Periodontitis Associated with Chediak-Higashi Syndrome in a Young African American Male

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Abstract

Background: Chediak-Higashi syndrome (CHS) is a rare autosomal recessive genetic disease. The primary defect is abnormal granule formation in the cells secondary to a mutation of a lysosomal trafficking regulator protein. CHS patients have immune system abnormalities, bleeding abnormalities, and multiple infections including periodontitis. *Methods*: A 13-year-old African American male presented with severe gingival inflammation, generalized gingival bleeding, and tooth looseness. Comprehensive dental, medical and laboratory evaluations were performed. *Results*: All teeth exhibited excessive mobility. The gingival tissues were swollen and bled easily. Most sites had probing depth in excess of 10 mm. Dental radiographs showed advanced generalized alveolar bone loss. Areas of skin depigmentation were noted. Blood smear showed presence of intracellular large granules in white blood cells. Platelet function was altered. Gingival histopathology showed an intense chronic inflammatory cell infiltrate and presence of numerous filamentous bacteria. Subgingival microbiological culture showed the presence of *Porphyromonas gingvalis, Prevotella intermedia* and *Tannerella forsythia*. Based on the periodontal, medical and laboratory findings a diagnosis of CHS was established. Because of the advanced periodontal condition and the risk of fatal bacterial infections, exodontias were performed. Because of platelet abnormalities the patient developed postoperative bleeding complications that required management with coagulation factor 7. *Conclusions*: Advanced periodontitis is an important symptom of CHS and may be the first step in the diagnosis of the condition. Due to the weakened immunity of CHS patients, periodontal management is usually unsuccessful. Tooth extractions are recommended to eliminate the periodontal problems and reduce the risk of fatal bacterial infections.

Key words: Chediak-Higaashi syndrome, leukocyte function, periodontitis, periodontal diseases/microbiology, periodontal diseases/therapy, hemorrhage.

Introduction

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive genetic disorder of granule morphology and function affecting multiple organ systems. Cuban pediatrician Beguez-Cesar (1943) was the first to describe this rare disease. Later Chediak (1952) and Higashi (1954) further described and characterized the syndrome and their names became associated with it. The primary defect is abnormal granule formation in the cells secondary to a mutation of a lysosomal trafficking regulator protein (Ward *et al.,* 2002). This results in impaired function of multiple body cells and systems. White blood cells and other cells characteristically exhibit large granules in the cytoplasm. Patients with CHS have immune system abnormalities, multiple infections, bleeding abnormalities and muscle weakness. Progressive damage to the peripheral nervous system, partial albinism, and sensitivity to light are associated with the disease. In addition, patients with CHS tend to have slight cognitive deficits. The disease is lethal and life expectancy is usually short, with a majority of patients dying in childhood. Fatality is associated with infections and lymphoproliferative disorders in multiple organs (Introne *et al.*, 1999; Certain *et al.,* 2000). Treatment with bone marrow transplantation may be helpful in correcting neutrophil dysfunction in some patients (Trigg and Schugar, 2001).

CHS is associated with significant periodontal problems, including profound gingival inflammation and advanced alveolar bone loss. Our knowledge of periodontal abnormalities in CHS patients is derived mainly from a few case reports (Tempel *et al.,* 1972;

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Hamilton and Giansanti, 1974; Delcourt-Debruyne *et al.,* 2000; Shibutani *et al.,* 2000). Previous reports did not specifically address recommended periodontal management and possible bleeding complications. The rarity of CHS makes it impossible to study the disease in a large population of patients. The greater the number of cases documented the greater would be our understanding of the disease and its management. This case report will describe the periodontal findings and recommended periodontal management in an African American child.

Case report

Patient information

The patient described is a thirteen-year-old African American male. He was a single child who lived with his mother in a rural area near Augusta, Georgia. His father was deceased. His mother brought him to the Medical College of Georgia School of Dentistry for periodontal evaluation as per the recommendation of the local dentist. The chief complaint was swollen bleeding gums and loose teeth. He was having difficulty chewing his food. He was about 5 ft tall (~150 cm) and weighed 95 lbs (43.2 kg). He had a friendly personality, looked relaxed and was cooperative.

Oral/dental examination revealed a somewhat asymmetrical face with the lower jaw slightly prognathic. Palpation of the neck detected swollen and indurated submandibular lymph nodes. Intra-oral evaluation showed malpositioning of all teeth (*Figure 1*). The teeth were normally shaped; however, they were rotated and pushed out of place. Diastemas were present between most teeth. All teeth exhibited grade 2 to 3 mobility. Generalized abundant amounts of plaque and calculus were noted (*Figure 1*). The gingival tissues were swollen and easily bled on provocation. There was generalized loss of interdental papillae. Most sites showed probing depth in excess of 10 mm.

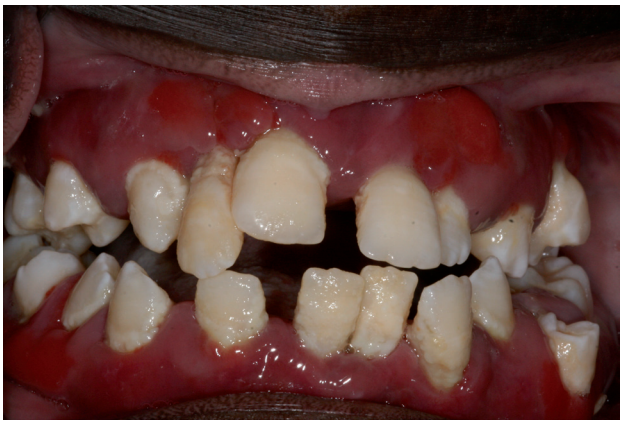

Figure 1. Clinical image showing tooth malpositioning, generalized swelling of gingival margins, loss of interdental papillae, and heavy accumulations of dental plaque.

Radiographic examination, including a panoramic x-ray and a full mouth series of periapical intraoral radiographs, showed generalized advanced alveolar bone loss reaching the apical third of most teeth (*Figure 2*). Several teeth appeared to have no remaining bone support.

In addition to the clinical and radiographic evaluations, a gingival biopsy was obtained under local anesthesia. Also, subgingival plaque samples were collected from multiple sites for microbial analysis.

The severity and extent of the periodontal lesions aroused suspicion of an underlying medical condition. The patient was referred to the pediatric department at the Medical College of Georgia for a comprehensive medical evaluation and blood analysis. Pertinent find-

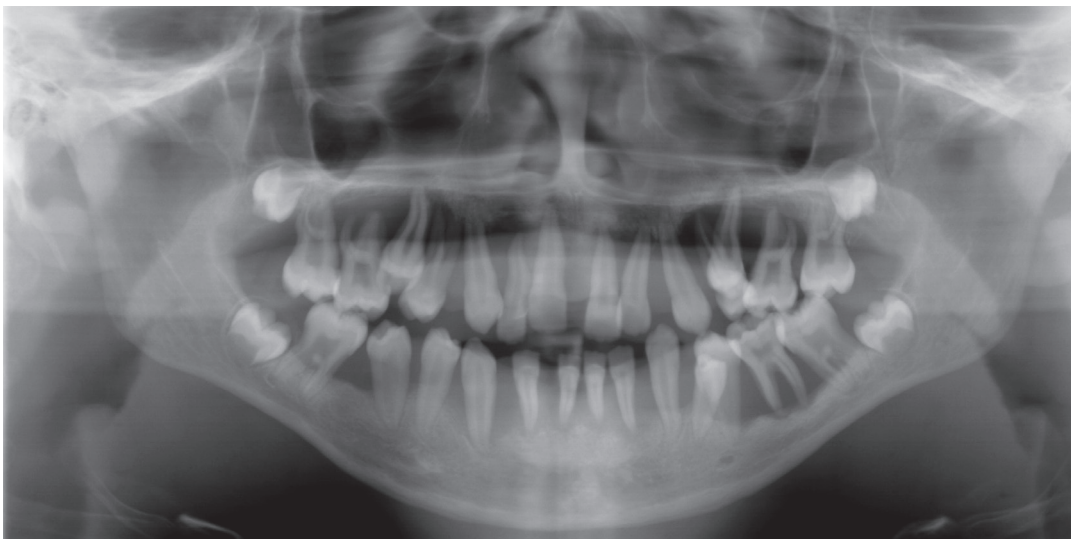

Figure 2. Panoramic x-ray showing generalized extensive alveolar bone loss.

ings that suggested a diagnosis of CHS were areas of depigmentation in the skin and some hypopigmentation of the eyelashes. Pertinent negatives were the absence of optic atrophy and a normal neurologic exam. Most conspicuous for a neutrophil disorder was the severe oral dental findings as detailed above.

Laboratory findings

A complete blood count revealed a hemoglobin level of 9.3 g/dl, and white blood cells at 4.8 x 10^6/dl with normal differential, establishing that the patient was not neutropenic. The patient's platelet function analysis showed normal platelet aggregation in response to ADP, collagen and arachidonic acid, but abnormal platelet aggregation in response to ristocetin. The patient's Epstein-Barr virus serology was positive, thus placing him at risk for fulminant lymphoproliferative syndrome, as has been observed in CHS. A peripheral blood smear showed the presence of large, intracellular granules in neutrophils and other white blood cells.

Gingival histopathological findings

Hematoxylin and eosin-stained sections revealed granulation and fibrous connective tissues lined with non-keratinized stratified squamous epithelium, and bacterial colonies (*Figure 3*). The granulation tissue and fibrous connective tissues intertwine and are composed of dense intertwining bundles of collagen interspersed by fibroblasts, fibrocytes and occasional small blood vessels engorged with erythrocytes. This framework supports an intense chronic inflammatory cell infiltrate, chiefly consisting of plasma cells and lymphocytes (*Figure 4*). At the periphery of the specimen, multiple basophilic calcified fragments supporting bacterial colonies are noted. Sections stained with Gram stain revealed numerous filamentous Gram-positive bacteria (*Figure 5*).

Microbiological findings

Three interproximal sites with pockets 10 mm or greater were randomly selected in different regions of the mouth. Supragingival plaque was first removed with a curette. Subgingival plaque samples were then collected with sterile paper points. A paper point was placed in each of the selected sites for 30 seconds. After sample collection, the paper points from the three selected sites were immediately placed in a vial containing a transport solution. The vial was sealed and mailed overnight to a commercial laboratory for culture analysis. The microbiological culture report identified the presence of the following periodontopathic bacteria: *Porphyromonas gingivalis* 3.8%, *Prevotella intermedia* 10%, *Tannerella forsythia* 5.4%, *Campylobacter* species 4.6%, and *Fusobacterium* species 6.2%.

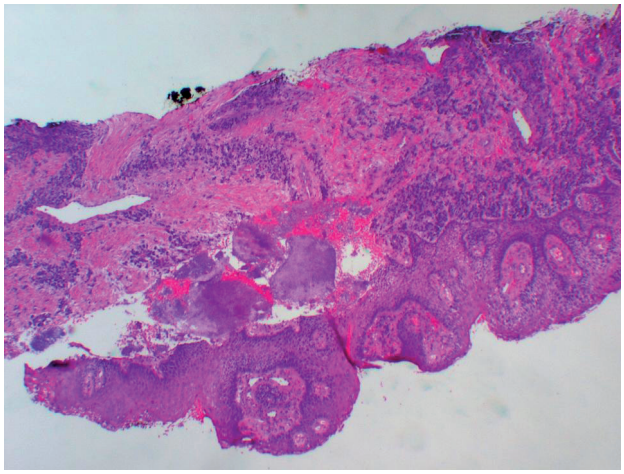

Figure 3. Sections of granulation and fibrous connective tissues lined with non-keratinized epithelium and supporting mononuclear chronic inflammatory cells (hematoxylin and eosin stain, original magnification 40x)

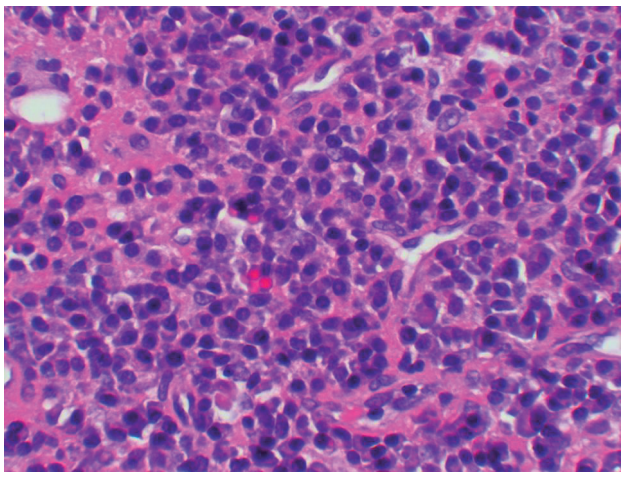

Figure 4. Intense chronic inflammatory cellular infiltrate predominantly consisting of plasma cells and lymphocytes (hematoxylin and eosin stain, original magnification 400x)

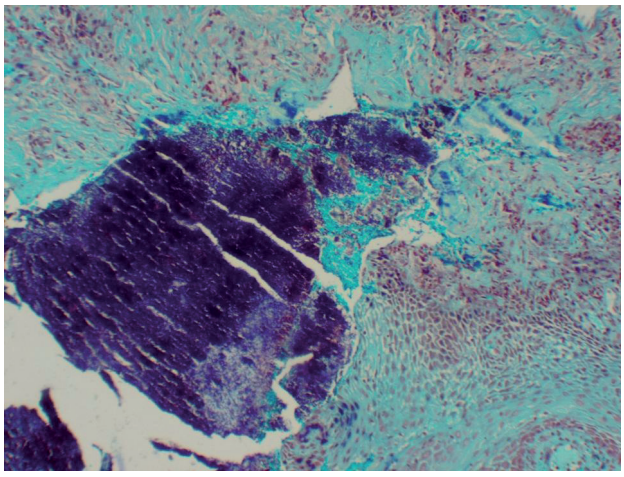

Figure 5. Sections of filamentous bacteria wedged inbetween non-keratinized epithelium (sulcular epithelium) and the underlying connective tissue (Gram stain, original magnification 200x)

Periodontal diagnosis and management

Based on the periodontal and medical findings a diagnosis of periodontitis as a manifestation of systemic disease was established. Due to the severity of alveolar bone loss, the significant depth of the periodontal pockets and the advanced mobility of the teeth, it was not feasible to attempt to periodontally treat and maintain the teeth in the mouth. Previous reports in the literature that attempted to treat periodontally involved teeth in patients with CHS failed to arrest disease progression. In addition, retaining periodontally involved teeth with deep pockets in these immune compromised patients carries the risk of subjecting the patient to a continuous source of infections that can be life threatening. All teeth were deemed hopeless. They were not able to provide function and could not serve as reliable abutments. It was for the patient's best interest to recommend extraction of all teeth. A meeting with the mother was scheduled to present to her the medical and dental findings. Both dental and medical teams were present. The mother was counseled regarding the diagnosis and management of the condition. The seriousness of the medical condition was explained to her. She was advised that it was not feasible to save the teeth. Tooth extraction and fabrication of immediate dentures was recommended and accepted by the patient's mother. The patient was referred to the pediatric dentistry department at the Medical College of Georgia for an immediate-denture fabrication prior to scheduling the extraction of the teeth. Due to the risk of bleeding, full mouth extractions were done under general anesthesia in a hospital setting with the supervision of a pediatric hematologist. Immediate all-acrylic dentures were provided following the extractions.

Bleeding complications

Immediately after the extraction procedure the patient developed protracted bleeding from the extraction sites. Several units of packed red blood cells in addition to fresh frozen plasma and recombinant activated coagulation factor 7 (Novo7, NovoNordisk, Princeton NJ) were administered.

Discussion

CHS is a rare autosomal recessive genetic disease that has been described in humans, mice and other animals. The different species share the same disease characteristics (Perou and Kaplan, 1993). The disease is characterized by generalized cellular dysfunction due to lysosome-related organelle abnormalities (Ward *et al.,* 2002). The lysosome-related organelle abnormalities lead to immunological dysfunction in immune cells, aggregation dysfunction in blood platelets and pigmentation dysfunction in melanocytes. The disease is fatal because of increased susceptibility to bacterial infections (Spritz, 1998). Many patients with CHS enter into an accelerated fatal phase characterized by a lymphoproliferative syndrome associated with Epstein-Barr virus infections (Rubin *et al.,* 1985; Okano and Gross, 2000). The only available treatment for CHS is bone marrow transplantation, which may be helpful in correcting the genetic defect (Trigg and Schugar, 2001; Gordon *et al.,* 2003). With increasing age CHS patients develop peripheral neuropathy that is characterized by Parkinsonian symptoms (Uyama *et al.,* 1994; Jacobi *et al.,* 2005). Peripheral nerves show axon loss and rarefaction of large myelinated fibers.

The gene discovery

Enlarged lysosomal granules in the cell cytoplasm are important diagnostic features of CHS in humans. The observation that other animal species affected with the gene mutation express a similar phenotype, characterized by enlarged lysosomal granules in the cell cytoplasm, as in man, suggested that the genetic defect in man and other animals might also be similar. Perou and Kaplan (1993), using cell fusion studies, showed that indeed the same gene was responsible for the abnormally enlarged lysosomes in CHS among different animal species. These early studies paved the way to use the beige mouse to identify the human gene.

Mice affected with the mutated gene have a beige coat color due to the hypopigmentation effect associated with dysfunctional melanocytes (Shiflett *et al.,* 2002). The altered coat color makes it easy to identify mutant animals. The beige mouse also shows all other CHS characteristics seen in humans. For these reasons, the beige mouse was used as a model of human CHS. The mutated gene associated with CHS was identified by two independent groups of researchers in both the beige mouse and in humans (Barbosa *et al.,* 1996; Barbosa *et al.,* 1997; Perou *et al.*, 1996a; 1996b). Nagle *et al.* (1996) mapped the human gene to chromosme 1q43. Twenty-six mutations have been identified in the CHS gene including nonsense and missense mutations, deletions and insertions. Recently Zarzour *et al.* (2005) described two new mutations: a nonsense mutation and a pair deletion mutation. The severity of the disease is proportional to the number of mutations present. The current name of the mutated gene is CHS1 (Zarzour *et al.,* 2005).

The product of the normal (un-mutated) human CHS gene is a large protein composed of a predicted 3801 amino acids with a weight of 429 kDa (Ward *et al.,* 2002). The protein has several characteristic architectural features that may be important for its function. On the amino-terminus it has a large stretch of ARM/HEAT repeats (Nagle *et al.,* 1996). ARM motifs facilitate membrane binding and HEAT repeats help

with vesicle transport. On the carboxyl terminal it has a BEACH domain and four to seven WD-40 repeats (Nagle *et al.,* 1996). The exact function of the protein product of the gene is not fully known. It is a cytosolic protein (Perou *et al.,* 1997). The presence of a BEACH domain suggests that it is important in regulating lysosomal trafficking in the cytoplasm. It may also have a role in sorting endosomal proteins. The protein product of the mutated gene in CHS is truncated and nonfunctional (Ward *et al.,* 2002). The mutated gene and its defective protein product are associated with the formation of enlarged lysosomes.

In addition to cell organelle morphologic aberrations, CHS cells show biochemical imbalance characterized by altered cyclic nucleotide levels (Katz *et al.,* 1982), increased sphingomyelin turnover, increased production of ceramide and lowered protein kinase C (PKC) activity (Tanabe *et al.,* 2000). PKC is an important enzyme that catalyzes the transfer of phosphates to a variety of target proteins. It is recruited to the cell membrane to perform its function. Ceramide is a lipid molecule byproduct of the cell membrane. It is an important signaling molecule that can influence PKC activity. Tanabe *et al.* (2000) showed that in fibroblasts obtained from the beige mouse unstimulated breakdown of sphingomyelin and production of ceramide were elevated. The elevated ceramide levels down-regulated PKC activity inside the cell. The down-regulation of PKC was associated with the formation of giant granules and cellular dysfunction. The connection between the mutated CHS gene and its dysfunctional protein product with elevated ceramide levels and down-regulation of PKC activity is not known.

Cellular abnormalities

All body cells in CHS patients are affected. It is well documented that patients with CHS have impaired neutrophil function (Bellinati-Pires *et al.,* 1992; Wilkinson, 1993). The impaired function is secondary to chemotaxis defects and myeloperoxidase deficiency (Kimball *et al.,* 1975). Neutrophils in CHS patients cannot mobilize efficiently and cannot successfully kill their targets (Root *et al.,* 1972). B cells from CHS patients, because of intracellular vesicular abnormalities, show significantly delayed peptide loading and antigen presentation (Faigle *et al.,* 1998; Lem *et al.,* 1999). Thus, antibody production in CHS is impaired. In patients with CHS cytotoxic T cells produce defective lysosomes incapable of destroying the infected cell (Baetz *et al.,* 1995; Stinchcombe *et al.,* 2000). Therefore, patients with CHS are more susceptible to viral infections.

Natural killer (NK) cell activity in patients with CHS is significantly diminished. CHS NK cells fail to initiate the post-binding lytic mechanism (Haliotis *et al.,* 1980; Klein *et al.,* 1980). In patients with CHS there are defects in melanosome formation and transfer (Windhorst *et al.,* 1968). The melanosome abnormalities result in partial albinism. Platelets of CHS patients are deficient in delta granules, and platelet aggregation in response to collagen is impaired (Buchanan and Handin, 1976; Rendu *et al.,* 1983). The platelet deficiencies in CHS patients result in prolonged and excessive bleeding. Curiously, in the reported case the platelet function analysis showed normal platelet aggregation in response to ADP, but abnormal platelet aggregation in response to ristocetin, indicating normal delta granule function and abnormal alpha granule function associated with a deficiency in von Willebrand factor. The abnormal platelet aggregation was associated with bleeding complications following exodontia.

Periodontal disease in CHS patients

Due to the rarity of CHS, reports of oral/periodontal manifestations of the disease in the dental literature are sparse. Tempel *et al.* (1972) described two young Caucasian female patients with severe gingival inflammation, tooth mobility and increased probing depth. Histopathology of the gingival tissues showed heavy infiltration of chronic inflammatory cells. Hamilton and Giansanti (1974) reported a case of CHS in a 10-year-old African American boy. They described excessive early periodontal breakdown, gingival swelling and tooth migration. More recently, Delcourt-Debruyne *et al.* (2000) reported a case of a 14-year-old Caucasian male patient with severe gingival inflammation, spontaneous gingival bleeding, and extensive alveolar bone loss. Shibutani *et al.* (2000) reported a longitudinal follow-up of a case of a young Asian female patient with severe gingival swelling and mobility. Their attempts to control the periodontal problems were unsuccessful. The clinical periodontal manifestations in the case we report corroborate those previously described. Periodontitis in CHS patients is characterized by severe radiographic alveolar bone loss, extensive gingival swelling, gingival bleeding, advanced increase in probing depth and excessive tooth mobility.

Understanding the pathogenesis of periodontitis in CHS may help increase our understanding of the pathogenesis of periodontitis in the general population. Periodontitis is initiated by bacterial build-up in the dentogingival region (Page and Schroeder, 1976). The bacteria are contained within a plaque biomass on the tooth surface in proximity to the gingival tissues (Socransky and Haffajee, 2005). Bacterial cell invasion inside the gingival tissues is rare (Manor *et al.,* 1984; Liakoni *et al.,* 1987; Listgarten, 1988). Bacterial byproducts instigate an immune/inflammatory response in the gingival tissues (Page, 1991). The immune/inflammatory response involves the participation of several cells and biological mediators. The biological mediators induce the release

of host-produced degrading enzymes (Page, 1991). The host-produced degrading enzymes are responsible for the periodontal tissue breakdown (Page, 1991). Thus, bacteria are not directly involved in the destructive process (Van Dyke and Serhan, 2003). Eventually, when the host defenses succeed in controlling the bacterial infection, the destructive process is halted (Page and Schroeder, 1976).

For the immune/inflammatory response to succeed it requires the presence and participation of several defense cells such as neutrophils, lymphocytes and NK cells (Page and Schroeder, 1976). Neutrophils are the first line of defense against the bacteria in the dentogingival area. They literally migrate into the sulcus/pocket space to form a barrier between the bacteria and the gingiva (Brecx and Patters, 1985). Specialized immune cells such as B-lymphocytes, T-lymphocytes and NK cells are recruited to the gingival tissues to aid the neutrophils in their fight against bacteria. A well-coordinated cellular immune response is essential to prevent bacterial cells from invading the gingival tissues and helps with the production of antibodies to neutralize the bacterial irritants/toxins.

The microbiologic findings from this report and previous reports show a microbiological profile consistent with periodontopathic bacteria associated with periodontitis in the general population (Socransky and Haffajee, 2005). Yet the associated periodontal damage in CHS patients far exceeds the periodontal damage in the general population. The histopathologic findings from this report and previously published reports suggest that in patients with CHS, because of mass immune cell dysfunction, the bacterial cells gain access to inside the gingival tissues. The bacteria inside the gingival tissues seem to be directly involved in the destructive process. The direct bacterial tissue destruction combined with indirect tissue destruction through the release of host inflammatory degrading enzymes may explain the massive and uncontrollable periodontal tissue loss in CHS patients. These observations emphasize the importance of a robust and dynamic immune cell response in defending the periodontium. When the immune cell response is dysfunctional, bacterial tissue invasion and massive tissue damage ensues.

Periodontal management

Based on previously published reports, attempting to treat the periodontal disease in these patients is unsuccessful. Taking into consideration that these patients are highly susceptible to bacterial infections that may be fatal, we feel it is prudent, for the well-being of the patient, to recommend exodontia. Because of platelet dysfunction and bleeding abnormalities, it is recommended that tooth extraction be performed in a hospital setting in coordination with a hematologist. In the case presented, following tooth extractions, the patient developed uncontrollable bleeding and significant blood loss. The bleeding complication required administration of red blood cells, frozen plasma and coagulation factor 7.

In conclusion, we presented a case of periodontitis associated with CHS in a young African American male. We reviewed the genetic background of the disease. We discussed an altered pathogenesis of periodontitis in these patients due to immune cell dysfunction and bacterial invasion within the gingival tissues. We also discussed bleeding complications and their management. Because of the great risk of bacterial infections and the related fatal consequences, we recommend exodontia as a management option for periodontal problems in CHS patients.

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