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Manifestations of Hematological System in Jaws

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Abstract

A wide array of systemic diseases encountered in internal medicine have manifestations in the yawning abyss that internists call the oral cavity. The oral cavity has an important anatomical location with a role in many critical physiologic processes, such as digestion, respiration, and speech. It is also unique for the presence of exposed hard tissue surrounded by mucosa. The oral cavity might well be thought as window to the body because oral manifestations accompany many systemic diseases. Hematologic abnormalities are varied in nature, in its causation as well as in its clinical manifestations, most of which manifest in the oral cavity. Careful examination of the oral cavity may reveal findings indicative of an underlying systemic condition, and allow for early diagnosis and treatment.

Keywords: Oral Manifestations, Haematological, Anemia, Glossitis

Introduction

The mouth is a mirror of health or disease, a sentinel or early warning system[2] which has the potential to reflect the human body's internal condition.[1] Oral clinicians are at pains to emphasize that mouth is a part of the body and not merely a gateway for delicacies.[2] Irrespective of the organ system involved, changes frequently occur in the oral cavity reflecting disease elsewhere in the body.[3]

A wide array of hematological 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 hematological disorder or a latent one that may subsequently manifest itself.[4]

Hemoglobinopathies occur widely across the world and an increased numbers of affected births and high rates of mortality and morbidity are still observed in the majority of affected countries of the developing world. According to **Chaudhary et al in 2012,**[5] in India, frequency in terms of carrier rate is 0-44% and an estimated 5 million carriers are living with the gene. Hematopoeisis is the physiological production of blood cell elements consisting of red blood cells, white blood cells and platelets.[6]

Red Blood Cell Disorders

Anemia: It is defined as a condition in which there is less than the normal hemoglobin level in the body, which decreases oxygen carrying capacity of red blood cells to the tissues. According to **Vinall C et al in 2007**,[7] anemia may arise from bleeding, or from increased destruction or decreased production of red /blood cells.

Iron Deficinecy Anemia- It develops when the amount of iron available to the body cannot complete the need of iron for the production of red blood cells. Iron deficiency

anemia is a global public health problem, as compelling and harmful as the epidemics of infectious disease. According to **Maternal Mortality in India, 2008**, 20% of all the maternal deaths are attributed to anemia during pregnancy.[8] Twitching, flinching, or an uncontrollable urge to move the legs, a condition called as Restless Legs Syndrome, are common symptoms of iron deficiency anemia. Pallor or pale skin is often observed in a person with anemia. The person may have a ghostly pale appearance (**DeMaeyer E et al in 1985**).[9]

Oral manifestations

It include angular chelitis, atrophic glossitis or generalized oral mucosal atrophy (**McIntyre AS et al in 1993**[10]; **Kaur N et al in 2015**[8]).Palatal pallor and narrowed mouth opening are also found. The most frequent symptoms are glossodynia and glossopyrosis. The surface of tongue is smooth, glistening and reddened.[3] This is often accompanied by tenderness or a burning sensation. Recurrent aphthous stomatitis, erythematous mucositis and burning mouth also are evident in patients of iron deficiency anemia. Iron deficiency predisposes the patient to candidal infection, which results in the changes seen at the corners of the mouth and on tongue (**Zegarelli DJ et al in 1993**).[11]

Hemolytic Anemia- It result from excessive destruction of red blood cells.[6] According to **Tefferi A et al in 2003**,[12] in all types of hemolytic anemia, laboratory evidence of increased cell destruction (suggested by increased lactate dehydrogenase), increased hemoglobin catabolism (suggested by increased levels of indirect bilirubin), decreased levels of haptoglobin (a serum protein that clears free hemoglobin), and bone marrow regenerative effort (suggested by reticulocytosis) may be appreciated.

a) Sickle cell anemia

According to **Vinall C et al in 2007**[7], this is caused by a mutation in the gene encoding the beta-globin chain, causing the formation of sickle hemoglobin (HbS). On de-oxygenation, HbS undergoes polymerization. This results in distortion of the red blood cells leading to a sickle shape.

Oral manifestations

It may manifest in orofacial manifestations such as angular cheilosis, pallor of lips and oral mucosa, sore or burning tongue, atrophy/ denudation of filliform papillae, increased risk of candidiasis, glossitis (**Adeyemo TA et al in 2011**).[13]

According to **Chaudhary et al in 2012,**[5] the following changes were observed in enamel, dentin and cementum: decrease in number of dentinal tubules, decrease and irregular dead tract formation, decrease in thickness of the secondary tubules, increase in enamel lamellae, presence of gnarled enamel not below the cusp but more towards the DEJ, hypercementosis and calcified canals.

Radiographic manifestations- The 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 (**Brown DL et al in 1986**).[14] The lamina dura appears more distinct and paranasal frontal sinuses appear reduced in size. In skull radiographs, resorption of inner surface of diploe and new growth on the outer surface produce trabeculae with a “hair-on-end” appearance.

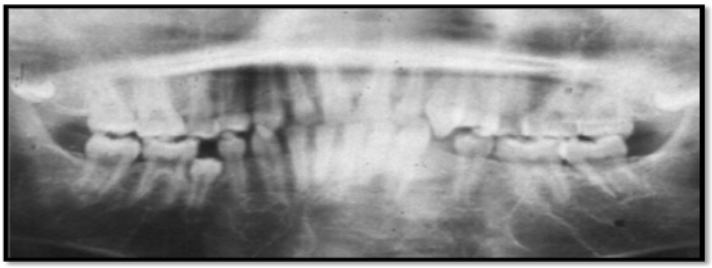

Figure 1: Radiograph of a patient with sickle cell anemia, demonstrating Horizontal trabeculation creating a ladder like effect

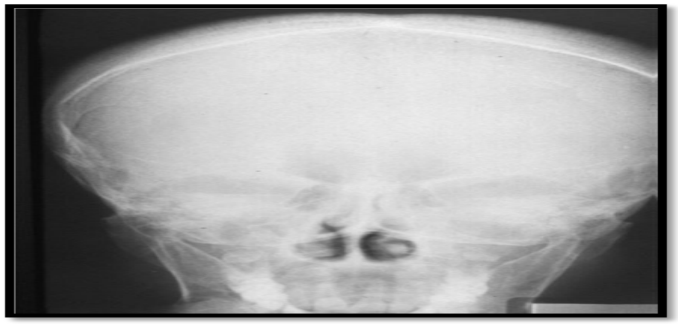

Figure 2: Lateral skull film demonstrating thinned cortex with wavy lines, called "hair on end.

b) Thalassemia

This is a heterogeneous group of genetic disorders characterized by a decreased synthesis of globin chains, leading to decreased production of hemoglobin and a hypochromic microcytic anemia (**Vinall C et al in 2007**).[7] In more severe types of thalassemia, such as **Cooley's anemia,** signs of severe anemia are seen in early childhood and may include fatigue and weakness, pale skin or jaundice, protruding abdomen with enlarged spleen and liver, dark urine, abnormal facial bones, and poor growth, ineffective erythropoiesis and expansion of the bone marrow in every part of the skeleton of individuals with untreated thalassaemia result in skeletal changes, including osteoporosis, growth retardation, platyspondyly, and kyphosis. It is chiefly seen in Mediterranean populations with prevalence as high as 15-20% in Greece, Turkey, Cyprus and southern Italy (**Weatherall JD et al in 1981**).[15]

Oral manifestations

Enlargement of the maxilla occurs due to hypertrophy and expansion of erythroid marrow. This results in flaring and spacing of the maxillary anterior teeth, increased overjet, anterior open bite and varying degrees of malocclusion (**Hattab FB in 2001**).[16] The osseous changes cause prominent cheekbones, sunken root of the nose, labial inclination of the maxillary incisors and inadequate lip seal. These facial features have led to the description "rodent" facies.[6]

Craniofacial deformities include universal Class II skeletal base relationship with a short mandible, a reduced posterior facial height, increased anterior facial proportions, and with severe facial disfigurements (grade 3 or "chipmunk faces"). Patients may have gingival inflammation and anterior dental caries because of the inability to close their mouth and mouth breathing. Introrally, the oral mucosa may be pale, owing to the anemia or yellow tinged, owing to jaundice.[17]

Radiographic manifestations

It includes the appearance of spiky-shaped and short roots, taurodontism, attenuated lamina dura, enlarged bone marrow spaces, small maxillary sinuses, absence of inferior alveolar canal, and thin cortex of the mandible (**Adeyemo TA et al in 2011**[13]). At the superior aspect of skull, the skull widens by the expansion of diploe and subperiosteal bone formation.[17] Thin bone spicules radiating circumferentially from the inner table produce a "hair-on-end" appearance.[6] Within the jaws, paticulary in the posterior mandible, the medullary portions are widened, honeycombed or generally rareified.[13]

Pernicious Anemia- It is an autoimmune gastritis resulting from the destruction of gastric parietal cells and consequent impairment of intrinsic factors secretion to bind the ingested vitamin B12. Other autoimmune disorders, especially thyroid disease, diabetes mellitus, and vitiligo, are also commonly associated with pernicious anemia.[18]

Oral manifestations

The classic oral symptoms of pernicious anemia are- Glossitis and Glossodynia. The tongue is "beefy red" and inflamed, with small erythematous areas on the tip and margins. A sore, burning tongue (glossopyrosis) is present

in about half of the patients. Patients may complain of dysphagia and taste aberrations.[19]

Discomfort described by denture wearers who have pernicious anemia is probably due to the weakened mucosal tissues. Although the "burning mouth" sensation diagnosed in pernicious anemia can be due to a neuropathy, other causes of oral burning, including candidiasis, should be considered.[20]

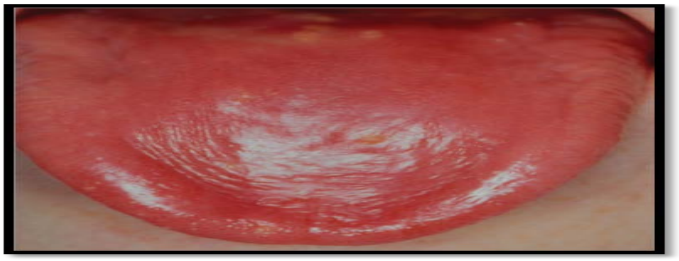

Figure 3: Atrophic glossitis in a patient with vitamin B12 deficiency

Aplastic Anemia

Aplastic anemia (AA) is a serious hematologic disease characterized by hypocellular bone marrow that produces insufficient numbers of hematopoietic stem cells, leading to deficient production of erythrocytes, granulocytes, and platelets.[21] The etiology is typically unknown, but associations have been noted with certain medications, benzene exposure, insecticides, viruses, and hepatitis. The initial symptoms of AA include fatigue, increased bruising, epistaxis, and gingival hemorrhage.[22]

Oral Manifestations

Submucosal hemorrhages, gingival swelling, herpetic lesions, spontaneous gingival bleeding, pallor, and periodontal disease in associated with patients with Aplastic anemia.[23]

Causes Of Anemia	Orofacial Manifestations
Iron Deficiency Anemia	Angular cheilosis, pallor of lips and oral mucosa, sore or burning tongue, atrophy/ denudation of filliform papillae, increased risk of candidiasis, glossitis
Vitamin B12 Deficiency	Angular cheilosis, mucositis, stomatitis, sore or burning mouth, haemorrhage gingiva, halitosis, epithelial dysplasia of oral mucosa, oral paresthesia, detachment of periodontal fibers, loss or distortion of taste, glossitis, oral pain, ulceration, ulcerative gingivitis, denuded tongue, glossodynia, tongue is beffy red, smooth and glossy, delayed wound healing , xerostomia, bone loss, apthous ulcers
Folic Acid	Angular cheilosis, mucositis, stomatitis, sore or burning mouth, increased risk of candidiasis, inflamed gingiva, glossitis, oral pain, ulceration, ulcerative gingivitis, denuded tongue, glossodynia, tip or borders of tongue red or swollen, slick bald pale, apthous ulcers
Sickle Cell Anemia	Orofacial pain, paresthesia of 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.
Thalassemia	Enlargement of maxilla, bossing of skull and prominent molar eminences. The overdevelopment of maxilla 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

Table 1- Summary of Orofacial manifestations of anemia

Polycythemia Vera

Polycythemia vera is a myeloproliferative disorder characterized by excessive proliferation of erythroid elements along with granulocytic and megakaryocytic cells. In polycythemia vera (PV) red blood cell (RBC) volume increases to an erythrocyte count of 6 to 12 million/ mm, with a hemoglobin concentration of 18 to 24 g/dL, leading to increased blood viscosity and thrombosis. Polycythemia is divided into absolute erythrocytosis (a true increase in red-cell mass) and relative erythrocytosis (the red cell mass is normal, but the plasma volume is reduced due to the loss of tissue and intravascular fluid).[24]

Oral Manifestations

Polycythemia may initially present with sontaneous bleeding from the gum, purplish or red areas on the tongue, cheeks, lips and gums, poor oral hygiene, inflamed & edematous gingiva and periodontal disease.[25] Angular chelitis, atrophic glossitis and koilonychia may be concurrent, because iron deficiency is common with polycythemia vera.[6] Facial plethora (red, florid complexion) is a cardinal sign particularly evident around the ears, nose and lips. In absolute erythrocytosis reactive keratosis, and different forms of candidiasis, mucosal ulcers are observed.[25]

White Blood Cells Disorders

Leukemia: It is a hematological disorder which is caused by proliferating white blood cell-forming tissues resulting in a marked increase in circulating immature or abnormal white blood cells.[26] The etiology of leukemia is poorly defined, most authors considering that it is multifactorial. General manifestation of leukemia may include fatigue, anaemia, lymphadenopathy, recurrent infection, bone and abdominal pain, bleeding and purpura.[27]

Oral Manifestations

According to **Hou GL et al in 1997,**[28] oral manifestations may occur in any of the leukemia's, but they are more common in AML. An increased incidence of numerous oral problems such as generalized ulcers; spontaneous bleeding of mucosa and gingivae; coated tongue; limited mouth opening; foul odor; oral infections (mucositis, candidiasis, herpes simplex, varicella/zoster, and cytomegalovirus); shallow papillae; differences in salivary flow rate and pH; Numb Chin syndrome; mucosal pallor; swallowing and chewing difficulties; ulceration and edematous areas; erythema; trigeminal nerve neuropathy; reticular lesions; ecchymoses; neuropathy; xerostomia; reddened, tender, and painful mucosa; gingival pain and hemorrhage have been reported.Temporomandibular joint arthritis is usually found in AML, and osteolytic lesions in the mandible have been reported (**Chung SW et al in 2011**).[29]

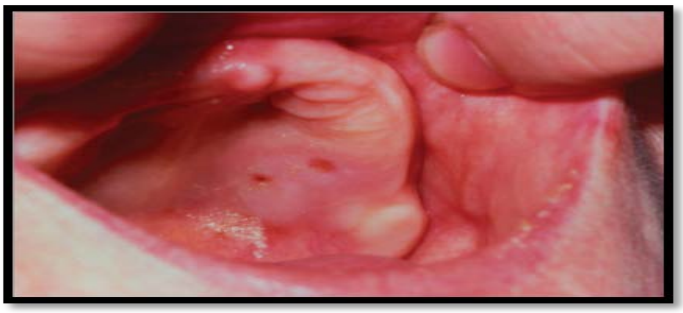

Figure 4: Palatal chloromas in a patient with acute myelogenous leukemia.

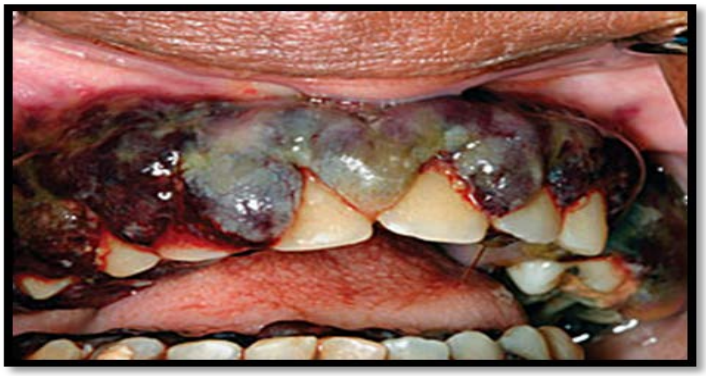

Figure 5: Diffuse, hemorrhagic enlargement of the gingiva in a patient with acute monocytic leukemia

Lymphoma: It is a heterogenous malignant disease of the lymphatic system, characterized by a proliferation of lymphoid cells or their precursors. Lymphomas are the third most common cancer worldwide and constitute 3% of malignant tumors.[30] They make up 2.2% of all malignancies of the head and neck and are the second most frequent in that region surpassed only by epithelial malignancies (**Epstein JB et al, 2001**).[31]

The Hodgkin's lymphoma, by definition, is a disseminated or located malignant proliferation of tumoral cells primarily derived from lymphoreticular system, involving the lymphonodal fabric and the bone marrow.[32] Non-Hodgkin's lymphoma comprises a heterogeneous group of lymphoid neoplasm with a spectrum of behavior ranging from relatively indolent to highly aggressive and

potentially fatal. The etiology of these lymphomas remains unknown, although radiation, chemotherapy, viral infection, and immune deficiencies have been associated factors.[33] Burkitt's lymphoma, a high-grade, diffuse malignant disease of small, non-cleaved lymphocytes, is most common in children of central Africa.[6] The main findings in the intraoral and extraoral examinations were swelling, pain, dental displacements, and facial asymmetry.[34]

Oral manifestations

First, the initial signs usually include cervical lymphadenopathy with associated symptoms. The head and neck may be the only area involved early in the disease (**Epstein JB et al in 2001**).[33] Oral manifestations usually include asymptomatic soft swelling with or without ulceration that primarily affect the tonsils, palate, buccal mucosa, gums, tongue, floor of the mouth, salivary glands, and retromolar region (**Ardekian L et al 1999**).[35] Alveolar bone loss with edema and pain may also occur which often mimics periodontal diseases. Lip paresthesia and pathologic fractures may also occur, and are common signs of jaw involvement (**Solomides CC et al in 2002**).[36] Oral lesions may appear as an erythematous, painless enlargement, often with surface ulceration secondary to trauma, but rarely with deep oral ulceration.[37]

Radiographic manifestations- Radiographically, it appears as noise traces with radiolucent edges, while cortical bone is expanded, eroded, or perforated by infiltration of soft tissues (**Takahashi H et al in 1992**).[38]

Multiple Myeloma

Multiple myeloma (MM) is a relatively rare malignant hematological disease, which is characterized by the multicentric proliferation of plasma cells in the bone marrow.[31] The clinical manifestations of the disease occur due to an expanding mass of plasma cells in the bone marrow. The common clinical signs and symptoms of multiple myeloma include pain in the bone, fatigue, anemia and infectious diseases.[40]

Oral manifestations

Oral lesions rarely occur as the first indication of the disease. Jaw lesions may be the primary manifestation of multiple myeloma. These include swelling, mass formation paresthesia of the lower lip, pain, bleeding and fracture of the jawbone, tooth mobility and migration, macroglossia and radiolucent lesions.[41]

Radiographic manifestations- It includes multiple punched-out radiolucencies in the jawbones or generalized rarefaction of the bone, a result of osteoporosis from marrow replacement with the malignant cells (**Mozaffari E et al in 2002** and **Pisano JJ et al in 1997**).[41] MM can exhibit three distinct radiographic aspects in the skeletal system, including, in the maxillaries: bone with no apparent alteration, multiple radiolucent areas**,** generalized bone rarefaction and osteoporotic alterations.[42]

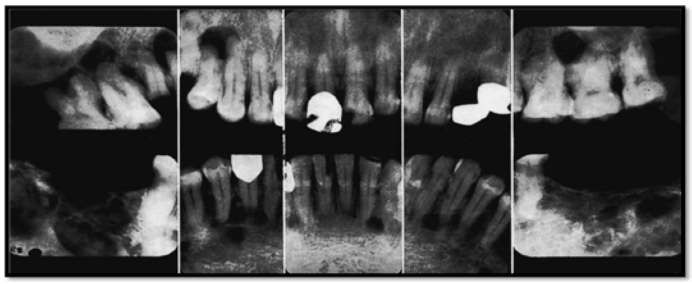

Figure 6: Intraoral radiographic series showing multiple involvement of the maxilla and the mandible in multiple myeloma.

Neutropenia

Neutropenia is a relatively common disorder most often due to chemotherapy treatments, adverse drug reactions, or autoimmune disorders. It is defined as a total circulating neutrophil count lower than $2000x10^6$/litre. It is not a disease but a sign of an underlying disorder with a wide range of underlying causes.[43]

Kostmann's syndrome- It is characterized by severe neutropenia (<500 cellsx106/ litre), recurrent bacterial

infections and failure in the maturation from promielocytes into mielocytes.[44]

Oral manifestations

In the oral cavity, agranulocytosis can appear as necrotic ulcers with a white or greyish surface without signs of inflammation.[45] Neutropenic ulcers differ from other oral ulcers in that they usually lack surrounding inflammation and are characterized by necrosis. The other most common oral complications is severe gingivitis and periodontitis.[37] Neutropenia predisposes to respiratory or cutaneous bacterial infections (**Page & Good, 1957**).[46]

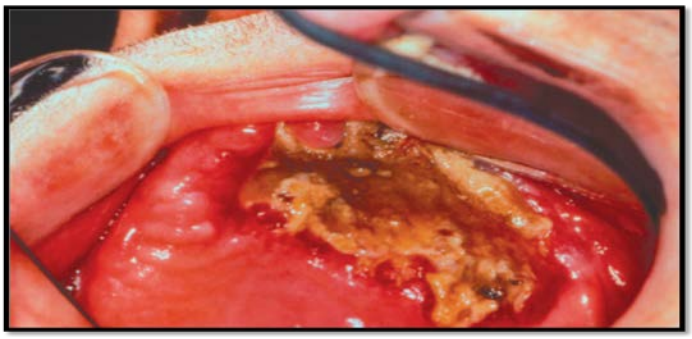

Figure 7: Oral ulcers in patients with severe neutropenia involving the palate.

Bleeding And Clotting Disorders

Platelet deficiency and vascular wall disorders result in extravasation of blood into connective and epithelial tissues of the skin and mucosa, creating small pinpoint hemorrhages, called petechiae, and larger patches, called ecchymoses. Platelet or coagulation disorders with severely altered hemostasis can result in spontaneous gingival bleeding, as may be seen in conjunction with hyperplastic hyperemic gingival enlargements in leukemic patients. Continuous oral bleeding over long periods of time fosters deposits of hemosiderin and other blood degradation products on the tooth surfaces, turning them brown.

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.[47]

Oral manifestations

Bleeding from multiple sites, frequently manifested in the mouth as gingival and post-extraction hemorrhages. Hemarthrosis is a common complication in hemophiliacs' weight-bearing joints, yet it rarely occurs in the temporomandibular joint (TMJ). Poor oral hygiene and iatrogenic factors can also induce the oral bleeding. In toddlers, oral ulcerations and ecchymosis involving palate, lips and tongue are common.[4]

According to **Nishioka GJ et al in 1988**[48] there are very few reported cases of TMJ hemarthrosis. Chronic hemophilic TMJ arthropathy may also occur, which requires arthrotomy, arthroscopic adhesion lysis, factor replacement, splint therapy and physical therapy.

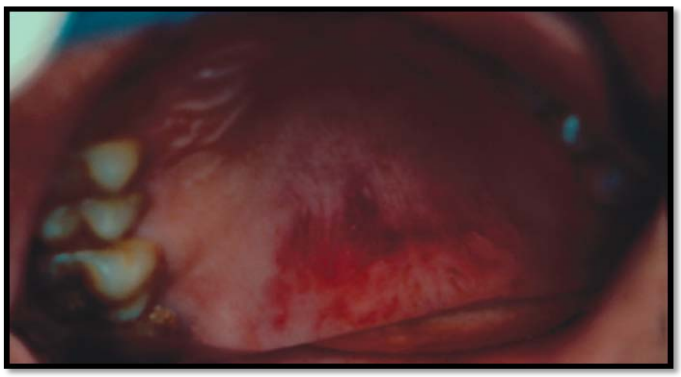

Figure 9- Palatal ecchymoses

Conclusion

Often oral manifestations are the first sign or the most significant sign of systemic disease.[1] So, to familiarize dentists and even other physicians with theses manifestations is important for them to have a better

recognition, diagnosis and correct decision upon treating these manifestations in such patients.

References

1. Amanat D, Zahedani SM. Oral Manifestations of systemic diseases: a review. Int. J. Dent.Clinics 2013;5(1):13-9.
2. Mehrotra V, Devi P, Bhovi TV, Jyoti B. Mouth as a mirror of Systemic Diseases. Gomal Journal of medical science 2010;8(2).
3. Patil S, Khaandelwal S, Doni B, Rahuman F, Kaswan S. Oral manifestations in chronic renal failure patients attending two hospitals in North Karnataka, India. Oral Health Dent Manag. 2012;11(3):100-6
4. 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.
5. Chaudhary M, Agarwal R, Holani A, Gawande M. Histological changes in tooth enamel, dentin and cementum of patients with sickle cell anemia. Journal of Oral Health Research 2012;3
6. Burket's Oral Medicine, Diagnosis and Treatment – 10th edition
7. Vinal C, Stassen LF. Dental management of the anaemic patient. 2007;53(4):191-95.
8. Kaur N, Goyal G, Padda S, Kaur B, Sunidhi. Iron deficiency anemia and oral health prospective – a review. Indian Journal of Comprehensive Dental Care 2015;5(2):655-60.
9. DeMaeyer E, Adiels-Tegman M. The prevalence of anaemia in the world. World Health Statistics Quarterly 1985;38:302–16.
10. McIntyre AS, Long RG. Prospective survey of investigations in outpatients referred with iron deficiency anemia. Gut 1993;34:1102–7.
11. Zegarelli DJ. Fungal infections of the oral cavity. Otolaryngol Clin North Am. 1993;26(6):1069-89.
12. Tefferi A. Anemia in Adults: A Contemporary Approach to Diagnosis. Mayo Clin Proc. 2003;78:1274-80.
13. 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.
14. Brown DL, Sebes JI. Sickle cell gnathopathy: Radiologic assessment. Oral Surg Oral Med Oral Pathol 1986;61:653-6.
15. Weatherall JD, Clegg JB. The thalassaemia syndromes. 3rd Oxford: Blackwell Scientific: 1981:132-74.
16. Hattab, F.N., Hazza'a, A.M. Caries risk in patients with thalassaemia major. IntDenl 2001;51(1):35-8.
17. 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.
18. Catherine Qiu Hua Chan, Lian Leng Low, Kheng Hock Lee. Oral Vitamin B12 Replacement for the Treatment of Pernicious Anemia. Front Med (Lausanne) .2016;3: 38.
19. Steinberg MH. Management of sickle cell disease. N Engl J Med 1999:340;1021–30.
20. Faccini JM. Oral manifestations of vitamin B12 deficiency. Faccini JM. Br J Oral Surg. 1968.
21. Brennan MT, Sankar V, Baccaglini L, Pillemer SR, Kingman A, Nunez O, Young NS, Atkinson

JC. Oral manifestations in patients with aplastic anemia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;92(5):503-8.

22. Rappeport JM, Bunn HF. Bone marrow failure:Aplastic anemia and other primary bone marrow disorders. In: Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL, editors. Harrison's principles of internal medicine. 13th ed. New York: McGraw-Hill, Inc.; 1994;1754-6.
23. Luker J, Scully C, Oakhill A. Gingival swelling as a manifestation of aplastic anemia. Oral Surg Oral Med Oral Pathol 1991;71:55-6.
24. Grover HS, Kapoor S, Kaushik N (2016) Polycythemia Vera Dental Management -Case Report. J Anesth Crit Care 2016;5(2).
25. Gordon Atherle Y, Lisa Taylor. Polycythemia. CDHO Advisory 2012;1-14.
26. Deliverska EG, Krasteva A. Oral signs of leukemia and dental management– literature data and case report. J of IMAB 2013;19(4):388-91.
27. G Guan, N Firth. Oral manifestations as an early clinical sign of acute myeloid leukaemia: a case report. Australian Dental Journal 2015;60:123–27.
28. Hou GL, Huang JS, Tsai CC. Analysis of oral manifestations of leukemia: a retrospective study. Oral Dis 1997;3:31–38.
29. Chung SW, Kim S, Choi JR, Yoo TH, Cha IH. Osteolytic mandible presenting as an initial manifestation of an adult acute lymphoblastic leukaemia. Int J Oral Maxillofac Surg 2011;40:1438-40.
30. Diehl LF,, Karnell LH. Menck HR. The American College of Surgeons Commission on Cancer and the American Cancer Society. National Caneer Data Base report on age, gender, treatment, and outcomes of patients with chronic lymphoeytic leukemia. Cancer 1999:86:2684-92.
31. Epstein JB, Epstein JD, Gorsky M. Characteristics of oral and paraoral malignant lymphoma: a populationbased review of 361 cases Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92(5):519–25.
32. Scardina GA, Ruggieri A, Carini F, Cacioppo A, Valenza V, Messina P. Hodgkins Disease and its oral manifestation. Current Research Journal of Biological Sciences 2007;2(4):387-91.
33. Schubert MM, Peterson DE, Silverman JR. Leukemia and Lymphoma. Ch -9:152-173.
34. Chihuam GG. Plasmablastic lymphoma: a case of rectal disease with boné marrown involvement in a HIV positive patient Ver Gastroenreol Peru 2014;34(4):347–50.
35. Ardekian L. Burkitt's Lymphoma oh the oral cavity in Israel J Cranio-MaxillofacSurg 1999;27(5):294–7.
36. Solomides CC. Lymphomas of the oral cavity: histology immunologic type, and incidence of Epstein-Barr virus infection Hum Pathol 2002;33(2):153–7.
37. Mancheno Franch A, Gavalda Esteve C, Sarrion Perez MG. Oral manifestations and dental management of patient with leukocytes alterations. J Clin Exp Dent. 2011;3(1):53-9.
38. Bernardes Silva TD, Tavares Ferreira CB, Leite LB, Menezes Pontes JR, Antunes JS. Oral manifestations of lymphoma: a systematic review. ecancer 2016;10:665.
39. Vieira-Leite-Segundo A, Lima-Falcao MF, Correia-Lins-Filho R, Marques-Soares MS, Lopez-Lopez J, Chimenos-Kustner E. Multiple Myeloma with primary manifestation in the

mandible: A case report. Med Oral Patol Oral Cir Bucal. 2008;13(4):232-4.

40. Kasamatsu A, Kimura Y, Tsujimura H, Kanazawa H, Koide N, Miyamoto I, Sakamoto YE, Shiiba M, Tanzawa H, Uzawa K. Maxillary Swelling as the First Evidence of Multiple Myeloma. Case Reports in Dentistry 2015.
41. Oral and General Health – Exploring the Connection Research Review Oral Health of Non-Head & Neck Cancer Patients Part 1: Oral Manifestations of Non-Head & Neck Cancer 2010.
42. Epstein JB, Voss NJ, Stevenson-Moore P. Maxillofacial manifestations of multiple myeloma. An unusual case and review of the literature. Oral Surg Oral Med Oral Pathol 1984;57:267-71.
43. Munshi HG. Severeneutropenia:adiagnostic approach. West J Med 2000;172:248–52.
44. Thomas ED, Blume KG, Forman SG. Hematopoietic cell transplantation. 2nd ed. Oxford, England: Blackwell Science 1999.
45. Tewari S, Tewari S, Sharma RK, Abrol P, Sen R. Necrotizing stomatitis: a possible periodontal manifestation of deferiprone-induced agranulocytosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;108:13-9.
46. Scully C, Macfadyen E, Campbell A. Oral Manifestations in Cyclic Neutropenia. British Journal of Oral Surgery 1982;20:96-101.
47. Kasper CK. Hereditary plasma clotting factor disorders and their management. Haemophilia 2000;6:13-27.
48. 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.