Autoimmune Neutropenia as a Cause of Periodontal Disease in Preschool Children

Evlambia Hajishengallis*/ Stephanie Rashewsky /Cyelee Kulkarni***/ Panagiota Stathopoulou******

In autoimmune neutropenia, autoantibodies attack neutrophils resulting in their destruction or alteration of their function. Since neutrophils have important immunologic functions, aberrations in their homeostasis lead to increased susceptibility to diseases, such as periodontitis. Periodontitis as a manifestation of neutropenia can affect adults and children. In this paper, we describe the treatment of periodontal disease in a 2-year-old female with autoimmune neutropenia. The importance of an interdisciplinary approach, frequent recalls, and meticulous mechanical therapy in stabilizing her periodontal condition, despite ongoing systemic infections is emphasized.

Key words: *periodontal disease, autoimmune neutropenia, children*

INTRODUCTION

All types of periodontal disease can potentially affect children. However, while gingivitis is common, the destructive forms of periodontal diseases, i.e., aggressive periodontitis, chronic periodontitis, and periodontitis as a manifestation of systemic disease, are rare in the pediatric population.[1]

Periodontitis as a manifestation of systemic disease in children can appear at any time after the eruption of primary teeth and occur in localized or generalized form.[2] Systemic diseases associated with early onset of periodontitis include the Papillion-Lefèvre syndrome, hypophosphatasia, leukocyte-adhesion deficiency, Chédiak-Higashi syndrome, histiocytosis X, leukemias, acrodynia, and neutropenia.[3-5]

From Penn Dental Medicine,the University of Pennsylvania, Philadelphia, , USA.

*Hajishengallis Evlambia, DDS, MSc, PhD, Associate Professor, Chief of Pediatric Dentistry, Pediatric Dentistry Division, Department of Restorative and Preventive Sciences.

**Stephanie Rashewsky, DMD, Pediatric Dental Resident, Pediatric Dentistry Division, Department of Restorative and Preventive Sciences,.

***Cyelee Kulkarni, DMD, Instructor, Pediatric Dentistry Predoctoral Program Director, Pediatric Dentistry Division, Department of Restorative and Preventive Science.

*****Panagiota G. Stathopoulou DDS, MS, PhD, Assistant Professor, Department of Periodontics, Assistant Dean of Clinical Affairs.

Send all correspondence to:

Evlambia Hajishengallis
Robert Schattner Center, 240 South 40th Street Philadelphia, Evans PQ18, PA 19104-6030
Phone: (215) 573-2650
Fax: (215) 573-8358
E-mail: Evlambia@dental.upenn.edu

Neutropenia is a granulocyte disorder, characterized by a low absolute neutrophil count (ANC) in blood circulation. ANC below 1500/ml in children older than 1 year of age, or below 2000/ml in children 2 -12 months indicates neutropenia.[6] Neutropenia is classified as mild (ANC between 1000–1500/ml), moderate (ANC between 500–1000/ml), and severe (ANC < 500/ml).[7] Besides ethnic differences (i.e., in people of African origin an ANC of 1000/ml is normal), there are significant random, nycthemeral and seasonal fluctuations in the ANC.[6,8] This explains the requirement for repeated blood tests (i.e., 3 samples per week over a 6-week period) for the definitive diagnosis of chronic neutropenia.[6] Based on the duration of the decreased ANC, chronic neutropenia is classified as permanent (ANC is constantly low), intermittent (periods of normal ANCs), and cyclic (low ANC every 21 days).[6]

The etiology of chronic neutropenia in children is multifactorial and sometimes difficult to determine.[9,10] In most patients, neutropenia is secondary to viral infections, drugs, malignancy, hypersplenism, or autoimmunity, whereas congenital neutropenias are less prevalent.[11]

Neutrophils play a significant role in inflammation and wound healing, and function as the first line of defense against pathogenic microorganisms.[12,13] Therefore, reduced number or impaired function of neutrophils result in infections that appear most often at the mucous membranes (mouth ulcers and periodontal disease) and in the skin of the genital and perirectum area (rashes and abscesses).[6]

In this paper, we present a case of a 2-year-old female with a history of autoimmune neutropenia and periodontitis. We review the autoimmune type of neutropenia and also discuss the treatment of her periodontal disease.

Case report

A 25-month-old Caucasian female was referred by her hematologist to the Pediatric Clinic at the University of Pennsylvania School of Dental Medicine for evaluation of gingival hyperplasia/hypertrophy on maxillary anterior teeth.

Review of her medical history revealed severe chronic neutropenia (Table 1), resulting in numerous infections such as periorbital cellulitis, respiratory syncytial virus infections, pustular diaper rashes, bilateral suppurative otitis media, right third-toe cellulitis, hand-foot-mouth disease, and recurrent fevers. A bone marrow aspiration biopsy was normal and genetic testing for mutations in the *ELA2* gene was negative. However, her serum tested positive for anti-neutrophil antibodies, and based on this, she was diagnosed with autoimmune neutropenia. On the other hand, the high frequency of the infections she suffered was not consistent with this diagnosis.

Review of the patient's dental history revealed a visit to a general dentist one month earlier for inflammation associated with a popcorn kernel trapped on the buccal gingiva of the primary maxillary right central incisor. The kernel was removed and local debridement was performed. After persistence of inflammation accompanied by suppuration for two weeks, clindamycin and hydrogen peroxide were prescribed.

The intraoral examination at initial visit showed inflammation of the anterior maxillary gingiva from primary canine to canine, with erythema, edema, and bleeding upon pressure on both the buccal and palatal sides (Figure. 1). For maxillary right central and lateral incisors Probing Depth (PD) measurements ranged from 2 to 5 mm, Clinical Attachment Level (CAL) measurements ranged from 1-3 mm, and bleeding on probing was present. The rest of the sites had PD measurements of 3 mm or less, no attachment loss, and bleeding on probing was generalized. No oral ulcers or tooth mobility were observed, and radiographic examination showed no significant findings (Figure. 2). The patient's parents reported significant bleeding on tooth brushing. The periodontal diagnosis was Localized Slight Periodontitis as a Manifestation of Systemic Diseases. Mechanical debridement was performed, and oral hygiene instructions were given including a power toothbrush and alcohol-free chlorhexidine applications twice daily. The parents were also advised to discontinue the administration of clindamycin and hydrogen peroxide.

A gingivectomy and biopsy of the persistent hyperplastic maxillary gingiva was performed at the time of the bone marrow aspiration, and revealed normal inflammatory tissue and typical anaerobic oral bacteria. One week following the gingivectomy, the patient presented with reduced signs of inflammation and healing within normal limits, while post-surgical recession of 1-3 mm was evident (Figure.3). A thorough dental prophylaxis was performed (under antibiotic prophylaxis), oral hygiene instructions were reinforced and chlorhexidine application was reduced to one time daily. Soon after this visit, the patient was hospitalized for right third-toe cellulitis and received intravenous antibiotics and granulocyte colony-stimulating factor (G-CSF). She responded well to G-CSF, and at re-evaluation, six weeks after her release from the hospital, an improvement in her gingival condition was noted. The edema and erythema had subsided, and there was absence of bleeding on probing, pressure, or tooth brushing. The patient was placed on 3-month periodontal maintenance, and her periodontal disease has been under control for more than 20 months, as evident by stable attachment loss measurements and lack of bleeding on probing (Figures. 4, 5, 6). Periodontal stability has been achieved despite her continuing to have low ANCs (Table 1) and repeated episodes of systemic infections and fevers.

DISCUSSION

In autoimmune neutropenia, autoantibodies attack molecules on the neutrophil membrane leading to their accelerated destruction or alterations in their function.[14] The origin of the autoantibodies is unknown, but it may involve molecular mimicry of microbial antigens, modification of endogenous antigens as a result of drug exposure, loss of suppressor activity against self-reactive lymphocyte clone, etc.[14] Detection of anti-neutrophil antibodies is challenging due to the fragility of the neutrophils, their autofluoresence, and tendency to aggregate and release autolytic enzymes during processing.[14,15] A minimum of two tests is frequently required for the autoantibody detection[14], and still the findings may not be conclusive.

Our patient had a history of positive anti-neutrophil antibodies, but the etiology of her neutropenia was complicated by the frequency of her systemic infections. More than 2/3 of children diagnosed with autoimmune neutropenia are under 3 years of age, but despite their severe neutropenia, they are asymptomatic or present with mild skin and upper respiratory infections.[14] This is probably due to bone marrow reserves being normal and not affected by the autoimmunity, as well as to the often observed compensatory monocytosis. Only 10-12% of patients suffer from severe infections, like in the present case.[14]

Two other types of neutropenias with serious oral manifestations were considered in the differential diagnosis of the patient, the severe or permanent and the cyclic neutropenia. Both of these neutropenias often involve mutations in the *ELA2* gene, which result in apoptosis of neutrophil precursors.[6] In both of them, the ANC is usually below 200/ml although in cyclic neutropenia the low ANC appears approximately every 21 days. Severe permanent neutropenia is diagnosed typically before the age of 6 months whereas cyclic neutropenia is usually diagnosed around the second year of life. Testing of our patient for *ELA2* gene mutations was negative.

The oral manifestations of neutropenias include oral ulcers, stomatitis, edematous and fiery-red gingiva, and severe periodontal pathology similar to aggressive periodontitis.[16,17] Our patient presented with generalized inflammation and periodontitis localized in the anterior teeth. The treatment plan therefore, was focused on eliminating any local factor, which could exacerbate the effect of the patient's systemic condition on her periodontal health.

Treatment of periodontitis as a manifestation of systemic disease in children is similar to that of aggressive periodontitis, and includes nonsurgical and surgical mechanical therapy, antimicrobials, frequent maintenance appointments, and thorough home plaque control.[18] The hyperplastic inflamed gingiva in the maxillary anterior area of our patient was removed, a full-mouth mechanical debridement was performed, and oral hygiene instructions including use of chlorhexidine were stressed. After control of the inflammation, the patient was placed on a 3-month recall. The typical 6-month recall interval has been shown to be inadequate for patients with periodontitis[19], while a more frequent interval,

Fig. 1 **Enlargement of buccal gingival tissue associated with maxillary anterior teeth of our patient**

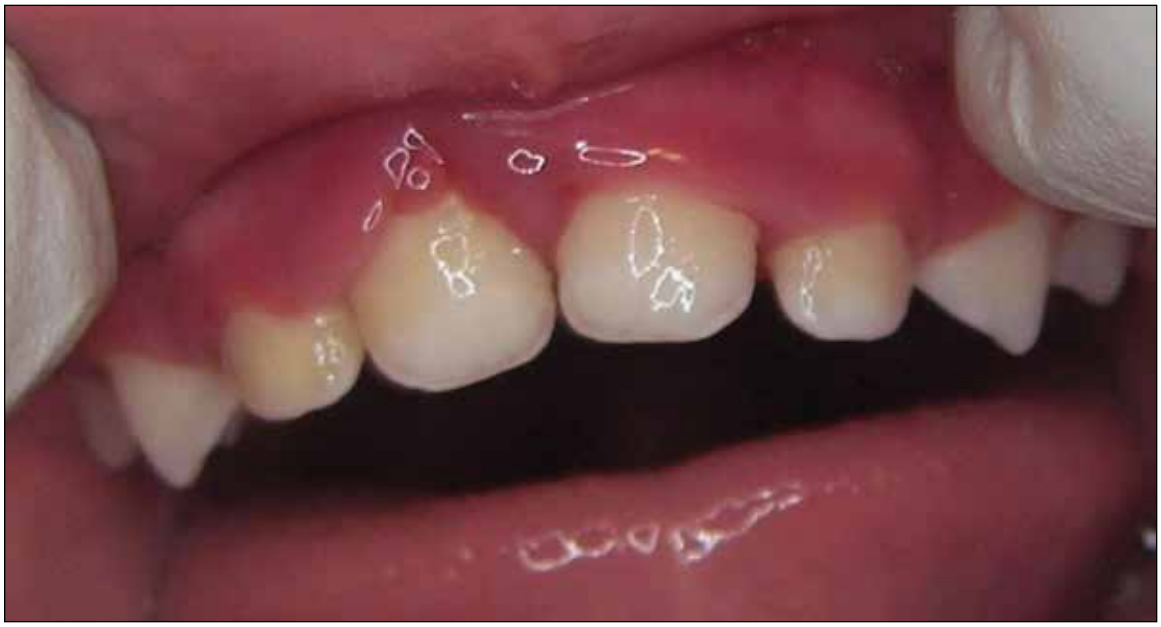


Fig. 2 **Maxillary occlusal radiograph**

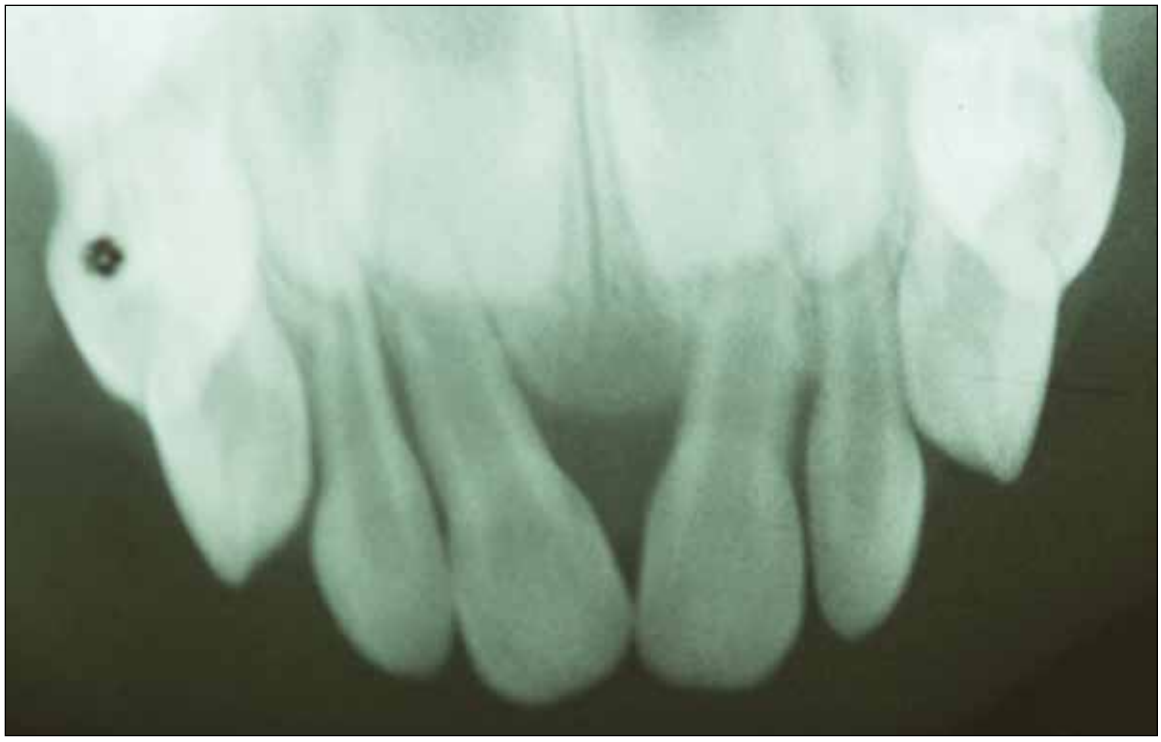


Fig. 3 **Gingiva on maxillary buccal side 1 week after the hyperplastic gingiva tissue excision in the operating room**

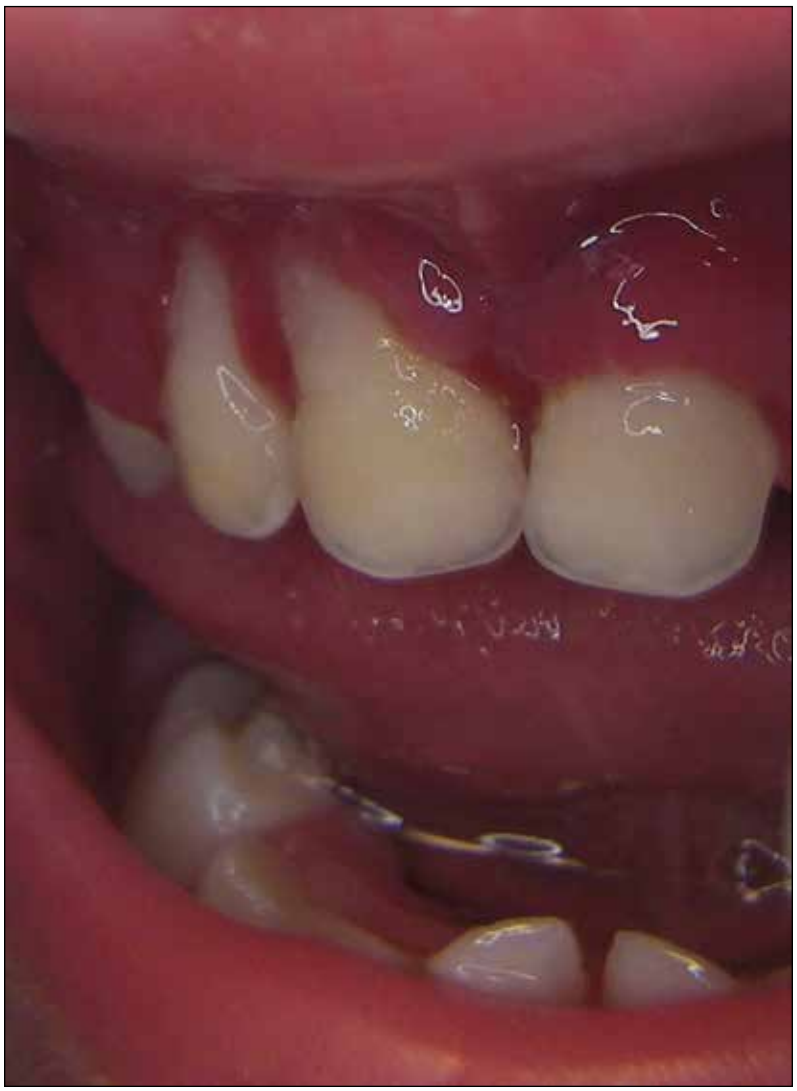


Fig. 4 **Maxillary (a) and mandibular (b) gingival tissue of our patient six months after her initial presentation in our clinic**

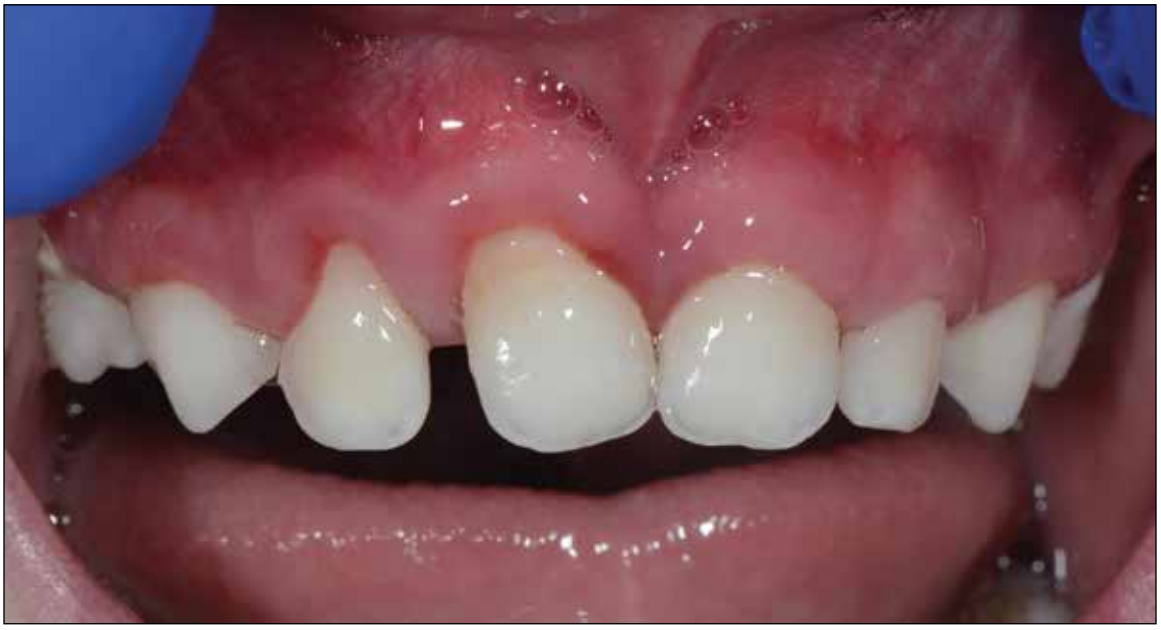


Fig. 5 **Gingival tissue of our patient one year after her initial presentation in our clinic**

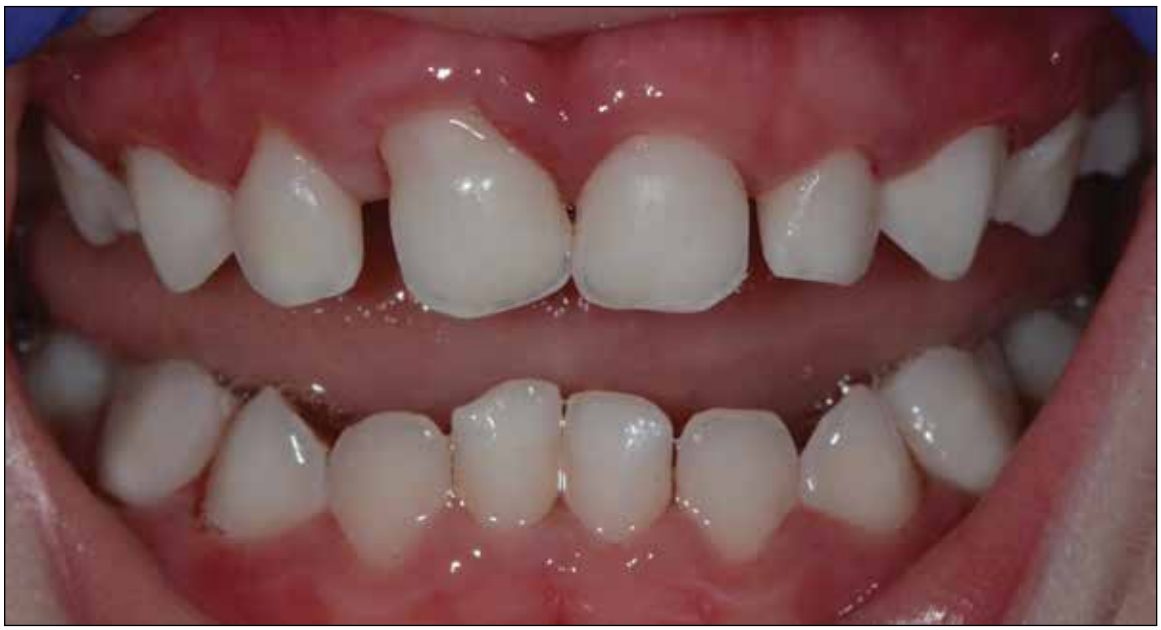
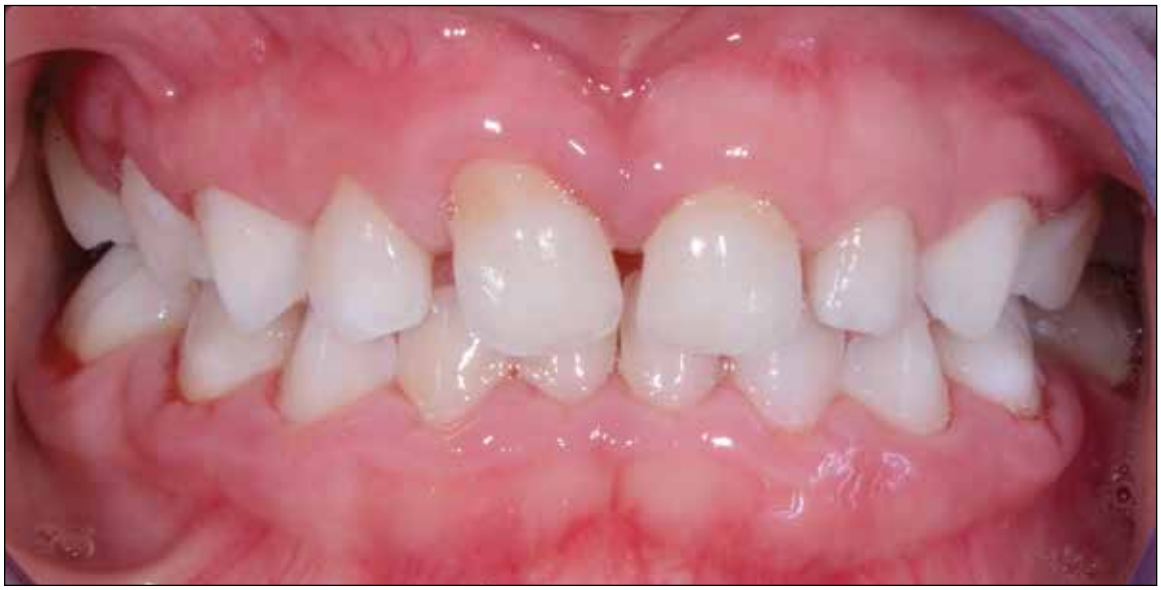


Fig. 6 **Gingival tissue of our patient twenty months after her initial presentation in our clinic**



usually every 3 months, is essential for the maintenance of periodontal health and prevention of further periodontal attachment loss.[4,20-23]

Bacteria associated with periodontitis in neutropenic patients include *Porphyromonas. gingivalis, Prevotella. intermedia, Capnocytophaga ochracea, Capnocytophaga sputigena, Aggregatibacter. actinomycetemcomitans,* etc.[24] Although these bacteria are susceptible to amoxicillin and metronidazole,[25,26] systemic antibiotics are not routinely used for the treatment of periodontal disease due to the potential side-effects and mainly the development of antibiotic resistance.[27] The decision to use antibiotics in conjunction with mechanical periodontal therapy is influenced by the clinical situation, the immunological status of the patient, and the subgingival microbiota.[28] In our case, since stability of the periodontal condition was achieved by mechanical therapy, plaque control, chlorhexidine application, and 3-month recall visits, we elected not to use antibiotics.

Severe infections in neutropenic patients are addressed with recombinant G-CSF[14] which acts by regulating the production and mobilization of neutrophils from the bone marrow, stimulating phagocyte function, reducing neutrophil apoptosis and membrane antigen expression.[2,14,29]L.</author><author>Dale, D. C.</author></authors></contributors><auth-address>Department of Pediatrics, University of Washington, Seattle, WA 98195-6422, USA.</auth-address><titles><title>Neutropenia: causes and consequences</title><secondary-title>Semin Hematol</

Table 1. Absolute neutrophil counts (ANC) on repeated hematologic examinations

Date (month/day/year)	ANC/ml
5/10/2012	1992
5/30/2012	336
7/11/2012	546
8/3/2012	294
8/24/2012*	111
8/25/2012	616
9/5/2012	1703
10/26/2012	486
11/30/2012	400
1/19/2013	2112
2/13/2013	658
4/17/2013	111
7/24/2013	46

*On 8/24/2012 the patient started a 20 day-course of Granulocyte-Colony Stimulating Factor (G-CSF)

secondary-title><alt-title>Seminars in hematology</alt-title></titles><periodical><full-title>Semin Hematol</full-title><abbr-1>Seminars in hematology</abbr-1></periodical><alt-periodical><full-title>Semin Hematol</full-title><abbr-1>Seminars in hematology</abbr-1></alt-periodical><pages>75-81</pages><volume>39</volume><number>2</number><edition>2002/04/17</edition><keywords><keyword>Diagnostic Techniques and Procedures</keyword><keyword>Humans</keyword><keyword>Inflammation/etiology</keyword><keyword>Neutropenia/*complications/diagnosis/*etiology</keyword><keyword>Skin Diseases, Infectious/etiology</keyword></keywords><dates><year>2002</year><pub-dates><date>Apr</date></pub-dates></dates><isbn>0037-1963 (Print
However, long-term treatment with G-CSF may result in serious adverse effects, such as myelodysplastic syndrome, splenomegaly, osteopenia and leukemia.[30-32] Administration of G-CSF has been shown to also reduce gingival inflammation and bleeding in patients with chronic severe neutropenia[33] and cyclic neutropenia.[34,26] In the present case, the patient received one round of G-CSF which resulted in increased ANC (Table 1) and was followed by an improvement in her gingival condition. At the same time, mechanical plaque removal was performed and therefore, it is impossible to assess the effect of G-CSF administration alone on the improvement of periodontal parameters.

The prognosis of autoimmune neutropenia of childhood is very good; 80-95% of the cases resolve spontaneously usually within 36 months from the time of diagnosis.[14] Consequently, periodontal parameters are expected to stabilize after recovery of the neutrophil counts, and periodontal disease is not anticipated to continue in permanent dentition. In the meantime, a conservative treatment approach, including plaque control with mechanical therapy, meticulous oral hygiene, and 3-month periodontal maintenance has the potential for halting periodontal disease, as well as reducing the possible risk for systemic infections as a result of transient bacteremias in these immunocompromised patients.

CONCLUSION

The present case report emphasizes the importance of an interdisciplinary approach in the treatment of pre-school children with periodontitis as a manifestation of neutropenia. It is essential that the dental team, comprising of a general dentist or pediatric dentist and a periodontist, collaborates with the medical team, often a pediatrician and a hematologist. In addition, the patient's parents should be considered a part of this team, since compliance with home care and frequent maintenance are absolutely necessary for long-term periodontal stability. Such an organized interdisciplinary approach results in early accurate diagnosis and appropriate treatment, which in turn provides the opportunity to control periodontal disease at early stages using mechanical therapy alone. In the present case, and due to the parents being proactive, the disease was diagnosed at an early stage, at which both severity and extent could be controlled and limited. Early accurate diagnosis, early appropriate treatment, and compliance with the recommended recall interval actually resulted in periodontal stability in our patient. .

REFERENCES

1. Jenkins WM, Papapanou PN. Epidemiology of periodontal disease in children and adolescents. Periodontol 2000 26:16-32, 2001.
2. Periodontal diseases in children and adolescnets. Am Acad Ped Dent Reference Manual 35:338-45, 2012-2013.
3. Kinane DF, Hodge PJ. Periodontal disease in children and adolescents: introduction and classification. Periodontol 2000 26:7-15, 2001.
4. Myele J, Gonzales JR. Influences of systemic disease on periodontitis in children and adolescents. Periodontol 2000 26:92-112, 2001.
5. Hajishengallis E, Hajishengallis G. Neutrophil Homeostasis and Periodontal Health in Children and Adults. J Dent Res 93:231-7, 2014.
6. Donadieu J, Fenneteau O, Beaupain B, Mahlaoui N, Chantelot CB. Congenital neutropenia: diagnosis, molecular bases and patient management. Orphanet J Rare Dis 6:26-50, 2011.
7. Coates TD. Overview of neutropenia. UpToDate Available at: "http://www.uptodate.com"). Accessed September 25/2012.
8. Hsieh MM, Tisdale JF, Rodgers GP, Young NS, Trimble EL, Little RF. Neutrophil count in African Americans: lowering the target cutoff to initiate or resume chemotherapy? J Clin Oncol 28:1633-7, 2010.
9. Roskos RR, Boxer LA. Clinical disorders of neutropenia. Pediatr Rev 12:208-12, 1991.
10. Walkovich K, Boxer LA. How to approach neutropenia in childhood. Pediatr Rev 34:173-84, 2013.
11. Oski FA. Neutropenia in children. Pediatr Rev 3:108-12, 1981.
12. Amulic B, Cazalet C, Hayes GL, Metzler KD, Zychlinsky A. Neutrophil function: from mechanisms to disease. Annu Rev Immunol 30:459-89, 2012.
13. Kobayashi SD, DeLeo FR. Role of neutrophils in innate immunity: a systems biology-level approach. Wiley Interdiscip Rev Syst Biol Med 1:309-33, 2009.
14. Capsoni F, Sarzi-Puttini P, Zanella A. Primary and secondary autoimmune neutropenia. Arthritis Res Ther 7:208-14, 2005.
15. Shastri KA, Logue GL. Autoimmune neutropenia. Blood 81:1984-95, 1993.
16. Defraia E, Marinelli A. Oral manifestations of congenital neutropenia or Kostmann syndrome. J Clin Pediatr Dent 26:99-102, 2001.
17. Deas DE, Mackey SA, McDonnell HT. Systemic disease and periodontitis: manifestations of neutrophil dysfunction. Periodontol 2000 32:82-104, 2003.
18. Chauhan VS, Chauhan RS, Devkar N, Vibhute A, More S. Gingival and periodontal diseases in children and adolescents. J Dent Allied Sciences 1:26-9, 2012.
19. Nyman S, Rosling B, Lindhe J. Effect of professional tooth cleaning on healing after periodontal surgery. J Clin Periodontol 2:80-6, 1975.
20. Becker W, Becker BE, Ochsenbein C, et al. A longitudinal study comparing scaling, osseous surgery and modified Widman procedures. Results after one year. J Periodontol 59:351-65, 1988.
21. Kaldahl WB, Kalkwarf KL, Patil KD, Dyer JK, Bates RE, Jr. Evaluation of four modalities of periodontal therapy. Mean probing depth, probing attachment level and recession changes. J Periodontol 59:783-93, 1988.
22. Ramfjord SP, Morrison EC, Burgett FG, et al. Oral hygiene and maintenance of periodontal support. J Periodontol 53:26-30,1982.
23. Parameter on periodontal maintenance. American Academy of Periodontology. J Periodontol 71:849-50, 2000.
24. Kamma JJ, Lygidakis NA, Nakou M. Subgingival microflora and treatment in prepubertal periodontitis associated with chronic idiopathic neutropenia. J Clin Periodontol 25:759-65, 1998.
25. Belibasakis GN, Thurnheer T. Validation of Antibiotic Efficacy on in Vitro Subgingival Biofilms. J Periodontol 85:343-8, 2014.
26. Schmidt JC, Walter C, Rischewski JR, Weiger R. Treatment of periodontitis as a manifestation of neutropenia with or without systemic antibiotics: a systematic review. Pediatr Dent 35:E54-63, 2013.
27. Walter C, Weiger R. Antibiotics as the only therapy of untreated chronic periodontitis: a critical commentary. J Clin Periodontol 33:938-9, 2006.
28. Slots J. Systemic antibiotics in periodontics. J Periodontol 75:1553-65, 2004.
29. Boxer L, Dale DC. Neutropenia: causes and consequences. Semin Hematol 39:75-81, 2002.
30. Cottle TE, Fier CJ, Donadieu J, Kinsey SE. Risk and benefit of treatment of severe chronic neutropenia with granulocyte colony-stimulating factor. Semin Hematol 39:134-40, 2002.
31. Dale DC, Cottle TE, Fier CJ, et al. Severe chronic neutropenia: treatment and follow-up of patients in the Severe Chronic Neutropenia International Registry. Am J Hematol 72:82-93, 2003.
32. Masood N, Shaikh AJ, Memon WA, Idress R. Splenic rupture, secondary to G-CSF use for chemotherapy induced neutropenia: a case report and review of literature. Cases J 1:418, 2008.
33. Hasturk H, Tezcan I, Yel L, et al. A case of chronic severe neutropenia: oral findings and consequences of short-term granulocyte colony-stimulating factor treatment. Aust Dent J 43:9-13, 1998.
34. Chen Y, Fang L, Yang X. Cyclic neutropenia presenting as recurrent oral ulcers and periodontitis. J Clin Pediatr Dent 37:307-8, 2013.