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"Differential Responses of Oral Mucosa to Injury"

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Abstract: Responses to cell injury are characterized as cellular adaptations, and they can be either degenerative, regenerative, or restorative in nature. These responses vary depending on the cell types and level of damage caused. Aside from growth disruptions, cell injury can cause a variety of vascular, inflammatory, and immune-mediated reactions. These responses can happen simultaneously or quickly after one another, and they can affect not just the wounded cell but also the organ or organism level. Oral tissue is known to respond differently to chronic irritation\injury by developing either simple keratosis/ traumatic ulcers/ innocuous tumor-like proliferations or life-threatening ulceroproliferative malignancies. This article discusses the differential oral tissue reactions owing to chronic\ recurrent tissue injury leading to extreme or exuberant tissue response.

Keywords: Keratosis, Ulcer, Tumour-Like Proliferations, Ulceroproliferative Malignancies

Introduction-

Cells have a finite range of injury responses that depends on the type of cell and nature of the injury. Adaptation, degeneration, and death are the three types of responses. A cell can either favorably adapt to a stimulus or sublethal insult by increasing efficiency or productivity, or degenerate, losing functional capacity.[1] The response to repeated injury to the oral mucosa by deleterious agents, can produce several alterations depending upon the duration of contact and intensity of the harm produced.[2]It may result in a minor injury which is reversible, reverting cells to their normal or nearly normal structure and function, or it may cause irreversible alterations that lead to cell death.[3] The effects may perhaps range from a proliferative epithelial response i.e. frictional keratosis, if the stimulus is mild, whereas different intensities of tissue injury may possibly cause atrophy, erosions and ulcers.If the tissue irritation is for a longer period of time it may produce traumatic ulcer or may result in fibrous connective tissue growth termed as Reactive Hyperplasia, e.g. Denture-induced fibrous hyperplasia.Likewise, inflammation can act at several stages releasing chemical mediators such as cytokine, prostaglandins, and tumor necrosis factor leading to oxidative stress which in turn can induce genetic and epigenetic changes damaging DNA, inhibiting its repair, altering transcription factors, preventing apoptosis, stimulating angiogenesis thus resulting in cancer formation.[4]

Common causes of cell injury

Cell injury is defined as a variety of stresses a cell encounters as an outcome of changes in its internal and external environment.[5]Lesions resulting from physical and chemical injuries in the oral cavity are frequently identified during routine oral examinations and are a common occurrence. These include traumatic occlusion, sharp occlusal anatomy, acidic and alkaline food products or drugs, and food or drink at varying temperatures. Physical agents that can cause cell injury include mechanical trauma, extreme temperatures, radiation, and electric shock. These agents can cause damage directly (by crushing or tearing the cell) or indirectly (by disrupting the blood supply to these cells). Cell injury arises from the activation of one or more of the four primary biochemical mechanisms that affect cellular homeostasis at the molecular level: ATP depletion, permeabilization of cell membranes, disruption of metabolic pathways, and DNA damage. 1, 5 Increased workload and injury can be made up for by cells growing larger (hypertrophy, in the case of muscle) or multiplying (hyperplasia, in the case of gingiva), or if they are not able to meet the increased demand, they may degenerate or die. As a result of cumulative damage to their proteins, lipids, and nucleic acids, cells age.

Oral mucosa

Based on morphology, functional requirements, and specific pattern of differentiation, oral mucosa is divided into three types: keratinized stratified squamous epithelium (masticatory mucosa - hard palate and gingiva), non-keratinized or lining stratified squamous epithelium (buccal mucosa, labial mucosa), and specialised mucosa, which includes lingual papillae and taste buds as specialised structures allowing taste perception on the dorsal surface of the tongue. The cells of stratified squamous epithelia go through a final differentiation procedure that result in the formation of a mechanically resistant and toughened surface composed of cornified cells with keratin filaments but no nuclei or intracellular organelles. The cell membrane is replaced in these squames by a proteinaceous cornified envelope that is covalently cross linked to the keratin filaments, resulting in a highly insoluble yet flexible structure that protects the epithelial cells beneath. [6]The oral epithelial cells are frequently replaced by cell division 14 to 21 days, owing to high functional demands. The homeostasis of the epithelium is maintained through a balance between cell division and surface differentiation with desquamation. Disruption of this balance due to factors like aging or pathological conditions can lead to the development of hyperplastic or atrophic epithelium.[7]

Oral mucosal responses to injury

Likewise oral tissues respond differently to chronic irritation, by hypertrophy (e.g., gingival hypertrophy), or inflammatory papillary hyperplasia, a type of denture stomatitis or traumatic ulcer, keratosis (e.g., frictional \traumatic

keratosis), or form innocuous tumor-like proliferations (traumatic fibroma) or life-threatening ulceroproliferativemalignancies.[8]Histopathologically, these lesions may demonstrate either hyperkeratosis overlying dense fibrous connective tissue, or granulomatous tissue extending deep into the mucosal layers or may demonstrate epithelial hyperplasia with papillary projections with varying degrees of subepithelial chronic inflammation and fibrosis or loss of surface epithelium and\or basement membrane depending on the extent of damage, in ulcerations or erosions on the affected tissues. [9, 10]

Pathology of keratinization shows various patterns. These disorders can be the result of mutations in genes that code for keratin proteins, or lesions that show aberrant keratinization histopathologically due to a variety of causes. Keratinization can be altered in various ways, including increased keratinization, decreased keratinization, or aberrant keratinization. Hyperkeratinization is a specific defect observed in epithelial cells. Normally, oral epithelial cells for e.g. gingiva takes 41–75 days and buccal mucosa 25 days to shed or desquamate. This process is disrupted in hyperkeratinization due to an excess of keratin production and accumulation due to a lack of sufficient desquamation.[6] It happens as a result of prolonged inflammation, infection, or malignancies. Chronic irritation leads to hyperkeratinization, which is caused by a greater rate of epithelial cell proliferation. Decreased keratinization or a lack of keratin production occurs when epithelial cells fail to fully differentiate and mature to the stage of keratin formation.Premature keratinization happens in individual cells or groups of cells in different strata of the epithelium before they reach the surface, and is known as dyskeratosis. These dyskeratotic cells are large and spherical, with a deep eosinophilic cytoplasm and a hyperchromatic nucleus that separates them from their neighboring cells.[6]

When there is greater functional demand, the cell may adapt to the alterations that are expressed morphologically and then return back to normal if the stress is eliminated (cellular adaptations). When the stress is mild to moderate, the injured cell may recover, resulting in reversible cell injury; but, when the harm is severe, cell death may result, resulting in irreversible cell injury. Reversible cell injury may leave lingering consequences in the cell, such as evidence of subcellular injury or alterations, or metabolites may accumulate within the cell (intracellular accumulations).[2] Altered physical stimuli may cause cellular adaptations such as: increased demand, increased trophic stimulation (e.g. growth factors, hormones) leading to hyperplasia, hypertrophy whereas decreased nutrients and decreased stimulation causes atrophy. Chronic irritation (chemical or physical) may cause metaplasia.
Described as "an increase in the size of an organ or tissue due to an increase in the number of its constituent cells, as a local response of tissue to injury," an oral

inflammatory hyperplastic (IH) lesion is a common entity.One could characterize it as an excessively jubilant reparative reaction. Traumatic irritants include calculi, protruding restoration edges, foreign objects, persistent biting, sharp bone spicules, and overextended appliance borders. Whatever causes the initial chronic injury, inflammation results. Inflammation then drives the development of granulation tissue, which is made up of proliferating endothelial cells, a rich, patent capillary bed, chronic inflammatory cells, and a small number of fibroblasts. Stratified squamous epithelium quickly covers the granulation tissue.[12]

The asymptomatic, smoothly contoured or lobulated erythematous IH lesion is caused by the rich vascularity and transparency of the nonkeratinized epithelial layer. It blanchs when gently compressed digitally and is somewhat spongy and soft. Lesions vary in shape; most are sessile and have a wide base, but some are polypoid. The lesion shrinks considerably as the inflammation and vascularity decrease if further injury is avoided at this point. Should the insult be allowed to persist, the granulomatous lesion enlarges further, with the exception of the areas furthest away from the sites of irritation, where some fibrosis might show up. On the reddish surface of the lesion, these fibrotic areas show up as pale pink patches.[11]

If the initiating factor is removed during the mixed stage, the lesion will shrink in size in direct proportion to the level of inflammation. In other words, less shrinkage will occur if the lesion is primarily composed of fibrous tissue; however, significant shrinkage will occur if the lesion contains noticeable granulation tissue and inflammation. These lesions typically exhibit an injury, healing, and reinjury pattern that is fairly consistent. If excision is necessary, allowing the lesion to regress (sclerose) before excising it will simplify the process and reduce blood loss. Since fibrous tissue makes up the majority of the lesion's bulk, almost no reduction should be expected when it is pale pink and quite firm (FH). The recommended procedure is to remove the specimen and then examine it under a microscope.

Proliferative oral lesions

Different clinical terminologies have been applied depending on the traumatic agent and anatomic site involved: Inflammatory papillary hyperplasia (palatine papillomatosis), peripheral giant cell granuloma, fibrous hyperplasia (FH), pyrogenic granuloma, hormonal tumor, pulp polyp (chronic hyperplastic pulpitis), Epulis granulomatosum, and Parulis A misnomer known as peripheral ossifying fibroma or peripheral fibroma with calcification. The clinical appearance of IH lesions, which is influenced by their microstructure, dictates how they should be managed. Basically, if the irritant source can be removed and the lesion is red and mushy, there may be a noticeable shrinkage that could potentially negate the necessity for excision.

Fibrous hyperplasia (traumatic or irritational fibroma) - It is the healed end product of an inflammatory hyperplastic lesion and is not a true neoplasm. They occur commonly on the gingiva, tongue, buccal mucosa, and palate. These reactive lesions are most often sessile or slightly pedunculated with a smooth contour, pale pink in colour, and firm on palpation (Figure 1a). An excisional biopsy is the indicated treatment.[12]

Pyogenic Granuloma- This lesion develops into an ulcer on the IH. The oral flora may infect the ulceration, which is typically caused by damage during mastication, triggering an immediate inflammatory response. Clinically, the asymptomatic reddish papule, nodule, or polyp typically exhibits rough, ulcerated, and necrotic surfaces on at least a portion of its surface (Figure 1b). Although there is no pus in the lesion, early clinicians referred to it as a pyogenic granuloma because of the clinical resemblance of this necrotic white material to pus.14 The anterior gingiva is the most typical site. Additional locations include the vestibule, palate, lips, tongue, buccal mucosa, and alveolar mucosa in edentulous areas. More often than not, women are impacted than men. Upon histopathologic analysis, polymorphonuclear leukocyte clusters are seen insome areas of the granulation tissue, especially areas adjacent to the necrotic or ulcerated surface. Treatment includes surgical excision or Laser therapy.

Hormonal tumour- These lesions occur during puberty and pregnancy (first and second trimester) due to the higher levels of sex hormones during these periods, triggered by trauma\chronic irritation.[16] These IH lesions of the gingivae characteristically involve the interdental papillae and are usually deep red in colour (Figure 1c). The physiologic alterations is brought on by higher oestrogen levels and marked rise in the progesterone levels. Treatment includes surgical excision.[12]

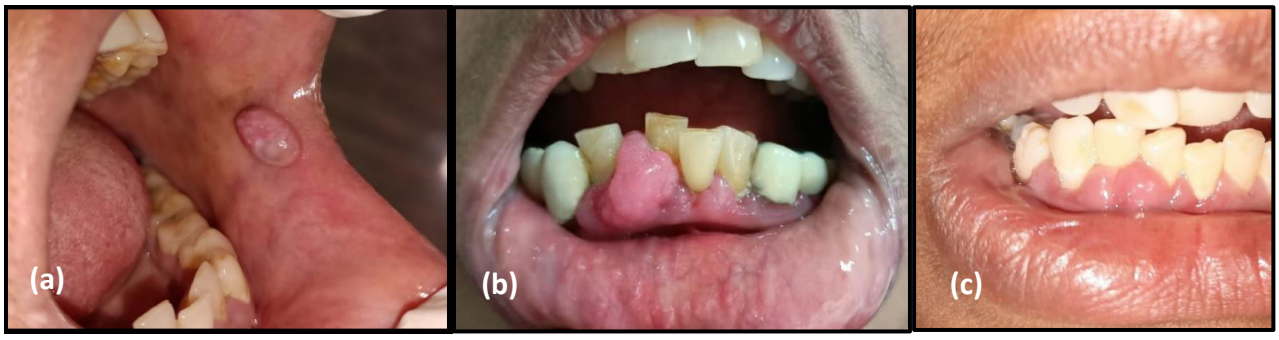

Figure 1a: Traumatic fibroma on the left buccal mucosa

Figure 1b: Pyogenic granuloma i.r.t. lower incisors

Figure 1c: Gingival hyperplasia i.r.t. lower anterior teeth due to hormonal imbalance in a female patient

Epulis Fissuratum-It is an IH lesion resulting from chronic low-grade trauma induced by denture flange of ill-fitting dentures. It's commonly observed at the

borders of the denture. It is an exophytic lesion, usually asymptomatic in nature, occurring with greater incidence in the maxilla than in the mandible and the anterior regions of both jaws are more often affected than the posterior regions (Figure 2a). It is seen predominantly in female patients. [7] Treatment includes surgical excision and addressing the causative factor to prevent recurrence of the lesion.

Parulis- It is a small IH lesion that appears on the alveolar mucosa at the oral end of a draining sinus. This lesion is commonly found in conjunction with a draining chronic alveolar abscess and a non-vital tooth (Figure 2b). The most common sites are the maxillolabial and buccoalveolar mucosae.[18] A drop of pus from the sinus aperture can be forced by slight digital pressure on the parulis' margin, and this is almost diagnostic. After the persistent odontogenic infection is eliminated, the lesion normally disappear on its own. The lesion may continue as FH if it is large and has a lot of fibrosis, and it will need to be removed.[12]

Papillary Hyperplasia of the Palate (PHP) - Palatine papillomatosis, another name for an IH lesion, is virtually exclusively found on the palate behind a full or partial removable denture. This issue affects about 10% of maxillary denture wearers, the majority of whom wear their dentures all the time. Its exact etiology is unknown, however it seems to be connected to the palatine tissue's frictional irritation caused by loose-fitting dentures.19 There may be an etiologic role for Candida albicans. While large lesions typically require surgical removal (by knife, cryosurgery, electrosurgery, or laser) before the denture is put, milder cases respond to antifungal treatment.

Peripheral Giant Cell Lesion- This lesion is classified as IH, and it most likely results in a reactive reaction in the gingiva, periosteum, and periodontal ligament (Figure 2c). It is unlikely that this lesion is a real tumor; instead, it may be reactive in character, thought to be triggered by trauma or local irritation, however the exact etiology is unknown. It differs from other IH lesions in that multinucleated giant cells, the origin of which is unknown, are present. Under a microscope, different levels of vascularity and inflammation are visible, along with a dispersion of the previously stated large cells. There are different concentrations of hemosiderin and extravasated erythrocytes. Because of this pigment or because unoxygenated erythrocytes are close to the periphery, the lesion may appear bluish. Depending on the amounts of collagen and vascular components present, the lesion may appear red to pale pink. The polypoid or nodular lesions are rubbery to soft in substance, and they are situated on the gingiva or edentulous alveolar ridge. It is more prevalent in the mandibular premolar and molar regions and is primarily present in Caucasian people. While people of all ages may be impacted, those between the ages of 30 and 70 seem to be more susceptible, and more women than males are affected. Additionally, they

frequently penetrate interdentally, eroding nearby bone and causing neighboringteeth to separate. The underlying bone may be undergoing a cupped form of resorption. Complete surgical excision, extending to the underlying bone, is the course of treatment.21 Scaling the neighboring teeth is necessary to remove any potential cause of irritation that could lead to the lesion's recurrence, which is thought to occur in 10% to 18% of cases.

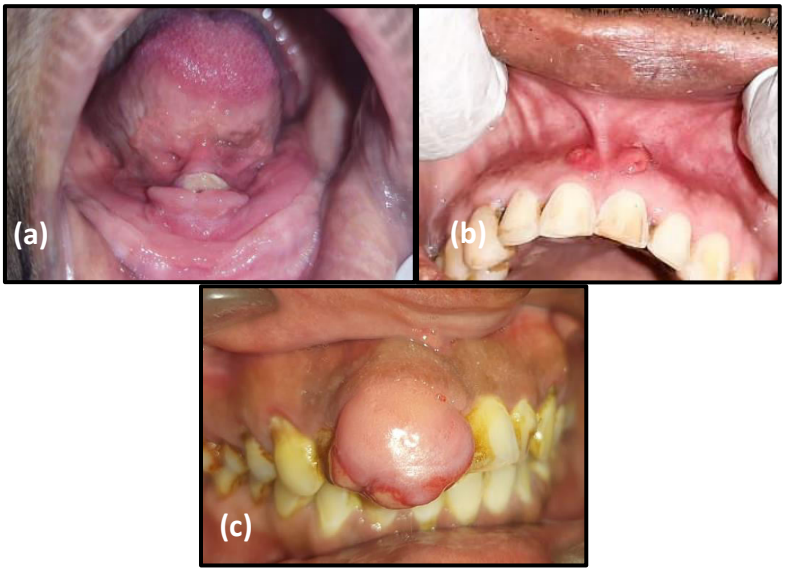

Figure 2a: Epulis Fissuratumi.r.t. floor of the mouth

Figure 2b:Parulis bilaterally i.r.t. upper central incisors

Figure 2c: Peripheral Giant Cell granuloma i.r.t. upper anterior teeth

Pulp Polyp - An IH lesion of the pulp tissue that develops when the tooth crown covering the pulp chamber is completely or partially damaged by caries. Because deciduous and permanent first molars in children and young adults have large pulp chambers, pulp polyps, also known as chronic hyperplastic pulpitis or pulpitis aperta, are typically detected in these teeth (Figure 3a). They usually grow to occupy the pulpal chamber or complete cavitated area of the tooth. It arises due to a combination of mechanical irritation and bacterial invasion into the dental pulp. The lesion acquires a stratified squamous covering, apparently as the result of a fortuitous grafting of vital exfoliated epithelial cells from the adjacent oral mucosa. Its histopathologic characteristics are identical to those of the other types of IH lesions.[22] Treatment includes pulpotomy in selected cases and in permanent tooth either root canal therapy or extraction of the tooth.

Gingival Polyp - Gingival polyps, also referred to as localized gingival enlargements, are focal fibrous hyperplastic lesions. They represent reactive hyperplasia of fibrous connective tissue in response to trauma or irritation.[15] The primary reason for the occurrence of gingival polyp is attributed to local factors such as caries, overhanging margin, calculus and tooth malposition (Figure

3b). Gingival polyp can grow into the proximal tooth cavity near the gum area like as class II cavity, however its origin can be traced to the gingiva. Sometimes, the swollen pale pink gums, enlarge to fill the area in the tooth cavity. The gold standard for treatment is surgical excision, which can be performed using a scalpel, electrocautery, or lasers.

Epulis Granulomatosum- This specific IH type of lesion grows from a tooth socket after the tooth has been extracted or otherwise lost. The precipitating cause in most cases is irritation by a sharp spicule of bone left in the walls of the socket.[23] The growth may become apparent in a week or two after the loss of the tooth and the clinical characteristics are similar to those of other IH lesions.Surgical excision is the most common treatment.

Acquired Hemangioma- While some hemangiomas are acquired later in life, the majority are congenital. IH lesions, primarily on the gingivae, may give rise to certain of the oral cavity's acquired capillary hemangiomas. Certain IH lesions with a large number of patent capillaries can have the ideal circumstances to establish a considerable blood flow during the IH stage. When the irritant is removed and the inflammation goes down, these capillary networks are still present. The resulting lesion is often nodular, bluish-red in color, bleeds readily, and may turn blanching when pressure is applied. Treatment options include carbon dioxide laser, excisional biopsy, and intralesional corticosteroid injection.

Peripheral Fibroma with Calcification- A benign proliferation of gingival tissue, peripheral fibroma with calcification (PFC) is also known as peripheral ossifying fibroma. Dental appliances, restorations, calculus, plaque, and microbes are thought to be the irritants that cause the lesion. It is believed to affect the periodontal ligament superficially and frequently has calcified deposits strewn across a fibrous tissue backdrop that resemble cementum or osteocementum. Radiopaque foci within the soft tissue tumor mass are seen on radiographs if the calcified element is considerable. PFC often affects the interdental papillae and appears on the gingiva. The lesion may cause the neighboring teeth to separate, and on occasion, there may be some visible bone resorption beneath the lesion. As with other IH lesions, causative irritants can usually be identified, and early inflammatory and late fibrotic stages are typical. The fibrotic PFC may be more common. Treatment includes surgical excision and histopathologic examination.[25] Any predisposing causes should be treated such as plaque or irritation from a dental prosthesis.

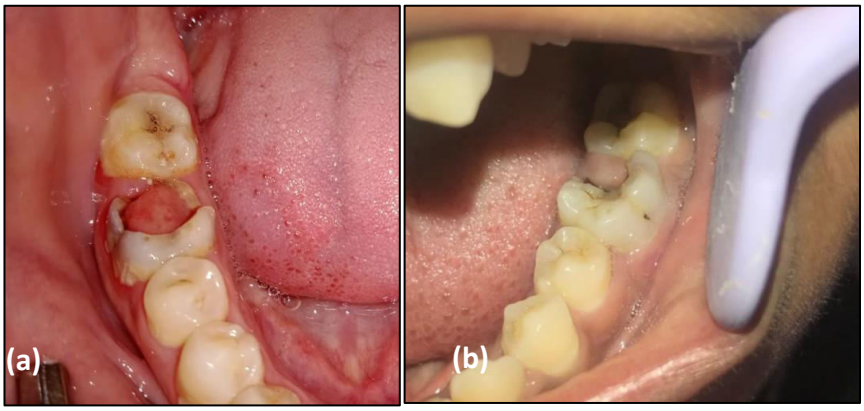

Figure 3a: Pulp polyp i.r.t. lower molar

Figure 3b: Gingival polyp i.r.t. lower molar

Ulcerative oral Lesions:-

Traumatic ulcers: Ulceration of the oral cavity may result from chemical, thermal, electrical, or mechanical trauma, either acute or chronic. Physical causes include injury by sharp or broken tooth, rough or over hanging restorations, dental instruments, self-inflicted, denture irritation, sharp foreign bodies prosthetic appliances (Figure 4a and 4b), and chemical causes include contact with chemicals, e.g., include local application of medications (e.g. aspirin), recreational drugs (e.g. cocaine), dental materials such as sodium hypochlorite, formocresol, topical oral care products such as hydrogen peroxide, denture cleaners, and mouthwashes.[26] Thermal trauma to oral tissues results most frequently from contact with high temperature substances (hot food or drinks, particularly microwaved food items), and also as a result from extreme cold temperatures as well (cryogenic burns) such as from contact with frozen metal, dry ice, or liquid nitrogen (Figure 4c). Although they can present in a variety of clinical ways, they typically manifest as a single, painful ulcer with a smooth red or whitish-yellow surface and a thin erythematous halo. They generally feel soft to the palpation and heal without leaving scars after 6 to 10 days, either on their own or after the source has been removed. Chronic traumatic ulcers, however, could clinically resemble a malignancy. Common sites include the buccal mucosa, tongue, and lip. The history and clinical features are used to make the diagnosis. However, a biopsy is required to rule out malignancy if an ulcer lasts for more than 12 to 15 days. Topical analgesics, steroids, and removal of traumatic components are the treatment.

Chemical burn clinical features include red, painful erythema that may undergo desquamation, leaving erosions.[26] The lesions usually heal spontaneously in about 7 days. The diagnosis is made exclusively on based on history and clinical grounds.

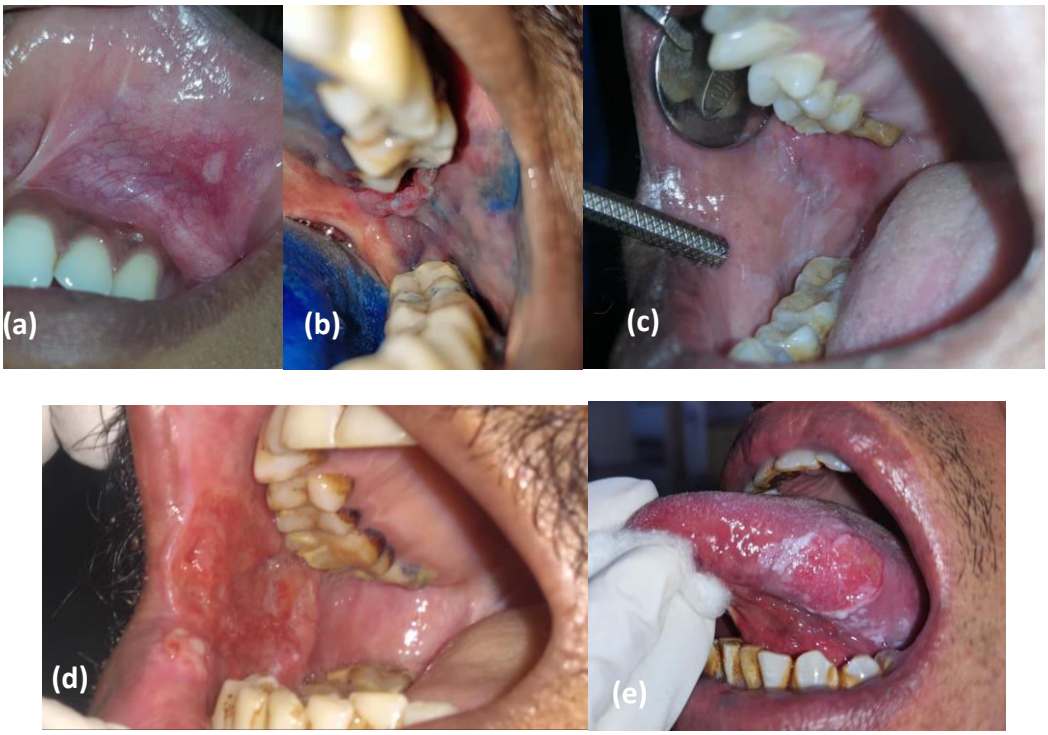

Figure 4a: Traumatic ulcer i.r.t. upper labial mucosa
Figure 4b: Major ulcer mascurading as malignancy on the buccal mucosa distal to upper third molar
Figure 4c: Chemical burn i.r.t. right buccal mucosa
Figure 4d: Ulcerative lesion on the right buccal mucosa extending from the angle of the mouth to the retromolar region
Figure 4e: Ulceroproliferative lesion i.r.t. left lateral border of the tongue

Ulcerations of neoplastic etiology

The oral mucosa goes through Chronic Mechanical Irritation (CMI) as a result of repetitive injury caused by the mechanical action of an intraoral injury source. Mechanical irritation can result from defective teeth (such as misaligned or sharp teeth), ill-fitting dentures, or parafunctional habits like oral mucosa biting, sucking, tongue interposition, or thrusting.CMI has been linked to dysplasia and carcinogenesis, and is thought to be a risk factor for oral cancer (OC). OC is detected mostly in areas that could be exposed to prosthetic or dental CMI, especially in nonsmokers with no other risk factors.[27] Irritation of the oral mucosa on a repeated basis pinpoints the tumour site, increases the incidence and malignancy index, and shortens the latency period. Breaks in mucosal integrity caused by CMI are thought to promote carcinogen absorption. Similarly, the increased cell proliferation generated by wound healing may expose cells to more random or carcinogen-driven mutations, causing malignant changes. CMI may meet the criteria to operate as a promoter cofactor in malignant transformation when it causes an open wound such as a chronic traumatic ulcer.

The classic ulcerative SCC is described as a craterlike lesion having a rolled, indurated border and a velvety base. It may be covered with a crust when

occurring on the vermilion border. The most affected sites in the oral cavity are lower lip, floor of the mouth, and ventral and lateral borders of the tongue(Figure 4d and 4e). Lesions are usually solitary, and require biopsy to rule out dysplasia or invasive OSCC.[26]

Conclusion

Oral traumatic lesions are diverse in which some present as acute lesions while majority present as chronic lesions. Oral mucosal lesions react differently to injury based on type of trauma, duration of trauma, intensity of trauma, type of oral mucosa involved etc. Thorough clinical examination and attention to all possible aspects of causative factors are mandatory for complete resolution of the lesion.

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