

# Periodontal disease as a manifestation of cyclic neutropenia: case report with a 34-year follow-up

## Précis

Case report: oral manifestations of cyclic neutropenia.

## Abstract

**Introduction:** Cyclic neutropenia is an autosomal-dominant haematological disorder. It is characterised by a periodic depression of peripheral blood neutrophils at 21-day intervals. Patients have a decreased ability to fight infection and commonly experience fever, ulceration, skin infections and lymphadenopathy.

**Case report:** A 17-year-old patient was referred by her consultant haematologist for periodontal assessment due to painful oral tissues and loose teeth. Clinical and radiographic examination revealed advanced periodontal destruction. A course of cause-related, non-surgical periodontal treatment, followed by an orthodontic and reconstructive phase, was carried out to arrest disease progression and stabilise her dentition. This case was followed up intermittently for over 34 years.

**Discussion:** The oral manifestations of cyclic neutropenia include oral ulcerations, angular cheilitis, periodontal destruction and early tooth loss. Early identification and regular follow-up should be employed for this patient cohort. Restorative procedures should be meticulously planned and executed to facilitate plaque control.

**Conclusion:** This case report illustrates the challenges of long-term management of severe periodontitis in a young individual who suffers from cyclic neutropenia. Delivery of dental and periodontal care was complicated by long travel distances, periods of non-attendance and financial issues. Early interventions to improve periodontal health and align the teeth proved successful, and this case report illustrates the benefit of planning periodontal care on a case-by-case basis. Regular supportive oral care is essential.

*Journal of the Irish Dental Association* 2020; 66 (4): 195-200.

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FIGURE 1: Pre-treatment photograph (1985).



FIGURE 2: Pre-treatment orthopantomogram (1985).

### Introduction

Severe periodontal disease is rare in young people. The presence of severe attachment loss in children and adolescents usually coincides with the presence of systemic conditions such as Down syndrome,<sup>1,2</sup> Papillon-Lefèvre syndrome,<sup>3,4</sup> hypophosphatasia<sup>5,6</sup> or cyclic neutropenia.<sup>7</sup>

Cyclic neutropenia (also called cyclic haematopoiesis) is a rare autosomal-dominant inherited haematological disorder with an estimated worldwide prevalence of one to two per million inhabitants.<sup>8</sup> The prevalence in the Republic of Ireland is reported to be at 2.6 cases per million inhabitants according to the EU registry.<sup>9</sup>

The disorder is characterised by a periodic depression of peripheral blood neutrophils at approximately 21-day intervals.<sup>7,10</sup> Neutrophils, or polymorphonuclear leukocytes, are part of the body's innate immune response system, accounting for 50-70% of our circulating white blood cells. Normal neutrophil levels range from 1,500-8,000 cells/mm<sup>3</sup> with neutropenia occurring when levels fall below the lower range.<sup>11</sup> They have important roles

in the body's immune defence system, carrying out functions such as phagocytosis and degranulation to fight infection.<sup>12</sup>

The role of the immune system in the pathogenesis of inflammatory periodontal disease was reported by Page and Schroeder in 1976.<sup>13</sup> The neutrophil was placed as the "front line" defence cell against bacterial attack at the dento-gingival junction. However, over the decades our understanding of the complex interactions of the immune system has increased. A recent review highlighted the expanded role of neutrophils, which are traditionally regarded as merely antimicrobial effectors in acute conditions and protagonists of the 'initial' lesion described by Page and Schroeder, but are currently appreciated for their functional versatility and critical roles in chronic inflammation.<sup>14</sup>

Cyclic neutropenia is caused by a mutation in the *ELA-2* gene, which encodes neutrophil elastase. This mutation results in defective early haematopoietic precursor cell development, in turn leading to failure of neutrophil production in the bone marrow.<sup>15,16</sup> Manifestations of the disease vary in severity and can present as early as the first year of life. They include recurrent fevers, oral ulceration, gingivitis, skin infections and lymphadenopathy.<sup>17,18</sup> A diagnosis of cyclic neutropenia is confirmed by obtaining a number of leukocyte counts at least two to three times per week for a minimum of six weeks.<sup>19</sup>

Currently, management includes regular administration of granulocyte colony-stimulating factor (G-CSF), which is given to promote granulopoiesis. The G-CSF binds to specific receptors on the neutrophils' surface, elevating the neutrophil count in the bloodstream.<sup>16,20</sup>

Periodontitis as a manifestation of cyclic neutropenia is mentioned in previous classifications of periodontal disease as a disease that is associated with clinical attachment loss (**Table 1**). The most recent 2017 classification of periodontal disease mentions systemic disease but does not list any specific associated conditions.<sup>21</sup>

Here we describe the case of a young patient affected by cyclic neutropenia presenting with advanced periodontal destruction. We take the opportunity to discuss the importance of early and regular oral assessment of patients who have increased susceptibility to infection, to identify and manage the occurrence of such advanced periodontal breakdown.

### Presenting complaint

A 17-year-old female patient was referred to the Periodontology Department of the Dublin Dental University Hospital by her consultant haematologist in 1985. She lived with her family 180km from Dublin. She complained of loose

**Table 1: Periodontitis as a manifestation of systemic diseases.<sup>22</sup>**

#### A. Associated with haematological disorders:

1. Acquired neutropenia
2. Leukaemias
3. Other

#### B. Associated with genetic disorders:

1. Familial and cyclic neutropenia
2. Down syndrome
3. Leukocyte adhesion deficiency syndromes
4. Papillon-Lefèvre syndrome
5. Chediak-Higashi syndrome
6. Histiocytosis syndromes
7. Glycogen storage disease
8. Infantile genetic agranulocytosis
9. Cohen syndrome
10. Ehlers-Danlos syndrome (Types IV and VIII)
11. Hypophosphatasia
12. Other

#### C. Not otherwise specified (NOS)



FIGURE 3: Post periodontal therapy (1985).



FIGURE 5: Periodontal splint (1986).

teeth and recurrent painful ulcers of the oral mucosa, which lasted up to three months at a time. She was especially concerned about the unsightly spaces developing between her front teeth. Her medical history was unremarkable other than her diagnosis of cyclic neutropenia. She was a non-smoker and an irregular dental attender at the time.

#### Examination

Clinical examination revealed poor plaque control and calculus deposits. There was extensive gingival inflammation and widespread periodontal attachment loss, with multiple mobile, drifting and furcation-involved teeth (**Figure 1**). The patient had a class II division 1 incisor relationship with a complete vertical overlap. Orthopantomogram radiograph displayed moderate-to-severe generalised bone loss (**Figure 2**).



FIGURE 6: Orthopantomogram in 2007.



FIGURE 4: Post-orthodontic alignment (1986).

#### Treatment

The treatment plan included cause-related therapy, and corrective and reconstructive phases. The cause-related therapy phase included oral hygiene instruction and plaque control measures. Following review of oral hygiene, a corrective phase of full mouth non-surgical periodontal therapy was carried out, and the patient responded well to treatment (**Figure 3**). Following an improvement in oral hygiene, the patient reported a decrease in the frequency and severity of oral ulceration.

The reconstructive phase consisted of fixed orthodontic treatment to align the teeth and correct the traumatic, increased vertical overlap (**Figure 4**). This was followed by provision of resin-retained metal splints and bridges for retention and stabilisation of the occlusion. The palatal inflammation seen following placement of the fixed bonded retainer in **Figure 5** resolved on reinforcing good oral hygiene. The patient was followed up at regular intervals until 1999. Due to relocation for work, she was lost to review for eight years (1999–2007). She re-attended briefly in 2007 but did not wish to have treatment due to personal circumstances, preferring to attend her local general dentist. Examination at that time revealed that the 1.8 and 4.8 had been extracted. There was also progression of the periodontal attachment loss at sites 3.5 and 3.6 (**Figure 6**).

The patient returned to the Dublin Dental University Hospital in 2018 for advice regarding stabilisation of her remaining teeth. Her medical history now included a diagnosis of osteoporosis in 2016, for which she was on oral bisphosphonates. She reported frequent chest infections requiring antibiotics and hospitalisation on occasion. She also receives infusions of granulocyte colony-stimulating factor (G-CSF). In the time since her previous review in 2007, she had lost several posterior teeth due to dental abscesses (**Figure 7**).

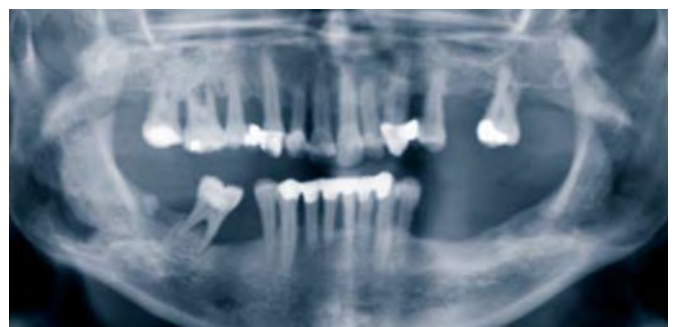


FIGURE 7: Orthopantomogram in 2018.



FIGURE 8: Maxillary view of dentition (2019).



FIGURE 9: Mandibular view of dentition (2019).



FIGURE 10: Frontal view of dentition (2019).



FIGURE 11: Extension of occlusal table on lower left first premolar to provide an occlusal contact with the upper left second premolar.

Clinical examination revealed generalised progression of periodontal attachment loss in spite of excellent oral hygiene. The remaining teeth, including the 4.6, were surprisingly stable despite the attachment levels (**Figures 8, 9 and 10**).

The primary focus for ongoing oral and dental care was a preventive plan including oral hygiene instruction, dietary advice including fluoride therapy, and supportive periodontal care to prevent further periodontal loss.

Restorative treatment options to stabilise the remaining teeth and increase occlusal function were discussed with the patient. These included:

- maintaining her current dentition and providing no active restorative treatment;
- provision of a mandibular removable partial denture;
- resin-bonded bridge to replace the mandibular right second premolar; and,
- dental implants.

The patient wished to have the edentulous space 45 restored. Following discussion of the associated risk factors, she was reluctant to consider dental implants as she was taking oral bisphosphonates, as well as the risk of clinical

attachment loss due to the cyclic neutropenia.<sup>23-25</sup>

A conservative fixed prosthodontic approach was planned for the patient along with oral hygiene instruction, dietary advice and periodontal supportive therapy. The occlusal table on the mandibular left first premolar was extended with a direct composite resin restoration to provide an occlusal contact between 3.4 and 2.5 (**Figure 11**). A resin-bonded fixed-partial denture was provided to restore the edentulous space in the mandibular right premolar area (**Figure 12**). This improved occlusal function bilaterally. A resin and fibre retainer was placed on the palatal of the maxillary incisors where the original metal retainer had recently failed. The patient was advised to use a high-fluoride toothpaste at bedtime and to apply chlorhexidine using interdental brushes.

### Discussion

Neutropenia increases patient susceptibility to infections, particularly those of a bacterial origin affecting the skin and mucosal surfaces,<sup>26</sup> with the risk of infection increasing when the neutrophil count drops below 1,500 cells/mm<sup>3</sup>.<sup>16</sup> Unlike the persistent nature of symptoms experienced in other neutropenias,



FIGURE 12: Buccal view of fixed partial denture.

such as benign familial neutropenia, those seen in cyclic neutropenia occur in episodes corresponding with the periodic fall in levels of neutrophils.<sup>27</sup> The oral manifestations of neutropenia presented in this case report include:<sup>7,17,28,29</sup>

- mucosal ulceration;
- angular cheilitis;
- increased susceptibility to advanced periodontal destruction; and,
- early tooth loss.

These signs are similar to those of recurrent aphthous stomatitis and aggressive periodontitis, making their clinical differential diagnoses challenging without further haematological investigations.

Painful oral ulceration, which occurs in cyclic neutropenia, can deter patients from carrying out good oral hygiene measures; therefore, they commonly present with poor plaque control and advanced periodontal destruction.<sup>28</sup> Improved oral hygiene may result in the improved healing of the ulcers, as occurred in this case.

Given the periodontal complications of systemic diseases such as cyclic neutropenia, restorative procedures should be conducive to periodontal health. The following should be considered when planning for such a patient:

- regular recall and supportive therapy to encourage patient compliance in carrying out oral health measures;
- periodontal splinting, if required, may be used to ensure stabilisation of remaining teeth;
- margins of fixed restorations should be supra-gingival to prevent gingival irritation, and pontics should be hygienic in design and relieved of the alveolar crest as shown; and,
- removable prostheses should be favourably contoured and tooth supported so as not to impinge on soft tissues.<sup>30</sup>

## Conclusion

Predictable, long-term maintenance is challenging in patients who present with advanced periodontal destruction at a young age. Early detection of periodontal problems and intervention are essential and necessitate close co-operation between medical and dental professionals. Excellent oral hygiene is essential in the neutropenic patient to control gingival inflammation and

periodontal destruction. It also results in the reduction of oral microbes, which may promote early healing of recurrent ulceration. The possible need for future bisphosphonate therapy, as in this case, highlights the importance of periodontal maintenance over extraction of teeth, which could lead to the development of medication-related osteonecrosis of the jaw (MRONJ). This patient cohort should be reviewed regularly, with long-term follow-up in general dental practice to control progression of periodontal destruction and to manage acute episodes of infection.

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## CPD questions

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CPD

1. Oral manifestations of cyclic neutropenia include which two of the following?

- ☐ A: Chronic periodontitis
- ☐ B: Halitosis
- ☐ C: Oral ulceration
- ☐ D: Black hairy tongue
- ☐ E: Angular cheilitis

2. Neutropenia occurs when neutrophil levels drop below:

- ☐ A: 1,500 cells/mm<sup>3</sup>
- ☐ B: 800 cells/mm<sup>3</sup>
- ☐ C: 1,000 cells/mm<sup>3</sup>
- ☐ D: 1,200 cells/mm<sup>3</sup>
- ☐ E: 8,000 cells/mm<sup>3</sup>

3. Which of the following has not been associated with periodontal disease?

- ☐ A: Down syndrome
- ☐ B: Papillon-Lefèvre syndrome
- ☐ C: Gardner syndrome
- ☐ D: Hypophosphatasia
- ☐ E: Cyclic neutropenia