ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 11, pp.75681-75686, November, 2018

DOI: https://doi.org/10.24941/ijcr.33312.11.2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

ORAL MANIFESTATIONS OF RED BLOOD CELL DISORDERS: A RECENT ANATOMIZATION

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ARTICLE INFO

Article History:
Received 17th August, 2018
Received in revised form
03rd September, 2018
Accepted 26th October, 2018
Published online 30th November, 2018

Key Words:
Red Blood Cells, Oral Manifestations, Anaemia, Glossitis, Ulceration, Chelitis.

ABSTRACT

Primary objective of the literature is recognize and evaluate the wide array of oral manifestations associated with red blood cell disorders which would eventually aid in diagnosis of the lesions associated with the disorders for the practitioners. It starts with petechiae, spontaneous gingival bleeding, herpetic infection in aplastic anaemia to hunter's glossitis in pernicious anaemia. Literature also includes enamel hypoplasia associated with erythroblastis fetalis, atrophic glossitis in iron deficiency anemia with symptom of glossodynia in megaloblastic anemia. Marked manifestations of pharyngo-esophageal ulcerations and esophageal webs seen in plummer Vinson syndrome and periodontitis, taurodontism, agenesia, supernumerary teeth to be seen in fanconi's anemia. Literature ends with midfacial overgrowth, radiographic dentofacial abnormalities in sickle cell anemia and brodie syndrome, chip munk facies to be seen in thalassemia patients.

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***Citation: Swatantra Shrivastava, Sourabh Sahu, Pavan Kumar Singh, Rajeev Kumar Shrivastava, Soumendu Bikash Maiti and Stuti Shukla,* 2018.** "Oral manifestations of red blood cell disorders: A recent anatomization", *International Journal of Current Research*, 10, (11), 75681-75686.

INTRODUCTION

Blood is unique due to its existence as the only fluid tissue, a blood cell can be any type of cell normally found in blood which falls into four categories which are red blood cell (RBC), white blood cell (WBC), platelet and plasma. The differences between these groups lie on the texture, color, size and morphology of nucleus and cytoplasm. In blood smear, number of red cells is many more than white blood cells. Blood cells form in the bone marrow, the soft material in the center of most bones. Leukocytes or WBC are cells involved in defending the body against infective organisms and foreign substances. Leukocytes cells containing granules are called granulocytes (composed by neutrophil, basophil, eosinophil). Cells without granules are called agranulocytes (lymphocyte and monocyte). These cells provide major defense against infections in organisms and their specific concentrations can help specialists to discriminate the presence or the absence of very important families of pathologies. When infection occurs, the production of WBCs increases. Abnormal high or low counts may indicate the presence of many form of disease, since blood counts are amongst the most commonly performed blood test in medicine (Adollah *et al.,* 2008).

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Oral manifestations of disorders

Aplastic Anemia is caused by lack of bone marrow activity, reduction of red blood cell count, white blood cell count and platelets which causes pancytopenia (Richa Wadhawan *et al.,* 2014; Sepúlveda *et al.,* 2016). Most common manifestations include pale and atrophic oral mucosa, smooth, bald and sore tongue, angular stomatitis, bleeding from the gingiva due to deficiency of platelets (Richa Wadhawan *et al.,* 2014) (Fig 1). In a case-control study of 79 patients with AA, the most commonly observed findings attributed to the disorder were were petechiae, spontaneous gingival bleeding, herpetic infection (Richa Wadhawan *et al.,* 2014). The most common orofacial manifestation of the disease is multiple hemorrhages, which most often develop in patients with platelet counts <25 $\times 10^9$ microliter. The other common manifestations are oral ulceration, candidiasis and viral infection (Richa Wadhawan *et al.,* 2014; Sepúlveda *et al.,* 2016; Rai *et al.,* 2016; Nabiel AlKhouri, 1999). Petechiae purpuric spots or frank hematomas of the oral mucosa may occur at any site, while hemorrhage into the oral cavity, especially spontaneous gingival

hemorrhage, is present in some cases. Such findings are related to the blood platelet deficiency. As a result of the neutropenia there is a generalized lack of resistance to infection, and this is manifested by the development of ulcerative lesions of the oral mucosa or pharynx. These may be extremely severe and may result in a condition resembling gangrene because of the lack of inflammatory cell response (Neal Young, 2010; Eva Guinan *et al.,* 2011).

Pernicious anemia is a relatively common chronic hematologic disease. It is an adult form of anemia that is associated with gastric atrophy and a loss of intrinsic factor production in gastric secretions and a rare congenital autosomal recessive form in which intrinsic factor (IF) production is lacking without gastric atrophy. The term pernicious anemia is reserved for patients with vitamin B12 deficiency due to a lack of production of IF in the stomach. Intrinsic factor in gastric secretions is necessary for the absorption of dietary vitamin B12 (Lahner and Annibale, 2009). Examination may include pallor, glossitis and oral ulceration (Andres and Serraj, 2012). Glossitis (Hunter's glossitis) characterized by a slick or bald tongue, papillary atrophy, and burning sensation on contact with certain foods is usually associated with this disease, although much less described in a recent series devoted to concerned anemia (Fig 2).

Fig. 1. Bleeding gums in aplastic anemia

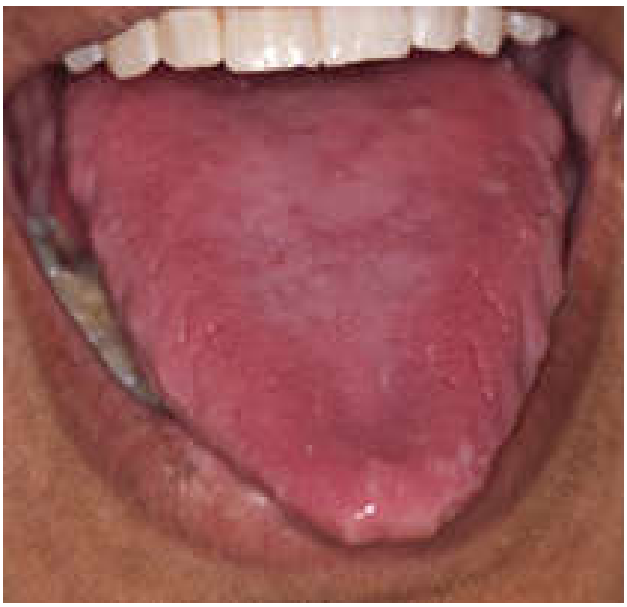

Fig. 2. Glossitis in pernicious anemia

Polycythemia is first described by Vasquez in 1892. So, called Vaquez's disease and other name includes polycythemia rubra vera, Osler's disease, and erythema. It an abnormal increase in the number of red blood cells in the peripheral blood, usually with an increase in haemoglobin level (Sambandan, 2010). Oral Manifestations includes purplish red discoloration of the oral mucosa is visible on the tongue, cheeks, and lips. The gingiva is red and may bleed spontaneously. Petechiae and ecchymoses are observed in patients with platelet abnormalities. Varicosities in the ventral tongue, a frequent normal finding, are exaggerated in cases of polycythemia (Sambandan, 2010). Erythema of oral mucosa, glossitis, gingivitis, gingival bleeds spontaneously but no tendency to ulcerate (Lele, 1965; Jepson, 1969). It can manifest intra orally with erythema (red–purple color) of mucosa, glossitis, and erythematous, edematous gingiva. Spontaneous gingival bleeding can occur because the principal sites for hemorrhage, although rare, are reported to be the skin, mucous membranes, and gastro-intestinal tract (Brian *et al.,* 2004). Oral mucous membranes appear deep purplish red, the gingiva and tongue being most prominently affected. The cyanosis is due to the presence of reduced hemoglobin in amounts exceeding 5 gm/dl. The gingiva are often engorged and swollen and bleed upon the slightest provocation. Submucosal petechiae are also common, as well as ecchymosis and hematomas. In current infection may occur, but this is not related directly to the disease (Richa Wadhawan *et al.,* 2014).

Erythroblastosis fetalis is a hemolytic disease of fetal or neonatal life due to fetal-maternal blood group incompatibility the fetus having a blood factor that its mother lacks, and the mother producing antibodies against that factor. These maternal antibodies are capable of agglutinating the RBC's of both the fetus and the father. Erythroblastosis Fetalis includes at least three clinical types: (a) Hydrops fetalis, (b) Icterus gravis of the newborn (c) Hemolytic anemia of the newborn. Erythroblastosis fetalis may be manifested in the teeth by the deposition of blood pigment in the enamel and dentin of the developing teeth, giving them a green, brown or blue hue. Ground sections of these teeth give a positive test for bilirubin. The stain is intrinsic and does not involve teeth or portions of teeth developing after cessation of hemolysis shortly after birth. Enamel hypoplasia is also reported occurring in some cases of erythroblastosis fetalis. This usually involves the incisal edges of the anterior teeth and the middle portion of the deciduous cuspid and first molar crown. Here a characteristic ring-like defect occurs which has been termed the Rh hump by Watson. Many infants with this disease are stillborn, but an increasing number of those born alive have survived after a total replacement of their blood by transfusion at birth (Sambandan, 2010). Iron deficiency anemia (IDA) is defined as a reduction in total body iron to an extent that iron stores are fully exhausted and some degree of tissue iron deficiency is present. It may occur as a consequence of low dietary intake, impaired absorption, or excessive iron loss (Terri *et al.,* 2011). 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. Migratory glossitis, also known as geographic tongue. 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 (Frewin

et al., 1997). 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. Angular cheilitis, however, is often associated with fungal infections (Candida albicans), dehydration and ulceration due to atropy of mucosa (Adeyemo *et al.,* 2011; Wasiu *et al.,* 2011; Long *et al.,* 1998; Pontes *et al.,* 2009).

Megaloblastic anemias are a subgroup of macrocytic anemias caused by impaired DNA synthesis that results in macrocytic red blood cells, abnormalities in leukocytes and platelets and epithelial changes, particularly in the rapidly dividing epithelial cells of the mouth and gastrointestinal tract.[28] Megaloblastic anemias occurs due to deficiency of vitamin B12 or folate or both, resulting in disordered cell proliferation leading to Megaloblastic anemias (Truswell and Vitamin, 2007). Various oral manifestations are: pale oral mucosa, Glossitis, Glossodynia, Beefy red tongue, Erythematous macular lesions on the dorsal and border surfaces because of marked epithelial atrophy, Soreness of the tongue, Reduced taste sensitivity. stomatitis as well as mucosal ulceration (recurrent aphthous ulcers) in vitamin B12 and folate deficiency have long been recognized. 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 (Smith, 2008). 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 (Fragasso *et al.,* 2010; Aslinia *et al.,* 2006; Christopher, 1999). 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 (Celik *et al.,* 2003). The presence of oral signs and symptoms, including glossitis, angular cheilitis, recurrent oral ulcer, oral candidiasis, diffuse erythematous mucositis and pale oral mucosa (Smith and Refsum; Wang; Puntambekar *et al.,* 2009).

Plummer-vinson syndrome is otherwise called the Patterson–Brown–Kelly syndrome or sideropenic dysphagia, iron-deficiency anemia and esophageal webs. Even though the syndrome is very rare nowadays, its recognition is important because it identifies a group of patients at increased risk of squamous cell carcinoma of the pharynx and the esophagus (Samad *et al.,* 2015; Hoffmann and Jaffe, 1995). Oral characteristics include glossitis, glossopyrosis, glossodynia, and angular cheilitis. Its etiology is unknown although autoimmune, genetic, infectious and nutritional factors have been proposed as a cause. Approximately 10% of patients suffering Plummer-Vinson syndrome develop squamous cell carcinoma principally in the hypo pharynx and esophagus. pagophagia and dysphagia due to pharyngo-esophageal ulcerations and esophageal webs (Samad *et al.,* 2015; Mansell *et al.,* 1999; Anthony *et al.,* 1999). Furthermore, it is characterized by glossitis, angular cheilitis, mucosal pallor and occasionally hyperkeratotic lesions are seen in the oral mucosa (Samad *et al.,* 2015; Lopez Rodriguez *et al.,* 2002; Chisholm, 1974; Messmann, 2001).

Fanconi Anemia (FA) is a recessive genetic disorder, in which individuals present congenital alterations associated with consanguinity. It was described for the first time by Fanconi in 1927, in a case report of three brothers with a condition of progressive anemia, pancytopenia, physical anomalies and hyper pigmentation of the skin. This disease is characterized by the malfunctioning of the DNA repair mechanism, which present an increase in the rate of spontaneous damage, among these spontaneous chromosomal instability, and hypersensitivity of cells to the chromosomal breaking effect induced by clastogenic agents (D'agulham *et al.,* 2014). Oral manifestation were Gingivitis and periodontitis are the most cited oral manifestations in individuals with the disorder (Fig 3). Gingival bleeding and hyperemia are remarkable findings in patients with fanconi's anemia. Poor oral hygiene is added to the systemic condition that makes it an aggravating agent of gingivitis and periodontitis in these individuals. It is important to remember that bio-film is the etiologic agent of gingivitis and gingival bleeding is one of the main clinical signs of this inflammation. Therefore, thrombocytopenia acts as a modifying agent of the systemic condition, and we suggest that this exacerbates gingival bleeding in these individuals. Another common hematological alteration in individuals with FA is chronic anemia, of which the main oral clinical characteristics are pallor of the mucosa and gingival. The continuous and daily consumption of sucrose, presence of specific cariogenic microbiota, low socio-economic condition and reduced access to dental care are relevant factors for the development of caries, a multifactorial disease (D'agulham *et al.,* 2014). The use of fluoride may be of great help in the control of dental caries (Solomon *et al.,* 2015). Dental anomalies found in radiographic studies, diverse dental anomalies have been observed in this population. With regard to number, agenesia and supernumerary teeth are the most common anomalies. The tooth with the highest prevalence of agenesia is the maxillary central incisor. With respect to position, rotation of permanent teeth and tooth transposition are the most reported anomalies. The permanent canine is the tooth with the highest prevalence of transposition (De Araujo, 2007). Curved, tapered roots with apical dilacerations, enamel pearl, taurodontia, microdontia, and enamel hypoplasia are the alterations in shape, dimension and dental structure described in these patients (Goswami *et al.,* 2016). Alterations in calcium metabolism during odontogenesis related to Vitamin D resistant rickets, explain some of the dental alterations in individuals with FA, such as agenesia and presence of supernumerary teeth. The other alterations may be justified by the cranio-facial anomalies such as microcephaly and retro/micrognathia. Furthermore, it is common for these patients to present low stature, growth hormone deficiency and hypothyroidism. This may occur due to hypoactivity of the hypothalamus causing insufficiency of growth hormone, resistance to its action and hypothyroidism. Sialochemical and sialometric alterations Reduction in salivary flow (hyposalivation) is an important oral manifestation in individuals with FA. This occurs both in patients submitted to BMT, and in those who did not undergo transplantation. However, there is not report of dry mouth sensation (xerostomia) or apparent clinical sign (Younghoon Kee *et al.,* 2012). This diminished salivary flow may be justified by the pathogenesis of FA, related to endocrine alterations and or those of the central nervous system and due to the use of drugs, particularly on the central action Alterations in urea and calcium concentrations in saliva have also been reported in individuals with FA, while amylase and total proteins have shown no alteration. Changes in salivary flow may lead to increase in the prevalence of caries, and increased predisposition to development of infections, however, this is not an isolated factor. In spite of these individuals presenting a

low level of salivary flow, and high indices of urea and calcium in saliva being expected, these present reduced values when compared with individuals without systemic alterations. This may be justified by dysfunction in calcium and urea absorption by the body. This applies to calcium by the gastrointestinal atresia, and urea by the renal and hepatic alterations (De Araujo, 2007). Recurrent aphthous ulcers are the most common lesions in soft tissues in individuals with FA. As they present a painful symptomatology, these lesions are responsible for the increase in the frequency of these patients visiting the dental office (Younghoon Kee *et al.,* 2012).

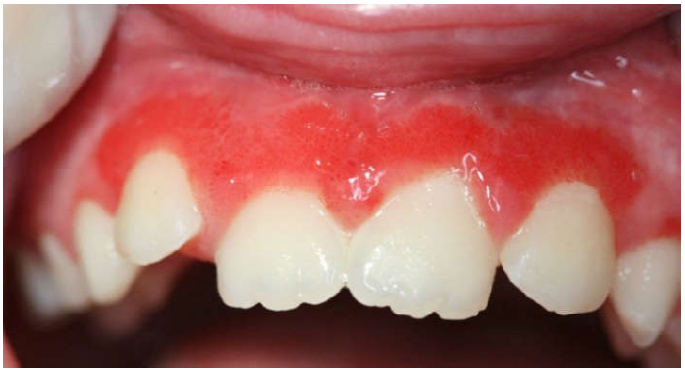

Fig. 3. Gingivitis in a child with fanconi anemia

Sickle cell anaemia is a genetic disease caused by replacement of glutamic acid by valine in position 6 at the N-terminus of the beta-chain of globin, thus resulting in haemoglobin S. Under conditions of hypoxia, erythrocytes that predominantly contain haemoglobin S take on a shape resembling a sickle (Kaur *et al.,* 2013). The reduction in oxygen-transport capacity results in circulatory difficulties, including vasoocclusive conditions, which diminishes the lifespan of the red blood cells to approximately 20 days (Konotey-Ahulu, 1974). These orofacial changes in HbSS as reported in the literature include mid-facial overgrowth attributable to marrow hyperplasia, other skull and jaw changes such as increased thickening of the skull and osteoporotic changes, mandibular infarction that may be followed by osteosclerosis, osteomyelitis of the mandible, anesthesia or paraesthesia of the mental nerve, asymptomatic pulpal necrosis, smooth tongue, orofacial pain, enamel hypomineralization and diastema (Morris and Stahl, 1954). (Fig 4 & 5).

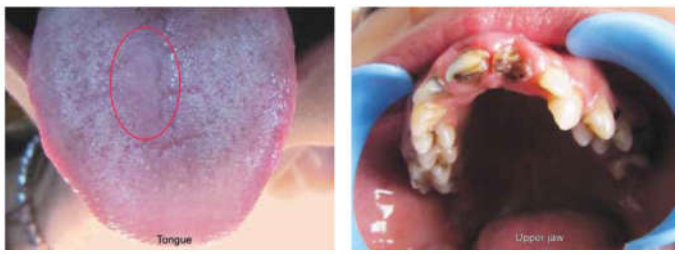

Fig. 4. and Fig. 5. showing smooth tongue and high arched palate in sickle cell anemia

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. 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 (Mourshed and Tuckson, 1974).The mandible is the most affected part of the face because the blood supply is relatively insufficient when compared with the maxilla (Walker and Schenck, 1973; Hammersley, 1984; Patton *et al.,* 1990).

Thalassemia (Mediterranean anemia) is an inherited blood disorder characterized by less hemoglobin and fewer red blood cells in your body than normal. It is a pediatric inherited disease caused by genetic disorder. There is an absence or reduction in the production of hemoglobin. There are two type of thalassemia –alpha or beta-depending on which globin chain is affected by a genetic mutation or deletion. Thalassemia is characterized by severe anemia, growth retardation, skeletal disturbances, and iron overload, cardiac and endocrine abnormalities which cut short the life of the affected patients (Herbert *et al.,* 2009). The most common orofacial manifestations are due to intense compensatory hyperplasia of the marrow and expansion of the marrow cavity and a facial appearance known as "chipmunk" face: enlargement of the maxilla, bossing of the skull and prominent molar eminences. Overdevelopment of the maxilla frequently results in an increased over jet and spacing of maxillary teeth and other degrees of malocclusion (Weel *et al.,* 1987). The most common orofacial manifestations are due to intense compensatory hyperplasia of the marrow and expansion of the marrow cavity (Cannell, 1988). Thalassemia major patients develop skeletal class II maloclussion subsequent to maxillary protrusion and mandibular atrophy. The early fusion of occipital sutures takes place concomitantly with medullary hyperplasia of the anterior maxillofacial structures, causing maxillary skeletal protrusion. Often the mandibular arch is telescoped within the maxillary arch (Brodie syndrome) in thalassemia major patients .Malocclusion due to maxillary protrusion, increased overjetand anterior open bite, malar prominence, saddle nose and frontal bossing give an appearance of 'chip-munk facies' orrodent facies. The mandible is generally less protruded than maxilla apparently because the dense mandibular cortical layer resists expansion (Abu Alhaija *et al.,* 2002; Sakshi Madhok *et al.,* 2014; Margot *et al.,* 1986). Overgrowth of marrow in frontal, temporal and facial bones consistently impedes pneumatisation of paranasal sinuses. Marrow overgrowth in maxillary bone may cause lateral displacement of orbits (hyperteleorism) (Margot *et al.,* 1986).

Summary and conclusion

The literature therefore emphasizes on a simple yet elaborate assemblage of oral manifestations. Many manifestations may be similar which requires further investigations but what it does is direct or makes the practitioner vigilant about the signs and symptoms and help in documenting a much proper and effective diagnosis for themselves and device a proper treatment plan. It is a field where a medico dental correlation becomes very paramount and work together for a better understanding of the lesion

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