

Orofacial manifestations of hematological disorders: Anemia and hemostatic disorders

Titilope A Adeyemo, Wasiu L Adeyemo, Adewumi Adediran, Abd Jaleel A Akinbami, Alani S Akanmu

Departments of Haematology and Blood Transfusion and Oral and Maxillofacial Surgery, College of Medicine, University of Lagos, Nigeria

ABSTRACT

The aim of this paper is to review the literature and identify orofacial manifestations of hematological diseases, with particular reference to anemias and disorders of hemostasis. A computerized literature search using MEDLINE was conducted for published articles on orofacial manifestations of hematological diseases, with emphasis on anemia. Mesh phrases used in the search were: oral diseases AND anaemia; orofacial diseases AND anaemia; orofacial lesions AND anaemia; orofacial manifestations AND disorders of haemostasis. The Boolean operator "AND" was used to combine and narrow the searches. Anemic disorders associated with orofacial signs and symptoms include iron deficiency anemia, Plummer-Vinson syndrome, megaloblastic anemia, sickle cell anemia, thalassaemia and aplastic anemia. The manifestations include conjunctiva and facial pallor, atrophic glossitis, angular stomatitis, dysphagia, magenta tongue, midfacial overgrowth, osteoclerosis, osteomyelitis and paraesthesia/anesthesia of the mental nerve. Orofacial petechiae, conjunctivae hemorrhage, nose-bleeding, spontaneous and post-traumatic gingival hemorrhage and prolonged post-extraction bleeding are common orofacial manifestations of inherited hemostatic disorders such as von Willebrand's disease and hemophilia. A wide array of anemic and hemostatic disorders encountered in internal medicine has manifestations in the oral cavity and the facial region. Most of these manifestations are non-specific, but should alert the hematologist and the dental surgeon to the possibilities of a concurrent disease of hemopoiesis or hemostasis or a latent one that may subsequently manifest itself.

Received : 06-08-09
Review completed : 09-11-09
Accepted : 06-02-10

Key words: Anemia, hemostatic disorders, manifestation, orofacial

A wide array of hematological disorders encountered in internal medicine has manifestations in the oral cavity and the facial region.^[1] Most of these manifestations are non-specific, but should alert the hematologist and the dental surgeon to the possibilities of a concurrent hematological disorder or a latent one that may subsequently manifest itself.^[1] These manifestations must be properly recognized if the patient is to receive appropriate diagnosis and referral for treatment. The importance of understanding

the orofacial manifestations of these disorders also lies in the fact that orofacial signs and symptoms may be the first clinical presentation that alerts the dentist/hematologist to an underlying hematological disorder.

Disorders of the erythroid (anemia and polycythaemia), lymphoid and megakaryocytic-platelet compartment of the bone marrow, immune system deficiencies, coagulation as well as human immunodeficiency virus infection have been widely reported to manifest in the orofacial region.^[1-6]

In this review of orofacial manifestations of hematological disorders, orofacial manifestations of anemia and disorders of hemostasis are discussed.

A computerized literature search using MEDLINE was conducted for published articles on orofacial manifestations of hematological diseases, with emphasis on anemia. Mesh phrases used in the search were: oral diseases AND anaemia; orofacial diseases AND anaemia; orofacial lesions AND anaemia; orofacial diseases AND anaemic disorders. The

Address for correspondence:

Dr. Titilope A Adeyemo,
E-mail: titilopeadeyemo@yahoo.co.uk

Access this article online	
Quick Response Code:	Website: www.ijdr.in
	DOI: 10.4103/0970-9290.87070

Boolean operator “AND” was used to combine and narrow the searches. The full texts of these articles were thoroughly examined. References in these articles were also manually searched for non-Medline articles. Only relevant articles were selected for the review.

OROFACIAL MANIFESTATIONS OF ANEMIA

Iron deficiency anemia

Iron deficiency anemia is the most common hematological disorder.^[2] It may manifest in the orofacial region as atrophic glossitis, mucosal pallor and angular cheilitis. Atrophic glossitis “flattening of the tongue papillae” resulting in a smooth and erythematous tongue may mimic migratory glossitis [Table 1]. Migratory glossitis, also known as geographic tongue, is a condition of unknown etiology that affects 12% of the population.^[1] It results in lesions on the tongue that are erythematous, non-indurate, atrophic and bordered by a slightly elevated, distinct rim that varies in color from gray to white. In atrophic glossitis, these areas do not have a white keratotic border and they increase in size rather than changing in position. In more severe cases, the tongue may be tender. Angular stomatitis (painful fissures at the corners of the mouth) and cheilosis (dry scaling of the lips and corners of the mouth) are also common findings associated with iron deficiency anemia.^[1] Angular cheilitis, however, is often associated with fungal infections (*Candida albicans*), lip-sucking and dehydration.^[7] Treatment must focus on correcting the deficiency state and providing adequate energy, protein, fluids and nutrients to promote healing. When angular cheilitis is due to opportunistic infections brought on by decreased resistance secondary to nutrient deficiencies, treatment should focus on antifungal therapy, correction of the nutrient deficiency and diet modification to make eating a more comfortable experience.^[7]

The Plummer–Vinson syndrome

This is otherwise called the Patterson–Brown–Kelly

syndrome or sideropenic dysphagia. It is a symptom complex caused by iron deficiency.^[8] This syndrome manifests as atrophic glossitis, or angular cheilitis, and, occasionally, hyperkeratotic lesions are seen in the oral mucosa. It is also associated with koilonychia (or spoon nails), pagophagia and dysphagia due to pharyngoesophageal ulcerations and esophageal webs.^[8]

Megaloblastic anemia

This may be caused by a vitamin B12 deficiency (commonly from pernicious anemia, surgical resection of the ileum or small intestinal diverticula) or by a folic acid deficiency (most commonly from malnutrition).^[9,10] Vitamin B12 deficiency manifests in the oral cavity as part of megaloblastic changes in the entire gastrointestinal tract, which are so well demonstrated morphologically in the bone marrow.^[9,10] The oral manifestations of painful atrophy of the entire oral mucous membranes and tongue (glossitis), stomatitis as well as mucosal ulceration (recurrent aphthous ulcers) in vitamin B12 and folate deficiency have long been recognized [Table 1].^[9,10] These oral changes may occur in the absence of symptomatic anemia or of macrocytosis. “Magenta tongue,” which is said to be rather characteristic, may herald a B12 deficiency.^[10]

Sickle cell anemia

Sickle cell disease is generically used to describe a group of disorders characterized by the production of abnormal hemoglobin S (HbS).^[11] The entities include sickle cell anemia (HbSS), sickle cell Hb C disease (HbSC) and sickle cell-β thalassaemia.

Sickle cell anemia (HbSS) is the most common type and represents the homozygous form where the individuals inherit a double dose of the abnormal gene that codes for hemoglobin S. The sickle hemoglobin abnormality is caused by substitution of valine for glutamic acid in the sixth position from the NH₂ terminal end of the β-globin chain.

Table 1: Orofacial manifestations of anemias

Cause of anemia	Orofacial manifestation
Iron deficiency	Angular cheilosis; pallor of lips and oral mucosa; sore, burning tongue; atrophy/denudation of filiform papillae; increased risk of candidiasis; glossitis
Vitamin B ₁₂ (cyanocobalamin) deficiency	Angular cheilosis; mucositis; stomatitis; sore or burning mouth; hemorrhage gingiva; halitosis; epithelial dysplasia of oral mucosa; oral paraesthesia; detachment of periodontal fibers; loss or distortion of taste; glossitis oral pain; ulceration; ulcerative gingivitis; denuded tongue; glossitis; glossodynia; tongue is “beefy,” red, smooth and glossy; delayed wound healing; xerostomia; bone loss; aphthous ulcers
Folic acid deficiency	Angular cheilosis; mucositis; stomatitis; sore or burning mouth; increased risk of candidiasis; inflamed gingiva; glossitis oral pain; ulceration; ulcerative gingivitis; denuded tongue; glossitis; glossodynia; tip or borders of tongue red and swollen; slick bald pale; aphthous ulcers
Sickle cell anemia	Orofacial pain, paraesthesia of the mental nerve, step ladder appearance of the alveolar bone of radiographs, pulpal necrosis and enamel hypomineralization, mandibular Salmonella osteomyelitis, prominent maxilla with severe malocclusion, acute facial swelling, gingival enlargement and buccal mucosal pallor
Thalassaemia	Enlargement of the maxilla, bossing of the skull and prominent molar eminences. The overdevelopment of the maxilla frequently results in an increased overjet and spacing of maxillary teeth and other degrees of malocclusion.
Aplastic anemia	Oral and facial petechiae, gingival hyperplasia, spontaneous gingival bleeding, oral hemorrhagic bullae, oral candidiasis, herpetic lesion

With decreased oxygen tension, the abnormal hemoglobin polymerizes, forming fluid polymers (tactoids) that cause the red cells to deform into a characteristic sickle shape that may plug different areas of the microcirculation or large vessels.^[11]

The hallmark features of sickle cell disease are chronic hemolytic anemia and vaso-occlusion resulting in ischemic tissue injury.^[11] While a wide spectrum of complications result from these, the major manifestation of concern is "sickle crisis" of aplastic, hemolytic or painful (vaso-occlusive) types leading to devastating multisystem complications, including stroke, pulmonary disease, delayed growth, osteomyelitis, organ damage and psychosocial dysfunction. All tissues and organs within the body are at risk of damage due to sickling.

Although relatively uncommon, a number of orofacial changes have also been observed in sickle cell disease.^[12] When it occurs, the basic pathogenicity is similar to that in other organs. These orofacial changes in HbSS as reported in the literature include midfacial overgrowth attributable to marrow hyperplasia,^[13,14] other skull and jaw changes such as increased thickening of the skull and osteoporotic changes,^[15,16] mandibular infarction that may be followed by osteosclerosis,^[17,18] osteomyelitis of the mandible,^[19-22] anesthesia or paraesthesia of the mental nerve,^[23,24] asymptomatic pulpal necrosis,^[25] orofacial pain, enamel hypomineralization and diastema [Table 1].^[26-28] These dentofacial deformities are radiographically characterized by a step-ladder appearance of the alveolar bone and areas of decreased densities and coarse trabecular pattern most easily seen between the root apices of the teeth and the inferior border of the mandible.^[13,14]

Mandibular osteomyelitis is an oral complication commonly observed in patients with sickle cell anemia, which is rarely manifested with other complications, making both its diagnosis and treatment easy.^[19] The mandible is the most affected part of the face because the blood supply is relatively insufficient when compared with the maxilla.^[20] Intravascular impairment can result in both ischemic infarct and osteonecrosis thus allowing bacterial proliferation by *Streptococcus* or *Salmonella*.^[19-22] Aches in the mandible can be preceded by widespread painful crises and be accompanied by neuropathy involving the inferior alveolar nerve and paraesthesia of the lower lip.^[29,30]

The possibility of blood extravasations and hematoma secondary to sickle cell anemia-induced hemorrhage should be considered as a working diagnosis of a facial swelling in sickle cell disease. Scipio *et al.*^[31] reported a case of a 14-year-old boy with sickle cell-related hemorrhage who developed an acute facial swelling, mimicking facial cellulitis of dental origin. Surgical exploration, however, revealed a

large hematoma between the periosteum and the lateral aspect of the ramus of the mandible. Pools of blood were also found within the buccinators muscle. The boy also exhibited gingival enlargement, which was considered to be an outcome of repeated hemorrhagic episodes and fibrous repair. Gingival biopsies reported the presence of erythrocyte-filled intraepithelial blood vessels in the gingival epithelium.

Saint Clair de Velasquez and Rivera reported, in a study, that the most common soft tissue oral manifestation of sickle cell anemia in a Venezuelan population was buccal mucosa pallor, while the most common hard tissue finding was enlarged medullary spaces.^[32]

The increased number of malocclusions in patients with sickle cell disease can be related to muscular imbalance, absence of labial sealing or changes in the osseous base thus leading to increased orthodontic intervention.^[26]

Thalassaemia

These are a group of inherited hemolytic anemia involving defects in the synthesis of either the α or the β polypeptide chains of hemoglobin (α -thalassaemia, β -thalassaemia). Based on genetic and clinical entities, thalassaemia are classified as homozygous, heterozygous or compound heterozygous. The heterozygous form of the disease (thalassaemia minor) is mild and usually asymptomatic, the only manifestation being hypochromic microcytic anemia.

Homozygous β -thalassaemia, also known as Cooley's anemia or Mediterranean anemia, is chiefly seen in Mediterranean populations with prevalence as high as 15–20% in Greece, Turkey, Cyprus and southern Italy.^[33]

The homozygous form of β -thalassaemia (thalassaemia major) exhibits the most severe clinical symptoms with marked orofacial deformities.^[33] The onset of symptoms occurs early in infancy and the patients are severely anemic and have a short life expectancy. Patients with the most severe form of the disease rarely survive into adulthood because of cardiac failure, chronic anemia and hypoxia.^[33,34] However, with modern management, the prognosis has greatly improved.

The most common orofacial manifestations are due to intense compensatory hyperplasia of the marrow and expansion of the marrow cavity [Table 1] and a facial appearance known as "chipmunk" face: enlargement of the maxilla, bossing of the skull and prominent molar eminences.^[35,36] Overdevelopment of the maxilla frequently results in an increased overjet and spacing of maxillary teeth and other degrees of malocclusion.^[37-40]

Aplastic anemia

Aplastic anemia commonly presents with oral manifestation

and can be the first clinical manifestation of the disease [Table 1]. The most common orofacial manifestation of the disease is multiple hemorrhages, which most often develop in patients with platelet counts $<25 \times 10^9/\text{liter}$. Figure 1a and b shows multiple orofacial hemorrhages in a 12-year-old patient with aplastic anemia. The other common manifestations are oral ulceration, candidiasis and viral infection.^[41]

Orofacial manifestations of disorders of hemostasis

Interaction of several basic mechanisms produces normal hemostasis, which can be divided into four general phases: the vascular phase; the platelet phase; the coagulation cascade phase, consisting of intrinsic, extrinsic and common pathways; and the fibrinolytic phase.^[3]

An abnormal tendency to hemorrhage or thromboembolism occurs in the mixed group of disorders known as hemostatic disorders. All hemorrhagic hemostatic disorders, both inherited and acquired, may produce a variety of orofacial manifestations, including petechiae, nose bleeding, spontaneous and post-traumatic gingival hemorrhages and prolonged post-extraction bleeding [Table 2].^[3] Minimal trauma, such as occurs in eating or in tooth brushing, may be sufficient to provoke gingival hemorrhage, which, when it does, is characterized by its persistence rather than its profusion, and the total volume of blood loss may be important.^[42]

Vascular disorders of hemostasis

The vascular disorders are a heterogeneous group of conditions characterized by easy bruising and spontaneous bleeding from the small vessels.^[43] Frequently, the bleeding is mainly in the skin, causing petechiae, ecchymoses or both and in some cases there is bleeding also from the mucous membrane.^[43] Vascular defect of hemostasis may be acquired or inherited.^[43] Most cases of bleeding from the vascular defect alone are not severe or life threatening. Hereditary hemorrhagic telangiectasia^[44]

and Ehlers–Danlos syndrome,^[45] in which some patients express the characteristic facial appearance of large eyes, small chin, thin nose and lips, lobeless ears are examples of hereditary vascular disorders that may present with petechiae or ecchymotic lesions on the lips, tongue and oral mucosa and epistaxis.

Platelet disorders in hemostasis

Abnormal bleeding associated with thrombocytopenia (low platelet count) or abnormal platelet function is characterized by spontaneous skin purpura, mucosal hemorrhages and prolonged bleeding after trauma.^[42]

Facial petechiae, conjunctivae hemorrhage and hemorrhagic bullae in the oral mucous membrane occur in primary deficiency of platelets. These features are also seen in secondary thrombocytopenia due to the myelophthistic syndrome, autoimmune disorder, aplastic anemia [Figure 1a and b], infections, collagen vascular disease, disseminated intravascular coagulopathy and drugs.^[42] These features may be seen in von Willebrand's disease (VWD) and have also been observed in severe hemophilia.^[42]

Thrombocytopenia secondary to an autoimmune disorder is called idiopathic thrombocytopenic purpura (ITP). It is an autoimmune disease characterized by the production of antibodies against one's own platelets. These antibodies adhere to the platelets and are recognized and destroyed by the reticuloendothelial system. Consequently, the platelet count gradually diminishes and is insufficient for the maintenance of primary hemostasis. Several reports have documented cases of ITP presenting as post-extraction hemorrhage.^[46,47]

Disorders of platelet function are suspected in patients who show skin and mucosal hemorrhages and in whom the bleeding time is prolonged despite a normal platelet count.^[48] Glanzmann thrombasthenia (GT) is an exceedingly rare

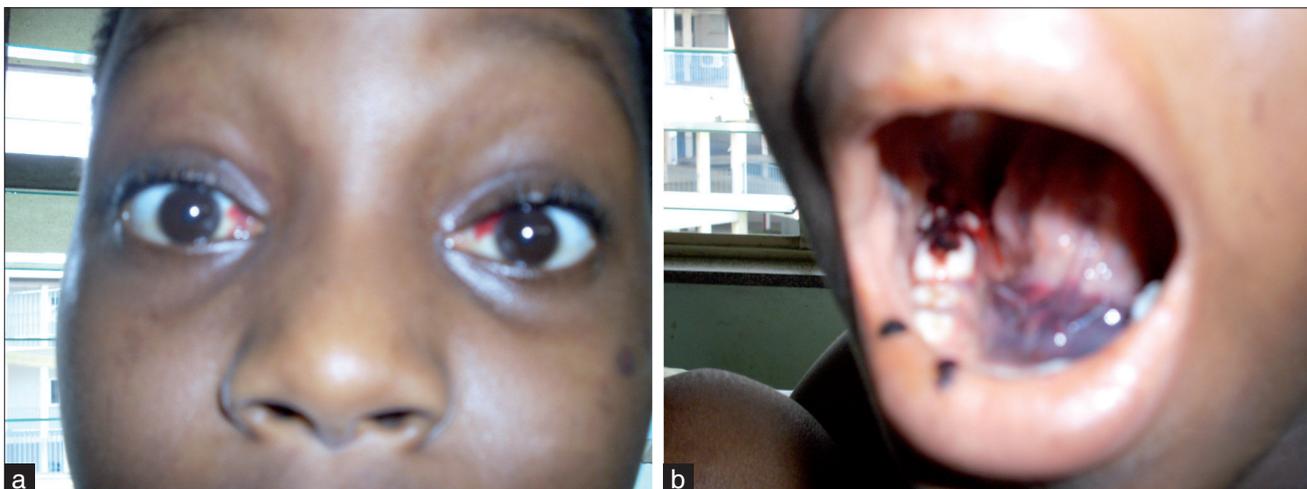


Figure 1: (a) A 12-year-old boy with aplastic anemia. Note the subconjunctival ecchymosis. (b) The same patient as in Figure 1a. Note ecchymosis of the lower lip and cheek as well as sublingual hematoma

Table 2: Orofacial manifestation of some disorders of hemostasis

Disorder of hemostasis	Mode of transmission and severity	Orofacial manifestations
Platelets abnormality		
Quantitative defects		
Secondary thrombocytopenias	Acquired	Facial petechiae and conjunctivae haemorrhage, Angina bullosa hemorrhagica, oral haematoma, palatal and tongue purpura, ecchymotic lesions on the lips, tongue and oral mucosa, epistaxis, spontaneous and post-traumatic gingiva hemorrhage, poor oral hygiene with cavities and gum disease, post-extraction hemorrhage.
ITP	Acquired	
Qualitative defects		
Glanzmann thrombasthenia (GT)	Autosomal recessive manner or acquired as an autoimmune disorder /clinically variable but may be severe.	Skin and mucosa telangiectasias on the tongue, oral hematoma, palatal and tongue purpura, ecchymotic lesions on the lips, tongue and oral mucosa, epistaxis, spontaneous and post traumatic gingiva hemorrhage, poor oral hygiene with cavities and gum disease, High and narrow palate, resulting in dental crowding. malocclusion, micrognathia Spongy gums and bleeding from the mucous membranes. Loss of teeth
Bernard–Soulier	autosomal recessive/ variable but may be severe.	
Grey platelets syndrome	autosomal dominant/ occasional autosomal recessive/ variable but may be severe.	
Anti-platelet drugs	Acquired	
Vascular abnormality		
Inherited	Autosomal dominant/clinical variability.	Angina bullosa hemorrhagica, oral haematoma, palatal and tongue purpura, ecchymosis on the lips, tongue and oral mucosa, epistaxis, spontaneous and post-traumatic gingiva hemorrhage, poor oral hygiene with cavities and gum disease, post-extraction hemorrhage. Prolong post-extraction bleeding, rare hemarthrosis. Angina bullosa hemorrhagica, oral haematoma, palatal and tongue purpura, ecchymotic lesions on the lips, tongue and oral mucosa, epistaxis, spontaneous and post-traumatic gingiva hemorrhage, poor oral hygiene with cavities and gum disease, post-extraction hemorrhage. TMJ hemarthrosis and arthropathy Same features as in hemophilias except that no hemarthrosis is seen. Facial petechiae and conjunctivae haemorrhage, Angina bullosa hemorrhagica, oral haematoma, palatal and tongue purpura, ecchymosis on the lips, tongue and oral mucosa, epistaxis, spontaneous gingiva hemorrhage.
Hereditary hemorrhagic telangiectasia (HHT)	Usually autosomal dominant/mild to life-threatening.	
Ehlers Danlos syndrome	Autosomal dominant/clinical variability.	
Marfans syndrome	Autosomal dominant/clinical variability.	
Acquired	Acquired.	
Scurvy	Acquired.	
Coagulation disorders		
Inherited	Usually autosomal dominant with variable penetrance/occasional autosomal recessive. Mild to severe disease.	von Willebrand's disease
von Willebrand's disease		
Hemophilia A (classic hemophilia)	Sex-linked inheritance/mild to severe disease.	Hemophilia A (classic hemophilia) Hemophilia B (Christmas disease)
Hemophilia B (Christmas disease)	Sex-linked inheritance/mild to severe disease.	
Factor XI deficiency (hemophilia C)	Autosomal dominant/mild disease	Factor XI deficiency (hemophilia C)
Acquired	Acquired	
Liver disease		
Uremia		
Hyperglobulinemia		

ITP - idiopathic thrombocytopenic purpura, TMJ - Temporomandibular joint

but well-defined inherited disorder of platelet function caused by a defect in the glycoprotein IIb/IIIa complex.^[3] The association of GT with consanguinity has been noted, especially in geographic regions in which such intermarriage is common. In most patients, GT is diagnosed during early infancy or before the age of 5 years. Common manifestations of this hemorrhagic disorder are gingival hemorrhage, purpura, epistaxis, petechiae and menorrhagia.^[6] Bernard–Soulier syndrome and grey platelet syndrome^[49] are the other well-defined, inherited disorders of platelet function while the use of antiplatelet drugs like aspirin and clopidogrel, uremia and hyperglobulinemia are some acquired disorders of platelet function with similar orofacial manifestations.^[50]

Coagulation disorders of hemostasis

In the 2007 World federation of hemophilia global survey where 89% of the world population was covered, 52,545 persons were identified with VWD, 105,018 with hemophilia A, 21,384 with hemophilia B, while 18,762 persons were identified with other bleeding disorders. In this survey, the total number of people identified with bleeding disorders was 213,904.^[51]

von Willebrand's disease

VWD is one of the most common hereditary coagulation abnormalities in humans and shows a worldwide distribution.^[52] It is classified into type 1, type 2A, 2B, 2M, 2N disease. Type 1 disease is the most common form of

VWD, accounting for approximately 80% of all cases. It is transmitted as an autosomal-dominant trait and thus there may be evidence of a family history of excessive bleeding. Most forms of the disease show incomplete penetrance of the phenotype and variable expressivity of bleeding symptoms within families.^[53] In contrast, the severe type 3 form of the disease shows a recessive pattern of inheritance with parents that do not usually manifest clinical symptoms. Type 2N VWD, in which isolated low FVIII levels occur, also shows a recessive pattern of inheritance and, thus, here again, a family history may be absent.^[53]

The diagnosis of VWD is established by finding a prolonged bleeding time, a low level of factor VIII procoagulant activity and abnormally low levels of factor VIII - von Willebrand protein by immunologic assay and diminished platelet aggregation in response to ristocetin.^[6,54] The clinical bleeding symptoms of this disorder are notoriously heterogeneous and may range from virtually no symptom to mild symptoms to a disease resembling factor VIII deficiency and include oral mucosal bleeding, soft tissue hemorrhage, menorrhagia in women and rare hemarthrosis.^[54] Continuous oral bleeding over long periods of time fosters deposits of hemosiderin and other blood degradation products on the tooth surfaces, turning them brown. If the history suggests VWD and oral surgery is contemplated in these patients, hematology consultation should be obtained and the patient's blood should be typed.^[54]

Hemophilia

Hemophilia is an X-linked hereditary disorder. Hemophilia A is a deficiency of factor VIII while hemophilia B (Christmas disease) is a deficiency of factor IX. Factors VIII and IX are important in the intrinsic phase of blood coagulation and their deficiency is considered severe when plasma activity of the deficient factor is <1 IU/dl (normal range, 50–100), moderate if it ranges between 2 and 5 IU/dl and mild if it is between 6 and 40 IU/dl.^[55]

The deficiency of factors VIII and XI is characterized by bleeding from multiple sites, frequently manifested in the mouth as gingival and post-extraction hemorrhages.^[56] Hemophiliacs may experience many episodes of oral bleeding over their lifetime. Sonis and Musselman^[57] reported an average 29.1 bleeding events per year, serious enough to require factor replacement in F VIII-deficient patients, of which 90% involved oral structures. Location of oral bleeding according to Sonis and Musselman are labial frenum, 60%; tongue, 23%; buccal mucosa, 17%; gingiva and palate, 0.5%.^[57] Bleeding occurrences were most frequent in patients with severe hemophilia, followed by moderate and then mild hemophilia, and most often resulted from traumatic injury.^[57] Bleeding events may also be induced by poor oral hygiene practices and iatrogenic factors.^[57] Kaneda and colleagues^[58] reported frequency of

oral hemorrhage by location in individuals' deficient of F VIII and F IX as follows: gingiva, 64%; dental pulp, 13%; tongue, 7.5%; lip, 7%; palate, 2%; buccal mucosa, 1%. Many minor oral bleeds, such as those from the gingiva or dental pulp, can be controlled by local measures while more major forms will require factor replacement.^[58]

Hemarthrosis is a common complication in a hemophiliac's weight-bearing joints, yet it rarely occurs in the temporomandibular joint (TMJ). There are very few reported case of TMJ hemarthrosis.^[59,60] Chronic hemophilic TMJ arthropathy may also occur, which requires arthrotomy, arthroscopic adhesion lysis, factor replacement, splint therapy and physical therapy.^[60] The treatment of patients with either hemophilia A or hemophilia B involves the replacement of the deficient clotting factors by intravenous infusion to either control or prevent bleeding.^[55] Patients with mild factor VIII deficiency may be treated with DDAVP to raise the factor VIII level.

There is a group of rare inherited coagulation disorders that may present significant difficulties in diagnosis and management,^[61] and with similar orofacial manifestations of hemophilia and VWD. These rare disorders include defects of fibrinogen, prothrombin, factor V, combined deficiency of factors V and VIII, factor VII, factor X, deficiency of vitamin K-dependent factors (II, VII, IX, X), factor XI, factor XII and factor XIII deficiency.^[61] The overall frequency of these disorders in the general population is low (with the exception of factor XI deficiency). Homozygous deficiency varies from 1 in 500,000 for factor VII deficiency to 1 in 2 million for prothrombin.^[62] All the disorders are autosomally inherited and, with the exception of factor XI deficiency, generally have no significant clinical manifestations in heterozygotes.^[63] Severe deficiencies are more likely to be found in populations where marriage between blood relatives is common and, in rare cases, individuals may inherit more than one disorder.^[63]

Factor XI deficiency, also known as hemophilia C, is the most common of the rare disorders and has a more variable bleeding tendency than hemophilia A or B.^[64,65] The deficiency is particularly common in Ashkenazi Jews, where the carrier rate is 8–9%. Severely deficient individuals (FXI < 10 IU/dl) have a mild bleeding tendency after surgery, especially in areas with high fibrinolytic potential such as the mouth, the nose and the genitourinary tract. Spontaneous bleeding is rare, and hemarthroses are not a feature.^[66,67]

Preventive and restorative dental care, particularly for the patient with hereditary hemostatic disorder, is of paramount importance for the fact that advanced dental conditions and subsequent treatments have proven to be more complicated

and risky.^[57-60] Quite often, dental health is neglected by hemophiliacs for fear of bleeding during procedures. Surprisingly, even dental specialists avoid these candidates and contribute to the conversion of a simple dental patient to an oral surgical patient.^[59,60] The complexities involved in diagnosing a bleeding disorder and the rarity of a standardized protocol to handle such patients contribute to this problem.

CONCLUSION

A wide array of disorders of red cells and hemostasis encountered in internal medicine has manifestations in the oral cavity and the facial region. Most of these manifestations are non-specific, but should alert the hematologist and the dental surgeon to the possibilities of a concurrent disease of hemopoiesis or hemostasis or a latent one that may subsequently manifest itself. These manifestations must be properly recognized if the patient must receive appropriate diagnosis and referral for treatment. Proper diagnosis is essential to initiate the correct treatment.

REFERENCES

- Long RG, Hlousek L, Doyle JL. Oral manifestations of systemic diseases. *Mt Sinai J Med* 1998;65:309-15.
- McFarlane DB, Pinkerton PH, Dagg JH, Goldberg A. Incidence of iron deficiency, with and without anaemia, in women in general practice. *Br J Haematol* 1967;13:790-6.
- Aster J, Kumar V. White cells and lymph nodes. In: Cotran RS, Kumar V, Collins T, editors. *Robbins Pathologic Basis of Disease*. 6th ed, Kidlington, Oxford: WB Saunders; 1999. p. 657-8.
- Hou GL, Huang JS, Tsai CC. Analysis of oral manifestations of leukaemia: A retrospective study. *Oral Dis* 1997;3:31-8.
- Stafford R, Sonis S, Lockhart P, Sonis A. Oral pathoses as diagnostic indicators in leukemia. *Oral Surg Oral Med Oral Pathol* 1980;50:134-9.
- Toygar HU, Guzeldemir E. Excessive gingival bleeding in two patients with Glanzman Thrombasthenia. *J Periodontol* 2007;78:1154-8.
- Zegarelli DJ. Fungal infections of the oral cavity. *Otolaryngol Clin North Am* 1993;26:1069-89.
- Hoffman RM, Jaffe PE. Plummer-Vinson syndrome: A case report and literature review. *Arch Intern Med* 1995;155:2008-11.
- Faccini JM. Oral manifestations of vitamin B12 deficiency. *Br J Oral Surg* 1968;6:137-40.
- Field EA, Speechley JA, Rugman FR, Varga E, Tyldesley WR. Oral signs and symptoms in patients with undiagnosed vitamin B₁₂ deficiency. *J Oral Pathol Med* 1995;24:468-70.
- Embury SH. The not so simple process of sickle cell vasoocclusion. *Microcirculation* 2004;11:101-13.
- Davies SC, Brozović M. The presentation, management and prophylaxis of sickle cell disease. *Blood Rev* 1989;3:29-44.
- Konotey-Ahulu FI. The Sickle cell disease: Clinical manifestations including the 'sickle cell crisis'. *Arch Intern Med* 1974;133:611-9.
- Brown DL, Sebes JI. Sickle cell gnathopathy: Radiologic assessment. *Oral Surg Oral Med Oral Pathol* 1986;61:653-6.
- Morris AL, Stahl SS. Intraoral roentgenographic changes in sickle cell anaemia, a case report. *Oral Surg Oral Med Oral Pathol* 1954;7:787-91.
- Prowler JR, Smith EW. Dental bone changes occurring in sickle cell diseases and abnormal haemoglobin traits. *Radiology* 1955;65:762-9.
- Mourshed F, Tuckson CR. A study of the radiographic features of the jaws in sickle cell anaemia. *Oral Surg Oral Med Oral Pathol* 1974;37:812-9.
- Walker RD, Schenck KL Jr. Infarct of the mandible in sickle cell anaemia: Report of a case. *J Am Dent Assoc* 1973;87:661-4.
- Hammersley N. Mandibular infarction occurring during a sickle cell crisis. *Br J Oral Maxillofac Surg* 1984;22:103-14.
- Patton LL, Brahim JS, Travis WD. Mandibular osteomyelitis in a patient with sickle cell anaemia: Report of a case. *J Am Dent Assoc* 1990;121:602-4.
- Shroyer JV 3rd, Lew D, Abreo F, Unhold GP. Osteomyelitis of the mandible as a result of sickle cell disease: Report and literature review. *Oral Surg Oral Med Oral Pathol* 1991;72:25-8.
- Olaitan AA, Amuda JT, Adekeye EO. Osteomyelitis of the mandible in sickle cell disease. *Br J Oral Maxillofac Surg* 1997;35:190-2.
- Friedlander AH, Genser L, Swerdloff M. Mental nerve neuropathy: A complication of sickle cell crisis. *Oral Surg Oral Med Oral Pathol* 1980;49:15-7.
- Gregory G, Olujohungbe A. Mandibular nerve neuropathy in sickle cell disease: Local factors. *Oral Surg Oral Med Oral Pathol* 1994;77:66-9.
- Andrews CH, England MC Jr, Kemp WB. Sickle cell anaemia: An aetiological factor in pulpal necrosis. *J Endod* 1983;9:249-52.
- Kelleher M, Bishop K, Briggs P. Oral complications associated with sickle cell anaemia: A review and case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996;82:225-8.
- Okafor LA, Nonnoo DC, Ojehanon PI, Aikhionbare O. Oral and dental complications of sickle cell disease in Nigerians. *Angiology* 1986;37:672-5.
- Taylor LB, Nowak AJ, Giller RH, Casamassimo PS. Sickle cell anaemia: A review of the dental concerns and a retrospective study of dental and bony changes. *Spec Care Dentist* 1995;15:38-42.
- O'Rourke CA, Hawley GM. Sickle cell disorder and orofacial pain in Jamaican patients. *Br Dent J* 1998;185:90-2.
- Stinson J, Naser B. Pain management in children with sickle cell disease. *Paediatr Drugs* 2003;5:229-41.
- Scipio JE, Al-Bayaty HF, Murti PR, Matthews R. Facial swelling and gingival enlargement in a patient with sickle cell disease. *Oral Dis* 2008;7:306-9.
- Saint Clair de Velasquez Y, Rivera H. Sickle cell anaemia oral manifestations in a Venezuelan population. *Acta Odontol Latinoam* 1997;10:101-10.
- Weatherall JD, Clegg JB. *The thalassaemia syndromes*. 3rd ed, Oxford: Blackwell Scientific; 1981. p. 132-74.
- Modell B. Management of thalassaemia major. *Br Med Bull* 1976;32:270-6.
- Weel F, Jackson IT, Crookendale WA, McMichan J. A case of thalassaemia major with gross dental and jaw deformities. *Br J Oral Maxillofac Surg* 1987;25:348-52.
- Kaplan RI, Werther R, Castano FA. Dental and oral findings in Cooley's anemia: A study of fifty cases. *Ann N Y Acad Sci* 1964;119:664-6.
- Cannell H. The development of oral and facial signs in b thalassaemia major. *Br Dent J* 1988;164:50-1.
- Van Dis ML, Langlais RP. The thalassaemias: Oral manifestations and complications. *Oral Surg Oral Med Oral Pathol* 1986;62:229-33.
- Hes J, van der Waal I, de Man K. Bimaxillary hyperplasia: The facial expression of homozygous b thalassaemia. *Oral Surg Oral Med Oral Pathol* 1990;69:185-90.
- Abu Alhaja ES, Hattab FN, al-Omari MA. Cephalometric measurements and facial deformities in subjects with b thalassaemia major. *Eur J Orthod* 2002;24:9-19.
- Sepúlveda E, Brethauer U, Rojas J, Le Fort P. Oral manifestation of Aplastic anaemia in children. *J Am Dent Assoc* 2006;137:474-8.
- Girolami A, Luzzatto G, Varvarikis C, Pellati D, Sartori R, Girolami B. Main clinical manifestations of a bleeding diathesis: An often disregarded aspect of medical and surgical history taking. *Haemophilia* 2005;11:193-202.
- Malfait F, De Paepe A. Bleeding in the heritable connective tissue disorders: Mechanisms, diagnosis and treatment. *Blood Rev* 2009;23:191-7.
- da Silva Santos PS, Fernandes KS, Magalhães MH. Osler-Weber-Rendu syndrome--dental implications. *J Can Dent Assoc* 2009;75:527-30.
- Létourneau Y, Pérusse R, Buithieu H. Oral manifestations of Ehlers-Danlos syndrome. *J Can Dent Assoc* 2001;67:330-4.
- Martini MZ, Lopez JS Jr, Gendler JL, da Fonseca EV, Soares HA, Franzi

- SA. Idiopathic thrombocytopenic purpura presenting as post-extraction haemorrhage. *J Contemp Dent Pract* 2007;8:43-9.
47. Chandra J, Ravi R, Singh V, Narayan S, Sharma S, Dutta AK. Bleeding manifestations in severely thrombocytopenic children with immune thrombocytopenic purpura. *Hematology* 2006;11:131-3.
48. Nurden AT. Inherited abnormalities of platelets. *Thromb Haemost* 1999;82:468-80.
49. Young G, Luban N, White JG. Giant platelet disorders in African-American children misdiagnosed as idiopathic thrombocytopenic purpura. *J Pediatr Hematol Oncol* 1999;21:231-6.
50. Hassan AA, Kroll MH. Acquired disorders of platelet function. *Hematology Am Soc Hematol Educ Program* 2005;1:403-8.
51. Report on the Annual Global Survey 2007. World Federation of Hemophilia; 2008.
52. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. *Blood* 1987;69:454-9.
53. Miller CH, Graham JB, Goldin LR, Elston RC. Genetics of classic von Willebrand's disease: I. Phenotypic variation within families. *Blood* 1979;54:117-36.
54. Goodeve A, Eikenboom J, Castaman G, Rodeghiero F, Federici AB, Batlle J, *et al.* Phenotype and genotype of a cohort of families historically diagnosed with type 1 von Willebrand disease in the European study, Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand Disease (MCMDM-1VWD). *Blood* 2007;109:112-21.
55. Kasper CK. Hereditary plasma clotting factor disorders and their management. *Haemophilia* 2000;6:13-27.
56. Rakocz M, Mazar A, Varon D, Spierer S, Blinder D, Martinowitz U. Dental extractions in patients with bleeding disorders. *Oral Surg Oral Med Oral Pathol* 1993;75:280-2.
57. Sonis AL, Musselman RJ. Oral bleeding in classic haemophilia. *Oral Surg Oral Med Oral Pathol* 1982;53:363-6.
58. Kaneda T, Shikimori M, Watanabe I, Minato F, Koide Y, Inoue N, *et al.* The importance of local hemostatic procedures in dental extractions and oral mucosal bleeding of haemophilic patients. *Int J Oral Surg* 1981;10:266-71.
59. Kaneda T, Nagayama M, Ohmori M, Minato F, Nakajima J, Shikimori M. Hemarthrosis of the temporomandibular joint in a patient with hemophilia B: Report of case. *J Oral Surg* 1979;37:513-4.
60. Nishioka GJ, Van Sickels JE, Tilson HB. Hemophilic arthropathy of the temporomandibular joint: Review of the literature, a case report, and discussion. *Oral Surg Oral Med Oral Pathol* 1988;65:145-50.
61. Bolton-Maggs PH, Perry DJ, Chalmers EA, Parapia LA, Wilde JT, Williams MD, *et al.* The rare coagulation disorders review with guidelines for management from the UKHCDO. *Haemophilia* 2004;10:593-628.
62. Mannucci PM, Duga S, Peyvandi F. Recessively inherited coagulation disorders. *Blood* 2004;104:1243-52.
63. Bolton-Maggs PH, Young Wan-Yin B, McCraw AH, Slack J, Kernoff PB. Inheritance and bleeding in factor XI deficiency. *Br J Haematol* 1988;69:521-8.
64. Bolton-Maggs PH. Factor XI deficiency and its management. Treatment of Hemophilia monographs. 3rd ed, vol 16. World federation of Hemophilia; 2008. p. 1-18.
65. Brenner B, Lupo H, Laor A, Zivelin A, Lanir N, Seligsohn U. Predictors of bleeding in factor XI deficiency. *Thromb Haemostas* 1995;73:1441.
66. Seligsohn U. Factor XI deficiency. *Thromb Haemost* 1993;70:68-71.
67. O'connell NM. Factor XI Deficiency. *Semin Hematol* 2004;41:76-81.

How to cite this article: Adeyemo TA, Adeyemo WL, Adediran A, Akinbami AA, Akanmu AS. Orofacial manifestations of hematological disorders: Anemia and hemostatic disorders. *Indian J Dent Res* 2011;22:454-61.

Source of Support: Nil, **Conflict of Interest:** None declared.

