The thalassemias: Oral manifestations and complications

Columbus, Ohio, and San Antonio, Texas

OHIO STATE UNIVERSITY COLLEGE OF DENTISTRY AND UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO DENTAL SCHOOL

The signs, symptoms, and potential complications of the thalassemias are discussed. A case of thalassemia minor is presented, with emphasis on how the condition may affect the dental management of the patient.

(ORAL SURG. ORAL MED. ORAL PATHOL. 62:229-233, 1986)

Human erythrocytes are subject to many genetic abnormalities that may produce or result in anemic or polycythemic states.1 Some of the abnormalities involve a disturbance in enzymatic function, such as glucose-6-phosphate dehydrogenase deficiency. Other genetic disturbances result in hemoglobinopathies.

Adult hemoglobin is normally a tetramer of two alpha (α) and two beta (β) chains. The thalassemias are a group of hemoglobinopathies characterized by a reduced rate of production of one or more of these globin chains. The imbalance is due to disturbances in the control mechanisms of protein synthesis and results in altered function of the hemoglobin molecule and aberrant erythrocyte morphology.

Thalassemias are classified according to the chain that is produced at the reduced rate. Disorders of α chain synthesis are complex and give rise to a variety of disease states. The most severe condition is a homozygous deletion defect that results in excessive γ chain production in the fetus. This gives rise to a group of severe developmental defects known as hydrops fetalis and is usually fatal before or shortly after birth. A less severe homozygous defect, in which each of two genes is defective in a different way, produces hemoglobin II disease. Victims of this disorder may reach adulthood and have varying degrees of anemia and splenomegaly. Hemoglobin values may range from 7 to 10 g/dL, and the erythrocytes may show marked hypochromia and variation in size and shape.2 The heterozygous state of α-thalassemia may produce erythrocytes with a reduced mean corpuscular hemoglobin (MCH) of 20 to 25 picograms (pg) (normal, 27 to 32 pg), and a mean corpuscular volume (MCV) of 60 to 70 cubic microns (μm³) (normal, 80 to 94 μm³). In other instances, heterozygotes may show only minimal evidence of hypochromic microcytic anemia.

The α-thalassemias are found most frequently in southeast Asia, in parts of the Middle East, and in some Mediterranean populations.3 It has been reported that approximately 25% of the American black population has single α chain gene defects.4,5 Hemoglobin H disease has been reported in children with mental retardation,6 and an acquired form of α-thalassemia has been found in patients with leukemias and other myeloproliferative diseases.7

The β-thalassemias also result from a wide variety of genetic defects and produce diverse clinical and hematologic findings. The terms major and minor used in conjunction with β-thalassemia usually refer to the degree of severity of signs and symptoms, but several different genotypes may produce similar clinical presentations.8 In general, homozygous states result in the severe anemia of thalassemia major. The peripheral blood smear shows marked anisocytosis, poikilocytosis, reticulocytosis, hypochromia, and basophilic stippling.9 Bone marrow studies often show erythroid hyperplasia.10 Radiographic changes resulting from expansion of the marrow spaces in
long bones include cortical erosions, subcortical lucencies, rarefaction, enlarged nutrient foramina, and "raindrop" spaces within the cortex. In the jaws, there is generalized rarefraction of alveolar bone, thinning of cortical bone, and a "chicken-wire" appearance of enlarged marrow spaces and coarse trabeculation. In some cases, the lamina dura may be thin, the roots of the teeth short, and the premaxilla prominent. In the skull, proliferation of the marrow may completely erode the cortex, leaving only periosteum, and produce a "hair-on-end" radiographic appearance. In addition, pneumatization of the paranasal sinuses may be delayed, and the nasal cavity or the middle ear may be encroached upon to the point of occluding the anatomic spaces.

The heterozygous states of β-thalassemia produce a milder degree of anemia referred to as thalassemia minor. Hemoglobin values for men may range from 9 to 15 g/dL (normal, 14 to 18 g/dL), and values for women may be 8 to 13 g/dL (normal, 12 to 16 g/dL). The mild anemia of heterozygous β-thalassemia may be confused with iron-deficiency anemia unless electrophoresis or other specific hemoglobin analyses are performed. Beta-thalassemias are more frequently found in Mediterranean and black populations.

---

Fig. 1. Clinical appearance of tongue. Note the absence of filiform papillae in the affected area.

Fig. 2. Contact lesions on hard palate. Note the presence of petechiae.
The treatment of thalassemia major includes multiple blood transfusions, and the primary complication of this treatment is iron overloading. Three factors may contribute to the deposition of iron in the tissues: (1) ineffective erythropoiesis with increased erythrocyte breakdown; (2) repeated transfusions; and (3) excessive iron absorption from the gut induced by chronic hypoxemia. Excessive iron deposition in tissues may result in damage to the myocardium, liver, spleen, pancreas, thyroid, para-thyroids, and gastrointestinal mucosa. In order to reduce iron overload, splenectomy, transfusion with young red cells, and chelation therapy with deferoxamine have been used. Transfusional chronic active hepatitis due to viral infection is also a frequent complication of thalassemia major.

Nontransfusion-dependent thalassemia minor patients also suffer complications from their condition. They appear to be at increased risk of chronic inflammatory liver disease, including viral hepatitis, typhoid fever, gastroduodenal ulcers, arthropathies, and possibly rheumatoid arthritis. Folic acid deficiency is quite common in heterozygotes because of the increased demand associated with chronic hyperactivity of the marrow. Ocular lesions are more common in thalassemia minor than in thalassemia major.

**CASE REPORT**

In October 1982, a 33-year-old man of Greek descent was seen in the Dental Diagnostic Science Referral Clinic at the University of Texas Dental School at San Antonio. He complained of a burning sensation over the entire dorsum of his tongue, particularly when consuming spicy foods or alcoholic beverages, and he had become aware of a "red streak" on his tongue. His medical history revealed a diagnosis of thalassemia minor, a condition he shared with his father and his son. He claimed to have never suffered any ill effects from the condition, and no treatment had ever been prescribed by his physician.

The treatment of thalassemia major includes multiple blood transfusions, and the primary complication of this treatment is iron overloading. Three factors may contribute to the deposition of iron in the tissues: (1) ineffective erythropoiesis with increased erythrocyte breakdown; (2) repeated transfusions; and (3) excessive iron absorption from the gut induced by chronic hypoxemia. Excessive iron deposition in tissues may result in damage to the myocardium, liver, spleen, pancreas, thyroid, parathyroids, and gastrointestinal mucosa. In order to reduce iron overload, splenectomy, transfusion with young red cells, and chelation therapy with deferoxamine have been used. Transfusional chronic active hepatitis due to viral infection is also a frequent complication of thalassemia major.

Nontransfusion-dependent thalassemia minor patients also suffer complications from their condition. They appear to be at increased risk of chronic inflammatory liver disease, including viral hepatitis, typhoid fever, gastroduodenal ulcers, arthropathies, and possibly rheumatoid arthritis. Folic acid deficiency is quite common in heterozygotes because of the increased demand associated with chronic hyperactivity of the marrow. Ocular lesions are more common in thalassemia minor than in thalassemia major.

**Table I. Abnormal laboratory findings**

<table>
<thead>
<tr>
<th>Test requested</th>
<th>Patient’s values</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate dehydrogenase</td>
<td>339 u/L</td>
<td>60-230 u/L</td>
</tr>
<tr>
<td>Totalbilirubin</td>
<td>3.1 mg/dL</td>
<td>0.2-1.5 mg/dL</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>2.9 mg/dL</td>
<td>0.2-1.0 mg/dL</td>
</tr>
<tr>
<td>RBC count</td>
<td>6.28 x 10^6/μl</td>
<td>4.7-6.1 x 10^6/μl</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12.5 g/dL</td>
<td>14.0-18.0 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>36.7%</td>
<td>42-52%</td>
</tr>
<tr>
<td>MCH</td>
<td>60 μg/ml</td>
<td>80-94 μg/ml</td>
</tr>
<tr>
<td>MCV</td>
<td>19.9 pg</td>
<td>27-33 pg</td>
</tr>
<tr>
<td>Folic acid</td>
<td>5.5 mg/ml</td>
<td>2-19 mg/ml</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>209 pg/ml</td>
<td>180-710 pg/ml</td>
</tr>
</tbody>
</table>

**Table II. Suggested prophylactic antibiotic regimen for asplenic patients**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin V</td>
<td>2000 mg taken 30 minutes to 2 hours prior to dental procedure, then 500 mg taken every 6 hours for 8 doses or Erythromycin</td>
</tr>
</tbody>
</table>

At the time of examination, the patient was exhausted. In addition to his career demands, he was also responsible for the care of his two young children and a pregnant, bedridden wife. Although the patient had an olive complexion, he appeared pale. Oral examination revealed that the central portion of the dorsum of his tongue was void of filiform papillae (Fig. 1). The affected area measured approximately 2 x 3 cm and was erythematous. The anterior margin of the lesion appeared hemorrhagic, although no fresh blood could be wiped off. The hard palate was also inflamed in the midline, and there were scattered pinpoint petechiae in the affected area (Fig. 2). The remaining tissues were unaffected, although the gingiva and other oral mucosa appeared paler than normal. Dark-field microscopy of cytologic scrapings of both tongue and palate revealed a few isolated hyphae compatible with the presence of the pathogenic form of *Candida albicans*. Additional samples were collected for culture on Sabouraud's medium.

Hematologic studies were ordered, and the findings were compatible with the diagnosis of thalassemia minor (Table I). The elevated levels of lactate dehydrogenase and prehepatic unconjugated bilirubin indicated the increased erythrocyte fragility and destruction that accompanies thalassemia. Other evidence suggestive of microcytic hypochromic anemia included a slightly elevated red blood cell count, along with decreased values for hemoglobin, hematocrit, MCV, and MCH. Although folic acid and vitamin B12 levels were within low normal limits, they reflected the tendency toward deficiencies in these areas that are often seen in patients with thalassemia. Radiographic evaluation of the skull, jaws, and hands did not reveal significant changes.

A tentative diagnosis of atrophic candidiasis was made, and the patient was started on a therapeutic trial of nystatin vaginal suppositories, one tablet (100,000 units) to be dissolved in the mouth six times a day for 2 weeks. The lesions improved somewhat but did not resolve. Although no *Candida* organisms could be grown on the culture medium, nystatin therapy was continued for 2 additional weeks. The lesions again failed to resolve, and
the patient remained symptomatic. Suspecting noncompliance with the use of the vaginal tablets, a systemic regimen consisting of 200 mg ketoconazole taken orally once daily for 4 weeks was prescribed. However, the lesions persisted during the course of the medication.

DISCUSSION

Reports of oral complications from the thalassemias are rare in the literature. Pain and swelling in the parotid glands of patients with thalassemia major have been reported, possibly as a result of iron deposits in the serous cells. However, it seems reasonable to believe that oral manifestations may be more common in thalassemias than the literature would indicate. Iron-deficiency anemia and folic acid deficiency may produce symptoms of glossodynia and loss of papillae on the tongue similar to those seen in the patient whose case is presented here. The hematologic findings in thalassemia minor are very similar to those of iron-deficiency anemia, and folic acid deficiency is a common complication of thalassemia minor. Therefore, a form of thalassemia may be considered in a differential diagnosis of glossodynia and loss of papillae.

Median rhomboid glossitis with contact lesions on the palate and palatal petechiae have been reported to be signs of candidiasis. Candida albicans is an opportunistic organism, and a lowered host resistance associated with a chronic anemia condition may provide an opportunity for increased virulence and resistance to treatment. It has been reported that candidiasis is associated with iron-deficiency anemia, and the infection may be resistant to treatment until the anemia is brought under control. In the case presented here, the lesions persisted several weeks.

Other considerations are also important in the management of patients with thalassemia. A patient who has had a splenectomy is at risk of massive infection following a bacteremia. It has been suggested that these patients receive prophylactic antibiotics prior to dental treatment, the regimen consisting of oral penicillin or erythromycin (Table II).26 Patients with thalassemia should be questioned specifically about a history of splenectomy (Table II).26 Thalassemia major and minor patients are at increased risk of viral hepatitis. All members of the dental team should be aware of this so that appropriate precautions are taken when a patient with thalassemia is being treated.

CONCLUSIONS

Thalassemia hemoglobinopathies produce a wide variety of signs, symptoms, and complications in those patients who inherit the diseases. The condition is relatively common, and clinicians may encounter patients with α- or β-thalassemia in daily practice. They should be aware of possible oral manifestations of the condition, the similarities to iron-deficiency anemia, and the complications that may arise as a result of the disease process or its treatment. Successful management of a patient with thalassemia depends on a proper diagnosis and a treatment plan that considers both the systemic and oral conditions.

REFERENCES


Reprint requests to:
Dr. Margot L. Van Dis
Division of Diagnostic Services
The Ohio State University College of Dentistry
305 W. Twelfth Ave.
Columbus, OH 43210-1241