Association of Human T Lymphotropic Virus 1 Amplification of Periodontitis Severity with Altered Cytokine Expression in Response to a Standard Periodontopathogen Infection

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Background. Periodontal diseases (PDs) are infectious diseases in which periodontopathogens trigger chronic inflammatory and immune responses that lead to tissue destruction. Recently, viruses have been implicated in the pathogenesis of PDs. Individuals infected with human T lymphotropic virus 1 (HTLV-1) present with abnormal oral health and a marked increased prevalence of periodontal disease.

Methods. In this study, we investigated the patterns of periodontopathogen infection and local inflammatory immune markers in HTLV-1–seropositive individuals with chronic periodontitis (CP/HTLV-1 group) compared with HTLV-1–seronegative individuals with chronic periodontitis (CP group) and periodontally healthy, HTLV-1–seronegative individuals (control group).

Results. Patients in the CP/HTLV-1 group had significantly higher values of bleeding on probing, mean probing depth, and attachment loss than patients in the CP group. The expression of tumor necrosis factor α and interleukin (IL) 4 was found to be similar in the CP and CP/HTLV-1 groups, whereas IL-12 and IL-17 levels trended toward a higher expression in the CP/HTLV-1 group. A significant increase was seen in the levels of IL-1β and interferon γ in the CP/HTLV-1 group compared with the CP group, whereas expression of the regulatory T cell marker FOXp3 and IL-10 was significantly decreased in the lesions from the CP/HTLV-1 group. Interestingly, similar frequency and/or load of periodontopathogens (*Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola,* and *Aggregatibacter actinomycetemcomitans*) and frequency of viruses (herpes simplex virus 1, human cytomegalovirus, and Epstein-Barr virus) characteristically associated with PDs were found in the CP/HTLV and CP groups.

Conclusions. HTLV-1 may play a critical role in the pathogenesis of periodontal disease through the deregulation of the local cytokine network, resulting in an exacerbated response against a standard periodontopathogen infection.

Periodontal diseases (PDs) are infectious diseases in which periodontopathogens trigger chronic inflammatory and immune responses that lead to tissue destruction [1, 2]. The presence of multiple gram-negative species in the subgingival biofilm triggers a robust proinflammatory reaction, which involves cytokines such as tumor necrosis factor α (TNF-α) and interleukin (IL) 1β, associated with disease progression [1, 2]. Conversely, anti-inflammatory cytokines, such as IL-10, are also expressed in diseased periodontal tissues and can counteract the effect of proinflammatory mediators [3]. T_H cytokines also can interfere in the progression of periodontal lesions, potentiating (T_H1 and T_H17) or attenuating (T_H2 and T regulatory [Treg] cells) the local host response [4–7]. Therefore, the overall proinflammatory and anti-inflammatory balance is supposed to regulate the balance of the matrix metalloproteinases

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Table 1. Clinical Features of the Control, Chronic Periodontitis (CP), and CP/Human T Lymphotrophic Virus (HTLV) Groups

Feature	Control group[a] (n = 42)	CP group (n = 64)	CP/HTLV group (n = 36)	P[b]
Sex, F/M, No.	20/22	31/33	16/20	.83[c]
Age, mean (SD), years	42.3 (7.61)	48.6 (8.40)	49.6 (8.11)	.56[d]
Plaque index, mean (SD)	0.3 (0.4)	1.4 (1.1)	1.4 (0.9)	.62
BOP, mean (SD), %	5.18 (1.63)	63.58 (12.41)	69.71 (10.66)	.01
Probing depth, mean (SD), mm	2.17 (0.65)	4.22 (0.73)	4.85 (0.93)	<.001
Probing depth at site, mean (SD), mm	2.24 (0.54)	7.05 (1.16)	7.12 (1.31)	.78
Attachment loss at site, mean (SD), mm	0	3.94 (1.12)	4.64 (1.65)	.01

Note. BOP, bleeding on probe; CP, chronic periodontitis; HTLV-1, human T-lymphotrophic virus 1.

[a] All clinical parameters of the control group are statistically different from the CP and CP/HTLV-1 groups (P < .001).

[b] P values for the CP group vs the CP/HTLV-1 group.

[c] Fisher exact test.

[d] Unpaired t test.

and their endogenous inhibitors, which are involved in the degradation of connective tissue, and the receptor activator of NF-κB ligand and osteoprotegerin (as the key molecular regulation system for bone remodeling, where the receptor activator of NF-κB ligand is the main stimulatory factor for the differentiation and activation of osteoclasts, counteracted by osteoprotegerin) and consequently determine the progressive or stable nature of the lesions [8, 9].

However, the etiology of PD is complex, involving several local and systemic factors that can interfere in the control of proinflammatory and anti-inflammatory balance in the periodontal environment. Highly virulent periodontopathogens, such as *Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola,* and *Aggregatibacter actinomycetemcomitans,* are especially associated with higher disease severity and also with systemic infectious and inflammatory complication conditions associated with PD [1, 10–12]. Functional single-nucleotide polymorphisms that effectively regulate cytokine gene transcription are also described to present a small but significant role in the determination of PD outcome [13, 14]. Finally, modifying factors, such as diabetes mellitus, were also described to modify the nature of the host response, increasing the strength of the proinflammatory reaction and determining increased disease severity [1, 12].

Recently, different viruses have been implicated in the pathogenesis of PD [15, 16]. Herpes viruses are frequently found in periodontal pockets and may initiate or accelerate periodontal tissue destruction because of a virally mediated release of cytokines or even an impairment of the periodontal defense, resulting in a heightened virulence of resident pathogenic bacteria [15, 17–19]. Human cytomegalovirus (HCMV), also frequently found in periodontal lesions, may contribute to disease progression through the activation of *IL1B* gene transcription [20].

Interferences in the cytokine transcription are also characteristically associated with human T lymphotropic virus 1 (HTLV-1) infection, an exogenous human retrovirus that infects 10 million to 20 million people worldwide [21]. HTLV-1 infection has also been associated with an increase in CD4 T cells expressing Tax, an increase in CD8 T cells expressing TNF-α and interferon γ (IFN-γ), and high levels of CXCL9 and CXCL10 chemokines, associated with IFN-γ production and recruitment of T cells to the site of inflammation [22]. Deregulated immune response due to HTLV-1 infection is associated with adult T cell leukemia and chronic progressive disease of the central nervous system termed *HTLV-1–associated myelopathy* (HAM)/*tropical spastic paraparesis* (TSP) [21] and also with T lymphocytic alveolitis, polymyositis, arthritis, uveitis, and sicca syndrome [23]. Indeed, the marked production of T_H1 and proinflammatory cytokines and the expansion of autoreactive T cells observed in HTLV-1–infected patients are in part due to the lack of regulatory T cell function and decreased ability of IL-10 and transforming growth factor β to downmodulate immune response [2, 24–28].

Therefore, HTLV-1 infection can be considered a potential modifying factor in the pathogenesis of PD. Indeed, recent studies demonstrate that abnormal oral health is a common feature in HTLV-1–seropositive patients and that such patients have a marked increased prevalence of PD [29, 30]. In this study, we investigated the patterns of periodontopathogen infection and local inflammatory immune markers in chronic periodontitis (CP), HTLV-1–seropositive, HAM/TSP symptomatic individuals (CP/HTLV group) compared with HTLV-1–seronegative individuals presenting with CP (CP group), or periodontally healthy individuals (control group). Herein, we show that HTLV-1 may play a critical role in the pathogenesis of PD through the deregulation of the local cytokine network, resulting in an exacerbated response against standard periodontopathogen infection.

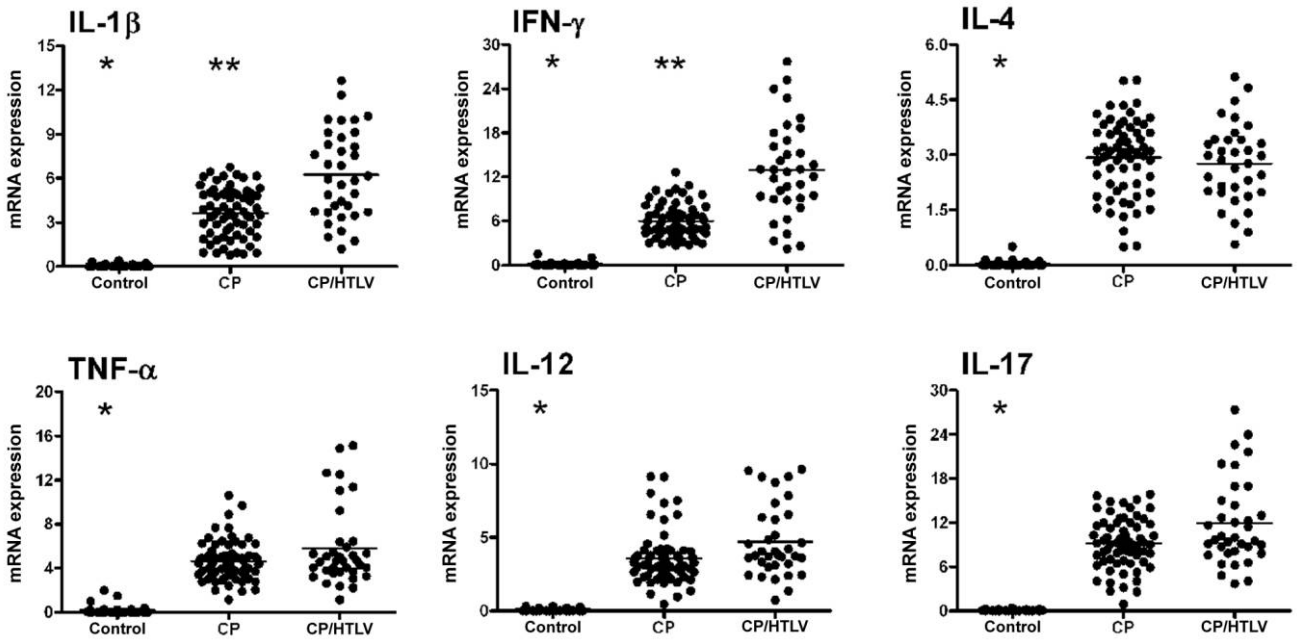

Figure 1. Exacerbated cytokine expression in periodontal lesions from patients infected with human T lymphotropic virus 1 (HTVL-1). Total RNA from gingival samples of control subjects, patients with chronic periodontitis (CP), and HTLV-1–positive patients with CP (CP/HTLV) was extracted, and levels of interleukin (IL) 1β, tumor necrosis factor α (TNF-α), interferon γ (IFN-γ), IL-12, IL-4, and IL-17 messenger RNA (mRNA) were measured quantitatively with real-time polymerase chain reaction (SYBR Green System). The results are presented as the fold increase of expression of the individual mRNAs, with normalization with the target internal control β-actin using the cycle threshold method. *$P < .001$ for the control group versus the CP and CP/HTLV groups; **$P < .05$ for the CP group versus CP/HTLV group (analysis of variance, followed by the Tukey test).

PATIENTS AND METHODS

Study population and clinical examination. This cross-sectional study contained 36 patients in the CP/HTLV group, 64 patients in the CP group, and 42 healthy controls. Patients and controls scheduled for treatment at the Dentistry School of University of Ribeirão Preto and Hospital Universitário Professor Edgar Santos had their histories taken and underwent clinical and periodontal examination. Before the beginning of the study, all individuals signed a consent form that was approved by an institutional review board.

The diagnosis of PD was made according to the American Academy of Periodontology, as previously described [3, 31]: patients were scored for bleeding on probing (BOP), probing depth, and clinical attachment loss (CAL) and then were placed into the CP/HTLV, CP, or control group [3, 31]. After the diagnostic phase, CP patients ($n = 64$) who presented with moderate to advanced PD ($\geq$1 tooth per sextant with a probing depth >6 mm and a CAL >3 mm) received basic periodontal therapy. Biopsy specimens of gingival tissue (1 sample from each patient) were obtained during surgical therapy of the sites that exhibited no improvement in clinical condition (ie, persistent bleeding on probing and higher probing depth) 3–4 weeks after the basic periodontal therapy, as previously described [31]. The control group ($n = 42$) was composed of individuals who presented with clinically healthy gingival tissues (<10% of BOP; no sites with a probing depth >3 mm or CAL) scheduled to undergo surgical procedures for restorative or prosthetic reasons. During these procedures, biopsy specimens of healthy gingival tissue (no BOP and a probing depth <3 mm) were taken. The clinical features of the groups are summarized in Table 1.

The diagnoses of HTLV-1 infection and HAM/TSP were made according to World Health Organization guidelines, as previously described [29–32]. Clinical features of HTLV-1–symptomatic HAM/TSP infection include muscle weakness in the legs, hyperreflexia, clonus, extensor plantar responses, sensory disturbances, urinary incontinence, impotence, and low back pain [29, 30]. Diagnosis of HTLV-1 infection was performed by enzyme-linked immunosorbent assay (Cambridge Biotech) and confirmed by Western blot analysis (HTLV blot 2.4; Genelab) [29, 30]. After HTLV-1 infection and HAM/TSP diagnosis, the patients were categorized into a seropositive and symptomatic group (CP/HTLV group, $n = 36$) or characterized as seronegative ($n = 106$, including the 64 patients in the CP group and the 42 individuals in the control group). Excluded from the study were patients who did not give informed consent, patients with a significant medical history indicating evidence of known systemic modifiers of PD (including human

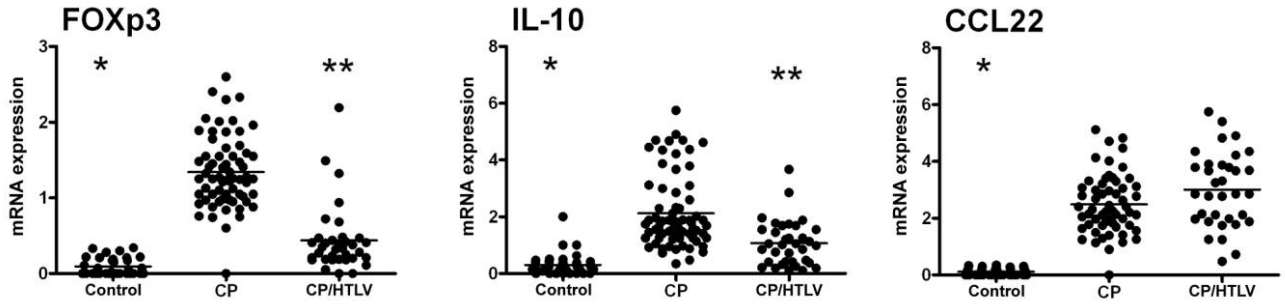

Figure 2. Human T lymphotropic virus 1 (HTLV-1) infection interferes with the regulatory T cell network in periodontal lesions. Total RNA from gingival samples of control subjects, patients with chronic periodontitis (CP), and HTLV-1–seropositive patients with CP (CP/HTLV) was extracted, and levels of FOXp3, interleukin (IL) 10, and CCL22 messenger RNA (mRNA) were measured quantitatively by real-time polymerase chain reaction (SYBR Green System). The results are presented as the fold increase of expression of the individual mRNAs, with normalization with the target internal control β-actin using the cycle threshold method. *$P < .001$ for the control group versus the CP and CP/HTLV groups; **$P < .05$ for the CP group versus the CP/HTLV group (analysis of variance, followed by the Tukey test).

immunodeficiency virus and diabetes mellitus), or those who had undergone periodontal therapy in the previous 2 years, as previously described [31]. Smokers were specifically excluded.

Real-time polymerase chain reactions. Real-time polymerase chain reactions (PCRs) were used to quantify cytokine expression in periodontal tissue samples and to detect and quantify the target pathogens in periodontal biofilm samples. The extraction of total RNA from periodontal tissues samples, performed with Trizol reagent (Invitrogen), and the complementary DNA synthesis were accomplished as previously described [13]. To allow the detection of *P. gingivalis*, *T. forsythia*, *T. denticola*, and *A. actinomycetemcomitans*, and also herpes simplex virus 1 (HSV-1), human cytomegalovirus (HCMV), and Epstein-Barr virus (EBV), periodontal crevice or pocket biofilm samples were collected with sterile paper point ISO No. 40 from the same site biopsied previously to the surgical procedure [33]. Bacterial DNAs were extracted from plaque samples with a DNA Purification System (Promega) [3]. Real-time PCR messenger RNA or DNA analyses were performed in an MiniOpticon system (BioRad), using SybrGreen MasterMix (Invitrogen), specific primers, and 2.5 ng of complementary DNA or 5 ng of DNA in each reaction, as previously described [4, 14]. For messenger RNA analysis, the relative level of gene expression was calculated in reference to β-actin using the cycle threshold method. Positivity to HSV-1, HCMV, and EBV was determined on the basis of positive and negative controls, similar to the method previously described [14]. Positivity to bacteria detection and the bacterial counts in each sample were determined on the basis of comparison with a standard curve composed of specific bacteria DNA (1×10^9 to 1×10^{-2} bacteria) and negative controls, similar to the method previously described [14], and then adjusted for sample dilution in the assay to accomplish the bacterial copy numbers in each site. The sensibility range of bacteria detection and quantification of our real-time PCR technique was of 10^1 to 10^8 bacteria to each of the 4 periodontopathogens tested.

Statistical analysis. The significance of the differences in observed frequencies of periodontopathogens was assessed by the χ^2 test. The possible differences between the genotype subgroups of the control and CP subgroups were evaluated by analysis of variance, followed by the Tukey test. $P < .05$ was considered statistically significant.

RESULTS

PD parameters in HTLV-1–seropositive and HTLV-1–seronegative patients. The study sample was similarly composed of male and female patients (Table 1), and as expected, the clinical parameters of periodontitis severity are strikingly lower ($P < .001$, for all parameters tested) in the control group. When comparing the CP group with the CP/HTLV group, similar scores of plaque index ($P = .62$) and probing depth ($P = .78$) of the biopsied sites were found, whereas the CP/HTLV group was found to have significantly higher values of BOP ($P = .01$), mean probing depth ($P < .001$), and attachment loss ($P = .01$) than patients in the CP group.

Cytokine messenger RNA expression pattern in periodontal lesions. Because cytokine patterns expressed in the periodontal lesions are thought to determine or influence disease outcome, we next investigated the possible interference of HTLV-1 infection in the cytokine milieu (Figure 1). In accordance with previous studies, cytokine expression in the control group was found to be strikingly lower than in diseased tissues. The expression of TNF-α and IL-4 was found to be similar ($P > .05$) in the CP and CP/HTLV groups, whereas IL-12 and IL-17 levels present a trend (nonstatistically significant, $P > .05$) toward a higher expression in the CP/HTLV group. Our results also demonstrate a significant increase in the levels of IL-1β

Table 2. Frequencies of Microbial Detection in the Control, Chronic Periodontitis (CP), and CP/Human T Lymphotrophic Virus (HTLV) Groups

Microbial parameters	Control group, no. (%) (n = 42)	CP group, no. (%) (n = 64)	CP/HTLV group, no. (%) (n = 36)	CP vs CP/HTLV P[a]
Porphyromonas gingivalis	5 (11.9)	42 (65.22)	22 (60.94)	.67
Treponema denticola	4 (9.52)	39 (60.84)	19 (52.63)	.53
Tannerella forsythia	4 (9.52)	37 (53.04)	18 (49.86)	.53
Aggregatibacter actinomycetemcomitans	1 (2.38)	11 (17.16)	5 (13.85)	.78
HSV-1	3 (7.14)	29 (45.24)	15 (41.55)	.83
HCMV	2 (4.76)	36 (56.16)	18 (49.55)	.68
EBV	3 (7.14)	29 (45.24)	16 (44.32)	>.99
HTLV-1	0 (0)	0 (0)	36 (100)	<.001

Note. EBV, Epstein-Barr virus; HCMV, human cytomegalovirus; HSV-1, herpes simplex virus 1.
[a] $P < .05$, Fisher exact test.

($P < .05$) and IFN-γ ($P < .05$) in the lesions from the CP/HTLV-1 group when compared with the CP patients. When cytokine levels from the HTLV lesions were compared with an age-, sex-, and clinically matched CP subgroup, similar results to the comparison with the whole group were found (data not shown).

Quantitative analysis of Treg marker expression. Because HTLV-1 was described to interfere with Treg networks, we next investigated the expression of Treg markers in periodontal lesions (Figure 2). As previously described, the expression of Treg markers was found to be significantly higher in diseased than in healthy tissues ($P < .001$, for all markers analyzed). When comparing the CP and CP/HTLV groups, we found that the expression of FOXp3, the transcription factor essential for Treg development and function, was notably decreased ($P < .05$) in the lesions from the CP/HTLV group. Similarly, the expression of IL-10 was also found to be lower ($P < .05$) in the CP/HTLV group when compared with the CP group. Interestingly, CCL22, described as a Treg chemoattractant in the periodontal environment, was found to be similarly expressed in periodontal lesions from the CP and CP/HTLV groups ($P > .05$). When Treg marker levels from HTLV lesions were compared to an age-, sex-, and clinically matched CP subgroup, similar results were found (data not shown).

Periodontopathogen frequency and load in periodontal lesions associated or not with HTLV-1 infection. In the view of the increased severity of PD and dysregulated cytokine production in the lesions associated with HTLV-1, we next investigated whether such a response could be due to differences in the frequency and/or load of periodontopathogens. Regarding the frequency of bacterial periodontopathogens and viruses in periodontal pockets, our data demonstrate that all the pathogens investigated were strikingly less frequent in the control group ($P < .001$), as expected (Table 2). When the CP and CP/HTLV groups were compared, no significant differences (see Table 2 for P values) were found in the frequency of *P. gingivalis, T. forsythia, T. denticola, A. actinomycetemcomitans*, HSV-1, HCMV, and EBV detection. When the load of the bacterial periodontopathogens in the different groups was investigated, we found the load of the periodontopathogens was markedly higher in diseased sites than in healthy ones ($P > .001$) (Figure 3). Comparing the CP and CP/HTLV groups, no differences were found in the load of any of the bacteria analyzed ($P > .05$) (Figure 3). When the frequency and load of periodontopathogens from HTLV lesions were compared to an age-, sex-, and clinically matched CP subgroup, similar results were found (data not shown).

DISCUSSION

PDs are infectious diseases in which the chronic inflammatory immune responses raised against periodontopathogens lead to tissue destruction. In this scenario, the balance between pro-inflammatory (TNF-α and IL-1β), T_H1, and T_H17 cytokines versus anti-inflammatory and T_H2 cytokines is supposed to determine PD outcome. Interferences in the patterns of host response are characteristically associated with HTLV-1 infection, which recently was demonstrated to be associated with increased prevalence of PD [34]. In accordance, our data demonstrate that HTLV-1–positive patients had higher scores of the clinical parameters of disease severity. Accordingly, HTLV-1 infection is characteristically associated with a systemic immune–mediated inflammatory disease that results in tissue damage [21, 24, 30]. Interestingly, HTLV-1 infection can modify the pathophysiology of osteoarthritis (a condition that shares several characteristics with PD, such as the chronic nature of the inflammatory reaction associated with bone resorption activity) by increasing the inflammatory activity in a subset of carrier patients but does not necessarily worsen the clinical outcome and local synovitis [35].

Therefore, to investigate the putative mechanisms by which

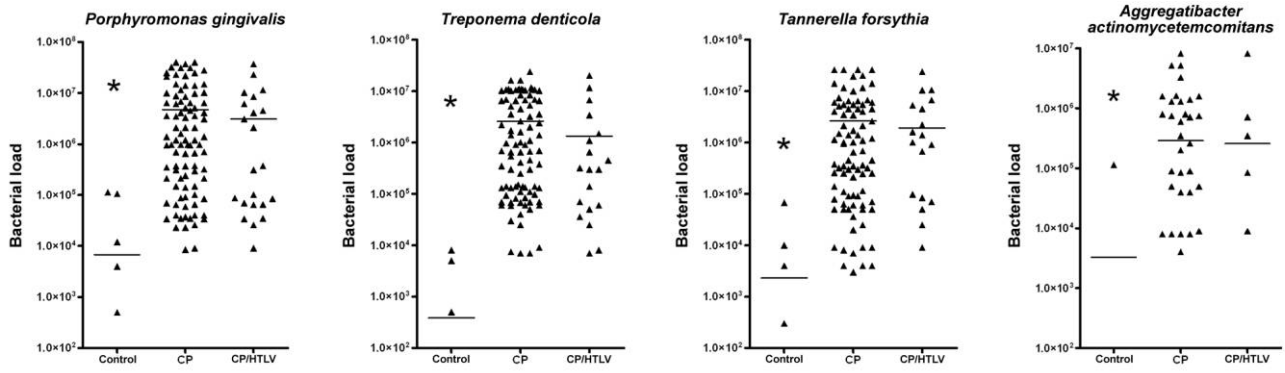

Figure 3. Quantitative assessment of the periodontopathogen load in the chronic periodontitis (CP) and human T lymphotrophic virus 1 (HTLV-1) and CP (CP/HTVL) groups. The loads of the periodontopathogens *Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola,* and *Aggregatibacter actinomycetemcomitans* in the periodontal crevice or pockets of control subjects, CP patients, and CP/HTLV patients were determined by real-time polymerase chain reaction. Only patients who tested positive for each bacteria are depicted in the figure; for prevalence consult Table 2. $*P < .001$ for the control group versus the CP and CP/HTLV groups; $**P < .05$ for the CP group versus the CP/HTLV group (analysis of variance, followed by the Tukey test).

HTLV-1 could increase periodontitis severity, we initially investigated the pattern of cytokine expression in the lesions. Although similar levels of TNF-α and IL-4 were found in the samples from both the CP and HTLV-1 groups, lesions from HTLV-1–positive patients presented a trend toward a higher IL-12 and IL-17 expression. In addition, the CP/HTLV group was found to have significantly higher levels of IL-1β and IFN-γ than the CP patients. Accordingly, HTLV-1 infection is characterized by spontaneous proliferation of $CD4^+$ lymphocytes that harbor a provirus, promoting an active expansion of infected T cells and leading to systemic and abundant secretion of cytokines, such as IFN-γ, TNF-α, and IL-6 [24, 28, 36]. In HTLV-1–associated tissue damage, a proinflammatory microenvironment is the hallmark of the immunologic profile, with increased levels of IFN-γ, TNF-α, and IL-6 a common finding [24, 28]. Interestingly, a similar skew toward a predominant proinflammatory T_H1-type response is verified in aggressive periodontitis, and a PD form is characterized by early onset and increased severity [6, 31].

Another important immunologic finding is that Treg activity is supposed to be impaired in the periodontal lesions from HTLV-1–positive patients, as suggested by the decreased expression of FOXp3 and IL-10. In accordance with our findings, HTLV-1 symptomatic patients exhibit reduced FOXp3 expression and Treg suppressor function compared with healthy donors, which could explain the marked cellular activation, spontaneous cytokine production, and associated disease development [26, 27]. In periodontal tissues, $CD4^+CD25^+FOXp3^+$ cells were found in inflammatory infiltrates in periodontal tissues and were associated with high expression of the regulatory cytokines IL-10 and transforming growth factor β [4]. Interestingly, the levels of CCL22, thought to be responsible for Treg chemoattraction to periodontal tissues [4], are similar in the lesions from the CP and HTLV-1 groups, suggesting that a defective function, and not a defective migration, is associated with the impaired Treg activity in the lesions. Conversely, a recent study suggests that the HTLV-1 infection leads to dissemination of *Strongyloides stercoralis* by augmenting Treg counts, which in turn down-regulate the immune response to the parasite [37]. However, a previous study suggests that the high production of IFN-γ observed in patients coinfected with HTLV-1 and *S. stercoralis* is responsible for the impaired T_H2 response against this helminth [38], reinforcing the complexity of the immunologic networks involved in coinfection processes. Interestingly, because our HTLV group was free of active *S. stercoralis* infection (data not shown), it is possible to rule out the possible additional influence of this coinfection in our results and to suggest that distinct coinfections (ie, HTLV-1 and periodontitis vs HTLV-1 and strongyloidiasis) may result in distinct immunoregulatory and pathological outcomes. However, further specifically designed studies are required to support deeper discussions in this field.

Another possibility for the increase in periodontitis severity due to HTLV-1 infection, besides the indirect interference in the immune response, is the interaction with the classic periodontopathogens. Indeed, EBV and HSV are thought to mediate overgrowth and increased aggressiveness of periodontopathic bacteria [15, 16]. However, our results demonstrate that both frequency and load of *P. gingivalis, T. forsythia, T. denticola,* and *A. actinomycetemcomitans* were similar in the CP and CP/HTLV groups. In addition, the frequency of EBV, CMV, and HSV infection was also similar between HTLV-1–positive and HTLV-1–negative individuals with PD. These findings, considered together with the similar plaque index scores between the CP and CP/HTLV groups, also rule out the possibility that immunologic abnormalities in HTLV-1–infected patients could

interfere with the proper mechanical control of oral microorganisms, which could favor periodontitis development. In addition, it is important to consider that HTLV-1 may also be an important local cofactor in the determination of tissue damage in periodontal lesions. An important point to be considered is the fact that healthy periodontal tissues of HTLV-1–infected patients were not evaluated for the pattern of cytokine expression (because of ethical and technical issues), and further studies are required to determine whether the cytokine imbalance reported in this study is the cause of PD or an adverse effect of HTLV-1 infection.

Increasing evidence suggests that immunosuppression associated with HTLV-1 infection may affect the risk and expression of several other infectious diseases, such as tuberculosis and leprosy [39, 40]. However, distinct from most infectious diseases, in which the intensity of the immune response seems to be associated with the control (at least partial) of the infectious agents, in human and experimental periodontitis even the development of robust responses does not allow the clearance of periodontal infection [13, 14, 41]. Indeed, the ability of the periodontopathogens to attach and colonize the subgingival biofilm, as well as to invade epithelial and endothelial cells, confers an efficient protection that possibly impairs its clearance [42, 43]. Therefore, the hyperinflammatory genotypes may not be an evolutionary advantage in view of the complex host-pathogen interaction of PDs.

In summary, our results show that infection with HTLV-1 presents as an exacerbated inflammatory immune response, possibly associated with an impaired Treg activity, in response to a usual pattern of periodontal infection. The first steps in solving the puzzle of microbial and immunologic contributions to the immunopathogenesis of PD have been achieved, but further studies are required to understand their exact contribution in periodontitis outcome.

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Potential conflicts of interest. All authors: no conflicts.

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