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Review Article

Oral Ulcers Presentation in Systemic Diseases: An Update

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Abstract

BACKGROUND: Diagnosis of oral ulceration is always challenging and has been the source of difficulty because of the remarkable overlap in their clinical presentations.

AIM: The objective of this review article is to provide updated knowledge and systemic approach regarding oral ulcers diagnosis depending upon clinical picture while excluding the other causative causes.

METHODS: For this, specialised databases and search engines involving Science Direct, Medline Plus, Scopus, PubMed and authentic textbooks were used to search topics related to the keywords such as oral ulcer, oral infections, vesiculobullous lesion, traumatic ulcer, systematic disease and stomatitis. Associated articles published from 1995 to 2019 in both dental and medical journals including the case reports, case series, original articles and reviews were considered.

RESULTS: The compilation of the significant data reveals that ulcers can be classified according to (i) duration of onset, (ii) number of ulcers and (iii) etiological factors. Causation of oral ulcers varies from slight trauma to underlying systemic diseases and malignancies.

CONCLUSION: Oral manifestations must be acknowledged for precise diagnosis and appropriate treatment.

Introduction

The breach describes ulcerations in the epithelium, underlying connective tissue or both [1]. The most frequent oral mucosal lesion that comes across is oral ulceration [2], [3], [4]. Patients having ulceration of oral cavity might report primarily to a dental consultant or a general physician.

Ulcerations can be classified based on (i) duration of onset (ii) number of ulcers and (iii) etiological factors; ulcerative lesion lasts for two weeks, is considered as the chronic ulcer. Acute ulcer lasts for no longer than two weeks and is typically painful [1], [5], whereas recurrent ulcers present with a history of comparable episodes with irregular healing and chronic ulcer may last for more than two weeks [6]. The solitary ulcer is the occurrence of a single ulcerative lesion, while the term multiple explains the incidence of numerous ulcerative lesions [6].

Because of the variety of presenting features and causative factors, identification of oral ulcerative lesions may be relatively challenging. Local or systemic factors can be contributing to developing ulcers [1], [6]. Ulcers have different parts: the floor (uncovered ulcer surface), the base (ulcer rest seat), the margin (interface among the wall of ulcer and normal epithelium) and the edge (the part of the

margin and floor). The extension phase, transition phase (preparation for healing) and the healing or repair phase are the three stages that are identified throughout a simple ulcer clinical course [7], [8].

The current review article aims to introduce a systemic approach for diagnosis of oral ulcers presenting in different systemic conditions based on their updated knowledge, structure and diagnostic features while ruling out other causative factors and this will also help the dental practitioner to reach the definite diagnosis.

Discussion

It is essential to keep in mind the differential diagnosis to reach a conclusive diagnosis. The differential diagnosis should include the lesions that cannot be skipped in the beginning and to achieve the definitive diagnosis; the additional laboratory investigations are carried out. Literature research revealed that before reaching a definite diagnosis, the malignant ulcerations of the oral cavity were wrongly detected for several months as benign lesions [9], [10].

Malignant Ulcers

Most patients presenting with oral ulcerations will have symptoms for more than two weeks, reflecting the early sign of malignancy. Some of these malignancies may include epithelial neoplasms, solid tumours like lymphomas and minor salivary malignancies can also be presented as ulcers.

Within the oral cavity, the most common malignancy of epithelial origin in oral squamous cell carcinoma (OSCC) [11], [12]. Oral squamous cell carcinoma characteristically appears as a non-healing and non-tender ulcer. In the initial stages, there are various clinical presentations which can often lead to the wrong diagnosis. The commonly affected sites are ventral and lateral borders of the tongue, the floor of the mouth, and lower lip [13]. Clinically it can be presented as the white, red, red-white, exophytic or ulcerative lesion. The typical clinical presentation of OSCC ulcer is crater-like ulcer with the indurated rolled border along with the velvety base. Ulcerative lesions of OSCC are mostly solitary, but it can be presented as multiple ulcerations in a few cases [14].

The malignant tumour of the skin (hair-bearing areas) is called basal cell carcinoma. It usually arises in the sun-exposed areas of the face; from the adjacent involved skin areas, it may spread to the mucous membrane. Initially, it appears as an elevated papule, and with the disease progression, it develops into a central crusted ulcer along with smooth rolled borders [15], [16]. The clinical site of the lesion and histopathology plays a significant role in diagnosis as the OSCC can be included in the differential diagnosis [15], [17].

Ulcer's Due to Microbial Agents

Ulcers due to microbial agents (virus, bacterial and fungal infections) are frequently encircled by an erythematous halo reflecting a healthy and inflammatory response [18]. Most of these ulcers usually have a typical clinical presentation. These ulcers typically appear as vesiculobullous lesions that initially appear as intact blisters which eventually rupture leading to ulcerations. One of the most frequent viral infections presenting with oral ulcers is symptomatic herpes simplex virus (HSV) infection known as primary herpetic gingivostomatitis. More than 90%of lesions are triggered by HSV type-1, and the rest are triggered by HSV2 [19]. After 2-3 days of initial onset, the lesion in the oral cavity usually comprises of pin-headed vesicles that often rupture resulting in painful ulcerations, enclosed by yellowish pseudo-membrane. Both non-keratinized and keratinised mucosa can be affected [20]. The mild form usually presents as a small, numerous punctate superficial ulcers which are confined to the lips and gingiva, whereas the most severe form may appear as diffuse large whitish ulceration consisting of erythematous halo surrounded by a scalloped border [10]. The ulcers typically heal within 5 to 7 days without scar formation [21]. The sores of primary herpetic gingiva-stomatitis may mimic with aphthous stomatitis and acute necrotising gingivitis [10].

Other virus-induced oral ulcers are seen in shingles (Herpes zoster infections) that are caused by the reactivation of dormant varicella-zoster virus [22]. The prevalence of Herpes zoster infections increases promptly, after the age of 50 years, with a decrease in cell-mediated immunity and immunosuppressive conditions [23]. After several days of infection, unilateral clustered and painful ulcers with 1-5 mm diameter were seen on the buccal gingivae and hard palate [6]. These ulcers will frequently rupture resulting in the formation of crater-like ulcers and erosive areas. Shingles can mimic with the herpes simplex lesions, and it can be differentiated by the distinctive pattern of the distribution of the lesion [5], [6]. Within 10-14 days, the ulcers most heal and are self-limiting [20].

Epstein-Barr virus (EBV) is affiliated to the herpes virus group, and it displays tropism for B lymphocytes. The most common lesions caused by EBV are infectious mononucleosis, nasopharyngeal carcinoma and Burkitt's lymphoma [24]. Ulcers caused by Epstein–Barr virus is infrequent but might be a characteristic of infectious mononucleosis. In oral mucosa, the ulcers typically consist of small shallow ulcers [25].

Strains of Coxsackie A virus frequently causes hand foot and mouth disease [26]. It is described as mouth ulcerations and vesicular rashes involving the extremities [26], [27]. After 1 to 2 days of infection, the oral ulcers are typically restricted to the posterior part of the mouth and most commonly present on the soft palate, buccal mucosa, hard palate and tongue. Primary herpetic gingivostomatitis, recurrent aphthous stomatitis, erythema multiform, herpangina will be considered in the differential diagnosis of hand foot and mouth disease. It can be differentiated from other lesions as it involves the extremities and oral cavity at the same time. It is a self-limiting and asymptomatic disease caused by coxsackie A virus. It commonly affects children [28].

Herpangina is typically related with soreness of throat, fever, blisters and ulcers involving the posterior part of the mouth (palate and throat) [29]. As the lesion caused by the herpangina mostly involve the posterior part of the mouth and it can help differentiate it from other viral infections and aphthous ulcers [29].

Oral lesions may be the first sign of HIV infection or HIV-disease advancement [30]. Ulcers seen in the oral cavity of HIV affected patients clinically mimic with aphthous ulcerations, but in contrast, these ulcers are more constant and are most challenging to treat with steroids [31].

The bacterial infection presenting with oral ulcerations are necrotising ulcerative gingivitis (NUG), toma, tuberculosis and syphilis. Acute necrotising ulcerative gingivitis identification can be created on clinical findings alone, as there are enough clinical signs to distinguish this disease from others. The most common symptoms are interproximal necrosis along with punched out ulceration, bleeding and soreness of the affected area and are always limited to gingiva predominantly the interdental spaces. The clinical presentation of acute necrotising ulcerative gingivitis may be different as it depends on the extent and degree of severity of the lesion [32]. Scurvy, Noma, herpetic gingivostomatitis, agranulocytosis and leukaemia can be considered in the differential diagnosis [33], [34].

Primary oral infection caused by Mycobacterium tuberculosis is uncommon. It characteristically presents as solitary, necrotic and ulcerative lesions with undermined edges most commonly affecting the tongue followed by gingivae, the floor of the mouth, palate, lips, and buccal mucosa [35], [36]. At the same time, the ulcer can be irregular, indurated and more painful. Oral SCC, traumatic ulceration, the syphilitic ulcer will be considered in the differential diagnosis of the oral tuberculous ulcer [36], [37].

Primary syphilitic ulcerative lesions caused by Treponema pallidum is generally resulted because of oro-genital or oro-anal contact with an infected lesion [38]. A chancre usually develops as a solitary ulcer after one to three weeks on the lips and rarely on the other sites of the oral cavity [34], [39]. The ulceration lesion is typically deep with a brown or red-purple base and ragged rolled border along with accompanying cervical lymphadenopathy [40]. Traumatic ulceration and squamous cell carcinoma can be included in the differential diagnosis [41]. The most common oral manifestation of secondary syphilis is mucous patches characterised by irregular ulceration, covered by a grey-white necrotic membrane and surrounded by erythema. Confluent mucous patches are known as “snail tracks “ which heals in a few weeks [42]. The most common opportunistic infection of the oral cavity is “Oral candidiasis” which is caused by increased growth of Candida albicans species [43]. Candidiasis infrequently results in oral ulceration [44].

The most common characteristic of oral blastomycosis is painless, nonspecific, verrucous ulcer with indurated borders that is frequently misdiagnosed as OSCC [44]. Moreover, South American Blastomycosis may produce a larger area of ulceration in immunocompromised patients and can be suggestive of OSCC [45]. Further, the most frequent oral manifestation of mucormycosis is palatal ulceration resulting from necrosis; lips, gingivae and alveolar ridge can also be affected [46].

Ulcers Due to Hormonal Imbalance

The imbalances in the hormones are present in numerous diseases related to the endocrine system of the human body as pregnancy and puberty. They may occur during pregnancy and puberty and also by the use of oral contraceptives [34]. Many researchers have recommended a direct relation among fluctuating hormonal status and oral health [47]. Hormonal imbalances expressed as increased salivary estrogen level provoke local physical changes such as increased exfoliation of the oral epithelium causing ulcerations in oral cavity among females during the normal menstrual cycle and pregnancy [34].

Ulcers Due to Systemic Disorders

Systemic disorders may lead to disturbances in oral conditions, and one of the most common oral presentations is ulceration. The differential diagnosis of these ulcers can include chancre, ANUG, early squamous cell carcinoma, leukaemia, traumatic abscess, cyclic neutropenia [48]. Most of the time, the oral site can act as the first indication of blood born disease before other signs and symptoms appear. An abnormal decrease in the circulating red blood cells is called anemia. Pernicious anemia and iron deficiency anemia may present with superficial and small ulcer which mimic aphthous like ulcerations. The periodic decrease in circulating neutrophils due todefects in maturation of neutrophils may lead to a lethal

systemic condtion called cyclic neutropenia, with oral manifestation characterized as solitary / multiple painful ulcers with an erythematous halo that may last for 10-14 days with healing results in scarring. These ulcers may resemble with major types of the aphthous ulcer; and can be differentiated from major recurrent aphthous stomatitis (RAS) by periodontal destruction [49], [50].

Ulcers Due to Inflammatory Bowel Diseases

The most frequent inflammatory bowel disease (IBD) includes ulcerative colitis and Crohn's disease. Lesions of the oral cavity may be apparent and last for months to a year before or at the same time with the abdominal symptoms when IBD disease appear [51], [52]. Aphthous ulcerations is proved to be the most common oral manifestation of IBD during its active phase [49]. In Crohn's disease, two types of oral ulcers can occur one is characterised as deep linear ulcers, having rolled edges which frequently involve the buccal vestibules. The other type of ulcer is superficial mucosal ulceration. The differential diagnosis of such ulcers includes other granulomatous diseases like sarcoidosis [53], [54], [55]. However, the oral lesions of ulcerative colitis include oral aphthous like ulcerations, diffuse pustules, lichen planus and Pyostomatitis vegetans [56].

Ulcers Due to Immune-Mediated Disorders

One of the most common inflammatory lesions of the oral cavity is known as “Recurrent Aphthous Stomatitis” (RAS) [57]. Clinically, it is described by oral ulceration recurrent episodes in an otherwise healthy individual. non-keratinized mucosa of the oral cavity is mostly affected. It can be categorised as minor aphthous, major aphthous and herpetiform [32]. Classically the ulcers appear as a rounded, tender mucosal surface covering with fibrin slough surrounded by an erythematous border. Major aphthous ulcers may result in scarring upon healing, and these ulcers may merge to produce large ulcerative areas [58]. Aphthous ulcers are similar in appearance and site to those ulcers observed in Bechet’s disease. Though in the Bechet’s disease number of ulcerations is greater and of longer duration and is more tender in comparison to aphthous [59]. Along with the aphthous ulceration in Bechet’s syndrome, anogenital and ocular ulceration and arthralgia are helpful in diagnosis [60].

Vesiculobullous Lesions of the Oral Cavity

Various vesiculobullous immune-mediated diseases like mucous membrane pemphigoid pemphigus vulgaris, erosive lichen planus can present with chronic and multiple oral ulcerations [61], [62]. Immune-mediated vesiculobullous lesion of the oral cavity causes blisters formation followed by ulceration of oral mucosa discomfort. Lichen planus is an immune-mediated chronic disease affecting the middle age with female prediction [63]. Oral lichen planus may present in the absence of skin lesions or can occur along with skin involvement. Erosive type present with ulcer covered with pseudomembrane slough along with erythema and keratosis with the multifocal pattern of spreading, bullous like lesion combined with reticular and erosive pattern [64], [65], [66]. Hypersensitivity disease characteristically comprised of irregular erythematous vesicles along with plaques resulting in the formation of the target like or bull’s eye lesions that can be precipitated by multiple factors like drugs, viral and fungal infections. The typically affected areas are lips and buccal mucosa. The lesions are usually ulcerated having an inflammatory halo with irregular margins. The characteristic finding of the disease is severe crusting lesion involving the lips [67], [68]. Erythema multiform is often mixed up with primary herpetic gingivostomatitis but can be differentiated by the appearance and pattern of distribution of lesions of the oral cavity. Another immune-mediated vesiculobullous disease is pemphigus vulgaris described by lack of adhesion of cells resulting in the formation of blisters [69]. Oral lesions are developed in 90% of cases of pemphigus vulgaris. In 50% of cases, it is the first sign of disease. The lesion of oral cavity first appears as bulla which has a very thin roof which ruptures rapidly because of any traumatic insult, resulting in the formation of chronic painful bleeding ulcers with irregular borders which heal with difficulty whereas mucous membrane pemphigoid is characterised by immune-mediated reaction at the level of basement membrane [69]. It has a female predisposition and occurs most commonly at the age of 40. The most frequently affected sites are gingiva before it involves other mucosal sites. Lesions of mucous membrane pemphigoid are usually hemorrhagic that typically result in scar formation upon healing.

Traumatic Ulcers/ Iatrogenic/Idiopathic Ulcers

Injuries due to trauma affecting the oral cavity may characteristically result in the surface ulcerations. Traumatic ulceration is among the most common oral cavity ulcerations [70]. Sublingual ulcerations are seen in newborns and infants; in case of Riga-Fede disease and this may result because of chronic mucosal irritation because of the premature eruption of deciduous teeth (natal or neonatal teeth) and it is frequently related with breastfeeding. The traumatic ulceration in children most commonly occurs because of thermal or electrical factors and affected mostly commissure and lip areas whereas in adults the traumatic ulceration is characteristically the result of mechanical injuries like malformed or fractured teeth; ill-fitting dentures; overheated foods and radiation

injuries [71], [72]. Traumatic ulcers involving the dorsum of the tongue may mimic to the ulcerations triggered by proliferative reactive processes like traumatic ulcerative granuloma, specific infections and lymphoma and definite diagnosis are made microscopically [70]. Traumatic ulcers mostly appear as erythematous, raised edges with a yellowish-white necrotic pseudomembrane which can be easily removed. The ulcerations involving the vermillion border of the lip typically have crusted appearance. Traumatic ulcers mostly heal within ten days after the removal of injurious factors. A differential diagnosis is made from following factors: (i) the lesion's size, (ii) location, (iii) number, (iv) onset, (v) the age of the patient, (vi) association of other systems of the body and (vii) progression of the disease [15].

Conclusions

Oral ulceration diagnosis is always challenging and needs a thorough history taking and clinical examination. The fact cannot be denied that oral presentation may be a sign of some larger underlying systemic disease. Any ulcer that lasts longer than two weeks should be examined histopathologically. This newly updated review included 20 oral ulcerative lesions which are established on the number and duration of oral ulcers. This helps the dental clinicians to create a stepwise method to rule out doubtful conditions to reach a definite diagnosis.

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