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Mild elevation of C-reactive protein in a young patient with severe periodontitis: a case report with 2 years of follow-up

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Abstract

Periodontal inflammation is associated with systemic disease. Low-grade inflammation (LGI) is critical to the link between periodontal disease and several systemic disorders. C-reactive protein (CRP) is a common circulating biomarker for acute-phase immune responses, and it is closely related to LGI. The present case demonstrated excellent results using a comprehensive approach for periodontitis in a young woman with severe periodontitis and mild CRP elevation. A 21-year-old Japanese woman complained of tooth mobility and bleeding during tooth brushing. She was pre-obese (body mass index = 29.9), and she had a mildly elevated CRP level (5.2 mg/L). Of all periodontal sites, 34.5% had deep pockets (≥6 mm). The patient was diagnosed with stage III, grade C periodontitis and generalized aggressive periodontitis. Comprehensive periodontal treatments, including regenerative procedures for vertical bone loss and furcation involvement, were performed. Periodontal tissue inflammation was resolved, and periodontal regeneration was achieved. During the 2-year follow-up period, her teeth did not exhibit any signs of instability, attachment loss, or bone loss. Despite the weak nature of the evidence, this case suggests that CRP is valuable for assessing LGI, and it may potentially be considered during periodontal grading in the future.

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Introduction

Periodontal disease is a chronic inflammatory disease triggered by an immune response to oral biofilm, resulting in alveolar bone and tooth loss. Periodontitis was the 11th most prevalent global disease in 2016, with a prevalence of 5% to 20% in middle-aged adults (35–44 years) and 40% in older people (65–74 years).[1]

Furthermore, periodontal inflammation is linked to systemic diseases such as cardiovascular disease, adverse pregnancy outcomes, stroke, and diabetes. The gingival pocket epithelium, which is in direct contact with subgingival biofilm, is the interface through which local inflammation influences systemic conditions. Low-grade inflammation (LGI) is a key concept that links periodontal disease with several systemic disorders.[2] The assessment of LGI involves the evaluation of circulating or cellular biomarkers.

C-reactive protein (CRP) is a common circulating biomarker for acute-phase immune responses. It is used to explain the pathophysiology of inflammatory processes and inflammatory diseases. High-sensitivity CRP (hsCRP) has been used as a sensitive marker for cardiovascular risk screening, and it is closely related to LGI. In the future, hsCRP could be considered in the periodontal classification framework.[3]

The present case reports the excellent results obtained using a comprehensive approach for periodontitis in a young woman with severe periodontitis and mildly elevated CRP levels.

Case report

A 21-year-old Japanese woman was referred to the Department of Periodontology, Nihon University Dental Hospital (Tokyo, Japan) in October 2017 with complaints of tooth mobility and bleeding during tooth brushing. She was systemically healthy, was receiving no medications, and was a non-smoker with no financial issues or cultural beliefs that prevented her from receiving specific treatments. A family history of similar complaints and early tooth loss was reported by the patient, specifically involving her parents. An extra-oral examination did not reveal any abnormalities. Her nutritional status was pre-obesity (body mass index [BMI] = 29.9). Blood tests, including the complete blood count (CBC) and fasting blood sugar (FBS), hemoglobin A1C (HbA1c), and CRP measurements, were performed. Her white blood cell (WBC) count and CRP level were mildly elevated at 9600/μL and 5.2 mg/L, respectively, indicating LGI. The results of other blood tests, including HbA1c, were within normal ranges.

She had no missing teeth. Her periodontium was generally inflamed, with marked edema and friable consistency. The anterior teeth were flaring and highly mobile with a diastema of approximately 2.0 mm between the maxillary central incisors (Figure 1). Detailed baseline periodontal parameters are presented in Figure 2. Of all periodontal sites, 34.5% had deep periodontal pockets (≥6 mm). Only 26.2% of the sites had a healthy periodontal pocket depth (≤3 mm). The O'Leary plaque index was

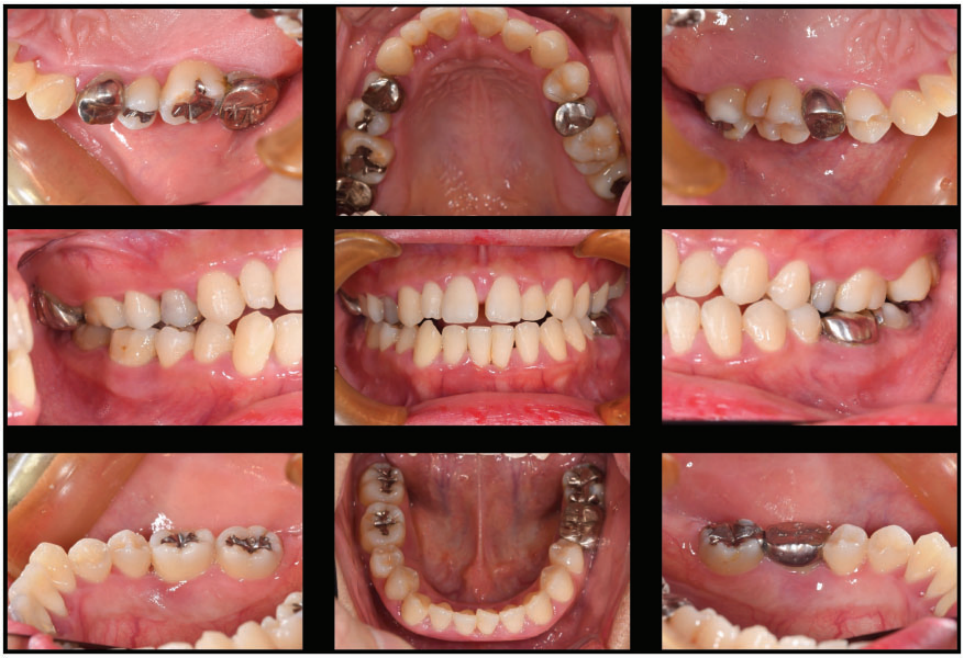

Figure 1. Pre-treatment intra-oral photographs.

PCR : O'Leary Mobility : Miller Furcation : Glickman PPD red number = BOP(+)

PCR																	
Mobility		0	0	0	1	1	1	1	1	1	1	1	0	0	0		
Furcation			I I												I	I	
PPD B		3 3 3	6 3 4	4 3 5	5 3 7	6 2 5	6 3 8	7 3 7	6 2 6	4 7 9	6 3 4	6 3 6	6 3 4	4 3 6	4 3 4		
PPD P		6 4 4	4 3 7	6 3 4	4 4 8	8 7 7	7 6 6	7 4 4	7 3 7	4 3 7	7 4 5	6 4 4	4 4 4	3 3 4	4 4 5		
	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7		8
	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7		8
PPD L		4 4 4	4 4 6	5 3 3	4 3 3	6 3 3	6 3 6	7 5 7	4 6 3	4 4 6	6 3 6	4 4 4	4 4 4	6 5 3	4 4 4		
PPD B		4 4 4	3 3 8	9 3 4	5 3 7	7 3 5	8 4 7	8 5 7	5 3 6	6 3 6	6 3 6	3 3 3	3 3 5	7 6 4	4 4 4		
Furcation			II											II			
Mobility		0	0	1	1	0	2	3	1	1	0	0	0	0	0		
PCR																	

Figure 2. Baseline periodontal charting (October 2017).
B, buccal; BOP, bleeding on probing; L, lingual; P, palatal; PPD, periodontal pocket depth.

64.3%, revealing poor oral hygiene status, and more than 72.6% of the sites displayed bleeding on probing (BOP). The patient presented grade III mobility in tooth #41, grade II mobility in tooth #42, and grade I mobility in most of the anterior teeth according to Miller's classification. According to Glickman's classification, furcation involvement was confirmed as follows: grade I mesial and distal furcation

of #16, grade I distal furcation of #26 and #27, and grade II lingual furcation of #36 and #47. Periapical radiographs revealed generalized horizontal bone loss with supporting bone of less than one-half or one-third of the root length, which was most severe in the lower incisors (Figure 3). Periradicular radiolucency with an angular bony defect involving the apex of the mesial sides of #36 and #46 was observed.

For microbiological examination, saliva was collected in a sampling tube supplied with a commercial kit (Saliva-Check Lab; GC, Tokyo, Japan) and sent to a microbiological testing laboratory (GC Oral Check Center, Tokyo, Japan) for the quantitative detection of periodontal pathogens by quantitative polymerase chain reaction. In total, 8×10^8 cells/mL were collected. Although *Treponema denticola* and *Tannerella forsythia* were detected, their contents were extremely small (0.0043% and 0.0017%, respectively). No other periodontal pathogens were detected. Thus, the hypothetical etiological relationship between specific periodontal pathogens and rapid disease onset was rejected.

According to the new classification of periodontal diseases, the patient was diagnosed with stage III, grade C periodontitis.[3] She was diagnosed with generalized aggressive periodontitis according to Armitage's classification.[4]

In the non-surgical phase of treatment, the patient was motivated to achieve better plaque control. The Bass technique was demonstrated to the patient, who was also educated about the use of interdental brushes. Supragingival scaling and sextant root surface debridement consisting of thorough ultrasonic scaling and root planing under local anesthesia were performed. Teeth #18, #38, and #48 were extracted to improve the cleanability of the second molars. Root canal was performed because apical radiolucency was detected in #17 and #36. Because the patient complained of hypersensitivity in the lower incisors, pulpectomy was performed for the four incisors, for which provisional restorations were fabricated and used during the non-surgical and surgical phases of treatment.

After the non-surgical phase of treatment (11 months), the O'Leary plaque index decreased to 24.1%, and only 26.8% of the sites exhibited BOP. Although non-surgical treatment reduced the probing depth at most sites, several deep periodontal pockets remained. Deep pockets were present in #36, #41, and #46, and extraction was planned for #41 because of its poor prognosis. Although the diastema decreased between the two maxillary central incisors, a midline diastema of 1.0 mm prevailed, and it was restored with composite resin. Prior to planning for the surgical

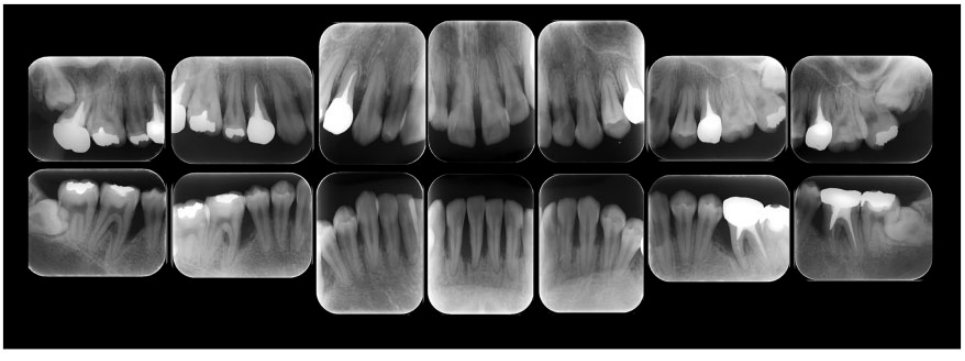

Figure 3. Baseline periapical radiographs (October 2017).

phase, reevaluation with cone-beam computed tomography was conducted for #36 and #46. Imaging revealed a two-walled vertical bone defect without furcation involvement in #36 (Figure 4). Therefore, a periodontal regenerative surgery with 0.3% recombinant human FGF-2 (rhFGF-2; REGROTH® Dental kit, 600 µg in hydroxypropyl cellulose; Kaken Pharmaceutical, Tokyo, Japan) was deemed appropriate for the mesial side of #36 (Figure 5). Furthermore, in the lower right sextant, a two-walled vertical bone defect with lingual furcation involvement was confirmed in #46 (Figure 6). Guided tissue regeneration (GTR), using a resorbable collagen membrane (Bio-Guide; Geistlich Biomaterials, Wolhusen, Switzerland) and bovine bone substitute (Bio-Oss; Geistlich Biomaterials), was conducted at the mesial and lingual sites of #46 (Figure 7). Furthermore, the thickness of the gingiva covering the lower incisors was extremely thin, and the risk of further destruction of the periodontium was high. Thus, connective tissue grafting was performed to increase the gingival thickness to develop a thick phenotype (Figure 8).

After the healing period, all periodontal pockets were eliminated. The lingual furcations of #36 and #46 improved to grade I. In the reconstructive phase of treatment, #17, 14, 25, and 36 were restored with porcelain or zirconia crowns. The lower incisors were also restored with a zirconia fixed partial denture.

After the active treatment phase, the patient has been followed in the maintenance phase since September 2019. Her CRP level decreased to a healthy range after active periodontal treatment. During follow-up, the teeth did not display any signs of mobility, attachment loss, or bone

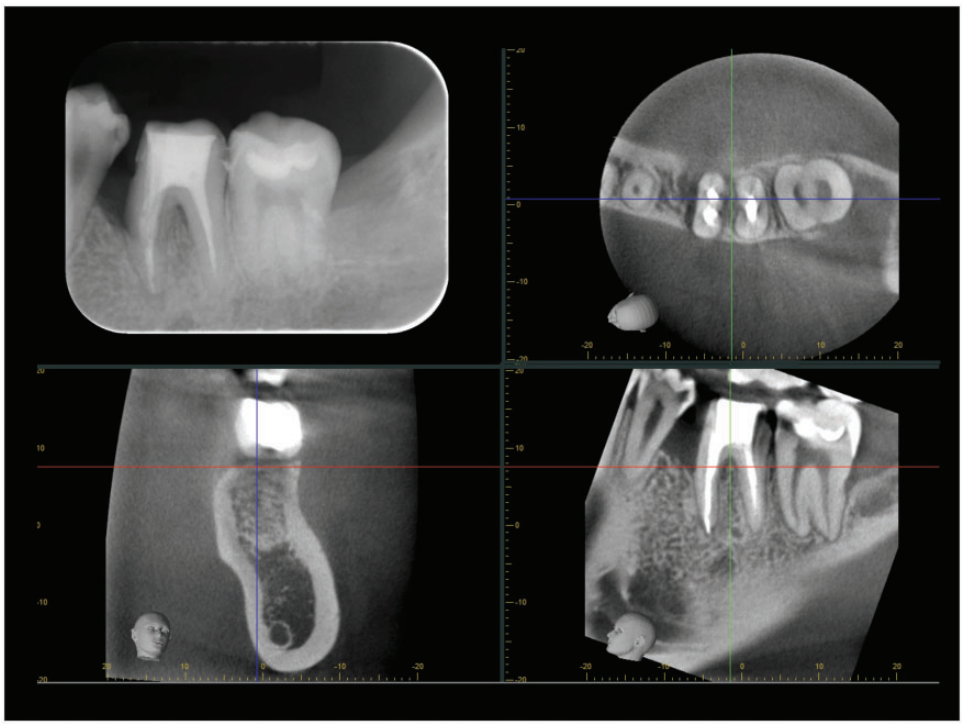

Figure 4. Micro-computed tomography of tooth #36.

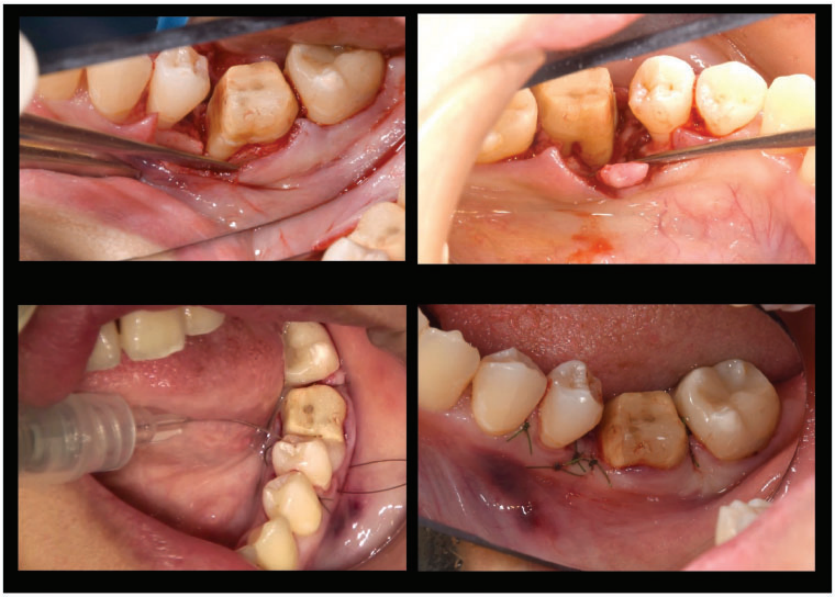

Figure 5. Periodontal regenerative surgery with 0.3% recombinant human FGF-2 for a vertical bone defect in tooth #36.

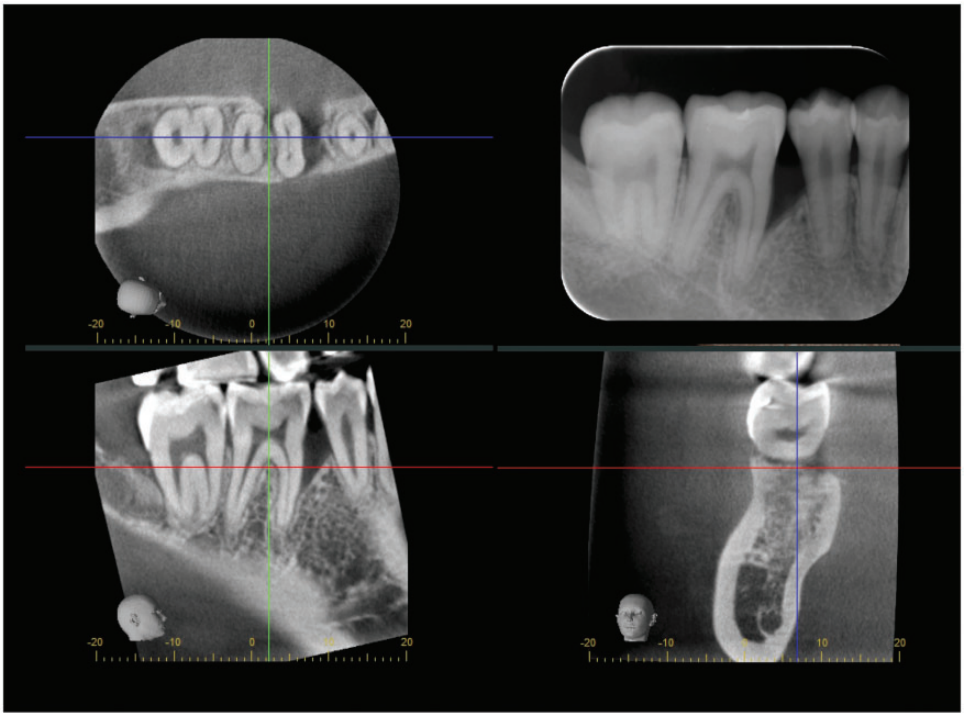

Figure 6. Micro-computed tomography of tooth #46.

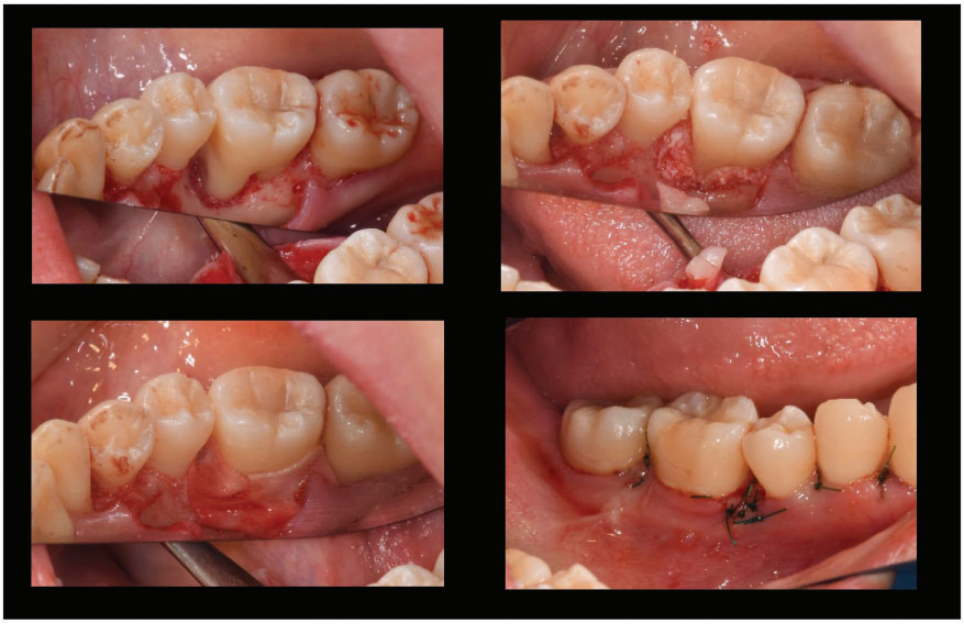

Figure 7. Periodontal regenerative surgery with guided tissue regeneration and bone grafting for a vertical bone defect connected to a furcation defect in tooth #46.

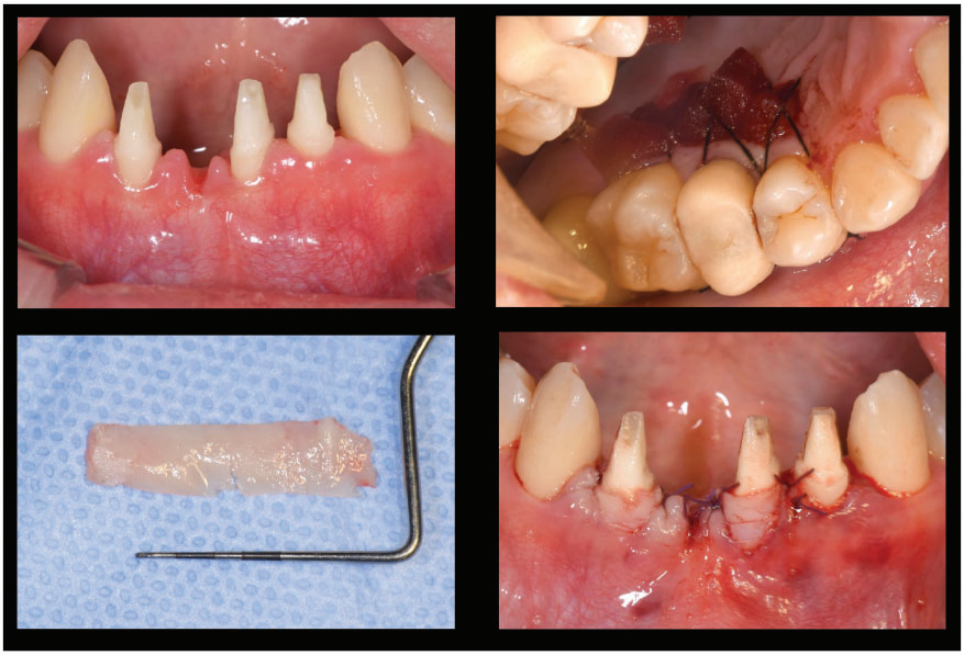

Figure 8. Periodontal phenotype alteration with connective tissue graft.

loss. Follow-up sessions were scheduled every 3 to 4 months. During the recall visits, almost all BOP-positive sites were scaled and irrigated. The 2-year post-treatment periodontal condition is presented in Figures 9 and 10. Detailed periodontal parameters over 2 years of follow-up are presented in Figure 11. After 2 years of follow-up, the patient's WBC count and CRP level were 6700/μL and 1.7 mg/L respectively, which were within normal limits. BMI at after 2 years of follow-up was same as that in the initial visit. The results of other blood tests, including HbA1c, were also within normal ranges.

The reporting of this study conforms to CARE guidelines,[5] and written informed consent to publish was obtained from the patient. Because this was a single case report, there was no requirement for institutional review board approval according to the regulation of Nihon University School of Dentistry.

Discussion

In the present case, a young, systemically healthy patient presented with severe destruction of the periodontium and a mildly elevated CRP level. The results illustrated that periodontal treatment improves both periodontal parameters and systemic outcomes regarding inflammation.

Periodontitis and systemic health are correlated, as periodontitis is influenced by systemic conditions and vice versa. In recent years, the concept of systemic LGI as a common background for several diseases, including periodontitis, has increasingly attracted scientific attention. According to this concept, periodontitis might contribute, at least in part, to the

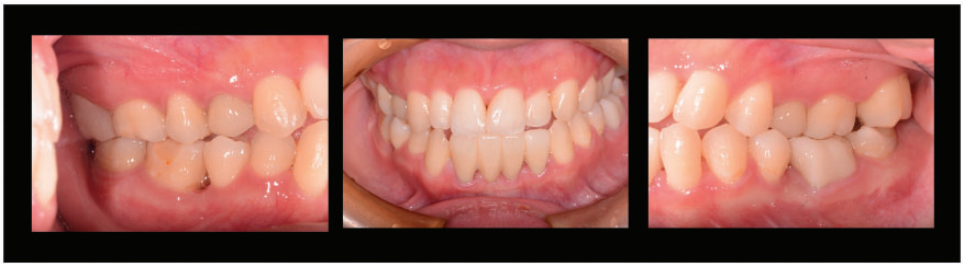

Figure 9. Intra-oral photographs after 2 years of follow-up (September 2021).

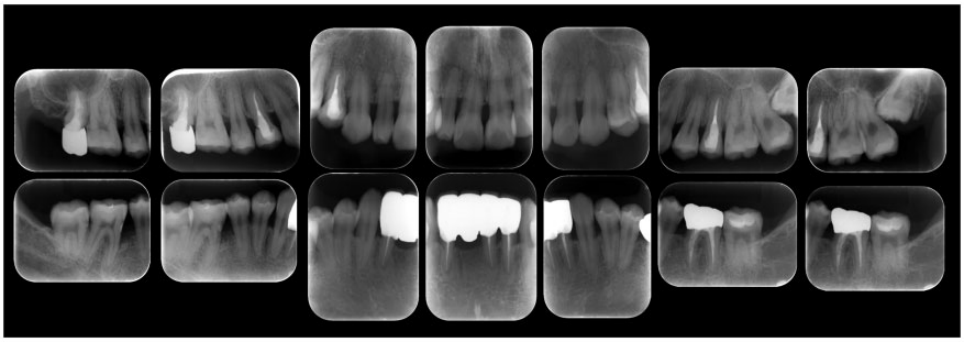

Figure 10. Periapical radiographs after 2 years of follow-up (September 2021).

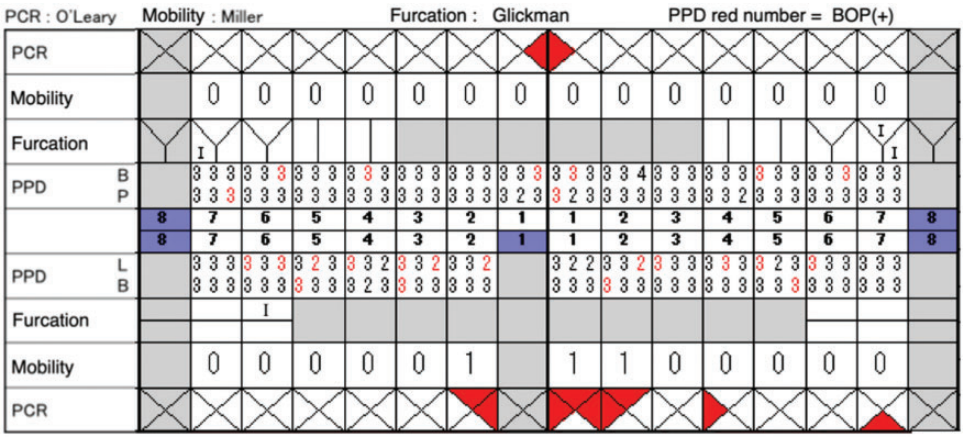

Figure 11. Periodontal charting after 2 years of follow-up (September 2021).
B, buccal; BOP, bleeding on probing; L, lingual; P, palatal; PPD, periodontal pocket depth.

development and progression of chronic systemic conditions by consistently inducing LGI. CRP values represent a summation of the patient's LGI, which may be partly influenced by periodontitis. CRP levels ranging from 3 to 10 mg/L have been accepted as indicative of LGI in several studies.[6–8] The CRP level of the patient at the initial visit was 5.2 mg/L. The WBC count was also mildly elevated in the blood test. Considering her good systemic condition, the mild increases of her CRP level and WBC count were suspected to be attributable to periodontal inflammation. During the World Workshop of Chicago in 2017, a new periodontitis classification that subdivided periodontitis according to a multi-dimensional staging and grading system was adopted.[3] The workshop focused on the effects of systemic diseases and conditions on the course of periodontitis. In the workshop, CRP was envisaged to be integrated into the periodontitis grade. The present case represents a fine example of how CRP level highlights the potential systemic impact of periodontitis.

The effects of periodontitis on the expression of pro-inflammatory cytokines are well known. Slade *et al.* examined the relationship between periodontitis and LGI and clarified how such a correlation might be modified by BMI.[9] In this study, periodontal patients with BMI ≤ 20 displayed 2-fold higher CRP levels than healthy participants. Contrarily, among individuals with BMI ≥ 35, the difference in CRP levels was negligible between periodontal patients and healthy individuals. They concluded that the systemic influences of local inflammation might be enhanced by mild obesity but largely masked by severe obesity. It is important to distinguish the systemic effects of local inflammation (e.g., periodontitis) and metabolic disorders (e.g., obesity). In the present patient, who was pre-obese (BMI = 29.9), both influenced her LGI and needed to be controlled to reduce the risk of systemic and oral burden.

According to the new periodontitis classification, the patient was diagnosed with "stage III, grade C periodontitis." Because more than 30% of periodontal pockets were deeper than 6 mm, the periodontal stage was categorized as stage III or IV according to the severity of disease at presentation. The stage also depends on the anticipated complexity of disease management and further includes a description of the extent and

distribution of the disease in the dentition. Although anterior teeth flaring and open bite were confirmed in the initial dentition in the present case, it was difficult to judge whether they were congenital or attributable to the periodontal disease burden. Thus, the initial stage of the present case was tentatively diagnosed as stage III. The grade provides supplemental information about the biological features of the disease. When previous periodontal records are unavailable, the bone/age ratio should be calculated from the radiographs. In the present case, the lower incisors were the most affected teeth. Because the bone/age ratio of these teeth exceeded 1.0, the diagnosis was grade C periodontitis.

Because the patient exhibited a rapid progressive course, she was diagnosed with grade C periodontitis, and the involvement of genetic factors was suspected. A leading hypothesis of increased susceptibility to progressive tissue destruction entails deficient host response to periodontal infection. The DNA methylation is an epigenetic mechanism that regulates the transcription of many genes, and it is associated with some forms of cancer and inflammatory diseases including periodontitis. A polymorphism in methylenetetrahydrofolate reductase (MTHFR), a key folate enzyme, may impair DNA methylation when folate intake is inadequate, and it might increase the risk of reproductive abnormalities.[10] In MTHFR deficiency, a disorder in the formation of methionine from homocysteine occurs and exposes the organism to both the reduction of methionine (and S-adenosylmethionine) and the toxic effects of homocysteine deposition. Thus, the assessment of polymorphism in MTHFR has the potential to clarify the susceptibility to progressive periodontal tissue destruction.[11] In future studies, host susceptibility outcomes, such as MTHFR polymorphism, should be examined.

The world workshop stated the possibility of including CRP as an assessment modality for grading in collaboration with medical physicians. In the workshop, a CRP level of >3 mg/L was tentatively regarded as grade C. Because the present case was already diagnosed as grade C without considering the CRP level, increasing the grade was impossible. To include these assessments in the future, more detailed categories must be set. Furthermore, the development of the "inflammasome" concept has opened new insights into the initial immune response to periodontal infection.[12] The inflammasome depends on the assembly of a sensor, for instance nod-like receptor family pyrin domain containing protein (NLRP) with its adaptor apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), allowing the recruitment and activation of an inflammatory caspase. It was demonstrated that patients with periodontitis had higher serum and salivary NLRP3 concentrations than healthy controls.[13] Periodontitis was demonstrated to be a significant predictor of both serum and salivary NLRP3 concentrations. Thus, NLRP would be one of the candidates linking periodontitis to systemic inflammation. Future studies are also expected to assess inflammatory markers including CRP and NLRP.

In the present case, different surgical approaches were used for teeth #36 and #46. In #36, a two-walled vertical bone defect without furcation involvement was confirmed. Because of the presence of a bone defect, biological agent monotherapy was selected as the regenerative procedure. Moreover, a two-walled vertical bone defect with lingual furcation destruction was confirmed in #46. Because the bone defect was connected to the furcation defect as a non-contained lesion, a bone graft with a GTR membrane was needed. Consequently, successful periodontal regeneration was achieved in both teeth. Takayama *et al.*

reported a successful case in which the same biological agent (0.3% rhFGF-2) was used for severe lingual furcation defects.[14] Thus, biological monotherapy may have been effective for periodontal regeneration for #46.

The extraction of a periodontally compromised tooth and its subsequent replacement are among the most complex and debatable decisions that a dentist must make during everyday clinical practice. The treatment of questionable teeth is influenced by the status of the dentition in which the tooth is located. Questionable teeth sandwiched between teeth with good prognoses have a wider range of clinical options, such as implant prosthesis or a fixed bridge. In the present case, the periodontal status of anterior teeth excluding #31 was improved drastically by periodontal initial therapy and surgical alternation of the gingival phenotype.[15] As a consequence of periodontal therapy, the patient complained of hypersensitivity in anterior region, and she selected to under pulpectomy. We selected restoration with a zirconia fixed partial denture for lower incisors because of anatomical restoration for both functional osseointegration and harmonious and natural blending of the restoration with the surrounding tissues.

Conclusions

This single case report demonstrated good clinical results using a regenerative periodontal approach for periodontitis in a young woman with severe periodontitis and mildly elevated CRP levels. Despite the weak nature of the evidence, this case suggests that CRP is valuable for assessing LGI in collaboration with other medical variables, and it has the potential to be included in future periodontal grading.

Declaration of conflicting interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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