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CASE STUDY

Surgical management of gingival recessions in patients with refractory gingival pemphigus vulgaris: A multidisciplinary challenge

Andrea Gabusi[1] | **Martina Stefanini**[1] | **Davide Bartolomeo Gissi**[1] | **Roberto Rossi**[1] | **Matteo Sangiorgi**[1] | **Camilla Loi**[2,3] | **Federica Filippi**[2,3] | **Lucio Montebugnoli**[1] | **Giovanni Zucchelli**[1] | **Federico Bardazzi**[2,3]

[1]Section of Oral Sciences, Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

[2]Division of Dermatology, Department of Experimental, Diagnostic and Specialty Medicine, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

[3]Division of Dermatology, IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico) Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

Correspondence
Andrea Gabusi, Section of Oral Sciences, Department of Biomedical and Neuromotor Sciences, University of Bologna, Via S.Vitale 59, 40159 Bologna, Italy.
Email: andrea.gabusi3@unibo.it

Abstract

Background: Mucogingival surgery for root coverage of gingival recessions (GRs) is usually performed in patients with unremarkable periodontal and systemic health. However, the predictable results of surgical procedures and increasingly high aesthetic expectations of patients necessitate optimal management of GR also in patients with systemic conditions that affect the oral cavity. In patients with pemphigus vulgaris (PV), mucosal fragility and complicated surgical management of inflamed soft tissues are major challenges.

Methods and Results: A 36-year-old female patient with PV and deep GR on the mandibular incisors is presented. After initial unresponsiveness to steroids and immunosuppressants, complete clinical remission was achieved through repeated rituximab infusions and topical platelet-rich plasma. After > 1 year of stable clinical remission off therapy the patient successfully underwent surgical procedures for vertically coronally advanced flap with connective tissue graft.

Conclusions: To the best of our knowledge, no studies have described the surgical management of GR in PV patients. Although controlled studies are required to confirm present results, complete and stable clinical remission is necessary to avoid complications. Collaboration among dermatologists, oral medicine specialists, and periodontologists is essential to determine whether mucogingival surgery for root surface exposure is indicated for PV patients.

KEYWORDS
autoimmune diseases, pemphigus, gingival recession, vertically coronally advanced flap

Key points

Why are these cases new information?

- This is the first report of root coverage in a patient with oral PV

What are the keys to the successful management of these cases?

- The achievement of complete and stable clinical remission from oral PV
- Multidisciplinary collaboration among dermatologists, oral medicine specialists, and periodontologists

What are the primary limitations to success in these cases?

- The refractoriness of gingival lesions induced by PV
- Poor mucogingival conditions of inflamed gingival tissues exacerbated by PV

INTRODUCTION

Gingival recession (GR) is characterized by the displacement of marginal tissue apical to the cemento-enamel junction.[1] The treatment of GR is challenging, particularly in the region of the mandibular incisors, where the bone plate is thin and the vestibulum is shallow. Additionally, inadequate plaque control, trauma, and poor mucogingival conditions may worsen recessions.[2]

Vertically coronally advanced flap (VCAF) and connective tissue graft (CTG) provide satisfactory aesthetic surgical outcomes to treat the deep GRs that affect the lower incisors.[3,4] Currently, mucogingival surgery for root coverage in patients with GR is performed in patients with unremarkable periodontal and systemic health.[2–4] However, the predictable results of surgical procedures and increasingly high aesthetic expectations necessitate optimal management of clinical recessions also in patients with systemic conditions that affect the oral cavity.

Pemphigus vulgaris (PV) is an autoimmune bullous disease that may affect the oral cavity.[5] The prevalence rate of PV is reported to be 65 per million[6] with a predilection for women and the elderly.[7] Mucosal lesions are typically caused by autoantibodies against desmoglein-3 (Dsg3) that split the epithelium.[8]

Any area of the oral cavity can be involved in PV. However, gingival erosions with erythema and/or vesiculobullous lesions are particularly common; their presence is termed desquamative gingivitis.[9]

When it arises in young patients and causes GRs, PV can be both aesthetically problematic and a major risk factor for early tooth loss.[10]

To the best of our knowledge, no studies have described the surgical management of GRs in PV patients.

We describe the case of a young patient with a long history of recalcitrant oral PV associated with deep GRs, resolved with mucogingival surgery only after the achievement of complete clinical remission from PV.

MATERIALS AND METHODS

Clinical presentation

A 36-year-old female patient with a long history of gingival PV managed by the Oral Medicine section (Department of Biomedical and Neuromotor Sciences, University of Bologna) and Dermatology Unit (S. Orsola Hospital, University of Bologna) was referred in 2021 to the Periodontology section of the Department of Biomedical and Neuromotor Sciences (University of Bologna) for the treatment of deep GRs on the mandibular incisors, which were caused or exacerbated by recalcitrant gingival lesions.

The initial PV symptoms appeared in 2012 and included both widespread extra-oral vesiculobullous lesions and erosions involving buccal mucosa and gingiva. The titers of circulating autoantibodies against Dsg1 and Dsg3 in the peripheral blood measured 167 and < 2 U/mL, respectively.

Despite the dermatological lesions completely regressed with the use of systemic steroids, the oral lesions were unresponsive. Attempts with different steroid-sparing agents (azathioprine, topical cyclosporin, mycophenolate mofetil, and intravenous immunoglobulin) were also ineffective. (Figure 1A).

The patient subsequently underwent seven rituximab infusions (five infusions of 500 mg e.v. and two of 1000 mg) since each rituximab cycle could achieve only partial clinical remission that lasted for < 12 months (Figure 1B). Not even low levels of circulating antibodies against Dsg3 (9 U/mL), recorded after the fourth rituximab infusion, prevented the occurrence of relapses.

Finally, 12 months after the seventh infusion of rituximab, clinical examination showed minimal residual gingival erosions related to PV. As an adjunctive topical treatment, the patient started applications of platelet-rich plasma (PRP) once a week for 2 months, which achieved complete clinical remission off therapy (Figure 1C).

PRP preparation required the collection of 3 mL of venous blood from compatible healthy donors under sterile conditions into PT tubes (with 3.2% sodium citrate), followed by centrifugation at 1500 rpm for 20 min.

Platelet activation was performed using human thrombin (5 mL of PRP + 3 mL of thrombin) or 1 mL of 10% calcium gluconate (v/v) in 9 mL of PRP (activation time: 10–20 min at 37°C). The final product contained a minimum platelet concentration of $1 \times 10^6 \pm 20\%$ according to Italy's current legislation (D.M. November 2, 2015). PRP was applied in direct contact with affected areas using sterile gauzes. The product was maintained in situ for at least 1 h with no food or water consumption. The detailed clinical management of PVs is summarized in Figure 2.

After > 1 year of complete and stable clinical remission off therapy, the clinicians considered the patient suitable to be referred to the periodontologist, to evaluate the optimal treatment for GRs.

Case management

The patient had multiple RT2 Cairo's class GRs that affected the lower incisors. Buccal periodontal parameters (recession depth [REC], probing pocket depth [PPD], clinical

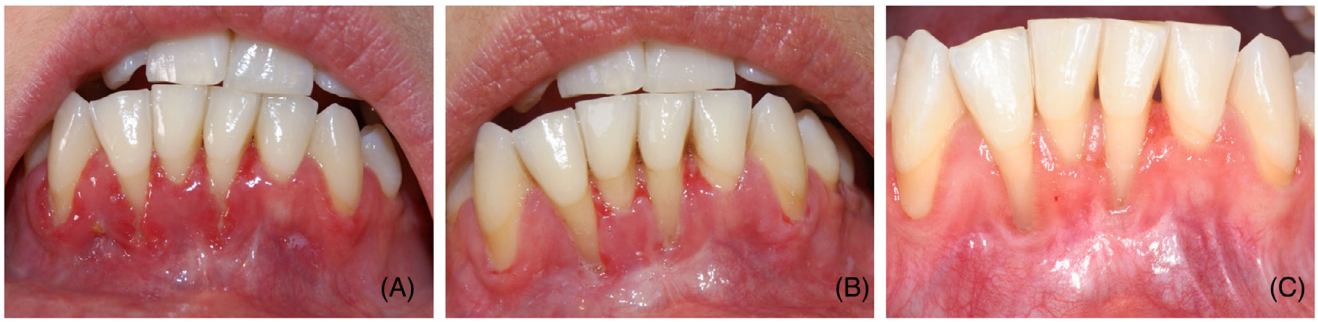

FIGURE 1 Clinical picture of the patient taken before the first infusion of rituximab showing the presence of erosive gingival lesions related to pemphigus vulgaris (PV) and gingival recessions (GRs) (A). The persistence of erosive gingival lesions related to PV has worsened the depth of GRs (B). Clinical picture of the patient taken at the end of platelet-rich plasma (PRP) topical applications (C).

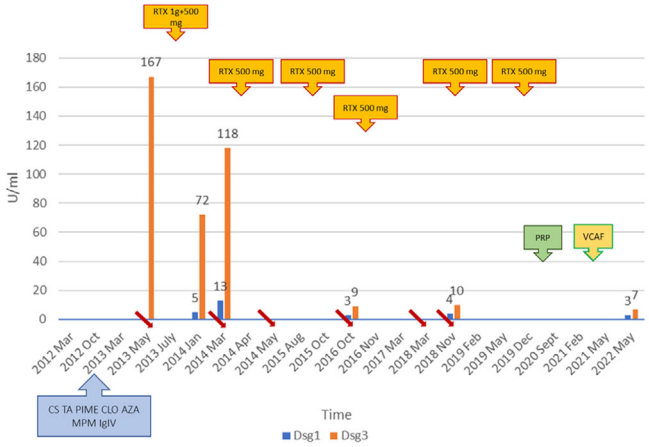

FIGURE 2 Clinical management of PV from baseline to periodontal surgery (VCAF). Red arrows represent relapses. Abbreviations: AZA, azathioprine; CLO, clobetasol; CS, prednisone; Dsg1, desmoglein-1; Dsg3, desmoglein-3; IgIV, intravenous immunoglobulins; MPM, mycophenolate mophetil; PIME, pimecrolimus; PRP, platelet-rich plasma; RTX, rituximab; TA, triamcinolone acetonide; VCAF, vertically coronally advanced flap.

attachment level [CAL], and keratinized tissue [KT]) were recorded at baseline (Figure 1C):

REC: 8 mm; PPD: 2 mm; CAL: 10 mm at the level of #26: absence of KT;

REC: 4 mm; PPD: 2 mm; CAL: 6 mm at the level of #25: 1 mm of KT;

REC: 6 mm; PPD: 3 mm; CAL: 9 mm at the level of #24: absence of KT;

REC: 1 mm; PPD: 2 mm; CAL: 3 mm at the level of #23; 1 mm of KT.

The patient underwent supragingival plaque removal and scaling 4 weeks before the surgical procedure for VCAF.

The designed flap consisted of five interdental horizontal incisions located at a distance from the tip of the interdental papilla equal to the REC plus 1 mm. Then, two slightly divergent vertical incisions distal to #26 and #23 that extended into the alveolar mucosa were made. The trapezoidal-shaped surgical papillae were elevated split-thickness (Figure 3A). At the level of #25 and #23, the KT apical to the root exposure was elevated to a full thickness up to the buccal bone crest; in areas with no apical KT, split-thickness elevation was performed.

Two different incisions were made: a "deep" (Figure 4A) incision (using a blade parallel to the bone) that detached the muscle insertions from the periosteum and a "superficial" (Figure 4B) incision (using a blade parallel to the external lining mucosa) that separated the flap from the muscle. The part of the submucosal labial tissue isolated by the two incisions was removed.[4]

Root surfaces were mechanically treated using Gracey's curettes and chemically conditioned with 24% EDTA gel for 2 min. A CTG derived from the extra-oral de-epithelialization of a free gingival graft from the hard posterior palate (Figure 3B) was sutured apical to the anatomical de-epithelialized papillae (Figure 3C).

The vertical incisions were sutured using simple interrupted sutures, and a sling suture was applied to adapt the flap to the crown convexity[11] (Figure 3D).

Clinical outcomes

At the 1-year follow-up visit, notable recession reduction was achieved (Table 1), and no signs of PV relapse were observed (Figure 5). The following parameters were recorded:

REC: 2 mm; PPD: 2 mm; CAL: 4 mm at the level of #26; 3 mm of KT;
REC: 2 mm; PPD: 2 mm; CAL: 4 mm at the level of #25; 5 mm of KT;
REC: 2 mm; PPD: 2 mm; CAL: 4 mm at the level of #24; 5 mm of KT;
REC: 1 mm; PPD: 2 mm; CAL: 3 mm at the level of #23; 3 mm of KT.

In addition, the level of circulating anti-Dsg3 antibodies measured 7 U/mL, suggesting that the PV disease was still quiescent.

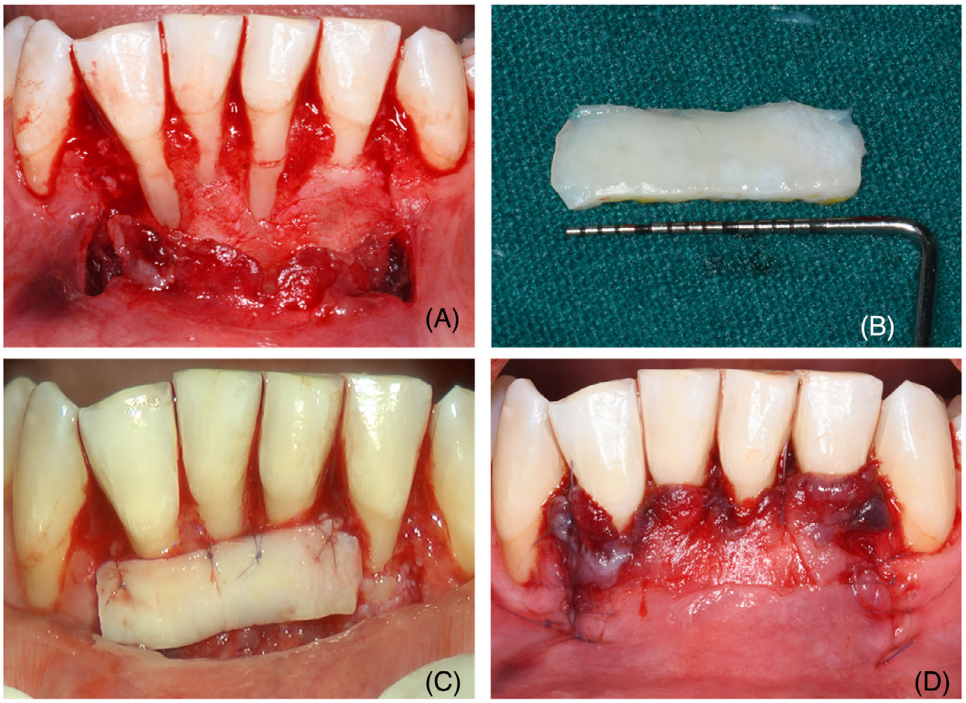

FIGURE 3 Clinical pictures from periodontal surgery: flap design (A). A connective tissue graft (CTG) deriving from the extra-oral de-epithelielization of a free gingival graft was harvested from the hard posterior palate (B). The CTG was sutured apical to the anatomical de-epithelialized papillae with a 7/0 polyglycolic acid (PGA) suture (C). The flap was sutured with simple interrupted sutures along the vertical incisions (7/0 PGA). A sling suture (6/0 PGA) suspended to the lingual cingulum of the treated teeth was done in order to adapt the flap to the convexity of the crown (D).

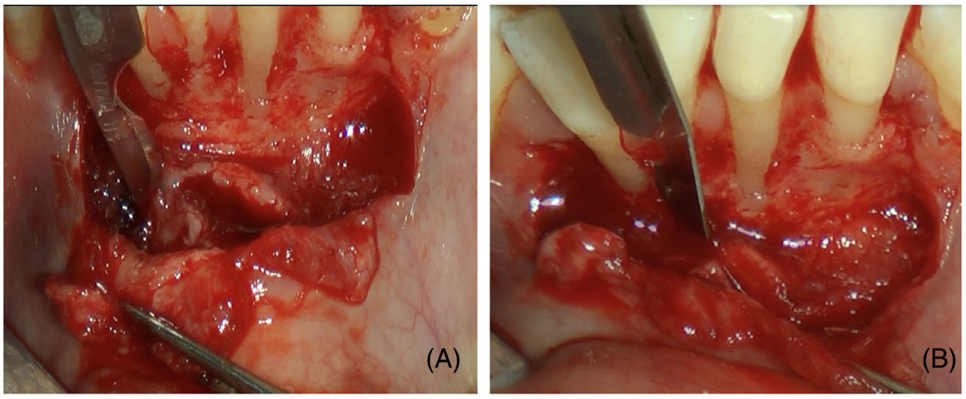

FIGURE 4 Details of muscular detachment during flap design showing deep (A) and superficial (B) incisions.

TABLE 1 Periodontal parameters at baseline and after mucogingival surgery.

	Baseline				After surgery			
Tooth	**#26**	**#25**	**#24**	**#23**	**#26**	**#25**	**#24**	**#23**
REC (mm)	8	4	6	1	2	2	2	1
PPD (mm)	2	2	3	2	2	2	2	2
CAL (mm)	10	6	9	3	4	4	4	3
KT (mm)	0	1	0	1	3	5	5	3
HS (yes/no)	no	no	no	no	no	no	no	no

Abbreviations: CAL, clinical attachment level; HS, hypersensitivity; KT, keratinized tissue; PPD, probing pocket depth; REC recession.

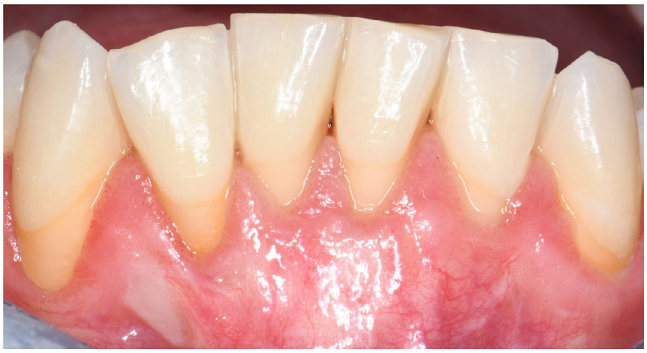

FIGURE 5 Clinical picture of the patient taken 12 months after surgery.

DISCUSSION

To the best of our knowledge, this is the first report of the treatment of GRs in a patient with oral PV.

PV is associated with periodontal disorders. Thorat et al. evaluated the periodontal status of PV patients and found increased PPD, CAL, and clinical severity score (CSS). The poor periodontal status of PV patients suggests that PV may be involved in the development or progression of periodontitis.[12]

Although it appears that PV patients may develop GRs due to their worsened periodontal status, some investigators have hypothesized that autoimmunity may lead to direct and synergic effects on plaque-related inflammation, which could exacerbate periodontal problems and the clinical severity of autoimmune blistering disease. This hypothesis is supported by studies reporting the release of inflammatory cytokines that drive both tissue injury and epithelial splitting (e.g. interleukin [IL]-1, IL-6, IL-8, Tumour necrosis factor alpha (TNFα), and matrix metalloproteinases).[13]

In addition, a major complication of dental management of patients with blistering diseases is the development of bullae and erosions in response to minimal trauma. Indeed, despite the lack of documented cases of failure, the fragility of epithelium and the development of bullous lesions during and after the surgery may hamper the healing process.

In our patient, clinical success may be related to several factors, including the degree of surgeon expertise in performing VCAF and patient age. However, the achievement of complete clinical remission of PV appears mandatory before a VCAF.

The achievement of clinical remission can be challenging. In the present case treatments with steroids, mycophenolate mofetil, and azathioprine were ineffective. Also, the effect of rituximab was delayed, and stable clinical improvement was achieved only after seven rituximab infusions and PRP.

Rituximab is a monoclonal antibody that binds avidly to the CD20 antigen, which is expressed on normally differentiated B-lymphocytes, but not on plasma cells.[14]

A similar delayed response to rituximab was documented also by Greenblatt et al.,[15] where partial remission was achieved early after successive infusions, suggesting a crescendo response to rituximab administration in oral PV.

Several hypotheses were proposed to explain the refractoriness of gingival lesions including the persistence of long-lived plasma cells that continue to produce pathogenic autoantibodies against Dsg 3 despite rituximab administration. This may explain the persistently high anti-Dsg3 level, which decreased to negative only after five infusions.[16]

Other investigators have proposed that autoreactive B cells "hide" in chronic oral lesions and may increase autoantibody production and make lesions recalcitrant.[17,18] This may explain the continued appearance of lesions even in the absence of circulating antibodies

Finally, it is plausible that some treatment-resistant PV lesions are associated with disturbed wound healing.[19] Although the mechanism underlying the effects of PRP is not clear, it is likely mediated by high concentrations of platelet-derived growth factors. In our patient, PRP may have promoted complete clinical remission by improving tissue repair and modulating local inflammation.[20] Topical use of PRP, instead of injections, is less traumatic and more appealing for patients. In a recent study, Ahmed et al. demonstrated the advantages of the topical use of autogenous platelet-rich fibrin mixed with Orabase in terms of pain alleviation and accelerated healing for oral ulcers in blistering skin diseases.[21] In addition, allogenic PRP used in this report offers several advantages over autologous formulations (i.e., standardized platelets concentration, no patient-related contraindications) and should be considered in future studies.

CONCLUSION

This is the first report of root coverage in a patient with PV. Mucogingival procedures appear effective in patients who achieve complete and stable clinical remission from PV. Multidisciplinary collaboration among dermatologists, oral medicine specialists, and periodontologists is essential to identify PV patients suitable for mucogingival surgery.

AUTHOR CONTRIBUTIONS

Conceptualization: Andrea Gabusi, Federico Bardazzi, and Camilla Loi. *Data curation*: Andrea Gabusi, Camilla Loi, and Martina Stefanini. Formal analysis: Andrea Gabusi, Martina Stefanini, Matteo Sangiorgi, Federica Filippi, Camilla Loi, Davide Bartolomeo Gissi, and Roberto Rossi. *Investigation*: Andrea Gabusi, Davide Bartolomeo Gissi, Martina Stefanini, Matteo Sangiorgi, Federico Bardazzi, and Camilla Loi. *Methodology*: Lucio Montebugnoli, Federico Bardazzi, and Giovanni Zucchelli. *Supervision*: Giovanni Zucchelli, Lucio Montebugnoli, Davide Bartolomeo Gissi, and Federico Bardazzi. *Validation*: Giovanni Zucchelli, Lucio Montebugnoli, and Federico Bardazzi. *Writing–original draft preparation*:

Andrea Gabusi and Martina Stefanini. *Writing, review, and editing*: Andrea Gabusi, Martina Stefanini, Matteo Sangiorgi, Roberto Rossi, Davide Bartolomeo Gissi, Federico Bardazzi, Federica Filippi, and Camilla Loi.

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CONFLICT OF INTEREST STATEMENT

This study is original, and all the authors declare no conflicts of interest or competing financial interests.

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