



# Oral Manifestations of Cyclic Neutropenia in a Japanese Child: Case Report With a 5-year Follow-up

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## Abstract

Cyclic neutropenia is an uncommon hematologic disorder characterized by a marked decrease in the number of neutrophils in the peripheral blood occurring at regular intervals. The neutropenic phase is characteristically associated with clinical symptoms such as recurrent fever, malaise, headaches, anorexia, pharyngitis, ulcers of the oral mucous membrane, and gingival inflammation. This case report describes a Japanese girl who has this disease and suffers from periodontitis and oral ulceration. Her case has been followed up for the past 5 years from age 7 to 12. The importance of regular oral hygiene, careful removal of subgingival plaque and calculus, and periodic and thorough professional mechanical tooth cleaning was emphasized to arrest the progress of periodontal breakdown. Local antibiotic application with minocycline ointment in periodontal pockets was beneficial as an ancillary treatment, especially during neutropenic periods. (*Pediatr Dent.* 2003;25:383-388)

**KEYWORDS:** CYCLIC NEUTROPENIA, PERIODONTITIS, MIXED DENTITION

*Received August 16, 2002 Revision Accepted December 23, 2002*

Severe periodontitis is extremely rare in children. The incidence of advanced alveolar bony destruction in primary and mixed dentition is particularly associated with systemic diseases, including hypophosphatasia,<sup>1-3</sup> Pappillon-Lefèvre syndrome,<sup>4,7</sup> histiocytosis X,<sup>8-11</sup> agranulocytosis,<sup>12,13</sup> leukocyte adherence deficiency,<sup>14,15</sup> neutropenias,<sup>16-26</sup> leukemias,<sup>27,28</sup> diabetes mellitus,<sup>29</sup> scleroderma,<sup>30-34</sup> Down syndrome,<sup>35-37</sup> and Chediak-Higashi syndrome.<sup>38-40</sup> The defective immune and neutrophil functions associated with these diseases are thought to increase patient susceptibility to infections and alveolar bone loss.

Cyclic neutropenia is an uncommon hematologic disorder characterized by a marked decrease in the number of neutrophils in the peripheral blood occurring at regular intervals. It was first recognized as a distinct entity in 1910 because of the regular recurrence of neutropenia, fever, and mouth ulcers in a 19-month-old boy.<sup>41</sup> Its etiology is unknown, but the episodes of neutropenia may be caused by the following mechanism: a regulatory abnormality involving early hematopoietic precursor cells that causes decreased entry of granulocyte progenitor cells into granulocytopoiesis, causing a reduction in the production of neutrophils. The episodes, which last from 3 to 10 days, occur in cycles with a mean duration of 21 days but can range from 14 to 36 days.

The clinical features of the neutropenic phase include recurrent fever, malaise, headaches, anorexia, pharyngitis, bacterial infections, ulcers of the oral membrane, and periodontal disease. Some patients show intermittent arthralgia, abdominal pain, sore throat, lymphadenitis, ischiorectal infections, mental depression, conjunctivitis, and cutaneous ulcers. The periodontal manifestations presented in earlier reports include rapid periodontal breakdown and alveolar bone loss.

While the periodontal status produced by this disease cannot be restored to normal, it is possible to retard progressive degradation by proper dental management.

This report describes (1) the oral manifestations in a Japanese child patient with cyclic neutropenia who has been suffering from periodontitis for the past 5 years; and (2) the dental management the authors have used. The definition, etiology, clinical features, laboratory tests, differential diagnosis, and treatment options of this disease are summarized in Table 1.

## Description of case

### Medical history

A Japanese girl born in 1989 with no family history of cyclic neutropenia had suffered from repeated episodes of

fever, upper respiratory tract infections, and otitis media since the age of 1 month. She was first admitted to a hospital to undergo treatment for severe fever, depressed white blood cell count, and anemia at the age of 10 to 11 months. Oral ulceration occurred at the age of 3 years. She had to be hospitalized again at the age of 6 years because of recurrent fever, oral ulceration, left ear pain, and bilateral cervical lymph node enlargement. Serial blood count tests with differential diagnosis were performed to confirm the existence of cyclic neutropenia (Figure 1). Regular cycles of both neutrophils and lymphocytes were noted with a 20- to 21-day periodicity, which were coincident with the symptom periods. During neutropenic episodes, the neu-

trophil count dropped below 500/mm<sup>3</sup>, often decreasing to 0. Lymphocyte counts were reciprocal to the neutrophil values. The total white blood cell count was equal to or slightly less than the lower limit of normal during the neutropenic phase. From then on she underwent periodic examinations at the hospital and was prescribed medications such as recombinant granulocyte colony-stimulating factor (rG-CSF) for daily administration, and antibiotics when she had recurrence of fever.

The patient was started on daily injections of rG-CSF at a dose of 50 µg intramuscularly in July 1997. It had been continued for some months, and, during that time, she had less recurrence of fever, less painful and smaller oral ulcers, and less infections as compared with those prior to rG-CSF treatment. This resulted in (1) an increased neutrophil count between 200 and 300 cells/mm<sup>3</sup> during the nadir period; and (2) a reduction in the duration of the nadir, although the neutrophil counts still continued to cycle. Consequently, reducing the injections from daily to 3 times per week was successful with no further symptoms. The patient had been administered twice-per-week injections with a dose of 75 µg since March 1998, and no further cyclic episodes of fever were reported.

#### Dental history and treatments

The patient's mother reported that oral ulceration occurred from 3 years of age and sometimes prevented her from eating, due to pain. She had received restorative treatment at a neighboring dental private practice in her early childhood but had not received any periodontal management.

A pediatrician referred the patient to the Okayama University Dental School Pediatric Dental Clinic at the age of 7 years in 1996 for evaluation and management of gingival swelling and anterior malocclusion.

The initial examination revealed a mixed dentition, of which the papillary, marginal, and attached gingiva surrounding the teeth at that time was erythematous and edematous. Gingival recession was seen in the right maxillary and mandibular primary canine regions. An anterior open bite caused by persistent thumb-sucking and tongue-thrust habits was noted (Figure 2), together with aphthous ulcers on the buccal mucosa. The left mandibular primary canine was excessively mobile due to supporting bone loss.

The maxillary permanent central incisors and the mandibular permanent central and lateral incisors had erupted. According to the hematologic examination the patient received at the medical hospital on the same day, she was in the neutropenic phase; thus, the neutrophil count was essentially 0. She had suffered a fever for a week immediately after returning home from the first dental visit. Radiographic examination 3

**Table 1. Cyclic Neutropenia: Summary**

<b>Definition:</b> A hematological disorder characterized by regular periodic reduction of the neutrophils.
<b>Etiology:</b> The etiology remains unknown, although an autosomal dominant trait has been described in some cases.
<b>Occurrence in children:</b> Rare
<b>Clinical features:</b> The symptoms and signs of cyclic neutropenia occur in a cyclic pattern of 3 weeks and persist for 5 to 10 days, after which the neutrophil count generally returns to normal. Painful oral ulcerations covered by a whitish membrane and surrounded by slight erythema are the most constant findings. The lips, tongue, buccal mucosa, and gingiva are the areas most commonly affected. Fever, malaise, headaches, oral ulcerations, stomatitis, periodontal disease, bacterial infections, pharyngitis, pneumonia, chronic cough, skin infections, arthralgia, lymphadenitis, otitis media may occur during an episode of neutropenia.
<b>Laboratory tests:</b> Repeated complete blood count
<b>Differential diagnosis:</b> Aphthous ulcers Herpetic stomatitis Congenital neutropenia Agranulocytosis Leukemia Primary and secondary syphilis
<b>Treatment:</b> Symptomatic and topical antiseptics for the oral lesions Corticosteroids and occasionally splenectomy in severe cases Granulocyte-colony stimulating factor (G-CSF) may also be effective Bone marrow transplantation

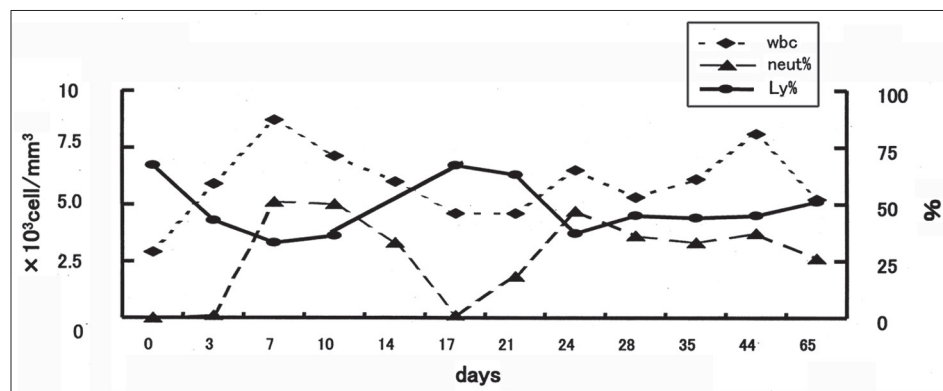


Figure 1. Total white blood cell count and percentage of neutrophils and lymphocytes over time.



Figure 2. Intraoral view at initial examination (6 years old, neutropenic period).

weeks after the initial visit showed severe bone loss around the mandibular anterior teeth and moderate bone loss around the maxillary and mandibular primary molars. The first permanent molars appeared to have suffered no bone loss (Figure 3). All the primary and permanent teeth present had periodontal pockets with a depth of 3 to 5 mm, and lesions in the buccal mucosa had developed. The patient stated that she had difficulty brushing her teeth because of gum soreness. She tried to wipe her teeth by using gauze during every neutropenic phase. She had eaten mainly rice gruel, pudding, and ice cream for meals, and, due to the mouth soreness, she could not even rinse out her mouth. Instead, she held the water in her mouth for a moment before expectorating.

During the first 4 years, treatment was focused mainly on improving oral hygiene, due to the patient's evident poor oral hygiene. Appropriate tooth-brushing and flossing techniques were demonstrated, and the importance of daily removal of plaque, especially around the gingival margin, was emphasized to the patient and her mother. At every dental visit, subgingival plaque and calculus were removed carefully. Thorough tooth cleaning using a prophylactic rubber cup and topical irrigation with 0.1% ethacridine lactate solution (Acrinol, Maruishi Seiyaku Co, Osaka, Japan) as an antiseptic agent were additionally performed to minimize plaque formation. Minocycline ointment (Perioline, Sunstar Co, Japan) was then applied into the periodontal pockets as an adjunct to reduce bacteria suspected of causing periodontal disease. The patient was placed on periodic recall (once or twice a month) at the authors' clinic for examination and professional tooth cleaning. To reduce plaque formation and gingival inflammation in neutropenic phases, an antiseptic mouth rinse with povidone-iodine solution was prescribed for use several times a day at home.

According to radiographic examinations taken at the age of 10 years, bone loss had appeared to have progressed, despite frequent periodic recalls and the improved plaque condition (Figures 4 and 5). At this point, the areas with pockets up to 5 mm deep had increased, particularly around the mandibular permanent anterior region. The marginal

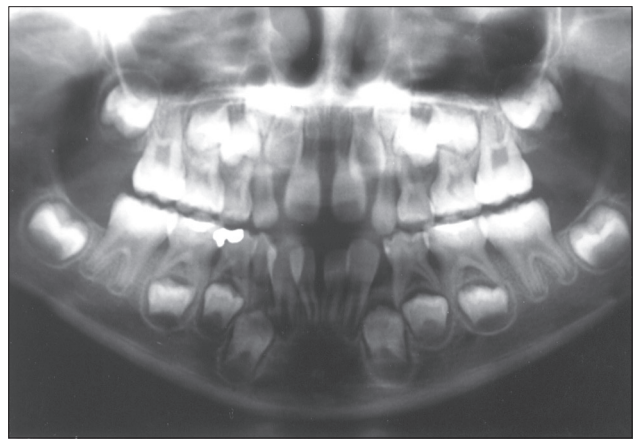


Figure 3. Panoramic radiograph at 3 weeks after initial examination.



Figure 4. Intraoral view at age 10 (neutropenic period).

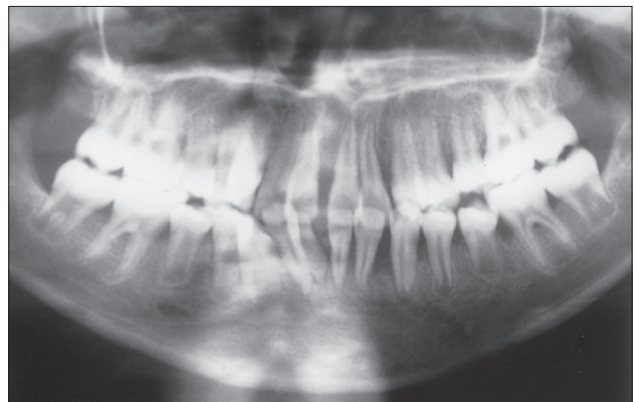


Figure 5. Panoramic radiograph at age 10.

gingiva around the maxillary and mandibular incisors was severely inflamed, hyperemic, and hyperplastic. The gingiva in some areas covered half of the teeth. Alveolar bone resorption was noted in the mandibular first permanent molars by age 10. It was judged impossible to improve the periodontal status because loss of supportive tissue had advanced, in spite of the periodic recalls. A periodontal specialist performed a gingivectomy surgically under local anesthetic at the time of the nonneutropenic phase. Because deepened pockets persisted around the maxillary and mandibular permanent central and lateral incisors and had



Figure 6. Intraoral view at age 11.

continued to make oral self-care difficult, it was necessary to eliminate the pockets which had developed at the age of 11. The antibiotic coverage for the gingivectomy was given prior to surgery. For 6 months following surgery, a good gingival condition was maintained during nonneutropenic phases. Though the patient maintained an improved oral hygiene regime, recurrence of erythematous and edematous gingiva continued during neutropenic phases. Periodic examination and evaluation involving probing would have been desirable, but in this case were difficult to perform because the procedures were very painful and were usually refused by the patient.

Cessation of thumb-sucking had been recommended to correct excessive overjet in the anterior region, but the habit had persisted. However, at age 11, the patient became cooperative and started to accept myofunctional therapy such as a button-pull exercise, designed to strengthen both lips, and a tongue-spot exercise, to correct the position of the tongue tip during the swallowing act. She also wished to stop thumb-sucking at that point because of her concern with its cosmetic consequences. Figure 6 shows the improvement of the anterior occlusion in the 9 months after myofunctional therapy started.

The cavities that were present in the patient at the initial visit had been treated and finally exfoliated normally, and from then on, no new carious lesions had developed in the permanent dentition. At the age of 12, she acquired caries-free permanent dentition without losing teeth from periodontal breakdown.

Assessments of caries activity using the Cariostat method<sup>42-46</sup> (Sankin Co, Japan), which had been performed at every dental visit, consistently revealed a score of 1 or 1.5, indicating low caries risk (high risk=2-3).

## Discussion

This report describes the case of a Japanese girl diagnosed with cyclic neutropenia who suffered from severe periodontitis. The oral manifestations described in this case were in accordance with previous case reports.<sup>16-21,23-26</sup> The periodontal status of this patient did not normalize, but, unlike

cases reported in earlier literature,<sup>16,17,23-25</sup> no permanent teeth had to be extracted. The periodontal disease that was observed in this patient was mainly associated with systemic disease, not local factors. However, a worsening periodontal status may also be correlated with poor oral hygiene. Hence, even in patients with cyclic neutropenia, it is important to persevere with a regular oral hygiene regimen—involving regular and thorough professional mechanical tooth cleaning and professional removal of subgingival plaque and calculus—to minimize progress in periodontal breakdown. Minocycline ointment application in periodontal pockets was also beneficial as an ancillary treatment, especially during the neutropenic phases. It was very difficult for the patient to achieve adequate oral hygiene during the neutropenic phases because of painful gingiva. It must be recognized that dental procedures such as tooth-brushing and probing may be unwelcome and even painful for such patients. Systemic antibiotic therapy was considered for periodontal disease, but local antibiotic treatment was mainly utilized to avoid the occurrence of antibiotic-resistant bacteria and deliver a high concentration of the antibiotic directly into the periodontal pockets for more effectiveness.

In addition to effective pain control, it is essential to consider infection control when any surgical procedure is required. Antibiotic coverage was discussed with the pediatrician but was only used prior to the periodontal surgery to reduce infection risks. Antibiotic coverage is not usually necessary for conventional dental treatments, although the patient is at higher risk of infection, except for oral surgery.

Periodontal surgery should be avoided, especially during the neutropenic episodes, because the risk of postoperative infections is very high. Nonetheless, gingivectomy was carried out at the time of the nonneutropenic phase in this case to achieve better periodontal management because the severely hyperplastic gingiva, which partly covered the teeth, prevented the patient from practicing appropriate oral hygiene. It had resulted in a temporarily improved gingival condition. However, it did not result in a complete cure, as the recurrence of severe gingival inflammation was found in spite of the patient's improved oral hygiene. The periodontal status and its treatment in cases where it is associated with systemic disease vary widely depending on the severity of the underlying disease. Progression of periodontitis in such patients is not avoidable in general. In this case, the periodontal condition was resistant to the authors' treatment, but its progression appeared to be successfully retarded.

This patient had been treated with recombinant granulocyte colony-stimulating factor (rG-CSF) by her pediatrician. It resulted in an increased neutrophil count between 200 and 300 cells/mm<sup>3</sup> during the nadir period and a reduction in the duration of the nadir. However, the neutrophil counts still continued to cycle, leading to a significant reduction of the number and severity of recurrent fever, infections, oral ulcers, and gingival inflammation in

this case. These findings suggest that rG-CSF treatment can affect oral status of neutropenic patients. Because the greatest concern is the potential induction of leukemia in patients treated with long-term rG-CSF,<sup>48</sup> it had been administered to possibly decrease the dose or frequency to attain the minimal effective dosage and injection frequency.

Orthodontic treatment with active appliances should be avoided, since there is a greater risk of accelerated periodontal breakdown. Regarding the management of the anterior open bite, the authors' primary focus was to (1) eliminate thumb-sucking and tongue-thrust habits as a cause of malocclusion; (2) strengthen the lips; and (3) correct the tongue tip position. The anterior occlusion was improved with no marked rapid breakdown of periodontal supporting tissue.

This patient had experienced restorative treatment but, it should be noted, had never received any periodontal management before being referred to the authors' clinic by her pediatrician. The dental profession can play a very important role in the early detection of systemic diseases that affect oral status, and it must, therefore, ensure that appropriate diagnoses and referrals are made.

According to the guidelines for periodontal diseases of children and adolescents in the 2000-2001 Reference Manual published by American Academy of Pediatric Dentistry,<sup>47</sup> it is imperative that children receive a periodontal examination as part of their routine dental visit since early diagnosis is important for successful treatment. Moreover, the presence of severe periodontitis in children may be an early sign of systemic disease. Hence, a general medical evaluation to determine if systemic disease is present should be considered for children who exhibit severe periodontitis, especially if the disease appears resistant to therapy.

Little is known about the effect of dental caries on patients with cyclic neutropenia.<sup>24</sup> Caries activity tests with the Cariostat method,<sup>42-46</sup> which has been employed widely in Japan, showed a consistently low-risk range for the acidogenicity of plaque samples. The patient never developed new carious lesions, despite plaque accumulation due to occasionally poor oral self-care. It is vital to keep caries activity low because of the difficulty of maintaining adequate oral hygiene during neutropenic phases with attendant gingival soreness. Caries prevention is also important because proximal restorations, which can be a cause of local periodontitis, should be avoided.

### Acknowledgements

The authors would like to thank Dr. Megumi Oda, professor, Faculty of Health Sciences, Okayama University Medical School, Okayama, Japan, for his medical assistance; Drs. Mika Kume and Takako Nakamura, pediatric dentists, for assisting in the preparation of this manuscript; and Dr. Peter Milgrom, professor, School of Dentistry, University of Washington, for his helpful comments on an earlier draft of this paper.

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