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Connective Tissue Disorders and Their Manifestation in Oral Cavity

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Abstract

Connective tissue diseases encompasses a wide range of heterogeneous disorders characterized by immune-mediated chronic inflammation often leading to tissue damage, collagen deposition and possible loss of function of the target organ. Connective tissue disorders (CTD) occur in 3–5% of the population. Malar rash, Raynaud’s phenomenon, Gottron’s rash, photosensitivity, and oral ulcer are the diagnostic features of connective tissue disorders. In this review, we are describing the oral manifestation and dental considerations associated with these disorders which will allow the practitioner to have a holistic approach in diagnosis and management of these patients.

Keywords: Connective Tissue, Oral Manifestation, Maxilla, Mandible.

Introduction

Connective tissue disorders are a heterogeneous group of systemic inflammatory diseases characterized by the presence of circulating auto antibodies and autoimmune-

mediated multi organ system involvement [1]. It is the most widespread and abundant type of tissue in the human body. These tissues connect and give support to the body and its organs. It generally consists of an indigenous population of cells surrounded by fibers and an amorphous ground substance. [2]

Connective tissues arise from an embryonic tissue called mesenchyme. Connective tissues fall into four main categories:

1. Loose connective tissues (adipose tissue)

2. Dense connective tissues (tendon)

3. Support tissue (cartilage and bone)

4. Blood and blood forming tissue (red marrow)

Connective tissue consists of cells surrounded by a compartment of fluid called the extracellular matrix. On the basis cells present and the extra cellular matrix structure, two types of connective tissue are: **Connective tissue proper**; further divided into loose and dense connective tissue specialised **connective tissue;** reticular, blood, bone, cartilage and adipose tissues [3]. The connective tissues include various types of fibrous tissue that vary only in their density and cellularity, as well as the more specialized and recognizable variants—bone, ligaments, tendons, cartilage, and adipose tissue. major function of the connective-tissue cells includes- binding and supporting, protecting insulating and transporting substances within the body.

The pathology of connective tissue is demonstrated by the most important example- the Inflammation, pathological reaction of connective tissue on the several irritation and injuries. [4]

There are around 200 connective tissue disorders; the etiology of these disorders can include autoimmune disease, genetic disorder and cancers. In the (table no 1) we have listed some of the common connective tissue disorders as per their etiology-

Table 1: Connective Tissue Disorders

Autoimmune Disorders	Heritable Disorders	Mixed Connective Tissue Disorders	Benign Tumors	Malignant Tumors
Rheumatoid Arthritis	Ehlers Danlos Syndrome	Systemic Lupus Erythematosus	Peripheral Giant Cell Granuloma	Hemangiopericytoma
Sjogren's Syndrome	Osteogenesis Imperfecta	Systemic Sclerosis	Central ossifying fibroma	Kaposi Sarcoma
Systemic Sclerosis	Marfans Syndrome	Polymyositis	Torus Palatines	Ewings Sarcoma
Systemic Lupus Erythematosus			Sturge Weber Syndrome	Hodgkin Lymphoma
			Osler Weber Rendu Syndrome	Non- Hodgkin Lymphoma
			Oral Hemangiomas	Burkitts Lymphoma
				Multiple Myeloma

Hereby, we are elaborating in detail some important disorders of connective tissue which have characteristic oral findings and would help the clinician in early diagnosis and treatment.

Rheumatoid Arthritis

Rheumatoid arthritis is chronic autoimmune inflammatory disease affecting the synovial membrane of diarthrodial joints. Chronic, bilateral and symmetric polyarthritis, joint pain, and inflammation that can result in deformity, instability, and destruction of synovial joints are the clinical features.[6] Its etiology is multifactorial. There is a female predominance with a peak incidence between 25 and 50 years. In 84% of patients with rheumatoid arthritis temporomandibular joint (TMJ) can be affected, clinically or radio logically. Such involvement may give rise to pain, tenderness, and possibly swelling, of the pre-auricular area, and some limitation of mandibular movement. [7] Patients with venerable active rheumatoid arthritis may have an increased incidence of periodontal disease, including an increase in pocket depths, furcation involvement, loss of alveolar bone, and teeth (fig-1). The oral mucosal consequences of rheumatoid arthritis include oral ulceration, glossitis and angular cheilitis secondary to anemia's. Radiographic findings include narrowed joint spaces, flattened condyles, erosions, subchondral sclerosis, cysts, and osteoporosis(fig-2). Differential diagnosis of rheumatoid arthritis includes- osteoarthritis,

Sjogren's syndrome, sarcoidosis, systemic lupus erythematosus.

The goals of treatment for rheumatoid arthristis are to reduce joint inflammation and pain, maximize joint function, and prevent joint destruction and deformity. Medications, considered to be fast-acting, are nonsteroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylate (Aspirin), naproxen (Naprosyn), ibuprofen (Advil and Motrin), and etodolac (Lodine). Fish oils and omega-3 fatty acid supplements are beneficial for the short-term symptoms of RA.

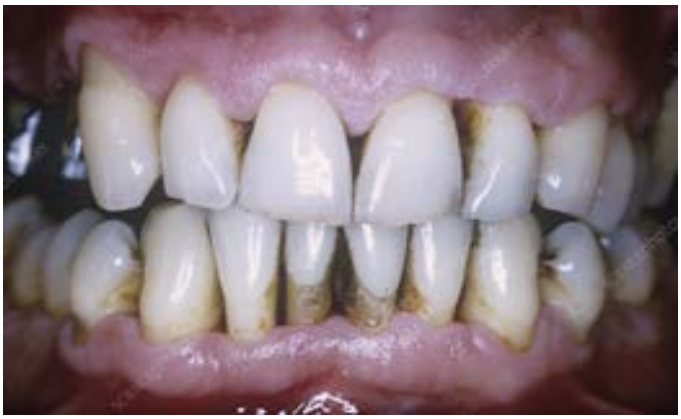

Figure 1: clinical feature of rheumatoid arthritis

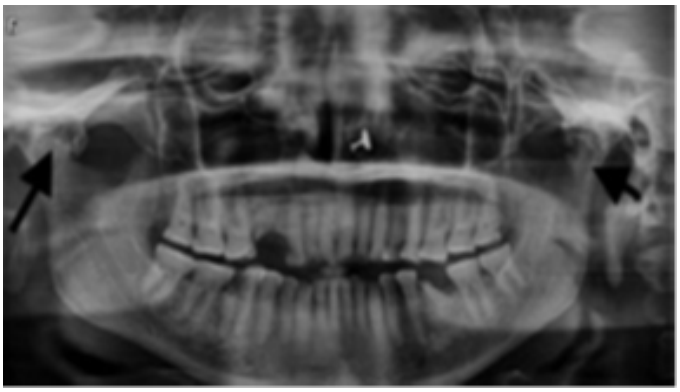

Figure 2: Panoramic view showing reduced joint space, Erosion of condylar surface

Sjogrens Syndrome

Sjogren's syndrome is an autoimmune disease affecting salivary and lacrimal glands and causing a reduction of the secretion activity due by lymphocytic infiltration and consequent destruction of the exocrine glands.[8] Etiology is unknown but certain genetic traits, stress, hormonal factors, and infections such as viruses or bacteria may act as a triggering factor in the pathogenesis of Sjogren's syndrome. It affects 0.5–3% of the entire population and is predominant in women compared to men (9: 1 ratio). It is sub classified into primary and secondary Sjogren's syndrome. If it occur alone in which there are symptoms and signs affecting mainly the eyes and mouth is called primary sjogren'syndrome and if it associated with other connective tissue disorders (rheumatoid arthritis,systemic lupus erythematosus) is called secondary sjogren's syndrome.[7] Oral manifestations of Sjogrens syndrome include parotid enlargement and findings related to decreased saliva, such as increased risk of dental caries, infections, and dysphasia (fig 3). Saliva is often thick or absent, and the oral mucosa may be dry, red, and wrinkled. The tongue possibly atrophic or fissured with deep grooves and malodorous due to food trapping (Fig 4). [9] Complication of Sjogren's syndrome is Non-Hodgkin lymphoma and neuropathy.

Dental treatment is mainly preventive, symptomatic, and supportive. Preventive therapy is aimed to prevent oral complications from the low salivary output, frequent oral examination once in every 4–6 months and radiographs should be performed annually, symptomatic treatment aimed to alleviate discomfort and pain as well as to prevent complications of xerostomia. A number of sialogogues in liquid, spray, or gel form have moistening and lubricating properties, and causes prolonged wetness of the oral mucosa,since adequate hydration of the oral mucosa is essential. Patients should be encouraged to sip water throughout the day. Patients should be cautioned to avoid having dry and bulky foods, spicy or acidic foods, beverages-containing alcohol, sugar, caffeine, or strong flavorings that may irritate sensitive, dry mucosa. Commercial available artificial saliva contains carboxymethyl cellulose, mucin, xylitol or sorbitol,

mineral salts, fluorides, and preservatives. It helps in the coating and moisturizing oral mucosa and teeth, but is for a short period.

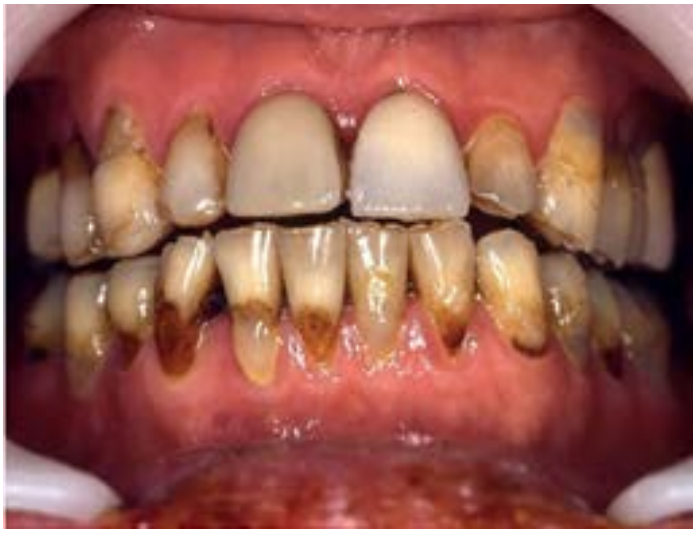

Figure 3: Root Surface Caries associated with xerostomia

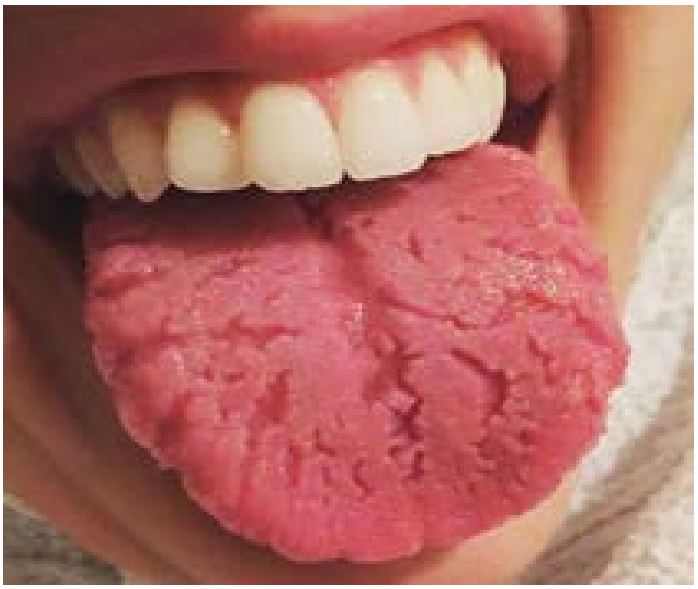

Figure 4: fissured tongue related to Sjogren's syndrome

Systemic lupus erytbematosus

Systemic lupus erythematosus is a multisystem autoimmune disease characterized by the formation and deposition of autoantibodies and immune complexes leading to inflammation and vasculopathy. The activation of type I IFN pathways, B and T cell dysfunction, and presence of antinuclear antibodies were demonstrated in the pathogenesis of systemic lupus erythematosus. Patients may also be predisposed to an erythematous maculopapular rash of sun-exposed facial skin. This '**butterfly' rash** usually extends across the bridge of the nose and zygoma. Associated oral lesions can vary greatly in appearance, manifesting as ulcerations, erythema, or hyperkeratosis (Fig 1), Cheilitis may also be present.

The prevalence of oral lesions varies between 6.5% and 21%. Oral ulcerations are frequent and listed among the minor criteria for SLE diagnosis and characteristically shallow in appearance with a tendency to occur in groups on the hard palate (fig 5). They are typically 1–2 cm in diameter and painless unless secondary infected. The associated oral ulcerations may persist for years or occur intermittently with cyclical remissions and exacerbations. SLE patients may also experience lupus cheilitis, honeycomb plaque, lichen planus like lesion, stomatodynia, dysgeusia, xerostomia, candidiasis, and periodontal disease. Lupus cheilitis has variable clinical presentations ranging from atrophic plaques to white/keratotic, purpuric, bullous, and verrucous lesions. The most common areas for lesions are buccal mucosa followed by hard palate and lower lip. Chronic lip enlargement or macrocheilia may also occur. Diagnosis of systemic lupus erythematosus is based on a multiple-organ condition and the study of antinuclear antibodies at a serum level. The differential diagnosis includes lichenoid reactions to dental fillings, traumatic or smoker's keratosis, and verrucous carcinoma. Preventive dental hygiene care in Lupus patients is very important. A Chlorhexidine mouthwash helps contain periodontal disease by chemical plaque control. Mucous membrane ulcers can be managed with hydrogen peroxide gargle or steroid impregnated gel. Intralesional injections of corticosteroids are also effective modality.[10]

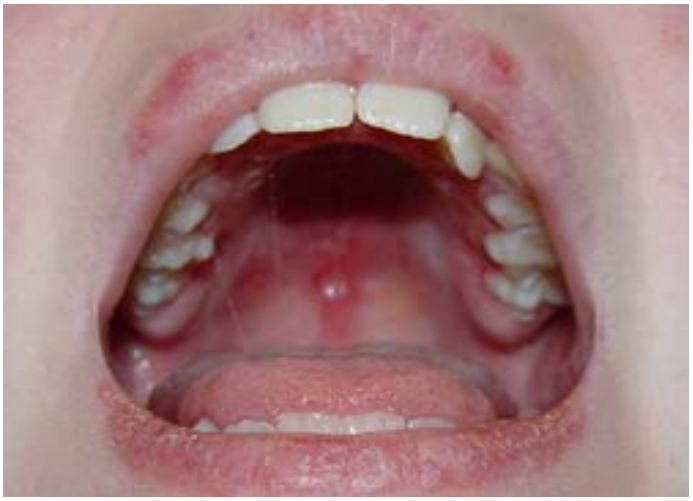

Figure 5: Shallow oral ulcers present on the hard and soft palate

Systemic Sclerosis

Systemic sclerosis is a chronic multisystem disorder, characterized by thickening of the skin caused by excessive accumulation of connective tissue [(11)]. Females are more commonly affected. Etiology of systemic sclerosis may be secondary to immunologic mechanisms, vascular endothelial cell injury, and activation of fibroblasts. It is classified into two groups as groups: limited cutaneous disease and diffuse cutaneous disease. Skin findings range from Raynaud phenomenon to masklike and "mouse" facies. [(9)] The oral manifestations include microstomia, xerostomia, telangietasia, increased decayed, missing and filled teeth. The radiographic findings include; uniform widening of the periodontal ligament space, especially around the posterior teeth (fig 6). Also the mandible shows varying degree of bone resorption. Treatment is focused on limiting further progression, although often the changes are irreversible. Range of motion Exercises may be beneficial to aid in mouth opening, and oral hygiene instruction should be provided to the patient. In patients with scleroderma patient advised to visit a dentist at least once in 3 months for the maintenance of oral health.

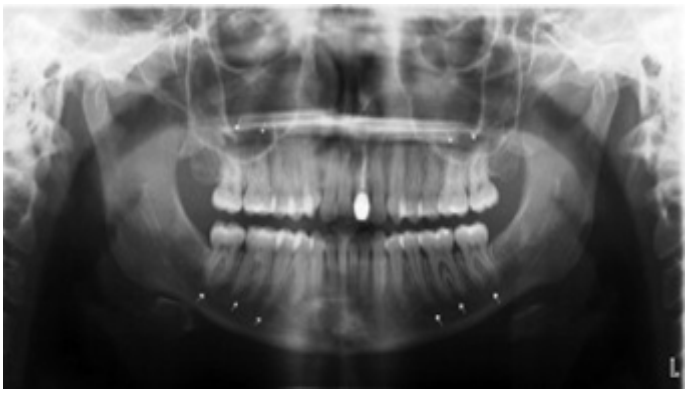

Figure 6: Panoramic radiograph of scleroderma patient with significant periodontal ligament space widening, particularly in the mandibular and maxillary posterior teeth.

Marfans Syndrome

Marfan syndrome is an autosomal-dominant genetic disorder of connective tissue that can affect different parts of the body, including the heart, blood vessels, lungs, eyes, bones, and ligaments. [(13)] Marfan syndrome arises out of mutation in the fibrillin-1 gene (FBN1) encoding the elastic fibers, a major component of connective tissue. This gene is localized in chromosome 15 (15q21) Cardiovascular disease is the cause of 90% of deaths among patients with this condition. Skeletal findings include tall stature relative to other family members (disproportionately long limbs), long digits (arachnodactyly), anterior chest deformity including protrusion (pectus carinatum) or sunken appearance (pectus excavatum) of the sternum and anterior ribs which is related to overgrowth of ribs, joint laxity or contractures, scoliosis, and craniofacial manifestations including highly arched palate(fig 7), crowded teeth, and overbite. Orofacial characteristics comprise of long and narrow face, maxillary or mandibular retrognatia, temporomandibular joint alterations, high arched palate, dental crowding, posterior crossbite, periodontal conditions.[(14)] There is greater risk of dental caries in patients with this syndrome. Supernumerary teeth and

severe dental crowding are considered highly atypical finding in this disorder. the diagnosis of Marfan syndrome is relies on the revised Ghent consensus criteria which requires major clinical signs in at least two systems and milder or less specific clinical signs in a third system. Differential diagnoses include Lujan- Fryns syndrome, Beals syndrome, MASS phenotype (mitral valve prolapsed aortic enlargement,skin and skeletal findings). Seek of treatment with Marfan syndrome is to improve life expectanc. Antibiotic prophylaxis should be used for oral procedures, such as orthodontic banding, tooth extraction, and periodontal treatment Oral administration of 50 mg/kg of amoxicillin (or 50 mg/kg of intravenous or intramuscular ampicillin for children who are unable to take oral medication) is recommended before surgery. Those who are allergic to amoxicillin or ampicillin should take 50 mg/kg of cephalexin or 20 mg/kg of clindamycin.

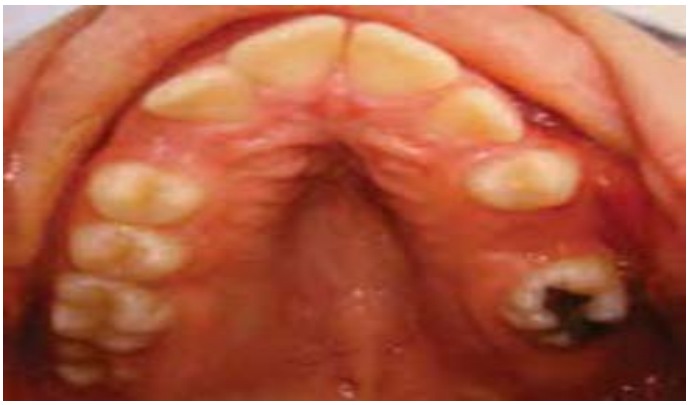

Figure 7: The palate is highly arched

Peripheral giant cell granuloma: Peripheral giant cell granuloma (PGCG) is the most common oral giant cell lesion appearing as a soft tissue extra-osseous purplish-red nodule consisting of multinucleated giant cells in a background of mononuclear stromal cells and extravasated red blood cells. [(15)] Peripheral giant cell granuloma originates from the interdental tissues (periosteum or periodontal membrane).lesion arise anywhere in the gingival or alveolar mucosa but commony occur in the anterior to the molar teeth. Peripheral giant cell granuloma is bringing into being more commonly in females than in males (2:1). Etiology of is unknown, but some local irritation factors such as poor dental restorations, dental extraction, plaque, and calculus accumulation play major role in the development of a peripheral giant cell granuloma. It is manifest clinically as a painless, soft, nodular mass, usually red to reddish-blue in color (fig 8). It seems to arise from deeper tissues and presents as a sessile or pedunculated lesion. The lesion is generally asymptomatic; however, repeated trauma due to occlusion can lead to its growth with eventual ulceration and secondary infection. Not often, the lesion is painful in nature. These lesions have a reported average diameter of less than 20 mm, but the extent of their growth capacity is not well-known, but usually is approximately about 0.5-1.5 cm.[(16)] Radiographic features are not that evident (fig 9) but, occasionally, bone involvement, widening of the periodontal ligament space accompanied by mobility of associated teeth are seen in periapical radiograph. Differential diagnosis include- central giant cell granuloma, pyogenic granuloma, peripheral ossifying fibroma, fibrous hyperplasia, inflamed irritation fibroma, hemangioma, lymphangioma, amelanotic melanoma.The treatment of preference is surgical excision with the suppression of the underlying etiologic factors.

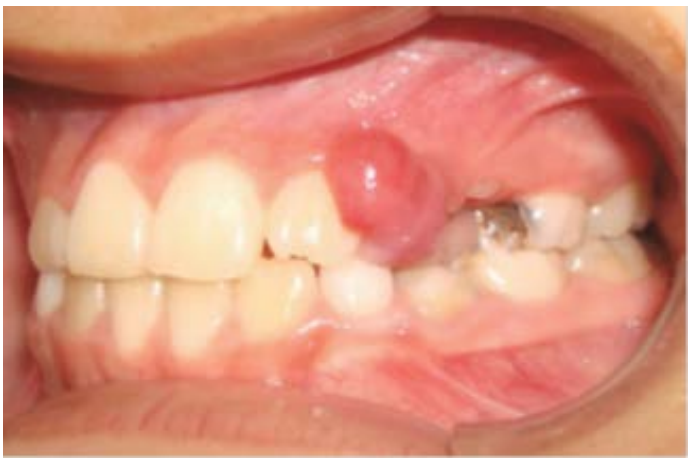

Figure 8: Nodular lesion between the upper left permanent lateral incisor and the primary canine

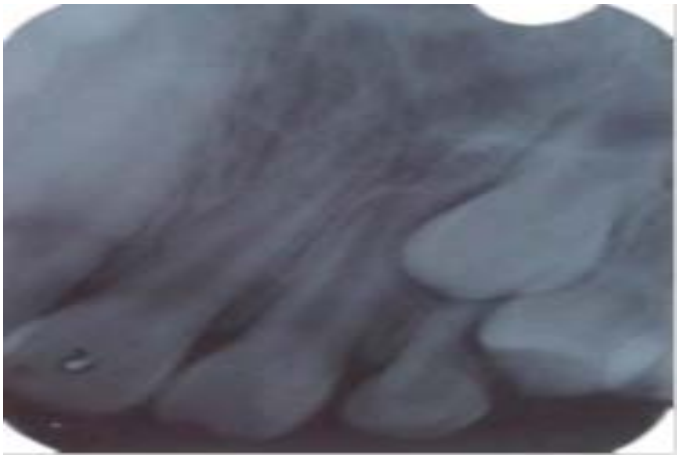

Figure 9: Radiographic aspect of the lesion without signs of abnormality.

Central ossifying fibroma

Central ossifying fibroma (COF) is a jawbone fibro-osseous lesion with the common microscopic features of trabeculae or spherules of bone or cementum-like material in a cellular fibrous connective tissue stroma.[18] This lesion occur in the second and third decades of life, commonly in women. Most commonly site of occurrence is mandibular premolar and molar areas. The aetiology of ossifying fibroma is unknown but odontogenic, developmental and traumatic origins have been suggested and thought to be of periodontal ligament origin because of their capacity to produce cementum and osteoid material.[19] This lesion usually presents clinically as a painless and expansive spherical or ovoid jawbone mass that may displace the roots of adjacent teeth and cause root resorption(fig 10). Radio graphically Six distinct radiographic patterns could be identified: (1) radiolucent, superimposed over teeth or residing in edentulous regions (28%); (2) radiolucent with opaque foci, lying in edentulous areas or superimposed over teeth (42%); (3) radiolucent, interposed between contiguous teeth (5%); (4) radiolucent with opaque foci, interposed between contiguous teeth (9%); (5) multilocular expansile (7%); and (6) aggressively expansile with opacification (9%) (fig 11). Differential diagnoses include other mixed radiolucent radiopaque lesions such as fi brous dysplasia, periapical cemental dysplasia, condensing osteitis, odontoma.

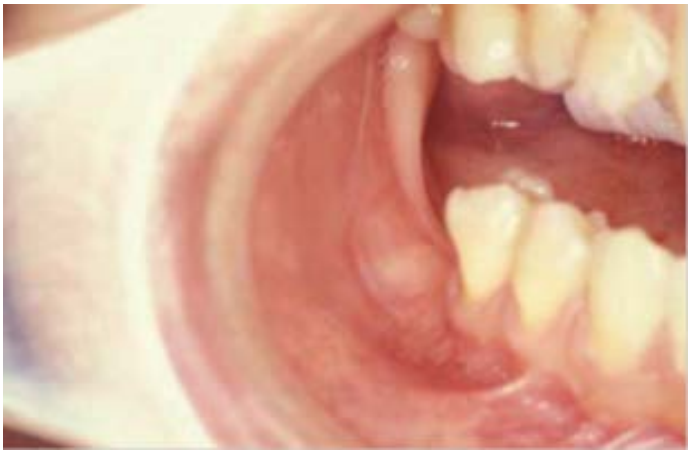

Figure 10: Intraoral picture of a central ossifying fibroma shows buccal cortical plate swelling at the edentulous alveolar ridge of the #46 and #47 areas.

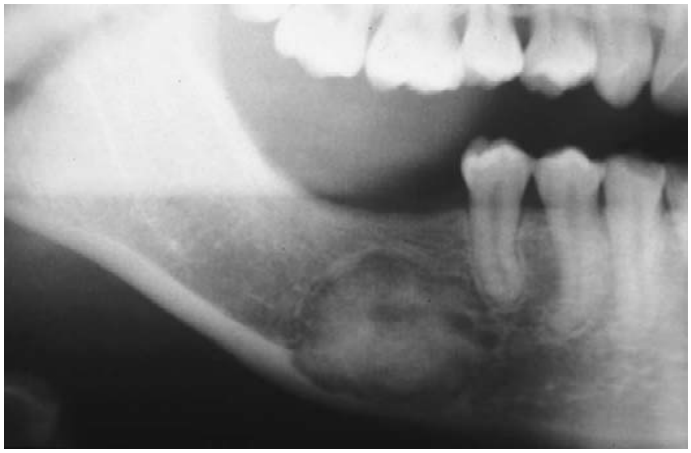

Figure 11: Panoramic radiograph of a central ossifying fibroma demonstrates a well-defined, radio-opaque lesion with sclerotic border at the edentulous alveolar ridge of the #46 and #47 areas.

Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi (Kaposi's Sarcoma, Angioreticuloendothelioma)

Kaposi sarcoma (KS) is a multifocal angioproliferative disorder of vascular endothelium, primarily affecting mucocutaneous tissues with the potential to involve viscera. Four clinical variants of classic, endemic, iatrogenic, and epidemic Kaposi sarcoma.[20] All forms of kaposi sarcoma may present in the oral cavity; however,

only epidemic variant are more likely to occur. KS-associated herpes virus or human herpesvirus-8 (HHV8) was detected in a Kaposi sarcoma lesion in 1994; by Chang et al. [21] Oral Kaposi sarcoma may also be the initial indication of undiagnosed HIV infection. Oral classic Kaposi sarcoma could present initially as well-demarcated, painless, brownish red to violaceous macule or papule. It could appear as a single or multiple lesions with dimensions varying from a few millimeters to centimeters, increasing slowly in size, forming nodules or tumors with or without ulceration (fig 12). Classic Kaposi sarcoma could invade bone and create tooth mobility. The most frequent locations are the hard palate and gingiva, whereas appearance on the buccal mucosa and tongue are rarer. Morbidity may be associated with pain, bleeding, and functional interferences caused by the tumor. Classic diagnosis of Kaposi sarcoma is made through a biopsy with other treatment modalities such as surgical excision, or electro-cauterization. The clinical differential diagnoses include bacillary angiomatosis, pyogenic granuloma, oral nevus, lymphoma, oral hemangiomas or other benign vascular proliferations.

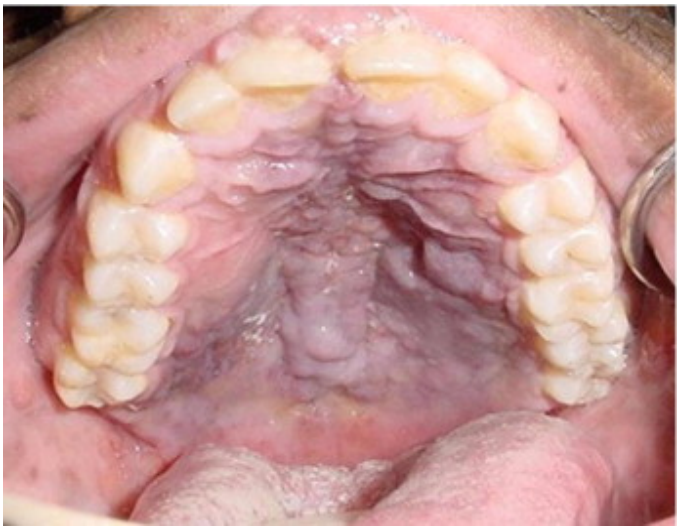

Figure 12: Clinical presentation of a bluish-purple mass affecting the palatal aspect of maxilla in an HIV-positive male.

Malignant Lymphoma

Lymphomas are a heterogeneous group of malignant diseases characterized by proliferation of malignant lymphoid cells or their precursors. [22] Lymphomas are generally classified into two major categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). They arise from the mutation of lymphocyte progenitor cells and are classified into Hodgkin's and nonHodgkin's lymphoma. Hodgkin's lymphoma occurs mainly in the lymph nodes (>90%). Intraoral finding includes ulcerations, pain, swelling, and tooth mobility, while the extraoral findings included facial asymmetry and cervical, submandibular, and submental lymphadenopathy. **Reed-Sternberg** cells are the main histopathological features for diagnosis of Hodgkin lymphoma. Treatment for Hodgkin lymphoma are chemotherapy alone or chemotherapy follow by radiotherapy sometimes steroid injection can also be given in few cases of Hodgkin lymphoma. Non-Hodgkin's lymphomas (NHLs) are a group of diverse malignancies that usually involves lymph nodes. Oral lesions of non Hodgkin lymphoma can manifest centrally within the bone or can occur in the soft tissues, most commonly the gingiva, palate, or the buccal vestibule. Patients often present with signs and symptoms such as tooth mobility, localized swelling with ulcer, unexplained dental pain, or ill-defined lytic osseous changes (fig 13). [23] Burkitt lymphoma (BL) is an aggressive form of non-Hodgkin B-cell lymphoma with 3 variants: endemic, sporadic, and immunodeficiency-associated types. The endemic form typically involves the mandible, maxilla. [24]The main findings in the intraoral and extraoral examinations were swelling, pain, dental displacements, and facial asymmetry (fig 14). Regarding imaging, the main findings were bone resorption, followed by lesions with diffuse boundaries. Signs and symptoms may include tooth mobility, dental and jaw pain, soft tissue and

gingival enlargement, and jaw expansion. Mitotic figures are abundant; as are tingible body macrophages that contain phagocytosed apoptotic debris creating the "**starry sky**" pattern visible at low-power microscopy.

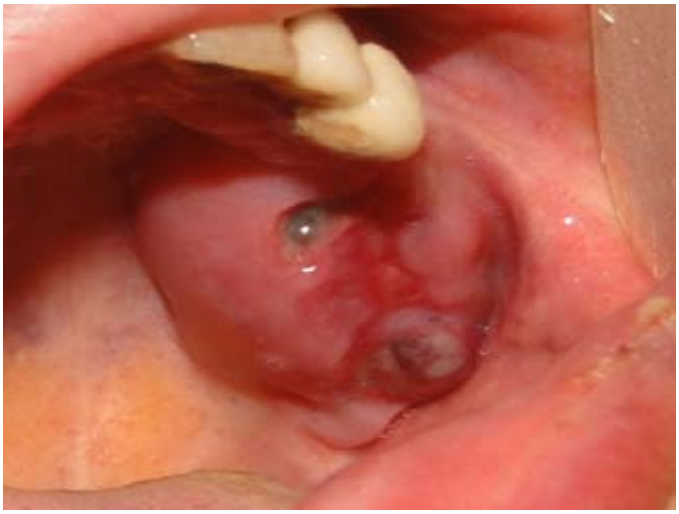

Figure 13: Gingival mass in the maxilla and mandible

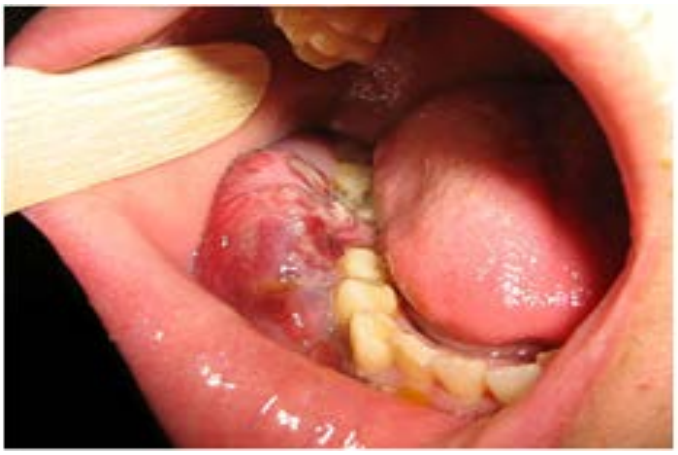

Figure 14: AIDS-associated Burkitt lymphoma of the oral cavity presenting with a rapidly growing mass of the gingiva

Multiple Myeloma

Multiple myeloma (MM) is a rare malignant hematological disease, characterized by proliferation of a single clone of plasma cells in the bone marrow. The prevalence of the oral lesions of multiple myeloma varies from less than 2–70 %[25]. It is most common in patients older than 40 years of age with a peak incidence rate at 60–70 years. Jaw lesions may be the primary manifestation of multiple myeloma with an incidence varying from 8 to 15%. 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. [26]. the common clinical signs and symptoms of multiple myeloma include pain in the bone, fatigue, anemia and infectious diseases. - Radiographic examination will usually reveal numerous sharply "**punched-out"** areas in a variety of bones, which may include the vertebrae, ribs, skull, jaws and ends of long bone(fig 15). Multiple myeloma is a deadly disease; the treatment only can prolong life span and symptom relief. Treatment protocols include administration of Dexamethasone or Prednisone, either alone or in combination with Thalidomide, remains a corner stone of multiple myeloma therapy.

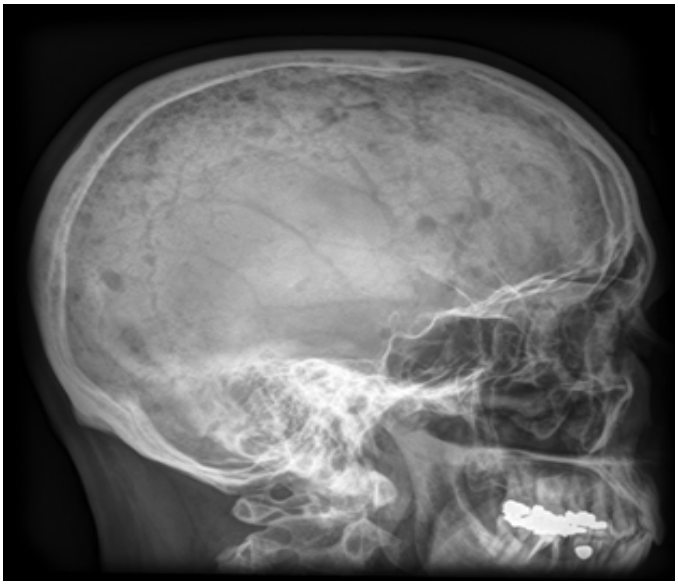

Figure 15: Multiple punched out lytic lesions are best seen in the skull vault.

Conclusion

The oral cavity provides a unique 'window into the body', and knowledge of the oral manifestations of systemic diseases will aid in diagnosis. Increasing evidence is emerging for a steady rise of autoimmune diseases in the last decades. Indeed, the growth in autoimmune diseases

equals the surge in allergic and cancer pathology; on the other hand, infections are shown to be less frequent in the western societies.

In the last 2 decades, the understanding of connective tissue structure and function has increased enormously. Dental care professionals have a key role in the management of patients with connective tissue disease, and can lessen the risk of common oral consequences, recognize oral disease that warrants specialist investigation or treatment and be able to modify the dental treatment to ensure that patients are not liable to further complications of the connective tissue disease, or its theray.

Oral manifestations of autoimmune disease are frequently the primary sign of autoimmune diseases. For many people a dental practitioner is the only healthcare professional they see on a regular basis. This review highlights the pivotal role a dental practitioner can play in the diagnosis of systemic conditions by piecing together information from a detailed history along with a thorough head and neck examination to diagnose dental, as well as medical, psychological and social problems.

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