Generalized Aggressive Periodontitis Associated With Plasma Cell Gingivitis Lesion: A Case Report and Non-Surgical Treatment

Andreas O. Parashis, * Emmanouil Vardas, † Konstantinos Tosios, ‡

* Private practice limited to Periodontics, Athens, Greece; and, Department of Periodontology, School of Dental Medicine, Tufts University, Boston, MA, United States of America.
† Clinic of Hospital Dentistry, Dental Oncology Unit, University of Athens, Greece.
‡ Private practice limited to Oral Pathology, Athens, Greece.

Introduction: Plasma cell gingivitis (PCG) is an unusual inflammatory condition characterized by dense, band-like polyclonal plasmacytic infiltration of the lamina propria. Clinically, appears as gingival enlargement with erythema and swelling of the attached and free gingiva, and is not associated with any loss of attachment. The aim of this report is to present a rare case of severe generalized aggressive periodontitis (GAP) associated with a PCG lesion that was successfully treated and maintained non-surgically.

Case presentation: A 32-year-old white male with a non-contributory medical history presented with gingival enlargement with diffuse erythema and edematous swelling, predominantly around teeth #5-8. Clinical and radiographic examination revealed generalized severe periodontal destruction. A complete blood count and biochemical tests were within normal limits. Histological and immunohistochemical examination were consistent with PCG. A diagnosis of severe GAP associated with a PCG lesion was assigned. Treatment included elimination of possible allergens and non-surgical periodontal treatment in combination with azithromycin. Clinical examination at re-evaluation revealed complete resolution of gingival enlargement, erythema and edema and localized residual probing depths 5 mm. One year post-treatment the clinical condition was stable. Radiographic examination indicated improved bone levels and formation of crestal lamina dura.

Conclusion: This case report highlights the unusual coexistence of GAP and PCG, where non-surgical treatment with elimination of all possible causes in combination with antimicrobials resulted in elimination of the gingival enlargement and significant improvement of periodontal parameters.

KEY WORDS (MeSH):
Gingivitis; plasma cell; gingival enlargement/therapy; periodontitis, aggressive/therapy.

BACKGROUND
Generalized aggressive periodontitis (GAP) most commonly affects healthy individuals under 35 years of age. It presents with a pronounced episodic generalized destruction of the attachment and alveolar bone in relation to their age affecting at least three permanent teeth other than first molars and incisors. In contrast to localized forms, clinical inflammation and amounts of plaque and calculus formation are similar to that observed in chronic periodontitis. Although the clinical distinction between chronic periodontitis and GAP is not clear cut, destruction in relation to age and family history are important criteria for its diagnosis. Prevalence of aggressive periodontitis remains elusive, which is reflective of the unresolved debate about its accurate and universally accepted case definition. It appears that among individuals younger than 35 years of age ranges from approximately 1% to a maximum of 15%, depending on the age of participants and the study.

Plasma cell gingivitis (PCG) is an unusual inflammatory condition clinically characterized by marginal gingival enlargement which extends to the attached gingiva. Contrary to plaque induced gingivitis the enlargement is located in the oral aspect of the attached gingiva. The attached and free
gingiva are diffusely enlarged, erythematous and edematous, with loss of normal stippling, a velvety texture and bleed easily. They are sharply demarcated along the mucogingival junction and are not usually ulcerated. PCG is asymptomatic, but some individuals may complain of pruritus, burning or pain. No loss of attachment or bone is usually seen. Microscopically, the gingival epithelium is spongiotic and infiltrated by inflammatory cells, while the underlying lamina propria is highly vascular and densely infiltrated by a polyclonal plasma cell infiltration. Similar lesions have been described on the tongue and lips, while the disease shows clinical and histopathologic similarities to plasma cell balanitis (Zoon’s balanitis). The term “plasma cell orificial mucositis” was also used to describe a similar reactive polyclonal plasma cell infiltration involving different anatomical areas, i.e. oral cavity, larynx, epiglottis and vulvae.

Although the exact etiology of PCG is not known, chronic infection, hormonal changes, Candida albicans infection and particularly a hypersensitivity reaction to certain allergens have been described. Such allergens can be flavoring agents, in particular cinnamon compounds or herbs, incorporated in chewing gums, mouthwashes and toothpastes as well as spices. To date, no definitive management is defined for PCG.

This report presents a unique case of severe GAP associated with a PCG lesion that was successfully treated and maintained non-surgically.

**CLINICAL PRESENTATION**

A 32-year-old white male was referred by his general dentist in September 2009 for treatment of gingival enlargement and periodontitis. According to the patient, the gingiva enlarged progressively and occasionally bled during the last few months; the teeth became progressively mobile; and there was a burning sensation on the gingiva. His medical history was non-contributory. He reported a family history of periodontal disease and a smoking history of two packs per day for 14 years till December 2008, when he quit smoking. His dental history included occasional visits to his dentist for “teeth cleaning”. He denied any habits or parafunctions. He reported using desensitizing toothpaste and chlorhexidine 0.12% rinse daily for the last two months.

Clinical examination revealed gingival enlargement with diffuse erythema and edematous swelling, predominantly around teeth #5-8. Those areas were sharply demarcated and showed no desquamation on friction. The rest of oral and pharyngeal mucosa was within normal limits.

High levels of plaque (PI =95%), gingival inflammation (GI=90%), bleeding on probing (BOP=87%) and calculus were also found. Generalized probing depths (PD) ≥ 5 mm were recorded with depths ≥ 7 mm on teeth #2-7, #10-12, #14-15, #18-19, #24-25 and #30, grade II furcation involvement on # 3 and 14, mobility 1 on #2-5, #14-15, #18-19 and #31, and mobility 2 on #7, #10 and #23-25 (Figs. 1a to 1d). All teeth tested vital. Occlusal analysis revealed generalized fremitus with prematurities on centric occlusion, protrusion and lateral movements without balancing contacts. Radiographic examination indicated generalized moderate bone loss with severe and angular loss on #2-7, #10-12, #14-15, #18-19, #24-25 and #30, widening of the PDL, and thickening of the lamina dura (Fig. 1e). The clinical and radiographic findings were consistent with severe GAP in association with gingival enlargement.

Due to the unusual appearance of enlargement of the gingiva around teeth #5-8, blood tests and histologic examination were suggested and accepted by the patient. A complete blood count and biochemical tests were within normal limits and HIV testing was negative. A biopsy was performed under local anesthesia from the area of #7. Five-micron thick formalin-fixed and paraffin-embedded tissue sections showed parakeratinized gingival mucosa with dense, chronic inflammatory infiltration (Fig. 2a). The epithelium displayed elongated and anastomosing rete pegs, spongiosis
and neutrophilic exocytosis, without micro-abscess formation (Fig. 2b). The underlying lamina propria was highly vascularized and densely infiltrated by plasma cells (Fig. 2b).

Immunohistochemistry was performed in a fully automated system, by applying a polymer detection system††. For antigen retrieval a high temperature technique with citrate buffer was utilized and the reaction product was visualized by incubation with the substrate/chromogen, 3,3’-diaminobenzidine (DAB) prepared from DAB chromogen and DAB substrate buffer (polymer), as a brown precipitate‡‡. Primary antibodies used were mouse monoclonal anti-human antibodies for CD138 (clone MI15, dilution 1:30) and CD20 (clone L26, dilution 1:300), and polyclonal rabbit-antihuman antibodies for kappa (κ) and lambda (λ) light-chains (dilution 1:200) §§. For negative control, the primary antibodies were substituted with non-immune serum of the same specificity.

Most cells were CD138/syndecan-1+ (Fig. 2c) and some of them CD20+ cells (Fig. 2f), while both κ or λ light-chains were expressed (Figs. 2d and 2e). No fungal hyphae or spores were revealed by Periodic Acid-Schiff stain. The microscopic diagnosis was chronic inflammation with plasma cell predominance. The clinical and microscopic findings were suggestive of PCG, and upon questioning the patient admitted regular use of cinnamon-flavored chewing gums, while mint flavor was contained in the desensitizing toothpaste he was using.

Thus, the clinical, radiographic, and laboratory findings were interpreted as severe GAP associated with a PCG lesion and secondary trauma from occlusion. The treatment plan, which included oral hygiene instruction (OHI), mechanical non- surgical therapy in combination with antibiotics, extraction of #1, #16 and #17, splinting of #6-8, occlusal adjustment, and construction of a bite guard followed by re-evaluation, was accepted by the patient.

CASE MANAGEMENT

The patient was instructed to refrain from using any cinnamon-flavored chewing gums. OHI with a rotating-oscillating electric toothbrush*** using a toothpaste containing triclosan and co-polymer††† and reinforcement in combination with ultrasonic supra and subgingival debridement was performed 3 times (Figs. 3a and 3b), followed by splinting of #6-8, occlusal adjustment, and construction of a bite guard (November-December 2009) (Fig. 3c).

Two months later (February 2010) quadrant scaling and root planing under local anesthesia with hand and ultrasonic instrumentation and extraction of #1, 16 and 17 was completed within a week. In addition, azithromycin 500 mgr‡‡‡ the day of the first appointment followed by 250 mgr for 4 days was prescribed. Postoperative instructions included twice daily use of antimicrobial gel§§§ (chlorhexidine 0.2%) for one month followed by daily use, soft foods for 10 days and analgesics (acetaminophen 1000 mg ****, every 4-6 hours) as needed.

CLINICAL OUTCOMES

Postoperatively, the patient tolerated treatment well, had no complaints, and reported having complied with the provided instructions. Re-evaluation was done two months later (April 2010). Clinical examination revealed complete resolution of gingival enlargement, erythema and edema despite average OH (PI=28%), significant reduction of gingival inflammation (GI=15% and BOP=10%) and mobility 1 on #5, #10, #14, and #23-25. PD 5 mm were recorded on # 3, #4, #10, #12, #14-15 and #18 (Figs. 4a to 4d). Surgical treatment for pocket elimination and periodontal regeneration in these areas in combination with a connective tissue graft for #7 to improve esthetics was suggested but the patient opted to delay this treatment because of financial reasons. At this point he was placed on a 3-month maintenance schedule.
The patient complied with all maintenance visits. Clinical examination one year post-treatment (April 2011) revealed again average OH (PI=35%), with moderate inflammation (GI=25% and BOP=14%) without gingival enlargement, erythema and edema. PD and mobility were stable (Figs. 5a to 5d).

Radiographic examination indicated improved bone levels on #2-7, #10-12, #14-15, #18-19, #24-25 and #30-31, reduction in the width of the PDL, and formation of crestal lamina dura (Fig. 5e).

**DISCUSSION**

The case presented herein fulfills the criteria of a diagnosis of GAP, i.e. an otherwise clinically healthy individual with a family history of periodontitis, presenting with rapid generalized attachment loss and bone destruction in a young age. The localized erythematous enlargement of the gingiva was not clinically consistent with GAP, as the latter is not usually associated with significant gingival enlargement or marked marginal inflammation.

An immunofluorescence study in PCG has reported IgG, but not IgM, IgA, or C3 expression by plasma cells, however there are no studies concerning the immunophenotype of inflammatory cells. In chronic periodontitis and GAP plasma cells constitute the dominant inflammatory population and immunohistochemically there is a predominance of CD20+ B-cells over plasma cells that are more numerous in GAP than in chronic periodontitis. In our case, a predominance of CD138/ syndecan-1+ cells was seen, while the presence of CD20+ B-cells was limited. CD138/ syndecan-1 is considered as a marker of plasma cells, but in gingivitis and chronic periodontitis syndecan-1 is reported to be expressed by plasma cells and B-cells. A preponderance of CD138/ syndecan-1+ mature plasma cell over CD20+ B-cells was evident in our case, not conforming to the histological picture of periodontitis. Thus, we suggest that the clinical and microscopic features are more consistent with PCG, possibly associated with a hypersensitivity reaction to cinnamon-flavored chewing gums or mint in the toothpaste.

To the best of our knowledge, this is the first report of severe GAP associated with a PCG lesion that was successfully treated and maintained non-surgically. Only a case of a 15 year old female with rapidly progressive periodontitis combined with marked enlargement of the gingiva with microscopic findings of dense infiltration of plasma cells similar to PCG, and a case of PCG associated with chronic periodontitis, with clinical and histological features very similar to our case, have been reported to date.

Differential diagnosis of PCG is very important due to its clinical similarity with other gingival pathologies, in particular desquamative gingivitis and granulomatous gingivitis that may represent manifestations of mucocutaneous and granulomatous diseases, respectively. In addition, plasma cell predominance in the inflammatory infiltrate necessitates exclusion of plasma cell neoplasms, in particular an unusual plasmablastic lymphoma that is usually located in the gingiva and palate of HIV positive or otherwise immunocompromised patients. Negative HIV testing, lack of clonality, as shown by the expression of κ and λ light chains, as well as recognition of other population of inflammatory cells, ruled out plasmablastic lymphoma in our case.

To date, there is little evidence and no agreement on the most appropriate treatment for PCG and no definitive standard of oral care has been defined. Further, there is little evidence and no agreement on the most appropriate surgical or nonsurgical periodontal protocols to PCG as well as on long-term management.
Although the exact etiological factors of PCG are not known and even the existence of the disease has been questioned, both the clinical and histologic features of this unique disorder suggest an enhanced inflammatory reaction characterized by normal plasma cells. The irritants of this exaggerated response can be traditional periodontal local factors such as plaque and calculus or allergens. The significant role of B-cells in periodontitis and the fact that B-cells and plasma cells are the majority of the cells in periodontitis lesions with no difference between chronic and aggressive periodontitis is well established in the literature. In addition, non-surgical mechanical therapy results in a marked decline of plasma cells both in chronic and aggressive periodontitis. These observations suggest that treatment of PCG can follow the same rational as treatment of periodontitis aiming at elimination of all the possible causes triggering an inflammatory response. Management of this case was based on this assumption.

As soon as the diagnosis of PCG was established the reduction or elimination of all possible causes triggering an inflammatory response has started. The patient was using cinnamon flavored chewing gums, while mint in toothpaste used daily could also act as allergens. PCG is frequently associated with cinnamon or other flavoring agents. Thus, elimination of those factors was the first treatment objective. In addition, OHI with a rotating-oscillating electric toothbrush that shows increase effectiveness of plaque removal over manual brushing, using a toothpaste containing triclosan, an anti-inflammatory agent, and ultrasonic supra- and sub-gingival debridement was performed 3 times. Trauma from occlusion was also eliminated. The reduction in gingival enlargement, erythema, swelling, and inflammation was very slow over a period of two months, but improvement was noticed after each visit (Fig. 3). This finding is in accordance with preliminary results of a case series, where standard professional oral hygiene procedures and non-surgical periodontal therapy including antimicrobials were associated with marked improvement of clinical and patient related outcomes in pediatric cases of PCG.

Definitive treatment with quadrant scaling and root planing under local anesthesia with hand and ultrasonic instrumentation completed within a week started after reduction of severe enlargement and inflammation were confirmed, an indication that the used approach was effective, to allow visibility and proper tissue manipulation. In addition azithromycin 500 mgr the day of the first appointment followed by 250 mgr for 4 days was prescribed. This approach was based on the effectiveness of this regiment in cases of generalized aggressive periodontitis and the need to use concomitantly all possible means to eliminate inflammation and avoid re-infection. Azithromycin use was decided based on the low side effects, suppression of periodontal pathogens and effectiveness in aggressive cases, and high concentration and slow and prolonged release in gingival tissues. In addition, emerging evidence is indicating a possible anti-inflammatory activity and healing through persistence at low levels in macrophages and fibroblasts in periodontal tissues and a reduction of drug-related gingival enlargement.

Postoperative instructions included twice daily use of antimicrobial gel (chlorhexidine 0.2%) for one month followed by daily use to avoid possible allergens included in mouthwashes. This combined treatment resulted in complete resolution of gingival enlargement, erythema, and edema despite average OH and significant reduction of gingival inflammation, PD, and mobility.

Clinical conditions remained stable during maintenance despite average OH and radiographic improvement was observed at one year post-treatment suggesting that all of the possible causes triggering an inflammatory response were maintained below the patient’s threshold level.
Summary

<table>
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<tr>
<th>Why is this case new information?</th>
<th>The present report documents an unusual case of severe GAP associated with a PCG lesion that was successfully treated and maintained non-surgically.</th>
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| What are the keys to successful management of this case? | - Establishing a diagnosis based on clinical, radiographic, histological and immunohistochemistry findings.  
- Reduction or elimination of possible causes triggering an inflammatory response with discontinuation of all possible allergens and non-surgical periodontal treatment in combination with local and systemic antimicrobials. |
| What are the primary limitations to success in this case? | - Compliance with OH and maintenance.  
- Possible recurrence of the disease. |

REFERENCES


CORRESPONDING AUTHOR: Dr. Andreas Parashis, 33 Sp. Merkouri Str., Athens, 11634, Greece. E-mail: parashis@perio.gr

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FIGURE 1.
(a, b, c, d) Clinical and e) radiographic images at initial presentation. Note generalized gingival enlargement interproximally with diffuse erythema and edematous swelling of the attached and free gingiva particularly in teeth #5-8.

FIGURE 2.
(a) Gingival mucosa, consisting of parakeratinized epithelium (EP) and vascular lamina propria (LP), with dense plasma cell infiltration (asterisks) (hematoxylin and eosin stain (H&E), original magnification x25). (b) Epithelium (EP) displays elongated and anastomosing rete pegs, spongiosis, and neutrophilic exocytosis. The inflammatory infiltrate consists mostly of mature appearing plasma cells (asterisks) (H&E, original magnification x100). Positive immunohistochemical expression for (c) CD138, (d) κ and (e) λ light-chains, and to a lesser extent for (f) CD20 (brown grains) (avidin-biotine-peroxidase, original magnification x100).

FIGURE 3.
(a, b) Clinical images following oral hygiene and ultrasonic debridement and c) splinting of #6-8 and construction of bite guard.

FIGURE 4.
(a, b, c, d) Clinical images at completion of treatment. Note complete resolution of gingival enlargement, erythema, and edema. Compare to Figure 1.

FIGURE 5.
(a, b, c, d) Clinical and e) radiographic images at one year post-treatment. Note stable periodontal conditions and radiographic improvement. Compare to Figures 1 and 4.

† Sensodyne rapid relief mint, GlaxoSmithKline, Greece.
** Plak Out, Omega Pharma, Greece.
†† Leica Biosystems Newcastle Ltd, Newcastle Upon Tyne, UK.
‡‡ Leica Biosystems Newcastle Ltd, Newcastle Upon Tyne, UK.
§§ Dako, Glostrup, Denmark.
*** Sonicare, Philips Electronic, Stamford, CT, USA.
††† Colgate Total, Colgate-Palmolive Hellas, Greece.
‡‡‡ Zithromax, Pfizer Hellas, Greece.
§§§ Plak Out Gel, Omega Pharma, Greece.
**** Depon, Bristol-Myers Squibb, Greece.