The Relationship Between Peripheral Levels of Leukocytes and Neutrophils and Periodontal Disease Status in a Patient With Congenital Neutropenia

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Background: *Congenital neutropenia is characterized by an almost total absence of neutrophils and increased susceptibility to infection. Oral manifestations include ulcerations of mucous membranes, acute gingival inflammation with focal necrosis, and rapid loss of attachment. Treatment with recombinant human granulocyte colony-stimulating factor (rhG-CSF) increases neutrophil numbers and ameliorates the periodontal status.*

Methods: *We report the treatment of a 22-year-old male with congenital neutropenia (Kostman syndrome), referred to us due to periodontal disease, and the effect of treatment on peripheral neutropenia. Diagnosis of neutropenia was made at year 1; at age 15, the patient started to receive injections of rhG-CSF, reducing the occurrence of infection and improving neutrophil count, although levels remained below normal. The patient underwent extraction of a molar at age 8; scaling, root planing, and modified Widman flaps at age 9; and oral hygiene maintenance every 2 to 3 months from age 18 to 21. At age 23, he initiated treatment at our periodontal clinic. The patient's gingiva was severely inflamed, and the dentition was covered with plaque and calculus. Attachment loss was advanced, all teeth were mobile, and bone loss was approximately 75% in most sites. Neutrophil counts were below normal, but other hematologic parameters were normal. Scaling and root planing were performed and the patient received antibiotics and chlorhexidine rinses twice each day for 2 weeks. Extracoronal splinting was performed, fluoride varnish was used to desensitize cervical areas, and tooth FDI #46 was restored. Root planing and deplaquing were repeated, and the patient received subgingival chlorhexidine irrigation 13 times over one year. Assessments were made on presentation, after the initial treatment, and at 1 and 2 years post-treatment.*

Results: *Mean probing depth was reduced post-treatment with a further reduction during the maintenance period. This was correlated with an increase in attachment levels. Total white blood cells increased, due in part to an increase in neutrophils, reaching normal levels.*

Conclusions: *This report demonstrates for the first time that periodontal therapy, resulting in decreased bacterial load, may result in restoration of normal levels of circulating neutrophils in individuals with congenital neutropenia under treatment with rhG-CSF. The results also suggest that periodontal pathogens may be associated with depressed neutrophil levels, even when patients receive treatment for neutropenia.* J Periodontol 2000;71:1499-1505.

KEY WORDS

Granulocyte colony-stimulating factor, recombinant; periodontal diseases/therapy; periodontal diseases/pathogenesis; neutropenia; neutrophils.

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Case Report

The neutrophil is the most commonly found leukocyte, comprising up to 70% of all white blood cells. As the primary phagocytic cell, the neutrophil plays a crucial role against bacterial infection, especially during the acute phase. In conditions in which leukocyte function is impaired, the importance of this cell to the host immune response is evident.

Neutropenia as defined by Kostmann[1] is a condition in which the number of neutrophils in the peripheral blood is less than 1,800/µl. Congenital neutropenia is an inborn defect characterized by a neutrophil cell-line specific impairment. In this disease, there is an almost total absence of neutrophils. The total number of leukocytes is markedly lower than in normal individuals. Persons with congenital neutropenia are more likely to contract respiratory tract and skin infections. They also suffer from infections of the ear, gastrointestinal tract, and genitourinary system. These recurrent infections may prove fatal during infancy. At present, the treatment of this condition includes the use of recombinant human granulocyte colony-stimulating factor (rhG-CSF).[2] The recombinant protein resembles the natural factor, releasing the neutrophil reservoirs from the bone marrow to the peripheral bloodstream, thus elevating the neutrophil count 10- to 12-fold. Treatment with rhG-CSF prolongs life expectancy of congenital neutropenia patients.

In situations in which there is an impaired host response to infections, as is seen in individuals with defects in the number or function of neutrophils, loss of periodontal attachment is frequently encountered.[3-8] Since congenital neutropenia is characterized by a severe neutrophil defect, some of its clinical signs are ulceration of mucous membranes, acute gingival inflammation with necrotic spots, and rapid loss of attachment. As a rule, the severity of the clinical signs is proportionate to the severity of the neutropenia. Treatment with rhG-CSF markedly improves the neutrophil count and concomitantly ameliorates the periodontal status of these patients.[9]

The aim of the present paper is to examine the relationship between periodontal treatment and peripheral neutropenia. We describe the treatment of a 22-year-old male with congenital neutropenia (Kostmann syndrome). The patient was referred to us by the attending hematologist because of his periodontal condition. This article describes the result of periodontal treatment and its effect on the peripheral neutropenia.

MEDICAL HISTORY

The patient's diagnosis of congenital neutropenia was made at the age of one year. No other family member is known to have this condition. In early infancy, he had constant skin, ear, eye, and upper respiratory infections. The patient stated that in late infancy, he had had a period of several years of relative quiescence, but infections started recurring around age 12. At age 15 (1991), he began to receive injections of rhG-CSF.§ Neutrophil counts were markedly increased, although their levels were lower than normal. Since then, he has not suffered from infections and leads a normal life.

Figure 1.
Pretreatment clinical appearance of patient with congenital neutropenia.

DENTAL HISTORY

The patient's oral problems started around age 4. His lower left first molar was extracted in 1984, at age 8. His right upper and lower first molars were extracted in 1990, at age 14. In 1985 (age 9), he underwent scaling and root planing, instruction in oral hygiene, and modified Widman flaps in the posterior lower sextants. The patient was placed on a maintenance regimen, but compliance was poor. Still, his periodontal condition between ages 12 to 18 was relatively free of acute episodes. In 1994, he was inducted into the army. During his 3-year military service, he participated in an oral hygiene maintenance regimen involving prophylactic treatment every 2 to 3 months. After his discharge, the patient discontinued dental care until he decided to resume treatment about a year and a half later. This treatment was performed in the Graduate Periodontal Clinic of the Hebrew University-Hadassah School of Dental Medicine (Jerusalem, Israel).

On presentation, the patient's gingiva was severely

§ Neupogen, Amgen, Inc., Thousand Oaks, CA.

Figure 2.
Clinical pretreatment radiograph of patient with congenital neutropenia. ***A.*** *Upper jaw;* ***B.*** *lower jaw.*

inflamed and the teeth were literally covered with plaque and calculus. The tissues were edematous and bled spontaneously (Fig. 1). The inflamed area covered the whole dentition, but was particularly severe in the anterior segments. Probing depths reached 10 mm and the gingival margins were apical to the cemento-enamel junction in most areas. Thus, the loss of attachment was very advanced. The patient complained of high sensitivity in the cervical areas of the teeth. All teeth were mobile, with mobility ranging between 1 to 3, and the lower incisors being the most mobile. All multi-rooted teeth showed different degrees of furcation involvement. There were no carious lesions except for one carious spot on the lower right first molar.

The radiological examination disclosed advanced bone loss of about 75% of the osseous support, except for the canine and wisdom teeth, which had a bone loss of about 30% (Fig. 2). The lower incisors fared

the worst. White blood cell counts were significantly lower than the normal range and the percentage of neutrophils was lower (Table 1). The other blood elements were in the normal range.

PERIODONTAL TREATMENT

Oral hygiene instructions were given and repeated at each treatment session. Scaling and root planing were performed and antibiotics prescribed, consisting of amoxicillin 500 mg tid and metronidazole 250 mg tid for 2 weeks, as well as twice daily oral rinses with 0.2% chlorhexidine gluconate.

Extracoronal splinting was performed on the lower anterior segment. Desensitizing therapy was instituted using fluoride varnish on the cervical areas and a restoration placed on tooth #46 (FDI). Root planing and deplaquing sessions were repeated and complemented with subgingival irrigation of chlorhexidine in 13 sessions during the course of a year. At the end of the long anti-infective period, a re-evaluation procedure was conducted.

During the course of the treatment, in both the initial preparation and in the maintenance period, we carefully monitored the patient's peripheral blood counts. Probing depths were measured using a Williams probe at pretreatment, post-treatment, and at every treatment period. The mean probing depth was determined and standard error calculated. The differences in mean probing depth were determined using Bonferroni's modification of Student *t* test.

Table 1.

Complete Blood Counts at the Beginning of Periodontal Treatment

Measurement	Blood Counts	Normal Range
WBC	2.4 x 10^3/µl	4.5-11.0 x 10^3/µl
RBC	4.3 x 10^3/µl	4.2-6.1 x 10^3/µl
HGB	12.7 mg/dl	12-17.5 mg/dl
PLT	121 x 10^3/µl	130-400 x 10^3/µl
Neutrophils	39%	40-64%
Lymphocytes	49%	22-44%
Monocytes	7%	0-7%
Eosinophils	1%	0-4%
Basophils	0%	0-2%

RESULTS

After a 2-year period (a year of initial preparation and a second year in which monthly maintenance sessions were performed), a notable improvement was obtained in the periodontal condition and the patient's overall well-being and self-esteem (Fig. 3). A marked improvement was also noted in clinical parameters such as probing depth (PD). As shown in Figure 4, the mean PD was reduced markedly post-treatment and was reduced even further during the maintenance period. Moreover, probing depths remained at 3 mm throughout the maintenance period.

The primary reason for the marked PD reduction was the elimination of edema. This resulted in shrinkage of the gingival tissue, with a concomitant apical migration of the gingival margin. A statistically significant gain of attachment level was also obtained (Fig. 5). This improvement in bone support could also be observed on the radiographs (Fig. 6).

Bleeding on probing almost disappeared and there was a significant improvement in clinical appearance. The total number of peripheral white blood cells (WBC) increased following periodontal treatment, with greater improvement during the maintenance period, eventually reaching normal levels (Fig. 7). The number of neutrophils increased with treatment (Fig. 8). As a function of total WBCs, there was a reciprocal relationship between the number of neutrophils and other types of leukocytes. The percentage of neutrophils was restored to normal levels by treatment and maintained at normal levels during the maintenance period.

Figure 3.
Post-treatment clinical appearance of patient.

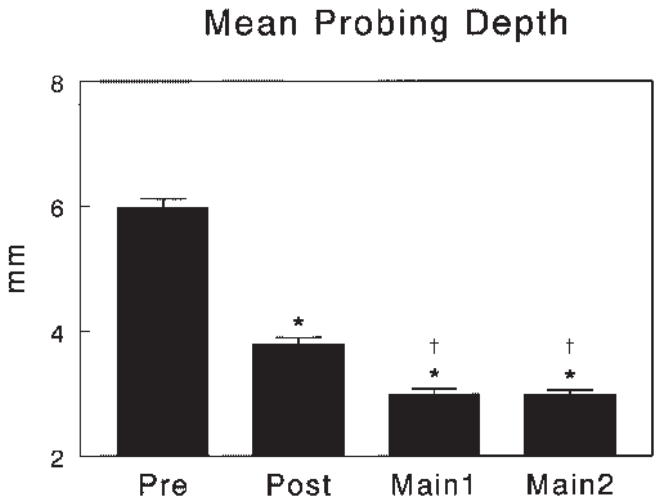

Figure 4.
*Change in mean probing depth (mm) prior to periodontal therapy (Pre), after treatment (Post), and at 2 maintenance appointments at year 1 (Main1) and year 2 (Main2) post-treatment. Values are the mean ± SEM (n = 174). *P <0.05, versus Pre; †P <0.05, Post versus Main1 or Main2. Statistical analysis was done using the Bonferroni correction to the Student t test.*

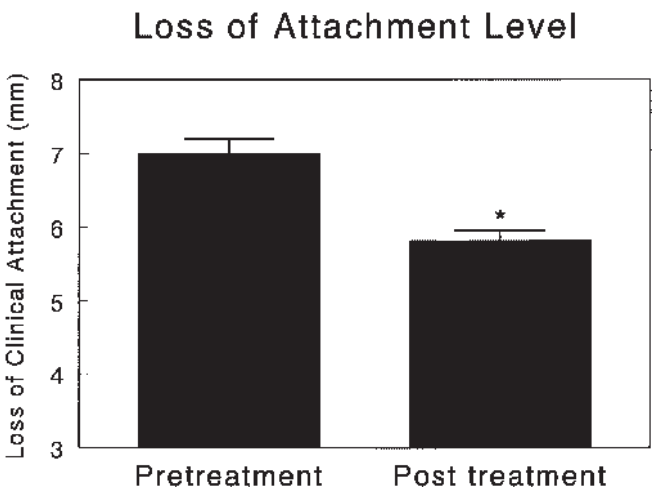

Figure 5.
Mean loss of clinical attachment (mm) pretreatment and post-treatment. Values are the mean ± SEM (N = 174); P <0.05, Pre versus Post. Statistical analysis was done using the Bonferroni correction to the Student t test.*

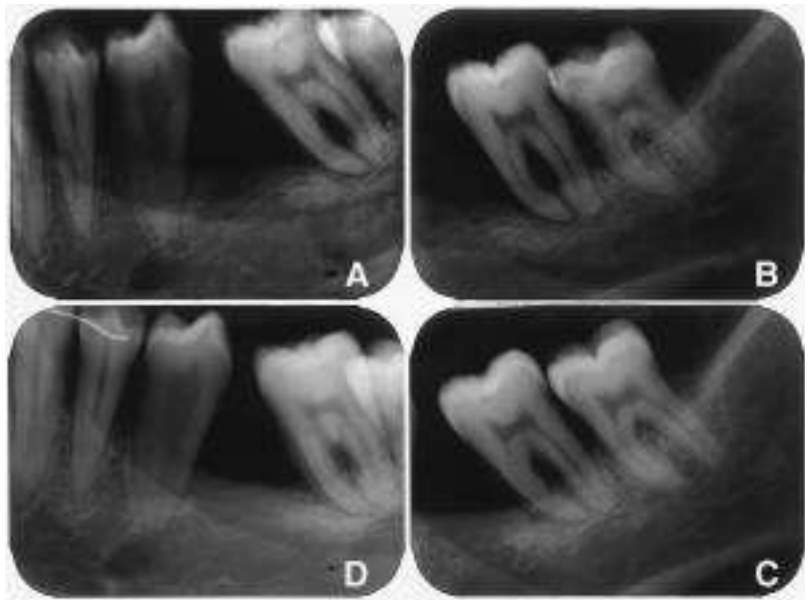

Figure 6.
*Pretreatment (**A** and **B**) and post-treatment (**C** and **D**) radiographs.*

DISCUSSION

Patients with mild neutropenia have been shown to have moderate loss of attachment compared with healthy subjects.[10] These patients responded well to conventional periodontal care and good plaque control measures. In contrast, patients with acute severe neutropenia require antibiotic therapy in addition to root instrumentation. Frequently, these patients also require surgery. The use of topical antimicrobial agents during the maintenance period has been advocated in addition to frequent instrumentation sessions.[6] In severe cases, periodontal destruction reaches levels at which extraction of all teeth is indicated.[7]

The report presented here suggests that non-surgical therapies may be effective as well. At the end of a 2-year period of non-surgical therapy, all of the patient's teeth remained functional, with a significant gain in attachment levels. This fact proves that, even in systemically compromised patients, adequate plaque control and meticulous instrumentation can result in a marked improvement in all clinical aspects, as demonstrated by various indices such as bleeding on probing, probing depth, attachment levels, and mobility. Teeth that were considered on presentation of questionable-to-hopeless prognosis remained in functional condition. This is particularly noteworthy because plaque control, although considerably improved, was not perfect.

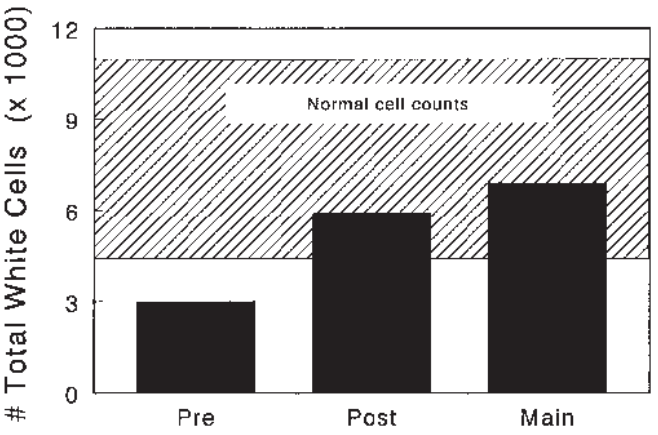

Figure 7.
Total white blood cell counts at pretreatment (Pre), after periodontal treatment (Post), and at a maintenance session 2 years after the end of active periodontal treatment (Main).

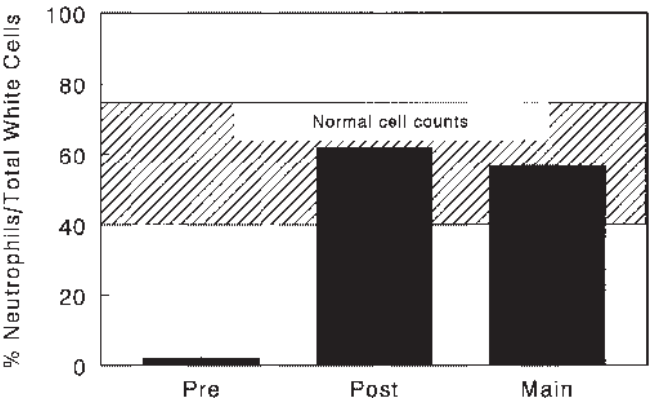

Figure 8.
Percentage of neutrophils per total white cells at pretreatment (Pre), after periodontal treatment (Post), and at a maintenance session 2 years after the end of active periodontal treatment (Main).

As the patient's medical records show, until 7 years before initiation of rhG-CSF therapy, his neutrophil count was below 500 per µl, which posed a life-threatening situation. The administration of rhG-CSF markedly improved his systemic condition. The patient ceased suffering recurrent infections and started leading a normal life. It is possible that the patient's improvement in neutrophil counts was unrelated to the periodontal therapy, since he had gone through periods of remission in the past. However, the WBC levels, and especially the neutrophil count, did not reach normal levels during an almost 7-year period of rhG-CSF therapy. The patient initiated periodontal treatment with severe neutropenia, even if the condition is defined more strictly as having a peripheral neutrophil count less than 1,000/µl.[11] It was only as the periodontal treatment progressed that the neutrophil count rose and finally reached normal levels. These normal neutrophil levels were maintained throughout the second year of periodontal care.

Periodontal diseases are infections that cause repeated bacteremias. These bacteremias consist of diverse bacterial strains that no doubt exert a negative influence on pre-existing systemic conditions. In diabetes, a favorable influence of periodontal care on the systemic condition has been shown,[8,12-14] although others have not noticed such an influence.[15] In chronic heart disease, poor dental health is associated with an increased risk of a fatal outcome.[16] The present case report is the first publication, to the best of our knowledge, which may indicate that periodontal care improves the systemic immune system in patients with severe neutropenia. These results may also suggest that periodontal status will affect the health of patients with impaired immune conditions.

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