Severe congenital cyclic neutropenia: A case report

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Abstract

Congenital cyclic neutropenia syndrome is a constitutional genetic disorder which is characterized by very low number of neutrophils (neutropenia). Patients suffering from this disorder clinically present with neutropenia at early age, history of recurrent fever, ulcerations in the oral cavity, gingivitis, and other recurrent infections. This paper describes a case report of a child with recurrent mouth ulcers, fever, and later diagnosed with severe congenital cyclic neutropenia. This also emphasizes the importance of identification of rare causes of immunosuppressive conditions in children presenting with recurrent oral ulcers and poor dental hygiene, to prevent long-term complications of oral cavity and also morbidity and mortality secondary to neutropenic sepsis.

Key words: Congenital neutropenia, elastase gene, oral hygiene, oral ulceration, periodontal breakdown

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Introduction

During acute inflammatory reaction and in host defense against bacterial infections, the neutrophils play an important role of first line of defense. If there is a deficiency of these cells, the organisms present on the body surfaces, predispose an individual to many infections.[1] In 1910, cyclic neutropenia was first recognized as a distinct entity in a 19-month-old boy who presented with periodic regular recurrence of neutropenia, mouth ulcers, and fever.[2] It is a rare hematologic disorder which is characterized by a significant decline in the number of neutrophils in the peripheral blood occurring at a regular interval.[3] Sometimes, the symptoms are cyclical with the intervals varying between 14 and 36 days.[4] In addition to consistent neutropenia, this condition is associated with lymphocytosis, variable eosinophilia, monocytosis, and decreased normal leukocyte count.[5] Berardinis and Reiman in 1949 suggested the cause to be an autosomal dominant inheritance which was later confirmed by Morley et al. in 1967. On the other hand, congenital neutropenia is a heterogeneous disorder of less well-defined entity.[2] Described by Kostmann in 1956, it is also known as Kostmann syndrome.[6] The etiology of this condition is suggested to be due to mutation in the neutrophils elastase gene (ELANE) resulting in arrested development of neutrophils at the promyelocyte stage within the marrow. This mutation is also associated with premature apoptosis of these myeloid cells. Although an autosomal dominant pattern of inheritance has been described in few cases, most are isolated.[7] This is a rare condition with prevalence of one in a million. Congenital neutropenia has estimated frequency of 2:1,000,000–3:1,000,000 in the general population, however, the cyclic variant has a frequency of 1:1,000,000 in general population including those cases of familial and simplex type.[8]
This article describes the history, clinical, radiographic, and hematologic findings of a female child with severe congenital cyclic neutropenia. Furthermore, this article emphasizes the dental management that can be used to halt the progression of the disease.

Case Report

An 8-year-old Asian female child born to nonconsanguineous parents of Indian origin was referred to the Department of Pedodontics and Preventive Dentistry by a pediatrician. She was suffering with the history of recurrent oral ulcerations, genital ulcerations, and fever every month from the age of 3 years. The symptoms had cyclical pattern of every 28 days and persisted for about a week. She was able to have only liquid diet during these episodes. In spite of the symptoms, her general growth was adequate for age. Fortunately, she was not admitted with severe febrile septic episodes. Dental examination of the child showed all of her deciduous teeth except for lower incisors, the permanent first molars, and lower incisors were in their eruptive stage. The deciduous molars clinically exhibited Grade 1 mobility. There was generalized marginal gingivitis and bleeding on probing. But no other local findings were clinically visible at the time of dental examination. Initial routine investigations advised by pedodontist were declined by parents. Unfortunately, the child did not keep regular dental appointments for 3 years.

Later, the patient presented when she was 11-year-old, and the oral health status had worsened. The parent gave the history that she showed the child to a pediatric rheumatologist where the child was diagnosed to be suffering from Behçet’s disease and was treated with steroids and colchicine (0.5 mg in divided dose) for the past 2 years. Although the oral and genital ulcerations were not clinically evident on steroid therapy still the child presented with bleeding gums and frequent febrile episodes. In between parents also consulted alternative medicine including the person who does black magic. However, the overall and dental health of the child worsened.

During this time, the dental examination of the child showed all her permanent teeth either erupted or in their eruptive phase except for the 3rd molars. There was erythematous marginal gingiva seen in relation to maxillary and mandibular anteriors. Gingival recession was seen lingually on the lower anteriors and in relation to 16, 26, 36, 44, 45, and 46 [Figures 1-3]. Pockets measuring 4–5 mm was seen among the posterior teeth. There was generalized bleeding on probing. The restoration was seen in relation to tooth 36, 46, 26. Grade 1 mobility was noticed with tooth 36 and 46.

The orthopantomogram showed alveolar bone loss along 16, 36, 45, and 46 region and along the maxillary and mandibular incisors [Figure 4]. Plaque was collected from gingival sulcus and was sent for culture. Colonies of Candida albicans was
grown on Sabouraud Agar plate [Figure 5]. One of the routine investigations showed child has neutropenia and so was referred to hematology department. On a lot of persuasions, parents agreed for the further investigations. Differential count of white blood cells done every week regularly revealed persistent neutropenia along with lymphocytosis and variable eosinophilia [Table 1].

The absolute neutrophil count (ANC) was persistently <200/mm³ was noticed. Bone marrow aspirate from posterior superior iliac spine revealed normocellular normoblastic marrow with maturation arrest at promyelocyte/myelocyte stage. Conventional cytogenetics showed normal karyotype. Sanger sequencing of ELANE gene was done from samples of blood collected from the patient, parents and a sibling. Sequence variation, c. 239T>G (p.V80G) in exon 3 of ELANE gene was observed in heterozygous state in the samples of the patient alone. With all the investigations and the mutation confirms that the child is suffering with severe congenital neutropenia syndrome.

The child was behaving like “cyclical neutropenia” but she had persistent neutropenia on laboratory investigations. She was started on filgrastim, granulocyte colony stimulating factor (G-CSF) 105 mcg thrice a week subcutaneous injections. She was symptomatically better with no febrile episodes including mouth ulcers. Initial dental treatment consisted of regular visits for oral prophylaxis every 2 months, re-restoration of 36, 46, and restoration with 45, parental education regarding oral hygiene maintenance of the child. Use of 0.2% chlorhexidine gluconate mouthwash was advised. The patient is kept on periodic recall.

Discussion

Severe persistent periodontitis in children is often a manifestation of underlying genetic or hematologic disorder. The polymorphonuclear neutrophils are important in maintaining the periodontal health; hence, their deficiency leads to recurrent bacterial and fungal infections.[6] The pedodontist often has the first opportunity to detect this disease of congenital neutropenia since it manifests uniquely in the oral cavity. However, clinical suspicion and further investigations like serial hematological tests at regular intervals are necessary to confirm this disease.[3] As in this case, the blood counts of neutrophils were low at every interval of testing.

There are many classifications of this disease. Based on the ANC, the disease has been classified into mild (ANC: 1000–1500/mm³), moderate (ANC: 500–1000/mm³), and severe (ANC <500/mm³).[6] Here, the patient manifested with the severe pattern since the ANC <200/mm³. So far 12 neutropenic disorders have been identified based on a molecular basis. Studies have shown that mutations of the gene encoding neutrophils elastase (the ELANE gene) as the most common cause for severe congenital neutropenia.[2,9]

Colonies of *C. albicans* was also noticed in the patient's oral cavity. This can be attributed to the suppurative of immunity due to long term use of systemic steroids. Earlier treatment strategies to cyclic neutropenia included systemic corticosteroids, corticotrophin, and androgens. These treatments had a moderate

| Date            | WBC count | Neutrophils | Lymphocytes | Eosinophil | Monocytes | Basophil | Band forms or immature granulocytes |
|-----------------|-----------|-------------|-------------|------------|-----------|----------|-----------------------------------|
| November 13, 2014 | 5900      | 11          | 73          | 6          | 10        | 00       | -                                 |
| November 19, 2014 | 5600      | 3           | 70          | 3          | 9         | 00       | 15                                |
| November 22, 2014 | 7600      | 3           | 54          | 4          | 21        | 00       | 18                                |
| November 25, 2014 | 6700      | 1           | 47          | 4          | 17        | 00       | 31                                |

WBC: White blood cell
subjective effect on the oral ulcerations but produced negligible improvement in the count of neutrophil count. Even prophylactic antimicrobial and antifungal treatments have been used in severe neutropenic patients. Currently, recombinant G-CSF is given to promote granulopoiesis. The G-CSF mediates its biological effect by binding to specific receptors on the neutrophils surface. It elevates the neutrophils count in the peripheral bloodstream by 10–12-folds by releasing the neutrophils reservoirs from the bone marrow.[6]

Currently, the patient, in this case, is on filgrastim 105 mcg thrice weekly and is showing improved oral health. Hematologist has planned to increase the dose depending on further ANC improvement or further febrile episodes. However, the periodontal status produced by this disease cannot be restored to normal, but the progression of the degradation of the periodontium can be reduced by proper systemic administration of G-CSF, maintaining personal oral hygiene and periodic medical and dental checkups.[3] Rinsing with 0.2% chlorhexidine gluconate during the episodes of neutropenia is seen to be beneficial. No surgery should be performed until sufficient absolute neutrophils count is attained as there are high risks of postoperative infection. In case of emergencies if surgery is an absolute necessary then it should be carried under appropriate antibiotic coverage and also increasing the G-CSF dose and in a hospital set up.[10]

To conclude, being a pedodontist one should be aware of the rare causes of systemic immunosuppressive conditions in children with persistent dental caries and bad oral hygiene.

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Conflicts of interest
There are no conflicts of interest.

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