Periodontal changes associated with chronic idiopathic neutropenia

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Abstract

This case report focuses on the periodontal status of a young patient with chronic idiopathic neutropenia. A four-year clinical course is presented. Chronic idiopathic neutropenia is a relatively rare blood dyscrasia characterized by a severe decrease in the number of circulating neutrophils. Young individuals exhibiting this problem experience rapid destruction of periodontal structures. A review of related literature reveals that the few discussions of dental symptoms available relate common findings: exaggerated gingivitis, premature exfoliation of the primary dentition and recurrent occurrence of aphthous-type lesions. While some mechanisms explaining the lack of circulating neutrophils have been postulated, the exact etiology of chronic idiopathic neutropenia is unknown. Dental therapy for individuals exhibiting this condition should be aimed at the reduction of local inflammation by careful and frequent removal of local irritational factors. Great care should be employed during dental therapy to reduce the possibility of bacteremias.

Introduction

Neutropenia is characterized by a severe decrease in the number of circulating neutrophils in the peripheral blood vessels. Classically, neutropenia occurs in adults, typically middle-aged women, and is a result of specific drug injection, radiation or severe infection. Several cases of infants and children exhibiting severe neutropenias of questionable or idiopathic origin have been reported in the literature. Due to differences observed in onset, severity, symptoms and etiology, a number of names have been used to describe the clinical entities: infantile congenital agranulocytosis, cyclic neutropenia, chronic benign neutropenia, reticular dysgenesis, congenital neutropenia, infantile aneucytosis, chronic idiopathic neutropenia and others. All children reported a history of persistent infections of the skin and respiratory tract. Several cases \cite{1,2,3,4,5,6,7} have discussed the response of the gingiva and periodontal supporting apparatus during the neutrophil disorder. Severe gingivitis, oral ulcers and destruction of the alveolar crest have been consistently noted.

Suggested therapy for children exhibiting this hematologic phenomena has included cysteine, blood transfusions, pyridoxine hydrochloride (vitamin B6), plasma transfusions, transfusion with packed white cells, non-specific fever therapy, splenectomy, cortisone, testosterone, and somatotropic hormone. Only antibiotic therapy has had predictable success in control of the systemic sequela. Newer methods of granulocyte transfusion appear to exhibit significant promise in future therapy regimes.

The purpose of this paper is to present a case report of a child exhibiting chronic neutropenia, discuss classification of such neutropenias and review dental management for children with such problems.

Medical History

The patient, a slight, well nourished 3\(\frac{1}{2}\)-year-old caucasian female, in no apparent distress, was referred to the Periodontics Department, College of Dentistry, University of Nebraska Medical Center, for evaluation and treatment of her gingival condition. A medical history revealed that initial problems were noted at age 2\(\frac{1}{2}\) weeks, when she developed an intense papular rash in the diaper area. A diagnosis of staphylococcal dermatitis was made and the patient was treated with ampicillin and oxacillin sodium. The rash cleared, but recurred two weeks following discontinuance of the antibiotics. The patient also experienced numerous early bouts of respiration difficulty and frequent febrile episodes, with temperatures ranging from 101-103°F. Each illness was treated with antibiotic therapy. The clinical picture recurred with cessation of each course of medication.

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The patient was evaluated at age three months and a diagnosis of hypogammaglobulinemia was made. She was treated with two injections of gammaglobulin. Multiple complete blood counts were completed during the course of her initial therapy. At no time was her granulocyte count above 3%.

At age five months the patient was referred to the University of Nebraska Medical Center for a hematologic evaluation. Laboratory data obtained at that time was as follows:

<table>
<thead>
<tr>
<th>Hemaglobin: 11.5</th>
<th>Platelets: 552,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC: 10,900</td>
<td>Urinalysis: normal</td>
</tr>
<tr>
<td>Differential:</td>
<td></td>
</tr>
<tr>
<td>76% Lymphocytes</td>
<td>IgG: 630</td>
</tr>
<tr>
<td>20% Monocytes</td>
<td>IgA: 45</td>
</tr>
<tr>
<td>3% Eosinophils</td>
<td>IgM: 97</td>
</tr>
<tr>
<td>1% Basophils</td>
<td></td>
</tr>
<tr>
<td>9% Neutrophils</td>
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A repeat blood count was comparable to the first. A bone marrow examination was reported to be consistent with congenital neutropenia. A diagnosis of congenital neutropenia, specifically of the congenital infantile agranulocytosis form, was made.

Following the diagnosis, the patient experienced numerous dermatologic infections that were treated with antibiotic therapy. At age two, severe otitis required lancing of the tympanic membranes. Ampicillin therapy was initiated at that time and continued in multiple two week courses.

**Family History**

Outside of a family history of allergic disorders, no significant familiar characteristics could be identified. Hematologic evaluations of the patient’s parents were within normal limits.

**Dental Findings**

Initial periodontal examination revealed swollen, edematous gingiva. A distinct granulomatous collar was evident at the cervical region of the teeth. It was crimson red in color and bled easily when manipulated (Figure 1). No evidence of perioral or other lesions within the oral cavity or pharyngeal region was present. Gingival recession had occurred in the anterior regions, resulting in exposed root surfaces. The gingival tissue was very tender and the patient resisted attempts at gentle probing. No clinical evidence of active carious lesions was detected. Moderate accumulations of plaque were present. The mother noted that the patient frequently complained of a “sore mouth” and resisted attempts at toothbrushing. Radiographic examination revealed exaggerated alveolar bone loss, particularly in the anterior regions of the mouth (Figures 2 and 3). No radiographic evidence of active caries was found.

The importance of plaque control was stressed to the mother. She was instructed in disclosing and cleaning her daughter’s mouth with an extra soft nylon brush, being careful to remove all traces of visible plaque. An emollient was prescribed to provide palliative relief to local regions devoid of epithelium. A thorough prophylaxis was performed and the patient was placed on a frequent maintenance regimen. The patient’s mother was told to call if any change in oral symptoms was noticed.

The patient was seen at one to three month intervals over the next four years. At maintenance appoint-
ments, plaque control was evaluated and discussed with the patient and her parents. Gingival contour, color and consistency were evaluated. Gentle debridement and polishing were accomplished as required. Kodachromes were obtained at six-month intervals for documentation. Bitewing and anterior radiographs were obtained yearly to evaluate osseous changes (Figures 2 and 3).

During the four years of observation, the patient's plaque control varied from fair to poor. From conversations with her mother it was determined that gingival inflammation periodically progressed to a point where use of even a soft toothbrush was very uncomfortable. During these periods, the parents would not insist that cleaning be performed and massive amounts of bacterial plaque would accumulate, resulting in increased gingival swelling and edema (Figure 4). The granulomatous collar remained present at each observation period, being more evident during some periods than others (Figures 1, 5 and 8).

Progressive gingival recession eventually resulted in advanced root exposure throughout the primary dentition. This was especially evident in the anterior regions of the mouth (Figures 5 and 6). Intrinsic staining became readily apparent in both the primary and permanent dentition (Figures 5, 6, and 7). Clinical evidence of active caries was not identified at any examination. Soft tissue lesions, appearing to be aphthous type ulcerations were occasionally present in the oral and perioral regions (Figure 9). Radiographic evaluations revealed progressing destruction of the alveolar bone about the primary dentition. This was especially evident about the anterior teeth and in the furcation regions of the primary molars (Figures 2 and 3).

The mandibular primary incisors were exfoliated at 5 years, 7 months. Eruption of the permanent incisors...
Figure 7: Age six years, plaque accumulation moderate. Maxillary incisors are mobile and show evidence of drifting. The deciduous mandibular incisors were exfoliated at age five years, seven months.

followed a normal pattern, although chronologically advanced. Alveolar support about the permanent teeth is within the normal limits through age seven.

Discussion

Several systemic conditions in children can initiate the oral manifestations of gingival inflammation, alveolar bone loss and mucosal ulceration. A differential diagnosis for a child presenting with these conditions must include such entities as juvenile periodontitis,\textsuperscript{34,35} Papillon-Lefevre syndrome,\textsuperscript{36} histiocytosis X,\textsuperscript{37} Chediak-Higashi syndrome,\textsuperscript{38} acatalasia,\textsuperscript{39} chronic granulomatous disease,\textsuperscript{40} hypophosphatasia,\textsuperscript{41} diabetes,\textsuperscript{42} and neutropenia.

Juvenile periodontitis and Papillon-Lefevre syndrome may be confirmed by the pattern of onset, clinical and radiographic features and lack of distinguishing laboratory features. Biopsy will confirm histiocytosis X. Chediak-Higashi syndrome exhibits identifying characteristics in peripheral leukocytes and lymphocytes as well as peculiar eosinphilia inclusion bodies in the myeloid cells of the marrow. Acatalasia may be identified by clinical or hematologic evaluation for blood catalase activity. Chronic granulomatous disease can be positively diagnosed by the qualitative nitro blue tetrazolium test. Hypophosphatasia may be confirmed by measurement of serum alkaline phosphatase. Hematologic evaluation will positively identify diabetes, leukemia or neutropenia.

Neutropenic conditions in childhood are separated into various classifications based upon clinical symptoms, age at onset, duration, white cell counts, immune function, familial tendencies and bone marrow alterations. Cyclic neutropenia is the most common form of granulocyte alteration exhibiting periodontal changes.\textsuperscript{43} In this disease, a predictably recurrent diminution of neutrophils occurs as a result of suppression or maturation arrest. The phenomenon occurs for five to seven days at regular 21-day intervals. The etiology of the process is unknown. In the time periods between these suppressions, the white blood cell counts increase, but neutrophil counts seldom exceed 50% of the total leukocyte population. Although the clinical symptoms exhibited in this case were similar to those reported for cyclic neutropenia by Telsey,\textsuperscript{44} and Wade,\textsuperscript{45} the persistence of the neutropenia exhibited by our patient does not allow duplicate classification.

Classifications such as infantile genetic agranulocytosis,\textsuperscript{46} as well as genetic, familial or hereditary neutropenias,\textsuperscript{47} were ruled out because of the apparent lack of hereditary ties. The term reticular dysgenesis\textsuperscript{14,15,16} cannot be utilized because the patient exhibits no evidence of an immunodeficiency. The term chronic benign neutropenia\textsuperscript{13,14} was not applied because this patient shows no evidence of spontaneous remission.

Several individuals\textsuperscript{17,20,31} have described cases of neutropenia in children which they labeled as chronic idiopathic neutropenia (granulocytopenia). The condition was so named because of the clinical course. A persistent neutropenia was present from birth with no apparent etiology; no familial tendencies were discovered. It differed from chronic benign neutropenia in that the children were followed for several years with no documentation of self-limitation. Clinical symptoms consisted of persistent, recurrent infections, including gingivitis, throughout the patient’s lifetime. Laboratory tests revealed severely depressed neutrophil counts with accompanying rises in the number of monocytes, lymphocytes and eosinophils. Bone marrow specimens revealed that granulopoiesis was active and orderly to the myelocyte level. Metamyelocytes, bands and segmented forms were rare. No decrease in immune functions was detectable. Therapy modalities other than antibiotics to control the recurrent episodes of infection were not successful. The condition apparently varied in severity from individual to individual. Some of the patients may survive into adolescence with suitable antibiotic therapy. This patient meets all those criteria and can be diagnosed as having chronic idiopathic neutropenia.

Her dental findings are similar to other reported neutropenia cases.\textsuperscript{15,20,46,47} While periodontal destruc-
tion, marked gingival recession, tooth discoloration and moderate to heavy accumulations of plaque were present, there was never any evidence of carious activity during the four years of follow-up. Tooth discoloration was primarily a result of intrinsic staining, probably due to antibiotic ingestion during formative periodontal was primarily a result of intrinsic staining, probably due to plaque control attempts that were below acceptable levels. The lack of carious activity in this patient and in others with neutropenic conditions is difficult to explain. It may be that the relative lack of certain inflammatory cells alter the microbial makeup to one incapable of initiating a carious process. Infected in children with chronic neutropenic conditions are common. With the lack of polymorphonuclear leukocytes in the circulation, it is assumed that the increased susceptibility to infections is due to the diminished phagocytic clearing of bacteria. The patients commonly exhibit a compensatory increase in eosinophils and monocytes in the bone marrow and peripheral blood. While these cells are also phagocytic, it has been shown that they are inferior to neutrophils in their ability to clear bacteria. Generally the infections reported in the medical literature are of dermal or upper respiratory origin. It stands to reason that the oral cavity, with its constant exposure to microorganisms, would be a common site for infections to appear.

While the exact role of the neutrophil in the protection of periodontal tissues has not been delineated, several investigators have determined that the cell may pass through junctional epithelium and reside in the gingival sulcus in a viable state. Decreased numbers of neutrophils have also been associated with development of gingivitis. Recent work has related decreased neutrophil function with increased susceptibility to certain periodontal diseases. It appears logical that the exaggerated periodontal destruction seen in patients with chronic idiopathic neutropenia is a result of decreased protection by the neutrophil.

Previous reports mention that the severe alveolar bone loss occurring around the primary teeth does not appear to interfere with the eruption pattern of the permanent teeth. Other observations that follow the children to a later age, report eventual alveolar bone destruction about the permanent teeth as a common sequela. This patient has exhibited a normal eruption sequence of the permanent dentition. The eruption schedule has been accelerated, probably due to the early loss of some primary teeth secondary to accentuated alveolar bone loss. It is expected that alveolar destruction about her permanent teeth will occur with time.

This patient, as well as others exhibited several episodes of recurrent aphthous lesions (Figure 9). Such problems have been noted to occur frequently, but there doesn’t appear to be a clear relationship with the circulating neutrophil count.

With the advent of more sophisticated antibiotic therapy, a greater number of children exhibiting hematologic disorders are surviving infections and requiring dental therapy. While some children with neutropenic conditions require no special management during dental therapy, many have an increased susceptibility to all infections, including periodontal disease. It is imperative that practicing dentists have a thorough knowledge of the dental management regimens required by these patients.

Mishkin et al. describe, in great detail, the biorationale for dental management of neutropenic patients. Although caries activity does not appear to be a major problem for individuals with chronic idiopathic neutropenia, daily stannous fluoride gel is recommended to retard the possibility of tooth loss or dental infection secondary to a carious lesion. Stannous fluoride application has also been shown to be capable of reducing plaque formation and potentially useful in the control of early periodontal disease. A strict oral hygiene program, complete with scaling and prophylaxis at short-term intervals, is suggested to decrease the intensity of gingival inflammation and slow the rate of alveolar bone loss. Maximum precautions, including antiseptic irrigation and antibiotic coverage, prior to tissue manipulation is suggested to reduce the possibility of bacteremias and postoperative infections.

Conclusion

Chronic idiopathic neutropenia is characterized by a severe decrease in the number of circulating neutrophils. The condition is characterized by oral symptoms consisting of: oral ulceration, gingival inflammation and rapidly advancing alveolar bone destruction.

It is important that the practicing dentist be aware of the dental ramifications exhibited by individuals with this disorder and be knowledgeable concerning their management.
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References
60. Temple, T. R. et al.: Host factors in periodontal disease: perio-
dental manifestations of Chediak-Higashi syndrome, J Peri-
61. Gillig, J. L. and Caldwell, C. H.: The Chediak-Higashi syn-
63. Wolf, J. E. and Ebel, L. K.: Chronic granulomatous disease:
report of case and review of the literature, J Am Dent Assoc, 96:
64. Baer, P. N. et al.: Hypophosphatasia: report of two cases with
65. Eversole, L. R.: Clinical Outline of Oral Pathology: Philadel-
66. Haas, R. J. et al.: Congenital immunodeficiency and agranulocy-
67. Howard, M. W. et al.: Infections in patients with neutropenia,
68. Kauder, E. and Mauer, M. A.: Neutropenias of childhood, J
69. Clime, M. J. et al.: Phagocytosis by human eosinophils, Blood,