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Inflammatory external root resorption following surgical treatment for intra-bony defects: a report of two cases involving Emdogain® and a review of the literature

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Abstract

Background: Enamel matrix-derived proteins have been shown to regenerate periodontal tissues lost as a result of disease in humans. Emdogain®, a commercial preparation of porcine enamel matrix derivative (EMD), has been shown to induce new cementum, periodontal ligament and bone formation in human periodontal defects. Although a number of studies have reported successful outcomes, local adverse effects have so far not been reported in the literature. This case report describes two examples of external inflammatory resorption following surgical root surface debridement and the use of Emdogain®.

Treatment: The treatment in both cases involved raising a full-thickness flap following completion of non-surgical therapy. The granulation tissue from the defect was removed and the root surfaces debrided. Emdogain® was applied following the manufacturers' instructions and involved conditioning the root surfaces with Pref-Gel and applying the Emdogain® to the defect. The flaps were sutured and the site reviewed regularly. Radiographs were taken before the treatment was undertaken and also at 6 months to assess the healing of the defect.

Results: External inflammatory root resorption was observed on the treated teeth 6–24 months after therapy.

Conclusion: External inflammatory root resorption may be an unusual adverse event following Emdogain® treatment.

Key words: dental enamel proteins; periodontitis; regeneration/adverse effects; root resorption

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The ultimate goal of periodontal treatment is to regenerate the periodontal ligament, cementum and alveolar bone lost as a result of disease. The crux of periodontal regeneration lies in the early induction of cementogenesis and the early assembly of newly formed periodontal ligament fibres onto the acellular cementum of the root surface (Pitaru et al. 1994, Ripamonti & Reddi 1997). Cementum is the first tissue of the periodontal attachment apparatus to form during periodontal development and regeneration. The deposition of cementum appears critical to the subsequent formation of periodontal ligament and bone. During root development, enamel matrix proteins secreted by the inner cell layer of Hertwig's epithelial root sheath, itself an apical extension of the enamel organ active in crown development, are deposited on the newly mineralised root dentine matrix. Upon contact with the enamel protein matrix, cells derived from the dental follicle differentiate into cementoblasts that deposit first acellular then cellular

cementum on the forming root (Hammarström 1997). Enamel matrix proteins, 90% of which are amelogenins, have also been shown to enhance the proliferation of periodontal ligament cells in vitro (Gestrelius et al. 1997) and also in the induction and spreading of human periodontal ligament fibroblasts (Van der Pauw et al. 2000). It has been shown that enamel matrix proteins synthesized and secreted by Hertwig's epithelial root sheath have the potential to stimulate the differentiation of mesenchymal cells in the dental follicle into cementoblasts which produce cementum (Slavkin & Boyde 1975).

Emdogain® (Biora AB, Malmö, Sweden) is a commercial product that consists of a gel containing hydrophobic enamel matrix proteins extracted from porcine-developing embryonic enamel. The proteins are solubilized in a neutral propylene glycol alginate vehicle for delivery to the surgical site, as the amelogenins are not soluble at physiologic pH. The propylene glycol alginate leaves the surgical site after the application allowing the amelogenin fraction to precipitate into an insoluble extracellular supra-molecular aggregate. This amelogenin matrix may then serve as a substrate for the pluripotential cells derived from the surrounding vital periodontal ligament to attach, differentiate and secrete cementum matrix. This product when applied to the root surface in conjunction with surgical periodontal therapy has been shown to promote periodontal regeneration as demonstrated in both animal and clinical experiments (Hammarström et al. 1997, Heijl 1997, Heden et al. 1999). A recent Cochrane systematic review (Esposito et al. 2003) has shown that sites treated with enamel matrix-derived proteins displayed significant improvements in pocket depth reduction when compared with open flap debridement alone. Studies have reported no differences in adverse post surgical experiences when Emdogain® was used for treatment (Zetterstrom et al. 1997, Hagenaars et al. 2004). Others have reported the clinical safety of Emdogain® with no negative impact on wound healing (Heard et al. 2000). Despite reports of adverse effects occurring with guided tissue regeneration (Blomlöf & Lindskog 1998), there appears to be a lack of reports in the literature on the possible effects of Emdogain® on the root surface. This paper reports two cases in which the roots of teeth treated surgically with enamel matrix-derived protein, Emdogain®, showed external inflammatory root resorption.

Case Reports

The two cases described below were referred to the Department of Periodontology of the Eastman Dental Hospital by their General Dental Practitioners for the management of periodontal disease. Both patients suffered from chronic periodontitis with no other obvious modifying risk factors. Their medical histories were clear and both patients were non-smokers. The periodontal disease presentation was generalized in both cases with extensive probing depths ranging from 5 mm to 10 mm throughout the mouth. The infection control phase of therapy had been initiated and consisted of oral hygiene instruction followed by a course of non-surgical root surface debridement with local anaesthesia. The cases were seen for re-evaluation 6 weeks following the infection control phase of therapy and the need for further intervention assessed.

Case Report 1

This was a 41-year-old female who had responded well to the infection (initial) control phase of therapy. At re-assessment she had a persisting probing depth of 10 mm localized to the distal aspect of tooth 47, which radiographically also had an intra-bony defect (Fig. 1). Her oral hygiene was excellent and a decision to undertake regenerative surgery using Emdogain® as the regenerative material was made. The rationale for the treatment was discussed with the patient and she was also informed about the use of the regenerative material and its origin. The patient was appointed to undergo the surgery that was carried out as follows.

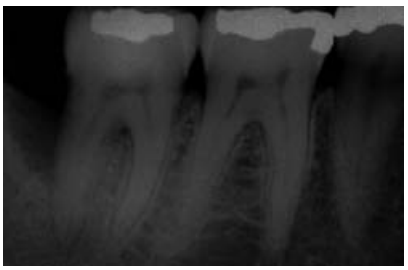

Fig. 1. Case 1: radiograph showing an intra-bony defect distal to tooth 47.

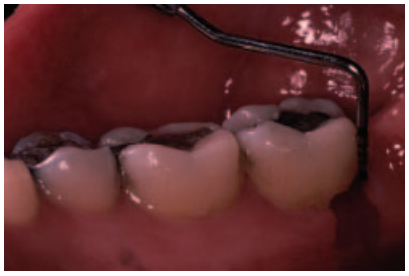

Fig. 2. Case 1: tooth 47 following probing.

A full-thickness mucoperiosteal flap was raised buccally and lingually to give good access to the site, taking care to preserve the papillary tissue to facilitate primary closure post-operatively.

The defect was identified and all granulation tissue removed and the distal root surface debrided. The defect and the root surface were examined for any abnormalities, and none were noted. The intra-bony defect was a two-walled defect coronally with the lingual plate missing, and three-walled more apically. The site was prepared for the application of the Emdogain®. The distal root surface was conditioned for 1 minute with Pref-Gel (Biora AB) and washed with saline. The Emdogain® gel was then applied into the defect taking care not to contaminate the conditioned root surface. The buccal and lingual flaps were replaced and sutured into position with interrupted 4/0 Vicryl sutures. The site was dressed with a periodontal dressing.

Post-operative instructions involved rinsing the area with 0.2% Corsodyl mouthrinse for 1 minute twice a day.

At review 1 week later, the healing was uneventful and the sutures removed. Regular appointments were arranged for the patient to be seen by the hygienist at 6 weekly intervals for supportive periodontal therapy, taking care not to instrument the distal surface of the 47 but checking the plaque control was optimal in this site.

At 6 months post-surgery she presented complaining of pain and discomfort from tooth 47. Clinical examination showed the site to be bleeding profusely with a 10 mm probing depth defect on the distal root surface (Fig. 2). A periapical radiograph taken of the area confirmed the presence of a subgingival radiolucency on the distal root surface of the 47 (Fig. 3). A provisional diagnosis based on the clinical and radiographic findings was made of external inflammatory root resorption. The prognosis of the tooth was deemed hopeless

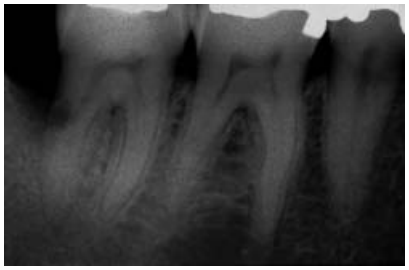

Fig. 3. Case 1: radiograph showing external inflammatory root resorption on the distal surface of the distal root of tooth 47.

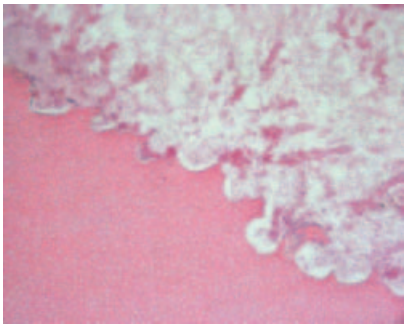

Fig. 4. Case 1: histopathological section of tooth 47, showing resorption cavity.

and the options discussed with the patient involved surgical repair of the defect, hemisection of the distal root, or extraction of the tooth. The patient initially opted for the hemisection because of the strategic value of the tooth in maintaining the occlusal stability of the opposing tooth. Arrangements were made for the root canal treatment to be initiated, however after the root canal treatment was started, she decided to opt for an extraction. The patient was consented for the extraction and the use of the tooth for a biopsy to confirm the clinical diagnosis. The tooth was removed with local anaesthesia taking care to preserve the distal root. The specimen was sent for histopathological analysis. The result confirmed the provisional diagnosis of root resorption and reported a mixture of debris and plaque in the cavity with vital pulp tissue present in the distal root canal of the 47 (Fig. 4). Healing of the site following extraction has been uneventful and to date the patients periodontal health remains stable.

Case Report 2

This was a 42-year-old female who had responded well to the infection control phase of therapy. At reassessment she presented with a localized persisting

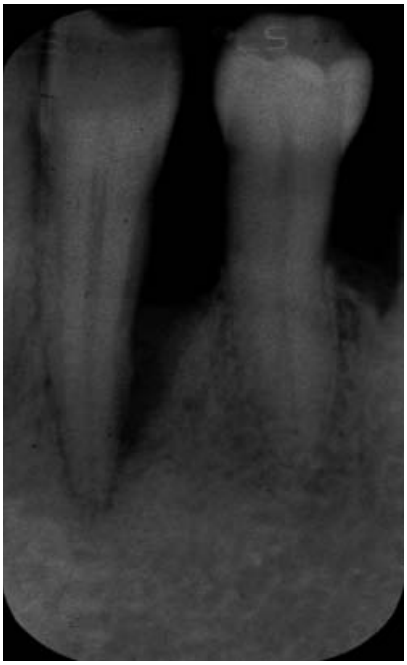

Fig. 5. Case 2: radiograph showing an intrabony defect distal to tooth 33.

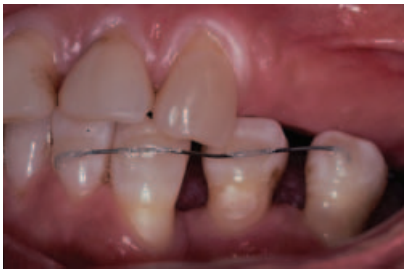

Fig. 6. Case 2: tooth 33 before regenerative therapy showing splinting with composite and orthodontic wire.

8 mm probing depth associated with the distal aspect of the tooth 33, which was also Grade II mobile. A radiograph taken of the site confirmed the presence of an intra-bony defect distal to the 33 (Fig. 5). The site was deemed suitable for regeneration and the proposed treatment discussed with the patient, which involved surgical debridement of the site with the use of Emdogain® to regenerate the defect. The patient was informed of the rationale for the use of the Emdogain® and was also informed of the origin of the material. The need for pre-surgical splinting of the tooth to eliminate the mobility, which would compromise the surgical outcome, was also discussed with the patient. The tooth was splinted with composite resin and orthodontic wire (Fig. 6) and scheduled for surgery. The surgery was undertaken as follows.

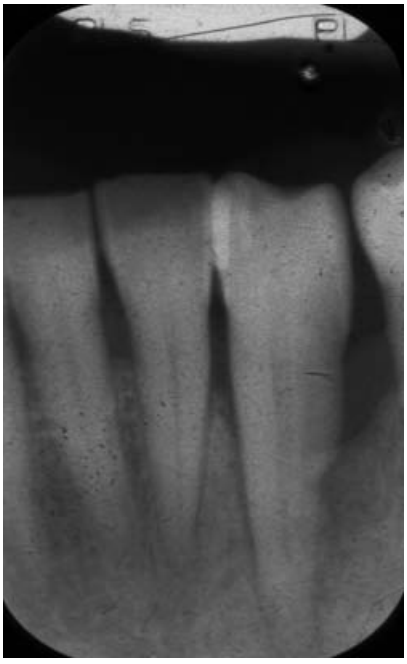

Fig. 7. Case 2: irregular outline of the distal surface of tooth 33.

Full-thickness mucoperisoteal flaps were raised buccally and lingually, taking care to preserve the papilla to facilitate primary closure post-surgery. The defect was cleaned of all granulation tissue and the root surface debrided. The defect was assessed and noted as a two-walled defect. No abnormality of the root surface was noted. The site was prepared for the application of the Emdogain® as per the manufacturers' instructions detailed above. The buccal and lingual flaps were then replaced and sutured into position with interrupted 4/0 Vicryl sutures.

Post-operative instructions involved rinsing the area with 0.2% Corsodyl mouthrinse for 1 minute twice a day.

Healing at 1 week was uneventful and the patient was kept on supportive periodontal therapy to assess the healing and her ability to maintain her plaque control. The composite resin splint was left in situ to facilitate healing immediately post-surgery. The patient was seen for review 4 weeks later when the splint had decemented. As the splint was scheduled to be removed at this visit it was not repaired. The patient was kept under review, but due to illness she did not return for review until over 4 months later when tooth 33 was firm with no mobility. Clinical examination at 6 months revealed the 33 sites to have responded well to the treatment with no

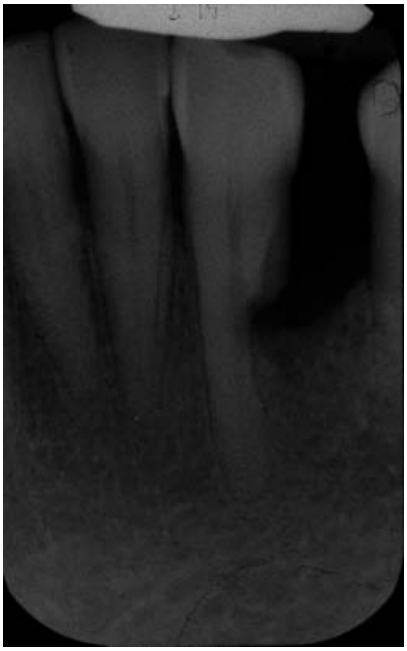

Fig. 8. Case 2: radiograph showing external inflammatory root resorption on the distal surface of tooth 33.

probing depths $\geqslant$5 mm. However, on percussion the tooth produced a ''ringing'' sound consistent with ankylosis. Radiographs taken at this visit showed infill of the intra-bony defect, but the outline of the distal root surface appeared irregular (Fig. 7). The tooth gave positive responses to both thermal and electric pulp tests. The patient was informed of our findings, and she was placed on a supportive therapy regime and the site monitored during this period. Two years post-surgery the patient was seen for her recall when she reported discomfort associated with the tooth 33. The periodontal health continued to remain stable with no probing depths and the tooth remained firm. A periapical radiograph taken revealed the presence of a radiolucency on the distal surface of the 33 root which appeared to be encroaching into the root canal (Fig. 8). The radiolucency was located just coronal to the level of the re-generated alveolar bone crest and the root apical to this appeared narrower when compared with the previous radiograph. A provisional diagnosis of external inflammatory root resorption was made. Because of the symptoms and the extent of the radiolucency the prognosis of the tooth was deemed hopeless. This was discussed with the patient and arrangements for the removal of the tooth were made and the replacement options

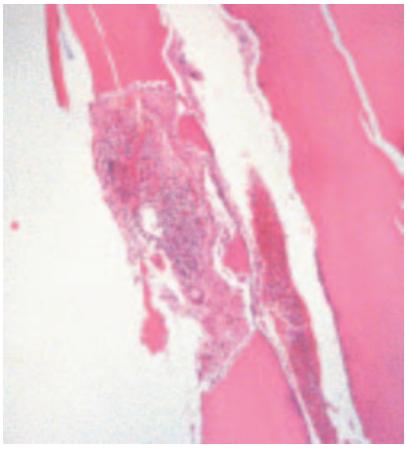

Fig. 9. Case 2: histopathological section showing external inflammatory root resorption on the distal surface of tooth 33.

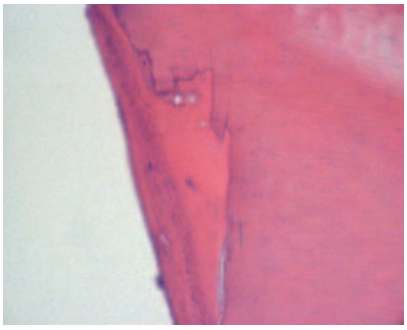

Fig. 10. Case 2: histopathological section showing intimate contact of bone with dentine on tooth 33, apical to the resorption cavity.

for restoring the space were also discussed. The patient was consented for the extraction and the retention of the tooth for histopathology. The tooth was removed and sent for histopathological analysis (Figs 9 and 10). The report confirmed the provisional diagnosis. The patient is undergoing treatment for the replacement of the missing tooth and will continue to be monitored for her periodontal health in conjunction with her dentist.

Discussion

Resorption of the hard tissues of the teeth is an uncommon event as the ''blast'' cells lining the surface of the roots protect the teeth. Injury or damage to the blast cell layer mobilizes the osteoclasts to come to the exposed hard tissue, which then excrete acids into the extracellular environment lowering the pH to facilitate further lysosomal activity thereby enhancing resorption. For resorption to occur, a trigger mechanism is necessary and a reason for the resorption to continue must also be present. A number of triggering factors have been implicated in the initiation of external root resorption and include damage to the root surface, orthodontic tooth movement, dento-alveolar surgery and periodontal disease and its treatment (Tronstad 1988). It has been reported that following this initial damage, the presence of bacteria either in the root canal or the gingival sulcus may sustain the resorptive process (Dragoo & Sullivan 1973).

It could be postulated in both cases that the trigger for the resorption is likely to be the periodontal disease and the subsequent debridement that had been carried out during the infection control phase. However the role of the surgery using Emdogain® in the enhancement and progression of the resorption needs to be considered. For the resorptive activity to occur the damaged root surface would have to have been repopulated by connective tissue/fibroblasts during the healing period. Under normal circumstances healing following periodontal surgery occurs with long junctional epithelial downgrowh, and healing by re-attachment. However with regenerative therapies, selective cell repopulation is encouraged to enhance regeneration. It has been shown that when connective tissue cells alone are allowed to populate the periodontal sites, resorption is seen on the root surfaces (Nyman et al. 1980). Following the regenerative surgical treatment, healing was observed in the apical third of the defects in both cases and is consistent with the findings of Karring et al (1980), who reported that apically, in the presence of viable periodontal ligament cells, the ligament was consistently re-established,. However, healing coronally was characterized by repair phenomenon including resorption and ankylosis.

It has been reported that damaged root surfaces not protected by the junctional epithelium is repopulated by connective tissue (Brosjö et al. 1990). Emdogain® has been shown to increase the migration of the gingival fibroblasts from the connective tissue as well as the periodontal ligament cells (Hoang et al. 2000). If this had happened in the two cases presented then the increased migration of the fibroblasts would have enhanced the risk of resorption. Whilst it can be argued that the fundamental

mechanisms by which Emdogain® has been postulated to work should have prevented the resorption, it has been shown that enamel matrix proteins do not protect the root surface from replacement resorption. (Araujo et al. 2003). Others have reported that the use of Emdogain® delays or prevents the recurrence of ankylosis (Filippi et al. 2002). However in this paper the teeth examined were trauma related and the roots had not been conditioned with EDTA before the application of the Emdogain. These findings are in contrast with those of Araujo et al (2003) who conditioned the roots and found that the Emdogain® did not prevent the resorptive activity. A clinical study by Schjøtt & Andreasen (2005) also showed that progressive root resorption was not prevented in patients following re-implantation of avulsed and previously ankylosed teeth. Whilst these studies may provide some explanation for the effects of the Emdogain® none of them involved periodontally affected teeth where the sites in question have been contaminated by bacteria. However, a recent case report (Majzoub et al. 2005) showed histologically both the presence of regeneration and ankylosis following the treatment of a periodontally compromised tooth with Emdogain®.

The use of the Pref-Gel (EDTA) to condition the root surface may have further contributed to the resorptive activity by increasing the exposure of the dentinal tubules to the osteoclastic activity, especially if some residues remained following rinsing with saline. Residual Pref-Gel may have also caused injury to the adjacent periodontal ligament, which contributes cells for regeneration of periodontal ligament and cementum.

In the two cases reported, if the conditioning agent and Emdogain® had a role in the initiation of resorption, the bacterial contamination in the sulcus may have played a role in sustaining the resorptive process.

Additionally, Lyngstadaas et al. (2001) and Van der Pauw et al. (2000, 2002) have shown that under the influence of the EMD, the periodontal ligament cells and the gingival fibroblasts release significantly higher levels of transforming growth factor TGFβ and increased production of alkaline phosphatase. Little is known about the levels of these factors and whether this could also have contributed to the ongoing problems. Jiang et al. (2001) reported that enamel matrix derivative may prolong osteoblast growth and influence periodontal tissue regeneration. They proposed that in sites with a narrow space (<0.5 mm) between the bone tissue and detached root, such osteoblast activity may promote early contact between bone forming cells and the hard tissues of the teeth. This type of contact may stimulate processes that involve replacement resorption and ankylosis. This may explain the signs of ankylosis seen in the second case.

The role of Emdogain® acting as the trigger factor for the resorption cannot be ascertained. The exact nature of the cellular effects of EMD are still relatively unclear and further work is necessary to establish this. In all the clinical papers published, the focus has been mainly on the outcome to the periodontal health but very little has been documented about the long-term effects of the material on the teeth themselves.

Summary

The above case report demonstrates two cases of external inflammatory root resorption following the treatment of intra-bony defects with Emdogain®. The true prevalence of this problem, and the contribution of the materials used in the procedure to the inflammatory resorption seen are unknown.

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Clinical Relevance

Scientific rationale for study: Resorption of teeth following the treatment of intra-bony defects with Emdogain® has not been reported in the dental literature. This report documents two cases of external inflammatory resorption following surgical treatment with Emdogain®.

Principal findings: External inflammatory root resorption was found in two teeth following surgical treatment with Emdogain®. In both cases, the teeth required extraction.

Practical implications: Resorption of teeth with intra-bony defects can be a rare complication following treatment with Emdogain®. Clinicians should be aware of this adverse effect and document cases if they occur.