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CASE STUDY

PDGF-BB-enriched collagen matrix to treat multiple gingival recessions with the tunneled coronally advanced flap

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Abstract

Background: With technological advancements in reconstructive periodontology, traditional protocols for the treatment of gingival recessions (GRs) can be challenged. This manuscript presents preliminary findings of a novel minimally-invasive approach for the regenerative treatment of multiple adjacent GR defects.
Methods: Two healthy adults were treated as part of this study. Multiple adjacent GRs in both subjects (1 in the mandible, and 1 in the maxilla) were treated employing a tunneled coronally advanced flap (TCAF) design, with the application of a cross-linked collagen matrix (CCM) that was enriched with recombinant human platelet-derived growth factor-BB (PDGF-BB) that was also applied on the prepared root surfaces. Clinical, ultrasonographic, esthetic, and patient-reported outcomes were observed at approximately 6- and 18-month time points.
Results: All sites healed uneventfully after the treatments. Complete root coverage was achieved and maintained throughout the follow-up observations, from 6 to 18 months. Patients reported minimal discomfort and reduction of dentinal hypersensitivity at the augmented sites. The areas augmented with CCM + PDGF-BB revealed an increased soft tissue thickness relative to baseline (pretreatment) measures, as well as reduction in the level of the facial bone dehiscences.
Conclusion: This article describes the success of two cases of a novel minimally invasive regenerative approach for the treatment of multiple adjacent GR defects by the TCAF, using a CCM loaded with PDGF-BB. This approach offers potential as a minimally-invasive method to repair multiple adjacent GRs.

KEYWORDS
gingival recession, platelet-derived growth factor, periodontics, regenerative medicine, tissue engineering, tissue scaffolds

INTRODUCTION

The occurrence of a gingival recession (GR) is a common finding in clinical practice.[1] When it comes to treatment, the scientific literature is in agreement that irrespective of the outcome of therapy—whether root coverage, or modification of the soft tissue phenotype—the traditionally applied autogenous connective tissue graft (CTG) still ranks as the "gold standard" approach.[2–4] Nonetheless, with routine implementation of this technique, and with realization of the path of contemporary periodontics to be moving in a direction of minimal invasiveness and optimized patient-centered outcomes,[5] many have recognized the drawbacks that are inherent, particularly the requirement of palatal harvesting.[6,7] Namely, in a recent study, we found that some patients, even after a decade had surpassed the date of their original treatment, still remembered the pain they experienced after a palatal harvesting procedure, which also negatively impacted their decision to accept a similar therapy in current day.[6]

Thus, clinicians now strive to adopt minimally invasive techniques for challenging the status quo and finding alternatives to the use of the autogenous CTG.[2,7,8] Among them, has been more routine implementation of autogenous soft tissue graft substitutes to enhance their efficacy using growth factors or bioactive agents, as well as employment of less invasive and novel surgical designs.[9]

An example is the newer generation of a xenogeneic collagen matrix, which has principally undergone chemical cross-linking to enhance its mechanical stability, which due to its porous structure, may also act as a viable carrier for a biologic agent, and a scaffold for the ingrowth of cells, enabling a growth factor-mediated root coverage procedure.[10] In particular, an in vitro study reported an increased cellular population and metabolic activity in this matrix when utilized as a scaffold for one of the most commonly utilized biologic agents, the recombinant human platelet-derived growth factor-BB (rhPDGF-BB).[11] Thus, in the current manuscript, we describe a minimally invasive approach for the treatment of multiple adjacent GRs, by virtue of a biologic-mediated root coverage procedure with the application of the cross-linked collagen matrix (CCM) incorporated with rhPDGF-BB.

MATERIALS AND METHODS

Design and objective of this feasibility study

The present manuscript illustrates the combined application of CCM + rhPDGF-BB with the tunneled coronally advanced flap (TCAF)[12,13] for the treatment of multiple GRs in two nonsmoking systemically and periodontally healthy individuals. Both patients were recruited and treated at the Department of Periodontics and Oral Medicine, School of Dentistry, University of Michigan between November 2019 and January 2020, and provided their informed consents. The study is in accordance with Declaration of Helsinki of 1975, as revised in Fortaleza in 2013 and the manuscript has been prepared according to the CARE guidelines for improving research reporting in case reports.[14]

To be considered, the selected patients must have had: (i) an esthetic concern or hypersensitivity associated with GR, (ii) age $\geq$ 18 years, (iii) presence of RT1 or RT2 multiple adjacent GRs,[15] (iv) at least 1.5 mm of keratinized tissue width (KTW) around the included teeth.

The following were considered as exclusion criteria: (i) subjects with an uncontrolled systemic disease (e.g., diabetes, etc.), (ii) smokers, (iii) presence of active periodontal disease, (iv) previous surgical procedure at the site to be treated, (v) individuals taking medications, which could interfere with the healing of the soft tissues, and (vi) known allergy to any of the biomaterials to be used.

Outcome measures

The clinical parameters of recession depth (REC), clinical attachment level (CAL) and KTW were assessed at baseline (pre-treatment), 6-month and 18-month follow-up. Gingival thickness (GT) and buccal bone dehiscence (BBD) were evaluated at the same time points using ultrasonography.[16–18] Briefly, this technology is commercially available as an ultrasound imaging device (ZS3, Zonare/Mindray, Mountain View, CA, USA) coupled with a 24 MHz (64 μm axial image resolution) and miniature-sized (approximately 30 mm long, x 18 mm wide x 12 mm thick) probe prototype (L30-8) to generate ultrasound images. The scans were taken at the midfacial aspect of each treated tooth and were saved in the Digital Imaging and Communications in Medicine (DICOM) format. A commercially available software (Horos, version 3.3.6, Horos Project) was utilized for evaluating GT at reference points 1.5, and 3 mm from the gingival margin and for assessing the distance between the buccal bone and the cemento-enamel junction (CEJ) at the midfacial aspect of the treated sites (BBD).[19] The professional esthetic evaluation was performed using the root coverage esthetic score (RES)[20] at the 6- and 18-month follow up.

Patient-reported outcome measures (PROMs) were assessed using a set of questionnaires with a visual analogue scale (VAS) from 0 to 100 to assess treatment satisfaction and esthetic outcomes at the final follow-up.

Case 1: TCAF + CCM loaded with rhPDGF-BB for multiple maxillary GRs

A 42-year-old healthy female patient presented with esthetic concerns for generalized RT1 and RT2 GRs in the maxillary region. She also reported substantial dental hypersensitivity on the right canine, which was also associated with a noncarious cervical lesion (NCCL). The GRs were characterized by the presence of at least 1.5 mm of KTW (Figure 1A–C).

It was decided to perform a minimally invasive approach, involving a combination of coronally advanced flap (CAF) and tunnel (TUN) technique (TCAF, as previously described)[12,13] with site-specific application of a CCM loaded with rhPDGF-BB for the maxillary right canine. The rationale for this approach was to open the flap only at the right premolar and canine area to gain access for the insertion and stabilization of the CCM soaked with the growth factor, aiming for root coverage and simultaneous gingival phenotype modification (Figure 1D). The presence of the NCCL was address by performing a bilaminar approach, with the biomaterial positioned over the NCCL to prevent the collapse of the flap.[21,22]

The other areas were tunneled and coronally advanced without receiving any graft materials, as previously described by Rasperini and coworkers.[23] The papillae at the level of the right premolars and the canine were incised using a miniblade (Salvin Dental Specialties, Charlotte, NC, USA), and a vertical incision was placed distal to the second right premolar. These areas were then raised split thickness interproximally and full thickness at the

FIGURE 1 Tunneled coronally advanced flap with a cross-linked collagen matrix loaded with recombinant human platelet-derived growth factor-BB (tunneled coronally advanced flap [TCAF] + cross-linked collagen matrix [CCM] + rhPDGF-BB) for the treatment of multiple maxillary gingival recessions. (**A–C**) Baseline. (**D**) Flap design involving the incision and opening of the papillae of the right premolars and canine only. The remaining areas were tunneled. (**E**) Cross-link collagen matrix. (**F**) Collagen matrix saturated with rhPDGF-BB. (**G**) Chemical root planing with 24% EDTA for 2 min. (**H–J**) Stabilization of the collagen matrix to the right premolars and canine. (**K**) The flap was coronally advanced and sutured approximately 2 mm coronally to the cemento-enamel junction. Note that the left quadrant until the right lateral incisor was tunneled and coronally advanced without receiving any grafts, given the overall thick gingival phenotype. (**L**) 2-week postop. (**M–O**) Outcomes at the 18-month follow-up

midfacial aspect of the premolars and canine until exposing 2 mm of bone.

The region distal to the right incisor and the left hemimaxilla were tunneled using straight and angulated tunneling miniblades (Butterfly, Cavenago di Brianza, Italy). Careful attention was made to maintain the integrity of the papillae. After removal of muscular insertions from the flap, the papillae were detached from the bone using tunneling miniblades (Butterfly, Cavenago di Brianza, Italy) and a papilla elevator (American Dental Systems, Vaterstetten, Germany). The incised anatomical papillae were de-epithelialized with a miniblade (Salvin Dental Specialties, Charlotte, NC, USA). A CCM (Geistlich Fibro-Gide, Geistlich Pharma North America, Princeton, NJ, USA) was trimmed and then saturated with rhPDGF-BB (GEM21, Lynch Biologics, Franklin, TN, USA) using a micro-injection needle (Figure 1E,F). The CCM were then left in the dappen dish for 15 min[24] The root surfaces were scaled, planed and chemically conditioned using 24% of EDTA for 2 min. rhPDGF-BB was also applied onto the dried root surfaces before stabilizing the CCM (Figure 1G). Simple interrupted sutures (6/0 and 7/0 PGA) (Butterfly, Cavenago di Brianza, Italy) engaging the matrix and the de-epithelialized anatomical papillae were performed to stabilize the CCM on the recipient bed, approximately at the level of the cemento-enamel junction (CEJ) or 1 mm apical (Figure 1H–J). The TCAF was then coronally advanced and stabilized approximately 2 mm above the CEJ with sling sutures and simple interrupted

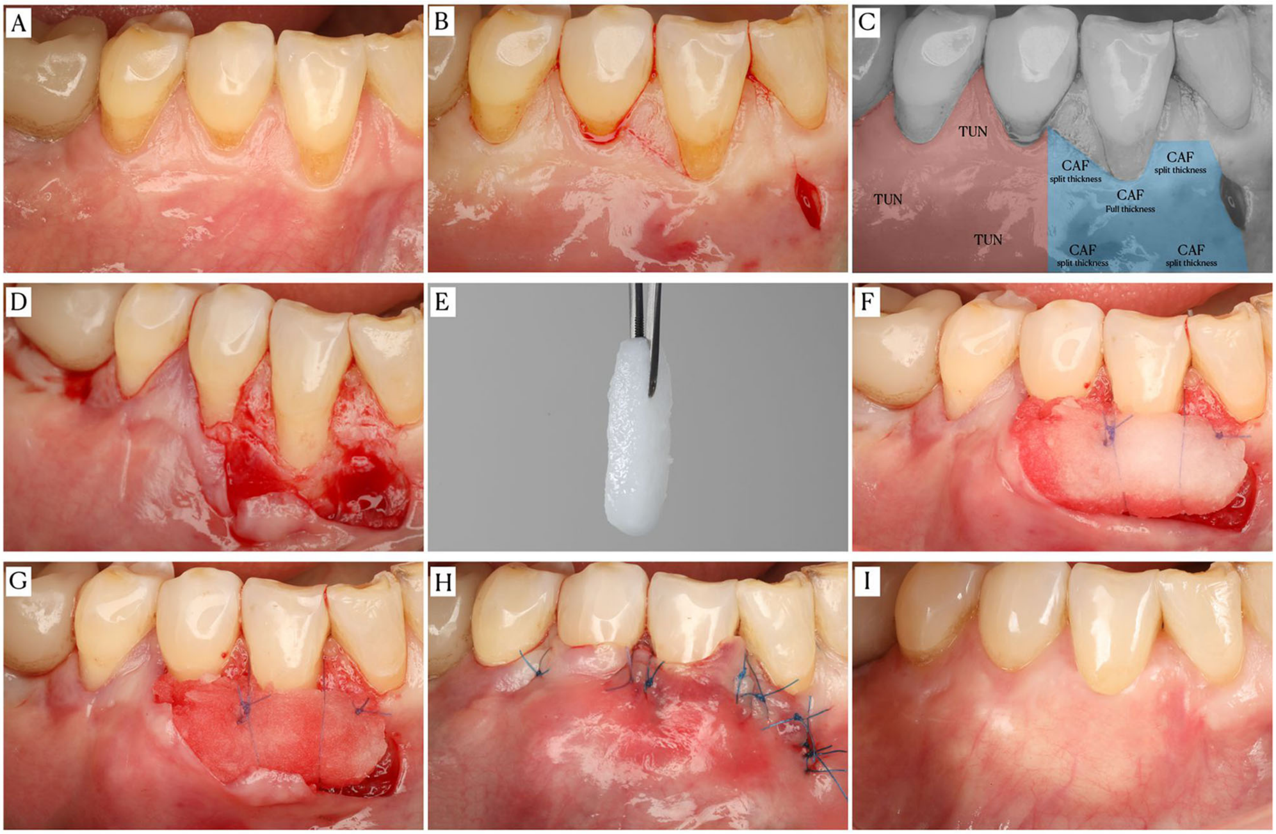

FIGURE 2 Tunneled coronally advanced flap with a cross-linked collagen matrix loaded with recombinant human platelet-derived growth factor-BB for the treatment of multiple mandibular gingival recessions. (**A**) Baseline. (**B–C**) Tunneled coronally advanced flap (TCAF) design, showing the different flap preparation areas. (**D**) De-epithelialization of the anatomical papillae of the canine after flap elevation. Note that the access provided by the selective flap preparation typical of the TCAF allowed for a better access at the level of the mental foramen region, facilitating flap releasing without damaging the mental nerve. (**E**) Cross-link collagen matrix saturated with rhPDGF-BB. (**F–G**) Stabilization of the collagen matrix on the recipient site. Note that there are two simple interrupted sutures stabilizing the matrix to the de-epithelialized papillae and an anchoring periosteal suture for further stabilize and compress the graft. (**H**) Flap colure. (**I**) 18-month follow-up

sutures (6/0 and/or 7/0 polypropylene) (Ethicon, Johnson & Johnson, Somerville, NJ, USA) at the level of the papillae, completely covering the graft. Simple interrupted sutures were performed at the level of the vertical incision, (7/0 polypropylene) (Ethicon, Johnson & Johnson, Somerville, NJ, USA) (Figure 1K).

Case 2: TCAF + CCM loaded with rhPDGF-BB for multiple mandibular GRs

A 49-year-old periodontally and systemically healthy female presented with multiple GRs in the lower right quadrant associated with esthetic concern and mild dental hypersensitivity at the level of the canine (Figure 2A). The patient reported that she had been previously treated with a graft from the palate in other areas of the mouth and, given the postoperative pain that she had experienced, she asked whether it was possible to address her concern with alternative techniques. After a discussion of advantages, disadvantages and expected outcomes of soft tissue graft substitutes compared to autogenous CTG, it was decided to use a CCM soaked with rhPDGF-BB.

A TCAF with one vertical incision on the mesial aspect of the canine was performed.[12,13] The papilla between the canine and the first premolar was also incised, with an oblique incision anticipating the rotation of the flap when coronally advanced (Figure 2B,C). Miniblades (Salvin Dental Specialties, Charlotte, NC, USA) were used to elevate the two papillae of the canine in a split-thickness manner, while the elevation of the midfacial portion of the flap at the level of the canine proceeded full-thickness until exposing 2 mm of labial bone. The other papillae, from the distal papilla of the first premolar to the distal papilla of the first molar (dental implant), were preserved in integrity, and detached from the underlying bone using tunneling miniblades (Butterfly, Cavenago di Brianza, Italy) and a papilla elevator (American Dental Systems, Vaterstetten, Germany). The flap was tunneled until the distal aspect of the first molar, in order to achieve adequate release and advancement of the flap (Figure 2C). The access provided by the incision of the papillae at the level of the canine allowed for inserting a miniblade (Salvin Dental Specialties, Charlotte, NC, USA) and releasing the muscular insertion, as well as identifying and protecting the mental nerve. The incised anatomical papillae were de-epithelialized using a miniblade and the root surfaces were chemically (24% of EDTA for 2 min) and mechanically treated (Figure 2D). A CCM (Geistlich Fibro-Gide, Geistlich Pharma North America, Princeton, NJ, USA) was trimmed and saturated with rhPDGF-BB (GEM21, Lynch Biologics, Franklin, TN, USA) as described above (Figure 2E). The CCM was inserted into the flap from the canine area until reaching the second premolar. The CCM was then sutured to the de-epithelialized anatomical papillae of the canine with two simple interrupted sutures and a suture anchoring to the periosteum apical to the graft (7/0 PGA) (Butterfly, Cavenago di Brianza, Italy) (Figure 2F,G). The TCAF was then coronally advanced and stabilized approximately 2 mm above the CEJ with sling and simple interrupted sutures at the level of the papillae, and simple interrupted sutures for the vertical incision (6/0 and 7/0 polypropylene) (Ethicon, Johnson & Johnson, Somerville, NJ, USA) (Figure 2H).

Both patients received similar oral and written postoperative instructions and were prescribed Ibuprofen (600 mg every 4–6 h for the first 3 days, followed by its prescription as needed), Amoxicillin (500 mg 3 times a day for 7 days), and a chlorhexidine mouth rinse (0.12% twice daily for 1 min for 14 days). The sutures were removed 2 weeks after the surgical procedure, at which point the subjects were instructed to resume mechanical tooth brushing at the operated area using an extra-soft bristle toothbrush for approximately 4 weeks, prior to switch to a soft bristle toothbrush.

RESULTS

The healing was uneventful and limited postoperative morbidity was reported by both patients.

In the case 1, complete root coverage was observed at the treated sites at 6 and 18 months (Figures 1 and 3). The patient reported reduced but mild residual dental hypersensitivity when using the air-spray test at the 6-month visit that however, disappeared at the 18-month follow-up. Patient's reported treatment satisfaction and esthetic assessment at the last visit were both 100. The professional esthetic evaluation using the RES was 9.13 ± 0.64, respectively. Ultrasonographic assessment of tooth #6 revealed that the GT at baseline was 0.756 and 0.692 mm, when measured 1.5-mm and 3-mm apical to the gingival margin respectively. The corresponding GT at 18 months was 1.541 and 1.306 mm, indicating that the increase in GT 1.5 mm below the gingival margin was 0.785 mm, and the GT gain 3 mm apical to the gingival margin was 0.614 mm. The BBD at baseline was 5.982 mm, as also confirmed intraoperatively using a periodontal probe. A BBD of 3.411 mm and 3.875 mm was observed on the ultrasonographic scans at the 6- and 18-month follow-up a, respectively, indicating a buccal bone level gain of 2.107 mm from baseline to 18 months.

In the case 2, complete root coverage was obtained at the canine and first premolar after 18 months, while the second premolar showed a residual recession of 1 mm, which was anticipated due to the interproximal attachment loss on the distal aspect of the tooth. The patient rated her treatment satisfaction and esthetic assessment 100 and 92.97. The professional esthetic score was 7.67 ± 2.31. In terms of ultrasonographic outcomes, a GT gain (from baseline to 18 months) of 0.458 mm and 0.671 mm was found when the soft tissue thickness was measured 1.5 and 3 mm below the gingival margin, respectively. The BBD at baseline was 4.492 mm (which was also confirmed intraoperatively), while at the last visit a BBD of 3.041 mm was noted on the ultrasound scan, indicating a reduction of BBD of 1.451 mm (Figure 4).

DISCUSSION

With development of novel technologies, and the emergence of biomaterials and bioactive agents, the field of regenerative periodontal medicine is progressively moving in a direction of highlighting patient-centered outcomes and increasing treatment efficiency by reducing intrasurgical time, postoperative morbidity, and complications. Conceivably, the impact of patients' own perception of our treatments, including intra- and postoperative discomfort, surgical chair time (also for clinicians) and the possibility of adverse events, will likely soon determine even more of the selection of our therapeutic approaches.

Appropriately, the concept of biologic factor-mediated root coverage, and the application of CTG-substitutes have been more so highlighted recently. As a result, several combination therapies involving biologic agents and CTG substitutes have been explored over the years to further enhance the properties of dermal or collagen scaffolds and matrices. Conceptually, the utilization of "enriched" and "enhanced" graft substitutes in the treatment of GRs can be a fundamental change in patient care, given the possibility to avoid a secondary surgical site for the CTG harvesting. Nonetheless, the literature has yet to support this notion, particularly as it relates to a generalized recommendation as a substitute to the gold standard autogenous graft.

In these two cases, we present the step-by-step protocol of treating multiple adjacent GRs with a collagen matrix that incorporated rhPDGF-BB, through a surgical design that was specifically used for this application, namely the TCAF.[12,13] Indeed, most of the stated advantages of the TCAF (stabilization of the matrix, avoiding vertical incisions, etc.) are inherent with the CAF or TUN, which traditionally have been denoted distinct from one another.[25,26] The proposed TCAF combines the advantages of the individual techniques of CAF and TUN, according to site-specific criteria and indications, such as reducing the number of vertical releasing incisions when possible (e.g., in the esthetic zone

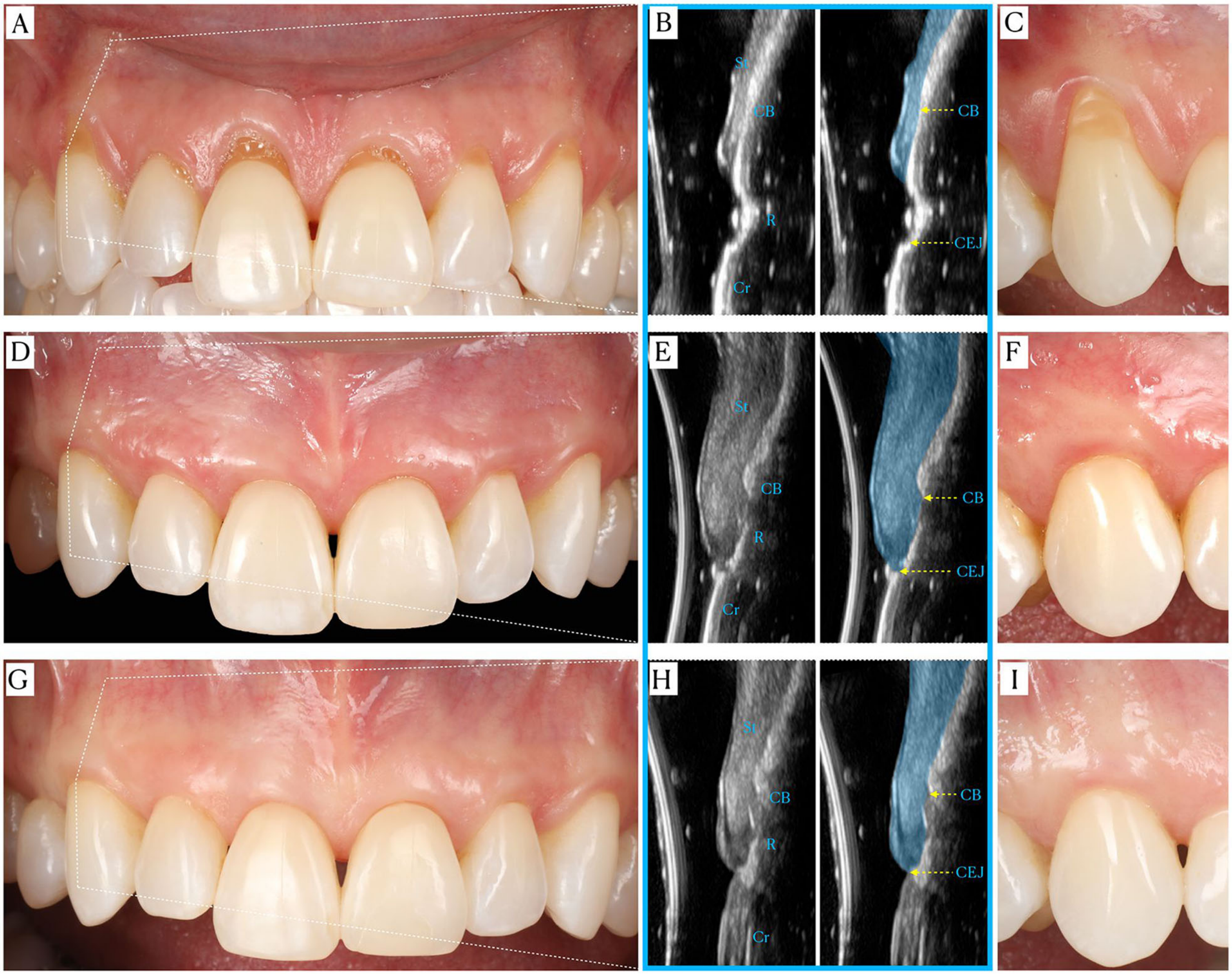

FIGURE 3 Clinical and ultrasonographic outcomes of case 1. (**A**) Baseline. (**B**) Ultrasonographic scan of the midfacial aspect of tooth #6, where the clinical crown ("Cr"), the root ("R"), the crestal bone "CB," the cemento-enamel junction ("CEJ") and the soft tissue ("St") are pointed out. Note that the CEJ, CB, and the soft tissue are highlighted in the second scan. (**C**) Clinical presentation of the canine at baseline. (**D**) 6-month outcomes. (**E**) Ultrasonographic scan of the midfacial aspect of tooth #6 at 6 months. Note the reduction of buccal bone dehiscence (distance between CEJ and CB) compared to the baseline. (**F**) Clinical presentation of the canine at 6 months. (**G**) 18-month outcomes. (**H**) Ultrasonographic scan of the midfacial aspect of tooth #6 at 18 months. Note the reduction of buccal bone dehiscence (distance between CEJ and CB) compared to the baseline. (**I**) Clinical presentation of the canine at 18 months

or a posterior region), increasing visibility for a particular site and enhanced ability for graft stabilization (particularly important as it relates to a biologic factor-soaked matrix), as well as maintenance of the integrity of weaker papillae such as those with interproximal attachment loss (resulting in a more favorable environment for early nutrition and integration of the graft).[12,13]

Indeed, the scope of minimal invasiveness in root coverage procedures does not only include avoiding palatal harvesting and vertical releasing incisions. It also encompasses the concept of site-specificity in rendering treatments,[5] which can translate into the avoidance of any additional biomaterials or grafts when applicable, through assessment of the local soft tissue phenotype. As we illustrated in this report, some of the treated sites did not receive any graft or biomaterials and were merely treated with the original soft tissues inherent. This concept of selective and site-specific gingival phenotype modification has been recently suggested in the literature,[23,27] and in line with these recommendations, we based our approach on presurgical clinical and ultrasonographic evaluation of periodontal structures of the teeth to be treated, in terms of KTW and GT. In addition, in light of the present findings of our pilot report, BBD could be another factor to consider in the scope of site-specific treatment recommendations, relative to the use of grafting materials and biologic agents. Indeed, an interesting finding from our pilot analysis, was the decrease in the level of the BBD that we noticed as a result of the treatments, at follow-up time points.

It is well known that rhPDGF-BB is a potent mitogen for fibroblasts and periodontal ligament cells.[28,29] When

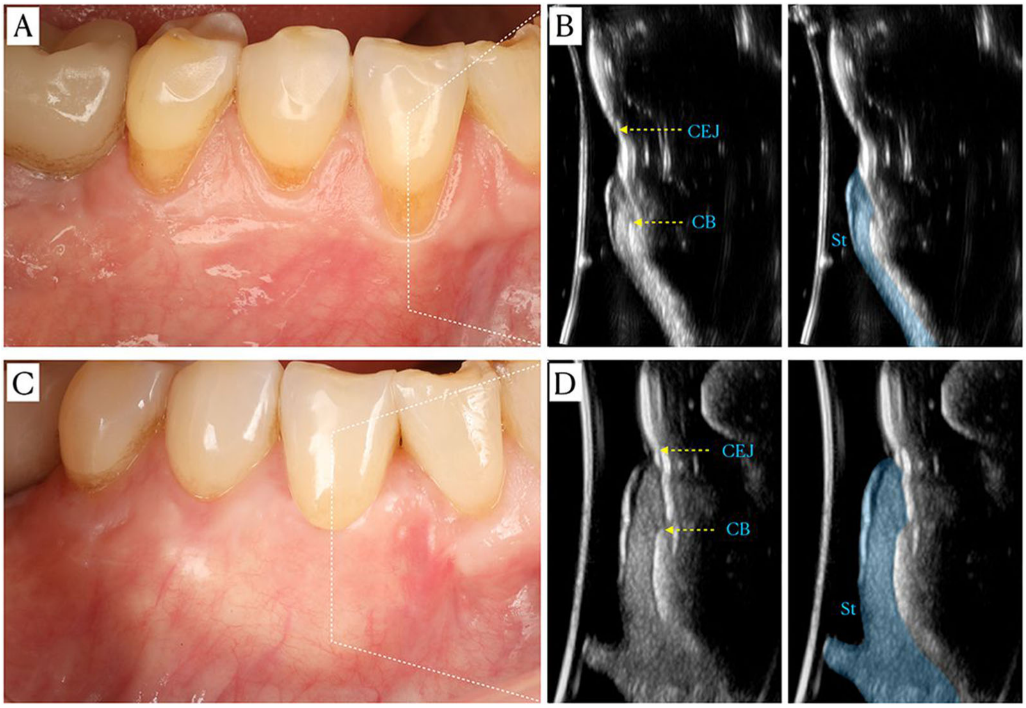

FIGURE 4 Clinical and ultrasonographic outcomes of case 2. (**A**) Baseline. (**B**) Ultrasonographic scan of the midfacial aspect of tooth #27, where the crestal bone "CB," the cemento-enamel junction ("CEJ") and the soft tissue ("St") are pointed out. (**C**) 18 months. (**D**) Note that the distance between the CEJ and the CB appeared to be reduced from baseline to 18 months

combined with beta-tricalcium phosphate for the treatment of isolated GRs in humans, rhPDGF-BB was found to promote regeneration of Sharpey's fibers, new cementum, and new bone.[30] The regenerative outcomes of rhPDGF-BB have also been showed clinically via re-entry procedures.[30,31] In our assessment of the two treated cases in this report, we observed a reduction of BBD of approximately 2 mm in an upper canine and 1.5 mm in a lower canine that received the CCM with rhPDGF-BB. Although the ultrasonographic nature of this finding does not allow for drawing conclusions in regard to periodontal regeneration, speculations can be made from this view. Firstly, readers should be aware that several studies have demonstrated ultrasonography to be a reliable and reproducible method for assessing oral and periodontal tissues,[32,33] with comparable outcomes to cone-beam computed tomography, in particular for assessment of BBD.[33–35] In line with a recent animal study showing that this novel CCM alone can promote periodontal regeneration when used in infrabony defects,[36] it can be assumed that the CCM could serve as an appropriate carrier for the sustained and progressive release of rhPDGF-BB, resulting in BBD reduction and possible periodontal regeneration. The sponge-like composition of the CCM which carried the rhPDGF-BB may have also contributed to the chemotaxis of cells from the periodontal ligament and alveolar bone,[36,37] that are characterized by the presence of receptors for PDGF on their surface.[38,39]

Ultrasonography also revealed a substantial gingival thickness gain at sites grafted with CCM + rhPDGF-BB. It has been suggested that a greater increase in soft tissue thickness may be expected following soft tissue grafting at sites with NCCLs compared to sites without these defects, due to the fact that the graft material is positioned on an unrestored concavity that may further enhance its properties of space maintenance resulting in an increased soft tissue thickness gain.[40]

It is important to bear in mind the limitations of this report. Indeed, the demonstration of two successfully treated cases does not stand alone as "evidence" for a generalized treatment recommendation or guideline, and neither was this the intent of this report. Adequately-designed and sufficiently powered randomized clinical trials, preferably with extended follow-up times are needed to validate our findings, as it pertains to the growth factor (rhPDGF-BB), the scaffolding matrix (CCM), and the benefits of the proposed TCAF approach. The intention of this paper is to describe the feasibility of a minimally invasive approach when attempting root coverage and inspire future application of such combination therapies with different growth factors and bioactive agents, in the common aim of enhancing patient-oriented outcomes. The concept of growth factor-mediated root coverage to substitute standard treatments, while certainly appealing, requires further validation through solid scientific evidence. In particular, noninferiority studies with adequate designs are required for challenging this status quo. Nonetheless, as we embark upon a new era in contemporary periodontal treatments and individualized approaches for our patients, such therapies, if validated and generalized can lead to a paradigm shift in our daily practice.

CONCLUSIONS

The present report describes a novel minimally invasive reconstructive approach for the treatment of multiple adjacent GRs (TCAF), with the application of a CCM, enriched with rhPDGF-BB. The described technique is based upon site-specific application of incisions on the papillary region or for the vertical release, as well as presurgical considerations of KTW, GT and BBD, which are assumed to be key factors for a minimally invasive root coverage approach.

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CONFLICTS OF INTEREST

The authors do not have any conflicts of interest pertaining to this article.

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