Severe Periodontitis in a Patient with Cyclic Neutropenia: A Case Report of Long-term Follow-up

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Cyclic neutropenia is a rare haematologic disorder. This case report presents a 6-year-old girl who was referred in order to treat gingival recession, and was finally diagnosed as having cyclic neutropenia based on an oral examination, complete blood counts and a sternal puncture bone marrow test. The patient received systematic granulocyte colony-stimulating factor therapy, full-mouth scaling and root planing and was followed up for 4 years. Due to irregular periodontal maintenance and poor oral hygiene, severe gingival inflammation and deep pockets persisted in the permanent dentition of the patient.

Key words: *cyclic neutropenia, periodontitis, oral hygiene, periodontal initial therapy*

Cyclic neutropenia (CN) is a rare haematologic disorder characterised by cyclic episodes of neutropenia, separated by periods of near-normal blood neutrophil counts, and a symptom complex presenting during the neutropenic nadirs. Classically, the patients present with severe neutropenia at the time of fever and infection. Clinical symptoms may resolve without antibiotics as the neutrophil counts recover[1,2]. Less frequently, patients get deeper tissue infections, such as pneumonia and bacteraemia.

Oral manifestations include recurrent painful ulcers and inflamed gingiva[3]. Gingivitis is common in patients with CN, and severe periodontitis may affect both deciduous and permanent dentition; spontaneous or periodic gingival bleeding may be observed[4-6], but sometimes only moderate periodontal lesions are found[7].

The clinical diagnosis of CN is made by recognising a fever cycle periodicity with a multiple of 7 days, most commonly in 21 or 28-day intervals. Blood neutrophil levels are usually nearly 0 for 3 to 5 days, followed by a period of recovering counts to levels near the lower limit of normal, clinicians should keep in mind that neutropenia may precede the patient‘s symptoms by 3 to 5 days, and a complete blood cell count should be obtained to detect neutropenia 3 to 5 days before episodes and at the onset of symptoms[1,2]. This case report presents the long-term effect of periodontal therapy on a 6-year-old girl, who was referred to treat gingival recession and was ultimately diagnosed as having CN.

Case report

A 6-year-old girl was referred to our department during the spring of 2005. The chief complaints stated by the patient’s mother were gingival recession and teeth mobility in the primary molars for 2 years. She also noticed that most of her daughter’s primary teeth had deep caries, and recurrent oral ulcers had been an ongoing problem for 4 years. The girl had received a dental scaling in paediatric dentistry 1 month ago, and all the dental caries were under treatment.

The medical history stated by the patient’s mother indicated that the girl caught a fever almost every month since she was 2 years old without obvious flu symptoms, such as coughing or nasal discharge. Dental ulcers appeared at the beginning of the fever. Systematic antibiotics were effective in controlling

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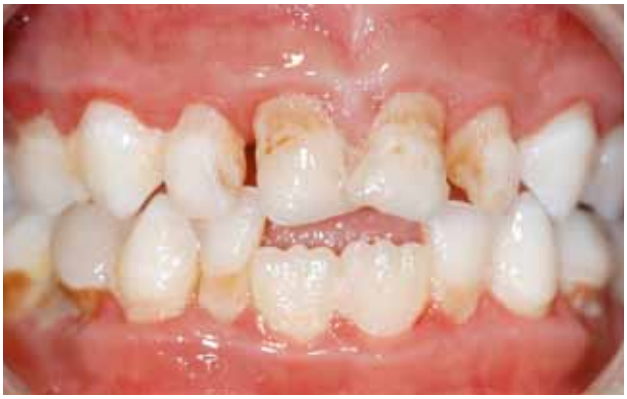

Fig 1 Clinical front view of the patient on first visit demonstrated generalised inflamed gingiva and gingival margins were fiery red.

Fig 2 Clinical buccal view of left mandibular primary first molar: on the first visit it showed obvious gingival recession and exposure of the furcation.

fever only before she was 4 years old. In the recent 2 years, the girl had repeatedly been admitted to hospital with the diagnosis of "fever of unknown origin". There was no family history of medical problems. The pregnancy with the patient ended in vaginal delivery after a full term.

Because the recurrent oral ulcers, teeth mobility and dental caries prevented the girl from taking in food efficiently, the overall nutrition status of the patient was poor. She was underweight and shorter than children of her age. Her cervical lymph nodes and neck were clinically normal, as were her cranium, face, hands, feet and elbows. Hyperkeratosis was not observed relating to systemic disease, such as Papillon-Lefevre syndrome. The patient's phosphorus, copper, zinc, calcium and iron levels in serum were within normal limits. Alkaline phosphatase and other liver function tests produced normal results. Blood tests for fungus, mycoplasma and chlamydia were negative.

The intraoral examination of the patient demonstrated poor oral health of the mixed dentition. The gingiva was fiery red and soft. For the primary incisors, gingival recession of 2 to 3 mm, probing depth (PD) of 2 to 4 mm and mobility of Grade II to III were noted (Fig 1). For the primary mandibular first molars, gingival recession of 4 to 5 mm, PD of 4 to 5 mm and mobility of Grade I were found, with Class III to IV furcation involvement according to Glickman (Fig 2). The PD of the other primary teeth was no more than 4 mm. Dental caries were found in upper primary incisors and all primary molars except tooth 2E. Two mandibular first primary incisors were missing and subsequent permanent teeth were in eruption. Two permanent mandibular first molars were not fully erupted.

A panoramic radiograph revealed a horizontal bone loss of ⅓ to ⅔ root length around primary teeth. Obvious radiolucencies were noted in the furcation area of the mandibular primary molars. Deep caries were observed in upper primary incisors and all the primary molars except tooth 2E, 3 of which had developed into apical periodontitis. All the succedaneous teeth were in normal development (Fig 3).

According to the medical history and periodontal examination of the patient, it was suspected that some systematic problem may be contributing to her periodontal status. Complete blood counts were taken 3 times in May and June 2005. Results demonstrated that there were significant decreases in the absolute neutrophil count (ANC) of 1.3 to 2.0 $\times 10^9$/L (normal: 1.8-6.4 $\times 10^9$/L) (Table 1). A diagnosis of CN was suspected and the patient was advised to go for a medical consultation with a paediatric haematologist for a definitive diagnosis.

Complete blood counts were taken once a week for 5 weeks in the paediatric haematology unit in Peking University People's Hospital revealed low ANC and neutrophil percentages, the neutropenic phase occurred approximately 21 days. The lowest ANC was 0.4 $\times 10^9$/L, while the maximum ANC was 0.8 $\times 10^9$/L. Fever and oral ulcers were recorded during the neutropenic nadirs (Table 1).

Immunological studies revealed increased serum IgG and IgM levels of 26.24 g/L (range, 6.46-14.51 g/L) and 3.50 g/L (range, 0.55-2.32 g/L), respectively. Serum IgA, IgE and T lymphocyte subsets of CD3, CD4 and CD8 were all within normal limits.

A sternal puncture bone marrow test indicated active bone marrow hyperplasia. Hypoplastic granulocyte

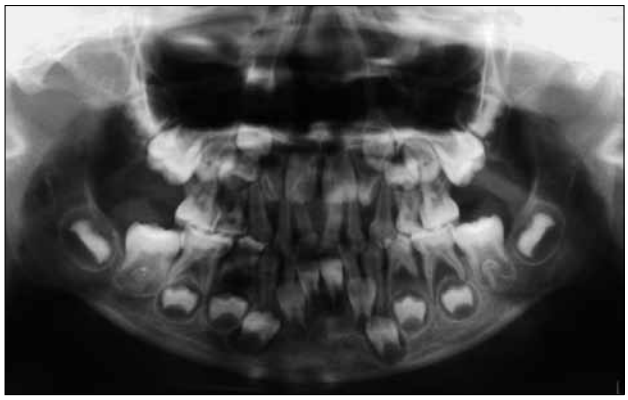

Fig 3 A radiographic examination revealed horizontal bone loss of 1/3–2/3 root length around primary teeth. Deep caries were observed in upper primary incisors and primary molars (except tooth 2E), tooth 1D, 2D and 4D had developed into apical periodontitis. All the succedaneous teeth were in normal development.

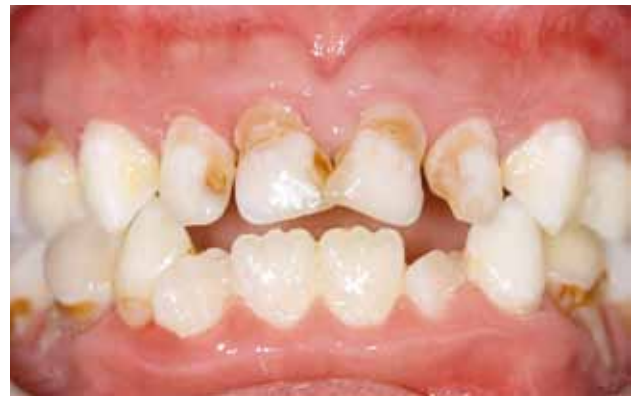

Fig 4 Clinical front view of the patient, 2 months after subcutaneous injection of G-CSF. Gingival inflammation has decreased compared to before injections (Fig 1), especially in the right maxillary primary teeth.

series were observed. There were increased numbers of promyelocytes to 8.0%, with atypical nuclei and vacuolisation of cytoplasm, and a marked absence of mature granulocyte fornation forms. Erythron proliferation was acceptable, cellularity was normal, but the myeloid erythroid was low. There was no decrease in macrocyte and platelet numbers.

Based on the serial blood and sternal puncture bone marrow tests, the patient was diagnosed as having CN. The haematologist treated the patient with subcutaneous injections of granulocyte colony stimulating factor (G-CSF) every other day. Therapy with G-CSF initially led to a WBC 'peak' of about 20 × 10^9/L, and subsequently normalisation for a few days.

Periodontal treatment and maintenance

Two months after the patient received G-CSF treatment, the ANC was > 0.5 × 10^9/L, the general status of the patient improved and acute gingival inflammation reduced (Fig 4). At this time, the patient received non-surgical periodontal treatment, including oral hygiene instruction, 0.12% chlorhexidine gluconate oral rinse, scaling and root planning with no prophylactic antibiotic.

During the first year after treatment, the patient came every 3 months for periodontal maintenance, including individualised oral hygiene instruction and supragingival scaling. The periodontal examinations revealed

Table 1 Sequential blood values of the patient in 2005

Date (month/date/year)	Oral symptoms	WBC	ANC	NEUT%	LYM	LYM%	PLT
5/19/2005	Oral ulcers	4.7	1.3	28.2	3.3	70.1	436
6/13/2005	Oral ulcers	4.4	1.4	30.7	2.7	62.3	458
6/21/2005	No oral ulcers	5.5	2.0	36.5	3.2	57.3	422
6/27/2005	No oral ulcers	5.0	0.8	7	3.7	73	496
7/04/2005	Begin of oral ulcers	4.6	0.6	13.8	3.2	69	485
7/11/2005	Healing of oral ulcers	4.0	0.4	7.9	3.0	57	389
7/21/2005	No oral ulcers	4.2	0.8	18	2.7	60	483
7/28/2005	Begin of oral ulcers	4.9	0.6	12.4	2.9	44	494
8/28/2005	7 days after G-CSF treatment	21.4	15.6	72.9	4.2	40	192

WBC: white blood cells count (range 4–10 × 10^9/L); ANC: absolute neutrophil count (1.8-6.4 × 10^9/L); NEUT%: neutrophil percentage (range 50–70%); LYM: lymphocyte percentage (range 1.8–3.3 × 10^9/L); LYM%: lymphocyte percentage (range 20-40%); PLT: platelet count (range 100-300 × 10^9/L)

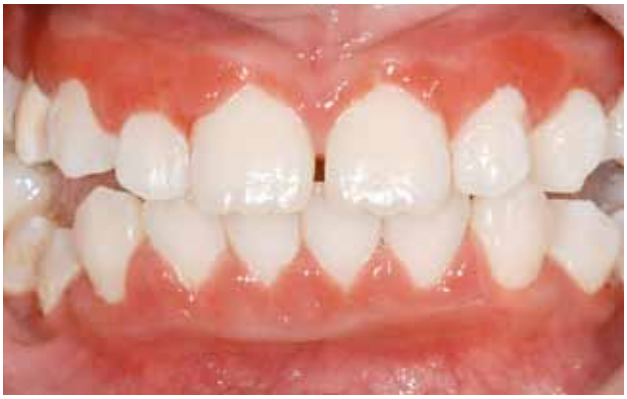

Fig 5 Clinical front view at her 2010 re-evaluation, severe gingival inflammation in both free and attached gingiva.

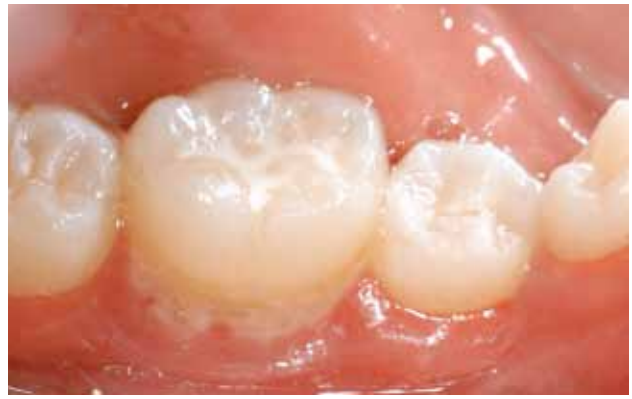

Fig 6 Multiple material alba and gingival recession in the lower first molar were found at her 2010 re-evaluation.

acceptable oral hygiene and PD of no more than 4 mm. The mobility of the lower primary molars and lower right primary canine was increasing to grade III, teeth extraction and space maintainers of these teeth were performed in the paediatric dentistry.

As it was difficult for the patient and her mother who lived far away to come for maintenance regularly, the patient was advised to adhere to a periodontal preventive programme, which involved measurement of her neutrophil cycles and supragingival scaling in her local oral department every 2 to 3 months. However, the patient was reluctant to receive regular teeth cleaning. When she was recalled back to our department in 2009, her oral hygiene was poor, with multiple dental calculus and inflamed gingiva. Although the girl was only 10 years old at this time, all the primary teeth had been lost. Scaling and root planing was given to the patient, with particular stress on the importance of oral hygiene and regular periodontal maintenance. But there was no obvious change of the periodontal status when the patient came back in August 2010. Erythematous areas were noted in both the gingival margin and buccal attached gingiva (Fig 5). Gingival recession and furcation involvement were observed in all first permanent molars (Fig 6), and PD was more than 5 mm in most teeth. A complete blood count revealed that the WBC was 3.8×10^9/L, ANC was 0.63×10^9/L, and the neutrophil percentage was only 0.63%. Non-surgical periodontal treatments, including scaling and root planing with mouth rinse of 0.12% chlorhexidine gluconate were given, and the patient was advised for further haematological treatment.

Discussion

The incidence of CN is 0.5 to 1 case per million[1]. In this case, the girl had remained undiagnosed for over 4 years until she was referred to our department. She had taken a massive amount of antibiotics and had repeatedly been admitted to hospital with a fever of unknown origin. This demonstrates the difficulty in diagnosing this unusual disorder. If a child presents with significant periodontitis, especially in primary or mixed dentition, the presence of systemic problems should not be ruled out without sufficient testing. Dental professionals should call for a thorough investigation of a patient's medical status, analyse their differential diagnosis, and make appropriate referrals.

Therapeutic protocols based on the use of G-CSF that increase the number and the function of neutrophils in the peripheral blood have been proposed, and patients with CN typically normalise their ANC upon G-CSF therapy[7,8], though chronic G-CSF therapy may develop malignancies[9]. Despite treatment with G-CSF, professional dental care is important[10]. The increase of ANC by G-CSF treatment leads to an alleviation in gingival inflammation, but periodontal inflammation and putative periodontal pathogens can persist without periodontal treatment. It is advised that periodontal treatment can be given when the ANC > 0.5×10^9/L.

Co-operation from the patients and their caregivers must be very high for a successful outcome; neglecting oral hygiene quickly leads to periodontal pathology[11]. Appointments once or twice a year were not sufficient to maintain periodontal health; progressive attachment loss was recorded in this patient who could only come once a year for periodontal maintenance. Regular

monthly professional removal of dental plaque and calculus has been recommended[11], and periodontal maintenance every 2 to 3 months may help to control periodontal inflammation. Daily rinsing with 0.12% chlorhexidine gluconate during the neutropenic episodes can help to supplement the mechanical cleaning of the dentition. But some reports find that even with the best professional and home care, teeth are often lost due to advancing periodontal disease[12]. Some report recommended that extensive extraction of primary teeth may reduce potential periodontal pathogens to a minimum before G-CSF treatment, which may prevent further deterioration[10].

Multiple proximal dental caries and apical periodontitis in 3 primary first molars were found in this patient. Recurrent painful oral ulcers and gingival inflammation may prevent the patient from daily tooth brushing, dentists should also pay more attention to caries prevention in patients with CN.

Conclusion

This case emphasises the importance of correctly diagnosing periodontal disease as an indicator of systematic disease, especially in young patients with severe periodontitis. Non-surgical periodontal treatment is effective in patients with CN. Patients' co-operation and 3-month interval periodontal maintenance or even more frequent visits are essential to long-term periodontal treatment success. Intensive preventive care for caries is crucial.

References

1. Wright DG, Dale DC, Fauci AS et al. Human cyclic neutropenia: clinical review and long-term follow-up of patients. Medicine (Baltimore) 1981;60:1–13.
2. Dale DC, Welte K. Cyclic and chronic neutropenia. Cancer Treat Res 2011;157:97–108.
3. Keshwara K, Zanganah Y. Cyclic neutropenia. Br Dent J 2011;210:197–198.
4. Rylander H, Ericsson I. Manifestations and treatment of periodontal disease in a patient suffering from cyclic neutropenia. J Clin Periodontol 1981;8:77–87.
5. Zaromb A, Chamberlain D, Schoor R et al. Periodontitis as a manifestation of chronic benign neutropenia. J Periodontol 2006;77:1921–1926.
6. da Fonseca MA, Fontes F. Early tooth loss due to cyclic neutropenia: long-term follow-up of one patient. Spec Care Dentist 2000;20:187–190.
7. Matarasso S, Daniele V, Iorio Siciliano V et al. The effect of recombinant granulocyte colony-stimulating factor on oral and periodontal manifestations in a patient with cyclic neutropenia: a case report. Int J Dent doi:10.1155/2009/654239.
8. Dale D. Neutropenia and neutrophilia. In Lichtman M, Beutler E, Kaushansky K et al (eds): Hematology, ed 7. New York: McGraw-Hill, 2006:907–919.
9. Pernu HE, Pajari UH, Lanning M. The importance of regular dental treatment in patients with cyclic neutropenia. Follow-up of 2 cases. J Periodontol 1996;67:454–459.
10. Lubitz PA, Dower N, Krol AL. Cyclic neutropenia: an unusual disorder of granulopoiesis effectively treated with recombinant granulocyte colony-stimulating factor. Pediatr Dermatol 2001;18:426–432.
11. Carlsson G, Fasth A. Infantile genetic agranulocytosis, morbus Kostmann: presentation of six cases from the original „Kostmann family" and a review. Acta Paediatr 2001;90:757–764.
12. Carlsson G, Wahlin YB, Johansson A et al. Periodontal disease in patients from the original Kostmann family with severe congenital neutropenia. J Periodontol 2006;77:744–751.
13. Deas DE, Mackey SA, McDonnell HT. Systemic disease and periodontitis: manifestations of neutrophil dysfunction. Periodontol 2000 2003;32:82–104.