Periodontal and Oral Findings in Two Siblings with Sickle Cell Disease: Case Report

Orak Hücre Anemili İki Kardeşe Ait Periodontal ve Oral Bulgular

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ABSTRACT Sickle cell disease (SCD) is a hereditary chronic disorder characterized by hemolytic anemia and crisis (vaso-occlusive, sequestration, and aplastic). The clinical manifestations of SCD, include a variety of orofacial changes such as midfacial overgrowth, facial swelling, increased thickening of the skull, osteoporotic changes, osteomyelitis, anesthesia of the mandibular nerve, asymptomatic pulpal necrosis, orofacial pain, enamel hypoplasia, diastema and gingival enlargement. SCD, periodontal disease and infections of the oral cavity can be a trigger for vaso-occlusive crisis. We report periodontal and oral findings in 2 male siblings with SCD, which in the older brother had been controlled for 3 years after the extensive laboratory investigation of pathogenetic determinants but remained uncontrolled in the younger brother. We concluded that frequent dental care is essential to ensuring the quality of life for patients with SCD. Although orofacial involvement is rare, periodontal/dental inflammation can result in a SCD crisis or complications such as osteomyelitis.

Key Words: Anemia, sickle cell; osteoporosis; hematologic diseases; periodontal diseases

ÖZET Hemolitik bir anemi olan orak hücre anemisi, üç tip krizle (vazooklüziv, sekestrasyonlu ve aplastik) karakterize, kronik herediter bir hastalıktır. Hastalığın klinik görünümü hastadan hastaya farklılık göstermekle beraber; orta yüz büyümesi, yüzde şişme, kafatasının incelmesi, osteoporotik değişimler, osteomiyelit, mandibular sinirin uyuşukluğu, asemptomatik pulpal nekroz, orofasiyal ağrı, mine hipoplazisi, hipodonti, diastema ve gingival büyüme gibi orafasiyal değişikliklerini içermektedir. Orak hücre anemisi olan hastalarda, periodontal hastalık ve ağız kavitesine bağlı enfeksiyonlar, vazooklüziv krizleri tetikleyebilmektedir. Bu olgu sunumunda, orak hücre anemisi olan iki erkek kardeşe ait oral ve periodontal bulgular sunulmaktadır. Büyük kardeş, orak hücre anemisi ile ilgili, ileri laboratuvar tetkiklerini takiben 3 yıldır kontrol altında olup, küçük kardeş tedavisine devam etmemiştir. Orak hücre anemili hastaların, yaşam kalitelerinin sürdürülebilmesi için dental bakımı ve takip çok önemlidir. Bu hasta grubunda, oro-fasiyal tutuluma nadir olarak rastlanmasına rağmen, periodontal ve dental enfeksiyonlar krize ve osteomiyelit gibi komplikasyonlara neden olmaktadır.

Anahtar Kelimeler: Anemi, orak hücreli; osteoporoz; hematolojik hastalıklar; periodontal hastalıklar

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The term "sickle cell syndrome" refers to a group of diseases characterized by the presence of hemoglobin S, but sickle cell disease (SCD) is the result of homozygosity for hemoglobin S, which causes rigid sickled erythrocytes.[1,2] The sickle hemoglobin gene demonstrates autosomal recessive inheritance.[1,3] Individuals with SCD are homozygous for the mutant globin gene, in which valine is substituted for glutamine at the sixth position

in the beta-subunit.[1] They exhibit chronic hemolysis and experience frequent infections and recurrent occlusions of microcirculation that cause painful crises and result in organ damage and chronic organ failure.[1, 4, 5] However, not only cellular components of the peripheral blood are responsible for the development of complications associated with SCD. Plasma factors such as cytokines, chemokines, oxidative radicals, factors that can alter endothelial apoptosis, and acute-phase proteins seem to be involved with several possible mechanisms in the vaso-occlusive phenomena of SCD.[4-6]

The common clinical manifestations of SCD are vaso-occlusive crises, avascular necrosis (AVN) and osteomyelitis.[7] An SC crisis may be precipitated by dehydration, acidosis, trauma, overexertion, surgery (including tooth extraction), periodontal infections, general anesthesia, temperature extremes, vascular occlusion, and pulmonary disease.[8] Patients with SCD are more prone to infections because of hyposplenism. Hyposplenism occurs as a result of repeated infarctions leading to atrophy and autosplenectomy. Impaired splenic functions lead impaired purification of microorganisms from the blood. As a result of infection, body temperature and tissue pH alter, and this may be precipitate crises. Patients may have fatigue and weakness; pain in the long bones, joints, and abdomen; cardiomegaly; systolic murmur, epistaxis; icteric sclera; bone deformities; and pallor of the oral mucosa.

The literature has very few studies of the relationship between SCD and oral health. Oral problems are not as common as other medical problems. Oral problems such as unilateral infarct of the mandible, pulpal necrosis, dental caries, orofacial pain, enamel hypoplasia, facial swelling, diastema, hypodontia, gingival enlargement, palatal pallor, anesthesia of the mandibular nerve, asymptomatic pulpal necrosis, osteomyelitis of the mandible, and midfacial overgrowth have been reported.[8-19] A number of orofacial changes such as midfacial overgrowth, increased thickening of the skull, osteoporotic changes, and multiple oral complications have also been observed in people with SCD.[18] Moreover, infections of the oral cavity and periodontal disease can be a source of focal infection for vaso-occlusive crisis. The two periodontal studies, concluded that individuals with SCD do not appear to be at increased risk for periodontal disease although one study only included adults while the other only included adolescents.[20,21]

The phenotypic heterogeneity of SCD is well known, and some patients with SCD experience more severe complications and have a poorer quality of life than do others with that disease.[1,22]

All tissues and organs of the body are at risk for damage from occlusions of the microcirculation. Severe bone changes can occur during the course of SCD. Chronic hemolysis and erythroblastic hyperplasia result in a widening of the medullary spaces, thinning of the cortices, and sparseness of the trabecular pattern.[1] The skull and vertebral bodies are the most commonly involved sites.[1]

It has been stated that genetic heterogeneity is associated with nonglobin genetic modifiers.[3] We report periodontal and oral findings in 2 male siblings with SCD. One of those patients underwent extensive laboratory investigation of the pathogenetic determinants of his disease.

CASE REPORT

Prior to any personal, medical and dental evaluation, written informed consents were obtained from both of the patients.

A 20-year-old Turkish man (patient 1) with homozygous SCD was referred from the Başkent University Department of Hematology to the clinic in the Department of Periodontology, where he has been treated for 3 years at the time of this writing. Because this patient's medical condition was stable when he presented to our periodontology clinic, the focus of examination has been his oral, facial, periodontal, and dental health.

The detailed medical and dental histories of patient 1 were recorded. He has 5 brothers, and his younger brother (patient 2) had also been diagnosed as having homozygous SCD, which had never been treated. Periodontal clinical parameters were recorded for both brothers (Table 1). There was no parental consanguinity in their family history, and they denied tobacco use and alcohol consumption.

TABLE 1: Periodontal measurements for two siblings with homozygous sickle cell disease.

	PI Values				GI Values				PD Value	BOP (+) Sites
Periodontal Parameters	PI 0 (%)	PI 1 (%)	PI 2 (%)	PI 3 (%)	GI O (%)	GI 1 (%)	GI 2 (%)	GI 3 (%)	PD (mm)	BOP (%)
Patient 1	37.5	46.4	4.46	11.6	78.6	21.4	0	0	1.53	4.46
Patient 2	93.7	3.57	2.68	0	99.1	0.9	0	0	1.60	0

PI, plaque index; GI, gingival index; PD, probing depth; BOP, bleeding on probing

In patient 1, the results of peripheral blood smear analysis revealed anisocytosis and normoblasts and showed that rigid erythrocytes accounted for 15% of all erythrocytes from peripheral blood. The results of hemoglobin electrophoresis indicated homozygous SCD. Serum biochemical test results showed in Table 2. The results of a direct Coombs' test and serologic tests for antinuclear antibodies and antibodies to hepatitis B virus, parvovirus B19, cytomegalovirus, and Epstein-Barr virus were negative. Inflammatory parameters such as C-reactive protein and the erythrocyte sedimentation rate were 96 mg/dL and 81 mg/dL, respectively. Nitrite concentrations were quantified by a colorimetric assay based on the Griess reaction, and the plasma nitric oxide concentration was 15.75 mmol/L. When compared with the results of a previous study, this concentration was less than the mean value in healthy controls (mean, 37.8 ± 17.5). The level of endothelial progenitor cells in circulation (identified by multicolor flow cytometry) was determined by the use of the endothelial-specific monoclonal antibodies anti-CD146 and-CD144. The antibodies were conjugated with fluorescein isothiocyanate (FITC-CD146, US Biological, Swapscott, 01907, MA, USA and phycoerythrin (PE-CD144, Beckman Coulter, Marseille, France); results were higher than mean historical healthy control level 2396.55 ± 658.375.95; range, 1200-3416). Oxidative burst (measured by multicolor flow cytometry) was identified as 448. Bio-Rad Laboratories External Quality Assurance Services (Bio-Rad Laboratories, Irvine, Calif, USA) periodically monitored the measurements for quality control.

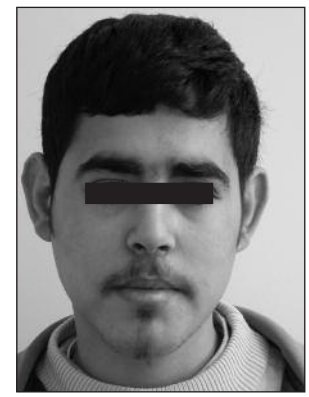

FIGURE 1: Patient 1, the older sibling (frontal view).

TABLE 2: Biochemical and serologic markers of the patient 1.

Patient 1 Laboratory Markers		Normal range
Serum Folate (ng/mL)	13.5	3.5-16.1
Serum Vit B12 (pg/mL)	231.5	208-960
Serum Ferritin (ng/mL)	911.04	7.00 - 140.00
Calcium (mg/dL)	8.6	8.40-10.00
Phosphorus (mg/dL)	5.0	2.30-3.70
Total Bilirubin (mg/dL)	2.0	0.2-1.2
Direct Bilirubin (mg/dL)	1.6	0-0.3
Alkaline Phosphatase (IU/L)	172	15-250
Alanine Aminotransferase (IU/L)	32	0-41
Aspartate aminotransferase (IU/L)	15	0-40
C-reactive protein (mg/dL)	96	0 - 50
Nitric oxide concentration (μmol/L)	15.75	<37.8 ± 17.5
Hepatitis B virus	Negative	Negative
Parvovirus B19	Negative	Negative
Cytomegalovirus	Negative	Negative
Epstein-Barr virus	Negative	Negative

Patient 1 was diagnosed as having steady-state SCD when he was examined, and he appeared physically healthy (Figure 1). He had attained his expected height (173 cm) and weight (59 kg). Subicterus was noted in the sclera, and he was asplenic. His left leg was paralyzed because of hip-joint calcification. No periodontal or dental infections or abnormalities were detected (Figure 2).

Patient 2 was 18 years old when he presented to our periodontology clinic. The focus of his examination was his oral, facial, periodontal, and

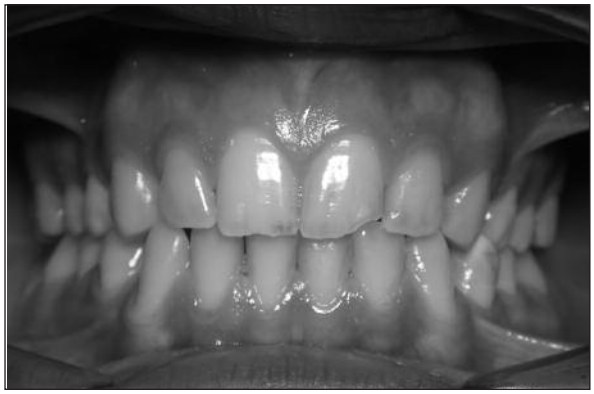

FIGURE 2: Patient 1, intraoral view. Note the healthy gingiva and oral tissues and the dentition.

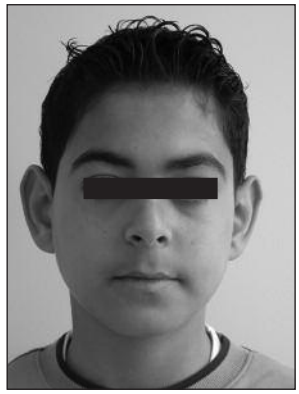

FIGURE 3: Patient 2, the younger sibling. This patient's height (147 cm) and weight (36 kg) were below the normal reference range for his age of 18 years.

dental health. This patient's height (147 cm) and weight (36 kg) were below the normal reference range for his age, but he exhibited no mental impairment (Figure 3). Abnormal cardiac enlargement was diagnosed, but no abnormalities were detected during his dental and periodontal examinations (Figure 4). Figure 5 reveals the physical features of these siblings.

In both patients, the plaque index and gingival index were recorded, the probing pocket depth was measured, and bleeding on probing was noted. To determine the status of alveolar bone level and osteoporosis, panoramic radiographs were obtained (Figures 6 and 7). In both patients, those radiographs revealed mandibular osteoporosis and increased trabeculation (especially in the interradicular and periapical regions around the teeth of the mandible and maxilla). No missing teeth

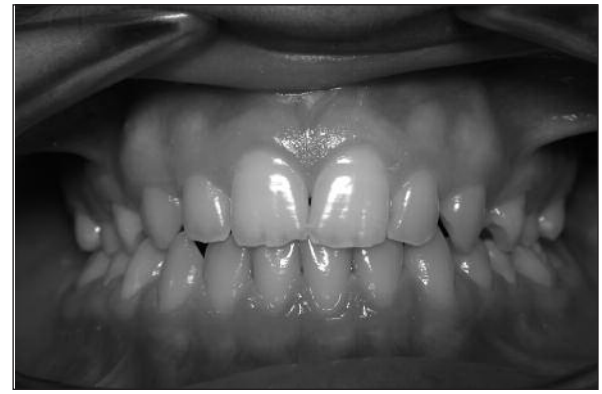

FIGURE 4: Patient 2; note the healthy gingiva and oral tissues and the dentition.

FIGURE 5: Two siblings with homozygous sickle cell disease. The younger brother is shorter than the normal range of height for his age.

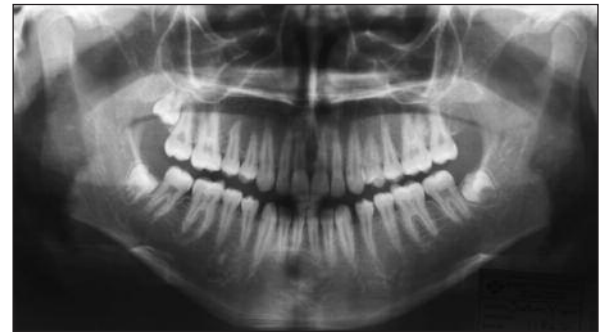

FIGURE 6: Patient 1; the panoramic radiograph reveals an osteoporotic mandible.

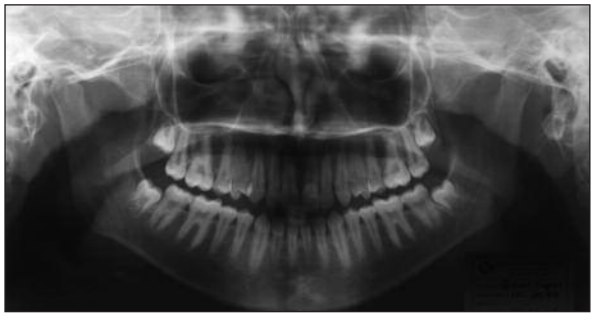

FIGURE 7: Patient 2; panoramic radiograph. The extent of osteoporosis in the mandible is greater than that in the mandible of patient 1.

were noted, but both brothers exhibited class I occlusion. The basis of the mandible was vertically shorter in younger brother than in the older one.

DISCUSSION

Orofacial involvement in SCD is rare. Clinical symptoms usually consist of gingival pallor and jaundice, ischemic necrosis in the periodontal tissues and pulp, delayed tooth eruption (which occurs during puberty), dentinal hypoplasia, and thinner trabecular composition caused by bone marrow hyperplasia.[11] The clinical problems associated with SCD are attributed to defective red blood cells; erythrocytes are carriers of oxygen to periodontal tissues and are responsible for tissue nutrition in the periodontium.[18] Oral signs may be the first clinical evidence of hematologic disorders, including SCD.

This case report has shown that there is no clinical periodontal disease associated SCD. Oral health was not a primary concern for these patients. Crawford suggests that SCD is not associated with increased levels of gingivitis and periodontitis in patients with SCD.[20] In agreement with the results of a study by Crawford, Arowojolu and Savage found no significant difference in alveolar bone loss patterns between patients and controls.[20,23] In the same study group, Arowojolu showed no clinical periodontal disease or attachment loss in patients with SCD.[21] In a study performed by our group (unpublished) have shown that plaque and gingival indexes were significantly higher in SCD patients than in healthy individuals. Furthermore, no significant differences existed regarding probing depth between patients with SCD and healthy individuals. The number of BOP positive sites was greater in SCD patients than in controls, but there was no clinical attachment loss and gingival recessions. Consistent with previous findings, in the present siblings, there was no periodontal diseases and alveolar bone loss.

Neutrophils that are activated in patients with SCD have an important role in the pathophysiology of that disease.[5, 24, 25] The observed neutrophil activation in SCD patients may lead to increased adherence of neutrophils to the endothelium in the microcirculation of SCD patients. Lard et al have shown that neutrophils are activated in SCD patients, suggesting an important role in the pathophysiology of SCD. Some investigators have found no association between periodontal disease and SCD.[20,21] In inflammation, the activation and recruitment of neutrophils are essential to remove pathogenic bacteria that can cause recurrent microbial infection and severe periodontal disease. Acute periodontal infection and periodontal disease can in turn precipitate an SCD crisis. Neutrophils in patients with aggressive periodontitis are thought to be already "primed" without exacerbating inflammation or cause.

In patient 1, detailed laboratory investigations could be made, and his inflammatory protein levels were found to be high. Levels of early apoptotic and late apoptotic neutrophils and an oxidative burst of neutrophils were found to be higher in patient 1 than in healthy controls described in previous studies; this suggests that cytokines, chemokines, and inflammatory mediators act on neutrophils, which are important in the initiation of endothelial activation.

High levels of endothelial progenitor cells in the circulation can indicate endothelial activation and inflammation.[5] Steady-state disease does not necessarily mean an absence of ongoing pathophysiologic activity, as shown by the elevation and fluctuation of acute-phase reactants and cytokines in patients with steady-state SCD.[1,6,26] Tissue oxygenation is associated with the tissue nitric oxide level. The level of nitric oxide can increase to maintain vasodilatation and protect against tissue

ischemia.[1,4] Acute-phase reactants, cytokines, and nitric oxide are markers for inflammation, and the accurate determination of their levels is essential to the diagnosis of SCD.

Transfusions should be used only for the prevention of the complications of SCD (e.g., in sequestration and plastic crises to restore the red blood cell mass). In other circumstances, such as central nervous system infarction, hypoxia with infection, stroke, acute chest episodes, and preperation for surgery, transfusions are used to decrease blood viscosity and percentage of circulating sickle cells.[27] The majority of patients with SCD require episodic blood transfusions on a chronic basis which makes them at risk for developing iron overload. Serum ferritin consistently >1000 ng/mL is commonly seen as an indication of iron toxicity. Serum ferritin levels belong to patient 1 was 911.04 ng/mL (normal range= 7.00-140.00 ng/mL). It is important to manage patients with evidence of transfusion-related iron toxicity. Generally this can occur when cumulative transfusions reach 120 mL of packed red blood cells per kg of body weight (or as few as 10 transfusions) and when serum ferritin is consistently at or above 1000 ng/mL.

Because ensuring the dental health of patients with SCD is essential, patients with that disease who are treated in our Department of Hematology must also be treated in our Department of Periodontology. In patients with SCD, dental treatment can be performed when the hemoglobin S concentration is 70% or more of the total hemoglobin content. Before dental treatment when active infection is present, antibiotic prophylaxis is recommended.[28,29] Prophylactic antibiotics should also administered before and after surgery to minimize the incidence of wound infection and osteomyelitis following surgery.[28,29] During dental and periodontal procedures, local anesthesia is more desirable than is the use of general anesthesia when possible, as local anesthesia does not lower the oxygenation of the blood.[28] Acetaminophen for treatment of pain could be prescribed because salicylates may induce acidosis.[28] After surgery, the patients need to be observed to ensure early and rapid detection of any untoward sequelae associated with the disease.[28]

Preventive dental therapy is the ideal approach for treatment of the SCD patient because dental infections can precipitate crises. Appointments should be kept short and stress reduction techniques should be used.[30] The goal of the dentist is to improve and maintain excellent oral health and to decrease the possibility of oral infections.[29] The impor- tance of adequate dental plaque control techniques in order to prevent inflammation, bleeding and infection in these patients are essential.[31] The treatment should never be initiated during a crisis unless in an emergency situation, and then treatment should be designed only to decrease infection and discomfort.[8] Rada and colleagues reported that perio- dontal infections, if severe enough, may precipitate a sickle cell crises.[8] Oral surgical procedures have the highest probability of an oral infection.[29]

The little information is available regarding the effects of not only sickle cell disease but also other hematologic disorders onto periodontal parameters. However, systemic disorders may become more complicated with ongoing periodontal inflammation. There was no relation between sickle cell disease and periodontal diseases. We concluded that frequent dental care is essential to ensuring the quality of life for patients with SCD. Although orofacial involvement in patients with that disease is rare, periodontal or dental inflammation can result in an SCD crisis or complications such as osteomyelitis. A team approach including the physician, dentist, and patient is vital to succesful dental management of the patient with SCD.

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