Chronic idiopathic neutropenia: A periodontist’s diagnosis

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Abstract:
Our aim is to report the periodontal findings of a 10-year-old boy who visited the outpatient department of periodontology, with the chief complaint of swelling in the right cheek region for the last 2 months, increasing mobility of the teeth, and frequent bleeding from the gums. Since the age of 4 years, he suffered from recurrent febrile episodes, with boils and furuncles on the face. After several hematological and immunological investigations, he was diagnosed with chronic idiopathic neutropenia. He was prescribed a 150 µg subcutaneous injection of recombinant granulocyte colony-stimulating factor, once daily for 8 days. For reducing oral inflammation, he was advised an oral rinse of 15 ml of chlorhexidine gluconate (0.12%) twice daily and advised for a routine periodontal checkup, every 3–4 weeks for evaluation, maintenance, and avoiding any acute inflammatory flare-ups.

Key words:
Gingival hyperplasia, neutrophil biology, pathology-oral

INTRODUCTION

Neutropenia is a severe decrease in the number of circulating neutrophils in the peripheral blood vessels. It may be a reaction to specific drugs, radiation, or severe infection.[1] Chronic idiopathic neutropenia (CIN) is a rare acquired hematological condition defined by an absolute neutrophil count (ANC) of 1.5–1.8 × 10^3/µL with an incidence ranging from 5 cases per million to 4.5% across the world.[2,3] However, there is only limited literature of persistent neutropenia in children. In fact, to the best of our knowledge, no such case has been reported in the Indian population.

The aim of this study is to present the periodontal findings of a 10-year-old boy exhibiting generalized gingival enlargement, mobility of teeth, and mucosal ulcerations. On conducting a series of hematological, immunological, and radiographic examination, he was diagnosed to be suffering from CIN. This study also reviews the clinical course of the disease through 3 years as well as documents the dental management of children having such predicaments.

CASE REPORT

A 10-year-old male child visited our department with the chief complaint of swelling in the right cheek region for 2 months [Figure 1]. There was an increasing mobility of the teeth and frequent bleeding from the gums. Medical history revealed that since the age of 4 years, the boy suffered from recurrent febrile episodes, temperatures recorded between 101°F and 103°F, accompanied with boils and furuncles on the face, and dull earache. Each episode was treated with appropriate antibiotic and antipyretic therapy.

General examination revealed boils on the face and extensor surface of the hands along with marked swelling extending from the right malar region to the inferior border of the mandible. Intraorally, there was diffuse gingival enlargement [Figure 2], generalized tooth mobility, spontaneous bleeding from the gums, the presence of local factors [Figure 3], and mucosal ulcers in the floor of the mouth [Figure 4].

Case management
Because there was a history of recurrent febrile episodes and severely mobile teeth along with gingival enlargement, the patient was advised for routine blood investigations, posteroanterior view of the skull [Figure 5], and cone-beam computed tomography (CBCT).

How to cite this article: Raj SC, Mahapatra A, Agrawal P, Patnaik K, Pradhan SS. Chronic idiopathic neutropenia: A periodontist’s diagnosis. J Indian Soc Periodontol 2020;24:173-7.
The CBCT [Figure 6] and orthopantomogram [Figure 7] revealed severe loss of alveolar bone up to or beyond apical third of the roots. Hematological reports revealed mild anemia, increased erythrocyte sedimentation rate (ESR), increased C-reactive protein (CRP), and marked decrease in ANC. Differential leukocyte count revealed marked lymphocytosis, neutropenia, and eosinophilia. Absolute eosinophil count was significantly raised (336 cells/mm^3).

The patient was referred to the department of hematology and was advised for differential leukocyte count twice every week for 3 weeks. He was advised a urine and stool culture along with blood malaria parasite (MP) and filarial parasite (FP). The reports were negative for MP and FP. Urine culture revealed the presence of Escherichia coli and stool examination revealed the presence of bacterial cells. All the subsequent blood examinations revealed pronounced neutropenia (10%-22%) and lymphocytosis (70%-88%). A peripheral smear was done to rule out leukemic gingival enlargement that reported no abnormality. Assessment of serum immunoglobulin revealed significantly raised levels of immunoglobulin G (IgG) and slightly raised levels of IgA. Liver function tests revealed increased levels of alkaline phosphatases.

Meanwhile, the boy had another febrile episode accompanied with increased gingival enlargement and pus discharge from the gingival sulcus of the upper left first molar. A gingival tissue biopsy, Gram staining, and culture of the pus were done. Biopsy reported a chronic inflammatory lesion. Gram staining of the pus revealed increased Gram-positive cocci in pairs and a few thick Gram-negative bacilli. Pus culture revealed normal oropharyngeal microflora. The boy was treated by 500 mg of amoxicillin TID and paracetamol 500 mg TID for 5 days and sent for a bone marrow examination. It reported an adequate particulate cell density and suppression of erythropoiesis and megakaryopoiesis. Myelopoiesis was grossly suppressed and maturation arrest was seen at metamyelocytic stage. Lymphopoiesis was accelerated and the bone marrow was hypoplastic [Figure 8].

Due to nonincidental family history, repeated hematological findings of neutropenia and lymphocytosis, and recurrent febrile episodes concurrent with gingival enlargement, mucosal ulcerations, and rapidly advancing periodontal disease, a diagnosis of CIN was made after excluding all other systemic conditions having similar clinical presentation.

He was prescribed a 150 µg subcutaneous injection of recombinant granulocyte colony-stimulating factor (G-CSF) (neukine 150 mcg, Intas Pharmaceuticals Ltd.), once daily for 8 days by the consulting hematologist. The aim was to stimulate proliferation and differentiation of granulocytes and to maintain ANC of 500–1000/mm^3.[3] For reducing gingival inflammation, he was advised an oral rinse of 15 ml of chlorhexidine gluconate (0.12%) twice daily 30 min after gentle tooth brushing using a fluoridated nonmedicated tooth paste and an ultrasonic toothbrush. He was asked to visit the dental out patient department every 3–4 weeks for 3 years of follow-up for the evaluation of oral hygiene and gingival inflammation. Acute inflammatory flare-ups were addressed by supragingival ultrasonic scaling and polishing as and when required.

Clinical outcomes

One month after the treatment, there was a significant reduction in the gingival inflammation [Figure 9]. There were no mucosal ulcerations [Figure 10] or lymphadenopathy. At 3-year follow-up, reasonable degree of stability was observed in the oral cavity, barring occasional episodes of bleeding gums which reportedly subsided spontaneously [Figure 11].

DISCUSSION

Albandar et al. suggested that bony destruction in the primary or mixed dentition in the absence of local factors is highly suggestive of systemic diseases such as leukemic gingival enlargement, osteolytic lesions of mandible (systemic sclerosis, Gorham’s syndrome, and Langerhans cell histiocytosis), inflammatory osteolysis, and neutropenia (drug induced, cyclic, and idiopathic).[4]

Generalized diffuse gingival enlargement, tendency of gingival bleeding, and lymphocytosis reported repeatedly in all the blood investigations are strongly indicative of leukemic enlargement.[5] However, the peripheral smear shows no blast cells. Furthermore, there is no reporting of constitutional symptoms such as cachexia and loss of appetite. The aggressive bone loss seen in CBCT may be indicative of osteolytic diseases such as systemic sclerosis.[6] It is reported to have a predilection for 30–50-year-old females and is associated with dry inelastic appearance of the skin and a characteristic osteolysis of condyles and coronoid process both of which were absent in this case. Gorham’s disease is another such rare condition involving massive locally aggressive osteolysis with resorption of the affected bone extending into adjacent soft tissues. In case of maxillofacial involvement, mandible is reported to be the most affected bone. It has predilection for children and young adults. However, the diagnosis is ruled out as the osteolysis seen in the child is generalized and also there is an absence of cellular atypia in the blood smear. Biopsy of the gingival tissue did not show any angiomatous tissue, which is typical of Gorham’s disease. The marked raise in the levels of alkaline phosphatase along with elevated ESR and CRP is strongly indicative of massive osteolysis.[7] The persistent reduction of total leukocyte count and neutropenia rules out the possibility of inflammatory origin. Furthermore, there is no history of vague bone pains or unexplained fractures due to increased bone porosity. The nonspecific oral ulcerations, precocious exfoliation of teeth, advanced periodontal disease associated with otitis media, and anemia as reported in some of the investigations resemble the clinical manifestations of eosinophilic granuloma.[8] However, it was ruled out by the biopsy report.

Several conditions related to qualitative defect of neutrophils also have similar periodontal presentation along with recurrent otitis media such as Papillon–Lefevre syndrome, Chediak–Higashi syndrome, leukocyte adhesion deficiency disease (LADD) syndrome, and lazy leukocyte syndrome.[9] The absence of peripheral leukocytes and lymphocytes as well as peculiar eosinophilic inclusion bodies in the myeloid cells of the marrow revealed in bone marrow biopsy ruled out the possibility of Chediak–Higashi syndrome.[10] LADD is always associated with leukocytosis along with raised IgG and IgM antibodies, which is contrary to all the blood

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investigations done so far. Papillon–Lefevre syndrome is ruled out due to the absence of hyperkeratosis of the palms and soles characteristically found in this condition. In addition, there were no reports of endocrinal derangement. All lung volume tests were performed to detect chronic pneumonitis. Negative reports ruled out the possibility of lazy leukocyte syndrome.\(^4\)

Figure 1: Extraoral swelling in the right malar region

Figure 2: Initial presentation of diffuse gingival enlargement

Figure 3: Presence of local factors along the gingival margins

Figure 4: Mucosal ulcers in the floor of the mouth with respect to 44, 45

Figure 5: Posteroanterior view of the skull showing generalized alveolar bone loss

Figure 6: Cone-beam computed tomography showing loss of alveolar bone beyond the apical third of the root
The most characteristic findings in this case were marked decrease in ANC and lymphocytosis strongly indicative of neutropenia. In children, neutropenic conditions are classified based on age at onset, white cell counts, clinical symptoms, duration, immune function, bone marrow alterations, and familial tendencies, with most common form being cyclic neutropenia which is associated with a cyclic decrease in neutrophil count due to suppression of neutrophil maturation for 5–7 days at a regular interval of 21 days. In this case, the weekly Differential leukocyte count (DLC) revealed no increase in the counts of neutrophil. Due to lack of any history of hereditary inheritance, familial or hereditary neutropenia is ruled out.

Because all investigations and the history revealed nonspecific etiology, it may be diagnosed as idiopathic chronic neutropenia, which is defined as the neutropenia lasting for at least 3 months not attributable to any drugs, specific genetics, infectious conditions, malignancy, or autoimmunity.

In CIN, infections and inflammatory symptoms vary considerably from patient to patient. The course is seldom self-limiting, and for many years, the management protocol was to maintain good hygiene, look out for early signs of infection, and treat the same with empiric antibiotic therapy. In children, nearly 1/3rd of the times, it resolves spontaneously, but in adults, remissions are very rare. G-CSF is the only predictably effective treatment documented so far. G-CSF stimulates the bone marrow to produce neutrophils and protects the body from infection and inflammation and improves the quality of life substantially.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be
published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgement
We would like to acknowledge the Department of Haematology, SCB Medical College and Hospital, Department of Oral Pathology, SCB Dental College and Hospital.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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