of the pocket epithelium deposits of microbial plaque were frequently observed (Fig. 4, area IV). Large bacteria resided in clusters in apparent contact with the connective tissue (Fig. 8).

Discussion

In the present study histopathological characteristics of periimplantitis lesions were analyzed. It was demonstrated (i) that all soft tissue units harbored large ICT that extended to a position apical of a pocket epithelium and (ii) that about 60% of the lesions were occupied by inflammatory cells, among which plasma cells dominated. Numerous PMN cells occurred not only in the pocket epithelium and associated connective tissue areas but also in perivascular compartments in more central areas of the ICT.

The finding that an inflammatory infiltrate occupied a large area of the periimplant soft tissue at sites with periimplantitis is in accordance with previous observations. Sanz et al. (1991) analyzed soft tissue biopsies from six patients with periimplantitis and reported that about 65% of the connective tissue portion was occupied by an inflammatory lesion. The authors further reported that ''the biopsies showed marked inflammatory changes both in epithelium and connective tissue'' and that plasma cells and other mononuclear cells dominated among the inflammatory cells. Piattelli et al. (1998) described some histological characteristics of periimplant tissues at 230 implants that were retrieved during an 8-year period. It was reported that at sites where implants were removed due to periimplantitis, an inflammatory lesion that included macrophages, lymphocytes and plasma cells, was found to occupy the connective of the periimplant mucosa. Esposito et al. (1997) in a study on immunohistochemical characteristics of soft tissues surrounding failing implants reported that the marginal portion of the specimens was ''characterized by an intense inflammatory and immunological response''.

On the other hand, Esposito et al. (2000) in a study on ''histopathological observations on late implant failures'' reported that only moderate inflammatory infiltrates were found in the connective tissue within the marginal portion of the periimplant tissues. In this context it should be realized that in 9 out of 10 implant sites examined by Esposito et al. (2000) there were no clinical signs of inflammation, i.e. redness, swelling or suppuration. Thus, the term ''implant failure'' may not describe a periimplantitis condition similar to the one examined in the current study.

The implant sites examined in the present sample included only units with obvious clinical signs of soft tissue inflammation and excessive bone loss.

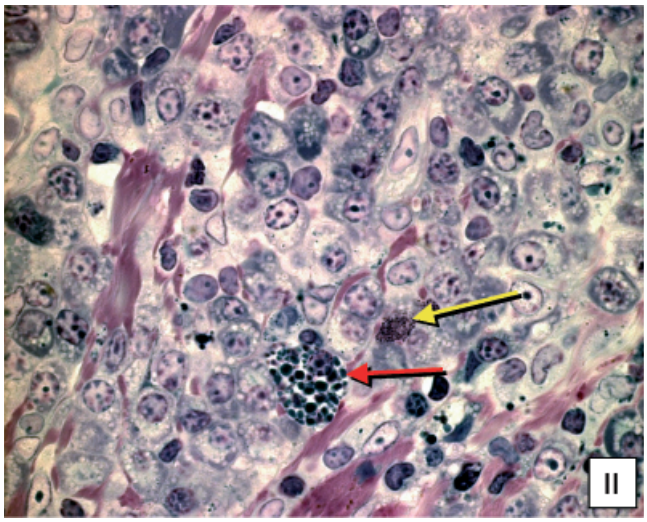

Fig. 6. Area II described in Fig. 4. Large numbers of plasma cells. A large macrophage (red arrow) adjacent to a mast-cell (yellow arrow). PAS and tolouidine blue. Original magnification × 1000.

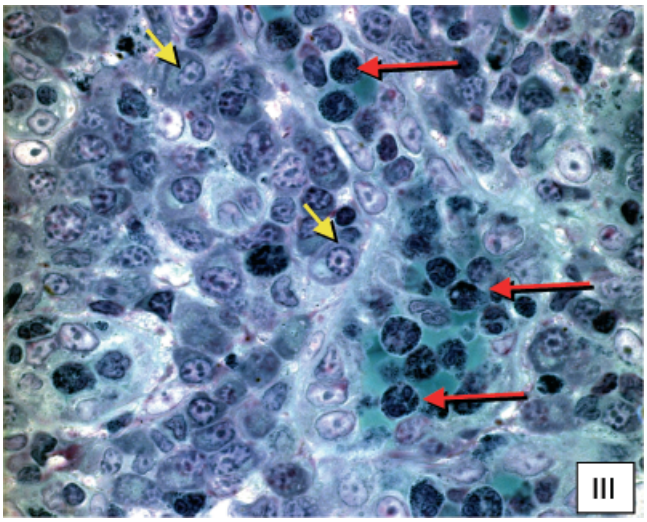

Fig. 7. Area III depicted in Fig. 4. Vast numbers of plasma cells (yellow arrows) and numerous PMN cells (red arrows). PMN cells occur within vessels and in perivascular compartments. PAS and tolouidine blue. Original magnification × 1000.

Other, more severe symptoms of inflammation, such as suppuration and fistula and abscess formation varied between subjects and sites. The histological examination, however, revealed that large inflammatory infiltrates were found in all specimens, i.e. also in biopsies from sites where the clinical symptoms of inflammation were less dramatic. It may therefore be suggested that the presence of clinical signs of inflammation, rather than the degree or severity of symptoms, together with radiographic signs of bone loss may serve as indicators for periimplantitis.

In the present study seven out of the 12 implants included exhibited mobility at the time of biopsy/explantation. At such sites (subject BS; L2, L3, subject SS; R1, L1 and subject GL; L1, L2, L3: Table 1) large inflammatory lesions were detected. The size of the ICT at mobile implant sites was on the average 3.39 mm^2, while the corresponding figure at sites with non-mobile implants was 3.88 mm^2 (data not shown). This indicates that the presence of inflammatory lesions in the periimplant soft tissues may not have been influenced by implant mobility. This observation is in contrast to findings reported by Piattelli et al. (1998). In their study particular attention was paid to a group of implants that were removed due to mobility. The authors reported that such implants were surrounded by a ''dense fibrous connective tissue'' and that no inflammatory infiltrate was present. Furthermore, in the study on late implant failures by Esposito et al. (2000) referred to above, the nine out of 10 implant sites that exhibited implant mobility were also apparently

Table 3. Results from the morphometric measurements

Subject	Site	Co	V	Fi	Mø	Ly	Pc	PMN	R
BS	L2	8.7	10.3	6.7	8.3	9.0	35.6	5.2	16.2
	L3	5.9	8.1	6.0	10.5	8.8	39.6	5.8	15.3
SS	R1	10.4	5.1	2.6	5.0	5.8	43.8	2.4	24.9
	L1	18.0	14.1	9.2	0.0	8.1	36.3	1.8	12.5
GL	L1	6.9	12.8	6.2	2.7	7.4	42.2	1.7	20.3
	L2	10.3	11.6	4.3	6.1	7.3	44.6	2.6	13.2
	L3	16.0	11.0	7.3	1.0	5.0	29.2	10.0	20.2
	R1	9.7	7.2	5.1	7.8	4.5	41.5	4.1	19.9
	R3	7.9	9.8	5.6	3.1	6.6	44.8	2.3	20.1
SL	L1	7.4	2.1	4.7	8.4	5.3	31.1	5.8	35.3
ES	L2	8.9	7.2	5.6	0.7	3.4	40.6	3.9	29.7
BA	R3	9.6	12.8	4.9	9.0	8.3	36.8	4.4	16.0
Group mean		10.0 ± 3.6	9.3 ± 3.5	5.7 ± 1.6	5.2 ± 3.6	6.6 ± 1.8	38.8 ± 5.1	4.2 ± 2.4	20.3 ± 6.8

% of the ICT occupied by collagen (Co), vascular structures (V), fibroblasts (Fi), macrophages (Mø), lymphocytes (Ly), plasma cells (Pc), polymorphonuclear cells (PMN) and residual tissue (R). Mean values for each site and group mean ± SD.

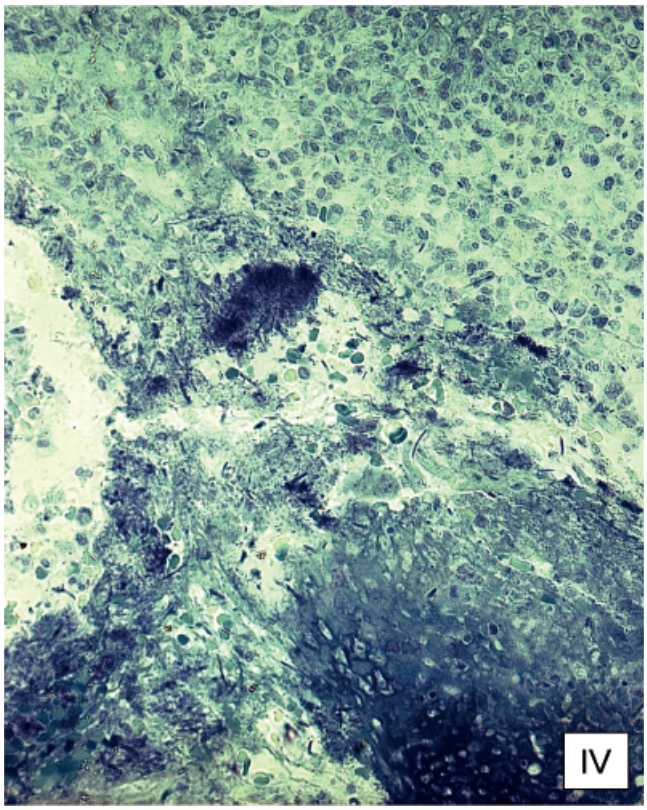

Fig. 8. Area IV showed in Fig. 4. Apical portion of the ''pocket area'' of the soft tissue. Note clusters of bacteria immediately lateral to the connective tissue between ulcerated portions of the pocket epithelium. PAS and tolouidine blue. Original magnification × 1000.

devoid of clinical and histological symptoms of inflammation. The reason behind the observed differences between the studies referred to and the current biopsy material may be related to apparent variations in causes for failures.

Gualini & Berglundh (2003) described some immunohistochemical characteristics of periimplant mucositis and periimplantitis lesions in biopsies obtained from 16 subjects. It was reported that periimplantitis lesions were considerably larger and contained significantly greater proportions of B cells and elastase positive cells (indicating PMN cells) than mucositis lesions. Gualini & Berglundh (2003) further reported that periimplantitis sites, in contrast to sites with mucositis, consistently displayed elastase positive cells in the central portions of the infiltrate. The finding that elastase positive cells, i.e. PMN cells, were detected in central areas of periimplantitis lesions is in agreement with observations made in the current study and indicates that effector systems of the host response, such as phagocytosis, are active in periimplantitis.

The finding that PMN cells, preferably neutrophil granulocytes, occurred in large numbers in different compartments of the lesions may indicate an enhanced PMN cell activity at sites with periimplantitis. This interpretation is consistent with results from studies on crevicular fluid at implants with periimplantitis. Thus, Hultin et al. (2002) analyzed the composition of the crevicular fluid at implants in 17 patients with periimplantitis and in 19 patients with ''stable marginal tissue conditions''. It was reported that sites with periimplantitis had higher elastase activity and concentration of lactoferrin than control sites. In a similar study, Plagnat et al. (2002) collected periimplant crevicular fluid (PICF) from 11 sites with clinical and radiographic signs of periimplantitis in eight subjects and from 11 implant units without symptoms of periimplantitis in 7 subjects. The authors reported that levels of alkaline phosphatase, elastase and α2-macroglobulin in PICF were significantly higher at diseased than at clinically healthy sites, and that the levels of the mediators correlated with clinical symptoms.

Acknowledgment

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