Cyclic Neutropenia Presenting as Recurrent Oral Ulcers and Periodontitis

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Background: *Cyclic neutropenia (CN) is a rare congenital disease that can present with recurrent oral ulcers and periodontitis. CN can easily be misdiagnosed as major recurrent aphthous stomatitis (MaRAS) or aggressive periodontitis (AP) in dental clinics. We describe the case of an 8-year-old boy with CN, and compare the oral manifestations of CN with those of MaRAS and AP.* ***Case report:*** *An 8-year-old boy presented with a history of recurrent oral ulcers, periodontal destruction, pharyngitis and otitis media since the age of 3 months. Repeated, routine blood tests showed 1-week-long neutropenic periods that occurred at intervals of 2 weeks. A bone marrow cytology test during a neutropenic period demonstrated a decrease in granulocyte count. During a 2-year follow-up, his symptoms were well controlled by regular administration of granulocyte colony-stimulating factor and periodontal maintenance.* ***Conclusion:*** *Several clinical features help to differentiate CN from MaRAS and AP. Early recognition of the systemic cause of oral symptoms is important.*
Keywords: *Cyclic neutropenia, Oral ulcers, Periodontal destruction*

INTRODUCTION

Cyclic neutropenia (CN) is characterized by a periodic decrease in circulating neutrophils that occurs every 21 days and lasts for 3–6 days.[1] CN is a rare congenital disease related to mutations in the *ELA2* gene, which encodes neutrophil elastase.[2] Defects in this enzyme decrease the ability of neutrophil progenitor cells to undergo granulocytopoiesis, leading to periodic neutropenia. During the neutropenic period, patients can experience repeated episodes of infections such as otitis media, pharyngitis, abscesses, oral ulcers and periodontitis.[2,3]

Oral manifestations in CN can easily be misdiagnosed in dental clinics. The literature describing these manifestations is very limited. The severity and recurrence of oral ulcers in CN are similar to those of ulcers in major recurrent aphthous stomatitis (MaRAS); additionally, periodontal tissue destruction in CN is as severe as that in aggressive periodontitis (AP). Therefore, early diagnosis of this complicated condition is challenging. To the best of our knowledge, no report has as yet summarized the characteristics of the oral manifestations of CN.

Here, we report the case of an 8-year-old boy with CN, and compare the oral findings of CN with those of MaRAS and AP.

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Case report

An 8-year-old boy with an uneventful family history was referred to us because of recurrent oral ulcers and periodontitis. The pregnancy, delivery and development of the patient were normal. He had a history of intermittent oral ulcers, pharyngitis and otitis media since the age of 3 months. The oral ulcers were usually located on the tongue, buccal mucosa or upper lips, and recurred every 3 weeks and lasted for 6–10 days. The ulcers could be temporarily and partially relieved by antibiotics.

On examination, we found two ulcers (Fig. 1A) covered by a dense yellowish-white pseudomembrane surrounded by an erythematous halo. Removal of the pseudomembrane revealed a granular base underneath. The ulcers were painful to slight touch and prevented the patient from maintaining good oral hygiene. No scars were found in the mouth. All posterior deciduous teeth were lost due to remarkable mobility although the boy was just 8 years old. The residual teeth showed class I–II mobility (Miller classification) and attachment loss (Fig. 1B). Severe destruction of the alveolar bone was found on pantomography (Fig. 1C). In addition, the lamina dura of most permanent teeth was disrupted

Repeated, routine blood tests showed an oscillation in neutrophil counts, suggestive of CN (Fig. 2). A bone marrow cytology test during the neutropenic period demonstrated a decrease in granulocyte count. During hospitalization, the neutrophil count quickly increased from 0.65×10^9/l to 1.36×10^9/l after administration of granulocyte colony-stimulating factor (GCSF). The patient was followed up for 2 years, and his symptoms were well controlled by regular GCSF treatments and an oral care program.

DISCUSSION

The oral manifestations of CN are similar to those of MaRAS and AP.[1–3] However, we found several features of CN that could be helpful in the differential diagnosis (Table 1). In both CN and MaRAS, the ulcers are recurrent, deep and self-limited, with a diameter greater than 10 mm. However, the location, number, duration and sequela of the ulcers are different in the two diseases. Severe

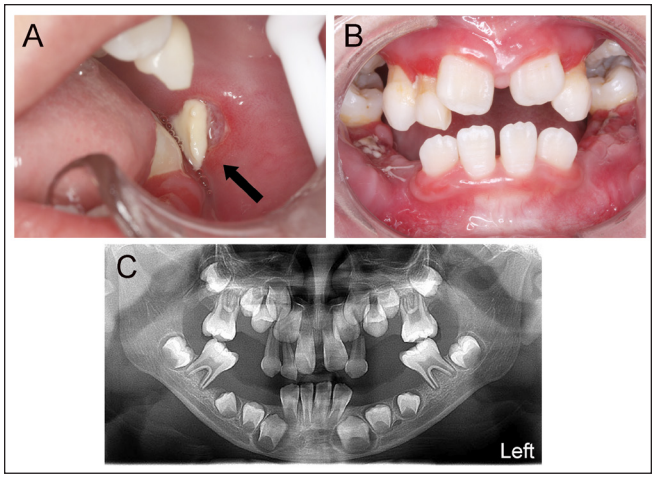

Figure 1. Oral findings in an 8-year-old boy with cyclic neutropenia. (A) An oral ulcer on the left buccal mucosa with a granular base (black arrow). (B) Severe attachment loss, gingival recession and diffuse swelling in the gingiva. (C) Pantomography showing severe alveolar bone destruction. Angular absorption of the alveolar bone reached the apex of the root of the lower right first molar and the apical one-third of the roots of the other first molars.

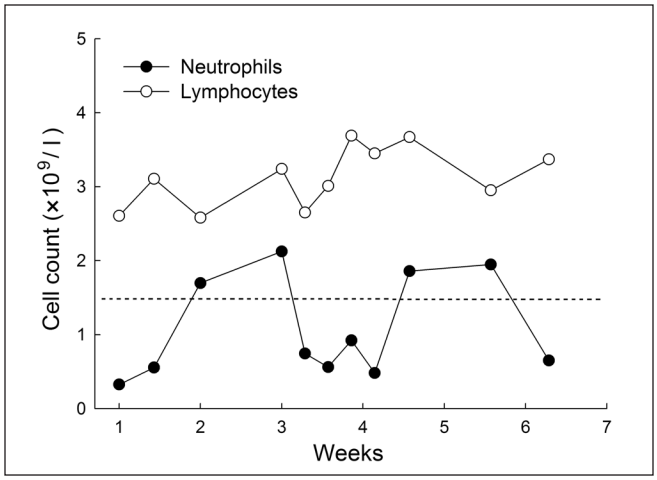

Figure 2. Fluctuation in circulating neutrophil counts. The neutropenic periods lasted for approximately 1 week, with intervals of approximately 2 weeks.

gingival inflammation and periodontal tissue destruction usually coexists with oral ulcers in CN. The extreme pain of the ulcers prevents patients with CN from maintaining good oral hygiene.[2,3] CN and AP both affect deciduous and permanent dentitions simultaneously in young patients. The pocket depth in both diseases is usually greater than 4 mm. However, the age at onset, oral hygiene and gingival inflammation are different in CN and AP (Table 1).

Early diagnosis of CN is difficult because of its rarity and the need for repeated, routine blood tests, over at least 6 weeks.[1] A history of recurrent infections, oscillation in neutrophil counts and the typical interval between and duration of neutropenic periods strongly suggest a diagnosis of CN. Early consultation with a pediatrician or hematologist is helpful to confirm the diagnosis. Our report highlights the importance of evaluating the systematic causes of oral symptoms.

The symptoms of CN can be well alleviated by GCSF, which promotes proliferation and differentiation of granulocytes.[1,2] In addition, the maintenance of good oral hygiene is essential to minimize periodontal destruction in CN. Mechanical tooth cleaning or subgingival scaling should be performed routinely. These treatments can make the patient feel more comfortable and attenuate attachment loss and bone destruction.

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Table 1. Comparison of the clinical features of cyclic neutropenia (CN), major recurrent aphthous stomatitis (MaRAS) and aggressive periodontitis (AP).

	CN	MaRAS	AP
Location in the mouth	Not specific[2, 3]	Usually in mobile, non-keratinized mucosa[4]	--
Number of ulcers	Usually multiple[2, 3]	Usually single[4]	--
Duration	6–10 days, consistent with neutropenic period	10–30 days or more[4]	--
Sequela	No scar[2, 3]	Scar[4]	--
Pseudomembrane	Dense and yellowish[2, 3]	Usually slim and gray-to-tan[4]	--
Onset	Usually in infancy or childhood[1–3]	--	Local type: circumpubertal onset[5] Generalized: under 30 yrs of age[5]
Oral hygiene	Usually bad, consistent with severity of periodontal destruction[2, 3]	--	Usually good, inconsistent with severity of periodontal destruction[5]
Gingival inflammation	General swelling[2, 3]	--	Slight