The Importance of Histopathological Diagnosis in the Management of Lesions Presenting as Peri-Implantitis

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ABSTRACT

Purpose: This study is a histopathological analysis of lesions clinically diagnosed as peri-implantitis (PI).

Materials and Methods: This retrospective study included microscopic findings in 117 peri-implant biopsies from lesions presenting clinical and radiographic features of peri-implantitis.

Results: The study group included 117 biopsies, mean age 55.2 years; 60.9% of biopsies were from failing implants during explantation, the remaining from surviving implants. All cases showed microscopic evidence for inflammation; however, although 41% exhibited only nonspecific inflammation, 29.9% exhibited actinomyces-related inflammation, 18.8% pyogenic granuloma (PG), and 10.3% giant cell granuloma (GCG). Differences in implant failure rates between pathological diagnostic groups were not statistically significant. Lesions with simple inflammation could not be distinguished clinically or radiographically from the potentially destructive lesions.

Conclusions: There were no clinical features which could distinguish PI with simple inflammation from potentially destructive lesions mimicking PI, such as GCG, PG, and actinomycosis. However, to control GCG and PG surgical procedures would be recommended, actinomycosis would indicate specific antibiotics, whereas in nonspecific inflammation, these measures may not be indicated. The results of the present study provide evidence for the importance of early microscopic examination of lesions presenting clinically as peri-implantitis, a step toward more accurate diagnosis and improved treatment of PI and lesions mimicking PI.

KEY WORDS: actinomyces, giant-cell-granuloma, inflammation, peri-implantitis

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Peri-implantitis (PI) is an inflammatory disease of tissues surrounding dental implants. The consensus paper from 2008 defines PI as an inflammatory lesion that affects the mucosa and the supporting bone, whereas peri-implant mucositis (PIM) affects only gingival mucosa.[1] PI presents clinically as erythema and swelling of the soft tissue, with bleeding on probing, often associated with suppuration and pocket formation and always presents loss of supporting marginal bone. In PIM, there is no bone loss, but all other signs mentioned for PI may be present .[1] PI is considered a multifactorial condition attributed to bacterial infections, poor oral hygiene, surgical trauma, genetic predisposition, implant surface characteristics, faulty or incorrect prosthetic design, occlusal overload, and/or improper surgical placement.[1–5]

There are no universally accepted protocols for the treatment of either PIM or PI;[6] moreover, in the majority of cases, the peri-implant tissue removed during treatment is not routinely submitted for histopathological examination. There is a very sparse information in the literature on the microscopic findings in PI; a review published in 2011 identified only four articles (printed 1991–2004) describing histopathological findings in a total of 35 human cases of PI.[7]

There are several pathological entities which mimic PI when they occur around implants, entities with distinct microscopic characteristics, as well as a locally destructive behavior. These include mainly giant cell granuloma (GCG) and pyogenic granuloma (PG) and rarely peri-implant malignancy, primary or metastatic.

There are more than 18 articles in the literature describing peri-implant malignancy,[8–11] 12 reported cases of peri-implant GCG,[12–19] and only two cases of PG around implants.[20,21] The majority of these lesions exhibit clinical characteristics which are consistent with PI; however, they do not behave like conventional PI and would not respond as expected to treatment modalities for conventional PI (debridement, improved hygiene, chlorhexidine rinses, short-term antibiotics, etc.)[6] Biopsy and histopathological evaluation are essential for correct diagnosis, identification of cases which mimic conventional PI, and optimization of treatment.

The objectives of the present study were to evaluate histopathological findings of cases clinically diagnosed as PI or PIM and to investigate the frequency of lesions clinically mimicking PI.

METHODS

The study was conducted as a retrospective study based on archival biopsy material submitted for analysis between 1999 and 2011. The study group included peri-implant biopsies taken from lesions diagnosed clinically as PI or PIM according to widely accepted criteria.[1] Lesions presenting erythema, swelling, bleeding on probing, with or without suppuration but had no bone loss were diagnosed as PIM; lesions presenting erythema, swelling, bleeding on probing, pocket formation with evidence of bone loss of at least 2 mm were diagnosed as PI.

The clinical status of the implants from which the biopsies were submitted was divided to two subgroups: failing implants when clinical signs of PI were present and explanation had been performed at the time the biopsy were submitted; surviving implants when signs of PIM or PI were present but at the time the biopsy was taken were not explanted but continued to be treated with various modalities. There were no uniform predetermined criteria set, as this was a retrospective analysis with many contributing dentists; the classification as failing or surviving was based on the information provided, if the biopsy material submitted was harvested during explanation procedures or from the mucosa around implants which had not been removed.

Tissues removed during these surgical procedures were submitted for microscopic analysis. The tissues were formalin fixed and paraffin embedded. Five micron-thick sections were routinely stained with hematoxylin and eosin (H&E). Periodic acid Schiff (PAS; PAS kit, Sigma-Aldrich, St. Louis, MO, USA) and gram stains were added when bacterial colonies suspected as actinomyces were observed in the H&E sections. Pathological analysis was performed by two experienced oral pathology specialists (I.K., A.H.) in a blinded fashion.

Due to the retrospective nature of this study, it was granted an exemption in writing by the University of Tel-Aviv and Tel-Aviv Sourasky Medical Center IRB.

SPSS® V.17 software (SPSS, Chicago, IL, USA) was used for statistical analysis. Descriptive methods have been applied as well as the Pearson chi-square test.

RESULTS

Study Group (PIM and PI)

A total of 117 biopsies from 86 patients (37 men and 49 women) were included in the analysis. The mean age was 55.2 years (range 21–78 years). In 31 patients, tissue from more than one implant was submitted for analysis, either concomitantly or at different occasions during the study period (repeated biopsies from the same location were not included).

The implants from which biopsies were obtained were located in the maxilla in 55.6% and in the mandible in 44.4%, (details in Figure 1).

Information allowing classification of the implant status at the time of biopsy was available for 64 biopsies. Of these, two (3.1%) showed only PIM, and 23 (35.9%) cases with clinical PI were classified as surviving, whereas 39 (60.9%) were classified as failing implants and were explanted at the same time the biopsy was obtained.

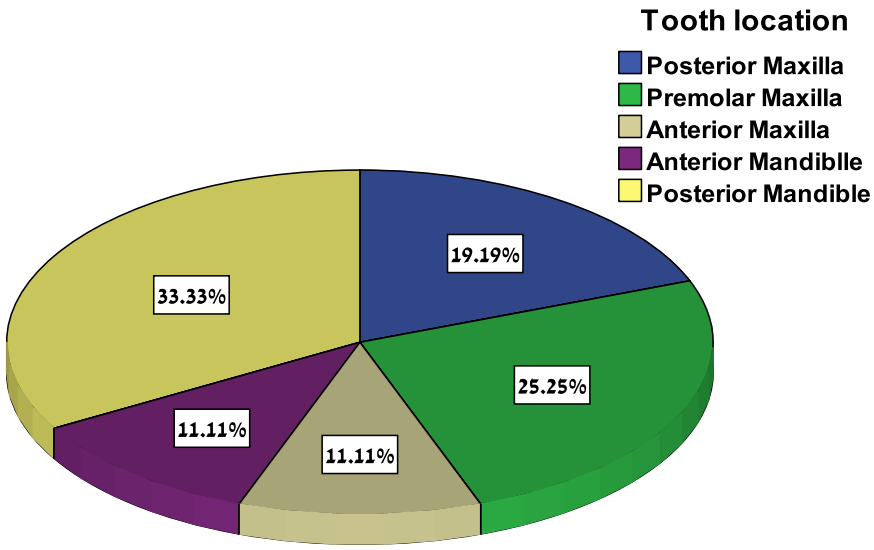

Figure 1 The location of the implants included in the study.

The implant age (time from implantation) at the time of the biopsy was known in 59 cases; ranging between 2 and 241 months, the mean implant age was 7.0 years (84.2 months).

The single case biopsied at 2 months did not fail, but exhibited signs of PIM, all the remaining cases, were late events.

Histopathological Diagnosis

Forty-eight (41%) biopsies were diagnosed as various nonspecific inflammatory reactions (Figure 2C) Actinomyces colonies surrounded by inflammation were found in 35 cases (29.9%) (Figure 3, C and D). The diagnosis of actinomyces-related inflammation was supported in all cases by the presence of typical morphology of the filamentous bacterial colonies, with variations in staining between the periphery and the center, and positive staining with both PAS and gram stains (Figure 3D). In addition, the presence of an inflammatory reaction bordering the bacterial colonies was considered mandatory for the diagnosis, thus ruling-out "floaters" that may have been innocent bystanders.

In 22 (18.8%) biopsies, the diagnosis was PG, and in 12 (10.3%), GCG (Figure 4). In 10 (8.5%) cases, foreign material with foreign body reaction was focally present. Comparison of the rate of implant failure between the different histopathological diagnostic groups found no significant differences.

For comparison, a group of 106 gingival biopsies (unrelated to implants) taken from lesions presenting with clinical characteristics which can also be found in PI (swelling, eryhtema, bleeding, or suppuration) was retrieved from the archives (2005–2011). In this group, 35 (33%) cases were diagnosed as PG, 11 (10.4%) were GCG, nine (8.5%) were nonspecific inflammation, and three (2.8%) were actinomyces-related inflammation.

Actinomyces-related inflammation was significantly more prevalent in the peri-implant group than in the gingival biopsies (29.9% vs 2.8%, $p < .01$), whereas for GCG and PG, there were no significant differences in frequency between the study group and the biopsies from lesions unrelated with implants. Biopsies specifically taken from lesions of periodontitis were not found in the archives.

DISCUSSION

PI and PIM are considered inflammatory diseases, resembling (but not identical with) periodontitis and gingivitis, respectively. As in the majority of cases the peri-implant tissue removed during treatment (such as during debridement) is not submitted for histopathological analysis, there is little information in the literature on the spectrum of microscopic findings in these lesions. The findings of the present study suggest that one-third of the cases clinically diagnosed as PI were found to be either PG or peripheral giant cell granuloma (PGCG). Both PG and GCG are reactive lesions, and although obviously benign, they have the highest frequency of destructive behavior among the reactive gingival lesions. In oral PG in general, a global recurrence

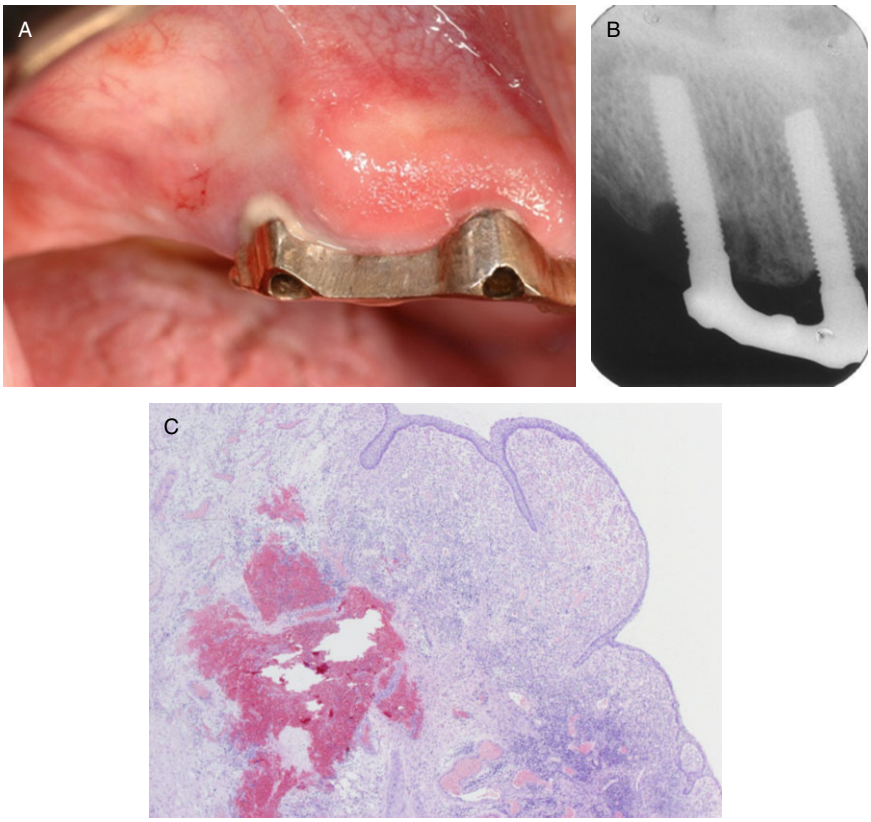

Figure 2 *A*, Clinical presentation of swelling, erythema, and suppuration around maxillary implants. *B*, Radiograph showing significant cervical bone loss. *C*, The microscopic features include vascular fibro-epithelial hyperplasia, and a dense inflammatory infiltrate (hematoxylin and eosin [H&E], original magnification ×40).

rate of 17% has been reported after conservative treatment, with a significantly higher rate in gingival lesions.[22] It has been demonstrated that PGCG can grow to sizes of up to 5 to 6 cm in diameter, with a recurrence rate of 10 to 15% after treatment.[23,24] PGCG has the highest rate of bone resorption among reactive gingival lesions, also a sign of its potentially destructive biological behavior.[22] PG and PGCG around implants have been rarely described in the literature; there are only two case reports of PG,[20,21] and only 12 cases of peri-implant GCG,[12–19] three of which have been previously reported from Tel-Aviv University and are included in the present study as well. The prevalence of peri-implant GCG was found in similar frequencies in both study and control groups. Analysis of the cases of GCG around implants (those from the literature and four new cases in the present series) indicates that they have a high tendency to recur after treatment, often several times, leading to implant failure in most cases.[12–19] Early microscopic diagnosis of GCG should lead to a more appropriate initial treatment and potentially improve outcome.

PG around implants was found to be less frequent than in nonimplant-related gingival biopsies (18.8% vs 33%); nevertheless, it is obviously not as rare as one would expect from only two previous case reports in the literature.[20,21] In a similar fashion to GCG, PG has a relatively high recurrence rate after conservative treatment, which may lead to bone loss and compromise implant survival. In order to control the disease in cases of peri-implant PG and GCG, meticulous surgical treatment is required. The patient would most probably not benefit from the essentially conservative treatment, which may be effective in conventional PI but not in GCG or PG mimicking PI. If biopsy material is not submitted, correct diagnosis could be delayed or completely missed, with a high probability of unwanted outcome.

Almost one-third of the cases exhibited bacterial colonies of actinomyces within the peri-implant tissue, as well as a dense inflammatory reaction. Actinomyces-related inflammation was 10 times more prevalent in the study group than in the control gingival biopsies. Actinomyces is filamentous anaerobic bacteria which

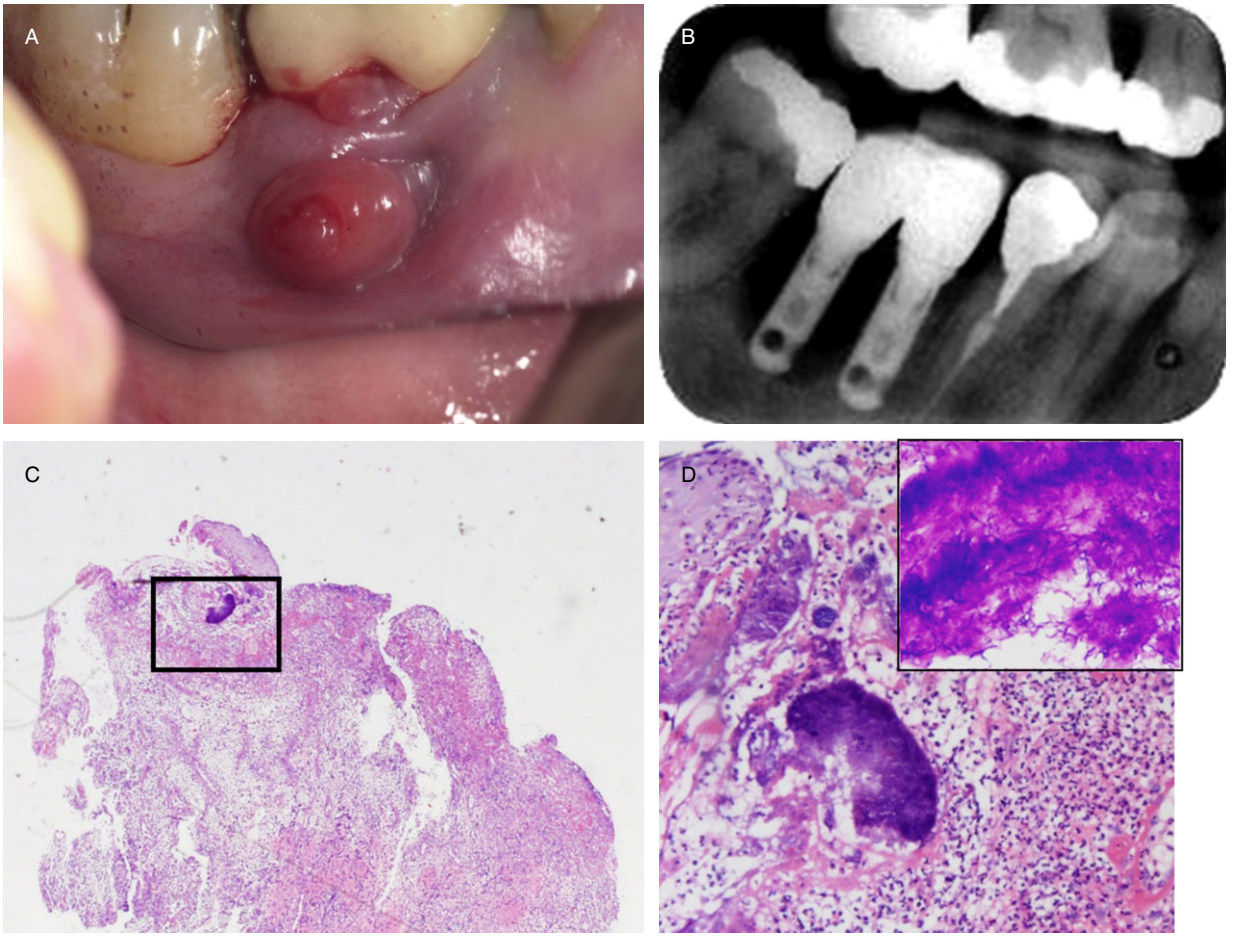

Figure 3 *A*, Clinical presentation of an erythematous exophytic mass adjacent to mandibular implants. *B*, Radiograph demonstrates severe bone loss. *C* and *D*, At low magnification, the micrograph exhibits an ulcerated polypoid mass, composed of loose vascular connective tissue (hematoxylin and eosin [H&E], original magnification ×20). The square surrounds a densely packed colony of microorganisms, surrounded by an acute inflammatory infiltrates (H&E, original magnification ×200). Gram stain demonstrates the thin filamentous features typical for actinomyces; periodic acid Schiff was also positive (Gram, ×400).

tends to aggregate in large compact colonies known as "sulphur granules," with an affinity for bone.[25] Actionomyces species are not considered primary periodontal pathogens as they have been isolated from normal oral flora, periodontal pockets, and around dental implants.[26,27] However, they can become pathogenic when the mucosal barrier is breached, allowing access to the submucosa or bone. Inflamed periodontal or peri-implant tissue, often ulcerated (Figure 5), may provide a path of entry for the bacteria. Infection with actinomyces may develop into cervico-facial actinomycosis, a destructive disease of soft tissue and/or jawbones, which requires prolonged antibiotic treatment.[28] None of the cases in the study developed this complication. Other less aggressive forms of actinomycosis, such as peri-apical actinomycosis, have also been described,[29] and there seems to be an important role for actinomyces species in the pathogenesis of bisphosphonate-related osteonecrosis of the jaws.[30,31] Except for one case report of the association of actinomyces with a failing implant, actinomyces has never been described in PI.[32] The exact role of actinomyces in the pathogenesis of PI and implant failure cannot be concluded from the present study; however, the presence of actinomyces colonies in a relative high proportions of the peri-implant tissues, which had not been recognized in the past, may point to a close relationship, either as a direct cause or as a secondary or contributing factor. As the cases with actinomyces mimic conventional PI clinically and radiographically (Figures 2 and 3), only routine biopsy of PI would reveal the presence of these bacteria within the tissue and allow for appropriate treatment intervention. Because in most cases the lesions included in the study were late events, with a mean implant age of 7 years, one

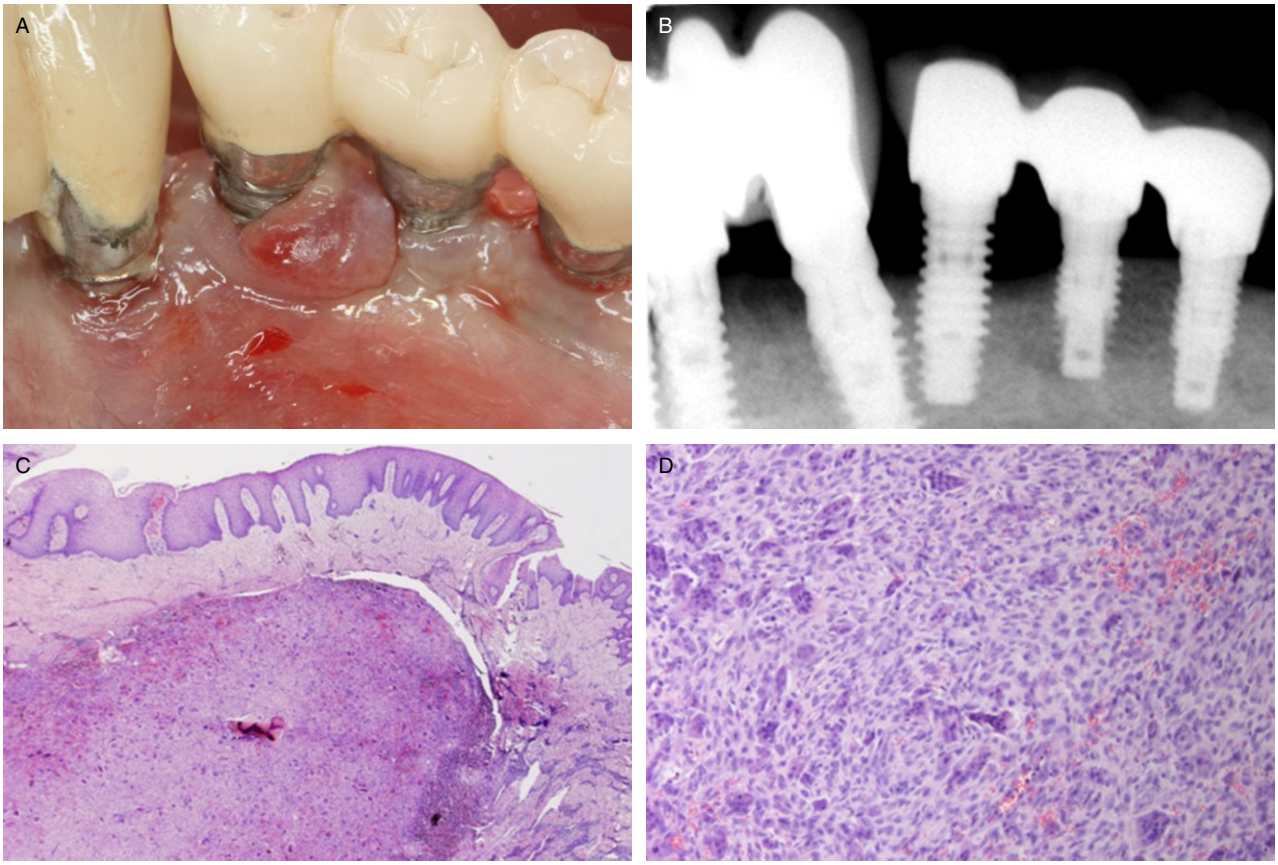

Figure 4 *A*, Clinical presentation of swelling, erythema, and partial exposure around left mandibular implants. *B*, Radiograph showing alveolar bone loss. *C* and *D*, Microscopic slide at low magnification showing a cellular and vascular submucosal mass, which at higher magnification is composed of multinucleated giant cells in a cellular matrix, features consistent with giant cell granuloma (hematoxylin and eosin [H&E], original magnifications ×40 and ×200, respectively).

can assume that actinomyces-related inflammation may also be a late event in PI.

Although peri-implant malignancy has not been identified in the present study, there are over 35 reported cases of peri-implant malignancy in the literature (mainly primary malignancy), which in the majority of cases also mimic PI.[8–11,33] Delayed diagnosis in these cases may have more severe implications than just implant loss, stressing the need for microscopic evaluation.

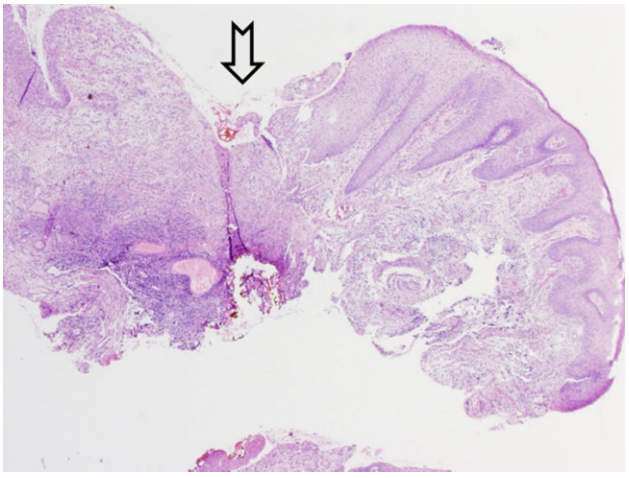

Figure 5 Micrograph showing inflammatory fibro-epithelial hyperplasia with central ulceration (*arrow*) (hematoxylin and eosin [H&E], original magnifications ×40).

Analysis of the frequency of implant failure between the various diagnostic groups in this study failed to find any significant differences. However, being a retrospective study, there is a possibility of bias in the cases submitted for biopsy; submitted cases may have presented with more severe clinical symptoms, may not have responded as expected to conventional treatment,or progressed more rapidly. These possibilities have been impossible to either confirm or reject based on the data available for this study.

There are obviously inherent limitations to retrospective studies; however, there are also benefits, such as the large number of cases available for analysis over a 12-year period, larger than any previous report on this subject in the literature.

Investigation of details such as implant type, depth of pockets, quantification of bone loss, medical, or lifestyle-contributing factors was beyond the scope of the present study as this has been thoroughly investigated in many previous works. However, regardless of the particular etiological factors, the role of biopsy and histopathological diagnosis in management of PI and lesions mimicking PI has not been addressed before.

The results of the present study provide evidence for the importance of early microscopic examination of the peri-implant tissue. As a significant proportion of cases which is clinically consistent with PI present entities with a high potential for destructive behavior mimicking PI, histopathology should become an integral part of management of PI to allow for more accurate diagnosis and treatment.

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